QUERI

Modifiable Risk Factors in the Progression of Multiple Sclerosis: A Systematic Review of the Epidemiology and Treatment

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Investigators:
Principal Investigator:
Susanne Hempel, PhD
Paul Shekelle, MD, PhD

Co-investigators:
Ning Fu, PhDc
Elena Estrada, BS, BA, MS
Annie Chen, BS, BA

Research Associates:
Isomi Miake-Lye, PhDc
Jessica Beroes, BS
Roberta Shanman, MS
Jeremy Miles, PhD

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4

PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

·   Develop clinical policies informed by evidence;
·   Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
·   Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces "rapid response evidence briefs" at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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TABLE OF CONTENTS

EVIDENCE REPORT

INTRODUCTION

Multiple sclerosis (MS) is the most common progressive disease of the central nervous system in young adults and the most common cause of serious physical disability in adults of working age.[1] [2] The estimated incidence is 7 per 100,000 per year and the median age of onset is 30 years.[3] For the military it is a significant neurological disease burden in terms of diagnosis, management, and disability retirement.

MS is characterized pathologically by focal areas of inflammation, demyelination, gliosis, and axonal damage throughout the central nervous system.[4,5] The course of MS is characterized by clinical relapses and disease progression. Relapse, exacerbations, or attacks, are acute, inflammatory events that occur episodically within the central nervous system. They can correspond to either the development of new focal inflammatory lesions or the reactivation of old lesions, and after an exacerbation, symptoms spontaneously remit, either partially or completely. Progression describes a steady deterioration in neurologic function associated with new symptoms and continuously worsening disability which takes place over a period of at least 6 (Poser criteria) or 12 months (McDonald criteria).[6,7] Once progression has developed, the course is continuous despite occasional plateaus and temporary minor improvements.[8]

MS disease presentation is very heterogeneous with variable clinical manifestations that evolve over time. About 80% of patients present with relapsing-remitting disease which manifests in relapses followed by periods of partial or complete recovery (remissions). Other subtypes of MS include secondary progressive MS (patients develop relapsing-remitting MS but then begin progressing with or without relapses). In about 50% of patients the course of MS changes from relapsing-remitting to secondary progressive disease after 10 years.[9] Active progressive MS shows a slow progression of disability from onset with periods of stability and occasional relapses, while patients with primary progressive MS show progressive worsening in disability from onset without exacerbations. It is estimated that while 15% of patients with MS will become severely disabled within a short time, for 25% of patients MS will never affect daily life.[10]

Epidemiologic data show that rates of MS appear to vary with environmental factors.[10] This suggests a role of potentially modifiable risk factors associated with the onset and phenotypic manifestation of the disease. Similarly, the course of MS varies with demographic variables and possibly other factors. Furthermore, the mechanism that changes the disease pattern from relapsing-remitting to secondary progressive MS is largely unknown.[9] Factors that may explain the diversity in clinical presentation, help predict the course of the disease, and identify potential triggers of disease progression are of great interest to patients and clinicians, in particular modifiable risk factors.[11]

Disease-modifying therapies for relapsing forms of MS are only partially effective in slowing short-term morbidity and there are no effective medication options for progressive MS.[12] Additional MS treatment and management options are needed to support patients with a diagnosis of MS. Some risk factors associated with the onset or progression of MS may be translatable into interventions, such as in the case of the potential risk factor vitamin D

deficiency, which can be tested in effectiveness trials by treating MS patients with a vitamin D supplement.[13]

This project focuses on empirical evidence on modifiable exposures and risk factors that are related to MS progression and approaches to reduce progression that are directed at modifiable risk factors. This review will be used by the VA Multiple Sclerosis Centers of Excellence to initiate new research studies, refine clinical guidelines, and plan for targeted disease-modifying and disease-prevention strategies.

METHODS

TOPIC DEVELOPMENT

This topic was developed in response to a nomination by the VA Multiple Sclerosis Center of Excellence-East, for an evidence review to examine the role of modifiable risk factors and military exposures in the progression of MS, as well as methods to reduce progression that are directed at modifiable risk factors.

The Key Questions (KQ) were:

(1) What modifiable epidemiologic factors are related to multiple sclerosis progression following diagnosis?

(2) What environmental exposures prior to or during military service are related to multiple sclerosis progression following onset symptoms?

(3) Among identified risk factors for progression, what treatment/risk factor modification therapies have been shown to delay or hasten the progression of multiple sclerosis once it has initiated?

SEARCH STRATEGY

We searched the electronic databases PubMed (medical literature); EMBASE (biomedical literature); AMED (Allied and Complementary Medicine Database); SCOPUS and Web of Science (broad research databases indexing conference papers and innovations); GreenFILE (environmental factors); DTIC (Defense Technical Information Center), and ProQuest Military Collection (databases for military research) for primary research studies published in English to March 2015 without date restriction. Dates of database inception varied; for example, PubMed systematically indexes research published since 1966, with some earlier publications.

For KQ1, we employed a search strategy that combined known presumed risk factors, and a more general search for prognostic study designs based on a published search filter[14] applied to PubMed, SCOPUS, Web of Science, and GreenFILE.

The KQ2 search strategy used search terms for military populations to identify MS studies without further study restrictions in the databases PubMed, EMBASE, AMED, SCOPUS, Web of Science, GreenFILE, DTIC, and ProQuest Military Collection.

For KQ3 we applied a search filter for randomized controlled trials (RCTs) to search the databases PubMed, AMED, SCOPUS, and Web of Science, to target eligible studies. The PubMed search encompassed all indexed RCTs in MS patients and was not restricted to a set of pre-defined interventions, to avoid missing relevant studies targeting uniquely-named or novel interventions.

Furthermore, we screened references of pertinent reviews and consulted with topic experts to ensure that all relevant studies were identified.

STUDY SELECTION

Two independent reviewers screened titles and abstracts of retrieved citations and recorded decisions in an electronic database. Citations deemed potentially relevant by at least one of the reviewers were obtained as full text. The full-text publications were screened against the specified inclusion criteria by 2 independent literature reviewers; disagreements were resolved through discussion within the review team. The literature flow was documented in an electronic database and reasons for exclusion of full text publications were recorded.

To be included in the systematic review, studies had to meet the following criteria, organized in the PICOTS framework.

Participants: Studies in human adult participants with a clinical diagnosis of MS were eligible for inclusion for KQ1 and KQ3. KQ2 was limited to active military personnel and Veterans with MS. Studies exclusively focusing on pediatric MS in children and adolescents were excluded. Studies targeting a range of clinical conditions were included as long as data on MS progression was reported separately. The sample composition of MS populations was not restricted but risk factor studies excluding all progressive forms and not reporting on MS progression were excluded (*eg*, studies describing disease severity in explicitly non-progressive forms).

Intervention: Studies reporting on modifiable epidemiologic factors and environmental exposures potentially associated with MS progression ("risk factors") were eligible for inclusion for KQ1 and KQ2. Eligible risk factors included (but were not limited to) the geographic region of residence, sun exposure, vitamin D intake, polyunsaturated fatty acid intake, diet, smoking, alcohol, exercise behavior, vaccinations, anesthesia exposure, radiation therapy exposure, use of oral contraception, fertility treatment, childbirth delivery variables, breastfeeding, salt intake, use of milk products, water sources intake, trace elements intake, mercury exposure, trauma exposure, military service/deployment, and military exposures. Non-modifiable risk factors such as genetic predispositions, physiological correlates, or demographic characteristics at MS onset were excluded. Descriptive factors such as quality of life or vitality with unclear modifiability, comorbidities, and concurrent psychological correlates of disability status that are more likely to be a reaction to than a predictor of MS (*eg*, coping strategies and perceptions of body image) were excluded. Factors directly associated with known MS medication, such as the use of disease-modifying treatment, type of medication, medication combinations, dosing schemes, adherence, and timing of therapy onset were also excluded.

Intervention studies evaluating the effect of modifying the intake or exposure to potential risk factors (*eg*, smoking cessation, weight loss, or exercise programs; nutritional interventions targeting vitamin D or Omega-3), alone or in combination with other therapies, were eligible for KQ3. Treatment studies testing potential risk factors were eligible for inclusion regardless of the current strength of association in empirical studies, but studies evaluating unspecific interventions not associated with potential or identified MS risk factors (*eg*, acupuncture) were excluded. Treatment studies evaluating the effect of existing, FDA-approved MS medications that aim to modify the disease course of MS (*eg*, interferon beta-1a), or aim to manage MS relapses (*eg*, prednisone), other suggested medication for MS (*eg*, laquinimod), treatments for autoimmune and immunodeficiency diseases (*eg*, corticosteroids), and medication given for their immunomodulatory properties (*eg*, statins) or tested for their use in MS (*eg*, lithium) were excluded regardless of any underlying risk factor hypotheses (*eg*, infection, hygiene hypothesis).

Comparator (design): Observational studies (*eg*, case-control, cohort studies comparing 2 cohorts, or cross-sectional studies including surveys), and experimental studies analyzing factors associated with MS progression were eligible for KQ1 and KQ2. Non-randomized experimental studies had to have a non-treated concurrent control group to identify standard progression rates and provide a power calculation to determine *a priori* whether differences between experimental groups could be identified. Risk factor studies had to report data on 10 or more participants with MS. Case studies speculating about associations were excluded.

RCTs in adults regardless of the comparator were eligible for KQ3. Only primary research studies were eligible for inclusion. Pertinent reviews and secondary data analyses were retained as background paper for reference mining.

Outcome: Studies reporting on the progression of MS were eligible for inclusion in the review. The primary outcome was Expanded Disability Status Scale (EDSS) scores or progression classifications based on EDSS score cut-offs. Studies reporting on earlier versions of the EDSS scale; other global patient-centered, clinical MS progression measures (*eg*, Multiple Sclerosis Functional Composite [MSFC], multiple domain assessments of the Functional System Score [FSS], Patient Determined Disability Scale [PDDS]); the clinical course of MS (*eg*, progression defined by clinical judgment, time to secondary progression); or comparing MS subgroups relevant to progression (*eg*, relapsing-remitting versus secondary-progressive stage) were eligible for inclusion. Studies reporting on disability measures focusing on the general ability to walk (*eg*, MS Progression: Disease Steps [DS]) were included. Studies only reporting on individual characteristics of walking (*eg*, gait, muscle strength, speed) were excluded. Studies reporting on other individual symptoms (*eg*, fatigue or depression) or individual diagnostic markers (*eg*, lesions shown with imaging techniques) without reporting on patient outcomes of MS progression were excluded. Studies reporting disability measures not specific to MS (*eg*, receiving a disability pension) were excluded. Studies reporting on MS-associated mortality were included if the endpoint was part of a continuum of progression and not an incidence measure of MS. Studies reporting on all-cause mortality in MS patient samples, for example investigating whether associations between epidemiologic factors and mortality found in the general population ('smoking predicts mortality') also apply to the MS population, were excluded. Studies exclusively reporting on the onset, rather than the progression of MS, and studies only reporting on the prevalence and incidence of MS without differentiating MS subtypes relevant to MS progression (*eg*, primary progressive MS) were excluded.

Timing: Risk factor studies were not limited by exposure duration and timing (*eg*, childhood exposure) and any follow-up points were eligible for inclusion in KQ1, but investigator-initiated exposures (ie, interventions) were restricted to long-term interventions if they did not report a statistical power calculation indicating that the study had sufficient power to show a difference between exposed groups. We included prospective (measuring the exposure before the outcome), retrospective (measuring the exposure of a past event retrospectively at the time of measuring the outcome), and concurrent (measuring the exposure status and the outcome at the same time point) studies. Studies eligible for KQ2 were limited to exposures prior to or during military service. Intervention RCTs including any intervention duration, regardless of the intervention timing, and any follow-up points were eligible for inclusion for KQ3.

Setting: Studies of any settings were eligible for inclusion in the review.

Other limiters: English-language studies were included.

The review was registered in PROSPERO, the international registry for systematic reviews PROSPERO http://www.crd.york.ac.uk/PROSPERO/. (PROSPERO 2015:CRD42015016461)

Protocol Deviations

Due to the overwhelming size of the literature identified through our literature searches that exceeded the available time and resources needed to complete the project, we removed co-morbidities such as stress, anxiety, depression, infections, sleep problems, or obesity regardless of their treatability and modifiability status from the eligibility criteria. We also excluded the large body of literature on pregnancy and parity given that the decision to have children may be directly associated with disease severity and anticipated progression (reverse causality is discussed in more detail in the discussion section). Finally, we excluded studies that reported on the physiological or clinical status of patients, such as body weight or serum fatty acid levels, without information on the intake or patient behavior (*eg*, diet regime) other than vitamin D. In sum, we excluded factors that could either be a reaction to, an independent comorbidity, or a predictor of MS progression, and concentrated primarily on behavior and choices or exposures somewhat under the control of the patient or their families.

DATA ABSTRACTION

Studies underwent standardized abstraction of study-level data in an electronic database. Data collection forms were designed by the project lead and discussed in the review team.

For KQ1 (risk factors) studies, we extracted information on the MS population (*eg*, proportion of patients with relapsing-remitting, secondary progressive, or primary progressive MS; age; % male; race/ethnicity distribution). We documented the number of participants in the study sample and the number of cases (ie, patients with progressive MS). We recorded the geographic region of the sample. We documented the study design (*eg*, cohort study), methods used to analyze the results (*eg*, linear mixed effects model, partial correlations), and the predictive timeframe (concurrent, retrospective, prospective data). We extracted analyzed, potential, modifiable risk factors of interest together with the time of exposure (*eg*, alcohol consumption in last 2 years). We recorded all independent variables entering the prediction model. We extracted the point estimate of effects and statistical significance of risk factors on MS progression. The evidence table differentiates predictions for EDSS scores and other clinical course characteristics relevant to MS progression.

Concurrent studies were defined as measuring the exposure status and the outcome at the same time point, such as current alcohol intake. Retrospective studies assessed at least some outcomes retrospectively (*eg*, cod liver oil consumption during childhood). Prospective studies had to report on at least 2 different points in time assessing the risk factor prior to the MS progression outcome to be classified as prospective.

For studies relevant to KQ2 (military service exposures), we extracted the information on the study population including: MS characteristics and military service status; number of study participants and cases, geographic region; study design; analytic method; assessed prior or post military service exposures; assessed military service exposures; other analyzed independent variables; predictive time frame; EDSS score results; and other clinical course results.

For intervention studies (KQ3, risk factor modification therapies), we extracted the study design and methodological characteristics, number of randomized participants per intervention group and proportion of participants with progressive MS, characteristics of participants, intervention components and co-interventions, comparator details, outcomes, followup points, statistical power analysis, EDSS results, other disease progression results, and adverse events.

Some studies were reported on in more than one publication. Studies, defined by the included participants, were only counted once, regardless of the number of publications the results were published in. The data extraction considered data from all publications available for the study.

QUALITY ASSESSMENT

For KQ1 and KQ2 we distinguished concurrent, retrospective, and prospective studies. Prospective studies were assessed with QUIPS (Quality In Prognosis Studies), a critical appraisal tool for prognostic studies.[15]

Intervention studies (KQ3) were assessed with the Cochrane risk of bias tool assessing selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias (where appropriate).

Quality criteria definitions and scoring guidelines for all domains are documented in Appendix C together with the assessment results.

DATA SYNTHESIS AND ANALYSIS

The evidence tables provide information on each included study to allow a comprehensive overview. Summary of findings tables summarize results for analyzed modifiable risk factor in the general population (KQ1) and military samples (KQ2), and results for individual interventions (KQ3) across all identified studies.

The evidence tables and summary of findings tables differentiated results based on EDSS scores, the primary outcome of the review, and other MS progression results. The EDSS[16] is widely used to assess the disability and the progression of MS. Scores range from 1 (no disability) to 10 (death due to MS). A milestone often used in research is EDSS 6, characterized by the need for a cane or other constant assistance to walk 100 meters.

Where possible, variables were pooled across studies in meta-analyses to identify reliable and valid effects across studies. We pooled studies where at least 3 studies were available for the risk factor of interest and the effect measure of interest (*eg*, correlations, time to event data, count data). Continuous outcomes were reported as standardized mean differences (SMD) to facilitate the comparison of effect sizes across outcome measures. We calculated weighted mean differences (WMD) to determine the clinical importance of the effect for studies reporting on the primary outcome EDSS scores. Dichotomous data were presented as relative risks (RR). For time to event data we computed hazard ratios (HR). Correlations (r) transformed to *z* statistics (using the Fisher transformation) to pool across studies. Point estimates were calculated together with the 95 percent confidence interval (CI). We used a restricted maximum-likelihood estimator and the Hartung-Knapp-Sidik-Jonkman method for random-effects models to pool across studies.

All studies relevant to KQ1 were summarized narratively. When at least 3 studies were available that reported on the same risk factor and the same outcome measure, we performed meta-analysis. The synthesis differentiated variables assessed as potential risk factors, and results indicating a statistically significant association with MS disability and progression. The synthesis addressed negative and positive associations indicating worsening of progression status or protective factors. In addition, it also documented the absence of associations.

Due to the diversity in study designs, analytic methods, and effect measures, and the small number of studies, studies in military personnel and Veterans relevant to KQ2 were summarized narratively. We differentiated assessed variables and statistically significant effects. The narrative synthesis emphasizes risk factors identified in more than one individual study.

Intervention studies (KQ3) were summarized narratively, grouped by intervention category. When at least 3 studies were available for the same intervention group and outcome measure (*eg*, EDSS scores, number of patients progressing, time to progression), we performed meta-analysis. Data were based on intention-to-treat results, where available. For continuous outcomes results were based on unadjusted post-intervention scores. Results of studies in military personnel and Veterans were an *a priori* planned subgroup analysis.

RATING THE BODY OF EVIDENCE

We rated the quality of the evidence for individual risk factors across all identified studies (KQ1), in military and Veteran populations (KQ2), and for individual interventions (KQ3) across all identified pertinent studies. Based on GRADE guidelines[17] the quality of the evidence was categorized as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Given the complexity of epidemiological data collection and interpretation, the synthesis focused on factors that have been assessed in more than one study. Other, unique assessment results were reported in evidence tables but not further documented in the summary of findings tables for KQ1 and KQ3 to provide a concise overview. Given the relevance to the VA, all available evidence was documented for KQ2.

For KQ1 and KQ2 we took the following criteria into account to determine the level of evidence quality. These are based on an adaptation of the GRADE framework for prognostic factor research.[18] The "phase of investigation" criterion was used as a starting point (high or moderate quality of evidence). The criteria "study limitations," "inconsistency," "indirectness," "imprecision," and "publication bias" were used to decrease the quality of evidence. The criteria

"moderate / large effect size" and "exposure-response gradient" were used to increase the evidence grade where applicable.

For KQ3 we took the number of identified studies and the criteria "risk of bias," "inconsistency," "imprecision," and "publication bias" into account. The starting point was high evidence because the data are based on RCTs.[17]

Publication bias was assessed with the regression test (Egger test) and the rank test (Begg test). Results indicating evidence of publication bias were reanalyzed using the trim-and-fill method to adjust for potentially missing studies.

TECHNICAL EXPERT PANEL

The technical expert panel (TEP) for the project included Mitchell T. Wallin MD, MPH, Clinical Associate Director, VA MS Center of Excellence-East; Glenn D. Graham, MD PhD, Deputy National Director for Neurology, Specialty Care Services, VA Central Office, Christopher Bever, Jr., MD, MBA, Director of the MS Center of Excellence-East, Professor, Departments of Neurology, Pharmacology and Physical Therapy, University of Maryland School of Medicine; Jodie Haselkorn, MD, MPH, Director, MS Center of Excellence-West, Professor, Rehabilitation Medicine, VA Puget Sound Health Care System; W. Joel Culpepper, MA, PhD, Associate Director of Epidemiology and Outcomes for the MS Center of Excellence-East; John W. Rose, M.D., Chief, Division of Neuroimmunology, VA Salt Lake City Health Care System; Gary M. Franklin, MD, MPH, Research Professor, Department of Environmental and Occupational Health Sciences Medicine (Neurology) and Health Services, University of Washington; Vijayshree Yadav, MBBS, MCR, Associate Professor, Neurology, Clinical Director, MS Center, Oregon Health & Science University; John F Kurtzke MD, FACP, FAAN, Professor Emeritus of Neurology, Georgetown University, Consultant in Neurology and Neuroepidemiology, Veterans Affairs Medical Center, Washington, DC; and Aaron Turner, PhD, Mental/Behavioral Health Psychology, VA Puget Sound Health Care System.

PEER REVIEW

A draft version of the report was reviewed by technical experts, clinical leadership, and additional peer reviewers where appropriate. Reviewer comments and how we have addressed them is documented in Appendix D.

RESULTS

LITERATURE FLOW

The literature search identified a large number of citations (N = 8,594). We selected 455 potentially relevant publications to be obtained as full text in order to screen them against the predetermined inclusion criteria.

We obtained a large number of publications as full text and checked studies for the outcome of interest after piloting the inclusion criteria in the first set of citations. Publications did not systematically mention progression in the title or abstract of the publication; hence, a large number of studies was obtained as full text and results sections were carefully screened for data relevant to MS progression.

In total, 300 publications were excluded because they did not meet one or more of the inclusion criteria. The list of excluded studies and the reasons for exclusion are documented in Appendix B. A large proportion of the studies was excluded because the full-text review showed that the study did not report on MS progression. The second-largest reason for exclusion was associated with studies not reporting on modifiable risk factors (Exclude-Intervention/Exposure).

In total, 95 studies[19-112] met inclusion criteria and contributed to answering the review questions. Of these, 59 studies contributed to KQ1. Despite the extensive search in general and specialist databases for military research, we only identified 4 studies that provided data for KQ2. In total, 36 RCTs were identified that contributed to KQ3.

Figure 1: Literature Flow Chart

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┌─────────────────────┐
│ Search results:     │─────────────►  Excluded = 8,2139 references
│ 8,594 references    │                    ·  Not MS, not progression, not empirical
└─────────┬───────────┘                       study, not English language
          │                              Could not be obtained
          │                                  ·  2 references
          │
          ▼
┌─────────────────────┐        Excluded references
│ Retrieved for full  │────┐       ·  Participants (not MS): 2
│ text review: N = 453│    │       ·  Intervention or exposure: 105
└─────────┬───────────┘    └──►    ·  Study design: 32
          │                        ·  Outcome: 159
          │                        ·  Language: 1
          │                        ·  Duplicate: 1
          │
          │                  Retained as background = 58 references
          ▼                      ·  More information on included studies or
┌─────────────────────┐             source of potential includes
│ Included studies:   │
│ N = 95              │
└─────────┬───────────┘
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Note: Some included studies contributed to more than one KQ.

KQ1 (progression risk factors): N = 59

KQ2 (military specific): N = 4

KQ3 (interventions): N = 36

KEY QUESTION 1: What modifiable epidemiologic factors are related to multiple sclerosis progression following diagnosis?

Risk factor studies meeting inclusion criteria were published between 1973 and 2015, with a large proportion of studies having been published in the last 3 years. Of note, no study was excluded due to the publication year for this review and all databases were searched without date restriction.

Studies were conducted in the US, Canada, Australia, Japan, Iran, Italy, Belgium, UK, the Netherlands, France, Sweden, Germany, Turkey, and Finland, and some were international samples based on online surveys. Studies identified participants through hospital records or surveyed members of MS registries. Most studies used unselected samples that included a range of MS forms.

