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RESEARCH PAPER



How people with multiple sclerosis experience the influence of nutrition and lifestyle factors on the disease

Astrid Karnoe^{a,b} , Lise M. Pedersen^a, Sashia Karlsen^a, Finn Boesen^c, Lasse Skovgaard^b and Lars Kayser^a 

^aDepartment of Public Health, University of Copenhagen, Copenhagen, Denmark; ^bSection of Research and Development, Danish Multiple Sclerosis Society Valby, Denmark; ^cDanish Multiple Sclerosis Hospital, Haslev, Denmark

ABSTRACT

Purpose: Increasing knowledge suggests that nutrition and lifestyle factors affect multiple sclerosis. This study explores how people with multiple sclerosis experience daily multiple sclerosis disease activity and the influence of nutrition and lifestyle factors (e.g., stress, sleep, and environmental temperature).

Methods: Four phases mix qualitative and quantitative elements in an exploratory study. The initial two phases consisted of an exploratory study with 14 participants followed by 15 semi-structured interviews. Results from the two first phases were substantiated in a survey completed by 425 respondents (response rate: 42.5%). Finally, findings and inconsistencies were elaborated in three focus group interviews.

Results: In the initial exploratory study, several of the participants linked nutrition and lifestyle factors to disease activity. Results from the semi-structured interviews showed that particularly stress, meat, fatty foods, and processed sugar were perceived to have a negative impact on disease activity, and some participants had experienced immediate effects of these factors on their disease activity. The survey supported these findings that were further elaborated in focus groups.

Conclusion: People with multiple sclerosis perceive nutrition and lifestyle to affect daily disease activity. Individuals who have experienced links between their multiple sclerosis, and nutrition and lifestyle attribute some of these changes to e.g., stress, and the consumption of sugar, meat, and fatty food.

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KEYWORDS

Multiple sclerosis; diet; exercise; fatigue; symptoms

► IMPLICATIONS FOR REHABILITATION

- A majority of the participants in this study perceived nutrition and lifestyle factors to have an effect on their multiple sclerosis, particularly stress, meat, fatty foods, and processed sugar.
- Some participants with multiple sclerosis experienced that nutrition, stress, environmental temperature, and physical activity had a direct effect on the severity of daily symptom manifestations.
- Nutrition and lifestyle factors that potentially influence multiple sclerosis disease activity should be considered when organizing rehabilitation and care to better meet the needs of the individual with multiple sclerosis.

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease that affects the central nervous system [1]. Disease onset is most common in individuals age 20–40 with a higher prevalence in women [2,3]. MS is accompanied by a wide range of physical and cognitive symptoms, and the disease severely impacts patient, patient's family, and society [4–6].

There is no cure for MS, but disease-modifying treatment can stabilize disease progression for patients in initial relapse-remitting phase and possibly delay transition to a secondary progressive phase of the disease. These medical treatments often have many side effects [7]. The primary and secondary progressive states of MS are less responsive to treatments, with the first pharmaceutical products entering the market recently [8,9].

Severe medical side effects and uncertainty of the disease-modifying treatments' long-term effect on disease progression, lead many MS patients to look for complementary treatments. This includes MS diets and changes in lifestyle [10,11]. An Australian study showed that 64.7% made changes to their diet

as a consequence of their MS diagnosis [11]. Research conducted in nutrition and MS have shown conflicting results when examining the impact of vitamin D, lower salt intake, and omega 3 on MS progression [12–17]. A recent epidemiological study in a sample of 6989 people with MS found that healthy diet and composite healthy lifestyle were associated with less disability and MS symptom burden [18]. However, further research is needed to examine the longitudinal perspective and specific dietary factors. Conclusive nutrition guidelines do not exist, and the content of currently published MS targeted diets varies greatly [14,19–21]. Consequently, people with MS receive little support and advice from their doctors [21], and instead on their own obtain information from the Internet, family and friends, and complementary health professionals.

Together with changes in diet, a number of lifestyle factors, and environmental temperature have also been found to impact MS disease activity. Increasing evidence suggests that physical activity and particularly exercise can decrease fatigue, restore function, and manage symptoms [22–24]. Furthermore, stressful life events have been associated with MS exacerbations [25].

Environmental temperature changes have been recognized as having an impact on MS. More than 80% of people with MS develop symptoms during cases of hyperthermia [26].

Clinically, disease activity in MS is defined as relapse rate and disability progression over time. However, many people with MS experience daily symptom manifestations that are caused by old scarring and environmental triggers that are not relapses or directly related to disease progression [27–29]. These symptom manifestations may affect the individual's functioning in everyday life through impairment, limitations, and restrictions [30]. From a clinical perspective, physical disability is used as a primary indicator for MS health, but 'invisible symptoms' (e.g., pain, cognitive impairment, and dizziness) are major contributors to health-related quality of life among people with MS [31–34]. Individuals with MS are often more concerned with mental wellbeing than physical disability [34], which illustrates a discrepancy between the clinical and the patient perspective. Hence, health professionals – as well as researchers – may benefit from a better understanding of how individuals with MS experience living with the disease and the factors experienced to affect MS. An improved understanding may lead to better patient-centred care and ensure that future research designs and outcomes are relevant to both clinicians and the individual with MS. Research indicates that nutrition and environmental factors affect MS, but to our knowledge, no studies have investigated the patient perspective of how these factors influence MS.

In this paper, we use disease activity as a broad term that contains both clinical definitions and daily MS symptom manifestations that affect individuals living with MS.

The aim of this study is to explore how people with MS experience disease activity and the impact of nutrition, temperature, stress, and physical activity.

Methods

Study design

Links between MS disease activity and nutrition, environmental temperature, stress and physical activity were explored in four sequential phases that combined qualitative and quantitative elements to substantiate and elaborate findings. See Figure 1 for an overview of study design and its four phases. Participants in phase one, two, and four only participated in one interview phase each, while survey invitations in phase three were sent to a randomized sample that did not exclude participants from interview phases.

