MS AUSTRALIA

MODIFIABLE LIFESTYLE FACTORS FOR MULTIPLE SCLEROSIS

For health professionals

Evidence-based lifestyle interventions to support MS management and health outcomes

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MS Australia is Australia's national multiple sclerosis (MS) not-for-profit organisation that empowers researchers to identify ways to treat, prevent and cure MS, seeks sustained and systemic policy change via advocacy, and acts as the national champion for Australia's community of people affected by MS.

MS Australia represents and collaborates with its state and territory MS Member Organisations, people with MS, their carers, families and friends, and various national and international bodies to:

- Fund, coordinate, educate and advocate for MS research as part of the worldwide effort to solve MS
- Provide the latest evidence-based information and resources
- Help meet the needs of people affected by MS

Contents

Executive summary

MS Australia hosted a workshop on modifiable lifestyle factors in MS on May 2, 2018, in Sydney. This workshop was organised in response to the 2016 MS Research Australia Research Priorities survey, which identified lifestyle factors as a key concern for the MS community. Addressing these factors offers people with MS a way to take control of their health and potentially reduce the impact of the disease. The workshop brought together clinicians, researchers, allied health professionals, and individuals living with MS to review the current evidence and discuss future research directions. A guide was subsequently published in 2020 to summarise the findings and recommendations.

Building on insights from this workshop, MS Australia and leading experts revisited the literature to ensure the latest evidence on lifestyle changes in MS was incorporated. As part of this effort, two new chapters, on sleep and stress-reducing behaviours, have been added to provide a more comprehensive perspective.

MS Australia has developed this guide as a trusted resource for clinicians, distilling the latest evidence on modifiable lifestyle factors in MS. It provides practical, evidence-based insights to support informed clinical discussions and decision-making. The guide covers key areas with recommendations, including:

Smoking

- Strongly advise smoking cessation as a priority intervention for all individuals, particularly those living with MS.
- Highlight the association between smoking and increased disease progression, relapses, and treatment failure.
- Provide resources for smoking cessation support, including pharmacological and behavioural interventions.
- Quitting at any stage has been shown to beneficial for people living with MS.

Diet

- Encourage a balanced diet (see Australian Dietary Guidelines) to support overall health.
- Emphasise whole foods, fibre, and healthy fats while minimizing ultra-processed foods, refined sugars, and saturated fats.
- Address common dietary deficiencies (e.g. vitamin D, B12) and consider dietitian referral for tailored advice.
- There is no strong evidence to support specific MS diets; general healthy eating patterns are recommended.

Weight management

- Assess and monitor BMI and other weight assessment tools (e.g. waist circumference, body composition analysis), as obesity is associated with increased MS disease activity and reduced treatment efficacy.
- Support weight management through sustainable dietary and physical activity strategies, rather than restrictive diets.
- Address weight concerns in a patient-centred way, considering mobility limitations and fatigue.
- Maintaining a healthy weight is beneficial at all disease stages.

Physical exercise

- Recommend regular, tailored exercise (aerobic, strength, balance) to improve mobility, fatigue, and cognitive function.
- Prescribe supervised or structured exercise programs with a physiotherapist or exercise physiologist when needed, ensuring safety and adaptation to disability level.
- Address common barriers such as heat sensitivity, fatigue, and pain by suggesting personalised strategies (e.g. cooling techniques, pacing).
- Exercise is safe and effective for people with MS and should be encouraged as part of routine care.

Sleep

- Screen for and address sleep disturbances (insomnia, obstructive sleep apnoea, restless legs syndrome) as they exacerbate fatigue and cognitive issues.
- Recommend good sleep hygiene practices, including consistent sleep schedules and reduced screen exposure before bed.
- Consider referring for cognitive behavioural therapy (CBT) for insomnia if poor sleep persists.

Stress reduction

- Recognise the bidirectional relationship between stress and MS symptom burden.
- Encourage evidence-based stress management techniques such as mindfulness, psychotherapy, and physical activity.
- Support mental health referrals when stress significantly impacts quality of life.

Lipids

- Monitor lipid profiles as part of cardiovascular risk management, given emerging links to MS disease activity.
- Promote heart-healthy dietary and lifestyle changes that align with MS recommendations.
- Consider lipid-lowering interventions in high-risk individuals per standard clinical guidelines.
- Regular screening for dyslipidaemia should be part of routine MS management.

Other comorbidities

- Actively manage comorbid conditions (e.g. cardiovascular disease, diabetes, depression) as they influence MS outcomes.
- Screen regularly for depression and anxiety, given their high prevalence in MS and impact on quality of life.
- Collaborate with multidisciplinary teams for holistic patient care.
- Early detection and optimal management of comorbidities in MS are key to improving health outcomes.

Gut microbiome

- Educate on the potential role of the gut microbiome in immune modulation, though clinical guidelines are still evolving.
- Support dietary diversity, fibre intake, and probiotic-rich foods to promote gut health.
- Avoid recommending unproven microbiome-targeted interventions until stronger evidence is available.

Vitamin D

- Assess vitamin D status in people living with MS, particularly those at risk of deficiency.
- Recommend supplementation only if deficiency is confirmed, following standard dosing guidelines.
- Advise against high-dose vitamin D supplementation without clear clinical indication, given lack of proven MS benefits.
- Recommend sun exposure guidelines from Cancer Council Australia to maintain healthy vitamin D levels.

Supplements

- Guide people living with MS to evidence-based supplementation, discouraging unnecessary or high-dose regimens.
- Address common queries regarding omega-3s, antioxidants, and other supplements with current evidence.
- Reinforce that a nutrient-rich diet is the foundation for optimal health, with supplements only as adjuncts.
- There is no strong evidence supporting supplements as a treatment for MS progression.

This document empowers healthcare professionals to provide evidence-based guidance to individuals with MS. By supporting informed lifestyle choices, it enables people with MS, in collaboration with their healthcare providers, to take an active role in managing their condition. Implementing evidence-based lifestyle changes may help improve disease outcomes, including relapse rates, disability progression, comorbidity risk, symptom management, and overall quality of life.

Introduction

Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is the most common chronic neurological disease that causes disability in young adults and is typically diagnosed between the ages of 20 and 40. In Australia, MS affects three times more women than men. While significant advancements in disease-modifying therapies (DMTs) have improved treatment options, there is still no cure.

The exact cause of MS remains unknown, but research has identified a combination of genetic and environmental factors that contribute to its development.

MS occurs when the immune system mistakenly attacks myelin, the protective fatty coating around nerves. Myelin is essential for insulating nerve fibres and ensuring that electrical signals travel efficiently between the brain and the rest of the body. During an MS attack, demyelination occurs, exposing and damaging the underlying nerve fibres. Over time, these damaged areas become scarred, disrupting nerve communication and increasing the risk of permanent nerve degeneration. This leads to a wide range of symptoms, including:

- **IMPAIRED MOBILITY (WALKING, HAND, AND ARM FUNCTION)**
- **NUMBNESS OR LOSS OF SENSATION**
- **PAIN**
- **FATIGUE**
- **VISION DISTURBANCE**
- **COGNITIVE CHANGES (THINKING AND MEMORY)**

Types of MS

MS presents in different forms, each with distinct disease patterns:

- **Relapsing-Remitting MS (RRMS):** The most common form of MS, characterised by relapses (episodes of new or worsening symptoms) followed by periods of partial or full recovery (remission).
- **Secondary Progressive MS (SPMS):** Develops after an initial RRMS phase, marked by gradual worsening of symptoms and increasing disability over time, often with fewer or no relapses.
- **Primary Progressive MS (PPMS):** Diagnosed in approximately 10-15% of people with MS, this form involves a steady progression of symptoms from the onset, without distinct relapses or remissions.

MS Australia and MS research

MS Australia is the leading national not-for-profit organisation dedicated to funding, coordinating, educating, and advocating for MS research. As part of the global effort to solve MS, MS Australia aims to accelerate research into the causes, better treatments, and prevention, with the ultimate goal of finding a cure.

Modifiable lifestyle factors in MS

The role of modifiable lifestyle factors in MS has gained increasing attention in recent years, driven by both scientific advancements and the priorities of the MS community.

In 2016, a national survey conducted by MS Research Australia revealed that people living with MS, caregivers, researchers, and healthcare professionals ranked modifiable lifestyle factors among the top research priorities. In response, MS Australia hosted a workshop on modifiable lifestyle factors in MS in 2018. This event brought together clinicians, researchers, allied health professionals, and people with MS to assess the current evidence and determine the best approaches to research and implementation.

A key outcome of this workshop was the formation of a working group to develop a guidance document, published in 2020, summarising the evidence on lifestyle factors that may influence MS disease progression, symptoms, and overall health. Since then, the evidence base has strengthened, and there is now a need to revisit the guide to incorporate more practical guidance for people with MS and to better support healthcare professionals in clinical conversations.

2025 Update

Since the 2018 workshop and the release of the 2020 guide, the evidence supporting lifestyle interventions in MS has continued to grow in depth and quality. In response, MS Australia has refreshed this guide to reflect the strengthened evidence base and to offer more practical, user-friendly recommendations for both healthcare professionals and people living with MS. This updated guidance document reflects:

- The latest research on the impact of modifiable lifestyle factors in MS
- Refined recommendations for healthcare professionals to support patient-centred care
- Practical strategies to empower individuals with MS in managing their condition through lifestyle choices.

This update also aligns with the recently published consensus recommendations[1,2] for people living with MS, which emphasise the importance of modifiable lifestyle factors. In addition to reinforcing these recommendations, this guide goes further by providing expanded information on areas such as sleep, stress management, and other emerging factors that can influence MS outcomes.

While gaps in the evidence remain in some areas, this guide serves as a trusted resource to help clinicians provide informed, evidence-based advice to people with MS.

Purpose of this document

This guidance document was developed in response to the priorities and concerns of people living with MS. It aims to empower healthcare professionals with evidence-based recommendations on modifiable lifestyle factors that may influence disease progression, symptoms, comorbidities, and overall quality of life.

Where applicable, the document also highlights modifiable risk factors that may impact the development of MS, including the risk of a first demyelinating event (FDE), radiologically isolated syndrome (RIS), or clinically isolated syndrome (CIS).

Scope of This Document

A working group of national experts with clinical and research expertise assisted in the development of this latest guide, covering the following key areas of interest in MS:

Aims of This Document

- Provide evidence-based lifestyle recommendations to improve MS disease progression, symptoms, and overall well-being.
- Identify modifiable risk factors that may influence the likelihood of developing MS.
- Where scientific evidence is available, summarise research findings and apply grading to indicate the strength of recommendations.
- Offer general health recommendations where MS-specific evidence is insufficient, ensuring guidance remains safe and beneficial.
- Clarify widely discussed lifestyle approaches in the MS community that lack robust scientific support, ensuring healthcare professionals have accurate information.

NHMRC Grading System

The National Health and Medical Research Council (NHMRC) Grading System was used to assess the strength of evidence for each recommendation. The grading system considers:

- The **quality, quantity, and consistency** of scientific studies
- The **clinical impact** of recommendations
- The **generalisability** of findings to people with MS
- The **applicability** of evidence within the Australian healthcare system.

NHMRC Grades of Recommendation:

STRONG EVIDENCE, TRUSTED TO GUIDE PRACTICE

GOOD EVIDENCE, APPLIES TO MOST SITUATIONS

LIMITED EVIDENCE, RECOMMEND WITH CAUTION

WEAK EVIDENCE, USE CAUTIOUSLY

If MS-specific evidence was insufficient for a topic, general health recommendations were included where applicable, but no NHMRC grading was assigned.

Review and Updates

This document has been reviewed and updated by a diverse panel, including:

SCIENTIFIC EXPERTS

NEUROLOGISTS

MS NURSES

MS SERVICE PROVIDERS

PEOPLE LIVING WITH MS

Cautions and Considerations

- This document does not replace standard medical treatment for MS.
- Individuals should consult their healthcare team before making significant lifestyle changes.
- Healthcare professionals should consider disability levels, mental health factors (e.g. depression, anxiety), and socioeconomic barriers when applying these recommendations.

Authors and Reviewers

MS Australia would like to acknowledge and sincerely thank the experts and contributors who dedicated their time and expertise to developing this guidance document. We extend our gratitude to the original expert working group for their foundational work, as well as to the clinicians, researchers, and individuals with lived experience who have contributed to this updated edition. Their insights have ensured that this document remains evidence-based, relevant, and valuable for healthcare professionals and the MS community. The full list of expert authors and review panel members is provided below.

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Smoking

Summary

Smoking tobacco and passive smoking (exposure to second-hand smoke) significantly harm health and are linked to an increased risk of many conditions, including MS, cardiovascular disease, and cancer.

There is consistent evidence that smoking negatively impacts MS progression, accelerating disability and advancing onset of progressive MS. There is currently no evidence about the impact of vaping or using e-cigarettes on MS, but there is evidence that these are harmful for general health and should be avoided.

People living with MS are strongly advised to avoid smoking and exposure to second-hand smoke.

The good news is that quitting is highly beneficial, reducing disability progression, symptoms, and progressive MS risk, in addition to reducing the risk of other conditions such as cancer and cardiovascular disease. The earlier smoking cessation occurs, the greater the benefits, though quitting is advantageous at any stage.

What is smoking (and passive smoking), and how common is it?

Smoking refers to the inhalation of smoke created by the combustion of organic material, most commonly tobacco, through products such as cigarettes, cigars, pipes, and waterpipes (shisha, nargile or hookah)[3]. This chapter focuses on tobacco products and excludes information about the harms or benefits of smoking marijuana or cannabis.

In 2022/2023, 10.6% of Australian adults (12.6% of men and 8.7% of women) reportedly smoked tobacco daily[4]. While exact smoking rates in Australians with MS are unknown, evidence suggests a higher rate than the general population. For example, an Australian survey by Weld-Blundell et al. about smoking and MS (which may have attracted people interested in the topic), found 26% were current smokers (n=73), 38% were former smokers (n=108) and 36% never-smokers (n=103)[5]. In contrast, the Australian MS Longitudinal Study (AMSLS) reported 11% of 1500 participants (n=165) were smokers in 2016[6]. Another Australian study of 282 people with a first demyelinating event (FDE) reported that 27% of people smoked at the time of enrolment between 2003-2006[7], with 20% still smoking five years later[8].

Exposure to second-hand smoke (passive smoking) is also harmful to health[4]. The Weld-Blundell study also found that 24% (n=67) of participants with MS were regularly exposed to passive smoke, with low awareness of its risks for MS onset and progression[5]. Despite the risks, there are currently no initiatives specifically designed to prevent smoking uptake, exposure to passive smoking, or to support cessation for people living with MS[9].

Does smoking affect the risk of MS or its onset?

Active smoking is a key risk factor for MS onset, increasing the risk of MS by approximately 50%[10,11]. Among those with clinically isolated syndrome (CIS), 67% of smokers progress to develop MS, compared to 36% of non-smokers[12]. This risk may be proportional to the number of cigarettes smoked, also known as a "dose-response effect"[13]. A review by Belbasis et al. confirmed that "ever-smoking" increased the risk of MS (odds ratio (OR) 1.52; 95% confidence interval (CI), 1.39–1.66)[14].

Other recent reviews (published in or after 2020), including those by Arneth[15] and Jasielski et al[16], support this. Further, Rosso and Chitnis attribute over 20% of MS risk to active and passive smoking combined[17]. However, inconsistent results were noted in a recent review by Maroufi et al. including only studies from the Middle East and North Africa region, where only five of the eight included studies (odds ratios ranging from 1.93 to 6.48) linked smoking to MS onset[18]. A Swedish case-control study estimated that the avoidance of tobacco smoking would prevent at least 13% of cases of MS[19].

Passive smoking also increases MS risk[20], particularly for genetically predisposed family members exposed to smoking[10]. Further, evidence indicates that paediatric MS risk in children is reduced when their parents stop smoking[20]. A 2024 review by Schlindwein et al. of two meta-analyses, two systematic reviews, and 11 observational studies found a consistent and positive association between passive smoking and MS onset[21].

Prenatal smoking exposure (active or passive smoking of the mother during pregnancy), does not appear to affect the risk of developing MS in offspring[22]. However, there is extensive evidence that prenatal smoking significantly harms the foetus, increasing the risk of stillbirth and pregnancy complications[4]. Pregnant individuals are advised to avoid smoking, or vaping, and passive smoke exposure[23].

Smoking a waterpipe at least once a week for a minimum of 6 months was found to have a significant association with MS onset (OR 1.73, 95% CI 1.38-2.17) according to a 2024 meta-analysis including 5 studies[24]. Sharing waterpipes could also facilitate transmission of several infectious diseases, such as Epstein-Barr virus, which has been associated with the onset of MS[24]. There is clear evidence that people living with MS or at risk of MS should avoid waterpipe smoking.

Does smoking have effects on MS disease progression?

High-quality research demonstrates that smoking accelerates MS disease progression, including disability worsening and the transition to secondary-progressive MS. Prospective population studies by Pittas et al[25] and Healy et al.[26] show a clear link between smoking and faster disability progression. Further, a 2017 systematic review (that analysed 1 concurrent, 9 retrospective, and 4 prospective studies) and a meta-analysis of seven studies (2 case control, 1 prospective, and 4 retrospective cross-sectional studies), found that smoking increased the risk of disease progression by ~55%. However, due to some variability in study estimates, this result can only be interpreted with moderate certainty of evidence[27]. Despite this uncertainty, most studies provide consistent and convincing evidence that people living with MS who smoke have an increased risk of their disability worsening compared to non-smoking people living with MS, as confirmed by another systematic review[28].

Recent reviews by Rosso and Chitnis (2020)[17], Jasielski et al. (2020)[16], and Maroufi et al. (2021)[18] reinforce this link. However, while another review found that ever smoking was associated with increased expanded disability status scale (EDSS) (SMD = 0.15, 95% CI = 0.01-0.28), they found no association with the risk of reaching EDSS 4 or EDSS 6[29]. In addition, smoking has also been associated with increased brain atrophy (decrease in total brain volume)[30] and comorbid conditions such as type 1 diabetes, vascular disease or stroke[31] which may further exacerbate disability progression.

Evidence linking smoking to more frequent relapses in relapsing-remitting MS is limited and inconclusive[16]. For passive smoking, a recent review concluded that there is insufficient evidence to determine its impact on MS progression[21].

Does smoking have effects on MS symptoms?

