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The Prevalence of Multiple Sclerosis in the Metropolitan Area of Rome: A Capture-Recapture Analysis

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Abstract
Background: Limited data are available on the prevalence of multiple sclerosis (MS) in central Italy. The objective of this study is to estimate MS prevalence in the metropolitan area of Rome. ***Methods:*** We used the capture-recapture method to calculate prevalence estimates in the study area. The selected prevalence day was December 31, 2015. A total of 1,007 patients, with a definite diagnosis of MS according to the revised McDonald's criteria, were considered for crude, age- and sex-specific prevalence estimation. ***Results:*** The overall crude prevalence rate was 146.2 cases per 100,000 (95% CI 119.9–172.5). A higher prevalence rate was recorded in females (194.1, 95% CI 149.6–238.6) than in males (93.0, 95% CI 67.2–118.8) with a female to male ratio of 1.8. Age-specific prevalence peaked in the 25–34 , 35–44 and 45–54 years class; moreover, it was found to increase up to the 45–54 years age group in females and the 35–44 years age group in males, decreasing thereafter. ***Conclusion:*** The results confirm that the metropolitan area of Rome is a high-risk area for MS.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system involving inflammation, demyelination, and axonal loss. Onset

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of the disease typically occurs during early adulthood, making MS the most common neurological disease affecting people under the age of 30 and the major cause of non-traumatic disability in young adults [1]. The increasing health care system inflicts burden due to progressive accumulation of cognitive and neurological impairment in MS patients. This leads to the importance of having up-to-date estimates of prevalence, so that the national and regional resources for the management of the disease are properly allocated. Last but not the least, updated prevalence estimates across different geographical areas might also help to better understand the contribution of genetic and environmental causes in MS etiology [2].

Italy is a country with a high prevalence for MS, with quite a particular heterogeneous pattern of different rates between regions. Sardinia and Sicily (the largest islands of the country) are high-risk areas, with an average prevalence of 299 and 176 per 100,000 population respectively; meanwhile, the rest of the country has a prevalence of approximately 110/100,000 [3]. Several studies have been conducted to address the incidence and prevalence of MS in different cities and provinces of Italy. Differing prevalence rates have been estimated among the largest cities of the mainland, where larger prevalence rates have been identified in the northern part of the country [3–6]. It has been speculated though that the variability of prevalence is in part simply due to the limited epidemiological data available from the central-southern regions [7–10]. Recently, Bargagli et al. [11] have argued that prevalence of MS in the Lazio region, a central region of Italy, could be actually larger than currently believed.

Prevalence and incidence estimates for MS are often simply based on self-reported records of patients recruited in MS centers, with no correction for under-count. When used, corrections for under-count are often only heuristic. This leads to biased estimates even after aggregation at larger area levels (e.g., regional, national or even European). Some authors indeed clearly point out the risk of underestimation of the true prevalence rates [3, 12]. An additional widespread problem limiting the possibilities for epidemiological comparisons over time and space is that methods of data collection and analysis are often non-standardized. Oftentimes, prevalence estimates are indirect, for example, being based on adjusting outdated direct estimates; and nonetheless, even direct counts are sometimes admittedly biased, as only patients available in incomplete lists are considered [11].

Recently an increasing interest on the possibility to match the data from MS centers with health care system administrative databases arose, hoping that this would lead to more precise and reliable estimates of incidence and prevalence of the disease [13]. Unfortunately, it is well acknowledged in several areas of epidemiology that even data based on a registry might lead to underestimated prevalence and incidence rates, and that, whenever possible, the extent of under-count should be at least assessed, and possibly corrected. Capture-recapture methods are specifically useful in this setting and formally, if the model is well specified, estimates are unbiased [14].

This study was mainly motivated by lack of updated and unbiased prevalence estimates for the metropolitan area of Rome, the capital of Italy and the most populated metropolitan area in central Italy. We have collected patient lists from 6 centers, and corrected for the (substantial) under-count through a state-of-the-art capture-recapture methodology.

