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Original research

Mortality and cause of death in multiple sclerosis in western Norway 1950–2021: a registry-based linkage study

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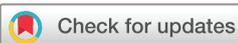
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ABSTRACT

Background Persons with multiple sclerosis (pwMS) have higher risk of mortality compared with the general population. Longitudinal studies are important for understanding the evolution of survival in pwMS.

Objective Examine changes in mortality among pwMS during the past seven decades.

Methods We followed pwMS from Hordaland and Møre and Romsdal in Western Norway, with disease onset from before 1950, identified from population-based epidemiological surveys and the Norwegian MS Registry and Biobank, until 1 January 2021. Data were linked to the Norwegian Cause of Death Registry to obtain underlying cause of death. We examined all-cause, and cause-specific mortality using standardised mortality ratios (SMR) and excess death rates (EDR). We calculated life expectancies and assessed survival stratified by sex, age and disease phenotype at onset. We compared hazard ratios (HRs) for mortality, in pwMS diagnosed before and after the era of disease-modifying treatment (DMT).

Results Of 3624 pwMS, 964 (55.5% women) had died, predominantly of multiple sclerosis (49.0%). Median life expectancy for pwMS was 74.3 years (95% CI 73.3 to 75.3), compared with 83.1 years for the general population ($p < 0.001$). From disease onset, pwMS survived 14.6 years shorter than the general population ($p < 0.001$). Overall, SMR was 2.3 (95% CI 2.13 to 2.42) and EDR was 6.8 (95% CI 6.42 to 7.09) for pwMS. Treatment-eligible pwMS diagnosed in the DMT era had the lowest risk of mortality, HR 0.49 (95% CI 0.34 to 0.70, $p < 0.001$).

Conclusion Excess mortality among pwMS declined during the past seven decades, possibly due to improved diagnostics, better symptomatic treatment and access to DMTs.

INTRODUCTION

Persons with multiple sclerosis (pwMS) have reduced life expectancy compared with the general population,¹ and longitudinal studies of temporal trends in multiple sclerosis (MS) survival have demonstrated inconsistent findings.^{2–6}

The era of disease-modifying treatment (DMT) in MS began almost 30 years ago with the pivotal randomised clinical trial comparing injectable interferon beta (IFN β)–1b to placebo.⁷ Long-term follow-up of the participants receiving active treatment demonstrated increased longevity more than

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies examining the temporal trends of survival in people with multiple sclerosis (pwMS) have demonstrated conflicting results. To better understand the evolution of survival in pwMS during the past seven decades, we examined population-based longitudinal changes in all-cause and cause-specific mortality.

WHAT THIS STUDY ADDS

⇒ Survival in pwMS has improved during the past seven decades, potentially due to access to disease-modifying treatment, better symptomatic treatment and reduced diagnostic delay.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ In practice, pwMS can be reassured that the prognosis of the disease has improved over time. Survival studies have unambiguous logical validity, and this study demonstrates the importance and feasibility of linking individual data held by national health registries to obtain outcomes otherwise unattainable in randomised clinical trials.

20 years later.⁸ Longer survival of pwMS exposed to IFN β –1b was confirmed more recently using real-world data,⁹ emphasising the importance of such studies and their ability to provide data otherwise unattainable in the clinical trial setting due to limited follow-up time.

In addition to their therapeutic benefits, DMTs may cause short-term and long-term side effects. A recent study from Norway indicated an increase in the incidence of cancer among pwMS compared with the general population after DMTs were implemented in routine clinical practice from 1996.¹⁰ Thus, longitudinal studies that allow comparison of time periods before and after DMTs became available are important to determine the natural course of MS and to evaluate the benefits and potential side effects of DMTs on mortality in pwMS.

To better understand the evolution of MS survival during the past seven decades, we examined all-cause and cause-specific mortality among pwMS in Hordaland and Møre and Romsdal counties in

Western Norway. We hypothesised that cancer and infectious disease-related mortality could change after the introduction of DMTs in Norway.

METHODS

Study design

We conducted a retrospective cohort study by linking data from The Norwegian MS Registry and Biobank (NorMSR) and the Norwegian Cause of Death Registry (CoDR). We report our results as suggested in the Strengthening the Reporting of Observational Studies in Epidemiology statement guideline.¹¹

Study population

We followed all pwMS registered in the databases of the local hospital trusts held by NorMSR until their time of death, or 1 January 2021, whichever came first. We also followed pwMS, not found in NorMSR, ascertained from previous longitudinal population-based epidemiological studies in the corresponding geographic areas under investigation in the present study.^{12 13} We avoided duplicate entries in the final data set by filtering the aggregated material using each person's unique 11-digit national identification number. We included data on the year of disease onset, date of diagnosis and initial disease course, that is, persons with relapsing onset MS (pwROMS) or persons with progressive onset MS (pwPOMS).¹⁴ Data on smoking history, time of conversion to secondary progressive MS (SPMS), longitudinal DMT exposure and symptomatic therapy were incomplete.

