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# Gender disparities in health resource utilization in patients with relapsing–remitting multiple sclerosis: a prospective longitudinal real-world study with more than 2000 patients

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**Dirk Schriefer, Nils-Henning Ness, Rocco Haase and Tjalf Ziemssen**

***Abstract***

**Background:** For the case of multiple sclerosis, research on gender differences from a health economics perspective has not received much attention. However, cost-of-illness analyses can provide valuable information about the diverse impact of the disease and thus help decision-makers to allocate scarce resources. The aim of this study was to describe healthcare resource use and associated societal costs from a gender perspective. In particular, we aimed to identify how resource utilization potentially differs in certain cost components between men and women.

**Methods:** Clinical and economic data were extracted from two prospective, multicentre, non-interventional, observational studies in Germany. Information on health resource use was obtained from all patients on a quarterly basis using a validated questionnaire.

Cost analyses were conducted from the societal perspective including all direct (healthcare-related) and indirect (work-related) costs, regardless of who bears them. Gender-related differences were analysed by a multivariable generalized linear model with a negative binomial distribution and log link function due to the right-skewed distribution pattern of cost data. In addition, costs for men and women were descriptively analysed within subgroups of two-year disease activity.

**Results:** In total, 2095 patients (women-to-men ratio of 2.7:1) presented a mean age of 41.85 years and a median Expanded Disability Status Scale of 2 (interquartile range 1–3.5) ($p > 0.30$ for gender-related differences). Women and men did not statistically differ in total quarterly costs (€2329 ± €2570 *versus* €2361 ± €2612). For both, costs were higher with advancing disease severity and indirect costs were the main societal cost driver. Regarding healthcare-related resources, women incurred higher costs for ambulant consultations [incidence rate ratio (IRR) 1.16, confidence interval (CI) 1.04–1.31], complementary medicine (IRR 2.41, CI 1.14–5.06), medical consumables (IRR 2.53, CI 1.69–3.79) and informal care (IRR 2.79, CI 1.56–5.01). Among indirect costs, we found higher costs for men for presenteeism (IRR 0.62; CI 0.53–0.72) and higher costs for women for disability pension (IRR 1.62; CI 1.23–2.13).

**Conclusions:** Multiple sclerosis poses a significant economic burden on patients, families and society. While the total economic burden did not differ between male and female patients, we found gender differences in specific cost items that are similar to those in the wider non-MS population.

***Keywords:*** gender disparities, multiples sclerosis, resource utilization, sex difference, societal costs

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Correspondence to:
**Tjalf Ziemssen**
Department of Neurology, MS Center Dresden, Center of Clinical Neuroscience, University Hospital Carl Gustav Carus, Fetscherstr. 74, Dresden, 01307, Germany
**Tjalf.Ziemssen@uniklinikum-dresden.de**

**Dirk Schriefer**
**Nils-Henning Ness**
**Rocco Haase**
MS Center Dresden, Center of Clinical Neuroscience, Neurological University Clinic Dresden, Germany

## Introduction

Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system with both clinical and pathological heterogeneity.[1] To date, no single treatment is available to cure MS. Current disease-modifying treatments (DMT) strategies focus on slowing down neurological impairments, notably disability accumulation and the incidence

of relapses.[2] In addition to disease-modifying therapies, patients require multidisciplinary symptomatic management (e.g. fatigue, cognitive impairment, pain, bladder function, spasticity). As patients are mostly diagnosed in their productive phase between 20 and 40 years, MS represents a lifetime source of physical, cognitive, social and economic burden profoundly affecting health-related quality of life. The chronic and overall progressive nature of the disease is associated with a continuous increase in healthcare-related resource use (cost-of-illness), affecting not only the patients and their families, but also the society as a whole. Annual societal costs range from approximately €21,174 (mild MS) to €64,270 (more severe MS) per patient in Germany.[3,4]

The ratio of women to men in MS incidence has increased in recent decades, from almost the same level at the beginning of the 20th century to 2–4:1 in most developed countries.[5,6] As the disease onset for women corresponds to the childbearing age, treatment choice for these women is additionally influenced by pregnancy plans. None of the DMTs to date is officially approved for use during pregnancy. An individual risk–benefit analysis is required, weighing up an increased likelihood for disease activity due to discontinuation of treatment against DMT safety.[6,7]

Research on sex and gender aspects in MS mainly focus on biological and behavioural differences affecting the epidemiology, pathophysiology, clinical manifestations and related outcomes.[6,8–12] The health economic perspective has not received much attention so far. However, cost-of-illness analyses are valuable to inform about the diverse impact of MS and thus help decision makers to allocate scarce resources. Mainly exploratory evidence to date suggests that costs of healthcare are similar for men and women, and gender differences are small compared with the influence of relapse activity, disability accumulation, MS phenotypes, age or disease duration.[13–18] Consequently, relatively large samples are required to detect gender-related differences beyond the statistical noise of variability. Secondary data such as big claims databases would have sufficient power, but they do not consider costs such as unpaid home help, over-the-counter medication or presenteeism, preventing a holistic societal perspective on resource use.[14,19] In addition, they fail to incorporate relevant clinical data, for example neurological disability and involvement of different neurological functional systems.