The interviews and focus group interviews are informed by a phenomenological approach that sought to explore the lived experience [35,36]. In this study we investigate people with MS's lived experience of possible links between their MS disease activity and nutrition and lifestyle factors. The sequential mixed methods design aims for a dynamic application of methods. Hence, the different phases are initiated in order to further understand and/or elaborate on the results of the preceding phase [37]. It has been debated if a phenomenological approach is compatible with focus group methodology. Opponents argue that by using focus groups one risks contamination of described experiences and a loss of the individual perspective [38,39]. However, focus groups may contribute with enrichment and clarification of data as a result of the interaction and reflection among participants, and between participants and interviewer [39,40].

Concepts and definitions

For people with MS, the lived experience is not limited to include disease activity as disability progression over time. Therefore, the data collection, does not distinguish between disease activity (relapses and/or progression over time) and symptom manifestations but on how MS is experienced by the people diagnosed with it. This may include the clinical definition of disease activity and relapses as well as symptoms and factors that influence people living with MS.

The semi-structured interviews, survey, and focus groups conducted in this study, also included data collection that explored factors for adoption of technology and eHealth project recruitment. These results will be published elsewhere.

Organization and data collection

Phase one: initial exploratory study

The initial exploratory study was conducted in a convenience sample of 16 people. The study included people diagnosed with MS, Danish speaking, above age 18, and with no significant cognitive impairment or aphasia.

Participants were identified and invited in April 2014 at the Danish MS Hospital in Haslev. The hospital admits patients for elective stays of two or four weeks, during which the patients participate in rehabilitation and patient education related to their condition and the impacts associated with living with MS.

Thirteen patients accepted the invitation and were interviewed on the premises by authors LP and SK. Three additional participants were recruited through Facebook, with one participant

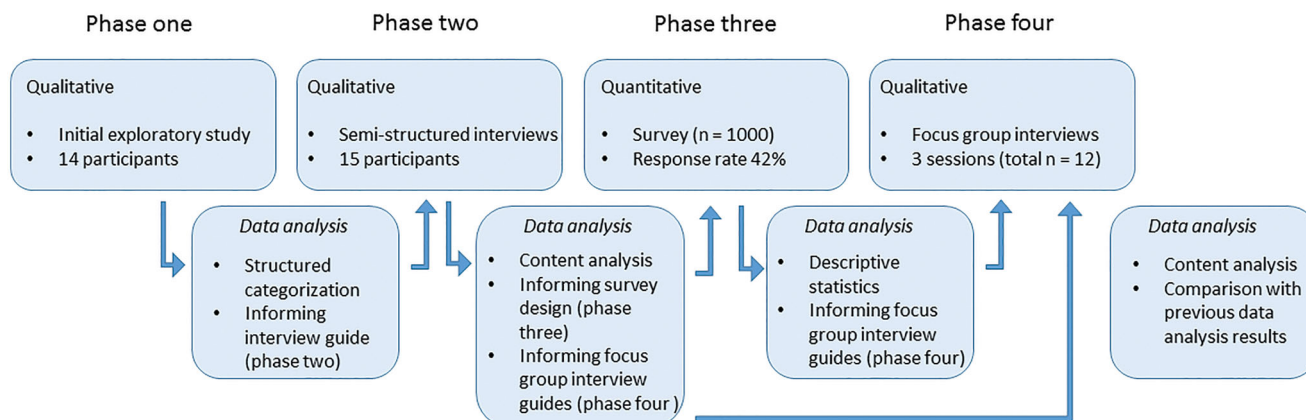


Figure 1. Overview of study design and its four phases.

responding to an advertisement on the Danish Multiple Sclerosis Society, and two participants via authors own Facebook network. These three interviews were conducted in the participants' own homes (April 14th, May 7th and 9th 2014).

The 16 interviews combined open-ended conversation with structured probing about nutrition and other factors affecting participants' MS. Probing was used to support the participants' awareness of daily habits. Interviews were digitally recorded and then transcribed. Two interviews were excluded prior to the analysis, due to technical problems with the recording device. Consequently, the dataset consisted of 14 interviews. Ten women and four men were interviewed.

Phase two: semi-structured interviews

Findings from phase one showed that several participants with MS had changed diet as a consequence of being diagnosed with MS, and that participants considered certain food groups and lifestyle factors to influence disease activity. Based on these results, semi-structured interviews were conducted to further explore people with MS's experience of links between nutrition and lifestyle factors and disease activity through an interview guide based on the findings from *phase one*. The interviews explored participants' dietary habits, and their experience of the links between MS disease activity and nutrition and lifestyle factors.

In the interviews, participants were asked about daily habits with regards to nutrition and lifestyle, how they experienced MS disease activity in everyday life, and how MS, and nutrition and lifestyle might be experienced to affect each other. Participants were not asked to relate to specific nutrition or lifestyle elements, but were asked open questions. If a participant mentioned specific elements, iterative questioning was used to learn more about the nature of their experience and to examine consistency [41]. Prior to each interview the participant would have time to read, ask questions and sign the consent form, as well as completing a short questionnaire on socio-demographic data. See Table 1 for socio-demographic distribution of participants. All interviews were recorded on Dictaphone.

Fifteen participants were included in the semi-structured interviews. Seven participants were identified in July 2016 through a Facebook status update on the Danish Multiple Sclerosis Society page. Eight participants were identified in July 2016 at the Danish MS Hospital, Haslev.

Table 1. Socio-demographic data.

	Phase two	Phase three (N = 425)	Phase four
<i>Gender</i>			
Female	10	79% (334)	10
Male	5	21% (91)	2
<i>Age</i>			
18–29	1	3% (14)	1
30–39	3	15% (64)	1
40–49	5	24% (100)	2
50–59	5	32% (135)	5
60–69	1	20% (87)	3
70–79		6% (25)	
<i>Type of MS</i>			
Relapse-remitting	9	60% (257)	8
Secondary progressive	2	13% (57)	2
Primary progressive	3	17% (74)	2
Don't know	1	9% (37)	
<i>Year of diagnosis</i>			
1989 or earlier		9% (41)	
1990–1999	2	20% (84)	3
2000–2009	7	37% (158)	8
2010 or later	6	33% (142)	1

All 15 interviews were conducted by author AK. Eight interviews were conducted at the Danish MS Hospital in Haslev on August 30th 2016 ($n=4$) and September 9th 2016 ($n=4$). Five interviews took place in participants' homes in the Northern and Capital region of Denmark July-August 2016. Two interviews were conducted at the Danish Multiple Sclerosis Society's offices in Valby.

