

ORIGINAL ARTICLE

Multiple sclerosis mortality trends by sex in Chile, 1997–2019



J. Arriagada Opazo^a, V. Farah González^a, M. González Delgadillo^a, L. Núñez-Franz^{b,*}, C. Morales García^c, P. Jiménez Rodríguez^d

^a Estudiante de la Escuela Medicina de la Universidad de Talca, Chile

^b Departamento de Salud Pública, Universidad de Talca, Chile

^c Hospital de Curicó, Curicó, Chile

^d Instituto Nacional de Estadísticas, Maule, Chile

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Abstract

Background: An increasing trend has been observed in the prevalence of Multiple Sclerosis (MS) globally. It is estimated that a total of 2.8 million people live with MS worldwide. In 2008, Chile started a pilot program for the Modifying Therapy of MS, and its clinical practice guideline.

Aim: This study aims to analyse the trend of the MS mortality rate in Chile from 1997 to 2019 disaggregated by sex and latitude.

Methods: MS mortality data (ICD-10, G35) from 1997–2019 were extracted from the Department of Health Statistical Information and population data from the National Institute of Statistics. Standardized mortality rates (SMRs) by age were calculated. The trend of the SMR was analysed using Joinpoint and with RiskDiff the effect of the risk of dying, the structure, and the size of the population on the crude mortality rate was evaluated.

Results: The trend of the TME has been decreasing significantly since 2005. When disaggregating by sex the decrease was not significant. According to latitude, the north and center south have a significant decreasing trend; in the south, the decreasing trend is not significant. There is an increase of 25% in the crude mortality rate due to the change in the structure of the population and a decrease of 25.46% is attributed to the risk of dying.

Conclusion: The SMR due to MS in Chile during 1997–2019 has decreased, in addition, a decreasing SMR is evidenced only in the northern zone. The crude rate has increased as a consequence of changes in the population, however, the risk of dying has decreased, especially in men.

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* Corresponding author.

E-mail address: lnunezf@utalca.cl (L. Núñez-Franz).

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PALABRAS CLAVE

Esclerosis múltiple;
Mortalidad;
Chile

Tendencia de la mortalidad por esclerosis múltiple según sexo: Chile 1997–2019**Resumen**

Introducción: Se ha observado una tendencia creciente en la prevalencia de la esclerosis múltiple (EM) a nivel mundial. Se estima que un total de 2,8 millones de personas viven con EM en todo el mundo. En 2008, Chile inició un programa piloto de Terapia Modificadora de la EM y su guía de práctica clínica.

Objetivo: Este estudio tiene como objetivo analizar la tendencia de la tasa de mortalidad por EM en Chile de 1997 a 2019 desagregada por sexo y latitud.

Métodos: Los datos de mortalidad de EM (CIE-10, G35) de 1997 a 2019 se extrajeron del Departamento de Estadísticas e Información de Salud y los datos de población del Instituto Nacional de Estadística. Se calcularon las tasas de mortalidad estandarizadas (TME) por edad. Se analizó la tendencia de la TME mediante *Joinpoint* y con *RiskDiff* se evaluó el efecto del riesgo de morir, la estructura y el tamaño de la población sobre la tasa bruta de mortalidad.

Resultados: La tendencia del TME ha sido decreciente significativamente desde 2005. Cuando se desagrega por sexo el descenso no es significativo. Según la latitud, el norte y centro sur tienen una tendencia significativamente decreciente; en el sur, la tendencia decreciente no es significativa. Se produce un aumento del 25% en la tasa bruta de mortalidad debido al cambio en la estructura de la población y una disminución del 25,46% se atribuye al riesgo de morir.

Conclusión: La TME por EM en Chile durante 1997–2019 ha disminuido, además, se evidencia una TME decreciente solo en la zona norte. La tasa bruta ha aumentado como consecuencia de los cambios en la población, sin embargo, el riesgo de morir ha disminuido, especialmente en los hombres.

