Radiologically isolated syndrome

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Individuals can be deemed to have radiologically isolated syndrome (RIS) if they have incidental demyelinating-appearing lesions in their brain or spinal cord that are highly suggestive of multiple sclerosis but their clinical history does not include symptoms consistent with multiple sclerosis. Data from international longitudinal cohorts indicate that around half of people with RIS will develop relapsing or progressive symptoms of multiple sclerosis within 10 years, suggesting that in some individuals, RIS is a presymptomatic stage of multiple sclerosis. Risk factors for progression from RIS to clinical multiple sclerosis include younger age (ie, <35 years), male sex, CSF-restricted oligoclonal bands, spinal cord or infratentorial lesions, and gadolinium-enhancing lesions. Other imaging, biological, genetic, and digital biomarkers that might be of value in identifying individuals who are at the highest risk of developing multiple sclerosis need further investigation. Two 2-year randomised clinical trials showed the efficacy of approved multiple sclerosis immunomodulatory medications in preventing the clinical conversion to multiple sclerosis in some individuals with RIS. If substantiated in longer-term studies, these data have the potential to transform our approach to care for the people with RIS who are at the greatest risk of diagnosis with multiple sclerosis.

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Introduction

An individual is deemed to have radiologically isolated syndrome (RIS) if brain or spinal cord MRI studies, done for reasons unrelated to multiple sclerosis, incidentally reveal demyelinating-appearing lesions in the absence of typical symptoms associated with CNS demyelination.[1–3] In some individuals, RIS might represent the earliest presymptomatic phase of multiple sclerosis. Although many people who have RIS will develop clinical signs consistent with multiple sclerosis, several post-mortem studies describe individuals with asymptomatic CNS demyelinating pathology, suggesting that some people with RIS might remain asymptomatic throughout their lifetime. There is equipoise regarding initiating multiple sclerosis disease-modifying therapies in people with RIS. Moreover, establishing whether a person has RIS can pose a major challenge to neurologists and multiple sclerosis clinicians because of the high prevalence of non-specific white matter disease lesions on MRI[4,5] and because, by definition, people with RIS do not have the clinical symptoms associated with CNS demyelination, which ordinarily aids the interpretation of MRI changes. Therefore, determining whether a person has RIS remains an important clinical challenge in neurology.

In this Personal View, we suggest how RIS relates to multiple sclerosis and we review RIS criteria, clinical risk factors and biomarkers for clinical multiple sclerosis, clinical pitfalls and risk for misclassification, therapeutic considerations, and future research directions. We aim to provide contemporary information that might improve clinical counselling, management, and care for people with RIS.

Stages of multiple sclerosis

Multiple sclerosis can be conceptualised as spanning different risk-related phases: (1) the multiple sclerosis risk phase, in which genetic, environmental, or epidemiological risk factors, and atypical paraclinical test results (eg, CSF, visual evoked potentials, and MRI not fulfilling RIS criteria) can be present; (2) the presymptomatic phase (or RIS), potentially including previous risk factors, in which demyelinating-appearing multiple sclerosis-like lesions become visible on structural MRI of the CNS, but clinical symptoms of multiple sclerosis are not present; and (3) the clinical disease phase, in which established multiple sclerosis criteria are met. Nevertheless, people in the first two phases will not necessarily develop symptoms, and approximately half of people with RIS will not develop clinical multiple sclerosis after 10 years.

Individuals in the multiple sclerosis risk phase are primarily identified during research studies, and no consensus criteria exist for defining this risk. Multiple sclerosis risk is most likely explained by genomic, epigenomic, environmental, gut microbiome, and metabolomic factors reviewed extensively elsewhere.[6–8] This phase might also include individuals occasionally encountered in clinical practice who have CSF-restricted oligoclonal bands or atypical visual evoked potentials or optical coherence tomography (OCT) findings but with no alternate explanation and no clinical or neuroimaging features of multiple sclerosis.[8–11] Eventually, some individuals with signs of disease biology might develop either asymptomatic MRI-visible white matter lesions (ie, RIS, if MRI criteria for dissemination in space [DIS, meaning demyelinating lesions in more than one location] are met) or clinical multiple sclerosis.[12] More work is needed to define other factors that determine the risk that an individual with RIS will subsequently be diagnosed with multiple sclerosis—a polygenic risk score has been proposed, using known genetic markers and environmental factors.[13] In the Genes and Environment Multiple Sclerosis cohort, 10% of women with a high polygenic multiple sclerosis score met the RIS criteria compared with 4% of women who did not have a high risk score.[14] A well defined multiple sclerosis risk score with a high predictive value would provide a major advance if a primary prevention strategy for CNS demyelination becomes available or if a high risk score could lead to a strong recommendation for screening

neuroimaging studies.[14] A validated score might allow the identification of some people with risk factors who will eventually be diagnosed with clinical multiple sclerosis. Although diagnostic criteria for multiple sclerosis have been revised, the fundamental tenet remains the demonstration of DIS and dissemination in time (DIT, defined clinically with a new relapse or radiologically with a new T2 lesion or new gadolinium-enhancing lesion), clinically or radiologically,[15] along with at least one clinical characteristic associated with CNS demyelination. Most people with clinical multiple sclerosis already have chronic white matter lesions suggestive of CNS demyelinating disease on MRI upon first clinical presentation, suggesting that many of these individuals went through the RIS phase before the clinical onset of the disease.[16]

Individuals with RIS fall between the at-risk and clinical phases. These individuals do not have a history of clinical symptoms typical of multiple sclerosis but have CNS white matter lesions highly suggestive of inflammatory demyelination based on lesion size, number, shape, and location. 10 years after being deemed to have RIS, around half of individuals will develop clinical symptoms of multiple sclerosis; these symptoms can take many forms, such as a first acute inflammatory demyelinating event or the onset of a progressive neurological syndrome fulfilling the criteria for primary progressive multiple sclerosis.[17–19] RIS is almost certainly not the beginning of multiple sclerosis disease biology; instead, it is intuitive that the mutliple sclerosis disease biology begins in some individuals during the multiple sclerosis risk phase and precedes the development of lesions visible on MRI.

