

Mortality trends from Multiple Sclerosis in Italy

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INTRODUCTION: According MSIF Atlas, Multiple sclerosis (MS) affects 2.3 million people worldwide and available epidemiological studies report an increasing prevalence of the disease [1-2], arising from one or more factors including normal linear rise due to increasing incidence, that already exceeded the mortality annual rate. Prevalence and incidence available data may report some limitations, because data are not routinely collected and usually refer to a small geographical area and specific limited periods. On the contrary, mortality data are collected routinely, in a standardized manner and they are available for longer periods and cover the entire country, allowing to obtain an estimation of mortality trends at a national level and also to confront data for different regions or countries. For Italy, the last published estimated mortality rate was 0.41 for males and 0.5 for females in the period 1974-1993 [4], quoted also by WHO at 2002 (0.4). **The aims of this study were to assess mortality trends for MS during the last 35 years (1980-2015) and to evaluate geographical differences for main geographic areas.**

METHODS: Mortality data were provided by the Italian Institute of Statistics. All deaths, with a death certificate that mentioned MS as the first cause of death (ICD9: 340; ICD10: G35) were included. Mortality data were aggregated into 5 time intervals in order to achieve a greater reliability smoothing out variability in number of deaths from one year to another, due to the relatively low number of annual deaths. Crude Mortality Rates (CRs) and Age-adjusted Mortality Rates (AMRs) were calculated to evaluate the mortality trend over time. Subsequently, we proceeded with the joinpoint regression to estimate the Annual Percent Change in mortality (APC, reported as %). The Standardized Mortality Ratios (SMRs) were calculated with the indirect standardization method, using as reference Italian age-specific mortality rates for respective period and area, to confront mortality among the 5 main geographical areas (North-West, North-East, Centre, South Italy and Islands).

RESULTS: During the study period 4,959 deaths for MS were observed in males and 7,434 in females. Overall AMRs were significantly higher in females (F: 0.71 vs. M: 0.56). Considering geographical areas, for both sexes significantly higher SMRs (compared to the national value) were observed for Islands (for males for both Sardinia and Sicily, for females only for Sardinia) and in North-East and North-West for females. On the other hand, significantly lower SMRs were observed for Central Italy for males and for South Italy for both sexes (Fig. 1). The analysis of the mortality trend, using the AMRs, revealed an initial decrease in mortality for males. However, the difference between the first and the last period was not significant. On the other hand, for females, a statistically significant increase in mortality was observed between the first and the last period (Tab. 1). The linear regression analysis for whole Italy showed an initial significant decrease in mortality, observed up to the year 1995 for males (APC -3.23%; $p < 0.05$) and up to 1999 for females (APC -1.01%; $p < 0.05$), followed by a significant increase more marked in females (APC 1.9%; $p < 0.05$ in males; APC 2.34%; $p < 0.05$ in females) (Fig. 2).

CONCLUSIONS: The initial decrease in mortality observed was consistent with the previously published study [4], whereas for subsequent years there are no data. The increase in mortality after 2000 may reflect the rising prevalence and incidence observed in Italy and in many other countries, but it can also reflect the improvement in the quality of diagnosis since the 80ties and medical coding of the cause of death, whereas the improvement in drug therapy and care should result in a decrease of mortality rates. Another possible reason is the growing knowledge of MS by general population, and then by medical examiners who certify the death. In fact, in Italy, in 1983 only 3-4% of general population have heard of MS, but in the following years there has been a continuous growth, reaching 97% in 2016 [5]. Mortality rates are consistently higher in female and in Sardinia, reflecting the higher MS prevalence and incidence amongst females and in that Island. The main limitation of mortality studies using ISTAT mortality data is the low accuracy of the death certificate and the impossibility of tracing back to clinical cases to confirm the cause of death. In chronic diseases, such as MS, several co-existing conditions may contribute to death. As a consequence, MS may be reported not as the main cause of death [6]. On the other hand, there could be an opposite problem, called "the sticky-diagnosis bias": the diagnosis of MS is considered so important by physicians, that it can "overcome" other causes of death and be reported incorrectly as the principal cause itself [7].

The strength of this study relies on the long period of time considered, providing a comprehensive picture, at national level, of disease trend and helping us to understand changes occurred over the last 35 years. So, despite their intrinsic limits, mortality data represent a valid tool useful for health planning due to the high cost of this disease [3]. The increasing mortality trends observed in this study, especially in females and in Sardinia, suggest that health care services destined to MS patients need to be increased in the close future.

Fig. 1: SMRs by sex and geographical area

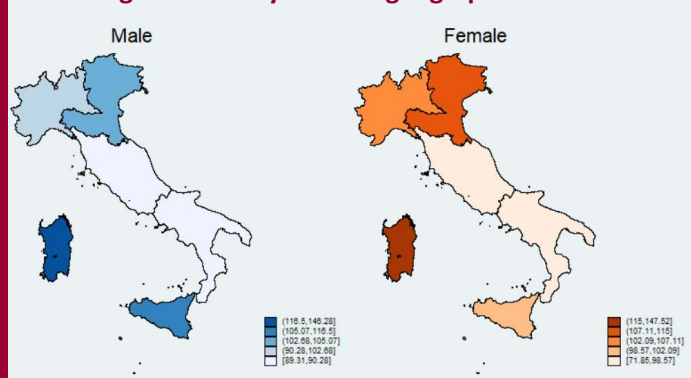
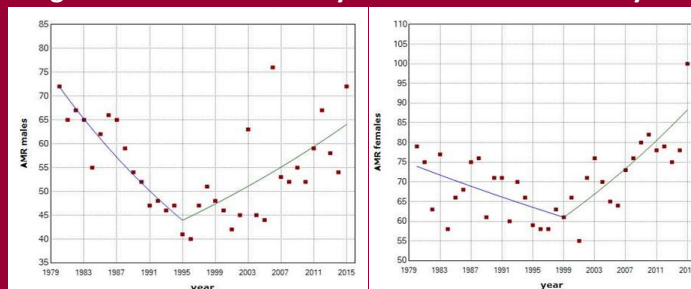


Fig. 2: Estimated mortality trend 1980-2015 in Italy



Tab. 1: Number of deaths, CRs, AMRs for aggregated data

	Period	N	CR	AMR	95%CI
Males	1980-86	971	0.50	0.65	0.60-0.69
	1987-93	847	0.44	0.52*	0.49-0.56
	1994-2000	803	0.42	0.46*	0.43-0.49
	2001-07	977	0.50	0.53*	0.49-0.56
	2008-15	1361	0.58	0.59	0.56-0.62
Females	1980-86	1239	0.61	0.69	0.65-0.73
	1987-93	1300	0.64	0.69	0.65-0.73
	1994-2000	1232	0.60	0.61	0.58-0.65
	2001-07	1462	0.70	0.68	0.65-0.72
	2008-15	2200	0.88	0.81**	0.77-0.84

* AMR lower than AMR observed in 1980-1986 ($p < 0.05$)

** AMR higher than AMR observed in 1980-1986 ($p < 0.05$)

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