Materials and Methods

Area Under Investigation

The area under study is the metropolitan city of Rome, located in the central part of Italy. Established in 2014, its territory corresponds to that of the old province of Rome, which it has replaced. It includes Rome, the capital and the largest city of the country, and several neighboring municipalities with close economic, cultural, and social integration relationships. The region covers an area of 5,352 km^2 and 121 municipalities (Fig. 1).

Patients born in the area were identified from their fiscal code (the unique taxpayer number assigned to Italian residents), which contains the string H501. The prevalence day was fixed as December 31, 2015.

Lists of patients with ascertained diagnosis of MS, according to the revised McDonald's criteria [15], were obtained from 6 different centers in Rome, namely, Azienda Ospedaliera Universitaria Policlinico Umberto I (267 patients, 66% females, average age 45.15 ± 11.21), Azienda Ospedaliera Universitaria Sant'Andrea (33 patients, 73% females, average age 50.94 ± 11.22), Policlinico Universitario Agostino Gemelli (183 patients, 62% females, average age 47.60 ± 10.73), Policlinico Universitario Tor Vergata (335 patients, 67% females, average age 45.64 ± 11.62), Presidio Ospedaliero San Filippo Neri (148 patients, 68% females, average age 45.10 ± 12.12), and Fondazione Santa Lucia (162 patients, 55% females, average age 54.22 ± 12.50). We included 6 out of the 13 MS centers in the metropolitan city, specifically 5 first-level centers and 1 second-level center (where first level, according to our Italian healthcare system, defines the center as qualified to administer advanced therapies for MS, that is, monoclonal antibodies).

Case ascertainment has been performed separately by each center (possibly more than once for patients appearing in more than one list). Several patients are well established, with only a very minor fraction of new diagnoses. We finally included patients with at least one visit in 2015 or later, who were alive at the prevalence date.

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The population count (number of subjects born in Rome and alive) at the prevalence day, December 31, 2015, together with its stratification by age and gender, was obtained directly from the official Italian National Institute of Statistics.

Capture-Recapture

We estimated, for the entire population and for each class made by gender, age class, and combinations thereof, the 32,768 possible log-linear capture-recapture models indexed by all possible one-way list effects and two-way list interactions. We also took into account unobserved heterogeneity, that is, the possibility that unobserved factors led to different list inclusion probabilities for each patient. To this end, list inclusion probabilities were deemed to arise from a latent distribution. Four possible distributions were compared: Darroch, Poisson, Gaussian, and Chao [16]. More formally, the count of patients available in a given subset of lists was modeled as list-parameters for the selected subset and two-way list-interaction parameters in the most general case. For example, the log number of patients counted simultaneously in the first, second, and fourth list was given by an intercept, 3 list parameters, and three two-way interactions (first-second, first-fourth, and second-fourth). A random effect to take into account unobserved heterogeneity might also be added. The most parameter-rich model was then compared to restricted models in terms of balance between goodness of fit and parsimony. The best model (according to the criterion specified below) was finally chosen separately for each stratum.

This resulted in 32,768 (number of one-way effects and two-way interaction models) * 21 (number of strata) * 4 (number of mixing distributions) = 2,752,512 different estimated models. For each stratum and for the overall population, the model minimizing the Bayesian Information Criterion (BIC) was selected (e.g., [17]). The BIC is deemed to be the best information criterion for estimating population sizes when the total population size is expected to be in the order of hundreds or even thousands.

Counts are based on 2011 census evaluation, extrapolated to the prevalence date by means of population ratios. Female to male ratios are obtained based on the estimates of the number of patients by gender (and age class).

Fig. 1. Map of Italy showing the metropolitan city of Rome (red).