Smoking is associated with worse MS symptoms, alongside its negative impact on disease progression and onset. A 2023 review by Vong et al. found that current and former smokers had a significantly higher risk of depression. The evidence linking smoking to anxiety was less clear[32]. One study showed that people living with MS who smoke experience a lower quality of life[33], and both smoking and MS are linked to reduced bone mineral density, increasing the risk of fractures and osteoporosis in later life[34] Jasielski *et al.* also identified associations between smoking and cognitive impairment in three studies[16]. A 2025 Swedish study further found that current smoking at MS diagnosis was associated with a higher risk of reaching Expanded Disability Status Scale (EDSS) milestones, physical worsening, and cognitive decline over time, even if smoking cessation occurred after diagnosis. The combination of smoking and obesity appeared to have additive negative effects across all outcomes[35]. The Australian survey by Weld-Blundell et al. found that previous smokers with MS experienced long-term improvements in MS symptoms and general well-being after quitting[5].

Does smoking influence premature mortality?

A UK study of more than 900 people living with MS found that smoking tobacco significantly increased the risk of early death compared to never-smokers. Within non-smokers, having MS did not increase the risk of early death compared to the general population[36].

How does quitting benefit people with MS?

Quitting smoking at any time is beneficial. Evidence shows that it reduces the risk of disease onset and slows disability progression, with greater benefits for those who quit earlier[37]. One study found that persistent smokers reach the progressive stage of MS approximately eight years earlier compared to those who quit around the time of diagnosis[38]. Additionally, every decade of smoking abstinence reduces the risk of increasing disability by approximately 30%[37].

It is never too late to stop smoking.

Does smoking interfere with MS medications?

Smoking may reduce the effectiveness of MS treatments[39–41]. For example, a study of 103 people living with relapsing-remitting MS, found that smokers treated with fingolimod or dimethyl fumarate were more than twice as likely to experience a relapse or have disease activity compared to non-smokers[42]. As these medications aim to prevent relapses and the progression of MS, this further adds to the negative effects of smoking on relapses and progression of MS.

Information that needs clarifying

How does smoking harm health?

Cigarette smoke contains more than 7000 compounds, including at least 100 compounds proven to be toxic to the central nervous system(CNS). These substances damage neurons, glia, and myelin, while triggering a pro-inflammatory cascade that harms the respiratory and cardiovascular systems, as well as the blood-brain barrier[17]. More information on how smoking harms your organs and brain can be found at https://www.quit.org.au/tools/effects-smoking-your-body.

Is nicotine responsible for harm or are other substances in tobacco the cause?

While nicotine is responsible for the addictive and stimulant effect of cigarettes, there is no evidence it plays a pathogenic role in MS[17]. A study on Swedish snuff use (smokeless tobacco) confirmed that the increased risk of MS in smokers is due to other compounds in tobacco smoke, rather than nicotine itself[43]. This supports the safety of nicotine replacement therapy for people living with MS as a quitting aid.

Nicotine-reduced and ultra-low nicotine cigarettes, marketed as healthier alternatives, may have even greater pro-inflammatory effects than regular cigarettes, although the evidence is limited[17].

Anecdotally, some people living with MS have reported symptom relief (e.g. pain or fatigue) from nicotine use[44,45], similar to observations in people with other conditions such as schizophrenia[46] and depression[47]. Early-stage studies in MS laboratory models suggest potential protective effects of nicotine against MS onset and severity[48]. However, current evidence does not support nicotine as beneficial for humans with MS.

Are e-cigarettes or vapes less harmful than regular cigarettes?

E-cigarettes (vapes) and heated tobacco products are marketed as “less harmful” nicotine delivery methods, but the industry is unregulated, with variable chemical compositions, doses, and technologies. All e-cigarettes, regardless of nicotine content, contain harmful substances, including carcinogens[49]. A 2023 umbrella review of 400 studies confirmed the harm of e-cigarettes, highlighting risks such as poisoning, lung injury, and device malfunctions[50]. There are no studies on e-cigarettes or vaping in people living with MS, but leading health organisations, including the Australian Department of Health[49], the Royal Australian College of General Practitioners[51] and the World Health Organization (WHO)[52], advise against their use. Nicotine-containing e-cigarettes combined with behavioural therapy may help those who have failed first-line cessation strategies, but this should be undertaken with medical guidance[53] and discussed with a healthcare professional[51].

Recommendations for people with MS

People living with MS, or at risk for MS, should avoid active and passive smoking, consistent with public health recommendations for the general population[3,49]. Harmful effects of tobacco on MS progression, along with the significant benefits of quitting smoking on these outcomes, make the case for action to quit and avoid tobacco smoking even more urgent for people living with MS. The highest level of evidence links active smoking to MS onset and disease progression. However, randomised controlled trials in this area are unethical due to the known risks of smoking, therefore the evidence comes from prospective and cross-sectional population studies, which may produce biased results.

Considerations for health professionals

Current practice often falls short in meeting the needs of people living with MS who smoke[5,45]. An Australian survey showed that while most people living with MS report that their neurologist (n=126, 75.4%) or other healthcare providers (n=125, 74.9%) assessed their smoking status, few receive assistance with quitting (neurologists: n=3, 1.8%, other healthcare providers: n=14, 8.4%)[5]. Similarly, another Australian MS study which interviewed 25 current or recent smokers, reported that the provision of evidence-based information and referrals to cessation support services were very infrequent[41]. Participants in both studies had low awareness of the harms of smoking on MS[5,45]. Survey participants preferred receiving cessation advice from neurologists or general practitioners, specifically tailored to MS[5]. Interview participants also gave more weight to quitting advice from MS specialist clinicians[45]. There was ambivalence around discussing smoking with healthcare providers, with people simultaneously wanting more information and support, while also feeling shame or guilt that they were currently smoking[45].

Although smoking cessation programs have been effective for other chronic diseases, no interventions have been tested specifically for MS. Current advice recommends behavioural interventions over multiple sessions (e.g. Quitline) and, where clinically appropriate, cessation medications.

What are the barriers to quitting for people with MS?

Common barriers preventing people living with MS to quit smoking include withdrawal symptoms, cost, and perceived coping benefits[5,45,54]. There are also MS-specific challenges such as cognitive difficulties[54,55], depression[54], and a complex relationship between cognitive function, coping, and depression among people living with MS[56]. Pain is another common symptom for people living with MS. Smoking has been shown to create a feedback loop with pain, increasing its long-term risk while providing short-term relief, which can strongly motivate continued smoking[55,57]. This makes quitting particularly challenging for those experiencing pain, depression, and/or anxiety[58]. Close monitoring and effective management of these symptoms can increase the likelihood of successful cessation. Additionally, as many people quit several times before succeeding long-term abstinence, regular follow-up is essential to provide long-term support for maintaining cessation.

Recommendations:

While MS-specific research into cessation strategies is ongoing, healthcare professionals should follow best practice guidelines for the general population.

The "Ask, Advise, Help" model is currently recommended.

1. **Ask**: Assess current and former smoking and vaping status, and exposure to passive smoking.
2. **Advise**: Provide personalised advice, including MS-specific benefits of quitting for both progression and symptom management.
3. **Help**: Offer behavioural interventions and referrals, such as Quitline, and consider cessation medications if appropriate.

The 2024 Royal Australian College of General Practitioners' guidelines "Supporting smoking cessation: A guide for health professionals" and "Supporting smoking & vaping cessation: A guide for health professionals" are comprehensive resources for healthcare providers[51,59]. These guides address topics such as pharmacology, quitting apps, and vaping. Key recommendations (including the level of evidence) relevant to all healthcare professionals are summarised below, while detailed pharmacotherapy guidelines can be found in the original documents.

1. A system for identifying all people who smoke and documenting tobacco use should be used in every practice or healthcare service. (Strong recommendation, high certainty)
2. All people who smoke should be offered brief advice to quit smoking. (Strong recommendation, high certainty)
3. Offer brief smoking cessation advice in routine consultations and appointments, whenever possible. (Strong recommendation, high certainty)
4. Offer follow-up to all people who are attempting to quit smoking. (Strong recommendation, high certainty)
5. Referral to telephone call-back counselling services should be offered to all people who smoke. (Strong recommendation, high certainty)

In summary, based on these guidelines and the evidence provided, we recommend the following actions aligned with the AACTT framework:

- **Action**: Assess and record whether individuals with MS, or at risk of MS, smoke, vape, or are exposed to second-hand smoke. If so, provide strong and specific advice to quit smoking or vaping and avoid passive smoke. Assist by outlining the benefits of cessation and connecting people living with MS to appropriate services. **Quitline** (phone 13 7848) is a free confidential support service for people who want to quit smoking. You can refer patients to receive a call from Quitline using the online referral form here: https://www.quitcentre.org.au/referral-form. Patients should consent to receiving a call from Quitline prior to an online referral form being completed.
- **Actor**: Healthcare professionals across all disciplines, including primary care, neurology, and allied health.
- **Context**: This should occur in all clinical settings including telehealth.
- **Target**: People living with MS or those at risk of MS.
- **Time**: During every interaction, whenever possible, with follow-up arranged to assess progress and provide further support as needed.

By embedding this approach into routine care, healthcare professionals can systematically reduce smoking-related risks in people living with MS or those at risk of developing the disease.

Diet and nutrition

Summary

A person's diet or pattern of eating includes all the foods and beverages that they consume. Nutrients are the components in foods and beverages that are essential for health, growth and repair. The nutrients in our foods and beverages interact in a complex matrix, and in the body lead to the health benefits that may be provided by the overall diet. Food is more than just nutrients; food extends beyond our biological needs for nourishment. For some, food provides joy, celebration, cultural and religious meaning. Scientific research into patterns of eating - or people's diets - are difficult to implement practically in real-life situations. Therefore, many studies for MS have focused on individual foods, individual nutrients or nutrient combinations. But, as humans, we eat combinations of foods which provide combinations of nutrients, which is important to consider. Studies investigating different patterns of eating, foods, and nutrients, and MS disease symptoms and progression, are outlined below. Note, dietary supplements are discussed in a separate chapter in this Guide.

Based on the currently available scientific evidence, the take-home message is that people living with MS should follow the same dietary guidelines as the general population - the Australian Dietary Guidelines[60]. Only about 4% of the general population adhere to both the fruit and vegetable messages of the Australian Dietary Guidelines, so aligning our eating patterns with the Australian Dietary Guidelines represents a substantial dietary change for many people. To ensure that the change can be maintained in the long term, people living with MS may benefit from consulting an Accredited Practising Dietitian to help them identify ways to incorporate healthy eating into their lives, factoring in their personal preferences, MS needs, and other considerations including finances.

Introduction

People living with MS are often highly motivated and eager to take an active role in managing their condition, including making positive lifestyle changes. Amongst these changes, diet holds a special place, as it can be deeply connected to our health, well-being and everyday life. Many studies have explored how different aspects of diet can impact health, including in the context of MS. This chapter will discuss some of the most researched diet and individual food types, as well as those which are of particular interest to people living with MS. We recommend that people living with MS consult their healthcare team before making any significant lifestyle changes such as diet, particularly if the goal is to improve and support their MS management.

‘Special diets’ and MS

Several ‘special diets’ have been promoted as having potential benefits for MS symptoms and disease outcomes. These diets include:

- Swank diet (restricted saturated fat)
- Wahls modified Palaeolithic diet (high in meat, vegetables and fruit; no dairy, eggs, legumes or grains)
- Overcoming MS diet (low in saturated fat; moderate in seafood, avocado and nuts; no meat, dairy, egg yolks or refined foods)
- McDougall diet (vegan, high-starch, low saturated fat),
- Ketogenic (low carbohydrate, moderate protein, high fat)
- Fasting-mimicking (often plant-based, low energy intake over some days of the week).

These diets share common elements, such as reducing discretionary (junk) and ultra-processed foods, but also have contradictions and frequently restrict whole food groups entirely.

Despite the good intentions behind the development of ‘special diets’ for MS, there is insufficient scientific evidence to recommend any of these diets for long-term use among people living with MS.

The details of each diet and the supporting scientific literature are outlined below.

Mediterranean and MIND diets

Other patterns of eating have been studied in relation to MS, even though they were not specifically designed for people living with MS.

These include:

- **The Mediterranean diet:** Characterised by a high consumption of fruits, vegetables, legumes, nuts and wholegrain breads; moderate to low intakes of lean meats, fish, dairy and eggs; and the use of olive oil as a primary source of dietary fat
- **The MIND (Mediterranean Dietary Approaches to the Stop Hypertension Intervention for Neurodegenerative Delay) diet:** Combines elements of the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets. The MIND diet encourages low fat dairy, low alcohol and limited intake of added sugars.

Both diets have scientific support for benefits in other chronic conditions[61,62], but few studies have evaluated their impact on MS. A retrospective analysis showed that greater adherence to the Mediterranean diet was associated with a lower risk of patient-reported disability and MS symptoms. However, the authors of that study recommended longitudinal follow-up and interventional trials specifically using the Mediterranean diet, before making clinical recommendations for people living with MS[63].

Palaeolithic diet

A Palaeolithic diet typically excludes legumes, grains, dairy and processed foods, whilst being high in meat, fish, fruit and vegetables[64]. Although the Palaeolithic diet has been studied in other health contexts, no clinical trials have studied the standard Palaeolithic diet in people living with MS. Instead, variants such as the **Wahls modified Palaeolithic** diet[65] and the follow-on Wahls Elimination Diet[66], a component of the Wahls Protocol[67], have been studied.

The Wahls diet differs from the typical Palaeolithic diet in that it allows some foods to be consumed that are usually restricted. The elimination variant further modifies the diet to exclude gluten-free grains, legumes and nightshade vegetables[66,67]. Studies summarising the effects of a Palaeolithic/Wahls diet in people living with MS have reported reductions in fatigue severity and improvements in quality of life[68].

However, these clinical trials included other intervention elements, such as supplementation and stretch and strength exercise, making it unclear whether the benefits were due to the diet alone[69].

Additionally, a Palaeolithic diet may be challenging to sustain long-term due to its exclusion of many foods and some food groups, potentially resulting in nutritional deficiencies. Therefore, the current evidence base is insufficient to support recommendations for its use for improving disease outcomes in people living with MS.

Low saturated fat diets: Swank, Overcoming MS, and McDougall diets

Low saturated fat diets are low-fat diets that primarily consist of starchy plant-based foods, while limiting animal products, dairy and vegetable oils. Several such diets are promoted for MS, each varying in the degree of restriction of saturated fat. These include:

- **Swank diet:** Reduced animal and dairy product consumption[70,71]
- **Overcoming MS diet:** Completely excludes animal and dairy product consumption but allows fish[72]
- **McDougall Diet:** Excludes all animal products, including fish and dairy[73].

A recent clinical trial compared the Swank diet with the Wahls modified Palaeolithic diet, finding that both diets reduced fatigue and improved quality of life[74]. The McDougall diet has also been evaluated in one clinical trial, where decreased fatigue was attributed to participants' weight loss[75]. The Overcoming MS diet, as part of a combined lifestyle program, is currently being assessed in a clinical trial, with results expected in 2025.

Although these diets have shown beneficial effects on fatigue, body mass index and some metabolic biomarkers in people living with MS, there have been no reported improvements in disability or physical function. Further studies are needed to assess the benefits of low-fat, plant-based diets for people living with MS[76]. Until stronger and more consistent evidence is available, it is not appropriate to recommend these diets for managing MS.

Intermittent fasting diets

Intermittent fasting encompasses various dietary models characterised by alternating periods of eating and voluntary abstinence from food and fluid intake. A recent review identified five clinical trials examining the effects of intermittent fasting in MS, reporting benefits such as weight loss, improved emotional wellbeing and enhanced quality of life[77]. One trial also reported a positive shift in the gut microbiome composition following a 15-day intermittent fast.

However, long-term adherence to an intermittent fasting diet is often reported to be low[78]. Further, current clinical trials are limited in number and often involve small cohorts. There is also uncertainty regarding the long-term effects of intermittent fasting and the variability in intermittent fasting dietary models makes it challenging to generalise findings[68,79]. Larger-scale, well-designed intervention studies are needed to confirm these preliminary findings before any model of intermittent fasting can be recommended for people living with MS.

Gluten-free diet

Gluten is a protein found in some grains, including wheat, barley and rye. A gluten-free diet aims to eliminate all sources of gluten from an individual's diet. Previous studies have suggested that a gluten-free diet may reduce disability progression, lesion activity shown on MRI, fatigue and quality of life in people living with MS[80]. However, there are currently few high-quality intervention studies, and many published findings have a significant risk of bias. Based on the existing evidence, a gluten-free diet cannot yet be recommended for people living with MS, except for those with coeliac disease[68] or other health considerations such as irritable bowel syndrome[81].

Furthermore, the European Society for Clinical Nutrition and Metabolism (ESPEN) does not support the use of a gluten-free diet to prevent MS and recognises its limited impact on disease outcomes in people living with MS[82].

Dairy-free diet

Dairy includes food products made from or containing milk, such as milk, yoghurt and cheese. A dairy-free diet excludes all sources of dairy. While one early study published in 1992 suggested a correlation between the intake of cow's milk and prevalence of MS, more recent studies exploring the relationship between dairy and MS are conflicting[83–86].

There is a need for larger-scale studies to better guide recommendations regarding dairy consumption for people living with MS. Exclusion of dairy may be necessary for individuals with a lactose intolerance, but this should be confirmed with a healthcare professional, as dairy products provide important key nutrients such as calcium. This is particularly important for women with MS who are at a higher risk of developing osteoporosis than the general population.

Currently, a dairy-free diet is not recommended for people living with MS, except for those with a diagnosed cow's milk allergy.

Fish consumption

Fish, particularly oily fish, is rich in both vitamin D and omega-3 polyunsaturated fatty acids, with studies supporting protective effects against cardiovascular disease, lipid metabolism and some cancers[87]. One study published in 2012 showed that consuming fish at least once per month (compared with less than once per month) was linked with lower disability in people living with relapsing-remitting MS[88]. However, many factors that might affect both fish consumption and MS, such as other dietary components and lifestyle characteristics, were not considered.

Furthermore, in a survey of people living with MS who were recruited through social media, those consuming fish reported a better quality of life and less disability[89]. However, the data were self-reported, and the participants were highly educated and engaged in other lifestyle changes, which may have biased the results. Therefore, there is no conclusive evidence on the role of fish consumption in MS disease progression.

