APPENDIX A. SEARCH STRATEGIES

This appendix documents the exact search strings for all searched electronic databases. We designed a search strategy for each key question in order to maximize relevance and retrieval success.

SEARCH METHODOLOGY KQ1

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY #1 (Study Design Filter):
multiple sclerosis[tiab] OR multiple sclerosis[majr]
AND
AND
"cohort studies"[mh] OR “follow-up studies”[mh] OR prognos*[tiab] OR predict*[tiab] OR multivariate[tiab]
NOT
(animal OR animals) NOT (human OR humans)

SEARCH STRATEGY #2 (Risk Factor Filter):
multiple sclerosis[tiab] OR multiple sclerosis[majr]
AND
AND
NOT
(animal OR animals) NOT (human OR humans)

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY #1:
TS = (multiple sclerosis)
AND
TS = (progression OR progressive OR progressing)
AND
TS = (cohort OR prognos* OR predict* OR multivariate)

SEARCH STRATEGY #2:
TS = (multiple sclerosis)
AND
TS = (progression OR progressive OR progressing)
AND
TS = (geographic OR sun OR sunlight OR vitamin D OR fatty acid OR diet OR dietary OR nutrition* OR obesity OR obese OR smoking OR tobacco OR alcohol OR exercise OR physical activity OR stress* OR anesthesia OR radiation therapy OR oral contracepti* OR fertility treatment OR pregnan* OR breastfeed* OR salt OR milk OR water OR trace elements OR trauma OR traumatic OR Epstein–Barr OR "Epstein barr")

DATABASE SEARCHED & TIME PERIOD COVERED:
SCOPUS – ~1800’s-3/2/2015
LANGUAGE:
English
SEARCH STRATEGY #1:
TITLE-ABS-KEY("multiple sclerosis")
AND
TITLE-ABS-KEY(progression OR progressive OR progressing)
AND
TITLE-ABS-KEY(cohort OR prognos*OR predict* OR multivariate)

SEARCH STRATEGY #2:
TITLE-ABS-KEY ("multiple sclerosis")
AND
TITLE-ABS-KEY (progression OR progressive OR progressing)
AND
vitamin d OR fatty acid OR diet OR dietary OR nutrition* OR obesity OR obese OR smoking OR tobacco OR alcohol ) OR ( geographic OR sun OR sunlight OR exercise OR physical activity OR stress* OR anesthesia OR radiation therapy OR oral contracepti* ) OR ( fertility treatment OR pregnan* OR breastfeed* OR salt OR milk OR water OR trace elements OR trauma OR traumatic OR epstein--barr OR "Epstein barr"

DATABASE SEARCHED & TIME PERIOD COVERED:
GreenFILE - ~1970’s- 3/2/2015
SEARCH STRATEGY:
"multiple sclerosis"

SEARCH METHODOLOGY KQ2

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – Earliest-3/16/2015
LANGUAGE:
English
SEARCH STRATEGY:
multiple sclerosis
AND
United States Department of Veterans Affairs[mh] OR Veterans Health[mh] OR Hospitals, Veterans[mh] OR Veterans Disability Claims[mh] OR Veterans[mh] OR military personnel[mh] OR military medicine[mh] OR veteran* or military or army or navy or naval or air force or marines or coast guard or
Modifiable Risk Factors in the Progression of Multiple Sclerosis

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DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY:
'multiple sclerosis'
AND
military OR army OR navy OR naval OR 'air force' OR marines OR 'army guard' OR 'national guard' OR
soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR
war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members' OR
'veteran'/exp OR 'veteran' OR veteran*:ti OR 'veterans health'/de OR 'veterans health'

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY:
TOPIC: ("multiple sclerosis")
AND
TOPIC: (veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'army guard'
OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces'
OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR
'veteran' OR 'veteran':ti OR 'veteran' OR 'veterans health'/de OR 'veterans health'

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY:
TITLE-ABS-KEY("multiple sclerosis")
AND
ALL(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'army guard'
OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces'
OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR
'veteran' OR 'veteran':ti OR 'veteran' OR 'veterans health'/de OR 'veterans health'

