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ORIGINAL ARTICLE

Standardized mortality ratios in multiple sclerosis: Systematic review with meta-analysis

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Objective: To perform a meta-analysis of all-cause, cause-specific and gender-specific standardized mortality ratio and crude mortality rate for people with multiple sclerosis. We also examined the temporal trends in this data.

Methods: Medline, Cochrane Library and Scopus were searched. Keywords were "multiple sclerosis" and "standardized mortality ratio" or "Standardized Mortality Ratio". We included longitudinal studies with available data on the number of deaths, follow-up period, person years and reports of standardized mortality ratio (SMR). Crude mortality ratio (CMR) was calculated and SMR was extracted. CMRs and log-SMR were pooled by the method of inverse variance. Meta-regression models were used to investigate temporal trends.

Results: Fifty-seven articles were screened. Fifteen studies were included covering a period 1949–2013 (160,000 patients; 21,225 deaths). The all-cause SMR for people with MS was 2.61 (95% CI 2.58 to 2.65). For men this was 2.47 (95% CI 2.42 to 2.52) and for women 2.57 (95% CI 2.53 to 2.61). The CMR was 13.45/1000 person years. Cause-specific SMR was 1.74 (1.67 to 1.81) for CVD, 4.70 (4.45 to 4.87) for respiratory disease and infection, 1.81 (1.64 to 2.0) for accident and suicide and 0.99 (0.93 to 1.06) for cancer. Meta-regression analysis of the SMR compared to midpoint follow-up year revealed no relationship (co-efficient 0.001, $p = .98$).

Conclusions: People with multiple sclerosis (MS) have reduced overall survival and increased risk of death from cardiovascular, respiratory and infectious disease as well as accidents and suicide. This does not appear to have changed over the last 65 years.

KEYWORDS
meta-analysis, mortality, multiple sclerosis, standardized mortality, systematic review

1 | INTRODUCTION

Multiple sclerosis (MS) is a progressive demyelinating disease characterized in the majority by acute attacks, separated by periods of stability.[1] The accumulation over time of MS lesions leads to disability and an increased risk of mortality over decades.[1,2] Due to the heterogeneity and the fact that disability often develops long after disease onset, short-term studies often fail to capture the full impact of the disease. Therefore, long-term population-based, observational studies from sources such as registries are required to accurately assess both morbidity and mortality in MS. The validated outcome of mortality reported as, standardized mortality ratio

(SMR), remains unambiguous and allows for comparison over time and between populations.

Mortality data may also allow for evaluation of the long-term effects of disease modifying treatments (DMTs) in a real-world setting, the impact of early and effective diagnosis, co-morbidities, lifestyle and environmental factors.[3] The SMR, which assesses the death rate, adjusted for age and sex, in the MS population when compared to the general population, assesses mortality risk. However, the SMR is dependent on duration of follow-up and the characteristics of those included in the studies, a factor that is influenced by the method and breadth of data collection.

In 2015, a meta-analysis of the SMR in MS by Manouchehrinia et al. (2015) found a 2.8 times greater risk of mortality in MS patients with no temporal trend over time from 1949–2012.[2] Consensus regarding the increased mortality compared to the general population was confirmed in later studies which showed an SMR for patients with MS between 2.45–2.92.[3–9] The lack of a temporal trend in the meta-analysis by Manouchehrinia et al. was in contrast to the improved survival over time demonstrated by the study by Koch-Henriksen et al., who found over fifty percent improvement in SMR in a 1990–1999 cohort compared to a 1950–1959 cohort.[7] While a study by Lunde et al. also reported a dramatic improvement in SMR of 0.7 in a cohort from 1997–2012.[9] This contrasting evidence was later supported by large-center studies in Denmark, Sweden and Norway which included 43,852 patients demonstrating an improved survival over time: citing early diagnosis, disease modifying treatment, improved treatment of co-morbidities and improved rehabilitation as potential causes.[7–9] However, differences in mortality trends are subject to a time bias and changing methods of data collection which may explain the dramatic improvements seen in later cohorts.

For this reason, we aimed to update the findings from the meta-analysis by Manouchehrinia et al. (2015), but also to investigate whether there is a temporal trend in all-cause mortality among people with MS. This knowledge can aid in the interpretation of treatment effects on overall mortality of people with MS going forward.

2 | MATERIAL AND METHODS

In performing this systematic literature review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol.[10]

2.1 | Search strategy and study selection

A comprehensive literature search was performed using Cochrane Library, Scopus and Medline by two independent investigators. The search strategy for all three databases was with the Mesh terms “Multiple Sclerosis Mortality” and “standardized mortality ratio” or “standardized mortality ratio” for publication in the period 2014–2020. This period was chosen as the previous meta-analysis included all published data up until November 2014. The last date searched was the May 18, 2020. Reference lists were screened for additional papers.

2.2 | Eligibility criteria

Original longitudinal cohort studies which reported overall all-cause SMR or age-matched hazard ratio for multiple sclerosis patients when compared to the age- and sex-matched counterparts were included. Studies were required to report total population size, number of deaths and length of study period to be included. Only studies published in English were included. For multiple studies using the same cohort, the study with the longest duration of follow-up that met the inclusion criteria was included.

2.3 | Ethics

No ethical approval was needed because data from previously published studies in which informed consent was obtained by primary investigators was retrieved and analyzed.