Phase three: survey

To substantiate the findings and validate the analysis from phase two, a survey was conducted among people with MS. The survey questionnaire contained 25 items related to nutrition and lifestyle factors, and for each item respondents were asked to state whether they had experienced the given nutrition and lifestyle factor to affect their MS. Furthermore, respondents were asked if they followed a specific set of MS diet guidelines, and if yes, which one. A text field allowed for comments on nutrition lifestyle that had not been stated in the structured part of the questionnaire. The questionnaire was set up in SurveyXact [42] and sent out to a random sample of 1.000 members of the Danish Multiple Sclerosis Society that was extracted from the member database. The sample only included members diagnosed with MS, who had given consent to receive information, and who had registered an email address. The sample was generated in December 2016.

Invitations were sent via emails that contained a brief introduction and a link. A reminder was sent out to those who did not reply within the first five days. Ten days after initial invitation, the questionnaire was closed. In total 425 respondents filled out the survey (response rate 42.5%). See Table 1 for a summary of participants' socio-demographics.

Phase four: focus group interviews

While the combination of phase one to three enhances our understanding of nutrition and lifestyle factors' effect on MS disease activity as perceived by participants, the first phases also reflected very different experiences among the participants. Focus group interviews were conducted to elaborate on participants perspectives through the discussions and synergy of focus group interviews [43,44]. Focus groups were assembled by sending out an invitation to potential participants who had already indicated an interest in the project. Furthermore, a status update was put up on the Danish Multiple Sclerosis Society's Facebook page. Twelve participants were identified with the invitation, and six were identified via the Facebook advertisement. Participant number for each focus group was as follows focus group 1 had five participants on 12th of January 2017 (one late cancellation), focus group 2 had four participants on 17th of January 2017 (two late cancellations), focus group 3 had three participants on 18th of January 2017 (three late cancellations).

Focus group interviews were conducted in Danish Multiple Sclerosis Society office facilities in Copenhagen, Denmark. Participants were invited to a 2.5 h long session. Participants were asked to fill out a participant consent form and a questionnaire on socio-demographic data. The focus group interview guide was inspired by Krueger and Casey [44]. Participants were informed that interviews were recorded on a Dictaphone and later transcribed.

Data analysis

Phase one: analysis of initial exploratory study

The collected data material from phase one, was analyzed by collecting the responses of the structured probing and categorizing

responses into structured categories. Categories described socio-demographic factors, symptom manifestations, the impact of nutrition on MS, and the impact of other lifestyle and environmental temperature on MS. Authors SK and LM went through transcriptions and supplemented the content of the response categories by identifying parts of open-ended conversation consistent with already existing categories.

Phase two: analysis of semi-structured interviews

The aim of the analysis of semi-structured interviews was to investigate nutrition and lifestyle factors that participants mentioned in relation to their everyday life living with MS. Content analysis was chosen to be able to classify these components into categories [45].

All interviews were transcribed in its complete form, and hereafter each interview was coded in NVivo (nVivo, vers. 11 [46]). Since data on nutrition and lifestyle was collected together with a part on adoption factors and eHealth, the whole dataset was initially coded into open themes to ensure that the two parts were properly separated before the main analysis. Data from part on adoption factors and eHealth is reported elsewhere. The two themes related to nutrition and lifestyle were analyzed by a qualitative deductive content analysis [47]. In the analysis, we focused on identifying nutrition and lifestyle factors linked to MS through the lived experience of the participants. The lived experience of living with MS was affected by both factors that participants had experienced to have an effect on their own MS, and factors that were believed to have an effect.

Initial coding was conducted by author AK. After coding of the first three interviews, the coding strategy was reviewed with author LK. After reviewing the code, the interview was re-coded to adjust to comments and discussions. Authors LSK, LK, and AK reviewed the codes together in three sessions that carefully examined the codes and the data behind each code. In the sessions, reflections were made on the nature of the patient experience, and how to best present the findings. A categorization matrix was developed, as a structured presentation of participants' experiences with nutrition [47]. The structure was the outcome of an abstraction process that divided the main categories into positive effects and negative effects, as well as distinguishing between the participants' experiences and beliefs.

Phase three: survey

Based on the results from the content analysis of the 15 semi-structured interviews, a survey was constructed to validate these findings. The survey included 25 items related to nutrition and lifestyle factors, and they were constructed by authors AK, LSK and LK. Nutritional factors that had been mentioned as having an impact on MS disease activity in the earlier studies were listed, and respondents had the options of responding "Yes, it has an effect" or "No, it does not have an effect" to each nutrition listed. In the selection of nutrition items, authors were particularly careful not to choose or divide items in a way that would favor

existing MS diets to avoid that respondents were guided in their responses. The same structure was used on sleep/rest, physical activity, cognitive training, stress, temperature, and smoking. Furthermore respondents were asked if they followed a specific MS diet, and in that case which one. In two items respondents indicated which symptoms (i.e., fatigue and pain) and conditions (i.e., mood and sex life) related to MS that they felt changing on daily or weekly basis. All items were followed with a text box, in which respondents could add options not represented in the categories. Socio-demographics are listed in Table 1.

Data was analyzed with focus on nutrition and lifestyle, and a comparison of the survey results and the results of the analysis. Data analysis was conducted in SurveyXact and R [42,48].

Phase four: focus groups

Focus groups were analyzed in a categorization matrix identical to the one developed in the analysis process of phase two. The three focus group interviews were transcribed and coded in nVivo [46]. Author AK, who coded all parts of the interviews related to nutrition and lifestyle, conducted the coding. Subsequently, the coded text was divided into the categories used in the phase two categorization matrix. Meetings with author AK and LK, and AK and LSK were held to discuss the findings and how they contributed to findings from previous phases.

Ethical consideration and data agency

In this study, no biological material or medical devices were used and the participants were not subjected to any kind of diagnostics or treatment. Consequently, approval from the Danish National Committee on Health Research Ethics (Den Nationale Videnskabetiske Komite), was not required, which is the case for all studies only involving interviews and questionnaires [49].

