



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

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PREFACE

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

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

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

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

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

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

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EXECUTIVE SUMMARY

INTRODUCTION

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. Epidemiologic data suggest that rates of MS vary with demographic and environmental factors. The disease presentation is very heterogeneous with diverse clinical manifestations. Progression of MS may vary with modifiable risk factors.

This systematic review focused on modifiable risk factors and exposures that are associated with MS progression, and interventions that are directed at modifiable risk factors to delay progression.

The Key Questions (KQs) were:

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 multiple sclerosis once it has initiated?

The 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 searched the databases PubMed, EMBASE, AMED, Web of Science, SCOPUS, GreenFILE, ProQuest Military Collection, and DTIC to March 2015; reference-mined reviews and included studies; and consulted with experts to identify pertinent studies. Literature searches were not restricted to a narrow set of known risk factors but were exploratory in nature.

Study Selection

The review focused on patient-modifiable risk factors, such as food intake or health behaviors of patients with MS. Studies meeting the following criteria were 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 risk factors (KQ3; *eg*, smoking cessation programs, dietary interventions)

Comparators (study design): Observational and experimental studies analyzing factors associated with MS progression (KQ1, KQ2), randomized controlled trials (RCTs) regardless of the comparator (KQ3)

Outcomes: Progression of MS, primary outcome measure Expanded Disability Status Scale (EDSS)

Timing: not restricted

Setting: No restriction but planned subgroup analyses for *Veteran* population.

Data Abstraction and Quality Assessment

For KQ1 we extracted sample characteristics, geographical region, and number of participants; study design, analysis, and assessment timing (*eg*, prospective); the predicted outcome, assessed potential risk factors, and controlled variables; EDSS results and other MS progression results. For studies relevant to KQ2, we extracted study details and MS progression results associated with prior military service exposure and exposure during military service. For intervention studies (KQ3) we extracted methodological characteristics; number and characteristics of participants; intervention and comparator content and duration; EDSS results and other MS progression outcomes together with the follow-up point, and adverse events.

For KQ1 and KQ2 we distinguished concurrent, retrospective, and prospective studies. Prospective studies were assessed with QUIPS, a critical appraisal tool for prognostic studies. The RCTs informing KQ3 were assessed with the Cochrane risk of bias tool.

Data Synthesis and Analysis

All included studies were presented in evidence tables, grouped by key question, to allow a comprehensive overview. We differentiated results based on standardized and common measures of disease status, the EDSS, and other results. Where possible, variables were pooled using a restricted maximum-likelihood estimator and the Hartung-Knapp-Sidik-Jonkman standard error method for random-effects models to identify reliable and valid effects across studies. Continuous outcomes were reported as standardized mean differences (SMD), dichotomous outcomes as relative risks (RR), time to event data as hazard ratios (HR), and correlations were transformed to z statistics (using the Fisher transformation) to pool across studies. Point estimates were reported with the 95 percent confidence interval (CI). Heterogeneity was assessed with the I^2 statistic, publication bias with the Egger and Begg test, and we used the trim-and-fill method in the presence of publication bias.

KQ1 studies were grouped by evaluated risk factors. A summary of findings table documented the number of available studies for all risk factors that had been addressed in more than one study, the strength of association with MS progression, and our confidence in the finding. For studies in military personnel and Veterans relevant to KQ2, we differentiated assessed variables and statistically significant effects across studies documented in a summary of findings table. Intervention studies (KQ3) were stratified by intervention category and summarized across studies in a summary of findings table. The quality of evidence assessment followed the standard GRADE approach for RCTs and an adaptation for prognostic factor research for KQ1 and KQ2. The quality of evidence indicates the confidence in the results that are drawn from the literature, and we distinguished high, moderate, low, and very low quality of evidence.

RESULTS

Results of Literature Search

The search identified 8,594 citations. In total, 94 studies met inclusion criteria.

Summary of Results for Key Questions

Fifty-nine studies contributed to KQ1, 4 studies contributed to KQ2 (all also relevant to KQ1), and 36 RCTs addressed KQ3.

KQ1: Modifiable Risk Factors

Studies assessed a number of risk factors and used a variety of progression measures, including EDSS scores, time to conversion from remitting relapsing to secondary progressive MS, and odds of reaching EDSS 6 (requiring a cane for walking). Thirteen studies were prospective studies, assessing risk factors and subsequent outcome measures at 2 different time points.

Vitamin D has been addressed in a large number of studies. Across studies, there was a negative correlation of -0.22 (CI -0.32, -0.12; 11 studies; I^2 66%) indicating that lower Vitamin D levels are associated with higher EDSS scores. The result is primarily based on concurrent predictor studies (measuring Vitamin D level and disability status at the same time).

Across studies, we identified an increased risk of faster progression in smokers than nonsmokers (HR 1.55; CI 1.10, 2.19; I^2 72%; 7 studies, 8 datasets). The result is primarily based on retrospective studies.

The use of epidural analgesics during childbirth delivery has been assessed in 3 studies and none reported a statistically significant association with EDSS or DSS scores.

Results for sun exposure, sunscreen use, month of birth, diet, fish consumption, alcohol consumption, exercise, trauma, oral contraception, geographic region, and education have been addressed in more than one study, but the differences in risk factor operationalizations and outcome measures did not allow concrete evidence statements to be made.

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

KQ2: Exposures Prior to or During Military Service

We identified 4 studies that reported on exposures prior to and during military services associated with MS progression (KQ2) in active military personnel or Veterans. Assessed risk factors were geographic location at entry to the military, occupational status at entry to the military, average fall/winter sun exposures before MS onset, cod liver oil intake at ages 6-15,

fish consumption at ages 6-15, deployment, being a Veteran, and dietary treatment. None of the studies assessed the same risk factors and outcome measures varied across studies.