Studies assessed a large variety of modifiable epidemiological factors and used different operationalizations of potential risk factors (*eg*, average number of cigarettes smoked per day, exercise / physical activities assessed with the revised Health Promoting Lifestyle Profile [HPLP-II]). Some studies assessed the current status while others assessed lifetime prevalence (*eg*, ever smokers).

Included studies used a broad range of outcome measures such as EDSS scores, other patient-reported scale scores, correlations with EDSS scores or other measures of disease status, time to EDSS 6, time to EDSS 4, time to secondary progression, or time to wheelchair dependency. Some studies used standardized scales such as the EDSS while others reported on clinician-defined outcomes (*eg*, clinical deterioration).

The research study pool included 13 prospective studies.[20,30,35,69,72,76,87,91,96-98,112,113] These studies assessed participants at 2 or more different points in time and are better suited to make predictions (rather than establish concurrent associations, or relying on retrospective assessments from memory about factors experienced in the past).

Details of all included studies are presented in the evidence tables. We grouped studies exclusively reporting on vitamin D or sun exposure, studies reporting on childbirth-related factors, studies investigating the role of smoking, studies reporting on diet and nutrition, and studies reporting on unique factors such as childhood trauma. The last evidence table summarizes studies that investigated more than one risk factor of interest for this review.

Of the single-factor studies, the largest group addressed vitamin D. Vitamin D can be absorbed from exposure from sunlight, from diet, or from dietary supplements. The first evidence table for KQ1 documents how published studies have operationalized this potential risk factor for MS progression.

Table 1. Evidence for KQ1 (MS Progression Risk Factors): Vitamin D or Sunshine Exposure

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Ascherio, 2014[20] prospective	18 European countries, Israel, and Canada	Sample from BENEFIT trial, presenting with first episode of neurological dysfunction suggestive of MS Form N/A; Poser criteria, McDonald 2001 criteria	EDSS changes	465	Time series Multivariate analysis	25(OH)D level	Sex, age at baseline, treatment group, baseline T2 lesion score, type of clinically isolated syndrome (BMI and steroid use explored)	A 50-nmol/L increase in 25(OR)D levels was associated with a reduction of 0.16 steps in EDSS scores (p = 0.11); 25(OH)D concentrations >/= 50nmol/L predicted lower EDSS during subsequent 4 years (p = 0.004)	
Dastagir, 2013[33] concurrent	US	MS center patients Relapsing MS patients (R-R or SP); criteria N/A	EDSS score	100	Cross-sectional Multiple regression	Vitamin D levels	Race, age, disease duration, time of onsite of Rx	Vitamin D level showed significant inverse correlation with EDSS (data N/A)	
Fragoso, 2012[39] retrospective	South America	Patients with MS from Argentina, Brazil, Chile, and Peru, mean age 40.8 (SD 12.6) years, mean disease duration 8.2 (SD 15.5) years, 29.1% female Form N/A, mean EDSS 2.48 (SD 2.34); Poser criteria, McDonald 2005 criteria, McDonald 2001 criteria	Progression to EDSS 6	1207 cases, 1207 controls	Case-control ANOVA, chi-square test, linear regression, correlation	Month of birth in different latitudes of South America	Latitude, age, disease duration, gender	No difference in disease progression in relation to the month or season of birth (numerical data N/A)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Gelfand, 2011[41] concurrent	US	African Americans with MS, mean age 21.9 (SD 11.2) years, 55.9% female, 18.7% European genetic ancestry Form N/A, MSSS 6.1(CI 4.8, 8.1); McDonald 2001 criteria	MSSS score	339 cases, 342 controls	Cross-sectional Correlation	25(OH)D levels	Age, gender, HLA-DRB1*15 status, latitude		No linear association between MSSS and vitamin D status (p = 0.57), no association between low vs high MSSS and deseasonalized or unadjusted vitamin D (OR 0.79, p = 0.86; OR 1.01, p = 0.97)
Hatamian, 2013[45] concurrent	Iran	Patients of MS Society with R-R confirmed by clinical findings and MRI, mean age 28.4 yrs, 70% female R-R with EDSS score < 5.5 and in remission; criteria N/A	EDSS score	52 MS patients, 52 healthy participants	Case-control Multiple linear regression analysis	25(OH)D level	Duration of disease, sex, age	Vitamin D was not associated with EDSS (beta = -0.01, p = 0.34) in univariate analysis; in adjusted model duration of disease was the only significant contributor to EDSS	
Lucenti, 2014[58] retrospective	Italy	MS patients, mean age 32 (SD 10.4) years, mean disease duration of 8.8 (SD 7.8) years, 65% female, 84% R-R and SP, 16% PP, median MSSS 3.86 (CI 3.55, 4.14); criteria N/A	MSSS score	1782	Cross-sectional Quantile regression	Month of birth	Gender, age at onset, clinical form		Month of birth had no impact on disease progression
Knippenberg, 2011[50] concurrent	The Netherlands	Outpatients with MS, 73% female, mean age 44.2 R-R, SP, PP; criteria N/A	EDSS score	59	Cross-sectional Correlation	25(OH)D serum level	N/A	Vitamin D did not reach statistical significance (r = -0.198)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Koch, 2008[51] retrospective	Canada, The Netherlands	Canadian MS database 29.6% males, mean age at onset 30.6, mean disease duration 20.1 years (SD 9.9); Dutch database 33.3% males, mean age at onset 32.9, mean disease duration 17.98 years (SD 10.4) Canadian: 12.4% PP, 87.2% R-R; Dutch 29.4% PP, 87.6% R-R; Poser criteria	Time to EDSS 6, time from MS onset to secondary progression, age at secondary progression	N = 2837; N = 810	Cross-sectional Kaplan-Meier survival analysis	Month of birth	N/A	No association between the month or season of birth and disease progression could be found that was reproducible in both cohorts	
Kragt, 2009[53] concurrent	Europe, The Netherlands	MS patients 68% female, 98% Caucasian, and mean 11.2 years duration, 98% born in the Netherlands, 64% of women premenopausal Definitive MS; Poser criteria	EDSS score	103 MS and 110 healthy controls	Case-control Correlation	Summer and winter serum 25(OH)D concentrations	N/A	No significant correlation between summer and winter vitamin D and summer and winter EDSS in sample; but in women r = -0.25 (summer, p = 0.044) and r = -0.29 (winter, p = 0.020)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Niino, 2013[70] concurrent	Japan	MS patients from Medical Center and Neurology Clinic, 90% female, mean age 40.8, mean age onset 30.1 years, mean and median age of disease duration 10.8 and 10.5 years 69% remitting phase, 33% relapsing phrase, 21% SP; McDonald 2010 criteria	Decreasing EDSS score and MSSS	43 cases, 34 controls	Case-control ANOVA	1,25(OH)2D, 25(OH)D, Vitamin D-binding protein	N/A	Negative correlation between 25(OH)D and EDSS (r = -0.53, p < 0.01)	25(OH)D levels in SPMS patients were decreased compared with R-R patients at remitting phase (p < 0.01); serum 25(OH)D correlates negatively with disease severity in R-R in the remitting phase and SP MS
Shahbeigi, 2013[86] concurrent	Iran	Neurology clinic patients, 76% women, mean age 34 (SD 9.1), mean disease duration 6 years (5.14) Mild (73%), moderate (11%), and severe (16%) MS; mean EDSS score 2.76 (SD 1.93); McDonald 2005 criteria	EDSS score	98	Cross-sectional Correlation	25(OH) Vitamin D3 concentration	N/A	Significant inverse correlation between EDSS and vitamin D level (r = -0.168, p = 0.049)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Smolders, 2008[90] concurrent	The Netherlands	Outpatient clinic patients, 75% female R-R 47%, SP 32%, PP 18%, unknown 3%; McDonald 2001 criteria	EDSS score	267	Cross-sectional T test, Mann-Whitney U test, linear regression model, poisson regression model	25(OH)D serum levels, 1,25(OH)2D	Sex, age, disease course (years)	Raw 25(OH)D levels correlated negatively with EDSS, there was no association between EDSS score and raw 1,25(OH)2D levels (p = 0.065); when vitamin D levels were tested as predictors of EDSS score, only the adjusted 25(OH)D level was an independent predictor, when the levels were considered as dependents of disability, only 25(OH)D was independently predicted by EDSS score (OR−3.155, CI -4.936, -1.374); 1,25(OH)2D level was not dependent upon disability	
Soilu-Hanninen, 2008[91] prospective	Finland	MS patients, mean age 34.1 (SD 1.5 years), mean time from the diagnosis of definite MS 5.6 years (range 6-15 years); healthy laboratory personnel living in the same area Form N/A, Mean EDSS 2.4 (range 0-5); criteria N/A	EDSS progression during 1 year	Treatment 23, Control 23	Case-control Logitudinal analysis	Vitamin D (25(OH)D) level	Grouped by winter, spring, summer, and autumn serum 25(OH)D levels	No correlation between vitamin D nutrition and EDSS progression (p = 0.07)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Sternberg, 2013[95] retrospective	US	MS patients: 75.7% female, mean age 55.6 (SD 11.5) years, mean disease duration 19.0 (SD 9.8) years 61% R-R, 31.6% SP, 7.4% PP; EDSS 4.1 (SD 2.2); criteria N/A	EDSS, MSSS score	206	Case control Regression analyses	Vitamin D3 plasma level	Cardiovascular drugs, smoking	Vitamin D level was inversely associated with EDSS (p = 0.05) and MSSS (p = 0.04)	
Thouvenot, 2014[100] concurrent	France	Files from MS clinic, age 45.3, 12.1 average years of disease, 72% women PP, SP, R-R; McDonald 2005 criteria	EDSS score	181	Other retrospective cohort analysis Kruskal-Wallis to compare vitamin D levels between MS types, Wilcoxon test comparing vitamin D levels in different origins	25(OH)D plasma level	N/A	Vitamin D level associated with EDSS score in bivariate model OR = 2.87 (p = 0.0012)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Van der Mei, 2007[103] concurrent, retrospective	Australia	Recruitment at local MS societies, eligible cases had cerebral MRI abnormalities and clinically definite MS RRMS, SPMS, PPMS; Poser criteria	EDSS score	136 MS patients, 272 matched community controls	Case control ANOVA F test Linear regression	25(OH)D status, time in the sun in summer and winter on leisure days in last 3 years, time in the sun in summer during work hours in the last year, past sun exposure, dietary intake last 12 months	Month serum sample was taken, duration of MS since first symptom	EDSS and 25(OH)D level correlation r = -0.38 (p < 0.0001); recent sun exposure was significantly associated with high EDSS (leisure r = 0.39, p < 0.01; during work hours r = 0.40, p < 0.01; no statistically significant correlation with past sun exposure or dietary intake	
Weinstock-Guttman, 2011[108] concurrent	US	MS patients mean age 46.6 (SD 10.6) years, disease duration 13.8 (SD 10.3) years, 71.9% female, 15.2% statin use 85.4% R-R, 11.8% SP, 2.8% PP; median EDSS 2.5, MSSS 3.5 (SD 5.43); McDonald 2010 criteria	EDSS and MSSS score, EDSS 4 or greater	178	Cross-sectional Stepwise regression	Vitamin D levels	Age, gender, race, statin use, lipid indicator variables	Deseasonalized 25-hydroxy vitamin D3 associated with MSSS (p = 0.021) but not included in EDSS prediction	

Note: N/A not available, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

The 17 identified studies provided data on patients in different European countries, the US, Canada, Iran, Japan, Israel, and Australia. Several studies recruited patients through MS registries. Total sample sizes ranged from 46 and 2,837. The majority of studies were concurrent studies, measuring the current status of the proposed risk factor and the outcome of interest simultaneously. Four studies assessed retrospective data (*ie*, predicted outcomes from exposures in the past).[39,51,58,95] Two studies were prospective studies[20,114] reporting on the risk factor and outcome sequentially, with the exposure preceding the outcome measure.

Assessed potential risk factors (as reported) were serum or plasma 25(OH)D levels at the time of assessment, 25(OH)D levels in the summer and winter, 1,25(OH)2D, vitamin D-binding protein, vitamin D levels not further specified, dietary vitamin D intake, sun exposure in the summer, sun exposure in the winter, time in the sun on leisure and on work days, and the month of birth.

Several studies reported on the correlation between 25(OH)D levels and EDSS scores, either reporting the correlation coefficient, the p-value, or paraphrasing the association. No other specific risk factor (*eg*, sun exposure) and specific outcome (*eg*, MSSS score) combination was assessed in more than one study. Only one study reported on the change between relapsing-remitting MS to secondary progressive MS. Koch et al[51] analyzed the month of birth and the time from MS onset to secondary progression in sample of patients with primary progressive or relapsing-remitting MS. Half the studies adjusted for potential confounders, such as age and duration of disease.

One of the prospective studies reported that 25(OH)D levels of 50nmol/L at up to 12 months predicted lower disability during the subsequent 4 years.[20] The other prospective study reported a statistically non-significant correlation between vitamin D nutrition and EDSS progression, but it was unclear whether the study had sufficient power to detect an effect.[91] The quality assessment of the two prospective studies is shown in the appendix. The study by Ascherio et al was a clinical trial sample,[20] rather than derived from a large and broader in scope MS registry sample. The study by Soilu-Hanninen was very small (23 patients with MS) and may also not be a good representation of the population of interest.[114]

Another large group of studies reported on smoking and effects on disease progression, as documented in the next evidence table.

Table 2. Evidence for KQ1 (MS Progression Risk Factors): Smoking

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Healy, 2009[46] retrospective	US	1465 out of 1745 patients who completed questionnaire at MS center R-R (N = 1020), SP (N = 212), primary progressive (PP) (N = 63), progressive relapsing (PR) (N = 24), CIS (N = 106), unspecified demyelinating disease (N = 39), or suspected MS (N = 1); McDonald 2005 criteria	EDSS score, MSSS, time to conversion from R-R to SP, proportion of patients who progressed on EDSS after 2 years/ after 5 years (increase in EDSS score)	1465	Cross-sectional Kruskal-Wallis, Wilcoxon, chi-square test, Cox proportional hazard model	Smoking history (smoking status, age of starting and quitting, average number of cigarettes smoked per day)	Age, disease duration from first symptom, gender	EDSS was significantly higher in current smokers (p < 0.0001) but not significantly different in ex-smokers (p = 0.22) compared to never smokers; EDSS was significantly lower in the light smoking group compared to the moderate smoking group (p = 0.040) and compared to the heavy smoking group (p = 0.025)	Conversion from R-R to SP occurred at faster rate in current smokers than never smokers (HR 2.50, CI 1.42, 4.41) but was similar in ex-smokers and in never smokers (HR 1.05, CI 0.59, 1.84); MSSS was significantly higher in the heavy smoking group compared to the light smoking group (p = 0.038) and the moderate smoking group (p = 0.048); probability of a PP course was higher among current smokers (OR 2.42; CI 1.09, 5.35) or ex-smokers (OR 1.91; 95% CI 1.02, 3.58) than never smokers

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Hernán, 2005[47] retrospective	UK	Individuals with a confirmed diagnosis of MS and 2 years or more of medical history prior to diagnosis available R-R; Poser criteria	R-R converting to progressive course (continuously worsening disability lasting 6 months or more as determined by 2 independent reviewers)	201	Case-control Cox proportional hazards regression	Current, past or never smokers; ever vs never smokers; according to medical records	Age at first symptoms, sex, first symptoms including motor deficits		Incidence rate ratio of secondary progression was 3.6 (CI 1.3, 9.9) for ever smokers compared with never smokers; 80% of progression occurred by 4.6 years of follow-up in smokers and by 5.3 years in nonsmokers
Jansons, 2011[48] retrospective	US	Patients with progressive MS Established progressive MS; criteria N/A	Time to progression from onset of MS in patients with relapsing-remitting MS; age at progression onset; time to EDSS 6 after progression onset	756	Cross-sectional Cox regression	Smoking (ever vs never; current vs previous; higher vs lower than mean pack-years)	Gender, age, number of 1st two year relapses, immune-therapy, PPMS vs SAPMS vs SPMS, post-progression relapses, symptoms at MS onset, CSF positivity		More than 19 pack-years of smoking was independently associated with shorter time to progression (p = 0.015); smokers reached EDSS 6 ~5 years earlier than never smokers (p < 0.001); smoking alone very strongly predicts an earlier onset of progression and disability after progression in MS

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Koch, 2007[52] retrospective	The Netherlands	Patients in MS database, definitive MS meeting Poser criteria Benign relapsing-remitting, R-R, SPMS, PPMS; Poser criteria	Benign relapsing-remitting, R-R, SPMS, PPMS; age at onset of SP, age at onset of PP disease; time from disease onset to EDSS 4, time from disease onset to EDSS 6; EDSS score	364	Case-control Conditional logistic regression and Cox hazard ratio	Smoking history: current status, starting and quitting dates, nonsmoking periods, number of cigarettes smoked, number of smoked pack-years before and after onset	Gender	No significant differences in the time to EDSS scores 4 and 6; total pack-years were not significantly correlated with EDSS in the total sample but in women (r = -0.16, p = 0.01)	In patients with PPMS, none of the variables had a significant effect on the age of progression
Maghzi, 2011[59] retrospective	Iran	Patients from MS registry; smoking group: 78.5% female, mean age 32.75 (SD 8,68) years, mean age at onset 27.42 (SD 7.91) years; control group: 46.5% female, mean age 32.86 (SD 9.65) 83.2% R-R, 2.9% PP, 13.9% SP course in the smoking group; McDonald 2005 criteria, McDonald 2001 criteria	Progression (EDSS/ disease duration)	516	Cross-sectional Conditional logistic regression	Ever/never smoker, smoking history, smoking duration, pack-years smoked	Age, gender	No difference in disease progression (EDSS/ disease duration) between smokers and nonsmokers (0.54, SD 0.42 vs 0.49, SD 0.48) in male patients	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Manoucherhrinia, 2013[61] retrospective	UK	Patients registered in MS specialist clinic database, 270 male, 625 female, mean age 49 years, mean duration of illness 17 years CIS, suspected MS, R-R, SP, PP; Lublin & Reingold criteria	Reaching EDSS 4, reaching EDSS 6	895	Cross-sectional Linear regression, Cox proportional hazard regression model	Smoking status (nonsmoker, stopped before onset, stopped after onset, current smoker)	Sex, onset age, use of DMT, initial course (R-R, PP)	RR of reaching EDSS 6 was higher in smokers compared to nonsmokers; risk of reaching EDSS 4 and 6 in ever-smokers vs never-smokers was 1.34 (CI 1.12,1.60) and 1.25 (CI 1.02, 1.51); current smokers showed 1.64 (CI 1.33, 2.02) and 1.49 (CI 1.18, 1.86) times higher risk of reaching EDSS 4 and 6 compared with nonsmokers; ex-smokers had a significantly lower risk of reaching EDSS 4 (HR 0.65, CI 0.50, 0.83) and 6 (HR 0.69, CI 0.53, 0.90) than current smokers, and there was no significant difference between ex-smokers and nonsmokers in terms of time to EDSS 4 or 6	No association between smoking status and PP vs R-R type at onset

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Pittas, 2009[76] prospective	Australia	Patients with MS, female 69.2%, mean age 48.2 years (SD 11.4), median age of MS onset 33.5 years, mean disease duration 14.1 (SD 10.3) years R-R at cohort entry 75%; mean EDSS 3.7 (SD 2.3); Poser criteria, McDonald criteria	MS progression (MS Severity Scale [MSSS])	203	Experimental Mixed effects linear regression	Pack-years smoked in the past 6 months at entry, ever smoker, total pack-years prior to MS, pack-years from onset, current smoker	Entry MSSS and EDSS, age, gender, IMT use, education level, and month of review		Cumulative pack-year smoked after cohort entry was associated with an increase in longitudinal MSSS (p < 0.001)

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Roudbari, 2013[115] retrospective	Iran	Patients registered in the MS Society (Guilan, Iran) database; mean age 34.8 (SD 9.5) years, 74% female, mean age at disease onset 1.7 (SD 2.3) years, 14% smokers, 86% nonsmokers R-R 64%, SP 36%; McDonald 2005 criteria	Risk of progression	524 included, 400 responded	Cross-sectional Cox regression	Smoking (pack-years smoked; 20 cigarettes smoked per day for 1 year = pack-year; nonsmokers vs < 10 pack-years vs > 10 pack-years)	Age on disease onset, number of relapses per year, gender		Compared with nonsmokers, current smokers who continued smoking after MS diagnosis and patients who started smoking after MS diagnosis showed a RR of 2.43 (CI 1.2, 4.8; $p < 0.001$) and RR 3.55 (CI 1.3, 9.2; $p = 0.007$) for MS progression; HR for smokers vs nonsmokers was 2.25 (CI 1.3, 3.99; $p = 0.004$); risk of SP was 2.43 times higher (CI 1.28, 4.6; $p = 0.007$) for greater numbers of cigarettes smoked per day vs nonsmokers

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Sundström, 2008[97] prospective	Sweden	Respondents MS epidemiological survey and interviews, 64% female R-R, SP, progressive from onset; criteria N/A	Progressive disease (PP, SP, or progressive relapsing) determined during interview, neurological exam, and medical records; progressive disease from onset, conversion to progressive disease (R-R, SP), time to progressive disease based on EDSS	122	Cross-sectional Multivariate Cox regression	Self-reported smoking habits; ever smoker (had to have started before MS onset to be included), never smoker; early start (15 or younger) or later start	Gender, age at disease onset, relapsing-remitting MS cases		After a median of 6 years disease duration, progressive disease was significantly more likely to occur in ever smokers compared to never smokers (p = 0.006); progression was most likely in patients who started smoking early compared to later (p = 0.005) or never smokers (p < 0.001); cases with late disease onset had 3x higher risk and ever smokers had 2x as high a risk for progression
Tepavcevic, 2010[112] prospective	Serbia	Patients with MS, age 18-60 years EDSS < 8; McDonald criteria	EDSS score	98	Prospective followup T-test, linear regression	Cigarette smoking status at baseline	Baseline EDSS, gender	The baseline smoking status showed independent predictive value on development of physical disability (p = 0.001)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Zivadinov, 2009[111] retrospective	US	Patients with MS at MS center with MRI exam, age 18-80 years, mean age 44 (SD 10.2), mean disease duration 12.1 years (SD 9.1), 93% white, 6% black; 79% female R-R: 68.6%, CIS: 5.7%, SP: 22.9%, PP: 2.8%; criteria N/A	EDSS score	368	Cross-sectional Polytomous universal model ordinal regression method	Smoking: never-smoker, ever-smoker, active smoker; mean duration; average number of packs per day	Age, disease duration, treatment duration	Median EDSS for the ever-smokers was 3.0 compared with 2.5 for the never-smokers; association of EDSS score with never-smoker/ever-smoker status (p = 0.004)	

Notes: N number of participants, N/A not available, SD standard deviation, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, RR relative risk, vs versus

We identified 11 studies that exclusively evaluated the effect of smoking on disease progression. Studies from the US, different European countries, Iran, and Tasmania contributed research. All but 3 studies were retrospective analyses. Participants were recruited at MS centers and registries. The number of included participants ranged from 98 to 1,465.

Specific assessed risk factors were: current smoking status; smoking status as baseline; age of starting and quitting; early (15 years or younger) or later smoking start; number of cigarettes smoked per day; current, past, or never smokers; ever versus never smokers; number of cigarette pack-years in total; pack-years smoked in past 6 months; smoking status before and after onset of MS; nonsmoking periods; and smoking duration in years. Information came from self-reported survey data or medical records. All studies used multivariate methods controlling for demographic and disease characteristics.

