

Modifiable Lifestyle Factors Workshop – Report

Workshop Summary

MS Research Australia held a workshop on modifiable lifestyle factors in MS on 2nd May 2018 in Sydney. This workshop was organised in response to a need identified by the 2016 MS Research Australia Research Priorities survey that modifiable lifestyle factors was an area of importance to the MS community as it provides a mechanism for people with MS to take control and potentially minimise the impact of MS on their lives. There is also growing evidence from epidemiological and clinical research that there is potential for modifiable lifestyle factors to change disease outcomes.

The workshop brought together clinicians, researchers, allied health professionals and people affected by MS to discuss the current evidence and the best way forward for research in this area.

While much is already known about the role of lifestyle factors in the risk of developing MS, this workshop focussed on whether lifestyle factors could impact progression and disease course in MS. The workshop aimed to discuss the current evidence for the effect of modifiable lifestyle factors on MS, determine the knowledge gaps and identify priorities and opportunities for further research to strengthen the evidence and the best way to design this type of research for the most meaningful outcomes. A key aim of the workshop was also to identify opportunities to translate and implement the current evidence to provide the most appropriate advice to the MS community.

The workshop opened with a brief overview of the current evidence on the environmental risk factors that contribute to MS onset and progression and also included a presentation from Ms Tara King about her personal MS journey and the positive lifestyle changes that she has made. She discussed the difference it has made to her, and her thoughts on what the MS community are looking for in the way of guidance and support to make positive lifestyle changes for themselves.

The first scientific session covered the current evidence for the role of lifestyle factors such as diet and physical exercise in MS. While research in this area is difficult, studies have shown that a healthy diet and exercise is of benefit to both quality of life and disease outcomes in MS. Dr Lucinda Black, Curtin University WA, discussed the role of diet in MS and the evidence that diets with higher levels of fruit and vegetables, less fat and sugar can improve outcomes such as disability and quality of life in MS. Associate Professor Ingrid van der Mei from the Menzies Institute for Medical Research, Tasmania, presented research about the role of comorbidities in MS outcomes.

The second session covered ways that evidence of lifestyle factors had been implemented into the MS community to date and aimed to learn from similar initiatives in other diseases and in the general population. Ms Jodi Haartsen, from Eastern Health, Victoria, spoke about the MS Brain Health Initiative, a global collaboration which aims to optimise the treatment and care of people with MS. It also aims to improve the understanding of people with MS of how they can keep their brains as healthy as possible and request the highest possible standard of care from healthcare professionals. Professor Mark Harris, University of NSW, described the implementation of SNAP, which are guidelines for smoking, nutrition, alcohol and physical activity for use by general practitioners to help people manage general health and long term health conditions. Professor Kaarin Anstey from NeuRA in Sydney, spoke about the successes and failures of implementation of lifestyle research outcomes in dementia.

The final session explored different types of study design for research on lifestyle factors in MS, as this has a major impact on the quality of the conclusions that can be drawn from the research. In this session, Professor Anne-Louise Ponsonby of the Murdoch Children's Research Institute, Victoria, spoke about her upcoming clinical trial which will investigate if specific supplements that support

mitochondria could improve fatigue and depression in MS. Professor Terry Wahls, University of Iowa, USA spoke about her clinical trial design which will compare two specific diets, the Wahls Diet and the Swank Diet, on outcomes in MS, especially fatigue. Professor George Jelinek, University of Melbourne, discussed research into lifestyle interventions that combine several aspects, such as nutrition, exercise, stress reduction and medication. This type of research can be very complex as many lifestyle factors are considered at once, providing additional challenges for study design. Dr Yvonne Learmonth from Murdoch University, WA spoke about the points to consider when designing research studies into physical activity in MS.

In depth discussion opportunities followed each session, allowing all delegates to contribute their perspectives, thoughts and expertise on this topic. Themes of the discussion included the strength of the current evidence for various modifiable lifestyle factors such as diets and exercise, as well as the best ways to improve this area of research and fill the gaps. A final discussion session aimed to draw together all the threads and themes that had been explored during the day, to arrive at some clear next steps to move the field forward.

The first clear outcome was the need for communication materials to be developed to provide consistent guidance to Australians with MS as well as neurologists and other clinicians dealing with people with MS based on the best-available evidence on modifiable lifestyle factors. A working group will now be convened to develop and produce guidelines. These guidelines may provide the basis for further resources which may include position statements, brochures, videos and toolkits.