2.4 | Data extraction

Total number of patients, number of deaths, mean follow-up period, person year, study type and duration were extracted from included studies meeting eligibility criteria without additional quality assessments regarding biases or certainty. Each investigator extracted data in a blinded approach from literature databases and references identified in the papers. Each study's corresponding author was contacted to provide information on people years where this information was not published. Where crude mortality ratio (CMR) was not reported, this was calculated using the person years. SMRs with 95% confidence interval (CI) were extracted for all-cause mortality, gender-specific mortality and cause-specific mortality for respiratory, cardiovascular disease, suicide and cancer. If cause-specific mortality was not reported, it was obtained from the relevant publications of the same cohort.

2.5 | Data analysis

2.5.1 | SMR

Included studies’ SMRs were pooled using inverse variance models for all-cause, cause-specific and sex specific SMR. Log-SMR was used in the analysis as it has a more normal sampling variance that is preferred when the reference populations between studies are different. The fixed effects model was applied.

2.5.2 | CMR

For studies where CMR was not reported, it was calculated by dividing the number of deaths during a study period by the person year follow-up time. Where person year was not reported it was estimated by mean follow-up time multiplied by number of persons.[9] The 95% CI for the CMR was obtained as below. CMRs were pooled by inverse variance model. The random effects model was also applied.

$$95\,\%\,\mathrm{CI} = \mathrm{CMR} \pm 1.96\sqrt{\mathrm{CMR}\,x\,(1-\mathrm{CMR}) \div \mathrm{Personyearfollow\,up}}$$

2.5.3 | Trends in SMR over time

A meta-regression model was used to determine whether study date was associated with effect size differences with log-SMR being the dependent variable and the middle year of follow-up period being the independent variable.

2.5.4 | Heterogeneity

Heterogeneity between studies was evaluated with the I^2 statistic. In the case of high heterogeneity, influence analysis was used to establish causes of high heterogeneity.

2.5.5 | Publication bias

A funnel plot was used for visual assessment of publication bias. An adjusted rank correlation test was used to complement the funnel graph. Egger's regression test was used for investigation of small study bias.

2.5.6 | Sensitivity Analysis

The cause-specific SMR were estimated excluding direct cause of death data to investigate whether cause of death reporting affected the findings.

Statistical analyses were performed using R version 4.0.3 20.20.10 and RStudio version 1.3.1093.

3 | RESULTS

3.1 | Study selection

A total of 56 studies were identified using the search strategy, with one additional study being identified through study citations. Of these, 18 duplicates were removed. Thirty-nine studies were screened for eligibility criteria through reading of abstracts. Thirty studies were excluded because they either did not include multiple sclerosis, reported on DMT, reported only co-morbidities, reported on incidence or were not longitudinal cohort studies. Nine articles remained for full text analysis of which two were excluded because no overall SMR/HR was reported.[11,12] Seven studies were used in qualitative synthesis and meta-analysis, in addition to the 12 studies identified through our search terms and which were already included in the meta-analysis by Manouchehrinia et al. in 2014 (Figure 1). Table 1 summarizes the 19 included studies. Of these 19 studies, seven were in addition to the previous meta-analysis adding 156,241 new patients and 1,312,210 person years to the original cohort of 27,423 patients and 437,832 person years. A total of 17 studies were included in the CMR meta-analysis. Two studies were excluded as person year could not be established.[9,13]

A pooled total of 185,557 individuals with 26,770 deaths and 1,750,042 person year follow-up were included in these analyses. Person year follow-ups ranged from 3.9/1000 in United Kingdom (UK) to 420/1000 person years in France. All observational cohorts were informed with register data and from high-income settings.

3.2 | CMR

The pooled CMR was 13.45/1000 person years (95% CI 9.56 to 17.34, $I^2 = 100\%$, $p = 0$) (Figure 2).

3.3 | SMR

The SMR ranged from 1.30 (95% CI 0.45 to 3.72) in France to 3.51 (2.63; 4.69) in the UK.[14,15] The pooled SMR from the fixed effects model for all-cause mortality was 2.61 (95% CI 2.58 to 2.65, $I^2 = 98\%$, $p < .01$) (Figure 3). When stratified by sex, the pooled SMR was 2.47 for men (95% CI 2.42 to 2.52, $I^2 = 95\%$, $p < .01$) and 2.57 (95% CI 2.53 to 2.61, $I^2 = 98\%$, $p < .01$) for women.

3.4 | Heterogeneity in SMR

Measures of heterogeneity confirmed a substantial proportion of variability between studies ($I^2 = 98\%$, $Q = 760$, $t^2 = 0.038$, $p < .01$). The prediction interval for SMR ranged from 1.63 to 3.83. Causes of high heterogeneity were determined by influence analysis (Figure S1). Four studies[3,7,8,16] were excluded due to a higher overall SMR of 2.66 (95% CI 2.58 to 2.75, $I^2 = 63\%$) with moderate heterogeneity.

3.5 | Cause-specific SMR

The pooled cause-specific SMRs are presented in Figure 4. Eleven studies in total reported cause-specific SMR: six of the studies.[1,10–12,15,16]

