

REVIEW

Mild Parkinsonian Signs: A Systematic Review of Clinical, Imaging, and Pathological Associations

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ABSTRACT: Mild parkinsonian signs (MPS) have been widely studied during the past 3 decades and proposed as a risk marker for neurodegenerative disease. This systematic review explores the epidemiology, clinical and prognostic associations, radiological features, and pathological findings associated with MPS in older adults free from neurodegenerative disease. We find that MPS as currently defined are strongly associated with increasing age and increased risk of development of Parkinson's disease (PD), all-cause dementia, disability, and death. Positive associations with later PD are found mainly in younger populations and those with other features of prodromal PD. There are currently no consistent radiological findings for MPS, and pathological studies have shown that MPS, at least in the oldest old, are often underpinned by mixed neuropathologies, including those associated with Alzheimer's disease,

cerebrovascular disease, nigral neuronal loss, and Lewy bodies. Different subcategories of MPS appear to convey varying risk and specificity for PD and other outcomes. MPS overall are not specific for parkinsonian disorders and, although associated with increased risk of PD, can reflect multiple pathologies, particularly in older individuals. "Mild motor signs" appears a more appropriate term to avoid prognostic and pathological implications, and larger future studies to prospectively examine outcomes and associations of specific MPS subcategories are required. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: parkinsonism; cognitive disorders; systematic review

The term *mild parkinsonian signs* (MPS) has been used to report subtle clinical findings characteristic of parkinsonian disorders. They have commonly been reported in aging populations, including older adults without known neurodegenerative disease. Their underlying basis, prevalence, clinical correlates, and prognostic value is, however, not well understood. Louis and Bennett¹ previously published a narrative review on this

topic in 2007, but to our knowledge no systematic review of the literature on MPS has been published. To understand their basis, define the concept of MPS, and help interpret the relevance of these signs and their prognostic value, we performed a systematic review of studies on epidemiology, clinical associations, and radiological and pathological features of MPS in older adults without neurodegenerative diseases.

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Methods

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses² reporting guidelines.

The search strategy was designed to detect peer-reviewed journal articles that included examination of MPS in adults without neurodegenerative disease using clear criteria distinguishing these individuals from those with other known causes of parkinsonism.

Study Types

Articles of the following types were included:

1. Descriptive studies of the prevalence, incidence, and associations of MPS from cohort and case-control studies of community-based older adults.
2. Cohort or case-control studies investigating the imaging features of MPS.
3. Cohort or case-control studies investigating the pathological features of MPS.

Exclusion Criteria

1. Studies lacking a clear definition of MPS distinguishing them from other causes of parkinsonism.
2. Studies that did not systematically assess a range of parkinsonian signs (bradykinesia, rigidity, gait, and tremor).

Studies Investigating MPS in the Context of Other Known Diagnoses (eg, Alzheimer's Disease)

Medline and Embase databases were searched up to August 25, 2020. Details of the search strategy are included in Appendix S1. As there may be a delay in categorizing recently entered articles, the most recent 24 months were searched without applying limits. Non-English-language titles were included. Data from relevant articles were collected using a standard template to record the number of participants, average age, cognitive status, prevalence, or incidence of MPS and key findings. Results were considered under the categories of epidemiology, clinical associations, radiological features, and pathological features.

Results

A total of 1875 titles and abstracts were scanned, and the majority excluded most describing parkinsonism in the context of other diagnoses, such as Alzheimer's disease (AD), Parkinson's disease (PD), and genetic and other neurodegenerative conditions. The full, de-duplicated list of articles and the final included articles are included in Appendixes 2 and Appendixes 3, and the flowchart of article selection in Figure S1. English abstracts were available for all articles not written in English. Two non-English-language articles^{3,4} were among the final 131 reviewed in full; use of translation software revealed that one did not meet the inclusion criteria,³ and data from the other cohort were reported elsewhere in English.⁴ A total of 98 articles were included in this review.

Classification and Definition

MPS have been defined and assessed in multiple ways. A general definition is that these are signs of parkinsonism not meeting the threshold for a diagnosis of PD.¹ Various alternative terms for MPS have been used including (subtle) extrapyramidal signs, parkinsonism, and parkinsonian-like. In most studies, with a few exceptions (mainly earlier studies),⁵⁻¹¹ MPS has been operationally defined using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor scale; UPDRS-III).¹² It should, however, be noted that this tool was not designed to diagnose PD or identify prodromal parkinsonian features but to measure severity in established PD.¹³ To define MPS, items from this scale have been variously used as a continuous measure or subgrouped in multiple ways with different thresholds applied to create categorical definitions. More recent studies¹⁴⁻¹⁹ have used the Movement Disorders Society-UPDRS (hereafter, MDS-UPDRS),²⁰ which was designed to capture abnormalities at the milder end of the spectrum in individuals with PD and is likely to have increased the sensitivity to motor changes in the general elderly population. Although similar, with the mapping of items and subscales available,^{20,21} the item definitions of the two scales are not identical, and the results of studies on MPS are therefore not completely comparable.