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY:
ti("multiple sclerosis") OR su("multiple sclerosis")
AND
ab(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'army guard' OR
'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR
'veteran' OR 'veteran':ti OR 'veteran' OR 'veterans health'/de OR 'veterans health'

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'darmed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR ti(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR su(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members')

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY:
multiple sclerosis
NUMBER OF RESULTS: 49

DATABASE SEARCHED & TIME PERIOD COVERED:
LANGUAGE:
English
SEARCH STRATEGY:
(ti("multiple sclerosis") OR ab("multiple sclerosis") OR su("multiple sclerosis")) AND (ab(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR ti(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members') OR su(veteran* OR military OR army OR navy OR naval OR 'air force' OR marines OR 'coast guard' OR 'national guard' OR soldier* OR guardsmen OR reservist* OR troops OR infantry* OR 'armed forces' OR 'armed services' OR war OR wars OR 'war related' OR combat* OR battle* OR 'service member' OR 'service members'))

DATABASE SEARCHED & TIME PERIOD COVERED:
SEARCH STRATEGY:
exact phrase: Multiple sclerosis
AND
Veterans
SEARCH METHODOLOGY KQ3

This section documents the exact search strings used to identify studies relevant for KQ3.

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – Earliest-1/13/2015
FILTERS:
   English, Randomized Controlled Trial
SEARCH STRATEGY:
"multiple sclerosis"

DATABASE SEARCHED & TIME PERIOD COVERED:
AMED – Earliest-3/3/2015
SEARCH STRATEGY:
"multiple sclerosis" AND interven* AND (random* OR rct*)

DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science – Earliest-3/3/2015
SEARCH STRATEGY:
TS = (multiple sclerosis)
AND
TS = (geographic OR sun OR sunlight OR vitamin D OR fatty acid OR diet OR dietary OR nutrition* OR obesity OR obese OR smoking OR tobacco OR alcohol OR exercise OR physical activity OR stress* OR anesthesia OR radiation therapy OR oral contracepti* OR fertility treatment OR pregnan* OR breastfeed* OR salt OR milk OR water OR trace elements OR trauma OR traumatic OR Epstein–Barr OR "Epstein barr")
AND
ts = (intervention* OR intervene*)
AND
LANGUAGE: (English)
APPENDIX B. STUDY SELECTION AND LIST OF EXCLUDED STUDIES

The search yield, title and abstract screening results; full text decisions, and the data extraction are documented in electronic databases which can be obtained from the authors, in compliance with standard data sharing requirements.

This appendix lists the citation of publications obtained as full text but not meeting inclusion criteria together with the reason for excluding the publication.

EXCLUDE: OUTCOME

Excluded publications not reporting on MS progression:


36. Dlugonski D, Motl RW, Mohr DC, Sandroff BM. Internet-delivered behavioral intervention to increase


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EXCLUDE: INTERVENTION/EXPOSURE

Publications not reporting on a risk factor of interest:

15. D’Alisa S, Miscio G, Baudo S, Simone A, Tesio L, Mauro A. Depression is the main determinant of quality
46. Locke S, Kruper DC, Yakovlev PI. FIVE-YEAR FOLLOW-UP ON MULTIPLE SCLEROSIS. REPORT ON VETERANS ADMINISTRATION COOPERATIVE STUDY. *Archives of Neurology.* Dec 1964;11:583-592.


84. Stroud N, Minahan C, Sabapathy S. The perceived benefits and barriers to exercise participation in persons
EXCLUDE: DESIGN

Publications not meeting study design inclusion criteria:

24. Pimentel ML. Multiple sclerosis in the Southern and Northern hemispheres: the month of birth at different latitudes has the same influence on the prevalence and progression of the disease in the Northern and Southern hemispheres. *Arq Neuropsiquiatr.* Sep 2013;71(9A):569-570.


