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Validation of a Self-Report Comorbidity Questionnaire for Multiple Sclerosis

Myles Horton[a] Richard A. Rudick[c] Claire Hara-Cleaver[c] Ruth Ann Marrie[a, b]

Departments of [a]Internal Medicine and [b]Community Health Sciences, University of Manitoba, Winnipeg, Man., Canada; [c]Mellen Center for Treatment and Research, Cleveland Clinic, Cleveland, Ohio, USA

Key Words
Multiple sclerosis · Comorbidity · Self-report · Questionnaire · Validation

Abstract
Background/Aims: Researchers increasingly recognize the high frequency of comorbidity in multiple sclerosis (MS) and the negative impact on quality of life and disability, but little work has evaluated methods of comorbidity measurement in MS. We aimed to validate a self-report questionnaire for assessing comorbidity in MS. ***Methods:*** Patients with MS were recruited from the MS Clinic in Winnipeg, Canada and the Mellen Center (Cleveland Clinic, Cleveland, Ohio, USA) from October 2008 to 2009. Using a questionnaire, participants reported the presence or absence of 36 comorbidities, sociodemographic characteristics, and disability status. Abstractors blinded to questionnaire results collected data regarding the comorbidities of interest and their treatments. Using the medical record as the gold standard, we determined the sensitivity, specificity, positive and negative predictive values of the questionnaire data. To measure agreement we calculated kappa (κ) statistics. ***Results:*** We enrolled 404 participants. Agreement between self-report and medical records was high (κ >0.82) for diabetes and hypertension; substantial (κ = 0.62–0.80) for hyperlipidemia, thyroid disease, glaucoma, and lung disease; moderate (κ = 0.43–0.56) for osteoporosis, irritable bowel syndrome, migraine, depression, heart disease, and anxiety disorders. Agreement was slight to fair for the remaining comorbidities. ***Conclusions:*** Self-report is a valid way to capture comorbidities affecting MS patients.

Introduction

Comorbidity is common in multiple sclerosis (MS) [1, 2] and may adversely influence health-related quality of life, and disability progression [3–5]. Despite increasing interest in evaluating the impact of comorbidity on MS, little work has evaluated methods of comorbidity measurement in this population, including the relative strengths and limitations of medical records, self-report, and administrative claims data [6].

Self-report questionnaires are easy to administer, less expensive than medical records review, and may better predict quality of life and functional status than medical records data [7]. Further, self-report questionnaires for comorbidity perform comparably for the prediction of mortality and health care utilizations to indices based on medical records or administrative data [8, 9]. A validated self-report questionnaire could be used inexpensively by researchers and health care administrators to gather co-

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Ruth Ann Marrie, MD, PhD
Health Sciences Center, GF-533
820 Sherbrook Street
Winnipeg, MB R3A 1R9 (Canada)
Tel. +1 204 787 4951, Fax +1 204 787 1486, E-Mail rmarrie@hsc.mb.ca

morbidity data for predicting health care utilization and other health outcomes, and by busy clinicians to capture comorbidities when multiple providers are involved in a patient's care.

In non-neurologic populations, however, the validity of self-reported comorbidities is variable [10, 11]. Furthermore, physical and cognitive disability, common features of MS [12], may affect the validity or reliability of self-reported health data [13, 14]. This makes the validity of self-reported comorbidity data in MS populations uncertain. We aimed to validate a self-report questionnaire for assessing comorbidity in MS against medical records data.

Materials and Methods

Study Population

We recruited study participants followed at the provincial MS Clinic at the Health Sciences Centre in Winnipeg, Man., Canada and the MS Clinic (Mellen Center) at the Cleveland Clinic in Cleveland, Ohio, USA. We obtained ethics approval from the appropriate review boards at each site. Participants had definite MS or a clinically isolated syndrome with high risk of MS [15], and were aged 18 years or older. Exclusion criteria included cognitive impairment that would preclude informed consent, or inability to complete the questionnaire due to impaired visual or upper extremity function. We anticipated that these criteria would exclude few potential participants.

