MODIFIABLE RISK FACTORS IN THE PROGRESSION OF MULTIPLE SCLEROSIS: PROTOCOL FOR A SYSTEMATIC REVIEW OF THE EPIDEMIOLOGY AND TREATMENT

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PREFACE

Quality Enhancement Research Initiative’s (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) clinicians, managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA, and some evidence syntheses inform the clinical guidelines of large professional organizations.

QUERI provides funding for four ESP Centers and each Center has an active university affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence;
- guide the implementation of 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.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

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

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EXECUTIVE SUMMARY

INTRODUCTION

Multiple sclerosis (MS) is the most common disabling disease of the central nervous system in young adults and the most common cause of serious physical disability in adults of working age. Epidemiologic data suggests that rates of MS vary with environmental factors, suggesting potentially modifiable risk factors. The disease presentation is very heterogeneous with versatile clinical manifestations. Progression of MS may vary with demographic and possibly other environmental exposures.

This project focuses on modifiable exposures and risk factors that are related to MS progression and approaches to reduce progression that are directed at modifiable risk factors.

The Key Questions (KQs) are:

KQ1: What modifiable epidemiologic factors are related to multiple sclerosis progression following diagnosis?

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

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?

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

Data Sources and Searches

We will search PubMed, EMBASE, AMED, Web of Science, SCOPUS, GreenFILE, ProQuest Military Collection, DTIC, DARE, and CDSR; reference mine reviews and included studies; and consult with experts to identify pertinent studies.

Study Selection

Studies meeting the following criteria will be eligible for inclusion in the review: Population: Adults with MS (KQ1, KQ3), military personnel/veterans with MS (KQ2); Interventions/exposure: potential MS progression risk factors (KQ1, KQ2: eg, smoking, nutrition) and interventions targeting modifiable risk factors (KQ3, eg, smoking cessation programs, dietary interventions); Comparators (study design): Observational (eg, case-control, cohort, cross-sectional) and experimental studies (eg, randomized controlled trials (RCTs)) analyzing factors associated with MS progression are eligible for KQ1 and KQ2; RCTs regardless of the comparator are eligible for KQ3; Outcomes: Progression of MS, primary outcome EDSS scores; Timing: Exposure and intervention duration, exposure timing (eg, during childhood), and
followup timing in intervention studies not restricted; Setting: No restriction for inclusion but planned subgroup analyses for veteran population

**Data Abstraction and Quality Assessment**

For KQ1 we will extract the study design; target population, time of diagnosis, and type/stage of MS; assessed potential risk factors, time frame; confounding factors; and results (effects of risk factors on disease progression). For studies relevant to KQ2 we will extract the study design and analytic method, prior military service exposure, exposure during military service, MS characteristics, confounding factors, and results with regard to disease progression. For intervention studies (KQ3) we will extract the study design and methodological characteristics; number and characteristics of participants; intervention and comparator details; outcomes, followup points, and corresponding results.

Studies addressing KQ1 and KQ2 will be assessed with QUIPS, a critical appraisal tool for prognostic studies, and intervention studies (KQ3) will be assessed with the Cochrane risk of bias tool.

**Data Synthesis and Analysis**

All studies relevant to KQ1 will be summarized narratively, differentiating variables assessed as potential risk factors and results indicating a statistically significant association with MS progression. Where possible, variables will be pooled across studies in a meta-analysis to identify reliable and valid effects across studies. Studies in military personnel and veterans relevant to KQ2 will be summarized narratively, differentiating assessed variables and statistically significant effects, and the synthesis will emphasize variables identified in more than one individual study. Intervention studies (KQ3) are likely to be summarized narratively due to the heterogeneity in interventions. Results will be grouped by intervention category.

**RESULTS**

**Results of Literature Search**

This section will describe the number and study design characteristics of studies relevant to the individual review questions.

