Cost-of-Illness Progression Before and After Diagnosis of Multiple Sclerosis: A Nationwide Register-Based Cohort Study in Sweden of People Newly Diagnosed with Multiple Sclerosis and a Population-Based Matched Reference Group

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Abstract

Background  Multiple sclerosis (MS) is a chronic disease associated with increased healthcare utilisation and productivity losses.

Objective  The objective of this study was to explore the progression of healthcare costs and productivity losses before and after diagnosis of MS in comparison to that of a population-based matched reference group.

Methods  We conducted a nationwide, Swedish register-based cohort study of working-aged people with MS diagnosed in 2010–12 (n = 1988) and population-based matched references without MS (n = 7981). Nine years of observation spanned from 4 years prior (Y−4) to 4 years (Y+4) after the year of diagnosis (Y0). Differences in annual all-cause healthcare costs (inpatient and specialised outpatient healthcare as well as pharmacy-dispensed prescribed drugs) and costs of productivity loss (days with sickness absence and disability pension) were estimated between the people with MS and references using t tests with 95% confidence intervals. The average excess costs of MS were estimated using generalised estimating equation models.

Results  People with multiple sclerosis had higher costs before the diagnosis of MS and also thereafter. The mean differences in healthcare costs and productivity losses between the people with MS and matched references in Y−4 were 216 EUR (95% confidence interval 58–374) and 1540 EUR (95% confidence interval 848–2233), with larger cost excesses observed in later study years. Summarising the 9 study years, people with MS had fivefold higher excess healthcare costs than references, and more than twice as high productivity losses.

Conclusions  Excess healthcare costs and productivity losses occur already before the diagnosis of MS and increase with time. The excess costs findings before diagnosis could suggest that an earlier diagnosis might lead to reduced excess costs of MS over time.

Plain Language Summary

Multiple sclerosis (MS) is a neurological disease that can affect many parts of everyday life, including work. We studied the extra costs related to MS. Extra costs were defined as the difference in costs between people with MS and the general population in Sweden. To do this, we compared the costs of working-aged individuals with MS from 4 years before to 4 years after the year of MS diagnosis with those of individuals without MS. For each year, we measured the healthcare consumption and days absent owing to sickness absence or a disability pension. We found that people with MS had larger costs already before the diagnosis of MS. For all types of costs we studied, there were extra costs. The extra costs became larger with time and had a steep increase around the year of MS diagnosis. When we summarised the costs from all 9 years, people with MS had five times higher annual costs related to healthcare consumption than those without MS. There were also twice as high costs for lost production from days absent with sickness absence or a disability pension. While our data from national registers had

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Objective measurements of the included costs, it did not include information on the costs for drugs administered in healthcare, rehabilitation or informal care from family members. We studied the costs of all people diagnosed with MS in 2010–12 in Sweden, related their disease trajectory with their costs, as well as compared their costs with the costs of a group from the general population. Our results of the extra costs of MS prior to diagnosis could suggest an unmet need. Earlier diagnosis and quickly starting treatment may lead to lower extra costs of MS over time.

### Key Points for Decision Makers

- People with multiple sclerosis (MS) have higher healthcare costs and productivity losses compared with the general population in Sweden.
- The excess costs of MS, in terms of healthcare costs and productivity losses, begin prior to diagnosis of MS and increase with time.
- The productivity losses for people with MS were the largest costs in terms of absolute costs; however, people with MS had a larger relative excess for healthcare costs in comparison with those costs of the matched references.

### 1 Introduction

Multiple sclerosis (MS) is a neurological disease often diagnosed when of working age [1–3] and is associated with increasing levels of both cognitive and physical disability along the clinical course [2, 4]. Sweden has an especially high prevalence at 189 per 100,000 [3, 5]. Although this prevalence estimate is relatively low compared with other chronic diseases, MS poses a significant socioeconomic burden to society. An increasing number of disease-modifying therapies (DMTs) to reduce disease activity and slow progression [2] are available in Sweden [6]. Updated population-based cost-of-illness (COI) estimates reflecting the recent advances in MS healthcare and potential changes to the work capacity of people with MS (PwMS) are therefore needed [7–10]. These estimates, in terms of healthcare costs and productivity losses, may assist in planning and resource allocation decisions [11].

Knowledge is limited of the progression of COI and the factors driving costs, both before and after being diagnosed with MS [12, 13]. Most recent studies consider costs among prevalent groups of PwMS with cross-sectional study designs [7, 10, 14, 15]. Yet, costs may be incurred already before the diagnosis of MS because of early signs and symptoms [16, 17]. Consequently, higher resource use among PwMS than among references has previously been observed prior to the diagnosis of MS [12, 13, 18, 19], and even around onset [17, 20]. How these higher resource use patterns translate into excess cost progression of MS is largely unknown regarding the pattern of cost progression and the magnitude of the excess [12]. Excess cost comparisons are especially important when studying a chronic and systemic disease such as MS, as there may be wider costs for resource use without direct attribution to the disease [12, 14, 21]. The excess costs of MS in Sweden in comparison with references have been investigated in one study with prevalent MS cohorts indicating a cost excess for MS [14]. However, the excess cost progression among newly diagnosed PwMS in Sweden remains unknown, necessitating assessment with an incidence-based cohort to map the excess costs to the clinical course prior to clinical diagnosis. Accordingly, we aimed to explore the progression of healthcare costs and productivity losses before and after diagnosis of MS in Sweden in comparison to that of a population-based matched reference group.

### 2 Methods

This nationwide, register-based longitudinal cohort study was conducted by the authors at the medical university Karolinska Institutet, Stockholm, Sweden, with the analyses performed in the Spring/Summer of 2020. We investigated the annual costs for 9 years among PwMS and their matched reference peers, with a relative time scale from 4 years before (Y−4) to 4 years after (Y+4) the year of MS diagnosis (Y0). The study period spanned 2006–16, with baseline referring to the match date (31 December Y−5). Individual-level Swedish register data were linked, using unique personal identity numbers, to build the study population and inform annual resource utilisation.

#### 2.1 Swedish Setting

Sweden has healthcare and social insurances with universal coverage for residents. Healthcare is predominantly financed from tax revenues with government-imposed caps for patient copayments within a 12-month period for healthcare visits and progressively discounted copayments for prescribed drugs [22, 23]. Healthcare utilisation is reported to the National Board of Health and Welfare that maintains nationwide registers, including the National...
Patient Register (NPR) [24, 25] recording all inpatient and specialised outpatient healthcare visits, the Swedish Prescribed Drug Register [26] for prescribed drugs dispensed at pharmacies, and the Cause of Death Register recording the dates of all deaths.

