Multiple sclerosis (MS) is a challenging and disabling condition, predominantly affecting individuals in their early life, and has an impact functionally, financially, and on quality of life. However, there is a lack of systematic approach towards assessing socioeconomic consequences of MS. Our objective was to systematically review observational analytical studies investigating the socioeconomic consequences of MS. We conducted a systematic review on socioeconomic consequences of MS with a focus on employment-, income-, work ability- and relationship-related outcomes between MS and the general population. Additionally, the educational characteristics were extracted. From 4958 studies identified, 187 were assessed for eligibility and a total of 27 studies from eight countries were included in this qualitative assessment; 32 different outcomes were identified. All studies indicated pronounced differences between MS patients and the general population, for example 15%–30% lower employment, lower earnings and higher social benefits, higher absenteeism and presenteeism proportions, higher work disability (eg, sick-leave days) among MS patients. Some studies also indicated differences in the family or relationship characteristics. There were no apparent differences with regard to educational level. In conclusion, socioeconomic data can serve as robust outcome measures to study various aspects of MS reflecting the broader consequences of the disease.

KEYWORDS
educational status, employment, family characteristics, income, multiple sclerosis, sick leave, socioeconomic factors, systematic review
in MS patients also concluded that most papers report observational studies or cross-sectional surveys focused on health-related quality of life and costs. Furthermore, socioeconomic outcomes can be investigated in many ways (e.g., income, employment, marital status, sick-leave days, etc.), and a comprehensive overview is warranted.

Thus, our aim was to systematically review studies investigating the socioeconomic consequences of MS.

2 | METHODS

We conducted a systematic review following the PRISMA statement. The study protocol was registered in PROSPERO: International prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/), ID: CRD42020182085. Published studies (full articles and abstracts) on socioeconomic consequences of MS were systematically searched in Medline (Ovid), Embase and Web of Science (Clarivate). A combination of relevant keywords to construct the search strategy, including MS, socioeconomic outcomes, employment, income, earnings, benefits, disability pensions, sickness absence, sick leave and marital status, was used (full search strategy is available in Supplemental Material 1). The search was limited to English language and publications prior to July 2019.

One author (AK) conducted the first screening of potentially relevant records based on titles and abstract, and two authors (AK, VDK) independently performed the final selection of included studies based on full-text evaluation using Rayyan, a web and mobile app for systematic reviews (https://rayyan.qcri.org/welcome). Consensus between the two reviewers was used to resolve any disagreement.

The main eligibility criteria were as follows:

- Population: adults of working age;
- Exposure: diagnosis of MS;
- Comparator: general population;
- Outcomes: socioeconomic outcomes (employment, income, work ability, education, relationship);
- Study design: observational analytical studies (e.g., cohort,
case-control), excluding descriptive studies and case reports, case series. Clinical trials and economic evaluations (e.g., cost if illness, cost-effectiveness studies) were not in the scope of this review.

Initially 4958 studies were identified (Figure 1) and 4783 records were screened after duplicates were removed. In total, 187 full-text articles (or abstracts) were assessed for eligibility and finally 27 studies were included in the qualitative synthesis. Studies that did not report any estimates (e.g., proportions, ratios), only pointing out to the direction (higher, lower) or association (e.g., significant, not significant) were not considered for the evaluation. Also, studies that did not have the control group in the study population, or did not perform the formal statistical comparison between the groups, or did not provide standardized rates, and suggesting only references about the various estimates in general population were further excluded.

Using a standardized data extraction form in Excel, study characteristics (as presented in the Tables and Supplemental Material 2) were extracted from the included studies. In case of possible overlap in a study population, the most recent study was selected.

### Table 1: The list of socioeconomic outcomes

| Outcome | Reference |
|---------|-----------|
| **1. Employment-related outcomes:** |
| 1.1. The proportion of the employed (fully or partially) or unemployed; | 11,12,16-19,21 |
| 1.2. The labour-force participation rate; | 18 |
| 1.3. The risk ratio (RR) for not being fully employed; | 14 |
| 1.4. The probability of remaining without early pension; | 15 |
| 1.5. The median time to early pension; | 15 |
| 1.6. The frequency of temporary unemployment. | 15 |
| **2. Income-related outcomes:** |
| 2.1. Percental difference in income/earnings/benefits; | 15,22 |
| 2.2. Difference in mean earnings/benefits; | 23,24 |
| 2.3. Proportion of those having a zero gross salary record; | 25 |
| 2.4. Personal annual income median; | 16,48 |
| 2.5. Personal annual income mean | 15 |
| 2.6 Personal annual earnings mean; | 21,22,24,25 |
| 2.7 Personal annual benefits mean; | 13,21,22 |
| 2.8. Disposable income mean; | 23,25 |
| 2.9. Proportion receiving earnings; | 11-13,23 |
| 2.10. Proportion receiving social benefits; | 11,13,23 |
| 2.11. Estimated difference for earnings; | 24 |
| 2.12. Adjusted regression coefficient for disposable income. | 23 |
| **3. Work ability-related outcomes:** |
| 3.1. Odds ratio for sick-leave/disability pension; | 49 |
| 3.2. Mean number of disability days per year; | 29 |
| 3.3. The mean annual prevalence of sick-leave/disability pension; | 28 |
| 3.4. Proportion having a short-term/long-term disability; | 21,24,27,29 |
| 3.5. Increase of the mean number of age-specific sick-leave days; | 31 |
| 3.6. Absenteeism; | 19,33 |
| 3.7. Presenteeism; | 19,33 |
| 3.8. Incidence rate for disability pension; | 32 |
| 3.9. Work disability (annual net days of sickness absence and disability pension); | 30 |
| **4. Relationship outcomes:** |
| 4.1. The proportions of divorced/separated/widowed/married/in civil union/never married; | 16,22,32 |
| 4.2. The cumulative incidence proportion of divorce; | 34 |
| 4.3. The hazard ratio (HR) of divorce; | 34,35 |
| 4.4. The cumulative probability of remaining in the same relationship. | 35 |
| **5. Educational level:** The proportion of those having school/high-school/university education. | 11,12,16,19,22,24,26,27,32 |
Two reviewers (AK and VDK) independently assessed the quality of the included studies focusing on such study characteristics as study design (cohort studies prioritized over cross-sectional), data sources (registries and databases prioritized over surveys and interviews), timeline and size of the study population. Consensus was used to resolve any disagreement. The quality assessment was performed ensuring at least one of the reviewers is not among the co-authors.