**Summary of Results for Key Questions**

This section will summarize the variables identified as associated with MS progression (KQ1). Furthermore, the exposures prior and during military services associated with MS progression (KQ2) will be summarized. Finally, evaluated treatment/risk factor modification interventions and their effects on MS progression will be summarized (KQ3).

**DISCUSSION**

**Key Findings and Strength of Evidence**

This section will summarize the key findings, place them in context of the existing literature, and state our confidence in the evidence to answer the review questions.

**Applicability**
This section will summarize the applicability of results to the VA, informed by KQ2 studies.

**Research Gaps/Future Research**

This section will summarize identified research gaps and outline future research needs.

**Conclusions**

This section will describe the conclusions that can be drawn from the evidence report.

[ES word limit 3,500]

**ABBREVIATIONS TABLE**

MS: Multiple sclerosis

KQ: Key question
EVIDENCE REPORT

INTRODUCTION

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

Multiple sclerosis is described by inflammation, demyelination, gliosis and axonal damage throughout the central nervous system. The course of MS is characterized by the expression of clinical relapse and disease progression. Relapse, exacerbations, or attacks, are acute, inflammatory events that occur episodically within the central nervous system. They can correspond to either development of new focal inflammatory lesions or reactivation of old lesions, and after an exacerbation, symptoms spontaneous 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 months (Poser criteria) or 12 months (McDonald criteria). Once progression has developed, the course is continuous despite occasional plateaus and temporary minor improvements.

MS disease presentation is very heterogeneous with versatile 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 an exacerbating remitting to a secondary progressive disease after 10 years. Progressive Relapsing 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 their daily life.

Epidemiologic data show that rates of MS appear to vary with environmental factors. 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. 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 environmental exposures or other modifiable risk factors.

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. 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, eg, the potential risk factor Vitamin D deficiency and treatment of...
MS patients with Vitamin D. 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.

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) are:

(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 MS once it has initiated?

SEARCH STRATEGY

We will search 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 without date restriction.

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

The KQ2 search strategy uses 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 will use a search filter for randomized controlled trials (RCTs), where applicable, to the databases PubMed, AMED, SCOPUS, and Web of Science, to target eligible studies.

We will search the databases PubMed using a systematic review search filter, DARE (Database of Abstracts of Reviews of Effects), and CDSR (Cochrane Database of Systematic Reviews) to identify existing systematic reviews. Furthermore, we will screen references of pertinent reviews and included studies. Finally, we will consult with topic experts to ensure that all relevant studies have been identified.
STUDY SELECTION

Two independent reviewers will screen titles and abstracts of retrieved citations and record decisions in an electronic database. Citations deemed potentially relevant by both, or either reviewers, will be obtained as full text. The full text publications will be screened against the specified inclusion criteria by two independent literature reviewers; disagreements will be resolved through discussion within the review team. The literature flow will be documented in an electronic database and reasons for exclusion of full text publications will be recorded.

To be included in the systematic review, studies must meet the following criteria organized in the PICOTS framework:

Participants: Studies in human adult participants with a clinical diagnosis of MS are eligible for inclusion for KQ1 and KQ3. KQ2 will be limited to active military personnel and veterans with MS. Studies exclusively focusing on Pediatric MS in children and adolescents will be excluded. Studies targeting a range of clinical conditions are included as long as data on MS is reported separately.

Intervention: Studies reporting on modifiable epidemiologic factors and environmental exposures potentially associated with MS progression (“risk factors”) are eligible for inclusion for KQ1 and KQ2. Risk factors eligible for inclusion in the review include (but are not limited to) the following: Geographic region, sun exposure, vitamin D deficiency, polyunsaturated fatty acid deficiency, diet, obesity, smoking, alcohol, exercise, stress, vaccinations, anesthesia, radiation therapy, oral contraception, fertility treatment, pregnancy and delivery variables, breastfeeding, salt intake, milk products, water sources, trace elements, mercury, co-morbidities amenable to direct intervention, gut microbiome, trauma, military service/deployment, military exposures, infections (viral infection, infectious causes), and Epstein–Barr virus. Non-modifiable risk factors such as physiological correlates, genetic predispositions are excluded.