A framework for multiple sclerosis has proposed that RIS could include the subclinical and prodromal stages before a person develops typical multiple sclerosis symptoms.[20,21] The prodromal phase of multiple sclerosis has been suggested as a phase in which subtle signs and symptoms occur before typical neurological symptoms of multiple sclerosis. Compared with matched controls, individuals who were ultimately diagnosed with multiple sclerosis showed increased use of health-care resources for non-specific or atypical symptoms 5 years before a diagnosis of a demyelinating disease was recorded by their health-care system.[20,21] Whether some of these individuals had MRI lesions that fulfilled RIS criteria before the diagnosis of multiple sclerosis, and whether the diagnosis of multiple sclerosis was accurate, are unknown, but further studies are exploring these questions.[14,22] Use of health-care resources by individuals with non-specific white matter disease, those with proposed multiple sclerosis prodromal symptoms, and people with RIS will be a key component in determining the value of health-care use patterns in identifying individuals at risk for multiple sclerosis. Sensitivity to the application of this approach in recognising individuals at-risk of multiple sclerosis in national health-care systems is also crucial to reduce the marginalisation of people in racial, ethnic, or other groups that can have reduced access to health-care resources.

Defining RIS

Criteria for RIS

Criteria for RIS were first published in 2009 and are defined by the presence of asymptomatic CNS white matter lesions on MRI that are ovoid, well circumscribed, 3 mm in length or more,[2] and hyperintense on T2-weighted images with or without the involvement of the corpus callosum.[1] These lesions must fulfil the 2005 multiple sclerosis criteria for DIS[23] (ie, three of the four following features: one gadolinium-enhancing lesion or nine T2-hyperintense lesions; one or more infratentorial lesion; one or more juxtacortical lesion; and three or more periventricular lesions) and must not be related to any other medical explanation. Although the number of lesions required for a multiple sclerosis diagnosis has been reduced in more recent iterations of the multiple sclerosis diagnostic criteria,[15,24] DIS criteria proposed in 2009 for RIS have remained unchanged. In 2017, it was suggested that the 2017 criteria for DIS and DIT in multiple sclerosis could be used in RIS.[25] However, scientific evidence did not support this recommendation, and the extrapolation of correlative data from people with multiple sclerosis to people with RIS might not be valid.

Some asymptomatic individuals might present with only one or two of the four DIS criteria but have lesions highly suggestive of multiple sclerosis. This clinical evidence inspired a new validation study, and an updated version of the criteria for RIS were proposed in March, 2023.[26] According to this update, when the 2009 RIS criteria are not fulfilled, an individual could be classed as having RIS if they have one or two DIS locations associated with two of the three following features: spinal cord lesions, oligoclonal bands in the CSF, or DIT on the follow-up MRI (figure 1). In such a situation, if a first clinical event eventually occurs, the individual can be diagnosed with multiple sclerosis.[15,29]

Differential diagnosis

Thorough investigation is needed in people suspected of having RIS, especially in children and adolescents, given their broad differential diagnosis, and in people of any age who have headaches as a presenting symptom. Mimics of demyelinating diseases in children include genetic or metabolic diseases (eg, leukodystrophies and mitochondrial disease), infections, and rarely malignancy.[30] Other differential diagnoses, such as vascular disease, nutritional deficiencies, other inflammatory diseases (eg, sarcoidosis), and rheumatological diseases (eg, lupus and antiphospholipid syndrome), can also occur in adults and children (panel).[31,32] In adults older than 50 years, the high prevalence of non-specific white matter hyperintensities adds to the diagnostic confusion. However, clear differences in MRI characteristics are generally apparent (figure 2). All of these mimics should

be considered when deciding whether a person has RIS.[33,34] A central principle of multiple sclerosis diagnosis is ruling out alternative explanations for the observed clinical features, and this rule also applies to RIS. Before a person can be deemed to have RIS, a thorough neurological history must be obtained to detect any potential clinical symptoms suggestive of multiple sclerosis, and a comprehensive medical investigation should also be done.

Migraines deserve particular attention as headaches are one of the most common reasons for the index MRI in people who have RIS. Additionally, migraines are often associated with white matter hyperintensities. Although most T2-weighted and fluid-attenuated inversion recovery white matter hyperintensities in migraine are subcortical, they can also be seen in the juxtacortical and periventricular regions and even within the posterior fossa,[35] which can mirror spatial patterns in people with multiple sclerosis. However, lesions in people with migraines are mainly distributed within the frontoparietal subcortical regions of the brain and usually spare the callosal and subcallosal areas and the spinal cord. Moreover, lesions in people who have migraines typically do not enhance with gadolinium.[35] Juxtacortical lesions in people who do not have multiple sclerosis lack the S or U shape that usually suggests multiple sclerosis-related demyelination. In multiple sclerosis, demyelinating periventricular lesions are expected to be ovoid, perpendicular to the ventricles, and should touch the ventricles (figure 2). Juxtacortical lesions should encroach upon the cortex.[36,37] Subcortical and deep white matter lesions fall in between the cortex and ventricle. Temporal periventricular lesions highly suggest inflammatory demyelination associated with multiple sclerosis rather than migraine.[27]