In total, 32 different outcomes were identified. We grouped the outcomes into the categories of employment-, income-, work ability- and relationship-related outcomes, also mapping the reported indicators for each of the included study (Table 1). Additionally, we extracted the information about the educational level from the selected studies. Results from the studies were qualitatively compared and summarized.

3 | RESULTS

A total of 27 studies from eight countries were selected for inclusion into this systematic review of socioeconomic consequences of MS. With respect to study design, 15 were cohort and 12—cross-sectional studies; 15 studies analysed data from the registries, whereas 10—data from surveys or interviews, additionally, one study investigated claims database. The selected studies are summarized in the Tables 2–6 and categorized according to the type of the outcome.

3.1 | Employment-related outcomes

Most of the identified studies reported the proportions of the employed or unemployed, with many studies11–15 pointing out to the 15%–30% observed differences for paid employment or full-time employment between MS and the general population (Table 2). A study from New Zealand14 indicated the largest difference between employed full-time MS patients and general population (25.2% and 71.8%, respectively), also this gap was significantly pronounced in Argentina (there were 51.5% unemployed among MS with cognitive impairment and 20.4% without, whereas this proportion in healthy controls was 3.8%).17 A study from United States12 reported the lowest proportion of 20.9% of full-time employed MS patients. Another study from United States44 showed that MS patients were approximately twice as likely to report not being fully employed as healthy controls (risk ratio at baseline—1.95 and at 24 months—2.07). However, an Australian study18 reported that from the longitudinal perspective, the employment gap between MS patients and the general population fell from 14.3% in 2010 to 3.5% in 2013. Interestingly, a study in Japan19 reported a very low difference between the two groups (4.4% and 4.7%, respectively).

Part-time employment was slightly more prevalent among MS patients when compared to general population in New Zealand (17.3% vs. 15.9%)16 and Australia (20.8% vs. 18.8%),20 however, not different (18.2% and 18.5%, respectively) in another Australian study.18 and significantly lower in United States12 (8.0% and 10.7%, respectively). The frequency of temporary unemployment for economically active persons at 5, 10 and 15 years after MS onset in Denmark was virtually the same for patients and control persons, with nearly no difference between men and women.15 The latter study, in contrast to the previous studies reporting the employment proportions, investigated the probabilities of remaining without early pension at 5 years (70% vs. 97%, respectively) and at 20 years (22% vs. 86%, respectively); the median time to early pension was 10 years for MS patients and 24 years for controls.15

3.2 | Income-related outcomes

From 11 studies investigating income-related outcomes, many reported mean annual income (total, or from earnings and benefits),13,16,21–23 whereas other studies chose more comparable indicators, such as percentual differences between the MS patients and general population, or proportions receiving certain type of income (Table 3).21–24 All studies investigating income in MS patients showed pronounced differences when compared to general population. A study in Denmark13 indicated 28% difference in the proportions of people receiving income from employment (39% and 67%, respectively). Also, there was a 34% difference in the proportions of people receiving income from public transfers (83% and 49%, respectively), and similarly in UK11–33.4% (76% and 42.6%, respectively). Both a higher proportion of patients receiving various social benefits and a higher average for the benefits among MS patients were also found in other studies.21–27 As reported in a Swedish study,22 both MS patients and the matched controls received most of their income from earnings followed by disability pension and sickness absence; MS patients had 15% lower earnings than the matched controls, and summed social benefits were 33% higher for MS patients.

The largest study in Sweden25 also pointed out there is a difference when these populations are compared to a period before the diagnosis of MS and after—there was no significant difference in the pre-diagnosis period, whereas during follow-up post diagnosis, patients with MS had on average EUR 5130 lower annual salary compared with controls, ranging from a loss of EUR 2430 the first year to EUR 9010 after 11 years. Another study24 confirmed that lower earnings by MS patients compared with the controls began shortly before MS diagnosis, and this gap increased thereafter.