Intervention studies evaluating the effect of modifying potential risk factors (eg, smoking cessation, stress reduction, weight loss, or exercise programs; nutritional interventions targeting vitamin D or Omega 3), alone or in combination with other therapies, are eligible for KQ3. Treatment studies addressing potential risk factors for the onset, relapse, or progression of diagnosed MS are 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, telehealth, acupuncture) are excluded. Treatment studies evaluating the effect of existing, FDA-approved MS medications, that aim to modify the disease course of MS (teriflunomide, interferon beta-1a, interferon beta-1b, glatiramer acetate, interferon beta-1b, fingolimod, alemtuzumab, mitoxantrone, peginterferon beta-1a, dimethyl fumarate, natalizumab) or to manage MS relapses (methylprednisolone, prednisone, adrenocorticotropic hormone) are excluded regardless of any underlying risk factor hypotheses (eg, infection, hygiene hypothesis).

Comparator (design): Observational studies (eg, case-control, cohort studies comparing two cohorts, or cross-sectional studies including surveys), and experimental studies analyzing factors associated with MS progression are eligible for KQ1 and KQ2. RCTs in adults regardless of the comparator are eligible for KQ3. Only primary research studies are eligible for inclusion,
pertinent reviews and secondary data analyses will be retained as background paper for reference mining.

**Outcome:** Studies reporting on the progression of MS are eligible for inclusion in the review. The primary outcome is Expanded Disability Status Scale (EDSS) scores or progression classifications based on EDSS score cut-offs. Studies reporting on other global patient-centered, clinical progression measures (eg, Multiple Sclerosis Functional Composite [MSFC]; multiple domain assessments of the Functional System Score [FSS]; Patient Determined Disability Scale [PDDS]), or the clinical course of MS (eg, time to secondary progression) are eligible for inclusion. Studies reporting on disability measures focusing on the ability to walk (eg, MS Progression: Disease Step[s [DS]) will be included but studies only reporting on individual characteristics of walking (eg, gait, muscle strength) will be excluded. Studies reporting on other individual symptoms (eg, fatigue or depression) or individual diagnostic markers (eg, lesions shown with imagine techniques) without reporting on patient outcomes of MS progression will be excluded. Studies reporting on MS-associated mortality will be included but studies reporting on all-cause mortality in MS patient samples, eg, investigating whether associations between modifiable factors and mortality found in the general population (such as smoking and mortality) also apply to the MS population, will be 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) are excluded.

**Timing:** Exposure and interventions studies including any exposure duration and intervention duration, regardless of the exposure and intervention timing (eg, childhood exposure) and any followup point are eligible for inclusion for KQ1 and KQ3. Studies eligible for KQ3 are limited to exposures prior or during military service.

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

Other limiters: English-language studies will be included.

The review will be registered in PROSPERO, the international registry for systematic reviews PROSPERO [http://www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/).

**DATA ABSTRACTION**

Studies will undergo standardized abstraction of study-level data in an electronic database. Data collection forms will be designed by the project lead and discussed in the review team and will be piloted by the reviewers to identify potential sources of disagreements and ambiguities.

For KQ1 (risk factors) studies, we will extract information on the MS population (eg, proportion of patients with relapsing-remitting, secondary progressive, progressive relapsing, or primary progressive MS; age; % male; race/ethnicity distribution). We will document the number of participants in the study sample and the number of cases (i.e., patients with progressive MS). We will record the geographic region of the sample. We will document the study design (eg, cohort study) and methods used to analyze the results (eg, linear mixed effects model, partial correlations). We will document analyzed potential, modifiable risk factors of interest together with the time of exposure (if applicable). We will record all independent variables entering the
prediction model. The evidence table will also document the prognostic time frame for each study. We will extract the point estimate of effects and statistical significance of risk factors on MS progression. The evidence table will differentiate predictions for EDSS scores and other clinical course characteristics relevant to MS progression.

