MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Low socioeconomic status was associated with a higher mortality risk in multiple sclerosis

Floriane Calocer, Huah Shin Ng, Feng Zhu, Yinshan Zhao, Olivier Dejardin, Emmanuelle Leray, Gilles Defer, Charity Evans, John D Fisk, Ruth Ann Marrie and Helen Tremlett

Multiple Sclerosis Journal

2023, Vol. 29(3) 466–470

DOI: 10.1177/13524585221129963

Abstract

Background: The relationship between socioeconomic status (SES) and mortality among persons with multiple sclerosis (PwMS) is poorly understood.

Objective: To investigate the association between SES and mortality risk in PwMS.

Methods: From health-administrative data, we identified 12,126 incident MS cases with a first demyelinating event (MS 'onset') occurring between 1994 and 2017. Cox proportional hazard model assessed the association between socioeconomic status quintiles (SES-Qs) at MS onset and all-cause mortality.

Results: Lower SES-Qs were associated with higher mortality risk; adjusted hazard ratios: SES-Q1 (most deprived) = 1.61 (95% confidence interval (CI) = 1.36–1.91); SES-Q2 = 1.26 (95% CI = 1.05–1.50); SES-Q3 = 1.22 (95% CI = 1.02–1.46); SES-Q4 = 1.13 (95% CI = 0.94–1.35) versus SES-Q5 (least deprived).

Conclusion: A lower SES was associated with higher mortality risk in PwMS.

Keywords: Multiple sclerosis, socioeconomic disparities, socioeconomic status, mortality risk, population-based study

Date received: 4 February 2022; revised: 13 September 2022; accepted: 14 September 2022

Correspondence to:
H Tremlett
Department of Medicine, Division of Neurology and the Djavad Mowafaghian Centre for Brain Health, University of British Columbia, UBC Hospital, Room S126, 2211 Wesbrook Mall, Vancouver, BC V6T 2B5, Canada.
helen.tremlett@ubc.ca

Floriane Calocer
Huah Shin Ng
Feng Zhu
Yinshan Zhao
Department of Medicine, Division of Neurology and the Djavad Mowafaghian Centre for Brain Health, University of British Columbia, UBC Hospital, Vancouver, BC, Canada

Olivier Dejardin
UNICAEN, CHU de Caen, INSERM U1086 ANTICIPE, Pôle de Recherche, Normandie University, Caen, France

Emmanuelle Leray
EHESP Rennes, Sorbonne Paris Cité, Rennes, France; CIC-P 1414, CHU Rennes, West Neuroscience Network of Excellence (WENNE), Rennes, France

Gilles Defer
UNICAEN, CHU de Caen Normandie Department of Neurology, MS Expert Center, Normandie University, Caen, France; Réseau Bas-Normand Pour la Prise en Charge de la SEP, Caen, France

Charity Evans
College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

John D Fisk
Nova Scotia Health Authority and the Departments of Psychiatry, Psychology and Neuroscience, and Medicine,

Introduction

Socioeconomic disparities have been associated with disability acquisition in persons with MS (PwMS),[1] and possibly with MS incidence.[2] While a lower socioeconomic status (SES) is associated with higher mortality rates in the general and chronic diseased populations,[3] little is known about this relationship in PwMS, despite their higher mortality risk. We examined the relationship between SES and mortality risk in PwMS.

Methods

In this retrospective cohort study, we accessed prospectively collected linked health-administrative data in British Columbia (BC), Canada, including dates/information of all physician visits (from the Medical Services Plan),[4] hospital visits (from the Discharge Abstract Database),[5] death dates (from Vital Statistics),[6] registration dates in the provincial healthcare plan (from the Registration and Premium Billing files),[7] and all prescriptions filled at community/outpatient pharmacies (from PharmaNet)[8].

SES was obtained using Statistics Canada's algorithm, which uses each person's residential postal code combined with census-derived mean neighbourhood income.[1] All data were available from 1 January 1994, except prescription data (available from 1 January 1996).