Hence, our primary aim was to investigate gender-specific healthcare resource utilization and associated societal costs from the societal perspective. In a large real-world sample of more than 2000 MS patients, we investigated how resource utilization potentially differs in certain cost components and examined how different presentations of clinical disease activity relate to gender-related cost differences.

## Methods

The results reported in this manuscript were derived from pooled data from two prospective, observational, non-interventional, phase IV cohort studies in Germany. Details on study design have been described previously.[20,21] In short, MS patients under first-line therapy with glatiramer acetate, interferon beta preparations (PEARL study) or fingolimod (PANGAEA substudy) were followed under real-world conditions for 2 years, with observational periods ending 2015 (PANGAEA) and 2013 (PEARL), respectively. Further inclusion criteria were a relapsing–remitting multiple sclerosis (RRMS) diagnosis and an age of 18 or older. There were no exclusion criteria except the contraindications mentioned in the respective summary of the product information of treatment. Studies were conducted following both the codex of the Voluntary Self-Regulation of the Pharmaceutical Industry and recommendations dealing with quality aspects of non-interventional observational studies. Approvals from independent, local competent ethics committees were obtained and all participants signed informed consent upon inclusion in the study. In both studies, outcomes were collected prospectively with equal regularity and congruent visit schedules at intervals of 3 months.

### *Health resource outcomes*

Data on health resource utilization were collected directly from the patient at each quarterly visit. Therefore, patients filled in the MS health-resource survey (MS-HRS), a recently psychometrically approved questionnaire in terms of its reliability, validity and practicability.[19] Resources were identified and valued using the most accurate approach of bottom-up microcosting. Unit prices were taken from official statistics and

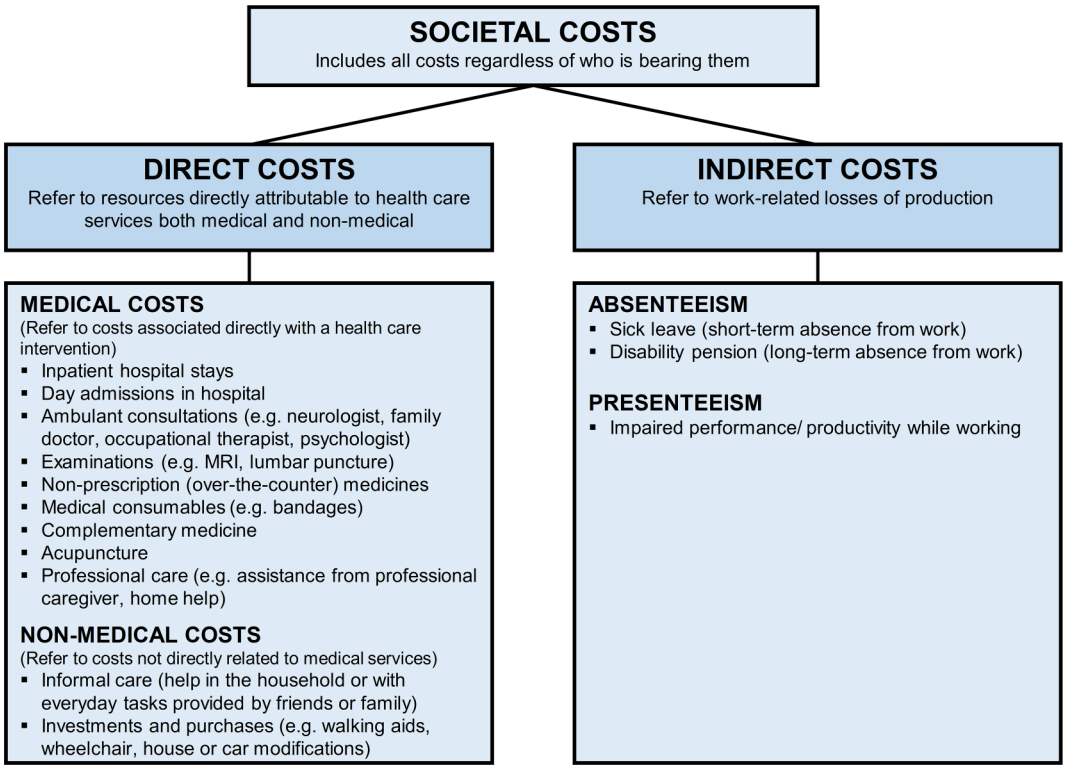


**Figure 1.** Direct and indirect societal costs.
Direct medical costs for DMTs not considered.
MRI, magnetic resonance imaging; DMTs, disease-modifying therapies (treatments)

administrative data, as described before.[19,22] Whenever necessary, we adjusted prices from different periods to 2011 Euro using the consumer price index. Mean costs per patient were reported quarterly in line with the recall periods in the MS-HRS. All costs were reported without expenditures for DMTs.