For studies relevant to KQ2 (military service exposures), we will extract 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 will extract 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.

**QUALITY ASSESSMENT**

Studies addressing KQ1 and KQ2 will be assessed with QUIPS (Quality In Prognosis Studies), a critical appraisal tool for prognostic studies. 14

Intervention studies (KQ3) will be 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 are documented in the appendix.

**DATA SYNTHESIS AND ANALYSIS**

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

All studies relevant to KQ1 will be summarized narratively. The synthesis will differentiate variables assessed as potential risk factors and results indicating a statistically significant association with MS progression. Where possible, variables will be pooled across studies in meta-analyses (eg, pooling time-to-event data expressed in hazard ratios [HR]) to identify reliable and valid effects across studies.

Due to the likely heterogeneity in study designs, analytic methods, and effect measures, and the anticipated small number of studies, studies in military personnel and veterans relevant to KQ2 will be summarized narratively. We will differentiate assessed variables and statistically significant effects. The narrative synthesis will emphasize risk factors identified in more than one individual study.

Intervention studies (KQ3) are likely to be summarized narratively due to the anticipated small number of studies available for each intervention and likely heterogeneity in existing studies. We
will group results by intervention category. Results of studies in military personnel and veterans will be presented in a subgroup analysis.

**RATING THE BODY OF EVIDENCE**

We will rate the quality of the evidence for individual risk factors across all studies (KQ1), in military and veteran populations (KQ2), and for individual interventions (KQ3) across all identified pertinent studies. Based on GRADE guidelines the quality of the evidence will be 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 the effect.

For KQ1 and KQ2 we will take the following eight criteria into account to determine the level of evidence quality following an adaptation of the GRADE framework for prognostic factor research: The Phase of investigation criterion will be used as a starting point (high or moderate quality of evidence). The criteria Study limitations, Inconsistency, Indirectness, Imprecision, and Publication bias can decrease the quality of evidence. The criteria moderate / large Effect size and Exposure-response gradient can increase the evidence.

The Phase of investigation will differentiate 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 will take the quality and risk of bias of the identified pertinent studies into account. Inconsistency will assess whether the identified association was consistently present across studies. Indirectness will take into account whether the available research studies do not accurately reflect the review question. Evidence will be downgraded for Imprecision if the sample size is insufficient, the confidence interval is wide and overlaps the value of no effect, there are less than 10 outcome events for each prognostic variable, or there are less than 100 cases reaching endpoints. Evidence will be 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 will be upgraded if Effects are moderate or large or there is evidence of Exposure-gradient response for factors measured at different doses.

For KQ3 we will take the Risk of bias, Inconsistency, Indirectness, Imprecision, Publication bias, Large effect, and 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 will be 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. 15

**TECHNICAL EXPERT PANEL**

The technical expert panel (TEP) for the project included Christopher Bever, Jr., MD, MBA, Director of the MS Center of Excellence-East; Jodie Haselkorn, MD, MPH, 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 will be reviewed by technical experts, clinical leadership, and additional peer reviewers where appropriate. Reviewer comments will be addressed in the final product and will be documented in the appendix.
RESULTS

LITERATURE FLOW

This section will report the number of citations identified in the systematic review searches, the number of studies screened as full text, and the number of studies meeting inclusion criteria. The figure will document the literature flow, the number of screened publications at each review stage, the number and reasons for exclusion, and the number of studies identified for each review question. Some studies will be relevant to more than one review question.
Figure ##: Literature Flow Chart

**Flowchart**

Search results: 657 references*

Excluded = XXX references
- Not MS, not empirical study, not English language

Pulled for full text review: N=XX

Excluded = XX references
- Participants (not MS): #
- Intervention (not modifiable risk factor): #
- Study design: #
- Outcome: #
- Duplicate: #

Included studies: N=XX

KQ1 (progression risk factors): N=X

KQ2 (military specific): N=X

KQ3 (interventions): N=X
KEY QUESTION 1: WHAT MODIFIABLE EPIDEMIOLOGIC FACTORS ARE RELATED TO MULTIPLE SCLEROSIS PROGRESSION FOLLOWING DIAGNOSIS?