The NorMSR is synchronised weekly with the National Population Register. This synchronisation automatically updates the vital status, that is, date of death, for pwMS in NorMSR within 1-week postmortem. We crosslinked the final data set with CoDR to identify the underlying cause of death (UCoD) for all participants, including the date of death for those not contained in NorMSR. The WHO defines UCoD as 'the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury'.¹⁵ The CoDR contains UCoD information from death certificates dating back to 1951. In CoDR, data are coded according to the 6th through 10th revisions of the International Classification of Diseases (ICD) and grouped according to the European Shortlist for Causes of Death (ESLCoD) published by Eurostat.¹⁶ We classified the UCoDs using the ESLCoD which comprises 17 main categories, with a total of 65 subspecific groups. For a particular UCoD subcategory to be reported and included in the statistical analyses, there had to be at least 10 deaths and the ESLCoD taxonomy had to be informative. Thus, we excluded main UCoD categories, in which less than 10 deaths occurred from the statistical analyses. Consolidated subcategories, consisting of several ICD codes, labelled using unspecific nomenclature, such as 'other diseases of the (organ) system', were reported without further specification under their respective main category. However, and since MS is included in the consolidated ESLCoD subcategory labelled 'other diseases of the nervous system and sense organs', we made one exception to this rule to gain access to disease-specific UCoD data.

Statistical methods

Survival

We estimated overall survival using the standard Kaplan-Meier estimator, following pwMS from date of disease onset to date of death, or date of administrative censoring, 1 January 2021. Life expectancy was estimated using the Ederer V.2 estimator using

lifetables stratified on sex, age and calendar year (in 1-year intervals). To evaluate the effect of age at onset on survival, we calculated the median age at death and median survival time in years for women and men based on disease course at presentation.

Mortality

To assess all-cause and cause-specific mortality in the study population, we used national aggregated population data on number of deaths, stratified by sex, 10-year age groups and calendar year to calculate the standardised mortality ratio (SMR) and the excess death rate (EDR).¹⁷ SMR is the quotient obtained by dividing the number of observed deaths in a sample population, by the number of expected deaths in a standard population matched by age group, sex and calendar-year of death, whereas EDR is the difference between the observed number of deaths per 1000 person-years and the corresponding expected number. Thus, SMR serves as a measure of relative risk, whereas EDR provides an absolute measure of excess mortality. Some authors hold EDR as a better measurement than SMR when performing longitudinal comparisons of mortality.^{1 4 5 18 19} We calculated overall SMR and EDR by sex, initial disease course and age at onset. To examine the temporal trend in all-cause mortality, we calculated SMR and EDR for seven cohorts defined by year of disease onset. The first onset cohort includes pwMS who experienced their first symptom of MS before 1950, while the second through sixth onset cohorts include pwMS with onset during the five following decades, 1950–2000. The seventh onset cohort includes pwMS with onset of MS between 2000 and 2015. To estimate the contribution of disease duration on excess mortality from all causes, we calculated EDR for different decades after MS onset in women and men based on disease course. Using UCoD data, we assessed cause-specific mortality across the seven onset cohorts stratified by sex, initial course of disease and age at onset.

To estimate the risk of mortality among pwROMS diagnosed before and after DMTs became available, we used multivariate Cox proportional hazards regression to estimate the HR for different cohorts based on time of diagnosis. The first DMTs, that is, injectable interferons, were introduced in Norway from 1996. To account for some delay in the implementation of novel drugs in routine practice, and to allow for inclusion of participants diagnosed recently leading up to DMTs becoming available, we selected the group of pwROMS diagnosed between 1990 and 1999 as the reference group. To adjust for potential confounding, we included sex, age at onset and diagnostic delay as covariates in the model. To account for differences in observation time across the cohorts, we performed a sensitivity analysis, restricting follow-up to 20 years.

The data were analysed in Stata V.17.

RESULTS

We identified 3624 pwMS, of which 3088 were held by NorMSR. 964 (26.6%) were deceased by 1 January 2021, of whom 535 (55.5%) were women, yielding a total of 79 897 person-years. Initial course of disease was unknown for 12 (1.2%), and we could not obtain the UCoD for 31 (3.2%), deceased pwMS. At the time of death, 109 pwMS were residing outside the geographic areas under investigation, but none was lost to follow-up. Among the deceased, 768 (79.7%) died in a health institution or hospital. Autopsy was performed in 86 (8.9%) cases. An overview of the study population, including demographics and clinical characteristics, is shown in [table 1](#).

