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Title: Incidence of multiple sclerosis in Germany: A cohort study applying different case definitions based on claims data

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Abstract

Background: Data on the incidence of multiple sclerosis (MS) on the national level is scarce. We aimed to estimate the incidence of MS in Germany and to compare different MS case definitions based on claims data.

Methods: We conducted a cohort study with the German Pharmacoepidemiological Research Database in 2012 and calculated age- and sex-standardized incidence rates (sIRs) for three case definitions. In addition, the effect of stepwise reduction of the look-back period without MS diagnosis on the incidence rate was evaluated.

Results: Our cohort comprised 4,175,877 individuals. The first case definition based on ICD-10 diagnoses yielded an sIR of 21.8 (95%-confidence intervals: 20.2-23.5) per 100,000 person years, whereas the second and third case definitions with additional requirements for drug treatment and diagnostic tests resulted in lower sIRs of 10.1 (9.1-11.3) and 6.6 (5.8-7.6), respectively. We observed a higher incidence for shorter look-back periods.

Conclusion: The incidence of MS in Germany might be substantially higher than suggested in earlier studies. In addition, our study highlights the importance of a look-back period of at least 36 months to identify incident MS cases based on claims data.

Introduction

Multiple sclerosis (MS) is one of the leading causes of neurological disability in young adults [1,2]. The condition is characterized by a high variability of symptoms and co-morbidities [3,4] which can severely impair the patients' quality of life [5].

In a systematic review on the epidemiology of MS in Europe, Kingwell et al. [6] found a general lack of studies providing incidence data on the national levels. Recent estimates of the absolute number of MS patients in Germany vary between 100.000 and 200.000 persons [7,8]. Data on the incidence of MS in Germany are rare, some dating back to the late 1980s [9]. In the most recent study based on registry data from the urban district of Erfurt, an average annual incidence of 8 per 100,000 persons was found between 1998 and 2002 [10]. Studies from other European countries provide more up-to-date information, but show a strong heterogeneity with the reported MS incidence ranging from 3.6 to 11.8 per 100,000 persons [11–22]. In general, the diverging results in studies may reflect regional differences of the MS incidence but could also be attributable to methodological inconsistencies with regard to MS case definitions [6,23,24] and the nature of the different data sources.

Large claims databases have recently been suggested as a valuable tool for studies on the epidemiology of MS, since analyses can be conducted rapidly and in a cost-efficient way [24]. In this study, we aimed to provide up-to-date estimates for the incidence of MS in Germany based on claims data using different MS case definitions.

Methods

Data source

Data source for this study was the German Pharmacoepidemiological Research Database (GePaRD) which has been described in detail elsewhere [25,26]. At the time of the study, GePaRD contained claims data of about 20 million insured members of four German statutory health insurance providers (SHI).. For this study, data up to the year 2013 from

approximately 10 million insured members of one SHI covering all regions of Germany were used.

In brief, GePaRD contains demographic characteristics including age and sex of the insured persons, standardized hospital records as well as data on ambulatory care and outpatient drug prescriptions. Hospital records include information on the dates of admission and discharge, diagnoses, diagnostic and therapeutic procedures with their respective dates as well as the reason for hospital discharge. Ambulatory care data contain information on diagnoses with the corresponding diagnostic certainty as well as treatments and diagnostic procedures. Due to reimbursement practices, ambulatory diagnoses can only be dated on a quarterly basis. All diagnoses in GePaRD are coded according to the German Modification of the International Classification of Diseases 10th Revision (ICD-10-GM). Data on outpatient drug prescriptions comprise information on the dates of prescription and dispensation as well as the specialty of the prescribing physician. Via linkage to a pharmaceutical reference database, further information on the Anatomical Therapeutical Chemical (ATC) classification code, defined daily dose and strength, packing size as well as generic and brand names can be obtained for each drug prescription [25,26].

The SHI as well as the governing authority approved the use of the data for this study. In accordance with the German Social Insurance Code, informed consent of the insured persons was not required.

Study design

We conducted a retrospective cohort study to estimate the incidence of MS in 2012. Claims data from 2004 through 2011 were used for the exclusion of prevalent MS cases while data from 2013 were used to assess diagnostic procedures and medications for MS case ascertainment.

To be eligible for inclusion in the cohort, patients must have had valid information on age and sex as well as continuous insurance during the whole study period (2004-2013), except for persons who were born between 2004 and 2012 or died after cohort entry. Furthermore,

prevalent MS cases with any MS diagnosis (ICD-10 GM code G35) from 2004 through 2011 (disease-free look-back period) were excluded. Hence, the cohort entry was defined as January 1, 2012, if inclusion criteria were fulfilled. The end of follow-up was either December 31, 2012, the first MS diagnosis according to the respective case definition or death, whichever occurred first.