This section will summarize the results of the literature search for KQ1. Details of all included studies will be presented in the Evidence Table for KQ1.
Table 1: Draft evidence table for KQ1 – MS progression risk factors

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Geographic region</th>
<th>Sample characteristics (MS subtype distribution, age, % male, race/ethnicity distribution)</th>
<th>Case definition</th>
<th>N sample, N cases</th>
<th>Analytic method</th>
<th>Potential, modifiable risk factors (assessment method, time of exposure)</th>
<th>Other analyzed independent variables</th>
<th>Predictive time frame</th>
<th>Results EDSS scores</th>
<th>Results other clinical course effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xx, xxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cox survival model</td>
<td>Smoking (current smokers, ex-smokers, non-smokers, ever smokers)</td>
<td>Age, disease duration, gender….</td>
<td></td>
<td></td>
<td>Current smokers vs never smokers: HR 2.08 (CI 1.15, 3.77) predicting conversion from RRMS to SPMS</td>
</tr>
<tr>
<td>Xx, xxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cox survival model</td>
<td>Sun exposure (childhood)</td>
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<td></td>
</tr>
</tbody>
</table>
Summary of Findings

This section will summarize the number of identified studies relevant to the review question and document the assessed potential modifiable epidemiologic factors across studies. Risk factors will be grouped by type of factor (e.g., nutrition), where possible.

A summary of findings table will document the number of studies, the study designs, and the number of participants included in the studies for each risk factor. Results (strength and statistical significance of the association) for EDSS scores and for other MS progression relevant findings will be summarized across studies. The table will show the presence and the absence of associations, i.e., document which risk factors and protective factors associated for progression have been assessed in the literature. Associations identified in only one study without any replication and conflicting results across studies will be highlighted. For each outcome, the GRADE summary will be documented.

Table: Summary of findings table KQ1: What modifiable epidemiologic factors are related to multiple sclerosis progression following diagnosis?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Study Design, # of Studies (# participants, # cases)</th>
<th>EDSS Findings: Direction, Magnitude of Effect</th>
<th>Other Progression Findings: Direction, Magnitude of Effect</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid</td>
<td>X cohort studies (N=XXXX, XX cases)</td>
<td>Cod liver oil: Fish consumption:</td>
<td></td>
<td></td>
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<tr>
<td>Vitamin D</td>
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<td>Sun exposure</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Stress</td>
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</tbody>
</table>

Quality of Evidence for Key Question 1

This section will highlight the identified risk factors that show a statistically significant association across studies, outline reasons for the overall GRADE assessment, and document the quality of the evidence and our corresponding confidence in the evidence to answer the review question.
KEY QUESTION 2: WHAT ENVIRONMENTAL EXPOSURES PRIOR TO OR DURING MILITARY SERVICE ARE RELATED TO MULTIPLE SCLEROSIS PROGRESSION FOLLOWING ONSET SYMPTOMS?

This section will summarize the results of the literature search for key question 2. Details of included studies will be presented in the Evidence Table for KQ2.
Table 2: Draft evidence table for KQ2 – Exposures Prior and During Military Service

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Geographic region</th>
<th>Sample characteristics (MS subtype distribution, age, % male, race/ethnicity distribution)</th>
<th>Case definition</th>
<th>Study design</th>
<th>N sample, N cases</th>
<th>Analytic method</th>
<th>Assessed prior/post military service exposure</th>
<th>Assessed military service exposure</th>
<th>Other analyzed independent variables</th>
<th>Predictive time frame</th>
<th>Result s EDSS scores</th>
<th>Result s other clinical course effects</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
Summary of Findings Key Question 2

This section will summarize the number of identified studies relevant to the review question and document the assessed potential environmental exposures prior or during military service across studies. Studies relevant to KQ2 may also be included in KQ1.