The Social Insurance Agency compensates lost income related to reduced work capacity due to disease or injury. All residents with work-related income can claim sickness absence if their work capacity is reduced because of a disease or injury [27]. A disability pension can be granted to those with long-term or permanently reduced work capacity, without any requirements of previous income [27]. Both sickness absence and a disability pension can be granted full time or part time (100, 75, 50, or 25%) of ordinary working hours [27]. The Micro Data for the Analysis of Social Insurance (MiDAS) register contains information on individuals’ full-time or part-time sickness absence and disability pension days [28].

### 2.2 Study Population

Newly diagnosed PwMS of working ages and population-based matched references formed the study population (Fig. 1). The PwMS were newly diagnosed individuals, defined as having the first MS diagnosis code ever registered as a main or side diagnosis in the NPR within 2010–12. Accordingly, these individuals did not have MS codes (International Classification of Disease and Health Related Problems (ICD)-8/9 340, or ICD-10 G35) prior to these years. In the next step, linking to the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) [29, 30], which provided sociodemographic and residency information, only individuals who were aged 19–55 years at baseline (31 December Y−5) were included. Exclusions were then applied to these working-aged PwMS identified from register data to strengthen assumptions that the MS code in the NPR represented a newly set diagnosis and to confirm
the diagnosis of MS. The Swedish Multiple Sclerosis Registry was also used in these steps [31].

After forming the PwMS group, each individual with MS was matched with four reference individuals without MS to form the matched reference group. Potential references from LISA eligible for matching were randomly selected to represent the general population in Sweden. Exact matching, without replacement, was based on sex (women/men), age (year), type of living area (Stockholm [including Södertälje], other large cities, medium-sized towns, rural areas), and country of birth (Sweden; yes/no) at baseline. This resulted in a group of references that was identical to the PwMS in each combination of strata of the matching variables.

2.3 Study Outcomes

Annual all-cause costs were calculated from the societal perspective. Cost estimations were prevalence based [11], including all costs incurred within the calendar year.

Healthcare costs, productivity losses, and total costs were estimated for each study year. Resource use was measured for each cost component and then the costs were calculated as a multiplication of the resource use count and unit cost. The unit costs for the cost calculations are summarised in Table 1.

Healthcare costs comprised the costs for inpatient and specialised outpatient healthcare visits and for prescribed drugs. Annual costs for inpatient and specialised outpatient visits, respectively, were derived from the diagnosis-related group (DRG) code classifying the visit in the NPR and patient copayments in the form of patient fees. The DRG code for each visit was translated to a cost with the retrospective weight assigned to the DRG [32]. Weights were multiplied by the relevant year’s national average unit cost per 1.0 DRG and then summed per person. Inpatient healthcare costs were assigned to the discharge year. Patient copayments were then added to the respective cost [22]. Annual drug costs for all prescribed drugs dispensed from pharmacies were summed from the costs recorded in the Swedish Prescribed Drug Register. Drug costs were specific to the quantity of and the substance (as per Anatomical Therapeutic Chemical Classification System code) dispensed and comprised the patient copayment and remaining portion paid by the county. Annual healthcare costs per person were calculated by summing the inpatient, specialised outpatient and drug cost components.

Productivity losses were estimated using the human capital approach [11], assuming full employment. As per the established methodology for counting productivity losses in COI studies, we did not measure the costs of the transfer payments from the benefits [11, 33, 34]. Rather, the net days of sickness absence and disability pension were used to infer the days of lost production (e.g., 2 gross days absent at 50% = 1 net day of absence). For each year, the net months of lost production were counted and then were multiplied with the sum of average gross monthly salary across all sectors [35] and the employers’ social security contribution [33, 36]. Only periods of sickness absence > 14 days were included to avoid introducing bias between employed and unemployed due to differences in when the Social Insurance Agency begins to pay for sickness absence by employment status [27]. Annual productivity losses per person were calculated by summing the production losses from both sickness absence and disability pension. In cases where the net days of sickness absence and disability pension exceeded the days in the year, the combined total was capped at the number of possible days in the year when calculating total productivity losses. Accordingly, there is a slight overestimation in the disaggregated productivity losses from sickness absence days (range 0.3–1.7% of the cohort per calendar year).

Annual total societal costs per person were the sum of healthcare costs and productivity losses. All costs were inflated to 2019 Swedish prices [37]. Results are presented in Euros (EUR), calculated with the 2019 exchange rate of 10.5891 [38].

2.4 Statistical Analyses

The study population was described with frequencies and proportions. Chi² tests were used to test for differences in proportions between all PwMS and the matched references.

Descriptive statistics for the annual costs per person were calculated for all of the PwMS and references, allowing for zero costs. For each study year, the mean costs of the PwMS and references were compared with two-tailed Student’s t tests assuming equal variance and reported as mean differences with 95% confidence intervals (CIs).

Adjusted cost comparisons between PwMS and references were performed using generalised estimating equation (GEE) models [39]. Generalised estimating equations estimate the population average response with repeated data [39], and are an extension of generalised linear models, a standard method for analysing cost data [40, 41]. Models were constructed separately for total costs, healthcare costs and productivity losses, specifying Poisson distribution, a log link function and an autoregressive correlation matrix to account for the within-individual correlation of the annually repeated cost measurements [42]. Costs can be considered to follow a count distribution when they are generated by counting the individuals’ resource use before multiplying the recorded volume of use with the corresponding unit cost [40]. We studied the excess costs for all PwMS rather than costs amongst resource users. Accordingly, resource use was counted for all within the study population, allowing for zero costs. Therefore, a gamma distribution could not be used as
these individuals with zero costs for a particular cost component would then be dropped.

Three main effect models were built to assess the association between MS and costs:

- **Model 1a:** MS and study year.
- **Model 2a:** Model 1a covariates as well as the cohort (2010, 2011, 2012) and matching variables (sex, age, type of living area, country of birth).
- **Model 3a:** Model 2a covariates and additional sociodemographic characteristics: educational level (university/college, yes/no); family composition dichotomised as...
married/cohabiting (yes/no) and living with children (age < 18 years) (yes/no); and type of work [43] (manager, office work, manual labour, unclassified work, not in paid work).

Additionally, an interaction term was included (Models 1–3b) between MS (yes/no) and study year (Y−4−Y+4) to identify time trends in the excess cost progression among PwMS compared with references. The matching variables were in the models because additional covariates were included in the analyses of this matched cohort [44].

The model results were reported exponentiated as incidence rate ratios with 95% CIs from the robust standard errors and p values [42]. The incidence rate ratios can be interpreted as population average multipliers indicating the excess cost due to MS [45, 46]. Last, adjusted annual mean costs with 95% CIs were estimated using Model 2b.