The initial exploratory study did not need to be registered, as it was part of a student research project. The remaining parts of the study were registered and approved with the Danish Data Protection Agency (2016-41-4723).

Results

Phase one: initial exploratory study

In the initial study, phase one, participants related a range of nutrition and lifestyle factors to changes in MS disease activity. When probed about nutrition and lifestyle factors and a potential impact on MS, particularly six factors were mentioned: psychological stress, hot/cold weather, sugar, exercise and beef (see Table 2). These results instigated the more elaborate investigation carried out in phase two to four.

Phase two and four: in-depth investigation

Seven men and 20 women participated in a semi-structured interview or a focus group interview; mean age was 48,7 (range 26 to 70). All participants were diagnosed with multiple sclerosis;

Table 2. Factors affecting MS.

Identified factor	Participant (ID)	Total
Psychological stress	1.1, 1.2, 1.6, 1.7, 1.8, 1.9, 1.11, 1.12, 1.13, 1.14	10 out of 14
Heat (temperature)	1.1, 1.2, 1.3, 1.4, 1.7, 1.9, 1.10, 1.11, 1.12	9 out of 14
Cold (temperature)	1.1, 1.7, 1.9, 1.10, 1.12, 1.13	6 out of 14
Sugar	1.2, 1.7, 1.11, 1.12, 1.13	5 out of 14
Exercise	1.7, 1.10, 1.11, 1.12, 1.14	5 out of 14
Beef	1.6, 1.12, 1.13	3 out of 14
No factors affecting MS	1.5	1 out of 14

Results from Phase 1: an initial exploratory study.

relapse-remitting MS ($n=17$), primary progressive MS ($n=5$), or secondary progressive MS ($n=5$), and one participant being unsure of the precise type of MS. All participants had been diagnosed with MS for mean 10.5 years (range 0–22 years), with disease burden ranging from mild, daily fatigue to being wheelchair bound most of the time. The participants had varying interest in nutrition and lifestyle factors; some mentioned diet and lifestyle to be a major priority in their everyday life with regular exercise and strict diets, while others expressed that quality of life to them equaled being able to eat whatever they felt like an not being bound to a specific diet or lifestyle. Seven out of 15 participants in the semi-structured interviews had made changes in their diet after they were diagnosed with MS (ID: 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.11).

Disease activity and symptoms

Participants in semi-structured interviews (phase two) and focus group interviews (phase four) experienced fluctuations in daily MS symptoms, both physical and neuropsychological symptoms. Physical symptoms included weak legs, sensory disturbances, decreased balance and headaches. Neuropsychological symptoms were related to cognition, energy levels, and mental wellbeing. The number and severity of symptoms varied among participants, and reflects the MS population as a heterogeneous group, and some participants experienced many and others few.

"I can feel 100kg heavier in my body. I become confused. I become forgetful. And as I said, I become a bit wobbly. And I sometimes get cramps." (Female, 39 years, diagnosed in 2009, ID: 2.12)

When asked about the experienced correlations between daily MS disease activity and nutrition and lifestyle factors, several participants reflected on the difficulty of distinguishing between

which parts of everyday life that potentially associate with changes in MS disease activity.

"(...) I'll say strange things or something. And then I start doubting if it is the MS, or if it's just because I'm confused and tired, right?"

(Female, 44 years, diagnosed in 2005, ID: 4.1)

While participants mainly used changes in daily symptoms to describe their MS and everyday life with the disease, relapse triggers and disease activity over time were only few times mentioned in relation to nutrition and lifestyle factors.

Nutrition and lifestyle factors

In the analysis, nutrition and lifestyle factors mentioned by participants in interviews and focus groups, were plotted into a categorization matrix [47] to distinguish between factors as having "Experienced positive impact on MS", "Experienced negative impact on MS", "Perceived positive impact on MS", and "Perceived negative impact on MS". "Experienced impact" describes nutrition and lifestyle factors that participants personally have experienced to have a positive/negative effect on their disease activity or symptom manifestations. "Perceived impact" describes factors that participants believe/perceive to impact disease activity based on information from other people, literature, diets, etc. The matrices for interviews and focus groups are shown in Tables 3 and 4.

A factor was categorized as "perceived impact" when a participant described the potential benefits or harms based on information from others, common knowledge of MS, or as something they try or had tried without having experienced an effect on their MS. For example wordings like: "I have also heard that of course you need to think about not getting too much animal fat" (Male, 49 years, diagnosed in 2000, ID: 2.14).

Table 3. Categorization matrix.

Experienced positive	Experienced negative	Perceived positive	Perceived negative
Nutrition	Meat (2.12)	Fish (2.1, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.11, 2.12, 2.13, 2.14) Vegetables (2.1, 2.2, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13)	Meat (2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.10, 2.13, 2.14) Fatty foods (2.4, 2.14(animal fat)) Legumes (2.5) Eggs (2.4) Sugar (2.2, 2.4, 2.5, 2.11) Fast food (2.4) Gluten (2.5, 2.11) Non-organic (2.4) Alcohol (2.2, 2.11)
	Sugar (2.6, 2.8) Fast food (2.6)	Legumes (2.6)	Dairy (2.5, 2.11)
	Alcohol (2.12)	Chicken (2.11) Avocado (2.3) Rice (2.9) Fibres (2.2)	
Vitamin D (2.3, 2.12)		Hemp (2.2) Ginger (2.1, 2.2)	
Other Factors	Smoking (2.1) Heat (2.1, 2.3, 2.4, 2.5, 2.11, 2.14) Cold water (2.9) Stress (2.1, 2.2, 2.4, 2.5, 2.9, 2.12, 2.14)		Smoking (2.15)

Table 4. Categorization matrix.

Experienced positive	Experienced negative	Perceived positive	Perceived negative
<i>Nutrition</i>	Fatty foods (4.8)	Fish (4.1) Vegetables (4.1)	Fatty food (animal) (4.3)
	Meat (4.2 (beef), 4.1, 4.6, 4.8) Sugar (4.1, 4.2, 4.3, 4.4, 4.6, 4.8, 4.10, 4.11)		Meat (4.3, 4.12, 4.10) Eggs (4.1)
	Alcohol (4.3)	Fibres (4.3)	
<i>Other Factors</i>			
Sleep and rest (4.1, 4.2, 4.6, 4.9, 4.11, 4.12)	Fever (4.2, 4.1, 4.9, 4.6, 4.7, 4.8, 4.10, 4.11) Heat/sun (4.6, 4.9) Artificial light (4.12, 4.6, 4.9) Stress (4.3, 4.11, 4.12, 4.10) Meno-pause (4.7)		

Participant 4.5 did not perceive or experience nutrition or lifestyle to have an effect.

