Medora

La community dei professionisti della salute By Roche

M-IT-00001115

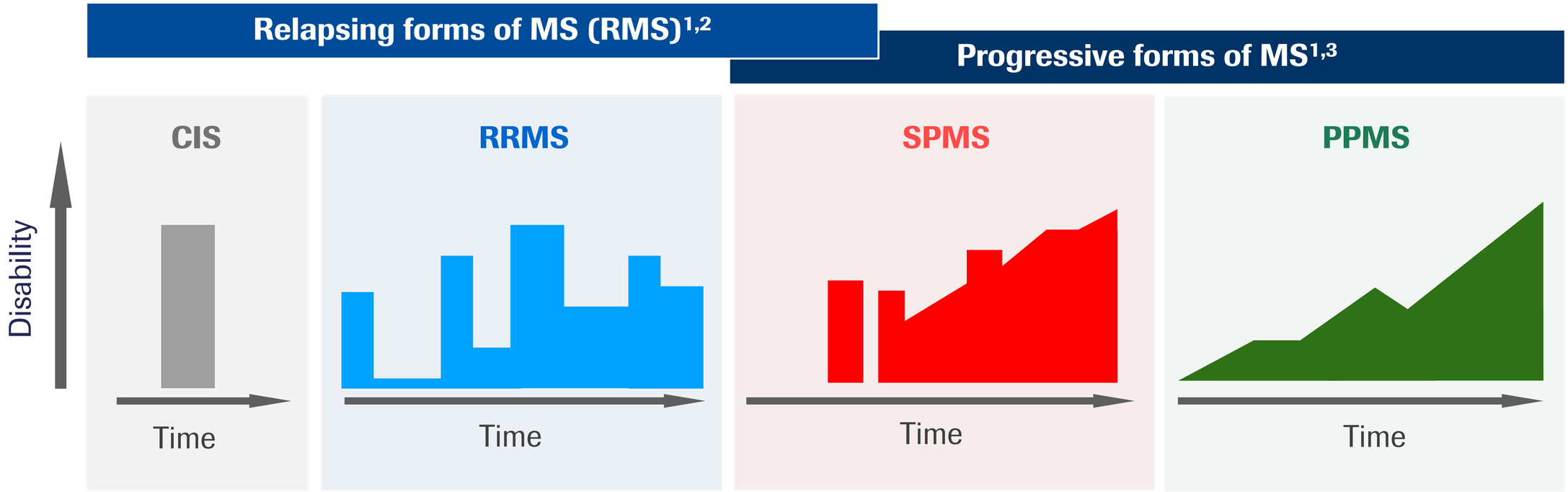
What are the different phenotypes of MS?

What are the different phenotypes of MS?

1. How do these clinical phenotypes differ?
2. What are relapses and why do they happen?

MS is a heterogeneous disease, conventionally defined in the clinical setting as either relapsing or progressive phenotypes

Based on the natural history of the disease, MS is typically described as having one of four phenotypes:



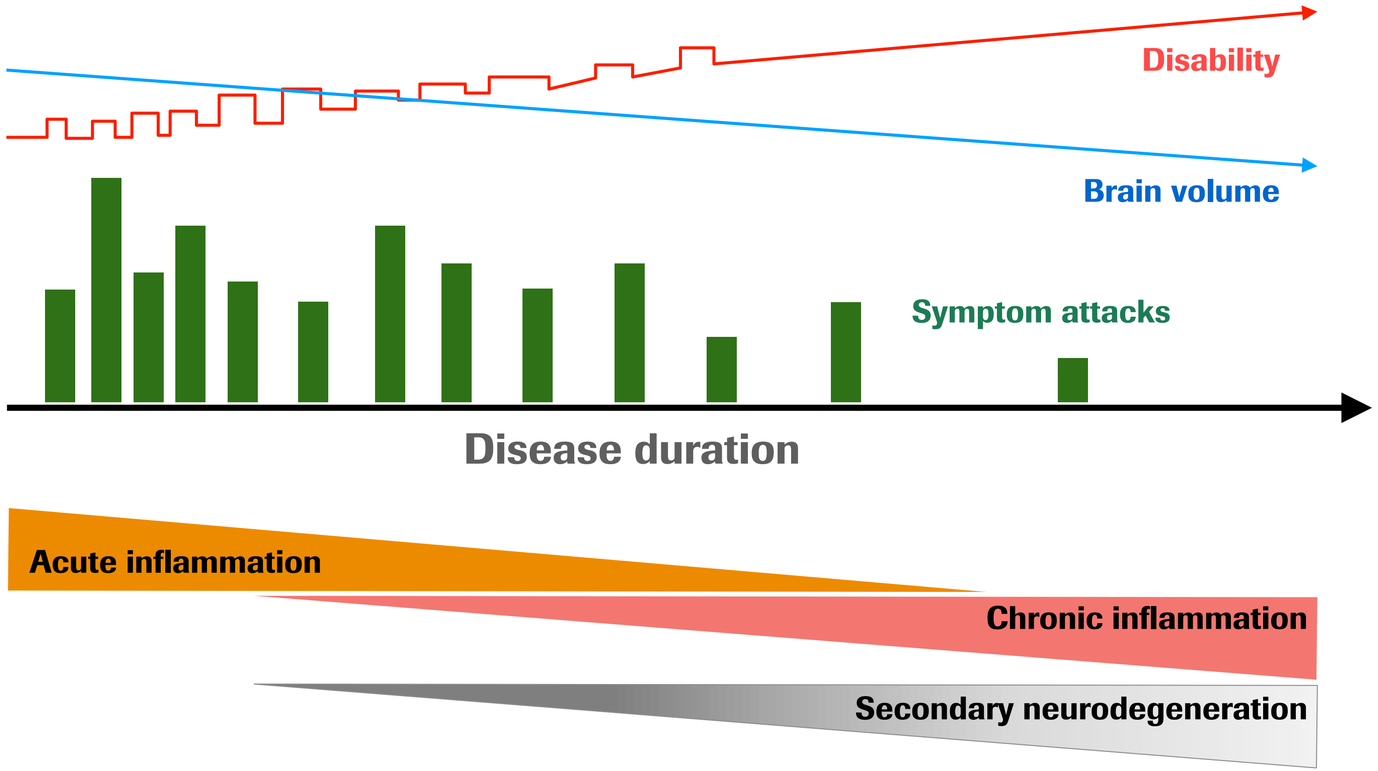
MS phenotypes are further subcategorised by disease activity (clinically or by MRI) and are deemed to be either ‘active’ or ‘non-active’

CIS, clinically isolated syndrome; PPMS, primary progressive MS; RRMS, relapsing remitting MS; SPMS, secondary progressive MS.

1. Lublin FD, et al. Neurology 2014;83:278–86;
2. National Multiple Sclerosis Society. Relapse-remitting MS (RRMS). http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS. Accessed January 2020;
3. National Multiple Sclerosis Society. Primary progressive MS (PPMS). http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS. Accessed January 2020.