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Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, autoimmune disease of the central nervous system (CNS) white matter. In MS, an inflammatory infiltrate causes myelin destruction; the disease is associated with high rates of morbidity and early mortality.^{1,2}

The precise aetiology of MS remains unknown and may be due to the interaction of several factors, such as loss of autoimmunity caused by T and B cells that generate inflammation and early neurodegeneration^{3,4}; genetic factors also play a role, such as polymorphisms that are relevant in the functioning or differentiation of T cells,⁵ or the HLA-DRB1*15 allele, which interferes with antigen presentation in the immune system.^{4,5} In turn, it also involves environmental factors such as Epstein-Barr virus infection, smoking, and/or low exposure to ultraviolet B light (UVB), resulting in vitamin D deficiency.^{4,5}

MS prevalence is high in developed countries, with a female-to-male ratio of 4:1.⁶ It usually manifests at 20–40 years of age, with a median age at diagnosis of 32 years.^{6,7} Furthermore, prevalence increases at higher latitudes, in association with low exposure to UVB rays.⁴

A total of 2.80 million people live with MS worldwide (35.90 cases per 100 000 population). Incidence amounts to 2.1 cases per 100 000 person-years, in 75 reporting countries. Europe reports the highest incidence, with 6.8 cases per 100 000 population, followed by the Americas with 4.8, and South-East Asia and Africa with 0.4 each in 2020.⁴ Between 2013 and 2020, prevalence increased from 29.6% to

43.95% due to improvements in the diagnosis and treatment of MS, and the number of individuals diagnosed.⁶ In 2012, incidence in Chile was estimated at 0.90 cases per 100 000 population, with a female-to-male ratio of 2:1.^{3,8}

Although the pilot program for disease-modifying treatment⁹ and the clinical diagnostic guidelines for MS in Chile were launched in 2008,¹⁰ no follow-up of MS mortality rates with a trend analysis has been performed to date. This information would contribute to a better understanding of the disease and to the implementation of prevention policies. With this in mind, the aim of this study was to analyse trends in MS mortality in Chile between 1997 and 2019, disaggregated by sex and latitude. This trend analysis aims to identify whether mortality due to MS has decreased in association with risk factors and changes in diagnosis.

Material and methods**Study design and population**

This is an ecological study of mortality in Chile between 1997–2019 (last year with available data) with MS reported as the basic cause of death on death certificates (DC), with code G35 according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).¹¹ From the DC, we obtained information on biological sex (man or woman). The Chilean Ministry of Health, specifically the department of healthcare sta-

tistical information, provided data on deaths. Data on the Chilean population were obtained from census (1992, 2002, 2012, and 2017) and intercensus estimations. The previous information was provided by the Chilean National Statistics Institute. Age-standardised mortality rates (ASMR) for the 23-year period were calculated with the direct method using the world standard population proposed by Segi.¹²

Ethical standards

This study complies with ethical standards.¹³ Mortality rates are public; therefore, no formal consent had to be obtained.

Statistical analysis

We analysed temporal trends in ASMR of MS in the period 1997-2019, using the Joinpoint regression program.¹⁴ This software was developed by the US National Cancer Institute to analyse data from the Surveillance Epidemiology and End Results Program. The aim was to describe the changes in trends. The program uses the registry of ASMR with self-correlated random error, starting with 0 points of change (a straight line) and continues trying up to a maximum of 4 points. Monte Carlo methods were used to determine statistical relevance. The annual percentage of change (APC) in ASMR was calculated with a 95% confidence interval. For the analysis of ASMR by latitude, we studied the period 2002-2019, as the population data per commune (the smallest administrative subdivision in Chile) has only been available since 2002. Two geographical areas were defined, from the Arica y Parinacota Region (XV), between 17° and 19° latitude, to the Magallanes Region (XII), between 48° and 56° latitude, with the cut-off point in La Araucanía Region (IX), between 37° and 39° latitude.

To assess the effect of demographic components (population size and structure by sex) and epidemiological data (risk of developing a disease), we used the RiskDiff® application.¹⁵ This method, which is available through a web-based application, was proposed by Bashir et al.¹⁶ First, the crude death rate per 100 000 population is calculated, then the differences in crude death rates per year are disaggregated into the difference due to risk and the difference due to population structure. This analysis was performed for the crude mortality rate and for cases. Furthermore, we conducted the analysis for the total population and disaggregated by sex.

Results

Between 1997 and 2019, 531 deaths were reported, of which 58.56% (n=311) were women. ASMR trends for the total population showed a joinpoint with a statistically significant downward trend from 2005 to 2019 (APC = -3.68; $P = .002$); the trend from 1997 to 2005 was not significant ($P = .113$). Deaths decreased from 0.16 to 0.09 deaths per 100 000 population between 2005 and 2019.

