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Mortality of multiple sclerosis in Iceland population-based mortality of MS in incidence and prevalence cohorts

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Abstract

Introduction: Mortality is an important feature of the natural history of multiple sclerosis (MS). We report the mortality of all individuals with MS in Iceland, identified in a nationwide population-based study.

Patients and Methods: The results are based on a prevalence cohort and an incidence cohort. The prevalence cohort consisted of all patients with MS (n = 526) living in Iceland on the 31 December 2007. The incidence cohort consisted of all residents of Iceland (n = 222) diagnosed with MS during 2002 to 2007. Mortality was determined by following both the incidence cohort (from diagnosis) and the prevalence cohort (from the prevalence day) until death or 31 December 2020. The mortality, associated with MS, was compared with that expected in the Icelandic population (*standardized mortality ratio* (SMR)).

Results: (a) Prevalence cohort (n = 526). The mean follow up was 12.0 years (range 0.3–13.0). The SMR was 1.6 (95% confidence interval (CI) 1.3–2.0). (b) Incidence cohort (n = 222). The mean follow up was 15.4 years (range 3.7–18.5). The SMR was 1.2 (95% CI 0.6–2.2).

Conclusion: During the follow-up period, there was a substantial increase in mortality among the patients with MS, compared with the general population. There was no increase in mortality among the incidence cohort, when followed for up to 18.5 years following diagnosis.

Keywords: Multiple sclerosis, epidemiology, mortality, standardized mortality ratio, survival

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Introduction

Multiple sclerosis (MS) is caused by an autoimmune-mediated inflammation in the central nervous system[1] and is the most common cause of nontraumatic neurological disability among young adults in Western countries.[2]

Mortality, together with the number of relapses and progression of disability,[3,4] are the three main clinical measures of the natural history of MS. Mortality is an unambiguous epidemiological parameter and very useful for global comparisons[5] of disease severity. Several studies have found an increase in mortality among individuals with MS and a recent meta-analysis reported increased all-cause mortality, among individuals with MS; standardized mortality ratio (SMR) 2.8 (95% confidence interval (CI) 2.7 to 2.9).[6] However the mortality of MS varies between different geographical regions and different time periods.[7,8]

Several studies have described the epidemiology of MS in Iceland,[9,12] but the mortality of individuals with MS, has not been previously reported. Iceland had a mean population of 296,835 during the period from 2002 through 2007.

We report the mortality in a population-based prevalence and incidence cohort of MS in Iceland.

Patients and methods

Inclusion criteria are identical for both the prevalence and incidence groups and all participants in this study are subjects of previously published incidence[9] and prevalence studies.[10] We used the 2010 update of the

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McDonald criteria when possible, but the available information was inadequate for some of the older cases, and then we used the Poser criteria.[13] All included in the study fulfilled at least one of the following criteria on the prevalence day (31 December 2007):

1. 2010 McDonalds criteria for relapsing-remitting MS (RRMS),[13]
2. Poser criteria for *Clinically Definite MS (CD-MS),*
3. Poser criteria for *Laboratory-Supported Definite MS (LSD-MS)*,
4. Poser criteria for *Clinically Probable MS (CP-MS),* or
5. *Primary-Progressive MS (PPMS)*.[13,14]

Identification of cases was done from multiple sources using the diagnostic codes: ICD10 (G35, G37.9), ICD9 (340,341), and ICD8 (340,341). This included (1) records of the Department of Neurology at Landspítali University Hospital (LSH); (2) all privately practicing neurologists in Iceland; (3) all regional hospitals and rehabilitation centers, caring for patients with MS; (4) *visual evoked potential* studies done at Department of Neurology LSH; (5) *Icelandic Social Insurance Administration* data base on all residents of Iceland receiving disability benefits for MS from 1990 through 2007, including information (1997–2007) on those applying for a walking aid because of MS; (6) central database on, all residents of Iceland, receiving disease modifying treatment for MS in Iceland during the study period.

Clinical data

Data collection used standardized abstraction form. Medical records were reviewed (OE and EO) for all suspected MS cases to confirm diagnosis, determine gender, age of onset and time of diagnosis, clinical type, results of diagnostic studies, and disability status according to the *Expanded Disability Status Scale* (EDSS). The EDSS was obtained from a visit to a neurologist, closest in time to the prevalence day, usually within 6 months. Magnetic resonance imaging (MRI) results were available for all (n = 526) and we reviewed the MRI results for all (OE and OK) to confirm the presence of lesions consistent with MS. We determined the *Dissemination in time* and *Dissemination in space* status of all (n = 526), based on the 2010 McDonald criteria.[13]

We excluded seven individuals from the study because of atypical symptoms for MS (n = 4) and a normal MRI (n = 3).