MS is characterised by inflammation, degeneration and accumulating disability

- Peripherally-initiated **inflammation** dominates in **early MS**, leading to **abnormal lesions** and **symptom attacks (relapses)**
- **Later stages** are characterised by **CNS-compartmentalised inflammatory responses**, **brain volume loss** and **neurodegeneration**
- The complex pathobiology of MS ultimately leads to **accumulation of clinical disability**



CNS, central nervous system.
Figure adapted from Kawachi I, Lassmann H. J Neurol Neurosurg Psychiatry 2017;88:137–45.
Bar-Or A. Semin Neurol 2008;28:29–45.

Patients with MS share common clinical manifestations and underlying neuropathological mechanisms of disease

Clinically, the symptoms and disease course of MS can manifest in a number of ways[1,2]

Acute relapses

Episodes of clinical worsening, which may be followed by complete remission or permanent disability[1]

Chronic symptoms

Ongoing signs and symptoms, that result from disease progression and adversely impact patients' lives

Accumulation of disability and functional worsening may occur following a relapse or independently[3]

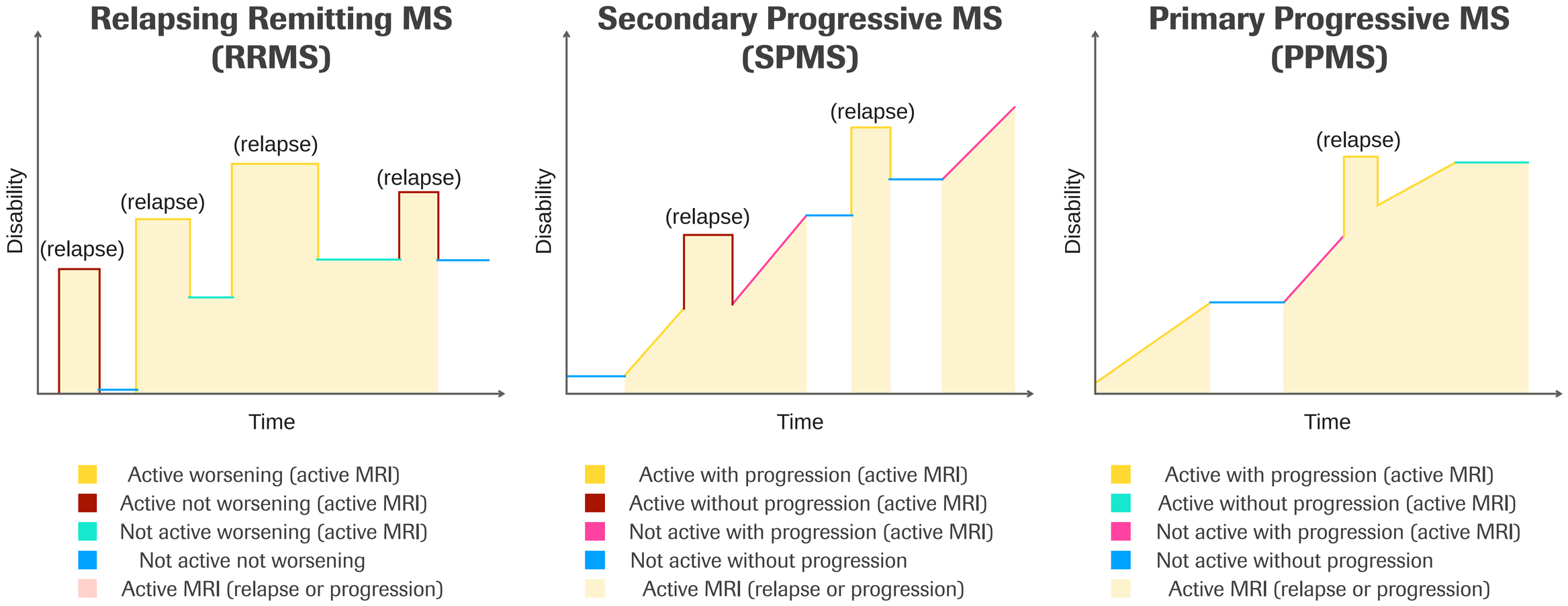
Disability progression

Periods where a patient's MS appears to be clinically non-active (sub-clinically this may not be the case)[3]

Episodes of non-activity

1. Correale J, et al. Brain 2017;140:527–46; 2. Kutzelnigg A, et al. Brain 2005;128:2705–12; 3. Multiple sclerosis: current status and strategies for the future (2001). National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK222397. Accessed January 2020.

Across phenotypes, MS is defined by continuous disease progression and acute and chronic disease activity[1–2]