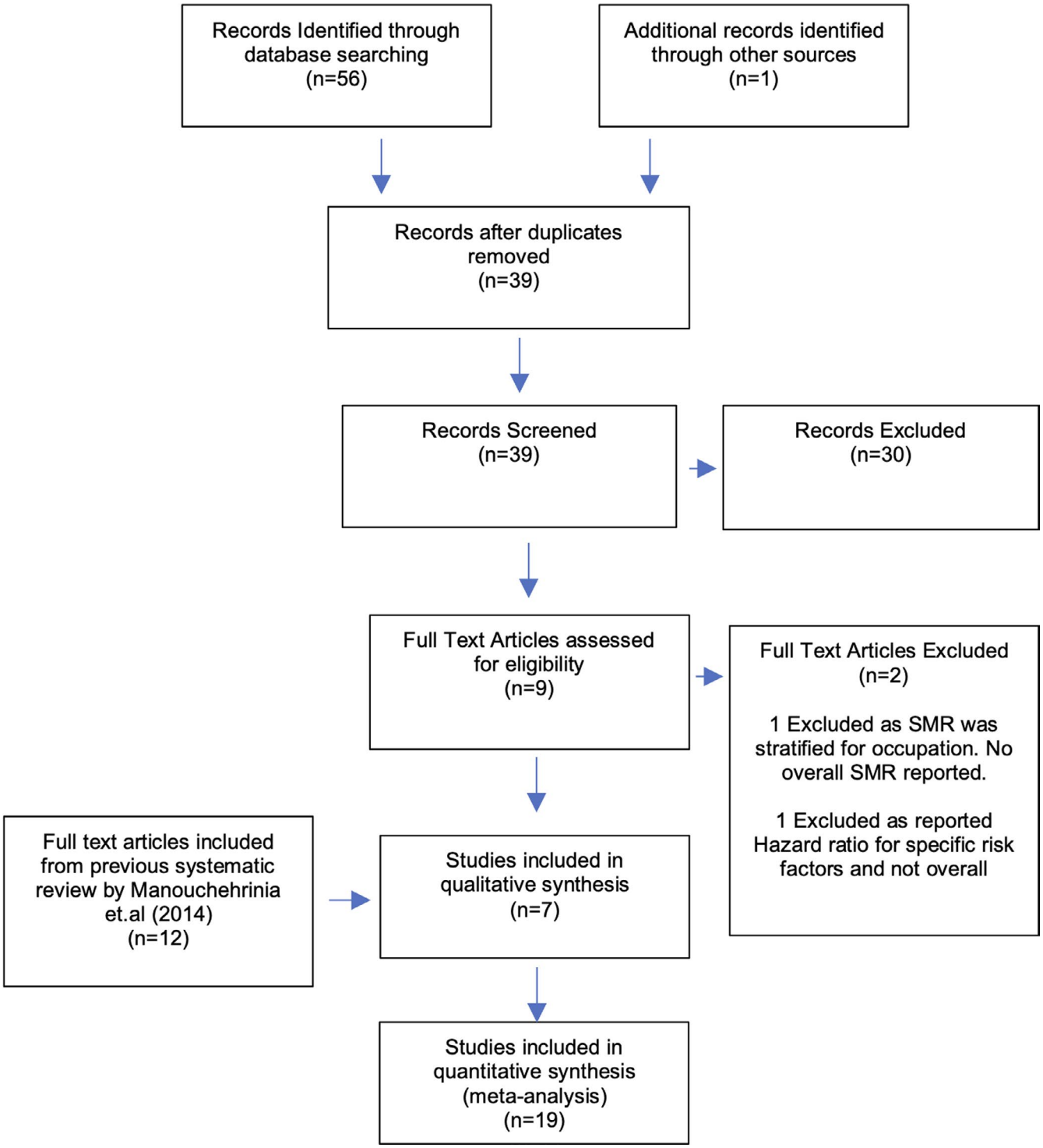

FIGURE 1 Flow chart of study procedure

used the underlying cause of death as their definition for cause-specific SMR, four used direct cause of death[3,5,7,17] and one did not specify.[18]

3.5.1 | Cardiovascular disease

A total of 10 studies reported SMR for cardiovascular disease. Of these 10 studies, four were in addition to the previous publication.[4,6,8,9] The SMR for cardiovascular disease was 1.74 (95% CI 1.67 to 1.81, $I^2 = 94\%$, $p < .01$).

3.5.2 | Respiratory illness and infection

Eight studies reported an SMR for respiratory illness and infection. Of these eight studies, three were new to the cohort of the previous