The two best described cohorts in which MPS have been studied are the Religious Orders Study/Memory and Aging Project (ROS/MAP) and Washington Heights-Inwood Columbia Aging Project (WHICAP); each has used different diagnostic criteria (Table 1). The number of items included differs: the ROS/MAP^{23,25} studies use 26 items from the UPDRS-III, including an additional turning item, grouped into four motor domains of parkinsonian gait, bradykinesia, rigidity, and tremor, whereas the WHICAP²² definition uses 10 items. The WHICAP definition excludes several items that are considered core features of PD, such as limb bradykinesia and gait,²² whereas the modified UPDRS-III (mUPDRS) used in the ROS/MAP group includes items not entirely specific for parkinsonian disorders, such as action or postural tremor^{12,20,23} (Table 1).

The ROS/MAP criteria have been variously used as a continuous score,²⁶⁻³⁴ binarized,³⁵⁻³⁸ or trinarized.^{25,39,40} Head-to-head comparisons of these criteria are rare; in the ROS/MAP cohort²⁵ (n = 2962; mean age, 78.3 years), the prevalence of "parkinsonism" (used as a binary category) was 26.2% compared with 57.9% using WHICAP; using the more lenient "possible parkinsonism" category (to create a "trinary" classification) took in a further 29.9%, making the combined prevalence similar to WHICAP (56.1% vs. 57.9%). These two definitions also gave similar results in the Bruneck cohort^{41,42}

TABLE 1 *Contrasting definitions of MPS*

WHICAP binary classification	ROS/MAP binary classification	MDS criteria for possible subthreshold parkinsonism
See reference 22	See reference 23	See reference 24
10 items from UPDRS-III, includes rigidity in five regions, facial expression, speech, posture, body bradykinesia, rest tremor (counted as a single item) Notably excludes limb bradykinesia, gait	26 items from the UPDRS-III with custom modifications to item descriptions, including an additional turning assessment	Entire UPDRS-III excluding action tremor, or entire MDS-UPDRS, excluding postural and action tremor
MPS defined as two or more UPDRS-III items with a score of 1, one item with a score of ≥ 2 , or UPDRS-III rest tremor item ≥ 1	Divided into four subscales, “parkinsonism” defined as a summed score ≥ 2 in two or more subscales, “possible parkinsonism” ≥ 2 in one subscale	UPDRS-III score >3 , or MDS-UPDRS score >6 , (Items confounded by comorbid conditions excluded when calculating score.)

MPS, mild parkinsonian signs; WHICAP, Washington Heights-Inwood Columbia Project; ROS/MAP, Religious Orders Study/Memory and Aging Project; UPDRS-III, Unified Parkinson’s Disease Rating Scale Part III; MDS-UPDRS, Movement Disorders Society–Unified Parkinson’s Disease Rating Scale.

($n = 393$; mean age, 66.5 years): annualized incidence 3.2% (ROS/MAP) versus 2.8% (WHICAP). However, when the binary categorization is used the prevalence is markedly different; additionally, due to differences in included items the classifications may not select the same group of individuals.

Many other definitions have been used; one of the most prevalent variations has been to apply the WHICAP cut-points to the entire UPDRS-III.^{41,43-51} Definitions have been proposed for prodromal PD, including adding bradykinesia to the WHICAP definition¹⁸ and the MDS criteria for subthreshold parkinsonism (Table 1).²⁴

In addition to forming categorical definitions, many studies define subcategories according to the clinical domains of PD, or using factor analyses,^{52,53} generally considered under headings such as rigidity,

bradykinesia, axial dysfunction, gait dysfunction, or tremor (see the MPS Subcategories section for a summary).

These variations in definitions are likely to explain some of the variation in results, which in turn hampers the comparison between studies and meta-analytical approaches.

Incidence and Prevalence

The estimated prevalence of MPS varies widely, from 4% to 46%.^{6,54} This is likely to be largely attributable to heterogeneity in classification (as noted previously) and differences in cohort characteristics. Age is highly associated with the prevalence of MPS: in one study, MPS increased from 14.9% at ages 65 to 74 years to 52.4% in individuals aged 85 years and older,⁷ with similar results in other studies.^{14,19,25,55-60} Average age also varies widely in cohorts, from 54.6 to 82.9 years in community-based epidemiological studies^{61,62} (Fig. 1).

Incidence rates for MPS are shown in Table 2. As with prevalence, differing classification approaches are likely to influence incidence rates (see the Classification and Definition section). Age is also a significant predictor of incidence of MPS⁴¹: Buchman et al³⁹ showed the incidence increasing from 36.0/1000 person-years at ages ≤ 75 years to 94.8 for ages 75 to 84 years, and 160.5 for ages ≥ 85 years.