Studies used a range of outcome predictors, assessing continuous outcomes, dichotomous status variables, and time to event data. The individual measures were EDSS scores, MSSS scores (measure of rate of disease progression, standardized for disease duration), EDSS score divided by disease duration, time to conversion to secondary progression from onset, time from disease onset to EDSS 4, time to EDSS 6, reaching EDSS 4 during study period, reaching EDSS 6, experiencing progression, age at onset of secondary progression, and proportion of patients who progressed on EDSS after 2 years/ after 5 years (increase in EDSS score).

Three prospective studies were identified. All reported a statistically significant effect of smoking on MS but reported on different outcome measures.[76,97,112] The detailed quality assessment of the prospective studies is shown in Appendix C. Two of the studies did not indicate major flaws. One was published as an abstract only and lacked detail.

The following evidence table shows studies that investigated childbirth-related factors such as the use of epidural analgesia during childbirth.

Table 3. Evidence for KQ1 (MS Progression Risk Factors): Childbirth-associated Factors

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Confavreux, 1998[30,116] prospective	Europe, multiple countries	Women had MS before pregnancy and were pregnant, referred by European neurologist; duration of MS before pregnancy 6 years, age at beginning of pregnancy 30 96.6% R-R, 3.14% SP; mean EDSS at baseline 1.32; Poser criteria	EDSS or DSS	254	Time series Logistic regression	Epidural analgesia, breast feeding	Age, duration of disease, occurrence of relapses before and during pregnancy		No acceleration of the progression according to use of epidural analgesia (p = 0.66) or breast-feeding (p = 0.27); same finding 2 years post-partum
Gava, 2014[40] retrospective	Italy	Women with MS at an academic medical center SP and R-R; McDonald 2010 criteria	EDSS score	174	Cross-sectional Logistic regression analysis	Oral contraceptives use	Age, duration of disease, age of menarche, use of DMT, parity	Ever users of combined oral contraceptives had lower EDSS scores compared to never users (p = 0.044)	
Lu, 2013[57] retrospective	Canada	Female MS patients with live births, British Columbia Perinatal Database Registry, mean age 32 years 99% relapsing-onset, 1% PP; Poser criteria, McDonald 2005 criteria	EDSS 1-1.5 vs 2-2.5 vs 3 or higher	431	Cross-sectional Multivariate models	Obstetrical epidural and spinal anesthesia use during delivery	Age, parity, comorbidities, mode of delivery, birth weight, gestational age in weeks	EDSS was not associated with use of either type of anesthesia (p > 0.1)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Pastò, 2012[72] prospective	Italy	Women with pregnancies between 2002 and 2008 in 21 MS centers, mean age at conception 31.8, mean age at onset 24.7, mean disease duration at conception 7.1 years Form N/A, mean EDSS at conception 1.5 (SD 1.0); McDonald 2010 criteria	Progression on EDSS	415	Cross-sectional Multivariate analysis	Epidural analgesia delivery, cesarean delivery	Age at MS onset, age, disease duration, EDSS at conception, DMT before pregnancy, number of relapses in year before pregnancy / during pregnancy, exclusive breastfeeding	Epidural analgesia delivery and cesarean delivery were not associated with disability progression after delivery	
Sena, 2012[85] retrospective	Europe	Female MS patients registered with hospital, with R-R MS, median disease duration 6.2 (SD 5.1) years, never-users vs past-users vs after-users: mean age 37.3 (SD 10.2) vs 38.6 (SD6.8) vs 32 (SD6.6) years, mean age at disease onset 29.9 (SD 9.8) vs 34.6 (SD R-R; McDonald 2005 criteria	EDSS, MSSS scores; benign course (MSSS < 2.5)	132 (53 never-users, 26 post-users, 54 after-users)	Cross-sectional Multivariate linear and logistic regression	Oral contraceptive use	Age, gender, smoking, childbirths, age at disease onset, disease duration, relapse rate, age of menarche, age at onset of OC use, OC use duration	After-user patients had lower EDSS and MSSS scores than never users (p < 0.001, p = 0.002) and past users (p = 0.015 and p = 0.002)	Patients who took oral contraceptives after disease onset were more likely to have a more benign disease course (MSSS < 2.5) than never / past users (OR: 2.97; CI 1.24, 6.54; p = 0.011)

Notes: DMT disease modifying treatment, N number of participants, N/A not available, SD standard deviation, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

We identified 5 studies reporting on pertinent risk factors. Study sample sizes in the studies varied widely, ranging from 174 to 2,105 included women. Studies used different outcomes measures: EDSS, DSS, or MSSS scores. One study included only patients with relapsing-remitting MS. It predicted EDSS and MSSS scores and reported on the odds ratio of having a more benign disease course defined as MSSS below 2.5.[85]

The studies evaluated a number of potential risk factors that may be associated with MS progression: epidural and/or spinal analgesia during delivery, breast feeding, use of oral contraceptives, and cesarean delivery. All studies adjusted for covariates in the analyses, in particular the age at the time of the first child and age at MS onset.

Three studies were retrospective analyses but 2 studies assessed women at the time of pregnancy and followed them for a number of years.[30,72] The quality assessment of the prospective studies are shown in the appendix. The main source of potential bias was confounding due to selection bias. It is possible that participants self-selected the exposure or intervention, such as breast feeding, because of their EDSS scores. Hence studies may show reverse causality with EDSS scores (the outcome) influencing the variable assessed as the risk factor.

We also identified studies that exclusively reported on diet and its effects on disability and progression of MS, as documented in the following evidence table.

Table 4. Evidence for KQ1 (MS Progression Risk Factors): Diet

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Aupperle, 2005[21] concurrent	US	Patients with MS, 84% female R-R; criteria N/A	EDSS	38	Case-control Analysis N/A	Red blood cell fatty acids, dietary fatty acids intake	N/A	None of the fatty acids were related to disability	
Foster, 2012[38] retrospective	US	MS patients, mean age 47.8 (SD 12.5) years, mean disease duration 15.2 (SD 10.5) years, median EDSS 3.0 (SD 4.0) 93.5% Caucasian American, 4.5% African American, and 5% other races, 76% female 66.2% R-R, 22.4% SP, 7% relapsing SP, 4.4% PP or primary relapsing; McDonald 2001 criteria	EDSS and MSSS scores	272 cases, 151 controls	Cross-sectional Regression analyses	Duration of alcohol consumption after MS diagnosis 15 years or fewer (compared to no consumption of alcohol or consumption for > 15 years)	Age, age of onset, sex, disease duration	EDSS scores were lower in patients who had consumed for 15 years or fewer after MS onset compared those who did not consume alcohol or consumed it for > 15 years; pattern of non-linear dependence suggests that moderate duration of alcohol use does not have adverse effects	
Kurtzke, 1973[54] retrospective	US	Men first diagnosed with MS in US Army hospitals during World War II Form N/A; Schumacher criteria	DSS score change (better, same, worse after hospitalization)	517	Other Count comparison	Diet	N/A		Diet: 28% better, 56% the same, 16% worse; patients with hospital routine without specific treatments: 19% better, 74% same, 8% worse.

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Plow, 2012[77] concurrent	US	N/ARCOMS registry, 292 respondents out of 1000 randomly selected surveyed patients, 79.7% female, average duration since diagnosis 15 (SD 8.30) years 63% R-R, 20% SP, 8.1% PP, 6.6% progressive relapsing MS; criteria N/A	Type of MS (R-R, progressive, unknown)	292	Cross-sectional Logistic regression	Healthy nutritional behavior indicator defined by whether participants answered 4 out of 5 questions with the response of "often": 1) make good food choices, 2) eat 5 servings of fruits and vegetables a day, 3) limit fat intake, 4) read labels, 5) eat regularly	Gender, optimism/ pessimism, BMI, physical activity, emotional self-management, communication with physician		Nonsignificant correlation type of MS-nutritional behavior ($p = 0.38$)
Swank, 1990[98,117] prospective	US, Canada	Patients who maintained contact with MS clinic Form N/A, minimum, moderate, and severe disability; other criteria	Average worsening in disability grade, percentage of deaths due to MS	144	Case series t-test	Good dieters (fat consumption = < 20 g/day) vs poor dieters (consumption > 20 g/day), period checks of eating habits (presumably) self-reported	N/A		In each of the disability groups the average worsening in disability grade and the percentage of deaths of the poor dieters significantly exceeded those of the good dieters; greatest difference occurred for minimum disability at study entry ($p < 0.0001$)

Notes: N number of participants, N/A not available, N/ARCOMS North American Research Committee on Multiple Sclerosis, SD standard deviation, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

We identified 4 studies that exclusively looked at dietary behavior. All studies were conducted in the US or the US and Canada.

One study reported concurrent data, meaning current dietary fatty acid intake, in patients with relapsing-remitting MS. The study, published as a conference abstract, lacked detail but stated that none of the assessed fatty acids were related to disability.[21]

Two studies were retrospective analyses.[38,54] One reported on the duration of alcohol consumption after MS diagnosis. The other focused on men on active duty in the US Army and reported on the disease course for patients that were put on a specific diet in the hospital, compared to patients without administration of a specific therapy.[54] The study did not report a statistical analysis but, applying Fisher's exact test to the raw data, we find that the difference between groups was not statistically significant. No information was available on the specific diet and approaches may have varied across patients and hospitals.

A fourth study reported on the Swank diet in multiple publications.[98,118,119] The prospective study compared "good dieters," meaning people with fat consumption of 20g per day or less, and "poor dieters" who exceeded the fat consumption limit. Patients who were given the diet advice were followed for 34 years. The study reported that in each of the disability groups, the average worsening in disability grade and the percentage of deaths of the poor dieters significantly exceeded those of the good dieters. The detailed quality assessment of the study is shown in Appendix C. The main concern is the ascertainment of the risk factor, which in this case is the compliance of the participants with the diet and self-reports that determined the classification into good or poor dieters.

A small group of studies exclusively reported on exercise behavior as shown in the following evidence table.

Table 5. Evidence for KQ1 (MS Progression Risk Factors): Exercise

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Marrie, 2009[62] retrospective	US, Canada	N/ARCOMS questionnaire respondents, 94.5% white, 75.8% women, mean age 52.7; mean age at onset 31.2, mean age of diagnosis 31.2, mean disease duration 21.5 Form N/A, PDDS mild disability 35.4%, moderate disability 11.95, severe disability 52.7%; criteria N/A	PDDS category	8983	Cross-sectional Multivariate regression	Physical activity, leisure-time activity (scale from 1 = inactive to 4 = heavy activity) in the last year	Smoking status, physical activity level		Physical activity decreased steadily with increasing disability
Milivojevic, 2013[64] retrospective	US	MS patients, 65.1% female, mean age 38 (range 21-58), mean disease duration 5.4 years (range 1-16) Form N/A, mean EDSS 1.7 (range 0-5.5); neurological evaluation	EDSS score	63	Cross-sectional T-tests	Use of physical rehabilitation	N/A	Patients who used inpatient, outpatient, and home-based rehabilitation had higher levels of impairment compared to patients who were not rehabilitated (p = 0.002, p = 0.004, p = 0.0021)	
Motl, 2012[68] prospective, retrospective	US	MS patients recruited through National MS Society, mean age 45.9 (SD 9.6) years, mean disease duration 8.8 years (SD 7.0), median PDDS 2, 86.6% female, 91% Caucasian, well-educated R-R; criteria N/A	Progression in PDDS	269	Time series Latent growth curve modeling	Premorbid physical activity	Gender, age disease duration since diagnosis, disease-modifying therapies		Premorbid physical activity predicts the linear change in disability scores (PDDS) (p < 0.005)

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Shammas, 2014[87] prospective	Germany	Patients with definite MS and EDSS < 5, 64% female, mean age 41 years (SD 9.3), mean disease duration 12.18 years (SD 10.67), recruited in MS clinic 8/11 R-R, 1/11 PP, 2/11 SP, mean EDSS 3.6 (SD 1.66); McDonald 2010 criteria	EDSS score	11	Other Correlation	Total number of steps taken during study period	Age, gender, weight, height, shoe sizes	Number of steps negatively correlated with EDSS score (r = -0.54, p = 0.01)	
Stuifbergen, 2006[96] prospective	US	Patients from MS Society patients and advertisments in rural newspapers, mean age 49.4 years, 83% women R-R, PP, SP, PR; criteria N/A	Incapacity Status Scale (ISS) scores	611	Time series Multivariate latent curve modeling	Exercise behavior (HPLP-II exercise/ physical activity subscale)	Age, sex, years since diagnosis, residency type, attrition		Exercise behaviors and functional limitations were negatively correlated (r = -0.34); time 1 exercise scores were negatively correlated with annual change rate in functional limitations (r = -0.17); increasing rates of change in functional limitations correlated with decreasing rates of change in exercise behavior (r = -0.25)

Notes: N number of participants, N/A not available, N/ARCOMS North American Research Committee on Multiple Sclerosis, SD standard deviation, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

The 5 studies addressing exercise were conducted in the US, US and Canada, and Germany. The number of included participants ranged from 11 to 8,983. The studies included retrospective and prospective analyses.

A large retrospective study used data from 8,983 survey respondents.[62] It reported an association between self-reported physical activity in the last 12 months and disability measured with the Patient Determined Disease Steps (PDDS), indicating that physical activity decreased steadily with increasing disability. The PDDS is a self-report measure of disability using a scale of 0 (normal) through 8 (bedridden), developed as a surrogate for the EDSS. Another retrospective study assessed the use of physical rehabilitation and reported that patients who had used inpatient, outpatient, or home-based rehabilitation had higher levels of impairment compared to patients who were not rehabilitated.[64]

A very small, prospective study in 11 participants reported a negative correlation between objectively measured physical activity over one year and EDSS scores.[87] No other data were reported that may inform the temporal association between the 2 variables, such as the effect of physical activity at baseline on MS progression.

A prospective study by Stuifbergen et al, on the other hand, assessed exercise behavior in a sample followed for 5 years. Exercise scores at the first assessment time point were negatively correlated ($r = -0.17$) with annual change rate in functional limitations due to MS (Incapacity Status Scale, ISS; self-reported degree of impairment).[96] A prospective study by Motl et al[68] reported that participants with higher premorbid physical activity levels reported less change in disability over time (PDDS scores) compared with those who reported lower premorbid physical activity.

The risk of bias evaluation for the prospective studies is shown in the Appendix C. The objectively measured study only included 11 patients and data were not prospectively analyzed.[87] The other prospective studies were higher quality but neither reported on EDSS scores, the primary outcome of this review.

The next evidence table summarizes studies that addressed other exposures not captured in previous evidence tables, such as exposure to trauma.

Table 6. Evidence for KQ1 (MS Progression Risk Factors): Other

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Baghizadeh, 2013[22] retrospective	Iran	Neurology and MS clinic-attending patients, 78% female, mean age 34 yrs, mean age of onset 24 yrs R-R, SP, PP; McDonald criteria	MSSS scores (chronic, mild-moderate, advanced-accelerated, aggressive-malignant disease severity)	338	Cross-sectional Ordinal logistic regression	Education	Unclear		Education did not predict getting worse (p = 0.074)
Detels, 1982[35] prospective	US	MS onset between Jan 1, 1960 and Dec 31, 1969, born in the US, white, residents in 1970 in either a low-prevalence (Los Angeles County, CA) or in a high-prevalence area (King and Pierce Counties, WA); LA: 67.7% female, WA: 74.8% female; mean age at onset 33.4 yrs Form N/A; Schumacher criteria	3-point scale: 1) walking without aids; 2) walking with aids such as braces, crutches, or canes; and 3) restricted to wheelchair or to bed (self-reported)	560 cases in LA, 326 cases in WA	Cross-sectional Multivariate regression	Geographic regions (high- vs low-prevalence area)	Age at onset, residence, sex, disability status at intake		Progression to a non-ambulatory status or death was significantly greater among patients who lived in LA county (low-prevalence area)
Sibley, 1990[89] retrospective	US	Patients in the community with clinically definitive MS, mean age 43 years, female to male ratio 1.6 to 1 Form N/A; Schumacher criteria	Mean increase in DSS/year	170 MS patients	Other design Chi-square test	Trauma, different subtypes (dental procedures, minor surgery, major surgery, fractures, sprains, burns, head injuries, abrasions/ lacerations/ contusions)	N/A		Peripheral trauma is not a risk factor for MS progression

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Covariates	EDSS results	Other results
Spitzer, 2012[93] retrospective	Germany	Patients with definite MS attending a MS outpatient clinic, age 18-50 years, mean age 39.7, 73% women, mean MS onset 29.2 years, mean MS duration 10.5 years, mean relapse rate 0.66% 70% R-R, 7% PP, 23% SP, mean EDSS score 3.2; McDonald 2001 criteria, McDonald 2005 criteria	EDSS score, disease progression (EDSS scores divided by years of disease duration)	234 with MS	Case-control Logistic and multiple linear regression	Self-reported childhood maltreatment (CTQ total score, emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect)	Age, sex, education, current depression		Childhood trauma was not associated with disease progression or EDSS
Tuzun, 2010[102] retrospective	Turkey	MS patients with R-R or SP MS; earthquake victim vs control: 66.7% vs 58.8% female, mean age of onset 26.8 (SE 1.3) vs 24.8 (SE 1.2), 68.6% R-R, 31.2% SP, EDSS 3.09 (SE 0.3) (earthquake); 64.7% R-R, 35.3% SP, 3.01 (SE 0.4) (control); McDonal criteria	EDSS score	82	Cross-sectional Logistic regression	Earthquake experience	N/A	Comparable EDSS scores between groups after the earthquake	
Vollmer, 2002[104] retrospective	US	US Veterans and non-veterans from NARCOMS patient registry Relapsing, PP; criteria N/A	PDDS score	2150 Veterans, 2107 non-VHA Veterans, 16119 non-veterans	Matched controls Paired t-test	VHA Veteran, non-VHA Veteran, non-veteran	N/A		PDDS scores 5.0 in VHA, 4 in non-VHA Veterans, 3.6 in non-veterans (p < 0.001 VHA Veteran vs non-veteran)

Note: N number of participants, N/A not available, N/ARCOMS North American Research Committee on Multiple Sclerosis, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, SD standard deviation, vs versus

We identified 6 studies that reported on unique risk factors of interest. Three were US studies, one was conducted in Iran, one in Turkey, and one in Germany. All but one were retrospective studies; one followed patients prospectively.[35] Where reported, studies included a range of MS subtypes. The largest study compared 2,150 VHA Veterans with 2,107 non-VHA Veterans and 16,119 non-veterans.

In terms of risk factors, studies reported on education, peripheral trauma (*eg*, surgery, head injuries), childhood maltreatment, geographic regions with high or low MS prevalence, recent earthquake exposure, and being a VHA Veteran.

A prospective study reported that progression to a non-ambulatory status or death was significantly greater among patients who lived in LA county, a low-prevalence area for MS.[35] The detailed risk of bias assessment for this study is shown in the appendix. Of note, the study measured disability status at follow-up by a self-administered mailed questionnaire; hence, the progression data are not based on physician assessments.

One study used a VA-relevant dataset and reported that VHA Veterans had higher PDDS scores than non-veterans.[104]

The other studies reported no associations between assessed predictors and outcome measures.

The last KQ1 evidence table summarizes all those studies that reported on more than one group of risk factor of interest for this review, for example studies reporting the effect of smoking *and* exercise.

Table 7. Evidence for KQ1 (MS Progression Risk Factors): Multiple

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
Bombardier, 2004[27] concurrent	US	Survey respondents with diagnosis of MS by MRI, 77% female, mean age 48.7 years, mean EDSS 5.7, mean disease duration 11.8 years Form N/A; criteria N/A	EDSS score	739 respondents (out of 1374 surveyed)	Cross-sectional T-test	Possible, current alcohol problems during preceeding month (4 items) vs no alcohol problems; drug or medication misuse during the past month (1 item) vs not	N/A	Respondents with possible alcohol-related problems (p = 0.001) and respondents with drug misuse (p < 0.05) had lower EDSS scores	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
D'hooghe, 2012[36,120-122] retrospective	Belgium	Flemish MS Registry, relapsing vs progressive onset patients: mean age 50.3 vs 58.6, mean age onset 31.5 vs 37.3, mean disease duration 18.8 vs 21.4, female 75.6% vs 62.2%, 33.3% relapsing onset, 34.9% progressive onset, EDSS >= 6 35.9% vs 80%; Poser criteria	Time from onset or from birth to sustained EDSS 6	1431 respondents (out of 3320 invited); 704 with EDSS 6 or more	Cross-sectional Kaplan-Meier survival and Cox proportional hazard regression	Alcohol, coffee, and fish consumption (compared to no consumption); smoking; sun exposure in summer (hours daily), sun exposure in winter, sun exposure compared to peers, sunscreen/protection, working place (inside, both, outdoors); age at starting oral contraception, duration of oral contraceptive intake; health promoting lifestyles profile II (HPLP total score, health responsibility, physical activity, nutrition, spiritual growth, interpersonal relationships, stress management)	Gender, age at MS onset, IMT use	In relapsing MS, alcohol, wine, coffee, and fish consumption were associated with a reduced risk to reach EDSS 6; in progressive onset MS, all n.s. Smoking was associated with an increased risk to reach EDSS 6 in relapsing onset MS; in progressive onset MS, all n.s. except for type of fish (fatty fish associated with increased risk to reach EDSS 6 compared to lean fish). In relapsing onset MS, respondents reporting equal or higher levels of sun exposure than peers had a decreased risk of reaching EDSS 6 In progressive onset MS, the use of oral contraceptives was related to an increased risk. For relapsing onset, HPLP (p = 0.030), health responsibility (p = 0.218),	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
								physical activity (p < 0.001), and nutrition (p < 0.001) were predictive of time from onset to EDSS 6 but not spiritual growth (p = 0,048); time from birth analyses showed physical activity and nutrition to be significant (p < 0.001); for progressive onset, all n.s.	
Goodin, 1999[43] concurrent	US	Survey respondent with definite MS, 78.6% female, 92.5% Caucasian, 2% African American, 2.5% Asian, 3.0% Hispanic, mean age 48.1, mean age at MS onset 31.1, mean duration of symptoms 17.1 years 57.8% R-R, 22.6% SP, 20.1% PP; mean EDSS 4.8 (SD 2.3); diagnosed by a physician, any criteria	EDSS score	168	Cross-sectional Multiple regression	Exercise, consumption of alcohol (5-point scale from never to daily), insurance coverage, physical therapy, getting a 2nd opinion, being happy with medical care or coverage, being denied medical coverage or treatment, other dietary factors	unclear	Exercising (p = 0.001) and consumption of alcohol (p < 0.001) associated with lower EDSS scores; medical insurance coverage (p < 0.001) and physical therapy (p < 0.001) associated with higher EDSS scores; getting a second opinion, being happy with or being denied medical coverage, other dietary factors not associated with EDSS (p > 0.05)	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
Lauer, 1992[55] retrospective	Germany	MS patients, 64.1% female 64.2% benign, 35.8% malignant MS	MS patients with benign (DSS = < 2.0 after 11 or more years' duration) vs malignant (DSS > = 7.0 after less than 16 years' duration) course	81 (52 benign, 29 malignant)	Cross-sectional Logistic regression	Ether anesthesia, brain trauma, vaccination (poliomyelitis, diphtheria, tetanus, influenza), childhood diet breast fed, diet rich in animal fat, predominantly butter, domestic slaughtering, milk daily, unpasteurized milk, 3 or more eggs per week, animal brain, often brain sausage; childhood animal exposures (dog, cat, bird, pig , rats, mice, other rodents, cattle); animal exposure within 5 years before onset (dog, cat, bird, domestic rodents, cattle, pigs); childhood coal heating, wood heating, humid flats, no sewage system, no piped water; frequent environments (farm, industrial plant, fields,	Covariates	Associated with benign course: milk daily (OR 3.03, p = 0.03), grew up with chickens (OR 2.77, p = 0.03), frequent environment meadows/pastures (OR 3.88, p = 0.007), close contact to wood (OR 3.31, p = 0.017); not associated with ether anesthesia, vaccination (poliomyelitis, diphtheria, tetanus, influenza), brain trauma, childhood diet breast fed, diet rich in animal fat, predominantly butter, domestic slaughtering, unpasteurized milk, 3 or more eggs per week, animal brain, often brain sausage, dog, cat, bird, pig , rats, mice, other rodents, cattle, within 5 years before onset dog, cat, bird, domestic rodents, cattle, pigs, childhood coal heating, wood heating, humid flats,	