Questionnaire Development

The details of the initial questionnaire development are reported elsewhere [1, 16]. Briefly, the questionnaire included comorbidities which were reported to be frequent in the general or MS populations, or were frequently included in existing, validated comorbidity measures [8, 9, 17–20] (Appendix I, Questionnaire). We did not attempt to include all possible comorbidities, and we specifically excluded stroke. In young persons with MS, stroke may be an incorrect diagnosis that precedes the MS diagnosis; in older individuals with MS, this could also be a misdiagnosis, and the information from our questionnaire alone would not be adequate to make a distinction. Further, stroke typically affects persons over age 65; the prevalence in persons aged 25–59 years is only about 0.8% [21]. Although sleep disorders may be more common in MS than in the general population [22, 23], we were uncertain whether we could accurately differentiate sleep disturbances secondary to MS from unrelated sleep disorders and opted to pursue this in subsequent studies. Participants were asked: 'Has a doctor ever told you that you have …?' [9]. For each comorbidity, participants reported the presence or absence of the condition, the year of diagnosis, and whether it was being treated currently.

Initial pilot testing of the questionnaire by 17 patients with MS followed at the Mellen Center showed that the questionnaire was easy to understand, and that the mean time for completion was 11 min (range 6–20) [1]. Following pilot testing we added epilepsy, migraine and osteoporosis to the list of comorbidities queried.

Study Procedures

Each participant completed the self-administered questionnaire querying comorbidities, and provided information regarding ethnicity, education level, and disability status, as measured using Patient Determined Disease Steps (PDDS). PDDS is a self-report measure which correlates highly with the physician-scored Expanded Disability Status Scale, and is scored ordinally from 0 (no disability) to 8 (bedbound) [24].

Following training by the senior investigator (R.A.M.), four abstractors reviewed the medical record using a standardized form which captured the year of MS symptom onset, the year of MS diagnosis, the clinical course, the presence of each comorbidity of interest, and current treatment status of that comorbidity. If a diagnosis was not noted in the record but a disease-specific medication (e.g. insulin) was noted, the comorbidity was recorded as absent but treatment was recorded as present. Medications which were not disease-specific were not recorded unless the medical record clearly indicated which condition was being treated with that medication. The senior investigator conducted random audits of the charts being reviewed to ensure ongoing consistency of data collection.

Statistical Analysis

Categorical variables were reported as frequency (percent). Continuous variables were reported as mean (standard deviation) or median (interquartile range) as appropriate. For each data source we calculated the frequency of the comorbidities, as well as the frequency of any physical comorbidity, or any mental comorbidity. We calculated sensitivity, specificity, positive and negative predictive value of each comorbidity queried on the questionnaire when compared to the medical record as the gold standard. To measure agreement wherein neither data source was considered the gold standard, we calculated kappa statistics in two ways. First, we compared self-reported comorbidities with those documented in the medical record. Second, we compared self-reported comorbidities with the presence of a documented comorbidity, or a disease-specific medication, or both. Kappas of 0–0.20 indicated slight, 0.21–0.40 indicated fair, 0.41–0.60 indicated moderate, 0.61–0.80 indicated substantial, and 0.81–1.0 indicated almost perfect agreement [25]. We do not report kappas for conditions with a frequency of less than 4% in the study population due to potential instability of the estimates related to small cell sizes.

For those comorbidities where kappa was ≥ 0.41 (moderate or better agreement), we examined whether sex, ethnicity, age, education level, disability status, or enrollment site affected agreement between our data sources using stratified analyses. Given the small number of non-White participants, we classified ethnicity as White or non-White. Age was dichotomized at the median. Similarly, education level was dichotomized at or below high school graduate level versus beyond high school graduate level. Disability status was dichotomized as PDDS score ≤ 3 (mild disability) versus PDDS ≥ 4 (moderate or severe disability).

We estimated that a sample size of 400 would be adequate to detect a kappa of ≥ 0.60 (substantial agreement) for comorbidities with a prevalence of 5% or more if the null hypothesis is $\kappa = 0.40$ (moderate agreement), $\alpha = 0.05$, and $\beta = 0.80$ [26]. Statistical analysis was performed using SPSS 12.0 and SAS V9.2.