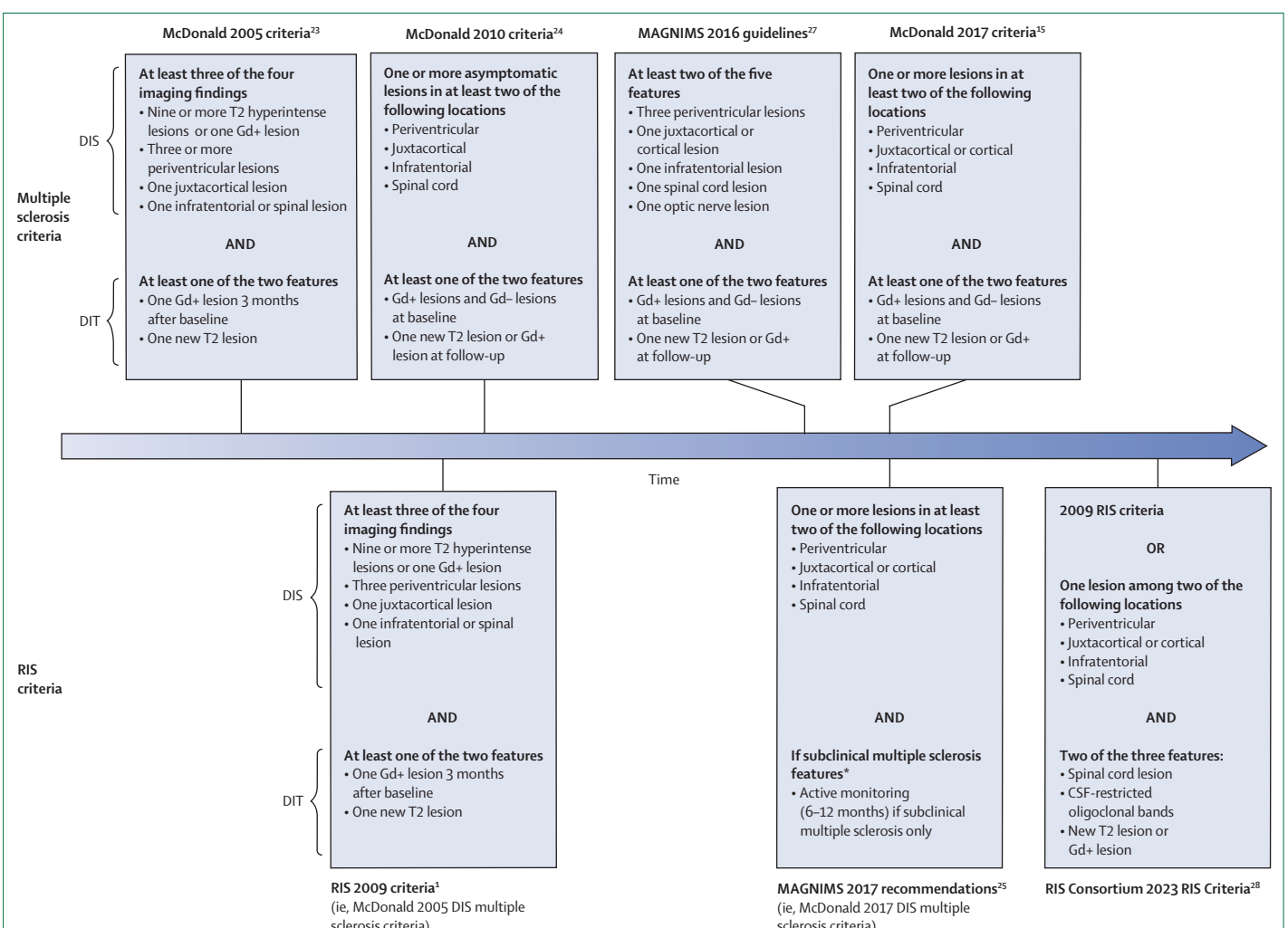

Figure 1: **Summary of criteria for multiple sclerosis and RIS**
DIS=dissemination in space. DIT=dissemination in time. Gd+=gadolinium enhancing. Gd–=gadolinium non-enhancing. RIS=radiologically isolated syndrome. VEP=visual evoked potentials. *Only if one or more: specific cognitive dysfunctions; CSF oligoclonal bands; abnormal visual evoked potentials; high T2 lesions load; cortico-juxtacortical, infratentorial, or spinal cord lesions; DIT on follow-up.

***Panel*: Imaging features suggestive of non-specific white matter demylination rather than RIS or multiple sclerosis**

- Bilateral and mostly subcortical lesions, rather than periventricular and juxtacortical white matter lesions
- Juxtacortical lesions, when present, are few in number, can be punctate, and do not have the S or U type shape seen with demyelinating lesions
- Lesions are mostly distributed within the frontal and parietal white matter
- Lesions often have symmetrical and umbrella-like distribution
- Lesions are often very small and punctiform
- Punctate and nodular-like lesions are common
- Absence of ovoid lesions
- Absence of cortical, posterior fossa, corpus callosum, and spinal cord lesions
- Absence of temporal periventricular lesions
- Absence of central vein sign
- Absence of iron rims
- Absence of gadolinium enhancement

Clinical and paraclinical features

Risk of a clinical event

Results from a large, multinational, prospective cohort of 451 people with RIS have been published with 5-year[17] and 10-year[18] follow-ups. Approximately 138 (79%) of the individuals with 10-year follow-up were female, 144 (82%) were White, 18 (10%) had a family history of multiple sclerosis, and the mean age when first meeting RIS criteria was 37·2 years. At baseline, 440 (99%) participants had periventricular lesions, 400 (90%) had juxtacortical lesions, 30% (137) had infratentorial lesions, 135 (35%) had spinal cord lesions, and 108 (28%) had gadolinium-enhancing lesions. A CSF profile suggestive of multiple sclerosis was observed in 60–65% of samples at baseline. The two most common reasons for the index MRI were headache (190 [42%]) and trauma (37 [8%]).[17,18]

94 (34%) participants had their first multiple sclerosis symptom within 5 years of the discovery of RIS and 173 (51%) within 10 years.[18] Younger age (<35 years) at the time of meeting RIS criteria, male sex, CSF-restricted oligoclonal bands or elevated CSF IgG index (positive CSF), and infratentorial or spinal cord lesions on the index MRI were predictors of a first clinical event at 5 years and 10 years.[17,18] The presence of gadolinium-enhancing lesions during follow-up also predicted a seminal clinical event at 10 years.[18] People with RIS can be stratified according to these factors, which is useful for clinicians and clinical trialists who study RIS. For example, the 10-year risk estimate for progression to clinical multiple sclerosis was greatly increased when all four risk factors (ie, age <37 years, positive CSF, the presence of infratentorial lesions, and the presence of spinal cord lesions) were present compared with none or just one risk factor: 87% probability of a first clinical event within 10 years versus *vs* 29%, respectively.[18] Individuals with two risk factors had a 54% probability of a clinical event at 10 years, and those with three risk factors had a 68% probability, indicating a stepwise increase in the likelihood with the number of risk factors present. Gadolinium-enhancing lesions on the index scan were identified as a risk factor in a prospective cohort in 2021.[38]

In the 5-year international cohort,[17,19] of the 128 people with RIS who became symptomatic after 5 years of follow-up, 15 (12%) developed primary progressive multiple sclerosis.[19] Those diagnosed with primary progressive multiple sclerosis were more likely to be men, had a higher mean age at RIS identification and symptom onset, and were more likely to have spinal cord lesions than people with RIS who were subsequently diagnosed with clinically isolated syndrome or multiple sclerosis. The mean age of primary progressive multiple sclerosis onset in people with RIS was similar to that of patients with primary progressive multiple sclerosis identified through population-based and clinic-based cohorts.[29,39] The similar prevalence, sex ratio, and age of onset of primary progressive multiple sclerosis in individuals first identified as having RIS, compared with people with primary progressive multiple sclerosis identified using clinical multiple sclerosis criteria,[29,39] lends further support to the notion that RIS in some people represents presymptomatic multiple sclerosis.