Longitudinal Stability of MPS

In keeping with age-related increases in prevalence, MPS severity increases over longitudinal follow-up. There is marked interindividual variability in the rate of

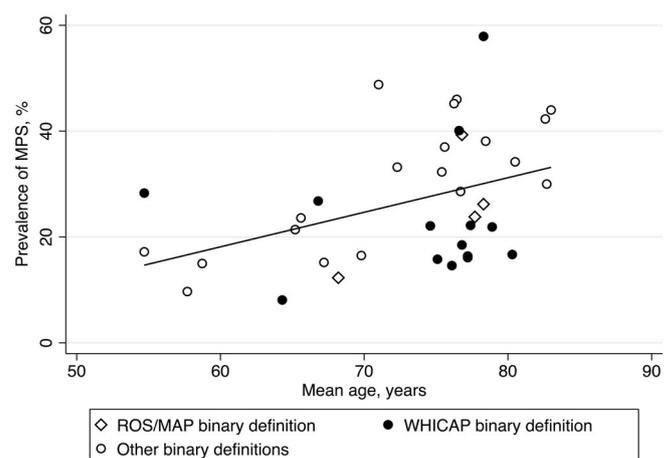


FIG. 1. Prevalence of MPS by age, from 39 studies where both a cross-sectional prevalence and mean age could be extracted. Note: “other” definitions were predominantly based on the entire Unified Parkinson’s Disease Rating Scale Part III (with a threshold applied to create a binary definition). MPS, mild parkinsonian signs; ROS/MAP, Religious Orders Study/Memory and Aging Project; WHICAP, Washington Heights-Inwood Columbia Aging Project.

TABLE 2 Incidence of MPS

Cohort, reference	n	Definition of MPS	Mean follow-up, years	Mean age, years (baseline)	Annualized incidence, %	Independent predictors of incident MPS
ROS/MAP ³⁹	2001	ROS/MAP (See Table 1)	5.4	76.8	8.9	Age, higher baseline mUPDRS, lower global motor score (a composite of 10 motor measures), smoking
MAP ³⁸	682*	ROS/MAP (See Table 1)	4.1	81.5	8.3	Higher number of vascular conditions and depressive symptoms; lower physical activity, global cognitive and global motor scores
Bruneck ⁴¹	393	Score of ≥ 2 for entire summed UPDRS-III, or resting tremor ≥ 1	5	65.8	5.5	Age, decreased olfactory function, SN echogenicity
Ama-cho ⁶³	299*	WHICAP (See Table 1)	3	74.7*	8.4	Not specified
Ama-cho ⁶⁴	316	WHICAP (See Table 1)	8	72.8	3.7	Higher scores on Tanner questionnaire (parkinsonian symptoms), PSQI; lower reported exercise, higher DWMH Fazekas score
CCMA ⁶⁵	115*	Summed UPDRS-III score > 0 in one of three domains: Bradykinesia (limb/axial), Rigidity, Rest tremor	1	74.6*	47.8	Higher number of cardiac conditions

*Numbers apply to “normal motor” group at baseline.

Abbreviations: MPS, mild parkinsonian signs; ROS/MAP, Religious Orders Study/Memory and Aging Project; mUPDRS, modified Unified Parkinson's Disease Rating Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale Part III; Ama-cho, cohort study from Ama-cho (Japan); WHICAP, Washington Heights-Inwood Colombia Aging Project; PSQI, Pittsburgh Sleep Quality Index questionnaire; DWMH, deep white matter hyperintensities; CCMA, Central Control of Mobility in Aging study.

progression. In the ROS cohort,³³ 79% of individuals showed increases in mUPDRS over 4.6 years of follow-up (range, 0.001–0.797 points/year). Factors influencing progression are detailed in the following sections. MPS can also regress^{33,63,65}; 21% of those studied by Wilson et al³³ showed improvement of between -2 and 0 points per year. This is further illustrated by two studies using (differing) binary definitions of MPS. In both, baseline MPS regressed to normal in $\sim 38\%$ of individuals.^{63,65} Younger participants were more likely to regress. Wada-Isoe et al⁶³ additionally found that a higher baseline Mini-Mental State Examination (MMSE) score, and lower periventricular and deep white matter hyperintensities (WMH; a measure of cerebrovascular pathology) predicted regression. Mahoney and colleagues⁶⁵ found that slower gait velocity at baseline predicted persistence of signs. The authors hypothesized that MPS regression might be attributed to the effect of exercise, or rehabilitative efforts,^{63,65} noting that individuals with regression tended to be younger, perhaps having

higher potential for neuroplasticity. A role for exercise is supported in other studies (see the Lifestyle Factors section). It is also likely that unmeasured factors

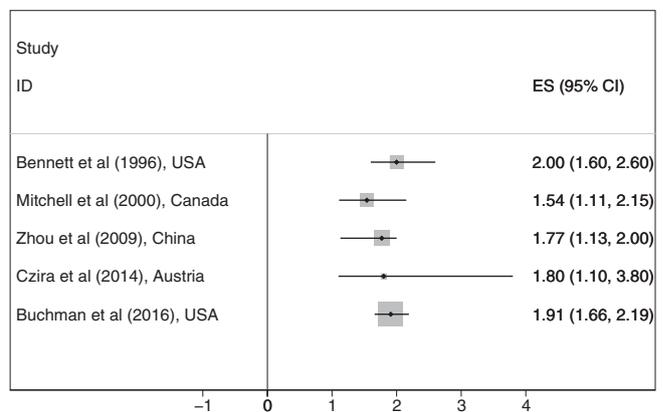


FIG. 2. Forest plot showing hazard ratios for mortality in individuals with baseline mild parkinsonian signs. CI, confidence interval; ES, effect size; ID, identification.

