The impact of comorbidities on outcomes in the multiple sclerosis population: a rapid review protocol

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Method Article

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Abstract

Introduction: People with multiple sclerosis (MS) experience higher comorbidity burden than the non-MS population. Research has shown that having comorbidities alongside MS can lead to worse MS outcomes, including faster rates of disability progression, delays in initiating disease-modifying treatments, and earlier death. A comprehensive overview of which comorbidities affect these outcomes has not yet been published. This review aims to summarize what is currently known about these relationships to inform the development of a comorbidity index specific to people with MS.

Methods and analysis: A rapid review structure will be implemented that is in line with the current recommendations by the Cochrane Rapid Review Methods Group. Two databases will be searched (MEDLINE and EMBASE) and a grey literature search will be included. The Newcastle-Ottawa scale will be used for a risk of bias assessment. Results will be displayed visually in tables and graphs, as well as through a narrative synthesis.

Ethics and dissemination: Ethics approval is not required for this review. The rapid review will be submitted for publication in peer-reviewed journals. The results will also be disseminated through conferences and seminars.

PROSPERO registration number: CRD42023475565

Introduction

Multiple sclerosis (MS) is a chronic, often debilitating disease of the central nervous system. An estimated 3 million people worldwide have MS. The countries with the highest estimated prevalence of MS include Canada, USA, Iceland, Norway, Sweden, Finland, Germany, and Italy, with a high prevalence in other European countries as well. Recent studies have shown that comorbidity is very common in people with MS, with conditions such as mood disorders, other autoimmune conditions (e.g., psoriasis) and cardiovascular disease occurring more frequently in people with MS than in the general population. A higher comorbidity burden is associated with multiple adverse clinical outcomes, in particular, delayed diagnosis of MS, greater disability at the time of diagnosis and greater disability progression after MS diagnosis, reduced quality of life, increased relapse rates, and increased mortality risk. We will focus on disability progression, treatment initiation, and mortality outcomes. Characterizing the role of comorbidity in MS and which comorbidities affect important health-related outcomes is an important step towards understanding how to best tailor treatment for people with MS with differing levels of comorbidity burden.

Additionally, it is important to have an accurate method to quantify the burden of comorbidity in people with MS. Current comorbidity indices were developed for often hospitalized populations without MS. These may not be completely accurate in an MS patient population, as the care for people with MS is usually in the outpatient/community setting. These indices also often include comorbidities that, in an
MS population, are actually more likely to be symptoms of MS than comorbidities.\textsuperscript{20–22} A comorbidity index specifically for people with MS could be developed to include only diseases that are known not to be symptoms of MS and that are associated with outcomes important to the MS population. Such an index would benefit MS research, particularly in observational studies that adjust for comorbidity. It could also be used by practitioners to classify a patient’s expected prognosis based on their comorbidity burden at the time of diagnosis.

The overall goal of this project is to develop a comorbidity index specific to people with MS. For the development of such an index, it must be understood which comorbidities are associated with which outcomes and therefore should be considered as potential predictors. Though it is known that individual comorbidities influence certain outcomes, a comprehensive summary of all comorbidities that impact disability progression, disease-modifying treatment (DMT) initiation, and mortality has not yet been established. This rapid review will establish a list of comorbidities that have been shown to have an association with these outcomes and should therefore be included in the comorbidity index. This will be useful in the development of an MS-specific comorbidity index, and will also contribute to the growing body of literature around comorbidities and their effects on the MS population and provide a foundation for future research by indicating which comorbidities may be most important to study.

**Objective**

This review is the first phase of a project aiming to create a comorbidity index specific to people with MS. The comorbidity index will be developed to predict three important disease outcomes in MS: (1) disability progression, (2) initiation of DMT, and (3) death. The objective of this review is to identify comorbidities that are associated with the three outcomes and are thereby important in the prediction of these outcomes. Comorbidities will be defined as any chronic disease co-existing with the person’s MS that is not a complication or secondary condition of MS.

**Rapid review question**

In people with multiple sclerosis, which comorbidities, impact disability progression, treatment initiation, and mortality (and by how much)?