TABLE 1 Study characteristics

ID	Study	Patients (*n*)	Deaths (*n*)	Person years	Study period	Underlying or direct cause of death	CMR (95% CI)	SMR (95% CI)	SMR Female (95% CI)	SMR Male (95% CI)
1	Hansen et al. (Denmark)[17]	9881	4254	207,862	1949–1997	Underlying	20.46 (19.85–21.7)	2.89 (2.81–2.98)	3.14 (3.01–3.17)	2.66 (2.54–2.78)
2	Sadovnick et al. (Canada)[13]	2348	115		1972–1985	NA		2.0 (1.63–2.36)		
3	Torklidsen et al. (Norway Hordeland County)[15]	878	198	35,120	1953–2005	Direct	5.63 (4.85–6.42)	2.66 (2.31–9.8)	3.11 (2.58–3.27)	2.23 (1.81–9.12)
4	N. Koch-Henriksen et al. (Denmark)[7a]	12,847	6102	339,483	1950–2015	NA	17.98 (17.53–18.42)	2.45 (2.39–2.51)	2.53 (2.41–2.65)	2.36 (2.25–2.48)
5	Lunde et al. (Norway Hordeland County)[9a]	1388	291		1953–2012	Direct		2.7 (2.4–3.0)	2.9 (2.903–3.4)	2.5 (2.1–2.9)
6	Ragonese et al. (Italy)[19b]	183	30	4188	1960–2007	NA	7.16 (4.6–9.71)	2.12 (1.32–3.46)	2.22 (1.23–4.0)	2 (0.89–4.46)
7	Smestad et al. (Norway- Oslo)[18]	386	263	12,172	1972–2005	Direct	6.8 (5.9–7.7)	2.47 (2.09–6.38)	3.4 (3–3.9)	2.2 (1.9–6.16)
8	Sumelahti et al. (Finland)[27]	1614	219	32,165	1971–2006	NA	21.6 (19.02–27.22)	2.8 (2.6–6.15)	2.94 (2.36–3.62)	2.02 (1.56–6.17)
9	Leray et al. (France)[19]	1879	68	23,906	1976–2003	NA	2.84 (2.15–3.52)	1.3 (1–8.18)	1.5 (1.1–2.1)	1.1 (0.8–8.9)
10	Burkill et al. (Sweden)[8 a,b]	29,617	9563	358,366	1968–2012	Underlying	26.68 (25.78–27.59)	2.92 (2.86–2.99)	2.06 (2.97–3.15)	2.75 (2.65–2.84)
11	Kingwell et al. (Canada)[28]	6917	1025	77,950	1980–2007	Underlying	13.14 (12.34–13.94)	2.88 (2.71–3.07)	3.01 (2.79–3.25)	2.68 (2.43–2.96)
12	Hirst et al. (Wales)[29]	366	218	5609	1985–2006	Underlying	38.86 (33.8–43.92)	2.79 (2.44–3.18)	1.65 (1.55–1.76)	1.3 (1.21–1.4)
13	Leary et al. (France)[3a]	27,603	1569	420,801	1980–2012	NA	3.79 (3.55–3.92)	1.48 (1.41–1.55)	3.14 (2.67–3.69)	2.26 (1.79–2.85)
14	Rodríguez-Antigüedad Zarranz et al. (Spain)[20]	1283	89	16,422	1987–2011	NA	5.41 (4.29–6.54)	2.78 (2.2–3.38)	2.73 (1.94–3.51)	3.26 (2.27–4.24)
15	Kingwell et al. (Canada)[6a]	6629	1416	104,236	1986–2013	Underlying	13.58 (12.88–14.29)	2.71 (2.55–2.87)	2.79 (2.61–2.98)	2.53 (2.32–2.76)
16	Sandi et al. (Hungary)[4a]	740	121	10,303	1993–2013	Underlying	11.74 (9.66–13.82)	2.52 (2.1–3.01)	2.57 (2.03–3.2)	2.46 (1.82–3.25)
17	Manouchehrinia et al. (UK)[30]	923	80	18,717	1994–2012	Not specified	4.27 (3.34–5.2)	1.99 (1.7–2.33)	1.8 (1.4–2.3)	2.41 (1.95–2.69)
18	Lalmohamed et al. (UK)[15]	1270	69	3937	2001–2008	Direct	17.52 (13.42–21.62)	3.51 (2.63–4.69)	3.94 (2.73–5.68)	2.96 (1.84–4.77)
19	Foloun et al. (France)[5a,b]	78,805	1080	78,805	2012–2013	NA	13.7 (12.88–14.58)	2.56 (2.41–2.72)	2.55 (2.5–2.75)	2.58 (2.34–2.83)

Note:: Person years estimated from mean follow up period.

Abbreviations: CMR, crude mortality ratio; SMR, standardised mortality ratio.

[a]Studies in addition to previous meta-analysis.

[b]Calculated 95% CI. Used in cause specific SMR analysis. Cause of death definitions were not applicable in those studies that did not investigate this.

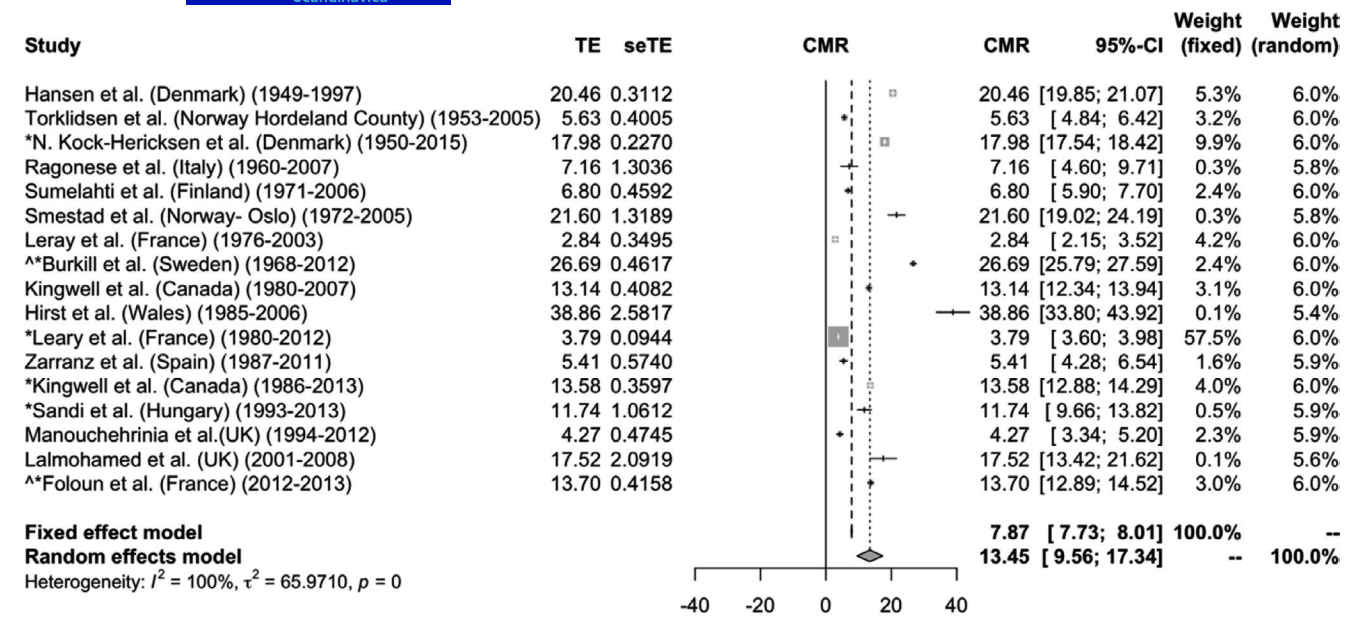

FIGURE 2 Forest plot of crude mortality ratio sored by cohort's follow-up period midpoint year (*studies added to updated meta-analysis)

