

Use and users of Complementary and Alternative Medicine among people with Multiple Sclerosis in Denmark

- a Sequential Mixed Methods Study

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THE 5 ORIGINAL PAPERS ARE

1. Skovgaard L, Nicolajsen PH, Pedersen E, Kant M, Fredrikson S, Verhoef M, Meyrowitsch D. Use of Complementary and Alternative Medicine among people with Multiple Sclerosis in the Nordic Countries. *Autoimmune Diseases*, Volume 2012, Article ID 841085, 13 pages

2. Skovgaard L, Nicolajsen PH, Pedersen E, Kant M, Fredrikson S, Verhoef M, Meyrowitsch D. Differences between users and non-users of Complementary and Alternative Medicine among people with Multiple Sclerosis in Denmark: A comparison of descriptive characteristics. *Scandinavian Journal of Public Health*. 2013; 0: 1-8

3. Skovgaard L, Nicolajsen PH, Pedersen E, Kant M, Fredrikson S, Verhoef M, Meyrowitsch D. People with Multiple Sclerosis in Denmark who use complementary and alternative medicine – do subgroups of patients differ?. *European Journal of Integrative Medicine*. Vol. 5, Issue 4, Pages 365-373

4. Skovgaard L, Pedersen IK, Verhoef M. Use of bodily sensations as a risk assessment tool. Exploring people with Multiple Sclerosis' views on risks of negative interactions between herbal medicine and conventional drug therapies. *BMC Complementary*. 2014, 14:59

5. Skovgaard L, Pedersen IK, Verhoef M. Exclusive Use of Alternative Medicine as a Positive Choice. A Qualitative Study of Treatment Assumptions among People with Multiple Sclerosis in Denmark. *International Journal of MS Care*. 2014;16:124-131

1. INTRODUCTION

1.1 THE SETTING

Medical and health care systems, practices, and products that are not generally considered part of conventional medicine are often in a Western context referred to as complementary and alternative medicine (CAM) (1). CAM represents a large variety of treatment modalities, including alternative medical systems such as traditional Chinese medicine and Ayurveda, mind-body interventions such as meditation and yoga, biologically-based therapies such as herbs and vitamins, manipulative and body-based methods such as osteopathy and cranio-sacral therapy as well as so-called energy therapies such as qi gong or healing (1).

Use of CAM is widespread in the Western world and has increased markedly over the past 20 years (2-6). CAM is often used among people with chronic conditions (7, 8). In Denmark, the proportion of the population that has used CAM at some point in their life has increased from 23% in 1987 to 52.8% in 2010. In 2010 26.3% had used CAM within the past twelve months compared to 10% in 1987 (9). Several unpublished surveys have indicated that the use of CAM is highly prevalent in chronic patient groups in Denmark (10), including people with Multiple Sclerosis (MS) (11-13).

The reasons for the popularity of CAM are manifold. In Denmark, results of recent studies among the general population have indicated that the typical CAM user is female, aged 25-64 years and has 13-14 years of schooling as educational background (9). Treatment of mild symptoms, treatment of chronic conditions, prevention, as well as a wish to participate actively in one's course of treatment are among the motives most often mentioned by Danish CAM users (8). However, knowledge about CAM use among people with chronic diseases is limited and more knowledge is required in order to enhance the understanding of the growing popularity within this field (7, 14).

1.2 STUDY AIMS

The research presented in the present PhD thesis has aimed to contribute to a better understanding of the popularity of CAM by providing new research-based knowledge regarding use and users of CAM among people with Multiple Sclerosis (MS) in Denmark. The overall aim of the PhD study was to investigate how and why people with MS in Denmark include CAM in managing their life with

a chronic disease and to discuss their experiences and beliefs linked to CAM use.

The study populations were based on the respective Nordic MS organisations' member registers and reflections upon the representativity of these registers versus the Nordic national MS populations are included in the results section as well as in the discussion section.

The objectives addressed in each of the five papers, on which this PhD thesis is based, are:

- To determine the prevalence of CAM use and motives related to CAM use among people with MS in Denmark, as well as in the four other Nordic countries, and to perform comparative analyses between the five countries (Paper I);
- To compare differences in characteristics of CAM users and non-users among people with MS in Denmark (Paper II);
- To compare differences in characteristics of subgroups of CAM users among people with MS in Denmark (Paper III);
- To explore views on risks of negative interactions between herbal medicine and conventional drug therapy among people with MS in Denmark who combine these two types of remedies (Paper IV);
- To explore treatment assumptions among people with MS in Denmark who use CAM exclusively (Paper V).

1.3 FORMALIA

1.3.1 AN INDUSTRIAL PHD PROJECT

The PhD project on which this thesis is based was performed as an industrial PhD project, meaning a collaboration between a university and an organization in the private sector. In this project, the collaboration took place between Department of Public Health at Copenhagen University and the Danish MS Society. The National Research Center in Complementary and Alternative Medicine at University of Tromsø, Norway provided a co-supervisor with specific knowledge of CAM research and the Norwegian, the Swedish, the Finnish and the Icelandic MS organisations took part in the collaboration.

The PhD project has combined a public health research interest in expanding the existing knowledge about the use of CAM in Denmark with a patient organization's interest in obtaining a deeper understanding of their members' interest in the field of CAM.

1.3.2 THE CONTENT OF THE PHD THESIS

The thesis presents and discusses the results from the three-year research project as well as relevant issues linked to the research process. It includes five published papers.

Thus the thesis contains:

- a presentation of the research approach – the mixed methods design, the theoretical foundation and the methods applied
- a presentation of the data sources – selection criteria and analyses of representativeness
- the main results of the five papers
- the overall results of the mixed methods study and a description of how the study has contributed to the existing knowledge in the field
- a discussion of themes derived from the analyses, including the application of relevant theoretical perspectives not presented in the papers
- a discussion of strengths and limitations linked to the research approach applied as well as to the data material
- a conclusion

1.3.3 LITERATURE SEARCHES

As the project has been conducted as a mixed methods project, where results from one part of the research process inform the initiation and design of a subsequent part, literature searches have been conducted in the initial phase of the project as well as during the research process (15). The literature searches have been conducted within the following themes:

- CAM use among people with MS, prevalence and motives
- Characteristics of CAM users and CAM non-users among people with MS
- Typologies of CAM users (in general, not only those linked to MS)
- Patients' beliefs, perceptions and convictions regarding risks linked to the combination of CAM and conventional medicine
- Patients' motives linked to exclusive use of CAM and foregoing of conventional medicine

Pubmed, Cinahl and PsychInfo were used as databases in the literature search. Key concepts were identified for each of the five searches and relevant search terms were found for each concept. As an example, the following concepts and MESH-terms were identified in relation to the Pubmed search linked to theme nr.1: "Multiple Sclerosis/epidemiology"[Mesh] OR "Multiple Sclerosis/therapy"[Mesh] AND "Complementary Therapies"[Mesh] and "alternative medicine".

Searches were initially performed on the terms individually and secondly by using Boolean "AND" and "OR". Furthermore, free-text searches were performed, using truncation, on the basis of the key concepts. In the free-text searches, related articles were included.

1.3.4 THE DEFINITION OF CAM

The definition of CAM is not obvious (16). The field is broad and constantly changing. Generally, CAM is defined relationally as being different from conventional medicine, although elements such as the level of evidence, the inclusion in public health care insurance or the way a certain treatment is perceived by the user have also been suggested as relevant criteria (17-19). A relational definition has been applied in this project, as the division between conventional medicine and CAM constitutes an important part of the data analyses. However, the boundaries between CAM and conventional medicine are not absolute, and specific treatment modalities defined as CAM at this point may, over time, become widely accepted as conventional, as for example chiropractic has been in Denmark since 1992.

In Denmark, nor internationally, no single definition of CAM exists. In this research project, I have chosen to follow the definition proposed by the American National Center for Complementary and Alternative Medicine (NCCAM) as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine" (1). I have found this definition relevant to apply in the project, partly because it is widely applied in international CAM research, and partly because it defines CAM relationally and leaves room for adaptation to specific cultural contexts, in this case a Nordic context. The criteria used in the analytical phase for categorizing specific treatment modalities as either CAM or conventional medicine are presented in section 2.2.1.

In the present research project, no distinction has been made between "complementary" and "alternative". In some parts of the literature, "complementary medicine" refers to use of CAM together with conventional medicine and "alternative medicine" re-

fers to use of CAM in place of conventional medicine (20, 21). However, such a distinction is not applicable in relation to a survey as it requires specific knowledge about the way a given CAM modality has been applied by the user. Therefore, CAM has in this project analytically been applied as one category.

1.3.5 TERMINOLOGY

Troughout the thesis I use the term “people with MS” when I refer to the target group in question – partly because it is a neutral term and partly because it is the term internationally applied within MS research. I refer to the term “user”, when I distinguish analytically between users and non-users of CAM. I use the term “patient” on a more general level, e.g. methodologically when referring to “a patient perspective” or in the discussion section when referring to “the empowered patient”. I also use the term “patient” when distinguishing between patient and practitioner, e.g. when referring to “patient-doctor communication”.

1.3.6 THE RELEVANCE FOR PUBLIC HEALTH RESEARCH

The relevance of addressing CAM as an important issue in public health research has increased both nationally and internationally over the last decades as the use of CAM among general populations, as well as within specific patient groups, has developed rapidly (22-25). In Denmark, the use of CAM has increased markedly over the past 25 years (9). Furthermore, recent developments have indicated that CAM research represents a field of growing importance in the Western world, not least within the EU countries, and that issues within the CAM field are relevant in a broader health care perspective (6). Thus, research within the CAM field may contribute to public health research by providing knowledge of general relevance, e.g. regarding patients’ treatment preferences, their attitudes towards various parts of the health care system, their motives for engaging in different types of treatments as well as their beliefs and convictions related to their various health care choices. Furthermore, the present research project has a specific focus on chronically ill patients – a focus of increasing relevance as the number of chronically ill patients is expected to grow markedly in Denmark as well as globally over the next 10-15 years (26, 27).

1.4 BACKGROUND

1.4.1 MULTIPLE SCLEROSIS

MS is a severe neurological disease, characterized by a chronic course of exacerbation and remission of symptoms, leading to severe disability (28). The absolute number of individuals with MS is increasing in the Western countries (29) and represents a substantial challenge to treatment, prevention, health promotion and rehabilitation.

People with MS face many challenges in their everyday life, like other groups of people with chronic illness (30, 31). The causes of MS are still unknown (28, 29) and there is hence no cure for MS. Medical treatment options are limited for some types of MS and treatments often have many side effects. In addition, MS is often characterized by a wide range of accompanying symptoms (28, 32).

1.4.2 PREVALENCE OF USE OF CAM AMONG PEOPLE WITH MULTIPLE SCLEROSIS

Several recent studies have indicated high prevalence of CAM use among people with MS (33-45). Internationally, survey results indicate that the prevalence of CAM use among people with MS ranges from 41% in Spain to 70% in Canada and 82% in Australia (39, 40, 46). In Denmark, results of previous small scale and unpublished studies among members of the Danish MS Society have until now suggested that the prevalence of CAM use lies within the range of

48-54% (11-13). Typically, people with MS who use CAM combine it with conventional medicine, although exclusive CAM use exists as well (the prevalence ranges from 10-30% in the literature) (33, 36, 40, 42, 44).

1.4.3 REASONS FOR USE OF CAM AMONG PEOPLE WITH MULTIPLE SCLEROSIS

The reasons for CAM use vary from treatment of concrete symptoms (12, 13, 34, 47, 48) to “bodily exploration” and development of strategies for disease coping (14, 37, 49-51). A number of studies have shown that CAM is often used for non-specific purposes among people with MS (36, 38, 49, 52), although a recent review found the main reasons for using CAM to be treatment of symptoms and disease modification (37). In Denmark, a few unpublished studies have suggested that CAM is used by people with MS primarily to relieve pain, fatigue and problems with balance and walking (12, 13). A recent Norwegian study has showed that CAM is also used for non-specific purposes by people with MS and as part of overall self-care management (49).

1.4.4 CHARACTERISTICS OF CAM USERS AMONG PEOPLE WITH MULTIPLE SCLEROSIS

Although results regarding background characteristics of CAM users among people with MS are not fully consistent, most studies have shown associations between use of CAM and gender (more women than men use CAM), high education, high income, low self-assessed state of health and long MS duration (34, 36, 38, 44, 53). Regarding age there is no concordance in existing studies of CAM use among people with MS; CAM use has been found to be associated with high age (42), as well as with low age (40), and some studies have found no associations (33, 53).

1.5 THE NEED FOR FURTHER RESEARCH

Whereas some knowledge exists regarding the prevalence of CAM use, the motives for CAM use and predictors for CAM use among people with MS internationally, little research has been carried out within this field of research in a Danish context. Hence, very little is known about how and why people with MS in Denmark use CAM.

As indicated above, the existing international literature indicates some variations regarding prevalence, motives and characteristics linked to the use of CAM among people with MS. The lack of consistency in the international literature points to the relevance of investigating the issue of CAM use among people with MS specifically within the national Danish context. Furthermore, the multitude of aspects presented in the existing international literature with regard to the use of CAM among people with MS points to the relevance of investigating this issue from different perspectives, using different methodological approaches. On this basis, the present study has applied a mixed methods research design with the aim of exploring this field of research and hence providing new knowledge about how and why people with MS in Denmark include CAM in managing their life with a chronic disease.

2. RESEARCH APPROACH, METHODS AND MATERIAL

2.1 THE MIXED METHODS PERSPECTIVE

2.1.1 THE OVERALL APPROACH

The overall research design applied in this study is a sequential mixed methods design, where quantitative and qualitative research methods have been integrated in a sequential and dynamic way (54). The study has been based on an overall exploratory approach in the sense that no predefined theoretical frame has been

applied. Analytically, the study has been based on an overall phenomenological approach, and specific tools for data gathering have been selected on the basis of the specific research questions – hence following the exploratory aim of letting data guide the methodological choices (54).

2.1.2 ABOUT MIXED METHODS DESIGNS

The combination of quantitative and qualitative methods

The combination of quantitative and qualitative research methods has long been discussed within the social sciences (55). Within the last couple of decades, a more integrated approach to the investigation of social phenomena has become common. Whereas a combination of quantitative and qualitative research methods, carried out as parallel use, has been applied for quite some years within the social sciences, the integration of the two approaches, as suggested by mixed methods research, has only recently gained broader acceptance (54-57).

Mixed methods research is the subject of methodological debate. There is agreement that mixed methods research describes research that integrates quantitative and qualitative methods in one single study or in a study of multiple phases (58). The combination can take place in some or all of the stages of the research project (59), e.g. sampling, data collection, analysis and description of results. Tashakkori and Creswell emphasize this by defining mixed methods as: "Research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or programme of inquiry." (60).

Bazeley underlines the difference between mixed methods and multi-methodology by emphasizing the non-parallel character of mixed methods research: "I tend to distinguish between mixed methods and multimethod, although if I need a generic term, I used mixed methods. Multimethod research is when different approaches or methods are used in parallel or sequence but are not integrated until inferences are being made. Mixed methods research involves the use of more than one approach to or method of design, data collection or data analysis within a single program of study, with integration of the different approaches or methods occurring during the program of study, and not just at its concluding point." (61).

In the present study, the aim has been to exceed the multi-methodological parallel use of different research methods. I have applied a sequential mixed methods research design (54), where quantitative and qualitative methods have been integrated at several stages in the research process – in the sampling, in the data collection, in the analysis and in the description of results.