A sensitivity analysis (Model 4a) was conducted to further investigate the contribution of comorbidity to the excess costs of MS beyond the indirect adjustments through comparison with the matched reference group. To do this, comorbidity (0; 1–2; 3–4; 5+ comorbidity categories) was added to Model 2a. The modified RxRisk Comorbidity Index [47, 48] was constructed for Y−4, with drug information (excluding MS DMTs) from the Swedish Prescribed Drug Register and supplemented with information from the Swedish Cancer Register (included in the register, yes/no) to reduce underestimation of cancers. Anxiety/depression (yes/no) and pain (yes/no) were identified from the index.

Statistical analyses were performed using SAS Version 9.4 except for costing data management using STATA Version 15. The Regional Ethical Review Board of Stockholm, Sweden approved the project.

3 Results

The included study population comprised 1988 PwMS and 7981 population-based matched references. The matching procedure resulted in 2024 PwMS and 8096 references. However, individuals were subsequently excluded if they died, emigrated within Y+1−Y+4, or if being a matched reference with sickness absence or disability pension for MS (n = 36 PwMS and n = 115 references excluded). The 98.5% (PwMS: 98.2%; references: 98.6%) of the identified study population that had complete follow-up were included in the analyses. The characteristics of PwMS and matched references included in the analyses are presented in Table 2. There were no statistical differences between the PwMS and matched references regarding the matching variables after the subsequent exclusions, nor for most of the other measured sociodemographic characteristics. Differences between the PwMS and the references were observed regarding comorbidity.

The annual numbers and proportions with costs and the mean costs for all are presented in Table 3 with the mean healthcare costs and productivity losses plotted in the Electronic Supplementary Material (ESM). Healthcare costs among PwMS steeply increased in the years around diagnosis of MS and peaked in Y+1. Afterwards, there was a slight decreasing trend in the annual mean per person healthcare costs, with high proportions of PwMS having healthcare costs (> 98% per year). Productivity losses were higher than healthcare costs. The mean annual productivity losses among PwMS increased over the study period, with a sharp increase in Y0.

The cost components as a proportion of the total costs are presented in the ESM. The distributions among the references were stable, whereas among PwMS the relative contribution of component costs differed across study years. The three components that consumed the most resources among PwMS before diagnosis of MS were sickness absence, disability pension and inpatient healthcare costs, while sickness absence, disability pension and drug costs were the largest cost components after diagnosis of MS. Healthcare costs among the PwMS went from 14% of the total costs in Y−4 to 31% in Y+4. Productivity losses contributed 63–86% of the total costs in all years for PwMS and 81–86% for references.

An excess in both healthcare costs and productivity losses was observed already before the diagnosis of MS when comparing the costs among PwMS with those of the matched references. The mean differences in Y−4 indicated an excess cost per person with MS of 216 EUR (95% CI 58–374) for healthcare costs and 1540 EUR (95% CI 848–2233) for productivity losses (Table 3). Thereafter, the magnitudes of the mean differences increased.

Reporting the excess cost estimates for MS from Model 2a, PwMS had on average 5.25 times higher healthcare costs (95% CI 4.97–5.55) and 2.38-times higher productivity losses (95% CI 2.24–2.54) throughout the study compared with matched references (see ESM). After including comorbidity, the excess cost estimates for MS for both healthcare costs and productivity losses attenuated slightly from those in Model 2a to 5.06 (95% CI 4.79–5.34) and 2.25 (95% CI 2.12–2.39), respectively.

The estimates from the three models including the interaction term were consistent with each other and showed that MS was associated with increasingly greater excess costs (total, healthcare and productivity losses) with time (see ESM). Significant excess costs among the PwMS compared with references were observed from Y−2 with Y−4 as the reference year, with the largest cost excesses for MS observed for Y0 and Y+1.

