

# Recommendations for observational studies of comorbidity in multiple sclerosis

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For the attendees of the  
International  
Workshop on  
Comorbidity in  
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## ABSTRACT

**Objective:** To reach consensus about the most relevant comorbidities to study in multiple sclerosis (MS) with respect to incidence, prevalence, and effect on outcomes; review datasets that may support studies of comorbidity in MS; and identify MS outcomes that should be prioritized in such studies.

**Methods:** We held an international workshop to meet these objectives, informed by a systematic review of the incidence and prevalence of comorbidity in MS, and an international survey regarding research priorities for comorbidity.

**Results:** We recommend establishing age- and sex-specific incidence and prevalence estimates for 5 comorbidities (depression, anxiety, hypertension, hyperlipidemia, and diabetes); evaluating the effect of 7 comorbidities (depression, anxiety, hypertension, diabetes, hyperlipidemia, chronic lung disease, and autoimmune diseases) on disability, quality of life, brain atrophy and other imaging parameters, health care utilization, employment, and mortality, including age, sex, race/ethnicity, socioeconomic status, and disease duration as potential confounders; harmonizing study designs across jurisdictions; and conducting such studies worldwide. Ultimately, clinical trials of treating comorbidity in MS are needed.

**Conclusion:** Our recommendations will help address knowledge gaps regarding the incidence, prevalence, and effect of comorbidity on outcomes in MS. *Neurology*® 2016;86:1446-1453

## GLOSSARY

**CI** = confidence interval; **EDSS** = Expanded Disability Status Scale; **ICD** = *International Classification of Diseases*; **MS** = multiple sclerosis; **NARCOMS** = North American Research Committee on Multiple Sclerosis.

Substantial heterogeneity in multiple sclerosis (MS)-related outcomes exists, but this remains incompletely understood. Comorbidity may account for some of the observed heterogeneity in outcomes in MS, yet its effect has only recently received attention. Comorbidity is common in the general population, and is associated with higher mortality and increased health care utilization.<sup>1</sup> Despite evidence that comorbidity is common<sup>2</sup> and affects outcomes in MS,<sup>3</sup> important knowledge gaps remain.

An international group of investigators in MS, epidemiology, clinical trial design, and comorbidity met in Toronto, Canada, on March 27–28, 2015, under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the European Committee on Treatment and Research in Multiple Sclerosis and the US National Multiple Sclerosis Society. The workshop goals were to reach consensus about the most relevant comorbidities to study in MS with respect to incidence, prevalence, and impact on outcomes; prioritize outcomes for such

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studies; and review datasets that may support these studies. Comorbidity was also discussed in the context of clinical trials, as described elsewhere.<sup>4</sup> The current article summarizes the evidence related to comorbidity in MS that was collated and reviewed in preparation for the workshop, describes the limitations of the existing literature regarding comorbidity and MS, and reports recommendations for future research regarding comorbidity in MS that resulted from the workshop. Specifically, we review core concepts related to the definition of comorbidity, findings from an international survey regarding research priorities in comorbidity research, the key findings from a systematic review of the incidence and prevalence of comorbidity in MS, and a systematic review of the effect of comorbidity on outcomes in MS, health behaviors in MS, and issues related to measurement and analysis of comorbidity in MS, which guided our recommendations.

**CORE CONCEPTS** Comorbidity is conceptualized differently depending on whether the perspective is clinical, epidemiologic, or health policy-based.<sup>5</sup> The core concept is that more than one distinct condition exists in an individual.<sup>5</sup> Traditionally, comorbidity refers to the total burden of illness other than the index disease of interest, and typically focuses on chronic conditions. This definition excludes complications that are a direct result of the index disease. While both comorbidity and complications may influence outcomes, their etiologies and types of interventions may differ. Throughout this article, we focus on comorbidity. For some conditions, such as immune-mediated neurologic disease, it may be difficult to determine whether 2 distinct conditions exist (that is, MS and another condition) or not (that is, the other condition alone or MS alone), but such diagnostic decisions are not the focus of this article. We also recognize that for some conditions, such as depression or anxiety, it may be difficult to distinguish between comorbidity and complication or symptom of disease. However, we have chosen to consider these conditions as comorbidities rather than symptoms of MS because in some individuals they appear to occur independent of MS, such as when onset is many years before clinical onset of MS, multiple factors may contribute to depression or anxiety in MS, which may or may not be MS-related, such as genetic factors or psychosocial stressors, and they have specific diagnostic criteria, unlike symptoms such as fatigue.