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
						meadows/pastures, natural waters, forest, close to wood)		no sewage system, no piped water, other frequent environments (farm, industrial plant, fields, natural waters, forest)	
Mandia, 2014[60] retrospective	Italy	MS patients mean age 45 (SD 11.0) years, disease duration 13.6 (SD 9.1) years. Form N/A, mean EDSS 3.0 (SD 2.4), MSSS 3.2 (SD 2.6); McDonald 2001 criteria	MSSS score, MSSS 1 or less (mild) vs MSSS 6 or more (severe)	131	Cross-sectional Multiple linear regression	Smoking (ever, never, ex, current smoker, active/passive exposure), sunlight exposure (frequent vs rare, > 2h/day vs < 2h/day, sunscreen use), diet (vegetarian, egg consumption, fish consumption, consumption of dairy products, liver consumption, vitamin supplementation, fortified foods) in previous 2 years	Age, sex, covariates		Severe MS was predicted by vitamin D (p = 0.001) and sun exposure (p = 0.005) but not smoking or diet

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
McDowell, 2011[63] retrospective	US	Patients with progressive MS, mean age 61 (SD 9.6), between 18 and 65 years old at time of onset, 77% male, born and raised in the USA, registered in the VHA Multiple Sclerosis Surveillance Registry Progressive MS (progressively worsening from symptom onset with or without any recovery from symptoms later in the course), PP, and progressive relapsing MS; McDonald criteria 2001	Time to PDDS 8	219	Other Kaplan-Meier analysis, log rank tests, Cox proportional hazards models	Average fall/winter sun exposure before MS onset, cod liver oil intake at ages 6-15, fish consumption at ages 6-15	Age at symptom onset, MS subtype, onset symptoms, demographics, mononucleosis before symptom onset, smoking before disease onset, type of skin		Median time from disease onset to PDDS 8 was 20 years (CI 16, 29) for low average fall/winter sun exposure compared to 29 years (CI 14, 42) for higher exposure; fall/winter sun exposure HR 2.13 (CI 1.20, 3.78, p = 0.01), cod liver intake HR 0.44 (CI 0.20, 0.96; p = 0.04), fish consumption HR 0.79 (CI 0.45, 1.41; p = 0.43)

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
Mowry, 2012[69] prospective	US	EPIC cohort (5-year longitudinal MS cohort), white MS patients over 18, with EDSS score < 8 from MS center MS or CIS; McDonald 2001 criteria, McDonald 2005 criteria	EDSS score	469	Time series Multivariate regression	25 hydoxyvitamin D level, smoker at baseline (5 years earlier)	Age, sex, ethnicity, DMT	EDSS was not associated with smoking at baseline (IRR 0.09, p = 0.49) but each 10 ng/mL higher vitamin D level was associated with lower subsequent disability (IRR -0.047, CI -0.091, -0.003; p = 0.037)	
Teter, 2008[99] retrospective	US	Female MS patients age 45 and older, NYSMSC registry, mean age 54.2 (SD 7.3), mean disease duration 18 (SD 10.8) years 48% progressive disease at enrolment; criteria N/A	EDSS > 6	2935	Cross-sectional Logistic regression	Educational attainment, sun exposure	Age, disease duration, MS type	Lower educational attainment (OR 1.5, 95% CI 1.2, 2.8) and less sun exposure (OR 1.8, 95% CI 1.2, 2.8) predict EDSS > 6	
Wallin, 2015[105] retrospective	US	Gulf War-era MS cohort with US military service between 1990-2007 Form N/A; criteria N/A	Progression to DSS 6 and DSS 7	2691	Cross-sectional Cox proportional hazard model	Geographic location and occupational status at entry to the military, deployment to a war theater			Deployment to a war theater , geographic location and occupational status at entry to the military were not predictors of progression to DSS 6 and DSS 7

ID Assessment timing	Region	Sample MS form	Predicted outcome	N	Design Analysis	Risk factors	Co-variates	EDSS results	Other results
Weiland, 2014[106,123,124] retrospective, concurrent	Australia, US, Europe	Internet survey, adults diagnosed with MS by a physician Form N/A, physician diagnosis	PDDS converted to normal/ some disability, gait/ cane disability, major mobility support	2469	Cross-sectional Multiple regression	Alcohol (frequency of alcohol use, amount; non-drinker, low level vs high level of consumption, binge drinking; moderate drinking [up to 30g/day for women, up to 45g/day for men] vs low or no alcohol consumption); smoking (current, former, or never smoker; frequency, time since quitting; physical activity; meditation practice, frequency	Gender, age		Disability associated with moderate alcohol consumption (p < 0.001) and smoking status (p < 0.001); being a current smoker increased odds of requiring major mobility support (OR1.9, CI 1.44, 2.5; p < 0.001), being a former smoker associated with increased odds of 1.24 (CI 1.0, 1.5, p = 0.23) compared with never smokers. Those with higher disability had a lower level of physical activity and vice versa (p < 0.001) No association between those who did and did not meditate in PDDS scores but significant association with frequency of meditation and PDDS (more-disabled respondents were more likely to meditate, p < .001)

Note: IRR incidence rate ratio, N/A not available, n.s. not statistically significant, NYSMSC New York State Multiple Sclerosis Consortium, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, RR relative risk, vs versus

The 10 studies that each addressed multiple risk factors of interest were 6 US studies, one which included the data from the Flemish MS registry, one study which was conducted in Germany, one in Italy, and one study which reported on an internet survey which international responders.

The studies addressed a wide range of potential risk factors such as alcohol, wine, coffee, fish, cod liver oil, and fat consumption. Studies also addressed health-promoting nutrition and other dietary factors; alcohol-related problems, drug misuse, smoking; vitamin D levels, sun exposure; oral contraceptive intake; physical activity; meditation practices, spiritual growth; interpersonal relationships; and stress management behaviors. Some studies associated MS progression with insurance coverage and treatment-associated factors; latitude and geographic location; and deployment to a war theater.

Three studies primarily reported on concurrent data[27,43,106] (that is, linking current behavior such as current alcohol intake to EDSS scores). Most studies assessed the effects of prior events, exposures, or behaviors in retrospective studies.[36,55,63,105,106 60,99] The retrospective study by D'hooghe was based on a 2009 survey of people registered in the Flemish MS society, and the data were reported in multiple publications focusing on the effects of alcohol, coffee, fish, and smoking;[36] sunlight exposure;[120] and menarche, oral contraceptives, and self-reported health promotion behaviors.[122] A German study assessed a catalogue of potential risk factors, ranging from exposure to vaccines, childhood diet, exposures to pets and livestock, and environmental factors such as living near an industrial plant.[55]

One prospective study addressed vitamin D levels and smoking. The longitudinal US study reported that EDSS scores were not associated with smoking at baseline but each 10ng/mL higher vitamin D level was associated with lower subsequent disability.[69] The detailed risk of bias assessment for this high-quality study is documented in Appendix C.

Summary of Findings and Quality of Evidence

We identified a large number of studies reporting on potential modifiable risk factors for MS progression. However, studies assessed very specific risk factors (*eg*, vitamin D serum level, sun exposure in the summer 2 hours or more daily, *etc*) and predicted very specific outcomes (*eg*, EDSS scores, time to reach EDSS 6, *etc*). The following summarizes the available evidence for individual risk factors across all identified risk factor studies.

Vitamin D

Vitamin D and sun exposure-associated variables have been addressed in a large number of studies; however, the risk factor analyses used many different approaches, as documented in the evidence tables (see Table 1 and Table 7). The following figure summarizes the correlation between EDSS scores and the physiological vitamin D level of participants. The figure shows a risk factor and outcome measure that was reported in multiple studies that all reported a correlation as the measure of association or allowed computing a correlation from the reported data.

Figure 2: Correlation between EDSS Score and Vitamin D Level
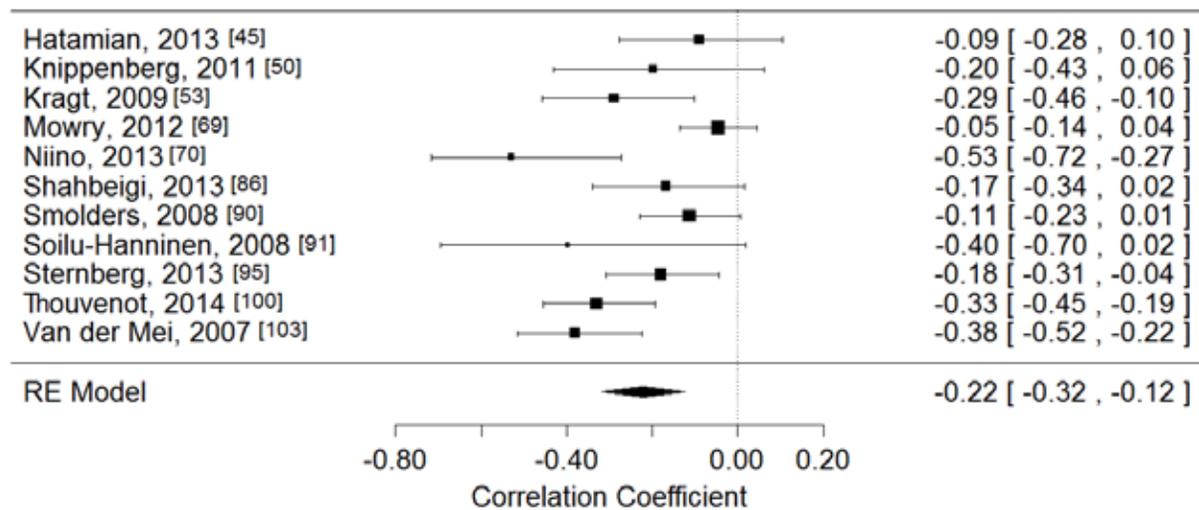
Eleven included studies reported a correlation between vitamin D levels and EDSS scores. Across all available data, there was a weak negative correlation of -0.22 (CI -0.32, -0.12; 11 studies) indicating that lower vitamin D levels are associated with higher EDSS scores. All individual studies suggested the same direction of effects but not all were statistically significant and there was evidence of heterogeneity (I^2 66%). We also identified evidence of publication bias (regression test p = 0.045, rank test p = 0.087). Using the trim-and-fill method of correcting for potentially missing studies, the estimate was slightly lower but still statistically significant (r = -0.20; CI -0.29, -0.11).

Eight data points in the meta-analysis came from concurrent data analyses, assessing current vitamin D level and EDSS scores at the time of data assessment. One retrospective chart review also reported an association.[95] Of the 2 included prospective studies, one highlighted that there was not a statistically significant negative correlation between vitamin D nutrition and EDSS progression.[91] However, the finding is likely to be linked to the small sample size; the reported correlation is in range with other reported results seen in the forest plot. The other prospective study showed higher vitamin D levels to be associated with lower subsequent disability in a multivariate analysis.[69]

An additional prospective study assessing on vitamin D was identified that could not be added to the meta-analysis because it reported on other measures of association. The study reported that values greater than or equal to 50nmol/L at up to 12 months predicted lower EDSS scores (p = 0.004).[20]

The evidence suggesting a correlation between vitamin D levels and EDSS scores was downgraded to only moderate quality of evidence due to *indirectness*. For this systematic review, the correlation between the physiological measures of vitamin D serum or plasma level is an indirect outcome. The review evaluated patient-modifiable risk factors, such as exposure, intake, or behavioral risk factors. The meta-analysis shows a correlation between the physiological level and a progression measure and whether the physiological levels can be directly influenced by the participant is an unresolved question. We did not identify more than one study reporting on intake of vitamin D and a measure of MS progression.

Sun Exposure

Five studies reported on sun exposure and MS progression.[36,60,63,99,103] All were retrospective studies. Four reported a negative association of sun exposure and MS progression or a positive association of increasing disability and reduced sun exposure. One reported an association in patients with relapsing onset MS but not in progressive onset MS. However, all studies used different assessment tools (EDSS, PDDS, and MSSS) and different predictors (time to sustained EDSS 6, time to PDDS 8, a score of MSSS 6 or above, odds of reaching an EDSS score greater than 6, EDSS scores). Hence it was not possible to estimate the size of the potentially protective effect across studies and the quality of the evidence base is currently insufficient for concrete effect estimates.
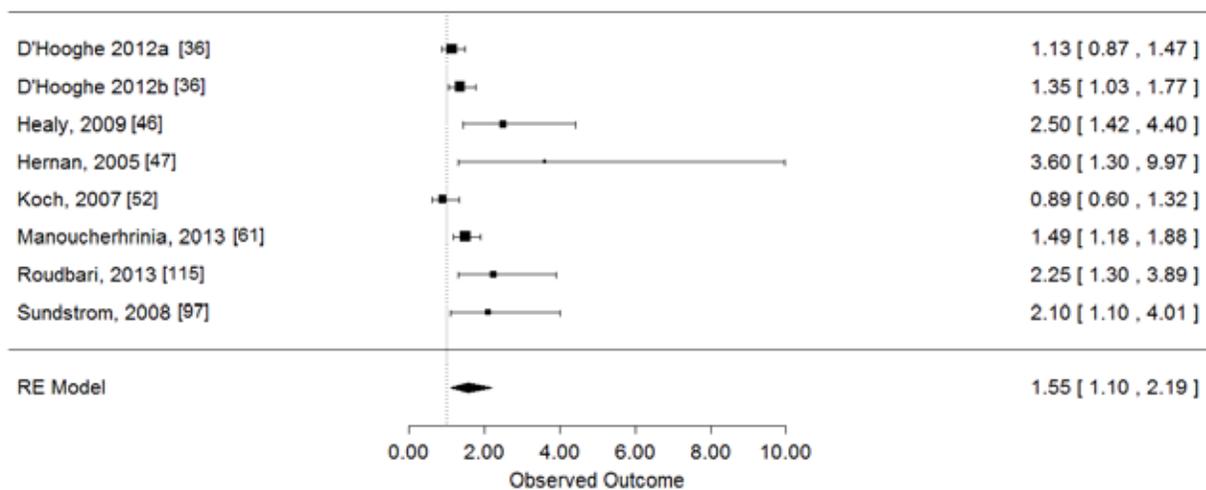
Sunscreen Use

Sunscreen use has been addressed in 2 studies.[36,60] Both reported no association with MS progression but both used different outcome measures (reaching EDSS 6, MSSS scores), precluding concrete evidence statements.

Month of Birth

Three studies assessed whether the month of birth was associated with disease progression, often hypothesizing this affects the amount of sunshine a newborn is exposed to.[39,51,58] One study reported on the time from onset to secondary progression, one on progression to EDSS 6, and one on MSSS scores. All reported no impact on disease progression but studies did not report on the same outcome measure and did not report numerical results other than the statistical significance of the association that would allow further analyses. The quality of the evidence base was determined to be insufficient for specific evidence statements.

Smoking

A large number of studies reported on smoking but studies used a variety of operationalizations of the risk factor and a range of different outcome measures. The forest plot summarizes the studies that reported on disease progression, either operationalized as time to reach EDSS 6, time to conversion to secondary progression, or time to progressive disease. The studies compared current and/or ever smokers with nonsmokers and/or never smokers. Data are primarily based on retrospective data collections.

Figure 3: Time to Progression and Smoking

D'Hooghe 2012a [36]	1.13 [0.87 , 1.47]
D'Hooghe 2012b [36]	1.35 [1.03 , 1.77]
Healy, 2009 [46]	2.50 [1.42 , 4.40]
Hernan, 2005 [47]	3.60 [1.30 , 9.97]
Koch, 2007 [52]	0.89 [0.60 , 1.32]
Manoucherhrinia, 2013 [61]	1.49 [1.18 , 1.88]
Roudbari, 2013 [115]	2.25 [1.30 , 3.89]
Sundstrom, 2008 [97]	2.10 [1.10 , 4.01]
RE Model	1.55 [1.10 , 2.19]

Across studies we identified an increased risk of faster progression in smokers than nonsmokers (HR 1.55; CI 1.10, 2.19; I^2 72%; 7 studies, 8 datasets). However, there was evidence of substantial heterogeneity (that is, unexplained variation in results across studies). A subgroup analysis restricting to studies predicting time to secondary progressive MS (rather than progression to EDSS 6 or progression in all samples) showed a larger effect estimate, but the pooled effect was not statistically significant in this subset and substantial heterogeneity remained (HR 1.90; CI 0.73, 4.94; I^2 77%; 4 RCTs). There was also evidence of publication bias (rank test p = 0.179, regression test p = 0.038). A sensitivity analysis computing the trim-and-fill method to account for potentially missing studies estimated a smaller effect (HR 1.33, CIs 1.05, 1.85; 2 estimated missing studies), but nonetheless a still statistically significant effect.

The forest plot includes one out of 4 identified prospective studies.[97] The other prospective studies could not be added to the meta-analysis because they reported on different measures. These studies reported conflicting results: one found no association between smoking status at baseline and EDSS scores over a period of 5 years (incidence rate ratio [IRR] 0.09; -0.17, 0.36)[69] while another one found baseline smoking status to be a predictor of physical disability after 6 years.[112] The third reported that the cumulative cigarette pack-years smoked after cohort entry was associated with an increase in longitudinal MSSS scores (p < 0.001).[76]

The body of evidence regarding an effect of smoking on the risk of progression was downgraded to moderate evidence quality due to unexplained heterogeneity in effect estimates across studies (*inconsistency*).

Diet

Evidence on dietary regimen was sparse and lacked detail.[21,36,38,54,60,63,98] We did not identify more than one study reporting on the same diet or diet variable except fish consumption (see below). Studies addressing fat consumption did not report on the same outcome measure. Results across individual studies varied, with some studies showing associations with MS progression, others not; and results also varied within studies (comparing relapsing and progressive onset MS).[36]

The only identified prospective study reported on the Swank diet for MS patients and showed that for poor dieters, operationalized as participants with an intake of more than 20g fat per day, the average worsening significantly exceeded those of the good dieters, but the size of the effect was not reported.[98] The quality of the evidence base was judged to be insufficient overall.

Fish Consumption

Fish consumption specifically, which is associated with vitamin D as well as fatty acid intake, has been evaluated in 3 studies: the Flemish registry survey, a study in patients with progressive MS registered in the VHA Multiple Sclerosis Surveillance Registry, and an Italian cohort.[36,60,63] The studies differed in risk factor timing (current; in the last 2 years; intake as a child) and used different outcome measures. The existing retrospective studies reported conflicting results with regard to the presence or absence of a negative association with MS progression. The quality of evidence was determined to be insufficient for specific evidence statements.

Alcohol

Alcohol consumption or alcohol misuse has been addressed in 5 studies in total.[27,36,38,43,106] Possible alcohol-related problems,[27] moderate duration of alcohol use after MS onset (15 years or less as compared to those who did not consume alcohol or consumed it for more than 15 years),[38] higher levels of alcohol consumption (using a 5-point scale ranging from never to daily)[43] have been associated with lower EDSS score categories, that is less disability in participants consuming alcohol, in 3 identified studies. One study found an association of alcohol consumption (compared to no consumption) with a reduced risk to reach EDSS 6 in relapsing MS patients but not in patients with progressive onset MS.[36] One study found that engaging in moderate alcohol consumption (up to 30g/day for women, up to 45g/day for men) compared to low or no alcohol consumption was associated with reduced odds of increased disability based on the PDDS (OR 0.59, $p < 0.001$).

No prospective study exists, and the identified studies reported predominantly on concurrent associations (measuring current intake and current disability status). We did not identify more than one study reporting on the same operationalization of alcohol consumption and the same progression or disability measure; hence, the quality of evidence was insufficient for effect estimates across studies.

Exercise

Although a handful of studies on physical exercise is available, we did not identify more than one study reporting on the same specific exercise variable and the same measure of MS progression.[36,43,62,64,68,87,96,123] All identified studies reported an association between exercise and EDSS score or another measure of progression or disability, but the direction of effects varied by study design.

Only 2 identified studies were prospectively analyzed, predicting later progression from baseline physical activity.[68,96] Both highlighted the possible role of premorbid or baseline physical activity on future progression. Neither reported on the primary outcome of the review. One reported that premorbid physical activity statistically significantly predicted the linear change in PDDS scores in patients with relapsing-remitting MS and emphasized the possible role of physical activity for lessening disability progression.[68] The other reported that baseline exercise scores were negatively correlated with the annual change rate in functional limitations assessed

with a self-reported incapacity status scale and discussed the potential positive impact of exercise on MS progression.[96] The overall quality of evidence was determined to be insufficient for concrete evidence statements, given the differences in outcome and predictor measures.

Trauma

Two studies addressed exposure to brain trauma.[55,89] Both reported that it is not a risk factor for MS progression, but studies used different outcome measures (mean increase in DSS per year, benign MS defined as DSS equal or lower than 2 after 11 or more years of MS duration). No concrete evidence statement could be formulated for an individual outcome that has been shown in more than one study.

Epidural Analgesia

The association with MS progression and epidural analgesia has been addressed in 3 studies, including 2 prospective and one retrospective study.[30,57,72] None reported a statistically significant association with EDSS or DSS scores. We did not identify studies that reported on the change to secondary progression.

The quality of the evidence for the statement that epidural analgesia does not affect progression was downgraded due to *phase of investigation* and *imprecision*. The risk factor was identified in exploratory, not confirmatory, studies and the point estimate of the association was not reported in either study. Hence, the strength of association is not known (studies only reported the statistically significance of the association).

Oral Contraception

Three studies reported on oral contraceptive use with conflicting results within and across studies.[36,40,57] The Flemish registry survey reported that use of oral contraceptives was related to an increased risk of reaching EDSS 6 in progressive but not in relapsing onset MS.[36] A second study reported that patients who had used combined oral contraceptives continuously for at least one year had lower EDSS scores compared to never users, indicating a protective effect.[40] A third study reported that women who started oral contraceptives after disease onset had lower EDSS scores than both never users and past users. A benign disease course was predicted by current oral contraceptive use compared to never or past users.[85] Given that none of the studies compared an identical combination of risk factor and outcome measure operationalization, the quality of evidence was determined insufficient for concrete evidence statements.