Results from Phase four: focus group interviews.

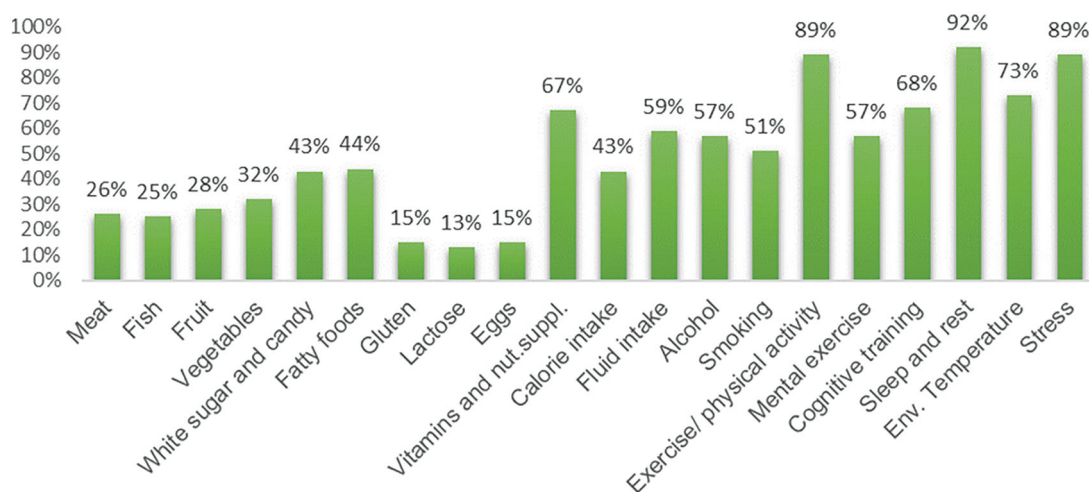


Figure 2. Phase three: survey results. Percentage of respondents who indicated the included factors to have an impact on MS ($n = 425$).

Contrarily, a factor was categorized as “experienced impact”, if a participant had experienced that factor to have an impact on their MS disease activity, potentially causing flare-ups. For example: “If I have eaten a big, red/rare steak... Then I can feel it. Right away”. (Female, 39 years, diagnosed in 2009, ID: 2.12).

Survey results from phase three are gathered in Figure 2, as a percentage of participants that perceived each of the nutrition and lifestyle elements to affect their MS. See Figure 2.

Nutrition

All participants had at least one nutritional factor that they perceived to have an impact on their MS – either on disease activity in general or disease activity related to a specific symptom manifestation. Three participants had personally observed specific diet components to have a negative impact on daily MS disease activity fluctuations (ID: 2.6, 2.8, 2.12).

These findings were supported in the phase three survey, where results of the survey showed that respondents perceived many dietary components to affect their MS.

Sugar

Findings from both the exploratory study and the survey (phase one and three) showed that sugar was the most common nutritional element to be linked to MS disease activity by

participants and respondents. For three participants in the semi-structured interviews, the MS diagnosis was the tipping point that urged them to remove sugar completely from their daily diet (ID: 2.2, 2.4, and 2.6). In total, four participants in phase two perceived sugar to have a negative impact on MS (see Table 3). However, this perception might also be influenced by society’s view on sugar consumption, as one participant described it as common knowledge that sugar is bad for everyone – not only people with MS. Two interview participants had experienced direct effects of sugar consumption on specific changes in disease activity. One participant described that he within a few hours after larger sugar intakes would feel light-headed and got sensory disturbances moving in specific patterns across one arm (Male, 51 years, diagnosed in 2012, ID: 2.6). Further one participant felt dizziness after extensive consumption of sugars, i.e., juice or chocolate (Female, 41 years, diagnosed in 2002, ID: 2.8).

In the phase three survey, 43% of the respondents’ reported sugar to have an impact on their MS disease activity. Based on findings from phase one and two, these results were a bit higher than expected. Consequently, focus group interview participants were presented with the results from the survey with seven out of 12 participants stating that they had experienced a negative impact of sugar on their experienced MS symptoms.

Participant (ID: 4.6): *I will say that the thing about sugar and things containing lots of sugar ... That doesn't surprise me. I feel the same.*

Participant (ID: 4.7): *But how does it affect you, if I may ask? Just to compare.*

Participant (ID: 4.6): *I think I get ... My body goes weak. (...) I can feel it if I have had a lot of sugar in a day. Normally, I don't eat sugar. So in the beginning I thought, that it is just because I'm not used to sugar. But then my [symptoms] increase. I get sensory disturbances in my whole left side. And it is just on small scale, but they do increase"*

Participant (Male, 51 years, diagnosed since 2012 ID: 4.6)

Participant (Female, 40 years, diagnosed since 2016 ID: 4.7)

Meat

Nine out of fifteen participants in phase two had the perception that meat, and in particular red meat, might have a negative effect on MS disease activity (see Table 3). This seemed to be a general opinion: "When you've heard what people say, then you try to avoid beef. [...] I don't think it makes a difference" (Male, 70 years, diagnosed since 2004, ID 2.13) None of the people participating in phase two had eliminated meat completely from their diet, but five participants had following the MS diagnosis, limited their intake to smaller amounts, poultry and wild rabbit (ID: 2.3, 2.4, 2.5, 2.6, 2.14). Other participants stated that meat was an important part of daily diet, and they enjoyed too much to eliminate it despite the potential harmful effects on MS (ID: 2.2, 2.7, 2.8, 2.12). Participant (Male, 49 years, diagnosed since 2000, ID: 2.14): "I do consider these things. I do. Probably not enough, but you also need to remember to live". While the perception of meat as having a negative impact on MS was widespread, only one participant (Female, 39 years, diagnosed since 2009, ID: 2.12) experienced a direct effect of eating red meat, which made her feel more tired and fatigue compared to fish and poultry.