Analyses were conducted from the societal perspective so that all resources are taken into account regardless of who bears them (Figure 1). We distinguished between direct costs that can be directly attributed to medical health care services (e.g. inpatient stays, day admissions, ambulant consultations or over-the-counter medications), direct non-medical costs (e.g. informal care, adaptions to the house or car) and indirect costs that denote work-related losses of productivity (Figure 1). Informal care was assessed as MS-related help in the household or with everyday tasks provided by friends or family members. To value informal care, we applied the opportunity cost method. The foregone benefits of informal carers were approximated by multiplying the hours spent on informal care by the opportunity cost of leisure time.

Loss of productivity in paid work encompasses absenteeism, either short-term (sick leave) or long-term (disability pension), but also presenteeism, which refers to limited performance while working (Figure 1). Indirect costs were valued using the human capital approach. For sick leave, the hours absent from work were multiplied with the average labour costs in Germany. For disability pension, the average daily labour costs were multiplied with the average number of working days and the disability percentage (0–100%). Costs due to presenteeism were calculated by multiplying the average reduction in labour productivity by the average labour cost in Germany, taking into account the hours effectively worked. Work productivity was assessed on a 10-point Likert scale, where '0' refers to 'work productivity not affected by MS' and '10' refers to being 'completely affected by MS'.[19,23]

### Clinical outcomes

Relapse data were sampled every 3 months. Disability was scored by means of the Kurtzke's Expanded Disability Status Scale (EDSS) every 6 months.[24] Based on EDSS and relapse data, we retrospectively categorized patients into four subgroups of disease activity as follows: disease activity free (DAF; no relapses and no confirmed disability progression); relapse without worsening (RWW; relapse event, no confirmed disability progression); progression independent of relapse activity (PIRA; no relapse, confirmed disability progression); and relapse associated worsening (RAW; relapse event, confirmed disability progression). For all conditions, a $\geqslant$6 month increase in EDSS had to be confirmed after another $\geqslant$6 months. We used a 'roving' EDSS as a reference for identification of disability progression/worsening events rather than the conventional (fixed) study baseline EDSS.[25] Consequently, subsequent EDSS assessments beyond baseline could serve as reference for the EDSS increase and confirmation. This definition is closer to the nature of a real-world setting and has been shown to increase sensitivity in detecting disability progression events.[25] Three most commonly applied strata were used for the definition of progression events:[26] required increase in EDSS by $\geqslant$1.5 points if reference EDSS was 0, increase in EDSS by $\geqslant$1 points if EDSS was between 1 and 5.5, or increase in EDSS by $\geqslant$0.5 points if reference EDSS was 5.5 or higher.

Of those patients achieving DAF, the proportion of patients with confirmed disability improvement (CDI) was further evaluated. CDI was defined as $\geqslant$1.0-point reduction in EDSS score from a reference EDSS score $\geqslant$2, as recommended before.[27] In line with the definition of a confirmed disability progression event, we referred a CDI associated change in EDSS to a 'roving' EDSS reference and a $\geqslant$6-month change had to be confirmed $\geqslant$6 months apart. Patients with less than three recorded EDSS scores were grouped as 'others', as no indication of sustained progression or improvement could be given.

### Other outcomes

We utilized information on age, employment, housing conditions (living alone), work-related conditions (employment), and year of MS diagnosis (disease duration).

### Statistical analyses

Quantitative variables were summarized as mean and standard deviation or median and interquartile range. For categorical variables, percentages and frequencies were reported to summarize the study population. To compare the difference in sociodemographic, work-related and clinical characteristics between the male and female subpopulation, independent samples *t*-test, Mann–Whitney U test or chi-squared test were used according to the scale and distribution of the data.

Cost data were analysed by a generalized linear model with a negative binomial distribution and log link function due to the right-skewed distribution pattern of cost data. Statistical significance in costs between men and women was estimated from corresponding models. In order to simultaneously control for possible confounding effects, we adjusted each model for age, baseline EDSS, disease activity (RWW, RAW, PIRA, DAF, others), study affiliation (i.e. DMT group interferon beta/glatiramer acetate *versus* DMT group fingolimod) and follow-up time. In case of significant gender-related differences, we reported associated incidence rate ratios and 95% confidence intervals (CIs) as measures of effect sizes, with male gender as the reference category.