Incident PwMS were identified using a validated algorithm,[9] requiring: ⩾3 hospital or physician-related MS diagnoses (the *International Statistical Classification of Diseases and Related Health Problems–Ninth Edition/Tenth Edition* (ICD-9/10)-CA codes 340/G35) or ⩾1 prescription filled for an MS disease-modifying treatment (DMT) (Supplemental Figure e-1). The index date was the earliest of the first MS or demyelinating diagnostic code in either the physician or hospital data or the first

Dalhousie University, Halifax, NS, Canada

Ruth Ann Marrie
Departments of Internal Medicine and Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Helen Tremlett
Department of Medicine, Division of Neurology and the Djavad Mowafaghian Centre for Brain Health, University of British Columbia, UBC Hospital, Vancouver, BC, Canada

MS-specific DMT prescription filled (1 January 1994/1996 onwards). Two years of residency in the province before the index date was required to identify incident cases. Cases were followed to the earliest of death, emigration from BC (the first discontinuation date in the registration files lasting >90 days) or 31 December 2017 (the study end). SES was captured at the index date (±3 years) and assessed as quintiles (ranging from least (SES-Q1) to most (SES-Q5) affluent).

Stratified Cox proportional hazard model was used to assess the association of the SES-Qs and all-cause mortality, with findings expressed as adjusted hazard ratios (aHRs) with 95%CIs. Initially, the model was adjusted for sex, and at the index date: age and calendar year (categorized as: 1994–1999, 2000–2005, 2006–2011, 2012–2017). Additional adjustments included the Charlson comorbidity index based on the physician and hospital data in the year pre-index date (excluding hemiplegia/paraplegia;[10,11] scores were categorized: 0, 1 or ⩾2) and any DMT prescription filled (ever: yes/no) during follow-up (as a time-dependent covariate).

Complementary analysis included restricting the cohort to either PwMS aged 18–65 years at the index date, or to PwMS with an index date from 1 January 1996 onwards (to coincide with the first available prescription data). Analyses were performed using SAS version 9.4 and STATA IC/SE 14. $p < 0.05$ was considered statistically significant.

Results

A total of 12,126 PwMS were included; 73% (8803) were women and 26% (3175) were DMT exposed (Table 1; Supplemental Table e-1 and Figure e-1); 46 people were excluded due to missing SES. At the index date, the median age was 44 years (interquartile range (IQR): 34–52 years), and 26% (3111) of participants had at least one comorbidity. Over the 10.8 years of follow-up (mean), 1324 (11%) died of whom 58% (769) were women.

The most deprived PwMS (SES-Q1) exhibited a lower survival compared to the least deprived PwMS (SES-Q5) (the initial analysis, Figure 1). Findings did not change substantially with additional adjustment for comorbidity and DMT use (Figure 1 and Supplemental Table e-2); each of the lower SES quintiles (SES-Q1 to SES-Q3) were associated with a higher hazard of mortality relative to the highest quintile (SES-Q5) in the adjusted models ($p < 0.05$). Relative to the highest, most affluent SES-Q5, the aHRs (which included the additional model adjustments) ranged from 1.61, 95% CI = 1.36–1.91 (SES-Q1) to 1.26, 95% CI = 1.05–1.50 (SES-Q2), 1.22, 95% CI = 1.02–1.46 (SES-Q3) and 1.13, 95% CI = 0.94–1.35 (SES-Q4).

The results from the complementary analyses were consistent with the main findings (Supplemental Table e-2).

Discussion

We found that a lower neighbourhood-level SES was associated with higher mortality risk in PwMS in a population-based study (where one in four were DMT exposed). For example, the lowest SES (most deprived; SES-Q1) was associated with a 61% higher mortality hazard compared to the highest SES (least deprived; SES-Q5). Furthermore, the all-cause mortality hazard exhibited a clear gradient across the SES quintiles.

While we were unable to find a directly comparable study, our results were broadly consistent with two studies examining mortality risk in PwMS in Canada, which also identified SES as an independent risk factor for mortality.[12,13] A complex network of factors may contribute to the association between SES and mortality risk. For example, lower SES may result in barriers to accessing timely or appropriate healthcare and treatment and has also been associated with a higher risk of chronic and severe comorbidity.[14]

Strengths of this study included access to a large population-based cohort comprising 12,126 PwMS with minimal missing data, and capture of SES close to the index date, minimizing selection or recall bias and reverse causation. Limitations included a lack of information regarding potential confounders in our health-administrative data, such as smoking, exercise or other lifestyle-related factors, as well as a lack of MS-specific clinical information. However, we were able to adjust for sex, age, the Charlson comorbidity index and DMT exposure. Furthermore, restricting the cohort to those aged 18–65 years or those with an index date after our prescription data were available did not change interpretation of results.