**General approach**

Due to time and funding constraints, we have elected to conduct a rapid review because it will be efficient and cost-effective. The Cochrane Rapid Reviews Methods Group defines a rapid review as: “a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through
streamlining or omitting a variety of methods to produce evidence in a resource-efficient manner."\(^{23}\) Compared to a systematic review, methods to streamline the review process include reducing or eliminating the grey literature search and performing a staged search looking first at existing systematic reviews before studies with other designs. Additionally, the reviewing team may enlist one reviewer for screening, data extraction, and risk-of-bias assessment with verification performed by a second reviewer.\(^{24,25}\)

In compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) recommendations,\(^{26}\) this protocol has been registered on PROSPERO (id: CRD42023475565), an international register of systematic reviews.\(^{27}\) Any amendments to the protocol will be updated on PROSPERO. We will also follow PRISMA guidelines as closely as is possible for a rapid review, in the final manuscript.\(^{28}\)

**Reagents**

**Equipment**

**Procedure**

1. *Establish eligibility criteria.*

All types of observational studies (excluding case reports and case series) of any sample size will be included. There will be no geographical restrictions. For inclusion, the study population must consist of people with a diagnosis of MS. Ideally a diagnosis would be made using internationally recognized criteria or a validated algorithm applied to health administrative data or similar recognised approach, but self-reported diagnoses will also be included. Any form of multiple sclerosis (relapsing-remitting, primary progressive, secondary progressive, clinically isolated syndrome) will be included. Included studies must examine the effect of at least one chronic condition co-existing with MS on disability progression and/or initiation of DMT and/or death. It does not matter whether the comorbidity was diagnosed before or after the MS diagnosis but must have been diagnosed before the outcome.

Case reports and case series will be excluded. Studies published in languages other than English will be excluded as recommended by the Cochrane Rapid Reviews Methods Group.\(^{25}\) Studies not conducted with humans or examining diseases as potential symptoms or complications of MS rather than separate, co-existing diseases will also be excluded. Studies focusing exclusively on MS pediatric populations (persons <18 years old) will be excluded because comorbidities may have different impacts on the outcomes of this group. Finally, studies on the longer-term effects of COVID-19 will be excluded because this is an emerging topic that was only relatively recently recognized, with much remaining unknown.

2. *Construct search strategy.*
The primary literature search will be conducted by the first reviewer (HF) using MEDLINE and Embase, as recommended by the Cochrane Rapid Reviews Methods Group, with medical subject headings and keywords related to MS and comorbidities (Appendix A, Appendix B). The timeframe for study publication will be limited to the years 2002 to current (i.e., 2023) due to the introduction of the McDonald diagnostic criteria for MS in June 2001 which substantially reduced diagnostic and treatment delays. The identified articles will first be searched for previous relevant systematic reviews covering parts of this time frame. If there are high quality relevant reviews available for some periods of time, these will be summarized and evaluated using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2). Primary articles will then be screened only for the time periods not already covered by acceptable systematic reviews.

We will perform a grey literature search following the primary search to identify any additional studies. As recommended in several rapid review guidelines, the grey literature search will be limited in the interest of time. We will limit the grey literature search by restricting to conference abstracts from 2021 to current for American Academy of Neurology (AAN), European Committee for Treatment and Research in MS (ECTRIMS), and Americas Committee for Treatment and Research in MS (ACTRIMS), which represent some of the largest MS related conferences, to include abstracts for which the authors have not yet had a chance to publish in full. Additionally, we will include pre-prints found in MEDLINE and Embase from 2022 to current. This search will be performed using the same search strategy as for the primary literature search but including only pre-prints and conference abstracts.

3. **Screen articles.**

As recommended by the Cochrane Rapid Reviews Methods Group, one reviewer (HF) will screen all titles and abstracts, and a second reviewer (MC) will screen 20% of abstracts as verification. The abstracts to be screened by the second reviewer (MC) will be chosen randomly after all duplicates have been removed. If agreement is 80% or higher, we will proceed with title and abstract screening with a single reviewer. If the agreement is lower than 80%, the two reviewers will discuss and clarify the eligibility criteria and continue screening with two reviewers until agreement of 80% or higher has been achieved. Any disagreements will be resolved through discussion between reviewers with input from other team members if necessary. The same process will be implemented for the full-text screening. All screening will be performed using the Covidence online review management software. The screening process and results will be detailed in a PRISMA flow diagram.