There was also discussion of future research avenues. These included controlled clinical trials of interventions in MS, which could compare people making changes to diet or exercise or both with others who did not make the changes or made smaller changes. Some of the simplest interventions would be to find ways to support people with MS to follow the current Australian Healthy Eating Guidelines and physical activity guidelines. Further research is also needed to determine the validity of different approaches to support people making lifestyle changes and assist them beyond the initial phase to create sustained change. It is hoped that the guidelines could also be used to develop an implementation tool that will provide a framework for MS nurses and other healthcare providers to either screen healthy lifestyle behaviours in people with MS or provide support to help them make lifestyle changes sustainable over the long term.

Workshop Proceedings

Background and aims

MS Research Australia held a workshop on modifiable lifestyle factors in MS on 2nd May 2018. This workshop was organised in response to a need identified by the 2016 MS Research Australia Research Priorities survey that modifiable lifestyle factors was an area of importance to the MS community as it provides a mechanism for people with MS to take control and potentially minimise the impact of MS on their lives. There is also growing evidence from epidemiological and clinical research of the role for modifiable lifestyle factors to change disease outcomes.

Development of the workshop was led by a steering committee of researchers and clinicians in the field of modifiable lifestyle factors in MS: Professor Robyn Lucas, Professor Bruce Taylor, Professor Anne-Louise Ponsonby, Associate Professor Ingrid van der Mei and Dr Lisa Melton.

45 delegates participated in the workshop from around the country. Delegates included epidemiologists, MS nurses, neurologists, allied health professionals, data scientists, clinical trialists, service providers, discovery researchers and people living with and affected by MS.

Delegates were welcomed by Dr Lisa Melton, Head of Research at MS Research Australia. Dr Melton spoke about the reasons for the development of the workshop and the objectives of the day.

The workshop had the following aims:

- Establish the current strength of the evidence for the effect of modifiable lifestyle factors on MS onset and progression
- Determine the knowledge gaps in this field
- Identify further research areas and appropriate research designs to fill the knowledge gaps
- Determine translation opportunities of current evidence to improve outcomes for people with MS

Introduction

Professor Robyn Lucas (Australian National University) and Professor Bruce Taylor (Menzies Institute for Medical Research TAS)

The role of modifiable lifestyle factors on the risk of developing MS and MS onset is well researched. Professor Lucas discussed the evidence that modifiable factors including smoking, low vitamin D, low sun exposure, stress and obesity in adolescence increase the risk of MS. The role of diet, in particular low intake of omega-3 dietary fats (particularly from fish), low non-processed red meat and a Western diet (high fat, high processed foods) is thought to increase risk of MS. It is likely that there are no other major risk factors for MS onset yet to be discovered, but the timing of exposures over a person's lifetime is still unclear. Interest in risk factors for the onset of MS are still important to people with MS as they influence whether family members may develop MS in the future.

Professor Taylor spoke about the current evidence of the role of lifestyle factors on the progression of MS. This evidence is much less robust than that for onset. This is due to a range of factors including the difficulty of study design, persistence of participants with the intervention, difficulty in maintaining blinding and the placebo effect, reverse causality and a lack of sensitive measurements for MS progression and outcomes. While a blinded randomised controlled trial is the ideal design, meaningful information may be gained from long term longitudinal studies where confounding factors are identified and accounted for. Presently, there is evidence that smoking and low vitamin D lead to worse outcomes in MS. A recent study also showed that risk of relapse can be modified by changing sun exposure behaviour in people with MS (1).

Ms Tara King

Perspective of a person with MS

Ms King spoke about her personal experience and journey with her MS. She described her fear and feelings of helplessness when she was diagnosed and her search for answers. Changing her diet and lifestyle allowed Ms King to take control of her MS and she credits improvements in her overall health and her MS to changes she made to her diet and lifestyle. She feels that further research in this area will allow more positive interactions between people with MS and their neurologists and help clear the confusion that people with MS experience when confronted with a large array of lay information on diet and lifestyle when compared to the lack of evidence-based information from health professionals. Ms King also discussed that there is a disconnect between the level of evidence health professionals require and the need and desire for people in the MS community to have reasonable advice to enact in their lives right now. For people with MS, Ms King feels this could be as important as finding a cure.