MIXED METHODS WITHIN HEALTH SCIENCE

The use of mixed methods within the health sciences is relatively new. During the last decade, however, a growing interest has been seen regarding the relevance of using mixed methods research to obtain more comprehensive, integrated knowledge about complex health issues, e.g. in relation to chronic diseases (62). It has been argued that the multifaceted character of contemporary challenges within health care demands multifaceted methodological approaches, and that mixed methods research designs may offer such approaches (62). It has further been argued that mixed methods approaches are especially relevant within research in CAM due to the complex character of this area; for example, in the 2012 "Roadmap for European CAM Research", mixed methods research strategies are pointed out as highly relevant with regard to obtaining knowledge that reflects existing complexities and thereby real-world settings of health care (6).

2.1.3 THE SEQUENTIAL DESIGN

In the present study, a quantitative and a qualitative approach are implemented in two distinct phases. The first phase involves collecting and analyzing quantitative data. Based on a need to further understand the quantitative results, or to focus on specific issues emerging from the quantitative results, a second, qualitative phase is implemented that is designed to help explain and/or complement the initial quantitative results. This type of sequential mixed methods design uses a quantitative phase partly 1) to identify possible trends linked to a given research issue (e.g. prevalence of use of a specific treatment or patterns of combination use of different treatments) and partly 2) to inform the sampling plan and interview protocol applied in a subsequent qualitative phase that might provide knowledge about possible mechanisms or reasons behind identified trends (e.g. why some people or subgroups of people within a specific patient group deviate from official recommendations in their behavior) (54).

Given the fact that very little is known about how and why people with MS in Denmark use CAM, an initial survey was relevant in order to provide basic, statistical knowledge about prevalence of CAM use, motives for CAM use as well as characteristics of CAM users, non-users and different subgroups of CAM users. On the basis of such statistical data, relevant qualitative interview studies were conducted, where the research questions as well as the selection of informants were informed by the statistical data collected in the first phase. Papers I-III are based on the quantitative data derived from the first phase. Papers IV and V are based on the qualitative data derived from the second phase. Research issues approached in the two qualitative interview studies (Papers IV and V) were selected on the basis of trends/significant results identified in the quantitative phase. In the same way, informant groups used in the two qualitative interview studies were strategically selected on the basis of predictors identified in the quantitative phase. The issue of bias linked to this type of strategic selection of informants is discussed in section 2.3.3 and 4.4.1-4.4.2.

2.1.4 THE PHENOMENOLOGICAL APPROACH OF THE OVERALL STUDY

It has been debated how mixed methods research relates to various philosophical traditions. Creswell and Clark use the concept of "worldview" to describe the philosophical assumptions that guide the inquiries of a certain study and emphasize that there is no consensus as to whether a specific worldview fits a mixed methods study best (54). Various authors have offered worldview possibilities for mixed methods research, including the position that multiple paradigms may be used in mixed methods research (63).

Creswell and Clark distinguish between four different worldviews – the postpositivist, the constructivist, the participatory and the pragmatic. The present study is based on a pragmatic worldview. Combining a quantitative phase and a qualitative phase, one could argue that two worldviews are combined in the study – a postpositivist worldview, where the aim is deductively to test an a priori theory or hypothesis through empirical measurement, and a constructivist worldview where the aim is to inductively identify common understandings or patterns from the participants' subjective views (54). However, when aiming at integrating quantitative and qualitative approaches, I have based the study on a worldview that accommodates methodological pluralism. Therefore, I have based the study on a pragmatic worldview. The pragmatic worldview is exploratory and it is first and foremost characterized by focusing on the research questions asked rather than on the methods (54). This means that the re-

search process is oriented towards a dynamic application of methods of data collection and data analysis, rather than based on specific hypotheses or guided by specific preselected theories (such as feminist theories or racial theories). Within this exploratory approach, multiple methods of data collection are used – if relevant – to inform the problems under study, valuating both objective and subjective knowledge (54). In section 4.3.2, the issue of different worldviews within mixed methods research is further discussed.

Analytically, I have been inspired by a phenomenological approach. Fade (64) argues that the phenomenological approach is highly relevant within health care research when the aim is to investigate perceptions of a given situation or phenomenon within a specific group of health care users or practitioners. Aiming at describing and exploring how and why people with MS in Denmark include CAM in managing their life with a chronic disease, a phenomenological approach offers a frame of understanding that allows the patient perspective to be in focus. Phenomenology may be defined as the study of structures of consciousness as experienced from the first-person point of view, i.e. based on a persons' everyday activity in his/her surrounding life-world (65). Patton (66, 67) and Creswell (65) emphasize the phenomenological approach as a path to gain knowledge about the way human beings make sense of their experiences and the meaning they give to experiences within a certain context. By applying a phenomenological frame of understanding in the present study, I have aimed to gain knowledge about patients' reflections on how and why different treatments are chosen, used or foregone in their everyday life.

The phenomenological approach has been applied to the study's overall analytical frame of reference. One might question the applicability of a phenomenological approach in relation to quantitative research. However, as shown by e.g. Miles (68) and William (69), the phenomenological approach is not necessarily incompatible with quantitative research, but may contribute to enhancing the integration of quantitative and qualitative concerns in mixed methods studies by constituting a common frame of reference. In the present study, the phenomenological approach is most explicit in the two qualitative interview studies, but it has constituted an analytical frame of reference to the entire mixed methods study.

2.2 THE SURVEY

2.2.1 THE DEVELOPMENT OF THE QUESTIONNAIRE

THE AIM AND PREPARATION OF THE QUESTIONNAIRE

The aim of the questionnaire was to collect information about the respondents' use of CAM and conventional treatments within the past 12 months as well as relevant background characteristics in order to identify possible trends linked to the use of CAM among the respondents.

Two main sources of knowledge were included in the development of the questionnaire: previous survey research targeting use of CAM among people with MS in a Danish context (70, 71) and input from an expert group consisting of five Nordic neurologists with a specialization in MS and five representatives of the Nordic MS societies, who commented on the development of the questionnaire in several phases.

Firstly, the main content of the questionnaire was determined. Following the overall aims of the study, it was decided that the questionnaire should collect information about:

- The types of treatment modalities which had been used within the past 12 months;
- For which symptom/health issue the specific treatment modality had been used;

- If any side effects/adverse effects had been experienced in relation to the specific treatment modality used;
- How the specific treatment modality used for a specific symptom/health issue was assessed by the user.

Collecting information about these issues aimed partly at identifying possible trends linked to the prevalence of use of different treatment modalities as well as motives for use among the respondents, but also at identifying possible trends linked to the respondents' experienced outcomes from using different treatments. The latter aspect is less often included in questionnaire studies and I found it to be a relevant variable in an exploratory mixed methods approach as previous research has emphasized self-assessed outcomes as an important factor in developing personal treatment strategies among people with MS (50). From a phenomenological perspective, the inclusion of a self-assessed outcome variable was seen as a way to approach the aspect of the patients' experiences, embedded in an everyday context. Overall, the questionnaire was developed with the aim of gathering knowledge about the way the respondents link their treatment behavior to various motives as well as outcome assessments and thereby provide a basis for interpreting the use of CAM from a patient perspective.

In the preparation phase, experiences from previous research (70), as well as assessments from the expert group, were taken into consideration. Particularly, the importance of taking the challenges related to the MS symptomatology into account when performing questionnaire studies within this patient group was emphasized by the expert group. This aspect will be further described below in connection to the arguments for applying an internet-based questionnaire.

DEFINING THE VARIABLES

Background variables

The following background variables were included in the questionnaire: Gender, age, highest level of education, yearly income per person in each household, self-assessed state of health, self-assessed quality of life, years since diagnosis, treatment with disease-modifying drugs (DMD) for MS and prevalence of other conditions than MS (defined as one or more additional severe or chronic diseases). These background variables were selected partly on the basis of variables included in the Danish National Health Interview Survey (72) and partly on variables relevant specifically within the MS area (years since diagnosis, treatment with disease-modifying drugs) as they are typically applied in MS questionnaire studies in a Danish context (73, 74). Accordingly, the definition of the variables included in the present study were based on the abovementioned sources; e.g. the variables regarding self-assessed state of health and self-assessed quality of life, both consisted of single Likert-scale responses as applied in the Danish National Health Interview Survey.

Variables related to treatment use

The main aim of the questionnaire was to collect data about the respondents' use of CAM. However, as mentioned in section 1.3.4, no universal definition of CAM exists, and previous Nordic studies have shown a lack of consensus regarding the definition of CAM among respondents (75-77). Inspired by these experiences, the questionnaire was developed with the aim of collecting information about the use of conventional treatments as well as CAM treatments. The terms "conventional" or "CAM" were not applied in the questionnaire in order to avoid response bias related to

these specific terms. Specific treatment modalities labels (conventional as well as CAM) were listed in random order. This strategy also provided the opportunity of exploring the use of conventional and CAM treatments in combination.

For each treatment, participants were asked whether they used it and what were their motives for use. As mentioned in section 1.3.4, the definition of CAM treatments was based on the National Center for Complementary and Alternative Medicine's (NCCAM) definition of CAM as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine" (1). Some treatment modalities, such as psychotherapy, diet and massage, are regarded as either conventional or CAM, depending on the subtype of treatment modality in question (e.g. conventional massage, shiatsu massage or healing massage). Therefore, linked to these treatment modalities, the respondents were asked to specify the subtype of treatment modality in use and the treatment modality in question was accordingly defined as either CAM or conventional treatment in the analyses. Acupuncture is partly accepted within conventional medicine in some countries. However, it is still widely regarded as CAM within CAM research, also in the Nordic countries, and it was therefore defined as CAM in the analyses. The specific CAM treatment modalities as well as conventional treatment modalities used in the questionnaire were chosen on the basis of known prevalence of use in the Nordic general populations (3) as well as among MS patients specifically (11-13). Some treatment modalities were used by very limited populations (e.g. Samic medicine among the Northern Norwegian population) and were not listed among the pre-defined treatment modalities. Room was left open for addition of not pre-defined modalities by respondents.

A pre-defined list of motives was included in the questionnaire, based on known MS symptoms (32) as well as experiences within the expert group. A list of side effects was included, based on the most common side effects reported to the Danish Health and Medicines Authority (78). In connection to both variables, room was left open for addition of not pre-defined motives/side effects by respondents.

A variable of self-assessed outcomes linked to the treatments used (the way of linking the treatments used with various motives and self-assessed outcomes through programming are presented below) was included in the questionnaire. The variable was presented as a -3 to +3 Likert scale accompanied by guiding phrasing. No previous use of such health outcome assessment applied in questionnaires was found relevant and this element was brought much into focus in the cognitive validation of the questionnaire (see below).

Using an internet-based questionnaire

As mentioned above, previous research has pointed to the importance of taking different challenges linked to MS symptomatology into consideration when performing questionnaire studies within a group of MS patients. A Danish study has shown that MS patients may have problems with their motor skills, making it difficult for them to fill out questionnaires in paper form (50, 70, 79). Cognitive challenges may also constitute a challenge with regards to the quality of survey results - previous research has shown that MS patients may have difficulties in providing usable responses due to lack of logical perception (50, 70, 79).

Quite early in the process, I decided to use an internet-based questionnaire. Firstly, through validations of survey questions, use of an internet-based questionnaire may contribute to insuring data quality by limiting invalid responses by guiding the respondents

through validations. Secondly, the use of an internet-based questionnaire may contribute to insuring data quality by limiting the cases of unreadable written response as well as compensating for possible motor skill challenges linked to hand writing. Thirdly, the use of an internet-based questionnaire is time-efficient as data entry is done instantly by respondents. I estimated the risk of non-response due to lack of internet access as limited on the basis of current prevalence of internet access in the Nordic countries, showing that more than 90% of the Nordic populations have internet access (80-82). Despite this high percentage of internet access, a certain risk of non-response due to lack of internet access or lack of technical skills must be taken into consideration. While the aspect of Internet demographics cannot be influenced, precautionary measures were taken against the risk of non-response due to lack of technical abilities by illustrating the process of entering the questionnaire with screen shots in the letter sent to all respondents. Furthermore, a telephone number and an email address were provided in the letter, giving access to technical assistance. The aspect of selection bias will be further discussed in section 4.4.1-4.4.2.

THE PROGRAMMING

The questionnaire was programmed in Inquisite IBM – a software program that allows far-reaching skip-sections and branching of questions. The questionnaire was programmed, so that the respondent in the first section of questions was asked which treatment modalities he/she had used within the past 12 months. As described above, a predefined list of the most commonly used conventional treatments among people with MS and the most commonly used CAM treatments in the Nordic countries was presented together with an open text field for addition of not pre-defined modalities by respondents. Secondly, the responses to the first section of questions were used to construct the next section of questions through branching. Thus, for each selected treatment modality in the first section of questions, a question was constructed, asking the respondent for which symptoms/health issues he/she had used the specific treatment modality. Thirdly, the responses to the second section of questions were used to construct a third section, asking the respondent to assess the perceived outcomes of the use of a specific treatment modality for a specific symptom/health issue on a seven point scale from -3 - +3.

In this way, the questionnaire offered a dynamic, ongoing construction of individually accommodated questions. While such dynamic construction of questions may entail the possibility of targeting individual treatment issues – in this case the use of specific treatment modalities, as well as motives and experienced outcomes linked to the use of the given specific treatment modalities - it may also entail a risk of confusing the respondents by the complexity in the three-section constructions of questions. Therefore, a thorough phase of validation through cognitive interviews was performed.

VALIDATION BY COGNITIVE INTERVIEWS

Cognitive interviewing aims at identifying and analyzing sources of response error in survey questionnaires by focusing on the cognitive processes used by respondents when answering questions in a survey. The purpose of the method is to gain knowledge about the way subjects understand questions applied, both across subjects and in the way intended by the investigator (83). The interviewer is not focused on the subject's cognitive processes for their own sake, but as related to the validity of the survey question (83). Izumi et al. (84) point out cognitive interviewing as a relevant tool to examine whether quantifiable questions capture the qualitative

characteristics of respondents' experiences. They emphasize the relevance of applying a phenomenological approach when performing cognitive interviewing as a validation of survey questions; the participants' interpretations of the survey questions are seen as affected by their prior experiences, and the interviewer may benefit from asking the participants to share their experiences relevant to the specific question. In this way, the interviewer may elicit the participants' responses and thereby explore their understanding and interpretation of the questions as linked to their prior experiences within a certain context (84).

In the present study, three sessions of cognitive interviews were performed with three test-informants participating in each session. The 9 test-informants all had MS. Overall, the application of cognitive interviewing was inspired by a phenomenological approach as outlined above – focusing on strengthening the questions' ability to link to the participants' prior experiences. Concretely, the process of cognitive interviewing was based on the model by Tourangeau (85), focusing on four phases of the cognitive process that is followed during an interview: Comprehension of the questions, retrieval from memory of relevant information, judgement/estimation process and response process. The participants were encouraged to verbalize thoughts as much as possible while answering questions ("think aloud" procedure), including sharing experiences relevant to specific questions. In cases of difficulties in this matter, specific additional follow-up questions were included, generally referred to as "verbal probes" (86-88).