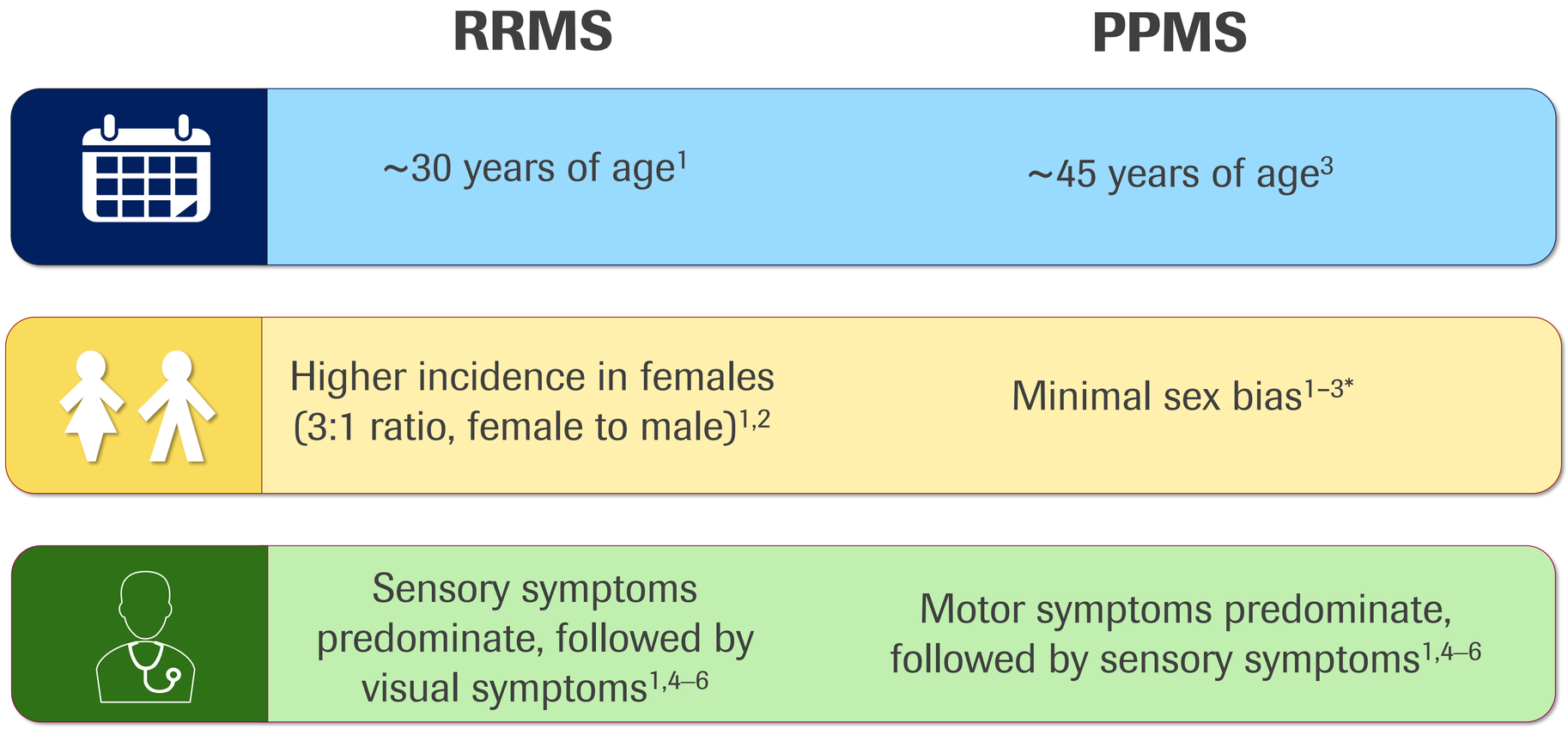


1. Lublin FD, Reingold SC. Neurology 1996;46:907–11; 2. Lublin FD, et al. Neurology 2014;83:278–86.

1

How do these clinical phenotypes differ?

Relapsing-remitting MS typically has an earlier age of onset than PPMS, sex bias and different initial presentation



*Although clinical studies have uniformly reinforced a lack of a gender difference in PPMS, a 2017 study of 600 patients with PPMS included in the NARCOMS Registry3 suggested the disease could be more prevalent in females. The discrepancy may have arisen from misclassification and selection biases in the registry, mortality rates being higher in males or an inherent bias in clinical trial cohorts.3

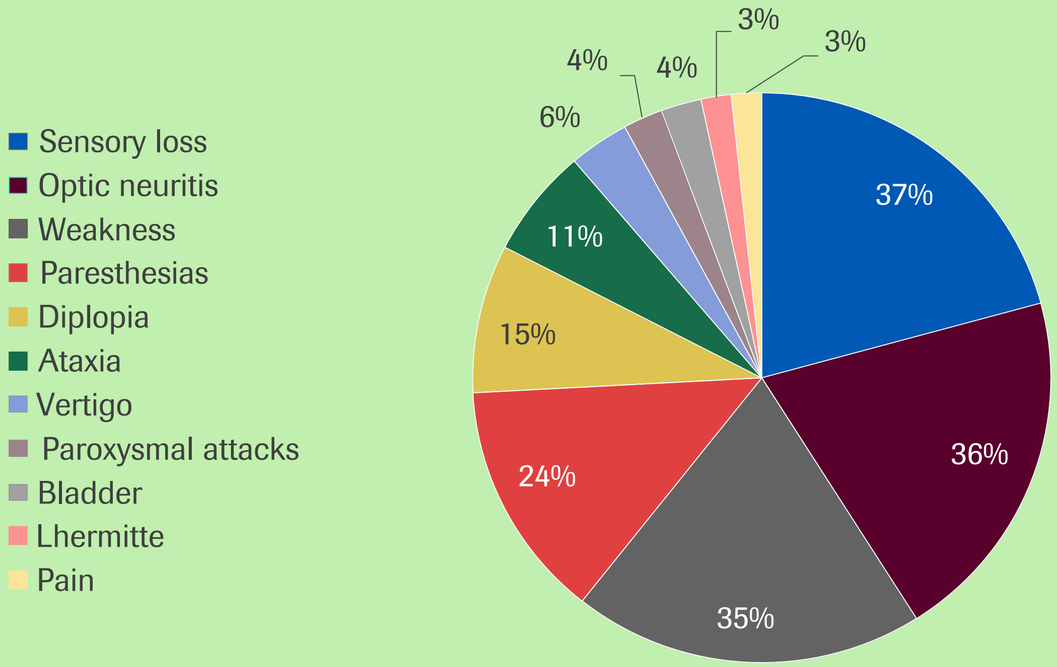
NARCOMS, North American Research Committee on Multiple Sclerosis; PPMS, primary progressive MS; RMS, relapsing MS.

1. Rice CM, et al. J Neurol Neurosurg Psychiatry 2013;84:1100–6; 2. Antel J, et al. Acta Neuropathol 2012;123:627–38; 3. Salter A, et al. Mult Scler 2018;24(7):951-962;
4. Cottrell DA, et al. Brain 1999;122:625–39; 5. Sola P, et al. Mult Scler J 2011;17:303–11; 6. Compston A, Coles A. Lancet 2008;372:1502–17.

The frequency any type of presenting symptoms differs between patients with RRMS and PPMS

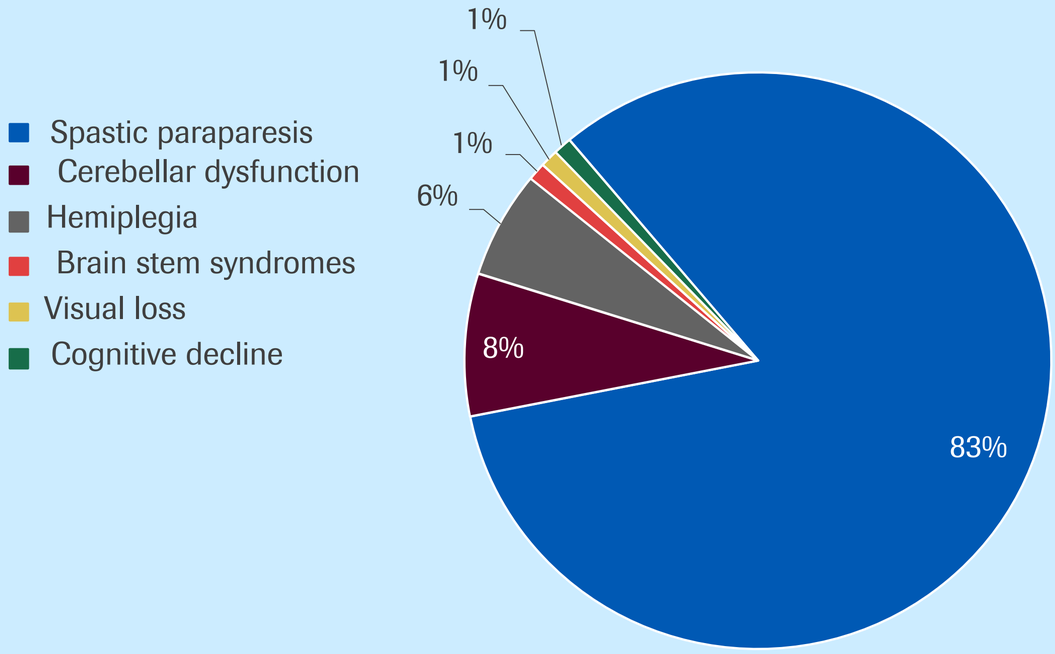
Presenting symptoms of patients with RRMS*[1,2]