Session 1

The pathway from epidemiological evidence to interventions
Chair – Professor Bruce Taylor, Menzies Institute for Medical Research TAS

Dr Lucinda Black, Curtin University WA
Nutrition and MS

Dr Black discussed the current evidence on whether nutrition plays a role in the progression of MS. 40% of people with MS make dietary changes after diagnosis, but the changes that they make are inconsistent and often not evidence based. People with MS also list dietary counselling as an important part of what they feel they need in the management of their disease. There is some evidence that a healthy diet can improve outcomes in MS and as only 4% of Australians follow the Australian Healthy Eating Guidelines (see [Australian Dietary Guidelines – Scientific Evidence](#) and [Australian Dietary Guidelines – Summary](#)), encouraging a generally healthy diet should be a fundamental message for people with MS.

There is some evidence that diets with higher levels of fruit and vegetables and less fat and sugar can improve outcomes such as disability and quality of life in MS (2,3). There is also evidence for individual nutrients being associated with better outcomes in MS including lower lipids, higher omega 3 polyunsaturated fatty acids, higher antioxidants (including vitamin E, vitamin C, carotenes, glutathione, lipoic acid and curcumin) and lower sodium (4).

However, to date, clinical trials into nutrition and MS have shown that omega 3 and omega 6 polyunsaturated fatty acids did not have a significant effect on outcomes (5,6). Another study of a very low fat vegan diet showed improvements in fatigue, BMI and metabolic markers, but no improvement on brain MRI, relapse rate or disability (7). Many clinical trials are ongoing into outcomes and symptom management. High quality dietary intervention research is needed to provide the evidence base for advice to patients, but the difficulties include adherence, diet design and assessment.

Associate Professor Ingrid van der Mei, Menzies Institute for Medical Research TAS
Lipids and comorbidities in MS

Common comorbidities in MS are depression, anxiety, hypertension, hyperlipidemia and chronic lung disease (8). Comorbidities were associated with greater diagnostic delays and higher disability at diagnosis, especially for obesity and musculoskeletal, vascular and mental comorbidities (9). This means that people with comorbidities are already disadvantaged at the time of diagnosis. Generally, comorbidities accelerate disability progression but have smaller effects on relapses and MRI (10, 11, 12, 13). MS is associated with only a small increase in risk of death, but optimising comorbidity management may improve survival. Comorbidities do have a substantial effect on quality of life in MS, especially musculoskeletal disorders and depression and anxiety (14). It is difficult to know the underlying mechanisms, but may be due to genetic commonalities, synergistic or additive effects on disability, symptoms or behavioural differences due to MS (such as reduced activity).

Discussion

General Discussion

- The discussion noted the importance of modifiable lifestyle factors to people with MS and consequently the importance of evidence based guidance in this area.
- People in the MS community are already looking for advice and will find it themselves, but this information and advice may not be based on research. There is a disconnect between research outcomes and the currently available advice.

- There are two questions that research can answer with respect to lifestyle factors. Firstly, does changing a particular lifestyle factor change quality of life or secondly does it change disease pathology? Research is generally interested in the second question, but the first question is still very important to people with MS.
- With lifestyle factors, it is reasonable to provide the best available evidence-based information to the MS community and allow them to choose, even if the most appropriate scientific level of evidence is not yet attained in the eyes of the scientific community. This situation was compared to that of a potentially toxic drug around which more stringent controls and clinical trial methodology may be warranted.
- There is also value in smaller step changes to lifestyle that people can make. If a perceived “ideal lifestyle” for MS is too burdensome for patients it will result in lower adherence and the feeling of failure if people are unable to continue, with a consequential decrease in quality of life.

Current evidence

- There was discussion of the limitations of the current evidence in lifestyle factor research generally and in MS.
- Measures of exposure, particularly self-reporting for diet, are difficult and inaccurate. Other potentially more accurate measurement options, such as sodium levels in the urine or apps that monitor physical activity may be better suited.
- Comorbidities can overlap with symptoms of MS, for example anxiety and depression, or musculoskeletal disorders. This means that in comorbidity research, studies need to be carefully designed to allow these differences to be distinguished. This is particularly important when considering measurements for disease progression, as musculoskeletal comorbidities would affect accurate measurement of EDSS related directly to symptoms caused by MS.
- Similarly cognitive decline, anxiety and depression, all of which are associated with MS, will lead to participation bias (people with less cognitive decline tend to participate) and adherence levels (lower motivation for those with anxiety and depression). Therefore, conclusions drawn may be from a subset of the MS population rather than a representative sample.