The three sessions of cognitive interviews showed that difficulties were mainly related to the comprehension of the questions (regarding aspects of phrasing linked to the variables of socio-economic status, quality of life, time of diagnosis, disease-modifying treatment of MS, treatment modalities used, experienced outcomes and experienced side effects). A number of changes in phrasing were made and help text was revised/incorporated with the aim of informing the respondent clearly about the aim of the overall questionnaire as well the aim of specific questions. In a few cases, difficulties were detected linked to the judgement/estimation process and to the response process. Most importantly, this was the case with regards to the experienced outcome variable, which was constructed as an individually accommodated variable, based on responses in two prior sections of the questionnaire. Challenges were partly linked to specific sub-variables in the prior sections and partly to the act of assessing specific treatments that were used in combination with other treatments. Changes were made in the phrasing of the questions and help text was incorporated, emphasizing that outcomes from a specific treatment linked to a specific symptom/health issue might be difficult to assess, but that the respondent should assess as far as he/she found it possible. An additional response category, labeled "Don't know/cannot be answered" was furthermore included.

The questionnaire was revised after each of the three sessions. The third session showed no challenges for the test-informants in the comprehensibility of the survey questions.

PILOT TESTING

Following the process of cognitive interviewing, the questionnaire was tested in March 2011 among 400 randomly selected respondents from the Danish MS society's member register. A letter with an invitation to participate in the survey was sent, including a personal code to access the survey on a specific internet address, which was also presented in the letter. Two reminders were sent. An open text field for comments was inserted at the end of the questionnaire. Based on survey responses and comments from respondents, the pilot testing indicated that:

- The response rate was 50-55% in all age groups
- The questionnaire was comprehensible
- The questionnaire's length was acceptable
- The size of letters should be further enlarged in some of the questionnaire batteries (this issue was also indicated in the cognitive interviews)

Sub-variables had to be added in relation to certain treatment modalities in order to clarify the labeling of conventional or CAM for the analyses (e.g. in relation to massage, diet, and psychotherapy)

More response categories had to be added to the list of treatment goals (not symptom-based variables)

Technical guidance should be provided in the letter sent to respondents and optimally a hotline of technical support should be offered

VALIDITY AND RELIABILITY

As presented above, cognitive interviewing and pilot testing was applied to assess and strengthen the validity and reliability of the questionnaire. The face validity of the questionnaire (does the questionnaire appear to measure what it claims to?) was assessed through pre-testing and through the cognitive interviewing. Through the three phases of cognitive interviewing in Danish, as well as through pre-testing of the four other Nordic versions of the questionnaire (the process of translation is presented below), the coherence between the aim of the questionnaire (as phrased in the introductory text) and the overall content was assessed and an acceptable face validity of the questionnaire was ensured. The content validity of the questionnaire (does the questionnaire represent a relevant range of possible items necessary for meeting the study aim?) was assessed through a recurrent involvement of the expert group. The expert group (consisting of neurologists as well as representatives of the Nordic MS organizations – ensuring a clinical perspective as well as a more coping-related perspective) was presented with the questionnaire at several points in the process, ensuring that aspects relevant to the overall study aim were included in the questionnaire.

Through the cognitive interviewing process, pre-testing and pilot testing of the questionnaire, the reliability of the questionnaire (are the questions/questionnaire items constructed in an explicit and comprehensible way that enhances the probability of achieving similar results if repeating the questionnaire under similar circumstances?) was assessed. The majority of the questions appeared to have an acceptable reliability, being interpreted consistently and unambiguously by respondents over time and across national borders (comparative analyses of the Nordic survey data indicated consistence in the interpretation of the questionnaire items). However, the question linked in the questionnaire to the assessment of self-experienced outcome of specific treatments used for specific symptoms/health issues, and presumably also the variable linking a specific treatment modality used to one or more specific symptoms/health issues, encompass a degree of complexity that makes them likely to represent a questionable level of reliability. This aspect can be regarded as a logical consequence of the phenomenological approach in the overall mixed method study design, entailing an immanent aspect of exploration and thereby an initiation of reflection within the respondent.

Reflections upon the internal and external validity of the overall study results are further discussed in sections 4.4.1-4.4.2.

TRANSLATION

The questionnaire was developed in Danish. After the assessment by the expert groups, validation by cognitive interviews and pilot

testing, the questionnaire was translated into the four other Nordic languages. The translation process proceeded as follows: The Danish version of the questionnaire was translated into each of the other four Nordic languages by persons with a health care background and with the specific Nordic language as mother tongue and Danish as first foreign language. Hereafter, the questionnaires were translated back to Danish by persons with a health care background and with Danish as mother tongue and the specific Nordic language as first foreign language. Mostly, medical students were used for these tasks. The original Danish version was compared to each of the four translated Danish versions and revisions were made in the Nordic versions. Challenges were mostly encountered with regard to the Finnish version due to differences in the construction of sentences, making it difficult to maintain the dynamic construction of personally accommodated questions as described above. However, solutions were found in collaboration with linguistic consultants and the five questionnaires were found to constitute a valid basis for parallel data collection, followed by comparative data analyses.

COLLECTION OF DATA MATERIAL

The survey was conducted in all five Nordic countries during the period from April 2011 to June 2011. A letter with a personal code was sent to all randomly selected respondents from the respective MS societies, asking the respondents to fill out the questionnaire online by using this personal code. Receiving the questionnaire in paper form was not an option. Reminders to non-respondents were sent twice. The response rates varied from 50.9 in Norway to 61.7 in Iceland.

Due to data protection rules it was not possible to use the national MS registers for the sampling. Hence, in all five Nordic countries, the MS societies' member registers constituted the populations from which the samples were selected.

2.2.2 SAMPLES AND RESPONDENTS

NORDIC MS EPIDEMIOLOGY AND REGISTERS

The amount of knowledge related to MS epidemiology differs in the five Nordic countries. Studies of MS prevalence are not consistent, although recent studies have indicated prevalence in the range of 170-190 per 100.000 in Denmark, Norway and Sweden (89). In Finland and Iceland prevalence is estimated to be in the range of 105-120 per 100.000. There are no obvious explanations to these differences, but they may be linked to differences in existence and/or quality of national MS registers as presented in the following.

In Denmark, all persons with an MS diagnosis are registered in the national MS register (90). The register comprises data on 11.189 patients alive. In Norway and Sweden, the national MS registers have a lower degree of coverage. The Norwegian register comprises data on 4810 patients alive. It is estimated by the register that the national MS prevalence is similar to the Danish and that about 8000 persons with MS are living in Norway. In Sweden, the national MS register comprises data on 11.893 patients alive and it is estimated that about 17.000 persons with MS are living in Sweden. In Finland and Iceland, no national MS registers exist, but it is estimated that about 7.000 persons with MS are living in Finland (91) and about 430 in Iceland (92).

Hence, the most accurate knowledge about MS epidemiology among the Nordic countries relates to the Danish context. Within the Swedish and Norwegian contexts, register data exist, however with a lower degree of coverage. Within the Finnish and Icelandic contexts, only data from the MS organizations' member registers are available.

THE MS ORGANIZATIONS' MEMBER REGISTERS VERSUS THE NATIONAL MS POPULATIONS

In Table 1, analyses of representativeness regarding distribution of gender and age are presented, comparing the Nordic MS organizations' member registers and the national MS registers in Denmark, Norway and Sweden.

Table 1 Characteristics of the register populations

	Denmark		Norway		Sweden		Finland		Iceland	
	OR	(CI)	OR	(CI)	OR	(CI)	OR	(CI)	OR	(CI)
National register	nr	11189	4810		11893		Data missing		Data missing	
Male n (%)	3479 (31.1)		1521 (31.6)		3437 (28.9)		Data missing		Data missing	
<40 years n (%)	2199 (19.6)		650 (13.5)		2542 (21.4)		Data missing		Data missing	
41-60 years n (%)	5543 (49.9)		2546 (53.1)		6163 (52.0)		Data missing		Data missing	
>60 years n (%)	3419 (30.5)		1510 (31.4)		3189 (26.6)		Data missing		Data missing	
Member register (OR vs national register)	nr	7133	4593		3435		5845		394	
Male n (%)	2078 (29.2)	0.94 (0.88-0.99)	1321 (28.8)	0.91 (0.83-0.98)	579 (23.8)	0.82 (0.75-0.91)	1534 (25.9)	Data missing	Data missing	
<40 years n (%)	1404 (19.7)	1.01 (0.93-1.08)	862 (18.8)	1.39 (1.24-1.55)	362 (14.9)	0.70 (0.62-0.78)	1224 (20.9)	Data missing	Data missing	
41-60 years n (%)	3607 (50.6)	1.02 (0.97-1.07)	2370 (51.6)	0.97 (0.91-1.04)	1251 (51.4)	0.99 (0.92-1.07)	3070 (52.6)	Data missing	Data missing	
>60 years n (%)	2112 (29.7)	0.97 (0.91-1.03)	1361 (29.6)	0.94 (0.87-1.03)	821 (33.7)	1.27 (1.16-1.38)	1551 (26.5)	Data missing	Data missing	

As shown by the table, the data of the Danish MS organization's member register (holding a fairly high degree of coverage) is representative of the national MS register (the latter covering all people in Denmark diagnosed with MS). The Norwegian and Swedish MS organization's member registers represent skewnesses regarding both gender and several age groups compared to the national MS registers. According to the Norwegian national MS register, people <40 years may very well be underrepresented in the register. However, the limited degree of coverage of the member registers and the national registers in both countries makes it difficult to interpret the skewnesses in relation to the national populations. Hence, the representativeness, concerning age and gender, of the Norwegian, Swedish, Finnish and Icelandic samples, compared to the national populations, is unclear.

The high external validity of the Danish register data constitutes one of the main reasons why the present study has focused on exploring the use of CAM in a Danish context. The low external validity related to the register data in the four other Nordic countries must be taken into consideration as a bias related to the comparative analyses presented by Paper I.

SAMPLE SIZES

Based on power calculations for comparative analyses of CAM use prevalence, 1050 people with MS were selected randomly from each of the member registers of the Swedish, Norwegian and Finnish MS societies. The power calculations were based on an 80% level of statistical power, a 5% significance level and an expected response rate of 60%. The sample sizes included expected dropout due to members who were deceased, lived abroad or did not have MS (registration error). As additional comparative analyses (CAM users vs. CAM non-users and selected subgroups of CAM users vs. each other) were to be performed on the Danish data material, the practically/economically (with regards to the distribution of letters) highest possible number of participants - 3500 people with MS - were selected randomly from the member register of the Danish MS society. In Iceland, the sample included the total number of all individuals who appeared in the member register of the national MS society. In Iceland it was not possible to distinguish between members with MS and supporting members in the register. Letters were therefore sent to all members of the Icelandic MS society (n=780), asking only people with MS to respond to the questionnaire.

REPRESENTATIVENESS OF SURVEY RESPONDENTS

Analyses of representativeness among survey respondents showed no major differences regarding distribution of gender and

age between the national member registers and the samples. However, as shown in Table 2, participants of <40 years and those >60 years were slightly underrepresented in the Danish data when comparing respondents with sample groups. Participants of 41-60 years were consequently slightly overrepresented. These differences were borderline significant.

Table 2 Characteristics of the study population

	Denmark	Norway	Sweden	Finland	Iceland
	OR (CI)	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Member register (sex and age known)	7123	4591	2495	5845	584*
Male n (%)	3278 (46.1)	1212 (26.4)	1199 (48.1)	1214 (20.8)	Data missing
<40 years n (%)	1404 (19.7)	862 (18.8)	362 (14.5)	1224 (20.9)	Data missing
41-60 years n (%)	3607 (50.6)	2370 (51.6)	1251 (50.1)	3070 (52.5)	Data missing
>60 years n (%)	2112 (29.7)	1359 (29.6)	822 (32.7)	1551 (26.5)	Data missing
Survey sample (OR vs. member register)	9361	1014	1046	1045	584*
Male n (%)	576 (29.8) 0.99 (0.91-1.08)	261 (25.8) 0.99 (0.88-1.10)	253 (24.3) 0.99 (0.85-1.16)	274 (26.2) 1.01 (0.87-1.16)	Data missing
<40 years n (%)	871 (19.9) 1.01 (0.91-1.12)	389 (18.6) 0.99 (0.83-1.17)	137 (13.0) 1.01 (0.81-1.23)	222 (21.3) 1.01 (0.86-1.18)	Data missing
41-60 years n (%)	1690 (50.3) 0.99 (0.92-1.06)	1201 (51.3) 0.99 (0.88-1.11)	536 (51.3) 0.99 (0.88-1.12)	953 (92.9) 1.01 (0.90-1.12)	Data missing
>60 years n (%)	1001 (29.8) 1.00 (0.90-1.09)	305 (30.1) 1.01 (0.89-1.16)	353 (33.7) 1.00 (0.86-1.15)	270 (25.8) 0.97 (0.84-1.12)	Data missing
Respondents (OR vs. survey sample)	1885 (55.5)	516 (50.9)	617 (59.1)	551 (52.7)	236 (61.5)*
Male n (%)	520 (27.9) 0.96 (0.85-1.08)	150 (29.0) 1.01 (0.81-1.26)	149 (23.8) 0.99 (0.79-1.24)	138 (25.0) 0.95 (0.75-1.20)	54 (22.8)
<40 years n (%)	351 (18.6) 0.94 (0.81-1.08)	176 (14.7) 0.78 (0.59-1.05)	81 (13.0) 0.86 (0.64-1.14)	109 (18.7) 0.97 (0.80-1.13)	61 (26.3)
41-60 years n (%)	1047 (56.1) 1.11 (1.01-1.22)*	304 (58.9) 1.14 (0.96-1.37)	373 (59.5) 1.16 (0.98-1.36)	523 (58.6) 1.11 (0.95-1.31)	137 (57.8)
>60 years n (%)	468 (25.1) 0.84 (0.74-0.95)*	136 (26.4) 0.87 (0.69-1.10)	173 (27.8) 0.81 (0.66-1.01)	125 (22.7) 0.88 (0.69-1.11)	38 (18.0)

In the present study, survey data from Norway, Sweden, Finland and Iceland are only included in Paper I as part of the comparative analyses between the five data sets (see section 2.2.2 regarding the external validity of these data). Papers II-V are based on the Danish survey data.

2.2.3 ANALYTICAL APPROACH

Comparative analyses between the five Nordic countries included prevalence of total CAM use, prevalence of use of specific CAM modalities as well as of specific symptoms/health issues addressed by CAM users as rationale for use. As none of the five countries constitute a natural a priori reference, I found it most correct to employ a changing reference. Thus, in Paper I, the country with the lowest prevalence of a specific variable was used as reference for presenting Odds Ratios (OR), indicating the comparative relations for each variable. The same principle was applied in Paper III, where the subgroup of CAM users with the lowest prevalence of a specific variable was used as reference. Comparative analyses between subgroups of CAM users included background variables and selected variables related to treatment use. The same variables were included in the comparative analyses in Paper II, focusing on CAM users and CAM non-users. In this Paper, CAM non-users constituted the reference.

P-values were not included in any of the tables due to risk of visual complexity, but statistical significance was determined by interpretation of 95% Confidence Intervals (CI) and is marked by “+” in the tables. As the choice of performing multiple comparisons entails the risk of multiple significance and thereby finding statistical significance that is due to random chance rather than real differences, I have been highly aware of interpreting significant differences in single variables in an overall perspective. In the discussion (section 4.4.1), the aspect of multiple significance is further discussed.

2.3 COMPLEMENTING QUANTITATIVE ANALYSES WITH QUALITATIVE INTERVIEW STUDIES

2.3.1 PAPER IV

Following the principles of the sequential mixed methods design, the results of the survey formed the basis for the choice of issues for further qualitative investigation as well as the selection of informants for the two qualitative studies. The exploratory approach of the sequential mixed methods design suggests that the identification of themes for further investigation in a second qualitative phase is based on an overall assessment of the quantitative results.