Table 1. Demographic and clinical characteristics of study participants

Variable	Total population (n = 404)	Winnipeg (n = 336)	Cleveland (n = 68)	p value
Sex, n (%)				
Female	307 (76.0)	256 (76.4)	51 (75.0)	0.80
Male	97 (24.0)	79 (23.6)	17 (25.0)	
Race, n (%)				
White	370 (92.0)	311 (93.4)	58 (85.3)	0.02
Non-White	32 (8.0)	22 (6.6)	10 (14.7)	
Education, n (%)				
≤High school	147 (36.6)	122 (36.5)	24 (35.8)	0.91
>High school	255 (63.4)	212 (63.5)	43 (64.2)	
Mean age, years (SD)	46.5 (11.8)	47.0 (11.9)	44.4 (10.4)	0.13
Mean age of onset, years (SD)	32.2 (9.9)	32.6 (9.9)	30.5 (9.9)	0.13
Mean disease duration, years (SD)	13.9 (10.1)	13.9 (10.4)	14.1 (8.7)	0.44
PDDS, median (IQR)	1.0 (0–4)	1.0 (0–4)	2.0 (0–5)	0.44
Clinical course, n (%)				
CIS	10 (2.5)	10 (3.0)	0	<0.0001
RRMS	286 (70.8)	232 (69.0)	54 (79.4)	
SPMS	65 (16.1)	58 (17.3)	7 (10.3)	
PPMS	31 (7.7)	23 (6.8)	5 (7.3)	
Unknown	12 (3.0)	13 (3.9)	0	

IQR = Interquartile range; CIS = clinically isolated syndrome; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS; PPMS = primary progressive MS.

Results

Between October 2008 and October 2009, we enrolled 336 participants from Winnipeg and 68 participants from Cleveland (total n = 404). Most participants were Caucasian, female, and mildly disabled, with an average (SD) age of 46.5 (11.8) years (table 1). Generally, participants from the two sites were similar with respect to demographic and clinical characteristics (table 1). A greater percentage of participants from Cleveland were non-Caucasian, and none of the participants from Cleveland were classified as having a clinically isolated syndrome whereas the Winnipeg cohort enrolled 10 participants with this clinical course. The characteristics of the entire study population were similar to the characteristics of the general MS patient population in North America [27, 28].

Using the questionnaire, 140 (34.7%) participants reported no physical comorbidities, while 116 (28.7%) reported one, 65 (16.1%) reported two, and 83 (20.5%) reported three or more. One third of participants (n = 125) reported having one or more mental comorbidities. The most frequent comorbidities reported were depression (27.4%), hypertension (18.8%), migraines (18.0%), hyperlipidemia (14.9%), and vitamin B_{12} deficiency (12.0%) (table 2).

Based on medical records data, including documentation of a diagnosis or disease-specific treatment, 175 (43.3%) participants had no physical comorbidities, while 103 (25.5%) had one, 76 (18.8%) had two, and 50 (12.4%) had three or more. The most frequent comorbidities were depression (31.7%), hypertension (18.8%), hyperlipidemia (15.6%), migraines (13.6%), and autoimmune thyroid disease (9.4%). With few exceptions, the frequency of comorbidities was higher based on the questionnaire than on medical records review. Based on medical records diagnoses alone, liver and thyroid disease were identified more often by records review than questionnaire. Based on medical records diagnoses and treatments, depression, hyperlipidemia, peptic ulcer disease, liver and thyroid diseases were identified more often by records review than questionnaire.