Priorities for translation

- As the number of people that are following the Government’s Australian Healthy Eating Guidelines is very low, there is likely to be value in providing this level of general dietary advice. This would be to improve overall wellbeing and/or “brain health” and minimise comorbidities rather than necessarily having an effect on disease progression.
- Evidence based guidelines for healthy eating and physical activity are already devised - translation and communication of this advice to people with MS would be straightforward.
- Sufficient vitamin D levels is already a part of the advice given to people with MS and there is enough evidence for general advice on maintaining vitamin D sufficiency even though evidence on optimal dose and disease modifying benefits is still pending.
- MS Research Australia and MS Societies are ideally placed to develop a guidance document on these topics for the MS community. In the meantime we can continue to explore research avenues to identify whether there is an optimal or specific types of physical activity or diet that is needed for MS.

Practicalities of translation

- Who is best placed to offer evidence based lifestyle advice was discussed extensively. It was noted that patients most want to hear this advice from their neurologists, but short appointment times and the necessary and complex discussion regarding MRI and clinical results and treatment planning with neurologists means that they may not be best placed to also cover lifestyle advice. The lack of substantial evidence that lifestyle modifications can make as much of a difference as disease modifying therapies means that this is less of a priority for discussion for neurologists.
- MS nurses are ideally placed to have a lifestyle discussion with patients, in terms of this fitting with other advice that they provide and the fact that they have serial discussions with patients, offering the opportunity to follow up and track progress. However, resourcing issues must be kept in mind if further lifestyle items are to be added to an MS nurse appointment.
- The importance of psychological support when people are attempting behavioural change was highlighted, and ideally this would be provided by someone who also has knowledge of MS. There is a difference between initiating change and implementing sustained change and this type of support would be valuable for maximising sustained change.
- Behavioural change can be difficult for everyone, not just people with MS. It is important to understand how other initiatives have tackled translation. However, the mode of translation may need to be different for the MS population as compared with the general population. Motivation is different for these two groups and any advice would need to be tailored to the individual (i.e. cognitive symptoms and mood).

Session 2

The pathway from interventions to implementation and uptake of evidence

Chair – Professor Robyn Lucas, Australian National University

Ms Jodi Haartsen, MS Nurse Practitioner, Eastern Health VIC

Brain Health: Time Matters in MS initiative

- The Brain Health initiative launched a report in October 2015 that focussed on overall lifelong brain health rather than disease activity (see [Brain Health: Time Matters Report](#)).
- The report notes the following about MS: disease activity can persist even if symptoms are absent, neurological reserve must be preserved to protect against disability progression, cognitive impairment has practical implications, and cognitive impairment predicts physical disability progression.
- Three recommendations came out of the report: minimise delays to diagnosis and treatment, monitor disease activity and treat to a target, and generate and use robust evidence to support decision making.
- Lifestyle recommendations from the report include keeping physically active, keeping mentally active, keep weight under control, avoid smoking, reduce alcohol and continue medications for other conditions. There are Brain Health handbooks specifically aimed at MS nurses, GPs and people with MS.
- The report was used as an audit tool by the Eastern Health MS Service to look at their service delivery (such as time to diagnosis, waiting times for MRI, access to MS medications, waiting times to MS specialists). This led to the implementation of steps to improve these services for people with MS.
- There is now an Australian MS Brain Health Community which aims to strategically and purposefully facilitate the implementation of the MS brain health recommendations as detailed in the MS brain health report in Australia. This group is currently focussing on disseminating the Brain Health information to GPs.