**EXCLUDE: PARTICIPANTS**

Excluded publications not reporting on participants with MS and risk factor studies excluding progressive MS:


**EXCLUDE: LANGUAGE**

Excluded non-English language publications:


**EXCLUDE: DUPLICATE**

Duplicate publications:

BACKGROUND

Reviews screened for additional references and multiple publications of included studies:


APPENDIX C. CRITERIA USED IN QUALITY ASSESSMENT

This appendix documents the individual risk of bias criteria used to assess included studies. In addition, it documents the criteria used to rate the quality of evidence across studies.

RISK OF BIAS ASSESSMENT OF KQ1 AND KQ2 STUDIES

A large number of diverse studies contributed to the review. We broadly categorized risk factor studies into concurrent, retrospective, and prospective studies. Concurrent and retrospective studies can provide only limited information on questions of progression, regardless of their methodological quality, and these studies were not further differentiated.

The identified prospective studies relevant to KQ1 and KQ2 were assessed with QUIPS (QUality In Prognosis Studies), a critical appraisal tool for prognostic studies. QUIPS assesses the domains study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. For each domain we determined whether the study indicates high risk of bias, moderate risk of bias, or low risk of bias.

Appendix Table 1. Risk of Bias: KQ1 and KQ2 Prospective Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Participation</th>
<th>Study Attrition</th>
<th>Prognostic Factor Measurement</th>
<th>Outcome Measurement</th>
<th>Study Confounding</th>
<th>Statistical Analysis and Reporting</th>
<th>KQ1 and KQ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascherio, 2014</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Confavreux, 1998</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Detels, 1982</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Mowry, 2012</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Pasto, 2012</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Pittas, 2009</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Runmarker, 1995</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Shammas, 2014</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
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<tr>
<td>Soilu-Hanninen, 2007</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
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<tr>
<td>Stuifbergen, 2006</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Sundstrom, 2008</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Swank, 1990</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Tepavcevic, 2010</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
Legend:

**Study participation:** Prompting items: a. Adequate participation in the study by eligible persons, b. Description of the source population or population of interest, c. Description of the baseline study sample, d. Adequate description of the sampling frame, and recruitment, e. Adequate description of the period and place of recruitment, f. Adequate description of inclusion and exclusion criteria. Ratings: High risk: The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants; Moderate bias: The relationship between the PF and outcome may be different for participants and eligible nonparticipants; Low bias: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants.

**Study attrition:** a. Adequate response rate for study participants, b. Description of attempts to collect information on participants who dropped out, c. Reasons for loss to follow-up are provided, d. Adequate description of participants lost to follow-up, e. There are no important differences between participants who completed the study and those who did not. Ratings: High bias: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants; Moderate bias: The relationship between the PF and outcome may be different for completing and non-completing participants; Low bias: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants.

**Prognostic Factor Measurement:** Prompting items: a. A clear definition or description of the PF is provided, b. Method of PF measurement is adequately valid and reliable, c. Continuous variables are reported or appropriate cut points are used, d. The method and setting of measurement of PF is the same for all study participants, e. Adequate proportion of the study sample has complete data for the PF, f. Appropriate methods of imputation are used for missing PF data. Ratings: High bias: The measurement of the PF is very likely to be different for different levels of the outcome of interest, Moderate bias: The measurement of the PF may be different for different levels of the outcome of interest, Low bias: The measurement of the PF is unlikely to be different for different levels of the outcome of interest.

**Outcome Measurement:** Prompting items: a. Clear definition of the outcome is provided, b. Method of outcome measurement used is adequately valid and reliable, c. The method and setting of outcome measurement is the same for all study participants. Ratings: High bias: The measurement of the outcome is very likely to be different related to the baseline level of the PF, Moderate bias: The measurement of the outcome may be different related to the baseline level of the PF, Low bias: The measurement of the outcome is unlikely to be different related to the baseline level of the PF.

