A contemporary study of mortality in the multiple sclerosis population of south east Wales

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Abstract
Background: Mortality studies in multiple sclerosis (MS) are valuable to identify changing disease patterns and inform clinical management. This study examines mortality in a British MS cohort.

Methods: Patients were selected from the southeast Wales MS registry. Hazard of death was analysed using Cox proportional hazards regression, adjusted for onset age, annualised relapse rate, initial disease course, time to EDSS 4.0, sex, socioeconomic status, and onset year. Age- and sex-stratified standardised mortality ratios (SMRs) were calculated by EDSS scores.

Results: Median time from MS diagnosis to death was 35.5 years and median age 73.9. Older onset age (hazard ratio [HR] 1.05, 95% confidence interval 1.03–1.06) was associated with increased hazard of death. Primary progressive course was associated with increased hazard of death in women (HR 2.04, 1.15–3.63) but not men (HR 1.23, 0.61–2.47). Slow time to EDSS 4.0 (HR 0.41, 0.28–0.60) and high socioeconomic status (HR 0.54, 0.37–0.79) were associated with reduced hazard of death. SMR increased from EDSS 6.0 (3.86, 2.63–5.47) but more substantially at EDSS 8.0 (22.17, 18.20–26.75).

Conclusions: Risk of death in MS varies substantially with degree of disability. This has important implications for clinical management and health economic modelling.

1. Introduction

Disease-specific mortality data remains a core epidemiological resource. Death is a universal and recognizable outcome, and mortality data therefore has value in informing clinical management, deriving case fatality, and identifying changing patterns of disease frequency. It is also an essential component in health economic modelling in chronic diseases such as multiple sclerosis (MS). High quality mortality data can be used to compare effects of new treatments on overall burden of disease, which can then be translated into estimates of long-term treatment efficacy and quality-adjusted life years (QALYs).[1] Over the last decade this has become particularly significant for MS as multiple new disease-modifying therapies (DMT) have become available.

Mortality studies in MS have commonly focused on analysis of cause of death.[2–8] Among those studies that have examined mortality in more detail, MS has consistently been observed to be associated with a higher risk of death,[9–15] with this effect most apparent for younger patients[13] and those with primary progressive disease.[11,14] However, few studies have linked mortality statistics to detailed prospective clinical data from disease onset, and where mortality has been reported as part of a prospective study, data have largely been derived from MS populations where deaths all occurred in the twentieth century,[16] lessening relevance to current clinical practice. This has also been compounded by a general trend of improvement in life expectancy in successive decades as a result of advances in public health and nutrition together with improvements in medical management and survival from common conditions, particularly cardiovascular disease.[17] For these reasons it is important to employ contemporary mortality statistics for comparator data where possible in order to ensure that any observed differences in disease specific survival are not attributable to confounding factors.

In this study we examine a contemporary cohort of British MS patients, with a particular focus on clinical variables associated with risk of death. In addition we have explored the relationship between disability level and standardised mortality ratios (SMR), as well as providing descriptors of cause of death according to death certificate data.

2. Methods

2.1 Patient selection

The MS registry of southeast Wales was first established in a prevalence study in 1985,[18] and since 1999 longitudinal data has been collected prospectively on all patients seen in the neuroinflammatory clinics at the University Hospital of Wales (a tertiary referral centre) and the Royal Gwent Hospital, which serve the cities of Cardiff and Newport and the surrounding areas; a population of 1.4 million. The registry has been estimated to include over 97% of MS patients in the region.[19] Patients are recruited at time of first presentation to the clinics, when demographic data and details of onset event, including degree of recovery, are collected. At all encounters (recruitment and follow-up) data is collected on current disease course, relapses since last encounter, disability (measured using the Expanded Disability Status Scale[20] (EDSS)), and disease modifying therapy (DMT) and its effects. Socioeconomic status was classified using the Welsh Index of Multiple Deprivation (WIMD),[21] which is the Welsh Government's official measure of deprivation in Wales and is based on residential postcode. For this analysis, socioeconomic status quartiles were used. Data is stored securely in a custom-built database on National Health Service (NHS) servers. Written consent is obtained from all patients. This study was approved by the South East Wales Research Ethics Committee (ref no.05/WSE03/111).