- Usually present with sensory symptoms related to a single organ class
- May have resolved by the time the patient is seen



Presenting symptoms of patients PPMS[1,3]

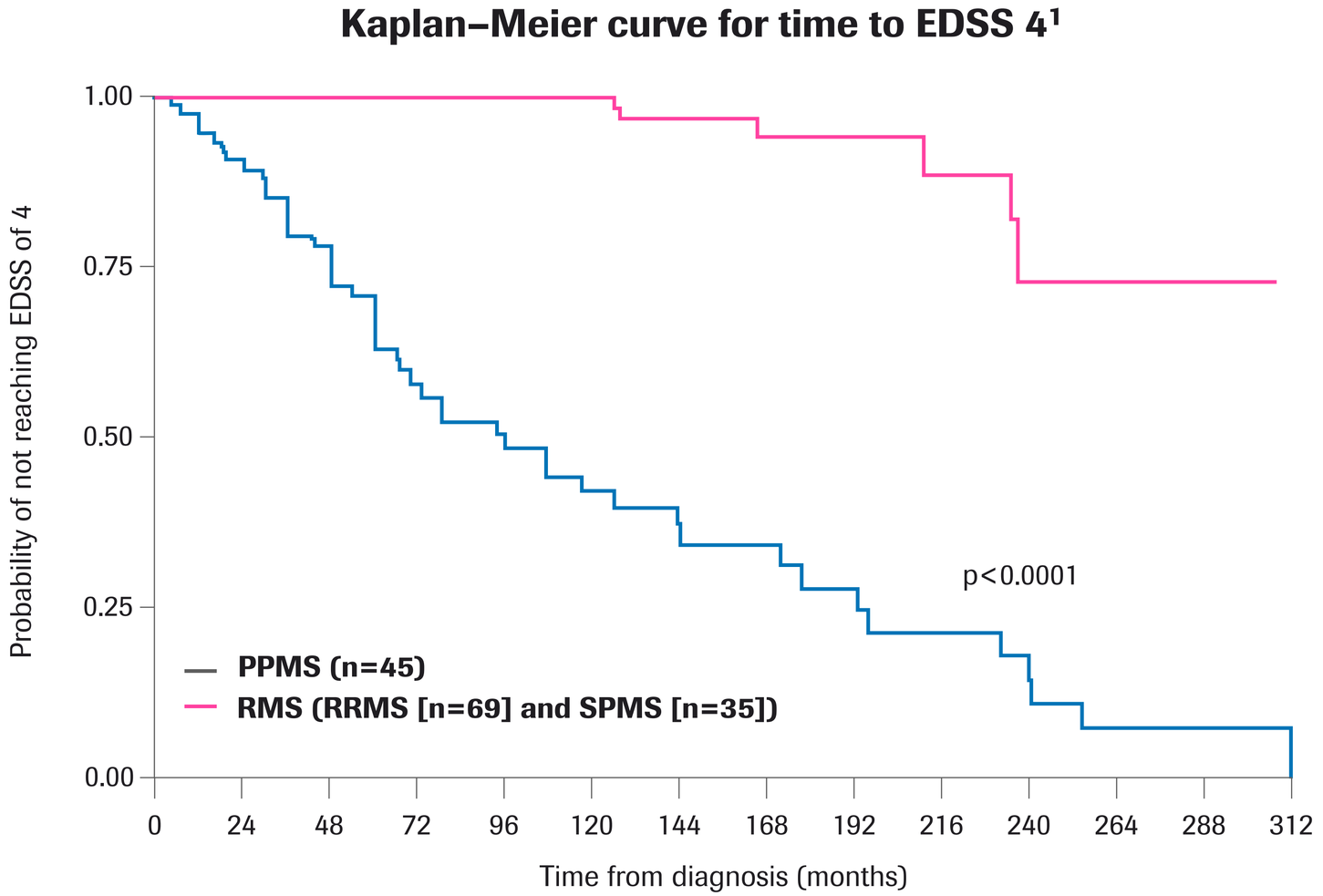
- Usually present with a progressive gait disorder
- Symptoms often predate referral to a neurologist by a number of years



*Incomplete list; symptoms reported in ≤2% of patients are not shown.
PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis.

1. Palace J. J Neurol Neurosurg Psychiatry 2001;7:ii3–ii8;
2. Hauser SL, Goodin DS (2008) in Fauci A, et al (Eds.). Harrison's principles of internal medicine (17th Edition, Volume II). McGraw Hill Medical;
3. Antel J, et al. Acta Neuropathol 2012;123:627–38.

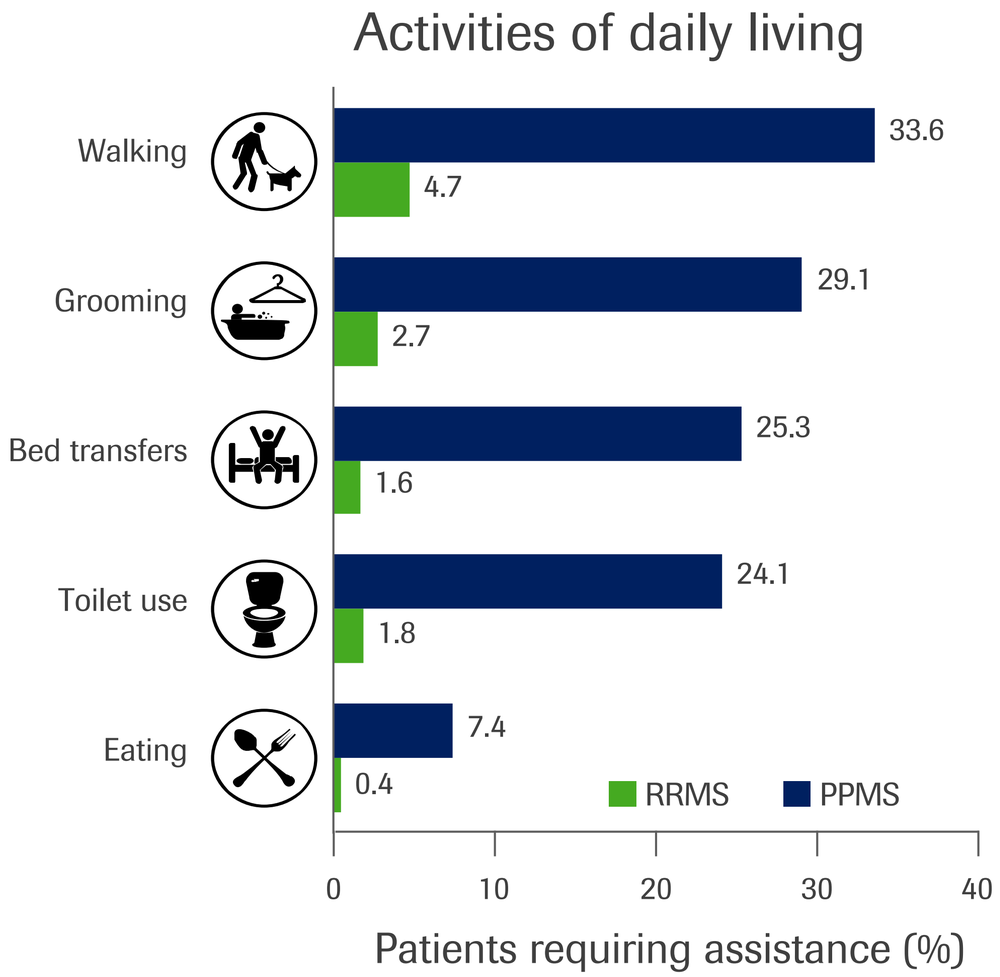
Disability progression is faster in patients with PPMS compared with RMS