Definition of incident MS cases

For the identification of incident MS cases, three definitions with different sensitivity and specificity were applied (**Figure 1**). The first case definition (C1) required at least one main hospital discharge diagnosis or two other diagnoses (i.e. secondary hospital or verified ambulatory diagnoses) coded as either G35.0 (initial manifestation), G35.1 (relapsing-remitting), G35.2 (primary progressive), G35.3 (secondary progressive) or G35.9 (without further specification) in the same or in two consecutive quarters. The second case definition (C2) additionally required a prescription of a disease-modifying drug (DMD), i.e. interferon beta-1a (ATC code L03AB07), interferon beta-1b (L03AB08), glatiramer acetate (L03AX13), natalizumab (L04AA23) or fingolimod (L04AA27), within 365 days after the incident MS diagnosis. Medications frequently prescribed for diseases other than MS or as third line-treatment (e.g. azathioprine and mitoxantrone) were not considered as DMD for case definition. For the third case definition (C3), a documented magnetic resonance imaging, lumbar puncture and an evoked potential test within in the same quarter of the initial MS diagnosis or the following quarter were additionally required. These diagnostic procedures are recommended by the German Society for Neurology for the ascertainment of the diagnosis once MS is suspected [27].

Statistical Analyses

For all three case definitions, crude incidence rates (IRs) as well as direct age- and sex-standardized incidence rates (sIRs) were calculated per 100,000 person years (PYs). We used the German general population from 2011 as well as the European standard population

from 2013 as standard populations. The corresponding 95%-confidence intervals (CI) were calculated assuming a Poisson distribution for crude IRs (28) and based on the Gamma distribution for sIRs [29]. In further analyses, the female to male ratio for all case definitions was obtained and crude IRs were stratified by age and sex. In addition, the effect of reducing the look-back period without MS diagnosis stepwise from 96 to 12 months was evaluated.

Results

The cohort comprised 4,175,877 persons fulfilling the inclusion criteria (**Figure 2**). The mean age was 41.8 years (standard deviation: 24.5) and 46% were female.

The characteristics of MS cases as well as the IRs and sIRs for all case definitions are displayed in **Table 1**. For C1, we identified 780 incident MS cases resulting in a crude IR of 19.0 (95%-CI: 17.7-20.4) per 100,000 PYs and an sIR of 21.8 (20.2-23.5) for the German population, respectively. Using C2, the number of incident MS cases was reduced to 348 with a crude IR of 8.5 (7.6-9.4) and an sIR of 10.1 (9.1-11.3) for Germany. Finally, we found a crude IR of 5.4 (4.8-6.2) and an sIR of 6.6 (5.8-7.6) in the German population for C3 based on 223 MS cases. The mean age of incident MS cases decreased with higher restriction of the case definition from 44.3 (C1) to 40.6 (C2) and 40.1 years (C3). For all case definitions, women were younger than men, but differences were less pronounced for C2 and C3. The female to male ratio of incident MS cases was higher for C2 and C3 with 2.5 and 2.6 compared to C1 with only 1.9.

The age-specific IRs for all case definitions are displayed in **Figure 3**. With 49.7 (39.8-61.4), the age-specific IR for C1 had a peak in the age-group of 35-39 years. Applying C2, the highest IR of 24.3 (16.9-34.0) was found in the age-group 25-29 years while the peak for C3 was in the age-group 30-34 years with 17.1 (11.5-24.4). After the respective incidence peak, the age-specific IRs steadily decreased with rising age for all case definitions except for a small increase from 40-44 years to 45-49 years. While the IR for C1 was higher in all age-groups, the IR for C2 and C3 were similar in the age-groups of 60 years and older. In

contrast to C2 and C3, incident MS cases were also identified in patients older than 70 years based on C1.

With C1 and C2, the majority of incident MS cases were first diagnosed in ambulatory care with 59.4% and 53.2%, respectively (see **Table 2**). In contrast, 56.1% of incident MS cases were first diagnosed in the hospital setting when C3 was applied. Across all case definitions, about 60-65% of all incident hospital MS diagnoses were coded as a first manifestation of MS (ICD-10 GM G35.0), whereas most incident diagnoses in the ambulatory setting were documented as MS without further specification (ICD-10 GM code G35.9).