Scientia Professor Mark Harris, University of NSW

SNAP (smoking, nutrition, alcohol, physical activity) Guidelines in General Practice

- The SNAP initiative started in 2003 and has been incrementally implemented since. Originally the initiative aimed to prevent type 2 diabetes and cardiovascular disease through obesity but has now become relevant to long term conditions, especially cancer.
- Implemented through the five As framework.
 - Assess: risk and motivation, health literacy
 - Advise/agree: advice, goal setting, motivational interviews
 - Assist: plan, treat, monitor (e.g. potentially with apps, photographing meals)
 - Arrange: referral, follow-up with groups outside clinical practice. (e.g. telephone coaching to maintain change, local walking groups). This step is important to prevent a return to previous behaviour.
- There has been low implementation rates of the SNAP guidelines.
- Health literacy was an important factor in implementation from a patient perspective. A lack of health literacy can appear as a lack of motivation. It has been found that it is important to bring in family networks to maintain motivation.
- Low referral rates by GPs and a lack of resourcing for longer in depth appointments were identified as an important factor in the implementation on the professional side. The GP's previous experience of referral success was a key factor in whether they decided to refer people on, but it was found that GPs responded to direct requests from patients for referrals meaning that patient self-advocacy is key. Patients must be empowered and motivated to request referrals and demand services they need.

Professor Kaarin Anstey, NEURA University of NSW

Successes and failures in dementia risk reduction

- Dementia is different to MS but may have lessons for MS in terms of implementation of lifestyle factor research. 65% of dementia is Alzheimer's Disease (AD). In dementia, there is a focus on primary prevention rather than progression as in MS, the patient population (onset) is older and have increased exposure over this longer time (with up to three decades of pathology). Cognitive decline over time also gives dementia research a more sensitive outcome measure.
- Of lifestyle factors, physical activity, high social engagement and being cognitively active decrease the risk of dementia. Being sedentary and smoking increases risk. Diet is complicated but oily fish reduces risk and high fat diet increases risk.
- The MIND diet has been suggested for reducing the risk of developing AD, this is a variant of the Mediterranean-DASH diet with an emphasis on berries.
- Age of exposure is important for dementia, obesity at 40-60 years increases risk while obesity at over 60 years of age does not change risk.
- Clinical trials looking at modifiable lifestyle factors have largely been unsuccessful in dementia due to the short term nature of trials and difficulties defining measurable outcomes.
- Dementia is declining in some parts of the world. This is due to successes such as the WHO Action Plan and convincing evidence for low physical activity as a risk factor.

Discussion

Practicalities for implementation

- Separate interventions for people with MS are not needed, but interventions must be individualised for the patient and take into account their life and family circumstances.

- Intervention at the primary care level (i.e. through GPs and practice nurses) is the pathway most likely to succeed but is not well defined. Strong links between GPs and neurologists are missing to integrate shared care plans and reinforce advice from other people on the medical team.
- There is the potential to use electronic health records to support long term follow up at the primary healthcare level. GP Health Pathways is already established to supply local referral ideas for GPs.
- There is good evidence that phone coaching for obesity, diet and physical activity is comparable to face to face coaching, with weekly calls over ten weeks. This type of support is helpful for maintenance. However, phone coaching is expensive and funding has been lost.
- Incremental increases are beneficial, particularly for physical activity (i.e. increasing 1000 steps to 2000 steps per day, rather than insisting on the recommendation of 10,000 per day).
- Similarly, there are also changes that people with advanced disease can make (such as exercising that can be undertaken in bed or in a wheelchair, weight control through diet) that will make small improvements for them that increase their quality of life.
- The Diabetes Educators model, which ‘actively promotes evidenced-based best practice diabetes education to ensure optimal health and wellbeing for all people affected by, and at risk of, diabetes’ provides is a good example of management of a long term condition for optimal health (see [Australian Diabetes Educators Association](#)).
- There is also crossover with the HeartMoves initiative which encourages low and moderate exercise and is designed to get people moving if they have stopped exercising. It is designed to be safe for people with stable long term heart conditions such as heart disease, diabetes or obesity (see [HeartMoves](#)).
- There is a need to develop Australian-based guidelines for MS. There are several examples in other diseases and other countries that would be useful to compare. These include
 - [Clinical Practice Guidelines for Dementia](#) – Australian guidelines that are mostly around care not prevention.
 - [Clinical Guidelines for Stroke Management](#) – Australian guidelines also around treatment of stroke.
 - [Living Well with MS](#) – Information and strategies covering a wide range of areas to improve wellness from the US National MS Society. This includes a module on [diet, exercise and healthy behaviours](#).
 - [Physical Activity Guidelines](#) – guidelines for physical activity for adults with MS developed by the Canadian MS Society.
- It was noted that the implementation of the NDIS has led to less interaction with the MS community making implementation more difficult, however the position of the MS nurse was again highlighted as an ideal one for lifestyle advice that can be tailored to the person’s disease and circumstance.