**Study Confounding:** Prompting items: a. All important confounders are measured, b. Clear definitions of the important confounders measured are provided, c. Measurement of all important confounders is adequately valid and reliable, d. The method and setting of confounding measurement are the same for all study participants, e. Appropriate methods are used if imputation is used for missing confounder data, f. Important potential confounders are accounted for in the study design, g. Important potential confounders are accounted for in the analysis. Ratings: High bias: The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome, Moderate bias: The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome, Low bias: The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome.

**Statistical Analysis and Reporting:** Prompting items: a. Sufficient presentation of data to assess the adequacy of the analytic strategy, b. Strategy for model building is appropriate and is based on a conceptual framework or model, c. The selected statistical model is adequate for the design of the study, d. There is no selective reporting of results. Ratings: High bias: The reported results are very likely to be spurious or biased related to analysis or reporting, Moderate bias: The reported results may be spurious or biased related to analysis or reporting, Low bias: The reported results are unlikely to be spurious or biased related to analysis or reporting.

**RISK OF BIAS ASSESSMENT OF KQ3 STUDIES**

Studies relevant to KQ3 were assessed with the Cochrane risk of bias tool. The tool assesses random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), completeness of reporting outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias (if appropriate) for each of the included studies. For each domain...
we determined whether the study indicates a high risk of bias, a low risk of bias, or an unclear risk of bias.

### Appendix Table 2. Risk of Bias: KQ3 Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants/providers</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
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<tbody>
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<td>Armutlu, 2001</td>
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<td>Low risk</td>
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<td>Low risk</td>
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<td>Unclear</td>
<td>Low risk</td>
<td>Low risk</td>
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<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
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<td>Low risk</td>
<td>High risk</td>
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<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
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<td>Unclear</td>
<td>High risk</td>
<td>Low risk</td>
<td>Unclear</td>
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<td>High risk</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>High risk</td>
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<tr>
<td>Romberg, 2004</td>
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<td>High risk</td>
<td>Low risk</td>
<td>Unclear</td>
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<td>High risk</td>
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<td>Schwartz, 2012</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Shaygannejad, 2012</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Sollu-Hanninen, 2012</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Unclear</td>
<td>High risk</td>
</tr>
<tr>
<td>Solari, 1999</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Study</td>
<td>Random sequence generation</td>
<td>Allocation concealment</td>
<td>Blinding of participants and personnel</td>
<td>Blinding of outcome assessment</td>
<td>Incomplete outcome data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
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<td>---------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stein, 2011(^1)</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torkildsen, 2012(^2)</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinstock-Guttman, 2005(^3)</td>
<td>Unclear</td>
<td>Low risk</td>
<td>Unclear</td>
<td>High risk</td>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiles, 2001(^4)</td>
<td>Unclear</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yadav, 2014(^5)</td>
<td>Unclear</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**

**Random sequence generation:** Low risk: The investigators describe a random component in the sequence generation process such as: Referring to a random number table, Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization; High risk: The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number; Allocation by judgment of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention; Unclear: Insufficient information about the sequence generation process to permit judgment of ‘Low risk’ or ‘High risk’.

**Allocation concealment:** Low risk: Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based and pharmacy-controlled randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes. High risk: Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (eg, a list of random numbers); Assignment envelopes were used without appropriate safeguards (eg, if envelopes were unsealed or non-opaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure. Unclear: Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

**Blinding of participants and personnel:** Low risk: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. High risk: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. Unclear: Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’; The study did not address this outcome.

**Blinding of outcome assessment:** Low risk: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. High risk: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. Unclear: Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’; The study did not address this outcome.

**Incomplete outcome data:** Low risk: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods. High risk:
Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; ‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation. Unclear: Insufficient reporting of attrition/exclusions to permit judgment of ‘Low risk’ or ‘High risk’ (eg, number randomized not stated, no reasons for missing data provided); The study did not address this outcome.

Selective reporting: Low risk: The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). High risk: Not all of the study’s pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (eg, subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study. Unclear: Insufficient information to permit judgment of ‘Low risk’ or ‘High risk’. It is likely that the majority of studies will fall into this category.

