ADAPTING YOUR LIFESTYLE

A GUIDE FOR PEOPLE WITH MS

MS AUSTRALIA

RESEARCH
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Document published August 2020.

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Introduction

Trying to keep up with the latest health information and determine fact from fiction can be confusing and time consuming. Recognising what is credible and safe advice to follow is particularly important when it's being used to help you manage multiple sclerosis (MS).

Diet and nutrition, gut health and supplementation are popular health topics. They are also examples of modifiable lifestyle risk factors – factors that can influence disease progression and disability.

They are 'modifiable' because they can be eliminated or reduced through changing our behaviour or environment, unlike our age or genetics which we can't do anything about.

Modifiable lifestyle factors are of particular interest as they provide a way to take control and potentially minimise the impact of MS on your life.

However, it's important to make decisions based on evidence and relevance to MS rather than media hype.

MS Australia worked with national experts in modifiable lifestyle factors – clinicians, researchers, allied health professionals – and people affected by MS, to review and assess the latest evidence and subsequently, develop practical recommendations for people with MS.

The aim is to equip you with a tool to help you make evidence-based lifestyle changes that may benefit aspects of your MS including relapses, disability and other symptoms, as well as improve your overall quality of life. These discussions and decisions are always best made with your doctor and other healthcare professionals.

The result is this document, ***Adapting Your Lifestyle: A Guide for People with MS***.

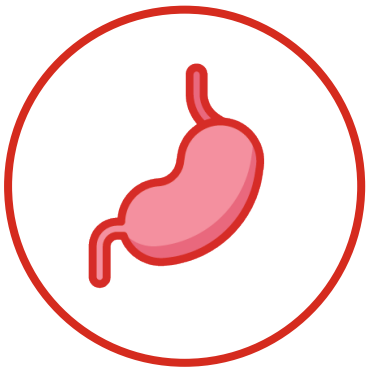
smoking **physical activity** **diet**

Nine modifiable risk factors are reviewed – smoking, physical activity, diet and nutrition, gut health, supplements, vitamin D and sun exposure, weight and obesity, other medical conditions and lipids.

To provide you with a comprehensive understanding of each factor, there is topline information relating to the background, key evidence, core recommendations and a common myth that we've busted.

If you'd like to dig deeper, there's a full reference list at the end of this document as well as more detailed guidelines that have been developed for the medical community.

We hope this guide helps you to better understand the role these lifestyle factors can have on MS and provides you with the confidence to make any changes in consultation with your healthcare team.



gut health

supplements

vitamin D and sun exposure

weight and obesity

other medical conditions

lipids

Smoking

When we discuss smoking, it's not just tobacco and cigarettes. Smoking also includes marijuana and opium, as well as combustible tobacco products such as cigars, pipes, cigarillos, little cigars and waterpipes (also known as shisha, nargile or hookah).

While the dangers of smoking have been a constant message for decades in Australia, 14% of men and 11% of women still smoke tobacco daily.

In comparison, data from a key MS study – the Australian MS Longitudinal Study – suggests 11% of people with MS report smoking tobacco, while data from another Australian study looking at those at the earliest stage of their disease found that 27% smoked at the start of the study and 20% were smoking five years later.

SNAPSHOT

Smoking increases the risk of MS progression by approximately 55%

One study estimates that up to 27% of people at the earliest stage of their MS smoke

There is good evidence, as defined by the National Health and Medical Research Council (NHMRC) for the link between smoking and MS

Experts strongly recommend that anyone with MS, at any stage, stops smoking ASAP

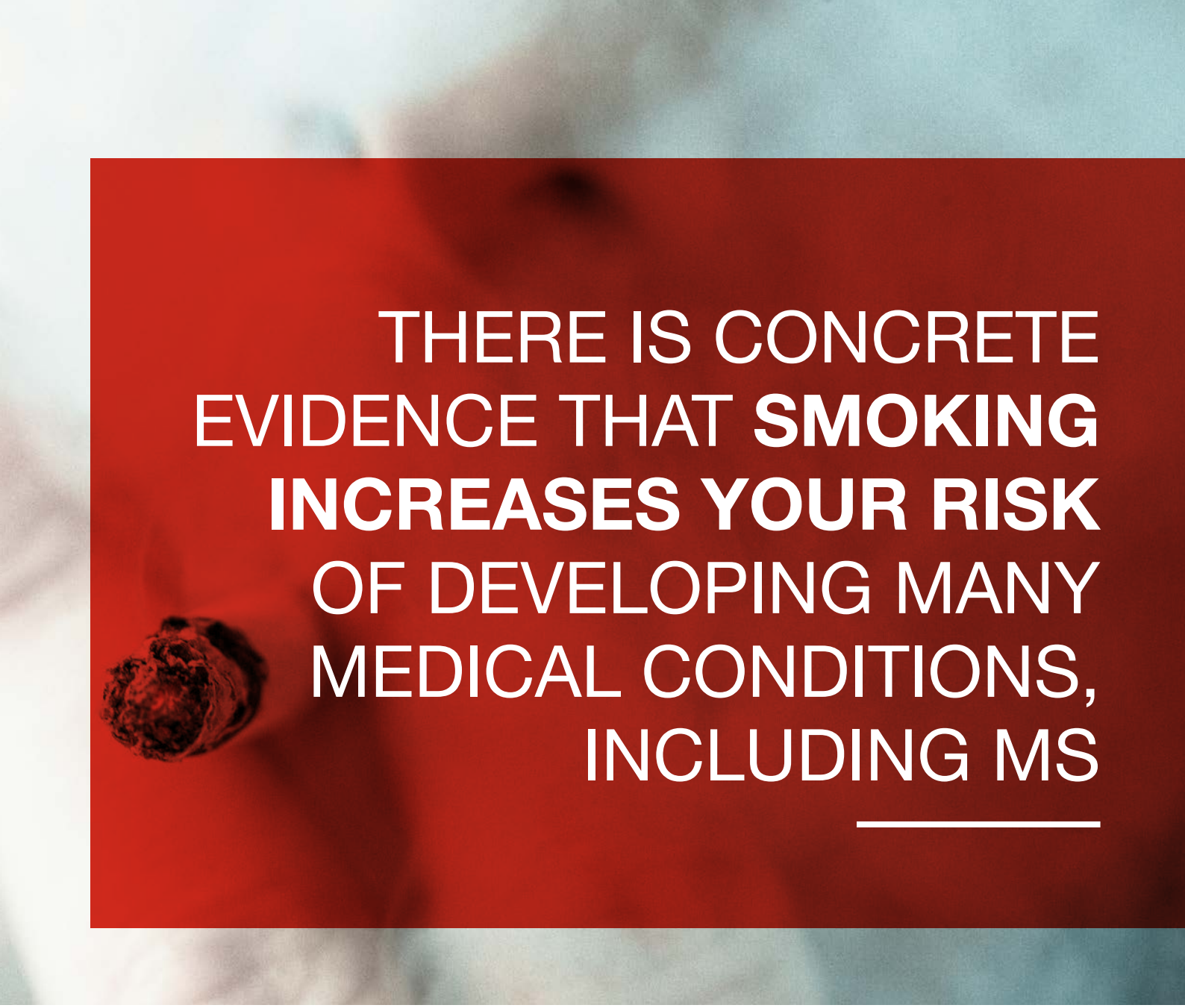
While e-cigarettes and heated tobacco products (tobacco products that produce aerosols containing nicotine and other chemicals which are inhaled through the mouth) might be less harmful than cigarettes, there is currently no evidence to support that these products are harmless or have benefits compared to being nicotine-free.

Evidence

There is concrete evidence that smoking increases your risk of developing many medical conditions, including MS.

Higher risk of developing MS, faster progression and worse symptoms of MS are all linked to smoking.

- Smoking increases the risk of developing MS
- Passive smoking increases the risk of developing MS
  - Family members of people with MS exposed to smoking may be at particularly increased risk if they are also genetically predisposed to MS
- Smoking increases the risk of MS progression by around 55%, making it a key risk factor for disease progression
- People with MS who smoke experience a lower quality of life, as well as increased risk of depression and anxiety
- Smoking increases the risk of early death in people with MS compared with those with MS who have never smoked



THERE IS CONCRETE EVIDENCE THAT **SMOKING INCREASES YOUR RISK** OF DEVELOPING MANY MEDICAL CONDITIONS, INCLUDING MS

- Medications that aim to prevent relapses and progression of MS

On the flip side:

- The risk of paediatric-onset MS is reduced in children whose parents stops smoking
- The risk of disability progression is significantly reduced when a person gives up smoking, and the earlier people with MS quit, the greater the benefits
  - Persistent smokers reached the progressive stage of MS eight years earlier than those who quit around the time of diagnosis
  - For every ten years that people did not smoke, the reduction in the risk of increasing MS disability was approximately 30%
- Quitting smoking at any time is beneficial

Recommendations

To reduce the risk of MS progression, quit smoking – the sooner, the better!

The ‘quit smoking’ message is the same for people with MS as it is for the general public. However, the specific evidence relating to smoking and MS makes the quit smoking message so much more urgent and compelling for people with MS or those at risk of developing it.

Quitting smoking is relevant and beneficial to anyone with MS at any stage and the earlier people with MS quit, the stronger these benefits are.

People with MS who stop smoking also decrease their chances of developing other conditions caused by smoking, such as cancer and cardiovascular disease.

Tip

Quit is a good place to start, as well as chatting with your doctor.

Common MS symptoms such as pain, depression and anxiety make it more difficult to quit. Don't be afraid to ask for support from healthcare professionals, friends, and family to help you quit.

MYTH BUSTER

MYTH: Nicotine is harmful for people with MS

People worry that nicotine is the harmful substance in tobacco, however evidence shows that this is not the case. Nicotine replacement products such as gum or spray are safe, and often recommended to help people quit.

Physical activity

Exercise may be the closest thing to a magic pill we have but for some people with MS, summoning up the energy for any type of physical activity can also feel like a bit of magic is needed!

Physical activity includes exercise, sport, occupational work, transportation and household chores.

Many people with MS have low levels of physical activity which can affect their movement, quality of life and increase the chances of developing other conditions such as depression, heart disease and obesity.

So, while taking it easy may seem like a good option, there's plenty of excellent reasons to 'get moving'.

Keep in mind that any physical activity recommendations should be adapted according to your specific needs, abilities and preferences.

SNAPSHOT

Exercise can help with mobility, fatigue and pain in MS

Many people with MS have low levels of physical activity

There is excellent evidence (as defined by the NHMRC) for the link between physical activity and MS

For people with a general level of fitness and experience, moderate aerobic exercise two to three times per week and strength training exercises two to three times per week is recommended

Evidence

There are many studies that support exercise training for the management of MS symptoms as well as the possibility of treating MS itself.

Exercise can help:

- physically – movement, fatigue, balance, sleep quality
- mentally – cognition (thinking, processing and memory)
- psychologically – symptoms of depression and mood changes

Exercise can also be used to manage pain in MS and it has been linked with a reduced rate of relapse. It is considered to be one of the most effective things you can do alongside your MS medication to help with pain.

Importantly, studies have shown exercise can slow disability progression in some cases.

THERE ARE MANY STUDIES THAT SUPPORT **EXERCISE TRAINING** FOR THE MANAGEMENT OF MS SYMPTOMS

Recommendations

Build physical activity into your weekly routine

People with MS aged 18 years and older with mild to moderate levels of disability should follow the guidelines below, adapted from the Canadian MS Society's *Physical Activity Guidelines*.

For those with a general level of fitness and experience *(these are people who are not physically active on a regular basis)*

- moderate aerobic exercise 2 to 3 times per week – upper body exercises such as arm cycling or seated shadow boxing (boxing without an opponent), lower body exercises such as walking or leg cycling and combined body exercises such as using an elliptical trainer
- moderate strength training exercise 2 to 3 times per week which may include using weight machines, free weights and cable pulleys

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

- moderate to vigorous aerobic exercise 5 times per week which may include running or road cycling
- moderate to vigorous strength training exercise 2 to 3 times per week, which may include using weight machines, free weights and cable pulleys

For those with more severe disability *(these are people with more severe disability who spend most of their day in a wheelchair)*

- breathing exercises, flexibility exercises and exercises of the arms and legs for up to 20 minutes per day (10 minutes per day for those who spend most of their day in a wheelchair or bed) three to seven times per week

Further information about physical activity for those with severe disability can be found in the American National MS Society Physical Activity Recommendations.

Tips

Try balance exercises

Australian research has shown that balance exercises are important and can be done 2 to 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 Exercises website.

It is recommended that you practise balance exercises in a safe environment. They can also be practised while supervised by an accredited health professional, such as a physiotherapist.