When we gradually reduced the duration of the required look-back period without MS diagnosis from 96 to 12 months, the greatest impact was observed for C1 (see **Figure 4**). Here, the crude IR steadily increased with each year of shortening the required look-back period up to 21.1 (19.8-22.6) for the 36-month period and further increased to 26.3 (24.8-28.0) for the 12-month look-back period. A similar but less pronounced trend was found for the C2 definition with an increase from 8.5 (7.6-9.4) for the 96-month period to 10.1 (9.2-11.2) for the 12-month period. In contrast, the IR remained relatively stable when we used C3 with an IR of 5.5 (4.9-6.4) for 12 months.

Discussion

We used claims data to analyze the incidence of MS in Germany in 2012 by applying different case definitions to identify incident MS cases. The observed IR strongly varied in dependence of the applied case definition and substantially decreased with additionally required components of drug treatment (C2) and diagnostic procedures (C3) compared to the definition based on the ICD-10 diagnoses only (C1). Further analyses revealed a substantial increase of the incidence with a shorter prior disease-free look-back period, i.e. without MS diagnosis, especially when only diagnoses were used for case ascertainment (C1).

So far, data on the incidence of MS on the national level is missing for Germany. Older studies found an annual incidence of 4.6 per 100,000 persons from 1975 to 1985 and of 8.0 per 100,000 persons from 1998 to 2002 based on a regional registry data in Lower Saxony and the urban area of Erfurt, respectively [9,10]. In our study, we found a substantially higher incidence when C1 was used to define incident cases and still a slightly higher incidence when C2 was used, the sIR for definition C3 was slightly lower. In this context, we consider C1 and C2 the most accurate case definitions to estimate the incidence of MS based on claims data. C1 is based on the ICD-10 diagnosis only and can be considered the most sensitive case definition. The high number of incident MS diagnoses coded in the ambulatory setting in combination with a high proportion of ICD codes without further specification and coding of secondary progressive MS as incident MS indicates that misclassification might have led to an overestimation of incident MS cases with definition C1. However, the comparison to C2 and C3 also illustrates that patients hospitalized with a main discharge diagnosis of MS and more specifically with an ICD-10 code for an initial manifestation of MS were not captured when further DMD treatment and diagnostic criteria were required for C2 and C3. In a study from Canada [30], a case definition similar to C1 requiring one hospital diagnosis or at least five billings for MS within 2 years was most accurate with a sensitivity of 84% and a positive predictive value of 86%. A further explanation for the large difference between C1 and C2 might be that we did not consider relapse treatment with methylprednisolone and unspecific DMDs such as azathioprine or mitoxantrone for case ascertainment. In addition, patients with a mild form of the disease or a primary progressive course may not have received DMD treatment in the first year after diagnosis. C3 was the most restrictive case definition with a high proportion of incident MS diagnoses in the hospital setting and more specific ICD-10 codes suggesting a high specificity. Therefore, this case definition may be particularly relevant to identify MS as a study outcome in comparative studies based on claims data in which a high positive predictive value is required [31], e.g. in studies investigating vaccinations as a risk factor for MS.

Our results indicate that the MS incidence in Germany might be substantially higher than expected. This is in line with other studies demonstrating a trend towards an increasing incidence of MS during the last decades [6] which may reflect actual changes over time, but may also be related to earlier diagnoses and relaxed diagnostic criteria [7,8,10,27]. In France, the national incidence was estimated to be 7.5 per 100,000 persons based on the main French insurance system [11]. In a Dutch study, incidence calculations based on a medical records database showed an increase of the IR from 4 per 100,000 PYs from 1996 to 2004 to 9 per 100,000 PYs in 2007 and 2008 [12]. Ahlgren et al. investigated the IR of MS in Sweden from 2001 to 2008. Here, the population-wide average IR was 10.2 per 100,000 PYs [13]. For 2010, a population-based study using the Clinical Practice Research Datalink found an overall IR of 9.6 cases per 100,000 PYs for the United Kingdom [14]. The highest incidence for Europe was recently reported from Buskerud in Norway with 11.8 per 100.000 persons [15].

The main strength of this study is the large sample size, which allowed us to investigate age- and sex-specific IRs of MS in Germany for the first time. In addition, we were able to use a long look-back period of 8 years decreasing the amount of misclassification of prevalent MS cases as incident ones. In fact, we observed that the IR strongly depends on the duration of the look-back period without MS, especially when case ascertainment is based solely on diagnoses.

This study also has some limitations. Since linkage to external data sources was not possible, further case validation based on MRI findings or documentation of patient history could not be performed. However, we used three case definitions with different sensitivity and specificity to prove consistency of our results. As a further limitation, we were not able to provide accurate information on different types of disease, e.g. primary progressive compared to relapsing remitting courses, due to unspecific coding. In addition, the sample was not large enough to estimate the incidence of MS on a smaller regional level. Although a previous study [8] indicated a possible West-East gradient with a higher prevalence

observed in the Western Germany. If regional differences also exist for the incidence rate of MS, this might also affect the generalizibility of our results. However, we would assume only small impact of this possible selection bias on the sIR, since we used data from an SHI that covers all regions of Germany and approximately 12 percent of the German population.