In the analysis by sex (Fig. 1), ASMR in women showed a downward trend (APC = -1.18), but this was not statistically significant ($P = .303$). The mortality rate decreased

from 0.12 to 0.09 deaths per 100 000 population between 1997 and 2019. ASMR in men showed a downward trend (APC = -1.82), but this was not statistically significant ($P = .053$). This rate decreased from 0.15 to 0.09 deaths per 100 000 population between 1997 and 2019. ASMR values for men and women were disperse throughout the study period.

Analysis of the effect of demographic changes and the risk of mortality in the total population revealed an upward trend in the crude rate due to population structure, whereas the risk of mortality due to MS and the total change in the crude rate fluctuated (Fig. 2). Disaggregation by sex revealed similar patterns. The total number of deaths amounted to 20 in 1997 and 25 in 2019, which represents a crude rate of 0.135 and 0.130 deaths per 100 000 population, respectively. The net change in the crude rate amounts to -0.004 deaths per 100 000 population (-3.29%). This can be disaggregated into -0.038 deaths (-28.46%) due to a decreased risk and 0.034 deaths (25.17%) due to changes in population structure. The net change in the total number of deaths amounted to 5 deaths (25%), which may be divided into -5.69 deaths (-28.46%) due to decreased risk; 5.03 (25.17%) due to changes in population structure, and 5.66 (28.19%) due to the increased population size.

Among women, the total number of deaths amounted to 10 in 1997 and 14 in 2019, which represents a crude rate of 0.133 and 0.144 deaths per 100 000 population, respectively. The net change in crude rate amounted to 0.011 deaths per 100 000 population (8.60%), which may be divided into -0.011 deaths (-8.28%) due to decreased risk, and 0.022 deaths (16.88%) due to changes in population structure. The net change amounted to 4 deaths (40%), which may be divided into -0.82 deaths (-8.28%) due to decreased risk; 1.68 (16.88%) due to changes in population structure, and 3.13 (31.39%) due to the increased population size.

Among men, the total number of deaths amounted to 10 in 1997 and 11 in 2019, which represents a crude rate of 0.138 and 0.117 deaths per 100 000 population, respectively. The net change in crude rate amounted to -0.02 deaths per 100 000 population (-15.13%), which may be divided into -0.06 deaths (-49.69%) due to decreased risk, and 0.04 deaths (34.56%) due to changes in population structure. The net change amounted to one death (10%), which may be divided into -4.96 deaths (-49.69%) due to decreased risk; 3.45 (34.56%) due to changes in population structure, and 2.51 (25.13%) due to the increased population size.

Trends in ASMR between 2002 and 2019 in the north of the country showed statistically significant differences ($P = .002$), with a decrease from 0.09 to 0.08 deaths per 100 000 (APC = -3.03) between 2002 and 2019 (Fig. 3). However, the trend in ASMR in the south showed no statistically significant differences ($P = .376$). We observed a decrease in rates (APC = -1.80), amounting to 0.20 and 0.11 per 100 000 population in 2002 and 2019, respectively. We should underscore that ASMR in the north and central areas are more homogeneous than in the south, where values are more disperse.

Discussion

Our study shows downward trends in ASMR for MS in men and women, although we observed great variation in ASMR over