Coffee consumption

One study found that consuming caffeinated coffee (compared with never drinking coffee) was associated with lower disability in people with relapsing-remitting MS[90]. However, factors, such as disease course and relapse, which might influence both coffee consumption and MS outcomes, were not considered. A more recent study reported no association between coffee consumption and MS disease severity compared to non-coffee drinkers[91]. Currently, there is insufficient evidence to support any specific recommendations regarding coffee consumption for people living with MS.

Alcohol consumption

Few studies have examined the impact of alcohol consumption on MS progression[92]. One study found that, compared with never drinking, people with relapsing-remitting MS who had consumed alcohol moderately (ranging from one drink weekly to two or more drinks daily) had a longer time to reach higher levels of disability[88]. However, this study did not specify the types of alcoholic beverages consumed and, being cross-sectional, did not account for cumulative consumption or changes in drinking habits over time. Therefore, the findings do not establish a protective effect of alcoholic beverages on the disease course in MS[88].

The largest alcohol study in MS reported that higher total alcohol consumption and red wine consumption were both associated with lower disability in people living with MS. However, it is also plausible that people with the higher disability scores drank less alcohol due to their condition, making the direction of the relationship unclear. In contrast, MRI studies showed that moderate red wine drinkers had larger T2 lesions compared to non-red wine drinkers[93]. Many factors influencing both alcohol consumption and disability progression were not considered.

Given these mixed findings, there is insufficient evidence to support any specific recommendations for alcohol consumption in people living with MS beyond adherence to the national guidelines.

Sodium (added salt)

Sodium is a mineral naturally present in many foods and is often added to packaged and processed items such as crisps, pizza and processed meats. The WHO recommends reducing sodium intake to lower blood pressure and decrease the risk of cardiovascular disease, gastric cancer, obesity, osteoporosis, stroke and coronary heart disease[94].

A review article reported that higher sodium intake was associated with worsened disease activity or an increased autoimmune response in people living with MS, suggesting it may be a risk factor for MS disease progression[95]. However, some individual studies assessed associations between sodium intake and positive health outcomes such as reduced disease activity, slower progression, or improved symptom severity. [95,96]. Another review highlighted the need for more human studies exploring dietary sodium in MS, including associations with inflammation and immunity, but no observed effect on the time to relapse[97]. Therefore, the impact of sodium intake on MS progression remains inconclusive.

Information that needs clarifying

Are any of the special diets beneficial for managing MS?

Currently, there is no conclusive evidence to support the effectiveness of any of the 'special diets' promoted for managing MS. Therefore, these diets, as described above, are not recommended for people living with MS.

Are the special diets safe for people living with MS?

Many of the 'special diets' are restrictive and may unnecessarily exclude key foods or food groups. If someone living with MS chooses to follow a special diet, it is important they work closely with their healthcare team to avoid potential risks such as unintentional weight loss, malnutrition and/or nutrient deficiencies.

Recommendations

We recommend that people living with MS follow the *Australian Dietary Guidelines*[98,99]. These guidelines include the following recommendations for adults:

- Enjoy a wide variety of nutritious foods from the core groups every day:
  - » Plenty of vegetables, including different types and colours, and legumes/beans
  - » Fruit
  - » Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties, such as breads, cereals, rice, pasta, noodles, polenta, couscous, oats, quinoa and barley
  - » Lean meats and poultry, fish, eggs, tofu, nuts and seeds, and legumes/beans
  - » Milk, yoghurt, cheese and/or their alternatives, mostly reduced fat
- Drink plenty of water
- Limit intake of foods containing saturated fat, added salt, sugars, and alcohol.

Following these guidelines may improve the overall health of people living with MS. However, further studies are needed to assess the impact of these recommendations on MS-specific outcomes. Additionally, people living with MS may benefit from consulting an Accredited Practising Dietitian to help identify practical ways to integrate healthy eating into their daily lives.

Considerations for healthcare professionals

When people living with MS are seeking to modify their diet, or require specific dietary guidance (e.g. obesity, malnutrition, metabolic comorbidities, or nutrition impact symptoms such as constipation, dysphagia etc), clinicians should refer them to an Accredited Practising Dietitian, preferably one with experience in MS. The Dietitians Australia website provides a search tool for locating an Accredited Practising Dietitian (*Find a dietitian | Dietitians Australia*). Additionally, the Australian Dietary Guidelines are an excellent resource for adults seeking general guidance on healthy eating.

Weight and obesity

Summary

Excess weight and obesity are recognised as harmful to overall health and have been implicated in various conditions, including MS[100]. Obesity, particularly during childhood or adolescence, increases the risk of developing MS, with a notable impact observed in females[101,102].

In adults already diagnosed with MS, being overweight or obese may contribute to faster disease progression and worsen symptoms such as depression and other comorbidities (Chapter, page 50). This can negatively influence the clinical course of MS[100,102,103]. Furthermore, obesity has been associated with a reduced response to MS treatments[103].

The key takeaway for healthcare professionals is that maintaining a healthy weight is beneficial for people with MS at any disease stage or time since diagnosis. Supporting people with MS in achieving or sustaining a healthy weight should be a priority to potentially improve outcomes and overall well-being.

The link between obesity and MS

Obesity is a growing global health concern[103]. At a population level the WHO classifies overweight and obesity based on the body mass index (BMI), calculated using an individual's weight and height: BMI = weight(kg) / height(m) * height(m)[104]. A BMI of 25kg/m^2 or greater is classified as overweight, and a BMI of 30kg/m^2 or greater, as obese. The 2025 obesity guidelines suggest a difference between pre-clinical and clinical obesity and risk of other health considerations. They also suggest that at an individual level, excess adiposity should be used as a measure of obesity and waist circumference, waist-to-height or waist-to-hip ratio using validated cut-off points in addition to BMI as a screening tool for those with a BMI <40kg/m^2. For those with a BMI above 40kg/m^2 adiposity can be assumed[105]. BMI alone[105] has its limitations. It does not differentiate between fat and muscle mass, leading to criticisms of its accuracy. Research indicates that BMI may underestimate obesity in people with MS, making it more effective for identifying those of healthy weight or moderately overweight, rather than those who are obese[106,107]. Where possible, alternative measures of obesity, such as percentage body fat, or muscle mass (measured using computed tomography (CT) scan or bioimpedance) should be considered for more precise evaluation of adiposity.

In 2022, the Australian Bureau of Statistics (ABS) reported that 34% of Australians were overweight, and 32% were obese[108]. While approximately 0.13% of the Australian population lives with MS, obesity data for this group are not included in ABS surveys. However, findings from AMSLS indicate that 61% of Australian people living with MS self-report a BMI in the overweight or obese range, comparable to the general population[6].

Recent research has focused on the mechanisms linking obesity to MS. Obesity contributes to a pro-inflammatory state in the body, characterised by elevated levels of cytokines such as interleukin-6 (IL-6) and hormones like leptin[109]. IL-6 is a key mediator of inflammation, while leptin, primarily involved in regulating appetite and metabolism, can also enhance immune responses. These elevated levels may exacerbate the neurological inflammation already present in people living with MS, contributing to disease activity[110,111].

Obesity has further been associated with a reduced brain volume and disruption of the blood brain barrier (BBB), a critical structure that protects the brain from harmful substances in the bloodstream[103]. BBB disruption allows immune cells and inflammatory mediators to access the CNS, potentially worsening MS pathology.

Additionally, obesity may lower the bioavailability of vitamin D[112]. Vitamin D is thought to play a protective role in MS by modulating the immune system. In individuals with obesity, vitamin D can become sequestered in adipose tissue, reducing its availability in the bloodstream and potentially diminishing its beneficial effects.

Other mechanisms include oxidative stress on oligodendrocytes (cells responsible for producing myelin), and microbiome disruption, which can alter the gut-brain axis and immune regulation[103]. These factors together may amplify the inflammatory environment in MS, highlighting the importance of managing obesity as part of MS care.

Does being overweight or obese have effects on the risk of getting MS or when MS begins?

Scientific evidence shows that being overweight or obese during childhood[113] and obese during adolescence[114] are established risk factors for developing MS in later life. While some recent studies suggest this link may partly reflect other health behaviours[115], evidence also suggests a causal relationship between BMI, visceral adipose tissue, and MS risk[116].

Does Being Overweight or Obese Affect MS Disease Progression?

Several studies have investigated the impact of excess weight on MS progression. Earlier research found no significant link between being overweight in adulthood and disease progression[117,118]. However, recent findings increasingly demonstrate that excess weight, particularly when measured by waist circumference rather than BMI, is associated with an increased rate of disease progression[101,107]. Obese individuals living with MS have been observed to reach higher disability levels more rapidly compared to those who are not obese[119]. A recent population-based Swedish study found that obesity at diagnosis was associated with a significantly increased risk of reaching EDSS 3 and 4, as well as greater physical worsening over time[35].

Furthermore, carrying extra weight is linked with comorbidities, such as high blood lipid profiles and diabetes. These conditions may worsen the clinical course of MS by increasing disability, lowering quality of life, and increasing the risk of relapse following a first demyelinating event (FDE)[120,121].

Does being overweight or obese influence MS relapse and symptoms?

Two studies have reported that being overweight or obese was associated with an increased risk of relapse[119,120]. Overweight and obese people living with MS also reported experiencing more symptoms of depression[121,122]. However, as these findings are based on cross-sectional studies, it remains unclear whether excess weight directly contributes to these outcomes, highlighting the need for further research.

Recommendations for people with MS

Maintaining a healthy body weight (BMI ≥ 18.5 kg/m^2 and ≤ 24.9 kg/m^2) is associated with numerous health benefits in the general population. For individuals with other chronic diseases, weight management has been linked to improved outcomes, and this may also be the case for people living with MS.

However, weight-based stigma within the MS community can present challenges. Such stigma may be both conscious or unconscious in healthcare settings and can also be internalised by individuals with MS who live with excess weight[123]. Addressing weight sensitively and without judgement is important when approaching this subject with people living with MS.

Behavioural treatment options for obesity in people with MS

While weight loss is often associated with positive health outcomes in MS a focus on weight may not be ideal for long term behaviour change. The focus may need to shift towards other elements of behaviour such as improving food choices rather than an emphasis on weight change alone. There are limited high-quality studies assessing the impact of weight loss specifically in people living with MS. One six-month trial demonstrated that calorie restriction combined with physical activity, another health behaviour, resulted in clinically meaningful weight loss, along with improvements in mobility, fatigue and quality of life[124]. However, further long-term studies are required to address the sustainability of this intervention and its impact on MS progression.

For all people, including those living with MS, maintaining or achieving a healthy weight range and waist circumference may be supported by a balanced approach that includes healthy eating, portion control, physical activity, and stress management[99]. This can be achieved with guidance from qualified professionals, such as dietitians, physiotherapists, and psychologists, as needed.

It is recommended that people living with MS follow the Australian Dietary Guidelines and the *Physical Activity and Exercise Guidelines* as outlined in pages 30 and 33 of this document. As current evidence specific to MS is insufficient to develop MS-specific recommendations, general public guidelines have been endorsed by experts. Consequently, the NHMRC method for grading evidence has not been applied in this context.

Pharmacological treatment options for obesity in people with MS

Emerging research is exploring the potential of repurposing weight-loss medications, particularly anti-diabetic drugs such as semaglutide (Ozempic), for use in people living with MS. In addition to addressing obesity and associated metabolic comorbidities, GLP-1 receptor agonists have shown promise for their anti-inflammatory and neuroprotective properties[125,126]. An analysis of the US Food and Drug Administration Adverse Event Reporting System revealed an inverse association between MS and several anti-diabetic drugs, including metformin, empagliflozin, liraglutide, dulaglutide, and semaglutide[126]. While these findings are intriguing, further research is needed to confirm their relevance to MS management. Another study found potential benefits to endothelial function, which could positively impact vascular comorbidities in people living with MS[125].

Currently, there is insufficient evidence to draw conclusions about the overall harms or benefits of pharmacological weight-loss treatments for people living with MS. Any consideration of anti-diabetic weight loss medications should be undertaken in consultation with the MS healthcare team, ensuring the approach is tailored to the individual's needs and overall health.

Surgical treatment options for obesity in people with MS

Metabolic and bariatric surgery, including gastric sleeve procedures, are recognised as the most effective treatment for all classes of obesity[127,128], with a typical weight loss of 32-37% and a low risk of complications (7-8%). However, neurological complications associated with these types of surgeries in the general population, often linked to nutrient deficiencies such as vitamin D, underscore the need for lifelong compliance with vitamin/mineral supplementation and careful monitoring with healthcare professionals[127].

In people living with MS, bariatric surgery may improve clinical outcomes by better managing metabolic comorbidities such as diabetes, hypertension, and dyslipidaemia[112]. Recent studies suggests that surgical outcomes in people living with MS are comparable to obese individuals without MS[127]. Furthermore, a reduced incidence of acute MS exacerbations has been reported in individuals with MS who have undergone bariatric surgery[127].

Decisions regarding bariatric surgery for people living with MS should be made in consultation with a multidisciplinary team, including bariatric surgeons, anaesthetists, endocrinologists, dietitians, and neurologists. Lifelong nutritional strategies such as supplementation are crucial to mitigate the risk of neurological complications and ensure optimal health outcomes.

Considerations for healthcare professionals

The NHMRC resource, the Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia is currently being updated. While the previous version[129] has been rescinded, it provided valuable guidance for assisting adults with MS who are overweight or obese in achieving weight loss. These guidelines addressed behaviour change, intervention strategies, and the importance of long-term follow-up. Key steps for weight management, also endorsed by global guidelines such as the National Institute for Health and Care Excellence (NICE)[130], include:

- **Ask and assess**: discuss the individual's readiness to change lifestyle behaviours. Include waist circumference, waist-to-hip, waist-to-height in addition to BMI screening in clinical measures.
- **Advise**: discuss the benefits of adopting healthy eating habits and barriers and enablers to improving overall health as well as other health conditions. Minimise the focus on weight loss.
- **Assist**: consider implementing multicomponent interventions that incorporate dietary, physical activity, and psychological strategies. Refer people to other appropriate healthcare professionals to assist and support them in making these lifestyle changes, or if considering weight loss medication/surgery options. Treatment goals should aim to improve overall health rather than weight loss alone.
- **Arrange**: promote and encourage self-monitoring and provide regular, ongoing monitoring to review progress behaviours, and goals.

In summary, based on these guidelines and the evidence provided, we recommend the following actions aligned with the AACTT framework:

- **Action**: Screen with BMI, assess and record waist circumference, waist-to-hip ratio or waist-to-height ratio and other relevant indicators (e.g. dietary habits and physical activity levels) in individuals living with MS or at risk of MS during every clinical interaction. Provide advice on the benefits of weight management, focusing on overall health improvements rather than weight loss. Assist by connecting individuals with appropriate services, such as dietitians, physiotherapists, or psychologists, to support healthy behaviour change.
- **Actor**: Healthcare professionals across all disciplines, including GPs, neurologists, nurses, dietitians, and allied health professionals, should routinely monitor and address goals and weight management in clinical practice.
- **Context**: This should be conducted in all clinical settings, including primary care, neurology, and allied health appointments, and tailored to the individual's specific needs and readiness to engage in lifestyle changes.
- **Target**: Individuals with MS or at risk of MS who are overweight or obese or are at risk of weight-related comorbidities.
- **Time**: Address weight, related health behaviours and related socio-ecological factors during every clinical interaction, with follow-up arranged to track progress and provide ongoing support as needed.

Physical activity and exercise

Summary

Many individuals with MS have low levels of physical activity and exercise participation. Limited participation in physical activity may lead to reduced fitness, limited mobility, and a lower quality of life. Inactivity can also increase the risk of developing comorbidities such as depression, cardiovascular disease, osteoporosis, and obesity.

Prior to the 1980s, the link between MS and physical activity was poorly understood. Since then, robust evidence has emerged demonstrating the benefits of physical activity and exercise in MS. This chapter outlines these potential health benefit, evaluates the quality of supporting research, and offers recommendations for optimal activity. Current exercise guidelines specific to MS are also discussed. Additionally, this chapter will provide practical guidance for all MS health professionals on implementing these recommendations. This includes detailing who promotes or prescribes physical activity and exercise when, to whom, at what time in the clinical journey, and in what setting[131].

The overall message is that physical activity and exercise should be considered a safe and effective strategy for enhancing quality of life in people with MS. Physical activity and exercise should be promoted to all persons with MS across the continuum of MS care. Evidence demonstrates that being active improves physical fitness, functional capacity, and quality of life in people with MS.

The link between physical activity and exercise, and MS

Physical activity and exercise are related but are distinct concepts. Physical activity encompasses a broad range of movements, including exercise, sport, occupational tasks, active transportation (e.g. walking your dog or cycling to the shops), and household chores. The research discussed in this section is primarily focused on physical activity in the form of walking. Exercise, by contrast, is considered to be a planned, structured, and repetitive activity performed over an extended period, often prescribed by a healthcare professional or exercise specialist to achieve specific health-related fitness[132,133].

Both physical activity and exercise offer clear benefits for people with MS[134] and the general population[135]. Inactivity poses a significant public health risk, with people with disabilities, including those with MS, being at much greater risk of serious health problems associated with inactivity[136]. In the general population, sustained participation in exercise has been shown to reduce the risk of developing illnesses such as heart disease, stroke and

type 2 diabetes, amongst many other diseases[137]. Additionally, The Royal Australian & New Zealand College of Psychiatrists guidelines for the management of mood disorder, such as clinical depression and anxiety, recommends physical activity as a form of treatment[8].

What are the benefits of physical activity and exercise for people with MS?

The latest evidence confirms that both physical activity (primarily measured as walking) and exercise have positive physical and mental benefits for people with MS[138–144].

Many research studies support the use of exercise training to manage MS symptoms and potentially alter the disease course of MS.

Evidence shows that exercise does improve physical fitness in people with MS[139,145–150], with both aerobic exercise (e.g. running, swimming and cycling) and strength/resistance training (e.g. lifting weights, using weight machines or resistance bands)[139,145–150] showing clear benefits for people with MS.

Physical activity (in the form of walking) and exercise (in the form of an exercise training program), when compared to no training, have been shown to improve:

- Mobility: Structured exercise programs improve walking related movement[138–140,144,148,151–154]
- Fatigue: Regular exercise reduces MS-related fatigue[140,143,145,148,155–158]
- Balance: Both physical activity and exercise enhance postural stability[138–140,143,154,159–161]
- Cognition: Improvements in thinking, memory, and processing have been observed[142,162]
- Depressive Symptoms: Exercise reduces depression and anxiety[141,155,163–165]
- Health-Related Quality of Life: Overall well-being is significantly improved[140,148,166–168].