In the present study, multiple aspects have been taken into consideration in this identification, as suggested by Creswell and Clarke who emphasize the relevance of significant as well as non-significant results, outlier results, surprising results or group differences (54).

The results of the survey pointed to the fact that the large majority of CAM users among people with MS use CAM as an add-on treatment, most often as a combination of CAM and conventional drug therapies (CDT). The results of the survey further showed that this group of combination users had a significantly higher prevalence of other conditions than MS compared to both of the other groups, increasing the probability of a high overall intake of CDT. At the same time this group had the highest prevalence of use of herbal medicine. Combined with the fact that communication with medical doctors about CAM treatments used did not occur in 37.7% of cases, that the assessment of side effects of CAM treatments was unclear in 23.3% of cases, and that the risk of negative interactions between herbal medicine and CDT is well known and well documented in the literature (93-97), the issue of possible negative interactions regarding the widespread combination of CDT and natural remedies was identified as a relevant issue for further qualitative investigation (the specific research questions of paper IV and V are presented in the articles, sections 3.2.4 and 3.2.5).

I also applied the results of the preceding survey to perform a strategically selected group of informants. Statistical analyses of the survey data indicated that users of CAM and CDT in combination differed significantly from CAM non-users on five variables: they were more often <40 years, women, educated at bachelor level or higher, belonging to a household with high income and affected by multiple diagnoses. While this analysis has not been included in any of the five papers, the data are presented in Table 3.

Table 3 Background characteristics of users of CAM and CDT and CAM non-users

		CAM non-users (n=898)			Users of CAM and farma (n=718)			
		n=	(%)	OR	n=	(%)	OR	(CI)
Gender	Female	583	(64.9)	1	582	(81.1)	1.24	(1.07-1.45) +
Age	<40	147	(16.4)	1	172	(24.0)	1.46	(1.15-1.86) +
	41-60	486	(54.1)	1	389	(54.2)	1.00	(0.84-1.18)
	>60	259	(28.8)	1	156	(21.7)	0.75	(0.60-0.94) -
Highest level of education	Primary school	182	(20.3)	1	73	(10.2)	0.50	(0.37-0.67) +
	PS + two years or more	602	(67.0)	1	467	(65.0)	0.97	(0.83-1.13)
	Bachelor or more	107	(11.9)	1	177	(24.7)	2.07	(1.59-2.68) +
	Not answered	7	(0.8)	1	1	(0.1)	0.17	(0.02-1.45)
Yearly income pr. person in household	<200.000 kr	371	(41.3)	1	236	(32.9)	0.79	(0.65-0.96) -
	200.000-400.000 kr	357	(39.8)	1	322	(44.8)	1.12	(0.94-1.35)
	>400.000 kr	70	(7.8)	1	91	(12.7)	1.63	(1.17-2.25) +
	Not answered	99	-11	1	62	(8.6)	0.78	(0.56-1.09)
Self-assessed state of health	Low (1-2)	67	(7.5)	1	65	(9.1)	1.21	(0.85-1.73)
	Medium (3-5)	558	(62.1)	1	468	(65.2)	1.04	(0.89-1.22)
	High (6-7)	270	(30.1)	1	184	(25.6)	0.85	(0.69-1.05)
Self-assessed QoL	Low (1-2)	62	(6.9)	1	53	(7.4)	1.06	(0.73-1.56)
	Medium (3-5)	466	(51.9)	1	383	(53.3)	1.03	(0.86-1.21)
	High (6-7)	363	(40.4)	1	279	(38.9)	0.96	(0.79-1.15)
Years since diagnosis	> 2	34	(3.8)	1	34	(4.7)	1.25	(0.77-2.03)
	2-10	330	(36.7)	1	315	(43.9)	1.12	(0.99-1.43)
	<10	493	(54.9)	1	356	(49.6)	0.90	(0.76-1.06)
Medical treatment of MS	No (total)	474	(52.8)	1	313	(43.6)	0.82	(0.69-0.98) -
	No - deselected	103	(11.5)	1	78	(10.9)	0.94	(0.69-1.29)
Other conditions	Yes	537	(59.8)	1	541	(75.3)	1.26	(1.08-1.47) +

I chose to apply three of these five variables as inclusion criteria for the qualitative interview study: age, gender and level of education, leaving out income and prevalence of multiple diagnoses. The choice of leaving out the income variable was based on the fact that income was assessed as average income per person in household and thereby saying less about the individual informant. Prevalence of multiple diagnoses was excluded based on the decision to focus primarily on the informants' use of treatments linked to their MS. Hence, as a result of this strategic selection, the group of

informants was limited to young women with a high level of education. Within this selection, those who had reported combined use of CDT and herbal medicine within the past twelve months, and who had accepted in their survey response to be contacted for an interview, were included in the final group of informants. This selection process provided a group of 13 informants. Semi-structured interviews were conducted with 11 informants, as two informants declined to participate in the study.

2.3.2 PAPER V

The results of the survey pointed to the fact that, although representing a minority (9.8%), statistical significant differences were found between the group of exclusive CAM users (defined as having used no conventional treatments for their accompanying symptoms) and other subgroups of CAM users, as presented in Paper III. The group of exclusive CAM users had by far the highest prevalence of foregoing DMD for MS (which was defined as a background variable in the questionnaire). The use of special diet was also the highest in this group – special diet being a typical self-initiated daily life style intervention. The group of exclusive CAM users had the lowest prevalence of experienced side effects as well as the lowest prevalence of doubt related to the occurrence of side effects related to CAM use. At the same time, this group also demonstrated the highest prevalence of doubt related to assessment of effect of the CAM treatments, as well as the lowest prevalence of positive assessment of CAM use. These characteristics suggested a group of CAM users among the respondents with high personal commitment to making choices about treatment strategies. I chose to further investigate the issue of exclusive CAM use by exploring overall beliefs and underlying convictions within the group of exclusive CAM users. This was done by applying the concept of “treatment mechanisms”, defined as the processes through which the treatment interventions are assumed (by e.g. a patient or a practitioner) to lead to an outcome (98, 99). This concept will be further presented in section 2.4.2.

As for Paper IV, the informants for this qualitative interview study were selected on the basis of the survey results. In the group of survey respondents who had informed to have used CAM exclusively (n=94), 24 respondents reported to have also foregone DMD for MS and thereby used CAM in total exclusivity. In their survey response, 7 of these 24 survey respondents had not accepted an invitation to participate in a qualitative interview study and could not be contacted due to rules of data privacy. The remaining 17 informants accepted to be interviewed. The 7 non-informants did not differ considerably from the 17 informants regarding gender, age and types of CAM treatments used.

2.3.3 THE STRATEGIC SELECTION OF INFORMANTS IN MIXED METHODS STUDIES

The process of strategic selection of informants applied in the present study entails a challenge regarding selection bias. In a sequential mixed method design, as in this study, it is important to be aware of the criteria used for informant selection (54). The aim of the sampling procedure is not to avoid selection bias by selecting informants randomly. Rather, the aim is to perform a purposeful sampling procedure that links the results of the quantitative strand with the subsequent qualitative phase by using the quantitative results to guide the sampling of informants. Hence, the aim of strategic sampling is to select a group of informants that may help refine and explain given quantitative results more in depth (54, 57, 62).

The sampling of informants can follow the identification of a theme, including all informants with characteristics linked to the theme. This is the case in Paper V, where all exclusive CAM users,

who had also foregone the use of DMD for MS, were included in the informant group. The sampling of informants can also be guided by quantitative results about respondent characteristics within a larger group of respondents. In Paper IV, the sampling of informants was based on those variables that significantly discriminated users of CAM and CDT in combination from CAM non-users, thereby aiming at identifying informants with characteristics “typical” of the group. This kind of strategic sampling procedure has been applied in different ways in other sequential mixed method studies (100, 101). Aiming at identifying and purposefully selecting a group of informants to explore in depth a certain theme derived from a quantitative study, these sequential mixed method studies entail a certain aspect of representativeness in their sampling procedures that is usually only associated with quantitative research. This is also the case in Paper IV. Conversely, as described in section 2.2.1, a certain qualitative aspect was integrated in the questionnaire used in the present study, e.g. through the inclusion of a self-assessed outcome variable linked to the patients’ everyday experiences. This integration of methodological elements from quantitative and qualitative research is immanent in the sequential mixed methods design. Possible limitations linked to this approach, e.g. connected to selection bias, will be further discussed in sections 4.3.2 and 4.4.1-4.4.2.

2.4 THE INTERVIEW STUDIES

2.4.1 THE OVERALL APPROACH

The overall analytical focus in the two qualitative interview studies was to investigate how two specific groups of informants, consisting of strategically selected people with MS, make sense of their experiences with regard to two specific issues: 1) possible risks related to the use of herbal medicine and CDT in combination, and 2) the choice of using CAM exclusively. In the overall mixed methods perspective, the aim of the two interview studies was to explore aspects of MS patients’ experiences with CAM use, based on their lived experiences with various treatments.

The analytical frame of reference, on which the two interview studies were conducted, was phenomenological. However, I have not followed one specific phenomenological methodology. Following a pragmatic approach to mixed methods research, I have applied tools of data collection, as well as of data analyses, that support the exploration of the specific research questions that emerged from the quantitative phase. In connection to data collection, I have applied a program theory tool (51, 98, 99, 102) and in connection to data analyses, I have applied the concept of meaning condensation as described by Kvale (103), combined with Hycner’s (104) analytical steps for phenomenological analysis. These approaches are further presented in the following.

2.4.2 THE USE OF PROGRAM THEORY

Program theory was originally developed within social policy as a tool to research and evaluate social policies and programs (51, 98, 99, 102, 105, 106). A program theory is an explication of the underlying assumptions about how a program (i.e. a social intervention) is expected to work (99). Within social evaluation theory, it has been suggested that formulating the program theory of a given social intervention – meaning making the underlying assumptions behind the intervention explicit – may be a relevant way to guide the evaluation of such intervention (99, 105).

In the two interview studies, I have applied program theory as a tool to facilitate the articulation of the informants’ various beliefs and assumptions related to their use of CAM treatments. The use of program theory in the present study is hence not to be regarded as a theoretical approach, but as a methodological approach – a

tool for supporting the data collection. Program theory is explicitly applied in Paper V, where the program theoretical notion of “treatment mechanisms” is included, whereas it is more implicitly applied in Paper IV where it has constituted a tool to facilitate the informants’ reflections regarding the specific issue risks of interactions between herbal medicine and CDT.

Various conceptual frameworks have been developed over recent years, suggesting ways to interpret/understand patients’ views and experiences related to CAM use (98, 107-109). These frameworks have emphasized the relevance of investigating whether specific beliefs about health and disease – meaning basic assumptions of how different interventions work - among the patients influence their views and experiences related to CAM use.

Such basic assumptions of how different interventions work constitute a program theory (also called intervention theory (98)). Although developed within social policy, program theory has in recent years been applied within health care research. E.g. it has been applied within research in integrative MS treatment as a tool to explore differences and similarities in basic assumptions about health and disease between conventional health care providers and CAM practitioners (51, 102). In these studies, program theory has proven valuable as a tool to facilitate the articulation of informants’ basic assumptions of how different interventions work.

In the present interview studies, I have built on this previous use of program theory by applying it as a tool to facilitate the informants’ assumptions of how conventional as well as CAM treatments work. By focusing on their experiences with different types of treatments, I have aimed at implicitly asking the informants to formulate of their personal program theory within a health care context, thereby gaining an insider perspective of their beliefs and assumptions of how different treatments used have led to different outcomes experienced.

If applying program theory in a health care context, such assumptions are often referred to as the “treatment mechanisms” – meaning the processes through which the treatment interventions are assumed to lead to an outcome (51, 98, 99, 102). By applying program theory in the process of data collection in the interview studies, I have aimed to explore the informants’ overall assumptions regarding treatment of MS. In this way, the use of program theory has supported the phenomenological approach by aiming at gaining knowledge about the informants’ perceptions of fundamental issues linked to treatment of MS, based on their everyday-life experiences.

2.4.3 THE ANALYTICAL APPROACH

In both interview studies, semi-structured in-depth qualitative interviews were conducted. The conceptual frame of the interviews was based on a program theoretical approach as outlined above, meaning that the main focus of the interviews was to gain insight into the participants’ treatment assumptions by exploring their experiences with different types of treatments and their beliefs on how the treatments used have led to the experienced outcomes. The interviews addressed these issues by asking the participants to relate broadly to how they had experienced the impact of various factors/interventions on their health. They were asked to relate how they assumed different factors/interventions had been of relevance with regards to the outcomes experienced. The interviews were only marginally structured, allowing as far as possible for narrative aspects of the participants’ reflections to have a strong presence. However, a certain structuring of the interviews was executed, assuring that a breadth of aspects (including i.e. physical, social and mental aspects) connected to the participants’ treatment assumptions was included in the interview.

Two methodological approaches were integrated and applied in the phase of data analysis. Overall, I used Hycner’s guidelines for phenomenological analysis of interview data (104) as an analytical frame. Hycner emphasizes a number of essential steps to follow, as well as a number of essential aspects to be considered, when aiming at capturing a phenomenon being studied through qualitative interviews. I supplemented Hycner’s guidelines with the process of meaning condensation as described by Kvale (103) specifically for the process of extracting themes from the data material. In both interview studies, my aim was to elaborate the quantitative findings by identifying consistent themes in the patient perspectives, linked to the two issues being studied in Papers IV and V, respectively.

Guided by these two methodological approaches – Hycner’s guidelines for phenomenological analysis and meaning condensation as describes by Kvale - the process of data analysis applied in the two interview studies was based on the following steps: In-depth summaries of the interviews were prepared. The summaries were read through and the recordings were listened to in order to get a sense of the whole. Following Hycner, the aim of this phase was to bracket as much as possible my own meanings and interpretations and let the interview speak for itself as well as to establish a context for the emergence of themes in the following process of analysis (104). Thereupon, clusters of meaning units as expressed by the informants were determined. A cluster of meaning unit could for instance be “The unpredictability of MS” or “The lack of medical treatment”. Those clusters of meaning units relevant to the given research question were selected for meaning condensation. In this phase, redundancies among the clusters of meaning units were eliminated (104). Meaning condensation was applied to abridge the meanings expressed by the informants into themes. Following Kvale, all aspects of the informants’ beliefs and assumptions, to which they had ascribed meaning in the interviews, were included in the analyses (103). The clusters of meaning units were thematized into overall themes for each interview. Finally, consistent themes were identified on the basis of the entire qualitative interview study, pointing to possible aspects of general relevance to the given research question.

2.4.4 FORMALITIES

The length of the interviews varied from 35-65 minutes. The interviews were conducted as one-time, open-ended interviews by telephone (reflections upon limitations in telephone interviews are included in section 4.4.1. The interviews were audio-recorded and illustrative quotations were extracted from the audio-recordings and used in the papers. The informants were guaranteed anonymity.

2.5 THE ORGANIZATION OF THE SEQUENTIAL MIXED METHODS DESIGN

The overall organization of the sequential mixed methods design, consisting of five papers, can be described as follows: The analyses of the data material from the five Nordic countries regarding the prevalence of CAM use and motives for CAM use constituted the content of Paper I. The analyses of the Danish data material regarding characteristics of CAM users and non-users and regarding subgroups of CAM users constituted the content of Paper II and Paper III, respectively. The analyses presented in Paper III on subgroups of CAM users inspired the issue addressed in Paper IV, in which the selection of informants was based on analyses presented in Paper II on CAM users and CAM non-users. The analyses presented in Paper III also inspired the issue addressed in Paper V, supported by analyses presented in Paper I on the Norwegian and Swedish data.