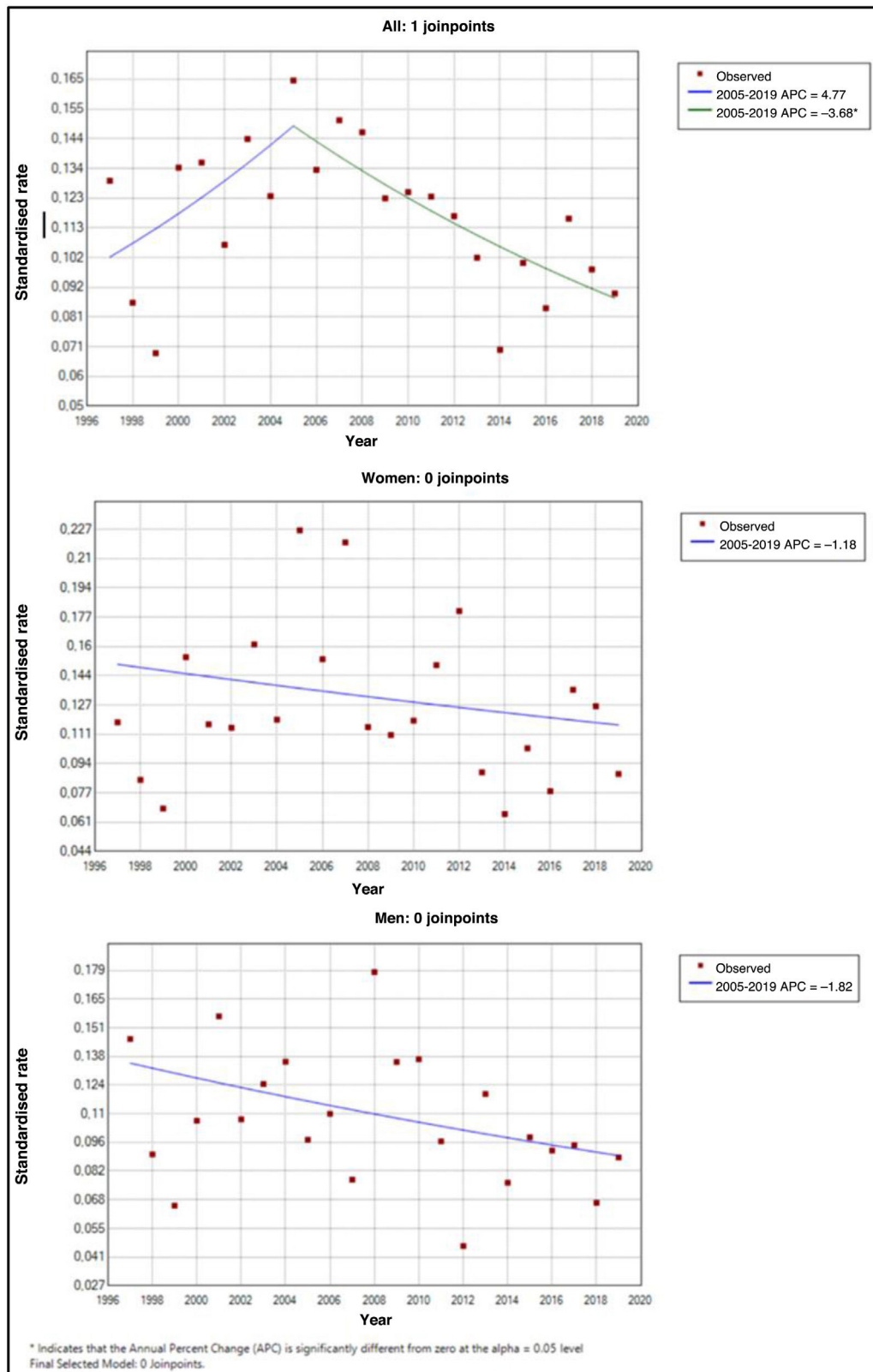


Figure 1 Standardised mortality rates due to MS in Chile, estimated by joinpoint regression, for the total population, women, and men, for the period 1997–2019.