Preliminary evidence indicates that exercise may improve:

- Risk of Falls: Home-based exercise programs lower fall risk
- Pain Management: Aerobic and resistance training help manage MS-related pain.

Additional benefits include, positive effects on memory[169,170], improved sleep quality[171,172] and a reduced risk of developing other comorbid conditions, such as metabolic disorders and cardiovascular disease[173,174].

Some studies have shown improvements post exercise in brain function, integrity and inflammation for people with MS[175–178]. However, most studies remain inconclusive about its ability to modify the disease process[179–183]. Despite this, exercise is considered by some experts to be the single most effective non-pharmacological approach for improving functional outcomes and managing symptoms, including aerobic capacity, walking performance, fatigue, gait, balance and quality of life[134,184].

Quality of the Evidence – NHMRC Grade

Health Benefits – A
Symptoms – B
Disability Progression - B

Which types of exercise are of most benefit to people with MS?

Systematic reviews of the literature generally examine a combination of aerobic, resistance and balance training, with fewer studies focused exclusively on a single type of exercise. Most studies explore the benefits of combined types of exercise[140–142,144,147–149,151,154,158,159,163,165–168,170,174], with one review each focusing on dosage of aerobic exercise[139] and resistance exercise[138] and two reviews focusing solely on balance exercise[160,161]. For all exercise types, safety is paramount, especially balance exercise, which should be practiced in a controlled, safe environment to minimise the risk of falls. Supervised balance exercises conducted under the guidance of an accredited health professional such as physiotherapists or exercise physiologists, are recommended to ensure safety and maximise benefits[185].

Quality of the Evidence – NHMRC Grade

Exercise overall - B
Aerobic exercise – B
Resistance exercise - B
Balance exercise - B
Yoga, Pilates and stretching exercise - A
High intensity aerobic exercise - B

Is exercise safe for people with MS?

In higher quality studies, exercise is safe for people with MS, and exercise is not associated with an increased risk of relapse[154,186,187].

Quality of the Evidence – NHMRC Grade

Safety - A

Despite this, people with MS participate in exercise at significantly lower rates than the general population, although comparable to other chronic conditions[188–192]. This reduced participation may stem from various concerns, including:

- Safety of exercise and fear of trips and falls
- Level of disability, and MS-related pain or fatigue
- Socioeconomic barriers, such as access to specialised exercise programs, trainers, or facilities to suit varying individual needs
- Psychological factors such as depression, which may reduce motivation to exercise.

Heat Sensitivity and Exercise

Heat sensitivity is a notable issue for those with MS, where exercising in warm environments may exacerbate their MS symptoms (Uhthoff's phenomenon)[193]. However, emerging research has identified strategies for people with MS to mitigate heat sensitivity, which allows them to exercise safely and for longer periods of time, even in warmer climates. Research suggests the following approaches:

- Drinking cold water[194] and staying hydrated with cold water can help regulate body temperature
- Wearing cooling garments (such as a cooling vest)[195] during exercise may be effective in reducing heat-related symptom worsening[194].

Are there considerations for those with more advanced levels of disability?

Most of the research and exercise guidelines described in this document are aimed at people with MS aged 18 years or over who have mild to moderate levels of disability.

However, exercise remains safe and beneficial for those with more advanced disabilities, provided it is appropriately adapted to their individual needs and capabilities.

Examples of adapted exercises include body weight-supported treadmill walking or total body recumbent stepping[149]. Exercise recommendations should be developed in consultation with the broader medical team[149,196–198]. These recommendations should take into account psychological factors such as depression that can affect motivation and engagement, and socioeconomic factors, where financial and geographical limitations to accessing supporting services can create barriers.

Participation in adapted exercise programs can lead to improvements in physical fitness, physical function, symptom management, and overall participation in daily life activities, even for individuals with more severe disability levels[149,196].

Recommendations for people with MS

Exercise guidelines for people with MS

Strong evidence demonstrates that exercising at least twice per week at a moderate intensity improves aerobic capacity and muscular strength in people with MS[148]. In 2013, exercise guidelines were produced for physical activity for people with MS,[199] and more recent recommendations now consider a person's previous experience with exercise training and level of fitness[200]. The guidelines below, adapted from the Canadian MS Society's *Physical Activity Guidelines*[201], are recommended for adults with MS who have mild to moderate disability.

There are two levels of exercises provided for people with MS based on a person's level of fitness and previous experience of exercise training:

1. **General Exercise Guidelines** (For individuals who are irregularly or infrequently active):
    - **Aerobic Exercise**: Moderate intensity 2–3 times per week for 30 minutes per session
        - » Examples: Arm cycling, seated shadow boxing, walking, leg cycling, elliptical trainer
    - **Resistance Training**: Moderate intensity 2–3 times per week
        - » Examples: Weight machines, free weights, cable pulleys
2. **Advanced Exercise Guidelines** (For individuals who are regularly participating in an exercise program and/or people who are seeking greater benefits from exercise training)
    - **Aerobic Exercise**: Moderate to vigorous intensity 5 times per week for 40 minutes per session
        - » Examples: Arm cycling, seated shadow boxing, walking, leg cycling, elliptical trainer
    - **Resistance Training**: Moderate intensity 2–3 times per week
        - » Examples: Weight machines, free weights, cable pulleys

3. **Considerations for all exercise levels:**
    - Professional Advice: The advice of an accredited health professional is recommended to help identify what types and amounts of physical activity are appropriate for each individual with MS. This could be a specialist physiotherapist, occupational therapist or exercise physiologist[202,203].
    - Symptom Management: Some MS symptoms, such as fatigue and heat sensitivity, should be identified and discussed before exercise begins.
    - Behavioural Support: Exercise programs may be more successful if they are accompanied with behavioural counselling to help people with MS identify expectations from exercise, relevant goals, monitor exercise and improve their exercise self-efficacy. In addition, health professionals can support people with MS to overcome barriers and use enablers to facilitate exercise participation[204,205].
    - If the general physical activity levels or ability levels are low, activities performed at a lower intensity, frequency and duration than recommended may still bring benefit. Exercise for people with higher support needs may need to be adapted to suit the individual and their capabilities.
    - It is recommended that people with MS gradually increase the duration, frequency and intensity of exercise as they feel comfortable, to progress towards meeting the recommended guidelines[199,200].
    - Safe and effective exercises for the more severely disabled population should be prescribed in consultation with the wider healthcare team. Exercises might include conventional exercise (aerobic, resistance and balance training as described in the general exercise section for people with MS above) and adapted exercise (e.g. body weight-supported treadmill walking, or total body recumbent stepping, which allows the person to be in a reclined position while performing exercise).

Additional Recommendations:

Stretching and balance exercises:

- It is recommended that people with MS practice stretching and balance exercises in a safe environment. Stretching exercises can be completed daily[199,200].
- Balance exercises can also be practiced when supervised by an accredited health professional such as a physiotherapist. You might complete balance exercises two to three times per week or more[199,200].

Considerations for health professionals: putting the recommendations into action in your practice

Exercise is safe and does not increase the risk of relapse in MS. In fact, regular exercise may reduce relapse rates in people with MS[174,189]. Allied health professionals, including physiotherapists, occupational therapists, and exercise physiologists are well-suited to prescribe and deliver exercise programs to people with MS. Other MS professionals, including nurses and neurologists, play a pivotal role in encouraging and supporting people with MS to be physically active by discussing the benefits of exercise and promoting the guidelines[199,200].

Health professionals should also identify appropriate referral options for tailored exercise programs and remain informed about local physical activity options that are inclusive of people with MS, such as sports, active transportation, or group exercise opportunities, which Australians with MS value[206].

To monitor behaviours and symptoms associated with outcome of physical activity and exercise validated tools are available for healthcare professionals. Such tools can:

- assess physical, psychological and behavioural readiness for exercise[207]
- monitor factors such as MS-symptoms[208–211]
- provide information on patients current exercise levels[212]
- identify functional limitations[213], and
- focus on exercise and physical activity behavioural outcome[205,214].

These assessments should be conducted before initiating or changing activity levels and repeated by healthcare professionals regularly and reported to the wider healthcare team to monitor progress and ensure suitability.

Healthcare providers can better support uptake of physical activity and exercise by coupling exercise prescription with behavioural change tools. These can include helping individuals set goals, increase their exercise self-efficacy and overcome perceived barriers to participation[204,215]. Given the significant benefits of exercise in MS[216], healthcare providers should address exercise behaviour at every stage of care, starting when MS is first suspected, at the time of diagnosis, during periods of stability, and focused discussion should be made to support persons with MS to maintain physical activity and exercise at the time of relapse and disease progression.

Discussions about exercise can be integrated into routine clinical interactions, including appointments, infusions, or telehealth sessions. Evidence supports both in-person and technology-based approaches as effective and acceptable to people with MS in Australia[206,217]. Healthcare professionals should leverage these opportunities to encourage exercise participation and adherence. (Please see our recommendations on putting these into action at your site below).

Implementing the recommendations in clinical practice

We recommend following a framework to embed these recommendations into the multidisciplinary care of persons with MS. That is, managers and healthcare professional teams should consider *who* should be doing *what* with *whom* at what *time* and in *what* location, regarding promotion and prescription of physical activity and exercise[145]. The answer to this question is based on factors unique to each clinical site, and situation.

The table below provides examples, which may vary depending on site specifics, which are relevant for putting the recommendations into action.

TABLE 1: ACTIONABLE RECOMMENDATIONS FOR HEALTH PROFESSIONALS

WHO should promote or prescribe exercise / physical activity?	Physiotherapist, nurse, neurologist, exercise physiologist, occupational therapist, other					
ACTION What should be done?	Education & explanation	Assessment of attitudes, habits, behaviour or capacity	Counselling	Exercise and physical activity prescription	Follow-up	Referral to program
CONTEXT where this happens	Clinical visits	When receiving other treatment	During clinic announcements (e.g. newsletters)	Telehealth sessions		
TARGET of who this should happen to	People under investigation for MS	People recently diagnosed	People with stable MS	People who are experiencing relapse	People whose MS is progressing	
TIME when this should happen	During initial investigation	At diagnosis	During stability	During relapse	During progression	

Examples of helping the team formalise putting these actions into place in your site may be:

The neurologist may assess the attitude and behaviour towards exercise of people newly diagnosed with MS and record this information for discussion with the wider team.

The nurse may educate and explain the benefits of exercise when persons with stable MS are receiving disease modifying therapies (DMTs) during times of stability.

The physiotherapist may use behaviour change counselling to discuss overcoming barriers to exercise during a clinic e-newsletter for people whose MS is progressing.

Opportunities exist for healthcare professionals to engage in discussion about physical activity and exercise at any stage of the disease process, with people with MS. Healthcare professionals are ideally situated to assist with implementing strategies to enable participation in appropriate exercise and physical activity with people with MS.

Sleep and multiple sclerosis

Current understanding and therapeutic approaches for addressing sleep difficulties in people with MS

Summary

Sleep is a fundamental biological function essential for maintaining good health. Good quality sleep is critical for everybody, including those living with MS. Poor quality sleep and diagnosed sleep disorders are common in people living with MS and exacerbate symptom severity and reduce health-related quality of life (HRQoL).

In MS, impacts of poor sleep on the quality of life of people living with MS result directly from MS-related lesions in brain regions that regulate sleep, and also via other MS symptoms such as pain or depression. While MS-specific sleep health guidelines are lacking in the literature, general guidelines from the Sleep Health Foundation can be safely applied to manage sleep health issues in people living with MS. Evidence-based strategies such as cognitive behavioural therapy (CBT) and moderate intensity exercise are effective for enhancing sleep in people living with MS.

Introduction

Sleep is a temporary state of unconsciousness during which the brain becomes less responsive to external stimuli[218]. It is vital for health and well-being[219], supporting growth, energy regulation, and metabolic and endocrine functions[220]. Sleep is now considered one of the three essential lifestyle behaviours, alongside diet and exercise, that are strongly linked to overall health[221,222]. Healthy sleep is defined by adequate duration, optimal quality, appropriate timing, regularity and the absence of sleep disorders[223,224].

The National Sleep Foundation (NSF) recommends 7 to 9 hours of sleep per night on a regular basis for optimal adult health[225]. Disruptions affecting sleep duration, quality, or architecture are associated with various health conditions, including hypertension[226], type 2 diabetes[227], obesity[228], cardiovascular disease[229], anxiety and depression[230], and cognitive impairment[231]. Insufficient sleep has been linked to worse neurological outcomes in healthy individuals[232–234], suggesting that poor sleep may exacerbate neurodegeneration in people living with MS, whose neurological functions are already compromised.

Poor sleep affects 33%–45% of the general population[235], and approximately 70% of people living with MS [236,237]. In MS, poor sleep may arise from lesions in brain areas that regulate sleep, such as the brainstem for sleep apnoea[238,239] and spinal cord lesions for restless legs syndrome (RLS)[239]. Impacts of poor sleep on quality of life can also be secondary to MS symptoms including pain, depression and anxiety[239]. This dual impact highlights the complex interaction between MS pathology and sleep disturbances.

Which sleep problems are common in people living with MS?

Individuals with MS experience a higher prevalence of sleep disorders compared to the general population[240,241]. Common sleep problems include insomnia, sleep apnoea, RLS, narcolepsy, circadian rhythm disorder, and rapid eye movement sleep behaviour disorders[238,240–242]. These disorders and their characteristics are summarised in the box below (Box 1).

Poor sleep quality is strongly associated with worse MS symptoms including fatigue, pain, depression, and disability[245–248] as well as reduced HRQoL[236,249,250]. Addressing sleep disturbances has been shown to improve HRQoL and alleviate MS symptoms[251], including fatigue, depression, and anxiety[252–254]. Emerging evidence also suggests that poor sleep negatively impacts the structure and function of the brain[255], indicating that effective treatment of sleep disorders may have neuroprotective benefits for people living with MS.

BOX 1: DEFINITIONS OF SLEEP DISORDERS COMMONLY EXPERIENCED BY PEOPLE WITH MS[256]

- **Insomnia:** Difficulty falling asleep, staying asleep, or waking too early and unable to go back to sleep.
- **Sleep Apnoea:** A sleep disorder where breathing repeatedly stops, causing sleep disruptions.
- **Restless Legs Syndrome (RLS):** Tingling or crawling sensations that create an irresistible urge to move the legs.
- **Excessive Daytime Sleepiness (EDS)**: Difficulty staying awake or alert, with an increased desire to sleep during the day.
- **Narcolepsy:** A chronic neurological disorder that affects the brain's ability to regulate sleep-wake cycles, characterised by excessive daytime sleepiness and sudden sleep attacks.
- **Circadian Rhythm Disorder:** Disruptions to the body's natural sleep-wake cycle, leading to irregular sleep patterns or sleeping difficulties.
- **Rapid Eye Movement (REM) Sleep Behaviour Disorder:** A condition where individuals actively enact their vivid dreams during REM sleep, often with physical movements and vocalisations.

Recommendations for getting a good night's sleep

Specific recommendations for improving sleep in people living with MS are limited, as there is a lack of studies tracking sleep changes over time or evaluating therapeutic interventions. Consequently, the following general sleep tips (also known as 'sleep hygiene') from the Sleep Health Foundation are recommended:

- Maintain regular times for going to bed and getting up.
- Relax for an hour before going to bed.
- Avoid going to bed on a full or empty stomach.
- If unable to sleep after 20 minutes in bed, go to another room until feeling tired again.
- Avoid spending too long in bed.
- Keep distracting things out of the bedroom.
- Get some sunlight exposure during the day.
- Get 7-9 hours of sleep.
- Avoid evening naps, which can disrupt night sleep.

These tips are available in a downloadable fact sheet[257] from the Sleep Health Foundation[258].

Targeted advice for better sleep for people living with MS

Non-pharmaceutical strategies known to improve sleep include CBT, physical activity, sleep hygiene education and lifestyle changes.

Cognitive behavioural therapy (CBT)

CBT is an effective, first-line treatment for insomnia, targeting thoughts and behaviours that negatively impact sleep [259–261].While not extensively studied in people living with MS, CBT has demonstrated positive effects on sleep outcomes in people with mental health conditions and insomnia [262]. Typically delivered by a trained psychologist, CBT is likely beneficial for people living with MS experiencing insomnia, and is more effective than hypnotics for long-term treatment [263,264], with fewer side effects[264]. Advances in digital platforms over the last decade has also improved access to CBT for plwMS[265].

Physical activity

Physical activity improves both sleep duration and efficiency in the general population)[266,267]. Clinical trials undertaken in people living with MS have produced mixed results[260] ,which may reflect variability in interventions delivered rather than ineffectiveness. Moderate physical activity offers health benefits, making it a valuable add-on therapy for sleep management in people living with MS[268,269].

Multidisciplinary Interventions

Preliminary evidence also supports approaches combining sleep hygiene education, lifestyle changes (smoking cessation, physical activity) and environmental modifications to improve sleep quality and fatigue in people living with MS[251]. Further research is nevertheless needed to validate these preliminary findings.

Assessing sleep using wearable technology

Sleep disturbances have traditionally been assessed objectively using polysomnography (PSG), usually available in hospital-based sleep laboratories. This overnight assessment of sleep includes examinations of brain waves, breathing, eye movements and leg movements with specialised electrodes and belts attached to the skin and scalp. This allows sleep specialists to accurately define sleep quality, quantity, and diagnose any sleep disorder. Using PSG has significant limitations including cost, barriers to access and usually assess one night only. However, wearable devices such as actigraphs[270] which are wristwatch-sized devices equipped with multiple sensors record movement data and can be worn for multiple nights in the individual's natural sleep environment[271]. Actigraphs are validated against PSG[272], and offers a relatively inexpensive, user-friendly method for measuring sleep over extended periods in a research setting[273]. Actigraphy has been widely used to study sleep outcomes in people living with MS [274,275] in community settings. However, formal diagnosis of sleep disorders often requires referral to a sleep laboratory for PSG, the gold standard for objective measurement of sleep, and assessment by a sleep clinician.