In the survey, 26% responded that they experienced meat to have an impact on their MS, which was fewer than indicated e.g., alcohol and sugar to have an impact. When this result was presented in the focus group, majority of participants agreed that they perceived sugar to have a larger impact than meat.

However, participants (ID: 4.1, 4.2 4.6, and 4.8) had experienced meat intake to be directly related to their MS disease activity, and participants (ID: 4.2 and 4.6) experienced immediate effects of eating meat, and particularly "red meat" (beef, lamb, and pork):

"I definitely believe that beef is bad, you know? Especially for me. That's just my experience. I can't have meat. Then I can't sleep at all, and have pain, and sensory disturbances, and everything. I. It goes straight to my legs"

(Female, 56 years, diagnosed since 2007, ID: 4.2)

Participants who noticed links between meat and MS disease activity were more likely to distinguish between "red" meat and "white" meat. Red meat was by participants defined as beef, pork, lamb, and other four-legged animals. Participants both experienced and perceived red meat to be a bigger trigger for worsening in MS condition compared to white meat (e.g., poultry and rabbit).

Fast food, fatty foods, and alcohol

Compared to meat, more respondents in the survey replied that they believed fatty foods and fast food had an impact on their MS (45% compared to 26%). However, this high number was not reflected in semi-structured interviews or focus group interviews. In the phase two, one participant had observed a correlation

between fast food (defined as processed, fatty foods) and increase in symptoms: "Now I have completely stopped eating fast food and that kind of stuff, right? But those times I have had something that I didn't completely know what was, then I have registered an increased activity in my symptoms" (Male, 51 years, diagnosed since 2012, ID: 2.6).

In the focus group interviews, one participant (Female, 51 years, diagnosed since 1995, ID: 4.8) had experienced feeling an increase in fatigue following the intake of fatty foods.

Similarly, 57% of survey respondents reported alcohol to affect their MS disease activity. In the interviews, only one participant reported an experienced effect on MS from alcohol: "Alcohol, I feel that too. Ehhm. It simply goes straight to my legs, immediately" (Female, 39 years, diagnosed since 2009, ID: 2.12). When further explored in focus groups, a participant (Male, 31 years, diagnosed since, ID: 4.3) told how he would feel tired after drinking even one beer. However, none of the remaining participants reported direct correlations between their MS disease activity and alcohol.

Fish and vegetables

While some participants in phase two and four had experienced different diet factors to have a negative impact on their MS disease activity, none reported to have experienced a positive impact on MS linked by a specific diet factor. However, fish and vegetables were perceived by participants in both phases to have a positive effect on their MS (see Tables 3 and 4). Participants mentioned that it was a priority for them to eat fish regularly and several times during the week: "I have always eaten lots of fish, and that is of course something that I'm aware of" (Female, 40 years, diagnosed since 2016, ID: 2.7). And the intake of fish was associated with the positive effects of increased and/or sufficient intake of Omega 3 (fatty acid). "Preferably, I eat fish at least once a week. Minimum. But I don't think it is quite enough" (Male, 31 years, diagnosed since 2014, ID: 2.3).

Similarly, many participants in the semi-structured interviews perceived vegetables to have a positive effect on MS. To some participants vegetables were the center of their meals, while others considered it a healthy supplement to their nutrition.

But I think that it is just something I do [eat vegetables], because I have been told that it is healthy, but it is not something that I can feel. (Female, 39 years, diagnosed since 49, ID: 2.13)

Other nutrition that one or more participants perceived as having a positive effect on MS were legumes, avocado, rice, fiber, hemp, and ginger.

Dietary supplements and vitamins

Dietary supplements and vitamins were widely used among participants and perceived to have a potential positive effect on MS. All interview participants took at least one nutrition supplement or vitamin, but they had very different opinions on which supplements to take and why. The majority of participants took vitamin D, as their clinicians had recommended it. In addition, some participants took large numbers of various supplements, as it "can't harm anything" (Male, 70 years, diagnosed since 2004, ID: 2.11), and another participant saw it as a way of providing the body with the right building blocks to resist MS (Female, 31 years, diagnosed since 31, ID: 2.5). Contrary, other participants minimized their consumption: "I stick to basic stuff, so I don't confuse it [the body] too much" (Male, 51 years, diagnosed since 2012, ID: 2.6).

The wide use of vitamins and dietary supplements was confirmed in the survey, in which 67% replied that they believed that certain vitamins and dietary supplements affected their MS.

MS diets

Altogether, many participants perceived and experienced that a number of specific diet components affected MS disease activity. However, several participants in interviews and focus groups interviews emphasized that they considered the effects of diet to be long term, and that the diet as a whole was more important than one specific diet component. Participant (Female, 56 years, diagnosed since 1995, ID: 4.6):

"I hear somebody say that they have tried to avoid this or that for a month. Or two months. And then I tell them: 'Try with a year. Try with two years, and then try to see the difference'".

Environmental temperature, stress and sleep

Compared to nutrition, more participants reported links between their MS disease activity and non-dietary factors. Temperature/ weather and stress were experienced to have a negative effect on MS disease activity.

Contrary, participants experienced that sleep, rest, and physical activity had a protective effect on disease activity in MS.

Stress

Interview participants reported that stress noticeably influenced their MS (ID: 2.1, 2.4, 2.5, 2.9, 2.12, 2.14). "Stress affects it [MS] a lot. Both physically and mentally" (Female, 63 years, diagnosed in 2001, ID: 2.5). In the following survey, 89% indicated that stress affect their MS. This was the second-highest ranked influence of all nutrition and lifestyle factors listed in the survey. Stress was not included as a specific question in the interview guide for the focus group interview. However, participants several times mentioned it themselves in all three interviews, and they continuously linked stress to significant increase in experienced disease activity.

Participant (ID: 4.11): Yes, stress [affects my MS]

Participant (ID: 4.12): Yes

Participant (ID: 4.11): It's completely... Then I can't think. At all.