Agreement, as measured by kappa, was similar when we compared the questionnaire data to medical records documentation of comorbidities, and when we compared the questionnaire data to medical records documentation

Table 2. Comparison of comorbidity frequency between self-report questionnaire and medical records review

Comorbidity	Questionnaire	Medical record		Medical record as gold standard					
	diagnosis n (%)	diagnosis n (%)	diagnosis or treatment n (%)	sensitivity	specificity	PPV	NPV	κ	95% CI
Depression	110 (27.4)	118 (29.3)	128 (31.7)	0.62	0.87	0.65	0.84	0.52	0.43, 0.61
Hypertension	76 (18.8)	69 (17.1)	76 (18.8)	0.86	0.95	0.78	0.97	0.82	0.75, 0.89
Migraine	72 (18.0)	53 (13.1)	55 (13.6)	0.70	0.90	0.51	0.95	0.54	0.43, 0.66
Hyperlipidemia	60 (14.9)	55 (13.6)	63 (15.6)	0.86	0.96	0.78	0.98	0.80	0.72, 0.88
Vitamin B_{12} deficiency	48 (12.0)	9 (2.2)	–[a]	0.44	0.89	0.08	0.99	–	–
Lung disease	41 (10.2)	31 (7.7)	32 (7.9)	0.77	0.95	0.58	0.98	0.62	0.49, 0.76
Anxiety	40 (10.0)	33 (8.2)	36 (8.9)	0.53	0.94	0.42	0.96	0.43	0.28, 0.57
Irritable bowel syndrome	38 (9.4)	24 (5.9)	24 (5.9)	0.75	0.95	0.47	0.98	0.55	0.39, 0.70
Anemia	29 (7.2)	10 (2.5)	14 (3.5)	0.40	0.94	0.14	0.98	0.19	0.02, 0.36
Thyroid	26 (6.5)	38 (9.4)	38 (9.4)	0.68	0.99	0.96	0.97	0.78	0.66, 0.89
Arthritis	25 (6.2)	12 (3.0)	12 (3.0)	0.58	0.95	0.28	0.99	0.35	0.15, 0.55
Cataracts	24 (6.0)	3 (0.74)	3 (0.74)	1.0	0.95	0.12	1.0	0.21	0.01, 0.41
Osteoporosis	22 (5.5)	13 (3.2)	16 (4.0)	0.77	0.97	0.46	0.99	0.56	0.37, 0.75
Heart disease	17 (4.2)	11 (2.7)	13 (3.2)	0.64	0.97	0.41	0.99	0.52	0.29, 0.74
Diabetes	17 (4.2)	17 (4.2)	17 (4.2)	0.88	0.99	0.88	0.99	0.88	0.76, 1.0
Skin cancer	14 (3.5)	3 (0.74)	3 (0.74)	0.33	0.97	0.07	0.99	–	–
Peptic ulcer disease	9 (2.2)	9 (2.2)	10 (2.5)	0.22	0.98	0.22	0.98	–	–
Epilepsy	8 (2.0)	7 (1.7)	7 (1.7)	0.57	0.99	0.50	0.99	–	–
Rheumatoid arthritis	8 (2.0)	2 (0.50)	2 (0.5)	1.0	0.98	0.25	1.0	–	–
Glaucoma	8 (2.0)	5 (1.2)	5 (1.2)	1.0	0.99	0.62	1.0	–	–
Bipolar disorder	7 (1.7)	3 (0.74)	3 (0.75)	1.0	0.99	0.29	1.0	–	–
Fibromyalgia	7 (1.7)	5 (1.2)	5 (1.2)	0.80	0.99	0.57	0.99	–	–
Uveitis	6 (1.5)	6 (1.5)	6 (1.5)	0.33	0.99	0.33	0.99	–	–
Knee replacement	6 (1.5)	4 (0.99)	4 (0.99)	0.75	0.99	0.50	0.99	–	–
Liver disease	5 (1.2)	7 (1.7)	7 (1.7)	0.43	0.99	0.60	0.99	–	–
Peripheral vascular disease	3 (0.74)	0	0					–	–
Kidney disease	3 (0.74)	7 (1.7)	7 (1.7)	0.14	0.99	0.33	0.98	–	–
Breast cancer	3 (0.74)	3 (0.74)	3 (0.74)	1.0	1.0	1.0	1.0	–	–
Schizophrenia	3 (0.75)	1 (0.25)	1 (0.25)	1.0	0.99	0.33	1.0	–	–
Systemic lupus erythematosus	2 (0.50)	2 (0.50)	2 (0.5)	0.50	0.99	0.50	0.99	–	–
Lung cancer	2 (0.50)	2 (0.50)	2 (0.5)	1.0	1.0	1.0	1.0	–	–
Inflammatory bowel disease	2 (0.50)	2 (0.50)	2 (0.5)	0.50	0.99	0.50	0.99	–	–
Hip replacement	2 (0.50)	2 (0.50)	2 (0.5)	0.50	0.99	0.5	0.99	–	–
Rectal cancer	0	0	0	–	–	–	–	–	–
Colon cancer	0	0	0	–	–	–	–	–	–
Sjögren's syndrome	0	0	0	–	–	–	–	–	–