Conclusion

In conclusion, our study suggests that the incidence of MS in Germany is higher than reported in older studies, probably because of a general increase in the incidence of MS. Further research is needed to investigate regional differences within Germany as well as time trends over the last years and the underlying causes, e.g. the possible impact of changes in diagnostic criteria. Given the large heterogeneity between the different case definitions used in our study, further validation studies are required to examine the high number of newly diagnosed MS cases not receiving treatment in the following year. In addition, our study highlights the importance of a sufficient look-back period to identify incident MS cases based on claims data. We suggest a prior disease-free look-back period of at least 36 months without an MS diagnosis, especially when only data on diagnoses are available.

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The authors declare that there is no conflict of interest.

References

1. Milo R, Kahana E: Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmun Rev 2010;9(5):A387–A394.

2. Compston A, Coles A: Multiple sclerosis. Lancet 2002;359(9313):1221–31.

3. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al: Natural History of Multiple Sclerosis Symptoms. Int J MS Care 2013;15(3):146-58

4. Marrie RA, Hanwell H: General Health Issues in Multiple Sclerosis: Comorbidities, Secondary Conditions, and Health Behaviors. Contin Lifelong Learn Neurol. 2013;19(4, Multiple Sclerosis):1046–57.

5. Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klösch G, Kollegger H, et al: Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand 2004;110(1):6–13.

6. Kingwell E, Marriott JJ, Jetté N, Pringsheim T, Makhani N, Morrow SA, et al: Incidence and prevalence of multiple sclerosis in Europe: a systematic review. BMC Neurol 2013;13(1):128.

7. Höer A, Schiffhorst G, Zimmermann A, Fischaleck J, Gehrmann L, Ahrens H, et al: Multiple sclerosis in Germany: data analysis of administrative prevalence and healthcare delivery in the statutory health system. BMC Health Serv Res 2014;14(1):381.

8. Petersen G, Wittmann R, Arndt V, Göpffarth D: [Epidemiology of multiple sclerosis in Germany: regional differences and drug prescription in the claims data of the statutory health insurance]. Nervenarzt 2014 Aug 1;85(8):990–8.

9. Poser S, Stickel B, Krtsch U, Burckhardt D, Nordman B: Increasing Incidence of Multiple Sclerosis in South Lower Saxony, Germany. Neuroepidemiology 1989;8(4):207–13.

10. Fasbender P, Kölmel HW: Incidence of Multiple Sclerosis in the Urban Area of Erfurt, Thuringia, Germany. Neuroepidemiology 2008;30(3):147–51.

11. Fromont A, Binquet C, Sauleau EA, Fournel I, Bellisario A, Adnet J, et al: Geographic variations of multiple sclerosis in France. Brain 2010;133(7):1889–99.

12. Kramer MA, Maas NAT van der, Soest EM van, Kemmeren JM, Melker HE de, Sturkenboom MCJM: Incidence of Multiple Sclerosis in the General Population in the Netherlands, 1996–2008. Neuroepidemiology 2012;39(2):96–102.

13. Ahlgren C, Odén A, Lycke J: High Nationwide Incidence of Multiple Sclerosis in Sweden. PLOS One. 2014;9(9):e108599.

14. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J: Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry 2014;85(1):76–84.

15. Simonsen CS, Edland A, Berg-Hansen P, Celius EG: High prevalence and increasing incidence of multiple sclerosis in the Norwegian county of Buskerud. Acta Neurol Scand 2017;135(4):412–8.

16. O'Connell K, Tubridy N, Hutchinson M, McGuigan C: Incidence of multiple sclerosis in the Republic of Ireland: A prospective population-based study. Mult Scler Relat Disord 2017;13:75–80.

17. Brola W, Sobolewski P, Flaga S, Fudala M, Szczuchniak W, Stoiński J, et al: Prevalence and incidence of multiple sclerosis in central Poland, 2010–2014. BMC Neurol 2016;16(1):134.

18. Grytten N, Aarseth JH, Lunde HMB, Myhr KM: A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. J Neurol Neurosurg Psychiatry 2016;87(1):100–5.

19. Otero-Romero S, Ramió-Torrentà L, Pericot I, Carmona O, Perkal H, Saiz A, et al: Onset-adjusted incidence of multiple sclerosis in the Girona province (Spain): Evidence of increasing risk in the south of Europe. J Neurol Sci 2015;359(1):146–50.