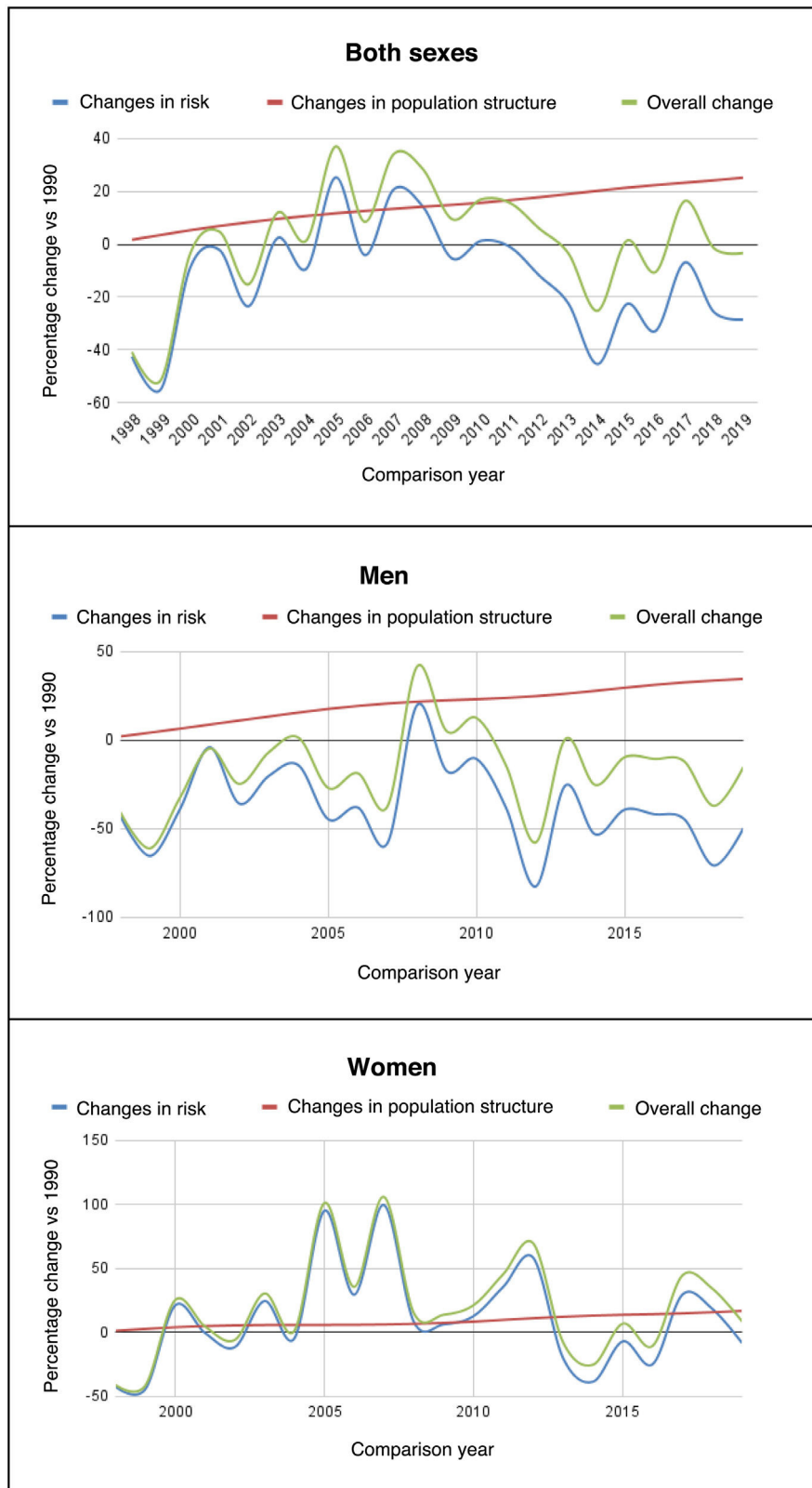


Figure 2 Percentage change in crude death rate due to MS in the total population, women, and men in Chile during the period 1998-2019, with respect to the reference year 1997.