Talk to a health professional

It's a good idea to talk to an accredited health professional, such as an exercise physiologist or physiotherapist, so they can identify what's going to work best for you – what exercise and how much.

Let them know about MS symptoms, such as fatigue and heat sensitivity, so they can consider that when developing your physical activity plan. The Support and Services resource on MS Australia's website can point you in the right direction for finding a local physiotherapist.

MYTH BUSTER

MYTH: Exercise makes MS symptoms worse

For many years, doctors advised people with MS to avoid any physical activity or exercise fearing it could trigger the onset or worsening of MS symptoms due to an increase in body temperature.

Australian research shows that drinking cold water during exercise can combat this, especially in warmer climates.

Research has also clearly shown that exercise is safe and beneficial for people with MS and can reduce relapse rates.

Diet

When we use the term 'diet' we're referring to all the food and drink a person typically consumes rather than a specific way of eating to lose weight.

There is a huge interest in the relationship between food and our health – what we should include or avoid in our diet to reduce the risk of developing or managing certain diseases.

While there has been research into nutrition and diet in MS as well as popular recommendations of diets for MS, robust evidence is lacking.

Additionally, the recommendations of individual diets are often conflicting, resulting in confusion rather than clarity.

Evidence

A number of 'MS diets' are circulating within the MS community, so we've reviewed the evidence for each diet as well as specific nutrients and foods.

Many of these diets have common themes such as no sugar, no processed foods, no dairy or meat and unfortunately, no robust evidence.

SNAPSHOT

There is not enough evidence to support a specific diet to improve outcomes in MS

People with MS should follow the nutritional guidelines for the general population – the Australian Dietary Guidelines

Speaking with a dietitian may help to implement these guidelines in daily life

Essentially, more studies, larger studies and better quality studies (e.g. ones that consider other factors that may affect study results) are required to ensure we have enough strong evidence to make specific dietary related recommendations.

A Paleolithic diet

This diet generally excludes legumes, grains and dairy, and increases meat, fruit and vegetables. Small research studies have shown some benefits of this diet relating to fatigue in people with MS, and improvement in quality of life in people with progressive MS. However, there may be other reasons for this change so further larger research studies are needed.

A low-fat, plant-based diet

High in starchy plant foods such as beans, peas and lentils, and excluding animal products and vegetable oils, this diet has helped with body mass index (BMI) and some MS-related issues including fatigue, but showed no improvement in disability outcome measures such as cognition and physical disability. Larger studies are needed.

A gluten-free diet

Gluten is a group of proteins found in cereal grains, such as wheat, barley and rye. In one small trial in people with relapsing-remitting MS, following a gluten-free diet improved disability outcomes, including physical disability and development of new MS lesions. While this is promising, further evidence is needed.

A dairy-free diet

One study has shown a link between cow's milk and prevalence of MS but as there is no evidence to suggest that dairy is associated with MS progression, we cannot recommend a dairy-free diet for those living with MS. More studies are required.

Coffee

Coffee has been the focus of several studies with most looking at the impact of coffee on the risk of developing MS. One study has shown that drinking coffee occasionally or daily, compared with never drinking coffee, was linked with lower disability in people with relapsing remitting MS. However many factors that might affect coffee-drinking and MS progression, such as changes in consumption habits over time, were not taken into account so currently there are no recommendations around drinking coffee.

Alcohol

While not a lot of research has been conducted in this area, moderate consumption of alcohol (two standard drinks per day) was linked with lower disability in people with relapsing remitting MS in one study. However various factors potentially affecting drinking alcohol and disability, such as changes in consumption habits over time and the type of alcoholic beverage consumed, were not considered.

Another study found higher total alcohol consumption and red wine intake were associated with lower disability in people with MS. However, it is possible that people with higher disability scores drank less alcohol than those with lower disability scores because of their disability, making the relationship between alcohol and MS unclear.

Sodium

Sodium is a major component of salt. Major sources of sodium are processed foods (e.g. pizza, cookies) and processed meats.

The World Health Organization (WHO) recommends a reduction in sodium to reduce blood pressure and the risk of cardiovascular disease, stroke and coronary heart disease.

One study showed that higher sodium intake was associated with increased disease activity including an increased risk of new lesions in people with MS while another study reported no association. This has resulted in no conclusive evidence on the role of sodium in MS progression.

Fish

Eating fish at least once a month was linked with lower disability in people with relapsing remitting MS, according to one study. 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.

Another study found people with MS eating fish were more likely to have a better quality of life and less disability. However, all data were self-reported and the participants were highly educated and engaged with lifestyle interventions shown to affect the risk of MS progression which may have biased the results. For general healthy eating, fish should be consumed twice per week.

Other

A review of the published studies related to MS and diet found no consistent evidence for improvements in disease outcomes when looking at nutrients, foods or eating patterns. 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.

Recommendations

Follow a balanced diet, eating a wide variety of nutritious foods rather than excluding any key food groups

In the absence of enough good quality scientific evidence to support any specific MS diets, we recommend following the *Australian Dietary Guidelines*:

- enjoy a wide variety of nutritious foods including vegetables of different colours and legumes/beans; fruit; mostly wholegrain and/or high fibre cereal varieties; lean meats, poultry, eggs, fish, tofu, nuts and seeds; milk, yoghurt and cheese, preferably reduced fat
- drink plenty of water
- limit foods containing saturated fat, added salt, sugars and alcohol

PEOPLE WITH MS SHOULD **FOLLOW THE NUTRITIONAL GUIDELINES** FOR THE GENERAL POPULATION – THE AUSTRALIAN DIETARY GUIDELINES

Tip

Talk to an Accredited Practising Dietitian

Only about 4% of the general population adhere to the *Australian Dietary Guidelines*.

For valuable support, talk to an Accredited Practising Dietitian who can work with you to incorporate these guidelines into your life.

MYTH BUSTER

MYTH: It's safe to follow 'MS diets'

Many of the 'MS diets' that are popular within the MS community exclude key foods and food groups which are important for a healthy, balanced diet.

In the absence of high-quality evidence to support a restrictive diet, this may cause more harm than good. The safest option is following the *Australian Dietary Guidelines*.

Gut health

Our guts are attracting a great deal of attention thanks to the gut microbiome. The human microbiome consists of trillions of complex and diverse microbial cells, primarily bacteria, with the majority residing in the gut.

Evidence continues to demonstrate the important function of gut bacteria in the maintenance of general health as well as certain physical and psychological conditions.

MS and the gut microbiome are also being studied. However, recommending any interventions – with the exception of diet and lifestyle – to change the microbiome of people with MS requires further research.

SNAPSHOT

There are significant differences in the gut microbiome – the complex and diverse populations of bacteria mainly found in the gut – of people with MS compared to people without MS

Diet and lifestyle are the best ways to attain a healthier gut microbiome

There is not enough evidence to recommend any other methods to change the microbiome of people with MS

Evidence

The evidence suggests there are significant differences in the composition and function of gut bacteria of people with MS compared to people without MS. This has been tested and confirmed in a variety of people with different genetics and of different ages and genders.

Laboratory studies have shown that transplanting microbiome samples from people with MS to laboratory models without MS, resulted in changes to the immune system similar to that seen in MS.

Taking these findings to the next step – specific interventions to change the microbiome of people with MS – is complex and more research is required to understand what a healthy microbiome looks like before any recommendations can be made.

Here is the evidence we currently have for these interventions.

Faecal microbiota transplant (FMT)

This involves a microbiota sample from a healthy donor being transplanted to another person. It has been used successfully to treat *Clostridium difficile* infections which can cause diarrhoea and more serious illnesses.

There are no results from clinical trials of FMT in MS (excluding individual case reports) although one is ongoing. Safety concerns of FMT include infection and death while the long-term effects of FMT are unknown.

DIET AND LIFESTYLE **ARE THE BEST WAYS** TO ATTAIN A HEALTHIER GUT MICROBIOME

Helminth therapy

A helminth is a parasitic worm (e.g. hookworm) which is exposed to the gastrointestinal tract in an attempt to alter the immune response and have a positive effect on MS.

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. However, one longer study found people with MS undergoing helminth treatment had severe gastrointestinal symptoms.

Probiotic supplements

Probiotics contain live micro-organisms that may be beneficial when consumed in adequate amounts. They are available as supplements (capsules) and in some foods (e.g. fermented foods such as yoghurt and sauerkraut).

Two clinical trials of probiotics found improvements in MS, including the reduction of some inflammation markers, and improvements in mood and quality of life. These initial results need to be confirmed in studies with larger numbers of people with MS over longer periods of time.

Recommendations

Follow diets that emphasise the consumption of plant foods including fruits, vegetables and legumes

Currently, the best and safest way to a healthier gut microbiome for people with MS is to follow the *Australian Dietary Guidelines* or traditional dietary patterns such as the Mediterranean, Norwegian or Japanese diets that emphasise eating plant-based food and have demonstrated their ability to increase beneficial gut bacteria.

In contrast, foods that are high in saturated fat, salt and sugar appear to have a negative effect on microbiota.

MYTH BUSTER

MYTH: There is 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.

Products and services that are advertised as aiming to restore the microbiome of people with MS are not currently supported by evidence.

Tip

Eating your way to a healthier gut is our key recommendation

But physical activity can also positively affect gut bacteria while smoking and alcohol have the reverse effect.

THE BEST AND SAFEST WAY TO **A HEALTHIER GUT MICROBIOME FOR PEOPLE WITH MS** IS TO FOLLOW THE AUSTRALIAN DIETARY GUIDELINES

Supplements

Vitamins (e.g. biotin), minerals (e.g. magnesium) and other compounds derived from plants (e.g. ginkgo biloba) are all types of supplements which are available as capsules, liquids and powders.

When people are diagnosed with the 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 that are necessary for good health.

Several dietary supplements have been studied for their possible benefits in people with MS and while these and others are advertised as being beneficial for MS, the evidence does not back this up.

SNAPSHOT

The use of supplements, including ginkgo biloba and biotin (vitamin B7), to improve MS is not supported by evidence

A recent review of dietary supplements in MS found that some produced unwanted side effects

Some dietary supplements showed promise in preliminary studies but further studies are critical to confirm their safety and effectiveness in people with MS

Evidence

These compounds have at least one study reporting that they improve at least one outcome relating to progression of MS such as reducing brain shrinkage, fatigue or depression:

- plant extracts – ginkgo biloba, green tea, ginseng, lemon verbena and King of Bitters (*Andrographis paniculata*)
- alpha lipoic acid (found in small amounts in foods such as organ meats [offal], spinach and yeast)
- vitamin A (found in fish liver oils, milk, green leafy vegetables, and red, orange, and yellow vegetables and fruits)
- high-dose biotin (vitamin B7 found in small amounts in unprocessed red meats, complex carbohydrates and dark, leafy greens)
- inosine (a man-made chemical also found in animal and fish meats)
- carnitine (derived from an amino acid which makes up proteins; red meat is a rich source with smaller amounts found in chicken, dairy, fish and beans)
- coenzyme Q10 (an antioxidant found in foods such as tuna, salmon, vegetable oils and meats)
- probiotics (living cultures of bacteria or yeast which can be found in foods such as yoghurt, sauerkraut, miso and kimchi)
- curcumin (the main component of the spice, turmeric)

Clinical improvements in disability levels were reported in three trials that investigated biotin, alpha lipoic acid and probiotics, respectively. Despite these interesting findings, more high quality research is needed before we can confidently recommend supplements for people with MS.

Polyunsaturated fatty acids are found in fish (omega-3) as well as in nuts, seeds and grains (omega-6).

Three studies have looked at the effect of polyunsaturated fatty acid supplementation in people with MS so far, but further research is needed to conclusively determine whether polyunsaturated fatty acids are beneficial for disease activity in people with MS.

MYTH: Supplements might not help my MS but they won't harm it

A recent review of dietary supplements in MS found some supplements – alpha lipoic acid, inosine and green tea extract – caused side effects including kidney problems, high levels of serum urea and abnormal liver function, respectively, so until we have the evidence that shows help without harm, supplements are not recommended to help manage MS.

Recommendations

Get the vitamins you need from a balanced diet

While it's encouraging to see preliminary studies demonstrating the potential benefits of some supplements, it's also critical to ensure that supplements are safe for people with MS to use. The long-term safety of supplement use needs to be examined, which also means ensuring they do not interfere with MS medications.

Until the science supports supplement use in MS, a balanced diet based on the *Australian Dietary Guidelines* will help you meet important nutritional needs.

Tip

Seek advice from a qualified health professional

People modifying their diets for ethical or religious reasons, those with known deficiencies or pregnant women should seek advice from a qualified health professional as supplements may be appropriate in these cases.