Healthcare professionals report that over half of people living with MS they see currently use a consumer sleep tracker to monitor their sleep[276], opening up a world of possibilities for individuals in self-monitoring sleep. While widely used and perceived as easy to use, consumer grade devices hold hidden complexity e.g. data access, fees, privacy and security issues[277] and may not be validated in clinical populations[270], in addition to the technical issues affecting all actigraphs e.g. difficulty in correctly differentiating light vs deep sleep, misclassification of sleep and wake[277].

Recommendations for people living with MS

While gaps remain in the evidence base for general recommendations for getting a good night sleep[278], following the Sleep Health Foundation's general advice for keeping good habits for getting a good night's sleep[258] is an appropriate and well validated first step.

People with MS whose sleep is causing them concern should visit their GP for further evaluation, regarding whether they may have symptoms of a sleep disorder. Following the GP consultation, the pathway typically involves a referral to a sleep specialist for further assessment and diagnosis. Based on the diagnosis, a comprehensive treatment plan can be developed. These include sleep hygiene education, lifestyle changes (diet, physical activity), CBT, medical interventions including medicines, and utilisation of sleep devices aimed at managing OSA e.g. continuous positive airway pressure (CPAP). Regular follow-ups ensure the treatment is effective, and adjustments are made as needed.

Secondary causes of poor sleep should be reviewed as these may be suitable for specific treatments. For example, low mood, anxiety or pain will respond to appropriate treatment (CBT, medications including antidepressants and pain modifying therapies) and may, in turn, improve sleep quality.

- Follow the Sleep Health Foundation's general advice for developing and maintaining good sleep habits[256].
- Referral to a sleep specialist may be required, for further assessment and diagnosis. Treatment may include CBT or medical interventions, such as CPAP for sleep apnoea. Regular follow-ups ensure treatments are effective and can be adjusted as appropriate.
- Address secondary causes of poor sleep, such as low mood, anxiety, or pain, with appropriate treatments (e.g. CBT, antidepressants, or therapies to treat pain), which may also improve sleep quality.
- Using consumer grade wearables (smart watches, fitness trackers) is common in people living with MS, and can be very helpful, but any abnormalities need to be followed up with healthcare professionals. It is important to note that the information provided by these devices is not always accurate and careful assessment by a health care professional is required to determine if findings are of significance.

BOX 2: FACTORS ASSOCIATED WITH POOR SLEEP IN PEOPLE LIVING WITH MS

- Being overweight or obese
- Recent MS relapse
- Higher MS disability levels
- Higher intensity of MS symptoms including pain and sensory symptoms, feelings of anxiety or depression, fatigue or cognitive symptoms
- Coexisting medical conditions other than MS
- Female sex
- Unemployment
- Not having attained university level education

List of factors derived from the following references:[236,279–281]

Considerations for healthcare professionals

Sleep health is essential for overall well-being, making poor sleep an important area for health professionals to address during consultations. This includes:

- Asking about sleep quality and identifying potential causes of poor sleep quality.
- Providing guidance on good sleep hygiene, referencing Sleep Health Foundation guidelines.
- Exploring treatable causes of poor sleep common in people living with MS, such as insomnia, sleep apnoea, and restless legs syndrome.

Use of a consumer grade sleep tracker may provide valuable information at this stage.

For individuals who are overweight or obese, discussing weight management may be appropriate, as obesity increases the risk of sleep apnoea and risk of other secondary sleep issues. Diagnoses may require referral to a sleep laboratory for PSG.

Effective treatment of poor sleep often requires a multidisciplinary approach to manage MS-related symptoms, including pain, depression, anxiety, and bowel and bladder dysfunction.

Recommendations:

- **Prioritise healthy lifestyle interventions:** Encourage regular moderate-intensity physical activity, smoking cessation, and weight management, all of which improve sleep quality.
- **CBT for insomnia:** Recommend CBT as an effective, evidence-based treatment for people with insomnia.
- **Medication as a lower priority:** Use medications to treat sleep issues only when absolutely necessary.

To ensure these strategies are effectively implemented in clinical practice, the **AACTT framework** provides a structured approach:

- **Actor:** Healthcare professionals (GPs, psychologists etc) should take the lead in assessing and managing sleep-related concerns in people living with MS.
- **Action:** Ask about sleep quality, provide advice on sleep hygiene, and identify treatable causes of poor sleep, and prioritise lifestyle interventions.
- **Context:** Address sleep issues during routine consultations and in discussions about overall health and MS-related symptoms.
- **Target:** Focus on improving sleep quality, managing secondary causes (e.g. pain, anxiety), and promoting lifestyle changes.
- **Timeframe**: Implement and evaluate interventions during regular follow-up appointments and ongoing care.

Stress and stress-reducing activities in MS

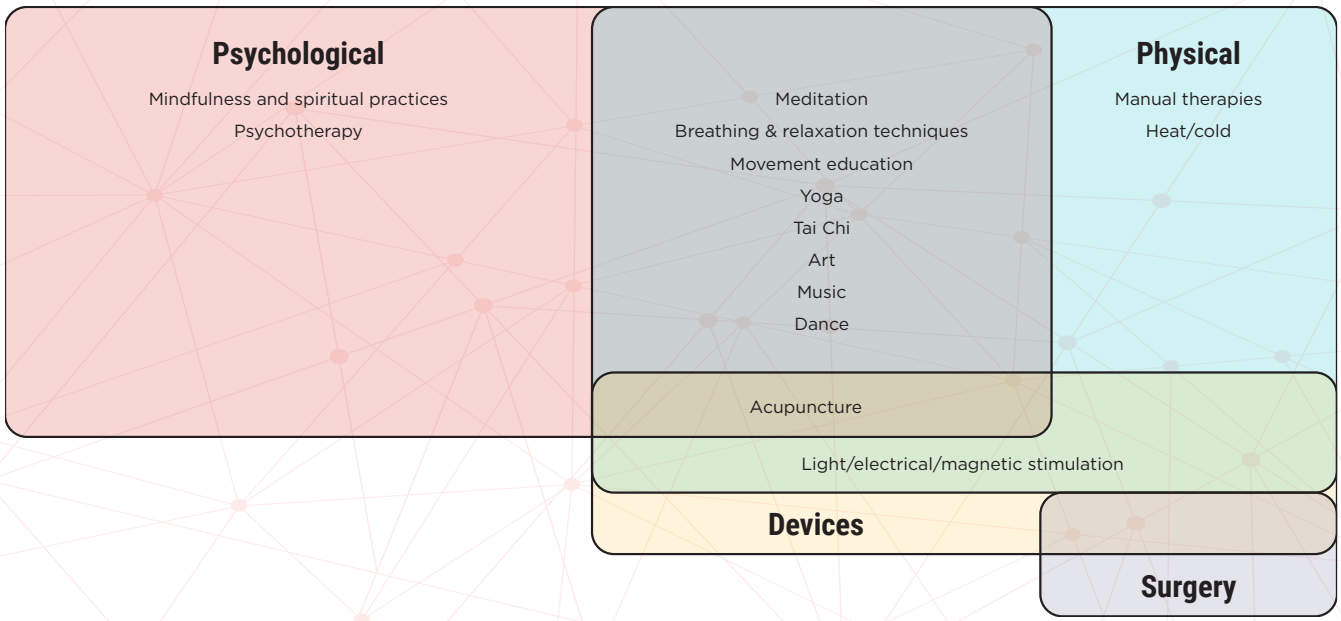
Summary

Acute stress is a normal part of life, but chronic stress can lead to systemic inflammation as well as significant mental and physical health concerns[282]. Given the impact of stress on health, MS experts have included this chapter to explore complementary stress-reducing practices for people living with MS.

Chronic stress is associated with increased MS risk, relapse rates and may exacerbate certain MS-related symptoms[282-285]. However, defining "stress" is challenging, as perceptions vary by culture, religion, and personal beliefs. Here, stress is defined as a physical and/or emotional reaction to life challenges[286].

This chapter reviews evidence from randomised controlled trials (RCTs) and high-level reviews on stress-reducing activities for people living with MS, and emphasises effective psychological practices, as defined by the National Centre for Complementary and Integrative Health (NCCIH, Figure 2. Complementary health approaches, categorised as psychological, physical, and nutritional (reproduced from the NCCIH)[286]). Additionally, we identify potential barriers to engagement, and strategies for supporting people living with MS in adopting these practices.

FIGURE 2. COMPLEMENTARY HEALTH APPROACHES, CATEGORISED AS PSYCHOLOGICAL, PHYSICAL, AND NUTRITIONAL (REPRODUCED FROM THE NCCIH)[286].



Evidence for stress-reducing activities in improving health outcomes in people with MS

Many stress-reducing practices have been investigated for their effectiveness in improving clinical and patient-reported outcomes among people living with MS. The diversity of these practices reflects the subjective nature of "stress-reducing behaviour" as what benefits one individual may be ineffective or counterproductive for another. The NCCIH provides a structured framework for identifying stress-reducing activities, which has been used to guide this chapter. These include:

- Meditation and mindfulness
- Mind-body therapies (Yoga, Tai Chi, Qi Gong)
- Art, music, dance
- Psychotherapy (including cognitive behavioural therapy)
- Breathing and progressive relaxation
- Movement education
- Mindful eating
- Acupuncture/acupressure
- Massage therapy
- Faith and spirituality.

This chapter focuses on the most prominent activities with the highest level of evidence, referencing relevant observational studies as applicable.

Cognitive Behavioural Therapy (CBT)

CBT, a structured form of psychotherapy, focuses on identifying and changing negative thought patterns and behaviours[287]. By developing practical skills for managing stress and enhancing emotional resilience, CBT may help better regulate emotions. CBT interventions have been tested in several clinical trials for treating depression and fatigue in people living with MS. Hind and colleagues reviewed seven trials, reporting a pooled protective effect of CBT on depression (standardised mean difference=-0.61)[288]. Similarly, another systematic review of four clinical trials showed a pooled beneficial effect of CBT on fatigue (standardised mean difference=-0.47)[289]. Taken together, these results suggest that CBT may be an effective approach for improving depression and fatigue for people living with MS.

Interpretations & recommendations

CBT has been shown to improve depression and reduce fatigue among people living with MS. Consider discussing CBT with people living with MS who may benefit, particularly those experiencing depression and/or fatigue.

Meditation & mindfulness-based practices

Meditation is "*the awareness that emerges through paying attention, on purpose, in the present moment, and non-judgmentally*"[290]. Meditation practices, including mindfulness and transcendental meditation, can reduce stress and improve emotional regulation, and has been shown to have effects on MRI-based outcome measures[291]. While no RCTs of meditation as a stand-alone intervention have been undertaken with people living with MS, one observational study has shown prospective associations of meditation practice with lower reports of depression and fatigue[292].

On the other hand, mindfulness has been assessed in many clinical trials with people living with MS and is shown to have beneficial effects on various clinical and patient-reported outcomes. The largest mindfulness RCT among people living with MS was conducted in 2010 where 150 were randomised to either an 8-week mindfulness-based intervention or usual care. Those in the intervention arm, showed a significant improvement in quality of life, and reduced depression, fatigue, and anxiety, at the end of eight weeks. This result was maintained six months later[293].

Mindfulness-based interventions among people living with MS have also shown to increase quality of life and coping skills, and reduce stress, depression, and anxiety[287,294] when delivered either face-to-face or online[293,295–297]. A systematic review of 14 RCTs of mindfulness-based interventions also reported a significant improvement in mental health-related quality of life[287]. However, of note, there was heterogeneity in the interventions across studies, including standard or modified mindfulness-based stress reduction, mindfulness-based cognitive therapy, and interventions incorporating additional elements such as physical activity.

Interpretations & recommendations

There is potential for mindfulness-based interventions to improve mental health-related quality of life, depression, fatigue and anxiety among people living with MS. However, further high-quality evidence is required before any recommendations can be made.

Mind-body approaches (e.g. yoga, Tai Chi)

Mind-body approaches such as yoga and Tai Chi, integrate physical movement with meditation and focused breathing[298].

Yoga has benefits for general mental health and chronic conditions[299–301], but evidence specific to people living with MS is limited. A meta-analysis of five RCTs assessing the effects of yoga practice on quality of life among people living with MS concluded no firm interpretations due to the heterogeneity between interventions[302]. However, a systematic review of six RCTs comparing yoga with usual care in people living with MS found a pooled standard reduction in fatigue, while an analysis of four RCTs of yoga compared to usual care failed to find a significant improvement in quality of life[303].

Studies of Tai Chi in people living with MS are also limited. A systematic review of 10 RCTs found that Tai Chi reduced depression but had no effects on fatigue[304]. Another systematic review of three RCTs showed benefits on quality of life[305]. Both reviews noted limitations, including small population sizes, intervention heterogeneity, low methodological quality, and insufficient follow up.

Interpretations & recommendations

Early evidence suggests yoga may improve fatigue and Tai Chi may reduce depression among people living with MS. Further studies with larger populations and clearly defined interventions are needed before any recommendations can be made.

Music and art therapies

Music therapy involves listening to and/or playing music, sometimes in combination with dance and other physical movement, to reduce stress and improve mood[306]. Two systematic reviews of studies among people living with MS showed some benefits of music therapy on gait, fatigue, and mental health. A systematic review of 10 RCTs concluded that different types of music therapy had varied benefits. For example, playing music improved manual dexterity, while neurological music therapy enhanced mood and quality of life[307]. A systematic review of 12 RCTs of music therapy for gait symptoms showed improvements in gait cadence, coordination, and speed[308]. However, small participant numbers and heterogeneity in interventions limited firm conclusions.

Art therapy, which involves creating and visualising physical art, has shown benefits for depression and mental health in the general population and some chronic neurological conditions[309]. In people living with MS, however, only one observational study of 14 women with MS found creative art therapy was positively associated with self-esteem and self-efficacy[310]. Further evidence to support these findings is needed.

Interpretations & recommendations

Early evidence suggests music therapy may improve gait cadence, coordination, speed, mood and quality of life. Further evidence from larger populations, and clearly defined interventions, is required before any recommendations can be made.

Engagement with mental health practitioners

The most effective and recommended approach to managing stress and mental health is to seek professional support rather than attempting to resolve issues alone. Many mental health services are available, including clinic-based counselling, psychology, psychotherapy, and psychiatry services. These may require referral from a GP. A 2016 systematic review of 10 RCTs of psychotherapy-based interventions, with or without pharmacological elements, found significant improvement in depression in nine trials (standardised mean difference=-0.45); anxiety and quality of life were only assessed in two and three studies, respectively[311].

Interpretations & recommendations

Discuss mental health and stress with people living with MS and consider potential referrals for ongoing counselling or other mental health services as appropriate.

Barriers to engagement with stress-reducing activities and potential support strategies

People living with MS may face barriers to participating in stress-reducing activities, including:

- **Physical symptoms** which may limit participation
- **Emotional symptoms** which may reduce motivation
- **Accessibility** which may limit access to programs and facilities
- **Financial constraints** which may prohibit engagement with available services.

Healthcare practitioners may support people living with MS by:

1. **Developing personalised plans**: tailored stress-reduction plans that consider an individual's baseline stress levels, capabilities, preferences, and medical history
2. **Accessibility**: facilitate access by recommending online classes, home visits, and community resources
3. **Motivation**: provide emotional support, goal setting, and progress tracking
4. **Education**: provide information regarding potential benefits of stress-reducing activities and how to integrate them into daily routines
5. **Resources**: discuss financial assistance programs and low-cost or free resources
6. **Monitoring and support**: regularly monitor the effects of stress-reducing activities on the individual's physical and mental health. Provide ongoing support and adjustments to the intervention as needed, ensuring it remains effective and sustainable
7. **Collaborative care:** foster a multidisciplinary approach involving neurologists, physical therapists, psychologists, and other healthcare providers to ensure comprehensive care**.**

Conclusions

Managing stress is a crucial component of comprehensive care for people living with MS. Stress-reducing activities such as CBT and mindfulness-based therapies provide the most promising evidence for reducing depression, anxiety, and fatigue, and improving the quality of life for people living with MS. However, due to small population sizes and intervention variability, it is difficult to recommend specific practices, forms, or frequencies to achieve these benefits.

Evidence for other stress-reducing activities and their impact on MS-related outcomes remains insufficient for any formal recommendations. Further research is required, particularly in studies evaluating more specific and definable MS-related outcomes. Nonetheless, stress-reducing activities should be tailored to individual needs and preferences to maximise their potential benefits.

Lipid profiles

Summary

Lipids play an important role in energy and cellular structure, including the myelin sheath that insulates nerves[312,313].

While lipids are biologically essential, abnormal or excessive lipid accumulation in the blood, often due to dietary factors or genetic predisposition, can lead to dyslipidaemia. This condition is a major contributor to the development of cardiovascular diseases[314,315].

Blood tests commonly measure triglycerides (TG), total cholesterol (TC), and apolipoproteins, which bind and transport lipids such as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).

Dyslipidaemia is prevalent in both the general population and in people with MS, increasing with age. Evidence suggests that adverse lipid profiles in people with MS are associated with disability progression and increased MRI lesion burden. **The key message is that clinicians should regularly screen people with MS for dyslipidaemia**, following established guidelines for vascular and metabolic comorbidities for the general population. People with MS, particularly those with lipid-related comorbidities, should consult with their clinical care team, including their GP, to adopt evidence-based lifestyle changes such as optimal physical activity and diet.

Healthcare professionals are encouraged to proactively monitor lipid profiles of people with MS and consider pharmaceutical interventions, including statins where appropriate. Statins are well-tolerated and safe for people with MS when combined lifestyle-based interventions.

The link between lipid profiles and MS

Do people with MS have different lipid profiles compared to the general population?

Similar to the general population, dyslipidaemia is one of the most prevalent comorbidities in MS[316]. Prevalence increases with age[317] and MS disease duration[318]. Evidence on whether people with MS are more likely to have an adverse lipid profile compared to the general population is inconsistent. Some studies suggest a higher likelihood of adverse lipid profiles in MS [319–321], while others show no difference[322–324] or even a lower likelihood[324–326].

Are lipid profile variables associated with worse outcomes in people with MS?

