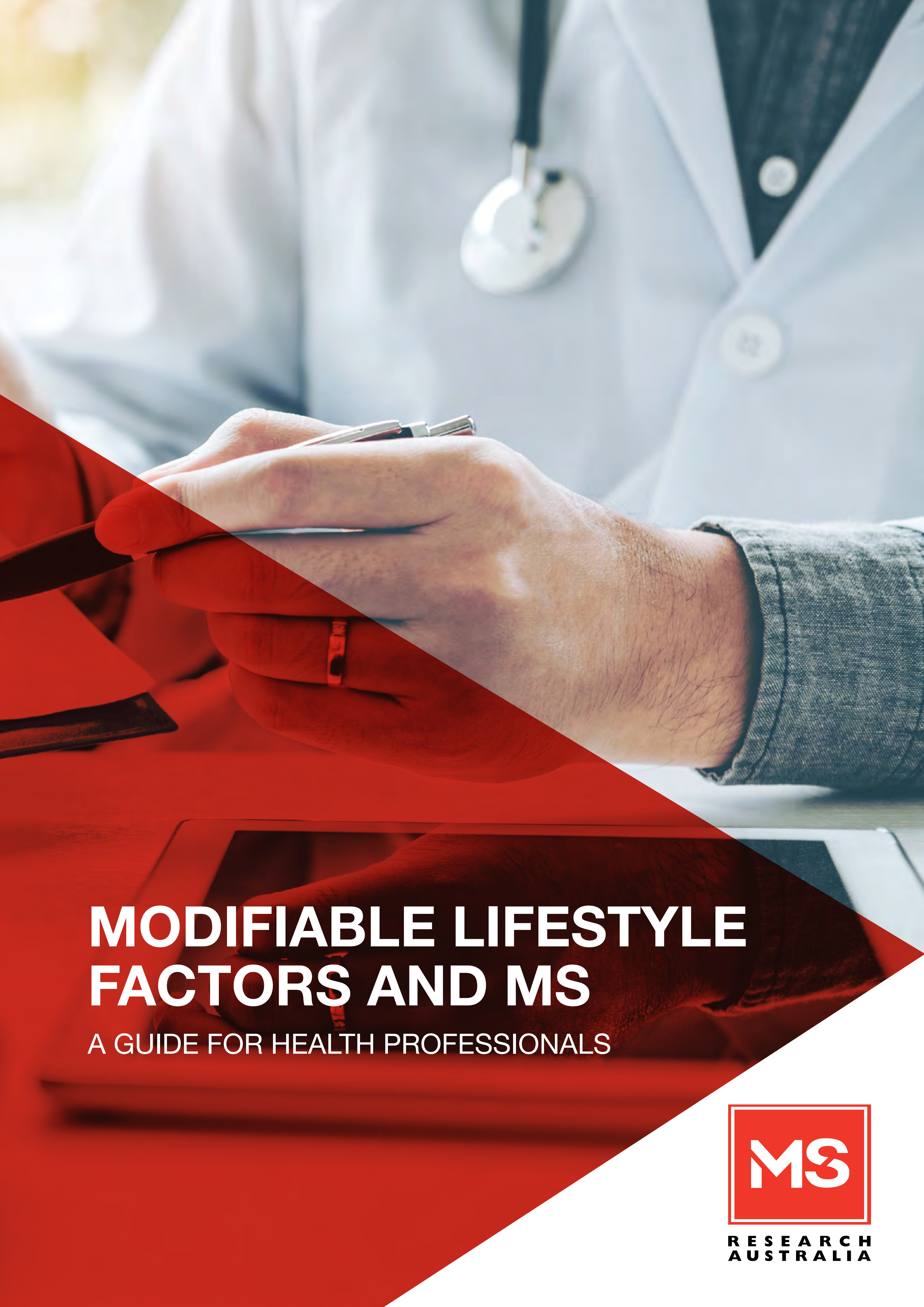

MODIFIABLE LIFESTYLE FACTORS AND MS

A GUIDE FOR HEALTH PROFESSIONALS

MS
RESEARCH AUSTRALIA

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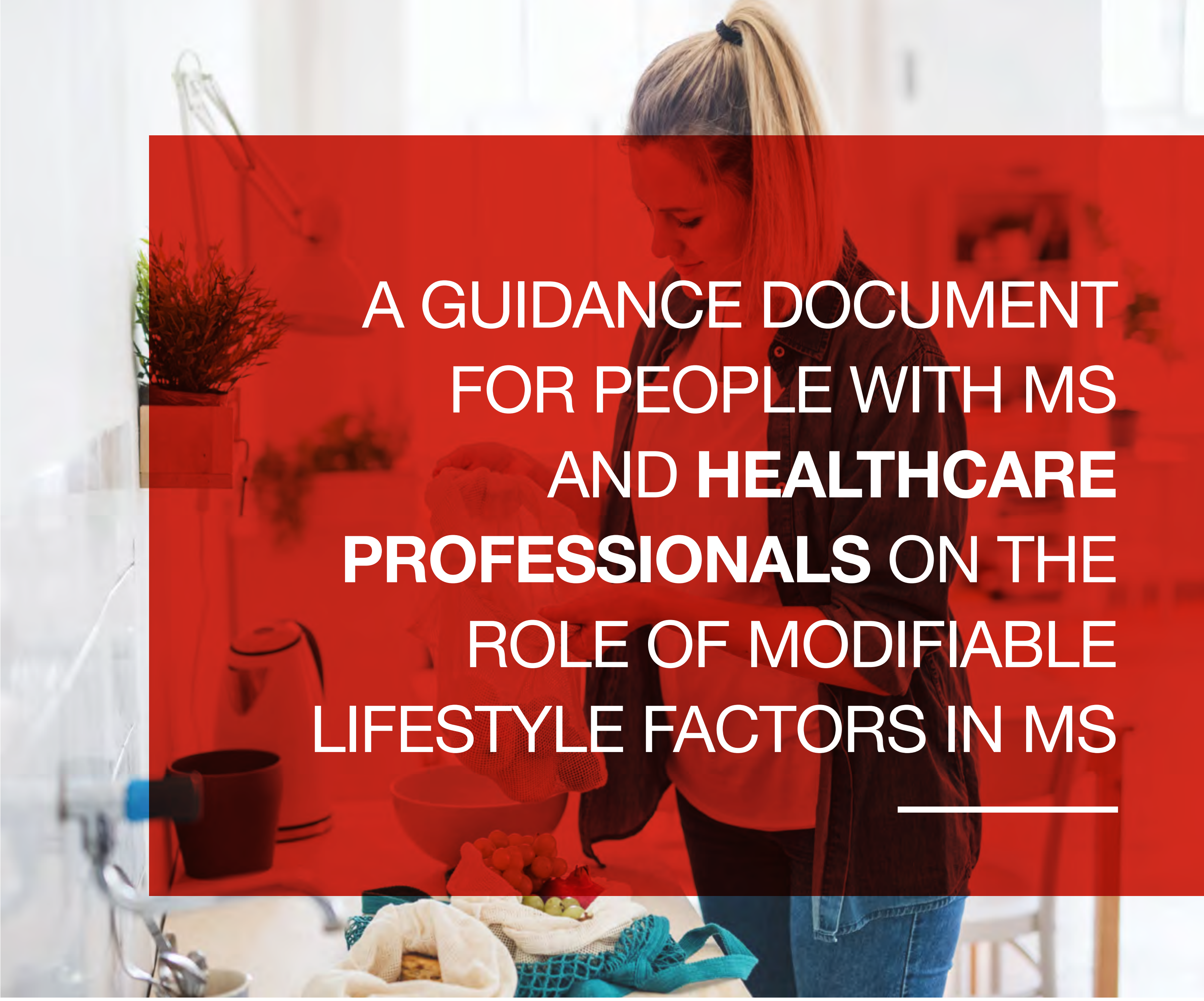


A GUIDANCE DOCUMENT FOR PEOPLE WITH MS AND **HEALTHCARE PROFESSIONALS** ON THE ROLE OF MODIFIABLE LIFESTYLE FACTORS IN MS

Publication Date

The information in this document is current as of August 2020.

Executive summary

MS Research Australia held a workshop on modifiable lifestyle factors in Multiple Sclerosis (MS) on 2nd May 2018 in Sydney. This workshop was organised in response to a need identified by the 2016 MS Research Australia Research Priorities survey that modifiable lifestyle factors was an area of importance to the MS community as it provides a mechanism for people with MS to take control and potentially minimise the impact of MS on their lives.

There is also growing evidence from epidemiological and clinical research that there is potential for modifiable lifestyle factors to change disease outcomes. The workshop brought together clinicians, researchers, allied health professionals and people affected by MS to discuss the current evidence and the best way forward for research in this area.

The first clear outcome was the need for communication materials to be developed to provide consistent guidance to Australians with MS as well as neurologists and other clinicians dealing with people with MS based on the best available evidence on modifiable lifestyle factors.

A working group of national experts with clinical and research expertise in the role of different modifiable lifestyle factors in MS were brought together for the development of this guidance document.

The topics covered in this document are related to both lifestyle choices and the impact of some environmental factors on MS. These include smoking, physical activity, diet and nutrition, gut health and microbiome, supplements, vitamin D and sunlight, weight and obesity, medical conditions in addition to MS (comorbidities), and lipid profiles.

The experts in each field provided the following recommendations for people with MS for each topic:

Experts strongly recommend that people with MS stop smoking irrespective of their stage of disease. Stopping smoking at any time is beneficial for people with MS, both for their MS and their risk of other conditions caused by smoking, such as cancer and cardiovascular disease.

Physical activity and exercise should be considered as a safe and effective means of improving the quality of life of people with MS. Evidence shows that being active can improve physical fitness, functional capacity and quality of life in people with MS.

People with MS should follow the same dietary guidelines as the general population - the Australian Dietary Guidelines. People with MS may benefit from consulting an Accredited Practising Dietitian to help them identify ways to best integrate these guidelines into their lives, factoring in personal preferences and needs.

There is not enough evidence to recommend any of the various methods which are sometimes advocated for their ability to change or improve the microbiome of people with MS and their claimed benefits on MS outcomes.

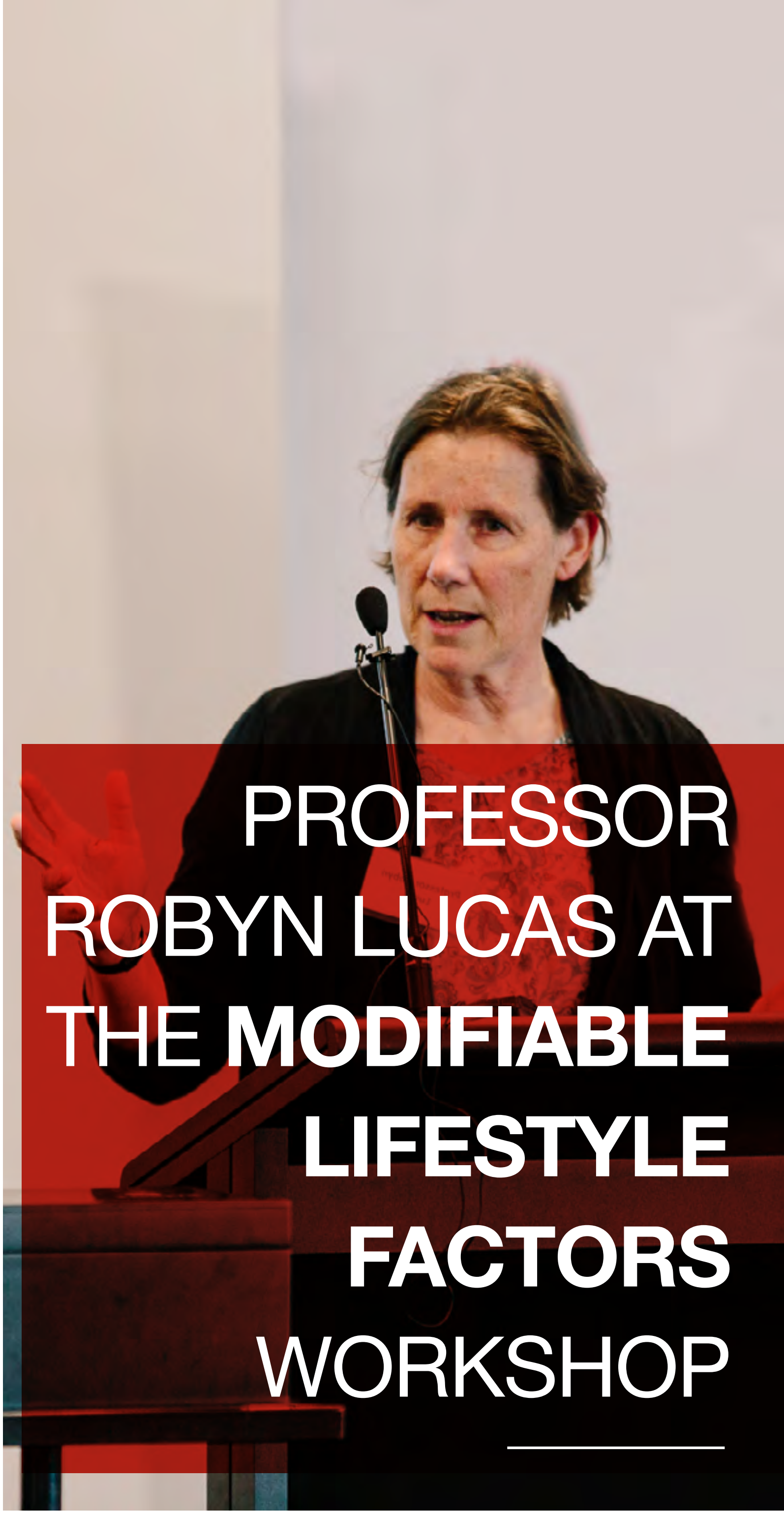
There is currently not enough evidence to support the use of any supplements for people with MS. A balanced diet, as recommended in the section on diet and nutrition in this document, in line with the *Australian Dietary Guidelines* and the help of an Accredited Practicing Dietician are the most effective ways to ensure all the nutritional needs of people with MS are being met.

There is currently not enough evidence to recommend sun exposure or vitamin D supplementation to reduce the risk of developing MS or the risk of disease progression. Experts recommend that people with MS follow the vitamin D recommendations of the National Health and Medical Research Council (NHMRC) of Australia and the Ministry of Health in New Zealand for the general public as well as advice for sun exposure for the general public by Cancer Council Australia, to maintain healthy vitamin D levels and obtain sufficient levels of sun exposure.

It is beneficial for people with MS to maintain or aim for their weight to be in the healthy range, irrespective of their stage of disease.

The early detection and optimal management of comorbidities in MS is key. People with MS and health professionals must both play a proactive role in the identification and management of comorbidities.

Clinicians should be vigilant about regularly screening people with MS for dyslipidaemia, using the screening and diagnostic guidelines for vascular and metabolic comorbidities that are common in the general population.


PROFESSOR ROBYN LUCAS AT THE **MODIFIABLE LIFESTYLE FACTORS** WORKSHOP

This document aims to empower healthcare professionals to provide evidence-based advice to their patients and clients with MS.

It will allow people with MS in conjunction with their health care providers to take an active role in the management of their MS by making evidence-based lifestyle changes that may benefit their MS disease outcomes such as relapse, disability, occurrence of comorbidities, symptoms, and to improve their overall quality of life.

Introduction

Multiple Sclerosis

Multiple Sclerosis (MS) is the most common chronic acquired neurological disease of young adults, often diagnosed between the ages of 20 to 40. In Australia, MS affects three times more women than men. Whilst we have more effective therapies emerging, there is no cure as yet.