PPV = Positive predictive value; NPV = negative predictive value.

[a] Due to frequent use of vitamin B_{12} supplementation in this population in the absence of confirmed vitamin B_{12} deficiency we did not consider recording of vitamin B_{12} use to indicate vitamin B_{12} deficiency in the absence of a physician-documented diagnosis.

of comorbidities or treatments; therefore, we report only the results of the latter analyses. Agreement (κ) was greater than 0.82 for diabetes and hypertension, and ranged from 0.62 to 0.80 for hyperlipidemia, thyroid disease, and lung disease; from 0.43 to 0.56 for osteoporosis, irritable bowel syndrome, migraine, depression, heart disease, and anxiety disorders (table 2). Agreement was slight to fair for arthritis, cataracts, anemia, and vitamin B_{12} deficiency.

Some of the conditions of interest, chiefly cancers, autoimmune disorders, liver and renal diseases, occurred too infrequently in our patient population for any meaningful interpretation regarding agreement. Although caution is warranted given the small number

Table 3. Stratified analyses showing the influence of demographic and clinical characteristics on the level of agreement (κ) between questionnaire and medical records for comorbidities

Characteristic	Depression		Hypertension		Migraine		Hyperlipidemia		Lung disease	
	κ	95% CI	κ	95% CI	κ	95% CI	κ	95% CI	κ	9% CI
Sex										
Female	0.52	0.42, 0.62	0.86	0.78, 0.94	0.53	0.41, 0.65	0.81	0.71, 0.91	0.55	0.38, 0.72
Male	0.49	0.28, 0.70	0.73	0.57, 0.89	0.52	0.15, 0.89	0.77	0.62, 0.92	0.80	0.60, 0.98
Race										
White	0.52	0.43, 0.62	0.83	0.75, 0.90	0.56	0.44, 0.67	0.80	0.72, 0.89	0.59	0.44, 0.74
Non-White	0.45	0.09, 0.82	0.63	0.16, 1.0	0.43	– 0.03, 0.88	0.71	0.34, 1.0	0.87	0.62, 1.0
Age										
<47 years	0.56	0.44, 0.69	0.77	0.60, 0.93	0.55	0.40, 0.70	0.82	0.65, 0.99	0.74	0.57, 0.91
≥47 years	0.48	0.35, 0.61	0.82	0.74, 0.91	0.53	0.37, 0.70	0.77	0.67, 0.88	0.52	0.32, 0.72
Education										
≤High school	0.51	0.36, 0.66	0.87	0.77, 0.96	0.32	0.07, 0.54	0.70	0.54, 0.86	0.85	0.71, 0.99
>High school	0.53	0.41, 0.64	0.78	0.68, 0.89	0.63	0.50, 0.75	0.85	0.76, 0.95	0.47	0.28, 0.66
Course										
RR/CIS[a]	0.55	0.44, 0.65	0.79	0.70, 0.88	0.54	0.42, 0.66	0.79	0.68, 0.89	0.66	0.51, 0.81
SP/PP[b]	0.47	0.27, 0.67	0.87	0.75, 0.98	0.52	0.15, 0.89	0.82	0.68, 0.96	0.64	0.35, 0.93
Disability										
Mild	0.55	0.43, 0.67	0.85	0.75, 0.94	0.57	0.43, 0.71	0.81	0.69, 0.93	0.66	0.47, 0.85
Moderate/severe	0.48	0.35, 0.62	0.80	0.69, 0.90	0.49	0.30, 0.68	0.79	0.67, 0.90	0.59	0.40, 0.78
Center										
Winnipeg	0.54	0.44, 0.64	0.83	0.75, 0.91	0.57	0.45, 0.70	0.80	0.70, 0.89	0.61	0.46, 0.76
Cleveland	0.41	0.19, 0.63	0.77	0.60, 0.94	0.39	0.12, 0.66	0.79	0.62, 0.97	0.70	0.39, 1.0