Table 1 Clinical and demographic data on deceased persons with multiple sclerosis by period of disease onset, in Hordaland and Møre and Romsdal counties, Western Norway

Period of onset (N)	≤1950 (n=141)	1950–1959 (n=122)	1960–1969 (n=191)	1970–1979 (n=376)	1980–1989 (n=538)	1990–1999 (n=644)	2000–2015 (n=1312)	Total
Sex								
Female	81 (8.5%)	67 (7.0%)	80 (8.3%)	139 (14.4%)	96 (10.0%)	57 (5.9%)	15 (1.6%)	535 (55.5%)
Male	60 (6.2%)	49 (5.1%)	67 (7.0%)	96 (10.0%)	91 (9.4%)	42 (4.4%)	24 (2.5%)	429 (44.5%)
MS-type								
PPMS	21 (2.2%)	32 (3.3%)	34 (3.5%)	51 (5.3%)	46 (4.8%)	35 (3.6%)	18 (1.8%)	237 (24.6%)
RRMS	118 (12.2%)	82 (8.5%)	113 (11.7%)	180 (18.7%)	141 (14.6%)	61 (6.3%)	20 (2.1%)	715 (74.2%)
Unknown	2 (0.2%)	2 (0.2%)	0 (0.0%)	4 (0.4%)	0 (0.0%)	3 (0.3%)	1 (0.1%)	12 (1.2%)
Age at onset								
<20	26 (2.7%)	5 (0.5%)	14 (1.5%)	13 (1.3%)	7 (0.7%)	3 (0.3%)	0 (0.0%)	68 (7.1%)
20–29	60 (6.2%)	44 (4.5%)	55 (5.7%)	82 (8.5%)	44 (4.5%)	19 (2.0%)	2 (0.2%)	306 (31.8%)
30–39	41 (4.3%)	40 (4.1%)	48 (5.0%)	72 (7.5%)	70 (7.3%)	20 (2.1%)	12 (1.2%)	303 (31.4%)
40–49	12 (1.2%)	20 (2.1%)	22 (2.3%)	42 (4.4%)	32 (3.3%)	33 (3.4%)	8 (0.8%)	169 (17.5%)
≥50	2 (0.2%)	7 (0.7%)	8 (0.8%)	26 (2.7%)	34 (3.5%)	24 (2.5%)	17 (1.8%)	118 (12.2%)
Age at diagnosis								
<20	1 (0.1%)	1 (0.1%)	1 (0.1%)	4 (0.4%)	5 (0.5%)	2 (0.2%)	0 (0.0%)	14 (1.4%)
20–29	17 (1.8%)	9 (0.9%)	34 (3.5%)	42 (4.4%)	28 (2.9%)	12 (1.2%)	2 (0.2%)	144 (14.9%)
30–39	42 (4.4%)	41 (4.3%)	44 (4.5%)	68 (7.1%)	57 (5.9%)	20 (2.1%)	8 (0.8%)	280 (29.1%)
40–49	43 (4.5%)	33 (3.4%)	36 (3.7%)	68 (7.1%)	47 (4.9%)	29 (3.0%)	9 (0.9%)	265 (27.5%)
≥50	38 (3.9%)	32 (3.3%)	32 (3.3%)	53 (5.5%)	50 (5.2%)	36 (3.7%)	2 (0.2%)	261 (27.1%)
Median diagnostic delay (years)	13.0	8.0	5.0	4.0	2.0	1.9	1.0	4.3
Autopsy*								
No	132 (13.7%)	110 (11.4%)	130 (13.5%)	208 (21.6%)	172 (17.8%)	92 (9.5%)	34 (3.5%)	878 (91.1%)
Yes	9 (0.9%)	6 (0.6%)	17 (1.7%)	27 (2.8%)	15 (1.6%)	7 (0.7%)	5 (0.5%)	86 (8.9%)
Place of death								
Private home	3 (0.3%)	6 (0.6%)	10 (1.0%)	28 (2.9%)	35 (3.6%)	13 (1.3%)	6 (0.6%)	101 (10.5%)
Hospital and other health institution	111 (11.5%)	96 (10.0%)	126 (13.1%)	198 (20.5%)	134 (13.9%)	77 (8.0%)	26 (2.7%)	768 (79.7%)
Not specified	27 (2.8%)	14 (1.5%)	11 (1.1%)	9 (0.9%)	18 (1.9%)	9 (0.9%)	7 (0.7%)	95 (9.8%)

*Including forensic, medicolegal and unspecified autopsies.

PPMS, Primary-progressive multiple sclerosis.; RRMS, Relapsing-remitting multiple sclerosis.

Categorical survival

The median life expectancy for pwMS was 74.3 years (95% CI 73.3 to 75.3), compared with 83.1 years for the general population ($p < 0.001$). For women with MS, the median life expectancy was 75.9 years (95% CI 74.6 to 77.6), and for men with MS, it was 72.0 years (95% CI 70.9 to 73.4), compared with 85.2 years for women ($p < 0.001$) and 80.0 years for men ($p < 0.001$) in the general population. The median life expectancy for pwROMS was 75.0 years (95% CI 73.8 to 76.3) and 69.7 years (95% CI 66.7 to 72.9) for pwPOMS ($p < 0.001$). The survival curves are shown in [figure 1A](#).