Emerging evidence suggests that adverse lipid profiles may negatively impact clinical outcomes of MS[318,320–328] . The findings are summarised below:

- **Disability** - A systematic review[327] and several cross-sectional studies[329–331] have shown associations between elevated levels of TC, LDL-C, and apolipoprotein B (ApoB) with disability progression and inflammatory MRI lesions in MS. Multiple studies also link dyslipidaemia to worse disability outcomes[120,332,333,334(p20121),335], supporting a consensus that dyslipidaemia contributes to greater disability.
- **Relapse** - There is inconsistent evidence about the association between lipid profiles and relapse risk. Some studies suggest an association between adverse lipid profiles and increased relapse rates[336,337], while others did not find an association[332,336,338].
- **MRI related outcomes** - Observational studies have linked adverse serum lipid profiles to increased contrast-enhancing lesions, markers of inflammation and acute disease. Prospective longitudinal studies have shown that an increase in TC and LDL-C, and a decrease in HDL-C, are associated with the appearance of new MRI lesions[338,339]. Associations between apolipoproteins (e.g. ApoAI, ApoAII, ApoE, and Lpa) and MRI outcomes are less studied, with insufficient data for consensus[340,341]. One longitudinal study indicates that higher HDL-C levels may reduce brain atrophy and grey matter shrinkage in people with MS[341], warranting further long-term research.

Evidence is inconclusive regarding altered lipid profiles, arterial blood flow[342–345], and their relationship to MS. Limited studies show insufficient support for associations between adverse lipid profiles and cognitive decline[346,347] or fatigue[348]. Currently, there is no evidence that links lipid profiles to pain or overall quality of life in MS.

Information that needs clarifying

Do MS medications have beneficial or detrimental effects on lipid profile variables?

Studies on DMTs, including interferon-beta, glatiramer acetate, natalizumab, fingolimod and dimethyl fumarate, show no strong adverse effects on lipid levels. Some evidence suggests a small reduction in HDL-C[349], while others report beneficial effects such as increased HDL-C or reduced TC and LDL-C[350,351].

Should statins be used in people with MS?

Statins are widely used to manage cholesterol levels and prevent cardiovascular disease[352,353]. In people with MS, statins are well-tolerated[354(p011)] and safe, with adverse events comparable to those in control populations[355].

Statins also exhibit immunomodulatory properties. A 2021 systematic review of seven randomised trials involving atorvastatin and simvastatin, found no significant impact on MS disease progression, relapse rates, or MRI markers (new T2 or gadolinium enhanced lesions)[356]. However, a 24-month trial of high-dose (80mg/day) simvastatin monotherapy trial in people with secondary progressive MS (SPMS) showed promising effects on disability, whole-brain atrophy, physical quality of life, and some measures of cognitive function[357,358]. Further trials are required before recommending high-dose statins for MS management.

Recommendations for people with MS

Physical activity and dietary interventions can result in modest improvements in cholesterol levels in adults not at high cardiovascular risk[359]. While evidence specific to MS is limited, people with MS, especially those with dyslipidaemia, should consult their clinical care team for guidance. Recommendations within the physical activity and diet chapters in this document provide helpful strategies. Due to insufficient evidence for MS-specific recommendations, guidelines for the general public are advised, and the NHMRC grading method has not been applied.

Considerations for healthcare professionals

Dyslipidaemia is common in both the general population and people with MS and is associated with worse clinical outcomes (e.g. disability progression and MRI lesions). Healthcare professionals should regularly screen for and treat dyslipidaemia in people with MS. As no MS-specific guidelines exist, general screening and diagnosis protocols for vascular and metabolic comorbidities should be followed[360]. Management strategies should include both pharmaceutical options (e.g. statins, which are well-tolerated and safe in MS) and non-pharmaceutical interventions, such as diet and exercise therapy.

Medical conditions

in addition to MS (comorbidities)

Summary

Comorbidities frequently co-occur with MS, often predating its diagnosis. Physical and mental health conditions are more common in people with MS than in the general population[316,361–366], and their presence is associated with reduced health-related quality of life[367–370]. Comorbidities also adversely affect MS outcomes, including MS relapses, disability progression, severity of symptoms such as pain and fatigue, MRI results, employment, hospitalisation and mortality[121,311,337,371–380].

The overall key message is that the early detection and effective management of comorbidities in MS are essential. Both people with MS and healthcare professionals should actively address these conditions. Prevention and self-management strategies, such as maintaining a healthy diet, smoking cessation, and engaging in regular physical activity, are beneficial when supported by a multidisciplinary care team.

For evidence-based guidance, please refer to the NICE guidelines Multimorbidity: clinical assessment and management[381] and the recent review on managing comorbidities in MS[360].

Comorbidities and MS

What is the prevalence of comorbidities in people with MS?

Eight systematic reviews[316,362,363,363–366,382] highlight that most physical and mental health comorbidities occur more frequently in people with MS than in the general population, despite variations in study designs, populations, and reporting methods.

Key findings include a higher prevalence of gastrointestinal, musculoskeletal, cardiovascular and respiratory comorbidities in people with MS[363,382]. Specific conditions more common in MS include:

- **Neurological and movement disorders:** Epilepsy, seizures, sleep disorders[365], and Parkinson's disease[383]
- **Psychiatric comorbidities:** Depression, anxiety, and bipolar disorder[366]
- **Chronic cardio-metabolic disorders:** Hypertension, hyperlipidaemia, diabetes[316], peripheral vascular disease[363], congestive heart failure[384,385], and stroke[316,319,384,385]
- **Autoimmune disorders:** Various conditions[316,364], fibromyalgia, and irritable bowel disease
- **Other conditions:** Vision problems.

Prevalence of comorbidities varies by sex[322]. Men with MS have higher rates of hypertension, diabetes, epilepsy, depression, and anxiety compared to women with MS[322].

Data from the AMSLS indicate that comorbidities are already common at MS symptom onset, with 65.2% of participants reporting at least one comorbidity, and 76.3% reporting multimorbidity (two or more comorbidities)[386]. The prevalence of certain comorbidities increased significantly after MS symptom onset, including depression (+27%), anxiety (+23%), hypertension (+22%), high cholesterol (+16%), osteoarthritis (+17%), eye diseases (+12%), cancer (+10%) and osteoporosis (+11%).

Are comorbidities independently associated with worse health outcomes in people with MS?

Evidence from cross-sectional and longitudinal studies shows that comorbidities significantly lower quality of life in people with MS compared to those without comorbidities[367–370,387,388]. AMSLS data identify mental-health disorders as having the largest impact on overall health-related quality of life, followed by musculoskeletal disorders[389].

The specific effects of comorbidities on MS-related outcomes and symptoms are summarised below.

What is the link between comorbidities and disease progression in people with MS?

- **Relapse:** Observational studies suggest that people with MS and multiple comorbidities experience higher relapse rates compared to those without comorbidities[121,332,337,390]. Rheumatoid arthritis, anaemia[332,337,390], and a higher cardiovascular risk (e.g. a 31% increased relapse risk per 1-point increase in Framingham score[391]) are associated with relapses. Associations with migraine[337,390] and hyperlipidaemia are mixed[332,337,338].
- **Disability/disability progression:** Cross-sectional and prospective studies show that comorbidities increase disability in early MS and accelerate progression[121,333,371,372,391–393]. MS-related and comorbidity-related disability are often indistinguishable.
- **MRI-related outcomes:** A recent review of studies of comorbidity and radiological outcomes from 2015-2022 linked vascular comorbidities to worse MRI measures, though findings vary by specific conditions[360]. Migraine and dyslipidaemia were the most studied conditions[360,394]. It remains unclear whether these MRI changes are MS-specific or comorbidity-related.
- **Symptom severity:** Observational studies have consistently shown that comorbidities exacerbate symptom severity in MS. Examples include:
    - » Pain: depression, arthritis and migraines reported a higher severity of pain[377]
    - » Fatigue: depression and cancer had higher fatigue severity[311,377]
    - » Physical impairments: osteoporosis and anxiety reported worsening of pain[378] coronary artery disease reported more weakness and imbalances[377]
    - » chronic obstructive pulmonary disease (COPD) reported worsening of fatigue[311,377]
    - » anxiety, irritable bowel syndrome (IBS), depression and migraine independently were at increased risk of fatigue[311,377].

AMSLS data indicate mental health disorders (particularly depression) significantly impact pain, fatigue, sexual dysfunction, and cognitive and sensory problems. Musculoskeletal disorders (particularly osteoporosis) mostly affected mobility, balance, bladder and bowel problems, and spasticity[395].

- **Employment outcomes:** Comorbidities adversely affect employment outcomes in people with MS, contributing to productivity loss and reduced workforce participation[379,396-400]. Mental health conditions, including anxiety and depression, drive absenteeism and occupational difficulties[398-400].
- **DMT initiation and choice:** A single retrospective cohort study found higher comorbidity burdens reduced DMT initiation likelihood, particularly with ischaemic heart disease and anxiety. Depression was linked to faster DMT initiation, while comorbidities did not affect initial DMT choice[372,401].
- **Mortality:** Comorbidities contribute to higher mortality risk in MS[402-404]. One large prospective study showed that at least 50% of deaths in people with MS were due to comorbidities. Specific conditions like psychiatric disorders, diabetes, cancer, and Parkinson's disease were associated with increased mortality[403]. Another large population-based study demonstrated mortality risk increased with higher comorbidity burden[404].
- **Hospitalisation:** Few observational studies[380,397,405,406] have looked at hospitalisation in people with MS in relation to comorbidities. Studies show comorbidities increase rates of all-cause and non-MS-related hospitalisations[380,405].

Recommendations for people with MS

Some comorbidities can be prevented or improved through a healthy lifestyle. People with MS are encouraged to adopt positive health behaviours, including a healthy diet, quitting smoking and engaging in regular physical activity, in consultation with their medical team.

Early identification and management of comorbidities are essential. People with MS should attend regular medical check-ups and proactively inform clinicians about any new or worsening symptoms between visits. As current evidence is insufficient to provide MS-specific recommendations, general public health guidelines have been recommended by the experts. Therefore, the NHMRC method for grading evidence has not been applied.

Considerations for healthcare professionals

The key message is that the timely recognition of comorbidities in people with MS is critical for achieving optimal health outcomes. Early screening is essential, as comorbidities often accumulate rapidly and worsen health outcomes early in the disease course in people with MS. GPs should routinely screen for prevalent comorbidities, such as mental health conditions (depression and anxiety), musculoskeletal disorders, and cardiovascular disorders, ideally during every clinic visit.

While evidence on effective models of care for comorbidity management in MS is limited, collaborative models of care, particularly in relation to mental health outcomes, show promise[360,394,407-409]. Interdisciplinary collaboration between clinicians and allied health professionals is essential to ensure comprehensive management of comorbidities and to provide tailored, evidence-based information to people with MS.

For guidance, refer to the NICE guidelines: *Multimorbidity: clinical assessment and management*[381].

These emphasise:

1. Discussing a tailored approach to care to improve quality of life.
2. Assessing disease and treatment burden.
3. Understand and establish patient goals, values and priorities.
4. Review medicines and other treatments considering evidence of individual benefits, harms, and patient priorities.
5. Agree on individualised management plan with the patient.

Additionally, there are also specific guidelines on:

1. Osteoporosis in MS[410]
2. The assessment and management of psychiatric disorders in MS[411,412].

Gut health and microbiome

Summary

The human microbiome refers to the complex and diverse populations of microbial cells, primarily bacteria, that naturally live within the body[413]. These microbial cells that live in the gut are an area of increasing interest due to the emerging evidence on their role in the maintenance of overall human health and the development and progression of some diseases (e.g. inflammatory bowel disease and depression)[414]. However, differences in the gut microbiome are seen even within people who are considered healthy and, therefore, more research is required in this area[415]. **While there is emerging evidence to suggest that the gut microbiome may influence the processes involved in MS, at this stage, there is not enough evidence to recommend any of the methods which are advocated for changing or improving the microbiome of people living with MS or their claimed benefits on MS outcomes.**

The overall message from the experts is that while there is evidence to suggest that the microbiomes of people living with MS may be different from healthy populations, there is currently insufficient scientific evidence to recommend any interventions or techniques targeting the microbiome for people living with MS.

The link between the gut microbiome and MS

There is an increasing scientific understanding of the ability of our gut microbiome to influence our immune system and overall health[416] with a recent study mapping specific profiles to disease types including MS[417]. As MS is an immune-mediated disease, the gut microbiome has been studied in people living with MS, and recent evidence has revealed there are significant differences in the composition and function of bacteria within the gut of people living with MS, compared with people who do not have MS[418]. This finding was upheld consistently in people with different genetics, ages and genders[419,420]. Studies in the laboratory setting have also shown that transplanting microbiome samples from people living with MS to laboratory (animal) models without evidence of MS, resulted in changes to the immune system similar to that seen in MS, i.e. an autoimmune basis[418,419]. This strengthens the evidence for the role that the gut microbiome plays for MS. However, more research is required to understand what a healthy microbiome looks like, as there are substantial variations seen within people who are considered healthy[415]. Therefore, more research is needed before any recommendations can be considered for MS.

Several methods are being investigated for their ability to change or improve the microbiome of people living with MS, with the aim of improving MS symptoms and outcomes. Due to the interest in the MS community, some of these interventions are discussed below, although the scientific evidence for these areas is very limited.

Faecal microbiota transplant

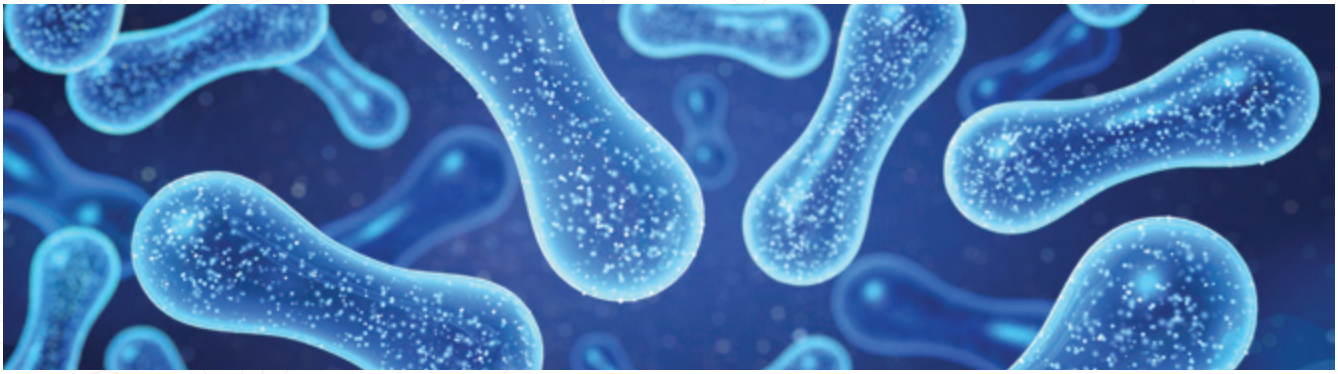
Faecal microbiota transplant (FMT) is a process whereby a microbiota sample from a healthy donor is transplanted into another person through an infusion in the colon, or delivery through the upper gastrointestinal tract[421]. This therapy has been successfully used to treat C. difficile infections. Due to the emerging role of the microbiome in several chronic diseases, including MS, the use of FMT as a treatment option is of growing interest. Excluding preliminary case report studies[422], there is only one pilot clinical trial of FMT in MS[423]. This trial did not confirm if FMT is a suitable therapy for people living with MS due to limitations in the study design and a small sample size. There are also potential safety concerns of FMT including infection and death[424], and the long-term effects are not yet known. Due to the lack of supporting evidence and possible associated risks, experts cannot recommend this therapy for the management of MS.

Helminth therapy

Helminth therapy involves deliberately exposing someone's gastrointestinal tract to a helminth, a parasitic worm (e.g. hookworms). This therapy is *theorised* to alter the immune response and influence MS[425,426]. It is thought that the immune response to the parasite can dampen the autoimmune response of MS[427,428]. Limited small studies have supported the safety of helminth therapy in the short term, and others have shown improvements in immune markers in people with MS[426]. However, one small study of longer duration (90 months) found people living with MS undergoing treatment had severe gastrointestinal symptoms[429]. While the strength of the evidence has increased for some areas such as Crohn's disease[430], based on the limited evidence, helminth therapy cannot be recommended for people living with MS.

Probiotic supplements

Probiotics contain live microorganisms that may be beneficial for people when administered in adequate amounts[431]. Probiotics are available in the form of supplements (capsules) and in some foods (e.g. fermented foods such as yoghurt and sauerkraut). To date, five clinical trials have investigated the use of probiotics in MS[432–437]. These trials have reported improvements in MS including the reduction of some markers of inflammation, and improvements in pain, fatigue, depression, mood and quality of life. However, further studies are required to confirm these results in larger samples with MS over longer periods of time.



Information that needs clarifying

What is the evidence for treating the microbiome with interventions or products on the market?

There is a wide variation between individuals on what a healthy gut microbiome looks like and therefore, products and services that are advertised as aiming to restore the microbiome of people living with MS are not currently supported by scientific evidence.

Recommendations for people with MS

There is insufficient scientific evidence to make specific recommendations regarding interventions such as FMT, helminth therapy or probiotics for people living with MS to improve their disease outcomes.

The best way to achieve a healthier gut microbiome for people living with MS is the same as that for the general population. This is to follow the Australian Dietary Guidelines (as recommended in the previous sections) or to follow traditional dietary patterns (e.g. the Mediterranean, Norwegian or Japanese diet) that emphasise the consumption of plant-based foods such as fruits, vegetables, wholegrains, legumes, nuts and seeds. Following plant-based eating patterns been demonstrated to improve beneficial gut bacteria[435,436,438,439]. The foods in these patterns of eating contain nutrients that can benefit the microbiota such as dietary fibre (i.e. soluble, insoluble, resistant starch), polyphenols, and omega-3 fatty acids. By contrast, regular consumption of foods that are high in saturated fat, salt, and sugar appear to have a negative effect on the microbiota profile[440]. Research is also starting to address the concept of xenobiotics, or the impact of synthetic components related to food from agriculture, industrialisation or pollution on the microbiome. Emerging research suggest that these components may result in a remodelling of microbiobal groups[441].

Other lifestyle factors such as physical activity[442], smoking[443], stress[444] and drinking alcohol[445] also influence the gut microbiome. The effects of microbiome changes on MS are currently unclear and improving the diet by consuming, fibre-rich foods, increasing physical activity, managing stress and not smoking are recommended to maintain overall good health in people living with MS.

As the evidence is insufficient to make recommendations that are specific for people living with MS, and guidelines that are applicable to the general public have been recommended by the experts. The NHMRC method for grading evidence has not been applied.