Classic definitions of comorbidity do not include health behaviors. However, behaviors such as smoking and alcohol intake affect the risks of, and outcomes of, chronic diseases, including MS.<sup>6</sup> In other diseases, such as lung cancer, health behaviors such as smoking have independent effects on outcomes.<sup>7</sup> Therefore, we considered health behaviors as a type of comorbidity rather than simple confounders when making our recommendations.

Conditions may co-occur due to chance, or be more likely to be diagnosed because of increased health system contacts due to the presence of a chronic condition.<sup>5</sup> Of greater interest is the co-occurrence of disease due to etiologic mechanisms such as direct causation, associated risk factors, heterogeneity, and independence. In direct causation, one condition leads directly to another condition, as observed when idiopathic thrombocytopenic purpura arises from the use of alemtuzumab to treat MS.<sup>8</sup> Common genetic or environmental risk factors may lead to increased comorbidity. Smoking may underlie the increased prevalence of lung disease in MS as persons with MS smoke more than the general population.<sup>6</sup> In heterogeneity, independent factors such as age may be associated with co-occurrence of disease. Finally, 2 conditions may coexist because they are secondary to a third, undiagnosed disease (independence). For example, asthma and peripheral neuropathy might both be due to Churg-Strauss syndrome. Such mechanistic questions are relevant to understanding comorbidity in MS, but were not the focus of our deliberations.

Comorbidity is one of several patient characteristics, including genetics, age, sex, race, ethnicity, and socioeconomic status, which are relevant to the clinical presentation and management of MS.<sup>9,10</sup> Socioeconomic status appears to account for some of the disparity in disability observed between African Americans and Caucasian Americans with MS.<sup>9</sup> These factors may modify the associations between comorbidity and outcomes in MS. Age, for example, is a critical determinant of the degree of disability experienced by persons with MS,<sup>11</sup> suggesting that progressive MS represents an age-related neurodegenerative process. Comorbidities such as hypertension, diabetes, and hyperlipidemia also increase in frequency with age, and can be conceptualized to accelerate brain aging,<sup>12</sup> potentially accelerating disability progression in MS.

Research regarding comorbidity can be grouped into the following areas: the incidence and prevalence of comorbidity; the effect of comorbidity on the affected individual, health system, and society; the mechanisms underlying the frequency of comorbidity and its effect; and evaluation of interventions to prevent comorbidities or to reduce their impact. Most

research regarding comorbidity and MS has focused on the first 2 areas.

**INTERNATIONAL SURVEY** Preparatory to the workshop, we surveyed experts regarding their views of the most relevant comorbidities and health behaviors to evaluate with respect to incidence, prevalence, and their effect on MS outcomes. Survey design and results are detailed in appendices e-1 and e-2 on the *Neurology*<sup>®</sup> Web site at Neurology.org. The top 3 comorbidities deemed to be in greatest need of study with respect to their effect on outcomes were psychiatric disorders, cancer, and autoimmune disease; the top 3 health behaviors were substance use, alcohol use, and diet. The most important research gaps identified were comorbidity as a prognostic factor for MS outcomes, followed by estimates of the frequency of comorbidity. With respect to health behaviors, the most important research gaps identified were their roles as prognostic factors for MS, followed by their effect on pharmacotherapy.

**Comorbidity, health behaviors, and MS. Incidence and prevalence of comorbidity.** Preparatory to the workshop, we reviewed the world (English-language) literature regarding the incidence and prevalence of comorbidity in MS.<sup>2</sup> Based on meta-analyses of population-based studies, the comorbidities with the highest incidence were hypertension (3.73%; 95% confidence interval [CI] 3.43–4.06%), stroke (2.73%; 95% CI 2.51–2.95%), and cancer (any cancer 4.3%; 95% CI 2.67–6.1); however, population-based studies were lacking for many conditions. The most prevalent comorbidities were depression (23.7%; 95% CI 17.4–30.0%), anxiety (21.9%; 95% CI 8.76–35.0%), hypertension (18.6%; 95% CI 13.9–23.2%), hyperlipidemia (10.9%; 95% CI 5.6–16.1%), and chronic lung disease (10.0%; 95% CI 0–20.9%). Several comorbidities occur more often in the MS population than the general population, including depression, anxiety, bipolar disorder, alcohol abuse, stroke, ischemic heart disease, inflammatory bowel disease, irritable syndrome, seizure disorders, and sleep disorders.<sup>2</sup>