Calculated from MS onset ([figure 1B](#)), the median survival time for pwMS was 14.6 years shorter compared with the general population ($p < 0.001$). Correspondingly, the median survival time for women and men with MS was reduced by 14.9 ($p < 0.001$) and 13.4 ($p < 0.001$) years. Similarly, survival from disease onset of pwROMS and pwPOMS was shortened by 12.0 ($p < 0.001$) and 19.3 ($p < 0.001$) years.

The median age at death, and the median time from MS onset to death, stratified by sex and initial disease course, is found in supplemental material (online supplemental table 1).

All-cause mortality

When assessing all-cause mortality, the overall EDR was 6.8 (95% CI 6.42 to 7.09) and SMR was 2.3 (95% CI 2.13 to 2.42, $p < 0.001$) for pwMS compared with the general population. The all-cause EDR and SMR for women were 6.1 (95% CI 5.75 to 6.46) and 2.5 (95% CI 2.25 to 2.67, $p < 0.001$), while the

corresponding numbers for men were 7.9 (95% CI 7.22 to 8.60) and 2.1 (95% CI 1.90 to 2.30, $p < 0.001$). For pwROMS, all-cause EDR and SMR were 5.6 (95% CI 5.28 to 5.98) and 2.2 (95% CI 2.03 to 2.35, $p < 0.001$), whereas for pwPOMS, EDR was 14.5 (95% CI 13.24 to 15.60) and the SMR was 2.6 (95% CI 2.25 to 2.92, $p < 0.001$). The all-cause EDRs and SMRs for the different age groups at onset and onset cohorts are shown in [table 2](#).

The all-cause EDRs for five decades after MS onset are shown in [table 3](#) stratified by sex and disease course.

Cause-specific mortality

Overall, during the study period, the most frequent UCoD was MS ($n = 473$, 49.0%), followed by diseases of the circulatory system ($n = 148$, 15.4%) and neoplasms ($n = 144$, 14.9%).

We found a marked excess in mortality due to epilepsy, SMR 22.4 (95% CI 14.9 to 32.3, $p < 0.001$). Similarly, we found increased cause-specific mortality from diseases of the respiratory system, SMR 1.6 (95% CI 1.17 to 2.09, $p < 0.01$). For this main UCoD category, we found an excess in the number of deaths in men, SMR 1.8 (95% CI 1.12 to 2.61, $p < 0.05$), in pwROMS, SMR 1.5 (95% CI 1.07 to 2.11, $p < 0.05$), in pwMS with onset before 30 years of age, SMR 2.3 (95% CI 1.37 to 3.65, $p < 0.01$) and those with disease onset before 1951, SMR 2.5 (95% CI 1.34 to 4.30, $p < 0.01$). Overall, twenty-one participants died due to pneumonia, SMR 2.3 (95% CI 1.14 to 3.49, $p < 0.01$). For this, UCoD subcategory we found excess