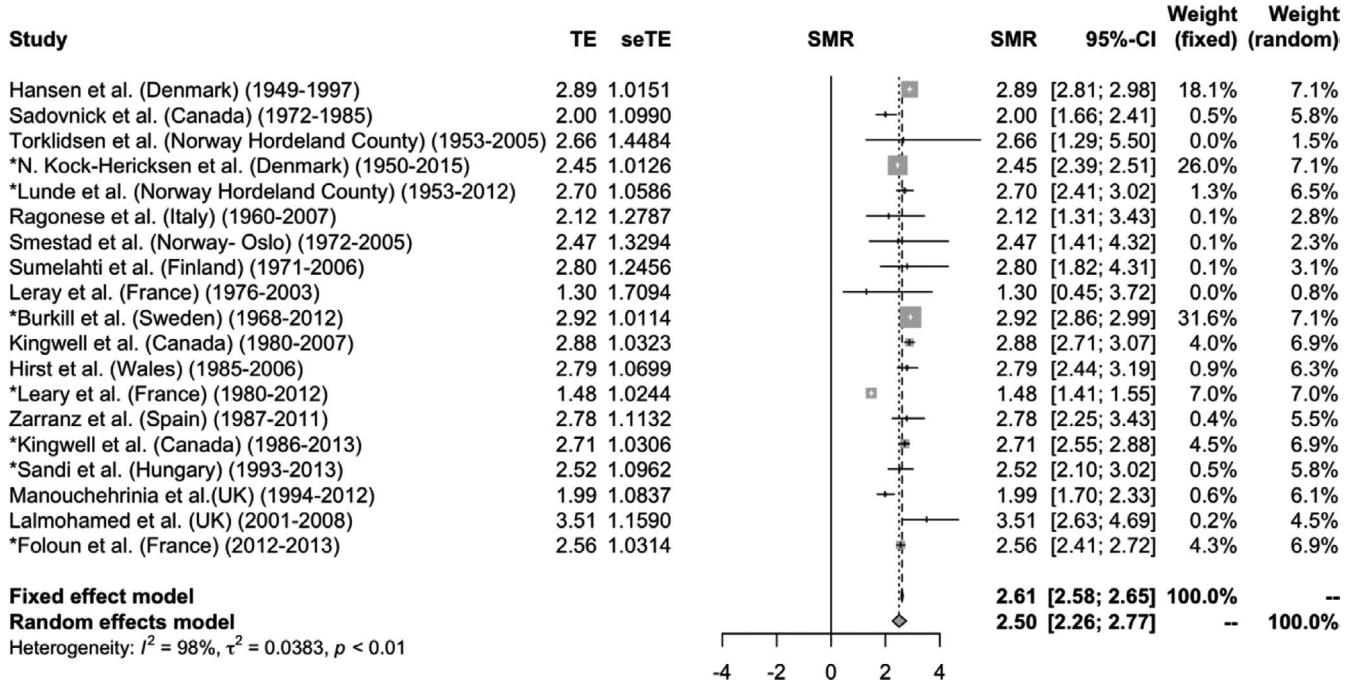

FIGURE 3 Forest plot of the pooled standardized mortality ratio (SMR) data, arranged by the respective cohort's midpoint year in the follow-up period (*studies added to updated meta-analysis)

meta-analysis.[6,8,9] The SMR for respiratory illness and infection was 4.70 (95% C.I. 4.54 to 4.87, I^2 = 97%, p < .01) in the main analyses and 4.60 (95% CI 4.43 to 4.8) when direct cause data was removed in a sensitivity analysis.

3.5.3 | Accident and suicide

Eleven Studies reported an SMR for accident and/or suicide. Two studies reported on accident only,[6,8] whereas four studies