Statistical analyses were performed using IBM SPSS software version 25 (Armonk, NY; USA). Figures were generated using GraphPad Prism 7.0 (GraphPad Software, Inc). All statistical tests were two-tailed and values of $p < 0.05$ were considered statistically significant.

## Results

### Study population

In total, 2095 patients with at least one completed questionnaire on health resources were eligible for analysis. Patients were predominantly female ($n = 1528$, 72.9%) corresponding to a women-to-men ratio of 2.7:1. At the time of documentation, the mean age was $41.85 \pm 10.13$ years and disease duration $7.55 \pm 6.12$ years (median 6 years). The mean EDSS at study onset was $2.43 \pm 1.57$ (median 2), with 21.2% of patients having reached EDSS milestone 4 (significant disability but able to walk without aid or rest for 500 m), and only 4.3% of patients having reached EDSS milestone 6 (requires unilateral assistance to walk about 100 m with or without resting). Further,

half of the patients achieved DAF status during follow-up, indicating an overall mild to moderately affected MS population.

### *Socio-demographic and disease characteristics*

As shown in Table 1, no gender-related differences in age ($p = 0.367$), disease duration ($p = 0.115$) and baseline disability (EDSS, $p = 0.600$) occurred. A comparable (small) proportion of patients presented EDSS scores beyond the EDSS milestones of 4 and 6, respectively (both $p > 0.05$). Looking at the composite measures of disease activity, we found a slightly lower proportion of female patients achieving DAF status compared with men (55.6% *versus* 60.8%, $p = 0.046$). Moreover, relapse related outcomes were slightly more prevalent among women (Table 1).

In terms of household living conditions, a higher proportion of male subjects were living alone ($p < 0.001$). The relative number of patients being employed ($p < 0.001$) was also increased in the male population as compared with women ($p < 0.001$, 70.2% and 58.4% respectively). Of those patients being employed, the proportion of part-time workers was higher among women ($p < 0.001$, 48.1% *versus* 10.5%) and accordingly, the relative frequency of full-time workers was pronounced among men (Table 1). Men and women did not differ in terms of study affiliation (DMT group) ($p = 0.355$) and length of study follow-up ($p = 0.197$), indicating that no gender-related dropout occurred.

### *Total costs*

On average, total quarterly costs were €2329 ± €2570 for women and €2361 ± €2612 for men, with a non-significant cost difference between both ($p = 0.534$). Indirect costs were the main cost driver and accounted for more than 82% of the total costs for both sexes, followed by direct medical and direct non-medical costs (Table 2).

### *Clinical disease activity measures*

For both women and men, direct costs, indirect costs and overall costs were largely determined by the degree of disability as measured by the EDSS (Figure 2). Further, patients who achieved DAF status were associated with lower costs as compared with patients showing disease activity (PIRA, RAW, RWW) (Figure 3). Women and men with RAW had highest expenditures. Within each subgroup of clinical disease activity, however, no gender-specific differences occurred (Figures 2–3).

### *Differences in direct medical costs*

Direct medical costs in total did not differ by gender in a significant way ($p = 0.160$, Table 2). Nevertheless, compared with men (reference), women utilized significantly more direct medical resources as follows: ambulant consultations ($p = 0.011$; IRR 1.16, CI 1.04–1.31), complementary medicine ($p = 0.021$; IRR 2.41, CI 1.14–5.06), medical consumables ($p < 0.001$; IRR 2.53, CI 1.9–3.8), professional care ($p < 0.001$; IRR 2.50. CI 1.44–4.36). Associated mean quarterly costs for men ($n = 567$) and women ($n = 1528$) are given in Table 2 in more detail. With the exception of inpatient care and ambulant consultation costs, associated mean (quarterly) costs were very modest (less than €50) as only a small proportion of patients claimed resources in these cost components (Table 3). Nevertheless, a significantly higher proportion of women at least once showed resource consumption regarding complementary medicine (7.9% *versus* 4.4%, $p = 0.007$), medical consumables (22.1% *versus* 13.6%, $p < 0.001$), professional care (11.1% *versus* 5.8%, $p < 0.001$) and over-the-counter medication (53.6% *versus* 46.9%, $p = 0.005$) (Table 3).

### *Differences in direct non-medical costs*

Gender-specific differences in direct non-medical costs ($p = 0.001$) were driven by informal care ($p < 0.001$; IRR 2.79 for females *versus* males, CI 1.56–5.01), with 28.9% of women compared with 19.2% men claiming associated healthcare resources at least once ($p < 0.001$).

### *Differences in indirect costs*

Total indirect costs did not significantly differ between men and women ($p = 0.936$). In terms of presenteeism, significantly more men utilized associated resources ($p < 0.001$, 45.5% *versus* 53.8%) and caused higher costs ($p < 0.001$, IRR = 0.62 for females *versus* males, CI 0.53–0.72). On the other hand, women on average utilized a higher amount of resources concerning disability pension ($p = 0.001$, IRR = 1.62, CI 1.23–2.13).