Vitamin D and sun exposure

A key role of vitamin D is calcium absorption and maintaining bone health. Its relevance for MS is its ability to reduce inflammatory immune responses.

Sunlight – ultraviolet light (UV) exposure – is the main way we produce vitamin D. Animal sources, such as oily fish, provide some vitamin D with dietary supplements providing significant amounts of vitamin D3.

Vitamin D2 can be obtained from plant sources including mushrooms exposed to sunlight and some dietary supplements. Vitamin D injections are used to treat acute deficiencies and are therefore only available when medically prescribed.

Evidence

There is some preliminary evidence suggesting vitamin D may have a role in the risk and progression of MS but, as is often the case, more robust clinical trials are needed.

SNAPSHOT

Vitamin D is well known for its vital role in bone health but it also plays a role in regulating the immune and neuromuscular systems

Studies have found that people who developed MS had lower levels of vitamin D in their serum compared with those who did not

There is some preliminary evidence suggesting vitamin D may have an effect on the risk and progression of MS but more robust clinical trials are needed

People with MS should follow vitamin D intake recommendations which vary according to age, and ensure they get adequate levels of sunlight based on their location, time of the year and skin colour

Vitamin D and the risk of MS

A number of individual studies, as well as a meta-analysis of 11 studies, found that people who went on to develop MS had lower levels of vitamin D in their serum (a part of blood) prior to MS onset compared with those who did not. Also, there are a number of inherited common variations in genes related to vitamin D metabolism that may potentially be involved in a slight increase in risk of developing MS.

The MS Australia 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) are currently assessing if vitamin D supplementation after the first attack suggestive of MS can reduce the development of Clinically Definite Multiple Sclerosis (CDMS). Results from the PrevANZ trial are expected in 2021, while the D-Lay-MS trial is scheduled for completion in 2023.

Vitamin D and disease progression

Several studies have concluded there are no significant benefits of vitamin D supplementation on the risk of relapse, disability progression or worsening of magnetic resonance imaging (MRI) outcomes in people with MS, with one meta-analysis finding it may have increased relapse rates. One study, which looked at vitamin D supplementation in people with relapsing remitting MS treated with interferon-beta, showed that the group treated with vitamin D and interferon-beta had a lower relapse rate, lower disability and lower number of lesions compared with the group treated with interferon-beta only. However, the weight of the clinical trial evidence suggests there may not be significant clinical benefit of vitamin D supplementation to improve outcomes relating to disease progression for people with MS.

Sunlight and MS risk or progression

One of the earliest pieces of evidence to suggest a role of sunlight in risk of developing MS is the observation that the rates of MS increase further away from the equator. This is seen in Australia where the incidence of MS is approximately seven times greater in Tasmania compared to North Queensland. There are several potential explanations for this phenomenon, however a strong candidate is the lower exposure to sunlight/UV radiation further from the equator.

No clinical trials have examined the effect of controlled sunlight exposure, or simulated sunlight exposure (using safe UV treatment, called “phototherapy”) on MS progression. However, results of a small clinical trial conducted on the impact of UV exposure on the clinical course of MS, showed a 30% reduction in the progression from a first demyelinating event (the first attack that may progress to full MS) to clinically definite MS (which requires multiple attacks to be diagnosed), suggesting that sunlight/UV exposure may have beneficial effects on the conversion to a full diagnosis of MS.

Vitamin D, sunlight and other MS symptoms

The findings on whether higher levels of vitamin D, vitamin D supplementation or sun exposure are beneficial for the treatment of other MS symptoms have been mixed. Some studies have found positive effects of these on depression, anxiety, fatigue and/or cognition, while other studies have found no effect on these symptoms.

At present, results are encouraging but the weight of the clinical trial evidence is insufficient to prove a clinical benefit of vitamin D supplementation or sun exposure for these symptoms.

Recommendations

Follow vitamin D intake recommendations and ensure you get adequate levels of sunlight

Follow vitamin D intake recommendations which vary according to age, and ensure you get adequate levels of sunlight based on your location, the time of year and skin colour.

Encouragingly, there are a number of studies investigating the role of vitamin D in MS but at this stage, evidence from clinical trials has not determined the optimal level of vitamin D or sun exposure required to see any beneficial effects in MS.

People with MS can follow the general vitamin D intake recommendations by the NHMRC and the Ministry of Health of New Zealand, as well as advice around sun exposure for the general public by Cancer Council Australia.

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

Tip

Test baseline vitamin D levels before starting supplementation which should occur under the supervision of a medical professional

Sun exposure

Adequate levels of sun exposure are recommended based on your location, time of the year and your skin colour. The following table shows the average monthly UV indices for Australian capital cities. Vitamin D production from sun exposure only occurs at a UV index above 3. During months where ambient UV is 3 or lower (indicated in red below), use of vitamin D supplements to maintain sufficiency may be appropriate.

UV Index

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

MYTH: Vitamin D has serious side effects

Vitamin D is essential for good health and supplementation is safe when taken as prescribed. There was some concern that vitamin D supplementation, particularly at high doses, may increase relapse rates. However, there were variations in the analysed study designs, with some looking at vitamin D supplementation alone and others as an add-on therapy. Since many studies have shown that a range of vitamin D doses are not harmful, it can be stated that supplementation is not hazardous. However, it is strongly recommended that all individuals avoid taking excess vitamin D.

Sun exposure, aside from the potential increase in skin cancer risk, has no negative impacts on vitamin D levels as the vitamin D produced from sun exposure is regulated within the body.

Weight and obesity

'Maintain a healthy weight' may be an old message but it's one of the most important evidence-based medical recommendations that applies to everyone, including people with MS.

Obesity and being overweight are global health epidemics as they are risk factors for many medical conditions.

The Australian MS Longitudinal Study found that over 60% of people with MS are either overweight or obese.

The WHO uses Body Mass Index (BMI) to determine what is healthy, overweight and obese. A healthy BMI is 18.5–24.9, overweight is 25–29 and a BMI of 30+ is obese. This method has its critics but it is simple and accessible to everyone.

Calculate your BMI

The formula is kg/m^2 – a person's weight divided by their height squared.

For example, a person who is 65 kg and 1.6 m tall would have a BMI of 25.4 – putting them in the overweight category.

Evidence

- **Risk factors** – being overweight or obese during childhood and obese during adolescence are risk factors for developing MS in later life
- **MS progression** – findings from studies investigating weight and MS progression have been slightly conflicting as early studies did not link excess weight during adulthood with disease progression, but more recent studies have
- **Symptoms** – one study found that being overweight or obese was associated with an increased risk of relapse

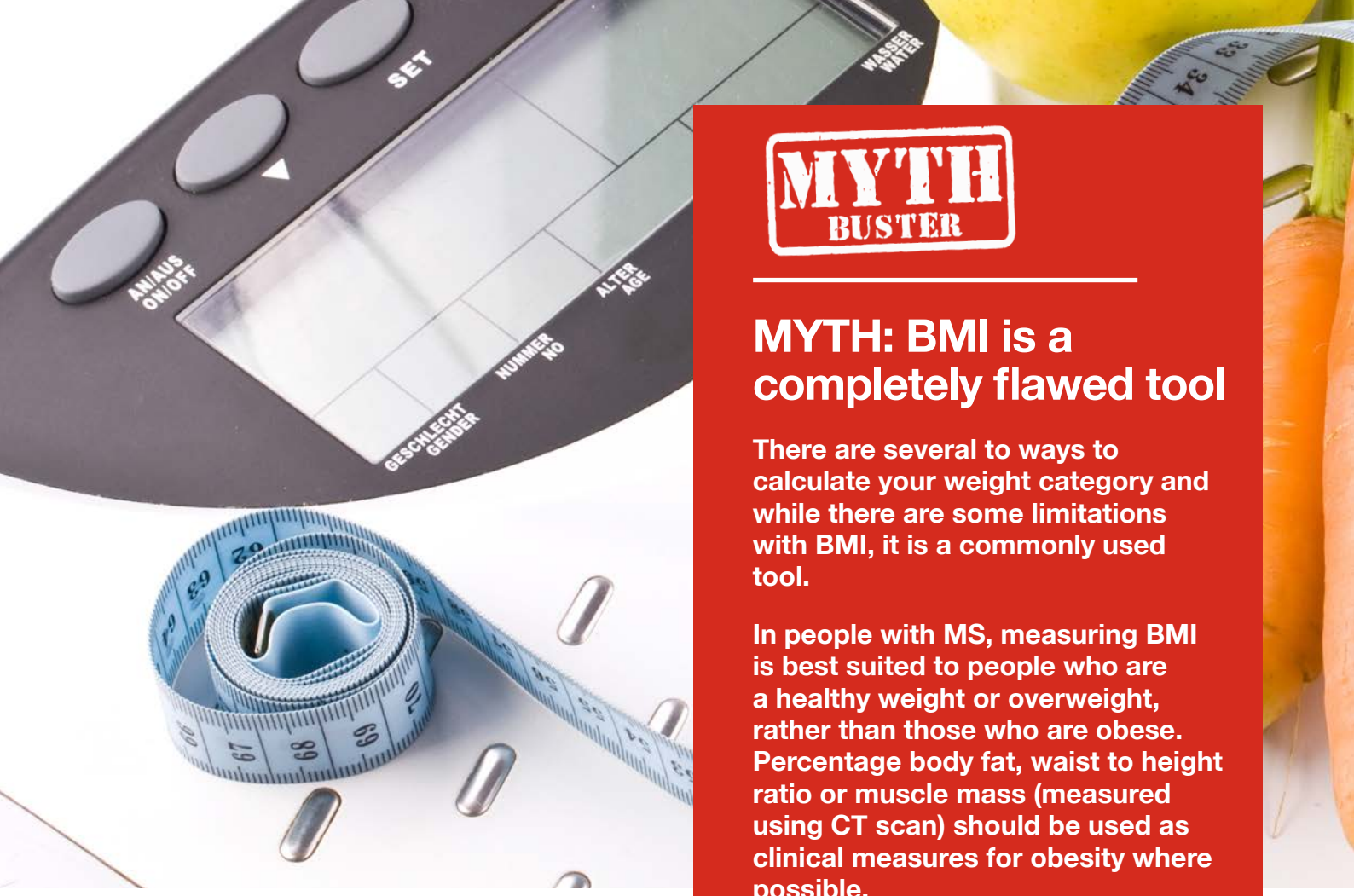
  Overweight and obese people with MS also reported more symptoms of depression, however it is unclear whether it is only the excess weight causing worse symptoms
- **Comorbidities (other medical conditions)** – extra weight is linked with comorbidities of MS, such as high cholesterol and diabetes. These conditions may also worsen MS leading to higher rates of disability, lower quality of life and an increased chance of relapse following an initial episode of neurological symptoms. Being overweight or obese is thought to put the body into a pro-inflammatory state and may add to the neurological inflammation present in people with MS

SNAPSHOT

Being overweight or obese during childhood and obese during adolescence are risk factors for developing MS in later life

Only a few high quality studies assessing the impact of weight on MS exist

Losing excess weight may be relevant as people with other chronic diseases have found improvements in their condition after weight loss



MYTH BUSTER

MYTH: BMI is a completely flawed tool

There are several to ways to calculate your weight category and while there are some limitations with BMI, it is a commonly used tool.

In people with MS, measuring BMI is best suited to people who are a healthy weight or overweight, rather than those who are obese. Percentage body fat, waist to height ratio or muscle mass (measured using CT scan) should be used as clinical measures for obesity where possible.

Recommendations

Maintain or aim for your weight to be in the healthy range, irrespective of your stage of MS

In the absence of MS-specific studies regarding weight, experts have looked at studies involving people with other chronic conditions and noted improvements in their condition following weight loss. Additionally, advice for the general population is to maintain a healthy weight. Based on this evidence, it is recommended that people with MS should also maintain a healthy weight.

Tip

Dietitians, physiotherapists and psychologists can provide support and guidance on how to achieve/maintain a healthy weight

The Diet section (page 14) contains key elements from the *Australian Dietary Guidelines* and guidelines for physical activity are outlined on page 10.

Other medical conditions

In addition to having MS, people may also have to manage a range of other medical conditions, known as comorbidities.

Many physical and mental health conditions occur more often in people with MS than the general public. This is a concern because people with conditions in addition to their MS have on average a lower health-related quality of life compared with those who do not. There is also increasing evidence that additional conditions have a negative impact on MS relapses and several other factors.