including fatigue, intercurrent illness, or transient musculoskeletal issues could cause small fluctuations in UPDRS-III in older adults. Finally, although interrater properties of the UPDRS-III are good, small variations are possible with re-rating, noting that interrater variability is increased when signs are extremely mild.⁶⁶

Clinical and Demographic Associations of MPS

Demographics

As discussed, increasing age is consistently associated with MPS, with the prevalence rising to more than 50% in the oldest old.^{7,25} Sex has not been consistently shown to influence the prevalence of MPS. Although three studies showed a higher prevalence in men,^{17,19,25} most studies show no sex differences in the incidence^{39,41,63-65} or prevalence of MPS.^{50,60,62,67,68} A higher prevalence of MPS has been reported in those with fewer years of education.^{17,56,57,60}

Vascular Risk Factors

The relationship between vascular risk and MPS is of key interest: vascular neuropathologies increase with age and are a recognized cause of both parkinsonism and dementia. Most^{26,27,65,69} but not all epidemiological studies^{16,19,70} have found an association between MPS and vascular risk factors; it is notable that studies that found an association had higher mean ages (late 70s to early 80s)^{26,27,65,69} than those that did not (in the 60s).^{16,19,70}

Diabetes mellitus (DM) has also been associated with both the severity and progression of MPS.^{14,26,27,50,69,71} In a subcategory analysis, DM was particularly related to the progression of gait and rigidity scores.²⁶ This relationship is not entirely clear, however, as adjusting for other vascular risk factors and peripheral neuropathy attenuated the association in one study.²⁷ Two cohorts found associations between lower limb vibration thresholds and increased mUPDRS scores,⁷² especially gait dysfunction,⁷³ but this has rarely been assessed.

Associations between MPS and other vascular factors including heart disease,^{69,71} peripheral vascular disease,^{69,71} higher body mass index,³⁹ and stroke^{69,71} have been reported: most of these associations were ameliorated but not eliminated when individuals with stroke were excluded, suggesting that this is not wholly explained by stroke-related disability.⁶⁹ In two cohorts, stroke was not associated with increased scores^{14,62}; however, it is possible that individuals with previous stroke may be less likely to participate in ambulatory research. An association between MPS and raised homocysteine levels has been reported.⁷¹ (See the Brain Imaging section for a discussion of imaging markers of vascular disease.)

Other Comorbidities

Because of the relatively nonspecific nature of some UPDRS-III items, other comorbidities may be associated with these scores. Arthritis and orthopedic conditions have been shown to associate with MPS.^{14,60,69,70} In the Canadian Longitudinal Study of Aging (CLSA),¹⁴ spondylosis or arthritis were associated with higher MDS-UPDRS scores (mean, 1.8 points). In a case-control study,⁷⁰ a group with orthopedic but no neurological complaints had nearly identical UPDRS-III scores (mean, 5.3; 95% confidence interval [CI], 4.6–5.9) to individuals with MPS (mean, 5.8; 95% CI, 4.6–7.0).⁷⁰ Essential tremor was also, unsurprisingly, associated with MPS in the CLSA (examining the MDS-UPDRS as a continuous measure), with higher scores (mean, 6.5 points).¹⁴ Depression has frequently been associated with MPS.^{9,15,22,38,54,57,59,63} This is a complex relationship as depression may directly cause psychomotor slowing as well as being associated with other conditions linked to MPS, including mild cognitive impairment (MCI), AD, PD, and cerebrovascular disease.

Limited evidence shows that MPS are associated with parkinsonian symptoms, measured, for example, via the Tanner questionnaire,^{56,61} but these measures are not sensitive enough to predict MPS.

Lifestyle Factors

In observational studies, previous dietary patterns consistent with the Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay diet and higher antioxidant intakes were associated with lower incidence and slower progression of MPS.^{34,37}

Higher baseline daily physical activity is associated with a lower incidence of MPS,^{38,64} and in one study⁷⁴ declines in physical activity over a 1-year period were associated with both motor and cognitive declines. It is possible that physical activity modifies the progression of MPS; conversely, motor and cognitive decline might underly the changes in activity.

