to date. Much of this strength is due to the breadth of studies included, assessment of bias, and depth of statistical analysis of outcomes and potential confounders. While we await results from RCTs such as the ongoing Aging and Cognitive Health Evaluation in Elders (ACHIEVE; NCT03243422) trial and the upcoming Early Age-Related Hearing Loss Investigation (EARHLI) trial, this meta-analysis provides substantial reason to pursue further study of the relationship between hearing loss and cognitive decline/dementia.[13]

In conclusion, Yeo and colleagues[12] offer a much-needed reminder that abundant evidence exists in support of an association between hearing loss and cognitive decline/dementia. While we await the completion of additional studies to test if hearing loss may cause cognitive decline/dementia—and if hearing restorative devices could mitigate that possible pathway—we recommend physicians consider hearing evaluation as part of a standard dementia workup. Thanks to the recent creation of over-the-counter hearing aids, access to hearing loss treatment will increase.[14] Clinicians have a unique opportunity to encourage hearing assessment and, if needed, use of hearing restorative devices such as hearing aids and cochlear implants. Not only can hearing loss contribute to symptoms of dementia, such as difficulty with communication, but hearing restoration remains an active area of investigation as a potential mitigator against the slow creep of cognitive decline. Simply put, assessment for hearing loss remains a crucial part of caring for patients with cognitive impairment.

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Time to Change the Current Clinical Classification of Multiple Sclerosis?

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People with multiple sclerosis (MS) have traditionally been classified has having relapsing-remitting (RR) or progressive (either secondary or primary progressive) MS based on (1) the presence of episodes of acute or subacute clinical worsening, followed by complete or partial recovery (relapses) or (2) more continuous—frequently insidious—disability worsening over time with or without superimposed relapses. This classification of disease course, established by an international expert consensus, heavily relies on the premise that relapsing disease is characterized by periods between relapses that are free of worsening while progressive disease presents a discrete period during which patients exhibit continuous decline of neurological functions. In the revisions of these criteria, imaging features of acute inflammatory activity (new,

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enlarging T2 or contrast-enhancing T1 lesions) were added to clinical relapses to provide more sensitive measures of episodic disease activity.[1] However, the committee did not reach a consensus on laboratory or imaging surrogates of steady clinical progression, which remained defined on purely clinical grounds.

Data from several recent observational studies[2,3] and controlled clinical trials[4,5] provided unequivocal evidence that steady progression independent of relapse activity (PIRA) is a frequent feature of typical RRMS and—more importantly—that PIRA is by far the most frequent manifestation of confirmed disability accumulation in RRMS in the era of immunomodulatory and immune-targeting therapeutics. This advancement in understanding was made possible by the availability of comprehensive and standardized longitudinal clinical observations in large groups of people with MS. In addition, our recognition of PIRA was critically facilitated by the availability of treatments that effectively suppress or even completely abrogate relapse activity—thus reducing the noise that may interfere with the detection of subtle signs of progression. In this issue of *JAMA Neurology*, Tur et al[6] expand the findings obtained in RRMS to people with MS presenting with a very first demyelinating event, classified as a clinically isolated syndrome (CIS). In the setting of the prospectively followed and thoroughly documented Barcelona inception cohort, these investigators assessed the frequency of PIRA vs relapse-associated worsening (RAW) in 1128 participants, all enrolled within 3 months from the first clinical episode. During a median follow-up of 10.5 years, 25% of the patients experienced PIRA at least once, 31% of these within the first 5 years after the first episode. In this CIS population, PIRA contributed to 66% of all confirmed disability worsening events, whereas RAW contributed to 34%. These figures are nearly identical to those recently reported from the Italian MS Registry[7]; among 5169 participants with CIS or relapsing MS included within 1 year after the first demyelinating event and during a median (SD) follow-up of 11.5 (5.5) years, 27% of patients experienced PIRA and 17.8% experienced RAW. While both studies are concordant in showing that approximately 1 of 4 patients develops confirmed disability worsening during the early stages of the disease, both probably underestimate the real incidence of confirmed disability accumulation. In fact, in these studies, the quantification of disability exclusively relies on a change in Expanded Disability Status Scale (EDSS) score, a measure that is notoriously coarse and that is heavily influenced by deficits in motor function. Combining EDSS score with measures of cognitive function, walking speed, upper limb function, and—more importantly—digital measures allowing more continuous, granular, and comprehensive monitoring of disability worsening should provide more precise estimates of the proportion of patients with RRMS experiencing relapse-independent confirmed progression.[8] Despite this limitation, both studies leave no doubt that PIRA is a common feature of MS from the earliest stages and contradict the conceptual distinction between relapsing and progressive disease courses or stages. Tur et al[6] also provide solid evidence that experiencing PIRA is a predictor of accelerated accumulation of disability; patients with PIRA had an 8-fold higher risk of reaching an EDSS score of 6.0 than patients without PIRA. Prognostically, early PIRA seems to portend a worse outcome: participants who developed PIRA within 5 years had significantly higher annual EDSS score increase rates than those who developed PIRA later and a 26-fold greater risk of reaching an EDSS score of 6.0. This underlines the importance of early monitoring and accurate detection of progression.