We included one EDSS score for each patient, which were available for 98% of all (n = 513). EDSS information was available from the medical chart for the majority and for the rest we reconstructed an EDSS score, when possible, based on the last visit, prior to the prevalence day (usually within 6 months).

Prevalence group (n = 526) included all residents of Iceland, alive on the prevalence day, and diagnosed with MS (1946–2007) prior to the prevalence day. Women were 73% (n = 382). The mean age at onset was 31 year (range 10–74) and the mean age at diagnosis was 36 years (range 13–77). The mean age on the prevalence day was 47 years and the mean duration from onset of MS symptoms till the prevalence day was 15 years; median 11 years (range 0–69 years). The mean EDSS on the visit closest to the prevalence day was 3.1 (range 0–8.5). The prevalence cohort was followed from the prevalence day till death or 31 December 2020, for a total of 6329 person years of observation (PYO), mean 12.0 years (range 0.3–13.0). The prevalence cohort is described in more detail in a previous publication.[10]

Incidence group (n = 222) included all residents of Iceland diagnosed with MS during a 7-year period preceding the prevalence day (1 January 2002 through 31 December 2007). Women were 74% (164 of 222) and the mean age of onset was 34 years (range 10–74) and the mean age at diagnosis was 37 years (range 13–75). These individuals were all alive and living in Iceland on the prevalence day and consequently they are also included in the prevalence group (42%). The incidence cohort was followed from diagnosis till emigration from Iceland, death or 31 December 2020, for a total of 3420 PYO, mean 15.4 years (range 3.7–18.5). The incidence group has been described in more detail in a previous publication.[9]

Six of the prevalence cases (n = 526), and none of the incidence cases (n = 222) emigrated from Iceland during the follow-up period.

Mortality

Date of death was obtained from Icelandic national registry.[15] The observed mortality of patients with MS was compared to the expected mortality, based on the gender and age-specific mortality of the Icelandic population, during the study period.[15] We calculated the SMR, defined as the number of observed deaths divided by the expected number of deaths.

Cause of death

Information on the cause of death was obtained from the *Causes of Death Registry* at the *Directorate of Health*. The Icelandic death certificates are based on

the *World Health Organization* recommendations and is a hierarchical form, where the first diagnosis is the *immediate cause of death* (e.g., pneumonia), the second diagnosis is an antecedent condition (e.g., dysphagia), and the third diagnosis is an *underlying* medical condition (e.g., MS). Additionally contributory conditions (e.g., diabetes mellitus) can be recorded.

Statistical analysis

We used independent sample t-test for continuous variables. The significance level was set at 5%. Observed and expected survival was determined with the life table method. Expected survival was calculated based on sex, age, and calendar year. For the SMR we calculated 95% confidence intervals. Analysis was done in Microsoft Excel version 14.4.5 and SPSS version 26.

Ethical issues

The study was approved by the Icelandic National Bioethics Committee and Data Protection Authority, reference numbers 2007090624 and VSNb2012010020/03.11, respectively.

Results

Mortality during the follow-up period

Prevalence group (n = 526). During the follow-up period 16% (83 of 526) of the prevalence cohort died and 51.5 deaths were expected, for an SMR 1.6 (1.3–2.0).

The mean age at death was 66 years (range 24–97). The crude mortality rate was 13.6 per 1000 PYO and the expected mortality rate was 8.1 per 1000 PYO. The observed cumulative survival at the end of the follow-up time was 84.2% compared to 90.2% expected. During the follow-up period the observed mortality increased progressively with time (Figure 1), compared to that expected.

Predictors of increased mortality (Table 1) in the prevalence cohort were: (1) age at diagnosis, and a significantly higher mortality was seen for those younger than 55 years of age: 0 to 34 years of age: SMR 2.2 (1.5–3.1); 35 to 54 years of age: SMR 1.6 (95% CI 1.2–2.2). (2) Disease severity. A higher mortality was seen for individuals with RRMS (SMR 1.7) but not PPMS (SMR 1.3). The mean age at death was 65.5 years for RRMS and 72.5 years of age for PPMS (p = 0.17).

Increased mortality was seen for those with EDSS score of 6 to 9.0 (Table 1), but not scores <6. EDSS was available for 98% of the cases (n = 513), including 95% (81 of 83) of those who died.