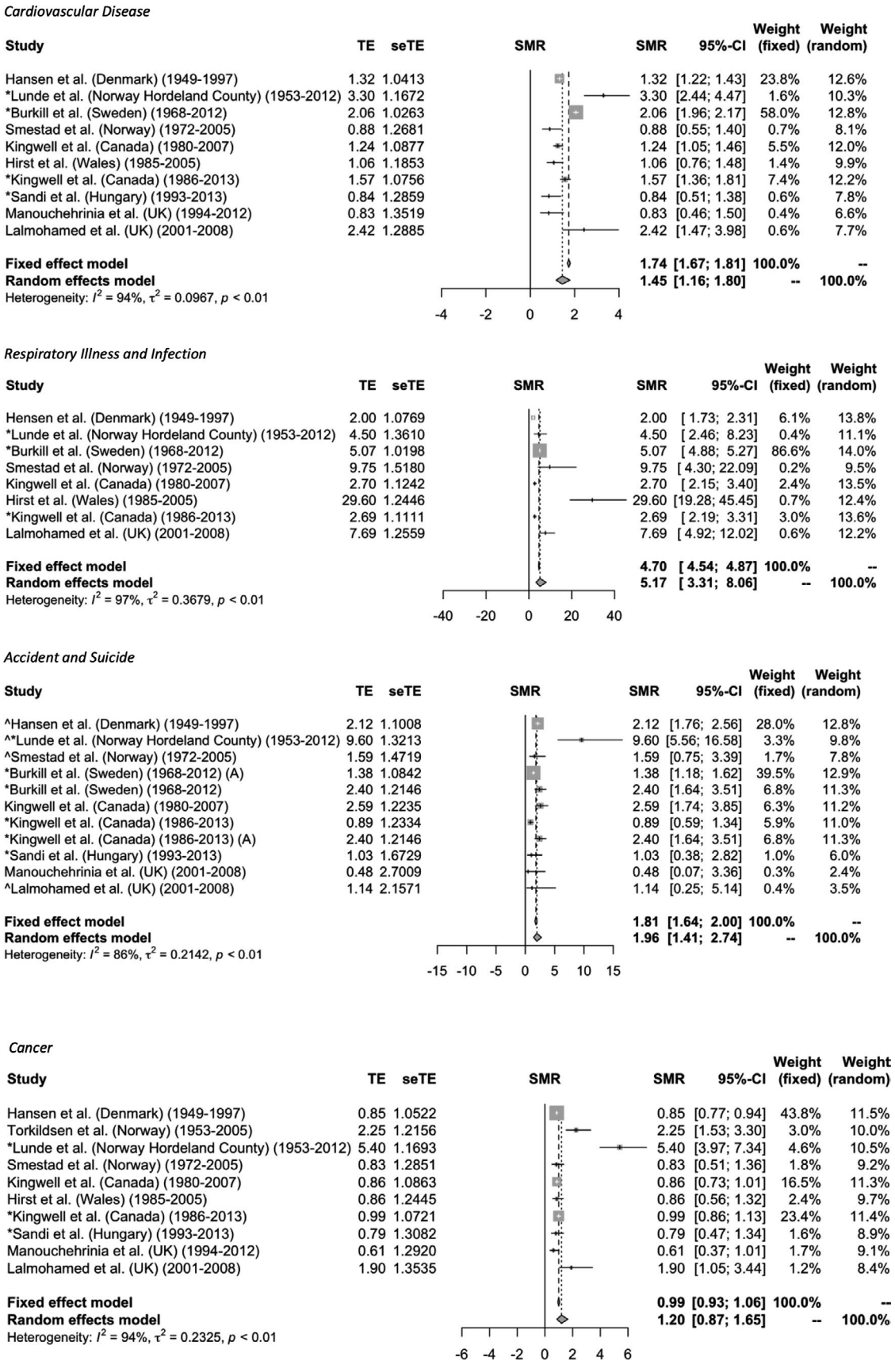

FIGURE 4 Forest plot of causes specific standardized mortality rates (SMR) due to cardiovascular disease, respiratory illness and infection, accident and suicide, and cancer. SMR, standardized mortality ratio; CVD, cardiovascular disease; *studies in addition to previous meta-analysis. ^accident and suicide. (A) accident only

reported on both accident and suicide.[9,15,17,18] The remaining five studies commented on suicide only. The pooled SMR for accident and suicide was 1.81 (95% CI 1.64 to 2.00, $I^2 = 86\%$, $p < .01$). In a subset analysis where studies that reported on accident only were removed, the SMR was 2.13 (95% C.I. 1.86 to 2.44, $I^2 = 85\%$, $p < .01$).

3.5.4 | Cancer

A total of 10 studies reported on cancer. Of the 10 studies, three were in addition to the previous meta-analysis.[4,6,9] The SMR for cancer was 0.99 (95% CI 0.93 to 1.06, $I^2 = 94\%$, $p < .01$).

3.6 | Time trends

Using meta-regression models, we were not able to reject the null hypothesis of no effect of time on SMR. This was true for both all-cause SMR (co-efficient 0.001 (change in log-SMR/year), 95% CI −0.0099 to 0.0102, $p = .98$) (Figure 5) and CMR (co-efficient −0.0655 (deaths/1000 person/year, 95% CI −0.43 to 0.3, $p = .72$). For males, the co-efficient was 0.0012 (CI −0.011 to 0.013, $p = .85$) and for females, −0.0036 (95% CI −0.15 to 0.01, $p = .53$).

3.7 | Publication bias

Visual inspection of the funnel plot did not reveal asymmetry in the result of all-cause SMR (Figure S1). Further inspection with rank correlation test ($p = .25$) and Egger's test ($p = .33$) supported this.

4 | DISCUSSION

In this study, we carried out a meta-analysis on the SMR for MS, updating results from a previous 2015 meta-analysis. A SMR is a valuable measure to identify the apparent risk of dying at a given age, given that the patient has also been diagnosed with MS. The SMR is calculated using the total number of observed deaths divided by the total number of expected deaths for patient's age- and sex-matched counterparts. If a SMR is greater than one, this suggests that there are more deaths in the studied group than would be expected for the general population. If the SMR is consistent over time, it suggests that any secular change in population survival over time is shared by both the MS group and general population. A total of seven large-center studies have been published since the meta-analysis by Manouchehrinia et al. (2015) was completed. Inclusion of the recent studies increased the total patient numbers to 160,000 compared to 27,423 in the previous meta-analysis. In this study which included the significant increase person years, we found the overall SMR for