20. Solaro C, Ponzio M, Moran E, Tanganelli P, Pizio R, Ribizzi G, et al: The changing face of multiple sclerosis: Prevalence and incidence in an aging population. Mult Scler 2015;21(10):1244-50

21. Izquierdo G, Venegas A, Sanabria C, Navarro G: Long-term epidemiology of multiple sclerosis in the Northern Seville District. Acta Neurol Scand 2015;132(2):111–7.

22. Yaouanq J, Tron I, Kerbrat A, Leray E, Hamonic S, Merienne M, et al: Register-based incidence of multiple sclerosis in Brittany (north-western France), 2000–2001. Acta Neurol Scand 2015;131(5):321–8.

23. Pugliatti M, Rosati G, Carton H, Riise T, Drulovic J, Vécsei L, et al: The epidemiology of multiple sclerosis in Europe. Eur J Neurol 2006;13(7):700–22.

24. Bezzini D, Battaglia MA: Multiple Sclerosis Epidemiology in Europe. Adv Exp Med Biol 2017;141–59.

25. Garbe E, Suling M, Kloss S, Lindemann C, Schmid U. Linkage of mother–baby pairs in the German Pharmacoepidemiological Research Database. Pharmacoepidemiol Drug Saf 2011;20(3):258–64.

26. Pigeot I, Ahrens W: Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf 2008;17(3):215–23.

27. German Society of Neurology Guideline: Diagnosis and therapy of multiple sclerosis. 2012. Available at: http://www.awmf.org/uploads/tx_szleitlinien/030-050l_S2e_Multiple_Sklerose_Diagnostik_Therapie_2014-08_abgelaufen.pdf

28. Daly L: Confidence limits made easy: interval estimation using a substitution method. Am J Epidemiol 1998; 15;147(8):783-90

29. Fay MP and Feuer EJ: Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med 1997;16(7):791-801.

30. Widdifield J, Ivers NM, Young J, Green D, Jaakkimainen L, Butt DA, et al: Development and validation of an administrative data algorithm to estimate the disease burden and epidemiology of multiple sclerosis in Ontario, Canada. Mult Scler 2015;21(8):1045-5

31. Lanes S, Brown JS, Haynes K, Pollack MF, Walker AM: Identifying health outcomes in healthcare databases. Pharmacoepidemiol Drug Saf 2015;24(10):1009–16.

Table 1 Characteristics of incident MS cases and MS incidence rates stratified by different case definitions and sex

	Case definition 1 (C1)	**Case definition 2 (C2)**	**Case definition 3 (C3)**
Total*			
MS cases, N	780	348	223
Mean age at diagnosis (SD)	44.3 (13.5)	40.6 (10.8)	40.1 (11.0)
Person years	4,099,696	4,099,909	4,099,971
Crude IR (95%-CI)	19.0 (17.7-20.4)	8.5 (7.6-9.4)	5.4 (4.8-6.2)
Standardized IR (95%-CI) for German population	21.8 (20.2-23.5)	10.1 (9.1-11.3)	6.6 (5.8-7.6)
Standardized IR (95%-CI) for European standard population	21.4 (19.8-23.1)	10.0 (8.9-11.2)	6.6 (5.7-7.6)
Women			
MS cases, N	515	249	161
Mean age at diagnosis (SD)	42.8 (12.8)	40.0 (10.9)	39.6 (11.1)
Person years	1,884,640	1,884,772	1,884,814
Crude IR (95%-CI)	27.3 (25.0-29.8)	13.2 (11.6-15.0)	8.5 (7.3-10.0)
Men			
MS cases, N	265	99	62
Mean age at diagnosis (SD)	47.2 (14.3)	42.1 (10.4)	41.2 (10.5)
Person years	2,215,056	2,215,137	2,215,157

Crude IR (95%-CI)	12.0 (10.6-13.5)	4.5 (3.6-5.4)	2.8 (2.2-3.6)

CI=Confidence interval; IR=Incidence rate; MS=Multiple sclerosis; SD=Standard deviation

*Note: All analyses were conducted based on a look-back period of 96 months (2004 to 2011) without MS diagnosis.