The selection of respondents in Paper V was based on the analyses presented in Paper III.

2.6 ETHICAL CONSIDERATIONS

All surveys and interview studies were approved by data protection agencies or committees on health research ethics as required in all five Nordic countries.

All respondents and informants participating in the study were guaranteed anonymity. All respondents were provided with information about the study aim, either as a written introduction to the survey or orally before beginning the interview. In relation to the interviews, informants were informed that they could withdraw at any time and that all information shared with the researcher would be confidential. Pseudonyms were used for informants' names when linked to quotes.

3. RESULTS

3.1 MAIN RESULTS FROM PAPER I

Aims: The aim of the study was to describe and compare: 1) the types and prevalence of complementary and alternative medicine (CAM) treatments used among individuals with Multiple Sclerosis (MS) in the Nordic countries; 2) the types of conventional treatments besides disease modifying medicine for MS that were used in combination with CAM treatments and 3) the types of symptoms/health issues addressed by use of CAM treatments.

Methods: An internet-based questionnaire was used to collect data from 6455 members of the five Nordic MS societies. The response rates varied from 50.9% in Norway to 61.5% in Iceland.

Results: A large range of CAM treatments were reported in use in all five Nordic countries. Supplements of vitamins and minerals, supplements of oils, special diet, acupuncture and herbal medicine were among the CAM treatment modalities most commonly used. The prevalence of the overall use of CAM treatments within the last twelve months varied from 46.0% in Sweden to 58.7% in Iceland. CAM treatments were most often used in combination with conventional treatments. The conventional treatments that were most often combined with CAM treatment were prescription medication, physical therapy and over-the-counter (OTC) medications. The proportion of CAM users who reported exclusive use of CAM (defined as use of no conventional treatments besides disease-modifying medicine for MS) varied from 9.5% in Finland to 18.4% in Norway. In all five Nordic countries CAM treatments were most commonly used for non-specific/preventative purposes such as strengthening the body in general, improving the body's muscle strength and improving well-being. CAM treatments were less often used for the purpose of improving specific symptoms such as body pain, problems with balance and fatigue/lack of energy. See Tables 4a+4b.

Conclusions: A large range of CAM treatments was used by individuals with MS in all Nordic countries. The most commonly reported rationale for CAM treatment use focused on improving the general state of health. The overall pattern of CAM treatment use was similar across the five countries.

3.2 MAIN RESULTS FROM PAPER II

Aims: The aim of this study was to investigate differences in socio-economic characteristics between CAM users and CAM non-users among people with MS in Denmark as well as differences in characteristics related to the use of CAM among CAM users and the use of conventional treatments among CAM non-users.

Table 4a+4b Comparison of use of CAM modalities among people with MS in the Nordic countries

CAM modality	Denmark (n=967)				Norway (n=272)			
	n	(%)	OR	(CI)	n	(%)	OR	(CI)
Supplements of vitamins and minerals	759	(78.5)	1.36	(1.02-1.82) *	101	(66.5)	1.16	(0.83-1.61)
Supplements of oils	423	(43.7)	1.74	(1.18-2.56) *	104	(38.2)	1.52	(0.98-2.34)
Special diet	101	(10.7)	1.53	(0.90-2.60)	40	(14.7)	1.20	(0.66-2.20)
Acupuncture	151	(15.6)	2.39	(1.47-3.98) *	51	(18.7)	2.07	(1.67-4.93) *
Herbal medicine	112	(11.6)	1.87	(1.13-3.08) *	31	(11.4)	1.84	(1.01-3.32) *
Reflexology	107	(11.1)	7.52	(2.75-20.60) *	4	(1.5)	1	
Yoga	106	(10.9)	1.40	(0.88-2.22)	25	(9.2)	1.17	(0.65-2.10)
Meditation	91	(9.4)	1.60	(0.93-2.70)	24	(8.8)	1.50	(0.80-2.82)
Alternative massage	49	(5.1)	2.76	(1.09-6.99) *	5	(1.8)	1	
Cranio sacral therapy	45	(4.6)	2.53	(0.99-6.44)	5	(1.8)	1	
Other supplements (probiotics, superfood, protein supplement, antioxidants, aloeic supplement, colloid silver, enzymes, fiber supplement, amino acid supplement, glucosamine, Mitochondrial Energy Optimizer, Gélé Royale)	42	(4.3)	2.01	(0.62-6.58)	10	(3.7)	1.70	(0.46-6.29)
Healing	41	(4.2)	6.49	(1.56-26.98) *	20	(7.3)	11.25	(2.61-48.57) *
Homeopathy	28	(2.9)	1.67	(0.64-4.36)	15	(5.5)	3.18	(1.14-8.86) *
Amalgam removal	22	(2.3)	1		11	(4.0)	1.78	(0.85-3.71)
Qi gong	18	(1.8)	1		9	(3.3)	1.78	(0.79-4.00)
Naprapathy	0	(0.0)	no data	no data	14	(5.1)	3.94	(1.28-12.11) *
CAM treatments with prevalence of use below 5% in all countries								
Denmark: Tai Chi, kinesiologi, Feldenkrais method, osteopathy, hypnosis, ortomolekylær behandling, cannabis, vacuum therapy, body SDS therapy, thought field therapy, Ayur vedic medicine, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy								
Norway: Tai Chi, Feldenkrais method, kinesiologi, osteopathy, ortomolekylær medicin, Bioresonans/quantum medical treatment, Mensendick treatment, aroma therapy, thought field therapy, Ayur vedic medicine, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy								
Sweden: Tai Chi, Feldenkrais method, osteopathy, kinesiologi, hypnosis, bioresonans/quantum medical treatment, antroposofisk medicin, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy								
Finland: Tai Chi, colonic therapy, kinesiologi, cannabis, lymphic therapy, osteopathy, CCSVI surgery, alternative psychotherapy								
Iceland: Tai Chi, aroma therapy, Feldenkrais method, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy								
Use of one or more alternative/energetic treatments (including traditional Chinese acupuncture, reflexology, shiatsu massage, healing massage, cranial sacral therapy, healing, homeopathy, spiritual psycho therapy, Qi gong, Tai Chi and kinesiologi)	223	(23.1)			56	(20.6)		
Number of CAM modalities in use	29				29			

CAM modality	Sweden (n=288)			Finland (n=306)			Iceland (n=139)		
	n	(%)	OR (CI)	n	(%)	OR (CI)	n	(%)	OR (CI)
Supplements of vitamins and minerals	171	(59.3)	1.03 (0.74-1.44)	244	(79.7)	1.39 (1.00-1.91) *	80	(57.5)	1
Supplements of oils	88	(30.6)	1.21 (0.79-1.89)	123	(40.2)	1.60 (1.04-2.44) *	35	(25.2)	1
Special diet	49	(17.0)	1.39 (0.77-2.50)	57	(18.6)	1.52 (0.86-2.71)	17	(12.3)	1
Acupuncture	34	(11.8)	1.81 (1.13-3.21) *	20	(6.5)	1	29	(20.8)	1.19 (1.13-5.41) *
Herbal medicine	31	(10.7)	1.29 (0.86-1.94)	19	(6.2)	1	18	(12.9)	2.09 (1.08-4.10) *
Reflexology	9	(3.1)	2.13 (0.65-6.98)	14	(4.5)	3.11 (1.01-9.57) *	15	(10.8)	7.34 (2.39-22.53) *
Yoga	42	(14.6)	1.06 (1.00-3.15) *	24	(7.8)	1	32	(23.0)	2.94 (1.67-5.17) *
Meditation	33	(11.4)	1.93 (1.07-3.54) *	18	(5.9)	1	19	(13.7)	2.32 (1.18-4.56) *
Alternative massage	14	(4.8)	2.64 (0.84-7.94)	15	(4.9)	2.67 (0.96-7.42)	8	(5.7)	3.33 (1.02-9.57) *
Cranio sacral therapy	8	(2.8)	1.51 (0.49-4.88)	0	(0.0)	no data	17	(12.2)	6.65 (2.40-18.41) *
Other supplements (probiotics, superfood, protein supplement, antioxidants, aloeic supplement, colloid silver, enzymes, fiber supplement, amino acid supplement, glucosamine, Mitochondrial Energy Optimizer, Gélé Royale)	28	(9.7)	4.50 (1.55-15.87) *	15	(4.9)	2.27 (0.68-7.97)	3	(2.2)	1
Healing	17	(5.9)	9.03 (2.07-39.44) *	2	(0.6)	1	17	(12.2)	18.71 (4.26-82.11) *
Homeopathy	5	(1.7)	1	10	(3.3)	1.68 (0.68-3.77)	7	(5.0)	2.96 (0.80-9.50)
Amalgam removal	8	(2.8)	1.22 (0.54-2.77)	8	(2.6)	1.55 (0.51-2.61)	7	(5.0)	2.21 (0.93-5.20)
Qi gong	30	(10.4)	5.60 (1.07-10.19) *	0	(0.0)	no data	0	(0.0)	no data
Naprapathy	11	(3.8)	2.82 (0.92-8.28)	4	(1.3)	1	0	(0.0)	no data
CAM treatments with prevalence of use below 5% in all countries									
Denmark: Tai Chi, kinesiologi, Feldenkrais method, osteopathy, hypnosis, ortomolekylær behandling, cannabis, vacuum therapy, body SDS therapy, thought field therapy, Ayur vedic medicine, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy									
Norway: Tai Chi, Feldenkrais method, kinesiologi, osteopathy, ortomolekylær medicin, Bioresonans/quantum medical treatment, Mensendick treatment, aroma therapy, thought field therapy, Ayur vedic medicine, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy									
Sweden: Tai Chi, Feldenkrais method, osteopathy, kinesiologi, hypnosis, bioresonans/quantum medical treatment, antroposofisk medicin, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy									
Finland: Tai Chi, colonic therapy, kinesiologi, cannabis, lymphic therapy, osteopathy, CCSVI surgery, alternative psychotherapy									
Iceland: Tai Chi, aroma therapy, Feldenkrais method, Birgitta Bruner's treatment, CCSVI surgery, alternative psychotherapy									
Use of one or more alternative/energetic treatments (including traditional Chinese acupuncture, reflexology, shiatsu massage, healing massage, cranial sacral therapy, healing, homeopathy, spiritual psycho therapy, Qi gong, Tai Chi and kinesiologi)	48	(16.7)		33	(10.8)	1	43	(30.9)	
Number of CAM modalities in use	26			22			28		

Methods: An internet-based questionnaire was used to collect data from 3361 patient members of the Danish MS society. A letter with a personal code was sent to all respondents, asking them to fill out the questionnaire online. Reminders to non-respondents were sent twice and the final response rate was 55.5%. Statistical associations were presented as odds ratios and with respective 95% confidence intervals.

Results: People with MS in Denmark use a wide range of CAM treatments for a variety of reasons. CAM users were more likely to be of female gender, 18-40 years of age, educated at bachelor level or above and have a high income compared to CAM non-users ($p < 0.05$). CAM users more often addressed non-specific/preventive treatment purposes through their use of CAM treatments, they communicated less often with a medical doctor about the CAM treatments used, and they experienced less side effects as well as less positive effects from the CAM treatments used when

tered, in-depth qualitative interviews were conducted with a strategic selection from the survey respondents. The study was inspired by a phenomenological approach and emerging themes were extracted from the data through meaning condensation.

Results: Four themes characterized the informants' views on risks of negative interactions when combining herbal medicine and CDT: 1) 'naturalness' in herbal medicine; 2) 'bodily sensations' as guidelines; 3) trust in the CAM practitioner; 4) lack of dialogue with medical doctor.

Conclusions: Generally, the combination of herbal medicine and CDT was considered by the informants to be safe. In particular, they emphasized the importance of their own bodily sensations as a warrant of safety. A trustful relation to the CAM practitioner furthermore made some of them feel safe in their use of herbal medicine and CDT in combination. The informants' use of bodily sensations as a non-discursive risk assessment may be a relevant element in understanding these issues.

MAIN RESULTS FROM PAPER V

Aims: A survey conducted among members of the Danish MS society has indicated that a minor proportion of these patients choose to forego all types of conventional treatments and use complementary and alternative treatment (CAM) exclusively. This paper draws on a qualitative follow-up study with the aim of gaining knowledge about the choice of using CAM exclusively by exploring treatment assumptions among a group of exclusive CAM users.

Methods: The study was inspired by a phenomenological approach. Semi-structured in-depth qualitative interviews were conducted with 17 participants, using program theory as analytical tool, and emerging themes were extracted from the data through meaning condensation.

Results: Four themes characterised the participants' treatment assumptions: 1) conventional medicine uses chemical substances that affect the body in negative ways; 2) CAM treatments can strengthen the organism and make it more capable of resisting the impact of the MS disease; 3) the patient's active participation is of significant importance to the healing process; 4) bodily sensations can be used to optimize the choice of appropriate treatments.

Conclusions: This paper indicates that the participants' exclusive use of CAM may reflect an embracement of CAM rather than a rejection of conventional medicine. Health personnel, patient organizations and health authorities within the MS field may benefit from being aware of possible changes in general attitudes towards conventional treatment interventions, e.g. with regards to the role of health enhancement.

4. DISCUSSION OF FINDINGS

4.1 THE OVERALL RESULTS

The overall results of the five papers indicate that among the Danish respondents the use of CAM is widespread - every second has used CAM within the past twelve months. CAM treatments are most often combined with conventional treatments and are most often used for non-specific/preventive purposes. Results regarding the use of CAM among the Danish respondents are consistent with results within the other four Nordic respondent groups, although some differences exist regarding the use of specific CAM modalities and regarding the prevalence of exclusive CAM use. Limited external validity related to the Norwegian, Swedish, Finnish and Icelandic register data constitutes a bias in the comparative analyses.

Analyses of the Danish survey data showed that among the respondents, users of CAM are more often women, they are more

often below 40 years, and they have more often obtained a high level of education compared to CAM non-users. There are few differences in characteristics of users when comparing subgroups of CAM users among the Danish respondents.

Among a selected group of Danish respondents, who combine herbal medicine and conventional drug therapies, the combination is generally considered to be safe due to the "natural" basis of herbal medicine. However, these informants' use of bodily sensations may be seen as a non-discursive risk assessment. Among Danish respondents, who use CAM exclusively, the choice of using CAM exclusively does not seem to represent a principled rejection of conventional medicine, but appears to be the result of the these informants' overall assessment, weighing beliefs and experiences regarding positive and negative impact of different types of treatments.

The overall results of the study indicate that the majority of people with MS in Denmark include a diversity of treatments in the managing of their life with a chronic disease, and that the motives for doing so are often embedded in a wish to strengthen a preventive and enhancing approach to treatment.

4.2 THE CONTRIBUTION TO EXISTING KNOWLEDGE

Previous research has indicated a high prevalence of CAM use, as well as a large variation of CAM modalities in use, among people with MS in the Western world (35-40, 46, 110, 111). Overall, the results of the present study support these previous findings by indicating a widespread use of CAM treatments among people with MS in Denmark as well as in the other Nordic countries.