Geographic Region

Two studies addressed geographic regions but in different operationalizations (*eg*, high vs low MS prevalence areas; geographic region of military personnel at entry to the military) and studies used different outcome measures (3-point scale differentiating walking without aids, walking with aids, and restricted to wheelchair; progression to DSS 6 and DSS7).[35,105] Only one of the studies reported an association; progression to a non-ambulatory status or death was significantly greater among patients who lived in Los Angeles County (a low-prevalence area). The different outcome measures, risk factor operationalizations, and conflicting results cannot be combined to a concrete evidence statement.

Education

Two studies investigated an association between education and MS progression.[22,99] Both studies were retrospective analyses, they reported on EDSS greater than 6 or MSSS scores, and they reported conflicting results. One study assessing MSSS did not find that education predicted getting statistically significantly worse in a sample of 338 patients, the other one reported that lower educational attainment predicted EDSS scores above 6 (OR 1.5; CI 1.2, 2.8). Given the lack of replication on outcome measures and the conflicting results, the quality of evidence was rated insufficient.

Other Factors

All other factors have been addressed in only one of the included studies and have not been replicated yet. The study details together with the results are shown in the evidence tables.

KQ1 Summary

The summary of findings table documents the available evidence for specific risk factors and specific outcome measures that were reported in more than one study. We did not include results that were based on a single study without replication by another, independent author group, given the complexity of epidemiological data collection.

Results (strength and statistical significance of the association) for EDSS scores and for other MS progression-relevant findings were summarized across studies. For each outcome, the GRADE summary is documented. The summary of findings tables is organized by outcome and where outcomes were not identical or not compatible across studies, no effect estimate could be determined and the evidence was consequently graded as insufficient for concrete evidence statements. The table shows the presence and the absence of associations, and factors delaying as well as hastening progression have been considered.

Table 8. Summary of Findings for KQ1

Risk factor and Outcome measure	Study Design, # of Studies	EDSS Findings: Direction, Magnitude of Effect	Other Progression Findings: Direction, Magnitude of Effect	GRADE
Vitamin D				
Correlation 25(OH)D level and EDSS	8 concurrent, 1 retrospective, 1 prospective study	Weak correlation (r -0.22; CI -0.28, -0.10) indicating lower levels of vitamin D are associated with higher EDSS scores		Moderate (indirect)*
Sun Exposure				
No outcome assessed in > 1 study	5 retrospective studies	N/A (see text)	N/A	Insufficient
Sunscreen Use				
No outcome assessed in > 1 study	2 retrospective studies	N/A (see text)	N/A	Insufficient
Month of Birth				
No outcome assessed in > 1 study	3 retrospective studies	N/A (see text)	N/A	Insufficient
Smoking				
Risk of progression comparing smokers and nonsmokers	6 retrospective, 1 prospective study	N/A	Smoking is associated with an increased risk of progression (HR 1.55; CI 1.10, 2.19)	Moderate (heterogeneity)*
Diet				
No outcome assessed in > 1 study	2 concurrent, 4 retrospective, 1 prospective study	N/A (see text)	N/A	Insufficient
Fish Consumption				
No outcome assessed in > 1 study	3 retrospective studies	N/A (see text)	N/A	Insufficient
Alcohol-related Variables				
No outcome assessed in > 1 study reporting on the same operationalization	3 concurrent, 2 retrospective studies	N/A (see text)	N/A	Insufficient
Exercise				
No outcome assessed in > 1 study	2 retrospective, 3 prospective studies	N/A (see text)	N/A	Insufficient
Trauma				
No outcome assessed in > 1 study	2 retrospective studies	N/A (see text)	N/A	Insufficient
Epidural Analgesia				

EDSS scores	2 prospective studies, 1 retrospective study	2 studies showed no association with EDSS scores (sign. N/A) or 3 EDSS score categories (p > 0.1)	One study showed no statistically significant association with EDSS or DSS (p = 0.66)	Low (exploratory, no point estimate)**
Oral Contraception				
No outcome assessed in > 1 study	3 retrospective studies	N/A (see text)	N/A	Insufficient
Geographic Region				
No outcome assessed in > 1 study	1 retrospective, 1 prospective study	N/A (see text)	N/A	Insufficient
Education				
No outcome assessed in > 1 study	2 retrospective studies	N/A (see text)	N/A	Insufficient

Note: The table only shows risk factors that were reported in more than one study; * quality of evidence downgraded by 1 level, ** quality of evidence downgraded by 2 levels

KEY QUESTION 2: What environmental exposures prior to or during military service are related to multiple sclerosis progression following onset symptoms?

Despite the extensive search, very few relevant studies were identified. In addition, only some of the studies addressed environmental exposures during military service. The remaining studies addressed other factors in samples of Veterans.

One of the studies has been presented in the context of diet risk factors (evidence table 4). The study evaluated MS in men on active duty in the US Army. It reported on the disease course for patients that were put on a specific diet in the hospital, compared to patients without administration of a specific therapy.[54] The reported data were not statistically significantly different between groups. However, no information was available on the specific diet and approaches may have varied across patients and hospitals.

A second study focused on disability and treatment patterns of MS patients in Veterans and non-veterans. The concurrent study reported that VHA Veterans had statistically significantly higher PDDS scores than non-veterans.[104] More information is presented in table 6, the evidence table summarizing "other" MS progression risk factors.

Two additional studies reported on multiple risk factors of interest and are shown in more detail in evidence table 7. One study reported on a Gulf War-era MS cohort which includes 2,631 patients.[105] The study reported that deployment to a war theater, geographic location, and occupational status at entry to the military were not predictors of progression to DSS 6 and DSS 7. The study was reported in a conference abstract and data on the exact point estimate and measure of dispersion were not available.

The fourth study addressed vitamin D exposure and reported on the average fall/winter sun exposure before MS onset, cod liver oil intake as a child (ages 6 to 15), and fish consumption between the age of 6 and 15.[63] The study reported on 219 Veterans with progressive MS registered in the Multiple Sclerosis Surveillance Registry. The study used the PDDS to assess

progression and predicted hazard ratios for the time to reach a PDDS score of 8 from disease symptom onset. This stage indicates that a wheelchair or scooter is the main form of mobility. The study reported low average sun exposure in the fall/winter before disease onset was associated with an increased risk of progression (HR 2.13; CI 1.20, 3.78) and cod liver oil during childhood and adolescence was associated with a reduced risk (HR 0.44; CI 0.20, 0.96). Fish consumption was not statistically significantly associated with PDDS progression in this sample. The study concluded that exposure to vitamin D before MS onset may slow disease-related neurodegeneration and thus delay progression to disability in patients with progressive MS.

Summary of Findings and Quality of Evidence for Key Question 2

The summary of findings table showing KQ2 evidence is grouped by exposures prior to or post military service and exposures during military service. All studies relevant to KQ2 also contribute to KQ1 and were already included in KQ1 evidence statements.

Table 9. Summary of Findings for KQ2

Risk Factor	Study Design, # of Studies	EDSS Findings: Direction, Magnitude of Effect	Other Progression Findings: Direction, Magnitude of Effect	GRADE
Prior or Post Military Service in Veterans				
Geographic location at entry to the military	1 retrospective study, N = 2631	N/A	Geographic location was not a predictor of progression to DSS 6 and DSS 7 (magnitude of effect N/A)	Insufficient
Occupational status at entry to the military	1 retrospective study, N = 2631	N/A	Status was not a predictor of progression to DSS 6 and DSS 7 (magnitude of effect N/A)	Insufficient
Average fall/winter sun exposure before MS onset	1 retrospective study, N = 219	N/A	Low sun exposure was associated with faster progression (HR 2.13; CI 1.20, 3.13)	Insufficient
Cod liver oil intake at ages 6-15	1 retrospective study, N = 219	N/A	Cod liver oil intake was associated with slower progression (HR 0.44; CI 0.20, 0.96)	Insufficient
Fish consumption at ages 6-15	1 retrospective study, N = 219	N/A	No statistically significant association with progression (HR 0.79; CI 0.45, 1.41)	Insufficient
Exposure During Military Service				
Deployment to a war theater	1 retrospective study, N = 2631	N/A	Deployment to a war theater was not a predictor of progression to DSS 6 and DSS 7 (magnitude of effect N/A)	Insufficient
Being a Veteran	1 concurrent study; N = 2150	N/A	VHA Veterans had higher PDDS scores than non-veterans (p < 0.001)	Insufficient
Diet in hospital	1 retrospective study, N = 517	N/A	Diet group: 28% better, 56% the same, 16% worse; patients with hospital routine without specific treatments: 19% better, 74% same, 8% worse (p = 0.131)	Insufficient

Note: N/A not reported, not available

None of the identified studies were prospective studies, which allow more confident interpretations of associations. In addition, all associations were based on only one study, and

without any replication in independent studies, the available evidence was graded as insufficient. Some of the factors shown in this summary of findings table were uniquely addressed in the KQ2-relevant studies, such as deployment. Other investigated factors, such as sun exposure, have been addressed in other studies documented in the KQ1 evidence synthesis; however, the exact operationalization of the factors, for example sun exposure during childhood and teenage years, also has not been replicated in other available studies by independent author groups.

KEY QUESTION 3: Among identified risk factors for progression, what treatment/risk factor modification therapies have been shown to delay or hasten the progression of MS once it has initiated?

We identified a substantial number of intervention evaluations; however, they addressed only a small range of interventions. Despite the comprehensive search and inclusive inclusion criteria, all identified studies evaluated either vitamin D supplementation, exercise interventions, or dietary interventions.

Details of included studies contributing to KQ3 are presented in 3 evidence tables in the following text.

The largest group of interventions addressed physical exercise.

Table 10: Evidence for KQ3: Effects of Exercise Interventions on MS Progression

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Armutlu, 2001[19]	26 No power calculation	Patients with ataxic MS, intervention group mean age 32.61 (23-44), 9 female, 4 male, EDSS 4.53 (3.5-5.5); control group mean age 34.61, (range 26-45), 7 female, 6 male; PP and SP; Poser criteria	Neuromuscular rehabilitation with pressure splints, 3x / week for 4 weeks		Neuromuscular rehabilitation alone	Significant improvements in EDSS scores in both groups, no difference between groups (p > 0.05)		N/A
Bjarnadottir, 2007[26]	16 (6 treatment, 10 control) No power calculation	Patients with mild MS aged 18-50 years with definite MS and EDSS < 4, and with the ability to ride a stationary bicycle; mean age 38.7 vs 36.1, mean EDSS 2.1 vs 1.8, mean duration of MS 8.7 vs 8.3 years; Poser criteria	Training 3x / week for 5 weeks or a total of 15 hours; aerobic exercise, resistance exercise and stretching and relaxation		No treatment	No change in EDSS was detected and groups did not differ in pre-post difference (-0.07, CI -0.7, 0.61)		1 patient in each group developed a relapse and was withdrawn, transient increase in symptoms was not observed
Carter, 2013[125]	28 No power calculation	Patients with MS, mean age 40 years (24-49) with mild to moderate EDSS = < 5.5; treatment vs usual care: female 87.5% vs 85.7%, mean age 39.5 (SD 6.5) vs 40.9 (SD 8.7), mean EDSS 3.0 (SD 1.1) vs 3.1 (SD 1.7); McDonald 2010 criteria	10 week pragmatic exercise intervention (2 supervised and 1 home-based session / week)		TAU	Lower EDSS scores in intervention group after 10 weeks (p = 0.07) and 3 months post-intervention (p = 0.48) compared to control		N/A
Conklyn, 2010[31]	10 No power calculation	Adult MS patients with gait disturbance, able to walk 100 feet without physical assistance; treatment vs control: mean age 47 (SD 10.51) vs 50.2 (SD 5.45), 60% vs 80% female, relapsing-remitting 80% vs 60%, SP 0% vs 40%, primary progressive 20% vs 0%; criteria N/A	2 week Rhythmic Auditory Stimulation		No treatment		No statistically significant changes in PDDS scores	N/A

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Dalgas, 2009[32] cross-over	38 Power unclear	Moderately impaired patients with MS, treatment vs control: female 10/16 vs 10/15, mean age 49.1 vs 47.7, mean EDSS 3.9 vs 3.7, mean time since diagnosis 8.1 vs 6.6; McDonald 2001 criteria	Biweekly 12-week lower extremity progressive resistance training program, participants encouraged to continue training afterwards		No treatment	EDSS remained unchanged in both groups		N/A
DeBolt, 2004[34]	36 (19 treatment, 17 control) No power calculation	Healthy adults with MS and the ability to walk (with or without assistive devices) at least 20m without rest, EDSS scores ranged from 2 to 6, 29 women (mean age, 50.3, SD 8.5) and 8 men (mean age 51.1, SD 7.1); criteria N/A	Home-based resistance exercise (8-week)		No treatment	No significant differences between groups after intervention (p = 0..552)		N/A
Fimland, 2010[37]	14 No power calculation	Maximal strength training vs control group: female 75% vs 75%, mean age 53 vs 54, mean EDSS 4.6 vs 3.5, years since diagnosed 8 vs 8; criteria N/A	A rehabilitation program, maximal strength training using high loads and few repetitions, 5 days/wk for 3 wks		No treatment	No changes were observed for the EDSS between groups.,scores remained unchanged in all participants		No adverse effects
Golzari, 2010[42]	20 No power calculation	Women from MS society and clinic, age 20-50, with clinically diagnosed R-R and EDSS 0-4; exercise vs control: mean age 32.5 (SD 7.57) vs 33.75 (SD 8.18), mean EDSS 2.14 (SD 1.06) vs 1.96 (SD 1.06); criteria N/A	Combined exercises for 24 sessions during 8 wks; 1-hour session with warm-up, stretch, aerobic, endurance, and resistance training, and relaxation		No treatment	Score was decreased in intervention group 8 weeks after training (p < 0.43) but not control group		N/A
Lo, 2008[56] cross-over	13 No power calculation	R-R, SP, and PP MS patients, mean age 49.8 (SD 11.1), EDSS 4.9 (SD 1.2), female 6/13, R-R 8/13, PP 5/13; McDonald 2001 criteria	Body weight supported treadmill training with or without robotic assistance training sessions, 2/week for 3 weeks, a total of 6 sessions of 40 mins		Reversed treatment order	Significant improvement in EDSS scores in both groups: -0.83 (SD 0.61, p = 0.06) and -1.1 (SD 0.7, p = 0.03)		No adverse events occurred

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Miller, 2011[66]	30 Insufficient power	Patients with PP or SP MS and EDSS scores 6.5-8; intervention vs control: 26.7% vs 46.7% female, mean age 56.3 vs 52.9, time since diagnosis 13 vs 18.7, EDSS 7 vs 7.1; definitive diagnosis, criteria N/A	8 week physiotherapy		TAU	EDSS: no interaction effect over time (p = 0.803) or group effect (p = 0.074)		None
Petajan, 1996[126]	46 No power calculation	Ambulatory MS patients recruited through MS society and physician referrals, exercise vs non-exercise: female 71.4% vs 76%, mean age 41.4 (SD 2) vs 39 (SD 1.7), EDSS 3.8 (SD 0.3) vs 2.9 (SD 0.3), years since first symptoms 11.6 (SD 1.7) vs 10.5 (SD 1.6), years since diagnosis 9.3 (SD 1.6) vs 6.2 (SD 1.1); Poser criteria	15 weeks aerobic training with 3 supervised training sessions per week (5 minute warm-up, 30 mins at 60% maximum aerobic capacity, 5 min cooldown)		No treatment	Overall EDSS scores did not change (-0.1 in exercise group, -0.1 in nonexercise group)		N/A
Pfalzer, 2011[75]	39 No power calculation	Ambulatory patients with clinically diagnosed MS; 22 with R-R, 5 SP, 5 PP, 3 PR, 4 unknown; clinically diagnosed, criteria N/A	Home-based exercise training (10 weeks)		No treatment	Intervention: EDSS mean 4.3 (SD 1.9, improvement pretest-posttest 0.2 (0.7)), Control: 3.7 (SD 1.6); pre-post 0.5 (SD 1.2) post-intervention		2 dropped out due to medical illness unrelated to MS
Rampello, 2007[79] cross-over	19 No power calculation	Patients aged 20-55 years with MS on waiting list for rehabilitation program with EDSS < 7; treatment vs control: mean age 44 vs 37, female 8/11 vs 6/8, mean disease duration 6 vs 10 years, mean EDSS 3.5 vs 3.25; Poser criteria	Aerobic training (8 weeks)		Other: neurological rehabilitation	No change over time was found in EDSS (p = 1.0)		2 dropped out due to perception of breathlessness and fatigue

◀◀   ◀   ▶

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Romberg, 2004[81] cross-over	114 Sufficient power	Patients aged 30-55 with definite MS and EDSS -5.5; exercise vs control: female 30/47 vs 41/48, mean age 43.8 vs 43.9, mean years after 1st symptoms 9.7 vs 9.6, mean years after diagnosis 6.0 vs 5.5, mean EDSS 2.0 vs 2.5; Poser criteria	Strength and aerobic training initiated during 3-week inpatient rehabilitation and continued for 23 weeks at home		TAU	No change (p = 0.93) over time in EDSS		No exercise-related injuries; 5 relapses in intervention group and 6 in control group in 9 patients
Sangelaji, 2014[83]	147 Power unclear	MS patients, EDSS score 0-4; criteria N/A	Aerobic, strengthening, balancing, and stretching exercises (10 weeks)		No treatment	No significant changes in EDSS at any follow-up, but both control and intervention increased EDSS scores at 1-year follow-up (intervention: 0.5 points, p = 0.001; control: 0.72 points, p = 0.001)		1 dropped out due to muscular pain in cuff muscles, 1 due to new attack and nonresponding symptoms
Schwartz, 2012[84]	32 Insufficient power	MS patients with chronic progressive pattern or relapsing-progressive with no relapse for 3 months (RP, SP, and PP); robot-assisted vs conventional: female 41% vs 43%, mean age 50.5 (SD 11.5) vs 46.8 (SD 11.5), disease duration 14.9 (SD 8.1) vs 11.3 (SD 6.7), EDSS 6 (SD 0.6) vs 6.2 (SD 0.5); McDonald 2001 criteria	12 sessions of robot-assisted gait training (gait orthosis) or conventional walking treatment 2-3 times a week (30 min net treatment) for 4 weeks		Conventional walking treatment	EDSS scores improved significantly post-treatment with no difference between the groups; mean changes in EDSS robot-assisted vs conventional post-intervention: -0.29 (SD 0.4) vs -0.31 (SD 0.3); at 3 months -0.22 (SD 0.4) vs -0.27 (SD 0.3); at 6 months -0.21 (SD 0.4) vs -0.25 (SD 0.4)		N/A

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Solari, 1999[92]	50 Sufficient power	MS patients aged 18-65, EDSS 3-6.5, mean EDSS 5.5; treatment vs control: 63 vs 48% female, mean age 44.6 (SD 10.2) vs 44.9 (SD 10.9), R-R 22.2 vs 21.7%, PP 14.8 vs 17.4%, SP 63 vs 60.9%; clinically definite or laboratory-supported MS	3 week inpatient physical therapy		Exercise at home	No changes in impairment occurred in either group (EDSS scores)		N/A
Wiles, 2011[109] cross-over	42 Power unclear	MS patients with walking difficulties, able to walk 5 meters without any physical assistance, mean age 47.2 (28.2-68.8), 35.7% female, mean duration of disease onset 4.4 (SD4.6); Poser criteria	Allocation to one of 6 permutations of three 8-week treatment periods separated by 8-week intervals: physiotherapy at home or no therapy		No treatment		Effects favored hospital- or home-based therapy over no therapy	N/A

Notes: AE adverse events, Co co-intervention, N/A not available, TAU treatment as usual, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

§ All studies are RCTs unless otherwise noted.

The 18 studies tested a range of physical interventions, including aerobic exercise, resistance training, physiotherapy, or rehabilitation with maximal strength training. Settings were home-based or rehabilitation centers. The majority of studies compared the program to no treatment; 3 studies compared to treatment as usual.[29,66,81] Two studies assessed the comparative effectiveness of a robot-assisted intervention[84,56] and one the effect of adding pressure splints to the training.[19] The training duration ranged from 2 to 26 weeks.

Studies enrolled between 10 and 147 participants. The majority of included studies was small and did not report a statistical power calculation. Four studies reported a power calculation but for a different outcome than MS progression or disability scores.[32,81,83,109] Two studies reported that power was insufficient even for the primary outcome.[66,84] Only one study took EDSS scores into account for the power calculation; the study reported no changes in impairment occurred in either group after 3-week inpatient physical therapy or exercise training at home.[92]

The identified studies were primarily in patients with mild MS who were ambulatory. However, 2 of the included studies were specifically designed to test the comparative effectiveness of robot-assisted gait training compared to conventional walking treatment or adding pressure splints to the training in patients with progressive MS; EDSS scores improved in both intervention arms.[19,84]

All included studies reported on disability of MS measured by the primary outcome of this review – EDSS scores. However, in none of the studies was MS progression a primary outcome, and only selected studies reported EDSS assessments to be a secondary outcome[42,74,75,83,84] to evaluate the intervention. Given the short duration of the intervention, many studies reported no substantial changes in EDSS levels after the intervention.

Half the studies did not report on adverse events. Reported adverse events were relapses,[26,81,83] breathlessness and fatigue,[79] muscular pain,[83] and unrelated illnesses.[75] Two studies assessed adverse events and reported that none occurred.[37,56]

The risk of bias assessment for the identified studies is shown in Appendix C. Performance bias was a prominent source of bias in the identified interventions because blinding of participants and personnel was not possible given the nature of the intervention. In addition, only selected studies ensured that the outcome assessors were blind to the treatment condition. Two studies, Fimland et al and Petajan et al, had noticeable imbalanced samples at baseline, with intervention patients that had higher EDSS scores than the control group.[37,127] While the internal validity of included studies varied, several studies were not particularly suitable to assess the outcome of interest due to the short duration of the intervention. Only 11 out of 18 studies reported on an intervention with a duration of 2 months or more.[29,32,34,42,66,74,75,79,81,83,109]

The second group of intervention studies reported on dietary interventions. The details of included RCTs are shown in the following evidence table.