Table 2 Distribution of incident MS diagnoses by health care sector

	Case definition 1		**Case definition 2**		**Case definition 3**	
MS cases, N	780		348		223	
MS cases by setting	Inpatient (N=317) (100%)	Outpatient (N=463) (100%)	Inpatient (N=163) (100%)	Outpatient (N=185) (100%)	Inpatient (N=125) (100%)	Outpatient (N=98) (100%)
G35.0	188 (59.3)	94 (20.3)	102 (62.6)	48 (26.0)	82 (65.6)	22 (22.5)
G35.1	66 (20.8)	126 (27.2)	43 (26.4)	65 (35.1)	31 (24.8)	37 (37.8)
G35.2	19 (6.0)	23 (5.0)	3 (1.8)	3 (1.6)	3 (2.4)	1 (1.0)
G35.3	2 (0.6)	10 (2.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
G35.9	42 (13.3)	210 (45.4)	14 (8.6)	69 (37.3)	9 (7.2)	38 (38.8)

MS=Multiple sclerosis

G35.0 Initial manifestation; G35.1 Relapsing-remitting; G35.2 Primary progressive; G35.3 Secondary progressive; G35.9 Without further specification

*Note: All analyses were conducted based on look-back period of 96 months without MS diagnosis of 96 months (2004 to 2011).

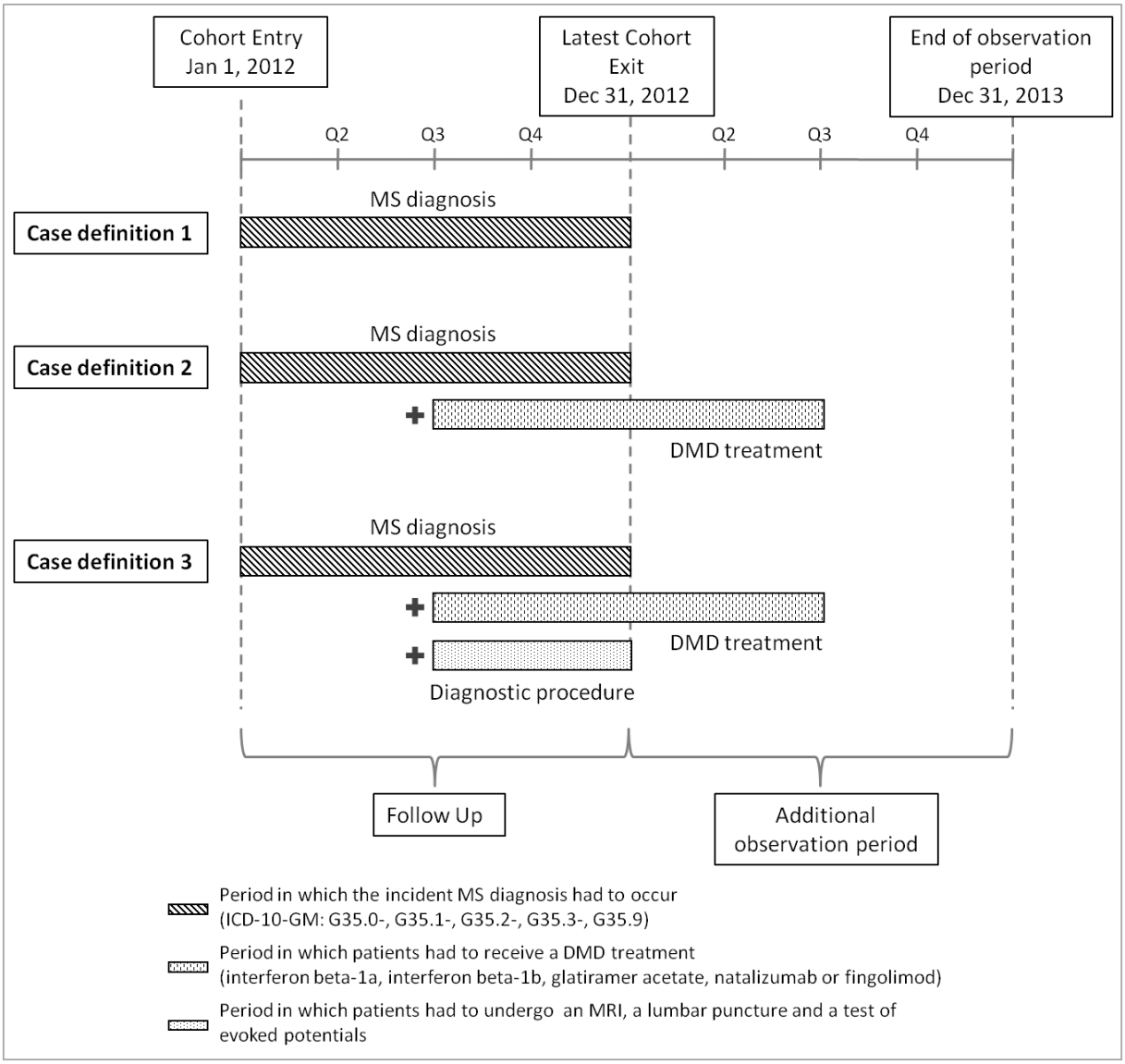

Figure 1 Case definitions for the identification of incident MS cases

DMD: Disease-modifying drug; ICD-10-GM: International Classification of Diseases, German Modification; MRI: Magnetic resonance imaging