Incident and prevalent MPS have been associated with self-reported sleep dysfunction.^{56,64}

In the WHICAP cohort, nonsmoking was associated with an increased prevalence of MPS, whereas no association with caffeine use was found.²² However, in other cohorts smoking was positively associated with MPS.³⁹

Prognostic Outcomes Associated with MPS

Mortality

In large community-based samples, MPS have been associated with increased mortality rates. The baseline presence of MPS,^{6,7,25,55,75} severity, and rate of

progression⁷⁶ have all been associated with higher death rates. In studies from the United States,^{7,25} Canada,⁶ Austria,⁷⁵ and China,⁵⁵ the relative risk of mortality among those with baseline MPS was similar (Fig. 2), between 1.5 and 2.0, with a mean follow-up ranging from 4⁵⁵ to 9.9 years.⁷⁵ These studies are, however, highly heterogeneous in their measurement and classifications of MPS, populations, and inclusion criteria, precluding meta-analysis of these data. Two studies examined subcategories of MPS^{7,55}; the gait⁷ and axial⁵⁵ categories were significantly associated with increased mortality in separate studies.

Physical Disability

MPS are associated with greater functional disability across both subjective and performance-based measures^{8,9,25,30,49,57,77} and with increased use of mobility aids.⁵⁷ These associations remained despite an adjustment for comorbidities such as depression and arthritis.⁷⁷ In subcategory analyses, all MPS categories were associated with disability in two studies,^{30,77} only gait and bradykinesia in one study,⁸ and axial and rigidity⁵⁷ in another study. MPS are also associated with falls in older adults.^{28,60,78}

MCI and Dementia

Parkinsonian features are a common finding in older adults with dementia and may be a marker of severity and predict more rapid decline in individuals with AD.^{6,79,80} Older adults with MCI have a higher prevalence of MPS (eg, 16.5% in older adults with normal cognition vs. 33% in MCI in a sample from Hong Kong⁴⁹), and MPS severity correlates with the severity of cognitive dysfunction in these individuals.⁸¹⁻⁸⁴ A consistent pattern of association with MCI subtypes (eg, amnesic, nonamnesic) has not been demonstrated.^{44,81,82,85} Note that operational definitions of MCI also differ, and studies vary in their inclusion of individuals with MCI, providing another source of heterogeneity.

In longitudinal studies, the baseline presence, severity, and rate of progression of MPS are associated with increased rates of development of all-cause dementia^{22,63,68} or clinically diagnosed AD.^{33,80,86,87} Further multivariate adjustment for stroke and diabetes^{67,68,80} did not alter these associations. Of the MPS subcategories, gait and axial signs were most often predictive of the development of dementia,^{33,63,67,68} with associations with rigidity and resting tremor each in two papers.^{33,63,68}

Cognitive Performance

MPS have been associated with poorer performance on cognitive testing both cross-sectionally and longitudinally.^{16,17,19,31,33,88} Detailed neuropsychological

assessment has found lower performance over multiple cognitive domains and that this associated with multiple subcategories of MPS. In the Tübinger Evaluation of Risk Factors for Early Detection of Neurodegenerative Disorders Study cohort¹⁷ (n = 480; mean age, 62.5 years) participants with persistent MPS had poorer global cognition at baseline and greater declines in global cognition and executive function over follow-up. The MPS group also had reduced β -amyloid-42 concentration in plasma, indicating a possible association with AD pathology.¹⁷ Aside from this finding, an investigation of AD biomarkers and MPS has not been reported.

Parkinson's Disease

Mild motor changes are present in the prodrome of PD, and subtle signs can be seen many years before clinical diagnosis,⁸⁹⁻⁹¹ including in prodromal cohorts with rapid eye movement-sleep behavior disorder (RBD)^{90,92} or glucocerebrosidase (*GBA*) genemutations.^{93,94} However, PD has rarely been reported as an outcome in large population-based cohorts describing MPS. Two studies have specifically examined the prognostic value of MPS for later development of PD: the Prospective Validation of Risk Markers for the Development of Idiopathic PD Study (PRIPS⁹⁵; n = 1260) found a 5.1% prevalence of MPS at baseline; at 3 years follow-up, 11 participants had developed PD, of which 63.6% were MPS positive at baseline, giving a sensitivity of 64% (31%–89%) and a specificity of 95% (93%–98%). However, of those developing PD between 3 and 5 years, none had MPS at baseline. A follow-up including some of these participants, the Bruneck study (n = 539), found that individuals with MPS at baseline had a relative risk of PD of 7.7 (95% CI 2.4–24.4) between 0 and 5 years of follow-up, but this decreased to 3.8 (95% CI 1.0–14.7) at 5 to 10 years.^{51,96} The results of both studies therefore suggest that MPS may be a late prodromal sign of PD. Work in other cohorts, including those with RBD, support this, suggesting that the sensitivity and predictive value of motor signs is best in the 2 years preceding diagnosis.^{89,97} As the authors of the Bruneck study note, the positive predictive value of MPS for a later diagnosis of PD was still too low to predict conversion to PD on an individual basis.⁵¹

However, it is recognized that motor features are only one sign of prodromal PD,^{24,98,99} and following MPS alone is unlikely to have sufficient sensitivity to detect PD. MPS associate with other risk markers for prodromal PD including hyposmia,^{15,16,32,41,100} RBD,⁹² self-reported autonomic symptoms,^{15,16} and increased echogenicity of the substantia nigra (SN).^{41,101} The Movement Disorders Society research criteria for prodromal PD include MPS among the factors for calculation of prodromal risk and have now

been validated in several studies.⁹⁶ Thus, for predicting PD, MPS are likely to have most value as part of a multifactor assessment algorithm.