Table 1. Characteristics of the incident multiple sclerosis (MS) cohort in British Columbia, Canada (1994–2017), overall and grouped by vital status by the end of the follow-up.

	Alive (*N* = 10,802)	Deceased (*N* = 1324)	Total (*N* = 12 126)
Sex, *n* (%)			
Men	2768 (25.6)	555 (41.9)	3323 (27.4)
Women	8034 (74.4)	769 (58.1)	8803 (72.6)
Age at index date, median (Q25%–Q75%)	41.6 (16.8)	58.8 (22.3)	43.0 (18.0)
Calendar year at index date, *n* (%)			
1994–1999	2657 (24.6)	595 (44.9)	3252 (26.8)
2000–2005	2829 (26.2)	406 (30.7)	3235 (26.7)
2006–2011	2819 (26.1)	245 (18.5)	3064 (25.3)
2012–2017	2497 (23.1)	78 (5.9)	2575 (21.2)
Time of follow-up from the index date, mean (SD)	11.0 (6.7)	8.6 (6.0)	10.8 (6.7)
Charlson comorbidity index,* *n* (%)			
0	8275 (76.6)	740 (55.9)	9015 (74.3)
1	1803 (16.7)	309 (23.3)	2112 (17.4)
⩾2	724 (6.7)	275 (20.8)	999 (8.2)
DMT exposure, *n* (%)			
Never treated	7760 (71.8)	1191 (90.0)	8951 (73.8)
Ever treated	3042 (28.2)	133 (10.0)	3175 (26.2)
SES quintiles, *n* (%)			
1 Lowest (most deprived)	1921 (17.8)	311 (23.5)	2232 (18.4)
2	2082 (19.3)	257 (19.4)	2339 (19.3)
3	2276 (21.1)	264 (19.9)	2540 (20.9)
4	2371 (21.9)	262 (19.8)	2633 (21.7)
5 Highest (least deprived)	2152 (19.9)	230 (17.4)	2382 (19.6)

N/n: frequencies; SD: standard deviation; SES: socioeconomic status; DMT: disease-modifying treatment; Q25%–Q75%: first and third quartiles.
Additional information is shown in Supplemental Table e-1, including select cohort characteristics grouped by SES-Q.
For those ever treated, their first DMT prescription filled were as follows (*n* = number of participants): beta-interferon (*n* = 1935), glatiramer acetate (*n* = 844), natalizumab (*n* = 44), fingolimod (*n* = 14), dimethyl fumarate (*n* = 247), teriflunomide (*n* = 153), alemtuzumab (*n* = 27) and daclizumab (*n* < 6). DMT exposure rates are comparable to (the few) other population-based studies conducted within a universal healthcare setting (see Supplemental Material for the relevant e-references and summary of this topic discussed in detail elsewhere: Ng HS et al. Characteristics of a population-based multiple sclerosis cohort treated with disease-modifying drugs in a universal healthcare setting. *Expert Rev Neurother* 2021 Jan; 21(1): 131–140. DOI: 10.1080/14737175.2021.1847085. Epub 2020 Dec 9. PMID: 33146570). This prior work also drew from the same source population and same universal healthcare setting, and used the same marker of SES as in this study; it found that the number of MS cases were evenly distributed across SES quintiles regardless of whether they were, or were not, treated with a DMT during follow-up.
*Modified to exclude hemiplegia/paraplegia.[10,11]
Of those who died, the age at death, median (Q25%–Q75%) = 67.6 (21.5) years.

While were able to access neighbourhood level SES, it would be valuable for future studies to access individual-level income or other markers of SES such as education attainment, occupation/employment status or composite indicators of socioeconomic deprivation.

Further studies are also required to better understand the influence of socioeconomic disparities on survival in PwMS, including, for example, the evolution of this relationship at different disease and disability-related stages,[1] or whether the effects are mediated by differences in health behaviours, effects of adversity, access to care or other unknown factors, and as different comorbidities accrue overtime, and across the different DMTs and racial/ethnic groups.

The present findings illustrate the importance of SES for PwMS and demonstrate its potential to alter important outcomes, such as mortality risk. Our findings suggest that efforts to improve economic stability, education, employment, social protection and the neighbourhood/built environment[15] for the most disadvantaged could improve survival.