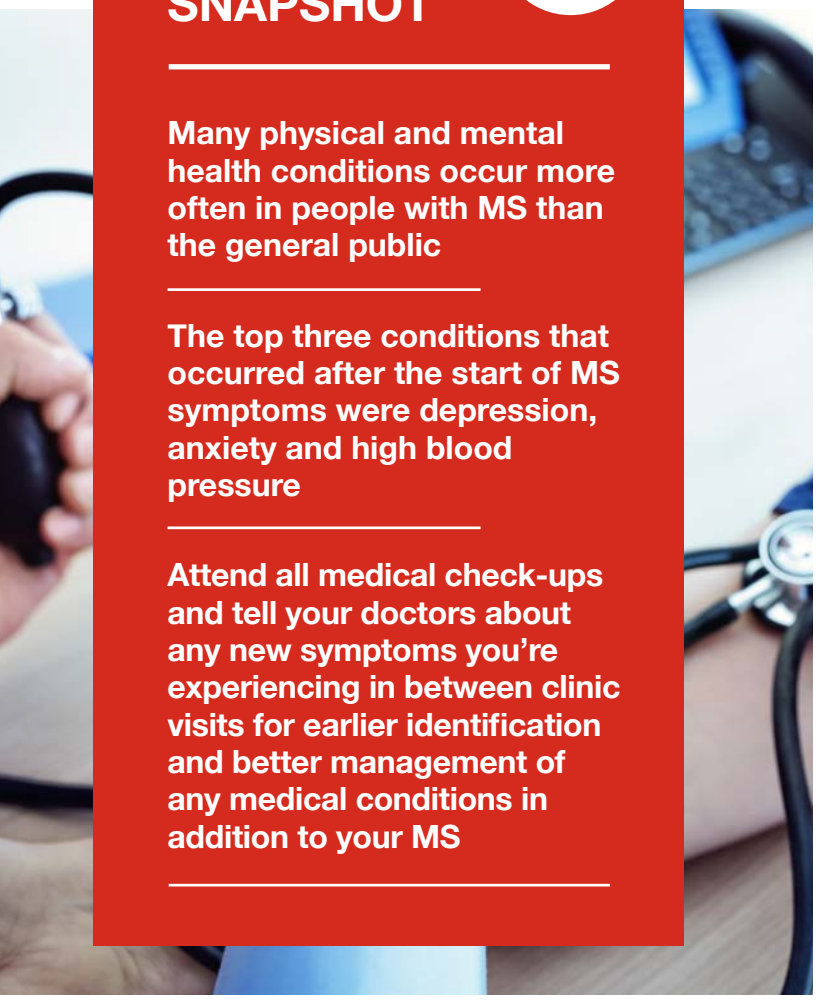
Additional medical conditions in people with MS are already prevalent at the start of MS symptoms with 65% of people with MS having one or more additional conditions.

SNAPSHOT

Many physical and mental health conditions occur more often in people with MS than the general public

The top three conditions that occurred after the start of MS symptoms were depression, anxiety and high blood pressure

Attend all medical check-ups and tell your doctors about any new symptoms you're experiencing in between clinic visits for earlier identification and better management of any medical conditions in addition to your MS



Evidence

- **Frequency –** conditions that occur more often in people with MS than the general public include depression, anxiety, hypertension, diabetes, chronic lung disease and hyperlipidaemia. The accumulation of other medical conditions seems to be beyond normal aging and may be due to changes in lifestyle behaviours, MS treatment effects and shared risk factors with MS
- **Quality of life –** people with additional medical conditions have a lower quality of life compared to those having MS only. Mental health and musculoskeletal disorders are the largest contributors to the reduction in overall health-related quality of life
- **Relapse** – people with MS with multiple additional conditions have an increased relapse rate compared with those who did not. Migraine, high blood lipid levels (see page 32), rheumatoid arthritis and anaemia were associated with an increased relapse rate when individual conditions were studied
- **Disability/disability progression** – the presence of any additional medical condition is associated with higher disability in early MS (i.e. maximum of two years after diagnosis) and a faster disability progression throughout the disease course
- **Magnetic resonance imaging (MRI) related outcomes** – additional medical conditions are associated with the worsening of MRI-related measures such as lesions and brain volume, but it is unclear if the decline is due to MS-specific reasons or whether the other medical conditions independently affect MRI outcomes

- **Symptom severity** – additional medical conditions are associated with higher symptom severity adding to the total symptoms commonly seen in MS. For example, people with MS experiencing depression, arthritis, migraine, osteoporosis or anxiety had more pain
- **MS medications** – one study has suggested that having a higher number of conditions in addition to MS may lower the likelihood of starting with a disease modifying therapy
- **Hospitalisations –** People with MS who have additional medical conditions have an increased chance of hospitalisation and mortality, but this is thought to be due to the other conditions rather than the MS itself
- **Employment outcomes –** additional medical conditions seem to reduce people's work productivity and likelihood of working, through an increase in symptom severity. The costs related to the loss of work productivity were highest for depression, allergy, anxiety, migraine and osteoarthritis

MYTH: Depression and anxiety are just something that people with MS have to live with

Around half of people diagnosed with MS will have a depressive episode. While this is common, no one 'just has to live with' any mental illness.

Understanding and support for Australians with mental illness has increased substantially over the years. Studies show that when people with MS work with health professionals mental health improves.

If you're feeling low or depressed, talk to your doctor, MS nurse or ask for a referral to a specialist ASAP. More information on recognising and managing depression can be found on MS Australia's website.

Recommendations

Attend all medical check-ups and tell your doctors about any new symptoms in between clinic visits

As with most medical conditions, the earlier they're identified, the better. The same applies to medical conditions that occur alongside your MS – early identification helps with better management of comorbidities to minimise the impact on your life.

Tip

Adopting a healthy lifestyle can also help to prevent and improve additional medical conditions

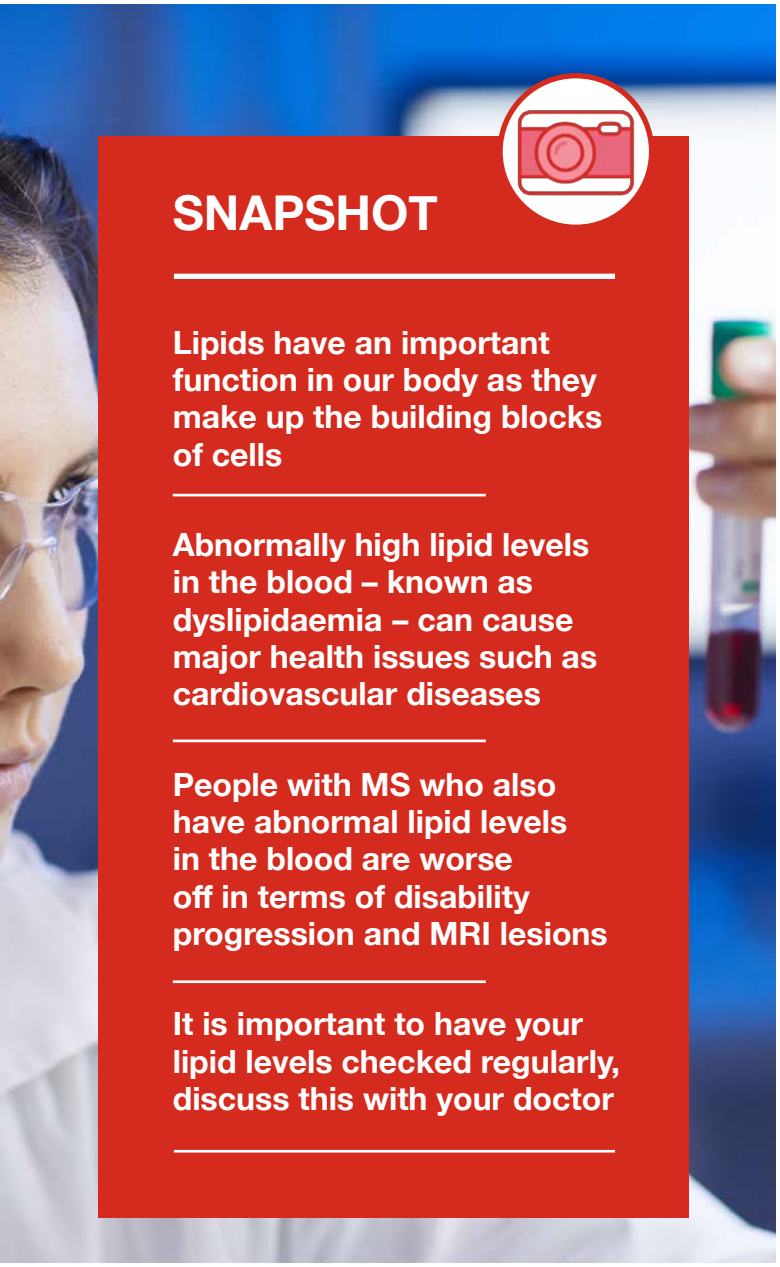
Take a look at the lifestyle sections (pages 6, 10 and 14) in this document.

Lipids

Lipids are an important structural part of cells in the body, and are a component of myelin, which protects and insulates nerve fibres and is the part of the brain and spinal cord that is attacked in MS. Lipids are also involved in signalling between cells and and store energy in the body.

Problems occur when lipid levels are abnormal or high, which is typically caused by eating too many fats or having genes that make this more likely.

Lipids are not the same as cholesterol; cholesterol is a type of lipid.



SNAPSHOT

Lipids have an important function in our body as they make up the building blocks of cells

Abnormally high lipid levels in the blood – known as dyslipidaemia – can cause major health issues such as cardiovascular diseases

People with MS who also have abnormal lipid levels in the blood are worse off in terms of disability progression and MRI lesions

It is important to have your lipid levels checked regularly, discuss this with your doctor

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

Abnormally high lipid levels are very common in people with MS, as they are in the general population.

In fact, this is one of the most common medical conditions to occur alongside MS. The prevalence increases with age and MS disease duration.

Evidence

There is inconsistent evidence around lipid levels in people with MS. Some studies have shown that lipid levels are increased in people with MS, while others have shown no difference or even the opposite effect.

There is increasing evidence that abnormal lipid levels may have negative effects on clinical outcomes of MS:

- **Disability** – there is consensus that high lipid levels contribute to worse disability outcomes
- **Lesions** – studies have found that abnormal lipid levels are linked with an increased number of lesions, indicators of inflammation in the brain and acute disease. However, one study indicates that increased HDL-C levels may be associated with less brain deterioration. Further studies with long-term follow-up are needed to confirm these findings

When it comes to medications, studies have looked at MS medications and statins:

- **MS medications** – based on limited evidence, there does not seem to be a pattern that MS medications have strong negative effects on lipid levels, with some studies noting a small reduction of the 'good cholesterol' HDL-C, while other studies observing beneficial effects (e.g. increase in HDL-C, or reduction in TC or LDL-C)
- **Statins** – used to reduce cholesterol for the prevention of cardiovascular disease, statins are well-tolerated and safe in MS but a major review did not find they had a beneficial effect on the disease course of MS. Encouragingly, a recent trial showed favourable effects on brain deterioration, physical quality of life and some measures of cognitive function but further trials are required

MYTH: Abnormal lipid levels can only be managed by medications

While medications such as statins are critical for many people to improve abnormal lipid levels or prevent cardiovascular events, physical activity and diet are also important. Your doctor will discuss the best management options.

Recommendations

Check your lipid levels

It is important to keep a check on your lipid levels as abnormal levels are common, both in people with MS and the general population. As these abnormal lipid levels are associated with worse clinical outcomes, such as disability progression, there are even more reasons for people with MS to have their lipids monitored regularly. This is done via a blood test. Discuss the testing with your doctor and the management options if you have abnormal lipid levels.

Tip

Adopting a healthy lifestyle can also help to prevent abnormal lipid levels

Take a look at the lifestyle sections (pages 6, 10 and 14) in this document.

References

Abbey R Tredinnick, Yasmine C Probst, Evaluating the Effects of Dietary Interventions on Disease Progression and Symptoms of Adults with Multiple Sclerosis: An Umbrella Review, Advances in Nutrition, , nmaa063, https://doi.org/10.1093/advances/nmaa063

Achiron, A. et al. Effect of Alfacalcidol on multiple sclerosis-related fatigue: A randomized, double-blind placebo-controlled study. Mult. Scler. 21, 767–775 (2015).

Adamson, B. C., Ensari, I. & Motl, R. W. Effect of Exercise on Depressive Symptoms in Adults With Neurologic Disorders: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil 96, 1329–1338 (2015).

Åivo, J., Lindsröm, B.-M. & Soilu-Hänninen, M. A Randomised, Double-Blind, Placebo-Controlled Trial with Vitamin D3 in MS: Subgroup Analysis of Patients with Baseline Disease Activity Despite Interferon Treatment. Mult Scler Int 2012, 802796 (2012).