Considerations for healthcare professionals

There is currently insufficient clinical data to recommend the use of therapies that target the microbiome in people living with MS. Probiotic and fibre supplements appear to be generally well-tolerated and have potential positive outcomes, although some therapies such as FMT and helminth therapy have potential risks associated with their use. In contrast, healthy dietary interventions appear to beneficially influence the gut microbiome without severe side effects. Therefore, referrals to an Accredited Practising Dietitian could be a way towards improving adherence to healthy dietary recommendations, which will have positive effects on the microbiome and overall health of people living with MS.

Vitamin D and sunlight

Summary

While observational studies have suggested links between vitamin D and MS risk[446,447] and progression, as well as of sun exposure and these outcomes, current evidence does not support either vitamin D supplementation or increasing sun exposure as ways to reduce the risk or progression of MS. Experts recommend that people with MS follow the vitamin D recommendations of the NHMRC and the Ministry of Health, New Zealand for the general public[448], and the advice for the general public about sun exposure for maintaining healthy vitamin D levels as recommended by a multi-organisational working group of 13 organisations, universities, and hospitals, including Cancer Council Australia and MS Australia [449].

The links between vitamin D, sunlight, and MS

The links between vitamin D and sunlight are well established, with ultraviolet (UV) radiation exposure from sunlight being essential for maintaining adequate vitamin D levels that are critical for overall health. Vitamin D plays many functions in the human body, but its major role is in the regulation of calcium homeostasis and maintaining bone health. In addition to this, and of relevance for MS, is its role in modulating the immune response[450]. It exists in two forms: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol)[451]. While vitamin D2 is available, both from dietary sources and supplements, vitamin D3 (cholecalciferol) is the predominant form available in most dietary supplements and is the major form consumed from animal sources and the form produced from sun exposure.

The primary source of vitamin D3 is UV exposure (UV index 3 or higher), with additional contributions from dietary sources like oily fish and supplements. In addition, vitamin D2 can be obtained from some UV-irradiated funghi and some supplements. While prescribed vitamin D injections can address acute vitamin D deficiencies, this is rarely needed[452]. In the Australian general population, the contribution of dietary intake to vitamin D is generally far less than that obtained by sun exposure[453]. A healthy diet alone will not achieve sufficient levels[454]. Vitamin D is converted in the liver to its circulating form, calcifediol (25(OH)D), which is measured to assess vitamin D levels. It is then activated in the body as calcitriol ($1,25(OH)_2D$)[455]. This active form of vitamin D interacts with the immune system and can reduce inflammatory immune responses[455], likely underlying its potential link with MS.

Additionally, UV exposure itself appears to influence immune function independent of vitamin D levels[456], including direct modulation of the activities of local immune system cells, particularly dendritic cells, most immediately those residing in the skin's inner layers. This UV exposure can lead directly to the inactivation of inflammatory dendritic cells, as well as to the development of anti-inflammatory tolerogenic dendritic cells. These cells can then interact with circulating immune cells, particularly T-lymphocytes, that can have systemic effects as these T-lymphocytes can have potent impacts upon the subsequent responsiveness of these cells to other antigen exposures[457,458].

What is the link between vitamin D and the risk of MS?

Several observational studies have indicated a relationship between vitamin D levels and/or vitamin D intake with MS risk and substantiated in systematic reviews[447]. Genetic risk variants in vitamin D metabolism and function, including the vitamin D binding protein, receptor, and cytochrome P450 enzymes, have also been associated with MS development[459,460]. Moreover, these risk variants have been utilised in Mendelian randomisation studies which have indicated a causal relationship of lower vitamin D with MS risk[461,462].

Until recently there had not been any substantive clinical trials assessing the effects of vitamin D supplementation on the risk of MS onset. In 2023, however, results from the Vitamin D MS Prevention Trial (PrevANZ), a world-first clinical trial funded by MS Australia, were published, PrevANZ assessed whether supplementation with vitamin D after the first attack suggestive of MS clinically isolated syndrome (CIS), could reduce the development of MS. In this trial, investigators randomised 199 eligible participants (presenting with a first clinical episode of CNS demyelination plus MRI evidence of at least 3 lesions, in keeping with contemporary diagnostic criteria[463] to three potential doses of cholecalciferol (1,000IU/day, 5,000IU/day, 10,000IU/day) or placebo, and followed them for up to 48 weeks to assess treatment effects on risk of conversion to diagnosed MS. This study showed no consistent or significant evidence of a treatment effect from vitamin D supplementation and were no different across the three vitamin D supplement doses compared to placebo (hazard ratio (HR)=0.87, HR=1.37, HR=1.28, respectively)[464]. Results did not differ materially on adjustment for factors like age, sex, participant location/ latitude, skin colour, season, and body mass index (BMI), nor did subgroup analyses by latitude or baseline vitamin D deficiency show any material or significant differences.

The D-Lay MS trial, a multicentre clinical trial of 316 patients with CIS, presentations substantiated by brain MRI (with or without additional spinal MRI) in line with the contemporary diagnostic criteria[465, 466] recruited across 36 MS clinics around France, evaluated 100,000IU/fortnight cholecalciferol vs placebo, followed over 24 months[467]. Unlike the PrevANZ trial, D-Lay MS did show a significant treatment effect of vitamin D supplementation versus its primary outcomes, (clinical and/or MRI disease activity) including a 34% reduction in clinical/MRI disease activity. However, when assessed separately, only MRI outcomes showed a significant benefit; relapse rates, disability progression, and patient-reported outcomes did not differ between groups. Notably, the treatment effect was more pronounced among participants who were vitamin D deficient at baseline, aligning with the understanding that while improving vitamin D deficiency is beneficial, there is not additive benefit of moving from replete to supra-replete[468]. Another important consideration for the D-Lay MS results is that most of the clinical/MRI disease activity occurred early in the trial – roughly in the first three months – while in the latter year of the study the failure trajectories were roughly parallel between groups. The interpretation of these dynamics requires interrogation of these data and further studies are needed to better understand whether and how vitamin D supplementation modulates clinical activity in early MS.

Several methodological and sample-related differences may explain the contrasting results between D-Lay MS and PrevANZ. The maximum daily dose in PrevANZ was 10,000 IU, compared to 100,000 IU every fortnight in D-Lay MS (averaging 7,143 IU/day). It is possible that higher, less frequent dosing has distinct biological or clinical effects, though this remains to be clarified. Although both trials had similar overall sample sizes (199 in PrevANZ vs. 303 analysed in D-Lay MS), PrevANZ used a four-arm design, meaning only 49 participants received the highest dose. In contrast, 157 participants in D-Lay MS received the full 100,000 IU/fortnight regimen. Follow-up periods also differed substantially, with 48 weeks in PrevANZ versus 24 months in D-Lay MS. Based on these two clinical trials and the low prevalence of vitamin D deficiency in the Australian and New Zealand populations, there is currently no strong evidence that people who have had a CIS should receive high dose vitamin D supplementation with the aim to reduce their risk of MS conversion. However, vitamin D levels should be checked and vitamin D deficiency treated, as it is for the general population, as there may be a moderate benefit to treating those who are vitamin D deplete at CIS.

What is the link between vitamin D levels and disease progression in people with MS?

Multiple observational studies have been undertaken assessing the relationships between vitamin D levels and vitamin D intake measures with clinical progression outcomes in MS. Systematic reviews aggregating these results have shown that serum vitamin D levels are inversely associated with relapse and with MRI outcomes[469].

However, there are many confounders to these associations and many published associations are confounded by reverse causality that is vitamin D levels are low because of the condition being studied rather than associated with the risk of progression of that condition (MS). For example,those with greater levels of MS disability are less physically active, spend less time outdoors, have higher body mass index, and are more likely to smoke, all associated with lower serum vitamin D levels.

Over the past two decades, several small clinical trials have evaluated the effects of different types of vitamin D supplementation at various doses, either alone or in combination with established MS medications such as interferon-beta, to assess the effects on MS progression, including relapses, MRI activity, disability progression, and other elements of MS clinical course and/or symptoms such as fatigue[470–475]. Meta-analyses have consistently concluded that there are no significant benefits of vitamin D supplementation on the risk of relapse[476], disability progression[476], MRI outcomes[477], or other outcomes like fatigue[478], in people with MS. While study limitations such as sample size, follow-up duration, insufficient vitamin D supplementation dose, limit interpretation of these trials, as described previously[479–481], the collective evidence is that vitamin D supplementation does not improve measured clinical outcomes in people with MS.

What is the link between sunlight and the risk of MS?

Studies indicate that people diagnosed with MS have significantly lower sunlight or UV exposure compared to those without MS. These findings are consistent across varying timeframes before the onset of clinical signs of MS, including three years prior to diagnosis, periods of childhood, and early adulthood[482–485]. as well as in a recent study of paediatric-onset MS[486] However, across all these studies, results were inconsistent as to what the optimal doses and life periods of exposure of sunlight or UV exposure were for realising benefits upon MS risk or progression outcomes. This may be attributable in some part to the long periods of recall required when asking people about their sun-related behaviours.

Even with assistive techniques like life calendars with key life events (starting school, getting drivers licence, etc.) to aid in recall[487], there are intrinsic limitations and biases that come with recalling behaviours like hours per day in the sun during childhood. The most ideal approach for assessing these relationships is a prospective study design, wherein exposures are measured and recorded at the time (e.g. childhood, adolescence, early adulthood) and then associations with subsequent outcomes evaluated. Such measurements of sun-related behaviours are not available in any studies at present, and in lieu of this, optimising methods for retrospective assessment of sun exposure, perhaps in line with the approaches developed for retrospective estimates of adiposity[114], are the best models available to enable assessment of early-life sun exposure with MS risk and progression outcomes. In the meantime, the best recommendations regarding sun exposure are to follow the standard guidelines for safe sun exposure, with a goal to minimising cancer-related deleterious effects.

In terms of studies of UV-based interventions, there has been a single clinical trial looking at a UV exposure-based intervention, the PhoCIS trial, which randomised 20 CIS participants to narrowband UVB phototherapy versus untreated (all were supplemented with sufficient vitamin D to increase their serum vitamin D levels to 80 nmol/L). While the intervention group showed a 30% lower frequency of main study outcome, conversion to diagnosed MS over 12 months' follow-up compared to the control arm, this difference did not reach statistical significance, due to the small sample size[488]. The phototherapy intervention also showed effects on immune system cell proportions, including changes that may indicate a shift in the immune cell responsiveness to inflammatory triggers[489]. Unfortunately, as no subsequent larger studies have been conducted which may be more statistically powered to assess these treatment effects, no firm conclusions can be drawn.

The paucity of studies of phototherapy as an intervention to reduce MS conversion among CIS patients precludes any recommendations for sun exposure-based treatments in preventing MS.

What are the links between sunlight and the progression of MS?

A limited number of studies have explored the relationship between sun exposure and MS disease progression[490–492]. One study found that higher sun exposure before a first demyelinating event (FDE) was associated with reduced progression to clinically definite MS[485]. Additionally, increased sun exposure during the 5-year follow-up after their FDE showed reduced conversion to MS, and those who were diagnosed with MS showed reduced relapse rates. A small pilot RCT of sun exposure as an intervention in people with MS was reported in 2019, the main analysis comparing 6 people with MS randomised to a narrow-band UVB (300-310nm) treatment (3 times weekly for 8 weeks) vs a sham light control treatment[493]. Although this study showed that the UVB intervention significantly increased serum vitamin D levels, no impacts upon clinical outcomes (ambulatory disability, cognitive performance, mood) were seen. No subsequent larger clinical trials have been reported which assessed sun exposure/UV therapy as an intervention to improve clinical outcomes in people with MS. This research gap highlights the need for further studies to determine whether sun/UV-based interventions may have utility in MS, as well as informing risk/benefit considerations of sun exposure benefits and skin cancer risk.

Are there any benefits of vitamin D or sun exposure to other clinical aspects of MS?

Few studies have examined sunlight's effects on MS symptoms, with most focusing on vitamin D. Observational studies suggest relationships between vitamin D supplementation and improvements in symptoms such as depression, fatigue[494,495], and quality of

life[496,497]. A recent meta-analysis of five clinical trials of vitamin D supplementation as an intervention against fatigue found a significant aggregate reduction in fatigue in the treatment groups[478]. However, the trials had small sample sizes and significant variability, particularly in dosing, warranting further research on vitamin D supplementation in MS fatigue. Accordingly, this suggestive but preliminary evidence is insufficient to justify recommending vitamin D supplementation for improvement of these outcomes.

Information that needs clarifying/further investigation before consideration for practice

Why are there disparities between the vitamin D and sun exposure studies?

Sun exposure and vitamin D are inescapably intertwined: as discussed earlier, sun exposure is the predominant source of vitamin D in people in Australia, as well as people with MS in Australia. It thus stands to reason that associations, both in observational studies and clinical trials, should show comparable effects from both exposure types, if only as one acting via the other. However, in fact there is appreciable heterogeneity in the studies of sun exposure and vitamin D. There are many more studies of vitamin D than sun exposure, both observational and interventional, and this likely reflects differences in the ease of measurement of serum vitamin D levels and administration of vitamin D supplement-based interventions, in contrast to the complexities of sun exposure recall and implementation of UV-based interventions. This greater volume of studies of vitamin D and potentially more accurate and systematic measures of vitamin D exposures (mostly using serum 25(OH)D)) contrasts with the relative paucity of sun/UV studies which have a remarkable heterogeneity in the modes by which sun exposure is queried[498], ranging from querying frequency/duration by season[483] to more diverse and multi-item sun measures[499]. That there are thus differences in the findings for these two related but distinct parameters is perhaps not as surprising as it might first seem. That said, there is still uncertainty about whether both vitamin D and sun exposure represent distinct and independent factors in MS. Work in observational studies in Australia has indicated that sun exposure and vitamin D have independent associations with MS[483], and the vitamin D supplementation clinical trials, particularly the D-Lay MS trial[467], suggest vitamin D may act independently. However, the extent to which sun exposure realises impacts upon MS independent of increasing vitamin D levels is uncertain, even despite UV having vitamin D-independent immune-modulating effects[456]. Further studies are needed and until greater clarity is achieved, neither can be recommended for the prevention or treatment of MS.

Is vitamin D supplementation safe?

Initially, there were concerns that high-dose vitamin D supplementation could cause hypercalcaemia (high calcium) and hyperphosphataemia (high phosphate), leading to significant and sometimes serious symptoms such as nausea, vomiting and gastrointestinal issues, as well as less frequent but more severe outcomes like renal calculi (kidney stones) and cardiovascular complications[500]. However, these effects are rare and typically associated with grossly excessive doses, and even at levels as high as 300nmol/L (6-times the threshold for vitamin D sufficiency) adverse effects were rare[501]. Most studies, including one involving doses up to 280,000 IU/week over 28 weeks, have found vitamin D supplementation to be safe, with no adverse effects on calcium or phosphate levels[502]. A comprehensive review of 52 clinical trials of vitamin D supplementation confirmed no impact on all-cause mortality, further supporting the safety of supplementation[503]. Importantly, aside from the potential impacts of sun exposure on skin cancer risk, there is no risk of excessive sun exposure leading to excessive vitamin D levels. The vitamin D photosynthesis pathway is inherently self-limiting – beyond a minimal erythemal dose of sun/UVR, the conversion of precursor sterols into pre-vitamin D plateaus[452].

While sun exposure poses a potential skin cancer risk[504], we would suggest it is in general a necessity as a source of vitamin D in most people in Australia. Nonetheless, routine testing of vitamin D is recommended for people living with MS who are at risk of deficiency. When vitamin D intake and sunlight exposure are both low, and serum levels indicate insufficiency (<50nmol/L) or significant deficiency (<25nmol/L), vitamin D supplementation is appropriate[454]. In all such things, people should consult with their medical practitioner before making any significant changes in use of supplements or other lifestyle changes.

Recommendations for people with MS

Currently, there is limited evidence to support high-dose vitamin D supplementation or sunlight exposure as interventions to either prevent MS onset or modulate disease progression in people living with MS. Instead, people with MS or those with CIS are recommended to follow the recommendations regarding vitamin D and sun exposure for the general public[448,449].

These guidelines, which are summarised below, aim to maintain healthy vitamin D levels and adequate sun exposure and align with similar national guidelines for people with MS[505,506]. Importantly, vitamin D requirements vary depending on factors such as sex, age, and location, as well as pregnancy status and other significant health conditions. In all such things, consultation with a medical practitioner before making any significant changes in use of supplements or other lifestyle changes is appropriate.

Vitamin D

TABLE 2: VITAMIN D RECOMMENDED INTAKE

ADEQUATE INTAKE FOR THE GENERAL PUBLIC	mg/DAY	DOSE (INTERNATIONAL UNITS)/DAY
For infants and children	5	200
Adults aged 19-50	5	200
Adults 50-70	10	400
Adults over 70	15	600
Pregnancy and lactation 14-50	5	200
UPPER LEVEL OF INTAKE FOR THE GENERAL PUBLIC	**MG/DAY**	**DOSE (INTERNATIONAL UNITS)/DAY**
Infants (0-12 months)	25	1,000
Children over 12 months old, and adults (including women during pregnancy and lactation)	80	3,200

Importantly, it is recommended that people with MS consult with their medical practitioner prior to starting vitamin D supplementation, including potentially having their vitamin D levels measured prior to commencing supplementation.

Sun exposure

Adequate levels of sun exposure vary depending on their latitude, the time of the year, and their skin colour. As per the conclusions of the multiorganisational working group about sun exposure recommendations for Australia and New Zealand[449], we recommend:

Those with dark brown to black skin (never burns) and dark brown skin (rarely burns):

- Routine sunscreen application is not needed. However, if outdoors for 2+ hours and UV index is 3+, consider sun protection/reduction.

Those with moderate brown skin (burns minimally, tans easily) to very fair, pale white skin (always burns, never tans). When the UV index is forecast to reach 3 or above: apply sunscreen as part of morning routine and if the UV index is 3 or above, use the Five SunSmart Steps:

- Slip on covering clothing
- Slop on SPF30+ broad-spectrum sunscreen
- Slap on hat
- Seek shade
- Slide on sunglasses[449]

All skin types are advised to seek sun protection such as covered clothing, sunscreen, a hat and sunglasses or to seek shade if outdoors for more than a few minutes in mid-August to the end of April, due to the UV levels usually being high.

As the evidence base is insufficient to make recommendations that are specific for people with MS, and guidelines that are applicable to the general public have been recommended by the experts, the NHMRC method for grading evidence has not been applied.