The adjusted mean annual healthcare costs and productivity losses among the PwMS and references are plotted in
| Characteristic                                      | PwMS 2010 cohort | PwMS 2011 cohort | PwMS 2012 cohort | All PwMS | Matched references n = 7981 | p value<sup>a</sup> |
|----------------------------------------------------|------------------|------------------|------------------|----------|-----------------------------|-------------------|
|                                                   | n = 611          | n = 706          | n = 671          | n = 1988 | n = 1988                    |                   |
|                                                   | n (%)            | n (%)            | n (%)            | n (%)    | n (%)                       |                   |
| **Sociodemographic characteristics**<sup>b</sup>  |                  |                  |                  |          |                             |                   |
| **Sex**                                            |                  |                  |                  |          |                             | 0.806             |
| Women                                              | 424 (69.4)       | 488 (69.1)       | 451 (67.2)       | 1363 (68.6) | 5449 (68.3)                |                   |
| Men                                                | 187 (30.6)       | 218 (30.9)       | 220 (32.8)       | 625 (31.4) | 2532 (31.7)                |                   |
| **Type of living area**                            |                  |                  |                  |          |                             | 0.993             |
| Stockholm                                          | 106 (17.4)       | 137 (19.4)       | 134 (20.0)       | 377 (19.0) | 1509 (18.9)                |                   |
| Other large cities                                 | 102 (16.7)       | 115 (16.3)       | 131 (19.5)       | 348 (17.5) | 1382 (17.3)                |                   |
| Medium-sized towns                                 | 215 (35.2)       | 266 (37.7)       | 203 (30.3)       | 684 (34.4) | 2741 (34.3)                |                   |
| Small towns/rural areas                            | 188 (30.8)       | 188 (26.6)       | 203 (30.3)       | 579 (29.1) | 2349 (29.4)                |                   |
| **Country of birth**                               |                  |                  |                  |          |                             |                   |
| Outside Sweden                                     | 68 (11.1)        | 68 (9.6)         | 83 (12.4)        | 219 (11.0) | 872 (10.9)                 | 0.908             |
| Sweden                                             | 543 (88.9)       | 638 (90.4)       | 588 (87.6)       | 1769 (89.0) | 7109 (89.1)                |                   |
| **Age (years)**                                     |                  |                  |                  |          |                             | 0.906             |
| 19–24                                              | 99 (16.2)        | 105 (14.9)       | 126 (18.8)       | 330 (16.6) | 1301 (16.3)                |                   |
| 25–34                                              | 188 (30.8)       | 213 (30.2)       | 192 (28.6)       | 593 (29.8) | 2357 (29.5)                |                   |
| 35–44                                              | 188 (30.8)       | 223 (31.6)       | 206 (30.7)       | 617 (31.0) | 2463 (30.9)                |                   |
| 45–55                                              | 136 (22.3)       | 165 (23.4)       | 147 (21.9)       | 448 (22.5) | 1860 (23.3)                |                   |
| **Educational level**                              |                  |                  |                  |          |                             | 0.497             |
| No college/university                              | 392 (64.2)       | 437 (61.9)       | 440 (65.6)       | 1269 (63.8) | 5029 (63.0)                |                   |
| College or university                              | 219 (35.8)       | 269 (38.1)       | 231 (34.4)       | 719 (36.2) | 2952 (37.0)                |                   |
| **Cohabiting/married**                             |                  |                  |                  |          |                             | 0.190             |
| No                                                  | 327 (53.5)       | 371 (52.6)       | 333 (49.6)       | 1031 (51.9) | 4008 (50.2)                |                   |
| Yes                                                 | 284 (46.5)       | 335 (47.5)       | 338 (50.4)       | 957 (48.1) | 3973 (49.8)                |                   |
| **Children living at home**                        |                  |                  |                  |          |                             | 0.002             |
| No                                                  | 363 (59.4)       | 397 (56.2)       | 366 (54.6)       | 1126 (56.6) | 4205 (52.7)                |                   |
| Yes                                                 | 248 (40.6)       | 309 (43.8)       | 305 (45.5)       | 862 (43.4) | 3776 (47.3)                |                   |
| **Type of work**                                    |                  |                  |                  |          |                             | 0.026             |
| Manager                                             | 14 (2.3)         | 25 (3.5)         | 12 (1.8)         | 51 (2.6)  | 304 (3.8)                  |                   |
| Office work                                         | 190 (31.1)       | 243 (34.4)       | 236 (35.2)       | 669 (33.7) | 2805 (35.2)                |                   |
| Manual labour and customer service                  | 276 (45.2)       | 298 (42.2)       | 292 (43.5)       | 866 (43.6) | 3373 (42.3)                |                   |
| Unspecified work                                    | 57 (9.3)         | 54 (7.7)         | 61 (9.1)         | 172 (8.7)  | 606 (7.6)                  |                   |
| Not in paid work                                    | 74 (12.1)        | 86 (12.2)        | 70 (10.4)        | 230 (11.6) | 893 (11.2)                 |                   |
| **Comorbidity in Y−4**                             |                  |                  |                  |          |                             |                   |
| Depression/anxiety<sup>d</sup>                     |                  |                  |                  |          |                             | 0.048             |
| No                                                  | 543 (88.9)       | 619 (87.7)       | 589 (87.8)       | 1751 (88.1) | 7152 (89.6)                |                   |
| Yes                                                 | 68 (11.1)        | 87 (12.3)        | 82 (12.2)        | 237 (11.9) | 829 (10.4)                 |                   |
| **Pain**                                            |                  |                  |                  |          |                             | <.0001            |
| No                                                  | 491 (80.4)       | 556 (78.8)       | 516 (76.9)       | 1563 (78.6) | 6599 (82.7)                |                   |
| Yes                                                 | 120 (19.6)       | 150 (21.3)       | 155 (23.1)       | 425 (21.4) | 1382 (17.3)                |                   |
| **Comorbidity categories**<sup>e</sup>              |                  |                  |                  |          |                             | 0.002             |
| 0                                                   | 169 (27.7)       | 196 (27.8)       | 196 (29.2)       | 561 (28.2) | 2533 (31.7)                |                   |
| 1–2                                                | 333 (54.5)       | 371 (52.6)       | 350 (52.2)       | 1054 (53.0) | 4082 (51.2)                |                   |
| 3–4                                                | 73 (12.0)        | 89 (12.6)        | 92 (13.7)        | 254 (12.8) | 1010 (12.7)                |                   |
| 5+                                                 | 36 (5.9)         | 50 (7.1)         | 33 (4.9)         | 119 (6.0)  | 356 (4.5)                  |                   |
in Y−4, 17,668 EUR (95% CI 15,906–19,629) in Y0, and ity losses for PwMS were 6815 EUR (95% CI 5956–7801) < 0.05 p 19,032 EUR (95% CI 17,167–21,104) in Y+4.

Cancer Register, excluding MS DMTs (ATC codes: L03AB07; L03AB08; L03AB13; L03AX13; L04AA31; L04AA23; L04AA27; L04AA34; L01XC02; L04AC01; and N07XX09). Comorbidity is according to a modified RxRisk Comorbidity index constructed by ATC codes from the SPDR or whether in the Swedish CancerRegister, excluding MS DMTs (ATC codes: L03AB07; L03AB08; L03AB13; L03AX13; L04AA31; L04AA23; L04AA27; L04AA34; L01XC02; L04AC01; and N07XX09). Comorbidity is according to a modified RxRisk Comorbidity index categories according to the SPDR by ATC codes: M01AB01-M01AX01; and N02AA01-N02AX09.

Table 2 (continued)
\( ATC \) Anatomical Therapeutic Chemical Classification System, \( DMT \) disease-modifying therapy, \( MS \) multiple sclerosis, \( SPDR \) Swedish Prescribed Drug Register
\( a \)P-value calculated with Pearson’s Chi\(^2\) tests. Differences in proportions were tested between all PwMS and the matched references without MS, \( p < 0.05 \)
\( b \)Sociodemographic characteristics measured at baseline (match date 31 December Y−3). Individuals with missing values were placed in the lowest category
\( c \)Variables used in matching 1:4, with age matched in exact years. Subsequent exclusions because of death or emigration, and for sickness absence or disability pension due to MS among the matched references, mean that the numbers presented no longer sum exactly to a 1:4 ratio
\( d \)Comorbidity and drug information with regard to the entire calendar year of the first (Y−4) study year
\( e \)Anxiety/depression was identified from the respective RxRisk Comorbidity index categories according to the SPDR by ATC codes: N05BA01-N05BA56; N05BE01; N06AA01-N06AG02; N06AX01-N06AX11; N06AX13-N06AX26; and N06AX12
\( f \)Pain drugs were identified from the respective RxRisk Comorbidity index categories according to the SPDR by ATC codes: M01AB01-M01AX01; and N02AA01-N02AX09

Fig. 2. The adjusted mean healthcare costs for PwMS were 1083 EUR (95% CI 919–1276) in Y−4, 8847 EUR (95% CI 8147–9609) in Y0, and 8360 EUR (95% CI 7682–9098) in Y+4 (data not presented). The adjusted mean productivity losses for PwMS were 6815 EUR (95% CI 5956–7801) in Y−4, 17,668 EUR (95% CI 15,906–19,629) in Y0, and 19,032 EUR (95% CI 17,167–21,104) in Y+4.

4 Discussion

In this register-based longitudinal cohort study, annual healthcare costs and productivity losses among working-aged PwMS from 4 years before to 4 years after the MS diagnosis year were compared with those of a population-based matched reference group. Excess costs of MS due to healthcare utilisation and production loss were observed already several years before the diagnosis year and increased over the 9-year study period. The productivity losses of PwMS were the largest cost in absolute terms. Yet, the relative excess costs for healthcare of PwMS were higher than the excess productivity losses.