On the other hand, despite coming to recognize the presence of PIRA from the earliest stages of MS, we learn disappointingly little from this study of patients with CIS about the predictors of PIRA.[6] Only age at first demyelinating event emerged as a statistically robust, although not particularly strong, risk factor for early development of PIRA (hazard ratio for each older decade, 1.43; 95% CI, 1.23-1.65; $P < .001$). In patients who had sufficient magnetic resonance imaging (MRI) documentation, the number of spinal cord lesions was also a risk factor, confirming the data reported previously in a smaller cohort.[9] It is additionally important to note that for methodological reasons inherent to the study designs, prior studies on PIRA have not provided conclusive evidence about the relation between PIRA and radiological activity. Despite such limitations, it is interesting to note that in this study by Tur et al,[6] half of the patients who experienced PIRA had inflammatory activity in MRIs performed within the previous 2 years.

In line with this, Portaccio et al[7] applied stringent criteria for defining true PIRA, when patients were not only relapse-free but also free of MRI activity within 90 days before and 30 days after documented disability worsening. In this subgroup, including 389 of 2349 confirmed disability accumulation events (16.6%), PIRA accounted for 48% and RAW accounted for 52% of these events, but true PIRA accounted for only 25% of all events.[7] Such observations as well as the current failure to consistently detect differential risk factors of PIRA and RAW are compatible with a complex multifactorial pathogenesis of disability accumulation in people with MS, following most probably the accumulation of both focal and diffuse tissue damage that occurs across all MS stages. In view of the mounting evidence of the detrimental implications of early PIRA and the emergence of treatment options with proven—though still only partial—efficacy in progressive disease,[4,10,11] a better characterization of the factors contributing to PIRA is urgently needed. Higher spatial resolution protocols that may reliably identify lesions below the current detection thresholds and more quantitative and tissue-specific imaging techniques[12] are currently being applied to elucidate this question. PIRA describes a clinical worsening in patients' disability but appears also to be associated with accelerated tissue loss in the brain, especially in the cerebral cortex[13] and spinal cord.[14] Interestingly, this was also true for a cohort of people with MS without any signs of radiological activity during the year preceding PIRA.[13]

Much remains to be done to advance our understanding of the factors underlying disability accumulation in people with MS and to improve our quantification and prevention of this disability. The study by Tur et al[6] brings us a step closer by documenting that accumulation of disability starts early in the disease course and by underlining the detrimental consequences of early PIRA in people with MS. Altogether, these

clinical observations and our current—growing but still incomplete—knowledge about the factors that contribute to disability accumulation suggest that we should revisit our traditional categorization of MS into relapsing and progressive courses. These previously devised clinical phenotypes have served their purpose in defining populations of patients that are most likely to be responsive to existing disease-modifying treatments. As we are moving toward developing treatments to help prevent disability accumulation, a more personalized understanding of a given patient's disability status is needed to help guide individualized treatment decisions. This new approach should be based on the comprehensive characterization of the different constituents of the disease process using advanced laboratory and imaging methods together with more granular, comprehensive, and meaningful digital measures of the functional consequences of MS.

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Functional Impairment Preceding Parkinson Disease Diagnosis—What's in a Prodrome?

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Recently, increasing attention has been focused on the years preceding Parkinson disease (PD) diagnosis. Criteria have been formulated for prodromal PD[1] with subsequent refinements.[2] Subtypes of prodromal PD have been promulgated, including body-first and brain-first classifications,[3] and different prodromal phenotypes have been associated with alternate disease trajectories. For example, the presence of rapid-eye movement sleep behavior disorder (RBD) at the time of PD diagnosis has been associated with a more severe disease course.[4] The recognition of a prodromal period has been viewed as potentially critical to the success of disease-modifying interventions, on the argument that it may be too late to enact meaningful clinical change once symptoms clinically manifest given the degree of neurodegeneration already present.

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Given the rising importance attached to prodromal PD research, the results of a case-control study by Miller-