

# Capture-Recapture as a Potentially Useful Procedure for Assessing Prevalence of Multiple Sclerosis: Methodologic Exercise Using Portuguese Data

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## Key Words

Capture-recapture methods • Epidemiology • Multiple sclerosis prevalence • Public health

## Abstract

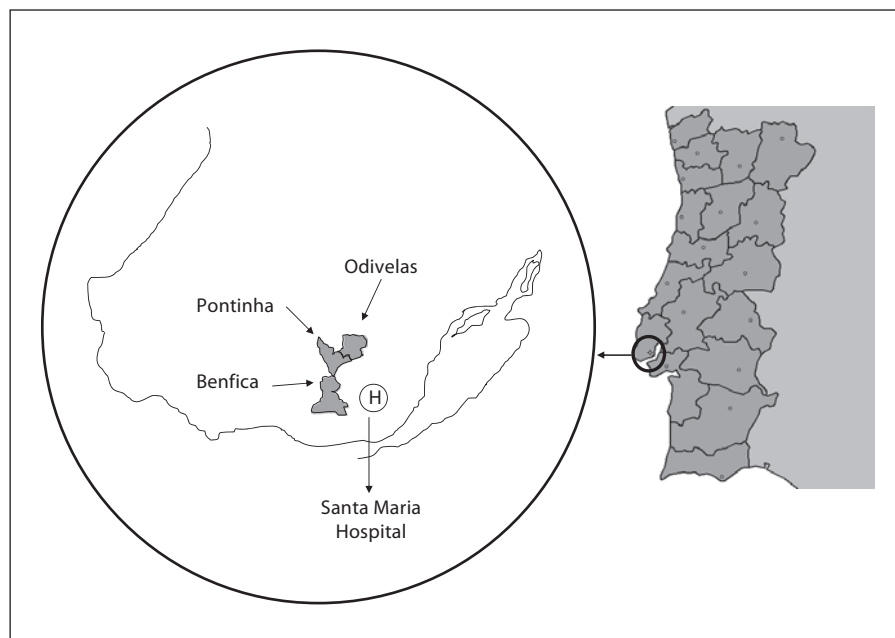
**Background:** Capture-recapture methods (CRMs) are well established in epidemiologic surveillance and considered useful for the task of correcting for case-finding limitations in multiple sclerosis (MS) prevalence surveys. To date, however, CRMs have been exclusively applied to crude prevalence figures. This study therefore sought to explore an age-specific application of this method to an urban Portuguese population of 229,342. **Methods:** We used a CRM to correct for the age-specific prevalence of MS obtained from two data sources, i.e. general practitioners in three primary-care districts and a neurology unit at the referral hospital. The corrected figures were adjusted for age using the European standard population as reference. **Results:** When applied to 95 MS patients, the CRM impact was highest at ages 50–59 years, with a 110% increase in cases where the corrected prevalence was highest, i.e. 181.8 (95% CI 75.7–287.9) per 100,000, and lowest, nil, at ages  $\geq 70$  years, with an unchanged corrected prevalence of 13.8. The crude prevalence

of 41.4 per 100,000 increased by 36% to 56.20 per 100,000 when it was CRM- and age-adjusted. Source independence was poor. **Conclusions:** CRMs can be differentially applied to MS counts. Valid comparisons may require simultaneous adjustment for age and other variables, such as diagnostic delay and diagnostic criteria. CRM applications to crude figures and dependent sources should be approached with caution.

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## Background

Potentially rising and still poorly understood trends in the incidence of multiple sclerosis (MS), occasional reports of MS as a side effect of vaccination, and the possible effects of the considerable decrease in childhood infections, among other things, may lead to epidemiologic surveillance or monitoring of MS [1–4]. Yet, despite some exploratory attempts, based on MS registries mainly in Scandinavian populations [5–8], neither the rationale for nor the structural and functional features of a public-health-based MS service has been proposed. One such initiative is the use of the capture-recapture method (CRM), a classic procedure intended to estimate or adjust



**Fig. 1.** Geographic location of the study populations.

for the extent of incomplete ascertainment when collecting cases from different sources, as generally occurs when proceeding with case-finding in MS surveys [9, 10]. As the name implies, the CRM has its antecedents in animal ecology.