Incidence group (n = 222). There were 11 deaths (5%) in the incidence group, compared with 8.9 expected; SMR 1.2, 95% CI 0.6–2.2. The mean age at death was 54 years (range 24–89). The mean duration from diagnosis of MS until death was 11.2 years (3.7–16.4). The observed crude mortality rate was 2.9 per 1000 PYO and the expected mortality rate was 2.3 per 1000 PYO. The observed cumulative survival at the end of the follow-up period was 95% compared to an expected survival of 96%.

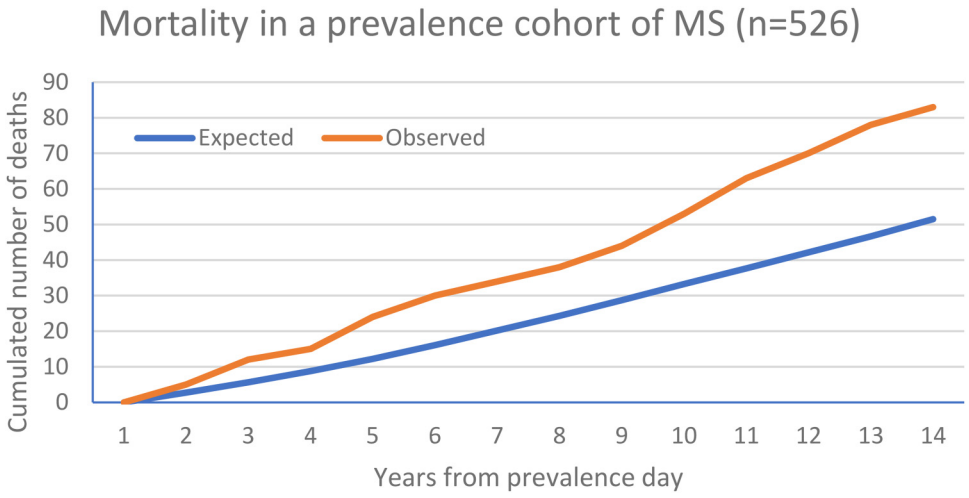

Figure 1. Observed deaths of the MS prevalence cohort (n = 526) and expected deaths based on the general Icelandic population, with respect to age, gender, and calendar year. During a follow up of 13 years. MS: multiple sclerosis.

Table 1. Predictors of early death in a prevalence cohort of MS in Iceland (n = 526), during 13 years follow up.

			Deaths (n)			
	n	%	Observed	Expected	SMR	(95% CI)
Gender						
Female	382	73	56	42.0	1.5	1.1–1.9
Male	144	27	27	12.9	2.1	1.4–3.0
Age at diagnosis						
0–34	271	52	30	13.8	2.2	1.5–3.1
35–54	226	43	44	27.3	1.6	1.2–2.2
≥55	29	6	9	10.4	0.9	0.4–1.6
Clinical phenotype[a]						
RRMS	486	93	69	41.3	1.7	1.3–2.1
PPMS	35	7	13	9.9	1.3	0.7–2.2
EDSS[b]						
0–2.5	305	59	23	21.2	1.1	0.7–1.6
3–5.5	98	19	9	7.3	1.2	0.6–2.3
6–9.0	110	21	49	21.3	2.3	1.7–3.0
Disease duration (years)						
0–9	304	58	22	12.8	1.7	1.1–2.6
10–20	131	25	29	11.4	2.6	1.7–3.7
≥21	91	17	32	27.3	1.2	0.8–1.7

[a]Clinical phenotype missing for 4 patients (1 death among them).
[b]EDSS missing for 11 patients (2 deaths among them).
CI: confidence interval; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; PPMS: primary-progressive MS; RRMS: relapsing-remitting MS; SMR: standardized mortality ratio.

Cause of death

Prevalence group. Death certificate was available for 74% (61 of 83) of those who died during follow up. The death certificate had a total of 95 diagnoses mentioned in the chain of events (immediate, antecedent, and underlying causes of death) and included: MS 48% (n = 29), infection 46% (n = 28), vascular disease 30% (n = 18), cancer 18% (n = 11), respiratory disease 7% (n = 4), drug abuse 7% (n = 4), and accident 2% (n = 1). The diagnosis of MS was not mentioned at all in 23% (14 of 61). None died of suicide.