Results

A total of 1,007 patients were included in at least one list, with 105 included in 2 and 8 included in 3 of the 6 lists considered. The prevalence population considered is made of 3,152,719 individuals. Hence, a naive prevalence estimate would be an unreliable 31.94 per 100,000 inhabitants. This is obviously due to severe under-coverage, that is, several patients are not included in the 6 lists considered. The optimal population size estimate (according to BIC criterion) is 4,610 per 100,000. This leads to an estimated prevalence of 146.2 per 100,000 inhabitants (194.1 for females and 93.0 for males, with a female to male ratio of 1.8). The estimated age at the prevalence date is 47.5 ± 13.4, with negligible gender differences. In Table 1 and Figure 2, we report the estimates stratified by age class and gender, also with 95% confidence intervals. The largest and smallest values for overall prevalence are, respectively, in 35–44 and 0–24 years age classes. According to gender, in females, the largest value is in the 45–54 class, while the lowest is in women aged over 65 years; in males, the largest prevalence is in the 35–44 class and the lowest is in the 0–24 class. The estimates of prevalence standardized to European Standard Population and to the general Italian population are comparable to those in the study area.

Discussion

Several studies assessed MS prevalence in European countries, revealing spatial heterogeneity in the distribution of the disease [18]. Those conducted in Italy yielded markedly different figures in the different regions of the country. Considering only the last 2 decades, prevalence estimates ranged from about 100 to 150 per 100,000 in the North [4–6] and from 120 to 230 per 100,000 in the islands [19–20].

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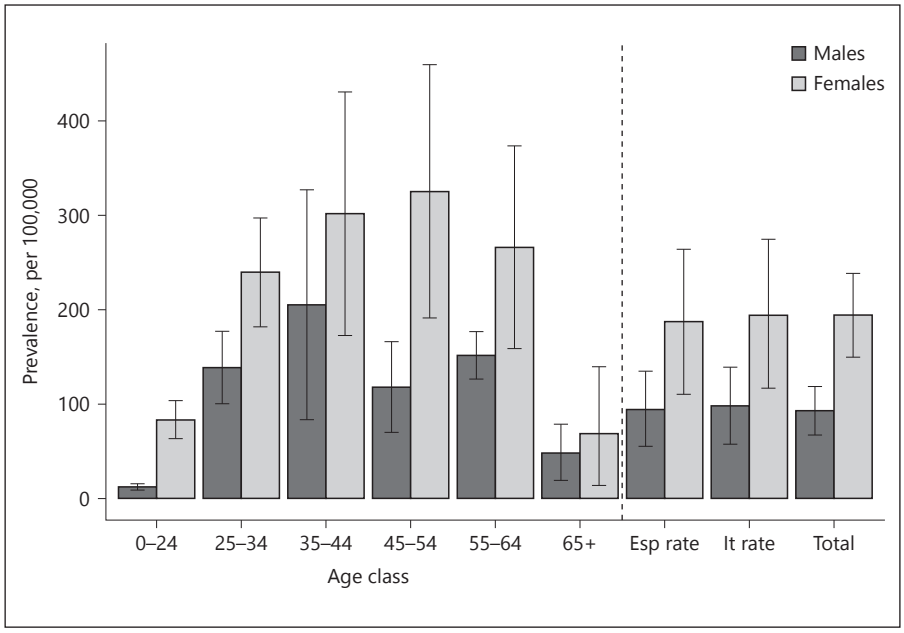

Fig. 2. MS prevalence distribution for 2015 in the metropolitan area of Rome (stratified by gender and age class). We also report the estimates standardized to the European and Italian Standard Population.

Table 1. MS prevalence estimates and male to female ratios for 2015 in the metropolitan area of Rome, also stratified by gender, age class, and both. We also report the estimates standardized to the European and Italian Standard Population