Results of applying CRMs to MS have been reported by six studies undertaken in Argentina, Colombia, France, Spain, the UK and the USA, in every case based on crude prevalence counts [11–16]. CRMs are considered useful in MS prevalence studies where cases are frequently diagnosed or registered in different data sources (hospitals, outpatient neurology clinics, patient associations, general practitioner (GP) lists, etc.), and reported increases in prevalence estimates versus uncorrected figures are high, reaching 38% in a recent study [12]. Comparisons of CRM-corrected crude prevalence figures are of limited value, however, when populations differ in age structure [17].

The aim of this study was to explore the impact of a CRM on correcting MS prevalence. Hook and Regal [18] stressed the importance of validating CRM using ‘real’ data instead of simulated information. The MS survey conducted on the 62,000 inhabitants of the Santarem district, which yielded a crude prevalence of 43 per 100,000 in 1998, may have become outdated due to technological improvements in diagnosis [19]. We therefore explored CRM effects as applied to recently updated, MS-diagnostic, population-based Portuguese data.

## Methods

### Study Populations and Medical Services

We studied the resident catchment population (2001 census) of three geographically adjacent primary-care districts in Lisbon’s Northern Health Area, i.e. Benfica, Pontinha and Odivelas. The sizes of the three subpopulations, as furnished by the health authorities, were 62,465, 33,031 and 133,846, respectively. These subpopulations are traditionally served by the Santa Maria Hospital (SMH), which also provides neurological care to a considerably larger population, totaling 517,872 persons. The geographic situation of the catchment areas of the above three primary-care districts and the SMH is shown in figure 1.

For the purposes of generating age-specific populations by district, we obtained age-specific 2001 census populations for administrative units that overlapped the residential areas of primary-care users (i.e. those of the Benfica and Pontinha parishes and the Odivelas municipal area) and yielded a reasonable fit with primary-care districts of the same name. The distributions of each of the three health district populations by age are shown in table 1.

The Portuguese health system is characterized by three coexisting systems, namely the country’s National Health Service (NHS), special social health insurance schemes for certain professions (health subsystems), and voluntary private health insurance. In addition, around 25% of the population is covered by health subsystems, 10% by private insurance schemes, and another 7% by mutual funds. The NHS provides universal coverage funded by taxation. In Portugal, primary care is provided at NHS primary-care centers (PCCs), with each center generally serving the catchment population residing in the geographic area in

which it is located; neurological care is provided by neurologists at a ratio of 1 per 31,600 inhabitants. Portugal's publicly run NHS provides neurological care at low cost, as follows: in the case of rural areas, at the hospital nearest to the resident population, and in the case of cities, on a less rigid basis whereby patients may be referred to different hospitals. Patients diagnosed with MS attend NHS hospital-based or private neurology clinics and PCCs. As the cost of MS treatment is wholly subsidized by the NHS, patients are required to be registered at the health centers in their respective residential areas. Insofar as the study populations are concerned, Lisbon's SMH, where this study's principal researcher (J.S.) practices, is the main referral center for their designated health regional area.

#### Case-Finding and Epidemiologic Classification

All PCCs in Lisbon's Northern Health Area were invited to participate in this survey. After the directors of the Benfica, Pontinha and Odivelas PCCs had presented the project to their staff, all three volunteered to participate. The project was approved by the SMH Ethics Committee in 2007.

#### Primary-Care-Based Case Search

During several meetings with a neurologist field researcher at the three PCCs, GPs received instructions and criteria for identifying patients suffering from MS, i.e. patients were required to present with diagnosis of MS, established by a department of neurology or a local neurologist. The GPs agreed to participate and complete a spreadsheet with patient data. At each center, the director appointed a local researcher to implement data collection. All GPs – 57 in Odivelas, 13 in Pontinha and 36 in Benfica – collaborated. Field data collection at the three centers was undertaken in the period from September 2009 through December 2010. When the data from the GPs were furnished to the research team, J.S. contacted the private neurologist who had made the MS diagnosis, or alternatively, other hospital departments, i.e. at the Capuchos and Egas Moniz Hospitals, to obtain confirmation of MS diagnosis of such patients and details enabling application of MS diagnostic criteria.