Table 11: Evidence for KQ3: Effects of Dietary Interventions on MS Progression

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Bates, 1977[24]	152 No power calculation	Patients with chronic progressive non-relapsing MS; criteria N/A	Group A: 8 capsules of 360mg linolenic and 3-42 g of linoleic acid daily; group B: placebo capsules (oleic acid oil); group C received 11.5 g/day of linoleic acid spread; group D placebo spread (oleic acid) for [presumably] 24 months		Placebo		No statistically significant difference between groups in the number of patients who improved, deteriorated, or remained unchanged	N/A
Bates, 1978[25] cross-over	116 (29 for each of 4 groups) No power calculation	Patients with remitting MS; Group A vs B, C vs D: female 19/29 vs 19/29, 24/29 vs 18/29; mean age 35 vs 32, 34 vs 33; mean duration of disease 7 vs 6, 7 vs 6; criteria N/A	Group A: 8 capsules daily (2 92g linoleic acid, 0 34g gamma-linolenic acid); Group B: 8 similar capsules (4 g oleic acid, control); Group C: 23g linoleic acid daily in a spread; Group D: 16g oleic acid in a spread (control) for [presumably] 24 months		Placebo		After 2 years, the number of patients who had deteriorated (DSS and additional assessment) in intervention group A was significantly greater than that in the control group B ($p < 0.05$)	N/A
Bates, 1989[23] multi-center	312 No power calculation	Patients aged 16-45 years with definite MS, suffered at least 2 relapses with 1 during last 24 months, EDSS =< 6.0, treatment vs control: female 102/155 vs 109/157, mean age 34 vs 33, mean duration of disease 6.5 vs 6.6; McDonald & Halliday criteria	20 capsules of 0.5 g of omega-3 fatty acid (1.71 g C20:5 and 1.14 g C22:6 per day) for [presumably] 24 months		Placebo	Intervention: 51% better, 43% worse, 1 patient died; placebo (olive oil): 41% better, 52% worse, no deaths (difference $p = 0.07$)		1 patient died

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Harbige, 2007[44]	36 No power calculation	Patients with active MS; international MS criteria	High or low dose of gamma-liolenic acid (18:3n-6)-rich borage oil (high in sn-2 GLA, low in monoenes, natural levels of vitamin E) for 18 months		Placebo	High-dose treatment significantly reduced disability progression (EDSS) compared with placebo and low dose treatment (no numerical results)		N/A
Millar, 1973[65]	87 (36 treatment, 39 control) No power calculation	MS patients, treatment vs control: mean age 37.8 vs 35.5, female 56% vs 64%, average age at onset 38 vs 36, mean duration of symptoms before entry 7.7 vs 9.2, mean disability score 2.9 vs 2.7; criteria N/A	Linoleate supplementation (30 ml sunflower seed oil, 8-6g of linoleic acid, 2/day) for 2 years		Placebo		Placebo (olive oil) deteriorated from 2.7 to 3.3 at the end of the trial, treatment group from 2.9 to 3.1 (n.s.)	N/A
Pantzaris, 2013[71]	80 (20 each in 4 groups) No power calculation	R-R patients aged 18-65 years, EDSS 0-5, with at least 1 documented clinical relapse; McDonald criteria	Intervention A: omega-3 and omega-6 polyunsaturated fatty acids at 1:1 wt/wt; Intervention B: combination of A and gamma-tocopherol; intervention C: gamma-tocopherol; Control: placebo (olive oil).; 19.5 ml / day for 30 months		Placebo	The cumulative probability of progression of EDSS with 1 point increase at 2 years was 10% in the combination group and 35% in the placebo group (p = 0.052), adjusted HR 0.22 (CI 0.04, 1.07; p = 0.06))		No significant AE, nausea N = 2, no abnormal values in biochemical and blood tests, no allergic reactions

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Paty, 1978[73]	96 No power calculation	Patients with definite MS, ambulatory (either on their own or with ambulatory aids); treatment vs control: mean age 45 for both, mean age onset 32 vs 30, duration of disease 13 vs 16, mean DSS 4.24 vs 4.26; Schumacher criteria	Linoleic acid (1 oz, 2/day, sun flower seed oil, 66.2% linoleic acid) for 30 months		Placebo		Final disability scale score for intervention vs placebo (olive oil): 3.52 vs 3.85, changes from baseline: -0.72 vs -0.41 (n.s.)	N/A
Ramirez-Ramirez, 2013[78]	50 Power unclear	Patients with R-R, at least 1 relapse in year before, EDSS score 0-5, treated with interferon beta-1b; intervention vs placebo: female 17% vs 18%, mean age 35 (SD 7.6) vs 35 (SD 7.8), mean EDSS 2.1 (SD 0.98) vs 2.06 (SD 0.84), years with disease 7.1 (SD 4.8) vs 6.7 (SD 6.7); McDonald 2005 criteria	Fish oil (4 g/day, 0.8g EPA, 1.6g DHA, and excipient) for 12 months	Interferon beta-1b	Placebo	EDSS changes from baseline to 12 months: 0.1 in intervention, 0.2 in placebo group (group differences n.s.)		No serious adverse effects; no changes in liver and renal tests, platelets, blood count, bleeding; fishy taste; < 5% reported nausea, stomach pain, diarrhea

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Rezapour-Firouzi, 2013[80]	100 No power calculation	R-R; group A vs B vs C: mean age 34.2 (SD 7.5) vs 35.9 (SD 7.8) vs 33.7 (SD 7.8); average age at onset 25 (SD 7.5) vs 30.3 (SD 8.1) vs 27.6 (SD 6.4); disease duration 6.23 (SD 3.9) vs 7.55 (SD 5.08) vs 6.6 (SD 4.0); female 69.6% vs 50% vs 75%; baseline EDSS 2.76 (SD 1.39) vs 3.45 (SD 1.41) vs 3.25 (SD 1.9); criteria N/A	Group A: hemp seed and evening primrose oils with Hot nature diet (foods with Hot nature; low intake of cholesterol, hydrogenated / trans fatty acids and saturated fats (fried food), olive / grape seed oil, fresh fruit and vegetables, nuts and seeds, fish and seafood, unrefined carbohydrates, plenty of water, cutting down sugar and refined starch, dairy products with honey or date, removing foods with Cold nature); Group B: hemp seed and evening primrose oils for 6 months		Placebo	Significant improvements in EDSS in intervention groups, significant increase in EDSS score in control group (olive oil)		No serious adverse effects in any of the patients
Torkildsen, 2012[101] multi-center	92 Power unclear	R-R patients, 18-55 years, EDSS = > 5.0; fatty acids vs placebo: female 30/46 vs 29/45, mean age 28.8 vs 28.3, mean EDSS at baseline, 1.94 vs 1.86, mean disease duration 5.4 vs 5.8 years, mean relapses the year prior 1.7 vs 1.6, mean time since diagnosis 2.2 vs 1.7; McDonald 2001 criteria	Oral omega-3 fatty acids (270mg EPA, 170mg DHA) and 4 units of alpha-tocopherol per gram for 18 months	Interferon beta-1a	Placebo	After 24 months, EDSS increased to 2.22 (1.34) in the fatty acids group and 2.19 (1.34) in placebo group (p = 0.63); 30% in the fatty acids group vs 30% in the placebo group had experienced disease progression (p > 0.99)	No differences in changes of MS Functional Composite scores after 6 (p = 0.53) or 24 (p = 0.57) months	74% intervention, 63% placebo experienced AE (*eg,* influenza-like symptoms, injection site reaction), n.s. between groups; 1 intervention patient (nausea) and 2 placebo patients (allergic reaction) withdrew

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	Other results	AE
Weinstock-Guttman, 2005[107] cross-over	31 No power calculation	MS patients, 18-60 years; intervention vs placebo: female 85.7% vs 84.6%, mean age 45.1 vs 39.9, mean disease duration 6.9 vs 4.6, mean EDSS 1.9 vs 2.0; Poser criteria	Very low-fat diet dietary advice (not to exceed 15% of total daily calories) plus fish oil supplement (6 capsules / day, 1.98g EPA, 1.32 DHA); control group received AHA diet advice (30% fat) plus placebo		Other	Weak trend towards an increase in EDSS (+0.35) in the control group vs a decrease of 0.07 points in the intervention group after 1 year		2 could not tolerate the diet (1 per group)
Yadav, 2014[110]	61 No power calculation	R-R (mean EDSS 2.5; mean age 41, range 24-55); criteria N/A	Low-fat plant-based diet (1 year)		Waitlist	After baseline difference adjustment, the groups showed no siginificant change in EDSS		"study demonstrated safety"

Notes: AE adverse events; Co co-intervention, N/A not available, n.s. not statistically significant, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

§ All studies are RTCs unless otherwise noted.

The majority of the 12 dietary intervention studies addressed effects of fatty acid supplementation. Three studies evaluated the effects of advice for a diet of foods with "Hot nature" according to traditional Chinese medicine, a very low-fat diet plus fish oil, and a low-fat plant-based diet.[80,107,110] Studies compared interventions primarily to placebo. One study compared to patients assigned to waitlist (patients will receive the intervention eventually).[110] Another compared to different, not very low-fat diet advice plus placebo instead of fish oil supplementation.[107] All studies tested long-term interventions; the duration ranged from 6 to 30 months.

Studies enrolled between 31 and 312 patients. Studies either reported no power calculation to determine the sample size necessary to detect a statistically significant difference between treatment groups, or it was computed for a different outcome than MS progression or disability scores. One of the included studies tested the intervention specifically in chronic progressive non-relapsing MS,[24] while other studies used unrestricted MS samples or did not report on the form and stage.

Several studies reported on EDSS results but not all reported EDSS endpoint values to allow a comparison between intervention and control groups. Some studies only stated the statistical significance of the difference, reported the statistical significance of the difference between baseline and endpoint for each group, or reported no specific numbers. Four included studies were published before the development of the EDSS and reported on the number of patients who deteriorated.[24,25,65,73] The adverse event assessment was sparse; 5 included studies did not report on adverse events at all, 3 reported adverse events but did not specify the treatment group patients were assigned to, and 2 gave no details on the experienced events. Only 2 studies reported on adverse events by intervention group and reported that one or 2 patients withdrew from the study.

The risk of bias assessment for the identified studies is shown in Appendix C. There was insufficient detail to assess the risk of bias in a number of dietary intervention studies, in particular the studies that were published 40 years ago, presumably due to differences in reporting standards.[24,25,65,73] Compliance in diet advice studies was judged to be a source of other bias, given the long duration of the intervention that required the participants to adhere to a demanding dietary schedule.[80,107,110]

Studies reporting on vitamin D supplementation are shown in the following, final evidence table. Studies exclusively gave dietary supplements to patients, rather than addressing more complex nutritional changes or dietary habits.

Table 12. Evidence for KQ3: Effects of Vitamin D Supplementation Interventions on MS Progression

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	AE
Burton, 2010[28] multi-center	49 Power unclear	MS clinic patients, mean age 40.5 years, EDSS 1.34, and 25(OH)D 78 nmol/L; treatment vs control: female 84% vs 70%, R-R/SP 23/2 vs 22/2, mean disease duration 8.2 vs 7.4; patients already taking > 4,000 IU/day were excluded; McDonald 2001 criteria	Escalating vitamin D doses up to 40,000 IU/day over 28 weeks followed by 10,000 IU/day, and further downtitrated to 0 IU/day; calcium 1,200 mg/day; for 52 weeks		Placebo	Treatment vs control EDSS (p > 0.5), % change in EDSS -0.23 vs 0.30 (p > 0.5), proportion completing with increased EDSS 0.88 vs 0.375 (p = 0.019) at end of trial	No adverse events observed
Kampman, 2012[49]	68 (35 treatment, 33 placebo) No power calculation	Patients aged 18-50 with clinically definite MS and EDSS = < 4.5; vitamin D vs placebo: female 69% vs 73%, mean age 40 vs 41, mean duration from first symptom (range) 11 (1-27) vs 10 (2-26) years, mean EDSS 2.5 vs 2.0, mean MSSS 3.6 vs 3.2; McDonald 2001 criteria	20,000 IU vitamin D3 once a week in capsule for 96 weeks		Placebo	No significant difference in EDSS between treatment and placebo groups (absolute difference -0.01, CI -0.35, -0.35, p = 0.091)	1 placebo patient dropped out due to nephrolithiasis
Mosayebi, 2011[67]	62 (28 treatment, 34 placebo) No power calculation	MS patients, 18-60 years, at least 1 relapse in the previous 12 months; > 3 lesions on spinal or brain-MRI or both; EDSS 0-3.5; vitamin D vs placebo: female 17/26 vs 25/33, mean age 37 vs 35, mean duration of disease 4.15 vs 6.4 years; patients with progressive MS were excluded; McDonald 2001 criteria	300,000 IU vitamin D3 as intra-muscular injections every month for 6 months		Placebo	EDSS increased by 0.21 from 2.10 after 6 month intervention and by 0.17 from 2.5 in placebo group	N/A
Shaygannejad, 2012[88]	50 Sufficient power	MRI, clinical, or laboratory-supported R-R, EDSS < 7, average age 38.6; PP and SP MS excluded; McDonald 2005 criteria	Low-dose vitamin D (calcitriol) for 1 year	DMT	Placebo	Intervention: EDSS 1.63 (SD 0.70, difference pre-post 0, CI -0.15, 0.15); Placebo: 1.94 (SD 1.41, difference pre-post -0.24, CI -0.40, -0.08; p < 0.01) at 12-month follow-up	Vitamin D was well-tolerated; most AE were mild. Most common in intervention vs placebo group: constipation (N = 6 vs 4), dyspepsia (N = 6 vs 2), fatigue (N = 4 vs 5), headache (N = 2 vs 1)

ID, Trial type[§]	N Power	Participants	Intervention	Co	Comparator	EDSS results	AE
Soilu-Hanninen, 2012[128] multi-center	66 (34 treatment, 32 placebo) Power unclear	R-R patients age 18-55 years with IFNB-1b use for at least 1 month and EDSS = < 5.0; vitamin D vs placebo: female 21/34 vs 20/32, mean age 39 vs 35, mean EDSS 2.0 vs 2.4, mean disease duration 3.0 vs 2.4, mean annual relapse rate from the 2 years before the study onset 0.49 vs 0.52, patients with relapses during the year preceding baseline 12/34 vs 13/32; McDonald 2005 criteria	Vitamin D3 (20,000 IU or 0.5 mg of vitamin D3 in capsule, once weekly) for 1 year		Placebo	EDSS score decreased in the vitamin D group by -0.2 from 1.8 and remained the same in the placebo group (-0.02) after the 12 months intervention (p = 0.071)	No hypercalcaemia or significant differences in any clinical chemistry parameters or AE between groups; diarrhea (intervention N = 5 vs control 2), fever (2 vs 5); SAE: 1 case of erysipelas treated with antibiotics in intervention, 2 hospitalizations in control group (elective hip surgery, elbow fracture)
Stein, 2011[94]	23 No power calculation	Patients with R-R older than 18 years, relapse within the preceding 24 months; intervention vs placebo, mean age 34 (29.5-49) vs 44.5 939.5 -47), female 63% vs 75%, duration of MS, 6 (1.5-10.5) vs 6 (2-12), EDSS 2.5 (2-4) vs 2 (1-3); PP and SP excluded; McDonald 2001 criteria	High-dose D2 group received 1,000 IU vitamin D2 daily plus a high-dose vitamin D2 supplement for 6 months		Other: low-dose D2 received 1000 IU vitamin D2 daily plus a placebo	OR for lower exit EDSS comparing high-dose with low-dose: 0.16 (CI 0.02, 1.34, p = 0.09)	N/A

Notes: AE adverse events, Co co-intervention, DMT disease-modifying therapy, N/A not available, R-R relapsing-remitting, PP primary progressive, SP secondary progressive, vs versus

§All studies are RCTs unless otherwise noted.

We identified 6 RCTs addressing vitamin D supplementation. Studies provided patients with different doses, and some studies explicitly tested high- or low-dose supplementation. Most studies administered vitamin D as a capsule. One study provided intramuscular injections. One study provided vitamin D and calcium.[28] All but one study compared intervention effects to placebo; 1 study provided the control group with a low-dose supplement.[94] The duration of interventions ranged from 6 to 24 months.

Samples were small and ranged from 23 to 68 randomized patients. One study[88] reported a power calculation for EDSS score differences. Two studies reported a power calculation, but for a different outcome, and 3 reported no power calculation; hence, it is unclear whether studies were adequately powered to detect a difference in MS progression. Only one study explicitly reported that the sample included 4 (out of 49) patients in secondary progression[28] and patients with progressive MS were excluded in 3 of the identified studies. [67,88,94]

All but one of the identified studies reported mean EDSS scores at the end of the trial for both experimental groups, some together with a statistical significance test for differences between groups. One study reported the proportion of patients completing the trial with increased EDSS, but none of the studies reported on the number of patients who entered progression, or reported on the time to progression. Adverse events were addressed in 4 out of 6 studies: one RCT reported no adverse events; one reported nephrolithiasis but did not specify the group; and 2 studies reported on minor adverse events.

The risk of bias assessment for the individual studies is shown in Appendix C. Studies gave supplements with matching placebos or injections with matching placebo injections, thereby reducing the risk of performance bias.

Summary of Findings and Quality of Evidence for Key Question 3

Results for KQ3 studies (risk factor modification therapies) are grouped by identified intervention type: exercise, diverse dietary interventions, and vitamin D supplementation.

Exercise

Across all identified physical exercise intervention studies, 7 reported post-intervention EDSS scores for both treatment arms. The results are shown in the following forest plot.

Figure 4: Effect of Exercise Interventions on EDSS Scores
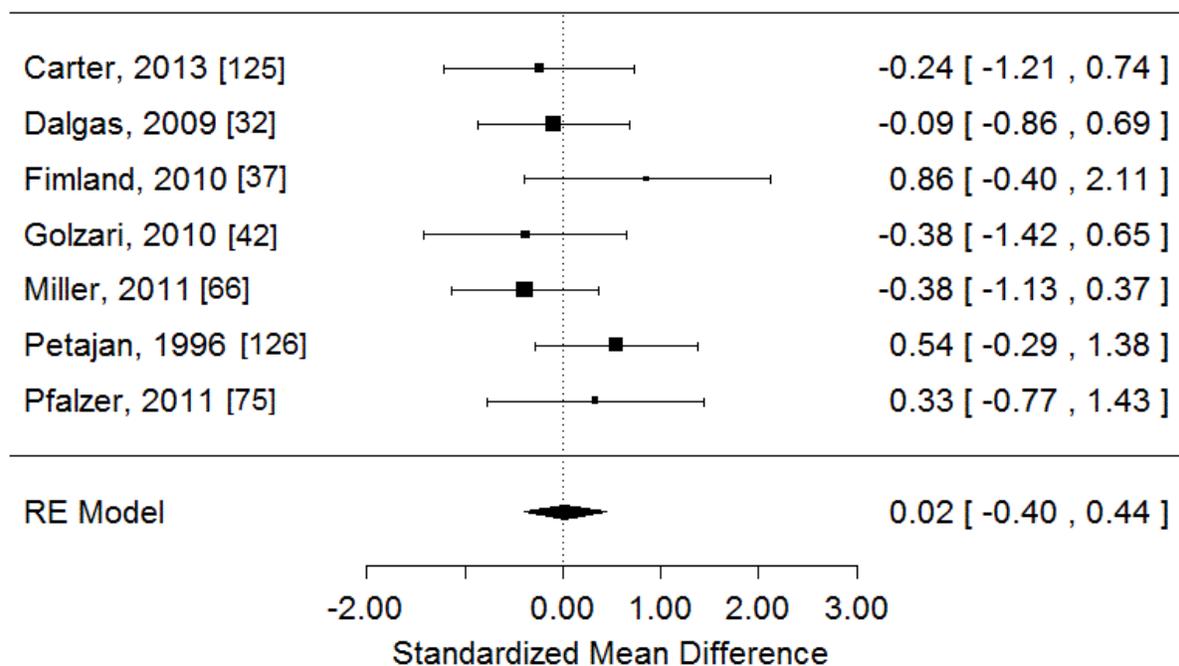
None of the individual studies reported a statistically significant effect, and the pooled result also did not provide evidence of statistically significant improvements in EDSS scores for exercise relative to an untreated control group (SMD 0.02; CI -0.40, 0.44; I^2 0%; 7 RCTs). However, several studies showed baseline imbalances, where intervention participants had higher EDSS scores than the control group. Using baseline-adjusted data for a sensitivity analysis, the result favored the exercise intervention (SMD -0.19; CI -0.34, -0.03; I^2 0; 7 RCTs). There was no indication of publication bias (rank test p = 0.562, regression test p = 0.850).

The quality of the evidence for the result of no difference between exercise interventions and untreated control groups on EDSS scores was downgraded by 2 due to severe *study limitations* and by 1 due to conflicting results in a sensitivity analysis (*imprecision*). Our confidence in the evidence summary showing the absence of an effect is limited because most studies were not designed to assess EDSS changes, study sample sizes were very small which could only detect a large treatment effect, and there were baseline imbalances. The intervention duration was not long-term but ranged between 4 weeks and 3 months, which may be too short to achieve, and to detect changes with standard diagnostic criteria. In addition, the difference between intervention and control groups was statistically significant when adjusting for baseline scores; hence an intervention effect in better-designed studies cannot be ruled out. Nonetheless, any treatment effect is likely to be very small; even adjusting for baseline imbalances, the estimate was an average of 0.20 points of improvement on the EDSS scale.

None of the studies reported on other outcome measures such as the change from relapsing-remitting to secondary progressive MS.

Dietary Interventions

Across studies, 4 dietary intervention studies reported on the number of patients deteriorating and entering progression in each group. The figure shows that none of the included studies reported a statistically significant effect between fatty acids supplementation compared to placebo. The intervention duration ranged from 18 to 24 months.

Figure 5: Effect of Fatty Acid Supplementation Interventions on the Relative Risk of Progression
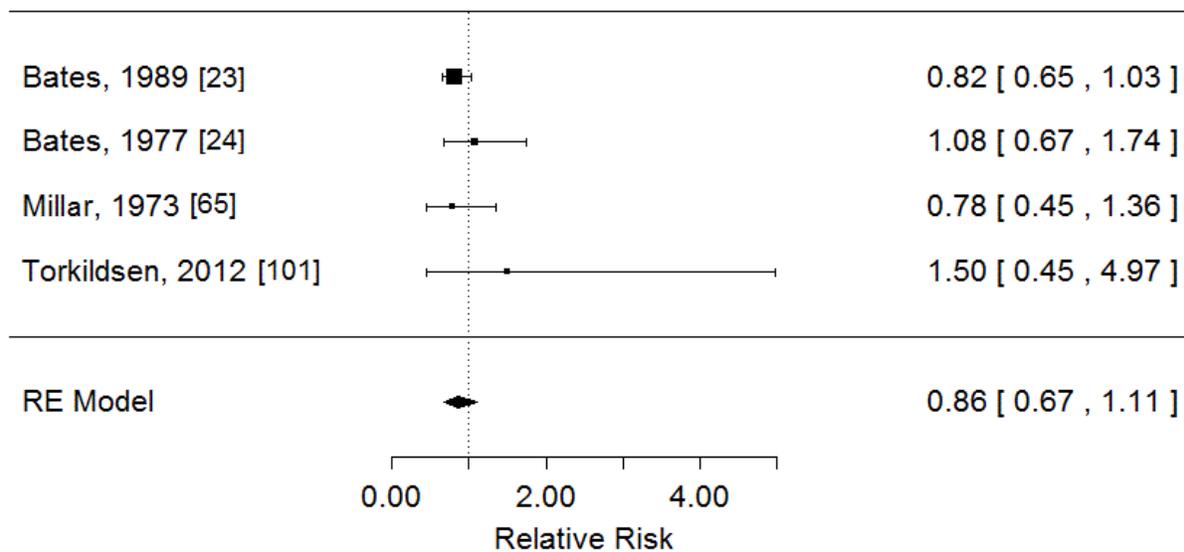
The pooled relative risk of experiencing progression was not statistically significantly lower in intervention groups (RR 0.86; CI 0.67, 1.05; I^2 0; 4 RCTs). Of note, Bates et al (1977) exclusively addressed patients with chronic progression.[24]

A similar result was shown for differences in EDSS scores between treatment and control groups across 3 dietary intervention studies testing fatty acids supplementation or Hot nature diet advice.