**Table 1.** Characteristics of the study population ($n = 2095$).

| Characteristics | | Male ($n = 567$) | Female ($n = 1528$) | $p$-value |
|---|---|---|---|---|
| **Study characteristics** | | | | |
| Participant PEARL study (IFN/GA) | *n* (%) | 422 (74.4%) | 1167 (76.4%) | 0.355 |
| Participant PANGAEA study (FINGO) | *n* (%) | 145 (25.6%) | 361 (23.6%) | |
| Follow-up time (month) | Median (IQR) | 24 (18–24) | 24 (18–24) | 0.197 |
| **Socio-demographics** | | | | |
| Age (years) | Mean (SD) | 41.51 (9.98) | 41.98 (10.19) | 0.367 |
| Living alone | *n* (%) | 121 (22.7%) | 247 (17.3%) | 0.006 |
| **Work-related characteristics** | | | | |
| Employed | *n* (%) | 394 (70.2%) | 882 (58.4%) | <0.001 |
| Employed in Full time | *n* (%) | 342 (89.5%) | 439 (51.9%) | <0.001 |
| Employed in Part time | *n* (%) | 40 (10.5%) | 407 (48.1%) | |
| **Disease characteristics** | | | | |
| Disease duration (years) | Median (IQR) | 6 (3–10) | 6 (3–11) | 0.115 |
| EDSS at baseline | Median (IQR) | 2 (1–3.5) | 2 (1–3.5) | 0.600 |
| Relapses 1-year prior baseline | *n* (%) | 229 (40.9%) | 681 (45.3%) | 0.023 |
| Relapses in follow-up period | *n* (%) | 160 (28.2%) | 510 (33.4%) | 0.072 |
| **Two-year disease activity**[a] | | | | |
| DAF | *n* (%) | 305 (60.8%) | 719 (55.6%) | 0.046 |
| CDI | *n* (%) | 45 (9.0%) | 106 (8.2%) | 0.597 |
| PIRA | *n* (%) | 55 (11.0 %) | 123 (9.5%) | 0.356 |
| RAW | *n* (%) | 34 (6.8%) | 126 (9.7%) | 0.048 |
| RWW | *n* (%) | 108 (21.5%) | 326 (25.2%) | 0.102 |

Missing values excluded from calculation of relative frequencies
[a]Patients grouped as 'others' (64 males, 234 females) excluded from calculation of relative frequencies.
CDI, confirmed disability improvement; DAF, disease activity free; FINGO, fingolimod; GA, glatiramer acetate; IFN, interferon beta preparation; IQR, interquartile range; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening; RWW, relapse without worsening.

## Discussion

Our results show that MS poses a significant economic burden on MS patients and society. Clinical disease activity and severity measures were highly correlated with resource utilization in the female and male study population. As to be expected, there were no significant gender-specific differences in total health care costs. No gender-specific differences in total costs were further found in subgroups of disease activity and severity. However, we identified some differences between men and women in specific direct (e.g. ambulant consultations, informal care) and indirect (e.g. disability pension) cost items.

**Table 2.** Mean costs (quarterly) per patient in Euro (€), stratified by gender ($n = 2095$).

| | Men ($n = 567$) | | | Women ($n = 1528$) | | | *p*-value* |
|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Median** | **Mean** | **SD** | **Median** | |
| **Total costs** | 2361 | 2612 | 1482 | 2329 | 2570 | 1349 | 0.534 |
| **Direct costs** | 385 | 884 | 126 | 426 | 801 | 160 | 0.044 |
| **Direct medical costs** | 344 | 832 | 119 | 369 | 732 | 142 | 0.160 |
| Inpatient care | 149 | 733 | 0 | 149 | 637 | 0 | 0.552 |
| Day admissions | 13 | 105 | 0 | 16 | 106 | 0 | 0.951 |
| Ambulant consultations | 139 | 198 | 68 | 158 | 197 | 88 | 0.011 |
| Examinations | 18 | 21 | 15 | 18 | 22 | 15 | 0.610 |
| Complementary medicine | 2 | 12 | 0 | 3 | 19 | 0 | 0.021 |
| Acupuncture | 1 | 8 | 0 | 2 | 11 | 0 | 0.563 |
| Medical consumables | 1 | 7 | 0 | 5 | 15 | 0 | <0.001 |
| Professional care | 12 | 96 | 0 | 19 | 39 | 0 | <0.001 |
| Non-prescription medication | 12 | 37 | 0 | 13 | 38 | 1 | 0.206 |
| **Direct non-medical costs** | 41 | 182 | 0 | 57 | 219 | 0 | 0.001 |
| Investments | 7 | 84 | 0 | 14 | 157 | 0 | 0.634 |
| Informal care | 34 | 150 | 0 | 43 | 146 | 0 | 0.001 |
| **Indirect costs** | 1976 | 2260 | 1150 | 1903 | 2252 | 934 | 0.936 |
| Sick leave | 217 | 868 | 0 | 197 | 803 | 0 | 0.753 |
| Presenteeism | 978 | 1431 | 287 | 659 | 1165 | 0 | <0.001 |
| Disability pension | 793 | 1756 | 0 | 1052 | 1998 | 0 | 0.001 |