Considerations for healthcare professionals

There has been an increasing interest in the impacts of sun exposure and vitamin D on MS risk and progression, which has led to some people with MS taking vitamin D supplements and increasing their sun exposure, hoping for disease-modifying benefits. However, the optimal vitamin D level and method of achieving it remain undefined.

The US National Institutes of Health defines vitamin D sufficiency as a serum level of >50 nmol/L, a cutoff that aligns with recommendations in Australia and New Zealand[507,508]. Accordingly, vitamin D supplementation is only recommended among people below this threshold.

In MS, some experts suggest aiming for summer-like levels (80–100 nmol/L) year-round, achievable with supplementation of up to 5,000 IU/day in winter and 2,000 IU/day in summer. Regular measurement of serum levels of vitamin D is not recommended in many countries, including Australia. Maintaining levels below 120 nmol/L is advisable, though evidence from well-conducted clinical studies is limited. As with any vitamin supplementation, excessive intake can be harmful, as the body tightly regulates vitamin levels, and over-supplementation may be as detrimental as deficiency.

Dietary supplements

Summary

Dietary supplements are becoming increasingly popular among people living with MS. However, evidence supporting their efficacy and benefits in people living with MS varies. General dietary recommendations, such as those outlined in the Australian Dietary Guidelines, remain the most reliable approach to support nutrition for overall health and well-being. It is essential for people living with MS to consult their healthcare team before initiating any new supplements.

Supplements in MS Management

Dietary supplements, sometimes referred to as nutraceuticals ("pharmaceutical" and "nutrition," referring to natural compounds with potential therapeutic effects), encompass the various vitamins, minerals, and other bioactive compounds consumed in addition to those in regular diets. Many people living with MS use these supplements, with one study reporting that 73% had taken over-the-counter vitamins or dietary supplements either in the past or were currently taking supplements, in an attempt to improve their MS symptoms[509]. Since the supplements outlined in this chapter are accessible in Australia without a prescription, their use is not always monitored by healthcare professionals, potentially leaving people living with MS at risk of adverse effects and/or interactions with their DMTs and other treatments.

This chapter aims to provide guidance for clinicians and other healthcare professionals regarding the evidence-based research findings for supplement usage by people living with MS. While there is an increasing diversity of supplements available, including vitamins and minerals and a multitude of herbal supplements, this chapter focuses on those supplements that have been researched in people living with MS, namely:

- Alpha-lipoic acid
- Biotin (vitamin B7)
- Coenzyme Q10
- Curcumin
- Ginkgo biloba
- Inosine
- Melatonin
- Omega-3 and omega-6 fatty acids
- Probiotics
- Vitamin A and carotenoids

Note – vitamin D, which is of significant interest and frequently used by people living with MS, is discussed in its own chapter in this Guide.

While some of these supplements have shown evidence of potential benefits to some MS outcomes, the evidence is inconsistent, as highlighted in a systematic review by Marx *et al*[510]. This chapter examines the evidence for selected supplements and provides recommendations for their use within the MS community.

Alpha-Lipoic Acid

Alpha-lipoic acid is found in certain foods such as spinach and organ meats such as liver. It is a potent antioxidant and anti-inflammatory compound that has been suggested as a potential therapeutic agent for improving neurological function, particularly in people living with MS[511,512].

A RCT by Khalili et al., examined a daily intake of 1,200 mg/day of alpha-lipoic acid in 52 people living with MS over a 12-week period[511]. Participants receiving alpha-lipoic acid daily showed significant increases in serum antioxidant capacity and significant reductions in their inflammatory cytokines (IFN-gamma, TGF-beta, and IL-4) compared to the control group. However, no significant changes were observed in EDSS scores or other cytokines.

Although this is the only RCT that has examined alpha-lipoic acid in people living with MS, alpha-lipoic acid supplementation has been shown to be effective in preventing and treating experimental autoimmune encephalomyelitis (EAE), the animal model of MS[513]. Currently, alpha-lipoic acid supplementation is being studied in two large multi-stage RCTs: the UK-based OCTOPUS study and the Australia-based PLATYPUS study[514]. These trials will investigate the efficacy and safety of multiple interventions simultaneously, including alpha-lipoic acid, with preliminary results expected in 2025. Participants in such trials will be closely monitored, including checks on kidney function, to ensure safety.

Based on current evidence, which is currently lacking in humans pending results from the OCTOPUS and PLATYPUS trials, alpha-lipoic acid supplementation is not recommended to people living with MSto improve their MS.

Biotin (Vitamin B7)

Biotin, or vitamin B7, is found in various foods, including eggs, organ meats, nuts, seeds, cow's milk, and certain vegetables. Biotin plays a crucial role in the synthesis of myelin. High-dose biotin (HDB) involves consuming significantly more biotin than what is typically obtained through diet, (often 100-300 mg daily) which is up to 10,000 times more biotin than the recommended daily intake. Several RCTs have investigated HDB for its safety and effectiveness safety in people living with MS.

A pilot RCT by Tourbah et al. included 154 MS people living with MS with moderate to severe disability who received either 300 mg/day of MD1003 (a high-dose pharmaceutical-grade biotin formulation, taken as 100 mg three times daily) for 12 months or a placebo, followed by 12 months of MD1003 for all participants[515]. This trial found that 13% of participants who received 300mg/day of MD1003 in the first 12-month period showed reduced disability over follow-up compared to none in the placebo group. In contrast, a large international clinical trial by Cree et al. involving 642 people living with MS recruited at 90 MS clinics across 13 countries, found that 300 mg biotin supplementation (100 mg, three times daily) did not significantly affect disability or walking speed in those with progressive MS[516].

Another trial by Tourbah et al. investigated biotin's effects on for the treatment of chronic visual loss related to optic neuritis in MS. This randomised, double-blind study involved 93 people living with MS, who were assigned to either biotin supplementation or placebo[517]. This study found no significant benefits in the biotin supplementation group compared to placebo.

The absence of consistent positive outcomes, especially in large, international clinical trials, suggests that biotin supplementation, including HDB, is not an effective intervention for improving disability outcomes in people living with MS. Furthermore, severe adverse events reported in the Cree et al. RCT[516] raise additional concerns. Until more extensive and well-designed trials are conducted, biotin supplementation, including HDB, cannot be recommended for people living with MS.

Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10) is an antioxidant found in various foods such as organ meats, tuna, salmon, and beef. It plays a crucial role in energy production and mitochondrial stabilisation in cells. CoQ10 has shown neuroprotective effects in people living with MS by addressing key disease mechanisms[518]. CoQ10 supplementation has been found to reduce inflammatory cytokines, oxidative stress, and improve mitochondrial function. CoQ10 supplementation has demonstrated potential in reducing the severity of EAE in animal models, by reducing inflammation and supporting remyelination[5519]. In observational studies of people living with MS, decreases in pro-inflammatory markers such as TNF-α, enhance antioxidant enzyme activities, and improvements in clinical symptoms such as depression and fatigue have been found[520].

In an RCT by Sanoobar et al., 500mg/day CoQ10 supplementation (N=22) vs placebo (N=23) was administered to 48 people living with MS over a 12-week period, resulting in significant reductions in fatigue, depression, inflammatory markers, and oxidative stress compared to the placebo group at 12-weeks[521]. In another trial by Moccia et al. involving 60 people living with MS, taking 200 mg/day of CoQ10 alongside subcutaneous high-dose interferon beta-1a was associated with improved cognition and reduction in pain[522].

While there is biological plausibility and promising evidence for the use of CoQ10 in MS, the current level of evidence from RCTs is insufficient to recommend its routine use in people living with MS.

Curcumin

Curcumin, the active component of turmeric, is thought to have significant therapeutic potential due to its anti-inflammatory and antioxidant properties. Some studies suggest that curcumin can modulate various cellular pathways and immune responses relevant in MS[523]. It has been shown to inhibit the production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, prevent axonal degeneration and modulate Th17 cell function, which plays a crucial in MS pathogenesis. Furthermore, curcumin can enhance the expression of neuroprotective factors and inhibit neuronal cell death.

Despite promising preclinical findings, clinical trials have not yet confirmed curcumin's efficacy in improving clinical outcomes for people living with MS. An RCT by Petracca et al. investigated the effects of curcumin (500 mg/day BCM 95- micronized curcumin with turmeric essential oils) in 80 participants with relapsing MS treated with IFN-beta-1a over two years[524]. While curcumin was found to be safe and well-tolerated, it did not result in significant improvements in inflammation, MRI changes, relapses, or disability progression compared to the placebo group. While curcumin is safe and well-tolerated, there is insufficient evidence to support its use to improve clinical outcomes in MS.

Ginkgo biloba

Ginkgo biloba is a herbal supplement derived from the leaves of the ginkgo tree. It contains various bioactive compounds, including flavonoids and terpenoids, known for their antioxidant and anti-inflammatory properties[525]. While ginkgo biloba has been widely investigated for its potential benefits on cognitive function and memory in the general population, including dementia[526], its effectiveness in people living with MS is not clear.

Two recent reviews summarised five studies examining the role of ginkgo biloba in managing cognition in MS[527,528]. A four-week trial showed positive effects on cognitive processing speed, verbal learning, and fatigue, while a 12-week trial noted improvements in concentration and memory. However, a larger 12-week follow-up study with 120 participants found no significant differences in cognitive measures, fatigue, or depression between the ginkgo biloba and placebo groups. Therefore, while the smaller studies reported potential cognitive benefits, these findings were not confirmed in larger trials. Overall, while ginkgo biloba is generally safe, its efficacy in managing MS symptoms remains inconclusive, warranting further research.

Inosine

Inosine is a naturally occurring nucleoside compound found in ribonucleic acid (RNA) and is known for its antioxidant properties. Inosine can increase uric acid levels in the body, offering potential neuroprotective benefits[529]. Available as an over-the-counter supplement, inosine has been studied for its potential health benefits, particularly in neurodegenerative diseases such as MS[530].

Three studies have investigated inosine use in people living with MS, either alone or alongside interferon-beta medications, with study sizes ranging from 6 to 159 participants, followed over periods of up to 2 years[531–533]. Doses of inosine ranged from 2–3 g/day or were adjusted based on participants' serum uric acid levels. These studies measured various outcomes, including EDSS, MRI changes, functional capacity, inflammatory markers, and relapse rates, but none found significant differences between the inosine and placebo groups.

A recent review of both preclinical and clinical studies[529], noted that inosine increased urate levels, and suggested potential benefits in people living with MS, including reduced relapse rates, slower disability progression, and fewer gadolinium-enhanced lesions on MRI[534,535]. However, inosine use was also associated with adverse events, such as an increased risk of kidney stones and gout[532].

Given the limited evidence of efficacy and potential risks of side effects, inosine supplementation cannot be recommended for people living with MS at this time.

Melatonin

Melatonin is a neurohormone secreted by the pineal gland that regulates circadian rhythms that has been linked to MS pathophysiology. Melatonin's antioxidant, anti-inflammatory, and immunomodulatory properties have made it a subject of interest for potential therapeutic effects in plwMS[536]. Research suggests that melatonin may reduce oxidative stress and inflammation, which are key factors in MS progression.

Preclinical studies in animal models of MS have also shown promising results. A systematic review and meta-analysis indicated that melatonin supplementation improved behavioural and cognitive outcomes, primarily due to its anti-inflammatory and neuroprotective effects[537].

Clinical trials in people living with MS have produced mixed results. A recent systematic review of seven RCTs, found that melatonin supplementation was safe and associated with improvements in sleep, cognitive outcomes, and fatigue for some participants[538]. However, variations in dosage, duration, and assessment methods among the studies led to the conclusion that the current evidence is insufficient to recommend melatonin for routine use in improving MS outcomes.

While current evidence suggests melatonin has potential benefits on cognitive outcomes and fatigue in people living with MS, larger and more rigorous RCTs are needed to confirm its broader clinical efficacy.

Omega-3 and omega-6 fatty acids

Omega-3 polyunsaturated fatty acids are found primarily in fish oil, plant-based oils and certain nuts and seeds. The three main types of omega-3 fatty acids are EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid; 'marine omega-3' found in fish) and ALA (alpha-linolenic acid) found in plant-based foods such as flaxseed, chia seeds, walnuts, soybeans and edamame.

Omega-3 fatty acids, particularly DHA, exhibit anti-inflammatory and neuroprotective properties, influencing gene expression and reducing inflammatory cytokines like TNF-α and IL-1[539,540]. Omega-6 fatty acids, found in safflower, sunflower, and canola oils, as well as tofu, walnuts, and almonds, promote inflammatory processes[541].

A 2019 systematic review and meta-analysis by Sedighiyan et al included four omega-3 supplement-based intervention studies where the study outcomes were change in EDSS[542]. None of the constituent trials showed significant treatment effects compared to the inactive comparators, and the pooled statistic also failed to indicate a treatment effect (mean pooled difference=-0.07, 95%CI=-0.27, 0.13). Of note – three of these trials were of omega-3 supplementation in addition to a pharmacotherapy (interferon-beta or fingolimod), whereas the other trial which evaluated omega-3 supplementation plus low-fat diet showed the strongest, though still nonsignificant effect[543]. However, no other systematic reviews with multiple comparable intervention studies of omega-3 supplementation are present in the literature.

Omega-3 and omega-6 fatty acids are essential for brain function and myelin synthesis, and people living with MS often have lower levels of these fatty acids. Early research suggested omega-3 and omega-6 fatty acid supplementation might not significantly reduce relapse severity or duration. However, recent trials using a nutraceutical formula containing both omega-3 and omega-6 fatty acids have reported significant improvements in disease progression, relapse rates, functional capacity, and quality of life[544,545].

Despite some evidence for the benefits of omega-3 and omega-6 supplementation in people living with MS, variations in study design, dosage, and study participant's characteristics limit interpretation. Further research is needed to determine the optimal dosage and effectiveness of omega-3 fatty acids before recommending them for people living with MS.

Probiotics

Probiotic supplements contain live microorganisms, such as bacteria and yeasts, that support digestive health and can alter gut microbiome composition. Given the gut microbiome interacts closely with the immune system, maintaining its health may help modulate immune responses, and potentially influence MS outcomes[434,546]. However, as highlighted in a recent article, there are many unknowns regarding probiotic therapy in general health, including the most effective strains, dosages, and duration, which may vary by the individual and the condition[547].

A small number of trials have shown probiotics may be beneficial for people living with MS. In one RCT, Ashghari et al. randomised 40 people living with MS to a *Saccharomyces boulardii* probiotic or placebo for four months. The probiotics group showed significant reductions in fatigue and improved quality of life, and decreased general inflammation, as measured by serum levels of high-sensitivity C-reactive protein (hs-CRP)[434]. In another RCT, Rahimlou et al. examined the effect of a multi-strain probiotic intervention versus placebo in people living with MS over a six-month period. The probiotics group experienced significantly reduced fatigue, depression, and inflammatory markers including hs-CRP and proinflammatory cytokines[437,548].

A further RCT conducted by Kouchaki et al. examined probiotic supplementation versus placebo in 60 people living with MS followed over a 12-week period. Probiotic supplementation was associated with reduced fatigue, stress and depression, as well as reduced inflammatory markers such as hs-CRP[433].

These studies suggest probiotics may reduce systemic inflammation and improve fatigue, mood, and quality of life in people living with MS. However, the small sample sizes and short durations of these trials limit their reliability. Further large-scale, long-term studies are necessary to confirm the efficacy of probiotics in managing MS.

Vitamin A and carotenoids

Vitamin A is a fat-soluble vitamin found in fish, particularly cod liver oils, organ meats such as liver, eggs, and dairy products. Vitamin A exists in different forms including retinol, retinal, retinoic acid or retinyl ester. Carotenoids, the precursors to vitamin A, are pigments responsible for the red, orange, and yellow colours in many vegetables and fruits. Both vitamin A and carotenoids help to maintain normal reproduction, vision and immune function[549].

Limited studies have examined the role of vitamin A supplementation in the management of MS. Research suggests that retinoic acid may modulate immune responses, potentially leading to clinical improvements.

An RCT involving 101 people with relapsing remitting MS found daily supplementation with vitamin A (25,000 IU for six months followed by 10,000 IU for another six months) led to significant improvements in disability using the MS Functional Composite (MSFC) scale, depression, and various measures of fatigue (total, physical, psychological, and cognitive). However, no significant differences were observed in disability, as measured using the EDSS, relapse rate or MRI measures such as lesion load[550].

Another RCT of 39 people living with MS assigned to either 25,000 IU of vitamin A (retinyl palmitate) daily or placebo over a six-month period found significant reductions inflammatory cytokines (IFN-gamma and TGF-beta) in the intervention group[551], suggesting a potential therapeutic mechanism.

While studies suggest possible benefits, the limited number and size of these studies are insufficient to recommend vitamin A supplementation for people living with MS. Importantly, people are not recommended to consume excessive vitamin A supplementation (typically over 100 times the recommended daily allowance), as vitamin A toxicity can be deleterious to their health.

Combined nutraceuticals

The term "nutraceutical" combines "pharmaceutical" and "nutrition," referring to natural compounds with potential therapeutic effects. Combined nutraceuticals can consist of a combination of multivitamins, zinc, and supplements listed in this chapter, designed to target specific biological pathways and potentially improve health outcomes in MS[552]. A combination of nutraceuticals is considered a safe integrative approach for treating neurodegenerative conditions such as MS due to their lower risk of adverse effects and compatibility with existing treatment regimens.

By combining biologically potent agents, nutraceuticals aim to achieve effects on clinical outcomes that individual components may not accomplish alone. Proposed nutraceutical combinations target pathways such as oxidative stress[553], mitochondrial function[554,555], or supporting neuronal health[552].

While nutraceuticals show promise and are actively researched, including by groups in Australia, no specific nutraceutical combinations targeting particular MS outcomes can currently be recommended for people living with MS and further studies are needed to establish their efficacy and clinical utility.

Current Recommendations

The role of dietary supplements in MS management is a rapidly evolving area of research. While some dietary supplements show promise, more evidence is needed to establish definitive recommendations. Currently, people living with MS are encouraged to maintain a balanced diet rich in plant-based foods, low in saturated fats, engage in regular physical activity, and consult healthcare professionals before starting any new supplement regimen.

Healthcare professionals are advised to stay informed about emerging research in this area to provide accurate advice and support. Treating physicians should be aware of the limitations and risks of supplementary treatments, including potential adverse effects and interactions with prescribed medications, to ensure a comprehensive approach to MS management.

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