Figure 6: Effect of Dietary Interventions on EDSS Scores
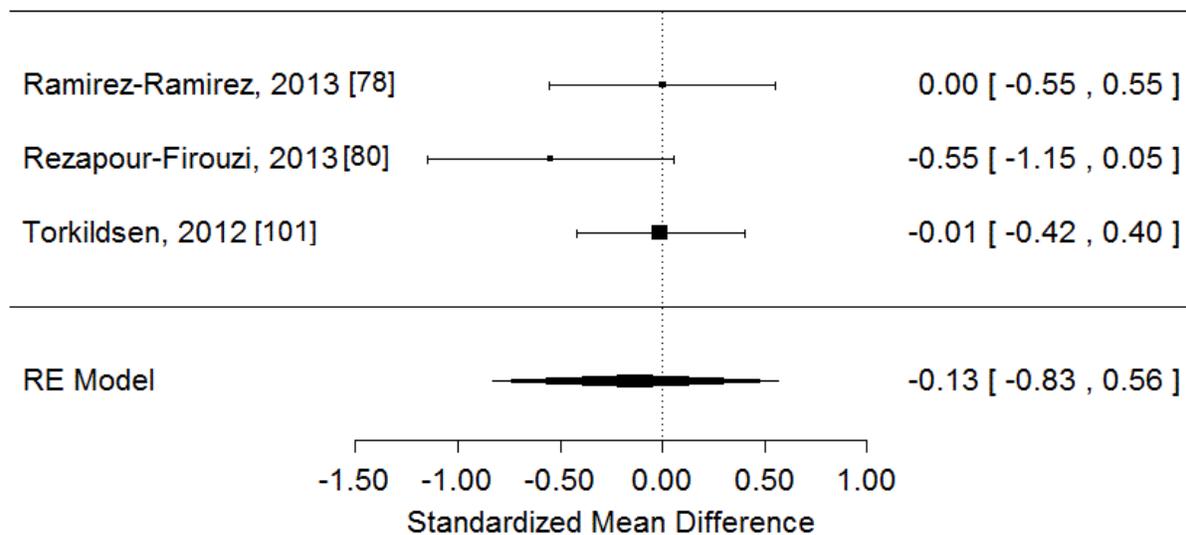
None of the individual interventions demonstrated a statistically significant effect on EDSS scores. Across studies, the difference in EDSS scores was not systematically different between intervention and control groups (SMD -0.13, -83, 0.56; I^2 5%; 3 RCTs).

One identified dietary intervention study reported a significant intervention effect, but this study could not be included in the meta-analysis. The study concluded that high-dose treatment of gamma-linolenic acid significantly reduced disability progression compared with placebo and low-dose treatment, but it did not report numerical data.[44]

The quality of evidence for the dietary intervention results showing the absence of an effect on MS progression (measured as the relative risk of progression [see figure 5] or based on EDSS scores [see figure 6]) were both downgraded to moderate due to study limitations. The early studies lack reporting detail while the more recently published studies were small and did not report statistical power calculations to determine whether studies were designed to detect an effect of the intervention on MS progression.

We did not identify studies reporting on other MS progression outcomes such as the time to secondary progression.

Vitamin D

The 5 RCTs comparing vitamin D supplementation to placebo and reporting on the same outcome measure are shown in the figure. All reported on EDSS scores.

Figure 7: Effect of Vitamin D Interventions on EDSS Scores
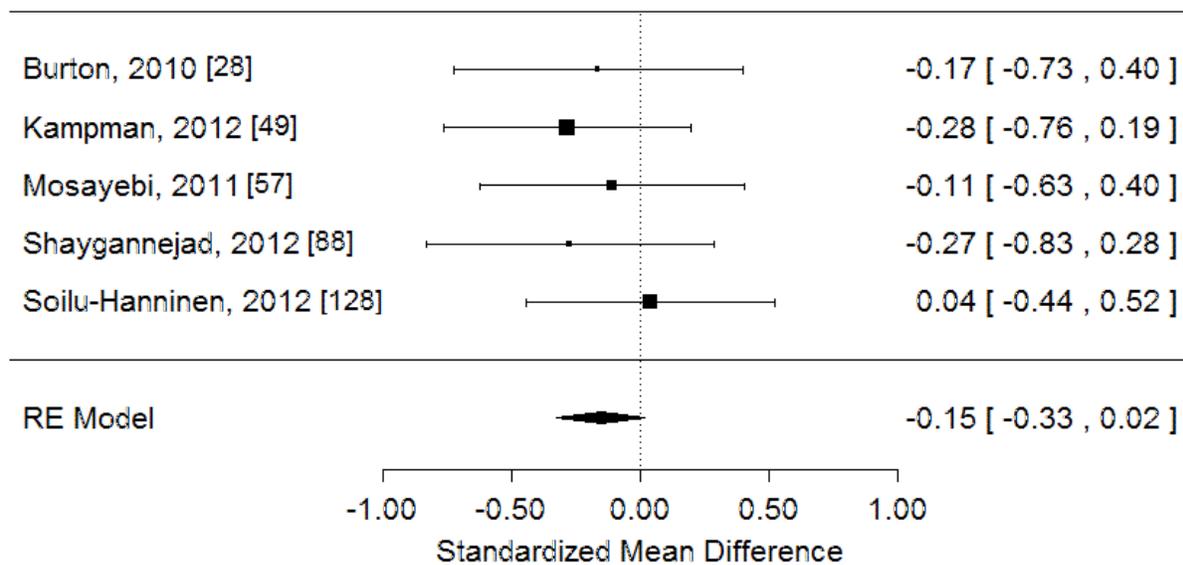
None of the individual studies reported a statistically significant effect of the specific intervention under evaluation. While the pooled result indicated a positive trend, we also could not show a significant difference in EDSS scores between intervention and control group across all studies using standardized mean differences (SMD -0.15; CI -0.33, 0.02; I^2 0; 5 RCTs). However, analyzing weighted mean differences to determine the clinical importance of the difference showed a statistically significant effect of vitamin D supplementation on EDSS scores (WMD -0.22; CI -0.39, -0.05; I^2 0; 5 RCTs). The result indicates a difference in EDSS scores of 0.22 between intervention and control groups. There was no evidence of publication bias for this result (rank test p = 0.82, regression test p = 0.99).

The quality of evidence for a non-significant effect of vitamin D supplementation on EDSS scores was downgraded by 2 due to *study limitations* and by 1 due to *imprecision*. The included studies were small and the lack of reported power calculations makes it unclear whether the studies were sufficiently powered to be able to detect small treatment effects. The statistical significance is dependent on the effect measure, showing that the effect estimate is not very robust.

Studies on vitamin D did not report on other MS progression-relevant outcomes.

Summary for KQ3

The following summary of findings table documents the results for all interventions or class of interventions for outcomes that were reported in at least 2 studies.

Table 13. Summary of Findings for KQ3

Intervention Outcome	# of RCTs	Findings: Direction, Magnitude of Effect	GRADE
Exercise Interventions			
EDSS score differences	7 RCTs	No statistically significant difference between exercise intervention and control group (SMD 0.02; CI -0.40, 0.44)	Very low (study limitations,** imprecision*)
Dietary Interventions			
Number of patients progressing	4 RCTs	No statistically significant difference between fatty acids supplementation intervention and control group (RR 0.86; CI 0.67, 1.05)	Moderate (study limitations*)
EDSS score differences	3 RCTs	No statistically significant difference between dietary intervention (fatty acids or Hot nature diet) and control group (SMD -0.13; CI -0.83, 0.56)	Moderate (study limitations*)
Vitamin D Supplements			
EDSS score differences	5 RCTs	No statistically significant difference between vitamin D supplementation and placebo (SMD -0.15; CI -0.33, 0.02)	Very low (study limitations,** imprecision*)

Note: * quality of evidence downgraded by 1 level, ** quality of evidence downgraded by 2 levels

VA Subgroup Analysis

The participants in Lo et al were recruited either from the MS clinic at the VA Connecticut Healthcare System or through chapters of the National Multiple Sclerosis Society.[56] The study compared body weight supported treadmill training, with or without robot assistance, and found an improvement in EDSS scales for both groups across the 13 participants.

The author affiliation of the study by Yadav et al[110] suggests that the participants were US Veterans. Patients were assigned to a one year low-fat, plant-based diet. The study reported no significant changes in EDSS scores in the groups after baseline difference adjustment. Only few study details were available; the study was published as a conference abstract.

SUMMARY AND DISCUSSION

Our systematic review focused on modifiable risk factors, such as health behaviors of patients with MS. We systematically searched for, documented, and synthesized studies available in the international literature on modifiable risk factors and the effect of modification therapies.

The review addressed a broad and very complex research field and a large number of studies contributed to this review. Literature searches were comprehensive and exploratory in nature and were not limited to a narrow set of known risk factors. Few prospective studies were identified to inform the association between modifiable risk factors and MS progression, limiting the conclusions that can be drawn from the existing literature for KQ1. Furthermore, while the review made every effort to locate studies relevant to KQ2 (exposure during military service), only a very small number of studies was identified. Although a number of interventions have been tested in RCTs, many were not designed to assess the effect on MS progression, also limiting the conclusions that can be drawn from the intervention literature addressed in KQ3.

We did not find variables that were identified as valid risk factors of MS progression and that have been shown in intervention studies to improve MS progression. However, the review systematically explores and catalogues what is currently known in this research field, highlights promising areas, and identifies future research needs to address the progression of MS.

SUMMARY OF EVIDENCE FOR KQ1: What modifiable epidemiologic factors are related to multiple sclerosis progression following diagnosis?

Our literature review identified a large number of modifiable epidemiologic factors that have been assessed in the context of MS progression. However, study designs, operationalizations of risk factors, and outcome assessment measures varied widely.

A substantial amount of research has been dedicated to the role of vitamin D in MS progression. Our synthesis shows a weak but consistent negative correlation between 25(OH)D levels and EDSS scores across studies. Evidence comes primarily from concurrent studies which assess the physiological level and the disability status at the same time. Hence, this result should be interpreted as an association without causal interpretation. Low vitamin D levels may be the cause, the effect, or a covariate of EDSS levels. In addition, whether the physiological levels can be directly influenced by patients is an unresolved question. The association has also been shown in 2 prospective studies that reported on this outcome and although there was some evidence of publication bias, an adjusted analysis found a very similar effect. We did not find studies reporting on other operationalizations of the role of vitamin D, such as sun exposure or use of supplements, that could be combined, and we did not find studies reporting on the effect of vitamin D on the change from relapsing-remitting to secondary progressive MS. The international literature has linked MS to vitamin D deficiency and suggests additional functions outlining why high levels of vitamin D may be beneficial for MS patients (*eg*, anti-inflammatory aspects of vitamin D).[4,129]

Smoking has also been addressed in a large number of studies and was associated with an increased risk of progression in MS patients. The association was shown in studies predicting time to EDSS scores of 6 (use of cane, crutch, or brace) as well as conversion to secondary

progression. Our confidence in the exact size of effect is somewhat limited due to unexplained heterogeneity (moderate quality of evidence). Our pooled estimate was statistically significant but lower than that reported by a 2011 meta-analysis. The earlier existing meta-analysis was based on fewer studies and did not find a statistically significant effect, and concluded at the time that smoking is important in determining MS susceptibility but the effect on the progression of disease is less certain.[130] The now available literature suggests that smoking is an important modifiable risk factor for MS progression. This is of particular importance as it is a risk factor that can be directly influenced by MS patients.

There is low quality of evidence that epidural analgesics during childbirth are associated with EDSS scores. This outcome has been addressed in retrospective as well as prospective studies but all existing studies report on disability levels across study samples, not direct measures of progression in individuals such as time to secondary progression.

The risk factors sun exposure, month of birth, diet, fish consumption, alcohol-related predictors, exercise, oral contraception, and education have been addressed in more than one study and were documented in detail in the summary of findings section. It was not possible to derive specific evidence statements due to the unique operationalization of risk factors and outcome measures; however, in particular the role of sun exposure and alcohol-related variables should be investigated further.

The evidence tables document a large range of potential risk factors such as: cesarean delivery; breast feeding; having been breast fed; obstetrical and spinal anesthesia; childhood maltreatment; working outdoors; individual health promoting lifestyle domains; meditation practice; insurance coverage; medical care satisfaction variables; exposure to different types of animals; coal heating; wood heating; humid living space; no sewage system; no piped water; type of environment (*eg*, farm); specific diet factors such as coffee consumption, liver consumption, vitamin supplementation, fortified foods, vegetarian diet; cod liver oil intake; occupational status; deployment to a war theater; being a Veteran; and earthquake experience. These were addressed in single studies and have not been replicated in other studies.

The review explored a large number of potential risk factors but shows that in many cases, the existing evidence base investigating an association is insufficient to make evidence statements for specific outcomes and results. This is illustrated by the following examples. Our systematic review showed that the evidence for an association between progression of MS and dietary factors is sparse. We did not identify more than one study reporting on the same diet and reporting on the same outcome measure. Similarly, a Cochrane review on dietary interventions in MS highlighted that a number of diets for MS (*eg*, Swank Diet) have been proposed; however, dietary habits in MS patients have not been extensively studied or reported.[12] Furthermore, physical exercise has been addressed in a number of published studies, both as a correlate of disability and its predictive validity for MS progression. Study results varied by analytic design. Lower physical exercise can be the cause, the effect, or a covariate of higher EDSS scores. We did not identify more than one study reporting on the same risk factor operationalization and MS progression outcome measure. Hence, the existing evidence base is still very limited. Approaches to offer physical exercise to MS patients are traditionally based on optimizing daily functioning, but whether exercise has a role in slowing progression of MS has also been raised as a research question.[131-133]

SUMMARY OF EVIDENCE KQ2: What environmental exposures prior to or during military service are related to multiple sclerosis progression following onset symptoms?

Only very few studies were identified that reported on exposures prior to and during military services associated with MS progression (KQ2) in active military personnel or Veterans. Evaluated risk factors in existing studies include only a small number of potentially relevant exposures such as deployment.

The quality of the evidence across studies was determined to be insufficient for evidence statements. None of the studies employed a prospective study design and risk factors were addressed in single studies without replication in other studies. All potential risk factors were reported in only one included study without replication in another participant sample. Hence, the available evidence is not suitable to answer the review question.

SUMMARY OF EVIDENCE KQ3: Among identified risk factors for progression, what treatment / risk factor modification therapies have been shown to delay or hasten the progression of MS once it has initiated?

Our literature searches identified a substantial number of studies that have addressed modifiable risk factors; however, all addressed exercise programs, dietary interventions, or vitamin D supplementation.

Exercise interventions did not demonstrate a statistically significant effect on EDSS scores comparing intervention and untreated control groups across all studies reporting on this outcome. However, sensitivity analyses indicated that, adjusting for baseline imbalances, small effects on EDSS become apparent (0.20 point difference between treatment groups). Studies were not designed to assess EDSS changes or other measures of progression, study sample sizes were very small with indications of baseline imbalances, and the interventions may have been too short to achieve and to detect changes with standard diagnostic criteria. The negative results should not be interpreted as exercise not being beneficial in MS in general. Exercise in MS patients may have many positive effects[132] and a recent systematic review[134] addressing a range of outcomes concluded that exercise may be recommended for rehabilitation. Our review aimed to detect an effect for a very specific outcome – progression of MS.

The identified data did not indicate a statistically significant positive effect of dietary interventions that affected the progression of MS. This result mirrors the conclusion of an existing Cochrane review on dietary interventions for MS that included studies published to November 2011.[12] The review reported that polyunsaturated fatty acids seem to have no major effect on disease progression but cautioned also that evidence statements are limited due to uncertain quality of the studies.

Individual studies and the pooled result showed a trend for an effect favoring vitamin D supplementation in MS patients but the statistical significance depended on the effect measure. Our confidence in the evidence for the absence of an effect is limited given that the existing studies were small and they may lack statistical power to detect small treatment effects. A Cochrane review that searched for intervention studies in May 2010 identified only one study; all

additional studies shown in our meta-analysis were published after this date. The review concluded that the level of evidence for the effectiveness of vitamin D supplementation does not allow confident decision-making about the use of vitamin D in MS.[4] Any potential treatment effects are likely to be small, with an estimated difference of 0.22 points in EDSS scores between intervention and control groups.

Finally, smoking, a risk factor for progression with a stronger evidence base, has not been addressed in RCTs to assess the effects of smoking cessation interventions on progression in MS patients. This is unfortunate because some risk factor studies suggested that negative consequences of smoking can be reversed in ex-smokers, suggesting that this risk factor could be amenable to intervention.[46]

LIMITATIONS

It should be noted that this review was restricted to patient-reported measures of MS progression and disability. Other progression measures such as MRI results are also of interest to clinicians and can make additional contributions to this complex research field.

Furthermore, due to resource constraints, this review was limited to English-language publications. Although we included several international studies, the language restriction will have missed some studies, in particular older studies contributing to research on MS progression.

This review identified a large number of studies contributing to the evidence base on modifiable risk factors associated with MS progression. However, the evidence base is limited due to the small number of prognostic studies and the small number of studies reporting on direct measures of progression (*eg*, conversion to secondary progressive MS) rather than proxies such as MS disability status.

We converted statistics to the extent possible for this review. Nonetheless we were often not able to summarize results across studies due to lack of reporting of key variables, such as point estimates and measures of dispersion, in addition to the statistical significance of the presence or absence of associations. Due to the timeframe and lack of resources the review is entirely based on published literature and did not contact authors for missing information or additional data; furthermore, several included studies have been published decades ago, making it unlikely that additional data is still available.

Applicability of Findings to the VA Population

We found no indication that risk factor results and treatment effects are not applicable to the VA population. However, the existing evidence does not permit analyses to test this hypothesis by identifying moderator effects linking study populations to differential effects. There are very few risk factor or intervention studies reporting specifically on VA samples.

RESEARCH GAPS/FUTURE RESEARCH

Our systematic review showed that more prospective research studies are needed to allow predictions and meaningful interpretation of risk factor analyses. Furthermore, it is imperative that risk factor studies report more details (*eg*, mean EDSS scores and a measure of dispersion), more measures of progression, and/or more analyses (*eg*, reporting on EDSS scores means as well as time to progression to specific EDSS benchmarks). While many individual studies do not

have sufficient statistical power to detect small effects of risk factors on progression, studies may contribute to future meta-analyses. We identified a number of areas with published research on a risk factor of interest, but due to the unique operationalization of predictor and outcome measure, it was not possible to adequately synthesize results across studies.

Although our review addressed a broad research field, there are other potential risk factors that were outside the scope of this review, such as comorbidities.[11] There is a growing literature on MS comorbidities, including obesity and the associations of body weight and MS progression, which warrants an individual systematic review.[135,136] Future reviews should in particular address the role of treatable comorbidities in MS progression. Scoping searches also identified a large literature base evaluating the effect of pregnancies. However, any association needs to be interpreted with caution. While the data may suggest a protective effect, reverse causality cannot be ruled out – a MS diagnosis and perceived progression may affect reproductive decision making.[137]

Furthermore, this review did not target psychological variables, such as depression, anxiety, coping strategies, social functioning, distress, anger, and other emotions and cognitive styles, which may be reactions to MS progression and/or contributing factors to MS progression. Although variables have been assessed in the literature, very often, these have been studied as correlates of the disease, and while many studies have tried to predict psychological variables with MS progression, some have used the psychological variables as predictors for MS progression. These variables should be assessed in prospective risk factor studies to establish the temporal chain of events in order to establish a prognostic link between these variables and MS progression. However, even if a link can be established, it is a different matter to show that the psychological variables can a) be modified and b) the modification has an effect on progression; hence, intervention studies testing the modification therapy will be subsequently needed.

Generally, more prospective risk factor studies are needed that allow determining a temporal sequence of events and that address the direction of associations. For example, a number of studies have reported on alcohol-related measures and showed better outcomes associated with specific operationalizations of alcohol use or misuse, but the available studies used primarily concurrent data (correlating current alcohol intake and current disability) and an alternative interpretation of this "protective" effect of alcohol is that more disabled people drink less alcohol because of their disability. Sun exposure should also be evaluated further in order to replicate identified associations of specific operationalizations of the predictor variable and MS disability and progression measures. Prospective studies are needed to provide more information on the role of sun exposure and alcohol consumption (and the optimum amount) in MS progression.[11]

Finally, intervention studies testing the effect of interventions on MS progression should determine the statistical power needed to detect a difference between treatment groups. This is in particular needed for vitamin D supplementation trials. In addition, more research on exercise interventions is warranted with studies that are adequately powered and interventions of sufficient duration to potentially influence MS progression. Effects of smoking cessation interventions should be determined in intervention studies given the association between smoking and MS progression. Furthermore, while a substantial number of intervention studies exist that have reported on disease status and disability measures, larger studies reporting on direct progression measures are urgently needed.

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CONCLUSIONS

A large number of studies is available to contribute to the growing research literature on modifiable risk factors and MS progression but the research field is very complex.

Risk factor studies used diverse operationalizations of risk factors and different outcome measures, and more prospective studies are needed. Most consistent results were shown for the association between EDSS scores and vitamin D levels. Smoking was associated with a faster progression of MS in smokers compared to nonsmokers.

Risk factors in Veterans and active military personnel were one of the key questions for this review but very few studies are available to inform on this participant subgroup.

We did not identify interventions that showed a statistically significant effect of exercise, diet, or vitamin D supplementation on EDSS scores across studies. However, studies were not designed to assess effects on MS progression. More research is needed, in particular, on interventions for smoking cessation, adequately powered vitamin D supplementation RCTs, and RCTs testing the effects of long-term exercise interventions.

REFERENCES

1. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Engl J Med.* Nov 16 2000;343(20):1430-1438.

2. Multiple sclerosis - management of multiple sclerosis in primary and secondary care. October 2014.

3. Veterans Health Administration The Office of Patient Care Services: Medical-Surgical Services. VHA HANDBOOK 1011.06 Multiple Sclerosis System of Care Procedures. Washington, D.C.December 7, 2009.

4. Jagannath VA, Fedorowicz Z, Asokan GV, Robak EW, Whamond L. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev.* 2010(12):CD008422.

5. Kuhlmann T, Lingfeld G, Bitsch A, Schuchardt J, Bruck W. Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain: a Journal of Neurology.* Oct 2002;125(Pt 10):2202-2212.

6. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology.* Mar 1983;13(3):227-231.

7. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology.* Jul 2001;50(1):121-127.

8. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* Jul 15 2014;83(3):278-286.

9. Herndon RM. Medical hypothesis: why secondary progressive multiple sclerosis is a relentlessly progressive illness. *Archives of Neurology.* Feb 2002;59(2):301-304.

10. Compston A, Coles A. Multiple sclerosis. *Lancet.* Apr 6 2002;359(9313):1221-1231.

11. D'Hooghe M B, Nagels G, Bissay V, De Keyser J. Modifiable factors influencing relapses and disability in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jul 2010;16(7):773-785.

12. Farinotti M, Vacchi L, Simi S, Di Pietrantonj C, Brait L, Filippini G. Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev.* 2012;12:CD004192.

13. Faridar A, Eskandari G, Sahraian MA, Minagar A, Azimi A. Vitamin D and multiple sclerosis: a critical review and recommendations on treatment. *Acta Neurol Belg.* Dec 2012;112(4):327-333.

14. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ.* Jul 28 2001;323(7306):224-228.

15. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine.* Feb 19 2013;158(4):280-286.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* Nov 1983;33(11):1444-1452.

17. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology.* Apr 2011;64(4):401-406.

18.   Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Syst Rev.* 2013;2:71.

19.   Armutlu K, Karabudak R, Nurlu G. Physiotherapy approaches in the treatment of ataxic multiple sclerosis: a pilot study. *Neurorehabil Neural Repair.* 2001;15(3):203-211.