Incidence group. Eleven died (5%; 11 of 222), and a death certificate was available for five of them. The cause of death was "multiple sclerosis" (3), "sepsis" (1), and "drowning" (1).

Discussion

We present the first nationwide population-based study from Iceland on the mortality of MS. Our study includes both a prevalence cohort (n = 526) and an incidence cohort (n = 222). The incidence cohort is included in the prevalence cohort. Observed mortality in both cohorts during the follow-up period was compared with that expected in the Icelandic population during the follow-up period, based on the age and gender composition of the respective cohorts.

The prevalence cohort was followed for up to 13.0 years and the mortality was increased with SMR of 1.6 (95% CI 1.3–2.0). Most previous studies have found elevated mortality in patients with MS above that expected and a meta-analysis from 2016 found the all-cause mortality to be increased; SMR 2.80 (95% CI 2.74–2.87).[6]

The mortality in the present study (SMR 1.6) is similar, but somewhat lower, than several recent[7,8,16] studies have reported (Table 2) with SMR between 2 and 3.[7,8,16,17,22] The same is true when we compare our results with studies based on only prevalence cases of MS and studies from Hungary[22] and Wales,[17] report SMRs of 2.5 and 2.8, respectively.

We found the mean age at death (n = 83) to be 66 years (range 24–97) in the prevalence cohort.

Table 2. Overview of population-based studies reporting SMR.

Country	Region	First author	Publication year	Time period of onset/ diagnosis	End of follow up	Patients (n)	Deaths (n)	SMR				
								Over-all	Females	Males	RRMS	PPMS
Canada	British Columbia	Kingwell	2012	1980–2004	2007	6917	1025	2.9	3.0	2.7	2.9	2.9
Denmark	Nationwide	Koch-Henriksen	2017	1950–1999	2015	18,847	6102	2.4	2.5	2.4		
Finland	Nationwide	Sumelahti	2010	1964–1993	2006	1595	464	2.8	3.4	2.2		
France	Nationwide	Foulon	2017	NA	2013	78,805	1080	2.6	2.6	2.6		
Hungary	Csongrád county	Sandi	2016	1993–2013	2013	740	121	2.5	2.6	2.5	2.3	4.1
Norway	Hordaland	Lunde	2017	1953–2012	2012	1388	291	2.7	2.9	2.5	2.4	3.9
Norway	Oslo	Smestad	2009	1940–1980	2006	386	263	2.5	2.9	2.0		
Spain	Bizkaia, Basque Country	Zarranz	2014	1987–2011	2011	1283	89	2.8	2.7	3.3		
Wales	South East	Hirst	2008	1947–1985	2006	379	221	2.8	3.1	2.3		

NA: not available; MS: multiple sclerosis; PPMS: primary-progressive MS; RRMS: relapsing-remitting MS; SMR: standardized mortality ratio.

Similar results were seen in a study from Wales reporting 221 deaths (58%) among 379 patients and a mean age at death of 65 years.[17] The deaths occurred at a younger age in a study from Spain, which reported 89 deaths (6.9%) among 1283 individuals and the mean age at death was similar for men (56.2) and women (56.9).[21]

The incidence cohort was followed for a mean of 15.4 years or 3420 PYO and the mortality in the incidence group was not increased, when comparing with that expected in the Icelandic population; SMR 1.2 (95% CI 0.6–2.2). The relatively short observation period may account for this and some previous studies[18,23] have not found any increase in mortality, during the first years following diagnosis of MS. A study from Norway reported 263 deaths (63%) among 386 patients with MS, followed up to 66 years from onset. The SMR for the first 10 years was 0.54 and 2.47 for the whole period.[18] A study from Finland reported 464 deaths (29%) among 1595 individuals; during the first 2 years the mortality was no different from the general population (SMR = 0.8) but elevated 2–3 fold thereafter.[19] Similarly, a study from France described 1569 (5.8%) deaths among 27,603 individuals with MS. No increase in mortality was observed during the first 20 years, but by 30 years of follow up the mortality was increased (the overall SMR was 1.5).[23]

Gender

Men had a higher mortality (SMR 2.1) in our study compared with women (SMR 1.5), but this may not represent a true difference as the numbers are small and confidence intervals overlap. Most previous studies have either described no difference in mortality between men and women, or higher mortality among women (Table 2). A large longitudinal study from Denmark did not find a significant difference in mortality between men and women,[7] and neither did a study from Hungary.[22] A study from Norway showed a significantly higher mortality among women (2.9 vs 2.5)[8] and similar findings have been reported from Canada and Finland.[19,20]