Our excess MS cost estimates were generally in line with previous studies. In particular, the excess healthcare costs in the years after the MS diagnosis are of similar magnitude to findings from a Swedish study with prevalent MS cohorts (mean annual excess in healthcare costs were EUR 7277–9748 and productivity losses were EUR 18,249–20,139) [14]. We also observed differences across all studied cost components. Excess healthcare costs have also been observed among prevalent PwMS in the USA for every studied healthcare cost component in a 12-month period, including inpatient services, radiology, visits and drugs [21]. With longer observation from the diagnosis of MS, it is likely that our estimates increase to closer reflect estimates from prevalence-based MS cohorts as the COI of MS is associated with disability level [7, 15, 49, 50] and time since diagnosis [51].

Multiple sclerosis was associated with higher costs already before receiving the clinical diagnosis. The excess costs already prior to MS diagnosis could represent diagnostic delays between MS symptom onset and clinical diagnosis [7, 16–18]. To the best of our knowledge, this is the first study considering excess cost progression before MS diagnosis in Sweden. A cost excess has been observed up to 8 years pre-diagnosis in a Danish study spanning 1998–2006 [12]. While the annual mean total societal excess cost per person of MS for all study years of EUR 13,901 [12] potentially reflects the limited DMT availability in those years, we observed similar excess cost progression trends. Specifically, that excess healthcare costs spike around MS diagnosis and excess productivity losses more steadily increase along the clinical course [12]. Furthermore, 63.9% of PwMS in Sweden have previously been observed to follow a similar healthcare cost trend to ours after the diagnosis of MS [52]. While our focus was on the excess between PwMS and references, previous COI studies suggest that the cost excess of MS likely differs among PwMS [52], for example, by sex [10], disability [15] or phenotype [53].

The observed spike in excess healthcare costs around diagnosis of MS, with a more than sevenfold excess cost among PwMS the year after MS diagnosis, is conceivably related to healthcare need arising from disease activity that resulted in the diagnosis and subsequent initiation of DMTs [13]. The sustained excess healthcare costs post-diagnosis are likely a combination of more PwMS requiring ongoing healthcare and DMTs [18, 54], and perhaps more complex and expensive care. Drug costs were increasingly important drivers of the excess costs of MS, likely owing to MS DMT initiation, as in previous findings among PwMS with low disability levels [50] and relapsing-remitting MS [53]. Similar to our observations of excess specialised outpatient costs,
Table 3  Number and percentage of users of the respective resource, mean per person costs\(^a\) with standard deviations (SDs) and 95% confidence intervals (CIs) for all of the people with multiple sclerosis (PwMS) and the population-based matched references, respectively, mean differences with 95% CIs between the PwMS and matched references, and the percentage of the mean costs among PwMS attributable to the excess, for each study year

|                           | PwMS (\(n = 1988\)) | Matched references (\(n = 7981\)) | Mean difference |
|---------------------------|----------------------|----------------------------------|-----------------|
|                           | Users (\(n\)) Users (%) Mean (EUR) SD 95% CI | Users (\(n\)) Users (%) Mean (EUR) SD 95% CI | Mean (EUR) 95% CI |
| (a) Total costs           |                      |                                  |                 |
| Year −4                   | 1530 77.0 8225 16,715 7490–8960 | 5926 74.3 6469 15,026 6139–6799 | 1756 1000–2512 < 0.001 21.3 |
| Year −3                   | 1546 77.8 8575 17,044 7826–9325 | 5878 73.7 6491 15,135 6159–6823 | 2085 1321–2848 < 0.001 24.3 |
| Year −2                   | 1593 80.1 9154 18,349 8347–9961 | 5937 74.4 6253 15,267 5918–6588 | 2901 2118–3683 < 0.001 31.7 |
| Year −1                   | 1702 85.6 11,408 20,903 10,568–12,247 | 5923 74.2 6234 15,101 5903–6566 | 5173 4388–5958 < 0.001 45.3 |
| Year 0                    | 1988 100.0 26,203 23,690 25,161–27,245 | 6000 75.2 6441 15,256 6106–6775 | 19,762 18,913–20,611 < 0.001 75.4 |
| Year +1                   | 1963 98.7 27,814 24,216 26,749–28,879 | 6043 75.7 6742 15,779 6396–7088 | 21,072 20,199–21,946 < 0.001 75.8 |
| Year +2                   | 1958 98.5 27,584 24,288 26,516–28,653 | 6039 75.7 7306 16,656 6941–7672 | 20,278 19,372–21,183 < 0.001 73.5 |
| Year +3                   | 1960 98.6 26,905 24,116 25,844–27,966 | 6015 75.4 7966 17,832 7574–8357 | 18,939 17,994–19,885 < 0.001 70.4 |
| Year +4                   | 1956 98.4 27,167 24,443 26,091–28,242 | 6097 76.4 8448 18,121 8050–8845 | 18,719 17,759–19,679 < 0.001 68.9 |
| (b) Healthcare costs      |                      |                                  |                 |
| Total healthcare costs    |                      |                                  |                 |
| Year −4                   | 1513 76.1 1121 3495 968–1275 | 5856 73.4 906 3138 837–974 | 216 58–374 0.007 19.3 |
| Year −3                   | 1525 76.7 1282 3247 1140–1425 | 5808 72.8 943 2801 882–1005 | 339 197–481 < 0.001 26.4 |
| Year −2                   | 1578 79.4 1605 5540 1361–1848 | 5874 73.6 1000 3886 914–1085 | 605 395–815 < 0.001 37.7 |
| Year −1                   | 1689 85.0 2272 4401 2078–2465 | 5867 73.5 1011 3291 939–1083 | 1261 1087–1435 < 0.001 55.5 |
| Year 0                    | 1987 100.0 8870 7656 8533–9206 | 5932 74.3 1132 3433 1057–1207 | 7378 7512–7964 < 0.001 87.2 |
| Year +1                   | 1962 98.7 10,312 8613 9933–10,691 | 5984 75.0 1202 3996 1115–1290 | 9110 8852–9368 < 0.001 88.3 |
| Year +2                   | 1954 98.3 9527 8260 9164–9891 | 5983 75.0 1364 4673 1261–1466 | 8164 7890–8438 < 0.001 85.7 |
| Year +3                   | 1955 98.3 8910 8417 8540–9280 | 5950 74.6 1423 5997 1292–1555 | 7487 7163–7809 < 0.001 84.0 |
| Year +4                   | 1950 98.1 8347 8184 7987–8707 | 6023 75.5 1405 4831 1299–1511 | 6943 6665–7221 < 0.001 83.2 |
| Inpatient healthcare costs|                      |                                  |                 |
| Year −4                   | 190 9.6 534 2865 408–660 | 684 8.6 443 2332 392–494 | 91 –30 to 211 0.139 17.0 |
| Year −3                   | 209 10.5 565 2355 462–669 | 694 8.7 418 1989 375–462 | 147 45–248 0.005 26.0 |
| Year −2                   | 207 10.4 707 4874 493–922 | 693 8.7 449 3230 378–520 | 258 80–436 0.004 36.5 |
| Year −1                   | 327 16.5 882 3116 745–1019 | 621 7.8 416 2495 362–471 | 465 336–594 < 0.001 52.7 |
| Year 0                    | 729 36.7 2449 5739 2196–2701 | 706 8.9 483 2434 430–537 | 1966 1800–2131 < 0.001 80.3 |
| Year +1                   | 353 17.8 1613 6161 1342–1884 | 650 8.1 508 3206 438–579 | 1105 909–1300 < 0.001 68.5 |
| Year +2                   | 340 17.1 1591 5349 1356–1826 | 710 8.9 622 3859 538–707 | 969 762–1175 < 0.001 60.9 |
| Year +3                   | 324 16.3 1459 5284 1226–1691 | 669 8.4 647 5162 533–760 | 812 557–1067 < 0.001 55.7 |
| Year +4                   | 297 14.9 1280 4640 1075–1484 | 631 7.9 608 3703 527–690 | 671 479–863 < 0.001 52.4 |
Table 3 (continued)