In 1985 the 379 patients of the original prevalence study [18] were registered with the Office of Population Censuses and Surveys, which allowed direct notification to the research team whenever a new death occurred in this patient group. Results from an interim analysis have already been reported,[22] and notification of deaths from this pilot cohort remains ongoing. For the remainder of the registry patients recruited since 1985, death was confirmed via several converging pathways. The disease registry is linked to NHS records, enabling automatic upload of any hospital record of death. Deaths are also notified during a weekly clinical meeting by specialist staff embedded in community and hospital care. Finally in order to confirm date of death and to identify any deaths not detected using the first two methods, data was cross-referenced with the Welsh Demographic Service (http://www.publichealthwalesobservatory.wales.nhs.uk/wds), which is government data from Public Health Wales providing demographic data on all residents of Wales who are registered with a general practitioner.

2.2 Death certificate data collection

Copies of death certificates were requested from the General Register Office (https://www.gro.gov.uk). Death certificates in the UK are structured according to international guidelines from the World Health Organisation,[23] usually described as Part 1 and Part 2. Part 1 is further classified into Part 1a, representing the immediate cause of death, and Parts 1b and 1c representing the events that led directly to the cause recorded in Part 1a. Part 2 is used to record conditions not directly leading to death but thought by the certifying clinician to be relevant to the death. Causes of death are classified using ICD codes. Information on cause of death documented in all parts of each death certificate was recorded for analysis.

Principal cause of death was based on Part 1a of the death certificate with the following exceptions: i) suicide was always considered the principal cause of death regardless of position on the death

certificate, ii) MS was considered the principal cause of death if the only entries which preceded

MS on Part 1 of the death certificate were those of cardiac or respiratory arrest/failure, iii) entries of

cardiac or respiratory arrest/failure were only considered the principal cause of death if no other

entries appeared on Part 1 of the death certificate.[6] Deaths considered to be due to MS or its

complications were also identified, based on i) MS listed in Parts 1a, 1b or 1c of the death

certificate, or ii) if bronchopneumonia or aspiration pneumonia were listed in Part 1 and MS was

listed in Part 2. Patients were grouped by principal cause of death into the following categories:

multiple sclerosis, cardiovascular disease, respiratory disease, respiratory infection, infection (non-

respiratory), cancer, gastrointestinal haemorrhage, renal failure or disease, accidents, suicide, and

other causes.

2.3 Statistical analysis

All statistical analysis was performed in R version 3.4.3.[24] Demographic data were analysed using

Students t-test and chi-squared test. To avoid immortal time bias, date of diagnosis of MS was used

as the entry point to the study. Kaplan-Meier survival analysis was used to compare time from

diagnosis to death by individual clinical variables. Cox proportional hazards regression was used to

analyse the association of the following covariates with risk of death: age at onset of MS (as a

continuous variable), annualised relapse rate in the first five years of disease (also as a continuous

variable), disease course at onset (progressive or relapsing), time to EDSS 4.0 (as a measure of the

rate of accumulation of early disability, dichotomised as slower or faster than the median time to

EDSS 4.0), sex, socioeconomic status, and calendar year of onset, for the whole cohort and also

separately by sex. Proportional hazards assumptions of the models were checked.

Standard statistical methods were used to derive sex- and age-stratified standardised mortality ratios

(SMRs)[25] by EDSS score as follows. EDSS scores were banded into <4.0, 4.0–5.5, 6.0–6.5, 7.0–7.5,

8.0–8.5, and 9.0–9.5. Next, sex and age group (under 30, 30–44, 45–59, 60–74, 75–89, ≥90 years) of patients in each EDSS band was tabulated using the whole cohort, to produce an age profile for each EDSS band for males and females separately. Expected deaths for each EDSS band were then calculated based on the age and sex profile for each band, using sex- and age-stratified comparative data for the population of southeast Wales.[26] Observed number of deaths in each EDSS band were counted, with EDSS score at death taken to be the EDSS score recorded nearest death (and not more than five years before death). The ratio between the observed and expected number of deaths was calculated (to provide the SMR) and tested using χ^2 test. SMR was not calculated for EDSS scores <4 to avoid immortal time bias, and because the number of patients dying at low EDSS scores was too small to allow reliable calculation.