	Males	Females	All	Female to male ratio
0–24	12.39 (8.96–15.82)	83.57 (63.44–103.69)	27.51 (22.56–32.45)	2.8
25–34	138.72 (100.32–177.12)	239.65 (181.94–297.36)	232.26 (190.48–274.04)	2.4
35–44	205.11 (83.39–326.83)	301.52 (172.42–430.62)	279.31 (172.97–385.65)	1.6
45–54	118.08 (70.18–165.98)	325.20 (191.04–459.37)	231.24 (161.96–300.53)	2.0
55–64	151.58 (126.42–176.73)	266.08 (158.80–373.37)	187.54 (122.95–252.14)	2.2
65+	47.89 (19.14–78.48)	68.74 (13.67–139.68)	58.37 (25.06–91.67)	0.9
Total	92.97 (67.24–118.71)	194.10 (149.57–238.64)	146.22 (119.92–172.52)	1.8
European standardized rate	94.28 (55.58–134.98)	187.34 (110.50–264.19)	142.90 (97.16–188.64)	2.0
Italian standardized rate	98.18 (57.69–139.00)	194.33 (117.05–274.68)	147.46 (99.33–195.59)	2.0

A recent study [3] noted how, as of 2015, Italy is a high-risk area for MS (average prevalence 110 per 100,000) with no north-south gradient, showing a trend toward an increased prevalence, in line with similar appraisals of nationwide prevalence in other European countries and in North America. Nonetheless, most of the epidemiological data on which these conclusions have been extrapolated have been collected from the islands and in the Northern part of the country. To date, the epidemiological data available from the central-southern regions are still limited [7–11, 21].

Our study specifically focused on the metropolitan city of Rome, a densely populated area in central Italy. The study was conducted by extrapolating an incomplete enumeration of cases to a well-defined population, using an innovative statistical approach to correct biases. We found an overall MS prevalence of 146.2 per 100,000 (95% CI 119.9–172.5). Our results confirm that the metropolitan area of Rome is an area of high risk for MS. Our prevalence estimates are actually the largest ever obtained for the area. This is due to the fact that previous surveys were either performed a few years ago, or based on an admittedly incomplete (however accurate) lists of patients [21].

The increased estimated prevalence over time can be due to several factors, including improved diagnosis tech-

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niques, increased attention by general physicians, increased survival of patients due to improved standard of care, and possibly even an increased morbidity likely due to environmental factors.

In agreement with previous studies, we identified a higher MS prevalence in females (194.1 per 100,000) than in males (93.0 per 100,000). Our estimated female to male to ratio is 1.8. The female to male ratio in the younger age classes is higher (considering classes 0–24 and 25–34, the average ratio is 2.6), decreasing then with age. This is consistent with the fact that disease manifestation is often earlier in females than in males [22].

Lastly, we calculated prevalence rates standardized to European and Italian Standard Populations. While there are currently no whole European-level estimates, it shall be reported that prevalence estimates in other regions of Europe are generally lower, with the notable exceptions of Southern Italy and Sardinia, Scotia, Northern Ireland, and specific regions of Scandinavia [12]. The Italian prevalence rate reported in [3] is 176 per 100,000 (when excluding Sardinia), which shall be compared with our 147.5 per 100,000 after standardization.

Our study has both strengths and limitations. The statistical model used to calculate prevalence rates is validated, and it enabled us to avoid bias related to small sample size, incomplete lists, and unobserved factors. From a methodological perspective, indeed, in this work, we outline how even with a clearly incomplete survey of patients in an area (as we have not included all centers treating patients in Rome) with the capture-recapture method one can obtain reliable estimates. On the other hand, even when a survey is deemed to have achieved a complete (or almost complete) census, we still recommend the use of the capture-recapture method to avoid bias, and at least check the extent of the population that might not have been included. In fact, we stress that our prevalence rates are slightly larger than prevalence rates previously published [11].

The major limitation of our study is, in our opinion, that due to the restricted number of patients included, we could not finely stratify by age class (e.g., we could not use 5 year intervals for age class-specific estimates, as these would have been associated with very large confidence intervals). Similarly, we were not able to compute precise incidence rates due to very limited number of new diagnoses in 2015. Finally, it shall be reported that we have focused on the prevalence for patients born in the area and alive, as we had no information on residency.

In conclusion, our study, by providing a reliable estimate for prevalence, demonstrates how the metropolitan city of Rome is a high-risk area for MS. Not surprisingly, this estimate is the largest ever obtained for the area.

Disclosure Statement

The authors declare that there are no conflicts of interest to disclose.

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