Another comprehensive study23 in Sweden reported a number of income-related outcomes from the longitudinal perspective: differences were found for all studied components of disposable income from diagnosis year, for example in the final study year (2013); earnings (~64,867 Swedish Krona (SEK) (~EUR 7500); 95% CI), −79,203 to −50,528); sickness absence (SEK 13,330 (~EUR 1500); 95% CI, 10,042–16,500); and disability pension (SEK 21,360 (~EUR 2500); 95% CI, 17,380–25,350). In addition, as showed by Wiberg et al.,24 educational level and type of occupation were highly correlated. Hence, MS patients classified as managers had larger differences in earnings than those in office work, and while a large proportion appeared to participate on the labour market to a high extent, many had low or no earnings at all.
| First author (year) | Country | Time | Population | Outcomes (main results) | In MS | In non-MS |
|---------------------|---------|------|------------|-------------------------|-------|-----------|
| Green (2007)        | UK      | 2001–2002 | 916 MS patients and matched general population | Paid employment | 29.9% | 59.6% |
| Gupta (2014)        | US      | 2009 | 536 MS patients and 74,451 controls | Full time | 20.9% (p = 0.001) | 36.7% |
|                     |         |      |            | Part time               | 8.0% (p = 0.044) | 10.7% |
|                     |         |      |            | Self employed           | 6.9% (p = 0.648) | 6.4% |
| Jennum (2013)       | Denmark | 1998–2006 | 402 MS+ON and 1606 controls | Income from employment | 66% | 82% |
| Kwon (2019)         | US      | N/A  | 48 MS patients taking natalizumab and 63 controls | Not currently fully employed at baseline | 40.4% (RR = 1.95; p = 0.023) | 20.6% |
|                     |         |      |            | Not currently fully employed at 24 months | 43.2% (RR = 2.07; p = 0.014) | 21.0% |
| Pearson (2017)      | New Zealand | 2006 | 1727 MS patients of working age (25–64 years) | Full-time employment | 25.2% | 71.8% |
|                     |         |      |            | Part-time employment (0–29 h) | 17.3% | 15.9% |
| Pfleger (2010)      | Denmark | 1980–2004 | 2538 MS patients and 60,760 controls | The probability of remaining without early pension was at 5 years | 70% | 97% |
|                     |         |      |            | The probability of remaining without early pension was at 20 years | 22% | 86% |
|                     |         |      |            | The median time to early pension | 10 years | 24 years |
| Simmons (2010)      | Australia | 2007 | 1273 respondents with MS | Full-time employment (≥35 h/week) | 29.0% (p < 0.001) | 40.8% |
|                     |         |      |            | Part-time employment (<35 h/week) | 20.8% (p < 0.05) | 18.8% |
|                     |         |      |            | Employed total | 49.8% (p < 0.001) | 59.6% |
|                     |         |      |            | Unemployed seeking employment | 0.6% (p < 0.001) | 3.5% |
|                     |         |      |            | Not in paid labour force | 49.7% (p < 0.001) | 36.9% |
| Van Dijk (2017)     | Australia | 2010–2013 | 1260 people with MS | Employed full time in 2010, 2013 | 33.3% (p < 0.001), 39.5% (p < 0.001) | 44.6%, 42.8% |
|                     |         |      |            | Employed part-time in 2010, 2013 | 15.5% (p < 0.001), 18.2% | 18.5%, 18.5% |
|                     |         |      |            | Total employed in 2010, 2013 | 48.8% (p < 0.001), 57.8% | 63.1%, 61.4% |
|                     |         |      |            | Unemployed in 2010, 2013 | 4.3% (p < 0.001), 4.1% | 3.1%, 3.7% |
|                     |         |      |            | Not in paid labour force in 2010, 2013 | 46.9% (p < 0.001), 38.1% | 33.8%, 35.0% |
| Vanotti (2016)      | Argentina | N/A  | 33 MS patients with cognitive impairment, 49 MS patients without cognitive impairment and 78 controls | Unemployment | 51.5% with cognitive impairment and 20.4% without | 3.8% |
| Yamabe (2019)       | Japan   | 2009–2014 | 85 MS and 145,759 without MS | Currently employed | 44.7% (p = 0.004) | 47.6% |

Abbreviations: N/A, not available (information extracted from an abstract only); RR, risk ratio.
TABLE 3  Studies that investigated income-related outcomes

| First author (year) | Country | Time       | Population                                      | Outcomes (main results)                                                                 | In MS                                                                 | In non-MS                |
|---------------------|---------|------------|-------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------|
| Frndak (2015)48     | US      | 2012–2014  | 221 MS patients and 63 healthy controls         | Annual income (median)                                                                  | USD 45,500 in patients with stable employment status                  | USD 42,000               |
|                     |         |            |                                                 | USD 37,000 in patients with deteriorating employment status                             |                                                                      |                          |
| Green (2007)11      | UK      | 2001–2002  | 916 MS patients and matched general population  | Under GBP 10,000                                                                        | 16.5%                                                                | 22.8%                    |
|                     |         |            |                                                 | GBP 10,000–29,999                                                                      | 55.0%                                                                | 41.5%                    |
|                     |         |            |                                                 | GBP 30,000                                                                             | 28.5%                                                                | 35.6%                    |
|                     |         |            |                                                 | Receiving state benefits                                                               | 76%                                                                  | 42.6%                    |
| Gupta (2014)12      | US      | 2009       | 536 MS patients and 74,451 controls             | Less than USD 25,000                                                                   | 25.8% (p < 0.001)                                                    | 18.4%                    |
|                     |         |            |                                                 | USD 25,000 to USD 49,999                                                               | 28.9% (p = 0.608)                                                    | 29.9%                    |
|                     |         |            |                                                 | USD 50,000 to USD 74,999                                                               | 19.8% (p = 0.356)                                                    | 21.4%                    |
|                     |         |            |                                                 | USD 75,000 and over                                                                    | 19.2% (p = 0.006)                                                    | 24.3%                    |
|                     |         |            |                                                 | Decline to answer                                                                      | 6.3% (p = 0.745)                                                     | 6.0%                     |
| Jennum (2012)13     | Denmark | 1998–2006  | 10,849 MS patients compared to matched 43,396   | Annual mean of social transfer income                                                   | EUR 12,275                                                           | EUR 5432                 |
|                     |         |            | citizens                                        | Income from employment                                                                  | 39%                                                                  | 67%                      |
|                     |         |            |                                                 | Income from public transfers                                                            | 83%                                                                  | 49%                      |
| Jennum (2013)21     | Denmark | 1998–2006  | 402 MS+ON and 1606 controls                     | Mean annual income from employment                                                      | EUR 20,365 (p < 0.001)                                               | EUR 27,609               |
|                     |         |            |                                                 | Mean annual public transfers                                                            | EUR 8,742 (p < 0.001)                                                | EUR 4,123                |
| Landfeldt (2018)25  | Sweden  | 1994–2012  | 5472 patients and 54,195 controls               | Difference in gross salary (during follow-up)                                          | EUR 5130                                                              | Reference                |
|                     |         |            |                                                 | Difference in gross salary the first year and 11 years after diagnosis                  | EUR 24,30 and EUR 9010                                               | Reference                |
|                     |         |            |                                                 | At least one record of zero gross salary within 10 years after diagnosis               | 45%                                                                  | 32%                      |