It remains unclear whether individual parkinsonian features, specific subcategories, or alternate definitions of global MPS might be more specific for the later development of PD. Decrement in rapid alternating movements, a pill-rolling tremor, or asymmetry and progression over time might have more predictive utility,¹³ and some evidence exists that rigidity is associated with progression or new development of parkinsonism.^{63,95} The more detailed investigation of individual MPS and that of novel electronic measures are likely to provide greater detail of the motor prodromal phase of PD.¹⁰²

Genetic Factors

There are limited data on the association of MPS with genetic factors. Shulman et al¹⁰³ found that MPS and individual subcategories associated with several single-nucleotide polymorphisms (SNPs) associated with idiopathic PD. A single SNP in *NMD3* associated with nigral neuronal loss in a nested pathology study.¹⁰³ A follow-up of this study found that the microtubule-associated protein tau gene (*MAPT*) H2 haplotype associated with MPS, although the potential mechanism of action is unclear.¹⁰⁴ Rosso et al¹⁰⁵ investigated relationships between MPS and the catechol-o-methyltransferase (*COMT*) Val genotype (associated with more rapid breakdown of dopamine at the synapse) and found that the *COMT* genotype was not associated with MPS, although it modified associations between MPS and WMH volume. Although these studies suggest that genetic factors may influence MPS, no clear conclusion can be drawn yet.

Brain Imaging

Global and Regional Atrophy

Associations between gray matter volume and MPS were examined in three studies with varying results. In the Health and Body Composition cohort, Rosano et al⁶² found that parkinsonian gait was associated with lower medial temporal lobe volumes and bradykinesia with smaller primary sensorimotor cortex. The tremor group and those with MPS overall did not have specific patterns of gray matter volume loss.⁶² Individuals from the same cohort with MPS had lower left dorsolateral prefrontal cortex and total gray matter volume cross-sectionally¹⁰⁵ and gray matter volumes associated with greater progression longitudinally,¹⁰⁵ but neither association survived adjustment. Louis et al¹⁰⁶ found that MPS did not associate with hippocampal volumes. Note that the discrepancy between the association found by Rosano et al⁶² (parkinsonian gait associated with smaller medial temporal lobe volume) and Louis

et al¹⁰⁶ (no association between MPS and hippocampal volumes) may be attributed to gait not being included in the WHICAP definition of MPS.²² Global atrophy was associated with MPS in the Cognitive Impairment through Aging Study study,⁴³ and Reitz et al reported higher odds of bradykinesia or rigidity in individuals with high cortical atrophy scores.⁴⁸

White Matter Macrostructural Imaging

Several studies have investigated associations between MPS and markers of cerebral small vessel disease (see Table 3).^{43,45,47,48,50,62,64,106} Positive findings have often been limited to specific patient subgroups or MPS subcategories; however, overall these studies support vascular disease having a role in the pathogenesis of MPS.

Microstructural Imaging

Similarly, limited evidence so far supports that loss of white matter microstructural integrity may play a role in MPS. De Laat et al found lower fractional isotropy of white matter in individuals with MPS, particularly in the frontal lobes, and in those in the rigidity subcategory.⁴⁶ Miller-Patterson et al⁵⁰ found that higher mean diffusivity predicted greater progression in MPS scores.

Dopamine Transporter Imaging

There is some evidence from dopamine transporter imaging that dopaminergic dysfunction is associated with MPS. In a biomarker study (n = 87) using dopamine-transporter positron emission tomography scanning,⁷² lower striatal dopamine transport was independently associated with greater MPS severity after adjustment for age. Associations were stronger for axial signs and bradykinesia.⁷²

Brain Pathologies and MPS

Brain pathologies associated with MPS have been specifically addressed in two pathological cohorts.

The Honolulu-Asia Aging Study

In a group of older men examined with the UPDRS-III, those with incidental Lewy bodies (ILB) on pathological examination (n = 29) had similar scores to controls (ILB = 17.0, control = 17.4); those with PD had, as expected, higher UPDRS-III scores (36.3, SD11.7).¹⁰⁷ In the control group (no ILB or PD, n = 50; mean age, 83.7 years), decreased neuron density in the dorsolateral and dorsomedial SN was significantly associated with the presence of (predominantly axial) parkinsonian signs. Excluding individuals with dementia partially attenuated these findings.¹⁰⁷