There is no known single cause of MS, but many genetic and environmental factors have been shown to contribute to its development.

In MS, the body's own immune system mistakenly attacks and damages the fatty material called myelin, which wraps around the nerves. Myelin is important for protecting and insulating nerves so that the electrical messages that the brain sends to the rest of the body travel quickly and efficiently.

As the myelin breaks down during a MS attack in a process called demyelination, patches of nerves become exposed and then scarred, which renders the nerves unable to communicate messages properly and at risk of subsequent degeneration. This results in a range of symptoms and disability (e.g. impaired walking, hand and arm function, loss of sensation, pain, fatigue, vision changes, and changes to thinking and memory).

Types of MS

Relapsing remitting MS (RRMS) is the most common form of MS; it is characterised by flare-ups of existing or new neurological symptoms of MS, also known as relapses or attacks, followed by periods of recovery or remission.

Secondary progressive MS (SPMS) is a secondary phase of relapsing remitting MS that can develop years to decades following the initial onset of relapsing symptoms. Secondary progressive MS is characterised by a progressive worsening of symptoms (accumulation of disability) over time, with no obvious signs of remission.

Primary progressive MS (PPMS) is diagnosed in approximately 10-15% of people with MS. Primary progressive MS is characterised by progressive worsening of symptoms and disability right from the beginning, without periods of recovery or remission.

Modifiable lifestyle factors in MS

In 2016, MS Research Australia conducted a survey to determine what the Australian MS community thought the priorities should be for the many different areas of MS research. The survey was completed by more than 1,000 people, including over 700 people with MS, their care givers, health professionals and professionals in the MS space.

It was identified that the role of modifiable lifestyle factors in MS was of great interest to the community, as it provides a mechanism for people with MS to be empowered to take control and potentially minimise the impact of MS on their lives. In response to these survey results, MS Research Australia held a workshop on modifiable lifestyle factors in MS on 2nd May 2018.

The workshop brought together clinicians, researchers, allied health professionals and

MODIFIABLE LIFESTYLE FACTORS PROVIDES A MECHANISM FOR PEOPLE WITH MS TO **TAKE CONTROL**

people living with and affected by MS to discuss the current evidence and the best way forward for research in this area. The workshop aimed to identify opportunities to translate and implement the current evidence to provide the most appropriate advice to the MS community.

While it was acknowledged that evidence was incomplete in many areas, a key outcome of the workshop was to bring together a working group of experts and stakeholders to provide a guidance document for people with MS and healthcare professionals on the role modifiable lifestyle factors can play in the development and progression of MS, based on currently available evidence.

MS Research Australia

MS Research Australia is the largest Australian not-for-profit organisation dedicated to funding, coordinating, educating and advocating for MS research as part of the worldwide effort to solve MS.

MS Research Australia's goal is to accelerate research into the cause, better treatments and prevention, with the aim of ultimately finding a cure for MS.

Purpose

The aims of this guidance document were developed based on the interests and concerns of people with MS. Ultimately, this document aims to empower healthcare professionals to provide evidence-based advice to their patients and clients with MS.

It will allow people with MS in conjunction with their health care providers to take an active role in the management of their MS by making evidence-based lifestyle changes that may benefit their MS disease outcomes such as relapse, disability, occurrence of comorbidities and symptoms, and to improve their overall quality of life. Where applicable, the benefits of modifying lifestyle factors on the risk of developing MS will also be identified.

For the purposes of this document, the risk of MS refers to the risk of having a first demyelinating event (FDE) or experiencing radiologically isolated syndrome (RIS) or clinically isolated syndrome (CIS). The progression from RIS or CIS to clinically definite MS (CDMS), relapses, disability progression and the appearance of new symptoms or worsening of existing MS symptoms following CDMS will be considered as disease progression.

A working group of national experts with clinical and research expertise in the role of different modifiable lifestyle factors in MS were brought together for the development of this guidance document.

The topics covered in this document are related to both lifestyle choices (including downstream effects such as changes in blood lipid levels) and the impact of some environmental factors on MS:

- **smoking**
- **physical activity and exercise**
- **diet and nutrition**
- **gut health and microbiome**
- **supplements**
- **vitamin D and sunlight**
- **weight and obesity**
- **comorbidities**
- **lipid profiles**

Aims of this document

Where scientific evidence is available, provide recommendations to people with MS on lifestyle changes to improve disease, symptoms and overall quality of life.

Where scientific evidence is available, provide recommendations to people with an elevated risk of developing MS, on the impacts modifiable lifestyle factors may have on the development of MS.

Where recommendations are being made, provide a summary of the supporting research, along with a grading of the strength of the scientific evidence.

Where recommendations cannot be made specifically for people with MS, provide general recommendations that are helpful and safe (so far as can be assessed at the current time) for people with MS to adopt.

Identify recommendations that are advocated within the MS community which are not based on robust scientific evidence and highlight the actual evidence in the area.

The NHMRC Grading System used in this document

The expert working group used the *NHMRC levels of evidence and grades for recommendations for developers of guidelines*[1] to grade the levels of evidence for each topic.

For topics where 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.

A grade was assigned to each recommendation based on the following:

- the evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias)
- the consistency of the study results
- the potential clinical impact of recommendations
- the relevance of the scientific evidence to people with MS (generalisability)
- the relevance of the scientific evidence to the Australian Healthcare setting (applicability)

The NHMRC Grading System definitions of grade of recommendation are as follows:

A = Body of evidence can be trusted to guide practice

B = Body of evidence can be trusted to guide practice in most situations

C = Body of evidence provides some support for recommendation(s) but care should be taken in its application

D = Body of evidence is weak and recommendation must be applied with caution

For more information on this system, please refer to the *NHMRC levels of evidence and grades for recommendations for developers of guidelines*[1].

Since this system is used to grade recommendations, no grade is given in the sections of this document where recommendations could not be made due to a lack of robust evidence.

Review

The content in this guidance document has been reviewed by a diverse panel, which included scientific experts, people living with and affected by MS, neurologists, MS nurses, and MS service providers.

The information in this document is current for August 2020. MS Research Australia will work with the working group authors and other experts to update these guidelines periodically to ensure that the advice remains in line with the most up-to-date scientific evidence.

Cautions and considerations

This document does not aim to replace standard medical treatment for MS.

Any person with MS looking to carry our major lifestyle modifications should do so in consultation their healthcare team.

Factors such as level of disability, psychological factors such as depression and anxiety, and socioeconomic factors such as financial and geographical barriers to accessing services must be considered by medical professionals when applying the recommendations in this document in practice.

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MS Research Australia would like to acknowledge and thank the people who provided their expertise and time to develop this document.

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Smoking

Smoking tobacco has been scientifically linked to an increased risk of many conditions, including development of MS, symptoms in people with MS, and disability progression in MS. Tobacco smoking also increases the risk of heart disease, a common comorbidity in people with MS.

There is conclusive evidence that smoking tobacco is a risk factor for MS as well as having a negative impact on the disease course. **Experts strongly recommend that people with MS stop smoking irrespective of their stage of disease.** Stopping smoking at any time is beneficial for people with MS, both for their MS and their risk of other conditions caused by smoking, such as cancer and cardiovascular disease.

The earlier people with MS quit, the stronger these benefits are.

EXPERTS **STRONGLY RECOMMEND** THAT PEOPLE WITH MS STOP SMOKING

The link between smoking and MS

Smoking refers to the inhalation of smoke created by combustion of organic material; most commonly tobacco, but can also include marijuana, opium, and others.

For the purposes of this document, we will be discussing combustible tobacco products which include cigarettes, the most common product in Australia[2], as well as cigars, pipes, cigarillos, little cigars and waterpipes (also known as shisha, nargile or hookah), but will not be discussing information about the harms or benefits of marijuana or cannabis.

It is well recognised that smoking has very harmful effects on the health of the smoker and those who inhale smoke passively.

Based on the Australian National Drug Strategy Household Survey 2016, 13.8% of men and 10.7% of women smoke tobacco daily[3].

It is not known how many people with MS in Australia currently smoke. Data from the Australian MS Longitudinal Study in 2016 showed that 11% of people with MS reported currently smoking tobacco[4]. An Australian study of 282 people with a first demyelinating event (FDE) reported that 27.4% of people with (suspected) MS smoked at the time of enrolment between 2003-2006[5], with 20.3% still smoking five years later[6].

Smoking is the leading cause of preventable death and disease in Australia[7], and Australia has implemented a comprehensive range of measures to reduce the number of people who smoke in the Australian population[8]. However, there are no initiatives addressing the prevention of smoking uptake or programs to assist people to quit smoking specifically designed for people living with MS.

Overall, the body of evidence showing the harmful effects of smoking tobacco on the onset and progression of MS is clear. Experts have been able to conclusively agree that smoking is a risk factor for MS, and highly recommend that people with MS stop smoking irrespective of their stage of disease to slow down progression.

A review of the research in this area was published in June 2019 and has been used to inform the sections below[9].

Does smoking have effects on the risk of getting MS or when MS begins?

Scientific evidence showing the impact of smoking in relation to the risk of MS is robust and clear. Smoking is a key risk factor for MS onset, increasing the risk of MS by approximately 50%[10,11]. It has also been shown that passive smoking increases the risk of MS onset[12].

Related family members exposed to smoking may be at particularly high risk as they may also be genetically predisposed to MS[13]. Furthermore, there is evidence to show that the risk of paediatric onset MS is reduced in children whose parent stops smoking[12].

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Does smoking have effects on MS disease progression?

There is a large body of high-quality research into the role of smoking on MS disease progression. A 2017 systematic review (that analysed 14 research studies) and a meta-analysis of seven retrospective studies and one prospective study[13] investigated the effect of smoking on MS progression (disability worsening or conversion to progressive MS).

The conclusion was that smoking was a key risk factor for faster disease progression and that smoking increased the risk of MS progression by around 55%, which can be said with a moderate level of certainty. There was some inconsistency between the estimates in the studies, meaning the overall quality of scientific evidence was moderate.

Despite the uncertainty around the precision of the estimate, this is convincing evidence that people with MS who smoke have an increased chance of their disability getting worse when compared to people with MS who do not smoke[14].

Furthermore, the well-established National Institute for Health and Care Excellence (NICE) *Multiple Sclerosis in adults: management* clinical guideline[15] recommend that, based on two prospective cohort studies[16,17] which show an increased risk of disability progression in people with MS due to smoking tobacco, people with MS should not smoke tobacco.

Does smoking have effects on MS symptoms?

In addition to its harmful effects on progression of disability, smoking is also associated with worse MS symptoms.

People with MS who smoke experience a lower quality of life[18], and more severe symptoms of depression and/or anxiety[19].

A UK database study that followed more than 900 people with MS over time showed that smoking tobacco increases the risk of early death in those who smoke compared with those who have never smoked. Within non-smokers, having MS did not increase the risk of early death compared to people without MS[20].

Are there benefits to quitting smoking on MS?

Quitting smoking at any time is beneficial. Evidence shows that the risk of disability progression is significantly reduced following a person giving up smoking, and the earlier people with MS quit, the greater the benefits[21].

Persistent smokers reached the progressive stage of MS eight years earlier than those who quit around the time of diagnosis[22]. Another study has shown that for every ten years when people did not smoke, the reduction in the risk of increasing disability was approximately 30%[21].

Does smoking interfere with MS medications?

Smoking may have adverse impacts on the effectiveness of medications people take to treat their MS[23,24]. As these medications are aimed at preventing relapses and progression of MS, this compounds the negative effects of smoking on progression of MS disability.

Information that needs clarifying

Is nicotine the cause of harm or is it other substances in tobacco?

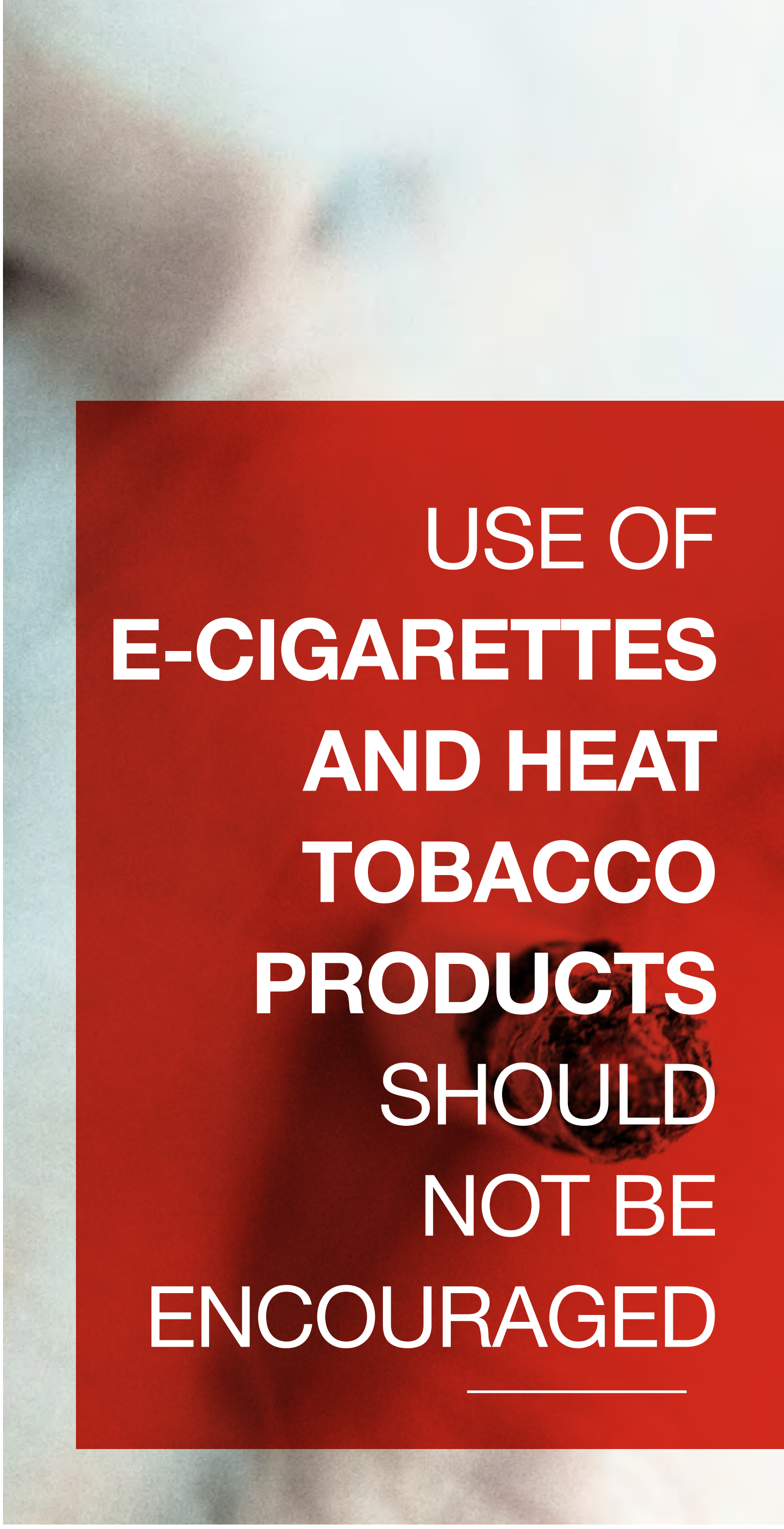
A study on Swedish snuff use (smokeless tobacco) suggests that the increased risk of MS onset in smokers is not due to the nicotine in tobacco, but other elements in the smoke[25]. This is an indication that nicotine replacement therapy is safe for people with MS, and an important tool in helping people quit.

Anecdotal evidence exists of some people with MS perceiving beneficial effects of nicotine on some MS symptoms such as pain or fatigue[26], which are similar to benefits that have been seen in other diseases such as schizophrenia[27] and depression[28].