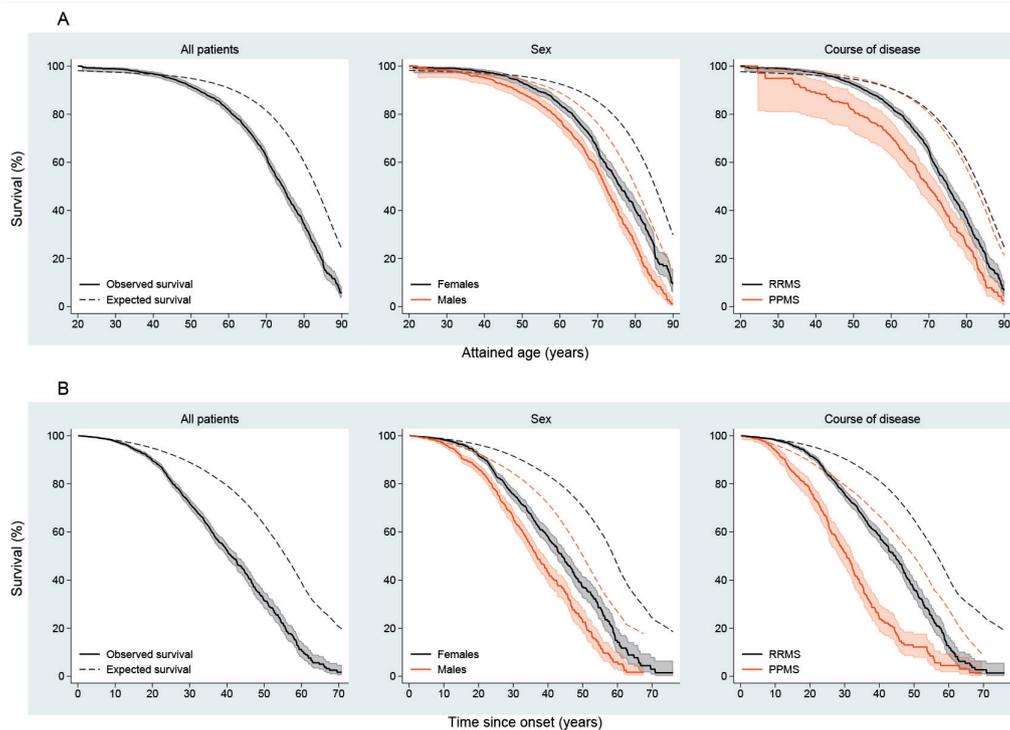


Figure 1 Survival for persons with multiple sclerosis, from birth (A) and disease onset (B), stratified by sex and initial course of disease, in Hordaland and Møre and Romsdal.

mortality both among women with SMR 2.3 (95% CI 1.13 to 4.03, $p < 0.05$) and men with SMR 2.3 (95% CI 1.11 to 4.25, $p < 0.05$), for pwROMS with SMR 2.4 (95% CI 1.34 to 2.82, $p < 0.01$) and among pwMS with disease onset before 1951 with SMR 2.8 (95% CI 1.45 to 6.03, $p < 0.01$) and those experiencing their first MS symptom before 30 years of age with SMR 3.1 (95% CI 1.23 to 6.30, $p < 0.05$).

We found excess mortality due to gastrointestinal cancers in the 1980–1989 onset cohort, SMR 2.2 (95% CI 1.02 to 4.24, $p < 0.05$), but, overall, we could not observe excess mortality due to neoplasms, SMR 1.0 (95% CI 0.82 to 1.15). Although we could not find excess mortality due to diseases of the digestive system in total, there was an increase in SMR among pwMS with onset before age 30 in this main category, SMR 2.4 (95% CI 1.11 to 4.62, $p < 0.05$).

Overall, there was no excess mortality due to diseases of the circulatory system, SMR 1.1 (95% CI 0.97 to 1.34). However, we found excess mortality from diseases of the circulatory system, among women with MS for the total study period, SMR 1.4 (95% CI 1.07 to 1.70, $p < 0.05$), and for the 1970–1979 onset cohort, SMR 1.7 (95% CI 1.20 to 2.39, $p < 0.01$). Death due to underlying acute myocardial infarction was increased in the same subgroups, SMR 1.6 (95% CI 1.02 to 2.33, $p < 0.05$) in women and SMR 1.9 (95% CI 1.05 to 3.22, $p < 0.05$) for the 1970–1979 onset cohort. For the latter subgroup mortality from cerebrovascular diseases was increased, SMR 2.5 (95% CI 1.27 to 4.55, $p < 0.05$).

The cause-specific SMRs for all the reported UCoD categories and selected subcategories are shown in [table 4](#).

All-cause mortality risk before and after the introduction of immunomodulatory therapy

We identified 715 deceased pwROMS. Of these, 559 were diagnosed before 1990, including 190 between 1980 and 1989.

Between 1990 and 1999, 112 pwROMS were diagnosed, and 44 in the subsequent years until 2019.

All-cause mortality risk was lower for pwROMS diagnosed between 2000 and 2019, HR 0.49 (95% CI 0.34 to 0.70, $p < 0.001$) compared with the reference group, that is, those diagnosed between 1990 and 1999 ([table 5](#)). For pwROMS diagnosed before DMTs became available, those diagnosed between 1980 and 1989 had lower risk of mortality, HR 1.7 (95% CI 1.30 to 2.10, $p < 0.001$), than those diagnosed before 1980, HR 2.4 (95% CI 1.94 to 3.05, $p < 0.001$). These findings remained consistent in the sensitivity analysis in which follow-up time was restricted to 20 years (results not shown).

DISCUSSION

In this longitudinal study, we found shortened lifespans and excess mortality in pwMS, corroborating the findings from a recent meta-analysis.⁶ Approximately, 8 out of 10 pwMS died while receiving care at a hospital or another health institution, which is similar to a study from Finland published recently.²⁰

The life expectancy for pwMS was, on average, reduced by 8.8 years, which is similar to the findings in a Canadian population-based study.²¹ The observed 3.9-year difference in median life expectancy between women and men with MS is comparable to the sex difference observed in the general Norwegian population. On average, pwROMS survived, 5.3 years longer than pwPOMS.

When evaluating survivorship from disease onset, the survival of pwMS started to diverge from that of the general population after approximately 10 years of disease duration. Furthermore, this decrement appears to occur earlier in men and is most pronounced for pwPOMS ([figure 1B](#)).

When assessing the effect of age at onset on survival, a later onset appears favourable when attained age is considered.