Characteristic	Anxiety		IBS		Thyroid		Osteoporosis		Heart disease		Diabetes	
	κ	95% CI	κ	95% CI	κ	95% CI	κ	95% CI	κ	95% CI	κ	95% CI
Sex												
Female	0.40	0.24, 0.57	0.56	0.40, 0.72	0.76	0.64, 0.89	0.56	0.36, 0.77	0.53	0.27, 0.78	0.85	0.71, 0.99
Male	0.52	0.15, 0.88	0.39	–0.15, 0.98	1.0	–	0.49	–0.11, 1.0	0.48	0.05, 0.91	1.0	1.0, 1.0
Race												
White	0.47	0.32, 0.62	0.52	0.36, 0.69	0.78	0.66, 0.90	0.57	0.38, 0.77	0.58	0.35, 0.80	0.85	0.71, 0.99
Non-White	–0.09	–0.18, 0	0.72	0.35, 1.0	0.65	0.02, 1.0	–		–		1.0	1.0, 1.0
Age												
<47 years	0.44	0.24, 0.63	0.62	0.41, 0.82	0.74	0.49, 0.98	0.32	–0.17, 0.81	0.35	–0.02, 0.71	0.79	0.52, 1.0
≥47 years	0.41	0.18, 0.64	0.48	0.26, 0.70	0.78	0.65, 0.92	0.20	0.01, 0.40	0.59	0.38, 0.80	0.91	0.79, 1.0
Education												
≤High school	0.39	0.13, 0.65	0.52	0.28, 0.77	0.61	0.32, 0.89	0.65	0.36, 0.94	0.38	0.0, 0.77	0.65	0.33, 0.97
>High school	0.44	0.26, 0.62	0.56	0.37, 0.76	0.84	0.72, 0.95	0.50	0.24, 0.75	0.58	0.32, 0.84	1.0	1.0, 1.0
Course												
RR/CIS	0.36	0.19, 0.53	0.52	0.35, 0.70	0.80	0.67, 0.94	0.54	0.18, 0.90	0.40	0.12, 0.69	0.91	0.79, 1.0
SP/PP	0.75	0.48, 1.0	0.64	0.32, 0.97	0.81	0.60, 1.0	0.46	0.19, 0.73	0.74	0.40, 1.0	0.85	0.56, 1.0
Disability												
Mild	0.38	0.19, 0.58	0.54	0.32, 0.77	0.82	0.66, 0.97	0.53	0.17, 0.90	0.38	0.06, 0.70	0.91	0.73, 1.0
Moderate/severe	0.49	0.26, 0.72	0.55	0.34, 0.76	0.74	0.57, 0.91	0.56	0.33, 0.79	0.65	0.37, 0.94	0.86	0.70, 1.0
Center												
Winnipeg	0.52	0.36, 0.68	0.53	0.37, 0.70	0.82	0.70, 0.93	0.48	0.25, 0.71	0.56	0.30, 0.82	0.88	0.74, 1.0
Cleveland	0.03	–0.22, 0.28	0.65	0.21, 1.0	0.57	0.21, 0.94	0.79	0.50, 1.0	0.41	0.0, 0.83	0.88	0.65, 1.0

IBS = Irritable bowel syndrome; RR = relapsing-remitting; CIS = clinically isolated syndrome; SP = secondary progressive; PP = primary progressive.