Session 3

Challenges and goals in designing intervention studies

Chair – Associate Professor Ingrid van der Mei, Menzies Institute for Medical Research TAS

**Professor Anne-Louise Ponsonby, Murdoch Children’s Research Institute
Combined mitochondrial agent supplements in MS (NutProMS)**

- Double blind randomised controlled clinical trial of combined mitochondrial agents for the treatment of fatigue and depression in MS. This trial has MRFF funding. Safety and tolerability have already been established for the combined mitochondrial agent being tested.
- Fatigue and depression are common in MS and can lead to a cascade of symptoms; they are also linked to worse disability outcomes.
- Mitochondrial dysfunction plays a significant role in active disease in MS and plays a role in the onset of disease.
- Single mitochondrial agents have been trialled in MS (Q10, alpha lipoic acid or biotin) and showed 25-50% benefit for fatigue and depression but the estimates are imprecise. Therefore the trial has been powered to detect a 15% reduction in primary outcomes. There are currently no effective routine treatments for fatigue in MS.
- Secondary objectives of the trial include the effect of the combined mitochondrial agent on physical activity, lactate/pyruvate ratio, total antioxidant capacity, adverse events, and a metabolomics profile (kynurenine pathway); and to assess the correlation between dietary intake, microbiome, metabolomics and genomic profile with fatigue and depression.
- The trial will run for 16 weeks, with one follow up at 20 weeks. Previous research has shown that 4 weeks is enough to see an effect.
- Aim to recruit 150 participants with stable RRMS, EDSS < 6, clinical fatigue at two time points over a fortnight.
- Genomic and metabolomics studies are planned to compare participants in each arm of the trial and there will be longer follow up of participants through the Australian MS Longitudinal Study and MSBase. It is hoped that these studies will provide information on the underlying mechanisms.

Professor Terry Wahls, University of Iowa, USA

Diet studies in MS (Wahls/Swank Diet Trial)

- There are a number of study designs for nutritional interventions in MS including feeding studies (metabolic kitchens), free living (with food weighing, phone follow up, food frequency questionnaires). Diets need to be nutritionally adequate.
- Supplement studies are more straightforward but there are potentially many supplements needed for neural repair. The Wahls Diet covers 36 neuronal nutrients.
- Parallel study design comparing Wahls Diet and Swank Diet, participants have a normal diet for 12 weeks and then intervention diet for 12 weeks. This way participants act as their own controls.
- Primary outcome is fatigue. Secondary outcomes are vision, cognitive function and microbiome changes.
- Participants are screened and tracked using motivational interview, food frequency questionnaire, weighed food record, surveys to determine if excluded foods were consumed and participants are given an overall diet adherence score.
- The surveys allow people to feel comfortable to admit when they have not followed the diet – this is an important mechanism for accurately recording adherence.

Professor George Jelinek, University of Melbourne

Multi-modal lifestyle modification studies in MS

- Methodological challenges have led to a paucity of controlled intervention data rather than observational data. Challenges include recruitment, blinding, randomisation, contamination between groups, adherence and choosing meaningful endpoints.

- Other disease research has successfully trialled lifestyle modification but the meaningful endpoints (or markers of endpoints) are more straightforward. In MS, disability is the ideal end point but this would make studies infeasibly long. Fatigue is a valid short term outcome in MS and could also use quality of life.
- Professor Jelinek has run week long intensive retreats for lifestyle modification which allows more control of the relevant lifestyle factors, but is unsustainable for the wider population. These people are also self-selected so they are highly motivated and not representative. Research has shown that this type of retreat does not conflict with adherence to MS medications.
- Priorities for future research include controlled multi-modal lifestyle intervention research, determining for whom and when an intervention would be effective and determining optimal delivery methods (effectiveness of online coaching or telehealth options) and determining if individual factors have significant effects in their own right (diet vs stress reduction).