With regards to the types of CAM modalities used, the results of the present study support previous findings that have pointed out supplements of vitamins and minerals, supplements of oils, herbal medicine, special diets, acupuncture and yoga as the most popular CAM modalities among people with MS (34-38, 46, 47, 112). However, the present study adds a focus on the distinction between CAM elements and non-CAM elements within specific treatment modalities that are usually defined as CAM (massage) or usually defined as conventional treatment (psychological intervention/psychotherapy). By applying a distinction that takes different "versions" of a specific treatment modality into consideration, the results of the present study suggest that involvement of aspects beyond the treatment modality itself may contribute to a more diverse and varied description - and thereby possibly a more accurate interpretation - of patients' treatment choices. The motives for CAM use among people with MS found in the present study include motives of specific as well as of general nature; the study results hereby contribute to previous research results (36-38, 46, 49, 52, 113, 114) by emphasizing that general health issues may constitute an important type of motive for CAM use.

The socio-economic characteristics of CAM users, found among the Danish respondents, are supported by comparable studies regarding gender, level of education and income (34, 36, 38, 53). However, the results of the present study are not consistent with previously reported associations between use of CAM and low self-reported health status or long MS duration among people with MS (33, 38, 42, 44, 53). Thereby, the results of the present study adds to the existing knowledge by indicating that CAM use is not necessarily associated with the level of disability among people with MS, possibly emphasizing the relevance of acknowledging the strengthening/preventive aspect of motives for CAM use. The characteristics found in the present study concerning variables related to CAM use are to some extent supported by previous findings; the prevalence of communication with a medical doctor about CAM use is relatively high in the present study (53.7%)

compared to other studies that have indicated that the major part of respondents do not to inform their medical doctor about their CAM use (41, 42). The low prevalence of experienced side effects from CAM use (15.8%) is comparable to findings from similar studies (33, 34) as is the prevalence of mainly positive outcome assessments of CAM use (33-35).

Whereas many studies have investigated predictors for CAM use, often by comparing CAM users with CAM non-users, only a limited number of studies have explored differences between subgroups of CAM users. No previous studies have investigated this issue among people with MS. Adams et al. have shown differences in characteristics when comparing CAM users from different geographical areas (115) as well as when comparing those using oral complementary medicines and those using alternative practitioners (116). Davis et al. have found differences when comparing adults who used CAM for health promotion and adult who used CAM to treat illness (117). Similar results have been shown by Grzywacz et al. (118) and by Kannan et al. (119). Differences in user characteristics regarding the use of specific CAM modalities have been shown by Pedersen et al. (120). The results of the current study add to the existing knowledge about typologies of CAM users by showing differences in characteristics of CAM users when basing the division of groups on the way the patients combine CAM and conventional treatments.

The analyses of the interview data indicated that among patients combining herbal medicine and CDT, possible risks of negative interactions were not subject to extensive reflection. Previous studies among CAM users in general have indicated similar tendencies, showing that the perception of CAM as risk-free is prevalent (97, 121-123), and that CAM users often consider CAM to be low-risk due to its 'natural' basis (121, 122, 124). A few studies have investigated users' beliefs and/or perceptions regarding the safety of use of herbal medicine specifically, indicating a similar trend [31-34]. The findings of the present study support these findings, indicating that the informants regard the combination of herbal medicine and CDT as being safe, not least based on the element of naturalness in herbal medicine. However, the results of the present study add to the existing knowledge by emphasizing bodily sensations as an important warrant of safety from a user's point of view. Thereby, the study suggests that the informants' way of addressing the issue of safety in a non-discursive way through the use of bodily sensations may contribute a clarifying perspective on the absence of reflection indicated by this and similar studies. Emphasizing the aspect of patients' use of bodily sensations, the study may also contribute to the interpretation of communicative challenges between patients and medical doctors regarding CAM by pointing to possible different epistemological approaches among patients and medical doctors, respectively.

No previous studies have investigated exclusive CAM use among people with MS, and the study has contributed with new knowledge on this field. A few studies have investigated the choice of foregoing conventional treatment among cancer patients (125-127). These studies show that a perceived severity of conventional treatment side effects, a wish of not harming or damaging the body, a high need for decision-making control, and strong beliefs in holistic healing appear to affect the decision by patients to forego some or all conventional cancer treatments. Such findings are widely supported by the findings of the current study. Previous studies have also emphasized that foregoing conventional treatment is not necessarily an indicator of distrust of the medical system, but rather a reflection of many personal factors (125, 127).

A study by Astin showed that among individuals in the general American population, those who relied primarily on alternative

forms of health care showed a different profile from those who used alternative medicine more in conjunction with conventional treatments (128). Primary reliance on alternative forms of medicine was predicted by a desire for control over health matters as well as by a belief in the importance and value of one's inner life and experiences (128). These findings are widely supported by the results of the present study, the latter suggesting that the choice to rely primarily or solely on CAM may refer to overall beliefs and convictions about health. Similar results were found in an English study of patient non-compliance in general, emphasizing that an apparently irrational act of non-compliance from the doctor's point of view may be a very rational action when seen from the patient's point of view, focusing on patients' assumptions and the personal and social circumstances within which they live as crucial to their decision-making (129). In a study among people with chronic benign conditions, Brien et al. found no patients who totally rejected use of conventional medicine in favor of CAM (130). Some patients used CAM solely for specific illnesses while using conventional medicine for other problems. Brien et al. emphasized the aspect of returning to use of conventional medicine after having used CAM as a neglected, however important, issue of research (130).

The results of the present study suggest that returning to conventional medicine may be a relevant issue for further research, as the informants did not reject such returning and indicated a dynamic approach to their use of various treatment modalities. The present study has contributed to existing knowledge by showing that the choice of using CAM exclusively may be linked to certain assumptions of treatment mechanisms by the informants, pointing out i.a. the issue of sustainability as an important aspect. Thereby the study has emphasized that foregoing of conventional medicine does not necessarily represent a rejection of conventional medicine, but may rather represent a favouritism of CAM in an overall assessment of advantages and disadvantages.

4.3 STRENGTHS AND LIMITATIONS IN THE OVERALL APPROACH

4.3.1 THE EXPLORATORY APPROACH

Use of CAM among people with MS in Denmark has been subject of very limited previous research. A few studies on people with MS in a Nordic context have been conducted, focusing on specific aspects of CAM use from a qualitative perspective. Hence, aiming at gaining knowledge about the use of CAM among people with MS in Denmark from an overall perspective, no obvious hypotheses could be established prior to the initiation of the present study, emphasizing the relevance of applying an exploratory approach.

The exploratory approach allowed for a multitude of aspects to be included in the study. The survey was developed with the aim of including whatever aspect of CAM use relevant to the respondents, and the interview studies were based on the results of the survey and not on pre-selected issues. Thereby, the exploratory approach entailed the opportunity of conducting the study with emphasis on the patient perspective. Constituting an open and inclusive frame of research, the exploratory approach however also entailed the risk of fragmenting the research process. Within an exploratory approach, the selection of aspects/issues for further investigation may be a challenge. In the present study, a certain element of fragmentation has been entailed by the exploratory approach.

4.3.2 THE SEQUENTIAL, MIXED METHODS DESIGN

The sequential, mixed methods design applied in the study provided a tool to frame the exploratory approach. This research design offered a dynamic research approach, where the qualitative study was based on what was learned from the initial quantitative

phase. Thereby, the sequential, mixed methods design supported the exploratory approach by allowing initially for a broad patient perspective to be present, but provided at the same time a tool to identify specific issues of relevance through strategic selection. Furthermore, the sequential, mixed methods design allowed for both quantitative and qualitative methods to be used and integrated, supporting the exploratory approach by investigating the research issue from different perspectives and thereby securing a breadth in the data collected.

While the sequential, mixed methods design constituted a relevant and useful design for an exploratory approach to the investigation of CAM use among people with MS in Denmark, it also entailed a number of challenges regarding the methodological stringency and coherence. Aiming at combining and integrating quantitative and qualitative methods, the sequential mixed methods design is difficult to anchor in a specific philosophical tradition. The widespread reference within mixed methods research to a pragmatic worldview (54) reflects this difficulty. Whereas specific philosophical traditions, such as post-positivism or constructivism, are based on certain terminologies and certain frameworks for ensuring scientific rigour, mixed methods research risks compromising the scientific rigour by relating to a diversity of traditions. This aspect has constituted a challenge in the present study. The sequential design has been time-consuming due to the two phases included in the study, and many resources have been allocated to the “practical” integration of the quantitative and qualitative strands. Thereby, fewer resources have been allocated to the theoretical integration, potentially challenging the scientific coherence and stringency of some parts of the study. This issue will be further elaborated in section 4.4.

4.3.3 THE PHENOMENOLOGICAL APPROACH

One of the ways in which I have aimed at establishing a methodological coherence in the study has been through the phenomenological approach, applied to the overall study. Even though the phenomenological approach has been most explicit in the qualitative interview studies, I believe that it has constituted a common frame of understanding that has supported the integration of the quantitative and the qualitative strands.

The phenomenological approach has supported the overall study aim by allowing the patient perspective to be in focus and by facilitating an exploration of patients’ perceptions linked to CAM use in the survey and notably in the qualitative interview studies. The phenomenological approach has supported the collection of data that are linked to patient experiences and patients’ real life situations. A challenge linked to the application of a phenomenological approach and a phenomenological methodology has been the possible presence of cognitive deficiency among participants. A phenomenological approach presupposes an ability to reflect upon lived experiences, as well as the ability to articulate these, among participants – an ability that is often affected among people with MS. Hence, it can be discussed whether an approach of greater methodological diversity could have generated more comprehensive data. An approach such as grounded theory might have offered useful approaches; the inclusion of different data sources from participants (e.g. diaries, observations, mail correspondence) could have provided a broader and more faceted data material. However, a grounded theory approach entails a high degree of complexity in the research process, making it very challenging to integrate with a quantitative strand.

Within a phenomenological approach, as within qualitative research in general, it is a challenge to establish and assess aspects

such as validity and reliability. It may also be a challenge to detect or prevent researcher induced bias. Even though these terms are primarily linked to quantitative research, reflections upon the trustworthiness are pertinent to the entire mixed methods study. As mixed methods research may entail the risk of compromising methodological stringency due to the unclear anchoring in philosophical traditions, I will - in the following - discuss the trustworthiness of the overall project with the aim of strengthening the transparency of the research process.

4.4 TRUSTWORTHINESS

Trustworthiness may be used as an overall notion to relate to the scientific rigour of a study (131, 132). The notion of trustworthiness is often applied within mixed methods research with the aim of bridging the different terminologies linked to evaluation of scientific rigour within quantitative and qualitative research methods, respectively (62, 132). Whereas concepts such as validity, reliability and generalizability are often applied within quantitative research, the terminology within qualitative research varies depending on the tradition in which the research is conducted.

Guba (133) and Shenton (following Guba) (134) suggest four criteria to be considered in pursuit of trustworthiness in a qualitative study, that correspond to criteria traditionally applied within quantitative research. These criteria are:

- credibility (corresponds to internal validity);
- transferability (corresponds to external validity/generalizability);
- dependability (corresponds to reliability);
- confirmability (corresponds to objectivity).

By establishing these four pairs of criteria, Guba and Shenton present a frame for evaluation of trustworthiness that applies to mixed methods research, as it embraces four basic aspects of common relevance for quantitative and qualitative research. In the following, I will use these four pairs of criteria to discuss the trustworthiness of the overall mixed methods study.

4.4.1 INTERNAL VALIDITY/CREDIBILITY

Internal validity is the question of whether a study measures what is intended. The survey aimed at investigating trends in use of CAM among people with MS. As described in section 2.2.1, various measures were taken to strengthen the test validity of the questionnaire; a thorough process of developing of the questionnaire, including a pilot test of 400 Danish respondents, three sessions of cognitive interviews as well as the application of skip-sections and branching, made it possible to collect data of rather high complexity among the respondent group, consisting of persons with physical as well as cognitive limitations. Although it cannot be assured that all respondents have understood the questions in the exact same way, the preparations undertaken have contributed considerably to the quality of data. However, some parts of the questionnaire entailed challenges in relation to the internal validity. In addition to the descriptive variables, the questionnaire aimed at collecting information about the respondents’ experienced outcomes. While this aspect contributed relevant information to the study’s overall exploratory approach, it may also have weakened the internal validity by applying a quantitative methodology to investigate patient experiences – forcing a subjective assessment to be stated within a standardized frame. E.g. the internal validity linked to the experienced outcomes variable was potentially weakened by the fact that outcomes could only be assessed as linked to the individual treatment modality and not as part of an integrated

treatment approach. Therefore, these responses were not interpreted independently, but as trends within an overall mixed methods perspective.

When asking about use of treatments within the past 12 months in a questionnaire, recall bias must be taken into consideration, not least within a group of respondents where the prevalence of cognitive challenges is higher than among the general population. This aspect was specifically taken into consideration in the validation of the questionnaire/the sessions of cognitive interviews.

Whereas the application of an internet-based questionnaire may have challenged the external validity (this will be further commented below), it has possibly strengthened the internal validity of the survey results. Previous questionnaire research among people with MS (70) has shown that data quality is likely to be weakened due to unreadable and/or irrational responses. This risk has been markedly reduced through the application of an internet-based questionnaire.

A challenge to the internal validity of the survey results is the risk of multiple significance. As described in section 2.2.3, the comparative analyses of the survey data were based on interpretation of 95% confidence intervals. I have been aware of interpreting significant differences in single variables as trends in an overall perspective, but no analytical precautions were taken against the risk of multiple significance, which weakens the internal validity of results. Different precautions could have been taken, e.g. application of a lower level of significance or a correction. In table 8, the results from Paper II regarding background characteristics of CAM users and non-users are presented as an example. Additional analyses are presented, based on a 0.03/0.01 level of significance and based on Holm's correction for multiple significance. The table shows that significant differences are maintained when the level of significance is lowered to 0.03 and 0.01. When applying Holm's correction for multiple significance, differences become borderline significant or non-significant regarding three of the seven variables. This aspect must be taken into consideration as a reservation linked to the analyses presented and it emphasizes the importance of interpreting the significant differences found in the entire study as trends in an overall perspective.