#### Hospital-Based Search

During the same period, the database of patients diagnosed with MS at the SMH unit directed by J.S. was explored by J.S. in order to identify residents in the above three primary-care districts. In addition, a few patients with MS but not shown on the GP lists were identified by J.S. after a request for information had been sent to neurologists in private practice. Patients were labeled as being known or unknown to the GPs, firstly by reason of the fact that their names were absent from the respective GP's list, and secondly on confirmation at the above-mentioned meetings of the fact that there was no record of MS diagnosis in the patient's clinical history at the PCC. The neurology records of patients attending the SMH were examined by J.S.

#### Diagnostic Criteria and Residence

Patients suspected of suffering from MS but still undergoing clinical evaluation or having symptoms difficult to interpret were not included in counts. A small number (around 3%) who had, at their most recent neurological visit, fulfilled McDonald's criteria for clinically isolated syndrome were deemed inappropriate for CRM correction and excluded from counts [20]. Patients who met

**Table 1.** Study population by primary-care center allocation, overall and age-specific

Age group	Odivelas	Benfica	Pontinha	All districts
0–19	28,497	9,455	7,093	45,045
20–29	22,880	10,111	5,265	38,256
30–39	19,502	7,206	4,583	31,291
40–49	19,781	7,206	4,785	31,772
50–59	19,845	10,085	4,720	34,650
60–69	13,238	9,766	3,552	26,556
≥70	10,103	8,636	3,033	21,772
All ages	133,846	62,465	33,031	229,342

Estimated using weights from population census for administrative units: Odivelas municipal area and Benfica and Pontinha parishes.

McDonald's 2001 MS diagnostic criteria [20] at the prevalence date (December 31, 2009) were included in the study and referred to as 'MS patients'.

Residence in PCC districts was verified from addresses shown in medical records. Four patients reported as having MS, identified at SMH or in the GP lists (2 from Odivelas, 1 from Benfica) without medical control for several years, were contacted. Due to severe disability (bedridden or wheel-chair bound), they had moved some years previously to charity homes located outside the study area.

#### Capture-Recapture Methodology

A potential usage of the CRM in epidemiology is the refinement of prevalence and incidence estimates when the investigator has clearly incomplete data from two or more sources [9].