Some early-stage studies have also shown that treatment with nicotine had some protective effects against disease severity and onset in a laboratory model of MS[29]. However, as it currently stands, the evidence is not sufficient to support these claims, and much more research is needed on the potential harms and benefits of nicotine in humans with MS.

Are e-cigarettes less harmful than regular cigarettes?

We now see an increased promotion of “less harmful” ways to use nicotine, such as e-cigarettes and heated tobacco products. There is currently no evidence to support that these products are harmless nor that their use has benefits compared to being nicotine-free[30].



USE OF **E-CIGARETTES AND HEAT TOBACCO PRODUCTS** SHOULD NOT BE ENCOURAGED

The overwhelming consensus of international health groups, including advice from the Australian Department of Health[31] and the World Health Organisation (WHO)[32] is that use of e-cigarettes and heat tobacco products should not be encouraged unless they have been approved as a tool to help people quit smoking entirely.

Recommendations for people with MS

Recommendations for people with MS are in line with the recommendations for the general public[33].

However, as summarised above, the harmful effects of smoking on disease outcomes and the specific benefits of quitting smoking on these outcomes make the case for action to reduce or preferably, quit tobacco smoking for people with MS more urgent and compelling.

The highest level of evidence available relates to the effect of smoking on MS onset and disease progression.

To minimise risk for disease progression, it is recommended that people with MS do not smoke.

NHMRC Overall Grade: B

Evidence base: B, consistency: C, clinical impact: A, generalisability: A, applicability: A.

Note regarding the levels of evidence for smoking in MS: due to the clear dangers of smoking, it is not ethical to undertake randomised controlled trials where participants are assigned to smoke.

Therefore, the highest level of evidence feasible in this area derives from prospective descriptive population studies.

Considerations for health professionals

Despite evidence for the effectiveness of programs to help people to quit smoking in other chronic diseases, surprisingly no interventions have been tested in people with MS or those at risk for MS.

As specific advice for people with MS is lacking, the current advice for quitting smoking is the same as that for the general population: behavioural intervention that runs over multiple sessions (such as that provided by Quitline) plus, if clinically appropriate, medications designed to help people to quit.

More research is needed to test if current programs to help people quit smoking are effective for people with MS and, if not, to modify or create new programs.

One survey reported on barriers preventing people with MS to stop smoking, which included unpleasant withdrawal symptoms and expensive treatment for tobacco dependence, and perceived benefits from smoking on boredom and coping[34]. However, these barriers are common to the general population and to specific cohorts such as people with mental illness.

Common MS symptoms such as difficulties with thinking and memory may be both motivators to continue smoking, and barriers to quitting[35,36].

Similarly, depression can reduce the chance of quitting successfully[37], and there is a complex relationship between thinking and memory function, coping and depression in people with MS[38].

Pain is another common symptom for people with MS. A positive feedback loop between smoking and pain has been described[39], where smoking may increase the risk of pain in the long term, while its ability to block pain in the short term can be a powerful motivator to continue smoking[40]. Therefore, people experiencing pain and/or negative emotions (due to depression or anxiety), may find it especially difficult to quit smoking[41].

Close monitoring and management of these symptoms may increase the chance of successfully quitting smoking, although further research is required in this area. Furthermore, it is known that attempts to quit are regularly unsuccessful in the general population, and regular follow-up may be needed to provide additional support.

While research is underway to better understand how to best help people with MS to quit smoking, health practitioners are advised to use best practice guidelines for the general population.

General guidelines and recommendations for healthcare providers to support people to quit smoking have been put together by Quitline, in collaboration with the Cancer Council, The Victoria Health Promotion Foundation and the Victorian State Government[42].

The key messages from this document follow a three-step process:

Ask – enquire whether a patient currently smokes, has smoked and if they have stopped recently.

Advise – provide clear, non-confrontational and personalised advice to smokers on stopping smoking, which includes the best way to quit in a way that is sustainable in the long term through behavioural interventions and/or medications that may assist them.

Help – offer to arrange referrals to services such as Quitline and to experts and tools (e.g. apps) that exist to help with behavioural and/or medications that may assist them.

More information can be found in the guideline document - *Helping patients to stop smoking: a guide for general practitioners*[42].

Physical activity

Many individuals with MS engage in low levels of physical activity including reduced exercise participation. Limited participation in physical activity may lead to a decrease in fitness, a reduced ability to move freely, and a general lower quality of life. The lack of activity can also increase the chances of developing other conditions such as depression, heart disease, osteoporosis, and obesity.

For many years, doctors advised people with MS to avoid any physical activity or exercise. This, in part, was due to some individuals with MS experiencing a temporary worsening of symptoms following an increase in body temperature. Prior to the 1980s, there was also limited understanding of the relationship between MS and physical activity or exercise. However, in this section, strong evidence of the associations between MS and physical activity and exercise is explored. It discusses optimal ways to be active, and clarifies the potential health benefits of physical activity and exercise in MS.

The overall message is that physical activity and exercise should be considered as a safe and effective means of improving the quality of life of people with MS. Evidence shows that being active can improve physical fitness, functional capacity and quality of life in people with MS. The recommendations provided below are general physical activity and exercise guidelines that may be followed for adults with mild to moderate MS. However, they should be adapted to the person’s needs, abilities and preferences.

The link between physical activity and exercise, and MS

Physical activity and exercise can be thought of as similar, but different, things. While physical activity can include exercise, sport, occupational work, transportation (e.g. walking your dog or cycling to the shops), and household chores, the research discussed in this section has mainly focused on physical activity in the form of walking.

Exercise is considered to be planned, structured, and repetitive; it is normally performed over an extended period of time and often prescribed by a healthcare professional or exercise specialist with a specific objective such as improved health-related fitness[43,44].

Physical activity and exercise have many clear benefits for people with MS and the general population[45].

Lack of physical activity is a serious public health concern, and people with disabilities, such as those with MS, are at much greater risk of serious health problems associated with inactivity[46].

In the general population, long term participation in physical activities, particularly exercise, is known to reduce the risk of developing illnesses such as heart disease, stroke and type 2 diabetes, amongst many other diseases[47]. The benefits to mental health outcomes such as depression and anxiety are also well documented[48].

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

Both physical activity (primarily measured as walking) and exercise have positive physical and mental benefits for people with MS[49–61].

Many research studies support exercise training for the management of symptoms

BEING ACTIVE CAN IMPROVE PHYSICAL FITNESS, FUNCTIONAL CAPACITY AND **QUALITY OF LIFE** IN PEOPLE WITH MS

of MS as well as the possibility of altering the disease course of MS itself. Evidence shows that exercising does improve physical fitness in people with MS[49–51].

In particular, both aerobic exercise (the type of exercise that increases your heart rate and breathing rate, and incorporates a high number of muscle contractions against low resistance loads for example, running, swimming and cycling) and strength/resistance training (the type of exercise which makes your muscles work harder than normal and incorporates a restricted number of muscle contractions against heavy loads, for example lifting weights, using weight machines or resistance bands)[49–51] are of benefit for people with MS.

Research has shown that exercise and physical activity in the form of walking, can help with mobility (being able to move freely)[52,53], fatigue[54–56], balance[57], cognition (thinking, processing and memory)[58], depressive symptoms[54,59,60] and health-related quality of life[61].

There is evidence that exercise can also be used to manage pain in MS[62]. Additionally, it has been shown that exercise may have positive effects on memory[63,64], sleep quality[65,66] and other diseases that may affect people with MS, such as metabolic disorders and cardiovascular disease[67,68].

Can exercise be used to treat MS alongside MS medications?

In addition to the benefits listed above for people with MS, exercise therapy has been associated with a reduced rate of relapses[69,70] and can also slow disability progression[71].

Exercise is considered by some experts to be the single most effective non-pharmacological approach for functional outcomes and managing symptoms (e.g. aerobic capacity and walking performance, and on fatigue, gait, balance and quality of life)[72].

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

There are many types of exercise, and there is consistently strong evidence of the benefits of aerobic exercise[61,73–75], resistance training[76,77] and balance exercises[78–80] in people with MS.

Balance exercises are developed by experts to help train a person with MS to improve stepping, standing and balance. These exercises can be practiced unsupervised at home using a balance board system such as computer-based technology[78,79,81]. It is important to practice balance exercises in a safe environment to reduce any risk of falls. Balance exercises can also be practiced when supervised by an accredited health professional such as a physiotherapist[82].

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

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

Exercise is safe and can be beneficial in people with MS who experience disability. Individuals who have more severe disabilities may need to participate in adapted exercise to suit the individual and their capabilities (e.g. but not limited to body weight supported treadmill walking or total body recumbent stepping).

Exercise recommendations should be made in consultation with the wider medical team[83–86], with considerations given to psychological factors such as depression, and socioeconomic factors such as financial and geographical limitations to accessing supporting services.

Information that needs clarifying

Is exercise safe for people with MS?

Studies have shown that exercise is safe and beneficial for people with MS and is not associated with an increased risk of relapse[69]. Furthermore, in exercise studies, people with MS who exercised showed improvements in their relapse rates when compared to those who did not exercise[68,87].

Despite this, overall participation in exercise by people with MS is significantly lower than the general population, but similar to that seen in other chronic conditions[87,88].

This could be due to the concerns of people with MS around a number of issues that include safety of exercise, fear of trips and falls, level of disability, MS-mediated pain or fatigue, socioeconomic issues around accessing specialised exercise programs, trainers and spaces to suit varying individual needs, and psychological factors such as depression, which may be impacting motivation to exercise.

One major issue for those with MS exercising in warm environments is heat sensitivity, and the worsening of their MS symptoms due to heat exposure (Uhthoff's phenomenon)[89]. Emerging findings have identified ways for people with MS to help combat heat sensitivity, which allows them to exercise for longer periods of time, especially in warmer climates.

Australian research shows that drinking cold water during exercise is an effective measure[90]. Strategies such as the use of a fan, pre-cooling in a cold bath and the use of an ice vest have also been used successfully by some people with MS. Research is ongoing in this area.

EXERCISE IS **SAFE AND BENEFICIAL** FOR PEOPLE WITH MS

Recommendations for people with MS

Exercise guidelines for people with MS

Strong evidence shows that exercise performed at least two times per week at a moderate intensity will increase aerobic capacity and muscular strength[61] and in 2013, exercise guidelines were produced for physical activity for people with MS[91]. More recently, advanced exercise guidelines have been produced which take into account a person's previous experience of exercise training and level of fitness[92].

We encourage that people with MS who are 18 years of age or over and have mild to moderate levels of disability should follow the guidelines below, adapted from the Canadian MS Society's *Physical Activity Guidelines for Adults with Multiple Sclerosis*[93].

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

For those with a general level of fitness and experience – *people who are irregularly or infrequently physically active*

- Moderate aerobic exercise 2-3 times per week and resistance training exercise 2-3 times per week.
- Suitable moderate aerobic exercises include upper body exercises such as arm cycling or seated shadow boxing, lower body exercise such as walking or leg cycling, and combined upper and lower body exercises such as using an elliptical trainer.
- Suitable moderate resistance training exercises include using weight machines, free weights and cable pulleys.

For those with an advanced level of fitness and experience – *people who are regularly participating in an exercise program and/or people who are seeking greater benefits from exercise training*

- Moderate to vigorous aerobic exercise 5 times per week and resistance training exercise 2-3 times per week.
- Suitable moderate to vigorous aerobic exercises include running or road cycling.
- Suitable moderate to vigorous resistance training exercises include using weight machines, free weights and cable pulleys.

For those with more severe disability *with an expanded disability status scale (EDSS) of 7.0+*

- Breathing exercises, flexibility exercises and exercises of the upper and lower extremities for up to 20 minutes a day (10 minutes a day for EDSS 8.0+) 3-7 times per week. Refer to the National MS Society of the USA physical activity recommendations for further details on recommendations for people with advanced MS[94].

Considerations

- 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. Some MS symptoms, such as fatigue and heat sensitivity, should be identified and discussed before exercise begins.

- 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 who are more severely disabled 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.
- In addition, stretching and balance exercises are also important. It is recommended that people with MS practice stretching and balance exercises in a safe environment. Stretching exercises can be completed daily.
- Balance exercises can also be practiced when supervised by an accredited health professional such as a physiotherapist. Balance exercises may be done 2-3 times per week.
- Suitable balance exercises include exercises undertaken when standing, minimising upper limb support and reducing the base of support. Examples can be found on the Physiotherapy Exercise website. Alternatives are group-based exercises such as Tai Chi.

NHMRC Grade: A

Evidence base: A, consistency: A/B, clinical impact: A, generalisability: A, applicability: A.

Considerations for health professionals

We now know that exercise is safe and is not associated with an increased risk of relapse in MS. In fact, people who exercised often showed reduction in their relapse rates[68,87].

The current physical activity guidelines for people with mild to moderate MS are prescribed at two levels; general (recommendations for people who are irregularly or infrequently physically active) and advanced (for people who are regularly participating in an exercise program and/or people who are seeking greater benefits from exercise training).

Care is needed to ensure that people with MS are exercising at a level that is suitable for them. It is likely that uptake of the recommendations by people with MS will be enhanced by the use of behavioural change tools; for example to assist individuals to establish goals and overcome perceived barriers to exercise[95].

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 and resistance 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).

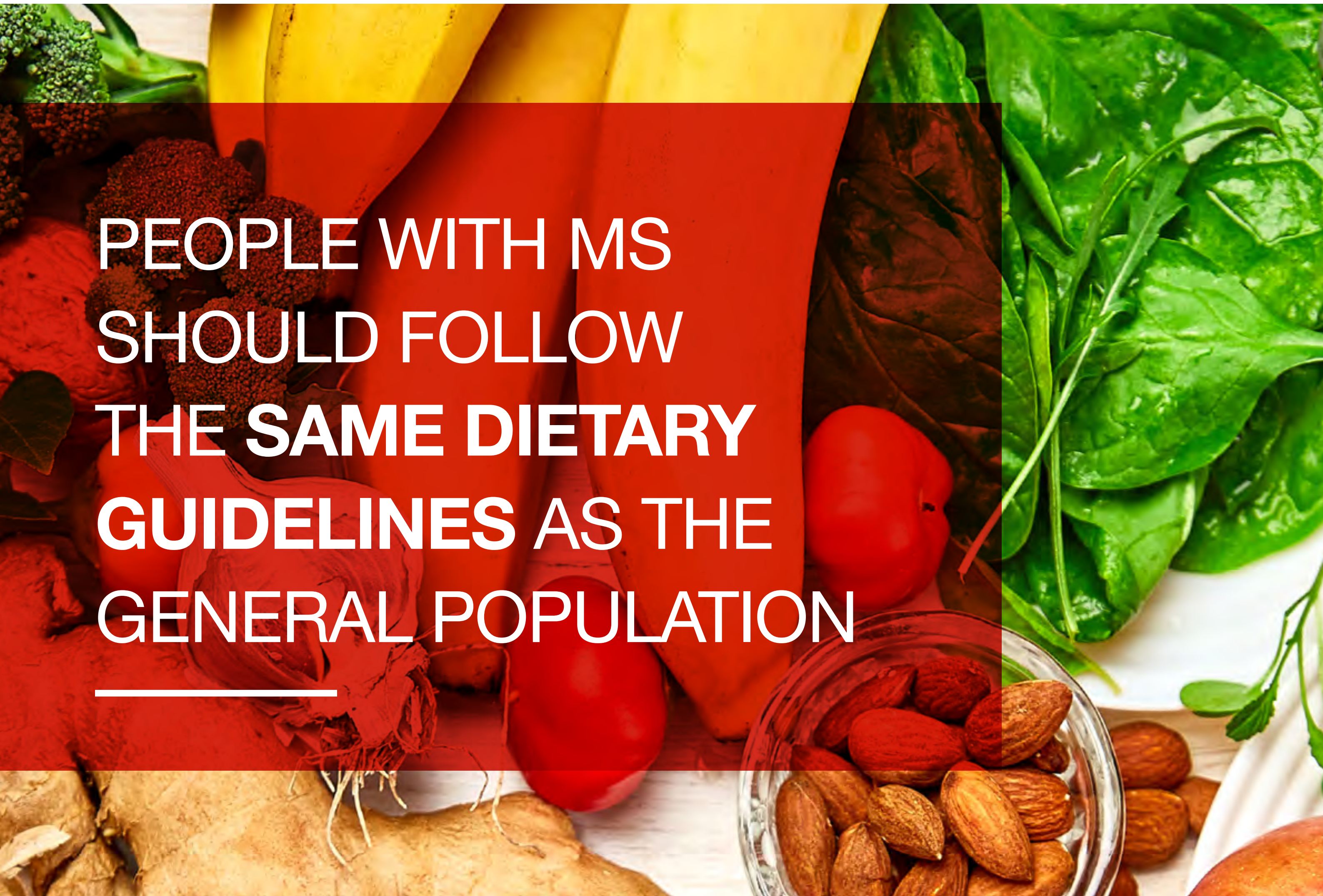
Improvements in physical fitness, physical function, and/or symptomatic and social participation outcomes may result from exercise participation in people with more severe disability[83,84].