Perhaps unsurprisingly, based on what is known in multiple sclerosis, pregnancy can trigger the symptomatic onset of clinically isolated syndrome in individuals with RIS.[40] Epstein-Barr virus infection might precede the clinical onset of multiple sclerosis, as seropositivity for Epstein-Barr virus is even greater in the multiple sclerosis population than in the general population.[41,42] The mechanism underlying multiple sclerosis development could be mediated by Epstein-Barr-virus-enhanced blood–brain barrier permeability, potentially in the RIS phase. Serum concentrations of neurofilament light chain, a marker of neuroaxonal injury, and studies of Epstein-Barr virus-infected memory B cells could provide evidence of neurodegeneration in response to Epstein-Barr virus infection. Triggers of relapses in people with multiple sclerosis are probably also relevant in RIS. Why approximately half of people with RIS do not develop clinical symptoms after 10 years of clinical follow-up is unclear. Some might not have, or might be resistant to, triggers, or older age and immune senescence might preclude a sufficient immune response to trigger symptomatic conversion. More longitudinal studies are needed to better understand this absence of transformation, especially in younger individuals (<37 years).

Paediatric and adolescent RIS

RIS has been reported in children and adolescents (aged 8·0–17·8 years).[43] This observation is fundamental, as such experiences might represent, as for adults, the earliest presentation of multiple sclerosis within the age

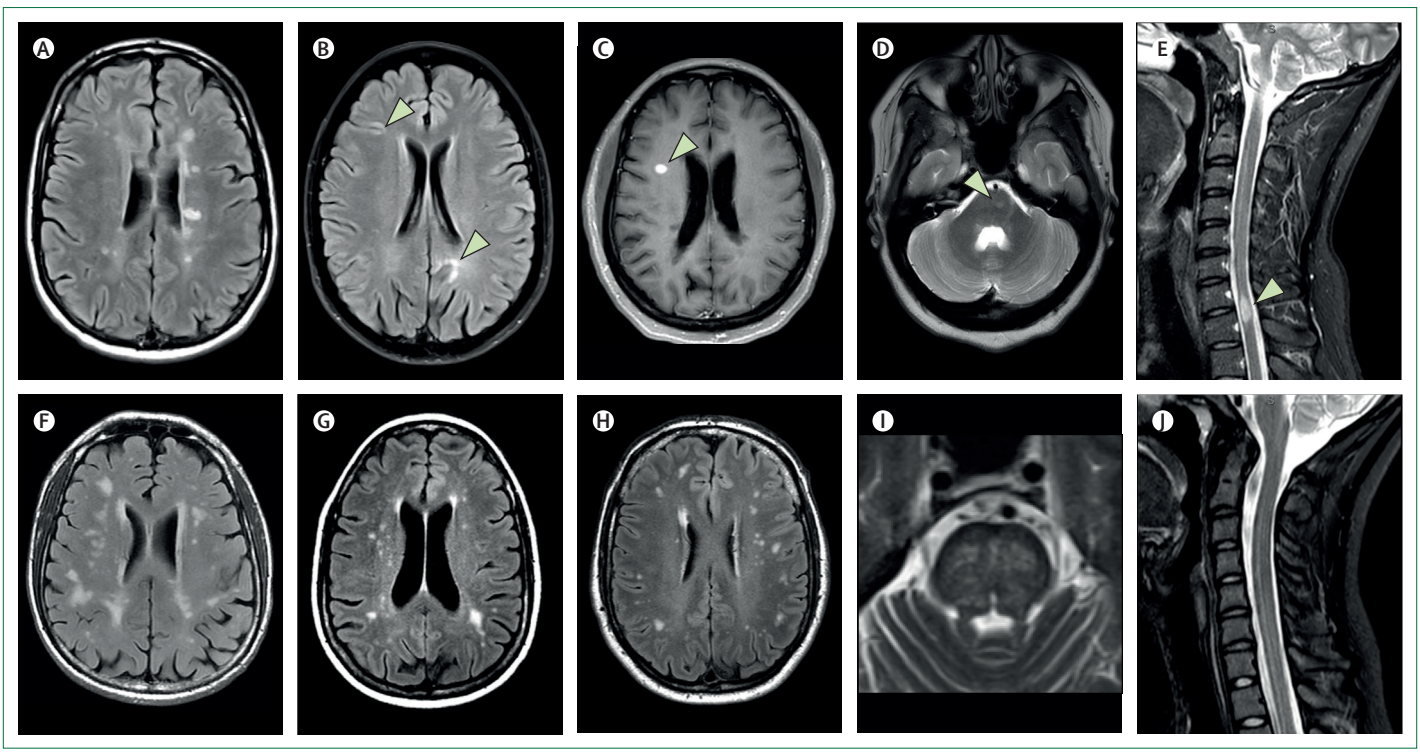

Figure 2: **MRI scans from the brain and upper cervical spinal cord**
Scans are from five people with radiologically isolated syndrome (A–E) and five people of similar ages with non-specific white matter disease (F–J). The scans from people with RIS show (A) incidentally identified T2-hyperintense anomalies within the brain highly suggestive of multiple sclerosis, (B) juxtacortical foci (arrows), (C) gadolinium enhancement (arrow) with obvious coexisting non-enhancing periventricular T1-hypointensities, (D) infratentorial involvement, and (E) intramedullary involvement of the lower cervical and upper thoracic spinal cord (C7–T1). Compare the morphology and spatial distribution of supratentorial foci observed in the non-specific white matter disease group (F–H) and the typical involvement of the pons (I). Healthy spinal cord imaging is typically observed in the non-specific white matter disease group (J).

continuum. Although the exact prevalence of RIS in the paediatric age group (aged 5–14 years) is unknown, one individual with RIS was identified among 5238 children aged 7–14 years (0·02%) in a Dutch study of incidental MRI findings in healthy children who were having scans in the large population-based Generation R study.[44] Further studies are needed to substantiate frequency estimates.

Risk of multiple sclerosis is substantial in children with RIS. In an international multicentre cohort study, 16 (42%) of 38 of children with RIS developed a first clinical demyelinating event 2 years from the index MRI.[45] Similar to adults, CSF-restricted oligoclonal bands and MRI abnormalities in the spinal cord were associated with an increased risk of a first clinical event. The similarities in risk factors for subsequent demyelinating events in children and adults with RIS argue for shared or at least overlapping biological mechanisms.