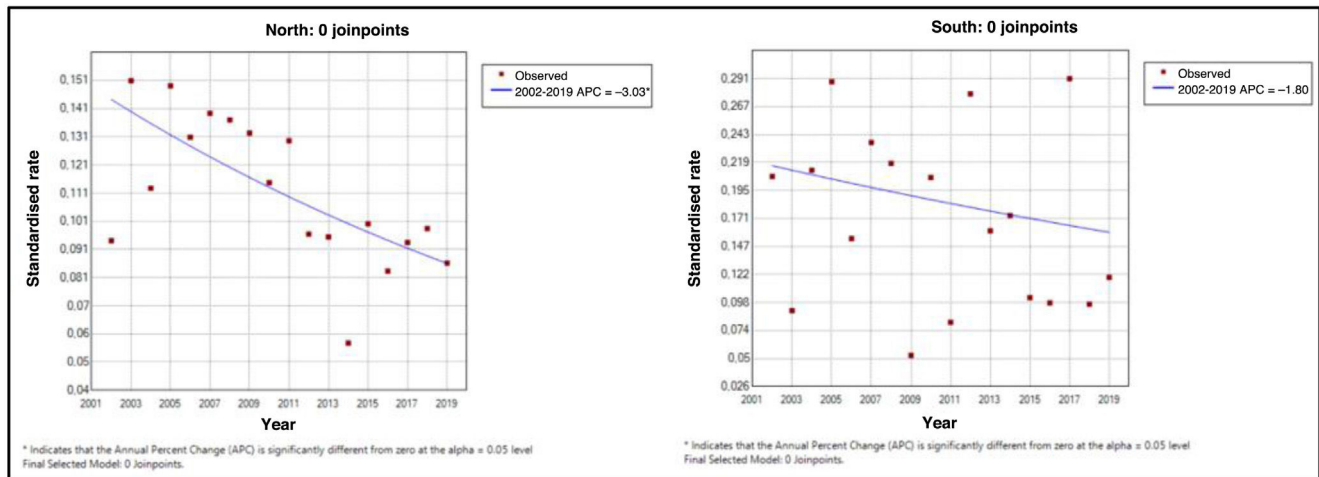


Figure 3 Standardised mortality rates due to MS in Chile, estimated by joinpoint regression, for the total population disaggregated by latitude, for the period 2002–2019.

the study period. When analysing the total population, we observed a downward trend from 2005. When disaggregating by latitude, a significant downward trend was observed in the northern and central regions, but not in the south. Finally, we observed a 25% increase in the crude mortality rate, due to a decrease in the risk of death due to MS (–28.46%), a change in the population structure (25.17%), and increased population size (28.29%).

The decreasing trend in mortality due to MS for both sexes began in 2005; this may be due to 3 reasons: a decrease in the prevalence of risk factors, improvements in diagnosis, and/or improvements in treatment.

Whereas risk factors do not directly influence the mortality rate, they may worsen disease progression and, consequently, outcomes. In this line, migration studies have shown that environmental factors prevail over genetics.⁴ Thus, smoking, obesity, and the climate at high latitudes, with limited hours of sun exposure (associated with low levels of vitamin D),¹⁷ increase the risk of developing MS. In Chile, the prevalence of overweight, obesity, and morbid obesity has increased from 64.50% in 2009–2010¹⁸ to 73.60% in 2016–2017.¹⁹ Smoking has decreased from 43.40% in 2009–2010 to 36.50% in 2016–2017, and is more prevalent in men (37.80% in 2016–2017) than in women (29.10% in 2016–2017).²⁰ Although the prevalence of smoking has decreased, it remains high. Furthermore, the prevalence of vitamin D deficiency amounted to 20.80% in 2016–2017 among adults aged ≤ 64 years.¹⁹ Thus, considering that the Chilean population displays high exposure to risk factors, the downward trend observed since 2005 cannot be attributed to a decrease in risk factors.

Diagnosis of MS was established using the 2001 McDonald criteria, which requires demonstration of dissemination in time (DIT) and in space (DIS) in separate events, with no other possible diagnoses.²¹ These criteria were updated in 2005, 2010, and 2017.²² In 2005, abnormal MRI findings in studies performed 30 days apart were implemented as a criterion²³; however, as only the number of lesions was evaluated, this was complicated for those with no neuro-radiological experience.²¹ The 2010 update is focused on showing DIS in the number of lesions and in their location.²¹

The 2017 update includes CSF oligoclonal banding, which enables diagnosis of MS after the first clinical event, increasing diagnostic sensitivity and specificity.^{22,23} In this area, the implementation of MRI has been essential. MRI first became available in Chile in 1989 thanks to private initiatives,²⁴ and began to be used in public hospitals in 2004.²⁵ In 2014, the Chilean Society of Radiology and the Chilean Ministry of Health reported that there were 120 MRI machines in Chile, 14 of which belonged to the public healthcare system.²⁶ This reflects the inequality and the delay in the diagnosis of patients treated within the public healthcare system (approximately 78% of the population, according to the latest Chilean national census of 2017),²⁷ which may have influenced the decrease in ASMR observed from 2005, as MRI is more easily available.

In clinical practice, the most recent McDonald criteria are used in Chile. This is relevant, as early administration of disease-modifying therapies prevents relapses and future disabilities; therefore, early diagnosis is crucial to reduce complications and mortality due to MS.^{9,22} As the updates published since 2005 have been implemented in Chile, the resulting improvement in diagnosis in that period may have been a cause of the decrease in ASMR.

Regarding treatment, Chile has programmes to increase the number of individuals with access to treatment, which started with the “Pilot national treatment program for Multiple Sclerosis patients belonging to the public health care system of Chile (FONASA) with immunomodulatory disease-modifying therapies,”⁹ later supported by the Explicit Health Guarantees program²⁸ and the Ricarte Soto law²⁹; however, the impact of these programmes on ASMR would require a counterfactual approach. Furthermore, a case-control study would be necessary to assess treatment. Both scenarios are beyond the scope of this research.