Diet

There is a great deal of interest in the impact of diet on the management of various chronic diseases, and MS is no exception. The MS community wants to know if there is any effect of diet on MS and to use this information to make informed choices.

Several special diets have been promoted to people with MS as having potential benefits on disease progression and outcomes. These include the Swank diet (saturated fat restricted to <20g/day), Wahls modified Paleolithic diet (high in meat, vegetables and fruits; no dairy, eggs, legumes or grains), the Overcoming MS diet (low in saturated fat; moderate in seafood, avocado and nuts; no meat, dairy, egg yolks or refined foods), a ketogenic diet (low carbohydrate, moderate protein, high fat), and a fasting mimicking diet. Many of these diets have common themes and call for the elimination of items such as sugar, processed foods, gluten, dairy, eggs or meat.

Despite the well-intentioned nature of these special diets, there is insufficient evidence to recommend any of these diets for people with MS. **Based on the available evidence, the take-home message is that people with MS should follow the same dietary guidelines as the general population - the *Australian Dietary Guidelines*[96].** It is important to note that only about 4% of the general population adhere to these guidelines. People with MS may benefit from consulting an Accredited Practising Dietitian to help them identify ways to best integrate these guidelines into their lives, factoring in personal preferences and needs.



PEOPLE WITH MS SHOULD FOLLOW THE **SAME DIETARY GUIDELINES** AS THE GENERAL POPULATION

The link between diet and MS disease progression

A person's diet includes all the foods and beverages they consume. Nutrients are the components found within foods and beverages that are essential to health and life. The nutrients within foods and beverages form a complex matrix and their interactions in the body lead to the health benefits of the overall diet.

Scientific research into overall patterns of eating or diet can be difficult to implement. Consequently, many studies have limited their scope to individual foods, individual nutrients or nutrient combinations.

Studies investigating diet and MS disease progression have been outlined below. Supplements are included as a separate topic in this document.

A Paleolithic diet and MS

A Paleolithic diet generally excludes legumes, grains and dairy, and is high in meat, fruit and vegetables. A small pilot study showed that a multimodal intervention, including a modified version of a Paleolithic diet, was beneficial for fatigue and quality of life in people with progressive MS; however, the study involved factors other than diet, and any benefit cannot be attributed to the diet alone[97].

Another small pilot trial by the same team showed benefits of a modified Paleolithic diet on fatigue in people with relapsing remitting MS[98]. However, further evidence from larger studies is needed before recommendations can be made regarding a Paleolithic diet for people with MS.

A low-fat, plant-based diet and MS

A low-fat, plant-based diet (high in starchy plant foods, and excluding animal products and vegetable oils), has been shown to have beneficial effects on fatigue, body mass index (BMI) and metabolic biomarkers in people with MS, but showed no improvement in disability outcome measures[99]. Larger studies are needed to assess any benefits of a low-fat, plant-based diet for people with MS.

A gluten-free diet and MS

Gluten is found in some grains, including wheat, barley and rye. A gluten-free diet excludes all sources of gluten. A small clinical trial found a positive effect of a gluten-free diet on disability outcomes and MS lesion activity in people with relapsing remitting MS[100]. Further evidence from larger studies is needed before recommendations can be made regarding a gluten-free diet for people with MS.

A dairy-free diet and MS

Although one study has shown a correlation between intake of cow's milk and prevalence of MS[101], there is no evidence to suggest that consuming dairy products is associated with MS disease progression. Therefore, recommendations cannot be made to support a dairy-free diet.

Coffee and MS

Drinking coffee has been the focus of several research studies[102–105]; however, most have focused on the impact of coffee intake on the risk of developing MS.

One study has shown that consuming coffee occasionally or daily (compared with never drinking coffee) was linked with lower disability in people with relapsing remitting MS[105].

However, many factors that might affect both coffee-drinking and MS progression were not taken into account. Therefore, there is insufficient evidence to support any recommendations regarding drinking or abstaining from coffee.

Alcohol and MS

One study showed that, compared with never drinking, moderate consumption of alcohol was linked with lower disability in people with relapsing remitting MS[105]. However, many factors that might affect both alcohol-drinking and disability were not taken into account.

A second study found that both higher total alcohol consumption and red wine intake were associated with lower disability in people with MS[106]. However, it is possible that people with the higher disability scores drank less alcohol than those with the lower disability scores as a result of their disability; hence, the direction of the relationship is unclear. There is insufficient evidence to support any special recommendations for alcohol consumption for people with MS.

Sodium and MS

Major sources of sodium are processed foods (e.g. pizza, cookies) and processed meats. The WHO recommends a reduction in sodium intake to reduce blood pressure and the risk of cardiovascular disease, stroke and coronary heart disease[107].

One study showed that higher sodium intake (as measured by sodium excretion in urine samples) was associated with increased disease activity in people with MS[108]; however, another study reported no association[109]. Hence, there is no conclusive evidence on the role of sodium intake in MS disease progression.

Fish consumption and MS

Fish, particularly oily fish, is high in both vitamin D and omega-3 polyunsaturated fatty acids.

One study has shown that consuming fish at least once a month (compared with less than once a month) was linked with lower disability in people with relapsing remitting MS[105].

However, many factors that might affect both fish consumption and MS progression, such as other dietary components and lifestyle characteristics, were not taken into account.

In a cohort of people with MS, recruited through social media and surveyed online, those consuming fish were more likely to have better quality of life and less disability[110]. However, all data were self-reported and the cohort was highly educated and engaged with lifestyle interventions shown to affect the risk of MS progression, which may have biased the results. Therefore, there is no conclusive evidence on the role of fish consumption in MS disease progression.

Other nutrients, foods or eating patterns

A review of the published studies related to MS and diet and found no consistent evidence for improvements in disease outcomes when looking at nutrients, foods or eating patterns[111]. While numerous dietary components and patterns have been studied in MS, those that were considered to be less relevant to MS outcomes have not been included in this document.

Information that needs clarifying

Are any of the special diets beneficial for treating MS?

There is currently no robust evidence to support any of the special diets promoted for people with MS, as outlined in the summary of this section; hence, these diets are not recommended for the treatment of MS.

Are the special diets safe for people with MS?

The restrictive nature of many of the diets that are popular within the MS community exclude key foods and food groups, perhaps unnecessarily. Further high-quality research is needed to support the safety of these special diets.

Recommendations for people with MS

There is insufficient scientific evidence to recommend any special diet for people with MS. More research is needed.

We recommend that people with MS follow the *Australian Dietary Guidelines*[96]. These guidelines include the following recommendations for adults:

- Enjoy a wide variety of nutritious foods from these five 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 general health of people with MS, although whether this will improve MS outcomes needs further research.

People with MS may also benefit from the help of an Accredited Practising Dietitian to help identify ways to best integrate these guidelines into their lives, factoring in personal preferences and needs.

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 health professionals

When people with MS are seeking to modify their diet, or where dietary guidance is needed (e.g. poor nutrition, obesity), clinicians should refer patients to Accredited Practising Dietitians.

The Dietitians Association of Australia website can help with locating an Accredited Practising Dietitian. Additionally, the *Australian Dietary Guidelines*[96] is an excellent resource for adults seeking general guidance on healthy eating.

Gut health

The human microbiome refers to the complex and diverse populations of microbial cells, primarily bacteria, that naturally live within the body[112]. The 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)[113].

However, differences in the gut microbiome are seen even within people who are considered healthy and therefore more research is required in this area[114]. While there is emerging evidence to suggest that the gut microbiome may influence processes involved in MS, at this stage, **there is not enough evidence to recommend any of the various methods which are sometimes advocated for their ability to change or improve the microbiome of people with MS and their claimed benefits on MS outcomes.**

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

The link between gut microbiome and MS

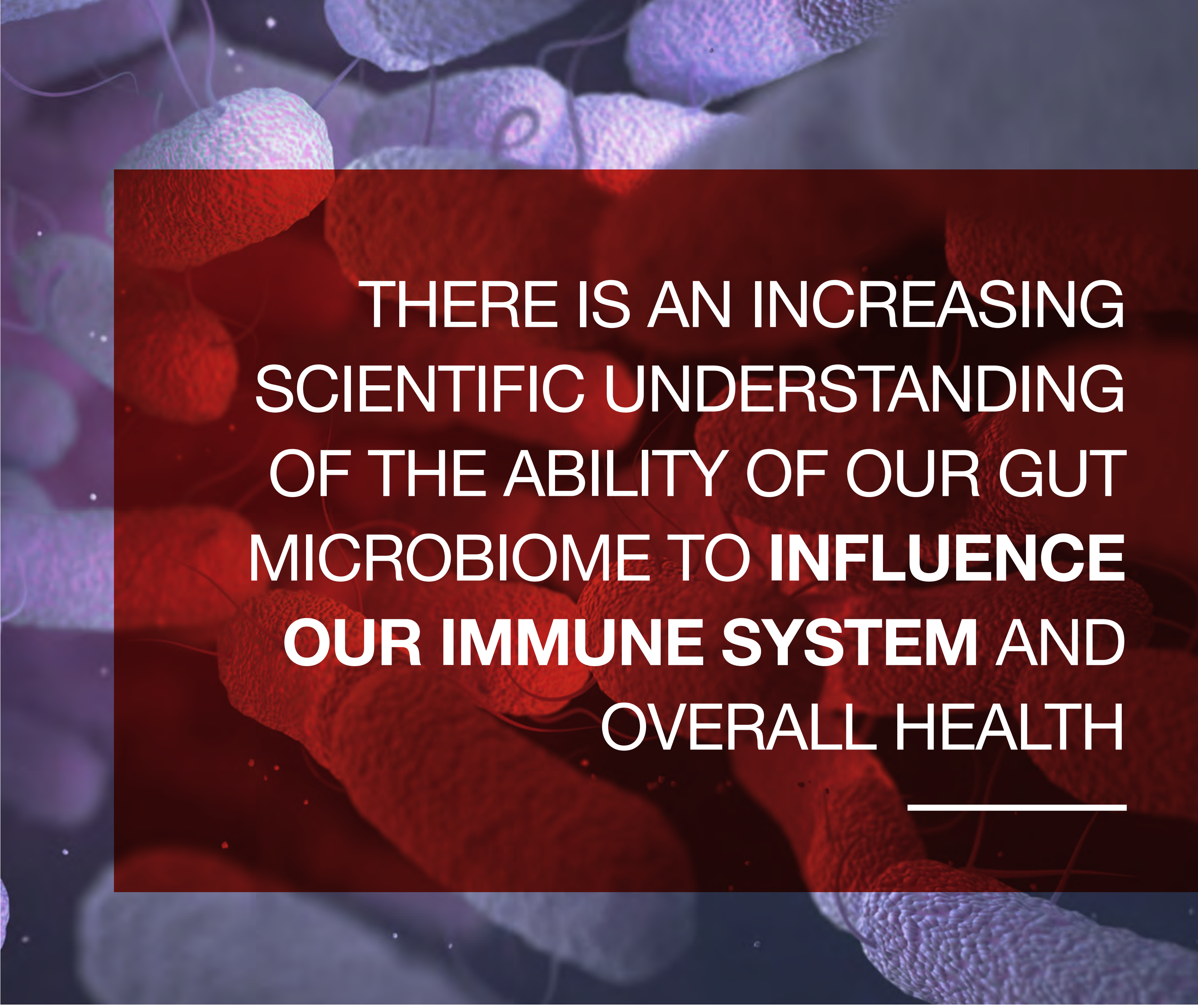
There is an increasing scientific understanding of the ability of our gut microbiome to influence our immune system and overall health[115].

As MS is an immune-mediated disease, the gut microbiome has been studied in people with MS, and one study has revealed there are significant differences in the composition and function of bacteria within the gut of people with MS, compared with people who do not have MS[116]. This finding has been confirmed and was consistent in people with different genetics, ages and genders[117,118].

Studies in the laboratory have shown that even transplanting microbiome samples from people with MS to laboratory (animal) models without MS, was enough to result in changes to the immune system similar to that seen in MS, which has an autoimmune basis[116,118].

This further strengthens the evidence for the role the gut microbiome may be playing in MS. However, it is clear that more research is required to understand what defines a health microbiome as there are variations seen even between people who are considered healthy[114].

Several methods are being investigated for their ability to change or improve the microbiome of people with MS, with the aim of improving MS outcomes. As these have been identified by the MS community as being of particular interest, some of these interventions are discussed in this section although the evidence in this area is limited.



THERE IS AN INCREASING SCIENTIFIC UNDERSTANDING OF THE ABILITY OF OUR GUT MICROBIOME TO **INFLUENCE OUR IMMUNE SYSTEM** AND OVERALL HEALTH

Faecal microbiota transplant

Faecal microbiota transplant (FMT) is a process whereby a microbiota sample from a healthy donor is donated to another person and is transplanted through an infusion in the colon, or delivery through the upper gastrointestinal tract[119].

This therapy has been previously used with success to treat *Clostridium difficile* infections, and due to the emerging role of the microbiome in several chronic diseases including MS, the use of FMT as a potential treatment option has been of growing interest.

Excluding preliminary case reports[120], there are no results from clinical trials of FMT in MS, although one is ongoing[121].

There are potential safety concerns of FMT including infection and death[122], and the long-term effects of FMT are not known. Due to the lack of supporting evidence and possible 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, i.e. a parasitic worm (e.g. hookworms). This therapy is theorised to alter the immune response and as such have an effect on MS[123,124].

Some small research studies support the safety of helminth therapy in the short term, and others have shown improvements in immune markers in people with MS[124]". However, one longer study found people with MS undergoing helminth treatment had severe gastrointestinal symptoms[125]. Based on the limited evidence, helminth therapy cannot be recommended for people with MS.

Probiotic supplements

Probiotics contain live microorganisms that may be beneficial for people when administered in adequate amounts[126]. Probiotics are available in the form of supplements (capsules) and in some foods (e.g. fermented foods such as yoghurt and sauerkraut).

Two clinical trials have investigated the use of probiotics in MS[127,128]. These initial trials have reported improvements in MS including the reduction of some markers of inflammation, and improvements in mood and quality of life. However, further studies are required to confirm these results in larger numbers of people 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 what constitutes a healthy microbiome across individuals[114]. Therefore, products and services that are advertised as aiming to restore the microbiome of people with MS are not currently supported by evidence.