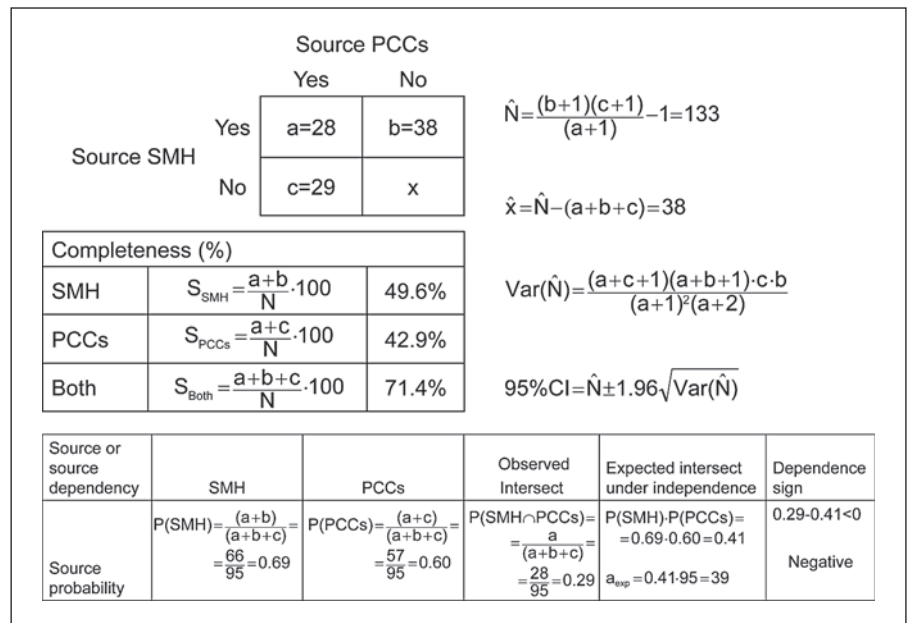
#### Data Source Design

In accordance with Hook and Regal's suggestions [9, 21], patient identification was followed by distinguishing (a) three 'original' sources, namely the SMH, three GP lists at PCCs, and some private practitioners, and (b) two 'analytical' sources, the SMH and PCCs, used for CRM calculations, after private practitioners and GPs at PCCs had been pooled into one source. Analytical sources were independent if the average probability of MS patients who appeared in their intersection or 'overlap' was equal to the product of average probabilities of appearing in each source separately. Independence of data sources was verified by testing the statistical significance of deviations between the expected and observed distribution of cases at the SMH and PCC intersect on a  $2 \times 2$  table obtained from product probabilities of the main analytical subsets (fig. 2).

#### Calculations for CRM

Assuming source independence, we used reported methods [9, 22–25] to obtain CRM-corrected prevalence estimates and their 95% confidence intervals (CIs) for pooled populations across all ages, each of the three subpopulations across all ages, and pooled populations by age-specific strata. The CRM-corrected preva-

**Fig. 2.** Methodologic outline and example of calculations of CRM correction, completeness and source dependency.



lence numerator was generated using the method described in 2000 by Hook and Regal [18], first reported by Sekar and Deming [22] and subsequently modified by Chapman [23] and Seber [24]. This numerator is known as the Chapman nearly unbiased estimator (NUE), as shown in figure 2 with an example for all districts across all ages. The estimated value for the unobserved cell was obtained, as indicated in figure 2, from the rounded Chapman NUE figure minus the three observed cell numbers. The 95% CI of the CRM-corrected prevalence was obtained from the 95% limits for the CRM-corrected value, by using the well-known Chapman NUE variance calculation procedure [23, 24], as suggested by Ferrer Evangelista et al. [26] and Gallay et al. [27] (fig. 2). Finally, CRM-corrected and age-adjusted prevalence figures and 95% CIs were calculated using standard European population weights provided by Zivadinov et al. [17] for MS prevalence strata, and the Epidat procedure for direct adjustment. The terms CRM-adjusted, completeness-adjusted and ascertainment-adjusted are indistinctly used in the literature.

#### Completeness

Heterogeneity of completeness (captured proportion of estimated cases) was tested using the test for  $2 \times 2$  or  $2 \times n$  contingency tables.

## Results

After detailed examination of neurology records kept by the SMH and by specialists (mostly neurologists) contacted by GPs and J.S., 96 patients were found to fulfill McDonald's 2001 criteria for MS at the prevalence date [20]. Age was not clearly identified for 1 patient who was

dropped from counts, so that the CRM was finally applied to 95 MS patients.

MS patients classified by source, original or analytical, are depicted in figure 3. Based on these figures, the CRM-corrected number of cases (n) was 133. Completeness for SMH and PCCs across all ages was 49.6 and 42.9%, respectively, rising to 71.4% for both sources combined. Source dependency for SMH and PCCs across all ages was 0.69 and 0.60, respectively. The expected intersect,  $0.69 \times 0.60 = 0.41$ , was higher than the observed intersect,  $28/95 = 0.29$ , with the dependency sign being negative ( $0.29 - 0.41 < 0$ ). Observed versus expected numbers at the intersect, 28 versus 39, and outside the intersect, 67 versus 56, yielded an OR = 0.60 (95% CI 0.31–1.14). The dependency sign for single districts and age groups (not shown) was systematically negative.

Shown in two sections, upper and lower, in table 2 is the  $2 \times 2$  breakdown of the two-source model when applied to eleven observations, four of which correspond to three separate and pooled districts across all ages (upper), and seven of which correspond to horizontally aligned age-specific strata for pooled districts (lower). In contrast, the second last row contains totals for all ages from vertically aligned age strata. The body of the table is divided into a left block with cases and completeness results, and a right block with prevalence figures, which are crude, age-specific, uncorrected or CRM-corrected, and age- and CRM-adjusted.