A summary of findings table will document the number of studies, study designs, and number of participants included in the studies for each environmental exposure. Variables will be grouped by exposures prior to or post military service and exposures during military service. Results (strength and statistical significance of the association) for EDSS scores and for other MS progression relevant findings will be summarized across studies. The table will show the presence and the absence of associations, i.e., document which environmental exposures have been assessed in the literature. Associations identified in only one study without any replication and conflicting results across studies will be highlighted. For each outcome, the GRADE summary will be documented.

Table: Summary of findings table KQ2: What environmental exposures prior to or during military service are related to multiple sclerosis progression following onset symptoms?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Study Design, # of Studies (# participants, # cases)</th>
<th>EDSS Findings: Direction, Magnitude of Effect</th>
<th>Other Progression Findings: Direction, Magnitude of Effect</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior or post military service</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
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<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Exposure during military service</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deployment</td>
<td></td>
<td></td>
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<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vaccinations</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Quality of Evidence for Key Question 2
This section will highlight the identified exposures prior/post and during military service that show a statistically significant association across studies, outline reasons for the overall GRADE assessment, and document the quality of the evidence and our corresponding confidence in the evidence to answer the review question.

**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?**

This section will summarize the results of the literature search for key question 3. Details of included studies will be presented in the Evidence Table for KQ3.
Table 3: Draft evidence table for KQ3 – Effects of Interventions on MS Progression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design, methods</th>
<th>N randomized</th>
<th>Participant characteristics, proportion with progressive MS</th>
<th>Intervention</th>
<th>Co-interventions</th>
<th>Comparator</th>
<th>Power calculation</th>
<th>EDSS score result by followup point</th>
<th>Results for other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proportion with progressive MS: Mean age: % male: Race/ethnicity distribution:</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Summary of Findings Key Question 3

This section will summarize the number of identified studies relevant to KQ3 (risk factor modifying interventions) and document the evaluated interventions across studies. Interventions will be grouped by type (eg, nutrition) where possible. Studies in military personnel / veterans will be presented in a subgroup analysis.

A summary of findings table will document the number of RCTs and number of participants in the studies for each intervention. We will highlight studies in patients with progressive MS. Results for EDSS scores and for other MS progression relevant findings will be summarized across studies. For each intervention and outcome, the quality of the evidence (GRADE) summary will be documented.

Table: Summary of findings table 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?

<table>
<thead>
<tr>
<th>Intervention Outcome</th>
<th># of RCTs and Participants</th>
<th>Findings: Direction, Magnitude of Effect</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise interventions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS score</td>
<td>Group training:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Robot-assisted gait training:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin D supplements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS score</td>
<td>Vitamin D2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin D3:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Polyunsaturated fatty acids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking cessation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stress reduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quality of Evidence for Key Question 3

This section will evaluate the quality of the evidence and our corresponding confidence in the evidence to answer the review question for the identified interventions.
MULTIPLE SCLEROSIS PROGRESSION

SUMMARY AND DISCUSSION

This section will summarize the key findings from the systematic review.

SUMMARY OF EVIDENCE KQ1: WHAT MODIFIABLE EPIDEMIOLOGIC FACTORS ARE RELATED TO MULTIPLE SCLEROSIS PROGRESSION FOLLOWING DIAGNOSIS?

This section will summarize the evidence available to answer KQ1 and place the findings in context of the existing literature reviews.

SUMMARY OF EVIDENCE KQ2: WHAT ENVIRONMENTAL EXPOSURES PRIOR TO OR DURING MILITARY SERVICE ARE RELATED TO MULTIPLE SCLEROSIS PROGRESSION FOLLOWING ONSET SYMPTOMS?