Allen, N. B. et al. Vascular disease among hospitalized multiple sclerosis patients. Neuroepidemiology 30, 234–238 (2008).

Alphonsus, K. B., Su, Y. & D'Arcy, C. The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: Systematic review and meta-analysis. Complement Ther Med 43, 188–195 (2019).

Armitage, J. et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 393, 407–415 (2019).

Ashtari, F., Ajalli, M., Shaygannejad, V., Akbari, M. & Hovsepian, S. The relation between Vitamin D status with fatigue and depressive symptoms of multiple sclerosis. J Res Med Sci 18, 193–197 (2013).

Australian Bureau of Statistics. Australian Health Survey: User's Guide. Cardiovascular Disease Biomarkers https://www.abs.gov.au/ausstats/abs@.nsf/

Australian Bureau of Statistics. National Health Survey: First results, 2017-18. https://www.abs.gov.au/ausstats/abs@.nsf/mf/4364.0.55.001 (2018).

Australian Government Department of Health. Are there safe smoking and tobacco options? https://www.health.gov.au/health-topics/smoking-and-tobacco/about-smoking-and-tobacco/are-there-safe-smoking-and-tobacco-options (2019).

Australian Government Department of Health. Australian Dietary Guidelines. https://www.eatforhealth.gov.au/sites/default/files/content/n55_australian_dietary_guidelines.pdf (2013).

Australian Government Department of Health. Tobacco control. https://www.health.gov.au/health-topics/smoking-and-tobacco/tobacco-control (2019).

Australian Government Department of Health. What are the effects of smoking and tobacco? https://www.health.gov.au/health-topics/smoking-and-tobacco/about-smoking-and-tobacco/what-are-the-effects-of-smoking-and-tobacco (2019).

Australian Government Department of Health. What is smoking and tobacco? https://www.health.gov.au/health-topics/smoking-and-tobacco/about-smoking-and-tobacco/what-is-smoking-and-tobacco (2019).

Australian Institute of Health and Welfare. Burden of disease Overview. https://www.aihw.gov.au/reports-data/health-conditions-disability-deaths/burden-of-disease/overview (2019).

Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2016: detailed findings. https://www.aihw.gov.au/reports/illicit-use-of-drugs/2016-ndshs-detailed/data (2019).

Aviv, R. I. et al. Decreased frontal lobe gray matter perfusion in cognitively impaired patients with secondary-progressive multiple sclerosis detected by the bookend technique. AJNR Am J Neuroradiol 33, 1779–1785 (2012).

Bates, D. et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. J Neurol Neurosurg Psychiatry 52, 18–22 (1989).

Benjamin, J. L. et al. Smokers with Active Crohn's Disease Have a Clinically Relevant Dysbiosis of the Gastrointestinal Microbiota. Inflamm Bowel Dis 18, 1092–1100 (2012).

Benjamins, J. A., Murphy, E. J. & Seyfried, T. N. Chapter 5 - Lipids. in Basic Neurochemistry (Eighth Edition) (eds. Brady, S. T., Siegel, G. J., Albers, R. W. & Price, D. L.) 81–100 (Academic Press, 2012).

Berer, K. et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc. Natl. Acad. Sci. U.S.A. 114, 10719–10724 (2017).

Birnbaum, G. & Stulc, J. High dose biotin as treatment for progressive multiple sclerosis. Mult. Scler. Relat. Disord. 18, 141–143 (2017).

Bisht, B. et al. Multimodal intervention improves fatigue and quality of life in subjects with progressive multiple sclerosis: a pilot study. Degener Neurol Neuromuscul Dis 5, 19–35 (2015).

Bouchard, C. & Shephard, R. J. Physical activity, fitness, and health: The model and key concepts. in Physical activity, fitness, and health: International proceedings and consensus statement. (eds. Bouchard, C., Shephard, R. J. & Stephens, T.) 77–88 (Human Kinetics Publishers, 1994).

Briggs, F. B., Gunzler, D. D., Ontaneda, D. & Marrie, R. A. Smokers with MS have greater decrements in quality of life and disability than non-smokers. Mult. Scler. 23, 1772–1781 (2017).

Britt, E., Hudson, S. M. & Blampied, N. M. Motivational interviewing in health settings: a review. Patient Educ Couns 53, 147–155 (2004).

Browne, R. W. et al. Apolipoproteins are associated with new MRI lesions and deep grey matter atrophy in clinically isolated syndromes. J. Neurol. Neurosurg. Psychiatry 85, 859–864 (2014).

Browne, R. W. et al. High-density lipoprotein cholesterol is associated with multiple sclerosis fatigue: A fatigue-metabolism nexus? J Clin Lipidol 13, 654-663.e1 (2019).

Burton, J. M. et al. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. Neurology 74, 1852–1859 (2010).

Cambil-Martín, J. et al. Influence of body mass index on psychological and functional outcomes in patients with multiple sclerosis: a cross-sectional study. Nutr Neurosci 19, 79–85 (2016).

Campbell, E. et al. Physiotherapy Rehabilitation for People With Progressive Multiple Sclerosis: A Systematic Review. Arch Phys Med Rehabil 97, 141-151.e3 (2016).

Camu, W. et al. Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE). Neurol Neuroimmunol Neuroinflamm 6, e597 (2019).

Canadian Society for Exercise Physiology. Canadian Physical Activity Guidelines for adults with Multiple Sclerosis. https://www.csep.ca/CMFiles/Guidelines/specialpops/CSEP_MS_PAGuidelines_adults_en.pdf (2013).

Cancer Council Australia. Position statement - Sun exposure and vitamin D - risks and benefits. https://wiki.cancer.org.au/policy/Position_statement_-_Risks_and_benefits_of_sun_exposure (2016).

Casey, B., Coote, S., Galvin, R. & Donnelly, A. Objective physical activity levels in people with multiple sclerosis: Meta-analysis. Scand. J. Med. Sci. Sports 28, 1960–1969 (2018).

Caspersen, C. J., Powell, K. E. & Christenson, G. M. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 100, 126–131 (1985).

Cekanaviciute, E. et al. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. Proc. Natl. Acad. Sci. U.S.A. 114, 10713–10718 (2017).

Chan, D. et al. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. Lancet Neurol 16, 591–600 (2017).

Chaseling, G. K. et al. Cold Water Ingestion Improves Exercise Tolerance of Heat-Sensitive People with MS. Med Sci Sports Exerc 50, 643–648 (2018).

Chataway, J. et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet 383, 2213–2221 (2014).

Chen, J. et al. Comorbidities are prevalent and detrimental for employment outcomes in people of working age with multiple sclerosis. Mult. Scler. (2019).

Chen, X.-L. et al. Vitamin D receptor gene polymorphisms and the risk of multiple sclerosis: An updated meta-analysis. Microb Pathog. 110, 594–602 (2017).

Christiansen, C. F. Risk of vascular disease in patients with multiple sclerosis: a review. Neurol. Res. 34, 746–753 (2012).

Clarke, S. F. et al. Exercise and associated dietary extremes impact on gut microbial diversity. Gut 63, 1913–1920 (2014).

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT03183869, Fecal Microbial Transplantation in Relapsing Multiple Sclerosis Patients; 2017 May 9. Available from: https://ClinicalTrials.gov/show/NCT03183869

Consortium of Multiple Sclerosis Centers and Nurse Practitioner Alternatives. Comorbidities in Multiple Sclerosis - A clinical resource guide. https://catmeded.weebly.com/uploads/1/4/2/6/14261658/comobidities_resource_guide.pdf (2018).

Correale, J. & Farez, M. F. The impact of parasite infections on the course of multiple sclerosis. J. Neuroimmunol. 233, 6–11 (2011).

Cruickshank, T. M., Reyes, A. R. & Ziman, M. R. A Systematic Review and Meta-Analysis of Strength Training in Individuals With Multiple Sclerosis Or Parkinson Disease. Medicine 94, e411 (2015).

D'hooghe, M. B., Haentjens, P., Nagels, G. & De Keyser, J. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. European Journal of Neurology 19, 616–624 (2012).

Dalgas, U. et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology 73, 1478–1484 (2009).

Dalgas, U., Stenager, E., Sloth, M. & Stenager, E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. Eur. J. Neurol. 22, 443-e34 (2015).

Dallmeijer, A. J. et al. Long-term effect of comorbidity on the course of physical functioning in patients after stroke and with multiple sclerosis. J Rehabil Med 41, 322–326 (2009).

De Filippis, F. et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut 65, 1812–1821 (2016).

de Souto Barreto, P., Cesari, M., Andrieu, S., Vellas, B. & Rolland, Y. Physical Activity and Incident Chronic Diseases: A Longitudinal Observational Study in 16 European Countries. Am J Prev Med. 52, 373–378 (2017).

Debernard, L. et al. Reduced grey matter perfusion without volume loss in early relapsing-remitting multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 85, 544–551 (2014).

Demaneuf, T. et al. Effectiveness of Exercise Interventions for Pain Reduction in People With Multiple Sclerosis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Arch Phys Med Rehabil 100, 128–139 (2019).

Derakhshandi, H. et al. Preventive effect of vitamin D3 supplementation on conversion of optic neuritis to clinically definite multiple sclerosis: a double blind, randomized, placebo-controlled pilot clinical trial. Acta Neurol Belg 113, 257–263 (2013).

Diaz-Cruz, C. et al. The effect of alcohol and red wine consumption on clinical and MRI outcomes in multiple sclerosis. Mult. Scler. Relat. Disord. 17, 47–53 (2017).

Ding, R. et al. Revisit gut microbiota and its impact on human health and disease. J Food Drug Anal 27, 623–631 (2019).

Ditre, J. W., Brandon, T. H., Zale, E. L. & Meagher, M. M. Pain, nicotine, and smoking: research findings and mechanistic considerations. Psychol Bull 137, 1065–1093 (2011).

Dörr, J. et al. High-dose vitamin D supplementation in multiple sclerosis - results from the randomized EVIDIMS (efficacy of vitamin D supplementation in multiple sclerosis) trial. Mult Scler J Exp Transl Clin 6, 2055217320903474 (2020).

Dougados, M. et al. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA). Ann. Rheum. Dis. 74, 1725–1733 (2015).

Drew, M., Tippett, L. J., Starkey, N. J. & Isler, R. B. Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. Arch Clin Neuropsychol 23, 1–19 (2008).

Duan, S. et al. Vitamin D status and the risk of multiple sclerosis: a systematic review and meta-analysis. Neurosci. Lett. 570, 108–113 (2014).

Ďurfinová, M. et al. Cholesterol level correlate with disability score in patients with relapsing-remitting form of multiple sclerosis. Neurosci. Lett. 687, 304–307 (2018).

Edwards, T. & Pilutti, L. A. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A systematic review and future research directions. Mult Scler Relat Disord 16, 31–39 (2017).

Engen, P. A., Green, S. J., Voigt, R. M., Forsyth, C. B. & Keshavarzian, A. The Gastrointestinal Microbiome: Alcohol Effects on the Composition of Intestinal Microbiota. Alcohol Res 37, 223–236 (2015).

Ensari, I., Motl, R. W. & Pilutti, L. A. Exercise training improves depressive symptoms in people with multiple sclerosis: Results of a meta-analysis. J Psychosom Res 76, 465–471 (2014).

Etoom, M. et al. Effectiveness of Physiotherapy Interventions on Spasticity in People With Multiple Sclerosis: A Systematic Review and Meta-Analysis. Am J Phys Med Rehabil 97, 793–807 (2018).

Fahy, E., Cotter, D., Sud, M. & Subramaniam, S. Lipid classification, structures and tools. Biochim. Biophys. Acta 1811, 637–647 (2011).

Farez, M. F., Fiol, M. P., Gaitán, M. I., Quintana, F. J. & Correale, J. Sodium intake is associated with increased disease activity in multiple sclerosis. J Neurol Neurosurg Psychiatry 86, 26–31 (2015).

Feinstein, A. Multiple sclerosis and depression. Mult. Scler. 17, 1276–1281 (2011).

Fiest, K. M. et al. Comorbidity is associated with pain-related activity limitations in multiple sclerosis. Mult. Scler. Relat. Disord. 4, 470–476 (2015).

Fiest, K. M. et al. Fatigue and Comorbidities in Multiple Sclerosis. Int J MS Care 18, 96–104 (2016).

Fitzgerald, K. C. et al. Sodium intake and multiple sclerosis activity and progression in BENEFIT. Ann Neurol 82, 20–29 (2017).

Fleming, J. O. Helminth therapy and multiple sclerosis. Int. J. Parasitol. 43, 259–274 (2013).