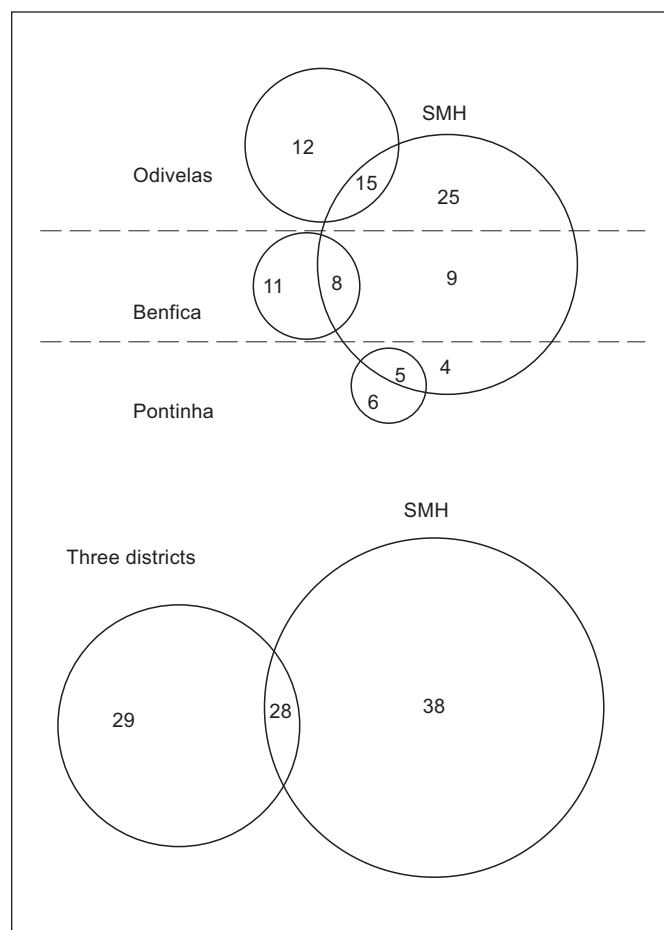
The left block of table 2 shows both observed data and rounded Chapman NUE numbers, which ranged from 19 for Pontinha to 133 for all districts and all ages, and from 3 for the  $\geq 70$  to 63 for the 50–59 age group on an age-specific basis. When NUE estimates for age groups were added, the number (141) exceeded the figure obtained by 6% when the method was applied to crude pooled populations (133). While the CRM-estimated number of patients at ages  $\geq 70$  years was low, i.e. 3, in other age groups it was higher than 7. Completeness for two sources, for single districts and all ages, ranged from 71.8 to 78.9%. Two-source completeness for age-specific groups was  $>78\%$ , except for the 50–59 age group in which it was 47.6%, and also proved to be significantly heterogeneous, with Fisher's exact test  $p = 0.001$ , Pearson's  $\chi^2_5 = 22.268$ .

Crude prevalence proportions, shown in the right block of table 2, ranged from 38.9 per 100,000 in Odivelas to 45.4 per 100,000 in Pontinha. Ascertainment-adjusted prevalence figures per 100,000 inhabitants, with their 95% CIs, were as follows: 53.0 (40.0–66.1), 62.4 (41.6–83.2) and 57.5 (37.5–77.6) for Odivelas, Benfica and Pontinha, respectively, and 58.0 (46.9–69.1) for the total study population.

Prevalence in age groups shown in table 2 (bottom right) displayed a considerably wide variation, ranging, after correction for ascertainment, from 13.8 at ages  $\geq 70$  years to 181.8 at ages 50–59 years. CRM impact was highest for the 50–59 age group, increasing from an observed 86.6 per 100,000 to a CRM-adjusted 181.8 per 100,000, i.e. by 110%. Prevalence at ages  $\geq 60$  years compared to that at ages 50–59 years was low, and CRM impact was limited, increasing from 33.9 to 37.7 per 100,000, i.e. by 11% at ages 60–69 years and nil thereafter. Finally, a complete overview of MS prevalence is shown in table 2 for all districts, for which crude observed prevalence per 100,000 was 41.4, increasing after CRM correction to 61.48, i.e. by 49%, and decreasing slightly after additional age adjustment to 56.20, i.e. by 36%.