KQ3: Risk Factor Modification Therapies

Despite the inclusive and extensive systematic search, all identified risk factor modification interventions targeted either physical exercise, dietary interventions, or vitamin D supplementation. Across the 36 predominantly small RCTs, we did not detect interventions with statistically significant treatment effects compared to passive control groups on MS progression.

The pooled effect of exercise interventions on EDSS scores was not different from untreated control groups (SMD 0.02; CI -0.40, 0.44; I^2 0%; 7 RCTs). However, using baseline-adjusted data for a sensitivity analysis, the result favored the exercise intervention (SMD -0.19; CI -0.34, -0.03).

The 12 identified dietary intervention evaluations primarily assessed the effects of fatty acid supplements. We did not identify a statistically significant effect on the relative risk of progression (RR 0.86; CI 0.67, 1.05; I^2 0%; 4 RCTs) or EDSS scores (SMD -0.13; -0.83, 0.45; I^2 5%; 3 RCTs) compared to placebo.

Vitamin D supplementation showed a trend for improved EDSS scores but the pooled standardized mean difference was not statistically significant from placebo groups (SMD -0.15; CI -0.33, 0.02; I^2 0; 5 RCTs). However, the weighted mean difference favored vitamin D supplementation and showed that supplements were associated with a 0.22-point difference in EDSS scores (WMD -0.22; CI -0.39, -0.05).

DISCUSSION

Key Findings and Strength of Evidence

Our systematic review and meta-analysis focused on modifiable risk factors. We systematically searched for, documented, and synthesized evidence available in the research literature on MS progression. A large number of relevant studies is available to contribute to the evidence base but the research area is very complex.

We did not identify factors that were shown to be significant risk factors in epidemiological studies and published evidence that shows their amenability to intervention and their effects on MS progression.

KQ1

There was great variation in assessment and prediction details across studies relevant to KQ1 and only 13 prospective studies were identified, limiting the conclusions that can be drawn from the literature. There is moderate-quality evidence of a correlation between vitamin D levels and EDSS scores. Our confidence in the result was downgraded to moderate quality of evidence due to *indirectness*. The correlation does not allow causal inferences and prospective studies are needed linking vitamin D intake to MS progression. There is moderate-quality evidence (downgraded due to unexplained heterogeneity) suggesting an association between the time to progression and smoking. There is low-quality evidence (due to study design limitation and lack of point estimates) suggesting that epidural analgesia during childbirth is not associated with

EDSS scores. A large number of potential risk factors have been reported in the literature; however, the existing evidence is insufficient for providing concrete evidence statements for individual outcomes.

KQ2

The quality of the evidence for research on environmental exposures during military service was determined to be insufficient for evidence statements because all factors were reported in only one included study without replication in another participant sample.

KQ3

Despite substantially more available literature on risk factor modification therapies, we confirmed earlier reviews showing that currently no statistically significant evidence exists to supports specific interventions for MS progression and more research is needed.

The quality of the evidence for the result of no difference between exercise interventions and untreated control groups on EDSS scores was downgraded due to severe *study limitations* and conflicting results in a sensitivity analysis (*imprecision*). Our confidence in the evidence summary is limited because studies were not designed to assess EDSS changes, study sample sizes were very small, there were baseline imbalances, and the interventions may have been too short to achieve and detect changes with standard diagnostic criteria. Nonetheless, any treatment effect is likely to be very small; adjusting for baseline imbalances, the estimate was 0.20 points on the EDSS scale.

The quality of evidence for the dietary intervention results showing the absence of an effect on MS progression measured as deterioration or EDSS scores were both downgraded to moderate due to *study limitations*. The early studies lack reporting detail while the more recently published studies were small and did not report statistical power calculations to determine whether studies could detect an effect of the intervention on MS progression.

The quality of evidence for a non-significant effect of vitamin D supplementation on EDSS scores was downgraded due to *study limitations* and *imprecision*. The included studies were small and the lack of reported power calculations makes it unclear whether the studies were sufficiently powered to be able to detect small treatment effects. The statistical significance was dependent on the effect measure, showing that the effect estimate is not very robust. Nonetheless, any potential treatment effects are likely to be small with an estimated difference of 0.22 points in EDSS scores between intervention and control groups.

Applicability

Very few studies reported specifically on VA samples. However, there is no indication that risk factor results and treatment effects are not applicable to the VA population.

Research Gaps/Future Research

Our systematic review showed that more prospective research studies are needed to allow predictions and meaningful interpretation of risk factor analyses. Furthermore, future studies should report more details and statistical analyses in order to facilitate evidence synthesis in

meta-analyses. Specific areas that need more research are the consumption of alcohol and sun exposure and their potential effects in slowing progression.

The existing intervention studies testing the effect on MS progression should determine the statistical power needed to detect a difference between treatment groups, in particular for vitamin D supplementation trials. Effects of smoking cessation should be investigated given the association between smoking and MS progression. Based on sensitivity analyses we found that more studies evaluating the effects of long-term exercise interventions are warranted.

Finally, although our review addressed a broad research field, there are other, potential risk factors of interest that are outside the scope of this review, including the effect of treatable comorbidities of MS.

Conclusions

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

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

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

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

ABBREVIATIONS

EDSS Expanded Disability Status Scale

HR Hazard ratio

OR Odds ratio

KQ Key question

MS Multiple sclerosis

r Correlation

RR Relative risk