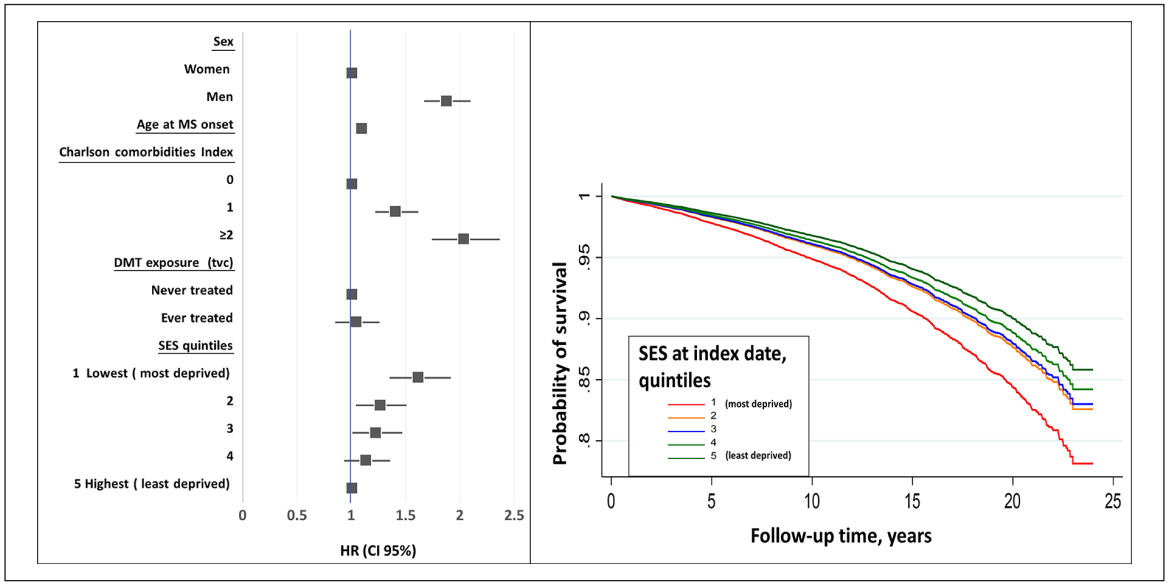

Figure 1. The association between socioeconomic status (SES) and mortality in the multiple sclerosis cohort, depicted Kaplan–Meier curves (left) obtained from a multivariate Cox proportional model,[a] and a forest plot (right) which also shows the additional model adjustments.[a,b]

[a]Adjusted for sex, and at the index date: age and categorized as four groups: 1994–1999, 2000–2005, 2006–2011 and 2012–2017.

[b]Additional adjustments: the Charlson comorbidity index based on the physician and hospital data in the year pre-index date (modified to exclude hemiplegia/paraplegia[10,11]), categorized as: 0, 1 or ⩾2 and any DMT prescription filled (ever: yes/no) during follow-up as a time-varying covariate (TVC).

Acknowledgements

Access to and use of British Columbia (BC) data were facilitated by Population Data BC, and approved by the BC Ministry of Health, BC PharmaNet and the BC Vital Statistics Agency. All inferences, opinions and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the British Columbia Data Stewards.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: F.C. received funding from the ARSEP foundation for a Postdoctoral Fellowship which supported this research. During the past years, received a fellowship from the 'Réseau Bas-Normand pour la SEP' and from the Regional Council of Normandy and a travel grant from ECTRIMS Scientific Programme Committee and from ARSEP foundation for MS Research for presenting works. H.S.N. received funding from the MS Society of Canada's endMS Postdoctoral Fellowship, and the Michael Smith Foundation for Health Research Trainee Award. G.D. received personal compensation for scientific advisory boards and funding for travel and/or speaker honoraria from Biogen, BMS, Merck Serono, Novartis, Sanofi Genzyme and Teva Pharmaceuticals; institutional research grants from Biogen, Merck Serono, Novartis and Sanofi Genzyme. C.E. received research funding from CIHR. J.D.F. received research funding from CIHR, the MS Society of Canada, Crohn's and Colitis Canada, Research Nova Scotia, and consultation and distribution royalties from MAPI Research Trust. R.A.M. receives research funding from: CIHR, Research Manitoba, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, CMSC and US Department of Defense. She is supported by the Waugh Family Chair in Multiple Sclerosis. She is a co-investigator on studies funded by Roche and Biogen Idec. H.T. is the Canada Research Chair for Neuroepidemiology and Multiple Sclerosis. Current research support received from the National Multiple Sclerosis Society, the Canadian Institutes of Health Research, the Multiple Sclerosis Society of Canada and the Multiple Sclerosis Scientific Research Foundation. In addition, in the last 5 years, he has received research support from the UK MS Trust; travel expenses to present at CME conferences from the Consortium of MS Centres (2018), the National MS Society (2016, 2018), ECTRIMS/ACTRIMS (2015, 2016, 2017, 2018, 2019, 2020) and American Academy of Neurology (2015, 2016, 2019). Speaker honoraria are either declined or donated to an MS charity or to an unrestricted grant for use by