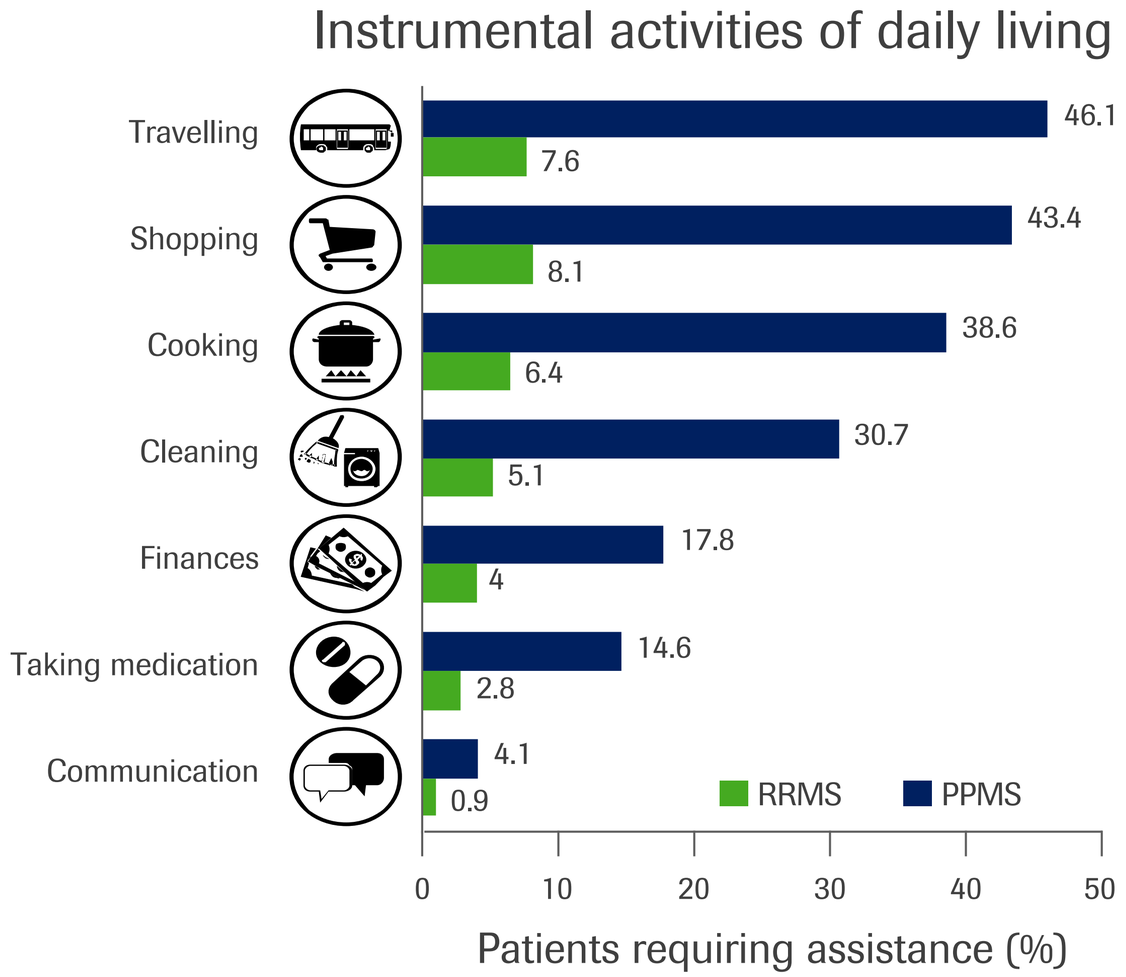


These curves are not age adjusted – patients with RRMS are typically diagnosed at a younger age, during which time they are better able to compensate against the effects of demyelination and neurodegeneration, in turn delaying disability progression.[2] This is in contrast to their PPMS counterparts, who are often included in such analyses at an older age[3]

Curves are not age adjusted.
EDSS, Expanded Disability Status Scale; PPMS, primary progressive MS; RMS, relapsing-onset MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.
1. Sola P, et al. Mult Scler 2011;17:303–11; 2. Musella A, et al. Frontiers Aging Neurosci. 2018;10:238; 3. Salter A, et al. Mult Scler 2018;24(7):951-962..

Patients with PPMS require more assistance with activities of daily living than patients with RRMS





p<0.001 for all RRMS vs PPMS comparisons.
PPMS, primary progressive MS; RRMS, relapsing-remitting MS.
Wu N, et al. Presented at ECTRIMS 2017 (Poster EP1427).

Overall, progressive MS has greater impact on patients and their caregivers than relapsing MS

Compared with patients with RRMS, patients with PPMS or SPMS:

Are less able to walk[1,2]

Feel more hopeless and resigned about the future[2]

Are more likely to require time off work, or stop working completely[1,2]

Need more help with daily activities[1,2]

PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

1. Gross HJ, Watson C. Neuropsychiatr Dis Treat 2017;13:1349–57; 2. Holland NJ, et al. Int J MS Care 2011;13:65–74.

Whilst clinical presentation and disease burden of RRMS and PPMS are distinct, there is little evidence that they differ in aetiology or pathogenesis

Up to 10% of patients with PPMS experience relapses, supporting common disease mechanisms[1,2]

RRMS and PPMS are not easily distinguishable based on the following[2]:

CSF banding
Visual evoked potentials
Genetics
Neuropathology

Clinical features (not distinct from SPMS)

- RRMS and PPMS should be viewed as two ends of a continuum or spectrum[1,2]