| Year  | PwMS (n = 1988) | Matched references (n = 7981) | Mean difference |
|-------|----------------|-------------------------------|-----------------|
|       | Users (n) Users (%) Mean (EUR) SD 95% CI | Users (n) Users (%) Mean (EUR) SD 95% CI | Mean (EUR) 95% CI p value Percent-age excess b |
|       | Specialised outpatient healthcare costs | Drug costs | Sickness absence costs c |
| Year −4 | 685 34.5 313 727 281–345 | 2477 31.0 253 837 235–272 | 60 20–100 0.004 19.2 |
| Year −3 | 762 38.3 389 827 353–426 | 2572 32.2 310 858 291–329 | 79 37–121 < 0.001 20.3 |
| Year −2 | 890 44.8 479 919 439–520 | 2738 34.3 333 859 314–352 | 146 103–189 < 0.001 30.5 |
| Year −1 | 1141 57.4 762 1263 706–818 | 2770 34.7 362 972 341–383 | 400 349–451 < 0.001 52.5 |
| Year 0 | 1950 98.1 2221 1622 2150–2292 | 1019 37.7 407 1019 385–429 | 1814 1757–1871 < 0.001 81.7 |
| Year +1 | 1840 92.6 1736 1701 1542–1692 | 3221 40.4 482 1099 458–506 | 1138 1077–1198 < 0.001 74.1 |
| Year +2 | 1807 90.9 1620 1644 1548–1692 | 3221 40.4 482 1099 458–506 | 1138 1077–1198 < 0.001 70.2 |
| Year +3 | 1782 89.6 1617 1701 1542–1692 | 3268 41.0 503 1128 478–528 | 1114 1052–1176 < 0.001 68.9 |
| Year +4 | 1754 88.2 1678 1783 1600–1756 | 3268 41.1 533 1217 507–560 | 1114 1052–1176 < 0.001 68.2 |
| Year −4 | 1339 67.4 275 1153 224–326 | 5078 63.6 209 987 188–231 | 65 15–116 0.011 23.6 |
| Year −3 | 1287 64.7 328 1393 267–389 | 4843 60.7 218 1069 194–241 | 201 140–261 < 0.001 48.1 |
| Year −2 | 1313 66.1 418 1723 342–494 | 4901 61.4 218 1069 194–241 | 201 140–261 < 0.001 48.1 |
| Year −1 | 1397 70.3 628 2118 535–721 | 4875 61.1 232 1203 206–259 | 396 325–466 < 0.001 63.1 |
| Year 0 | 1830 92.1 4200 4549 4000–4400 | 1322 40.4 482 1099 458–506 | 1138 1077–1198 < 0.001 70.2 |
| Year +1 | 1830 92.1 6963 5911 6703–7223 | 5001 62.7 245 1328 216–274 | 6718 6576–6860 < 0.001 96.5 |
| Year +2 | 1804 90.7 6316 6173 6045–6588 | 4937 61.9 259 1408 228–290 | 6057 5908–6206 < 0.001 95.9 |
| Year +3 | 1785 89.8 5834 6173 5556–6113 | 4978 62.4 274 1783 235–313 | 5560 5401–5720 < 0.001 95.3 |
| Year +4 | 1747 87.9 5390 6412 5108–5672 | 5052 63.3 263 1473 230–295 | 5127 4972–5282 < 0.001 95.1 |

(c) Productivity losses

| Year  | Total productivity losses | Sickness absence costs c |
|-------|---------------------------|--------------------------|
| Year −4 | 405 20.4 7104 15,328 6430–7778 | 1370 17.2 5563 13,763 5261–5865 | 1540 848–2233 < 0.001 21.7 |
| Year −3 | 406 20.4 7293 15,742 6601–7986 | 1322 16.6 5547 14,010 5240–5855 | 1746 1040–2452 < 0.001 23.9 |
| Year −2 | 425 21.4 7549 16,124 6840–8258 | 1256 15.7 5254 13,754 4952–5555 | 2296 1595–2996 < 0.001 30.4 |
| Year −1 | 530 26.7 9136 17,212 8379–9893 | 1229 15.4 5223 13,802 4921–5526 | 3913 3198–4627 < 0.001 42.8 |
| Year 0 | 987 49.7 17,333 20,680 16,423–18,243 | 1264 15.8 5309 13,859 5005–5613 | 12,024 11,265–12,784 < 0.001 69.4 |
| Year +1 | 403 45.4 17,502 21,396 16,561–18,443 | 1309 16.4 5540 14,156 5229–5850 | 11,962 11,183–12,742 < 0.001 68.3 |
| Year +2 | 921 46.3 18,057 21,665 17,104–19,010 | 1393 17.5 5943 14,640 5622–6264 | 12,114 11,314–12,914 < 0.001 67.1 |
| Year +3 | 925 46.5 17,995 21,716 17,040–18,950 | 1509 18.9 6542 15,382 6205–6880 | 11,453 10,626–12,280 < 0.001 63.6 |
| Year +4 | 941 47.3 18,819 22,296 17,839–19,800 | 1579 19.8 7043 16,094 6690–7396 | 11,776 10,916–12,637 < 0.001 62.6 |
Table 3 (continued)