Table 8 Background characteristics of CAM users and CAM non-users – additional analyses

		CAM users (n=907)				CAM non-users (n=898)					
		n (%)	OR (CI)	p*	Level of significance 0.05	Level of significance 0.03	Level of significance 0.01	Holm's correction	n (%)	OR	
Sex	Female	762 (78.8)	1.21 (1.05-1.39)	0.007	*	*	*	0.126	1	583 (64.9)	1
Age	<40	237 (24.5)	1.49 (1.19-1.87)	0.0004	*	*	*	0.008	*	147 (16.4)	1
	41-60	222 (23.9)	0.99 (0.85-1.16)	0.974						466 (54.1)	1
	>60	207 (21.4)	0.74 (0.61-0.92)	0.004	*	*	*	0.08	1	259 (28.8)	1
Highest level of education	Primary school	108 (11.1)	0.55 (0.42-0.71)	0.00003	*	*	*	0.00069	*	182 (20.3)	1
	PS + two years or more	618 (63.9)	0.95 (0.82-1.10)	0.516						602 (67.0)	1
	Bachelor or more	217 (24.5)	2.05 (1.61-2.62)	1.00E-08	*	*	*	2.40E-07	*	107 (11.9)	1
	Not assessed	4 (0.4)	0.53 (0.15-1.83)	0.385						7 (0.8)	1
Yearly income per person in household	<200.000 kr	309 (31.9)	0.77 (0.64-0.92)	0.004	*	*	*	0.076	1	371 (41.3)	1
	200.000-400.000 kr	437 (45.1)	1.13 (0.96-1.34)	0.132						357 (39.8)	1
	>400.000 kr	121 (12.5)	1.60 (1.17-2.18)	0.002	*	*	*	0.042	*	70 (7.8)	1
	Not assessed	91 (9.4)	0.85 (0.63-1.15)	0.399						99 (11)	1
Self-assessed state of health	Low (1-2)	83 (8.5)	1.15 (0.82-1.61)	0.411						67 (7.5)	1
	Medium (3-5)	604 (62.4)	1.01 (0.89-1.16)	0.945						558 (62.1)	1
	High (6-7)	279 (28.9)	0.95 (0.79-1.16)	0.671						270 (30.1)	1
Self-assessed QoL	Low (1-2)	61 (6.3)	0.91 (0.63-1.31)	0.628						62 (6.9)	1
	Medium (3-5)	500 (51.7)	0.99 (0.85-1.16)	0.964						466 (51.9)	1
	High (6-7)	308 (31.1)	1.02 (0.86-1.20)	0.834						363 (40.4)	1
Years since diagnosis	> 2	47 (4.9)	1.28 (0.81-2.01)	0.376						34 (3.8)	1
	> 2-10	415 (42.9)	1.16 (0.98-1.38)	0.075						330 (36.7)	1
	< 10	484 (50.5)	0.91 (0.78-1.06)	0.242						493 (54.9)	1
DMM* for MS	No (eval)	460 (47.6)	0.90 (0.77-1.05)	0.195						474 (52.8)	1
	No - desinstit	126 (13.0)	1.13 (0.86-1.49)	0.364						103 (11.5)	1
Other conditions	Yes	662 (68.4)	1.14 (0.99-1.32)	0.069						537 (59.8)	1

Whereas internal validity relates to quantitative research, credibility may be seen as the qualitative investigator's equivalent concept (135). The aspect of credibility in a qualitative study relates to the

question of how congruent the findings are with reality. Shenton points to a number of criteria relevant for a qualitative study's credibility (134).

Firstly, adoption of research methods well established. In the present study, methods well established as well as less well established have been applied. The phenomenological approach is widely applied within health care research, also specifically within CAM research, strengthening the credibility of the study. Likewise, Hycner's steps for phenomenological analysis are broadly applied as guidelines within phenomenological research. In the present study, this approach was supplemented by the use of meaning condensation and program theory. These two approaches are less well established, potentially weakening the credibility of the study if following Shenton. However, Kvale's concept of meaning condensation is wellknown in a Danish/Nordic context, and program theory has been successfully used in previous studies comparable to the present.

Secondly, the development of an early familiarity with the culture of participating organizations before data collection takes place. In this perspective, the study's credibility has been strengthened by the fact that I have previously been engaged in qualitative research among people with MS. This previous research has provided me with insight into aspects of specific relevance among people with MS (such as cognitive challenges). This insight has been valuable when preparing and performing the interviews. I have been aware of the risk of previous research results guiding the data collection and analyses of the present study; not least the ongoing involvement of the Nordic expert group has contributed to strengthening a non-biased approach.

Thirdly, random sampling of individuals to serve as informants. No random sampling of informants has taken place in the present study. As described in section 2.1.3 and 2.3, a strategic sampling of informants is immanent in the sequential, mixed methods design as a part of the integration of quantitative and qualitative methods. In Paper IV, the sampling of informants was based partly on the research question identified from the overall survey results and partly on statistical analyses of user characteristics. In Paper V, the sampling of informants was based on the research question identified from the overall research results. Such purposive sampling entails a certain selection bias. Such bias may have weakened the credibility of the study if following Shenton, as it entails the risk of reducing the variety of expressions presented in the interviews.

However, in the present study, the aim was not to obtain a variety of expressions in the entire study population, but to investigate a variety of expressions within strategically selected informant groups.

Fourthly, triangulation of different qualitative research methods. The qualitative strand of the present study has been limited to individual qualitative interviews. The inclusion of additional qualitative methods such as focus groups or observation, might have provided a broader range of data (cf. section 4.3.3), potentially strengthening the credibility of data by the different methods compensating for their individual limitations and exploiting their respective benefits. In the present study, however, the performance of a large survey did not allow for multiple qualitative methods to be applied for reasons of time consumption. Furthermore, triangulation of different methods of data collection in the qualitative strand of a mixed methods study entails a risk of high complexity in the research process as well as in the overall data material, potentially weakening the scientific coherence of a study. In the present study, individual qualitative interviews were chosen as method of data collection within the qualitative strand, as I considered this approach adequate to procure data to meet the study's

research aims. Also, I considered this approach most relevant within the patient group in question (compared to e.g. focus groups interviews), due to cognitive challenges as well as challenges linked to transportation and fatigue.

Fifthly, tactics to help ensure honesty in informants when contributing data. All informants, who participated in the study, were given the opportunity to refuse participation twice – in the survey and when contacted by email or telephone. Thereby, the probability was strengthened that only persons who were genuinely willing got take part in the study, and prepared to offer data freely, participated. At the outset of each interview, the informants were assured that data would be anonymized. During the interviews, I was aware of indicating that there were no right or wrong answers – an aspect of potential relevance with regards to use of CAM. A challenge to the credibility of the qualitative data was the fact that the interviews were performed by telephone. One cannot rule out that the absence of face-to-face contact may have constituted a challenge with regard to obtaining confidentiality in the interview. However, the decision to perform the interviews by telephone was partly based on practical/logistic circumstances and partly on preferences among some of the informants – indicating that vanity linked to their physical appearance would influence negatively on their performance during the interview.

Sixthly, peer scrutiny of the research project. Over the duration of the studies, the work was commented by supervisors (co-authors of the articles), reviewers (both qualitative studies have been published in peer reviewed journals), the Nordic expert group and by colleagues (at several scientific conferences).

Seventhly, member checks. In the present interview studies, checks relating to the accuracy of the data took place during the interviews and particularly at the end of the interviews as a recapturing of the informants' expressions. The interviews were audio-recorded, which allowed for a subsequent check of accuracy in the capturing of articulations. Credibility might have been strengthened by asking informants to read in-depth summaries of interviews, asking them to consider if the summaries had captured their intended expressions. However, such member check might also have entailed the risk of weakening the accuracy of data by compromising the spontaneity and honesty of informant expressions.

Eighthly, examination of previous research findings. In the present study, previous findings were examined in order to assess the degree to which the study results were congruent with those of past studies within the area of MS (cf. section 4.2). In the literature searches, focus was laid on MS (rather than on chronic illnesses in general) due to the various characteristics specific to MS (this aspect will be elaborated in section 4.4.2).

4.4.2 EXTERNAL VALIDITY/TRANSFERABILITY

The external validity of a survey is concerned with the extent to which the findings of the study can be applied to a wider population – the generalizability of the study. The survey included in the present study was performed simultaneously in the five Nordic countries. The comparativeness was strengthened by a large number of respondents and by a very thorough process of translation, using the same methods in all four processes of translation. As described in section 2.2.2, the analyses of representativeness regarding the respondent groups compared to the survey samples, as well as of the survey samples compared to the member registers, did not show any major differences concerning gender and age. However, as described in section 2.2.2, analyses of representativeness regarding the member registers compared to the national registers showed several significant differences, indicating that the survey results were likely to be representative of the member registers

rather than of the national populations. Furthermore, the degree of coverage of several of the member registers as well as national registers was questionable. However, the Danish data – on which the vast majority of the present study is based – holds a high quality, which strengthened the external validity of the Danish survey results. Limited data on survey samples (including non-respondents) implies a limitation regarding analyses of representativeness. I.e. data on levels of disability would have been highly relevant, as the level of disability is likely to influence the likelihood of the respondent filling out the questionnaire.

The response rates varied from 50.9 to 61.9%. The response rate in the Danish survey was 55.5%. These rates are acceptable, however a certain sampling bias must be taken into consideration when interpreting the results.

The internet-based questionnaire entailed a challenge to the representativeness as it required internet access. Although widely prevalent, as presented in section 2.2.1, internet access is not universal in the Nordic countries and may have left some potential respondents without the possibility of participating in the survey. However, as also suggested in section 2.2.1, the application of an internet-based questionnaire may also have contributed to limiting invalid responses and cases of unreadable written response and thereby contributed positively to the data quality.

Within qualitative research, the concept of generalizability is often rejected as qualitative research findings are specific to a limited number of individuals. However, in the present study, the qualitative interview studies constitute a strand in an overall mixed methods design; through the strategic sampling of informants it is to some extent embedded in the research design that each individual can also be regarded as an example within a broader group – suggesting that the aspect of transferability (term presented by Guba (133)) should not be immediately rejected within qualitative research; on the one hand, the concept of strategic selection of informants entails a risk of weakening the transferability of study results to a broader group due to the lack of variety in informant expressions ensured by random sampling and saturation. On the other hand, strategic selection of informants may strengthen the transferability of study results to a broader group by aiming at selecting informants with characteristics "typical" of the broader group (as done in Paper IV).

It can be argued that the transferability of Paper V was somewhat limited by the fact that 7 of the 24 informants in the group of informants did not participate in the qualitative interview study. However, as presented in paper V, these 7 non-informants did not differ substantially from the 17 informants regarding gender, age and types of CAM treatments used.

According to Shenton (134), the transferability of qualitative study results to other informant groups or contexts may be strengthened by ensuring that sufficient contextual information about the fieldwork sites is provided to enable the reader to determine how far they can be confident in transferring the research findings to other situations. The researcher can e.g. demonstrate how the study locations compare with other environments or settings. In the present study, telephone interviews were performed, making it difficult to assess the transferability in terms of the setting. However, information about the study frame (i.e. the study's organization, the sampling procedures, the number of informants, the data collection methods, the length of the data collection sessions and the time period over which the data was collected) linked to the present study has been provided, strengthening the possibility of assessing the transferability of the study results to other situations (134). According to Shenton, to assess the transferability

of a qualitative study, ultimately similar studies employing the same methods, but conducted in different environments, should be performed. The performance of such studies, e.g. in other Nordic contexts, has not been possible within the frames of the present study, but could possibly provide useful knowledge in terms of assessing the transferability of study results.

According to Shenton, an important aspect of external validity/transferability is the question of whether the study results are applicable to other patient groups. As indicated in sections 4.2 and 4.5, many of the findings of the present study are supported by previous findings among general populations or related patient groups, indicating findings of broad relevance and applicability.

MS is a severe, progressive chronic diseases and one may suggest that the findings of the present study are in particular applicable to similar patient groups (e.g. Parkinson's disease, Alzheimer's, arthritis, fibromyalgia), who are likely to share overall motives and strategies linked to CAM use. However, MS differs from most other severe, progressive chronic diseases by an early outset of diagnosis, a highly unpredictable course of disease, the absence of disease modifying treatments available regarding more than half of the patients and a frequent impact on cognitive abilities. These aspects specific to MS should be taken into consideration in future comparative studies.

4.4.3 RELIABILITY/DEPENDABILITY

Within survey research, reliability is concerned with the degree to which a study would generate similar results if repeated in the same context, with the same methods and with the same participants (134). No test-retest within the same group of respondents was performed in the present study. One could argue that such rest-retest could potentially have strengthened the reliability of the questionnaire data. However, one could also argue that the exploratory elements in the questionnaire, aiming at initiating reflections among respondents (e.g. linked to the assessment of experienced outcomes), challenges the relevance of a test-retest, as the probability of responses having altered in a subsequent measurement lies immanent in the exploratory approach. In the present study, I chose to perform a thorough validation and pre-testing of the questionnaire applied, which is likely to have strengthened the reliability of the present survey results.

Within qualitative research, the changing nature of the phenomena under investigation makes it difficult to strive for reliability as it is interpreted within quantitative research. Shenton points to the concept of dependability as a relevant equivalent within qualitative research (134). Rather than focusing on the ability of others to replicate results, the intent of applying the concept of dependability is to enable readers to develop an understanding of the methods used and their effectiveness as well as to enable future research to repeat the work (135). In the present study, dependability has been addressed by describing and evaluating the methods applied as well as the process of determining which methods to apply (in chapter 2 and section 4.3). Following the exploratory approach, not all methodological details were determined from the beginning; the analytical approach has been pragmatic (and somewhat heuristic), supporting the aim of a dynamic integration of quantitative and qualitative methods.

4.4.4 OBJECTIVITY/CONFIRMABILITY

Within quantitative research, objectivity refers to use of instruments that are not dependent on human skill and perception (134). Within questionnaire research, the intrusion of the researcher's bias is inevitable as the questionnaire is developed by researchers

and based on words and phrasings that carry meaning. In the present study, much work was allocated to the validation of the questionnaire through cognitive interviews, ensuring that the phrasing of the questions was as objective as possible, e.g. in the sense that value-laden words were avoided. For instance, the absence of the term "alternative" in the questionnaire supported this aim by not pre-defining any treatment modalities as either alternative or conventional and thereby reducing the risk of the respondents' personal attitudes toward CAM influencing the objectivity of responses. As described in section 2.2.1, the scale used in the questionnaire for assessment of experienced outcomes was applied as a part of the survey's exploratory aim. The scale was not subject to investigation of construct validity as the aim was to identify possible trends in subjective experienced outcomes and not to assess objective treatment effects.

Within qualitative research, the concept of confirmability can be regarded as the comparable concern to objectivity (134). Confirmability refers to the aim of reducing investigator bias and ensuring as far as possible that the research findings reflect the informants' experiences and ideas and not the preferences of the researcher. One criterion for confirmability is the extent to which the researcher reflects upon his or her own predispositions (134). The fact that I have previously been engaged in qualitative investigation of CAM use among people with MS may have served as an advantage in terms of credibility as well as a risk in terms of confirmability. In the interviews, I aimed at meeting the informants with what Patton (66) refers to as "empathic neutrality" meaning that the researcher approaches the informants with interest and understanding, but in a non-judgemental and neutral way regarding the informants' thoughts, emotions and behaviors. In the present study, I have without doubt been influenced by previous experiences with the patient group in question, as well as my association with a patient organization, which may have impeded my neutrality. However, I believe that my previous experience with this patient group has improved my understanding of challenges specifically related to people with MS, many of which have cognitive challenges, creating a useful basis for communication.

The application of program theory served as a tool to facilitate the reflection and thereby articulation of the informants regarding their beliefs and assumptions linked to CAM. My previous experience with use of program theory refers to practitioners, who might have different prerequisites for engaging in such articulation. Therefore, during the interviews, I have been aware of not encouraging the informants to express reflections beyond their abilities, as such expressions – if enforced – entail the risk not being (or only partially being) embedded in their daily life experiences.

Another criterion relevant for confirmability is the structuring of the interviews. Although partly structured, and thereby potentially limiting the narrative breadth in the interviews, the present interview studies generally seem to have allowed for aspects not emphasized by previous research, and thereby not expected, to emerge. E.g. in Paper IV, where the emphasis on the absence of discursive reflection among the informants concerning the choice of combining herbal medicine and CDT, and their emphasis on the naturalness in herbal medicine, was accompanied by an insight into the aspect of individual bodily assessments, to which the informants ascribed profound value.

4.5 PERSPECTIVES

The widespread and growing use of CAM in the western world is subject to frequent debate; some emphasize that the absence of evidence for the effect of CAM indicates that its popularity should

be interpreted rather from a psychological perspective than from a health science perspective; e.g. it has been suggested that the popularity of CAM first and foremost reflects a collective need for control of fear of death – a need to believe in treatment options that transcend the limitations of conventional health care science (136). Turner (137) has suggested that in modern societies, medical science is a potential substitute for religion. However, according to Turner, conventional medical science has not succeeded in meeting people’s spiritual needs. Alternative medicine has to a larger extent succeeded in doing so, making of it a relevant replacement of religion (137). It has also been suggested that the popularity of CAM reflects a need in modern societies for people to oppose to authorities, but that it often reveals an absence of insight into scientific methodology (137).