Other bias: Low risk: The study appears to be free of other sources of bias. High risk: There is at least one important risk of bias. For example the study had a potential source of bias related to the specific study design used; has been claimed to have been fraudulent; or had some other problem. Unclear: There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.

CRITERIA TO RATE THE BODY OF EVIDENCE FOR KQ1 AND KQ2

The GRADE framework for prognostic factor research\(^8\) differentiates 8 criteria that are used to evaluate the quality of the evidence across all identified studies:

The phase of investigation differentiates whether the risk factor evidence is primarily based on a study that aimed to identify potential prognostic factors (moderate quality) rather than based on studies aiming to confirm identified associations or explanatory research aiming to understand prognostic pathways (high quality).

Study limitations took the assessment frame into account by differentiating whether the risk factor status and the outcome variable were assessed at the same time (concurrently), retrospectively, or prospectively. Prospective studies were further differentiated by the risk of bias based on the QUIPS scores.

Inconsistency assessed whether the identified association was consistently present across studies and across study designs (eg, present in concurrent and prospective studies).

Indirectness took into account whether the available research studies does not accurately reflect the review question. Examples are cases where the only available research studies reported on vitamin D status, rather than a directly patient-modifiable risk factor such as vitamin D intake.

Evidence was downgraded for imprecision if the sample size was insufficient, the confidence interval was wide and overlapped the value of no effect, there were less than 10 outcome events for each prognostic variable, or there were less than 100 cases reaching endpoints.
Evidence was downgraded for publication bias unless the value of the risk or protective factor in predicting the outcome has been repetitively investigated.

Evidence for individual risk factors may be upgraded if effects are moderate or large or there is evidence of exposure-gradient response for factors measured at different doses.

**CRITERIA TO RATE THE BODY OF EVIDENCE FOR KQ3**

For KQ3 we took the criteria risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect, dose response, and all plausible residual confounding would reduce a demonstrated effect and/or would suggest a spurious effect if no effect was observed into account. The starting point was high evidence because the data are based on RCTs.

Risk of bias, inconsistency, indirectness, imprecision, and publication bias can lower the quality. Large effect, dose response, and all plausible residual confounding can upgrade the quality of the body of evidence. 17

Risk of bias evaluations were based on the above documented Cochrane Risk of Bias tool assessments. Inconsistency took the direction and the size of effects across studies into account. Indirectness may assess whether comparative effects are based on head-to-head trial evidence or was obtained from meta-regressions and subgroup analyses. Imprecision takes the confidence interval around the point estimate into account. Publication bias was assessed to determine whether there is evidence that pertinent studies, in this case negative effect studies are missing.
## APPENDIX D. PEER REVIEW COMMENTS/AUTHOR RESPONSES