H.T.'s research group. F.Z., Y.Z., O.D. and E.L. have no conflicts of interests relevant to this study.

Ethical Approval

This study was approved by the University of British Columbia's Clinical Research Ethics Board (#H18-00407).

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported by the Canadian Institutes of Health Research (CIHR) Project and Foundation grant (PJT-156363 and FDN-159934, PI: H.T.) and the Fondation ARSEP (post-doctoral fellowship awarded to Calocer).

ORCID iDs

Floriane Calocer https://orcid.org/0000-0001-6021-7197
Huah Shin Ng https://orcid.org/0000-0001-8381-5253
Ruth Ann Marrie https://orcid.org/0000-0002-1855-5595
Helen Tremlett https://orcid.org/0000-0001-5804-2535

Data Availability

The data used for this study were accessed through Population Data BC (popdata.bc.ca) and resided on a limited access secure research environment. For legal and ethical reasons, the data cannot leave this secure research environment.

Supplemental Material

Supplemental material for this article is available online.

References

1. Harding KE, Wardle M, Carruthers R, et al. Socioeconomic status and disability progression in multiple sclerosis: A multinational study. *Neurology* 2019; 92(13): e1497–e1506.
2. Goulden R, Ibrahim T and Wolfson C. Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review. *Eur J Neurol* 2015; 22(6): 899–911.
3. Stringhini S, Carmeli C, Jokela M, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: A multicohort study and meta-analysis of 1·7 million men and women. *Lancet* 2017; 389(10075): 1229–1237.
4. British Columbia Ministry of Health. Medical services plan (MSP) payment information file (V2, Data Extract, MOH). Population Data BC, 2017, http://www.popdata.bc.ca/data
5. Canadian Institute for Health Information. *Discharge abstract database* (Hospital Separations, V2, Data Extract, MOH). Population Data BC, 2017, http://www.popdata.bc.ca/data
6. BC Vital Statistics Agency. *Vital statistics deaths* (V2, Data Extract, BC Vital Statistics Agency). Population Data BC, 2017, http://www.popdata.bc.ca/data
7. British Columbia Ministry of Health. *Consolidation file* (MSP Registration & Premium Billing, V2, Data Extract, MOH). Population Data BC, 2017, http://www.popdata.bc.ca/data
8. British Columbia Ministry of Health. *PharmaNet* (V2, Data Extract, Data Stewardship Committee). British Columbia Ministry of Health, 2017, http://www.popdata.bc.ca/data
9. Wijnands JMA, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and infection risk: A cohort study. *J Neurol Neurosurg Psychiatry* 2018; 89(10): 1050–1056.
10. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43(11): 1130–1139.
11. Marrie RA, Bernstein CN, Peschken CA, et al. Intensive care unit admission in multiple sclerosis. *Neurology* 2014; 82(23): 2112–2119.
12. Rotstein D, Maxwell C, Tu K, et al. Risk of mortality in immigrants with multiple sclerosis in Ontario, Canada. *Neuroepidemiology* 2020; 54(2): 148–156.
13. Marrie RA, Elliott L, Marriott J, et al. Effect of comorbidity on mortality in multiple sclerosis. *Neurology* 2015; 85(3): 240–247.
14. Marrie R, Horwitz R, Cutter G, et al. Comorbidity, socioeconomic status and multiple sclerosis. *Mult Scler* 2008; 14(8): 1091–1098.
15. Saunders M, Barr B, McHale P, et al. *Key policies for addressing the social determinants of health and health inequities*. Health Evidence Network (HEN) synthesis report 52, 2017. Copenhagen: WHO Regional Office for Europe, https://www.euro.who.int/__data/assets/pdf_file/0009/345798/HEN52.pdf