3. Results

3.1 Demographics

A total of 2604 patients was identified (1851 recruited since the original prevalance study in 1985[18]), with a total of 45379 patient-years of follow-up and a median of 19.3 years follow-up per patient. Of these, 579 (22.2%) were deceased, and 79.3% of these had died in the last twenty years. Thirty-one (5.4%) deceased patients had received DMT: two alemtuzumab, four mitoxantrone, and the remainder either interferon-1β or glatiramer acetate. Patient demographics are summarised in Table 1.

Table 1: Patient characteristics.

Clinical variable	Living	Deceased
Total number	2604	
Per group	2025	579
Female	1434 (70.8%)	368 (63.6%)
Relapsing initial disease course	1748 (89.3%)	454 (89.7%)
Mean age at onset (standard deviation)	32.4 yr (10.8)	34.7 yr (11.8)
Mean follow-up (standard deviation)	18.0 yr (11.7)	24.5 yr (13.9)
Socioeconomic status:		
Most deprived	464 (22.9%)	119 (20.6%)
Second most deprived	379 (18.7%)	90 (15.5%)
Second least deprived	302 (14.9%)	101 (17.4%)
Least deprived	639 (31.6%)	167 (28.8%)
Decade of diagnosis:		
pre-1976	40 (2.0%)	170 (29.4%)
1976-1985	145 (7.2%)	133 (23.0%)
1986-1995	292 (14.4%)	88 (15.2%)
1996-2005	643 (31.8%)	65 (11.2%)
2006-2015	724 (35.8%)	12 (2.1%)
Decade of death:		
pre-1976	-	0 (0%)
1976-1985	-	11 (4.0%)
1986-1995	-	109 (18.8%)
1996-2005	-	158 (27.3%)
2006-2015	-	301 (52%)

3.2 Cause of death

Death certificates were untraceable for 12 (2.1%) patients. Of the remaining certificates, MS was

listed on the death certificate in 399 patients (68.9%, supplementary table 1Mean age at death was

lower in patients who had MS on their death certificate (62.2 versus 68.6 years), and mean age at

onset was also lower (33.6 versus 36.7 years, supplementary table 2).

The commonest principal cause of death was respiratory infection (44.1%, supplementary table 2),

followed by cardiovascular disease (17.3%) which was more frequent in men than women (22.2%

males vs. 14.4% females). A similar proportion died of cancer (10.9%), MS (10.8%) and non-

respiratory infections (9.3%). There was no sex difference for other causes of death. Mean age at

death was lower for suicide (43.8 years) and accidents (46.7 years) compared to all other cause of

death categories (supplementary table 2). A larger proportion of patients who had progressive

disease at death (primary or secondary) died from MS or its complications (46.3% RRMS, 67.9%

SPMS, 57.7% PPMS, supplementary table 3). Of patients who had received a DMT, cause of death

was related to MS or its complications in 19 (61.3%).

3.3 Time to and age at death

Median time from diagnosis of MS to death was 35.5 years, and median age at death was 73.9

years. For those diagnosed since 1985, median age at death was 76.9 years. Female sex, younger

age at onset of MS, relapsing initial disease course and higher socioeconomic status (less deprived)

were all associated with a longer time from MS diagnosis to death. Female sex and higher

socioeconomic status were also associated with an older age at death. However, a younger age at

onset and a relapsing initial disease course were associated with a younger age at death (Figure 1,

Table 2).