(Continues)
| First author (year) | Country | Time       | Population | Outcomes (main results) |
|----------------------|---------|------------|------------|-------------------------|
| Murley (2018)        | Sweden  | 2002–2013  | 785 diagnosed with MS and 7847 controls without MS | Annual mean sum of income from sickness absence at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 10,829 (95% CI, 8,369–12,292) | SEK 6523 (95% CI, 7804–9243) |
|                      |         |            |            | Mean difference of income from sickness absence at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 26,685 (95% CI, 23,178–30,179) | SEK 3955 (95% CI, 3549–4442) |
|                      |         |            |            | Proportion receiving income from sickness absence at T − 7 (2002), T − 0 (2009), T + 4 (2013) 20% | Reference 17% |
|                      |         |            |            | Annual mean sum of income from disability pension at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 13,966 (95% CI, 10,281–17,654) | SEK 8396 (95% CI, 7480–9312) |
|                      |         |            |            | Mean difference of income from disability pension at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 13,548 (95% CI, 10,866–16,230) | SEK 8571 (95% CI, 7872–9270) |
|                      |         |            |            | Proportion receiving income from disability pension at T − 7 (2002), T − 0 (2009), T + 4 (2013) 13% | Reference 10% |
|                      |         |            |            | Annual mean sum of income from earnings at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 184,174 (95% CI, 172,691–195,658) | Reference 5% |
|                      |         |            |            | Mean difference of income from earnings at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 207,834 (95% CI, 195,427–220,242) | SEK 193,918 (95% CI, 190,357–197,467) |
|                      |         |            |            | Proportion receiving income from earnings at T − 7 (2002), T − 0 (2009), T + 4 (2013) 8% | SEK 248,352 (95% CI, 244,339–252,365) |
|                      |         |            |            | Annual mean sum of disposable income at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK 64,867 (95% CI, 79,203 to −50,528) | SEK 279,298 (95% CI, 275,050–283,534) |
|                      |         |            |            | Mean difference of disposable income from earnings at T − 7 (2002), T − 0 (2009), T + 4 (2013) SEK −9742 (95% CI, −21,763–2275) | SEK 89% |
|                      |         |            |            | Adjusted regression coefficient for disposable income (postdiagnosis): SEK 40,517 (95% CI, −53,558–27,476) | SEK 87% |
|                      |         |            |            | T + 4 (2013) SEK −64,867 (95% CI, −79,203 to −50,528) | SEK 88% |
|                      |         |            |            | T + 4 (2013) SEK 184,174 (95% CI, 172,691–195,658) | SEK 150,110 (95% CI, 148,530–151,700) |
|                      |         |            |            | T + 4 (2013) SEK 207,834 (95% CI, 195,427–220,242) | SEK 182,010 (95% CI, 179,750–184,280) |
|                      |         |            |            | T + 4 (2013) SEK −9742 (95% CI, −21,763–2275) | SEK 205,450 (95% CI, 202,950–207,950) |
|                      |         |            |            | T + 4 (2013) SEK 40,517 (95% CI, −53,558–27,476) | Reference |
|                      |         |            |            | T + 4 (2013) SEK −64,867 (95% CI, −79,203 to −50,528) | Reference |
|                      |         |            |            | T + 4 (2013) SEK 184,174 (95% CI, 172,691–195,658) | Reference |
|                      |         |            |            | T + 4 (2013) SEK 207,834 (95% CI, 195,427–220,242) | Reference |
|                      |         |            |            | T + 4 (2013) SEK −9742 (95% CI, −21,763–2275) | Reference |
|                      |         |            |            | T + 4 (2013) SEK 40,517 (95% CI, −53,558–27,476) | Reference |
| First author (year) | Country | Time         | Population | Outcomes (main results)                                                                                                                                                                                                 |
|---------------------|---------|--------------|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pearson (2017)      | New Zealand | 2006        | 1,727 MS patients of working age (25–64 years) | Personal income median for female NZD 15,000 Personal income median for male NZD 25,000 Personal income median for employed female NZD 30,000 Personal income median for employed male NZD 50,000 |
| Pfleger (2010)      | Denmark | 1980–2004 | 2,538 MS patients and 60,760 controls | The mean gross income for the control group showed a constant and stable growth over the years, while the patients' income, after remaining stable for about 10 years, began to decline. After 20 years of follow-up the mean gross income for patients was only 70% of that of the controls |
| Wiberg (2015)       | Sweden | 2010, 2005  | 13,979 with MS diagnosis compared to a propensity score matched control group (69,895) | Mean income from earnings and proportion SEK 149,700 and 64% Mean income from disability pension and proportion SEK 57,000 and 52% Mean income from sickness absence and proportion SEK 9800 and 21% Mean income from disability allowance and proportion SEK 3100 and 16% Mean income from unemployment compensation and proportion SEK 2200 and 4% Mean income from social assistance and proportion SEK 800 and 4% |
| Wiberg (2019)       | Sweden | 1994–2009  | 2,650 people with MS and 7,950 control individuals | Mean earnings (difference in mean earnings from the matched control group) at T = 5 at T − 2 SEK 169.00 (4000) at T − 1 SEK 182.00 (1000) at T0 (MS diagnosis) SEK 181.00 (10000) at T + 5 SEK 163.00 (28,000) Estimated difference for earnings at T0 and T + 5 SEK 166.00 (63,000) Estimated difference for earnings at T0 and T + 5 SEK −36,900 (95% CI, −43,000 to −30,800) and −84,400 (95% CI, −91,500 to −77,300) | Reference |
### Table 4: Studies that investigated work ability-related outcomes