Friend, K. B., Mernoff, S. T., Block, P. & Reeve, G. Smoking rates and smoking cessation among individuals with multiple sclerosis. Disabil Rehabil 28, 1135–1141 (2006).

Frohman, T. C. et al. Uhthoff's phenomena in MS--clinical features and pathophysiology. Nat Rev Neurol 9, 535–540 (2013).

Gallagher, L. G. et al. Lifetime exposure to ultraviolet radiation and the risk of multiple sclerosis in the US radiologic technologists cohort study. Mult. Scler. 25, 1162–1169 (2019).

Gascoyne, C. R., Simpson, S., Chen, J., van der Mei, I. & Marck, C. H. Modifiable factors associated with depression and anxiety in multiple sclerosis. Acta Neurol. Scand. 140, 204–211 (2019).

GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 393, 1958–1972 (2019).

Gee, J. R., Chang, J., Dublin, A. B. & Vijayan, N. The association of brainstem lesions with migraine-like headache: an imaging study of multiple sclerosis. Headache 45, 670–677 (2005).

Gianfrancesco, M. A. et al. Causal Effect of Genetic Variants Associated With Body Mass Index on Multiple Sclerosis Susceptibility. Am. J. Epidemiol. 185, 162–171 (2017).

Gies, P. et al. Global Solar UV Index: Australian Measurements, Forecasts and Comparison with the UK. Photochem Photobiol 79, 32–39 (2004).

Gilbody, S., Bower, P., Fletcher, J., Richards, D. & Sutton, A. J. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Arch. Intern. Med. 166, 2314–2321 (2006).

Giubilei, F. et al. Blood cholesterol and MRI activity in first clinical episode suggestive of multiple sclerosis. Acta Neurol. Scand. 106, 109–112 (2002).

Gomes, J. P., Watad, A. & Shoenfeld, Y. Nicotine and autoimmunity: The lotus' flower in tobacco. Pharmacol. Res. 128, 101–109 (2018).

Graziano, E., Hagemeier, J., Weinstock-Guttman, B., Ramasamy, D. P. & Zivadinov, R. Increased contrast enhancing lesion activity in relapsing–remitting multiple sclerosis migraine patients. Neuroimage Clin 9, 110–116 (2015).

Grech, L. B. et al. Coping mediates and moderates the relationship between executive functions and psychological adjustment in multiple sclerosis. Neuropsychology 30, 361–376 (2016).

Gunn, H., Markevics, S., Haas, B., Marsden, J. & Freeman, J. Systematic Review: The Effectiveness of Interventions to Reduce Falls and Improve Balance in Adults With Multiple Sclerosis. Arch Phys Med Rehabil 96, 1898–1912 (2015).

Hart, P. H. et al. A randomised, controlled clinical trial of narrowband UVB phototherapy for clinically isolated syndrome: The PhoCIS study. Mult Scler J Exp Transl Clin 4, 2055217318773112 (2018).

Hart, P. H., Gorman, S. & Finlay-Jones, J. J. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? Nat. Rev. Immunol. 11, 584–596 (2011).

Healy, B. C. et al. Smoking and Disease Progression in Multiple Sclerosis. Arch. Neurol. 66, 858–864 (2009).

Hearn, A. P. & Silber, E. Osteoporosis in multiple sclerosis. Mult. Scler. 16, 1031–1043 (2010).

Hedström, A. K. et al. High consumption of coffee is associated with decreased multiple sclerosis risk; results from two independent studies. J Neurol Neurosurg Psychiatry 87, 454–460 (2016).

Hedström, A. K. et al. Smokers run increased risk of developing anti-natalizumab antibodies. Mult. Scler. 20, 1081–1085 (2014).

Hedström, A. K. et al. Smoking and risk of treatment-induced neutralizing antibodies to interferon β-1a. Mult. Scler. 20, 445–450 (2014).

Hedström, A. K. Smoking and its interaction with genetics in MS etiology. Mult. Scler. 25, 180–186 (2019).

Hedström, A. K., Bäärnhielm, M., Olsson, T. & Alfredsson, L. Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. Neurology 73, 696–701 (2009).

Heine, M., van de Port, I., Rietberg, M. B., van Wegen, E. E. H. & Kwakkel, G. Exercise therapy for fatigue in multiple sclerosis. Cochrane Database Syst Rev CD009956 (2015).

Hempel, S. et al. A systematic review of modifiable risk factors in the progression of multiple sclerosis. Mult. Scler. 23, 525–533 (2017).

Hoang, P., Schoene, D., Gandevia, S., Smith, S. & Lord, S. R. Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis--a randomized controlled trial. Mult. Scler. 22, 94–103 (2016).

Holick, M. F. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80, 1678S-1688S (2004).

Holmøy, T., Lindstrøm, J. C., Eriksen, E. F., Steffensen, L. H. & Kampman, M. T. High dose vitamin D supplementation does not affect biochemical bone markers in multiple sclerosis - a randomized controlled trial. BMC Neurol 17, 67 (2017).

Hooker, S., Punjabi, A., Justesen, K. & Sherman, M. D. Encouraging Health Behavior Change: Eight Evidence-Based Strategies. Fam Pract Manag 25, 31–36 (2018).

Hupperts, R. et al. Randomized trial of daily high-dose vitamin D3 in patients with RRMS receiving subcutaneous interferon β-1a. Neurology 93, e1906–e1916 (2019).

Imani, D., Razi, B., Motallebnezhad, M. & Rezaei, R. Association between vitamin D receptor (VDR) polymorphisms and the risk of multiple sclerosis (MS): an updated meta-analysis. BMC Neurol 19, 339 (2019).

Irish, A. K., Erickson, C. M., Wahls, T. L., Snetselaar, L. G. & Darling, W. G. Randomized control trial evaluation of a modified Paleolithic dietary intervention in the treatment of relapsing-remitting multiple sclerosis: a pilot study. Degener Neurol Neuromuscul Dis 7, 1–18 (2017).

Ismailova, K., Poudel, P., Parlesak, A., Frederiksen, P. & Heitmann, B. L. Vitamin D in early life and later risk of multiple sclerosis-A systematic review, meta-analysis. PLoS ONE 14, e0221645 (2019).

Jacobs, B. M., Noyce, A. J., Giovannoni, G. & Dobson, R. BMI and low vitamin D are causal factors for multiple sclerosis: A Mendelian Randomization study. Neurol Neuroimmunol Neuroinflamm 7, e662 (2020).

Jadidi, E., Mohammadi, M. & Moradi, T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. Mult. Scler. 19, 1336–1340 (2013).

Jafarirad, S. et al. The Effect of Vitamin A Supplementation on Biochemical Parameters in Multiple Sclerosis Patients. Iran Red Crescent Med J 15, 194–198 (2013).

Jakimovski, D. et al. Decrease in Secondary Neck Vessels in Multiple Sclerosis: A 5-year Longitudinal Magnetic Resonance Angiography Study. Curr Neurovasc Res 16, 215–223 (2019).

James, E. et al. The effect of vitamin D-related interventions on multiple sclerosis relapses: a meta-analysis. Mult. Scler. 19, 1571–1579 (2013).

Jangi, S. et al. Alterations of the human gut microbiome in multiple sclerosis. Nat Commun 7, 1–11 (2016).

Janzen, W., Turpin, K. V. L., Warren, S. A., Marrie, R. A. & Warren, K. G. Change in the Health-Related Quality of Life of Multiple Sclerosis Patients over 5 Years. Int J MS Care 15, 46–53 (2013).

Jelinek, G. A. et al. Association of fish consumption and Ω 3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis. Int J Neurosci 123, 792–800 (2013).

Kalb, R. et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. Mult Scler 1352458520915629 (2020).

Kampman, M. T., Steffensen, L. H., Mellgren, S. I. & Jørgensen, L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. Mult. Scler. 18, 1144–1151 (2012).

Kang, J.-H., Chen, Y.-H. & Lin, H.-C. Comorbidities amongst patients with multiple sclerosis: a population-based controlled study. Eur. J. Neurol. 17, 1215–1219 (2010).

Kau, A. L., Ahern, P. P., Griffin, N. W., Goodman, A. L. & Gordon, J. I. Human nutrition, the gut microbiome and the immune system. Nature 474, 327–336 (2011).

Kawada, T. Prediction of Adiposity by Body Mass Index in Patients With Multiple Sclerosis. Arch Phys Med Rehabil 97, 1598–1599 (2016).

Khallli, M. et al. Lipoic acid and multiple sclerosis: A randomized controlled clinical trial. Curr Top Nutraceutical Res 10, 95–100 (2012).

Khan, K. M. et al. Sport and exercise as contributors to the health of nations. Lancet 380, 59–64 (2012).

Kim, K. O. & Gluck, M. Fecal Microbiota Transplantation: An Update on Clinical Practice. Clin Endosc 52, 137–143 (2019).

Kim, Y. et al. Exercise Training Guidelines for Multiple Sclerosis, Stroke, and Parkinson Disease: Rapid Review and Synthesis. Am J Phys Med Rehabil 98, 613–621 (2019).

Kimball, S. M., Ursell, M. R., O'Connor, P. & Vieth, R. Safety of vitamin D3 in adults with multiple sclerosis. Am. J. Clin. Nutr. 86, 645–651 (2007).

Kinnett-Hopkins, D., Adamson, B., Rougeau, K. & Motl, R. W. People with MS are less physically active than healthy controls but as active as those with other chronic diseases: An updated meta-analysis. Mult Scler Relat Disord 13, 38–43 (2017).

Kjølhede, T., Vissing, K. & Dalgas, U. Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler 18, 1215–1228 (2012).

Knippenberg, S. et al. Higher levels of reported sun exposure, and not vitamin D status, are associated with less depressive symptoms and fatigue in multiple sclerosis. Acta Neurol. Scand. 129, 123–131 (2014).

Knippenberg, S., Bol, Y., Damoiseaux, J., Hupperts, R. & Smolders, J. Vitamin D status in patients with MS is negatively correlated with depression, but not with fatigue. Acta Neurol. Scand. 124, 171–175 (2011).

Kopin, L. & Lowenstein, C. Dyslipidemia. Ann. Intern. Med. 167, ITC81–ITC96 (2017).

Kouchaki, E. et al. Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial. Clin Nutr 36, 1245–1249 (2017).

Kowalec, K. et al. Comorbidity increases the risk of relapse in multiple sclerosis: A prospective study. Neurology 89, 2455–2461 (2017).

Lamers, I. et al. Upper Limb Rehabilitation in People With Multiple Sclerosis: A Systematic Review. Neurorehabil Neural Repair 30, 773–793 (2016).

Langeskov-Christensen, M., Heine, M., Kwakkel, G. & Dalgas, U. Aerobic capacity in persons with multiple sclerosis: a systematic review and meta-analysis. Sports Med 45, 905–923 (2015).

Latimer-Cheung, A. E. et al. Development of evidence-informed physical activity guidelines for adults with Multiple Sclerosis. Arch Phys Med Rehabil 94, 1829–1836 (2013).

Latimer-Cheung, A. E. et al. The effects of exercise training on fitness, mobility, fatigue, and health related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch Phys Med Rehabil 94, 1800–1828 (2013).

Lavela, S. L., Prohaska, T. R., Furner, S. & Weaver, F. M. Chronic diseases in male veterans with multiple sclerosis. Prev Chronic Dis 9, E55 (2012).

Learmonth, Y. C., Ensari, I. & Motl, R. W. Physiotherapy and walking outcomes in adults with multiple sclerosis: systematic review and meta-analysis. Phys. Ther. Rev. 21, 160–172 (2016).

Leavitt, V. M. et al. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: preliminary findings. Neurocase 20, 695–697 (2014).

Lemire, J. 1,25-Dihydroxyvitamin D3--a hormone with immunomodulatory properties. Z Rheumatol 59 Suppl 1, 24–27 (2000).

Lovera, J. et al. Polyphenon E, non-futile at neuroprotection in multiple sclerosis but unpredictably hepatotoxic: Phase I single group and phase II randomized placebo-controlled studies. J. Neurol. Sci. 358, 46–52 (2015).

Lucas, R. M. et al. Associations between silicone skin cast score, cumulative sun exposure, and other factors in the ausimmune study: a multicenter Australian study. Cancer Epidemiol. Biomarkers Prev. 18, 2887–2894 (2009).

Lucas, R. M. et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology 76, 540–548 (2011).

Maillart, E., Mochel, F., Acquaviva, C., Maisonobe, T. & Stankoff, B. Severe transient myopathy in a patient with progressive multiple sclerosis and high-dose biotin. Neurology 92, 1060–1062 (2019).

Makkawi, S., Camara-Lemarroy, C. & Metz, L. Fecal microbiota transplantation associated with 10 years of stability in a patient with SPMS. Neurol Neuroimmunol Neuroinflamm 5, e459 (2018).