Formal criteria for RIS in children are needed. The aforementioned international study of children with RIS[45] used the 2010 MRI DIS criteria[24] to determine eligibility; these criteria require fewer MRI lesions than the current adult RIS criteria.[1] Given the high risk of a first clinical demyelinating event in children, the 2010 MRI criteria were proposed for use in future studies.[45] A separate international study of 61 children with RIS assessed the performance of the 2010 MRI criteria for DIS, instead of the 2005 DIS criteria that are used to define RIS in adults. The main findings were that specificity declined as the MRI criteria became less stringent (ie, as fewer lesions were needed for the 2010 MRI criteria) and that the MRI criteria with the highest specificity were the 2005 DIS criteria[23] (53·9%, 95% CI 37·2–69·9). Specificity was further increased with the addition of CSF-restricted oligoclonal bands (specificity 83·3%, 95% CI 58·6–96·4). Together, these findings suggest that combining a raised MRI lesion threshold, as found in the 2009 criteria for RIS in adults, and the addition of CSF-restricted oligoclonal bands might improve the accuracy of identifying children with RIS.[45]

Advanced MRI in RIS

Although the focal white matter lesions in RIS are indistinguishable on conventional imaging from those seen in multiple sclerosis, some advanced imaging data suggest that the degree of overall tissue damage might be milder at the RIS stage than at the multiple sclerosis stage. Using diffusion tensor imaging, people with RIS were found to have lower fractional anisotropy in lesions than people with multiple sclerosis. By contrast, people with relapsing-remitting multiple sclerosis had lower

fractional anisotropy, both in lesions and in normal-appearing white matter than those with RIS, suggesting that the microstructural damage in RIS might be confined to lesions. Furthermore, functional connectivity did not differ in people with RIS compared with controls who had no evidence of neurological disease on brain MRI, possibly because people with RIS do not have clinical deficits that require the brain to compensate.[46] Another group reported an absence of diffusion tensor imaging changes in the healthy-appearing white matter of people with RIS compared with people with no evidence of neurological disease on brain MRI.[47] These findings are consistent with studies showing that magnetisation transfer ratio values were similar in the healthy-appearing brain areas of people with RIS and compared with people with no evidence of neurological disease, but statistically significantly higher than those of people with relapsing-remitting multiple sclerosis.[48] Similar findings have been shown in the spinal cords of people with RIS, in which diffusion tensor imaging and magnetisation transfer ratio values in healthy-appearing areas did not differ from values in controls with no evidence of neurological disease.[49] Data using proton MR spectroscopy are mixed. One study showed a lower N-acetyl aspartate-to-creatine ratio in lesions and perilesional regions, healthy-appearing white matter, and cortical grey matter of people with RIS compared with people with no evidence of neurological disease.[50] Another study reported no difference in N-acetyl aspartate-to-creatine ratios in cortical grey matter in people with RIS compared with healthy controls.[51] These findings have led some researchers to hypothesise that the microstructural tissue damage in RIS could be confined to lesions or is at least milder than in clinical multiple sclerosis. These are small, cross-sectional studies, and the duration of RIS is still being determined, making it challenging to make conclusions about disease severity.

Several groups have shown that brain volume loss is already present at the RIS stage, indicating substantial tissue damage. Reductions in whole-brain volume,[50,52,53] cortical volume,[47,51,52] cortical thickness,[51,54] thalamic volume,[51,54] and cerebellar volume[55] have been reported. Data regarding whole-brain volume and total grey matter volume are mixed, as other groups have reported no volume reductions in people with RIS compared with people with no evidence of neurological disease.[54] Similarly, although some studies have reported no difference in MRI in the cervical spinal cord area between people with RIS and people with no evidence of neurological disease,[49] other studies have reported the presence of spinal cord atrophy in RIS, similar to relapsing-remitting multiple sclerosis and less severe than in progressive multiple sclerosis.[56]

Specific advanced imaging techniques might be of particular interest in RIS, to increase confidence in whether white matter hyperintensities seen on MRI are likely to be demyelinating. Central veins,[57] paramagnetic rims,[58] and cortical lesions[59] have been identified in people with RIS, similar to people with clinical multiple sclerosis.[60,61] Furthermore, three-dimensional conformational metrics[62]and lesion dynamics[63] have shown utility in differentiating multiple sclerosis lesions from those related to small vessel disease. Further studies investigating the utility of these techniques to increase specificity for CNS demyelination and help distinguish RIS from white matter hyperintensities of other causes will be clinically relevant and of high interest.[64] The techniques most valuable to clinicians will be those that are easily integrated into routine practice and widely available without the need for complex MRI sequences and post-processing.

Optical coherence tomography

Using OCT, some groups have reported reductions in macular retinal nerve fibre layer (RNFL), macular ganglion cell inner plexiform layer (GCIP),[65] and temporal peripapillary RNFL thickness in people with RIS compared with people who have no evidence of neurological disease on brain MRI. Another group found no difference in overall RNFL thicknesses between people with RIS and those with no evidence of neurological disease. However, people with RIS who had spinal cord or infratentorial lesions had lower GCIP thicknesses than healthy controls and individuals with RIS who did not have a spinal cord or infratentorial lesions, suggesting that lower GCIP thickness in RIS could support the presence of more widespread disease.[65] A prospective study of 30 people with RIS independently predicted conversion to multiple sclerosis using OCT, peripapillary RNFL, and GCIP, even in the absence of spinal cord lesions.[66] Another study showed that peripapillary RNFL was thinner in individuals with RIS who had a clinical event during the follow-up period than in people with RIS who did not have a relapse.[67] Future studies will continue to examine the value of OCT metrics to predict which people with RIS are at the highest risk of clinical multiple sclerosis.

Laboratory markers

When a person is suspected of having RIS, there are two major challenges: differentiating CNS demyelination from white matter hyperintensities associated with other causes (eg, migraine and small vessel disease) and determining whether the person is at high risk of developing clinical symptoms.[68] There is a clear need for laboratory biomarkers to provide specificity for diagnosing CNS demyelination and identifying which people with RIS are at high risk. In a 2022 study, a global transcriptome signature analysis of people with RIS showed 57 differentially expressed genes, indicating 16 different signalling pathways, compared with people without evidence of neurological disease; however, these numbers of genes and pathways were similar to those of

people with multiple sclerosis, suggesting a similar dysregulation of the immune processes. These common biological signatures are known to regulate the immune response, cytokine production, and chemokine production, substantiating the link between the pathways that are dysregulated in RIS and multiple sclerosis.[69] If validated in a larger RIS cohort, such biomarkers would help to explain the mechanisms of transition from RIS to multiple sclerosis. Moreover, transcriptional signatures could inform management and monitoring decisions and help clinicians to talk with people with RIS about future risk of being diagnosed with multiple sclerosis. A small but growing body of literature suggests that serum and CSF biomarkers might refine the ability to predict which people with RIS will develop clinical symptoms.[70] In a study of 75 people with RIS, high levels of CSF neurofilament light chain and CSF-restricted oligoclonal bands independently predicted occurrence of a first clinical symptom, particularly in people older than 37 years.[71] CSF concentrations of neurofilament light chain did not differ between people with RIS and people with multiple sclerosis. In a study of 71 people with RIS, high CSF concentrations of CHI3L1 were associated with a shorter mean time to clinical symptoms when combined with positive CSF and four 2005 MRI criteria for DIS, but CHI3L1 in CSF was not an independent predictor of conversion to multiple sclerosis.[72] When meeting the criteria for having RIS, elevated concentrations of neurofilament light chain in CSF and serum are independent predictive factors of disease activity and clinical conversion.[73] Serum neurofilament light chain is more accessible than CSF neurofilament light chain and can be considered when a lumbar puncture is not performed. Large studies are underway investigating the added value of many candidate biomarkers in serum and CSF to predict clinical disease activity and disease severity in people with RIS. Detection of kappa free light chains in CSF has also recently been identified as a predictor of whether people with RIS will subsequently have symptoms of multiple sclerosis.[74]