Recommendations for people with MS

There is not enough evidence to make specific recommendations regarding interventions such as FMT, helminth therapy or probiotics for people with MS to improve their disease outcomes.

At the moment, the best way to achieve a healthier gut microbiome for people with MS is the same as that for the general population. This is to follow the *Australian Dietary Guidelines*[96] (as recommended in the previous sections) or 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 diets such as these has been demonstrated to improve beneficial gut bacteria[129,130]. These foods contain nutrients that benefit the microbiota such as dietary fibre (i.e. soluble, insoluble and resistant starch), polyphenols, and omega-3 fatty acids[131].

In contrast, regular consumption of foods that are high in saturated fat, salt, and sugar appear to have a negative effect on the microbiota profile[131].

Other lifestyle factors such as physical activity[132], smoking[133], and drinking alcohol[134] also influence the gut microbiome.

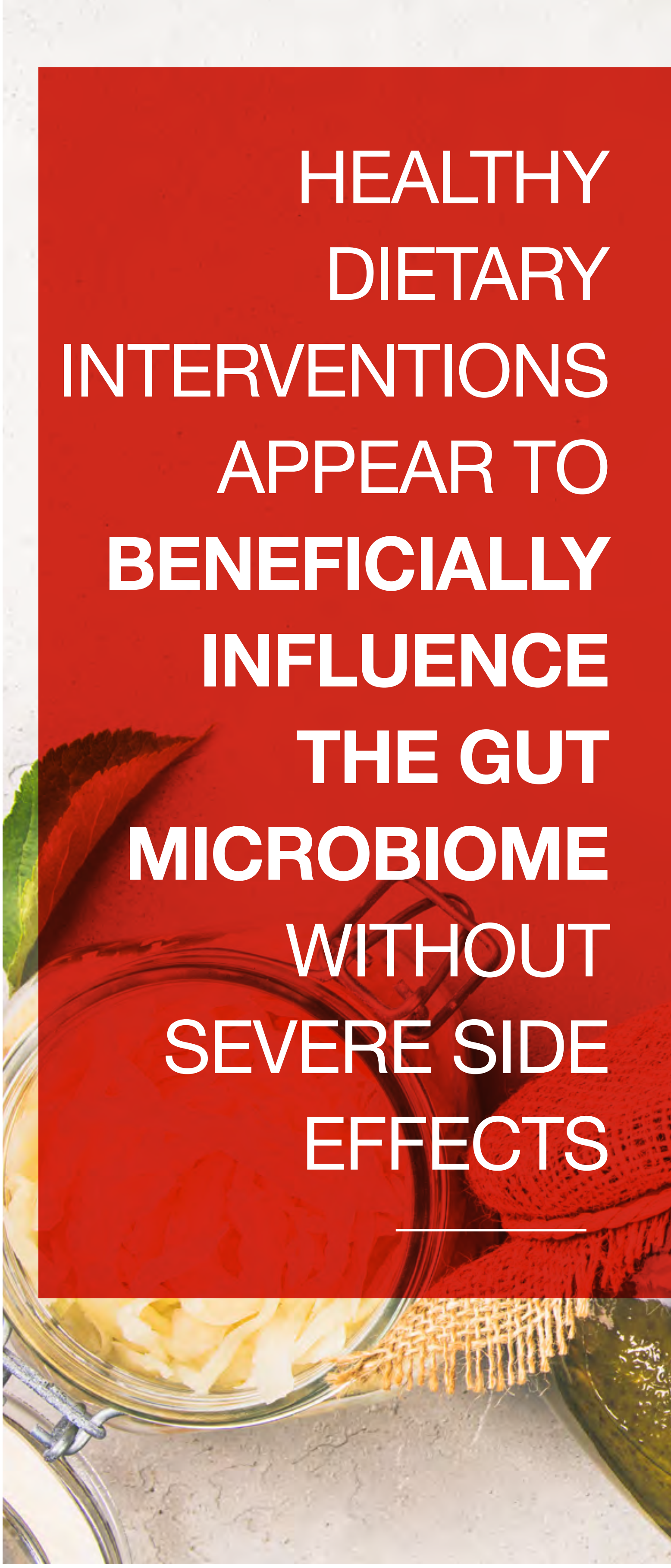
The effects of microbiome changes on MS are currently unclear and so improving diet, increasing physical activity and not smoking are recommended to maintain overall good health in people with MS.

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 health professionals

There is currently insufficient clinical data to recommend the use of therapies that target the microbiome in people with MS. Probiotic and fibre supplements appear to be generally well-tolerated although some therapies such as FMT and helminth therapy have potentially significant risks associated with their use.

In contrast, healthy dietary interventions appear to beneficially influence the gut microbiome without severe side effects. Therefore, referrals to Accredited Practising Dietitians may assist with adherence to healthy dietary recommendations, which will have positive effects on the microbiome and overall health of people with MS.



HEALTHY DIETARY INTERVENTIONS APPEAR TO **BENEFICIALLY INFLUENCE THE GUT MICROBIOME** WITHOUT SEVERE SIDE EFFECTS

Supplements

Supplements include vitamins (e.g. biotin), minerals (e.g. magnesium) and various other compounds either synthetic or plant derived (e.g. ginkgo biloba), designed to increase the quantity of the specific nutrient consumed. Supplements are available in various forms, such as capsules, liquids and powders.

When people are diagnosed with a deficiency of a particular vitamin or mineral, or in special circumstances (e.g. when pregnant or breastfeeding), supplements can be effective in replenishing and maintaining amounts of vitamins and minerals in the body that are necessary for good health.

Several dietary supplements have been studied for their possible benefits in people with MS. Some of the most commonly studied supplements are the antioxidant alpha lipoic acid, the herbal supplement ginkgo biloba and high-dose biotin (vitamin B7). Despite these supplements and others being advertised for their supposed benefits in people with MS, the body of evidence is not conclusive or robust enough to recommend their use for people with MS.

The overall take home message is that there is currently not enough evidence to support the use of any supplements for people with MS. A balanced diet, as recommended in the section on diet and nutrition in this document, in line with the *Australian Dietary Guidelines*[96] and possibly implemented with the help of an Accredited Practising Dietitian are the most effective ways to ensure all the nutritional needs of people with MS are being met.

Note: this section will not discuss vitamin D. There is a separate section dedicated to vitamin D in this guidance document.

FURTHER **HIGH-QUALITY RESEARCH IS NEEDED** BEFORE SUPPLEMENTS CAN BE RECOMMENDED

The link between supplements and MS

Despite many supplements being advertised for their possible benefits in MS, the evidence is not strong enough to make recommendations for their use.

A recently published systematic review has thoroughly critiqued and summarised the findings from studies that exist to-date on the various supplements which have been investigated for their effectiveness in MS, except vitamin D and polyunsaturated fatty acid supplements[135]. The information from this review has been used to inform the section below.

Are there benefits of any supplements on MS?

Of the abundance of supplements that exist on the market today, only a relatively small number have been studied in a scientifically rigorous way, and an even smaller proportion studied specifically in people with MS.

The supplements that have been most studied in people with MS are:

- alpha lipoic acid (an antioxidant fatty acid that can be found in foods such as organ meats, spinach and yeast)
- ginkgo biloba (a plant extract)
- vitamin A (found in fish liver oils, milk, green leafy vegetables, and red, orange, and yellow vegetables and fruits)
- high-dose biotin (vitamin B7)
- inosine (chemically synthesised antioxidant)
- carnitine (derived from an amino acid which makes up proteins)
- green tea extracts (a plant extract)
- coenzyme Q10 (an antioxidant)
- probiotics (living cultures of bacteria or yeast)
- curcumin (a compound which is the main component of turmeric)
- *Andrographis paniculata* (a plant extract)
- ginseng (a plant extract)
- lemon verbena (a plant extract)

All of these compounds have at least one study reporting that they improve at least one outcome relating to progression of MS such as reduced brain atrophy as measured by MRI or other symptoms of MS such as fatigue and depression compared to placebo[135].

Clinical improvements in disability levels were reported in three trials that investigated either biotin, alpha lipoic acid or probiotics[136-138].

Despite these findings, further high-quality research is needed before supplements can be recommended for use in people with MS.

Polyunsaturated fatty acids

Polyunsaturated fatty acids are found in fish (omega-3) as well as in nuts, seeds and grains (omega-6). Three intervention studies investigated the effects of polyunsaturated fatty acid supplementation in people with MS, although the results were contradictory. One study showed that fish oil supplementation reduced proinflammatory cytokine levels in the serum of people with relapsing remitting MS, but had no effect on MS relapse rate or disability progression[139].

Two other studies that investigated the effect of polyunsaturated fatty acid supplementation on disease activity in people with MS found no significant effect[140,141], although one of the studies did show a trend towards reduced disease progression[141].

Overall, the studies were underpowered to detect small to medium changes in disease outcomes and had other substantial limitations, such as high rates of dropout and multimodal interventions.

Information that needs clarifying

What is the evidence for supplements treating MS?

There are many supplements that are advocated as being beneficial for people with MS. Apart from the supplements that have been investigated in clinical trials discussed in the above section of this document, there are no other supplements that have scientific evidence to support their use in MS.

Most dietary supplements have been investigated in only a small number of short-term studies, usually with small numbers of participants. Therefore, while some dietary supplements may have promise for their use in MS based on preliminary studies discussed above, further studies are required to determine their safety and effectiveness in people with MS.

What about high-dose biotin?

The use of high-dose biotin as a treatment for MS is of great consumer and research interest, due to studies initially showing promising results.

The mechanism by which high doses of biotin might be effective in treating MS is currently unclear; however, it is hypothesised to aid in remyelination and improve energy production within the brain[142].

There is a growing number of clinical trials that have investigated the use of high-dose biotin. Most notably, there were two randomised controlled trials that investigated a specific formulation of high-dose biotin called MD1003.

One trial of 154 people with progressive MS reported that those that received 12 months of high-dose biotin had higher rates of disability reversal, using the EDSS decrease and timed 25-foot walk, compared to placebo[143]. However, a second six month long study of 93 participants reported that high-dose biotin did not improve MS-related vision loss[144].

Are supplements safe for people with MS?

Many dietary supplements which are available to the general public are generally safe for people with MS. However, in a recent review of dietary supplements in MS[135], undesirable side effects have been reported with some of them.

Some notable undesirable effects that people with MS experienced when consuming supplements have been reported in studies of alpha lipoic acid[145], inosine[137,146] and green tea extract[147].

Adverse reactions include: dehydration and kidney problems with alpha lipoic acid[145], unusually high levels of urea in the serum of participants taking inosine[146] and abnormal liver function in participants taking green tea extract (leading to early termination of the trial)[147].

Can vitamin levels be too high?

Having levels of vitamins that are too high can be as harmful as having levels that are too low. In particular, excess amounts of vitamin A are stored in the liver and may be harmful[148], particularly during pregnancy. Consuming multiple supplements may also create increased health risks and should only be done under the guidance of a suitably qualified health professional.

Recommendations for people with MS

While some research has shown positive results with the use of supplements in people with MS, there is not enough evidence to recommend the use of any supplements in this population (also refer to the vitamin D section).

Furthermore, long term safety of some supplements also needs further investigation in people with MS and it is not known whether they interfere with MS medications. It is important that people with MS consult their medical team prior to taking any supplements.

We recommend that people with MS who already use dietary supplements and those interested in taking dietary supplements consult with their healthcare team to ensure that they are using supplements in a safe manner. We recommend a healthy diet in line with the *Australian Dietary Guidelines*[96] to ensure the nutritional needs of people with MS are being met.

Those modifying their diets for ethical or religious reasons or those with known deficiencies and pregnant women may be exceptions; and it is recommended that these people seek advice from a qualified professional to determine the most appropriate supplement(s) and dose to meet requirements in each case.

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 health professionals

A large proportion of people with MS consume dietary supplements without being advised to do so by a health professional. It is recommended that clinicians advise appropriately regarding the use and misuse of supplements and screen for prior and current dietary supplement use to make sure any are identified.

For people who are interested in taking high-dose biotin, it is important that they speak to a health professional to ensure they are consuming biotin in a safe way. The existing clinical trials suggest that high-dose biotin is generally well-tolerated; however, one case-report documented one person with MS who experienced myopathy that resolved after ceasing biotin[149].

High doses of biotin may also result in incorrect blood test results (e.g. troponin and thyroid-related outcomes[150]), which health professionals should be aware of when interpreting blood test results of patients consuming high-dose biotin.

Furthermore, there are some reports that high-dose biotin may have a negative effect on MS-related outcomes; however, this may be related to the study design and formulation used[151,152].

Vitamin D and sun exposure

There is strong evidence from observational studies suggesting that there is a role for vitamin D in the risk of developing MS and the risk of disease progression[153-155]. However, direct clinical supplementation trials have not substantiated the results from the observational studies.

To date, there are no published clinical trials investigating the effects of vitamin D supplementation on preventing the development of MS, or on the conversion rate from a first demyelinating event (FDE), including clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS), to clinically definite MS (CDMS). The clinical trials which have looked at vitamin D supplementation as a treatment or an intervention in the progression of MS have largely shown no beneficial effects[156-164].

There have been several observational studies that have investigated sun exposure in people with MS prior to diagnosis, and these have shown that people with MS have had lower exposure to sunlight than those without MS[165-168]. However, there are no published clinical trials to date that have looked at sun exposure and conversion from a FDE to CDMS.

Only one small clinical trial has been conducted evaluating the impact of ultraviolet (UV) light exposure on disease progression. In this trial, participants with CIS were randomised to exposure to narrowband UV-B phototherapy or placebo, which resulted in a 30% reduction in MS progression in those exposed to UV-B phototherapy. However, the results were not statistically significant due to the small sample size[169], but suggest that a larger trial is warranted.

The take home message here is that there is currently not enough evidence to recommend sun exposure or vitamin D supplementation to reduce the risk of developing MS or the risk of disease progression. More robust clinical trials are needed to determine the possible benefit of vitamin D supplementation and sun exposure for people with MS and the associated optimal doses.