Malosse, D., Perron, H., Sasco, A. & Seigneurin, J. M. Correlation between Milk and Dairy Product Consumption and Multiple Sclerosis Prevalence: A Worldwide Study. Neuroepidemiology 11, 304–312 (1992).

Mandoj, C. et al. Anti-annexin antibodies, cholesterol levels and disability in multiple sclerosis. Neurosci. Lett. 606, 156–160 (2015).

Manouchehrinia, A., Weston, M., Tench, C. R., Britton, J. & Constantinescu, C. S. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. J Neurol Neurosurg Psychiatry 85, 1091–1095 (2014).

Marck, C. H. et al. Pain in People with Multiple Sclerosis: Associations with Modifiable Lifestyle Factors, Fatigue, Depression, Anxiety, and Mental Health Quality of Life. Front Neurol 8, 461 (2017).

Marck, C. H., das Nair, R., Grech, L. B., Borland, R. & Constantinescu, C. S. Modifiable risk factors for poor health outcomes in multiple sclerosis: The urgent need for research to maximise smoking cessation success. Mult. Scler. 1352458519858730 (2019).

Marck, C. H., Neate, S. L., Taylor, K. L., Weiland, T. J. & Jelinek, G. A. Prevalence of Comorbidities, Overweight and Obesity in an International Sample of People with Multiple Sclerosis and Associations with Modifiable Lifestyle Factors. PLoS ONE 11, e0148573 (2016).

Markowitz, C. E. et al. The treatment of multiple sclerosis with inosine. J Altern Complement Med 15, 619–625 (2009).

Marrie, R. A. Comorbidity in multiple sclerosis: implications for patient care. Nat Rev Neurol 13, 375–382 (2017).

Marrie, R. A. et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Mult. Scler. 21, 282–293 (2015).

Marrie, R. A. et al. A systematic review of the incidence and prevalence of cancer in multiple sclerosis. Mult. Scler. 21, 294–304 (2015).

Marrie, R. A. et al. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult. Scler. 21, 318–331 (2015).

Marrie, R. A. et al. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. Mult. Scler. 21, 263–281 (2015).

Marrie, R. A. et al. A systematic review of the incidence and prevalence of sleep disorders and seizure disorders in multiple sclerosis. Mult Scler 21, 342–349 (2015).

Marrie, R. A. et al. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology 72, 117–124 (2009).

Marrie, R. A. et al. Comorbidity increases the risk of hospitalizations in multiple sclerosis. Neurology 84, 350–358 (2015).

Marrie, R. A. et al. Differing trends in the incidence of vascular comorbidity in MS and the general population. Neurol Clin Pract 6, 120–128 (2016).

Marrie, R. A. et al. Effect of comorbidity on mortality in multiple sclerosis. Neurology 85, 240–247 (2015).

Marrie, R. A. et al. Rising prevalence of vascular comorbidities in multiple sclerosis: validation of administrative definitions for diabetes, hypertension, and hyperlipidemia. Mult. Scler. 18, 1310–1319 (2012).

Marrie, R. A. et al. Sex differences in comorbidity at diagnosis of multiple sclerosis: A population-based study. Neurology 86, 1279–1286 (2016).

Marrie, R. A. et al. The incidence and prevalence of comorbid gastrointestinal, musculoskeletal, ocular, pulmonary, and renal disorders in multiple sclerosis: a systematic review. Mult. Scler. 21, 332–341 (2015).

Marrie, R. A. et al. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. 21, 305–317 (2015).

Marrie, R. A. et al. Traditional risk factors may not explain increased incidence of myocardial infarction in MS. Neurology 92, e1624–e1633 (2019).

Marrie, R. A. et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology 74, 1041–1047 (2010).

Marrie, R. A., Cutter, G. & Tyry, T. Substantial adverse association of visual and vascular comorbidities on visual disability in multiple sclerosis. Mult. Scler. 17, 1464–1471 (2011).

Marrie, R. A., Horwitz, R., Cutter, G. & Tyry, T. Cumulative Impact of Comorbidity on Quality of Life in MS. Acta Neurol Scand 125, 180–186 (2012).

Marrie, R. et al. High frequency of adverse health behaviors in multiple sclerosis. Mult. Scler. 15, 105–113 (2009).

Martínez-Lapiscina, E. H., Mahatanan, R., Lee, C.-H., Charoenpong, P. & Hong, J.-P. Associations of serum 25(OH) vitamin D levels with clinical and radiological outcomes in multiple sclerosis, a systematic review and meta-analysis. J. Neurol. Sci. 411, 116668 (2020).

Marx, W. et al. The effect of emerging nutraceutical interventions for clinical and biological outcomes in multiple sclerosis: A systematic review. Mult Scler Relat Disord 37, 101486 (2019).

Massa, J., O'Reilly, E., Munger, K. & Ascherio, A. Caffeine and alcohol intakes have no association with risk of multiple sclerosis. Mult Scler 19, 53–58 (2012).

Mathew, A. R., Hogarth, L., Leventhal, A. M., Cook, J. W. & Hitsman, B. Cigarette smoking and depression comorbidity: systematic review and proposed theoretical model. Addiction 112, 401–412 (2017).

McKay, K. A. et al. Adverse health behaviours are associated with depression and anxiety in multiple sclerosis: A prospective multisite study. Mult. Scler. 22, 685–693 (2016).

McKay, K. A. et al. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. Neurology 90, e1316–e1323 (2018).

McLaughlin, L. et al. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. J. Neurol. 265, 2893–2905 (2018).

Mikaeloff, Y., Caridade, G., Tardieu, M., Suissa, S. & KIDSEP study group. Parental smoking at home and the risk of childhood-onset multiple sclerosis in children. Brain 130, 2589–2595 (2007).

Minden, S. L. et al. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 82, 174–181 (2014).

Mock, D. M. Biotin: From Nutrition to Therapeutics. J Nutr 147, 1487–1492 (2017).

Mokry, L. E. et al. Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. PLoS Med. 12, e1001866 (2015).

Moss-Morris, R. et al. Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. Behav Res Ther 103464 (2019).

Motl, R. W. & Sandroff, B. M. Benefits of Exercise Training in Multiple Sclerosis. Curr Neurol Neurosci Rep 15, 62 (2015).

Motl, R. W. & Snook, E. M. Physical Activity, Self-Efficacy, and Quality of Life in Multiple Sclerosis. Ann Behav Med 35, 111–115 (2008).

Motl, R. W., Dlugonski, D., Pilutti, L., Sandroff, B. & McAuley, E. Premorbid physical activity predicts disability progression in relapsing-remitting multiple sclerosis. J. Neurol. Sci. 323, 123–127 (2012).

Munger, K. L. et al. 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort. Neurology 89, 1578–1583 (2017).

Munger, K. L., Chitnis, T. & Ascherio, A. Body size and risk of MS in two cohorts of US women. Neurology 73, 1543–1550 (2009).

Munger, K. L., Levin, L. I., Hollis, B. W., Howard, N. S. & Ascherio, A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 296, 2832–2838 (2006).

Muñoz García, D. et al. Associated Inosine to interferon: results of a clinical trial in multiple sclerosis. Acta Neurol. Scand. 131, 405–410 (2015).

Murali, N. et al. Cholesterol and neurodegeneration: longitudinal changes in serum cholesterol biomarkers are associated with new lesions and gray matter atrophy in multiple sclerosis over 5 years of follow-up. Eur. J. Neurol. 27, 188-e4 (2020).

National Health and Medical Research Council & Ministry of Health. Nutrient Reference Values for Australia and New Zealand: Vitamin D. https://www.nrv.gov.au/nutrients/vitamin-d (2014).

National Health and Medical Research Council. CEO Statement: Electronic cigarettes | NHMRC. https://www.nhmrc.gov.au/about-us/resources/ceo-statement-electronic-cigarettes (2019).

National Health and Medical Research Council. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. https://www1.health.gov.au/internet/main/publishing.nsf/Content/obesityguidelines-index.htm (2013).

National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. https://www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf (2008).

National Institute for Health and Care Excellence (NICE). Multiple Sclerosis in adults: management clinical guideline. https://www.nice.org.uk/guidance/cg186 (2014).

National Institute for Health Care Excellence. Multimorbidity: clinical assessment and management. https://www.nice.org.uk/guidance/ng56. (2016).

Newland, P. K., Lorenz, R., Budhathoki, C. & Jensen, M. P. The Presence of Symptoms With Comorbid Conditions in Individuals With Multiple Sclerosis (MS). Clin Nurs Res 25, 532–548 (2016).

Nilsagård, Y. E., Forsberg, A. S. & von Koch, L. Balance exercise for persons with multiple sclerosis using Wii games: a randomised, controlled multi-centre study. Mult. Scler. 19, 209–216 (2013).

Noordman, J., van der Weijden, T. & van Dulmen, S. Communication-related behavior change techniques used in face-to-face lifestyle interventions in primary care: A systematic review of the literature. Patient Educ Couns 89, 227–244 (2012).

Noori, H. et al. The correlation between dyslipidemia and cognitive impairment in multiple sclerosis patients. Mult Scler Relat Disord 36, 101415 (2019).

Novotna, K. et al. Biofeedback Based Home Balance Training can Improve Balance but Not Gait in People with Multiple Sclerosis. Mult Scler Int 2019, 2854130 (2019).

Palavra, F. et al. New markers of early cardiovascular risk in multiple sclerosis patients: oxidized-LDL correlates with clinical staging. Dis. Markers 34, 341–348 (2013).

Paltamaa, J., Sjögren, T., Peurala, S. H. & Heinonen, A. Effects of physiotherapy interventions on balance in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. J Rehabil Med 44, 811–823 (2012).

Patnode, C. D., Evans, C. V., Senger, C. A., Redmond, N. & Lin, J. S. Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 318, 175–193 (2017).

Pearson, M., Dieberg, G. & Smart, N. Exercise as a Therapy for Improvement of Walking Ability in Adults With Multiple Sclerosis: A Meta-Analysis. Arch Phys Med Rehabil. 96, 1339-1348.e7 (2015).

Pekmezovic, T. et al. Lifestyle Factors and Multiple Sclerosis: A Case-Control Study in Belgrade. Neuroepidemiology 27, 212–216 (2006).

Pelizzari, L. et al. Five-Year Longitudinal Study of Neck Vessel Cross-Sectional Area in Multiple Sclerosis. AJNR Am J Neuroradiol 39, 1703–1709 (2018).

Pierrot-Deseilligny, C. & Souberbielle, J.-C. Vitamin D and multiple sclerosis: An update. Mult. Scler. Relat. Disord. 14, 35–45 (2017).

Pihl-Jensen, G., Tsakiri, A. & Frederiksen, J. L. Statin treatment in multiple sclerosis: a systematic review and meta-analysis. CNS Drugs 29, 277–291 (2015).

Pilutti, L. A. & Motl, R. W. Body Mass Index Underestimates Adiposity in Persons With Multiple Sclerosis. Arch Phys Med Rehabil 97, 405–412 (2016).

Pilutti, L. A., Dlugonski, D., Sandroff, B. M., Klaren, R. & Motl, R. W. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. Mult. Scler. 20, 594–601 (2014).

Pilutti, L. A., Greenlee, T. A., Motl, R. W., Nickrent, M. S. & Petruzzello, S. J. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med 75, 575–580 (2013).

Pilutti, L. A., McAuley, E. & Motl, R. W. Weight status and disability in multiple sclerosis: An examination of bi-directional associations over a 24-month period. Mult. Scler. Relat. Disord. 1, 139–144 (2012).

Pilutti, L. A., Platta, M. E., Motl, R. W. & Latimer-Cheung, A. E. The safety of exercise training in multiple sclerosis: a systematic review. J. Neurol. Sci. 343, 3–7 (2014).

Pittas, F. et al. Smoking is associated with progressive disease course and increased progression in clinical disability in a prospective cohort of people with multiple sclerosis. J. Neurol. 256, 577–585 (2009).

Platta, M. E., Ensari, I., Motl, R. W. & Pilutti, L. A. Effect of Exercise Training on Fitness in Multiple Sclerosis: A Meta-Analysis. Arch Phys Med Rehabil 97, 1564–1572 (2016).

Ponsonby, A.-L. et al. The physical anthropometry, lifestyle habits and blood pressure of people presenting with a first clinical demyelinating event compared to controls: The Ausimmune study. Mult Scler 19, 1717–1725 (2013).

Poorolajal, J., Bahrami, M., Karami, M. & Hooshmand, E. Effect of smoking on multiple sclerosis: a meta-analysis. J Public Health (Oxf) 39, 312–320 (2017).