Valid, reliable estimates of the incidence and prevalence of comorbidity in MS are needed to inform the design of studies assessing the impact of comorbidity, support pharmacovigilance efforts, and direct clinical programs aimed at mitigating the impact of comorbidity. However, we identified gaps in knowledge regarding the epidemiology of comorbidity in MS. First, most studies were conducted in few geographic regions, mainly western Europe and North America. Given worldwide variation in the burden of many chronic diseases,<sup>13</sup> estimates are needed from other regions. Second, estimates of the incidence and prevalence of comorbidity varied widely, likely due to

heterogeneity in study design, bias, and true differences between populations. Common limitations included the failure to report diagnostic criteria or validation of the approach used to identify the MS population or the comorbidity, lack of information regarding the time period when the study was conducted, and lack of a population-based design. Thus, homogeneous and more rigorous study designs are needed to clarify the true variation in incidence and prevalence of comorbidity across regions and socio-demographic groups. Reporting of age, sex, and ethnicity-specific estimates, and standardization of findings to a common population, would also improve comparability of study findings. Third, many potentially relevant comorbidities were infrequently evaluated. Finally, although many studies evaluated the incidence and prevalence of multiple comorbidities, the relationship of these comorbidities to one another was rarely considered.

**Effects of comorbidity.** With increasing age, the prevalence of comorbidity increases in MS, typically when disability is also accumulating. Therefore, the effect of comorbidity on MS is likely to be important as MS progresses. Preparatory to the workshop, we also systematically reviewed the association of comorbidity with outcomes commonly reported in clinical trials (relapses, disability, functional status, cognition, MRI outcomes, pain, and fatigue; for methods, see appendix e-3). We chose the same comorbidities as those considered in our systematic review of the incidence and prevalence of comorbidity in MS.<sup>2</sup>

We identified 35 publications from 32 unique studies (table e-1 and appendix e-3).<sup>3,10,14–46</sup> Most studies evaluated psychiatric comorbidities (17) or vascular comorbidities, including diabetes, hypertension, hyperlipidemia, ischemic heart disease, and peripheral vascular disease (6). Overall, the findings suggest that comorbidity is associated with adverse outcomes in MS. Depression, anxiety, and sleep disorders are consistently associated with the presence and severity of fatigue. Depression is also associated with impaired cognitive function, but not relapses or disability. The presence of physical comorbidities is associated with greater disability at the time of MS diagnosis<sup>10</sup>; the effect increased with an increasing number of comorbidities.<sup>10</sup> Vascular comorbidities are associated with more rapid progression of ambulatory disability.<sup>31</sup> Serum lipid measurements not necessarily meeting criteria for dyslipidemia have been associated with new hyperintense and contrast-enhancing lesions on MRI,<sup>43</sup> and with disability progression,<sup>39,43</sup> but not with relapses.<sup>38</sup> None of the studies evaluated the effect of treating comorbidities on outcome.

However, most potentially relevant comorbidities have not been studied and we identified few population-based studies.<sup>40</sup> Most study populations

were clinic-based. Secondary analyses of clinical trial data included even more selected populations. Definitions of comorbidities differed across studies, and most studies did not consider the potential confounding effects of treatment of the comorbidities on outcome. Many studies were cross-sectional, precluding causal inferences. Finally, it was often unclear if outcomes were assessed blind to comorbidity status. Future studies should be longitudinal, and need to enroll representative populations, use validated methods to assess comorbidity status and outcome, and assess potential confounding factors. Harmonization of data collection would facilitate comparisons across studies.

**Prevalence and effect of health behaviors.** Nearly 50% of persons with MS report ever smoking before MS symptom onset, and up to 39% actively smoke at the time of MS symptom onset.<sup>10</sup> The prevalence of definite or probable alcohol abuse or dependence ranges from 3.96% to 18.2%.<sup>47</sup> Excessive weight and obesity are highly prevalent in the MS population, affecting nearly 50% of individuals.<sup>48</sup> Although some inconsistencies exist,<sup>49</sup> smoking appears to be associated with more rapid disability progression, accumulation of hyperintense lesions on MRI, and greater brain atrophy.<sup>50</sup> In a cross-sectional study of 423 persons with MS, those who consumed alcohol for 15 years or less after MS onset had lower disability on the Expanded Disability Status Scale (EDSS) and higher brain volume than those who did not consume alcohol or who consumed it for more than 15 years.<sup>24</sup> In a Belgian study of 1,372 persons with MS, moderate alcohol consumption was associated with a reduced risk of progression to an EDSS score of 6.0 (cane).<sup>19</sup> In the North American Research Committee on Multiple Sclerosis (NARCOMS) cohort, obesity was associated with an increased likelihood of presenting with a relapsing, rather than progressive, course at onset among women, independent of age.<sup>51</sup> In a cohort of Australians, body mass index was not associated with relapse risk,<sup>38</sup> but was associated with greater disability.<sup>39</sup> An important limitation is that most of these studies considered the effect of only one health behavior on outcome, and did not consider the confounding effects of comorbidity. Future observational studies would benefit from considering the effects of comorbidities and health behaviors concurrently, and should attempt to disentangle the direction of causation between comorbidity and MS outcomes.