| First author (year) | Country | Time | Population | Outcomes (main results) | In MS | In non-MS |
|---------------------|---------|------|------------|-------------------------|-------|-----------|
| **Beiki (2016)**    | Sweden  | N/A  | 10,852 MS patients and 202,976 controls | Increase of the mean number of age-specific (18–55) sick-leave days at the time of MS onset | 0.94% (95% CI, 0.89–0.99) | 0.63% (95% CI, 0.58–0.67) |
| **Brenner (2014)**  | Sweden  | 2005–2010 | 10,750 MS patients and 5,553,141 non-MS individuals, aged 17–64 | On disability pension | 61% | 10% |
| **Gyllensten (2016)** | Sweden | 1998–2011 | 3,686 diagnosed with MS and 18,424 matched controls | Difference in mean number of work disability days at T−5 - T−1 T0 (MS diagnosis) T+1 T+5 | 20 days (p < 0.05), 41 days (p < 0.05), 82 days (p < 0.05), 98 days (p < 0.05), 106 days (p < 0.05) | Reference |
| **Ivanova (2009)**  | US      | 1999–2006 | 989 employees with MS and 989 controls | Short-term or long-term disability Mean number of disability days per year | 21.4% (p < 0.0001), 29.8 days (p < 0.0001) | 5.2%, 4.5 days |
| **Jennum (2013)**   | Denmark | 1998–2006 | 402 MS+ON and 1606 controls | Proportion of receiving sick pay | 27% | 13% |
| **Landfeldt (2016)**| Sweden  | 2001–2012 | 6,092 patients and 60,345 controls | The mean annual prevalence of sick leave, the first year after diagnosis to 11 years after diagnosis The mean annual prevalence of disability pension, the first year after diagnosis to 11 years after diagnosis | 12%–23%, 12%–55%, 13%–13%, 7%–9% | Reference |
| **Nohara (2017)**   | Japan   | 2009–2016 | 96 respondents with MS and 480 matched controls | Absenteeism Presenteeism | 17.5% (p < 0.001), 38.11% (p < 0.001) | 5.57%, 21.62% |
| **Sundström (2003)**| Sweden  | 1997–2001 | 399 prevalent cases | The risk of full sick leave due to MS The risk for disability pension | OR = 5.7 (95% CI, 4.5–7.2), OR = 6.6 (95% CI, 4.4–10) | Reference |
| **Tinghög (2013)**  | Sweden  | 2005 | 9,768 MS patients and 5,644,275 controls | Partial or full disability pension ≤ 1 sick-leave spell | 61.7%, 36.8% | 14.2%, 14.5% |
| **Tinghög (2014)**  | Sweden  | 2005 | 45,19 MS patients and 4,972,174 non-MS patients | Incidence rate for disability pension (per 100,000 person-years), women and men | 69.1 and 61.6 | 7.0 and 4.6 |
| **Wiberg (2019)**   | Sweden  | 1994–2009 | 2,650 people with MS and 7,950 control individuals | Had sickness absence in the year of MS diagnosis (T0) and 5 years later (T + 5), part time Had sickness absence at T0 and T + 5, full time Had disability pension at T0 and T + 5, part time Had disability pension at T0 and T + 5, full time | 10.0% and 6.2%, 46.7% and 16.9%, 5.2% and 21.0%, 9.1% and 25.1% | 2.1% and 1.1%, 13.7% and 10.4%, 2.3% and 2.9%, 6.3% and 7.9% |
| **Yamabe (2019)**   | Japan   | 2009–2014 | 85 MS and 145,759 without MS | Absenteeism (adjusted for age and comorbidities) Presenteeism (adjusted for age and comorbidities) | 12.0% (p < 0.001), 33.8% (p < 0.001) | 3.7%, 19.8% |

Abbreviation: N/A, not available (information extracted from an abstract only); OR, odds ratio; ON, optic. neuritis.
### TABLE 5  Studies that investigated relationship outcomes

| First author (year) | Country | Time       | Population                                                                 | Outcomes (main results)                                                                 |
|---------------------|---------|------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Landfeldt (2018)    | Sweden  | 1975–2012 | 3998 patients and 15,992 controls                                           | HR of divorce for men                                                                  |
| Pearson (2017)      | New Zealand | 2006   | 1727 of working age (25–64)                                                | Divorced/separated/widowed                                                              |
| Pfleger (2010)      | Denmark | 1980–2004 | 2538 with MS and 50,760 matched and randomly drawn control persons          | Married/civil union                                                                    |
|                     |         |            |                                                                            | Never married                                                                          |
|                     |         |            |                                                                            | The cumulative probability of remaining in the same relationship five years after the onset and at 24 years |
|                     |         |            |                                                                            | 86% and 33% (p < 0.001)                                                                  |
|                     |         |            |                                                                            | 89% and 53%                                                                           |
| Tinghög (2014)      | Sweden  | 2005      | 4519 MS patients and 4,972,174 non-MS patients                             | Living with partner                                                                    |
|                     |         |            |                                                                            | 54.9%                                                                                  |
|                     |         |            |                                                                            | 49.7%                                                                                  |
| Wiberg (2015)       | Sweden  | 2010, 2005| 13,979 with MS diagnosis and 5,203,176 non-MS (before matching)            | Partner, no children                                                                    |
|                     |         |            |                                                                            | 21%                                                                                   |
|                     |         |            |                                                                            | Partner, with children                                                                  |
|                     |         |            |                                                                            | 34%                                                                                    |
|                     |         |            |                                                                            | Single, no children                                                                     |
|                     |         |            |                                                                            | 36%                                                                                    |
|                     |         |            |                                                                            | Single, with children                                                                    |
|                     |         |            |                                                                            | 8%                                                                                     |

Abbreviation: HR, hazard ratio.