Death certificate

We found MS to be listed as the primary cause of death for 48% of all, which is similar to most previous studies, which have found MS to be the main cause of death in around or over 50%.[8,19,24,25] Nevertheless, direct comparison of studies is difficult as coding practices are likely to vary and coding errors are reportedly common.[26] Death due to cerebral vascular diseases may be more common in patients with MS.[6] Accurate information, was not available, on the prevalence of specific causes of death for the whole Icelandic population. However, infections and vascular diseases were reported the cause of death in 3.0% and 25%, respectively, for the whole population during the study period.[15] This is compared with 46% for infections and 30% for vascular diseases for the MS prevalence cohort. There were 17% (14 of 83) that did not have the diagnosis "*multiple sclerosis*" mentioned on the death certificate. This is similar to studies from other countries,[27] Norway (22%),[18] Wales (27%),[17] and Leeds (23%).[28] Thus, it has to be concluded that using death certificates as a primary method for identifying deaths among patients with MS is unreliable, and likely to underestimate the true number.

EDSS score

For the great majority of our patients the EDSS score was either available from the records or could be reconstructed, based on the last visit, prior to the prevalence day (usually within 6 months of the prevalence day). We included only one EDSS score for each patient. Only the higher scores (6–9) were associated with higher mortality (SMR 2.3) than expected. A study from Wales showed a great increase in SMR according to higher EDSS.[27]

Strengths and weaknesses

This study presents the first analysis of mortality of patients with MS in Iceland. This is a relatively recent cohort and thus diagnosed by modern methods.

This is a total population-based study and we believe we have identified the great majority, likely all, who met the inclusion criteria of MS in Iceland during the study period.

The population-based study design is a powerful method to eliminate selection bias, a concern in epidemiological studies, thus minimizing the risk of both exclusion of milder cases and patients with high comorbidity.[29]

Incidence studies include all with the disease and provide information about the natural spectrum of disease severity, and a mortality study is an important addition.

Prevalence cohort reflects the burden of disease in society indicating the need for healthcare for this patient group and the mortality in the prevalence cohort must be interpreted accordingly. Prevalence cohort gives less information about natural history of MS, as patients diagnosed during the same period as those included, may have passed away prior to

the prevalence day. This would underestimate mortality associated with MS.

We use "time of diagnosis of MS" as reference, rather than "time of first symptoms." We believe this to be a more accurate way of describing, as than onset of symptoms is often difficult to time accurately and can be subject to recall bias. This point has been debated in the past and we have used this approach in our previous peer reviewed studies. This may become less important in the future with the ready availability of MRI and mounting pressure for early diagnosis, due to availability of effective treatment.

A potential weakness of this study is the limited information gained from the death certificates and obviously a longer follow up would provide additional information.[7]

Conclusion

No increase in mortality is detected in an incidence cohort after a follow up of up to 17.3 years.

In a prevalence cohort, with a mean disease duration of 15 years and after 12 years of follow up from the prevalence day, the mortality was 1.6 times higher than expected in the general population of Iceland. These results are comparable to previous studies, in particular studies from neighboring countries in Europe.

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Author contributions

OE was involved in conceptualization, design, data acquisition, analysis, interpretation, writing, and reviewing and editing. ÓK was involved in data acquisition, interpretation, and reviewing and editing. EO was involved in conceptualization, design, analysis, interpretation, writing, and reviewing and editing.

Data availability

The data that support the findings of this study are not publicly available due to information that could compromise patient privacy, but are available from the corresponding author, OE, upon reasonable request.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Statement of ethics

The study was approved by the Icelandic National Bioethics Committee and Data Protection Authority, reference numbers 2007090624 and VSNb2012010020/03.11