People with RIS in the clinic

Clinical monitoring

Using evidence from the literature, we propose a monitoring algorithm for people who have met RIS criteria, including risk stratification and clinical and MRI follow-up (figure 3). In addition to brain MRI, we recommend, as shown in the revised RIS criteria,[26] that all people with RIS undergo baseline cervical and thoracic spinal cord imaging.[75] The presence of spinal cord lesions can support the diagnostic criteria if the brain MRI shows only one suggestive T2 lesion. A spinal cord MRI showing T2 lesions can also, along with a lumbar puncture, identify features suggestive of inflammatory demyelinating disease and represent risk factors for clinical multiple sclerosis. People with RIS should then be followed up and monitored for evidence of clinical or radiological disease activity with annual clinic visits and MRI studies. Cognitive tests can be added to eliminate the possibility of a prevalent cognitive form of multiple sclerosis.[76] Continued clinical vigilance regarding a better explanation for the observed MRI features is also recommended.

Therapeutic trials

Given the relatively high risk of clinical multiple sclerosis over time, particularly in people with RIS who have more than one risk factor and grey matter atrophy, an argument could be made for initiating disease-modifying therapies in some individuals with RIS. Despite the absence of randomised controlled trial data showing the benefit of disease-modifying therapies in RIS when clinical cohorts were collected,[17,38] 44 (17%) of 277 individuals in the multinational RIS Consortium cohort had previously been exposed to a disease-modifying therapy.[17] Surveys of 239 US-based and 350 European-based practising neurologists indicated that 50–80% would initiate disease-modifying therapy in a hypothetical person with RIS if new MRI lesions appeared during follow-up.[77,78] However, because some people with RIS remain asymptomatic throughout their lifetime, whether it is appropriate to commit individuals with RIS to long-term therapy with multiple sclerosis disease modifying therapies—some of which have substantial risks and side-effects—is the subject of active debate.[28–80]

Two multicentre, randomised, double-blind clinical trials have been conducted in people with RIS. The ARISE study randomly assigned people with RIS in a 1:1 ratio to dimethyl fumarate or placebo,[81] and the TERIS study randomly assigned people with RIS in a 1:1 ratio to teriflunomide or placebo.[82] The primary endpoint in both studies was the time to the first demyelinating clinical event related to CNS demyelination. Secondary endpoints included the number of gadolinium-enhancing lesions, the number of new or enlarging T2 lesions, T2 lesion volume, and whole-brain volume. The TERIS study also collected patient-reported outcomes with yearly fatigue, cognitive, and quality-of-life scales. These studies were designed as sister studies (ie, identical study duration, schedule of assessments, core MRI protocols and analysis, inclusion and exclusion criteria, and study endpoints) in anticipation of future pooled analyses.

Primary outcome results from the ARISE study showed that treatment with dimethyl fumarate resulted in an 80% reduction in the risk of a first clinical demyelinating event in individuals with RIS compared with placebo (hazard ratio [HR] 0·2, 95% CI 0·11–0·35; p=0·006)[81] over 2 years, providing the first scientific evidence of the prevention or delay of a first clinical event in people with RIS. Furthermore, compared with placebo, the number of new or newly enlarging T2-weighted hyperintense lesions in the dimethyl fumarate group was significantly reduced compared with placebo (HR 0·20, 95% CI 0·04–0·94; p=0·042).