### TABLE 6  Studies that reported education level

| First author (year) | Country | Time       | Population                                                                 | Outcomes (main results)                                                                 |
|---------------------|---------|------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Brenner (2014)      | Sweden  | 2005–2010 | 10,750 MS patients and 5,553,141 non-MS individuals, aged 17–64             | Compulsory school (to 9 years)                                                         |
|                     |         |            |                                                                            | High school (10–12 years)                                                               |
|                     |         |            |                                                                            | University (13+ years)                                                                  |
| Green (2007)        | UK      | 2001–2002 | 916 MS and matched general population                                       | Degree level or higher                                                                  |
|                     |         |            |                                                                            | 16.2%                                                                                  |
|                     |         |            |                                                                            | 15.1%                                                                                  |
| Gupta (2014)        | US      | 2009      | 536 MS patients and 74,451 controls                                        | High school graduate or less                                                           |
|                     |         |            |                                                                            | More than high school                                                                  |
|                     |         |            |                                                                            | 22.4%                                                                                  |
|                     |         |            |                                                                            | 22.4%                                                                                  |
|                     |         |            |                                                                            | 77.6%                                                                                  |
|                     |         |            |                                                                            | 77.6%                                                                                  |
| Pearson (2017)      | New Zealand | 2006   | 1727 of working age (25–64)                                                | Post-school                                                                           |
|                     |         |            |                                                                            | School                                                                                 |
|                     |         |            |                                                                            | 53.9%                                                                                  |
|                     |         |            |                                                                            | 46.1%                                                                                  |
|                     |         |            |                                                                            | 42.4%                                                                                  |
|                     |         |            |                                                                            | 57.6%                                                                                  |
| Tinghög (2013)      | Sweden  | 2005      | 9768 MS patients and 5,644,275 controls                                     | Compulsory (≤9 years)                                                                   |
|                     |         |            |                                                                            | High school (10–12 years)                                                              |
|                     |         |            |                                                                            | University (≥13 years)                                                                 |
|                     |         |            |                                                                            | 17.7%                                                                                  |
|                     |         |            |                                                                            | 22.2%                                                                                  |
|                     |         |            |                                                                            | 49.3%                                                                                  |
|                     |         |            |                                                                            | 46.9%                                                                                  |
|                     |         |            |                                                                            | 33.0%                                                                                  |
|                     |         |            |                                                                            | 30.8%                                                                                  |
| Tinghög (2014)      | Sweden  | 2005      | 4519 MS patients and 4,972,174 non-MS patients                             | Compulsory (≤9 years)                                                                   |
|                     |         |            |                                                                            | High school (10–12 years)                                                              |
|                     |         |            |                                                                            | University (≥13 years)                                                                 |
|                     |         |            |                                                                            | 17.1%                                                                                  |
|                     |         |            |                                                                            | 18.5%                                                                                  |
|                     |         |            |                                                                            | 49.1%                                                                                  |
|                     |         |            |                                                                            | 47.8%                                                                                  |
|                     |         |            |                                                                            | 33.7%                                                                                  |
|                     |         |            |                                                                            | 33.7%                                                                                  |
| Wiberg (2015)       | Sweden  | 2010, 2005| 13,979 with MS diagnosis and 5,203,176 non-MS (before matching)            | Lower education                                                                        |
|                     |         |            |                                                                            | Secondary education                                                                     |
|                     |         |            |                                                                            | Higher education                                                                        |
|                     |         |            |                                                                            | 14%                                                                                    |
|                     |         |            |                                                                            | 14%                                                                                    |
|                     |         |            |                                                                            | 49%                                                                                    |
|                     |         |            |                                                                            | 48%                                                                                    |
|                     |         |            |                                                                            | 37%                                                                                    |
|                     |         |            |                                                                            | 38%                                                                                    |
| Wiberg (2019)       | Sweden  | 1994–2009 | 2650 people with MS and 7950 control individuals                            | Elementary/college                                                                      |
|                     |         |            |                                                                            | High school                                                                             |
|                     |         |            |                                                                            | University/college                                                                       |
|                     |         |            |                                                                            | 10%                                                                                    |
|                     |         |            |                                                                            | 14%                                                                                    |
|                     |         |            |                                                                            | 53%                                                                                    |
|                     |         |            |                                                                            | 50%                                                                                    |
|                     |         |            |                                                                            | 37%                                                                                    |
|                     |         |            |                                                                            | 35%                                                                                    |
| Yamabe (2019)       | Japan   | 2009–2014 | 85 MS and 145,759 without MS                                               | University education                                                                   |
|                     |         |            |                                                                            | 44.7%                                                                                  |
|                     |         |            |                                                                            | 47.6%                                                                                  |
Besides having less income from earnings, MS patients in Denmark received an annual mean excess social transfer income of EUR 6843.13 Here, 20 years after follow-up, the mean gross income for patients was only 70% of that of the controls.15

Several studies also estimated the differences in earnings,23,24 for example 5 years after MS diagnosis it was SEK −84,400 (~EUR 9700) (95% CI, –91,500 to −77,300).24

### 3.3 | Work ability-related outcomes

Here, we identified a group of 12 studies with a range of outcomes related to absenteeism, presenteeism, sick-leave and disability pension days, but also expressed as odds ratios or incidence rates (Table 4). Two studies in Sweden26,27 identified a ~50% difference in the proportions of people with disability pension (61% in MS patients and 10% in general population26; 61.7% and 14.2%, respectively7), and one more Swedish study26 illustrated how this gap widens through the years after MS diagnosis: from 12% in the first year to 55% in 11 years after the diagnosis, compared to 7% and 9%, respectively, in the matched control group. Also, the mean annual prevalence of sick leave increased from 12% to 23%, respectively, in MS, while no increase was detected in general population (13% and 13%). To add, a study in United States29 showed that annually MS patients had 25.3 disability days more than control group, and a Swedish study30 illustrated how this changes in a longer time horizon—work disability, defined as annual net days of sickness absence and disability pension, of patients with MS increased gradually between 5 years (T − 5) and 1 year (T − 1) before diagnosis (mean: 46–82 days) followed by a sharp increase after diagnosis (T + 1, 142 days), after which only a marginal increase was observed (T + 5, 149 days). The matched controls had less work disability, slightly increasing during the period to a maximum of ~40 days.30 Also, the sharpest increase in the mean number of sick-leave days overlapped the recorded onset age; however, in the 30–34 and 35–39 onset age groups, sickness absence days in about 41% of individuals started to increase from seven years before the recorded onset age.31 As estimated by Tinghög et al.,32 the incidence rate for disability pension (per 100,000 person-years) was 69.1 for women and 61.6 for men in MS, but only 2.1 and 1.1 in general population.