While such explanations may hold some truth, the results of the present study indicated that other aspects – aspects related i.a. to empowerment, patient autonomy and bodily exploration – may contribute to an understanding of the widespread use of CAM among people with MS in Denmark. The results of the present study indicated that the use of CAM is often combined with conventional treatment and often embedded in a wish to strengthen a preventive and enhancing approach to treatment, suggesting that CAM is used as part of individual treatment strategies. Recently, it has been emphasized by social scientists such as Rose and Chrysanthou (138, 139) that in modern societies, patients may be regarded as autonomous health care consumers (rather than recipients of health care offers) and that CAM constitutes an important element in these modern health care consumer’s exploration of options for treatment, prevention and health enhancement (138). Such perspective is in many ways supported by the emphasis, put by the participants in the present study, on e.g. the relevance of the patient’s bodily sensations, of the active participation of the patient, of the individual patient’s own experiences as well as of a critical layman approach to medical science (e.g. linked to the concept of evidence and to the sustainability of pharmacological treatments). In the following, I will address a few of these perspectives and link them to the current debate on CAM use.

4.5.1 THE INFORMED BODY

The results of the present study have indicated that CAM use among people with MS is in several ways related to prevention and health promotion rather than treatment of specific symptoms. In Paper IV, and especially in Paper V, the informants emphasize the importance of the use of CAM representing preventive, strengthening and health promoting initiatives, and they emphasize the importance of such initiatives being taken actively by themselves. As shown in Papers IV and V, the relevance of such active, personal involvement seems to be embedded in a perception of the personal, bodily experiences being of high epistemological value; to the informants, the experience-based knowledge constitute an important element in their overall assessment of treatments used and/or foregone (as presented in Paper V).

Various CAM researchers have shown that the use of CAM often represents a health strategy in which patients try to regain or gain control over their disease (49, 140, 141) i.e. by building embodied knowledge and developing the body as a personal capacity. Previous research, including MS patients as well as other chronic patient groups, has shown that developing the body as a personal capacity may play a substantial role in patients’ ability to navigate their way through a chronic illness (49, 109). If following Chrysanthou (139), patients’ focus on the importance of bodily sensations, as also indicated by the results of the present study, can be understood as an aspect of modern health-orientated consumer culture,

where self-screening and self-diagnosis among the lay public is increasing rapidly and where the development of “the informed body” is crucial for the patients as a tool to navigate.

The importance of the informed body as a navigation tool in a health care context is also mentioned by Csordas (142-144). He emphasizes the importance of the body as an experiencing and informing agent, pointing to bodily experiences as a crucial element in patients’ ongoing construction of knowledge – the knowledge that they employ to interpret and act on the world. According to Csordas, the use of bodily experiences may be of specific importance to people with physical disabilities (144), a very common consequence of MS. For a person with physical disabilities, a bodily awareness may help preventing a feeling of alienation from the body (144). This aspect may be of particular relevance with regards to MS due to the common problem of sensory disturbances (30) and may thereby contribute to an understanding of the emphasis placed by informants in Paper IV and V on the importance of bodily experiences.

4.5.2 THE “PERSONAL EVIDENCE”

The notion of an informed/informing body may constitute a controversial issue. By emphasizing the importance of personal, bodily experiences, the informants in Papers IV and V demonstrate a highly individualized and experience-based approach to the concept of evidence when referring to personal, bodily experiences as being of high epistemological value. By doing so, the informants refer to lay knowledge as epistemologically valuable on a basis equal to professional, scientific knowledge.

A positive valuation of lay knowledge may be subject to criticism due to the lack of a scientific basis. Whereas such criticism is regarded as relevant by some, one may also regard the individual, experience-based approach to evidence as a rational challenge of traditional, medical approaches to evidence; Saks (145) has argued that while randomized controlled trials (RCT’s) constitute the gold standard within research in both conventional medicine and CAM, the results of individually targeted qualitative research appears in many ways to be more relevant to patients. Barry (146) has emphasized that the widespread use of RCTs entails a number of methodological challenges, which are also debated among patients. Such debates might lead to the questioning of the universality of conventional medico-scientific knowledge among patients (147). The results of the present study indicate that such questioning is prevalent among the participants and that lay knowledge is by some within this patient group regarded as a neglected source of knowledge. The relevance of including the lay perspective in health care science and development has been emphasized by studies within other chronic patient groups, e.g. diabetes (148, 149).

Järvinen and Mik-Meyer have pointed out the challenges in integrating clients’ experience-based knowledge and social/health care workers’ professional knowledge, emphasizing major differences in these two types of knowledge (150). However, epistemological differences linked to lay perspectives and professional perspectives should not necessarily be articulated dichotomically; McClean and Shaw have critiqued the lay-expert divide, suggesting instead a spectrum of knowledge about health and scientific issues (151). Whereas one may argue for the reasonableness in a spectrum of knowledge from a constructivist perspective, pointing e.g. to an absence of universality in current epistemological valuation within health care science, one may also from a more structuralist perspective question the reasonableness of accepting all types of knowledge as equally valid. Within CAM research, it has been ar-

gued that research designs should transcend the traditional hierarchy and aim for a typology of evidence, including lay knowledge as a valid contribution (152). Others have argued that a hierarchy of evidence should be maintained, securing thereby the generation of scientifically valid knowledge (153). In the present study, the informants in Paper IV and V express to a far extent a support for a spectrum of knowledge – partly directly by challenging the relevance of statistical research results for the individual patient and partly through their emphasis on the relevance of bodily experiences.

4.5.3 THE EMPOWERED PATIENT

In Denmark, as in other Western countries, much interest is at present being paid to patient empowerment as a way to strengthen patients' active participation in their own courses of treatment. It may be relevant to interpret the use of CAM among people with MS in Denmark in an empowerment perspective; using CAM as an element in managing life with a chronic disease through an enhancement approach fits in many ways well with the notion of empowerment. The Theory of Health Empowerment defines empowerment as a dynamic health process that emphasizes "purposefully participating in a process of changing oneself and one's environment, recognizing patterns, and engaging inner resources for well-being" (154). In many ways, the motives and reflections linked to the use of CAM as presented in the present study can be interpreted as manifestations of empowered patients – patients that take control over their illness and treatment. However, I believe it is relevant to question whether it is appropriate in the current study to link the use of CAM to the notion of health empowerment. Patient empowerment is also referred to as shared decision making (154) and one of the basic ideas of patient empowerment is that patients should be given sufficient information to enable informed choices (154). In this way, The Theory of Health Empowerment shares elements with The Theory of Planned Behavior (155) – presupposing that the patient has sufficient qualifications and resources to acquire relevant information and make choices/perform a behavior accordingly.

In the present study, the use of CAM can to some extent be interpreted as a result of informed choices – in some cases the informants indicate that CAM treatments have been included, or that conventional treatments have been foregone, on the basis of concrete information given to the patient or acquired by the patient. However, the overall results of the study suggest that the choice of using CAM may often be based on a wish to include a variety of treatment modalities in an overall treatment approach. Hence, it can be argued that the choice of using CAM may reflect the patients' personal beliefs and intuitive interpretations of relevant treatment strategies rather than being the result of a process of "purposefully participation" in a pre-defined course of treatment.

4.5.4 SUSTAINABILITY IN HEALTH CARE

Beliefs among the informants in fundamental differences between conventional medicine and CAM regarding their impact on the recipient's organism – particularly addressed in Paper V - may point to an important issue for further research. Although not articulating it explicitly, the informants expressed a strong belief in elements of sustainability of CAM treatments. As shown by the results of Papers IV and V, conventional medications were among the informants widely regarded as unsustainable in the way that they were considered to affect the human organisms in negative ways – de-strengthening, de-balancing and signal-blurring. CAM treatments, on the other hand, were considered as offering quite the

opposite – a way of strengthening the whole organism as well as enhancing the possibility of using bodily sensation actively in an ongoing regulation of interventions.

The issue of patients' perceptions of sustainability is fairly new within CAM research (Joos et al. have very recently addressed this issue in a German context (156)), but it may offer an important perspective for future research on motives for CAM use, e.g. in relation to including environmental aspects in the investigation of CAM users' convictions and beliefs. In 2010, a workshop on sustainability was scheduled for the annual International Conference in Complementary Medicine Research in Tromsø (157), but was cancelled due to lack of interest. In 2013, this annual conference, held in London, bore the title "Long Term Conditions – developing global, integrative and sustainable solutions" and the issue of sustainability in an overall health care perspective was given specific attention (158). The results of the present study suggest that the issue of sustainability in an individual, bodily perspective may constitute a useful aspect in future exploration of motives for CAM use.

4.5.5 DOCTOR-PATIENT COMMUNICATION ABOUT CAM

One of the issues pointed out in Papers II and III, and emphasized in Papers IV and V, is the issue of non-disclosure. The results of Papers II and III indicate that CAM users tend to not communicate with a medical doctor about their use of CAM, and the results of Paper V, and especially Paper IV, underline that this reluctance is to a large extent embedded in negative experiences and/or negative expectations. In most studies addressing safety and CAM, lack of communication with medical doctor appears a major issue. Thus, studies have indicated that of users of herbal medicine often do not inform their primary care provider about their CAM use (159-163). Supporting the results of the present study, the aspect of non-disclosure is in several other studies explained by expected lack of interest/knowledge of herbal medicine from the medical doctor or the patients' fear of negative response from medical doctor (159, 163). An Irish study from 2008 indicated that this issue is also relevant within MS treatment as only 25% of patients at an Irish neurological clinic had informed their medical doctor about use of CAM (41).

Several studies emphasize the importance of improving doctors' communication and openness regarding CAM treatments – not least regarding the safety aspect related to use of herbal medicine, as presented in Paper IV (97, 160, 163). The results of the present study suggest that communication between patients and medical doctors about safety issues linked to CAM may be an important issue. However, the results of the present study may also indicate that communication about motives and beliefs linked the patients' engagement in different types of treatments is equally important; theories on the modern health care consumer culture have emphasized that use of CAM is often embedded in an overall health strategy that encompasses different treatment approaches in the search of a holistic approach to treatment and to coping actively with chronic disease (138, 139). The results of the present study may be interpreted as emphasizing the importance of health care professionals engaging in understanding the background to patients' individual treatment strategies. As such, the results of the study may point to the importance of enhancing and qualifying communication between patients and representatives of conventional health care systems regarding motives, goals and rationales linked to CAM use – for reasons of safety, but also with the aim of mutual understanding. Differences in conceptions of valid knowledge - the lay perspective vs. the expert perspective - may constitute a relevant aspect with regards to such mutual understanding.

5. CONCLUSIONS

The results of the overall mixed methods study indicated that the use of CAM among people with MS is widespread in Denmark as well as in the other Nordic countries. The results of the study indicated that among the Danish respondents, about half had used CAM within the past twelve months. CAM treatments were most often used for non-specific/preventive purposes. Analyses furthermore indicated that among the Danish respondents, CAM users were more likely to be women, of young age and of high education when compared to CAM non-users. Analyses indicated few differences in background characteristics as well as characteristics linked to treatment use between subgroups of CAM users among the Danish respondents.

Comparative analyses of the Nordic survey data indicated no major differences between the Danish respondents and the other Nordic respondent groups, although some statistical differences were found regarding the use of specific CAM modalities and regarding the prevalence of exclusive CAM use. Some reservations should be made to the results of the comparative analyses due to challenges in the quality of the Swedish, Norwegian, Finnish and Icelandic register data, the limited number of variables included in the analyses of representativeness as well as the risk of multiple significance.

Based on a sequential, mixed methods design, two issues for further qualitative investigation were derived from the quantitative analyses: 1) beliefs on risks of negative interactions among users who combined herbal medicine and conventional drug therapies and 2) perceptions of treatment mechanisms among CAM users who used CAM exclusively, including having foregone use of disease-modifying drugs for MS. The two qualitative interview studies showed 1) that the informants, who were users of herbal medicine and conventional drug therapies in combination, generally considered such combination treatment to be safe due to the natural aspect of herbal medicine and 2) that the choice of using CAM exclusively did not seem to represent a principled rejection of conventional medicine, but appeared to be the result of the informants' overall assessment, weighing beliefs and experiences regarding positive and negative impact of different types of treatments.

The overall results of the study indicated that the majority of people with MS in Denmark include a diversity of treatments in the managing of their life with a chronic disease, that the motives for doing so are often embedded in preventative, enhancing approaches to treatment and that the users' choices regarding CAM may be related to many personal factors and hence not necessarily indicating a distrust of the medical system.

The results of the study are to a large extent supported by previous research, showing a widespread use of CAM among people with MS as well as among general populations in the Western world. The present study has emphasized the relevance of investigating use of CAM in connection to use of conventional treatments, indicating that CAM is primarily used as part of integrated approaches among people with MS, but also indicating that exclusive CAM use is prevalent, pointing to a research issue potentially relevant for further investigation. The present study has also emphasized that motives for CAM use may be multiple among people with MS; strengthening/preventive purposes are highly prevalent and motives for CAM use may refer to beliefs and convictions among patients that differ from conventional, medical science.

Theoretical perspectives on embodied knowledge, lay and expert knowledge, the notion of evidence as well as modern health consumer culture have supported the interpretation of the study

results. Although representing a patient group with specific challenges, the study results hence indicate that among people with MS in Denmark, some of the health care trends characterizing modern societies may be identified – trends such as autonomous search for individually accommodated treatment strategies, positive valuation of experience-based (embodied) knowledge and questioning of the universality of the research methodology traditionally applied within medical research.

The sequential, mixed methods design has entailed a number of challenges regarding the scientific stringency of the study and some reservations to the study results should be made, primarily linked to aspects of external validity/transferability. However, the application of a sequential, mixed methods design has offered a dynamic research design, where it has been possible to integrate quantitative and qualitative approaches in an exploration of CAM use among people with MS in Denmark.

ABSTRACT

Background: It is known that Complementary and Alternative Medicine (CAM) is popular among people with Multiple Sclerosis (MS) and that use is widespread. However, very limited knowledge exists about use and users of CAM among people with MS in a Danish context.

Aims: The overall aim of the thesis is to investigate how and why people with MS in Denmark include CAM in managing their life with a chronic disease and to discuss their experiences and beliefs linked to CAM use.

Methods: A mixed methods research design was applied, combining an internet based survey with two qualitative in-depth interview studies. A total of 6850 people with MS from the five Nordic countries, of these 3500 from Denmark, were invited to participate in the survey. The average response rate was 56.1%. Based on analyses of the Danish survey data, two specific issues regarding the use of CAM were selected for further investigation and two qualitative interview studies were performed (n=17, n=11), using program theory and meaning categorization as analytical tools.

Results: The results of the study indicate that the use of CAM among people with MS is widespread in Denmark as well as in the other Nordic countries. The results furthermore suggest that this use is generally embedded in a preventative, autonomous approach to treatment and that the users' choices regarding CAM may be related to many personal factors and do not necessarily represent a distrust of the medical system.

Perspectives: The results of the study point to the relevance of health care professionals engaging in understanding patients' different motives for – and experiences with - using different types of treatments. Thereby, the results of the study also point to the importance of enhancing and qualifying communication between patients and representatives of conventional health care systems regarding the patients' use of CAM, both with the aim of mutual learning and for reasons of safety.

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