Table 2: The association of clinical variables with time from MS diagnosis to death and age at death: univariate analysis

Variable	Time from diagnosis to death (years)		Age at death (years)	
	Time (95% CI)	**p**	**Age (95% CI)**	**p**
Sex:				
Female	35.7 (34.2-38.2)	0.048	75.4 (73.3-77.1)	0.005
Male	34.5 (31.2-37.4)		72.2 (71.3-74.3)	
Age at onset:				
Under 20	39.3 (37.7-48.1)	<0.0001	69.9 (66.9-73.1)	<0.0001
20-29	39.2 (37.3-43.1)		71.6 (69.6-75.8)	
30-39	34.0 (32.3-36.6)		73.7 (71.9-78.1)	
40-49	28.8 (24.8-31.1)		76.2 (73.5-79.3)	
50 and over	17.6 (15.3 - †)		78.0 (76.2-84.8)	
Initial course:				
Relapsing onset	35.9 (34.8-38.1)	<0.0001	73.5 (72.8-75.8)	0.002
Progressive onset	27.4 (21.9- †)		77.7 (75.7- †)	
Socioeconomic status:				
Most deprived	34.0 (29.9-43.4)	0.018	70.4 (69.1-76.2)	<0.0001
Second most deprived	37.4 (33.6-44.7)		76.1 (72.3-78.8)	
Second least deprived	34.2 (32.6-38.2)		72.2 (71.2-74.8)	
Least deprived	37.7 (35.5-41.1)		78.0 (76.1-79.9)	

Key: † upper confidence interval cannot be calculated

3.4 The association between clinical variables and hazard of death in MS: Cox proportional hazards regression

Older age at onset (hazard ratio [HR] 1.05, 95% confidence interval [CI] 1.03–1.06) and primary progressive disease course (HR 1.84, 95% CI 1.19–2.84) were associated with increased hazard of death. Median time to EDSS 4.0 was 14.4 years, and this was used to dichotomise patients into

either slow or fast time to EDSS 4.0. Slow time to EDSS 4.0 was associated with a reduced hazard

of death (HR 0.41, 95% CI 0.28–0.60). The least deprived socioeconomic quartile had a lower

hazard of death compared to the most deprived socioeconomic quartile (HR 0.54, 95% CI 0.37–

0.79). There was no association of annualised relapse rate in early disease (HR 0.80, 95% 0.39–

1.63), sex (HR 1.21, 95% CI 0.89–1.64), or year of onset (HR 1.01, 95% CI 0.99–1.03) with hazard

of death (Table 3). When analysed separately by sex, the only way in which findings differed from

the main analysis was that primary progressive disease course was associated with increased hazard

of death in women (HR 2.04, 95% CI 1.15–3.63) but not in men (HR 1.23, 95% CI 0.61–2.47, Table

3). None of the models violated the proportional hazards assumptions.

Table 3: The association between clinical variables and hazard of death in MS: Cox proportional hazards regression model for the total cohort and for women and men separately

Variable	Total cohort		Women		Men	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age at onset	1.05 (1.03-1.06)	<0.0001	1.03 (1.01-1.06)	0.001	1.07 (1.04-1.11)	<0.0001
Sex	1.21 (0.89-1.64)	0.22	-	-	-	-
Annualised relapse rate	0.80 (0.39-1.63)	0.54	1.09 (0.49-2.39)	0.84	0.35 (0.08-1.58)	0.17
Progressive onset	1.84 (1.19-2.84)	0.006	2.04 (1.15-3.63)	0.014	1.23 (0.61-2.47)	0.56
Slow time to EDSS 4.0	0.41 (0.28-0.60)	<0.0001	0.37 (0.23-0.60)	<0.0001	0.41 (0.20-0.84)	0.015
SES:						
Most deprived	Reference	-	Reference	-	Reference	-
Second most deprived	0.76 (0.49-1.19)	0.23	0.69 (0.39-1.22)	0.20	0.82 (0.40-1.69)	0.60
Second least deprived	0.96 (0.63-1.47)	0.86	1.01 (0.59-1.73)	0.97	0.71 (0.35-1.45)	0.34
Least deprived	0.54 (0.37-0.79)	0.001	0.53 (0.33-0.86)	0.01	0.47 (0.25-0.90)	0.023
Onset year	1.01 (0.99-1.03)	0.23	1.01 (0.98-1.03)	0.63	1.02 (0.98-1.06)	0.28

Key:
- Age at onset: hazard ratio is per one year increase in age at onset of MS
- Annualised relapse rate: hazard ratio is per unit increase in annualised relapse rate
- Slow time to EDSS 4.0 defined as slower or faster than the median time to EDSS 4.0 of 14.4 years

3.5 Disability and risk of death

184 patients had an EDSS score recorded within 2 years of death, and a further 47 within five years. EDSS score before death was ≤4.0 in four patients, and these were not included in the next steps of analysis. At EDSS scores of 6 or greater SMR was increased, most substantially at EDSS scores of 8 or greater (Table 4).