## Discussion

It should be emphasized that this study seeks only to serve as an illustration of ascertainment and age adjustment of MS prevalence using realistic data. The results show that adjustments for both age and completeness considerably modify crude figures, and that the impact of CRM adjustment is age specific, with the differential being highest for highest prevalence and lowest at ages



**Fig. 3.** Distribution of MS patients by original and main analytical sources.

$>70$  years. In addition, it suggests that CRM adjustment should be approached with caution, since source independence may be limited.

The need for age and age-and-sex adjustment when conducting MS incidence or prevalence studies has been stressed by Zivadinov et al. [17]. In our case, adjustment for age using the European standard population had a small impact, a result that was to be expected given the coincidence of the age structure of the European standard and Portuguese study populations. Since the impact of age and CRM adjustment is high and was not attempted previously [11–16], we propose that, if used, CRM should be systematically applied to age- and, likely, sex-specific measures, and that ascertainment-corrected MS prevalence comparisons should be subsequently adjusted for age, or compared by age-stratified analysis or using models controlling for age.

**Table 2.** Age distribution of MS patients: observed cases (OC) and estimated cases (EC) as well as percentage of completeness

Population denominators		Number of patients									Prevalence proportions per 100,000	
residence and age	number of persons	OC			EC	OC+EC		completeness (%)			observed	ascertainment-corrected with 95% CI
		at SMH and PCCs (a) <sup>1</sup>	unique to SMH (b) <sup>1</sup>	unique to PCCs (c) <sup>1</sup>	(x) <sup>1</sup>	total (N) <sup>1</sup>	Chapman NUE	SMH	PCCs	SMH and PCCs	crude point	crude, age-specific or age-adjusted
<i>All ages by district</i>												
Odivelas	133,846	15	25	12	19	71	70.75	56.3	38.0	73.2	38.9	53.0 (40.0–66.1)
Benfica	62,465	8	9	11	11	39	39.00	43.6	48.7	71.8	44.8	62.4 (41.6–83.2)
Pontinha	33,031	5	4	6	4	19	19.00	47.4	57.9	78.9	45.4	57.5 (37.5–77.6)
All districts	229,342	28	38	29	38	133	133.00	49.6	42.9	71.4	41.4	58.0 (46.9–69.1)
<i>All districts by age group</i>												
0–19	45,045	0	0	0	0	–	–	–	–	–	0	0.0
20–29	38,256	2	4	1	1	8	8.33	75.0	37.5	87.5	18.3	20.9 (11.9–29.9)
30–39	31,291	8	9	4	4	25	25.00	68.0	48.0	84.0	67.1	79.9 (59.7–100.1)
40–49	31,772	8	11	6	7	32	32.33	59.4	43.8	78.1	78.7	100.7 (70.2–131.2)
50–59	34,650	4	11	15	33	63	63.00	23.8	30.2	47.6	86.6	181.8 (75.7–287.9)
60–69	26,556	5	3	1	1	10	9.50	80.0	60.0	90.0	33.9	37.7 (31.3–44.0)
≥70	21,772	1	0	2	0	3	3.00	33.3	100	100	13.8	13.8 (13.8–13.8) <sup>2</sup>
All districts and all ages	229,342	28	38	29	46	141	–	46.8	40.4	67.4	–	61.48 <sup>4</sup>
All districts and all ages	229,342	–	–	–	–	–	–	–	–	–	–	56.20 (46.88–65.52) <sup>4</sup>

Prevalence figures are age-specific, crude, ascertainment-corrected and age-adjusted to the European standard population.