It is important to consider population changes, as MS interacts with natural ageing, comorbidities, and decreased effectiveness of the disease-modifying therapy due to the neurodegeneration that accumulates over time.²² An analysis of the crude mortality rate of MS revealed an increase of 25% for the total population, and disaggregated by sex, increases of 40% in women and 10% in men between 1997–

2019. However, when considering population changes, we can confirm that the risk of death due to MS has decreased by 28.46% in the total population, 8.28% in women, and 49.69% in men. This apparent increase in the crude rate may be due to the increase in population size and ageing of the Chilean population. Thus, in clinical practice, though there may be an increase in deaths due to MS, the risk of death has actually decreased.

Regarding latitude, a study published in *BMC Neurology* in 2022 reported a non-linear association between latitude and disease severity.³⁰ The most severe MS is associated with higher latitudes, which is explained by the lower exposure to UVB radiation and, therefore, lower vitamin D levels; in addition to being a risk factor, this is associated with increased level of disability before the ages of 6 and 18 years.³⁰ Therefore, latitude as a risk factor for MS is more significant in the first years of life, thus showing an increased frequency in individuals living their first 15 years of life in temperate zones (1/2000) than those living in tropical zones (1/10 000).³¹ According to our findings, no significant downward trend in ASMR was observed in the southern region of Chile as compared with northern areas, which may be due to the small number of cases. For this difference between regions, although it may be associated with low exposure to UVB radiation in the early years of life, the influence of European genetic inheritance (associated with higher incidence of MS) in the southern area should also be considered.⁶ In Chile, high levels of immigration were observed in this region from 1883 due to the hiring of French, German, Swedish, and Italian settlers.³² Furthermore, as Chile's population is concentrated in the northern and central areas,³³ a higher number of cases in the south may be in line with international data, with increased mortality rates in temperate zones.³⁴ This is reflected in the prevalence of MS in Brazil, which is 7 times lower than in Australia, 19 times lower than in Europe (with the exception of Croatia and Slovenia), and 42 times lower than in Canada.³⁰

In the international context, between 1990 and 2016, the ASMR of MS decreased by 11.5%; however, when data were disaggregated by country, these changes were not significant.³⁵ These findings are coherent with those obtained in our study when data were disaggregated by sex, but not when the total population is analysed, which revealed a significant downward trend. The international data may be explained by the fact that the 2010 and 2017 McDonald criteria enable earlier diagnosis of patients with MS; therefore, there is a decrease in relapses and symptoms, which results in lower mortality rates.²² Environmental factors may also explain a milder presentation of relapsing-remitting MS (RRMS). One example is smoking, whose prevalence has decreased in Europe and North America. Smoking is associated with higher numbers of relapses, worsening of the disease, and decreased efficacy of disease-modifying therapy.²² Furthermore, evidence reported in the USA shows decreased activity of RRMS, which may be attributed to new disease-modifying therapies, which are more efficacious in preventing relapses and disease progression.²²

In Chile, little information is available on the incidence, prevalence, or mortality rates of MS; therefore, this study provides evidence on this rare condition.

Among the limitations of our study, we could not calculate the median age of death due to MS, as the data provided by the Chilean Ministry of Health were categorised per 5-year periods. Furthermore, we could not evaluate trends in mortality rates by age group due to the low number of deaths, and therefore were unable to identify whether any age group was more affected. Additionally, there may be a bias in the recording of the basic cause of death listed on the DC, as a neurologist is not always present to confirm diagnosis at the time of death. The variability of mortality rates in the study period is the result of the low number of deaths: when this number increases, rates change considerably. Furthermore, as no incidence data are available, it is not possible to establish a complete picture of MS.

Conclusion

Over the period 1997-2019, the ASMR of MS in Chile decreased from 2005, possibly due to the implementation of the updated diagnostic criteria. We observed a decrease in the risk of death due to MS in women and men, despite the upward trend in crude death rates. This is explained by the increased sample size and population ageing. We also observed an association between the ASMR of MS and latitude, with a significantly decreased ASMR only being observed in the north area. Though the rate of mortality due to MS in Chile is low, this disease involves high costs for families and healthcare systems, and further studies are therefore needed to establish its incidence.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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