Dr Yvonne Learmonth, Murdoch University WA

Physical activity studies in MS

- Exercise has been shown to be of benefit in MS and can lower relapse rate and T2 lesion volume (15,16). Exercise also reduces depression and anxiety and increases participation in the community (17).
- Physical activity guidelines for people with MS are already written and the recommendations are 4 bouts of exercise per week: 2 resistance; 2 aerobic (18). There are no safety issues with physical exercise in MS (19).
- When designing intervention studies for physical exercise, they need to consider the scale of difference that is hoped to be achieved and select an appropriate target population where the difference will be measurable.
- Encouraging participation is key, factors that determine this include disability facilities at the location, distance of travel for participants, frequency, guidance from a professional and relevant motivation.
- Translation of physical activity research needs to get guidelines into clinical practice. Research has shown that people with MS most want to hear this advice from their neurologists and neurologists need training in this area to provide this advice.
- Feasibility studies are important but rarely conducted. Feasibility studies should cover retention, reasons for attrition, eligibility and participant outcomes. Practical considerations include equipment availability, sites, staffing, costs and data collection needs. Scientific considerations are challenges experienced during delivery, time to complete, acceptability and effectiveness of the intervention.

Discussion

Optimal intervention study design

- There was a discussion on the outcome measures in the mitochondrial agent trial. Fatigue is being used as the short term measure but the measurements taken of the kynurenine pathway will act as a proxy for longer term measurements of disease outcomes.
- There is a great need for markers that are relevant over the short term to track longer term outcomes. Research into immunomodulatory diseases have relapse rates as an outcome that can be used in short term clinical trials, but we need markers for regeneration and neuroprotection to track disability. This type of marker would also provide information on the underlying mechanisms.

- MRI markers are used in Phase II clinical trials and these are markers for longer term disability, including total lesion volume, total brain volume and grey matter measures. Issues exist for the standardisation of MRIs and protocols used can lack sensitivity and specificity.
- Multi-modal interventions need to assess the impact of the different components. Outcomes must be meaningful for the patient.

Future research questions

- Research is needed to determine if the specific MS diets provide benefits over and above that of following the Healthy Eating Guidelines. A clinical trial that has both a typical Australian diet and a healthy diet following the Australian guidelines as a control would be useful.
- Controlled clinical trials of multimodal approaches are also needed. These trials would benefit from arms which assess the effects of separate and combined components (i.e. diet and exercise vs. diet vs. exercise). Australia could be well placed to perform such trials given that Professor Jelinek has an established multimodal intervention set up in Victoria.
- Outcomes for any clinical trial need to encompass both measurements for wellness (i.e. quality of life) as well as determining if there is any outcome on disease pathology. The outcomes need to be weighed against the effort/quality of life impact of adhering to the program.
- Clinical trial participants must be representative, some subgroups of individuals may not be in a position to follow an intervention diet and it is important to determine for whom the intervention may be successful.
- Research is also needed to determine the validity of different approaches to support people making lifestyle changes. In some cases information is all that is required while in other cases face to face coaching is necessary. Depression, anxiety, health beliefs, coping mechanisms and denial all increase the coaching requirements. Health literacy and socioeconomic factors are also important.

Final Discussion

Chair – Associate Professor Ingrid van der Mei, Menzies Institute for Medical Research TAS

Rapporteur – Professor Robyn Lucas, Australian National University

Guidelines

- Guidelines are clearly required but guidelines produced to an NHMRC level are intensive, and guidelines already exist for Healthy Eating that have been approved by the NHMRC. There is scope for this to be tailored for people with MS and presented in a different way such as through the web and via video.
- Guidelines are also available for mild and moderate MS with respect to physical activity (18).
- Some kind of guidelines for healthcare professionals or factsheets for people with MS which cover multiple areas (such as healthy eating and physical exercise) and include grades of evidence and identify gaps for research would be useful for a range of applications including support for funding applications (for research or supportive care) and support for advocacy in policy development.
- These can be adapted from existing resources. Asthma Australia has national guidelines for asthma management aimed at health professionals (see [Australian Asthma Handbook](#)) and another document aimed at people with asthma (see [My Asthma Guide](#)). The [Clinical Practice Guidelines for Dementia](#) contain grades for the level of evidence for their recommendations.

Screening and Implementation Tool

- A tool could be developed for health professionals that would provide a framework for lifestyle interventions in MS similar to the SNAP template.
- There is also scope for an audit tool for use within a clinic to assess a patient's existing engagement with healthy lifestyles, for example, smoking levels. The guidelines could provide the benchmarks for the patient's current lifestyle within the audit tool.
- MS Nurses Australasia would be ideally placed to help develop these tools. These could then be disseminated using the MS Nurse network to the MS clinics as 80% of people with MS are managed in MS clinics in Australia (unpublished data from Bruce Taylor).