Table 4: Number of deaths and standardised mortality ratios by EDSS score

EDSS	Median time at EDSS score	Deaths observed	Deaths expected	Standardised mortality ratio (95% CI)	p
4-5.5	3.9 yrs	9	4.45	2.02 (0.98-3.71)	0.21
6-6.5	6.7 yrs	29	7.52	3.86 (2.63-5.47)	0.0004
7-7.5	3.7	16	3.36	4.76 (2.82-7.56)	0.004
8-8.5	9.2 yrs	104	4.69	22.17 (18.20-26.75)	<0.0001
9-9.5	3.3 yrs	69	1.14	60.74 (47.62-76.41)	<0.0001

4. Discussion

In this study we have presented a comprehensive analysis of mortality in a contemporary British MS population, with a median age at death of 73.9 years, and median time from MS diagnosis to death of 35.5 years. We found that older age at MS diagnosis, primary progressive disease course, rapid time to EDSS 4.0, and low socioeconomic status were associated with increased hazard of death. Additionally, clinical variables associated with hazard of death were similar for men and

women, with the exception of primary progressive disease course which was associated with an increased hazard of death for women only. We have also described standardised mortality ratios (SMR) by EDSS score, and shown that SMR increases with EDSS, most substantially when EDSS is ≥8.0.

Current life expectancy in Wales is 78.5 years for men and 82.3 years for women,[27] implying that MS is associated with a shortened lifespan relative to the general population. However, a valuable aspect of our study is the direct comparison with historical data from the 1985 prevalent cohort in the same region,[22] which reported a median age at death of 65.3 years for women and 65.2 years for men and thus an improvement of 8.6 years in life expectancy for MS patients in south Wales. This compares to an improvement of between 2 and 3 years in life expectancy in the general population of Wales since 2005,[28] so the improvement in survival for MS patients has been greater than that for the general population. Other studies have found a similar improvement, particularly in northern European cohorts,[8,9,13,15,29] which may reflect better symptomatic care over recent years and emphasises the value of contemporary data for current and future analyses which incorporate survival data. Not all studies have found improving life expectancy: no evidence was found for a change in survival over time in the British Columbia cohort in Canada.[11] In addition, a recent meta-analysis of SMRs reported between 1949 and 2012 found no evidence for an improvement in mortality ratios.[30] However, this meta-analysis was based on multiple cohorts each measured at a single point in time, rather than repeated observations in the same cohort over a period of years. It is possible that variation in life expectancy between different populations may mask the effect of improvements in life expectancy in individual cohorts over time within a single population.

Although women have both longer survival times[10,14,31] and are older at death than men,[11] adjustments to compare with the general population reveal that relative mortality is worse for women,[10,13] which may be most significant for women with PPMS compared to R-MS.[11] We also observed a difference in survival by sex and disease course: in our cohort PPMS was associated with increased hazard of death in women, but not in men. In addition, those with PPMS were older at death than those with relapsing onset MS, an effect which is largely explained by the older age at onset in PPMS patients (45 years versus 31 years), since other clinical variables within PPMS and relapsing-onset MS were either similar, or would be expected to have the opposite effect (i.e. PPMS is more common in men, who generally would be expected to have a shorter life expectancy). Differences in survival for sub-groups of MS patients are important as they may represent a group where targeted intervention may have most effect, and with the growing recent interest in potential DMTs in progressive disease, this is particularly relevant.