*Adjusted for age, baseline EDSS, disease activity (PIRA, RAW, RWW, DAF, other), study affiliation (DMT group) and follow-up time.
DAF, disease activity free; DMT, disease-modifying treatments; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening; RWW, relapse without worsening.

In order to contrast our overall cost estimates to previous research, we recalculated total costs on an annual basis and additionally included DMT costs for this purpose. Corresponding mean annual costs were €28,929 for women and €29,139 for men (both median EDSS 2, interquartile range 1–3.5). Cost were therefore higher than those most recently reported for German RRMS patients within a healthcare claim data set (€20,583).[28] One factor contributing to this deviation is that we captured a wide-ranging societal perspective by using the MS-HRS survey. However, as no clinical data could be provided (e.g. EDSS) by the authors, comparisons of the results cannot be carried out in a suitable manner as the degree of disability is the key cost driver.[13,14] However, when taking the mild to moderate degree of disability into account, our results are largely consistent with previous cost-of-illness studies.[3,4,29,30] Nevertheless, in the studies mentioned above, costs were not reported by gender. Also, cost data were only collected at a single point in time. In contrast, our results are based on longitudinal assessments. Consequently, we generated robust cost estimates (unit: quarterized mean

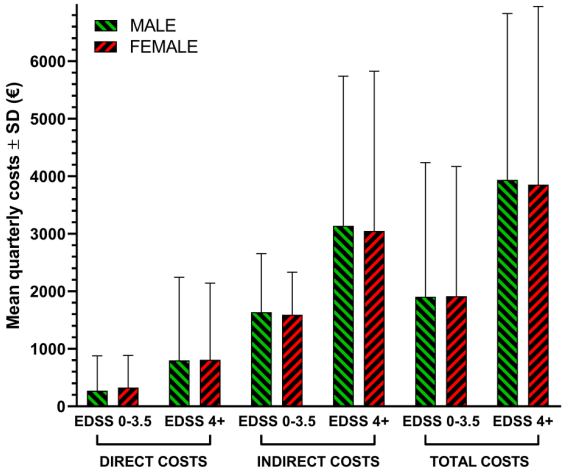


**Figure 2.** Mean quarterly direct, indirect and total costs in subgroups of baseline disability.
EDSS, Expanded Disability Status Scale.

costs per patient) with the potential to validly capture even those costs that arise less frequently.

### *Direct costs*

Although men and women with MS did not differ in total costs and were overall similar regarding their direct and indirect resource consumption, we were able to highlight some differences in detail. Regarding direct medical resources, our analysis revealed that women with MS tend to more frequently seek ambulant consultations, professional care, over-the-counter medication, complementary medicine and medical consumables compared with their male counterparts. These MS-related findings are consistent with previous research on patients' general health care-seeking behaviour in terms of physical and mental health.[31–33] Patients with chronic conditions and in particular women use health care and preventive services to a greater extent.[34] Another possible reason for this finding is that women are better socialized to seek health care because of earlier medical care contacts associated with reproductive health or screening for breast or cervical cancer.[35] We further found women to incur a higher amount of informal care. Beyond a greater help-seeking behaviour among women, the lower amount of informal care among men may be attributed to the socio-demographics of our study population, as men were significantly more often living alone.