of participants, our findings suggest that agreement is also adequate for epilepsy [κ = 0.52; 95% confidence interval (CI): 0.21, 0.83], glaucoma (κ = 0.77; 95% CI: 0.51, 1.0), and fibromyalgia (κ = 0.66; 95% CI: 0.35, 0.97). While only 2 participants were identified with a history of lung cancer and 3 participants with a history of breast cancer, the comparison of questionnaire responses to medical record documentation resulted in positive predictive values and negative predictive values for these conditions equal to 1.0. Agreement regarding the presence of any physical comorbidity was 0.56 (95% CI: 0.48–0.64), and for any mental comorbidity was 0.57 (95% CI: 0.48–0.65).

Sex, ethnicity, age, and disability status were not associated with the level of agreement between the two data sources. Education level was associated with a difference in agreement for lung disease, in which an education above high school level was associated with lower agreement values for this condition (table 3). This should be interpreted with caution because only 12 (5.7%) participants with a higher level of education reported lung disease. Except for anxiety disorders, agreement was similar at both sites. In Cleveland, there was no agreement between self-reported anxiety disorders and medical records diagnoses, but this finding should be interpreted with caution because only 9 patients reported an anxiety disorder.

Discussion

Although a growing literature describes the frequency and impact of comorbidity in MS [2, 29, 30], research regarding methods of comorbidity measurement in this population is lacking. Our findings indicate moderate or better levels of agreement between self-report and medical records for diabetes, hypertension, hyperlipidemia, thyroid disease, chronic lung disease, osteoporosis, irritable bowel syndrome, migraine, heart disease, depression, and anxiety disorders.

Our findings are consistent with research in other populations which suggested that diseases which are well defined, severe, and require ongoing care are accurately reported [31, 32]. As expected, agreement was weaker for less clearly defined conditions such as arthritis [32, 33]. Agreement was poor for skin cancer and anemia, which were captured more frequently by self-report [7, 32]; self-report may be more effective than medical records in identifying conditions in which effective intervention or spontaneous improvement may occur [7, 32]. Agreement was also poor for vitamin B_{12} deficiency, possibly reflecting aggressive treatment of vitamin B_{12} deficiency in MS patients, or patient-directed use of complementary therapies [34]. Due to their low frequency in the study population we cannot truly comment about the accuracy of self-reported solid organ cancers, autoimmune, liver and kidney diseases, but the literature consistently suggests that cancers are accurately reported [32, 33], and we found perfect agreement for the 5 non-skin cancers reported in our population.

We examined whether participant characteristics influenced agreement between data sources for those comorbidities where overall agreement was high enough to be useful for clinical research. With one exception, demographic and clinical factors did not influence agreement between self-report and the medical record. Agreement was substantial for lung disease in participants with education levels at or below high school but was moderate in participants with higher education levels. Very few participants in this group had lung disease, however; potentially rendering estimates of kappa unstable, and this finding could also reflect error due to multiple comparisons. Some studies suggested that self-reported comorbidity data may be less accurate in individuals who are older, non-White, more disabled, or less educated, but not consistently [11, 32, 35, 36].

We used the medical record as the reference standard because researchers are usually interested in what conditions health providers think patients have. Nonetheless, we need to recognize that the medical record is not the true criterion standard for comorbidity measurement, and that it has limitations. First, quality of documentation can vary across sites of patient care, and conditions may be under-reported in medical records because they have not been brought to attention or because they have not been assessed as specific problems during the medical visit examined by the chart review. Second, medical records must be used over a sufficient period of time to ensure complete identification of comorbidities. Third, patients often have multiple providers making it difficult to gather all medical records.