20.   Ascherio A, Munger KL, White R, et al. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA Neurology.* Mar 2014;71(3):306-314.

21.   Aupperle R, Denney D, Lynch S. Omega 3 fatty acid levels in multiple sclerosis: correlation of diet, disability, and depression. *Multiple Sclerosis.* Sep 2005;11:S28-S28.

22.   Baghizadeh S, Sahraian MA, Beladimoghadam N. Clinical and demographic factors affecting disease severity in patients with multiple sclerosis. *Iranian Journal of Neurology.* 2013;12(1):1-8.

23.   Bates D, Cartlidge NE, French JM, et al. A double-blind controlled trial of long chain n-3 polyunsaturated fatty acids in the treatment of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Jan 1989;52(1):18-22.

24.   Bates D, Fawcett PR, Shaw DA, Weightman D. Trial of polyunsaturated fatty acids in non-relapsing multiple sclerosis. *British Medical Journal.* Oct 8 1977;2(6092):932-933.

25.   Bates D, Fawcett PR, Shaw DA, Weightman D. Polyunsaturated fatty acids in treatment of acute remitting multiple sclerosis. *British Medical Journal.* Nov 18 1978;2(6149):1390-1391.

26.   Bjarnadottir OH, Konradsdottir AD, Reynisdottir K, Olafsson E. Multiple sclerosis and brief moderate exercise. A randomised study. *Multiple sclerosis (Houndmills, Basingstoke, England).* Jul 2007;13(6):776-782.

27.   Bombardier CH, Blake KD, Ehde DM, Gibbons LE, Moore D, Kraft GH. Alcohol and drug abuse among persons with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Feb 2004;10(1):35-40.

28.   Burton JM, Kimball S, Vieth R, et al. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology.* Jun 8 2010;74(23):1852-1859.

29.   Carter AM, Daley AJ, Kesterton SW, Woodroofe NM, Saxton JM, Sharrack B. Pragmatic exercise intervention in people with mild to moderate multiple sclerosis: a randomised controlled feasibility study. *Contemporary Clinical Trials.* Jul 2013;35(2):40-47.

30.   Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med.* Jul 30 1998;339(5):285-291.

31.   Conklyn D, Stough D, Novak E, Paczak S, Chemali K, Bethoux F. A home-based walking program using rhythmic auditory stimulation improves gait performance in patients with multiple sclerosis: a pilot study. *Neurorehabil Neural Repair.* Nov-Dec 2010;24(9):835-842.

32.   Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. *Neurology.* Nov 3 2009;73(18):1478-1484.

33.   Dastagir A, Alqallaf A, Bao F, et al. Vitamin D Levels in African-Americans and Caucasian with Relapsing Multiple Sclerosis: Relationship with Disease Course. *Neurology.* Feb 2013;80.

34.   DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Feb 2004;85(2):290-297.

35.   Detels R, Clark VA, Valdiviezo NL, Visscher BR, Malmgren RM, Dudley JP. Factors associated with a rapid course of multiple sclerosis. *Archives of Neurology.* Jun 1982;39(6):337-341.

36.   D'Hooghe M B, Haentjens P, Nagels G, De Keyser J. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. *European Journal of Neurology:The Official Journal of the European Federation of Neurological Societies.* Apr 2012;19(4):616-624.

37.   Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J. Enhanced neural drive after maximal strength training in multiple sclerosis patients. *European Journal of Applied Physiology.* Sep 2010;110(2):435-443.

38.   Foster M, Zivadinov R, Weinstock-Guttman B, et al. Associations of moderate alcohol consumption with clinical and MRI measures in multiple sclerosis. *Journal of Neuroimmunology.* Feb 29 2012;243(1-2):61-68.

39.   Fragoso YD, Adoni T, Almeida SM, et al. Multiple sclerosis in South America: month of birth in different latitudes does not seem to interfere with the prevalence or progression of the disease. *Arq Neuropsiquiatr.* Sep 2013;71(9a):573-579.

40.   Gava G, Bartolomei I, Costantino A, et al. Long-term influence of combined oral contraceptive use on the clinical course of relapsing-remitting multiple sclerosis. *Fertility and Sterility.* Jul 2014;102(1):116-122.

41.   Gelfand JM, Cree BAC, McElroy J, et al. Vitamin D in African Americans with multiple sclerosis. *Neurology.* May 2011;76(21):1824-1830.

42.   Golzari Z, Shabkhiz F, Soudi S, Kordi MR, Hashemi SM. Combined exercise training reduces IFN-gamma and IL-17 levels in the plasma and the supernatant of peripheral blood mononuclear cells in women with multiple sclerosis. *Int Immunopharmacol.* Nov 2010;10(11):1415-1419.

43.   Goodin DS. Survey of multiple sclerosis in northern California. Northern California MS Study Group. *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 1999;5(2):78-88.

44.   Harbige LS, Sharief MK. Polyunsaturated fatty acids in the pathogenesis and treatment of multiple sclerosis. *The British Journal of Nutrition.* Oct 2007;98 Suppl 1:S46-53.

45.   Hatamian H, Bidabadi E, Seyed Saadat SM, et al. Is serum vitamin D levels associated with disability in patients with newly diagnosed multiple sclerosis? *Iranian Journal of Neurology.* 2013;12(2):41-46.

46.   Healy BC, Ali EN, Guttmann CR, et al. Smoking and disease progression in multiple sclerosis. *Archives of Neurology.* Jul 2009;66(7):858-864.

47.   Hernan MA, Jick SS, Logroscino G, Olek MJ, Ascherio A, Jick H. Cigarette smoking and the progression of multiple sclerosis. *Brain: a Journal of Neurology.* Jun 2005;128(Pt 6):1461-1465.

48.   Jansons L, Tutuncu M, Tang J, et al. Does smoking really impact progression in multiple sclerosis? *Mult. Scler. J.* Oct 2011;17:S138-S138.

49.   Kampman MT, Steffensen LH, Mellgren SI, Jorgensen L. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Aug 2012;18(8):1144-1151.

50.   Knippenberg S, Bol Y, Damoiseaux J, Hupperts R, Smolders J. Vitamin D status in patients with MS is negatively correlated with depression, but not with fatigue. *Acta Neurologica Scandinavica.* Sep 2011;124(3):171-175.

51.   Koch M, De Keyser J, Tremlett H. Timing of birth and disease progression in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jul 2008;14(6):793-798.

52.   Koch M, van Harten A, Uyttenboogaart M, De Keyser J. Cigarette smoking and progression in multiple sclerosis. *Neurology.* Oct 9 2007;69(15):1515-1520.

53.   Kragt J, van Amerongen B, Killestein J, et al. Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jan 2009;15(1):9-15.

54.   Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, Nefzger MD. Studies on the natural history of multiple sclerosis. 7. Correlates of clinical change in an early bout. *Acta Neurologica Scandinavica.* 1973;49(3):379-395.

55.   Lauer K, Firnhaber W. Prognostic criteria in an epidemiological group of patients with multiple sclerosis: an exploratory study. *Journal of Neurology.* Feb 1992;239(2):93-97.

56.   Lo AC, Triche EW. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. *Neurorehabil Neural Repair.* Nov-Dec 2008;22(6):661-671.

57.   Lu E, Zhao Y, Dahlgren L, et al. Obstetrical epidural and spinal anesthesia in multiple sclerosis. *Journal of Neurology.* Oct 2013;260(10):2620-2628.

58.   Lucenti A, Galimberti S, Barizzone N, et al. Multiple sclerosis progression is not associated with birth timing in Italy. *Journal of the Neurological Sciences.* Nov 2014;346(1-2):194-196.

59.   Maghzi AH, Etemadifar M, Heshmat-Ghahdarijani K, et al. Cigarette smoking and the risk of multiple sclerosis: a sibling case-control study in Isfahan, Iran. *Neuroepidemiology.* 2011;37(3-4):238-242.

60.   Mandia D, Ferraro OE, Nosari G, Montomoli C, Zardini E, Bergamaschi R. Environmental Factors and Multiple Sclerosis Severity: A Descriptive Study. *Int. J. Environ. Res. Public Health.* Jun 2014;11(6):6417-6432.

61.   Manouchehrinia A, Tench CR, Maxted J, Bibani RH, Britton J, Constantinescu CS. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. *Brain: a Journal of Neurology.* Jul 2013;136(Pt 7):2298-2304.

62.   Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. High frequency of adverse health behaviors in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jan 2009;15(1):105-113.

63.   McDowell TY, Amr S, Culpepper WJ, et al. Sun exposure, vitamin D intake and progression to disability among veterans with progressive multiple sclerosis. *Neuroepidemiology.* 2011;37(1):52-57.

64.   Milivojevic I, Adamec I, Habek M. Utilization of physical rehabilitation among people with multiple sclerosis. *Irish Journal of Medical Science.* Sep 2013;182(3):429-432.

65.   Millar JH, Zilkha KJ, Langman MJ, et al. Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *British Medical Journal.* Mar 31 1973;1(5856):765-768.

66.   Miller L, Paul L, Mattison P, McFadyen A. Evaluation of a home-based physiotherapy programme for those with moderate to severe multiple sclerosis: a randomized controlled pilot study. *Clin Rehabil.* Aug 2011;25(8):720-730.

67.   Mosayebi G, Ghazavi A, Ghasami K, Jand Y, Kokhaei P. Therapeutic effect of vitamin D3 in multiple sclerosis patients. *Immunological Investigations.* 2011;40(6):627-639.

68.   Motl RW, Dlugonski D, Pilutti L, Sandroff B, McAuley E. Premorbid physical activity predicts disability progression in relapsing-remitting multiple sclerosis. *Journal of the Neurological Sciences.* Dec 15 2012;323(1-2):123-127.

69.   Mowry EM, Waubant E, McCulloch CE, et al. Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis. *Annals of Neurology.* Aug 2012;72(2):234-240.

70.   Niino M, Fukazawa T, Miyazaki Y, et al. Association of serum vitamin D levels in Japanese patients with multiple sclerosis. *Clinical and Experimental Neuroimmunology.* December 2013;4 SUPPL. 1:92.

71.   Pantzaris MC, Loukaides GN, Ntzani EE, Patrikios IS. A novel oral nutraceutical formula of omega-3 and omega-6 fatty acids with vitamins (PLP10) in relapsing remitting multiple sclerosis: a randomised, double-blind, placebo-controlled proof-of-concept clinical trial. *BMJ open.* 2013;3(4).

72.   Pasto L, Portaccio E, Ghezzi A, et al. Epidural analgesia and cesarean delivery in multiple sclerosis post-partum relapses: the Italian cohort study. *BMC Neurol.* 2012;12:165.

73.   Paty DW, Cousin HK, Read S, Adlakha K. Linoleic acid in multiple sclerosis: failure to show any therapeutic benefit. *Acta Neurologica Scandinavica.* Jul 1978;58(1):53-58.

74.   Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Annals of Neurology.* Apr 1996;39(4):432-441.

75.   Pfalzer L, Fry D. Effects of a 10-week inspiratory muscle training program on lower-extremity mobility in people with multiple sclerosis: a randomized controlled trial. *International Journal of MS care.* Spring 2011;13(1):32-42.

76.   Pittas F, Ponsonby AL, van der Mei IA, et al. Smoking is associated with progressive disease course and increased progression in clinical disability in a prospective cohort of people with multiple sclerosis. *Journal of Neurology.* Apr 2009;256(4):577-585.

77. Plow M, Finlayson M, Cho C. Correlates of nutritional behavior in individuals with multiple sclerosis. *Disabil. Health J.* Oct 2012;5(4):284-291.

78. Ramirez-Ramirez V, Macias-Islas MA, Ortiz GG, et al. Efficacy of fish oil on serum of TNF alpha , IL-1 beta , and IL-6 oxidative stress markers in multiple sclerosis treated with interferon beta-1b. *Oxidative Medicine and Cellular Longevity.* 2013;2013:709493.

79. Rampello A, Franceschini M, Piepoli M, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. *Physical Therapy.* May 2007;87(5):545-555.

80. Rezapour-Firouzi S, Arefhosseini SR, Ebrahimi-Mamaghani M, et al. Erythrocyte membrane fatty acids in multiple sclerosis patients and hot-nature dietary intervention with co-supplemented hemp-seed and evening-primrose oils. *African Journal of Traditional, Complementary, and Alternative medicine: AJTCAM / African Networks on Ethnomedicines.* 2013;10(6):519-527.

81. Romberg A, Virtanen A, Ruutiainen J, et al. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. *Neurology.* Dec 14 2004;63(11):2034-2038.

82. Roudbari SA, Ansar MM, Yousefzad A. Smoking as a risk factor for development of Secondary Progressive Multiple Sclerosis: A study in IRAN, Guilan. *Journal of the Neurological Sciences.* Jul 15 2013;330(1-2):52-55.

83. Sangelaji B, Nabavi SM, Estebsari F, et al. Effect of combination exercise therapy on walking distance, postural balance, fatigue and quality of life in multiple sclerosis patients: a clinical trial study. *Iranian Red Crescent Medical Journal.* Jun 2014;16(6):e17173.

84. Schwartz I, Sajin A, Moreh E, et al. Robot-assisted gait training in multiple sclerosis patients: a randomized trial. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Jun 2012;18(6):881-890.

85. Sena A, Couderc R, Vasconcelos JC, Ferret-Sena V, Pedrosa R. Oral contraceptive use and clinical outcomes in patients with multiple sclerosis. *Journal of the Neurological Sciences.* Jun 15 2012;317(1-2):47-51.

86. Shahbeigi S, Pakdaman H, Fereshtehnejad SM, Nikravesh E, Mirabi N, Jalilzadeh G. Vitamin d3 concentration correlates with the severity of multiple sclerosis. *International Journal of Preventive Medicine.* May 2013;4(5):585-591.

87. Shammas L, Zentek T, von Haaren B, Schlesinger S, Hey S, Rashid A. Home-based system for physical activity monitoring in patients with multiple sclerosis (Pilot study). *Biomedical Engineering Online.* 2014;13:10.

88. Shaygannejad V, Janghorbani M, Ashtari F, Dehghan H. Effects of adjunct low-dose vitamin d on relapsing-remitting multiple sclerosis progression: preliminary findings of a randomized placebo-controlled trial. *Multiple Sclerosis International.* 2012;2012:452541.

89. Sibley WA, Bamford CR, Clark K, Smith MS, Laguna JF. A prospective study of physical trauma and multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Jul 1991;54(7):584-589.

90.   Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Nov 2008;14(9):1220-1224.

91.   Soilu-Hanninen M, Laaksonen M, Laitinen I, Eralinna JP, Lilius EM, Mononen I. A longitudinal study of serum 25-hydroxyvitamin D and intact parathyroid hormone levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Feb 2008;79(2):152-157.

92.   Solari A, Filippini G, Gasco P, et al. Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. *Neurology.* Jan 1 1999;52(1):57-62.

93.   Spitzer C, Bouchain M, Winkler LY, et al. Childhood trauma in multiple sclerosis: a case-control study. *Psychosomatic Medicine.* Apr 2012;74(3):312-318.

94.   Stein MS, Liu Y, Gray OM, et al. A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis. *Neurology.* Oct 25 2011;77(17):1611-1618.

95.   Sternberg Z, Leung C, Sternberg D, et al. The prevalence of the classical and non-classical cardiovascular risk factors in multiple sclerosis patients. *CNS & Neurological Disorders Drug Targets.* Feb 1 2013;12(1):104-111.

96.   Stuifbergen AK, Blozis SA, Harrison TC, Becker HA. Exercise, functional limitations, and quality of life: A longitudinal study of persons with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation.* Jul 2006;87(7):935-943.

97.   Sundstrom P, Nystrom L. Smoking worsens the prognosis in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Sep 2008;14(8):1031-1035.

98.   Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. *Lancet.* Jul 7 1990;336(8706):37-39.

99.   Teter B, Weinstock-Guttman B, Mihai C, et al. Parity, education and sun exposure may predict long-term disability in female patients with multiple sclerosis. *Multiple Sclerosis.* Sep 2008;14:S203-S203.

100.   Thouvenot E, Orsini M, Daures JP, Camu W. Vitamin D is associated with degree of disability in patients with fully ambulatory relapsing-remitting multiple sclerosis. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies.* Mar 2015;22(3):564-569.

101.   Torkildsen O, Wergeland S, Bakke S, et al. omega-3 fatty acid treatment in multiple sclerosis (OFAMS Study): a randomized, double-blind, placebo-controlled trial. *Archives of Neurology.* Aug 2012;69(8):1044-1051.

102.   Tuzun E, Polat A, Akman-Demir G, et al. Impact of Earthquake on Multiple Sclerosis Attacks. *Noropsikiyatri Ars.* 2010;47(4):324-327.

103.   van der Mei IA, Ponsonby AL, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. *Journal of Neurology.* May 2007;254(5):581-590.

104.   Vollmer TL, Hadjimichael O, Preiningerova J, Ni W, Buenconsejo J. Disability and treatment patterns of multiple sclerosis patients in United States: a comparison of veterans and nonveterans. *Journal of Rehabilitation Research and Development.* Mar-Apr 2002;39(2):163-174.

105. Wallin M, Culpepper WJ, Kurtzke J. Risk Factors for Disease Progression in a Diverse US Population-based Multiple Sclerosis Cohort (S45.003). *Neurology.* 2015;84(14 Suppl 45.003).

106. Weiland TJ, Hadgkiss EJ, Jelinek GA, Pereira NG, Marck CH, van der Meer DM. The association of alcohol consumption and smoking with quality of life, disability and disease activity in an international sample of people with multiple sclerosis. *Journal of the Neurological Sciences.* Jan 15 2014;336(1-2):211-219.

107. Weinstock-Guttman B, Baier M, Park Y, et al. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients. *Prostaglandins, Leukotrienes, and Essential Fatty Acids.* Nov 2005;73(5):397-404.

108. Weinstock-Guttman B, Zivadinov R, Ramanathan M. Inter-dependence of vitamin D levels with serum lipid profiles in multiple sclerosis. *Journal of the Neurological Sciences.* Dec 15 2011;311(1-2):86-91.

109. Wiles CM, Newcombe RG, Fuller KJ, et al. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Feb 2001;70(2):174-179.

110. Yadav V, Marracci G, Kim E, et al. Effects of a low fat plant based diet in multiple sclerosis (MS): Results of a 1-year long randomized controlled (RC) study. *Neurology.* 2014;82(10):2014-2004.

111. Zivadinov R, Weinstock-Guttman B, Hashmi K, et al. Smoking is associated with increased lesion volumes and brain atrophy in multiple sclerosis. *Neurology.* Aug 18 2009;73(7):504-510.

112. Tepavcevic DK, Kostic J, Stojsavljevic N, et al. Cigarette smoking as a predictor for change in disability in multiple sclerosis patients: a 6-year follow-up study in Belgrade (Serbia). *European Journal of Neurology.* Sep 2010;17:487-487.

113. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. *Brain: A Journal of Neurology.* Feb 1995;118 (Pt 1):253-261.

114. Brandes DW, Bigley K, Hornstein W, Cohen H, Au W, Shubin R. Alleviating flu-like symptoms with dose titration and analgesics in MS patients on intramuscular interferon beta-1a therapy: a pilot study. *Curr Med Res Opin.* Jul 2007;23(7):1667-1672.

115. Maciejek Z, Wojcik-Draczkowska H, Wawrzyniak S, Niezgodzinska-Maciejek A. Evaluation of efficacy, safety and tolerability of fingolimod in patients with the relapsing form of multiple sclerosis - 12-month observation. A preliminary report. *Neurologia i Neurochirurgia Polska.* Mar-Apr 2013;47(2):145-151.

116. Vukusic S, Hutchinson M, Hours M, et al. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain: A Journal of Neurology.* Jun 2004;127(Pt 6):1353-1360.

117. Tavee J, Rensel M, Planchon SM, Butler RS, Stone L. Effects of meditation on pain and quality of life in multiple sclerosis and peripheral neuropathy: a pilot study. *International Journal of MS Care.* Winter 2011;13(4):163-168.

118. Swank RL, Goodwin J. Review of MS patient survival on a Swank low saturated fat diet. *Nutrition.* Feb 2003;19(2):161-162.

119. Swank RL. Multiple sclerosis: fat-oil relationship. *Nutrition.* Sep-Oct 1991;7(5):368-376.

120. D'Hooghe M B, Haentjens P, Nagels G, Garmyn M, De Keyser J. Sunlight exposure and sun sensitivity associated with disability progression in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2012;18(4):451-459.

121. D'Hooghe M B, Haentjens P, Nagels G, D'Hooghe T, De Keyser J. Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis. *Journal of Neurology.* May 2012;259(5):855-861.

122. D'Hooghe M B, Nagels G, De Keyser J, Haentjens P. Self-reported health promotion and disability progression in multiple sclerosis. *Journal of the Neurological Sciences.* Feb 15 2013;325(1-2):120-126.

123. Marck CH, Hadgkiss EJ, Weiland TJ, van der Meer DM, Pereira NG, Jelinek GA. Physical activity and associated levels of disability and quality of life in people with multiple sclerosis: a large international survey. *BMC Neurol.* 2014;14:143.

124. Levin AB, Hadgkiss EJ, Weiland TJ, et al. Can meditation influence quality of life, depression, and disease outcome in multiple sclerosis? Findings from a large international web-based study. *Behavioural Neurology.* 2014;2014:916519.

125. Thomas S, Thomas PW, Kersten P, et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* Oct 2013;84(10):1092-1099.

126. Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet.* Nov 8 2003;362(9395):1517-1526.

127. Solari A, Motta A, Mendozzi L, et al. Computer-aided retraining of memory and attention in people with multiple sclerosis: a randomized, double-blind controlled trial. *Journal of the Neurological Sciences.* Jul 15 2004;222(1-2):99-104.

128. Soilu-Hanninen M, Aivo J, Lindstrom BM, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon beta-1b in patients with multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry.* May 2012;83(5):565-571.

129. Pozuelo-Moyano B, Benito-Leon J, Mitchell AJ, Hernandez-Gallego J. A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in multiple sclerosis. *Neuroepidemiology.* 2013;40(3):147-153.

130. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV. Smoking and multiple sclerosis: an updated meta-analysis. *PloS One.* 2011;6(1):e16149.

131. Rietberg MB, Brooks D, Uitdehaag BMJ, Kwakkel G. Exercise therapy for multiple sclerosis - art. no. CD003980.pub2. *Cochrane Database Syst Rev.* 2005(1).

132. Feinstein A, Dalgas U. The benefits of exercise in progressive MS: some cautious optimism. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Mar 2014;20(3):269-270.

133. Dalgas U, Stenager E. Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? *Therapeutic Advances in Neurological Disorders.* Mar 2012;5(2):81-95.

134. Sa MJ. Exercise therapy and multiple sclerosis: a systematic review. *Journal of Neurology.* Sep 2014;261(9):1651-1661.

135. Marrie RA, Hanwell H. General health issues in multiple sclerosis: comorbidities, secondary conditions, and health behaviors. *Continuum (Minneapolis, Minn.).* Aug 2013;19(4 Multiple Sclerosis):1046-1057.

136. Overs S, Hughes CM, Haselkorn JK, Turner AP. Modifiable comorbidities and disability in multiple sclerosis. *Current Neurology and Neuroscience reports.* Oct 2012;12(5):610-617.

137. Miller DH, Fazekas F, Montalban X, Reingold SC, Trojano M. Pregnancy, sex and hormonal factors in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England).* Apr 2014;20(5):527-536.