In addition, employees with MS had a higher rate of medically related absenteeism and associated absenteeism days than employee controls.29 Also, the respective proportion were very different, for example in Japan absenteeism was 12% in MS and 3.7% in general population, whereas presenteeism—33.8% and 19.8%, respectively.15 Similarly, in another Japanese study,33 absenteeism proportions were 17.5% and 5.57%, respectively, and for presenteeism—38.11 and 21.62%, respectively.

### 3.4 | Relationship outcomes

A number of studies reported only point prevalence (proportions) of various family status, showing slightly higher proportions of living with a partner in MS patients than in the general population, for example 54.9% and 49.7%, respectively, in Sweden32; 60.8% and 54.0%, respectively, in New Zealand32 (Table 5). As the limitations with the cross-sectional designs are well-known, we highlight two longitudinal studies that specifically investigated the relationship outcomes: a Swedish study34 in crude analysis revealed no significant differences in the cumulative incidence proportion of divorce between patients and controls (p = 0.902), or women with MS and female controls (p = 0.157). In contrast, men with MS were estimated to have a notably higher incidence of divorce compared with male controls (p = 0.040). An adjusted model showed that men with MS had a 21% higher risk (hazard ratio (HR) = 1.21, p = 0.032) of divorce across follow-up compared with male controls when controlling for age, region of residency and year of diagnosis. No significant adjusted risk increase was found for women with MS.

A Danish study25 showed that after 24 years, the cumulative probability of remaining in the same relationship was much lower in MS patients when compared to general population—33% and 53%, respectively. Also, among MS patients with young onset (<36 years of age), those with no children had a higher risk of divorce than those having children less than 7 years (HR = 1.51; p < 0.001), and men had a higher risk of divorce than women (HR =1.33; p < 0.01).

### 3.5 | Educational level

Information on the formal education level was extracted from the selected studies only (Table 6). The reported proportions of MS patients having various educational levels were not apparently different when compared to the general population. Interestingly, many of the included studies11,16,24,26,32 pointed towards a trend that higher educational level was slightly more prevalent among MS patients, similarly the lowest educational category slightly more prevalent in general population.

### 4 | DISCUSSION

In this systematic review of the socioeconomic consequences of MS, we summarized findings of differences between MS patients and the general population in terms of employment, income, work ability and relationship. Work is salient to life, is central to well-being and is a mean by which individuals define themselves. Disease such as MS, however, can complicate the interaction between a person and work,26 hence seen in the majority of the studies indicating significant differences in employment rates between MS patients and the general population. As concluded in a literature review on factors related to difficulties with employment in MS patients, 59% of MS patients are unemployed,9 and many of the studies reviewed here revealed the 15%–30% observed differences for paid employment or full-time employment between MS patients and general population. However, as raised by Wiberg et al.,24 sorting individuals into conventional labor market categories as employed/unemployed obscures more nuanced information about the gradual effect of the disease on the individuals’ labor market attachment. Also, MS patients to a high extent work part time.
Interestingly, the difference in employment rates seems to be reduced with time, as observed in Australia: by 2013, the gap in employment for people with MS compared to the general population had decreased from 14.3% to 3.5%. The improved employment raises the question of what factors have contributed to the narrowing of the employment gap—the increased availability of more recent higher efficacy disease-modifying treatments is likely to be a key contributor, given that early and effective pharmaceutical symptom management has been argued to be the most important factor in employment maintenance. Also, difficulties with employment are a relevant issue in consideration with the variety of symptoms experienced by MS patients, and as summarized by Schiavolin et al., the symptoms that have frequently been reported to reduce MS patients’ ability to work are fatigue, mobility impairments and cognitive impairments.

Income-related outcomes, when reported by summary statistics, are particularly hard to compare, given the differences between the national currencies but also differences in economic status between countries. However, one could with no doubt conclude about a large gap between MS patients and general population in the proportion of those receiving earnings (28% difference between the two groups in Denmark), or 33%-34% more in MS group receiving social benefits, as in Denmark and UK. Interestingly, several studies concluded that MS patients’ earnings are lower than the controls’ beginning shortly before MS diagnosis, with this an increasing gap thereafter. Further, the results indicate that educational level and type of occupation are influential determinants of the large heterogeneity of MS patients earnings: the largest differences in absolute terms between MS and the controls were observed for those with elementary school education and for those working as managers. Also, men with MS had a sharper increase in work disability before diagnosis. High educational level was associated with less progression in work disability before and around diagnosis. In addition, MS patients with mental disorders had a higher risk for disability pension.

In general, absenteeism can be defined as missing work because of health problems, and presenteeism as impairment while working. However, the exact way of measurement may differ, for example Castelo-Branco et al. calculated labour-force absenteeism as the mean annual prevalence and number of sick-leave and disability pension days, whereas Ivanova et al. looked at medically related absenteeism as work absences due to the use of medical services. However, the two Japanese studies included in our review, did not specifically defined these types of outcomes, but did report higher proportions of both absenteeism and presenteeism in MS patients than controls. Glanz et al. suggest that absenteeism and presenteeism may be measuring separate dimensions of the impact of health problems on work productivity. In arthritis, for example, it has been estimated that presenteeism accounts for 41% of total productivity losses while absenteeism accounts for only 10%. In addition, presenteeism may correlate with health status better than absenteeism. Zhang et al. reported stronger correlations between presenteeism and health status measures including functional disability, pain, fatigue and disease activity than between absenteeism and the same health status measures in a group of subjects with rheumatoid arthritis.