To our knowledge, this is the most detailed examination of risk of death by EDSS score, although in general risk of death has been observed to increase with higher levels of disability[32,33] Our finding is consistent with observations of a divergence in survival after 20 years of MS,[13] which is the point at which significant disability commonly accumulates[34] and suggests that opportunities for modifying long-term prognosis may be most effectively instigated at lower EDSS scores. Furthermore it is directly relevant for clinical practice as it indicates the need to consider discussions concerning end-of-life care planning and advanced directives with patients who have EDSS scores of ≥7.5. These results may also be used to refine health economic models to calculate QALYs and cost-effectiveness of medications in countries that use cost utility analysis of health technologies, including the UK and Canada.[1]

Disease-modifying therapy (DMT) has only been widely available in Wales since 2002; 38% of our patients diagnosed since 2002 have had DMT, but only 11.7% of those diagnosed before 2002. Since only 31 of the deceased patients (5.4%) were diagnosed after 2002, this inevitably means that few deceased patients in this study had DMT so that these data largely represent a natural history cohort of untreated patients. It is as yet too soon to tell whether there are patients currently on DMT who might have died earlier without treatment.

The strength of this study is its basis in a large population-based cohort, with prospectively collected data on 70% of patients from onset of disease. This has allowed us to explore survival in detail, as well as SMRs by EDSS score. We were able to trace over 97% of death certificates, which reflects the high quality of the data and degree of follow-up. Another strength was the ability to directly compare mortality to that reports from MS patients prevalent in 1985,[22] providing valuable insights into the changing life expectancy for MS patients, and illustrates the value of analysing contemporary datasets.

In conclusion, we have shown an improvement in the life expectancy of patients in south east Wales since 1985 in a largely DMT-naive population. We have demonstrated that SMR increases substantially above EDSS 7.5, which will have implications for health economic modelling as new DMTs are developed, and for clinical practice regarding end-of-life care in patients with high EDSS scores. These data serve to illustrate that mortality studies remain relevant and important for understanding disease progression, long-term prognosis, and the effects of new interventions.

References

[1] World Health Organisation. Immunization, vaccines and biologicals: Estimates of disease burden and cost-effectiveness. Online, 2016. [Accessed 21st Dec 2016]. URL http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/

[2] Ford HL, Gerry E, Johnson M, et al. A prospective study of the incidence, prevalence and mortality of multiple sclerosis in Leeds. Journal of Neurology, 2002;249:260–265.

[3] Sumelahti ML, Hakama M, Elovaara I, et al. Causes of death among patients with multiple sclerosis. Multiple Sclerosis, 2010;16(12):1437–1442. doi:10.1177/1352458510379244.

[4] Lalmohamed A, Bazelier MT, Van Staa TP, et al. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. European Journal of Neurology, 2012;19(7):1007–1014. doi:10.1111/j.1468-1331.2012.03668.x.

[5] 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(4):219–225. doi:10.1159/000359971.

[6] Goodin DS, Corwin M, Kaufman D, et al. Causes of death among commercially insured multiple sclerosis patients in the United States. PLoS ONE, 2014;9(8):e105207. doi:10.1371/journal.pone.0105207.

[7] Jick SS, Li L, Falcone GJ, et al. Epidemiology of multiple sclerosis: results from a large observational study in the UK. J Neurol, 2015;262(9):2033–2041. doi:10.1007/s00415-015-7796-2.

[8] Burkill S, Montgomery S, Hajiebrahimi M, et al. Mortality trends for multiple sclerosis patients in Sweden from 1968 to 2012. Neurology, 2017;89:555–562. doi:10.1212/WNL.0000000000004216.

[9] Bronnum-Hansen H. Trends in survival and cause of death in danish patients with multiple sclerosis. Brain, 2004;127(4):844–850. ISSN 1460-2156. doi:10.1093/brain/awh104.

[10] Grytten Torkildsen N, Lie S, Aarseth J, et al. Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in western Norway. Multiple Sclerosis Journal, 2008;14(9):1191–1198. doi:10.1177/1352458508093890.

[11] 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;83(1):61–66. doi:10.1136/jnnp-2011-300616.

[12] Manouchehrinia A, Weston M, Tench CR, et al. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. J Neurol Neurosurg Psychiatry, 2014;85(10):1091–1095. doi: 10.1136/jnnp-2013-307187.

[13] 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(7):e0132033. doi:10.1371/journal.pone.0132033.