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References

1. Reich DS, Lucchinetti CF and Calabresi PA. Multiple sclerosis. *N Engl J Med* 2018 Jan 11; 378: 169–180.
2. Browne P, Chandraratna D, Angood C, et al. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology* 2014 Sep 9; 83: 1022–1024.
3. Uitdehaag BMJ. Disability outcome measures in phase III clinical trials in multiple sclerosis. *CNS Drugs* 2018 Jun; 32: 543–558.
4. Koch-Henriksen N, Sørensen PS and Magyari M. Relapses add to permanent disability in relapsing multiple sclerosis patients. *Mult Scler Relat Disord* 2021 Aug; 53: 103029.
5. Wallin MT, Culpepper WJ, Nichols E, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018 Nov 10; 392: 1736–1788.
6. Manouchehrinia A, Tanasescu R, Tench CR, et al. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. *J Neurol Neurosurg Psychiatry* 2016 Mar; 87: 324–331.
7. Koch-Henriksen N, Laursen B, Stenager E, et al. Excess mortality among patients with multiple sclerosis in Denmark has dropped significantly over the past six decades: a population based study. *J Neurol Neurosurg Psychiatry* 2017 Aug; 88: 626–631.
8. Lunde HMB, Assmus J, Myhr KM, et al. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. *J Neurol Neurosurg Psychiatry* 2017 Aug; 88: 621–625.
9. Eliasdottir OJ, Olafsson E and Kjartansson O. Incidence of multiple sclerosis in Iceland, 2002–2007: a population-based study. *Mult Scler* 2011 Aug; 17: 909–913.
10. Eliasdottir O, Kjartansson O and Olafsson E. Prevalence of multiple sclerosis in Iceland. *Neuroepidemiology* 2018; 51: 50–56.
11. Benedikz J, Stefansson M, Guomundsson J, et al. The natural history of untreated multiple sclerosis in Iceland. A total population-based 50 year prospective study. *Clin Neurol Neurosurg* 2002 Jul; 104: 208–210.

12. Sveinbjornsdottir S, Magnusson H and Benedikz JE. Multiple sclerosis in Iceland from 1900 to 2000: a total population study. *Mult Scler Relat Disord* 2014 May; 3: 375–383.
13. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011 Feb; 69: 292–302.
14. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983 Mar; 13: 227–231.
15. Statistics Iceland. Polulation;birth and death [Internet]. Iceland 2020 [updated 2020 June; cited 2023 January]. Available from:https://www.statice.is/
16. Foulon S, Maura G, Dalichampt M, et al. Prevalence and mortality of patients with multiple sclerosis in France in 2012: a study based on French health insurance data. *J Neurol* 2017 Jun; 264: 1185–1192.
17. Hirst C, Swingler R, Compston DA, et al. Survival and cause of death in multiple sclerosis: a prospective population-based study. *J Neurol Neurosurg Psychiatry* 2008 Sep; 79: 1016–1021.
18. Smestad C, Sandvik L and Celius EG. Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. *Mult Scler* 2009 Nov; 15: 1263–1270.
19. Sumelahti ML, Hakama M, Elovaara I, et al. Causes of death among patients with multiple sclerosis. *Mult Scler* 2010 Dec; 16: 1437–1442.
20. Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *J Neurol Neurosurg Psychiatry* 2012 Jan; 83: 61–66.
21. Rodriguez-Antiguedad Zarranz A, Mendibe Bilbao M, Llarena Gonzalez C, et al. Mortality and cause of death in multiple sclerosis: findings from a prospective population-based cohort in Bizkaia, Basque country, Spain. *Neuroepidemiology* 2014; 42: 219–225.
22. Sandi D, Zsiros V, Fuvesi J, et al. Mortality in Hungarian patients with multiple sclerosis between 1993 and 2013. *J Neurol Sci* 2016 Aug 15; 367: 329–332.
23. Leray E, Vukusic S, Debouverie M, et al. Excess mortality in patients with multiple sclerosis starts at 20 years from clinical onset: data from a large-scale French observational study. *PLoS One* 2015; 10: e0132033.
24. Scalfari A, Knappertz V, Cutter G, et al. Mortality in patients with multiple sclerosis. *Neurology* 2013 Jul 9; 81: 184–192.
25. Kingwell E, Zhu F, Evans C, et al. Causes that contribute to the excess mortality risk in multiple sclerosis: a population-based study. *Neuroepidemiology* 2019 Dec; 18: 1–9.
26. McGivern L, Shulman L, Carney JK, et al. Death certification errors and the effect on mortality statistics. *Public Health Rep* 2017 Nov/Dec; 132: 669–675.
27. Harding K, Anderson V, Willams O, et al. A contemporary study of mortality in the multiple sclerosis population of south east Wales. *Mult Scler Relat Dis* 2018 Oct; 25: 186–191.
28. Ford HL, Gerry E, Johnson M, et al. A prospective study of the incidence, prevalence and mortality of multiple sclerosis in Leeds. *J Neurol* 2002 Mar; 249: 260–265.
29. Kister I, Chamot E, Cutter G, et al. Increasing age at disability milestones among MS patients in the MSBase Registry. *J Neurol Sci* 2012 Jul 15; 318: 94–99.