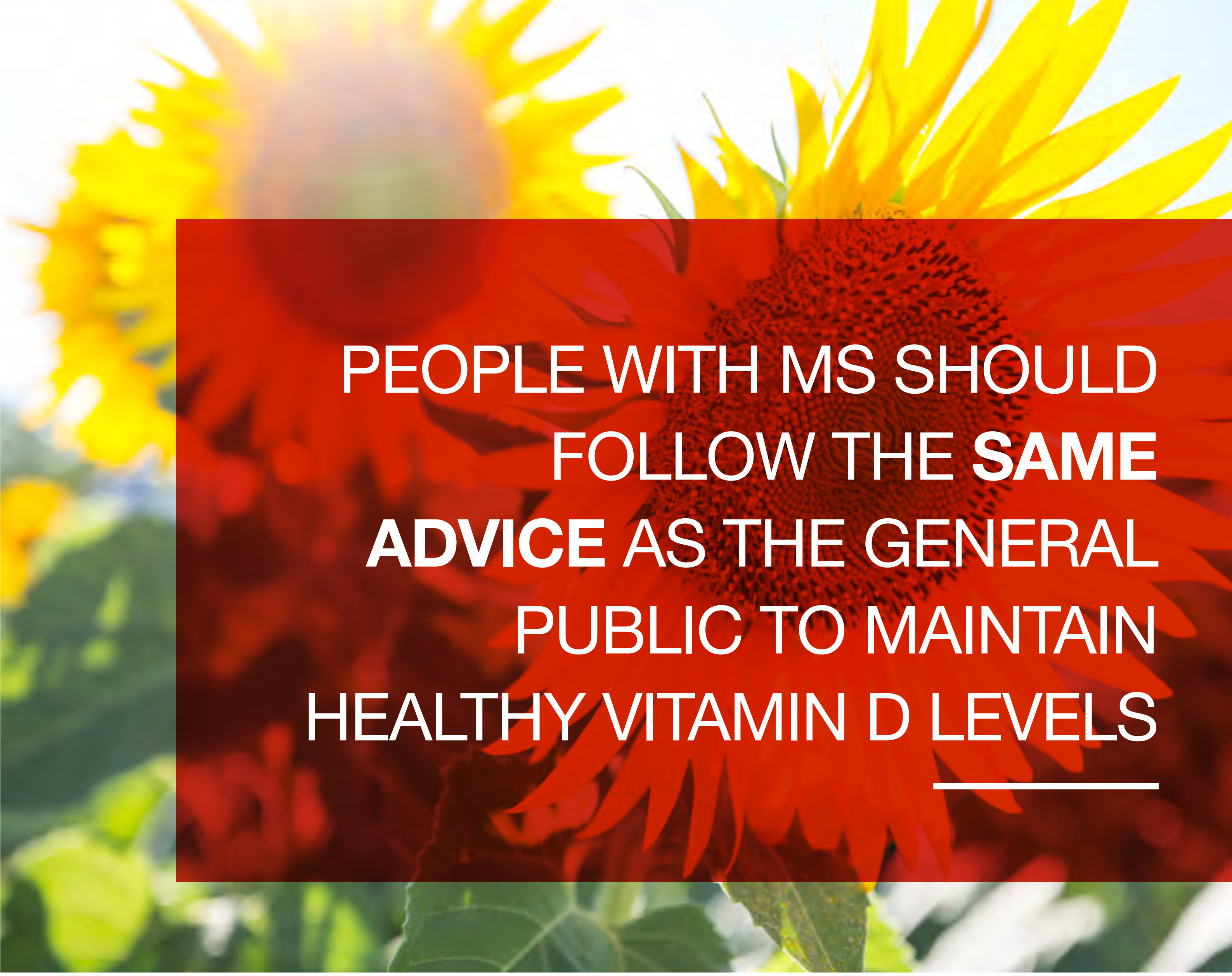
Experts recommend that people with MS follow the vitamin D recommendations of the NHMRC of Australia and the Ministry of Health in New Zealand for the general public[170], as well as advice for sun exposure for the general public by Cancer Council Australia[171], to maintain healthy vitamin D levels and obtain sufficient levels of sun exposure.

What are the sources and what is the biology of vitamin D?

Vitamin D has many functions in the human body. Its major role is in the regulation of calcium homeostasis and maintaining bone health.

In addition to this, and of relevance for MS, vitamin D has a potential role in modulating the innate and adaptive immune response[172].

Vitamin D is found in two forms, D3 (cholecalciferol), from animals, and D2 (ergocalciferol), from plants[173,174].



PEOPLE WITH MS SHOULD FOLLOW THE **SAME ADVICE** AS THE GENERAL PUBLIC TO MAINTAIN HEALTHY VITAMIN D LEVELS

The main source of vitamin D in Australia is exposure of the skin to sunlight (specifically the UV wavelengths). Other sources are dietary intake, with particularly high levels in oily fish (vitamin D3) and mushrooms grown in sunlight (vitamin D2), and dietary supplements (in Australia these are almost all vitamin D3).

Vitamin D can also be obtained by injections in cases where it is required immediately when treating acute deficiencies, although these are rarely used[173,175]. In Australia, the contribution of dietary intake to vitamin D is usually minimal[170].

Regardless of its source, vitamin D is transported from the skin or intestines to the liver where it is converted to the major circulating form known as calcifediol or 25-hydroxyvitamin D (25(OH)D). This circulating form is the one that is measured in the blood to determine vitamin D levels in the body. 25(OH)D is then converted to the active form responsible for its biological actions, known as calcitriol or 1,25-dihydroxyvitamin D (1,25(OH)2D).

Calcitriol production for systemic use, particularly for bone health, occurs in the kidneys but local conversion occurs in many tissues throughout the body[172].

Importantly, the major determinant of the blood 25(OH)D concentration in adult Australians is recent sun exposure.

The link between vitamin D, sun exposure and MS

The link between vitamin D and exposure of the skin to UV radiation from the sun is well-established.

The active form of vitamin D interacts with the immune system, and can reduce inflammatory immune responses[172]; this is a potential pathway for a beneficial effect in MS.

Additionally, exposure of the skin and eyes to UV radiation has impacts on immune function independent of a vitamin D pathway[174], suggesting that exposure to UV radiation may have an effect on the risk of MS development or progression through both vitamin D-dependent and vitamin D-independent pathways.

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

A meta-analysis of 11 studies[153] as well as other studies[176-178] that measured 25(OH)D levels in the blood (plasma or serum) prior to the onset of MS, found that people who went on to develop MS had lower 25(OH)D levels compared to those who did not.

In addition, a number of risk variants in genes related to vitamin D metabolism and function, including vitamin D binding protein, vitamin D receptor, and multiple cytochrome p450 vitamin D synthesis/catabolism enzymes have been implicated in the risk of MS development[179].

Moreover, these risk variants have been utilised in Mendelian randomisation studies which have indicated a causal relationship of low vitamin D with MS risk[180,181].

There have not yet been any published clinical trials which have looked at the effects of vitamin D supplementation on the risk of conversion from a FDE to CDMS.

However, studies are currently underway including the Vitamin D MS Prevention Trial (PrevANZ) and the Efficacy of Cholecalciferol (Vitamin D3) for Delaying the Diagnosis of MS After a Clinically Isolated Syndrome Trial (D-Lay-MS), which are assessing whether supplementation with vitamin D after the first attack suggestive of MS (FDE) can reduce the development of CDMS.

The results from the PrevANZ trial are expected in 2021, while the D-Lay-MS trial will be completed in 2023. Generally, conversion from a FDE to CDMS is considered progression of disease, but some studies do consider it as delaying disease onset and therefore classify any factor influencing time to conversion as risk factors.

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

Several clinical trials[156-164] have been conducted over the past two decades, which have evaluated the effects of different types of vitamin D supplementation at various doses, either alone or in combination with established MS medications like interferon-beta, on MS progression, including relapses, MRI activity, disability progression, and other elements of MS clinical course like fatigue.

Several meta-analyses have followed and have concluded that there are no significant benefits of vitamin D supplementation on the risk of relapse[182-184], disability progression[183,184] or MRI outcomes[184] in people with MS. One meta-analysis (including five studies) showed that there were increased relapse rates in groups that received vitamin D supplementation compared to placebo (+0.05)[183], while another meta-analysis (including twelve studies) suggested that higher doses of vitamin D supplementation were associated with higher relapse rates compared to low-dose supplementation (+0.15)[184].

However, the CHOLINE trial, which investigated the effects of 100,000IU cholecalciferol supplements every other week in people with relapsing remitting MS treated with interferon-beta, showed that the treated group had a lower two-year annualised relapse rate, lower EDSS and had fewer new hypointense T1-weighted lesions[185].

Despite the promising results from the CHOLINE trial, the weight of the clinical trial evidence suggests there may not be significant clinical benefit to vitamin D supplementation to improve outcomes relating to disease progression for people with MS, and there are possibly some deleterious impacts on relapse rate.

What is the link between sun exposure or UV radiation and the risk of MS?

Several observational studies have shown that people who have been diagnosed with MS have had significantly lower levels of exposure to sunlight or UV radiation than those without MS.

These studies looked at differences in sun exposure over varying periods of time before the first clinical signs of MS were seen in individuals - from three years prior to diagnosis, periods of childhood, to early adulthood - and found broadly consistent results[165-168].

However, the required dose of sun exposure or UV radiation has not yet been established, nor has a risk/benefit analysis been conducted to determine if the potential gains are worth the risks associated with increased sun exposure, such as skin cancer.

There has been a single clinical trial testing exposure to UV-B radiation (in a phototherapy booth) compared to no phototherapy on the conversion from CIS to CDMS. In this small trial (n=10 intervention; n=9 controls), there was a 30% reduction in the conversion from CIS to CDMS, although this did not reach statistical significance due to the small sample size[169].

However, this preliminary evidence suggests that exposure to the sun or UV radiation may have beneficial effects on the conversion to CDMS. Further clinical trials are needed to confirm these findings.

What are the links between exposure to the sun or UV radiation and the progression of MS?

There has been a relatively small number of studies that have looked at the relationship between sun exposure and MS disease progression[186-191].

One of the studies followed people after a FDE, and showed that higher sun exposure before a FDE was associated with reduced progression to CDMS[191].

Results from this study also showed that those who increased their sun exposure during the five years after their FDE showed reduced conversion to CDMS, and those that were diagnosed with CDMS showed reduced relapses.

This result is not suggestive of reverse causality but instead a potential beneficial effect of increasing sun exposure on clinical progression.

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

There have been far fewer studies on sun exposure than vitamin D supplementation in relation to possible benefits to MS symptoms.

Findings on whether vitamin D supplementation is beneficial for the treatment of MS symptoms are mixed.

One study has found that higher levels of vitamin D in serum correlated with lower levels of depression, but not fatigue[189], while another found that vitamin D supplementation over six months decreased fatigue significantly in people with MS[158].

Several studies have also looked at vitamin D supplementation or serum levels and found no significant effects on depression, anxiety, fatigue or cognition[161,190,192,193].

One longitudinal study showed an association between greater sun exposure and reduced depression and fatigue, although a similar effect was not seen for anxiety or cognition[193].

Noting that the 25(OH)D level is a marker of vitamin D status, derived from both dietary vitamin D and recent sun exposure (and does not distinguish between them). One study has found that higher serum 25(OH)D levels correlated with lower levels of depression, but not fatigue[189].

Taken together, the above results suggest that sun exposure and/or vitamin D supplementation may improve symptoms of MS, although the evidence is not strong enough to make any recommendations at this stage.

Information that needs clarifying

Why is there disparity between results from observational studies of 25(OH)D levels and trials of vitamin D supplementation in MS progression?

Observational studies consistently show that low sun exposure and/or low 25(OH)D levels are associated with increased risk of developing MS and, to a lesser extent, more rapid disease progression.

In contrast, findings from vitamin D supplementation trials provide little evidence to support a benefit. This could relate to the different source of vitamin D (sun exposure vs. oral intake), or that sun exposure and 25(OH)D levels reflect the combined immunomodulatory effects of vitamin D-dependent and independent pathways.

Alternatively, the apparent effects of sun exposure/25(OH)D could be due to an unmeasured confounding factor, although there is indirect evidence from epidemiological[154,194] and genetic[180,181,195] studies which would refute this.

Further studies are needed and until there is more clarity, neither sun exposure nor vitamin D supplementation can be recommended for the prevention or treatment of MS.

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Further studies are needed and until there is more clarity, neither sun exposure nor vitamin D supplementation can be recommended for the prevention or treatment of MS.

However, vitamin D supplementation, if required, for the maintenance of adequate 25(OH)D levels is important in the clinical management of people with MS for benefits for musculoskeletal health.

Is vitamin D safe?

Vitamin D supplementation has been found to be generally safe in people with MS and not associated with adverse effects on calcium or phosphate levels[161,196,197], even at reasonably high dosages of up to 280,000 IU/week over a 28-week period[198].

Recommendations for vitamin D intake are provided at the end of this section. For musculoskeletal health, the current recommendation is for maintenance of 25(OH)D level >50nmol/L.

There is some concern arising from the two meta-analyses of vitamin D supplementation in the treatment of MS, which have indicated that supplementation was associated with higher annualised relapse rate.

One meta-analysis showed a 0.05 increase in relapse rate among those receiving supplementation[183], while the other showed a 0.15 increase in relapse rate among those receiving high-dose supplementation (2,857-10,400 IU) compared to those receiving low-dose supplementation (800-1,000IU)[184].

As both meta-analyses note, there is a marked heterogeneity in the analysed study designs, with some studies investigating vitamin D supplementation alone and others as an add-on therapy, all with varying doses and comparators. Thus, although the studies are evaluated together to determine a pooled measure of association, there is marked heterogeneity such that these results should be evaluated with caution.

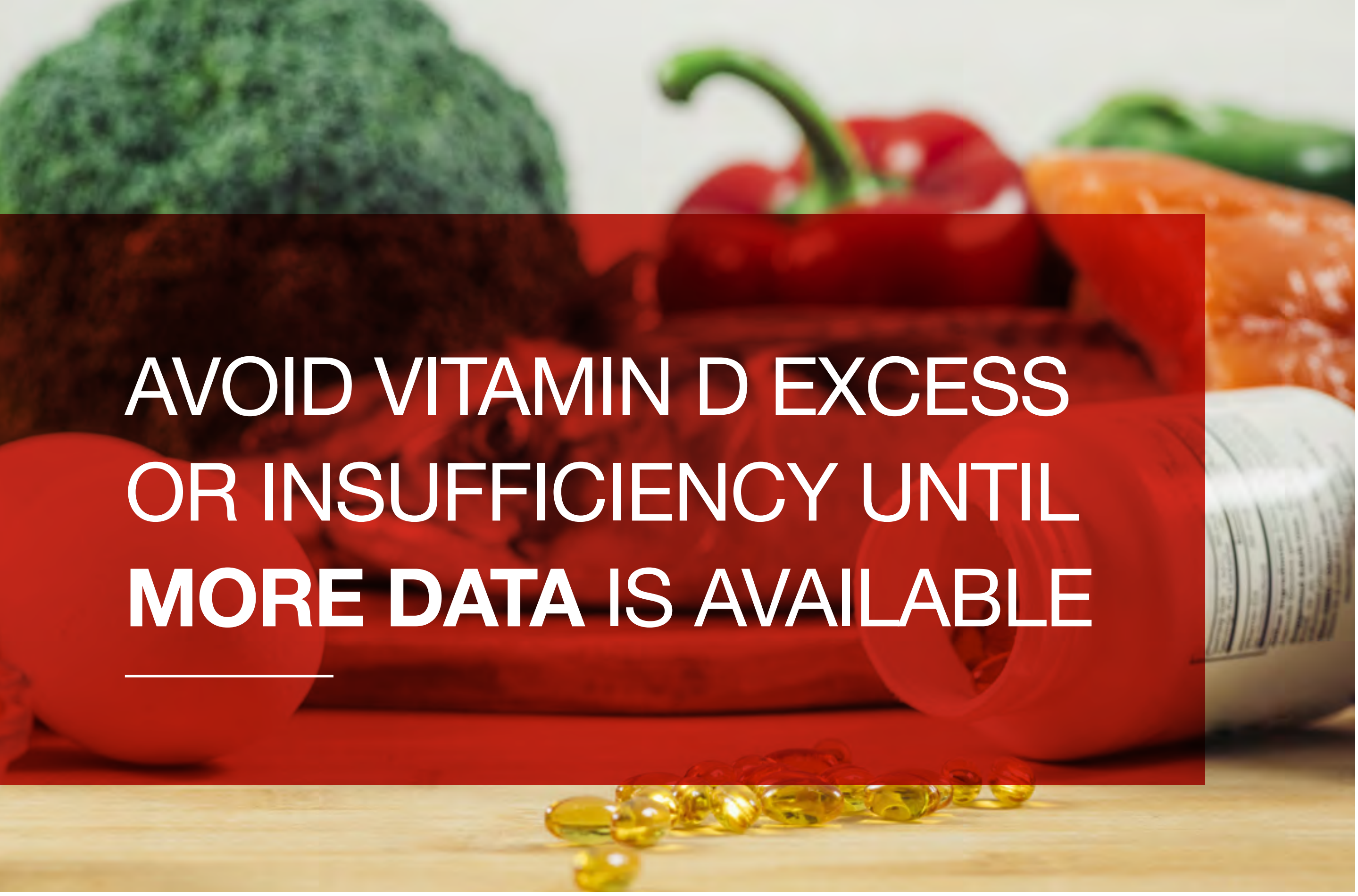
Moreover, the McLauglin et al. meta-analysis, which found the deleterious impact of high-dose supplementation compared to low-dose supplementation, was able to exclude such studies and just examine vitamin D supplementation compared to placebo[184].