<sup>1</sup> Notation from figure 2. <sup>2</sup> 95% CI limits equal point estimate because Var(N) = 0 due to b = 0. <sup>3</sup> Crude ascertainment-corrected prevalence obtained from added age-specific N estimates,  $\Sigma N = 141$  using the study population. <sup>4</sup> CRM- and age-adjusted.

The impact of CRM adjustment was poor at ages 20–29 years, modest at ages 30–49 years, and nil at ages >59 years. Different reasons would appear to account for this divergence. At ages with a high incidence, MS is known to both the SMH referral hospital and GPs. At ages >69 years, neither the SMH nor the GPs capture substantial numbers of MS-prevalent patients; however, if MS incidence has been stable in recent decades and excess mortality has been small (a relative risk ratio of 1.5), then such patients must be assumed to exist [28]. As suggested by surveys in Argentina where the reported prevalence was low, CRM does not substantially help correct for under-ascertainment in situations where ascertainment is poor at both PCCs and neurology department levels. This may call for case-finding efforts in Portuguese and other populations to be intensified and directed towards other sources of MS patients, particularly in the case of older age groups, e.g. retirement files. The fact that the largest 10-year increase in MS incidence in Newcastle, Australia, for 1986–1996 versus 1971–1981 was seen at ages >49 years may point to complex factors underlying the low accrual of patients at ages >69 years in our study [29].

When applying CRM to MS prevalence, evaluation of the presence of source dependency is essential. Contrary to what Hook and Regal [18] contended, namely that most datasets used by epidemiologists tend to have a net positive dependence, our results suggest the presence of negative source dependency, something that would tend to produce prevalence overestimates. A bias of this nature means that both the validity and interest of the application are diminished [9], since approximately 50% of the correction would be deemed inaccurate. Negative dependency, namely a situation in which the proportion of cases known to the SMH and PCCs is too low, could be viewed as applying here, in that the 28 cases captured by the SMH-PCC intersect are too low compared to the expected proportion of 41%, i.e. 39 cases. It may be difficult to establish whether patients with MS attending the PCCs tend to be diagnosed at the SMH due to the fact that its geographic proximity is comparatively greater than that of other hospitals, or whether losses in case-finding with respect to such patients correspond mainly to patients diagnosed at other hospitals. We believe the second alternative to be the more reasonable, particularly since the study was generated at the initiative of the SMH where

the tradition of MS registration is presumably better established. Other reasons may be higher MS prevalence or detection in the SMH's main catchment areas, or losses linked to collaboration by specialists from hospitals other than the SMH. Interestingly, use of CRMs may reveal underlying problems in case-finding when an MS survey is under way. The 6% difference between CRM-corrected crude and age-adjusted values might be attributable to non-compliance with sample size requirements at ages  $\geq 70$  years, the effects of rounding the Chapman NUE and, above all, variation in dependency across age strata (results not shown).

Aside from age-related simultaneous CRM adjustments, there are other types of adjustment which should perhaps be considered. One of these is adjustment for diagnostic delay, which has occasionally been performed in MS [30]. Finally, adjustment for diagnostic criteria could be proposed. Comparisons of CRM-adjusted figures obtained using different diagnostic criteria may require consideration of sensitivity and predictive value, and are likely to be affected by diagnostic delay. To date, incidence studies have mainly used selected traditional clinical categories, e.g. Poser's criteria [31], which differ considerably from magnetic resonance imaging-supported criteria, such as those of McDonald in 2001, that are capable of capturing even 'monosymptomatic' disease, a category absent from our study exercise into prevalent MS [20]. The higher proportion of such groups in newly diagnosed MS may require alarm thresholds adjusted for CRM and other variables, such as diagnostic delay and different, recently reassessed MS diagnostic criteria [32].

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To sum up, CRM may constitute a potentially useful tool for correcting for MS undercounts in epidemiologic studies or surveillance, subject to assessment of data source dependency, and for use in age-specific or custom-tailored applications. These results will be used to improve epidemiologic research into MS and to interpret results of specific, ongoing MS surveys being conducted in Portugal and Southern Europe. There may be shortcomings related to assessing the effect of CRM application to data of different types.

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## Disclosure Statement

The authors have no conflicts of interest to disclose.

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