Though education can be considered as a socioeconomic variable (and an outcome of consequence at some point), due to obvious reasons it would be hard to assess the relationship between education and a disease among adults, since absolute majority has already acquired their academic degree of before the onset of MS. Not surprisingly, the selected studies reported educational level among their study population characteristics, which is summarized here. However, due to declining cognitive function in MS patients, outcomes of the various educational forms (apart from formal education), such as shorter courses or training, could be further explored.

Among the strengths of our study is that we assessed a wide spectrum of socioeconomic outcomes. As listed in Table 1, it is a heterogeneous field of investigation. Our mapping of these outcomes could help to define study outcomes when designing a study aiming at more comparable results/outcomes. Thus, we suggest reporting ratios (eg, risk ratio for not being fully employed, odds ratio for sick leave, hazard ratio of divorce) instead of proportions. Also, in the context of the comparison to the general population, such analytical techniques as matching are valuable tools to overcome the underlying differences between the groups.

Due to this wide spectrum, it was not possible to assess the extracted information from the studies in quantitative manner. Also, besides underlying differences between MS and general population, MS patients are quite different in terms of progression of physical disability, reduction of cognitive function, etc., which can be explored further. Many of the included studies also focussed on MS diagnosis date, rather than the onset date; however, it is unknown whether there are systematic differences among the people with MS regarding the time between onset and diagnosis. Furthermore, the generalizability of the studies may be limited to countries with a similarly functioning labour market and welfare system.

The fact that seven countries out of eight are high-income countries according to the World Bank classification, shows also that to study socioeconomic factors in relation to a disease requires on one hand the well-developed societal databases and on the other hand a substantial research infrastructure, for example registries for which Scandinavian countries are well-known. Not surprisingly, 16 out of 27 (59%) studies were conducted in this region (with 12 of them in Sweden and four in Denmark). Also, when assessed for the quality, these studies were evaluated relatively higher (as employing longitudinal designs with matched control groups, large cohorts of people, longer time horizons, high quality nationwide registers). As addressed by Ludvigsson et al., personal identity number, established in all Nordic countries, has become a vital component of register linkages for research purposes and is used as the key number in all national linkages. It is extensively used in the public administration, and in more and more medical research, also used as the linkage tool between national register data and data collected through patient charts or biobank data. To add, specific quality registers (such as MS) can provide the kind of structured data collection necessary for assessing the outcomes in MS.
for studies of the long-term importance of modifiable risk factors. Therefore, the vast resources invested in the care of individuals with MS should be matched by equal investment into the documentation of interventions and outcomes.42

Given the importance of the socioeconomic outcomes, as summarized in this review, in the countries where information from the databases is not readily available for research purposes, other data sources and study designs may be exploited, such as surveys or interviews. We were able to identify and extract information from 10 cross-sectional studies with either survey or interviews as their main data source. However, these are usually subjected to various systematic biases and received lower grades in the quality assessment.

By reviewing and summarizing the studies investigating the socioeconomic consequences, we also illustrate how such outcomes can be used to study MS. In a number of studies, we have already shown how income highly correlates with physical disability and reflects the clinical course, for example increasing disability was associated with higher chance to receive social benefits and with lower chance to have earnings, primary and secondary progressive MS patients were similar from the perspective of patients’ income and sickness absence/disability pension, while relapsing remitting MS patients proved to have much higher earnings, less benefits, and lower levels of sickness absence and disability pension than the other two groups. Moreover, lower cognitive function affects the financial situation of MS patients negatively and independently of physical disability. In contrast to clinical scores such as EDSS, which are collected irregularly in the real-world setting, socioeconomic data when available from public registers, such as from tax authorities, have the additional benefits of minimal data loss and reflecting comprehensive time periods. Besides overcoming the ever-present challenge with missing data in observational studies, income data can encompass other aspects of the disease, such as fatigue and cognition, not captured by physical disability, thus serving as precise outcome measures that can be used as proxy parameters of disability or surrogate markers of global patient functioning.

In conclusion, this systematic review summarizes the pronounced differences in various socioeconomic outcomes between MS patients and general population and supports the idea that socioeconomic data can serve as a precise and robust outcome measure assessing a sum of composite of disability and global individual’s function, as well as reflecting the broader consequences of MS.

ACKNOWLEDGEMENT
For the help with the literature search, defining the search strategy, constructing the search string and performing the search in the databases, we would like to thank Gun Brit Knutssön, Information Scientist, Karolinska Institutet University Library.

CONFLICT OF INTEREST
AK is also employed by Takeda Pharma AB. VDK has received financial support from Stockholm County Council; Biogen (recipient of grant and scholarship, PI for project sponsored by); Novartis (Scientific Advisory Board member, recipient of scholarship and lecture honoraria); Merc (Scientific Advisory Board member, recipient of lecture honoraria). JH received honoraria for serving on advisory boards for Biogen and Novartis and speaker’s fees from Biogen, MerckSerono, BayerSchering, Teva and SanofiGenzyme. He has served as PI for projects sponsored by or received unrestricted research support from Biogen, SanofiGenzyme, MerckSerono, TEVA, Novartis and BayerSchering. His MS research is funded by the Swedish Research Council and the Swedish Brain Foundation.

ORCID
Andrius Kavaliunas https://orcid.org/0000-0003-3896-7332
Virginija Danylaitė Karrenbauer https://orcid.org/0000-0002-7166-8951

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.