4. **Extract data.**

As recommended by the Cochrane Rapid Reviews Methods Group, one reviewer (HF) will extract data using a standard form, with a second reviewer (MC) verifying the correctness and completeness. Extracted information will include study characteristics, comorbidities and outcomes studied, the authors’ conclusions and how they arrived at these conclusions. Conflicts will be resolved through discussion
between reviewers with input from other team members if necessary.\textsuperscript{35} A preliminary data extraction guide can be found in Appendix C. Extracted data will be organized into an Excel spreadsheet.

5. \textit{Perform risk of bias assessments.}

A risk of bias assessment will be performed by one reviewer (HF) using the Newcastle-Ottawa scale (NOS).\textsuperscript{38} A second reviewer (MC) will verify the first reviewer’s assessments, as recommended by the Cochrane Rapid Reviews Methods Group.\textsuperscript{35} The NOS is the most commonly used tool for cohort and case-control studies.\textsuperscript{39} The NOS consists of eight questions for each case-control and cohort study, which address selection, comparability of groups assessed, and the assessment of the outcome or exposure.\textsuperscript{38} Though more exhaustive criteria exist, the Cochrane Rapid Reviews Methods Group endorses the use of less complex, faster tools to complete risk of bias assessment in rapid reviews.\textsuperscript{35} By addressing the main aspects of bias in observational studies, this method will sufficiently characterize the quality of the studies included in our rapid review.

6. \textit{Synthesize data.}

Three tables will be used to display results for the outcomes. These tables will have subheadings for each comorbidity whose association with the outcome was assessed in at least one study selected from this literature search. Each table will include the reference, some study characteristics such as design, sample size, and demographic and MS characteristics, the author’s conclusions, and the methods or reasoning used to arrive at this conclusion (Appendix D). Bar graphs will be used to display the number of studies that examined the relationship between a given comorbidity and a certain outcome, as well as the proportion of studies that concluded an effect of a comorbidity on an outcome out of all those that examined this comorbidity and outcome (Appendix E).

Finally, a narrative synthesis will summarize the results as well as which comorbidities were found to have a statistically significant association with each outcome, and which were not. Additionally, we will discuss whether there are some comorbidities that affect several or all outcomes of interest in order to present an overview of which comorbidities may have the strongest overall effects on people with MS and their disease course.

\textbf{Troubleshooting}

See Troubleshootingtable.pdf in supplementary files.

\textbf{Time Taken}

1. Perform preliminary literature review and establish eligibility criteria: 1 month

2. Construct search strategy: 2 weeks
3. Screen articles: 1 month

4. Extract data: 2 weeks

5. Perform risk of bias assessments: 2 weeks

6. Data synthesis: 2 weeks

**Anticipated Results**

This rapid review will form the foundation for the development of a comorbidity index specific to the MS population, an important tool in the analysis of observational studies. Additionally, it will comprehensively identify which comorbidities are known to influence disability progression, initiation of DMT, and mortality in people with MS. This will provide the MS research community with an indication of how the treatment of certain comorbidities may improve outcomes for MS patients, and which comorbidity-outcome relationships warrant further study.

The findings from the rapid review will be disseminated through publication in a peer-reviewed journal and presentation at relevant seminars and conferences. We will also aim to broadcast the work through social media platforms hosted by the University of British Columbia and its School of Population and Public Health. The data from this review will be made available in the appendix, supplementary materials, or public repository. Furthermore, the results will inform future works including the development of a comorbidity index specific to people with MS. This will further disseminate the findings and demonstrate the importance of understanding the relationship between comorbidities and outcomes in the MS population.

**References**


27. National Institute for Health and Care Research. PROSPERO. York, United Kingdom;


36. Veritas Health Innovation. Covidence systematic review software. Melbourne, Australia;


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**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Troubleshootingtable.pdf