Prosperini, L. et al. Home-based balance training using the Wii balance board: a randomized, crossover pilot study in multiple sclerosis. Neurorehabil Neural Repair 27, 516–525 (2013).

Quisenaerts, C. et al. Acute nicotine improves social decision-making in non-smoking but not in smoking schizophrenia patients. Front Neurosci 7, 197 (2013).

Quitline, Cancer Council, VicHealth & Victoria State Government. Helping patients to stop smoking: a guide for general practitioners. https://www.quit.org.au/documents/274/AQ767_Quit_GP_Guide_v2.pdf (2019).

Ramanujam, R. et al. Effect of Smoking Cessation on Multiple Sclerosis Prognosis. JAMA Neurol 72, 1117–1123 (2015).

Ramirez-Ramirez, V. et al. Efficacy of fish oil on serum of TNF α, IL-1 β, and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. Oxid Med Cell Longev 2013, 709493 (2013).

Ranadive, S. M. et al. Vascular dysfunction and physical activity in multiple sclerosis. Med Sci Sports Exerc 44, 238–243 (2012).

Reale, M. et al. Nicotinic receptor activation negatively modulates pro-inflammatory cytokine production in multiple sclerosis patients. Int. Immunopharmacol. 29, 152–157 (2015).

Rhead, B. et al. Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk. Neurol Genet 2, e97 (2016).

Rimmer, J. H., Chen, M.-D., McCubbin, J. A., Drum, C. & Peterson, J. Exercise intervention research on persons with disabilities: what we know and where we need to go. Am J Phys Med Rehabil 89, 249–263 (2010).

Roberts, C. G. P., Guallar, E. & Rodriguez, A. Efficacy and safety of statin monotherapy in older adults: a meta-analysis. J. Gerontol. A Biol. Sci. Med. Sci. 62, 879–887 (2007).

Rodrigo, L. et al. Randomised Clinical Trial Comparing the Efficacy of A Gluten-Free Diet Versus A Regular Diet in A Series of Relapsing-Remitting Multiple Sclerosis Patients. Int J Neurol Neurother 1, 012 (2014).

Rolf, L. et al. Vitamin D3 supplementation in multiple sclerosis: Symptoms and biomarkers of depression. J. Neurol. Sci. 378, 30–35 (2017).

Roostaei, T. et al. Impact of Melatonin on Motor, Cognitive and Neuroimaging Indices in Patients with Multiple Sclerosis. Iran J Allergy Asthma Immunol 14, 589–595 (2015).

Rubak, S., Sandbæk, A., Lauritzen, T. & Christensen, B. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract 55, 305 (2005).

Sadeghi Bahmani, D. et al. In Patients With Multiple Sclerosis, Both Objective and Subjective Sleep, Depression, Fatigue, and Paresthesia Improved After 3 Weeks of Regular Exercise. Front. Psychiatry 10, 265 (2019).

Salin-Pascual, R. J. Relationship between mood improvement and sleep changes with acute nicotine administration in non-smoking major depressed patients. Rev. Invest. Clin. 54, 36–40 (2002).

Salonen, A. et al. Impact of diet and individual variation on intestinal microbiota composition and fermentation products in obese men. ISME J 8, 2218–2230 (2014).

Salzer, J. et al. Vitamin D as a protective factor in multiple sclerosis. Neurology 79, 2140–2145 (2012).

Sandroff, B. M., Johnson, C. L. & Motl, R. W. Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: a novel application of magnetic resonance elastography. Neuroradiology 59, 61–67 (2017).

Sandroff, B. M., Motl, R. W., Scudder, M. R. & DeLuca, J. Systematic, Evidence-Based Review of Exercise, Physical Activity, and Physical Fitness Effects on Cognition in Persons with Multiple Sclerosis. Neuropsychol Rev 26, 271–294 (2016).

Sangelaji, B. et al. The effectiveness of behaviour change interventions to increase physical activity participation in people with multiple sclerosis: a systematic review and meta-analysis. Clin Rehabil 30, 559–576 (2015).

Saroufim, P., Zweig, S. A., Conway, D. S. & Briggs, F. B. S. Cardiovascular conditions in persons with multiple sclerosis, neuromyelitis optica and transverse myelitis. Mult Scler Relat Disord 25, 21–25 (2018).

Scully, D., Kremer, J., Meade, M. M., Graham, R. & Dudgeon, K. Physical exercise and psychological well being: a critical review. Br J Sports Med 32, 111–120 (1998).

Sedel, F., Bernard, D., Mock, D. M. & Tourbah, A. Targeting demyelination and virtual hypoxia with high-dose biotin as a treatment for progressive multiple sclerosis. Neuropharmacology 110, 644–653 (2016).

Sena, A., Macedo, A., Ferret-Sena, V., Capela, C. & Pedrosa, R. Serum Lipoprotein Profile Is Associated With Protective Effects of Oral Contraceptive Use on Multiple Sclerosis Severity: A Cross-Sectional Study. Front. Neurol. 10, 60 (2019).

Shaygannejad, V., Janghorbani, M., Ashtari, F. & Dehghan, H. Effects of adjunct low-dose vitamin d on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized placebo-controlled trial. Mult Scler Int 2012, 452541 (2012).

Simpson Jr., S. et al. Anxiety, depression and fatigue at 5-year review following CNS demyelination. Acta Neurol. Scand. 134, 403–413 (2016).

Simpson, S. et al. Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis. J. Neurol. Neurosurg. Psychiatry 90, 1193–1200 (2019).

Simpson, S. J. et al. Sun Exposure across the Life Course Significantly Modulates Early Multiple Sclerosis Clinical Course. Front. Neurol. 9, 16 (2018).

Singh, R. K. et al. Influence of diet on the gut microbiome and implications for human health. J. Transl. Med. 15, 73 (2017).

Soilu-Hänninen, M. et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 83, 565–571 (2012).

Spain, R. et al. Lipoic acid in secondary progressive MS: A randomized controlled pilot trial. Neurol Neuroimmunol Neuroinflamm 4, e374 (2017).

Stampanoni Bassi, M. et al. Obesity worsens central inflammation and disability in multiple sclerosis. Mult. Scler. 1352458519853473 (2019).

Stein, M. S. et al. A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis. Neurology 77, 1611–1618 (2011).

Sternberg, Z., Leung, C., Sternberg, D., Yu, J. & Hojnacki, D. Disease modifying therapies modulate cardiovascular risk factors in patients with multiple sclerosis. Cardiovasc Ther 32, 33–39 (2014).

Sun, L.-M. et al. Increased breast cancer risk for patients with multiple sclerosis: a nationwide population-based cohort study. Eur. J. Neurol. 21, 238–244 (2014).

Sundström, P. & Nyström, L. Smoking worsens the prognosis in multiple sclerosis. Mult. Scler. 14, 1031–1035 (2008).

Tallner, A. et al. Multiple sclerosis relapses are not associated with exercise. Mult. Scler. 18, 232–235 (2012).

Tanasescu, R. & Constantinescu, C. S. Helminth Therapy for MS. Curr Top Behav Neurosci 26, 195–220 (2015).

Tanasescu, R., Constantinescu, C. S., Tench, C. R. & Manouchehrinia, A. Smoking Cessation and the Reduction of Disability Progression in Multiple Sclerosis: A Cohort Study. Nicotine Tob. Res. 20, 589–595 (2018).

Tankou, S. K. et al. A probiotic modulates the microbiome and immunity in multiple sclerosis. Ann. Neurol. 83, 1147–1161 (2018).

Tettey, P. et al. An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event. J. Neurol. Neurosurg. Psychiatry 88, 395–401 (2017).

Tettey, P. et al. An adverse lipid profile is associated with disability and progression in disability, in people with MS. Mult. Scler. 20, 1737–1744 (2014).

Tettey, P. et al. Frequency of Comorbidities and Their Association with Clinical Disability and Relapse in Multiple Sclerosis. Neuroepidemiology 46, 106–113 (2016).

Thormann, A., Sørensen, P. S., Koch-Henriksen, N., Laursen, B. & Magyari, M. Comorbidity in multiple sclerosis is associated with diagnostic delays and increased mortality. Neurology 89, 1668–1675 (2017).

Torkildsen, Ø. et al. ω-3 Fatty Acid Treatment in Multiple Sclerosis (OFAMS Study): A Randomized, Double-Blind, Placebo-Controlled Trial. Arch Neurol 69, 1044–1051 (2012).

Tourbah, A. & Sedel, F. Letter to the Editors – Multiple sclerosis and related disorders – Birnbaum et al., 2017. Mult. Scler. Relat. Disord. 20, 204 (2018).

Tourbah, A. et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. Mult. Scler. 22, 1719–1731 (2016).

Tourbah, A. et al. MD1003 (High-Dose Pharmaceutical-Grade Biotin) for the Treatment of Chronic Visual Loss Related to Optic Neuritis in Multiple Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Study. CNS Drugs 32, 661–672 (2018).

Tremlett, H. et al. Monthly ambient sunlight, infections and relapse rates in multiple sclerosis. Neuroepidemiology 31, 271–279 (2008).

Tremlett, H., Zhu, F., Ascherio, A. & Munger, K. L. Sun exposure over the life course and associations with multiple sclerosis. Neurology 90, e1191–e1199 (2018).

Turpin, K. V. L., Carroll, L. J., Cassidy, J. D. & Hader, W. J. Deterioration in the health-related quality of life of persons with multiple sclerosis: the possible warning signs. Mult Scler 13, 1038–1045 (2007).

Uher, T. et al. Serum lipid profile changes predict neurodegeneration in interferon-β1a-treated multiple sclerosis patients. J Lipid Res 58, 403–411 (2017).

Ursell, L. K., Metcalf, J. L., Parfrey, L. W. & Knight, R. Defining the Human Microbiome. Nutr Rev 70, S38–S44 (2012).

van der Mei, I. a. F. et al. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ 327, 316 (2003).

van der Mei, I. a. F. et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J. Neurol. 254, 581–590 (2007).

Wang, J., Xiao, Y., Luo, M. & Luo, H. Statins for multiple sclerosis. Cochrane Database Syst Rev CD008386 (2011).

Wang, S. et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. PLoS ONE 11, e0161174 (2016).

Warren, S. A., Turpin, K. V. L., Pohar, S. L., Jones, C. A. & Warren, K. G. Comorbidity and Health-Related Quality of Life in People with Multiple Sclerosis. Int J MS Care 11, 6–16 (2009).

Weinstock-Guttman, B. et al. Lipid profiles are associated with lesion formation over 24 months in interferon-β treated patients following the first demyelinating event. J. Neurol. Neurosurg. Psychiatry 84, 1186–1191 (2013).

Wens, I., Eijnde, B. O. & Hansen, D. Muscular, cardiac, ventilatory and metabolic dysfunction in patients with multiple sclerosis: Implications for screening, clinical care and endurance and resistance exercise therapy, a scoping review. J. Neurol. Sci. 367, 107–121 (2016).

World Health Organization. Guidelines for the evaluation of probiotics in food. https://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (2002).

World Health Organization. Guidelines on sodium intake for adults and children. https://www.who.int/nutrition/publications/guidelines/sodium_intake/en/ (2012).

World Health Organization. Tobacco fact sheet from WHO. https://www.who.int/news-room/fact-sheets/detail/tobacco (2019).

Yadav, V. et al. Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Mult. Scler. Relat. Disord. 9, 80–90 (2016).

Zale, E. L., Maisto, S. A. & Ditre, J. W. Anxiety and Depression in Bidirectional Relations Between Pain and Smoking: Implications for Smoking Cessation. Behav Modif 40, 7–28 (2016).

Zhang, T. et al. Effects of physical comorbidities on disability progression in multiple sclerosis. Neurology 90, e419–e427 (2018).

Zhang, T. et al. Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis. Neurology 86, 1287–1295 (2016).

Zheng, C., He, L., Liu, L., Zhu, J. & Jin, T. The efficacy of vitamin D in multiple sclerosis: A meta-analysis. Mult. Scler. Relat. Disord. 23, 56–61 (2018).

Zhornitsky, S., McKay, K. A., Metz, L. M., Teunissen, C. E. & Rangachari, M. Cholesterol and markers of cholesterol turnover in multiple sclerosis: relationship with disease outcomes. Mult Scler Relat Disord 5, 53–65 (2016).

Zivadinov, R. et al. Autoimmune Comorbidities Are Associated with Brain Injury in Multiple Sclerosis. AJNR Am J Neuroradiol 37, 1010–1016 (2016).

Zorzon, M. A nexus between lipids and multiple sclerosis? J. Neurol. Neurosurg. Psychiatry 84, 1181 (2013).

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