<table>
<thead>
<tr>
<th>Comment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies missing - Yes - Studies evaluating geography itself as a risk factor, studies prior to 1973, studies involving co-morbidity</td>
<td>The identified studies on associations between geography and progression are shown in the “other” and the “multiple” risk factor section. Studies published prior to 1973 were eligible for inclusion in the review and all databases were searched without date restriction. We have added the eligibility criteria after the description of the included studies in the result section to avoid ambiguity. In addition, we have emphasized that databases were searched from inception. Co-morbidities were outside the scope of this review but we have expanded the future research section to indicate that sufficient literature exists for systematic reviews on several individual co-morbidities.</td>
</tr>
<tr>
<td>It would have been useful to add obesity related studies in the review as it appears to be an important co-morbid condition and related information would have been of great research as well as clinical significance.</td>
<td>See above. In particular there is a growing literature on weight and MS progression; we have expanded on this issue in the future research section.</td>
</tr>
<tr>
<td>Several typographical errors are present in the draft, that I assume will be reviewed carefully towards the final draft.</td>
<td>Typographical errors will be correct before publication</td>
</tr>
<tr>
<td>Pg 1/Line 8: Traumatic brain injury is more common than MS in younger adults but is not progressive. I’d reword this sentence as follows: Multiple sclerosis (MS) is the most common progressive disease of the central nervous system in young adults and the cause of serious physical disability in adults of working age.</td>
<td>Revised as suggested</td>
</tr>
<tr>
<td>Pg 1/Line 21: Use “MS” throughout the manuscript after it’s defined.</td>
<td>We have revised the text accordingly but left the key questions as is to avoid ambiguity</td>
</tr>
<tr>
<td>Pg 1/Line 49: Is this a preliminary report vs. final?</td>
<td>The draft report is subjected to peer review</td>
</tr>
<tr>
<td>Pg 3/Line 16: “Concurrent” is not commonly used and is confusing. It should be replaced with retrospective.</td>
<td>To address this point, we have added a definition to avoid confusion (measuring the exposure status and the outcome at the same time point, eg, current alcohol intake)</td>
</tr>
<tr>
<td>Pg 5/Line 5: Change “Out” to Our.</td>
<td>Changed</td>
</tr>
<tr>
<td>Pg 5/Line 25: There are several redundant and inaccurate statements in the conclusion. The association between MS progression and vitamin D supplementation is not significant but the conclusions imply it is related. The conclusion should be modified to something like the following: Our systematic review documents the available evidence on modifiable risk factors for MS progression. Associations with MS progression are strongest for smoking. None of the intervention studies examining exercise, dietary, and vitamin D supplementation reported a statistically significant effect on MS disability. Other than smoking cessation, there are no other modifiable risk factors that can be given support from this review as an intervention worthy of slowing MS progression.</td>
<td>To address the perceived redundancy we have divided the conclusions into multiple paragraphs: one characterizes the overall evidence base, one summarizes the risk factor studies, one summarizes the intervention RCTs, and the last one describes the evidence for factors that were addressed in both, risk factor and in intervention studies. The correlation between EDSS scores and vitamin D level was statistically significant. We have revised the sentence to avoid the perceived inaccuracy.</td>
</tr>
<tr>
<td>Page Line</td>
<td>Text</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>Pg 8/Line 3:</td>
<td>There are several reviews of MS risk factors published in the literature. Some are comprehensive in scope. The statement below is confusing in implying there are multiple reviews of risk factors translated into treatment options. Is this referring to dietary or exercise treatments? There is an emerging body of research that evaluates risk factors translated into treatment options but no systematic review has to date comprehensively synthesized the available evidence.</td>
</tr>
<tr>
<td>Pg 18/Line 8:</td>
<td>Why was 1973 used as the starting year (vs. 1970)?</td>
</tr>
<tr>
<td>Pg 51/Line 5:</td>
<td>There is no figure in the box.</td>
</tr>
<tr>
<td>Forest plots:</td>
<td>There is no confidence interval represented on the summary measure of risk in the diagram. This should be included.</td>
</tr>
<tr>
<td>Please see editorial suggestions and comments in the uploaded document.</td>
<td>Thank you for your careful review; we have accepted all editorial changes</td>
</tr>
<tr>
<td>p. 10:</td>