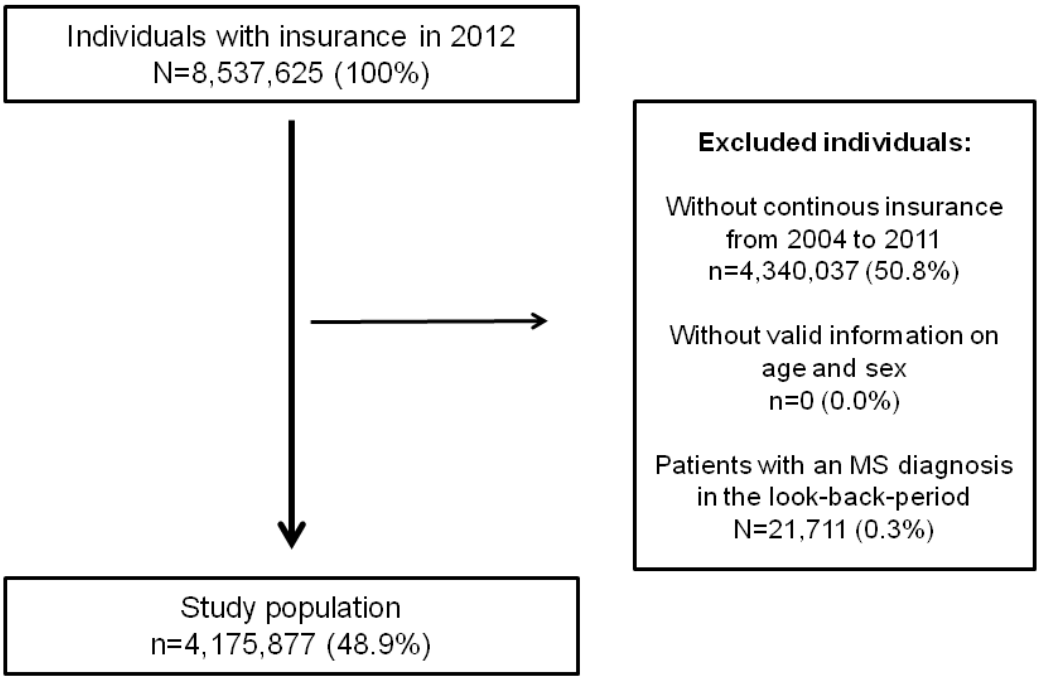

Figure 2 Study flow chart

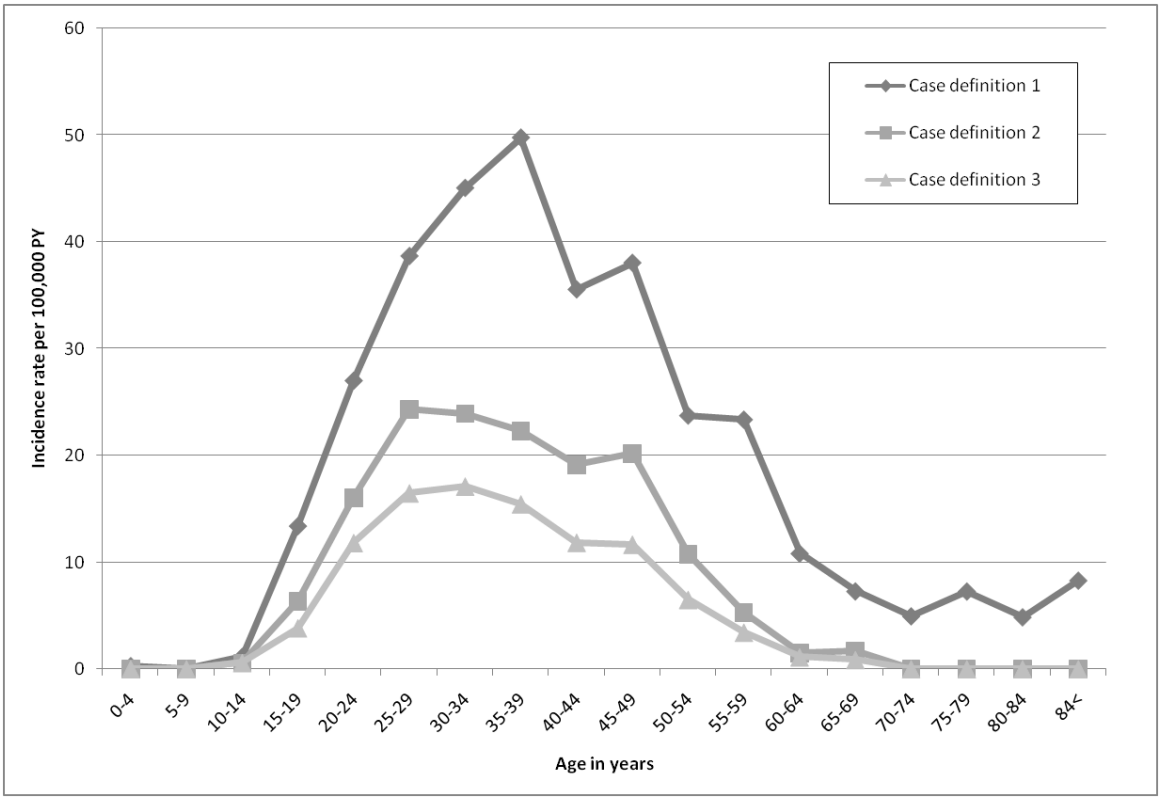

Figure 3 Age-specific MS incidence rates by case definition

PY=Person years