| Year   | PwMS (n = 1988) | Matched references (n = 7981) | Mean difference |
|--------|----------------|-------------------------------|-----------------|
|        | Users (n) | Users (%) | Mean (EUR) | SD | 95% CI | Users (n) | Users (%) | Mean (EUR) | SD | 95% CI | Mean (EUR) | 95% CI | p value | Percent-age excess$^b$ |
| Year −3 | 259 | 13.0 | 4214 | 12,234 | 3676–4752 | 840 | 10.5 | 3053 | 10,438 | 2823–3282 | 1162 | 630–1693 | < 0.001 | 27.6 |
| Year −2 | 270 | 13.6 | 4330 | 12,541 | 3778–4881 | 755 | 9.5 | 2641 | 9740 | 2428–2855 | 1688 | 1179–2197 | < 0.001 | 39.0 |
| Year −1 | 383 | 19.3 | 5966 | 14,289 | 5338–6595 | 748 | 9.4 | 2686 | 9873 | 2469–2902 | 3281 | 2746–3816 | < 0.001 | 55.0 |
| Year 0  | 838 | 42.2 | 14,164 | 19,684 | 13,299–15,030 | 798 | 10.0 | 2914 | 10,302 | 2688–3140 | 11,251 | 10,625–11,877 | < 0.001 | 79.4 |
| Year +1 | 740 | 37.2 | 13,766 | 20,118 | 12,881–14,651 | 844 | 10.6 | 3087 | 10,579 | 2855–3319 | 10,679 | 10,038–11,320 | < 0.001 | 77.6 |
| Year +2 | 708 | 35.6 | 13,197 | 19,961 | 12,319–14,075 | 931 | 11.7 | 3441 | 11,177 | 3196–3686 | 9756 | 9098–10,414 | < 0.001 | 73.9 |
| Year +3 | 621 | 31.2 | 11,366 | 19,123 | 10,525–12,207 | 1015 | 12.7 | 3885 | 11,959 | 3623–4147 | 7481 | 6808–8154 | < 0.001 | 65.8 |
| Year +4 | 553 | 27.8 | 10,407 | 18,904 | 9576–11,239 | 1069 | 13.4 | 4218 | 12,601 | 3942–4495 | 6189 | 5497–6881 | < 0.001 | 59.5 |

Disability pension costs

| Year   | 156 | 7.9 | 2915 | 10,538 | 2452–3379 | 536 | 6.7 | 2450 | 9709 | 2237–2663 | 465 | −21 to 950 | 0.061 | 16.0 |
| Year −3 | 176 | 8.9 | 3282 | 11,233 | 2788–3776 | 557 | 7.0 | 2616 | 10,147 | 2394–2839 | 666 | 156–1176 | 0.011 | 20.3 |
| Year −2 | 184 | 9.3 | 3423 | 11,450 | 2919–3927 | 557 | 7.0 | 2713 | 10,440 | 2484–2942 | 710 | 186–1233 | 0.008 | 20.7 |
| Year −1 | 178 | 9.0 | 3335 | 11,364 | 2836–3835 | 543 | 6.8 | 2629 | 10,299 | 2403–2855 | 706 | 189–1223 | 0.007 | 21.2 |
| Year 0  | 192 | 9.7 | 3474 | 11,456 | 2970–3978 | 526 | 6.6 | 2508 | 10,036 | 2288–2729 | 966 | 458–1474 | < 0.001 | 27.8 |
| Year +1 | 245 | 12.3 | 4251 | 12,551 | 3699–4803 | 507 | 6.4 | 2524 | 10,180 | 2301–2748 | 1727 | 1202–2253 | < 0.001 | 40.6 |
| Year +2 | 347 | 17.5 | 5680 | 14,158 | 5057–6303 | 524 | 6.6 | 2593 | 10,334 | 2366–2820 | 3087 | 2537–3638 | < 0.001 | 54.3 |
| Year +3 | 462 | 23.2 | 7671 | 15,896 | 6972–8370 | 551 | 6.9 | 2770 | 10,739 | 2534–3005 | 4901 | 4314–5488 | < 0.001 | 63.9 |
| Year +4 | 543 | 27.3 | 9553 | 17,590 | 8780–10,327 | 566 | 7.1 | 2932 | 11,181 | 2687–3177 | 6622 | 5997–7246 | < 0.001 | 69.3 |

EUR Euros, MS multiple sclerosis, SEK Swedish krona

$a$Mean costs were calculated for all 1988 PwMS and the 7981 population-based matched references without MS, respectively in the study population, irrespective of resource use. All costs are presented in Euros in 2019 values. The annual exchange rate for 2019 from SEK to EUR that was used was 10.5891 [38].

$b$The percentage excess refers to the mean difference between PwMS and references as a proportion of the mean of that cost component for PwMS.

$^c$In order not to introduce bias in relation to employment status, only sickness absence periods >14 days were included. There is a slight overestimation of the sickness absence-related productivity losses in the disaggregated costs (range: 0.3–1.2% of the cohort per year) due to capping of the net days of sickness absence and disability pension combined at the number of possible days in the year in calculating total productivity losses in cases where the number of net days combined exceeded the possible days in the year.
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A Canadian study observed excess physician (specialised outpatient and primary healthcare) visits already 5 years before the diagnosis of MS, with a peak in the year of diagnosis and elevated annual visits thereafter in comparison with both pre-diagnosis levels and the matched reference group [18]. The healthcare cost component trends are also consistent with findings from newly diagnosed PwMS in 2008–11 in the Netherlands, where hospital (inpatient and specialised outpatient healthcare) costs were observed to peak in the year of MS diagnosis compared with 2 years before, while drug costs peaked in the year after [13]. Furthermore, hospital costs 3 years after were observed to be 67% of the costs in the year of MS diagnosis [13]. We observed a similar peak, the corresponding percentages for the PwMS in our study are 59.6% for inpatient costs and 72.8% for outpatient costs.

Fig. 2  Adjusted annual mean a total societal cost of illness, b healthcare costs and c productivity losses per person with 95% confidence intervals for the people with multiple sclerosis (PwMS) [n = 1988] compared with the population-based matched references without multiple sclerosis (MS) [n = 7981] from Y−4 to Y+4. Costs are presented in Euros (EUR) in 2019 values. Adjusted results were calculated with generalised estimating equation models with the following specification: log link, Poisson distribution and autoregressive correlations. Model 2b is presented where cost = MS + year + MS*year + cohort + the matching variables (age, sex, living area and birth country).
Multiple sclerosis involves a substantial socioeconomic burden from productivity losses due to the age of onset and the disease’s relapsing and chronic nature [12, 55]. We add that the excess costs from productivity losses among PwMS are over twice as high early in the clinical course than among matched references. Productivity losses are high when occurring, with more skewness among references than PwMS in the proportions with days of lost production [56]. The excess productivity losses will likely further increase with time from the diagnosis of MS, owing to the clinical course affecting the functional ability and work capacity among a greater proportion of PwMS and to a greater degree, as well as more permanent reductions of work capacity [4, 19].