Research opportunities

- Intervention studies which are embedded within a larger cohort study (such as MSBase or AMSLS) could overcome self-selection bias. For example, one could identify participants using propensity weighting, select a subgroup for the intervention and use the rest of the group as a control.
- Intervention studies could test multimodal interventions and also each module separately (i.e. diet and exercise together vs. "MS diet" alone vs. healthy eating guidelines vs. exercise alone vs. control).
- An alternative is to use a sequential study design with more intensive diets first, and if these do not show a difference over and above a 'standard' healthy diet, there would be no need to test further types of intensive diets. For exercise, an example could be to attempt high intensity interval training three times per week first and then follow on with testing other exercise interventions.
- MRS biomarker or mfVEP (critical flicker fusion) in optic neuritis were suggested as possibilities that would allow the trial to have outcomes in the short-term in order to justify the long-term studies required for outcomes such as disability progression.
- Feasibility studies are important and designing the studies so that we are achieving a tangible and relevant outcome for the people with MS (why are we doing the study).
- Clinicians need a better way to track comorbidities. Comorbidity data can be included in MSBase but resourcing would be needed for data entry. Currently 4500-5000 Australians with MS are included in MSBase.

Final Recommendations/Conclusions

Guidelines for the Australian MS Community on modifiable lifestyle factors

- The evidence base from observational studies is reasonably strong for the following areas: smoking cessation, physical activity, adequate vitamin D and/or sunshine exposure, healthy lipids and healthy eating according to the Australian Dietary Guidelines.
- Information on "Living Well with MS" that cover diet and lifestyle advice needs to be produced (using different modes of delivery) and tailored to the Australian MS community. The information will include levels of supporting evidence and identify research gaps.
- Guidelines for health professionals should be accompanied by factsheets aimed at people with MS.
- A working group will be established to produce a guidance document on the different modifiable lifestyle factors. It can be adapted from available documents in order to create alignment with existing resources.

- The process will be coordinated through MS Research Australia. Relevant stakeholder groups and researchers will be involved, including the MS Research and Translation Network (set up by the Menzies Institute for Medical Research).
- The final guidance document will be disseminated to the MS community via MS Research Australia and through medical teams for people with MS (ideally MS nurses). This will allow tracking and follow up with individuals over time to encourage adherence.
- This document could also be used to develop an implementation tool that will provide a framework for MS nurses to either screen healthy lifestyle behaviours in people with MS or provide support and referrals for interventions to make lifestyle changes.

Avenues for future research

- Controlled intervention studies need to be designed that can more accurately measure the benefits of changes to modifiable lifestyle factors in MS. One option would be to run a multi-armed study that compared multimodal interventions to other arms with single interventions, following standard guidelines for diet and exercise and controls. Outcomes for any clinical trial need to encompass both measurements for wellness (i.e. fatigue, quality of life) as well as determining if there is any outcome on disease pathology. The outcomes need to be weighed against the effort/impact of adhering to a specific diet.
- Further research is also needed to determine the validity of different approaches to support people making lifestyle changes and assist them beyond the initial phase to create sustained change. This will aid implementation of any intervention studies and support the design of an implementation tool for use in the clinic (see above).

Acknowledgements

The workshop was developed in partnership with the steering committee made up of Professor Robyn Lucas, Professor Bruce Taylor, Professor Anne-Louise Ponsonby, Associate Professor Ingrid van der Mei and Dr Lisa Melton. MS Research Australia would like to thank our workshop sponsor Novartis for providing a grant contributing to the costs of the meeting. The agenda, speaker invitations and program have been entirely and independently designed by the Steering Committee.

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Resources

- Resource 1. [Australian Dietary Guidelines – Summary](#)
- Resource 2. [Australian Dietary Guidelines – Scientific Evidence](#)
- Resource 3. [Brain Health: Time Matters Report](#)
- Resource 4. [Clinical Practice Guidelines for Dementia](#)
- Resource 5. [Clinical Guidelines for Stroke Management](#)
- Resource 6. [Living Well with MS](#) Module on [diet, exercise and healthy behaviours](#).
- Resource 7. Canadian MS Society [Physical Activity Guidelines](#)
- Resource 8. [Australian Asthma Handbook](#)
- Resource 9. [My Asthma Guide](#)