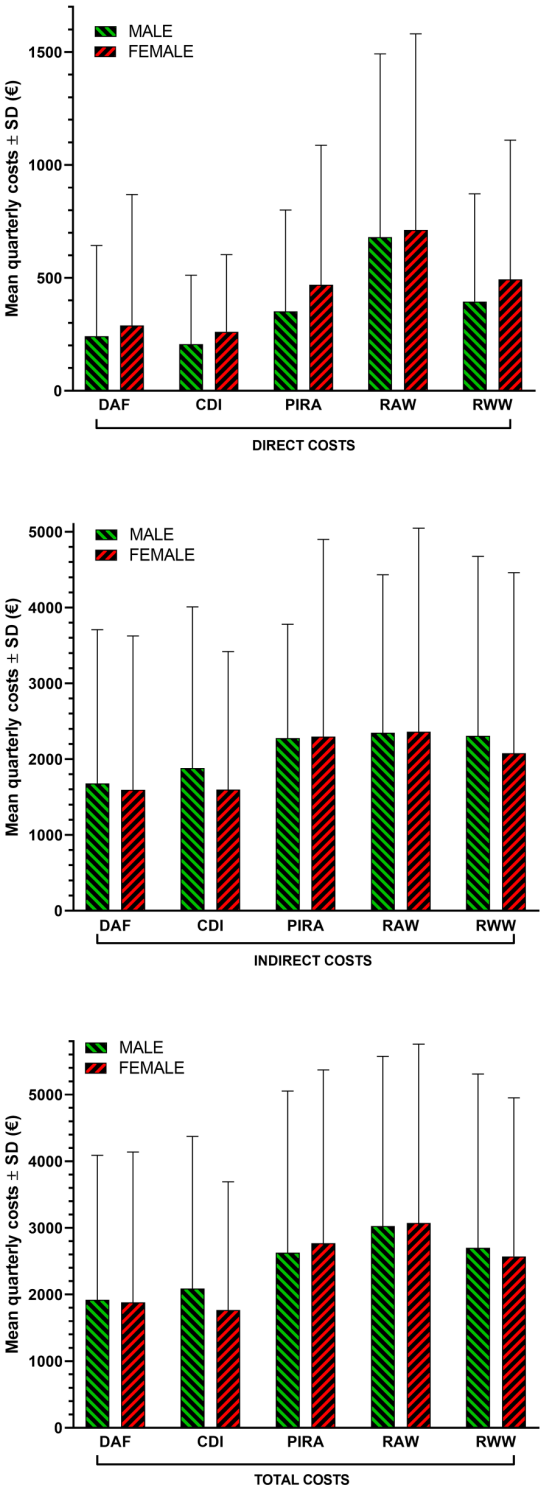


**Figure 3.** Mean quarterly direct, indirect and total costs in subgroups of 2-year disease activity.
CDI, confirmed disability improvement; DAF, disease activity free, PIRA, progression independent of relapse activity; RAW, relapse-associated worsening; RWW, relapse without worsening.

**Table 3.** Relative number of patients using resources at least once, stratified by gender ($n = 2095$).

| | Resource consumption | | |
|---|---|---|---|
| | **Men** $n = 567$ | **Women** $n = 1528$ | |
| | **%** | **%** | ***p*-value*** |
| **Total costs** | 98.2% | 98.8% | 0.357 |
| **Direct costs** | 96.6% | 97.7% | 0.099 |
| **Direct medical costs** | 96.6% | 97.6% | 0.120 |
| Inpatient care | 15.2% | 14.2% | 0.358 |
| Day admissions | 5.8% | 6.5% | 0.724 |
| Ambulant consultations | 93.3% | 94.4% | 0.175 |
| Examinations | 53.4% | 50.1% | 0.426 |
| Complementary medicine | 4.4% | 7.9% | 0.007 |
| Acupuncture | 3.2% | 4.2% | 0.216 |
| Medical consumables | 13.6% | 22.1% | <0.001 |
| Professional care | 5.8% | 11.1% | <0.001 |
| Non-prescription medication | 46.9% | 53.6% | 0.005 |
| **Direct non-medical costs** | 20.5% | 29.8% | <0.001 |
| Investments | 3.2% | 4.1% | 0.420 |
| Informal care | 19.2% | 28.9% | <0.001 |
| **Indirect costs** | 59.1% | 50.4% | <0.001 |
| Sick leave | 23.3% | 21.3% | 0.099 |
| Presenteeism | 53.8% | 45.5% | <0.001 |
| Disability pension | 10.1% | 10.6% | 0.686 |

*Adjusted for age, baseline EDSS, disease activity (PIRA, RAW, RWW, DAF, others), study affiliation (DMT group) and follow-up time.
DAF, disease activity free; DMT, disease-modifying treatments; EDSS, Expanded Disability Status Scale; PIRA, progression independent of relapse activity; RAW, relapse-associated worsening; RWW, relapse without worsening.

### *Employment rates*

With an overall 70.2% of males and 58.4% of females being employed at study baseline, our study revealed a significant gender employment gap of 11.8%. However, this is consistent with the employment gap that prevailed for the general population in Germany (10.2%) and Europe (12.5%) during the same time period.[36] Employment rates for both females and males were approximately 12% lower than in the general population (rates of 81.8% for males and 71.6% for females aged 20–64 years in Germany),[36] most likely due to the burden of the disease. The main reason for the underrepresentation of women in the German

labour market as compared with men is that women still carry out the bulk of private domestic and care work for children and other family members (unpaid work). Not only gender differences in the overall employment rate but also the proportion of working patients in part-time employment were in line with the general population in Germany. A rate of 10.5% male and 48.1% female employees with reduced working hours in our study compares with 8.6% and 46.2% in the general population,[37] resulting in a gender-related difference of 37.6% in both populations. The main reason why the part-time employment rate for women is substantially higher than for men is due to reasons similar to the lower general employment rate among women, namely unpaid work and a lower threshold for working part time as a result of societal pressures and expectations.[38]

### Indirect costs

In previous cost-of-illness evaluations, productivity losses due to presenteeism were rarely captured, although it has been shown that presenteeism accounts for significantly higher costs than absenteeism.[39,40] In our study, we found men on average to have significantly higher costs for MS-related presenteeism as compared with women. This may be partly attributable to the higher proportion of women who were not employed or working part-time, as reduced working hours may in general contribute to a lower risk of being unproductive at paid work and result in lower costs.