TABLE 3 Association between MPS and MRI markers of cerebral small vessel disease

Study	Cohort	Sample size	Mean age (years)	MPS prevalence (among dementia-free), %	Predictor	Effect size, outcome	Notes
Louis et al ¹⁰⁶	WHICAP	666	80.3	15.7	WMHV	OR, 1.27 for presence of MPS	Relationships only significant in the normal cognition group post adjustment (compared with aMCI, naMCI, dementia)
De Laat et al ⁴⁵	RUN DMC	430	65.2	21.4	WMHV Lacunes	For the upper quintile of WMHV, OR, 3.4 for the presence of MPS OR, 2.1 for the presence of MPS	Frontal, then parietal WMHV particularly associated Lacunes of deep gray matter structures, thalamus particularly associated
Hatate et al ⁴⁷	Osaka hospital	268	71.8	48.8	Microbleeds Lacunes	Deep microbleeds: OR, 2.67 for MPS Not associated overall, but mixed basal ganglia/thalamus associated with MPS: OR, 6.05	Lobar microbleeds not associated Total lacunes and isolated basal ganglia or thalamic lacunes not associated
Reitz et al ⁴⁸	MEMO	268	72.3	33.2	WMHV Lacunes	Periventricular WMH: OR, 1.34 Deep WMH: OR, 1.10 for MPS Resting tremor: OR, 1.95	Also associated with rigidity and gait subcategories No association between WMH/lacunes and bradykinesia/rigidity
Rosano et al ⁶²	Health ABC	307	83	44	Large WMH ≥ 10 mm WMHV	Resting tremor: OR, 1.91 No association in fully adjusted model	Individuals with MPS had higher WMHV adjusting for age only
Miller-Patterson et al ⁵⁰	Health ABC	205	82.7	30.2	WMHV	No association	No association with progression of UPDRS scores over 3.8 years (mean) follow-up
Camarda et al ⁴³	CogItA	1219	58.7	15	WMH	Periventricular WMH: OR, 2.6	WMH treated as binary variable
Kishi et al ⁶⁴	Ama-cho	316	72.8	29.7% incidence, 8 years follow-up	Deep WMH	OR, 1.62 for the incidence of MPS, per unit of Fazekas score	

Note: All studies are cross-sectional aside from Miller-Patterson et al⁵⁰ and Kishi et al.⁶⁵

Abbreviations: MPS, mild parkinsonian signs; MRI, magnetic resonance imaging; WHICAP, Washington Heights-Inwood Columbia Aging Project; WMHV, white matter hyperintensity volume; WMH, white matter hyperintensities; OR, odds ratio; aMCI, amnesic mild cognitive impairment; naMCI, nonamnesic mild cognitive impairment; RUN DMC, Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort; MEMO, Memory and Morbidity in Augsburg Elderly (Austria); Health ABC, Health and Body Composition Study; CogItA, Cognitive Impairment through Aging Study (Italy).

ROS/MAP

These studies have published successive waves of pathological findings. Key findings have been the following:

- 2006 (86 cases, ROS): the MPS gait dysfunction category was associated with higher levels of neurofibrillary tangles in the SN in individuals with and without dementia.¹⁰⁸
- 2011 (418 cases, ROS): macroscopic cortical and subcortical brain infarction were related to global scores; gait dysfunction showed significant associations with all vascular pathologies examined (macroscopic infarction, microscopic infarction, arteriosclerosis).²⁵
- 2012 (744 cases, ROS/MAP): nigral neuronal loss and Lewy bodies were significantly associated with MPS; AD pathology and vascular pathologies also had independent effects.¹⁰⁹
- 2016 (1160 cases, ROS/MAP): MPS were associated with vascular pathologies—atherosclerosis and arteriosclerosis—but not with micro- or macroinfarction, SN neuron density, Lewy bodies, or AD pathology.²⁵
- 2019 (1430 cases, ROS/MAP/Minority Aging Research Study): progression of MPS in older adults was related to the cumulative number of brain pathologies (nine pathologies investigated) rather than any individual pathology. The majority of individuals with MPS (>70%) showed neither nigral neuronal loss nor Lewy bodies; however, individuals with both of these features had a more rapid progression of parkinsonism.³⁹

Finally, one small study from this cohort found evidence of α -synuclein, nigral neuronal loss, and Lewy bodies in each of 18 brains from those with MPS. However, the mean MMSE score in the MPS group was 11/30 (ie, consistent with moderate to severe dementia), suggesting that other (unexamined) pathological processes may have complicated these findings.¹¹⁰

Overall, with the accumulation of cases in this case series, the emphasis has shifted from individual brain pathologies to investigating multiple pathologies. Notably, PD-associated pathologies are only seen in a minority of cases with MPS at autopsy.³⁶

MPS Subcategories

As discussed previously, many studies have investigated subcategories of MPS, for example, individuals with rigidity, bradykinesia, axial dysfunction, gait dysfunction, or tremor. Overall, gait dysfunction is most frequently associated with mortality,^{7,76} disability,^{8,30} dementia,^{33,76} and cognitive decline.³¹ However, the WHICAP definition of MPS does not include gait assessment—using this definition, axial dysfunction

(alteration in facial expression, speech, and posture) was most strongly associated with mortality.⁵⁵

However, gait (ROS/MAP) and axial (WHICAP) categories are each the most prevalent under their respective classifications^{7,25,55,57,67}; this may increase power and so increase the likelihood of a significant association.