Participant (Female, 52 years, diagnosed in 1995, ID: 4.11)

Participant (Female, 26 years, diagnosed in 2013, ID: 4.12)

Temperature

In addition, six participants experience that heat and warm temperatures affected their MS (ID: 2.1, 2.3, 2.4, 2.5, 2.11, 2.14), and especially leg strength: "It feels like I have lead weights on my legs. Then I have to focus when I move them [legs]. A lot. Somehow, the heat affects me a lot." (Female, 51 years, diagnosed in 2012, ID: 2.1).

These statements were supported by survey results, in which 73% had reported temperature and weather to have an impact on their MS.

Conversely to being affected by heat, one interview participant experienced that cold water made her limbs stiff, while warm water relieved her symptoms (Female, 56 years, diagnosed in 1997, ID: 2.9).

Sleep and rest

While stress and heat were reported to have a negative effect on MS disease activity, proper sleep and rest were regarded essential by participants (see Tables 3 and 4).

"And then I can go and be completely energized in the morning, but then the energy levels just fade, and in the afternoon, then I feel like 'ohhh', and then the battery runs out completely. And then you don't have anything for the rest [of the day], if you don't get some rest." (Female, 39 years, diagnosed in 2009, ID: 2.12)

In the survey, sleep and rest had the highest percentage of respondents indicating the factor to have an effect on MS (92%). In focus group interviews, participants talked about how the need for sleep changes and how daily energy levels can depend on taking a rest during the day:

"It really hits me from time to time. Then I need to sleep for 15 hours a day, and it is impossible to get up and. Yes"

(Female, 26 years, diagnosed in 2013, ID: 4.12)

And:

Participant (ID: 4.6): Do you need to rest during the day?

Participant (ID: 4.9): Yes (...) But I don't sleep. I just lie down and rest.

(Female, 56 years, diagnosed in 1995, ID: 4.6)

(Female, 54 years, diagnosed in 2006, ID: 4.9)

Physical activity

Physical activity was important to a majority of interview participants (10 out of 15), and there seemed to be an agreement on physical activity being beneficial for one's MS.

"I have definitely kept the active lifestyle, and I have a feeling that it has had an impact. I can't say how much or how little, but it does mean something. It is my... I don't doubt that at all" (Male, 51 years, diagnosed in 2012, ID: 2.6)

Nevertheless, the MS diagnosis imposes limitations, and some participants expressed that they didn't feel able to be as active as they used to (ID: 2.1, 2.2, 2.10). This could be due to physical limitations (Female, 51 years, diagnosed in 2012, ID: 2.1), or due to the effects in the days following intense physical activity (ID: 2.2, 2.5). A participant on physical activity:

"I can still do it, but it is the reaction afterwards that I don't feel good about. It can take me several days to recover. So that's just not an option" (Female, 43 years, diagnosed in 2014, ID: 2.2)

In the survey, 89% of the respondents stated that physical activity affects their MS. Unfortunately, we only have the percentage for how many respondents experienced physical activity as having an effect, and not whether the effect was positive or negative.

Discussion

Through four phases we explored how people with MS experience nutrition and lifestyle factors as correlated with disease activity.

Non-dietary factors such as stress, physical activity, and sleep and rest were more frequently associated to changes in MS disease activity. However, participants did perceive nutrition and many specific diet components to have an impact on their MS disease activity. These links between MS symptoms and nutrition were often based on perception and beliefs, instead of actual experiences. However, some participants reported having experienced sugar, meat, fatty foods and alcohol as causing an increase in their MS symptoms.

Sugars' i.e., mono- and di-saccharides' influence on MS disease activity or symptoms is unclear. A study have found increased sweets/candy consumption to be positively associated with risk of MS [20], and another study showed that poor nutrition quality with higher proportions of added sugars and meat were associated with increased symptom burden and disability [18]. However, to our knowledge, this is the first report which identifies sugars as an agent which may influence the patients perceived health symptoms.

Our results indicate that the di-saccharides such as those found in sweets (sucrose, fructose), but not necessarily lactose, may impact the MS patients' wellbeing.

The effect of disaccharides on the blood glucose concentration as an explanation would require changes which would either cause osmotic or electrolyte changes, initiate enzymatic processes or activate specific receptors, e.g., increases acetylcholine as shown in rats or be mediated by sugar-induced metabolites from the gut biota.

An explanation of a mechanism is not within the scope of this study, but the finding calls for further investigations.

Meat was another nutrient that appeared in all four study phases. This may be consistent with findings from 1950 by Swank, who showed that a diet low in total fat (especially saturated fat of animal origin) could significantly decrease the disease activity and deterioration in individuals with relapse-remitting MS [50]. Swank's research has been criticized for the lack of control group and high drop-out rates. Furthermore, a clinical control trial conducted in 2009–2013 tested the McDougall diet which is similar to the Swank diet with a very low fat, plant-based diet. The study did not find an improvement in MRI scans or relapse rates, but did show an improvement in fatigue after one year of following the diet [51]. At the same time, paleo diets with higher protein and fat intake are getting more popular among people with MS. So far, there is no conclusive evidence that support a complete removal of saturated fat from the diet – or an increased intake of protein and fat [15]. However, the reduction of red meat and saturated fat remains one of the most frequent elements in MS diets.

The reports of fatty food as a trigger for increased experienced disease activity may be related to the discussion on saturated fat in meat. Furthermore, fast food and fatty food often contain larger amount of sodium, which has been associated with MS disease activity [52]. However, a recent study by Fitzgerald et al. was not able to confirm this [16].

In general, the majority of participants in all four phases perceived certain food elements to influence MS. However, the analysis showed that fewer experienced a link between those food elements and their MS disease activity. This might be explained by the opinion of a general healthy lifestyle being good for ones MS, which could make respondents answer yes to elements affecting their MS, if it's an element that is generally considered unhealthy (e.g., alcohol and fatty foods).

The majority of participants reported temperature and weather to be a factor that they related to changes in their MS disease activity. Studies from as early as 1890 has registered a correlation between warm water and heat and exacerbations in MS symptom flares [53]. Even though these correlations have been identified in a number of studies, there is still very little knowledge on the mechanisms behind heating reactions among individuals with MS [26].