However, the Zheng et al. meta-analysis, with only five studies analysed, was not able to undertake such analyses[183].

Given the multi-varied studies which have shown a range of vitamin D doses are not deleterious to health, it can be asserted that supplementation is not hazardous.

The risks of sun exposure are well-described in Australia: primarily skin cancers (melanoma, keratinocyte cancers), eye conditions (cataracts, pterygium) and reactivation of latent virus infections (e.g. cold sores).

It seems likely that optimal sun exposure for vitamin D synthesis is short periods in the sun most days of the week. This is a pattern of sun exposure that is unlikely to incur an increased risk of adverse effects[171].



AVOID VITAMIN D EXCESS OR INSUFFICIENCY UNTIL **MORE DATA** IS AVAILABLE

Recommendations for people with MS

Despite the broad preliminary evidence base suggesting sun exposure and vitamin D may have a role in preventing MS onset and progression, evidence from clinical trials cannot currently answer questions around the optimal level of vitamin D intake, sun exposure, or 25(OH)D in people with MS.

The general advice is that people with MS should follow the vitamin D intake recommendations of the NHMRC of Australia and the Ministry of Health in New Zealand[170], and sun exposure guidelines for the general public provided by Cancer Council Australia[171], which are summarised below.

Vitamin D

Adequate intake for general public	**µg/day**	**IU**
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 general public	**µg/day**	**IU**
Infants (0-12 months)	25	1,000
Children, adults, pregnancy and lactation	80	3,200

Sun exposure

Adequate levels of sun exposure are recommended based on location, time of the year and skin colour.

Vitamin D production from sun exposure only occurs at a UV index above 3.

Consider the average monthly UV indices for these capital cities, as described by Gies et al[199] and replicated below.

During months where ambient UV is 3 or lower, use of vitamin D supplements to maintain sufficiency (>50nmol/L) may be appropriate.

Location	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Darwin	12.3	12.6	12.5	11.1	9.2	8.2	8.7	10.2	11.9	12.6	12.4	12.0
Brisbane	11.8	11.2	9.5	6.9	4.8	3.7	4.1	5.4	7.4	8.9	10.5	11.3
Perth	11.8	11.0	8.6	5.8	3.8	2.8	3.0	4.3	6.1	8.1	9.8	11.4
Sydney	10.5	9.5	7.5	5.2	3.2	2.3	2.5	3.6	5.3	7.1	8.7	10.0
Canberra	10.7	7.7	6.9	4.8	2.9	1.9	2.2	3.3	5.0	6.8	8.5	10.6
Adelaide	11.2	10.1	7.8	5.1	3.0	2.1	2.3	3.4	5.2	7.2	9.2	10.7
Melbourne	10.3	9.0	7.0	4.4	2.4	1.6	1.7	2.8	4.3	6.3	8.3	9.8
Hobart	8.0	7.0	4.0	3.0	1.0	1.0	1.0	2.0	3.0	4.0	6.0	7.0

Considerations for health professionals

There has been increasing interest in the impacts of sun exposure and vitamin D on MS risk and progression, which has led to many people with MS taking vitamin D supplements and increasing their sun exposure, hoping for beneficial effects on their disease progression. However, there are many uncertainties.

The desired 25(OH)D level to aim for is unclear, as is whether taking a supplement compared to vitamin D derived from sun exposure has a different effect. The US National Institutes of Health have defined vitamin D sufficiency, primarily for musculoskeletal health, as a serum 25(OH)D level of >50 nmol/L and recommend supplementation only if a patient is well below this level.

Within the MS field, there have been many different recommendations for the optimal 25(OH)D level, particularly in winter. One pragmatic approach to this is to aim for the levels that people without MS achieve in summer, around 80-100 nmol/L, year-round.

Measuring blood 25(OH)D levels on a regular basis is not recommended in many countries including Australia. Avoidance of high levels (>120 nmol/L) is probably wise, although this is not conclusively supported by well-conducted clinical studies.

It is important to note that, as with all vitamin supplementation, more is not necessarily better, so overloading the system with too much vitamin D could theoretically be as detrimental as not enough. Pragmatically, it would seem best to avoid vitamin D excess or insufficiency until more data is available.

Weight and obesity

It is known that being overweight or obese is harmful to human health generally, and has been scientifically linked to many conditions, including MS. Experts have suggested that being overweight or obese, particularly during childhood or adolescence, is a risk factor for developing MS.

There are some indications that being overweight or obese in adulthood is associated with more rapid disease progression in those already diagnosed with MS, and is linked with the exacerbation of symptoms such as depression and/or other conditions, further worsening the clinical course of MS.

The overall message is that it is beneficial for people with MS to maintain or aim for their weight to be within the healthy range, irrespective of their stage of disease.

IT IS BENEFICIAL FOR PEOPLE WITH MS TO **MAINTAIN OR AIM** FOR THEIR WEIGHT TO BE WITHIN THE HEALTHY RANGE

The link between obesity and MS

Obesity and being overweight are global health epidemics. The WHO classifies overweight and obesity based on the BMI of an individual, which is calculated from a measurement of a person's height and weight.

A BMI of 25kg/m^2 or greater is considered overweight and a BMI of 30kg/m^{2}or greater is considered obese. However, the use of BMI as a measure of obesity has been criticised as it does not separate lean body mass (including muscle mass) from body fat mass.

Studies have also shown that measures of BMI in people with MS underestimate the obesity of a person and are best suited to people who are of a healthy weight or overweight, rather than those who are obese[200,201]. Where possible, measures of obesity – percentage body fat, waist to height ratio or muscle mass (measured using CT scan or bioimpedance) – should be used as clinical measures.

In 2017-18, the Australian Bureau of Statistics (ABS) reported 67%[202] of the Australian population to be overweight with 31% classified as obese.

Approximately 1% of the Australian population are known to have MS, however, obesity data specific for people with MS have not been captured in the ABS surveys to date. Data from the Australian MS Longitudinal Study (AMSLS) show that 61% of Australian people with MS that participated in the study have a BMI that puts them in the overweight or obese categories[4].

Does overweight and obesity have effects on the risk of getting MS or when MS begins?

Scientific evidence suggests that being overweight or obese during childhood[203] and obese during adolescence[204] are risk factors for developing MS in later life.

Does overweight and obesity have an effect on MS disease progression?

Several studies have looked at the impact of being overweight or obese on MS progression, however, the results have been conflicting. While earlier studies did not find that carrying excess weight during adulthood was associated with disease progression[205,206], more recent studies have shown that excess weight is associated with an increased rate of disease progression[207-209].

Does being overweight or obese have an effect on MS symptoms?

One study found that being overweight or obese was associated with an increased risk of relapse[208]. Overweight and obese people with MS also reported more symptoms of depression[210,211].However, from these cross-sectional studies it is not clear whether the excess weight specifically caused the reported worse symptoms, and therefore further investigation is needed. Carrying extra weight is linked with comorbidities of MS, such as high blood lipid profiles and diabetes. These conditions may also worsen the clinical course of MS, leading to higher rates of disability, lower quality of life and an increased chance of relapse following a FDE[207,210]. Being overweight or obese is thought to put the body into a proinflammatory state, and may add to the neurological inflammation present in people with MS[209,212].

HAVING BODY WEIGHT IN THE **HEALTHY RANGE** HAS BEEN SHOWN TO HAVE MANY BENEFITS

Recommendations for people with MS

Having body weight in the healthy range (BMI $\geq 18.5\ \text{kg/m}^2$ and $\leq 24.9\ \text{kg/m}^2$) has been shown to have many benefits in the general population.

Few high-quality studies exist assessing the impact of being overweight or weight loss on the health of people with MS specifically. People with other chronic diseases have found improved disease outcomes after losing excess weight, and this may also be the case for people with MS.

A healthy weight range for people with all types of MS should be maintained or achieved by a balance of healthy eating and portion control, physical activity and stress management. This can be achieved with the guidance of suitably qualified health professionals including dietitians, physiotherapists and psychologists if needed.

We recommend people with MS follow the *Australian Dietary Guidelines*[96] and the guidelines for physical activity as outlined on page 18 of this document. People with MS with reduced mobility may need to adapt exercises accordingly (page 18).

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 health professionals

The NHMRC resource, the *Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults, Adolescents and Children in Australia*[213], provides guidance for health professionals to assist adults with MS who are overweight or obese to lose weight.

These guidelines discuss behaviour change, intervention strategies and long-term follow up.

The key steps relevant for weight management in adults are:

Ask and assess – Measure waist circumference in addition to BMI and discuss readiness to change lifestyle behaviours.

Advise – Discuss the benefits of weight loss in improving overall health as well as other health conditions, even for small amounts of weight loss.

Assist – use multicomponent interventions, including dietary, physical activity and psychological interventions, to achieve weight management goals. Refer people to other health professionals appropriately to assist them in making these lifestyle changes. Treatment goals should aim to improve overall health rather than weight loss alone.

Arrange – promote self-monitoring and provide ongoing monitoring to review weight and behaviours.

Other medical conditions

There are a wide range of comorbidities (medical conditions present in addition to a primary disease) that can co-occur with MS, and these may have been present prior to a diagnosis of MS.

Many physical and mental health conditions have been shown to co-occur more often in people with MS than the general public[214-220].

People with MS who also have comorbidities have on average a lower health-related quality of life compared to those without comorbidities[221-224].

There is increasing evidence that comorbidities also have a negative impact on MS relapses, disability progression, severity of symptoms such as pain and fatigue, MRI-related outcomes, employment outcomes, hospitalisation and mortality[210,225-236].

The overall message is that the early detection and optimal management of comorbidities in MS is key. People with MS and health professionals must both play a proactive role in the identification and management of comorbidities.

It is important that where possible, people with MS take initiative in the prevention and self-management of their comorbidities by making the beneficial lifestyle changes necessary around a healthy diet (page 24), smoking cessation (page 12) and maintaining adequate levels of physical activity (page 18), in consultation with their team of health professionals.

For health professionals seeking information on overall management strategies, screening and detection, we recommend the use of the *Comorbidities in Multiple Sclerosis: A Clinical Resource Guide*[237] on comorbidities in people with MS and the *NICE guidelines Multimorbidity: clinical assessment and management*[238] on multimorbidity in the general population.

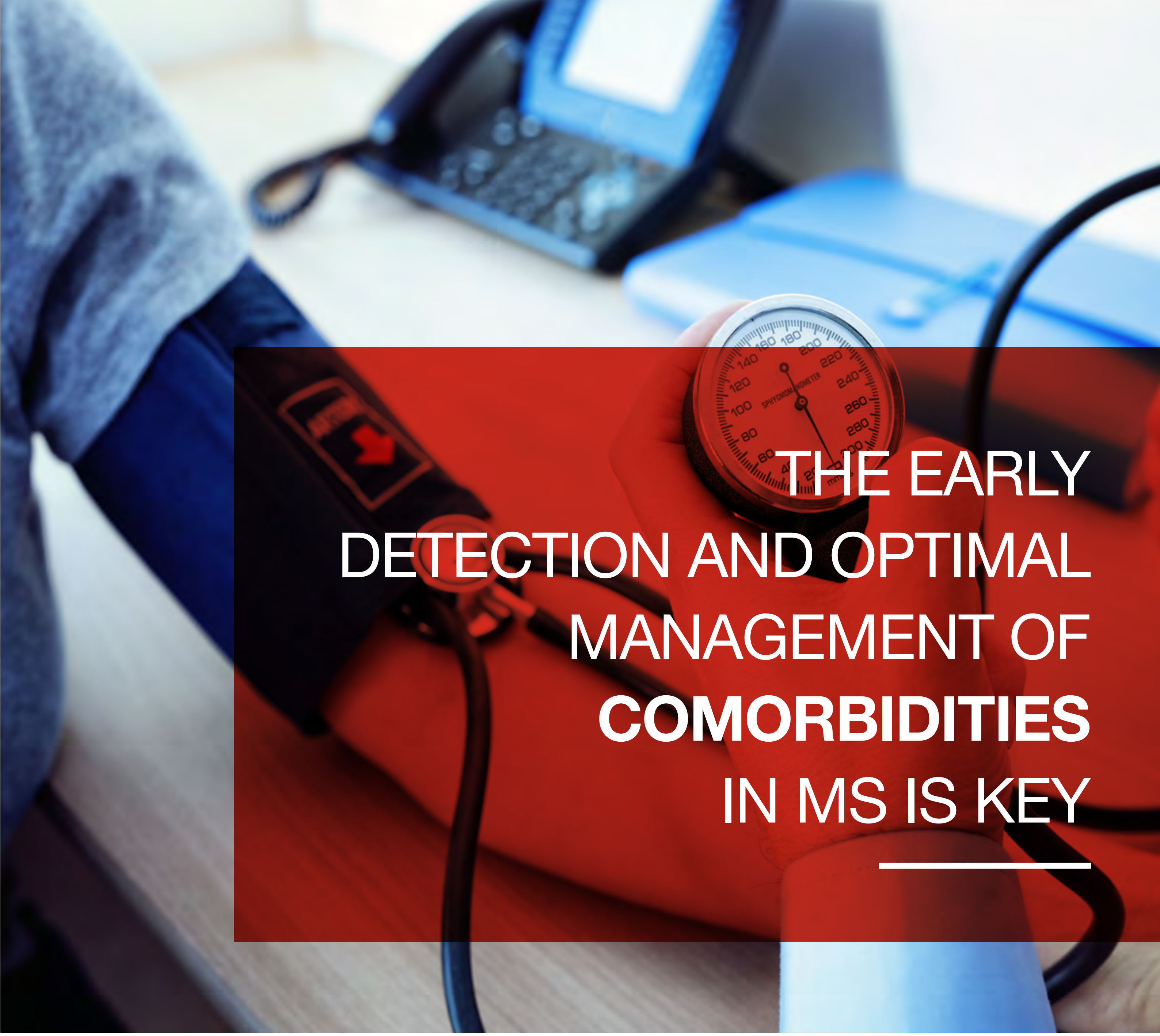
Comorbidities and MS

What is the prevalence of comorbidities in people with MS?

Seven systematic reviews[214-220] highlight that, despite some variances in results due to different study designs, included populations and methods of reporting findings, most physical and mental health comorbidities occur more frequently in people with MS than in the general population.

Some of the key findings from the above-mentioned studies were that gastrointestinal, musculoskeletal and respiratory comorbidities are more common in people with MS[217].

Furthermore, vision problems, irritable bowel syndrome, fibromyalgia, congestive heart failure[239,240], stroke[214,239-241], peripheral vascular disease[217], hypertension, hyperlipidaemia (page 54), diabetes[214], additional autoimmune disorders[214,218],



THE EARLY DETECTION AND OPTIMAL MANAGEMENT OF **COMORBIDITIES** IN MS IS KEY

epilepsy, seizures, sleep disorders[219] and psychiatric comorbidities such as depression, anxiety and bipolar disorders[220], were also shown to be more common in people with MS compared to the general population.

Based on the AMSLS data, comorbidities in people with MS were already prevalent at MS symptom onset (65.2% with > 1 comorbidity).

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

Cross-sectional studies consistently show that people with comorbidities have a substantially lower quality of life compared to those without comorbidities[221-224].