CSF, cerebrospinal fluid; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

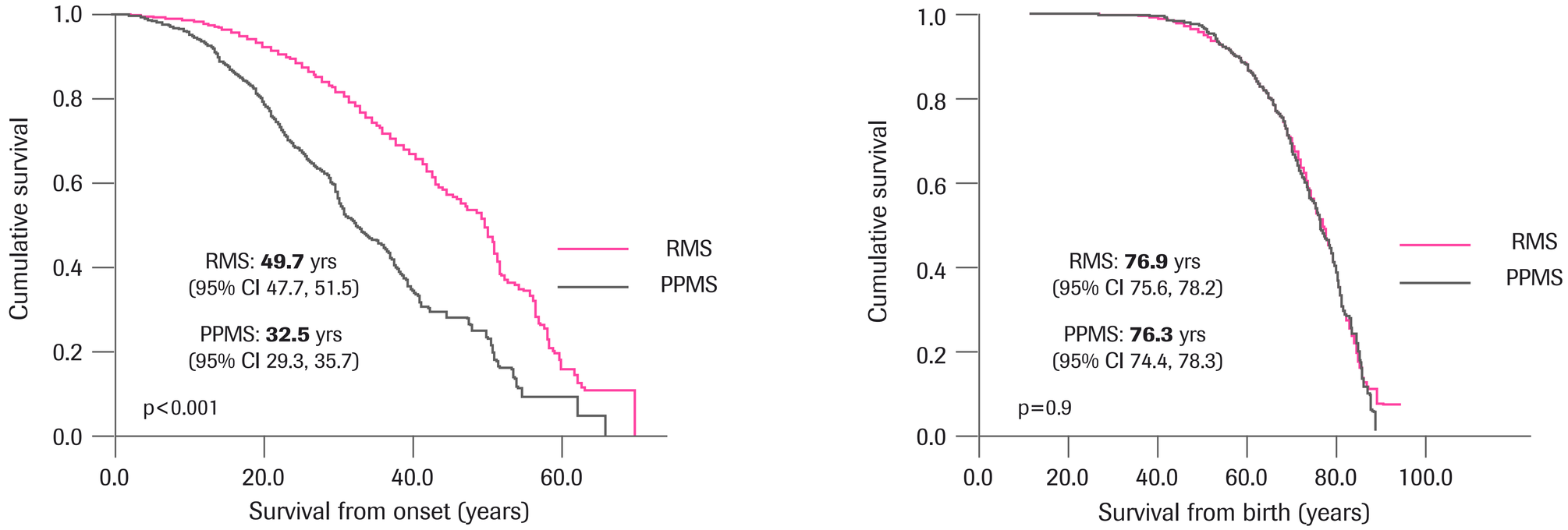
1. Antel J, et al. Acta Neuropathol 2012;123:627–38; 2. Rice CM, et al. J Neurol Neurosurg Psychiatry 2013;84:1100–6.

The average time from MS diagnosis to death is shorter in patients with PPMS than in patients with RMS

However…

- Age at death is similar in RMS and PPMS due to later age of onset of PPMS[1–4]
- Time to death from onset of progression does not differ between PPMS vs SPMS[1]

PPMS vs RMS Kaplan–Meier survival curves[2]



PPMS, primary progressive MS; RMS, relapsing MS; SPMS, secondary progressive MS.

1. Scalfari A, et al. Neurology 2013;81:184–92; 2. Kingwell E, et al. J Neurol Neurosurg Psychiatry 2012;83:61–6; 3. Smestad C, et al. Mult Scler 2009;15:1263–70;
4. Antel J, et al. Acta Neuropathol 2012;123:627–38.

2

What are relapses and why do they happen?

What is an MS clinical relapse?

Relapses, sometimes called attacks, exacerbations, flares or flare-ups, are acute clinical manifestations of MS disease activity[1–3]

A relapse presents clinically as an episode of neurological disturbance (such as paraesthesia, weakness/clumsiness or visual disturbance) in the absence of fever or infection, that lasts for at least 24 hours[1–3]

A clinical relapse is often associated with a trip to the emergency department or a hospital admission[3]

MS relapses are unpredictable and the relatively sudden onset of neurological symptoms may be functionally and socially incapacitating[4,5]

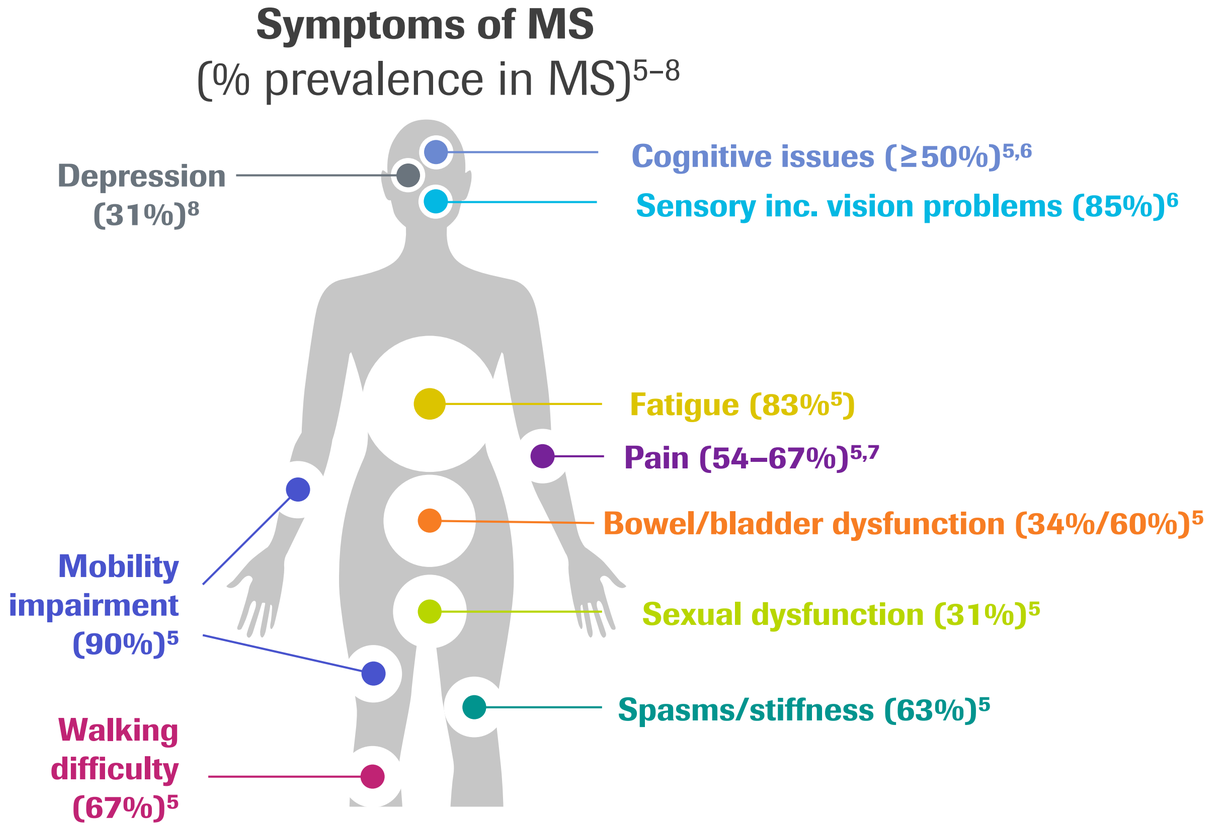
A relapse evolves over a few days, plateaus, then remits over a few weeks or months[3]

Attacks are separated by 30 days from the onset of the first event to the onset of the second.[6] Relapses may be followed by periods of recovery and be spread over time, or they may occur without full recovery[1]

1. Thompson AJ, et al. Lancet Neurol 2018;17:162–73; 2. Poser CM, et al. Ann Neurol 1983;13:227-31;
3. Brain Health: Time matters in multiple sclerosis. https://www.msbrainhealth.org/report. Accessed January 2020;
4. Leary SM, et al. Postgrad Med J 2005;81:302–8; 5. Vollmer T. J Neurol Sci 2007;256:S5–S13; 6. McDonald WI, et al. Ann Neurol 2001;50:121–7.