Participants in all four phases identified stress as a having a major influence on exacerbations in the participants perceived disease activity, and two participants even indicated stress as a

direct trigger of attacks in relapse remitting MS. These findings are consistent with the results of a meta-analysis from 2014, which showed a significantly increased risk of exacerbations among people with MS who had experienced stressful events in previous weeks or months [25]. While there is strong evidence of a link between stressful life events and exacerbations in MS, we still know very little on the psychological, neuroendocrine, environmental and immune mediators that cause these exacerbations [25].

Physical activity is often highlighted as an important factor for maintaining function and as part of rehabilitation following relapses. In this study, only few mentioned physical activity as having an impact on the experience of disease activity. Some participants even mentioned feeling worse after exercising. This may be due to increased body temperature [26]. It is possible that not many of the participants engaged in frequent exercise activities or that it opposite is part of everyday life and changes are not felt. Earlier studies have indicated that increasing levels of physical activity to be associated with increased levels of energy, social function, physical, mental, and overall quality of life [24,54].

The results from the initial study, semi-structured interviews, surveys, and focus group interviews were quite consistent and highlighted the same nutrition and lifestyle factors across methods. However, the tendencies for e.g., correlations between dietary factors and disease activity were stronger in the survey compared to semi-structured interviews and focus group interviews. This might be linked to the difference between believing that a dietary component is bad for MS, and actually experiencing its impact yourself. People with MS have been exposed to popular as well as scientific literature on nutrition and lifestyle factors and MS. All fifteen participants in the semi-structured interviews believed nutrition to be of influence on their MS, but only three participants had observed direct links between dietary factors and daily MS symptom fluctuations. Focus groups showed the same tendencies with eight participants who had observed links, while all believed nutrition to be of importance. This might mean that results from the survey could be affected by the mix of own experiences with what information respondents have received.

Methodological considerations

Some of the identified nutrition and lifestyle factors in this study that participants have experienced to impact MS, may be factors that are not unique to people with MS. They could illustrate something that people with other diseases or even healthy individuals may experience. However, while it may be difficult to distinguish between MS caused fatigue and postprandial somnolence, other of the identified cases illustrate flare-ups of more specific MS symptoms; such as sensory disturbances, dizziness and weak legs.

This study solely investigates people with MS's experience and perception of nutrition and lifestyle factors and MS. Several of the factors that were not experienced to have a positive or negative impact, may still have an effect that is not experienced by the individual, e.g more long-term effects on disease progression or relapse rate.

Participants were recruited through the Danish MS Society's social media accounts and other of the Danish MS Society's communication channels. All invitations emphasized that participation did not require a specific interest in nutrition or healthy lifestyle. However, it is possible that those who signed up were more interested in nutrition than the general population of people with MS.

In phase one, two participants were recruited through authors' own personal social media network. This might have affected how comfortable participants felt with being honest and open during the interview.

This study used a mixed methods approach that combined exploratory interviews (phase one and two), with a confirmatory survey (phase three), and finally reflecting and elaborating focus group interviews (phase four). The sequential mixed methods design allows us to triangulate and strengthen our results by combining qualitative and quantitative elements.

We recognize that in qualitative research, the subjectivity of the researcher is an integrated part of the research process [55]. In our frequent discussions we have encouraged awareness of this matter and continuously elaborated on the design of interview guides and survey, as well as the analysis process and findings to be able to explore the patients' lived experiences as openly as possible [56]. All authors present at the analysis and planning sessions were familiar with existing knowledge and theories. We were careful to examine our own involvement and impact on the process; for example in the design of the survey, we were aware of - and discussed how - our preexisting knowledge and beliefs could affect the selection and distribution of items chosen for the survey.

We deliberately avoided using a framework or including items based on existing knowledge or research conducted in the field of nutrition and lifestyle factors and MS, as we aimed to explore the lived experiences. However, individuals with MS are exposed to an abundance of information on diet, lifestyle, and health through patient communities and various online sources. Therefore, we used iterative questioning [41] to better understand how a factor was experienced to affect a participant's daily MS disease activity. In the analysis of phase two and four, the results of iterative questioning led us to divide nutrition and lifestyle factors into the categories of "perceived impact" and "experienced impact".

In this article, we have sought to provide a detailed description of methods and process, as well as to provide background information on both participants and researchers to strengthen the overall trustworthiness of the study. Throughout the study, measures were taken to enhance the study's trustworthiness, which can be described by the four criteria defined by Guba: credibility, transferability, dependability, and confirmability [41,57]. The use of iterative questioning, peer scrutiny of findings, and examination of previous research added to the study's credibility [41]. By addressing our research questions in a mixed methods approach, we have attempted to meet the criteria for dependability and confirmability by reducing investigator bias and using overlapping methods. The study was conducted in a Danish MS population, and the majority of participants across all four phases voluntarily signed up for the project. The nutrition and lifestyle factors perceived to affect MS are likely to be influenced by culture and available information in the population, and different aspects might be identified in other populations. We consider our study a contribution to the field but do not assume transferability.

Perspectives and future work

This study presents insight knowledge on nutrition and lifestyle factors' influence on MS disease activity - as experienced by individuals with MS. Results from this exploratory study, should be used as the foundation for further studies that collect real time data on nutrition and lifestyle factors and changes in perceived

MS disease activity in a larger scale, to allow for more structured analyses of these potential correlations. Sugar has consistently been linked to changes in MS condition in all four phases of this study. In earlier studies, sugar has mainly been linked to the onset of MS [20], and the effect of sugar on experienced disease activity as well as disease progression has not been thoroughly investigated. To further explore the links of sugar and MS, a controlled clinical trial would be needed.

Conclusion

A majority of the participants in this study perceived nutrition and lifestyle to have an impact on MS disease activity.

Fewer individuals experienced the potential impact of specific factors. However, some individuals had experienced temporary flare-ups of MS disease activity after the consumption of meat, sugar, alcohol, and fatty foods. Furthermore, some participants experienced associations between environmental temperature (in particular heat), sleep/rest, and stress. Further investigations are needed to explore links between MS disease activity, and specific nutrition and lifestyle factors.

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ORCID

Astrid Karnoe  <http://orcid.org/0000-0002-2571-1111>

Lars Kayser  <http://orcid.org/0000-0002-0909-4088>

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