Discussion

MPS occur in the prodrome of PD before a diagnosis of PD can be made, and their presence has been associated with an increased risk of later diagnosis of PD and with reduced dopamine transporter imaging. However, the prevalence of MPS in older adults is many times higher (5%–50%) than the estimated maximum prevalence of prodromal PD (0.5%–4%).²⁴ Although PD pathology is significantly associated with MPS, PD pathology does not account for all of this gap.³⁵ Conversely, PD pathology can be seen in older individuals without MPS.³⁵

The epidemiological, radiological, and pathological evidence of MPS suggests that most MPS, as currently defined, have heterogeneous causes and have a strong association with increasing age. This evidence also suggests that these signs are associated with poor outcomes, including mortality, dementia, and disability. The underlying pathologies, at least in the oldest old, are likely to be heterogeneous, including significant contributions from vascular disease, AD, PD, and other forms of neurodegeneration; combinations of pathologies may act synergistically to influence MPS.

Therefore, MPS (as currently defined) lack specificity for particular outcomes. Exploring subgroups within MPS may increase their utility to detect individual pathologies, particularly prodromal PD, the area in which MPS are especially relevant. The MPS most specific for PD have not been fully explored. Associations of characteristic parkinsonian features that may be most specific for PD (such as decrement in rapid alternating movements, a pill-rolling tremor, or asymmetry and progression over time) have not been well studied, although some evidence exists that rigidity is associated with progression or new development of parkinsonism.^{63,95} Conversely, gait and axial features may be more strongly associated with progression to dementia.^{63,67,68} Therefore, identifying the specific features of MPS related to underlying pathologies and confounding comorbidities will be crucial to improve the predictive power of MPS for PD or other outcomes.

MPS may have different underlying pathologies in different age strata.¹⁶ Further studies of MPS using in vivo biomarkers in different age groups and subgroups are needed to address this question.

A significant limitation to study in this area is the heterogeneity of criteria used to describe MPS, with disparate and often study-specific case definitions; this is particularly true when binary cut-offs (themselves arbitrary) are used to define MPS. Furthermore, as the UPDRS and MDS-UPDRS, on which these scales are mostly based, are designed for measuring the severity of PD-related features and are not validated for use in individuals without PD, it is acknowledged that they also capture non-PD-related abnormalities.^{13,20} In fact, the MDS-UPDRS specifically clarifies that, acknowledging the confounding of scores by other medical conditions, a “rate as you see” approach should be taken to ensure reproducibility.^{13,20} Even with adjustment for these potentially confounding comorbidities, underlying brain pathologies are difficult to distinguish.

Heterogeneity of terminology provides a limitation to this study; although our search terminology covers “mild parkinsonian signs,” “parkinsonian signs,” “signs of parkinsonism,” the search strategy may have missed some studies categorized by “parkinsonism” alone; using “parkinsonism” as a key word in Medline returns more than 18,000 articles, making this methodologically infeasible.

Although predicting PD is an important application of MPS, it is apparent that a significant proportion of the motor changes, pathologies, and outcomes are not “parkinsonian.” Where PD is not the focus, the term *parkinsonian* may be less relevant; in fact, some recent articles have moved away from this terminology, using broader terms such as *minimal motor features*¹¹⁰ or *mild motor signs*,¹¹¹ which may be clearer.

Moving forward, the definitions of MPS may need to be reconsidered. Recognizing heterogeneous underlying pathologies, specific definitions, and cut-points may be needed to investigate specific outcomes. The MDS-UPDRS is now frequently used, but its metric properties are not well explored in this population. Further studies illustrating its relationship with underlying pathologies, associated features, and progression in this population will allow data-driven approaches to developing new definitions and cut-points.

We suggest that where the aim is to use MPS to determine groups at risk of particular outcomes, for example, for PD, for trials of preventive or modifying interventions, there is a need to do the following:

1. Form consistent definitions of MPS and its subcategories to increase comparability across studies.
2. Define the individual MPS characteristics with the highest predictive value for development of PD or other outcomes.
3. Consider other comorbidities and factors that could affect ratings and address them in study design.
4. Include other prodromal features or risk factors specific for PD.

5. Consider specific age strata or subgroups.
6. Repeat assessment to incorporate progression and exclude unstable MPS.
7. Apply evidence-based in vivo biomarkers of neuro-pathologies to clarify the likely pathogenesis in different groups.

Conclusions

MPS are common in older adults and increase with age. Clinical, radiological, and pathological evidence suggests that pathologies underlying MPS, as currently defined, are heterogeneous and likely often mixed. Age, associated risk factors, and nonmotor and other neurological features contribute to diagnostic and prognostic outcomes. Specific parkinsonian signs and MPS subcategories need to be explored further for the predictive values, and further work is required to standardize and improve definitions of MPS across the field to identify MPS specific for the underlying pathologies and to investigate the associations of MPS in general and specific subdomains with biomarkers, clinical outcomes, and pathologies. This will be required to use these signs to aid prognostication, risk stratification for trials, or to recommend specific interventions. Given the heterogeneity in underlying pathology, clinical associations, and outcomes, “mild motor signs” may be a more accurate and useful terminology for some purposes. ■

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article

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Supporting Data

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(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

S.M.B.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

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