Another important unknown is whether there are interactions among co-occurring comorbidities and health behaviors leading to additive or synergistic effects on outcomes.<sup>5</sup> Metabolic syndrome, for example, is diagnosed when any 3 of the following are present: abdominal obesity, hypertension, elevated

fasting glucose, high serum triglycerides, and low high-density lipoprotein level. Metabolic syndrome increases the risk of cardiovascular mortality beyond that of its individual components.<sup>52</sup> Therefore, these associations need to be better understood. It is also unknown whether the timing of the development of a comorbidity, its severity, or its treatments are relevant to its effects.

**DATA SOURCES** In a series of presentations, we reviewed issues related to comorbidity measurement. Potential sources of comorbidity data include self-report, medical records, and administrative databases. None of these data sources is the gold standard in all circumstances. Briefly, the validity and reliability of self-reported comorbidity in MS varies by condition.<sup>53</sup> Accuracy is high for chronic conditions that are well-defined, require ongoing care, or cause disability.<sup>53</sup> Self-report is less accurate for conditions where diagnostic criteria are less precise, such as arthritis, and may vary in accuracy by sociodemographic characteristics.

The medical record offers information about comorbidity and MS, including disability status, and treatments used. However, medical records reviews may be costly and labor-intensive. When multiple health care providers are involved, it may be difficult to access complete information. Therefore, medical records reviews are often not feasible for large, population-based studies. Depending on the data sources used to construct a clinical database, they may be subject to the aforementioned limitations of self-report, medical records, or both.

Administrative data are obtained from enrolment into public and commercial health insurance plans as well as through the delivery of, and reimbursement for, health care services.<sup>54</sup> These data generally include demographic characteristics including a personal identification number, date of birth, sex, and region of residence, but race is often lacking. Most administrative datasets capture hospital and physician encounters, including the dates of service and diagnostic and procedure codes for the service delivered. Some datasets also capture prescriptions. Administrative datasets often use ICD codes. Widespread use of ICD codes may facilitate the conduct of similar comorbidity studies in multiple jurisdictions; however, the customization of ICD-10 in many countries threatens data comparability.<sup>55</sup> In many jurisdictions, administrative claims data are population-based, accessible, and cost-effective as compared to other data sources. However, their validity for research must be assessed,<sup>54</sup> and clinical details are lacking. The potential applications to comorbidity research are broad, including comorbidity surveillance, pharmacovigilance, and evaluation of the effect of comorbidity on health care utilization.

Appendix e-4 describes potentially useful datasets that include MS-relevant comorbidity and health behavior data, worldwide. While the validity of some of these datasets for MS research is established, further work is necessary to validate others.

**Analysis.** Analytically, comorbidity can be classified as a count of conditions, using an index, or by considering individual comorbidities. A count is the simplest to obtain and is associated with outcomes such as health care utilization,<sup>56</sup> but treats all comorbidities as equal. An index is a summary measure of comorbidities that may incorporate information about severity. Weighted indices apply more importance to some conditions than others. Some indices have been developed for use in specific populations or for specific outcomes (e.g., mortality); relative performance varies across populations and outcomes.<sup>57</sup> None has been developed for use in MS, and existing indices may be inappropriate for MS. For example, the Elixhauser index captures paraplegia, and other neurologic disorders (including MS),<sup>56</sup> potentially confounding MS severity with comorbidity. Consideration of individual comorbidities provides more opportunity to understand interactions between comorbidities, but requires larger samples. Further methodologic work is needed in this area.