Table 2 All-cause standardised mortality ratios (SMRs) and excess death rates (EDRs) among persons with multiple sclerosis in Hordaland and Møre and Romsdal counties, Western Norway

	Observed	Expected	SMR (95% CI)	EDR (95% CI)
Sex				
Female	535	218.3	2.5* (2.25 to 2.67)	6.1 (5.75 to 6.46)
Male	429	205.4	2.1* (1.90 to 2.30)	7.9 (7.22 to 8.60)
Course of disease				
PPMS†	237	92.3	2.6* (2.25 to 2.92)	14.5 (13.24 to 15.60)
RRMS‡	715	327.3	2.2* (2.03 to 2.35)	5.6 (5.28 to 5.98)
Unknown	12	N/A	N/A	N/A
Age at onset				
<20	68	17.8	3.8* (2.96 to 4.84)	6.4 (5.77 to 6.86)
20–29	306	102.7	3.0* (2.66 to 3.33)	6.9 (6.47 to 7.25)
30–39	303	134.4	2.3* (2.01 to 2.52)	6.7 (6.04 to 7.24)
40–49	169	93.9	1.8* (1.54 to 2.09)	6.0 (4.78 to 7.05)
≥50	118	74.8	1.6* (1.31 to 1.89)	9.2 (6.03 to 11.79)
Period of onset				
<1950	141	63.7	2.2* (1.86 to 2.61)	13.5 (11.52 to 15.22)
1950–1959	116	55.4	2.1* (1.73 to 2.51)	13.6 (11.07 to 15.61)
1960–1969	147	58.6	2.5* (2.12 to 2.95)	12.3 (10.85 to 13.48)
1970–1979	235	72.8	3.2* (2.83 to 3.67)	12.9 (12.13 to 13.61)
1980–1989	187	82.5	2.3* (1.95 to 2.61)	6.3 (5.50 to 6.93)
1990–1999	99	53.3	1.9* (1.51 to 2.26)	2.9 (2.19 to 3.54)
2000–2015	39	36.0	1.1 (0.77 to 1.48)	0.2 (-0.62 to 0.76)
Period of diagnosis				
<1980	475	177.5	2.7* (2.44 to 2.93)	15.8 (14.94 to 16.65)
1980–1989	249	97.2	2.6* (2.25 to 2.90)	10.3 (9.39 to 11.03)
1990–1999	152	73.3	2.1* (1.76 to 2.43)	4.4 (3.66 to 4.95)
2000–2019	88	75.7	1.2 (0.93 to 1.43)	0.4 (-0.19 to 0.94)
Total	964	423.6	2.3* (2.13 to 2.42)	6.8 (6.42 to 7.09)

*p < 0.001.
 †Primary progressive multiple sclerosis.
 ‡Relapsing-remitting multiple sclerosis.
 EDR, excess death rates; SMR, standardised mortality ratios.

However, in terms of absolute survival time in years, those who experience onset of MS at younger ages survive the longest (online supplemental table 1). A similar phenomenon has been observed for clinical, neuropsychological and radiologic markers of disease progression when comparing adult-onset to paediatric-onset MS, where the paediatric group requires longer

time to achieve specific disability and MRI milestones but does so at younger age.²²

As shown in table 2, the all-cause SMR initially increased for pwMS with disease onset from before 1950 and up to 1979, whereas EDR remained stable in the same period. For the subsequent onset cohorts, we observed a decrease in comparative

Table 3 Excess death rate (EDR) with 95% CIs by decade after disease onset in deceased persons with multiple sclerosis, in Hordaland and Møre and Romsdal counties, Western Norway

Decade after disease onset					
	First	Second	Third	Fourth	Fifth
Women	0.3 (-0.17–0.71)	3.6 (3.01–4.12)	13.0 (12.11–13.81)	16.3 (14.29–17.96)	23.8 (19.12–27.46)
RRMS*	0.2 (-0.36–0.56)	3.0 (2.41–3.51)	11.0 (9.98–11.76)	12.5 (10.26–14.35)	21.4 (16.30–25.33)
PPMS†	1.8 (-0.71–3.14)	8.7 (5.73–10.74)	30.1 (26.64–32.57)	48.5 (42.73–52.51)	45.2 (29.92–53.64)
Men	0.5 (-0.59–1.24)	5.9 (4.70–6.90)	16.1 (14.24–17.68)	24.9 (21.09–28.01)	23.2 (11.53–31.99)
RRMS‡	0.1 (-1.01–0.91)	4.2 (2.87–5.13)	14.3 (12.37–15.84)	18.8 (14.58–22.11)	24.0 (11.90–32.91)
PPMS§	2.0 (-1.57–4.06)	13.9 (9.95–16.79)	24.8 (18.28–29.48)	62.7 (50.73–70.96)	17.3 (-39.98–43.02)
Total	0.4 (-0.09–0.77)	4.4 (3.88–4.93)	14.1 (13.26–14.88)	19.2 (17.39–20.74)	23.6 (18.97–27.46)

*n=412.
 †n=115.
 ‡n=303.
 §n=122.
 PPMS, Primary progressive multiple sclerosis.; RRMS, Relapsing-remitting multiple sclerosis.