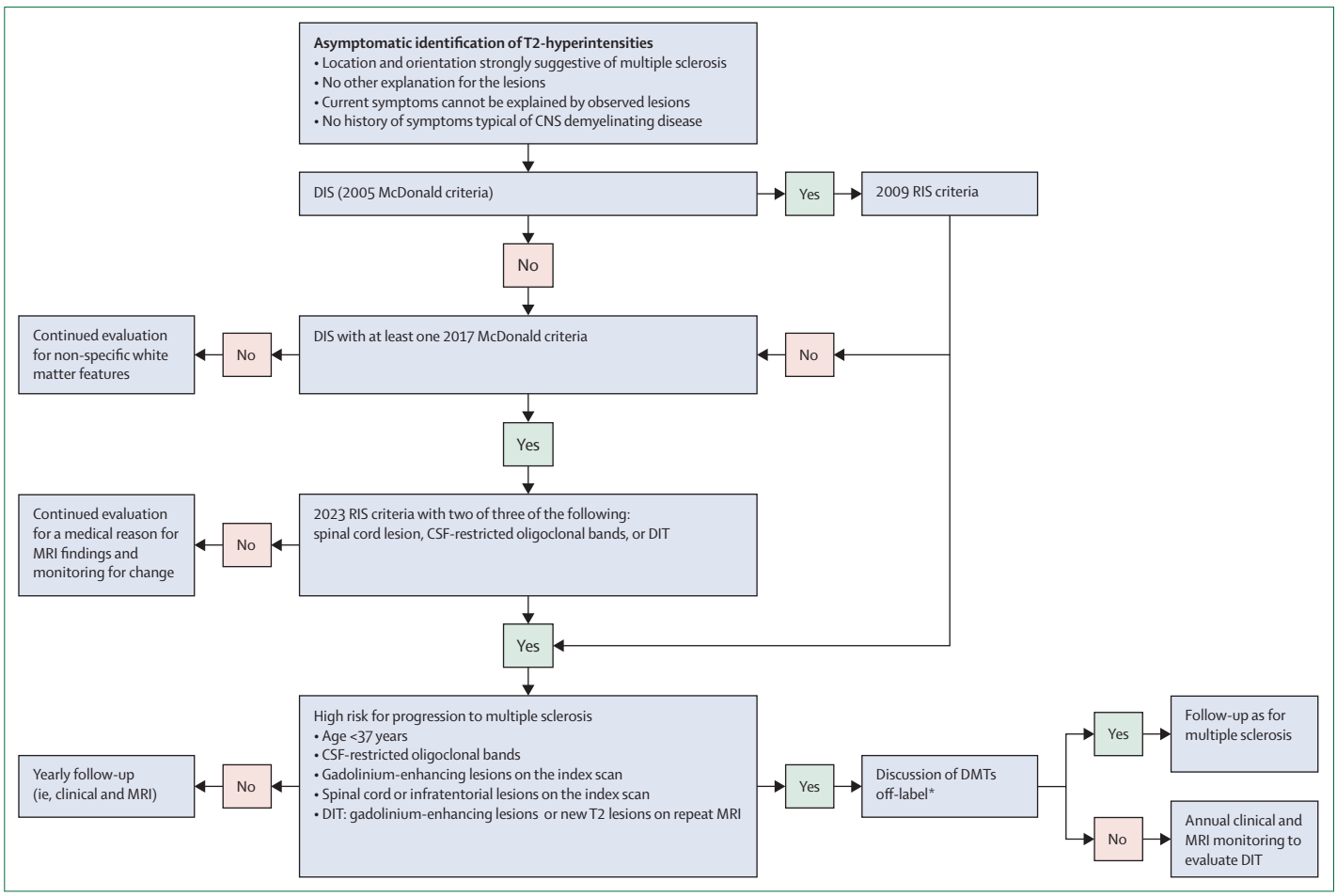

Figure 3: **Proposed guidelines for monitoring and counselling of individuals who have incidental T2 hyperintensities**
Suggested guidelines for investigation of and intervention for incidental T2 hyperintensities based on the opinion of the authors.[1,15,23,26] DIS=dissemination in space. DIT=dissemination in time. DMT=disease-modifying treatment. RIS=radiologically isolated syndrome. *If RIS has risk factors, a neurologist can decide to discuss oral DMTs as there is shown efficacy to extend time to the first clinical event in RIS.

Primary outcome results from the TERIS study supported the efficacy of teriflunomide, with a 62% reduction in the number of clinical events in the teriflunomide group compared with placebo (HR 0·38, 95% CI 0·17–0·88; p=0·025) over 2 years.[82] For teriflunomide compared with placebo, the odds ratio for the number of participants with gadolinium-enhancing lesions was 0·31 (95% CI 0·08–1·18; p=0·087) and the rate ratio for the cumulative number of new or enlarging T2 lesions was 0·69 (95% CI 0·34–1·40; p=0·31). These studies represent a major step in considering an active immune intervention at the presymptomatic stage of multiple sclerosis; however, caution is still needed. For example, we have yet to determine which people with RIS can benefit from disease-modifying therapy, owing to the absence of subgroup analyses, or whether the benefits persist beyond 2 years. CELLO,[83] a phase 4, multicentre placebo-controlled study, aimed to assess the effectiveness of three courses of the anti-CD20 drug ocrelizumab in people with RIS defined according to 2017 MAGNIMS recommendations,[25] but was stopped early due to the slow pace of recruitment.

Treatment with disease-modifying therapies might in theory be reasonable in people with RIS who have several risk factors for multiple sclerosis and have documented DIT by MRI criteria. However, studies with revised inclusion criteria, active comparator groups, subgroup analyses, and longer follow-ups are needed to substantiate this possibility. The drugs used in the two RIS studies (ie, dimethyl fumarate and teriflunomide) are currently not approved for use in people with RIS. Nevertheless, two drugs with different modes of action both having provided evidence of benefits represent a major step forward. If disease-modifying therapies are given off-label, it is crucial that the recipients have counselling regarding long-term therapy use, which mirrors the standards in multiple sclerosis care.[84,85] Currently available disease-modifying therapies are more effective in people with multiple sclerosis when prescribed earlier, but the individual with RIS who is receiving the treatment can be

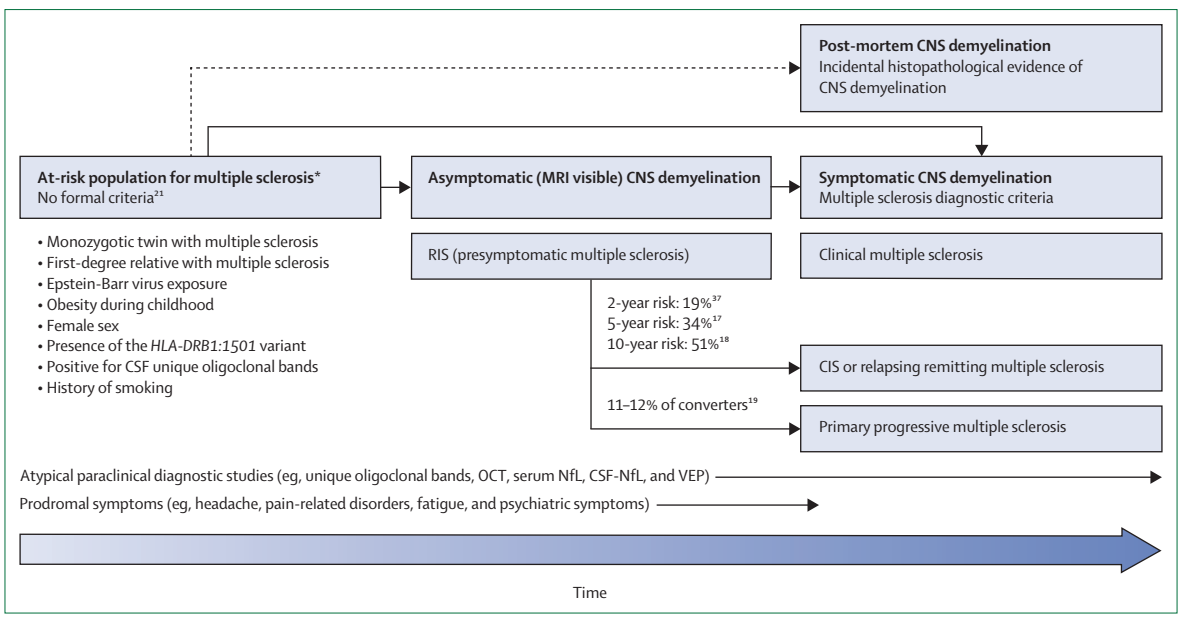

Figure 4: **Proposed phases of multiple sclerosis**
Our proposed scheme includes individuals at risk for future acute and progressive demyelinating clinical courses and those with histopathological features incidentally identified on post-mortem examination. The dotted line represents cases in which the individual died before any lesions were found. People who are at risk of multiple sclerosis or have only radiological evidence of multiple sclerosis can have atypical paraclinical findings and prodromal symptoms. Risk factors are shown in order from most to least evidence of an association. RIS=radiologically isolated syndrome. CIS=clinically isolated syndrome. VEP=visual evoked potentials. OCT=optical coherence tomography. NfL=neurofilament light chain. *Individuals at risk for multiple sclerosis might never manifest with asymptomatic or symptomatic CNS demyelinating lesions.

assured that the potential adverse events in the RIS trials mirror those in multiple sclerosis pivotal studies. However, the implication for people with RIS who agree to start a disease-modifying therapy with the aim of decreasing the risk of a clinical attack is that the long-term benefits must outweigh the risks of using an immunoactive treatment in a person who is asymptomatic.