This section will summarize the evidence available to answer KQ2 and place the findings in context of the existing literature reviews.

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?

This section will summarize the evidence available to answer KQ3 and place the findings in context of the existing literature reviews.

LIMITATIONS

This section will outline the limitations of the identified evidence base (eg, publication bias, study quality, or heterogeneity) and the limitations of the evidence review.

Applicability of Findings to the VA Population

This section will summarize the applicability of results to the VA, informed by KQ2 evidence.

RESEARCH GAPS/FUTURE RESEARCH

This section will outline identified research gaps (eg, absence of replication studies for individual identified risk factors or interventions) and provide specific suggestions for future research (content and methodology).

CONCLUSIONS

This paragraph will state the conclusions for each of the three key questions.
REFERENCES

2. Oct Care 2014.
APPENDIX XX. SEARCH STRATEGIES

This appendix will document the exact search strings for all searched electronic databases. We will design 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
OR disability[tiab]
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
OR disability[tiab]
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-12/16/2014

LANGUAGE:
English

SEARCH STRATEGY:
multiple sclerosis
AND
Multiple Sclerosis Progression Evidence-based Synthesis Program

medicine[mh] OR 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 service* or war or wars or war-related or combat* or battle* or service-member*

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – Earliest-12/23/2014
LANGUAGE: English
SEARCH STRATEGY:
'multiple sclerosis'
AND
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 '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 '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:
SCOPUS– Earliest-12/23/2014
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 '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:
AMED– Earliest-12/23/2014
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 '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:
GreenFILE – Earliest-12/23/2014
LANGUAGE:
English
SEARCH STRATEGY:
multiple sclerosis
NUMBER OF RESULTS: 49

DATABASE SEARCHED & TIME PERIOD COVERED:
Proquest Military Collection – Earliest-12/23/2014
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:
DTIC Technical Reports Collections – Earliest-12/17/2014
SEARCH STRATEGY:
effect phrase: Multiple sclerosis
AND Veterans

SEARCH METHODOLOGY KQ3

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

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – Earliest-1/13/2014
FILTERS:
English, Randomized Controlled Trial
**SEARCH STRATEGY:**
“multiple sclerosis”

**DATABASE SEARCHED & TIME PERIOD COVERED:**
AMED – Earliest-3/2014
**SEARCH STRATEGY:**
"multiple sclerosis" AND interven* AND (random* OR rct*)

**DATABASE SEARCHED & TIME PERIOD COVERED:**
Web of Science – Earliest-3/2014
**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)

**ADDITIONAL SEARCHES**
This section will document the exact search strings used to identify systematic reviews.

PubMed

CDSD

DARE
APPENDIX XX. STUDY SELECTION AND LIST OF EXCLUDED STUDIES

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

This appendix will list the citation of publications obtained as full text but not meeting inclusion criteria together with the reason for excluding the publication.
APPENDIX XX. CRITERIA USED IN QUALITY ASSESSMENT

The appendix will document the quality criteria, definitions and scoring details, and the results of the quality assessment for included studies.

Studies relevant to KQ1 and KQ2 will be assessed 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 will determine 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 studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Relevant to KQ1 and 2</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>
</tr>
</thead>
<tbody>
<tr>
<td>xxx</td>
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<td>xxx</td>
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</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.

Studies relevant to KQ3 will be 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 will determine whether the study indicates a high risk of bias, a low risk of bias, or an unclear risk of bias.

**Appendix Table 3: 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>
</tr>
</thead>
<tbody>
<tr>
<td>xxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>xxx</td>
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</tbody>
</table>

Legend: Unclear=● Low risk of bias=● High risk of bias=●

**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 into 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.
### APPENDIX XX. PEER REVIEW COMMENTS/AUTHOR RESPONSES

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