MS relapses are variable, unpredictable and highly disruptive for patients

- A relapse presents clinically as an episode of neurological disturbance in the absence of fever or infection, that lasts for at least 24 hours[1,2]
- The relatively sudden onset of neurological symptoms may be functionally and socially incapacitating[3,4]
- A relapse evolves over a few days, plateaus, then remits over a few weeks or months[4]
- Relapses may be followed by periods of recovery and be spread over time, or they may occur without full recovery[1]



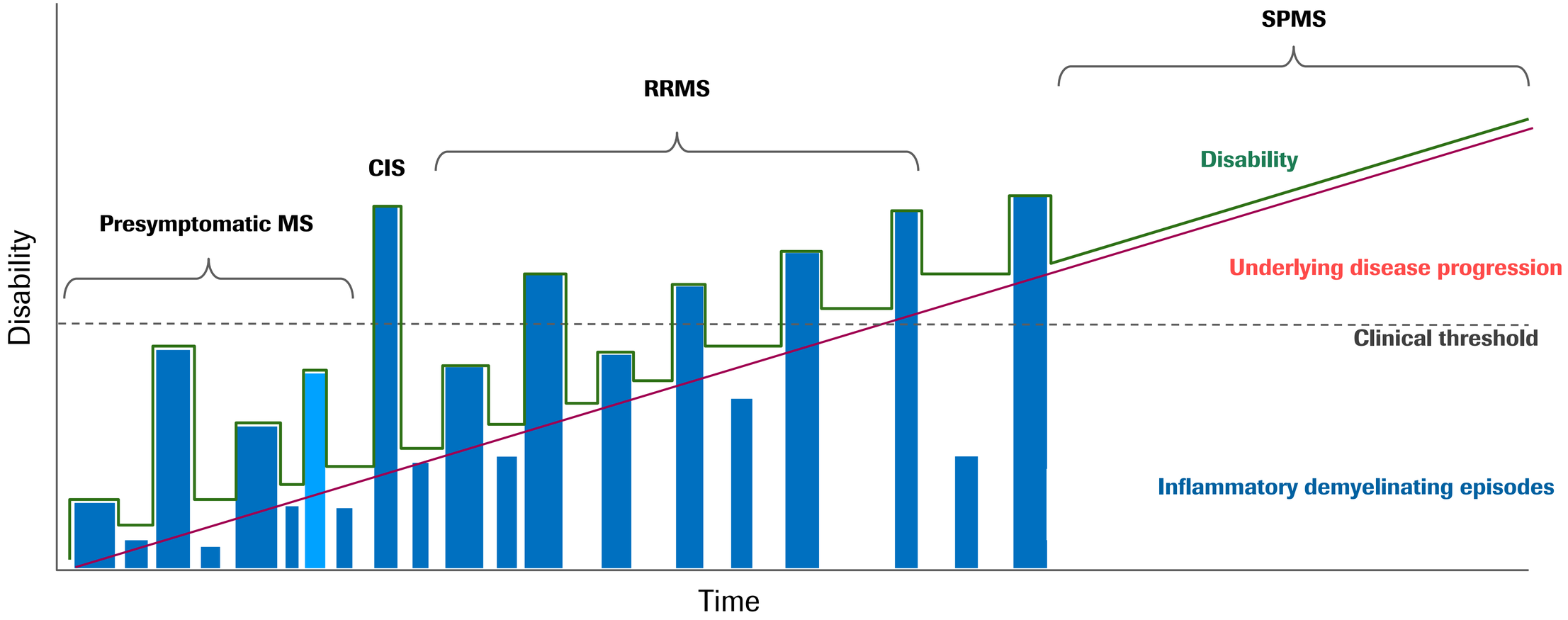
The most common symptoms of MS include fatigue, impaired mobility and sensory disturbances,[5,6] but loss of normal neuronal function throughout the CNS can also lead to seizures, sexual dysfunction and speech problems[5]

CNS, central nervous system.

1. Thompson AJ, et al. Lancet Neurol 2018;17:162–73; 2. Poser CM, et al. Ann Neurol 1983;13:227–31; 3. Vollmer T. J Neurol Sci 2007;256:S5–13;
4. Leary SM, et al. Postgrad Med J 2005;81:302–8. 5. Zwibel HL. Adv Ther 2009;26:1043–57; 6. Kister I, et al. Int J MS Care 2013;15:146–58;
7. Rae–Grant AD, et al. Mult Scler 1999:5:179–83; 8. Boeschoten RE, et al. J Neurol Sci. 2017;372:331–41.

Relapses are caused by underlying inflammation of the CNS and resulting demyelination that interferes with nerve conduction