Given the lower amount of paid work among women and in line with previous results, we found that females were likely to receive more disability pension.[41,42] This finding is most likely not MS-specific, as female gender is consistently associated with higher rates of disability pension, also in the general population.[43] Several hypotheses have been proposed for this observation, such as a greater workload of women in domestic and family work in addition to their paid work. Another reason for the higher level of disability pension for women could be the lower salaries that still exist today, less influence and a higher degree of repetitive work that are negatively linked with various health aspects for these women with MS.[42,43]

Our study further revealed that women and men did not differ in sick leave. Previous administrative data analyses concluded that women have higher rates of sick leave compared with their male counterparts, following the aforementioned reasons for disability pension.[41,42] One reason for this deviating result could be that different methodologies and types of study were used, which is common in cost-of-illness studies and makes comparisons often difficult.[14] For example, while we used patient reports, the two aforementioned analyses were based on data from the Social Insurance Agency in Sweden, in which absences due to illness were only taken into account if they exceed 14 days. As a result, some amount of short-term absence was not included in these analyses.

### Unpaid work

Out of the unpaid and paid work, only the amount of paid work that a patient no longer performs and the informal care that a patient receives is valued in terms of disease-related costs. Despite its acknowledged societal importance, unpaid labour (household work, care work, volunteer work) that a patient performs is rarely included in economic evaluations. Moreover, clear guidance on how to measure and value lost unpaid work is lacking in health economic guidelines.[44] Nevertheless, as reflected by lower full- and part-time employment rates in our study, women account for the majority of unpaid work. Quantifying this unpaid labour in the calculation of MS-related productivity losses would likely result in higher estimates of indirect costs, particularly for women.

Conversely, lower cost estimates for women may have resulted if we had considered socioeconomic factors in the valuation of indirect costs. For example, the level of work experience and individual salary (potentially reflecting a gender payment gap) were not taken into account in the cost valuation. In our real-word study setting, we particularly did not ask for the patient's income. Accordingly, gender-specific costs differences truly represent differences in resource use rather than overshadowing factors such as different payments for women and men.

As the gender gap in employment rates in our study was representative for Germany, we did not adjust for employment factors in the multivariable models. Nevertheless, we considered a number of potential confounding variables in the multivariate models to minimize the distortion by factors such as age, study affiliation (treatment group) and 2-year disease activity.

*Strengths and limitations*

One main strength of our analysis is the real-world nature of the data, a wide-ranging societal perspective on costs and the large sample size of 2095 patients. Nevertheless, limitations inherent in observational studies also apply to our study. Accordingly, the two underlying non-interventional studies were not primarily designed to assess gender-specific effects. The relationship between gender and outcome measures used in our study may have been influenced by unmeasured factors. Nevertheless, our study population reflected a typical real-world RRMS population with a women-to-men ratio of 2.7:1 and mean age of $41.85 \pm 10.13$ years. Further, no explicit exclusion criteria, except the contraindications associated with current DMTs (e.g. pregnancy), had been stated. On the other hand, patients in our study were required to be treated with injectable first-line treatment or fingolimod, which may limit the representativeness towards a real-world clinical practice setting to some extent. However, we reported all costs without DMTs in order to increase the generalizability of the results and to mitigate the influence of these high but varying cost drivers. As a limitation, our population mainly composed of mildly to moderately disabled patients, which means that more severely affected patients were rather underrepresented. An extrapolation of the results to the general German MS population was further restricted by the fact that only RRMS patients were part of the study.

## Conclusion

MS constitutes a significant economic burden for men and women, their families and society. While the total economic burden did not differ between male and female patients, we found gender differences in the distribution of specific direct and indirect cost items that show a similar pattern to those in a non-MS population.

Future analyses might focus on the quantification of additional areas of unpaid work, gender differences in costs in more severely affected RRMS patients as well as patients with primary or secondary progressive MS phenotypes.

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## ORCID iDs

Dirk Schriefer https://orcid.org/0000-0002-7524-7628

Rocco Haase https://orcid.org/0000-0003-2465-4909

Tjalf Ziemssen https://orcid.org/0000-0001-8799-8202

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