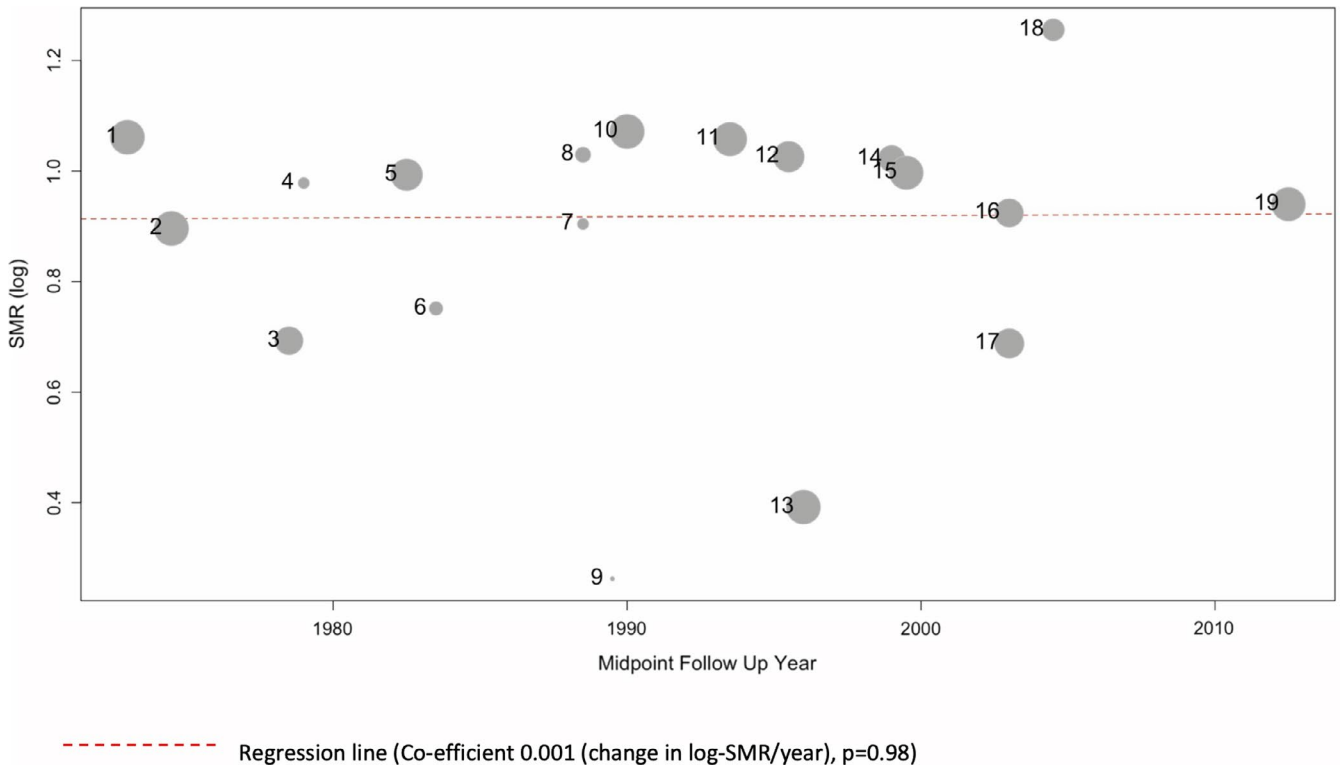

FIGURE 5 Bubble plot of meta-regression model with log standardized mortality ratio (SMR [log]) as the independent variable and midpoint of follow-up as the dependent variable. Numbers are used as study identifiers (Table 1)

MS patients was 2.6, which suggests MS patients have an almost three times greater risk of death compared to the general population. This rate is similar to what was found by Manouchehrinia et al, (2015) with an SMR of 2.8 and suggests the SMR for MS has been stable over time.

One limitation identified in the previous meta-analysis was that 79% of the cohort was made up of Danish and Canadian cohorts, our meta-analysis expanded this cohort with seven additional studies to include 58% from France and a further 27% from Sweden and Denmark, improving the generalizability of results for high-income countries.[2] SMR results between the two meta-analysis have varied between 2.8 and 2.6. The slightly higher SMR in the earlier study may be attributable to the heavy weighting of the Denmark study by Hansen et al., an issue that was overcome by the addition of later Denmark study by Koch-Henriksen that included a the more recent period of time, 1997–2015.[7] The CMR results were not significantly different between the two studies.

In regard to the SMR trends over time, we found no support of a reduced all-cause SMR for people with MS compared to counterparts over the last 65 years. Accordingly, mortality has decreased among people with MS at similar rates to the general population likely due to advances in modern medicine and lifestyle improvements. Although this is consistent with the systematic review by Manouchrinia et al, (2015), it contrasts with what single-population-based studies by Lunde et al (2017), Burkill et al (2017) and Koch-Henriksen (2017).[2,7–9] In these studies, improved coverage by the use of national databases allowing inclusion of outpatient healthcare over longer time frames, shorter follow-up periods for more recently enrolled patients inclusion of more benign MS cases and the increasing use of DMT's offers a potential explanation for the apparent improved survivorship in these individual studies. We sought, by using a meta-regression analysis that captured whole MS population for each time point to better understand the differences between studies. As DMTs were not widely available in the study periods for this meta-analysis, we believe that the mortality data from this review provides a more robust point from which differences over time, including the effects of DMT can be further assessed. To aid in this, we also recommend that future studies of MS mortality should include treatment information.