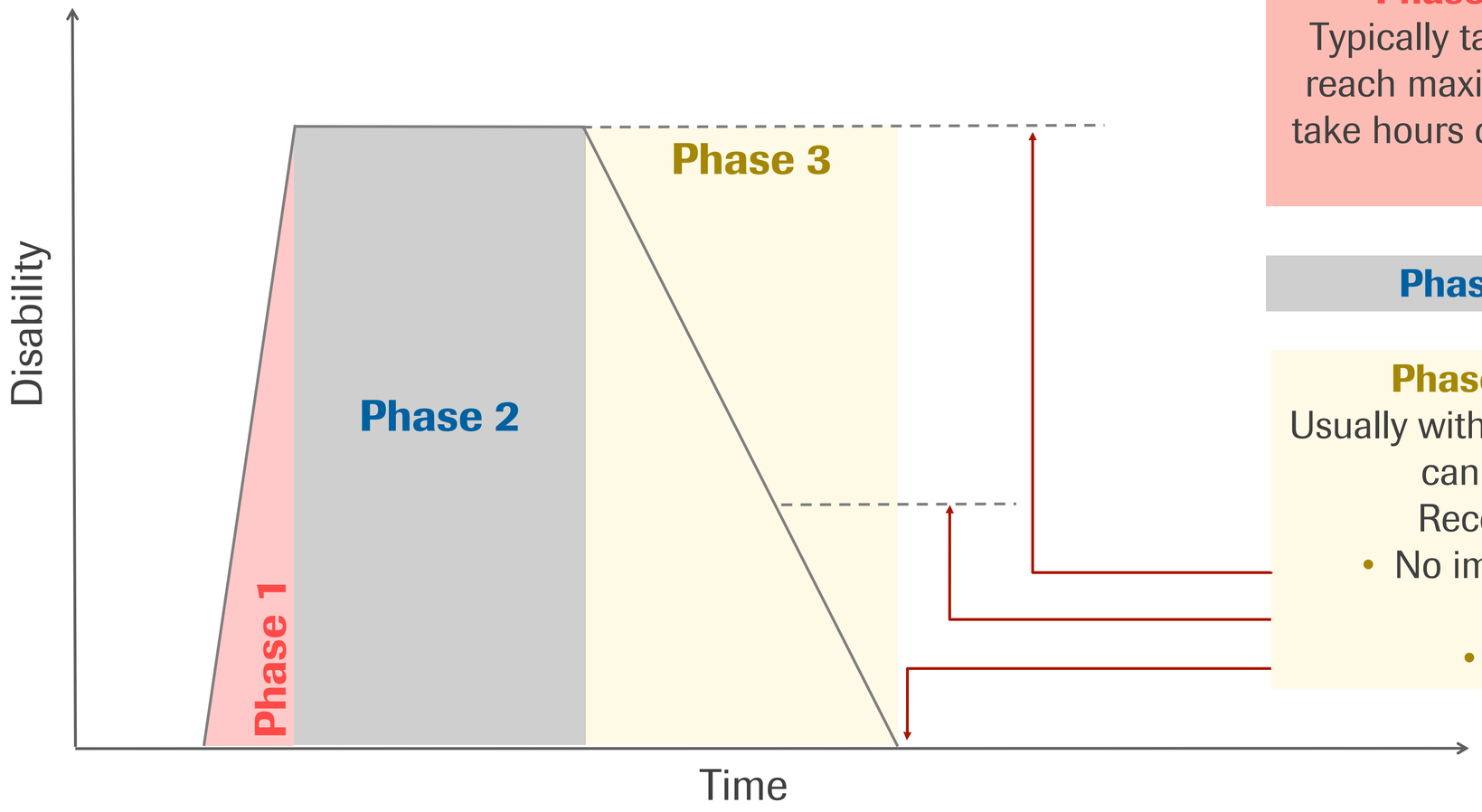
Relapses occur when inflammatory demyelinating episodes surpass a clinical threshold[1,2]



CIS, clinically isolated syndrome; CNS, central nervous system; RRMS, relapsing remitting MS; SPMS, secondary progressive MS.

1. Traboulsee A. J Neurol Sci 2007;256:S19–22; 2. Stys PK, et al. Nat Rev Neurosci 2012;13:507–14.

Acute relapses generally consist of three phases, then patients remain clinically stable until the next relapse



Phase 1: Worsening
Typically takes several days to reach maximal deficit, but may take hours or minutes or several weeks

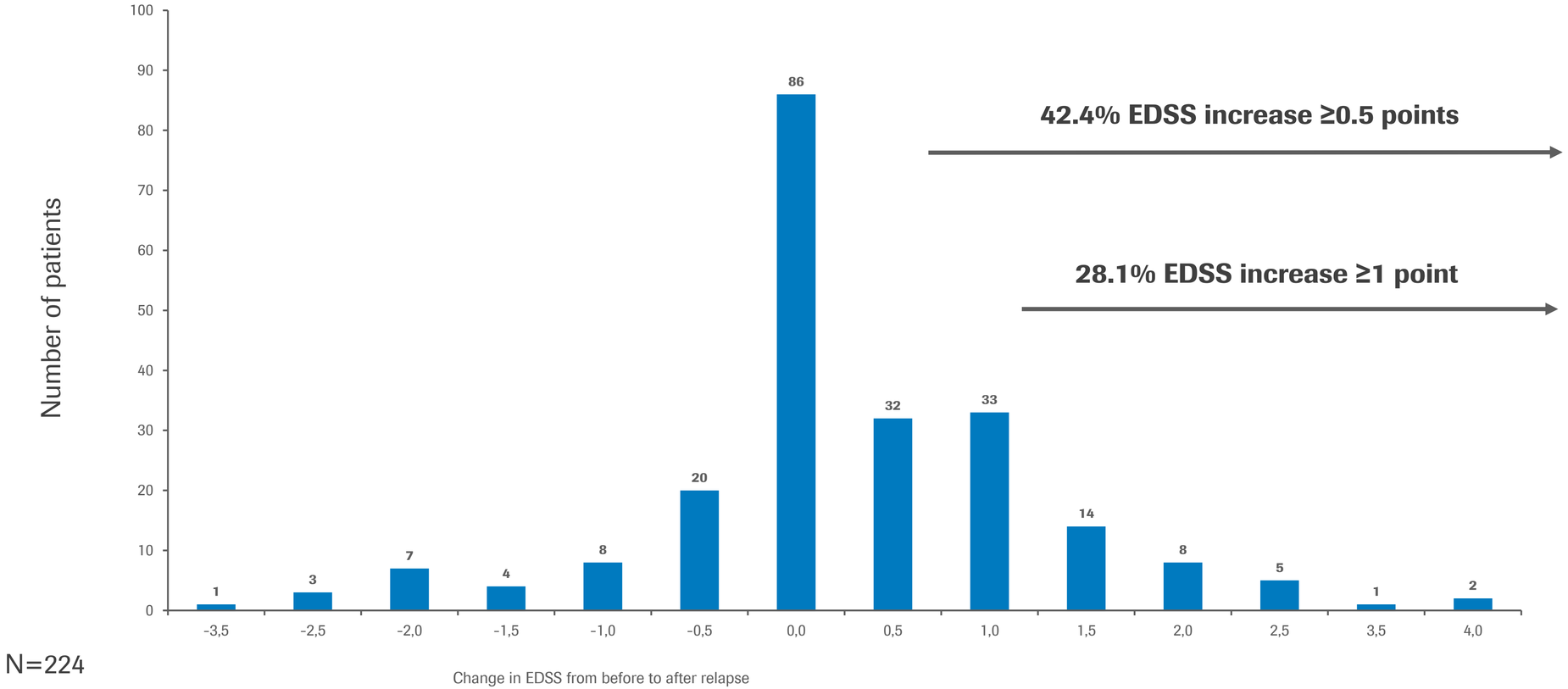
Phase 2: Stability

Phase 3: Recovery
Usually within 6 weeks; although can take months
Recovery can be:
- No improvement (4%)
- Partial
- Complete

Multiple sclerosis: current status and strategies for the future (2001). National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK222397. Accessed January 2020.

Relapses are often associated with an increase in disability

Net change in EDSS score from before to after a relapse (mean interval duration 114 days):
42% of patients demonstrated measurable residual worsening after a relapse



EDSS, Expanded Disability Status Scale.
Lublin FD, et al. Neurology 2003;61:1528–32.

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Il futuro della medicina, l’avanguardia di noi medici.

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