Table 4 Overall cause-specific standardised mortality ratios (SMRs) in persons with multiple sclerosis for selected* underlying causes of death (UCoDs)

	Observed	Expected	SMR	95% CI
Neoplasms (total)	144	147.5	1.0	0.82 to 1.15
Malignant neoplasm of colon, rectum and anus	23	18.8	1.2	0.78 to 1.84
Malignant neoplasm of trachea, bronchus, lung	30	28.5	1.1	0.71 to 1.5
Malignant neoplasm of breast	10	14.3	0.7	0.34 to 1.29
Diseases of the nervous system and the sense organs (total)	510	14.7	34.6†	31.7 to 37.8
Multiple sclerosis	473	1.9	248.9†	222.4 to 267.0
Epilepsy	28	1.3	22.4†	14.9 to 32.3
Diseases of the circulatory system (total)	148	129.4	1.1	0.97 to 1.34
Acute myocardial infarction	55	45.4	1.2	0.91 to 1.58
Other ischaemic heart diseases	23	19.9	1.2	0.73 to 1.73
Cerebrovascular diseases	35	29.4	1.2	0.83 to 1.65
Diseases of the respiratory system (total)	49	30.9	1.6‡	1.17 to 2.09
Pneumonia	21	9.2	2.3‡	1.14 to 3.49
Other chronic lower respiratory diseases	18	16.2	1.1	0.66 to 1.75
Diseases of the digestive system (total)	16	13.4	1.2	0.68 to 1.94
External causes of morbidity and mortality (total)	29	32.2	0.9	0.60 to 1.30
Accidents	18	20.3	0.9	0.53 to 1.40
Suicide and intentional self-harm	11	10.5	1.0	0.52 to 1.87
Unknown underlying cause of death	32	N/A	N/A	N/A

*The following main categories according to the European Shortlist for Causes of Death (ESLCoD) are not reported (see Methods); infectious and parasitic diseases, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, endocrine, nutritional and metabolic diseases, mental and behavioural disorders, diseases of the skin and subcutaneous tissue, diseases of the musculoskeletal system/connective tissue, diseases of the genitourinary system, complications of pregnancy, childbirth and puerperium, certain conditions originating in the perinatal period, congenital malformations and chromosomal abnormalities and symptoms, signs, ill-defined causes.

†p<0.001.

‡p<0.01.

and absolute excess mortality as measured by all-cause SMR and EDR, corroborating previous findings from Hordaland.³ However, and as pointed out by the authors of a recent meta-analysis, which failed to demonstrate a reduction in all-cause SMR in pwMS during the past 65 years⁶, shorter follow-up time for participants enrolled towards the end of a study period,

among other factors, offers a plausible explanation for the apparent improvement in survivorship observed in previously published reports from Scandinavia.^{2,4}

When assessing all-cause mortality by age of MS onset, SMR was highest for the youngest onset group, and lowest for the oldest onset group, implying a higher relative mortality risk for pwMS that experience early onset compared with the general population (table 2). This observation is expected when acknowledging that competing mortality risks increase with age, and when considering that mortality in the younger background population is low.

In absolute terms, however, we found similar EDRs for all the different age at onset groups, apart from the oldest (≥50 years) group (table 2). Current age was recently shown, in a study modelling EDR trajectories in a large cohort of pwMS from France, to have a stronger effect on mortality in pwROMS compared with duration of disease.²³ In the present study, we did not find an excess mortality during the first decade after disease onset, but after more than 10 years of disease duration, we found a time-dependent successive increase in EDR (table 3), which corroborates findings from previous reports.^{18,19}

As expected, the cause-specific mortality due to MS was high (table 4). The SMR for epilepsy was also considerable and comorbid epilepsy has been associated with increased risk of mortality in pwMS.²⁴ However, 26 out of 28 deaths in this subcategory occurred in patients experiencing onset before 1959. Thus, epilepsy appears to be a historical UCoD in this longitudinal study population.

Cancer mortality was not increased among patients with RRMS, nor among the latest onset cohorts, which constitute patients most likely exposed to DMTs. Excess mortality from

Table 5 All-cause mortality risk in relapsing-remitting multiple sclerosis by period of diagnosis, sex, age at onset and diagnostic delay

	HR	95% CI	P value
Period of diagnosis			
<1980	2.4	1.94 to 3.05	<0.001
1980–1989	1.7	1.30 to 2.10	<0.001
1990–1999	Reference	–	–
2000–2019	0.49	0.34 to 0.70	<0.001
Sex			
Women	Reference		
Men	1.4	1.18 to 1.59	<0.001
Age at onset			
<20	Reference	–	–
20–29	1.4	1.07 to 1.88	0.016
30–39	1.9	1.44 to 2.58	<0.001
40–49	3.2	2.33 to 4.52	<0.001
≥50	8.5	5.83 to 12.39	<0.001
Diagnostic delay			
<2 years	Reference	–	–
2–4 years	1.4	1.13 to 1.74	0.002
5–10 years	1.7	1.34 to 2.05	<0.001
>10 years	2.7	2.25 to 3.34	<0.001

gastrointestinal neoplasms was only observed for the 1980–1989 onset cohort, possibly due to fluctuations in cancer incidence.