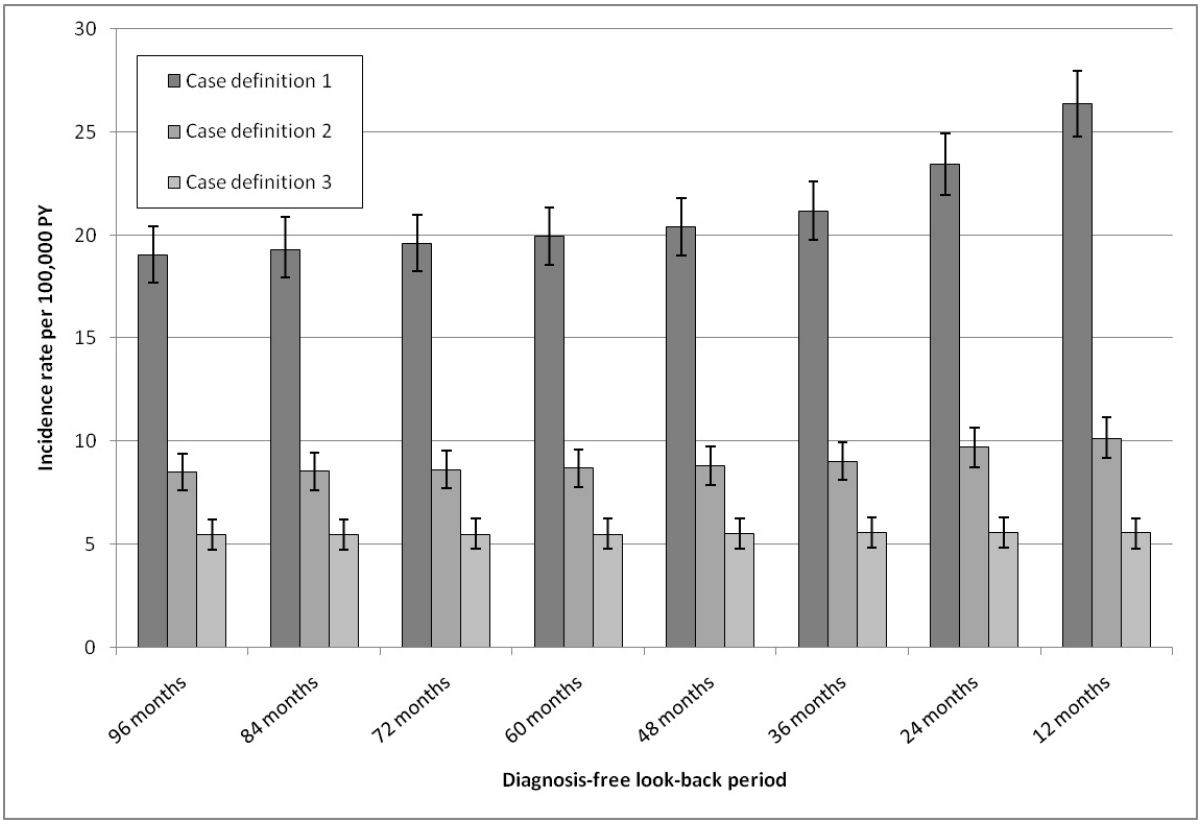

Figure 4 Comparison of MS incidence rates for all case definitions stratified by required look-back period without MS diagnosis

PY=Person years