### RECOMMENDATIONS FOR FUTURE RESEARCH

Following presentations that reviewed the findings of the international survey, systematic reviews, and issues related to the measurement and analysis of comorbidities, we held small group sessions to reach consensus regarding recommendations for future research. Recognizing that there would be challenges in studying all comorbidities in the short term, the charge to the small groups for the first and second recommendations was to prioritize 5 comorbidities, but these recommendations are not intended to discourage work that evaluates other comorbidities.

1. Establish age-specific, sex-specific, and ideally race/ethnicity-specific incidence and prevalence estimates for priority comorbidities in the MS population. Based on several considerations, we prioritized 5 comorbidities for future studies of their incidence and prevalence in MS, including depression, anxiety, hypertension, diabetes, and hyperlipidemia (table e-2). First, existing literature or clinical experience suggested they were prevalent in the MS population (depression, anxiety, hypertension, hyperlipidemia). Second, little or no information was available regarding their incidence (all), or regarding age- and sex-specific estimates of their incidence and prevalence (all). Third, these conditions may affect the risk of MS or differential outcomes in MS, and are potentially

treatable (all). Given the existence of some population-based data regarding the incidence of autoimmune disease and the low prevalence of many autoimmune diseases in MS, these conditions were given a lower priority.

2. Evaluate the effect of priority comorbidities on MS outcomes that are relevant from the perspective of the clinician, affected individual, health system, and society. Due to difficulties reaching consensus regarding the top 5 comorbidities, we prioritized 7 comorbidities for observational studies of the effect of comorbidity on MS outcomes, including depression, anxiety, hypertension, diabetes, hyperlipidemia, chronic lung disease, and autoimmune diseases. When selecting these comorbidities, physiologic and biological relevance to MS, existing knowledge regarding their effects on outcomes in MS, and their prevalence in the MS population were considered. Given its low prevalence, cancer was not prioritized, but was considered highly relevant for clinical trials.<sup>4</sup> Smoking, obesity, and physical activity were also considered priorities for both types of studies. However, future investigations should not be limited to these conditions. Preferred outcomes are summarized in table e-2.
3. Include potential confounders or effect modifiers as covariates in studies of the effect of comorbidity on MS outcomes. Key covariates include age, sex, race/ethnicity, socioeconomic status, and disease duration.
4. Design observational studies that have strong methodologic features. Given the methodologic limitations of the existing literature, we emphasized the importance of sound study design. We recognized that multiple data sources could be used to address these questions, but the validity of the methods used to assess comorbidity and the outcomes of interest are critical, along with inclusion of a representative study population. Specific efforts are needed to develop an MS-specific comorbidity index.
5. Harmonize measurement of key data elements such as sex, race/ethnicity, clinical course, comorbidity, and MS diagnostic criteria, and use common outcome measures to facilitate pooling and comparison of study findings. Such approaches are supported by the National Institute of Neurological Disorders and Stroke Common Data Elements Project.
6. Follow published guidelines when reporting study findings.<sup>58,59</sup> To be useful, observational studies need to be methodologically sound and be reported well. Reporting guidelines aim to improve the quality of reporting in observational studies, which is often poor, as is also true in the MS comorbidity literature. The Strengthening the

Reporting of Observational studies in Epidemiology statement provides guidelines for observational studies in general, while The Standards of Reporting of Neurologic Disorders checklist provides guidelines for reporting incidence and prevalence studies in neurologic disease.

7. Conduct observational studies of comorbidity in MS in all world regions. Since much of the comorbidity literature has arisen from few world regions and heterogeneity in MS outcomes is well-recognized, it is critical that investigators in areas beyond western Europe and North America be supported to conduct studies in their regions.
8. Explore the mechanisms of the effects of comorbidity on MS as a means of identifying potential approaches to mitigating their impact. This will require considering direct biological effects such as accelerated neurodegeneration (as might be assessed using measures of brain atrophy) or enhanced peripheral immune activation (as might be assessed by measuring cytokine profiles or immune cell behavior), and indirect effects such as diagnostic delays or differences in MS treatment or treatment responses.
9. Conduct clinical trials of the effect of comorbidity treatment on MS. In other diseases, there are comorbidity-based differences in disease management. For example, hypertension targets are lower in diabetic patients than in patients without diabetes to reduce the risk of diabetes-associated complications.<sup>60</sup> Observational studies of the incidence and prevalence of comorbidity and of the effect of comorbidity on outcomes in MS are needed to inform the design of these trials. Implementation research will be needed to move these interventions into clinical practice effectively.

#### AUTHOR CONTRIBUTIONS

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