This study had several limitations. Although we intended to include comorbidities which were frequent in the general or MS populations, we did not capture sleep disorders, which are increasingly recognized to be common in MS [22, 23]. Our participants only included patients from outpatient settings, but this is their usual source of care [37]. Study participants had mild to moderate disability, thus our findings may not apply to severely disabled patients. Further we did not assess the impact of

cognitive impairment, which affects 40–60% of persons with MS [38], on the validity of this questionnaire. Medical records review was limited to the documentation available at each MS clinic, including records from the hospitals in which the clinics were based, but did not include medical records from outside sources. This may underestimate the accuracy of self-reported conditions. Also, we may have underestimated the accuracy of self-report because we compared self-reported comorbidities with the presence of a disease-specific medication only when we were certain which condition was being treated with that medication. Due to their low frequency we could not assess the validity of the questionnaire for some conditions, such as cancer, but these had high negative predictive values; to evaluate conditions with frequency of 1% or less would require a sample size of more than 1,600 patients.

Nonetheless, this study has several strengths. Participant characteristics were similar to those of other MS populations, and the Winnipeg cohort represents approximately 20% of that clinic's population and more than 10% of the provincial MS population [39]. Few differences regarding agreement were identified when comparing the two study centers despite differences in the health care systems, including payor system, and the use of paper charts in Winnipeg and electronic medical records in Cleveland. This supports the validity of the questionnaire in a range of clinical settings.

Use of questionnaires to capture comorbidity has several potential advantages over other data sources. Questionnaires are less costly and resource-intensive than medical records review, particularly for large studies. They may be more sensitive at detecting comorbidities when individuals have multiple providers. Our study suggests that self-report is a reasonable way to capture the presence of several common comorbidities affecting patients with MS, and could be useful for clinicians and researchers. Future studies should compare the ability of this comorbidity questionnaire to predict mortality, disability, health care utilization, and quality of life relative to other sources of comorbidity data.

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Appendix

Comorbidity Questionnaire for MS

Has a doctor ever told you that you have any of the following conditions?

For each condition please mark 'No' or 'Yes'. If you do *not* have the problem, skip to the next problem. If you do have the problem, please write the *year* you were diagnosed in the second column. In the third column please indicate if you receive a medicine or some type of treatment for the problem.

Condition	No	Yes →	Year diagnosed →	Currently treated?	
				no	yes
High cholesterol (hyperlipidemia)	□	□		□	□
High blood pressure (hypertension)	□	□		□	□
Heart trouble (such as angina, congestive heart failure, or coronary artery disease)	□	□		□	□
Disease of arteries in the legs (peripheral vascular disease)	□	□		□	□
Lung trouble (asthma, emphysema, chronic bronchitis, or COPD)	□	□		□	□
Diabetes mellitus	□	□		□	□
Cancer of the breast	□	□		□	□
Cancer of the colon (large bowel)	□	□		□	□
Cancer of the rectum	□	□		□	□
Cancer of the lung	□	□		□	□
Skin cancer (specify type in this space)	□	□		□	□
Other cancers (specify type in this space)	□	□		□	□
Uveitis (inflammation of the eye)	□	□		□	□
Glaucoma	□	□		□	□
Cataracts	□	□		□	□
Migraine	□	□		□	□
Thyroid disease (such as Graves' disease, Hashimoto's thyroiditis; *not* thyroid cancer)	□	□		□	□
Vitamin B_{12} deficiency (pernicious anemia)	□	□		□	□
Lupus (systemic lupus erythematosus, SLE)	□	□		□	□
Sjögren's syndrome	□	□		□	□
Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	□	□		□	□
Rheumatoid arthritis	□	□		□	□
Degenerative arthritis (osteoarthritis)	□	□		□	□
Osteoporosis (bone disease causing thin bones – leading to fractures of the hip, wrist, and spine)	□	□		□	□
Hip replacement(s)	□	□		□	□
Knee replacement(s)	□	□		□	□
Fibromyalgia	□	□		□	□
Anemia or other blood disease	□	□		□	□
Kidney disease	□	□		□	□
Open sore or ulcer in the lining of the stomach, esophagus, duodenum (peptic ulcer disease)	□	□		□	□
Liver problems (such as cirrhosis)	□	□		□	□
Irritable bowel syndrome	□	□		□	□
Epilepsy (seizure disorder)	□	□		□	□
Depression	□	□		□	□
Anxiety disorder	□	□		□	□
Bipolar disorder (manic depression)	□	□		□	□
Schizophrenia	□	□		□	□

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