Conclusions and future directions

Since publication of the RIS criteria in 2009, there have been remarkable advances in our understanding of presymptomatic multiple sclerosis and the risk for clinical conversion to multiple sclerosis (figure 4). Updates to the 2009 criteria for adults with RIS[2] have been proposed,[26] prioritising accuracy, given the risk of psychological harm associated with an inaccurate diagnosis and unnecessary exposure to a disease-modifying therapy, and to align with the current radiological multiple sclerosis criteria.[15]

An international longitudinal study of children (<18 years) with RIS is also currently underway. The Isoelectric Focusing of Tears in Children With Radiologically Isolated or Clinically Isolated Syndrome (OBIT) study (NCT03979391) will aid in determining the frequency with which children with RIS develop a first clinical neurological event. As the presence of oligoclonal bands increases the specificity of criteria for RIS,[26,45] their detection in lacrimal fluid instead of CSF could facilitate diagnosis in children.[86] Studies in children with RIS also offer an opportunity to identify risk factors that might differ from those in adults.

Mobile apps are increasingly used to manage chronic health conditions, including multiple sclerosis.[87] Detecting deficits in neurological function using sensitive, practical, user-friendly, and time-efficient techniques could be highly relevant in future, especially in individuals with RIS. An engineered glove measuring finger motor performance detected subclinical impairments in people who had RIS without motor complaints.[88,89] Another app allows a smartphone to obtain digital biomarkers in 5 min that correlate to several dimensions of the neurological examination, showing subtle differences between people with RIS and people with no evidence of a neurological disorder on MRI.[87] Individuals with RIS have also shown subclinical deficits in eye movement detected by video oculography.[90] Since access to video oculography is scarce and its use in monitoring RIS is still under investigation (OCRIS Study, NCT03636789), mobile phone apps could be of value in detecting such subclinical deficits.[91]

An international RIS registry is ongoing, supported by the RIS Consortium, the French Multiple Sclerosis Society, the French Multiple Sclerosis Observatory,[92] and the ARISE and TERIS Study groups (RISC Cohort, NCT05388331), associated with other national efforts.[93,94] Pooling biological, imaging, and digital data in a large number of people with RIS will facilitate early identification of predictors for clinical conversion to

Search strategy and selection criteria

We searched PubMed for papers published between Jan 1, 2000, and June 30, 2023, without any language restrictions, with the following terms: "radiologically isolated syndrome", "central nervous system", "multiple sclerosis", "white matter lesions", "digital biomarkers", "MRI", "diagnostic criteria", "prodromes", " preclinical MS", "asymptomatic MS", "review", "incidentaloma", "diagnosis", "pathology", "preclinical disease", and "atypical symptoms". Additional references were gathered from the European Committee For Treatment And Research In Multiple Sclerosis library and American Academy of Neurology conference reports. Original research articles and high-impact reviews were included. The final reference list was generated based on the relevance and originality of the topics covered in this Personal View.

multiple sclerosis. International, multicentre, randomised, and other controlled RIS trials that provide evidence that could lead to regulatory approval for disease-modifying therapies already approved for multiple sclerosis are now warranted. For now, the prescription of disease-modifying therapies in people with RIS remains off-label.

Future worldwide efforts are needed to expand upon previously identified risk factors so that people with RIS might be better counselled on clinical surveillance recommendations and the risk for future disease activity. As the first randomised clinical trials have suggested a benefit in preventing or delaying the onset of a first symptom related to CNS demyelination, we expect to see further discussion regarding treatment of people with RIS and expansion of the definition of multiple sclerosis. The identification of additional biomarkers will assist in maintaining diagnostic accuracy, improving the sensitivity and specificity of criteria for RIS, and providing further insights into the risk for disease advancement. A prospective, international, comprehensive, standardised data registry involving worldwide collaboration, to enrich the RISC cohort, will be crucial to further understanding multiple sclerosis biology in this early presymptomatic phase. Such a registry might enable the effective exploration of biological reasons why some people with RIS do not develop symptomatic disease, and such findings might one day be essential in preventing clinical multiple sclerosis.

Contributors

All authors performed literature searches; drafted the manuscript; and critically edited, approved, and submitted the final draft.

Declaration of interests

CL-F is the principal investigator of the TERIS study. OK declares no competing interests. AS has received research grants from The Turkish Multiple Sclerosis Society and The Scientific and Technological Research Council Of Turkey and Istanbul University-Cerrahpasa Research Support Funds. He has received consultancy fees from Roche, Merck Serono, Biogen Idec/Gen Pharma of Turkey, Sanofi-Genzyme, Novartis, and Alexion, has received honoraria for lectures from Sanofi-Genzyme, Novartis, Roche, and Teva, and has received registration coverage for attending scientific congresses or symposia from Sanofi-Genzyme and Alexion. CJA receives grant support from the National Multiple Sclerosis Society and the National Institutes of Health (NIH). In the past 3 years, she has received honoraria or consulting fees from Sanofi-Genzyme, Novartis, Genentech, Alexion, EMD Serono, and Horizon Therapeutics for participation on advisory boards and data safety monitoring committees, and honoraria for lectures from the American Academy of Neurology, Spire Learning, Department of Defense, Catamount Education, Projects in Knowledge, and Oregon Health and Science University. NM has received research funding from the NIH (award number K23NS101099), the National Multiple Sclerosis Society, and the Charles H Hood Foundation, and speaker honoraria for MDedge. DP has received consulting honoraria from Roche and Novartis. DTO received personal compensation for consulting and advisory services from Alexion, Biogen, Celgene/Bristol Myers Squibb, EMD Serono, Genentech, Genzyme, Janssen Pharmaceuticals, Novartis, Osmotica Pharmaceuticals, RVL Pharmaceuticals, TG Therapeutics, and Viela Bio, and research support from Biogen and Merck Serono. He was also a study protocol author and served as the lead investigator of the ARISE study.

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