There has been inconsistency in the relationship of sex with SMR, with some studies reporting a higher SMR in men and attributing this to an increased risk of cardiovascular disease or a biological increased risk of more progressive disease.[19] However, in our analysis, in all but three included studies, women with MS were found to have a significantly higher SMR than men with MS compared to their counterparts without MS, this was confirmed in the meta-analysis data which showed women to have an SMR of 2.57 compared to 2.47 in men with no overlap in the confidence intervals.[2,5,20] In a study by Nakken et al. (2008) this difference was suggested to be caused by period differences in access to diagnosis and is therefore not as marked now as it had been in the past.[21]

Co-morbidity burden among people with MS remains an important influencer of disease progression, prognosis and management choice. Depression, anxiety, hypertension, hypercholesterolemia, and chronic lung disease remain at the forefront of most prevalent co-morbidities and so it is important that these were taken into account for our cause of death data.[22] For cause of death data, the greatest risk of mortality was for respiratory illness and infection with an SMR of 4.7 compared to the SMR of 1.74, 1.81 and 0.99 for cardiovascular disease, accident and suicide and cancer respectively. This large relative risk of death from respiratory illness is in keeping with the neurological effects of MS on respiratory function and reduced mobility increasing susceptibility to severe respiratory illness and associated mortality. However, it is important to note the variation in mortality data used in each study's analysis with some including only direct cause of death, while others, adhering to the more inclusive underlying cause of death definition. The wider underlying cause of death definition is recommended for mortality studies but this measure also may introduce bias in the estimates as it includes more events. This inconsistency, however, did not appear to overestimate the burden of respiratory co-morbidities given the similar SMR observed when including underlying cause of death only data compared to all causes data combined. Future studies should aim to use underlying cause of death for mortality statistics to ascertain if this finding is reflective of the disease process or indicative of an area to improve care.' Regardless, with such a dramatic increase in risk it is clear that significant inroads may be made to improving multiple sclerosis mortality through interventions that aim to improve the respiratory function of MS patients and adequate management of respiratory co-morbidities. Furthermore reduced respiratory functioning has been associated with a reduced quality of life through impaired physical performance and physical health related role limitations.[23] It is clear from this that enhancing respiratory function is a key modifier for mortality risk and quality of life.

In keeping with previous reports, we showed an increased relative risk of suicide in patients with MS.[24] This risk was understated in studies that combined accident and suicide into one category with subset analysis of suicide only presenting a risk of 2.13 compared to 1.81 for accident and suicide. This meta-analysis therefore presents a case for stratifying these two categories in future studies. It also demonstrates that suicidal ideation is an important pre-morbid risk factor that can be addressed in the healthcare setting. Patients who have MS should be screened for suicidal ideation by clinicians while keeping in mind associated factors, for example, depression, social isolation, alcohol abuse, younger age of onset and lower socioeconomic status and considering intervention in those factors that are modifiable.[24,25]

Of the different cause-specific SMR, all but cancer showed an increased risk of death compared to a population without MS. These findings are maintained with DMTs showing no increased risk of invasive cancer compared to the general population.[26] The equal risk of death from cancer for MS patients and the population suggests that perhaps access to regular healthcare review offers some protective factor for the diagnosis and therefore prognosis of cancer and suggests an unlikely biological link between cancer and MS.

Overall, risk of mortality from cause-specific data highlights areas that could be addressed to improve outcomes in multiple

sclerosis. This may include, but is not limited to, improved respiratory function with physiotherapy and aspiration prevention, improved cardiovascular profile with primary prevention, monitoring, exercise and enabling healthy diet and Improved support for mental health services and accident prevention through needs assessment and access to disability aids.

Limitations of our study included the substantial heterogeneity as a proportion of variability. It was not possible to significantly account for this by removing those studies identified in influence analysis. In addition to this, our study included heavy weighting on the Danish and Swedish cohorts, a large range of variability of follow-up and a lack of included reports from other OECD countries with lower MS incidence and prevalence including none from New Zealand, Australia or the USA. We were also limited by the availability of assigned MESH terms for newer studies. Furthermore, SMR depends heavily on duration of follow-up and the mortality within the given population, therefore there is heterogeneity in the reliability of studies where registry infrastructure may limit the breadth and length of data capture. In addition to this, the method of collection of MS data varied across and within studies with some studies relying on the accuracy of MS registries,[7,8] others relying on hospital acquired data[9] and others on outpatient clinic[4] or national insurance data.[3,5] This means that those studies that relied on hospital acquired data risk missing the inclusion of less severe cases, those studies that rely on registries are at the whim of the accuracy of this over time and those that rely on outpatient data risk missing more severe presentations. Future studies may wish to consider the use of registries for their data collection but take into account that the inclusivity of registries has likely improved in sensitivity and breadth over time. Further to this, they should ensure long-term follow-up taking into account that the average survival from age of onset in multiple sclerosis has been reported to be between 24.5 years in Scotland to 45 years in New Zealand.[3] Furthermore, a major limitation of mortality data includes the reliability of death certificates, especially in chronic diseases where the cause of death is open to interpretation and where understanding of direct and underlying cause of death may be muddied by a complex admission.

In conclusion, we have demonstrated that people with multiple sclerosis have reduced overall survival than reference peers without MS. People with MS also have an increased risk of death from cardiovascular disease, respiratory disease, infectious causes and accident and suicide when compared with their age and sex-matched counterparts. We did not find support for a temporal trend in mortality our study involving a significantly larger population than a previous meta-analysis including seven recent large-center studies. Accordingly, mortality has decreased among people with MS at similar rates to the general population to maintain a stable SMR over the last 65 years. We have also identified respiratory function as an important modifiable risk factor for MS and trials of DMT should include respiratory function as an outcome measure for further knowledge.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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