In the AMSLS, mental health disorders had the largest contribution to the reduction in overall health-related quality of life, followed by musculoskeletal disorders (unpublished data). Research in this area is ongoing.

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

The effects of comorbidities on specific MS-related outcomes and symptoms have been studied, and findings have been summarised below:

Relapse – Few observational studies have examined the association between comorbidities and the risk of relapse.

Overall, they showed that people with MS with multiple comorbidities had an increased relapse rate compared to those without comorbidities[225,242].

When individual conditions were studied, migraine, hyperlipidaemia (page 54), rheumatoid arthritis and anaemia were associated with an increased relapse rate[225,242].

Disability/disability progression – A number of cross-sectional and prospective studies have been carried out in this area[210,226,227,243,244], and findings showed that the presence of any comorbidity is associated with a higher disability in early MS (i.e. maximum of two years after diagnosis) and faster disability progression throughout the disease course.

While disability measures specific to MS were used, disability related to MS is likely to be indistinguishable from disability that is due to the comorbidity.

MRI-related outcomes – Three cross-sectional studies[229-231] have shown that comorbidities are associated with the worsening of MRI-related measures in people with MS. However, it is unclear whether these MRI measures are showing a decline due to MS disease activity or whether comorbidities independently affect MRI outcomes.

Symptom severity – Observational studies have consistently shown that comorbidities are associated with a higher severity of symptoms in people with MS, indicating that comorbidities are adding to the total load of symptoms commonly seen in MS.

For example, results show that people with MS experiencing:

- depression, arthritis and migraines reported a higher severity of pain[232]
- depression and cancer had higher fatigue severity[232,234]
- osteoporosis and anxiety reported worsening of pain[233]
- coronary artery disease reported more weakness and imbalances[232]
- chronic obstructive pulmonary disease reported worsening of fatigue[232,234]
- anxiety, irritable bowel syndrome, depression and migraine independently were at increased risk of fatigue[232,234]

The AMSLS found that mental health disorders (particularly depression) contributed most strongly to pain, fatigue, sexual dysfunction, cognitive and sensory problems.

Musculoskeletal disorders (particularly osteoporosis) contributed most strongly to walking difficulties, balance, bladder and bowel problems and spasticity (unpublished data).

Employment outcomes – Comorbidities seem to substantially negatively impact employment outcomes in people with MS, although only one study has been published on this topic. It showed that a variety of comorbidity measures were associated with employment outcomes such as MS-related work productivity loss and not being in the labour force[235].

Initiation of a disease modifying therapy (DMT) and choice of DMT – A single retrospective cohort study has suggested that having a higher number of comorbidities may lower the likelihood of starting a DMT by people with MS[245]. Comorbidities were not associated with the choice of initial DMT[245]. Specifically, the study showed that people with MS with ischemic heart disease or anxiety were less likely to start a DMT, while having depression seemed to shorten the time to DMT initiation.

Mortality – Two observational studies[246,247] have looked into whether comorbidities contribute to higher risk of mortality in people with MS.

One large prospective study showed that comorbidity status was associated with a higher mortality risk in both people with MS and a matched population but did not show a greater effect on the mortality in people with MS than in the matched population[246].

Further, the study found that at least 50% of deaths in people with MS were due to comorbidities or other health causes. Another large population-based cohort study found an increased mortality rate in people with MS who had a psychiatric comorbidity, diabetes, cancer or Parkinson’s disease compared to those without these comorbidities[247].

Overall, these two observational studies seem to suggest that having comorbidities increases mortality risk in people with MS mainly because of the additional burden brought by the comorbidities and not by the MS itself.

Hospitalisation – Only a single study[236] has looked at hospitalisation in people with MS in relation to comorbidities. Results have shown that people with MS who have comorbidities have a higher rate of hospitalisation for non-MS related reasons.

Recommendations for people with MS

Some comorbidities can be prevented or improved through a healthy lifestyle.

It is recommended that people with MS adopt positive health behaviours and self-management by making healthy lifestyle choices such as following a healthy diet (page 26), smoking cessation (page 14) and maintaining adequate levels of physical activity (page 20), in consultation with their medical team.

Early identification and management of comorbidities is important. To assist in that process, it is recommended that people with MS attend all relevant medical check-ups and be proactive in informing and updating their clinicians about any comorbidities or symptoms that they may experience in between clinic visits.

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 health professionals

The key message is that the timely recognition of comorbidities in people with MS is critical to achieving the best possible health outcomes.

Early screening is imperative to identify, treat and manage comorbidities because they tend to accumulate faster and worsen health-related outcomes of people with MS early in the disease process.

Specifically, GPs should ensure routine proactive screening for comorbidities in people with MS, particularly for those comorbidities that are more prevalent such as mental health conditions (depression and anxiety), musculoskeletal disorders and cardiovascular disorders, ideally during every clinic visit.

There is little evidence on the most effective models of care for comorbidity management in MS. However, collaborative models of care, particularly in relation to mental health outcomes, have shown promise[248-250].

Collaboration between clinicians and other health professionals involved in supporting the individual is essential to address comorbidities in people with MS, as well as providing the most relevant information regarding the management and treatment of their comorbidities.

THE **TIMELY RECOGNITION** OF COMORBIDITIES IN PEOPLE WITH MS IS CRITICAL

For detailed information on overall management strategies, screening and detection, we recommend the *Comorbidities in Multiple Sclerosis: A Clinical Resource Guide*[237] and NICE guidelines *Multimorbidity: clinical assessment and management*[238].

The approach to care in the general population that takes multimorbidity into account will:

- discuss the purpose of an approach to care that is to improve quality of life
- establish disease and treatment burden
- establish patient goals, values and priorities
- review medicines and other treatments taking into account evidence of likely benefits and harms for the individual patient and outcomes important to the person
- agree on individualised management plan with the patient

There are also specific guidelines on:

- osteoporosis in MS[251]
- the assessment and management of psychiatric disorders in MS[252]

Lipids

Lipids are an important form of energy storage in the human body and are key components of the structure of a wide range of living cells. This includes the cells of the nervous system, such as the myelin that protects and insulates nerves[253,254].

While lipids have important beneficial biological functions, there are conditions that arise due to the abnormal or high accumulation of lipids in the blood, often due to excessive dietary consumption of fats or genetic susceptibility. One such condition is dyslipidaemia, which is the most important contributing factor to the development of cardiovascular diseases[255,256].

Blood tests are used to measure the level of the most common types of lipids in the human body such as triglycerides (TG) and total cholesterol (TC), as well as apolipoproteins which bind to and help transport lipids such as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).

The prevalence of dyslipidaemia is high in the general population as well as in people with MS, and this increases with age. There is evidence suggesting that people with MS who also have an adverse lipid profile are worse off in terms of disability progression and MRI lesions.

The key message is that clinicians should be vigilant about regularly screening people with MS for dyslipidaemia, using the screening and diagnosis guidelines for vascular and metabolic comorbidities that are common in the general population.

People with MS, particularly those who have a lipid-related comorbidity such as dyslipidaemia, should consult with their clinical care team, including their GP, to receive guidance and follow recommended guidelines to achieve optimal levels of physical activity (page 20) and a healthy diet (page 26).

Furthermore, health professionals are encouraged to proactively monitor lipid profiles of people with MS and consider pharmaceutical interventions such as the use of statins where appropriate. Statins have been confirmed to be well-tolerated and safe for people with MS, in combination with non-pharmaceutical, lifestyle-based interventions.

The link between lipid profiles and MS

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

There is a growing body of evidence indicating that an adverse lipid profile may have negative effects on clinical outcomes of MS[257-265]. The findings are summarised here:

Disability - A recent systematic review[266] and some cross-sectional studies[267-269] have shown that higher levels of lipids, such as TC, LDL-C and apolipoprotein B (ApoB), are associated with worse disability progression and the appearance of inflammatory lesions seen on MRI in people with MS.

Similarly, a number of cross-sectional and cohort studies have also shown that dyslipidaemia is associated with worse disability outcomes in people with MS[207,242,244,270,271].

BE VIGILANT ABOUT **REGULARLY SCREENING** PEOPLE WITH MS FOR DYSLIPIDAEMIA

Thus, there is a consensus across current studies that dyslipidaemia contributes to worse disability outcomes.

Relapse – There is inconsistent evidence about the association between lipid profiles and hazard of relapse with some studies showing that an adverse lipid profile is associated with an increased relapse rate[207,225], while others did not find an association[207,242,272].

MRI related outcomes- Observational studies have documented that adverse serum lipid profiles are associated with an increased number of contrast-enhancing lesions in people with MS, which are indicators of inflammation in the brain and acute disease. Specifically, results from 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[272,273].

The relationships between apolipoproteins such as Apolipoprotein AI (ApoAI), Apolipoprotein AII (ApoAII), Apolipoprotein E (ApoE) and Lipoprotein(a) (Lpa) with MRI outcomes for people with MS are less investigated, and current findings are insufficient to reach a consensus[274,275]. A recent longitudinal study indicates that increased HDL-C levels may be associated with lower brain atrophy and grey matter shrinkage in people with MS[275]. Future longitudinal studies with long-term follow-up are needed to confirm these findings.

Research has been carried out looking at the altered lipid profiles and arterial blood flow in people with MS but currently the evidence is inconclusive[276-279]. Additionally, with only single studies available, there is insufficient evidence supporting the association of adverse lipid profiles with poorer cognitive function[280] and greater fatigue[281].

STATINS ARE **WELL-TOLERATED AND SAFE** IN PEOPLE WITH MS. LIFESTYLE AND BEHAVIOURAL MODIFICATIONS SHOULD ALSO BE CONSIDERED

Information that needs clarifying

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

Several studies have examined the effects of DMTs (interferon-beta, glatiramer acetate, natalizumab, fingolimod and dimethyl fumarate) on lipid profile-related measures.

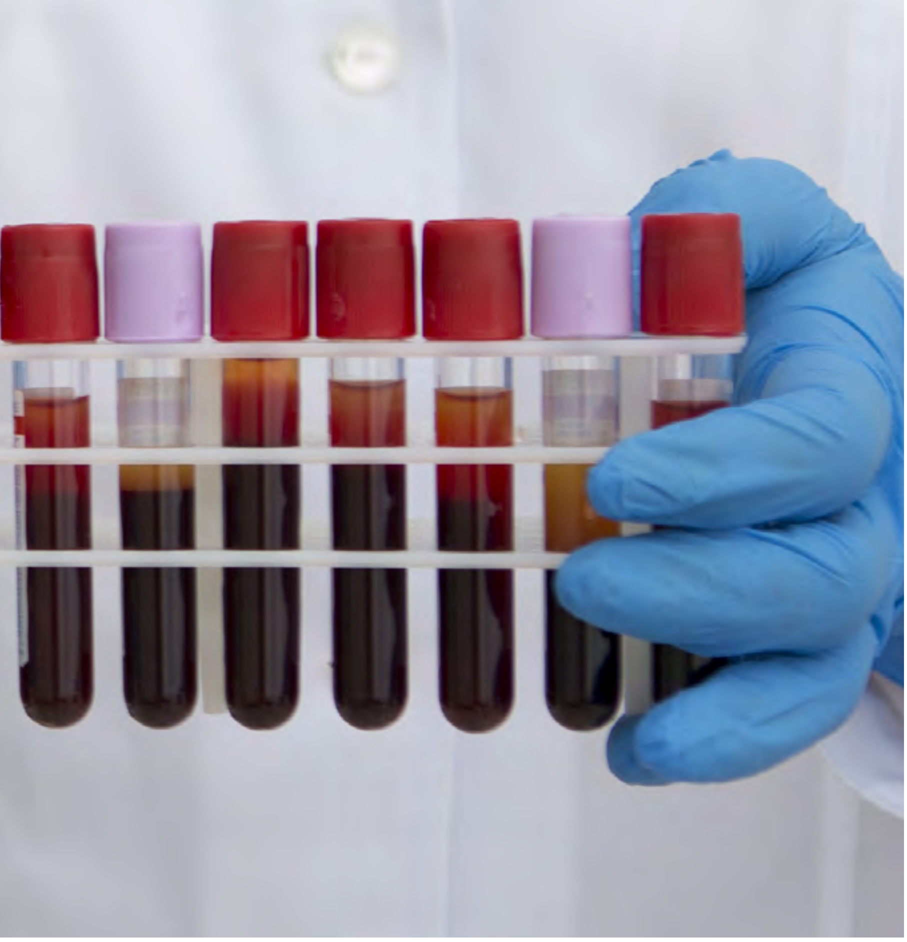
Based on the limited existing evidence, there does not seem to be a pattern that DMTs have strong adverse effects on lipid levels, with some studies noting a small reduction of the “good cholesterol” HDL-C[282], and other studies observing beneficial effects (e.g. increase in HDL-C, or reduction in TC or LDL-C)[283].

Should statins be used in people with MS?

Statins are approved medications for improving serum cholesterol levels and are widely used in the prevention of cardiovascular disease[284,285]. In people with MS, statins seem to be well-tolerated[286] and safe (i.e. the number of adverse events were similar compared to a control population)[287].

Statins also have immunomodulatory properties. A 2011 Cochrane systematic review failed to support that atorvastatin and simvastatin had a beneficial impact on the MS disease course in terms of relapse rate, disability progression and MRI markers (new T2 or gadolinium enhanced lesions)[286].

However, a recent 24-month high-dose (80mg) simvastatin trial showed favourable effects on whole-brain atrophy, physical quality of life, and some measures of cognitive function[288,289]. Further trials are required before using high-dose statins with the aim of controlling the MS clinical course.



Recommendations for people with MS

It has been documented that physical activity and diet behavioural interventions for adults who are not at high risk for cardiovascular disease could result in small to modest positive outcomes in improving cholesterol levels[290], although the data for people with MS is scarce.

It is recommended that all people with MS, particularly those who also have a lipid-related comorbidity such as dyslipidaemia, consult with their clinical care team for guidance. Additionally, the guidance outlined in this document regarding physical activity (page 20) and diet (page 26) will be useful.

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 health professionals

As dyslipidaemia is common in the general population and in people with MS, and it is associated with worse clinical outcomes in MS (e.g. disability progression and MRI lesions), clinicians should be vigilant about screening and treating people with MS for this condition regularly.

There are no specific guidelines to follow for diagnosing this comorbidity in people with MS. Therefore, clinicians should follow general screening and diagnosis guidelines for vascular and metabolic comorbidities. In terms of management, statins have been confirmed as being well-tolerated and safe in people with MS.

Non-pharmaceutical interventions such as lifestyle/behavioural modifications including diet and exercise therapy should also be considered where possible (in line with page 26 and page 20 of this document) as part of the management strategy.

Behaviour change resources

There are several sources of support available to health professionals to help individuals make the positive lifestyle changes that are recommended in this guidance document.

A systematic review of the relative effectiveness of face-to-face communication-related behaviour change techniques provided to health professionals to help change an individual's lifestyle has shown that behavioural counselling, motivational interviewing, education and advice are all effective behaviour change techniques[291].

Motivational interviewing is one counselling approach which may be more effective than traditional advice-giving[292,293]. It is a method that helps individual's resolve their feelings of ambivalence and barriers towards making positive changes by finding internal motivators.

Other brief evidence-based techniques to encourage healthy behaviour changes include 'SMART' goal setting, problem-solving barriers and self-monitoring[294].

It is important that health professionals relay to individuals that in most cases it has been shown that a great deal of preparation, contemplation and action/trying will be required to result in the maintenance of new behaviours.

BEHAVIOURAL COUNSELLING, MOTIVATIONAL INTERVIEWING, EDUCATION AND ADVICE ARE ALL EFFECTIVE **BEHAVIOUR CHANGE** TECHNIQUES

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