[14] Sandi D, Zsiros V, Fvesi J, et al. Mortality in Hungarian patients with multiple sclerosis between 1993 and 2013. Journal of the Neurological Sciences, 2016;367:329–332. doi:10.1016/j.jns.2016.06.035.

[15] 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. Journal of Neurology, Neurosurgery, and Psychiatry, 2017;88:626–631. doi:10.1136/jnnp-2017-315907.

[16] Cottrell DA, Kremenchutzky M, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain, 1999; 122(4):625–639.

[17] Tunstall-Pedoe H, Kuulasmaa K, Mhnen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 who monica project populations. Monitoring trends and determinants in cardiovascular disease. Lancet, 1999;353:1547–1557.

[18] Swingler RJ, Compston DA. The prevalence of multiple sclerosis in south east Wales. J Neurol Neurosurg Psychiatry, 1988;51(12):1520–1524.

[19] Hirst C, Ingram G, Pickersgill T, et al. Increasing prevalence and incidence of multiple sclerosis in South East Wales. J Neurol Neurosurg Psychiatry, 2009;80(4):386–391. doi:10.1136/jnnp.2008.144667.

[20] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology, 1983;33(11):1444–1452.

[21] Welsh Assembly Government. Welsh index of multiple deprivation (WIMD). Online, 2014. [Accessed 25th July 2016]. URL http://gov.wales/statistics-and-research/welsh-index-multiple-deprivation/?lang=en

[22] Hirst C, Swingler R, Compston DAS, et al. Survival and cause of death in multiple sclerosis: a prospective population-based study. J Neurol Neurosurg Psychiatry, 2008;79(9):1016–1021. doi:10.1136/jnnp.2007.127332.

[23] World Health Organisation. Medical certification of cause of death: instructions for physicians on use of international form of medical certificate of cause of death. Online, 1979. [Accessed 22nd August 2017]. URL http://apps.who.int/iris/handle/10665/40557

[24] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2017. URL https://www.R-project.org/

[25] Clayton D, Hills M. Statistical models in epidemiology. Oxford University Press (OUP), 2013.

[26] Welsh Assembly Government. Mid-yr estimates of the population. Online, 2014. [Accessed 29th February 2016]. URL https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates

[27] Office of National Statistics. Statistical bulletin: Life expectancy at birth and at age 65 by local areas in England and Wales: 2012 to 2014. Online, 2014. [Online: Accessed 13th March 2017]. URL
https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/lifeexpectancyatbirthandatage65bylocala2015-11-04

[28] Health Statistics and Analysis Unit, Welsh Government. Life expectancy by gender and year. Online, 2013. [Accessed 13th March 2017]. URL https://statswales.gov.wales/Catalogue/Health-and-Social-Care/Life-Expectancy/LifeExpectancy-by-Gender-Year

[29] Lunde HMB, Assmus J, Myhr KM, et al. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. Journal of Neurology, Neurosurgery, and Psychiatry, 2017;88:621–625. doi:10.1136/jnnp-2016-315238.

[30] Manouchehrinia A, Tanasescu R, Tench CR, et al. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. Journal of Neurology, Neurosurgery, and Psychiatry, 2016;87:324–331. doi:10.1136/jnnp-2015-310361.

[31] Hader WJ. Disability and survival of multiple sclerosis in Saskatoon, Saskatchewan. Canadian Journal of Neurological Sciences, 2010;37(1):28–35.

[32] Phadke JG. Survival pattern and cause of death in patients with multiple sclerosis: results from an epidemiological survey in north east Scotland. Journal of Neurology, Neurosurgery and Psychiatry, 1987;50(5):523–531.

[33] Leray E, Morrissey S, Yaouanq J, et al. Long-term survival of patients with multiple sclerosis in west France. Multiple Sclerosis Journal, 2007;13:865–874. doi:10.1177/1352458507077410.

[34] Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain, 2006;129(3):606–616. doi:10.1093/brain/awl007.

Figures

Figure 1: Kaplan-Meier survival curves showing time from MS diagnosis to death, and age at death by disease course (relapsing onset: unbroken line, primary progressive: dotted line).