<td>So if I understand correctly, a study on solely Relapsing Remitting MS (RR MS), the most common disease type, would have been excluded - even though patients with RR MS often progress over time?</td>
</tr>
<tr>
<td>p. 24:</td>
<td>Sentence is unclear. Which of the studies does this phrase refer to?</td>
</tr>
<tr>
<td>p. 50:</td>
<td>awkward wording</td>
</tr>
<tr>
<td>p. 51:</td>
<td>Figure missing from draft</td>
</tr>
<tr>
<td>p. 51:</td>
<td>I assume you mean since the Vit D values were dichotomized, rather than reported as a continuous variable? The statement is unclear as written, since the study did in fact use the EDSS.</td>
</tr>
<tr>
<td>p. 52:</td>
<td>Graphs have a diagonal line, which should be deleted.</td>
</tr>
<tr>
<td>p. 54:</td>
<td>Which - any alcohol consumption, or heavy drinking, or both?</td>
</tr>
<tr>
<td>p. 56:</td>
<td>Explain the &quot;downgrades&quot; (or refer to the text in the legend)</td>
</tr>
<tr>
<td>p. 69:</td>
<td>Unclear in this context</td>
</tr>
<tr>
<td>p. 78:</td>
<td>Would this be better expressed as &quot;pregnancy&quot; rather than &quot;children&quot;?</td>
</tr>
<tr>
<td>p. 82:</td>
<td>Unclear. Do you mean &quot;for which the published evidence demonstrates their amenability...&quot;? Need a clear statement to conclude the review!</td>
</tr>
<tr>
<td>Did any study examine the impact of moving to a different region/climate/latitude during childhood or early adulthood?</td>
<td>We did not identify such a study</td>
</tr>
<tr>
<td>I have a general concern that there may be confusion in discussion of studies between change from Relapsing-Remitting MS (RR MS) to Secondary Progressive MS (SP MS), and progression of disability caused by MS, which can occur both in RR MS and SP MS.</td>
<td>Yes, several studies did not restrict to RR MS and studies used a variety of outcome measures. To address this concern, we have highlighted those studies in the summary of findings section that specifically reported on the change from RR to SP MS and those that only included patients with RR MS at baseline</td>
</tr>
<tr>
<td>Page 5, line 5:</td>
<td>Change &quot;Out&quot; to &quot;Our&quot;</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Page 7, line 16:</td>
<td>Change &quot;described&quot; to &quot;characterized pathologically&quot; and add &quot;focal areas of&quot; before &quot;inflammation...&quot;</td>
</tr>
<tr>
<td>Page 7, lines 35 to 37:</td>
<td>Change &quot;Progressive relapsing MS&quot; to &quot;Active progressive MS&quot; The classification system for MS subtypes was revised in 2014 to remove the classification of &quot;progressive relapsing&quot; and replace it with the classification of &quot;active progressive&quot; This is given in Reference 8.</td>
</tr>
<tr>
<td>Page 10, line 60:</td>
<td>Azathioprine is listed as a medication specifically designed for MS, which . Azathioprine was originally developed as an antineoplastic agent it is now used for immunosuppression in autoimmune diseases and organ transplantation. Other drugs in this class that were omitted from the list include methotrexate and cyclophosphamide. Cladribine, listed later, probably belongs in the same list.</td>
</tr>
<tr>
<td>Page 13, line 54:</td>
<td>Move &quot;presented&quot; to after &quot;statistics&quot;</td>
</tr>
<tr>
<td>Page 15, line 14:</td>
<td>After &quot;East&quot; add &quot;, Professor, Departments of Neurology, Pharmacology and Physical Therapy, University of Maryland School of Medicine&quot;</td>
</tr>
<tr>
<td>Page 15, line 14:</td>
<td>After &quot;MPH&quot; add &quot;, Director, MS Center of Excellence - West&quot;</td>
</tr>
<tr>
<td>Page 15, line 26:</td>
<td>Change,&quot;PHD&quot; to &quot;PhD&quot;</td>
</tr>
</tbody>
</table>

Tables 1 to 7: I may not be reading the tables correctly but I did not see a column indicating the rating of the quality of the evidence in each study. I believe that Appendix C deals with that issue in detail but should some summary indication be included on these tables? | The studies were assessed with a number of individual risk of bias criteria which exceeded the available space in the evidence tables. To address this point we have systematically added information on the risk of bias to the result sections following the evidence tables |

Tables 1 to 7, case definition: I may not be understanding what is being reported here. I am used to this column being used to report whether an acceptable case definition was used by the study in question. In most cases this would involve a diagnosis of MS based on published criteria such as the Poser, McDonald or modified McDonald criteria. Cases might be further restricted based on disability range using a scale like the EDSS score. The entries in this column don't seem to fit this so I am unclear on what is being displayed here. I am also not clear on whether publications were reviewed to ensure that accepted case definitions were used. | We have revised the term to “predicted variable” to avoid confusion with MS diagnostic criteria. In addition, we have added the diagnostic criteria for prospective studies to the evidence tables. |