Among pwMS with onset before age 30, we found excess mortality due to diseases of the digestive system, but not in total (table 4).

Overall, we found excess mortality due to disease of the circulatory system in women and for the 1970–1979 onset cohort. Indeed, pwMS, and females more than males, appear to have an increased cardiovascular disease mortality.²⁵ The observed increase in comparative mortality for the 1970–1979 onset cohort is arguably a reflection of known cardiovascular risk factors, for example, smoking, and high dietary intake of saturated fats, which previously were more common.

We observed an excess in mortality from diseases of the respiratory system, particularly pneumonia, and most evident in pwMS with disease onset before 30 years of age. Progressive disability accumulation and immobility are known risk factors for developing respiratory infections, including aspiration pneumonia, which are common causes of death in pwMS.²¹

When comparing all-cause mortality risk for pwROMS before and after the start of the DMT era, and by using pwROMS diagnosed between 1990 and 1999 as the reference group, we found the risk to be highest among those diagnosed before 1980. Between 1980 and 1989, this risk decreased, and after DMTs were made readily available between 2000 and 2019, this risk was more than halved (table 5).

We suggest that several healthcare improvements, not only access to DMTs, are associated with the observed improvement in all-cause mortality risk for pwROMS, but also the implementation of MRI contributing to reduced diagnostic delay and better symptomatic therapies (table 1).

Strengths and limitations

The use of national health registries, a well-defined study population, and the long duration of follow-up are strengths of the present study.

However, our study has limitations. During the study period, different diagnostic criteria have been applied, including outdated revisions based primarily or exclusively on clinical assessment, and without the use of advanced ancillary examinations. The clinical application of different diagnostic criteria, in combination with early initiation of DMT, is associated with pwMS reaching disability milestones at a slower rate.²⁶ Following a diagnosis of MS, early exposure to DMTs, or treatment of disease related symptoms and signs, could convey beneficial effects on survival and mortality. However, and since we did not have detailed data on symptomatic therapy or DMT use, we are unable to elaborate on these potential effects.

Due to the longitudinal study design, pwMS diagnosed during the earliest periods may have inherent differences in disease severity and interval from onset to diagnosis. The median diagnostic delay from MS onset varied noticeably for the different onset cohorts (table 1). Using survival measures based on time of disease onset negates this effect partially, but a person's recollection of their first suggestive symptom of MS is subject to recall bias, particularly for pwMS brought to late diagnostic attention or who initially developed mild or unspecific transient symptoms. Furthermore, retrospective determination of disease onset based on suggestive symptomatology, as provided by pwMS themselves or through scrutinising medical records, is unlikely to be accurate, especially when considering the increasing amount of evidence of a protracted prodromal, preclinical and presymptomatic phase in MS.^{27–29}

For the survival and mortality analyses, we were unable to evaluate objective measures of individual disease severity, for example, frequency of relapses and clinical signs of disability progression, and paraclinical evidence of disease activity, that is, formation of new lesions on MRI and accelerated brain atrophy. We did not have comprehensive data on smoking history for estimating the amount of tobacco exposure in the study population. Smoking in pwMS has been associated with disability progression, conversion to SPMS and premature mortality.^{30–31} Similarly, we did not have access to data on comorbid conditions to assess individual disease burden beyond MS. Comorbidities are common in pwMS and affect disability progression and survival negatively.^{32–33} This also pertains to certain types of malignancies, which appear to be more prevalent among pwMS,³⁴ and the incidence of cancer was higher among pwMS in Norway after DMTs became available.¹⁰ However, in the present study, we did not find excess cancer mortality among persons considered eligible for treatment with DMTs, that is, pwROMS.

CONCLUSION

In summary, our study provides longitudinal real-world data in a well-defined cohort of pwMS demonstrating shortened lifespans compared with the general population. We observed a decrease in excess mortality parallel to the reduced delay from MS onset to diagnosis, which could imply a prognostic role of early diagnostic verification. For pwROMS, those diagnosed after the start of the DMT era had a more favourable outcome. We did not observe an increase in cancer or infectious disease-related mortality after DMTs were introduced.

To identify disease features associated with reduced longevity in pwMS, future studies should employ detailed clinical data, particularly exposure to specific DMTs and treatment of disease manifestations and comorbidities, as well as paraclinical measures of individual disease severity, including promising biomarkers.

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