Our findings of excess productivity losses pre-diagnosis suggest there may be an unmet need of PwMS. The observed progression of productivity losses was consistent with trends of higher annual net days of sickness absence and disability pension among PwMS in Sweden than among references already prior to diagnosis of MS [19, 57, 58]. The productivity losses pre-diagnosis suggest that the PwMS may experience early symptoms, such as fatigue, that even affect their work capacity [16, 59]. The diagnoses for these days of sickness absence and disability pension may be for diagnoses related to MS or represent other morbidities [58]. Individuals lacking an MS diagnosis and consequently not having MS DMTs potentially have worsening MS and larger excess costs. Our study period captures the increasing availability of DMTs, early initiation of which may be associated with maintaining work capacity and a reduced risk of sickness absence or disability pension [8, 9]. However, the long-term associations of these DMTs with work capacity or productivity losses remain largely unknown despite improving clinical outcomes [60]. Nonetheless, the costs of early DMT initiation may potentially be offset by other cost savings [61].

4.1 Methodological Considerations

A key strength of the study is the use of microdata from nationwide registers to identify the study population and inform real-world annual resource use, rather than annualising costs from self-reported information with short recall periods from a sample [11, 18, 50, 62]. Some bias may have been introduced in requiring 9 years of complete observation. Complete observation was needed in both assuming the MS ICD code represented a newly set diagnosis and in excluding individuals with incomplete observation, as a result of death or emigration in the 4 years post-diagnosis, to prevent biased parameter estimates in the GEE models [63].

Population-based matched references were used to estimate the cost excess of MS [62]. Therefore, costs related to comorbidity and wider problems related to MS were considered. Costs may be underestimated especially in register-based studies if only considering costs coded with MS as the main diagnosis [14]. It is not always obvious which disease costs relate to, as some comorbidity is independent of MS and yet others may be a result of MS [64]. Furthermore, comorbidity may alter the MS clinical course, as observed with depression [65], and consequently further MS-specific healthcare may be needed. The reference group and use of excess costs also adjusted for aging and wider societal changes over time [57]. Accordingly, our comparison of all-cause costs among PwMS with those of references captures the excess cost attributable to MS.

Multiple sclerosis is associated with substantial costs outside of healthcare [49, 50], thus the application of a societal perspective is especially important [49]. Productivity losses were estimated from high-quality data of sickness absence and the disability pension with the widely used human capital approach [11]. Friction cost methods may have led to lower cost estimates; however, friction periods were unknown and would assume that the available replacement was not already actively producing [11]. Our productivity losses are underestimated, with days of sickness absence only paid by employers (periods < 14 days) not captured in the data.

Retrospective DRG weights based on the nationwide average resource use of visits with that DRG classification were used to cost healthcare visits instead of micro-costing [66]. Using DRG weights may have underestimated the cost of visits due to diagnoses other than MS among PwMS, for example, PwMS may have required more resources than average because of MS and not all DRGs incorporate complication grades.

The main limitation of our study is the lack of information in the nationwide registers for other cost components. For example, we were unable to estimate costs related to informal care, sickness presenteeism, primary healthcare, rehabilitation and adaptation/investments. Additionally, information on drugs administered within healthcare was unavailable, including some DMTs. The inclusion of which would have been advantageous given the increasing interest in early initiation of high-efficacy DMTs [67] and their importance as cost drivers [15, 50]. Our productivity losses and healthcare costs should be interpreted with these considerations in mind.

The cost estimates may not be generalisable to other countries considering the differences in healthcare and social security systems that may influence consumption, unit prices and attitudes for use [49, 50, 68]. However, the costs are representative for newly diagnosed PwMS of working ages in Sweden 2010–12. The treatment landscape continues to change for PwMS, including new DMTs.
with varying prices. Accordingly, future studies will be required to update our cost estimates and these studies could also include cost profiles by first initiated DMT.

5 Conclusions

Newly diagnosed PwMS of working ages in Sweden incur significantly higher healthcare costs, over five times higher, and more than twice as high productivity losses compared with matched references in the country. These excess costs, which could be attributable to the presence of MS, begin already prior to the diagnosis of MS and continue to increase thereafter. Higher healthcare costs and productivity losses compared with matched references could indicate a high unmet need of PwMS before receiving the clinical diagnosis of the disease. Therefore, earlier diagnosis with immediate initiation of appropriate MS therapy aiming to tackle disease progression and reduce symptoms manifested because of the presence of the disease might lead to a reduced excess cost of MS over time.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-021-01035-4.

Declarations

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Conflict of interest Chantelle Murley, Kristina Alexanderson, and Emilie Friberg were partly funded by an unrestricted research grant from Biogen. Kristina Alexanderson has received unrestricted researcher-initiated grants from Biogen. Emilie Friberg has received unrestricted researcher-initiated grants from Celgene. Petter Tinghög has previously received salaries partly funded by Biogen and has no conflicts of interest directly relevant to the content of this article. Korinna Karampampa has previously been employed and received salaries from Karolinska Institutet that were partly funded by Biogen, but not for conducting this study and has not received any salary from Karolinska Institutet or Biogen since October 2019. Currently Korinna Karampampa is only affiliated with Karolinska Institutet, not receiving any financial compensation for her involvement in this study. Korinna Karampampa is working full time at a biopharmaceutical company, Gilead Sciences AB. Jan Hillert received honoraria for serving on advisory boards for Biogen and Novartis and speaker’s fees from Biogen, Merck-Serono, Bayer-Schering, Teva and Sanofi-Aventis. He has served as the principal investigator for projects sponsored by, or received unrestricted research support from, Biogen, Merck-Serono, TEVA, Novartis and Bayer-Schering. Jan Hillert’s MS research is also funded by the Swedish Research Council.

Ethics approval Approval for the research project was obtained from the Regional Ethical Review Board in Stockholm, Dnr: 2007/762-31; 2009/23-32; 2009/1917-32; 2010/466-32; 2011/806-32; 2011/1710-32; and 2014/236-32. The study was performed in accordance with the tenants of the Declaration of Helsinki and later amendments. Informed consent from the research participants was not applicable owing to the use of pseudonymised data from total population administrative registers and that we do not hold individual details revealing the identity of the participants. Individuals included in the voluntary Swedish MS Registry provide consent for the neurologist to enter their information into the register for both clinical and research purposes.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material No data are available. Please contact Prof. Kristina Alexanderson (kristina.alexanderson@ki.se) about why the data, according to the General Data Protection Regulation, the Swedish Data Protection Act, the Swedish Ethical Review Act and the Swedish Public Access to Information and Secrecy Act, cannot be made available.

Code availability Not applicable.

Authors’ contributions All authors contributed to the study conception and design. Data for this study were obtained by KA and JH. Data management and analysis were performed by CM. Statistical interpretation was conducted by CM, PT, EF and KK. The first draft of the manuscript was written by CM and all authors commented on versions of the manuscript. All authors have read and approved the final manuscript.

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