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Falling incidence of Parkinson's disease in Germany

Running title: Falling incidence of Parkinson's disease

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Abstract

Background

Idiopathic Parkinson´s disease (IPD) is a progressive neurodegenerative disorder that is strongly associated with age. The aim of the present study was to describe current sex- and age-specific trends and regional differences in the incidence of diagnosed IPD in older people in Germany.

Methods

This study was based on nationwide outpatient claims and drug prescription data of the German Statutory Health Insurance, covering roughly 87% of the general population. We conducted a cohort study in patients aged 50 years or older with observation time of at least four years. To assess the robustness of nation-wide annual IPD incidence trends from 2013 to 2019 three case definitions with varying levels of stringency regarding coded outpatient diagnoses and drug prescriptions were applied.

Results

In 2019, the population at risk comprised 30,575,726 persons. Using the primary and most specific case definition, annual age- and sex-standardised cumulative IPD incidence decreased stepwise from 137 (2013) to 106 (2019) new cases per 100,000 persons. The decline in incidence was seen in both sexes, in all age groups and in the majority of German regions. The relative decrease (2013-2019) in the annual age- and sex-standardised IPD incidence varied from 23% to 28% between case definitions.

Conclusion

Our findings indicate a nationwide decline in the age- and sex-standardised IPD incidence from 2013 to 2019 in Germany. This trend was consistent using different case definitions. Further research is needed to elucidate underlying factors of this trend.

Introduction

Idiopathic Parkinson´s disease (IPD) is a progressive neurodegenerative disorder associated with increased disability. The cardinal features are tremor, muscle stiffness, slowness of movement and impaired balance [1]. Other recognised IPD-related features include sleep disorders, constipation and postural hypotension as well as non-specific pain [2] mood disorders, dementia and neuropsychiatric complications[3,4]. Due to multifaceted clinical presentations, highly variable patterns of disease progression and a high comorbidity burden, clinical management of IPD patients is complex and requires a multidisciplinary approach [2]. There is no cure for IPD but medication can reduce motor and non-motor symptoms [5]. Men are at higher risk for IPD than women [6], and IPD primarily affects those aged 60 years or older [4,7]. Due to demographic ageing, particularly in western industrialized countries, the number of affected patients has more than doubled worldwide over the past generation [8] and is projected to further increase substantially [9,10].

For Germany, the pooled crude prevalence of IPD and secondary parkinsonism was estimated to amount to 588 patients per 100,000 persons in the year 2015 over all age groups [7]. In view of the aging population of Germany, a further increase in the number of patients with IPD was projected [9-11]. However, findings from a previous claims-based study showed a slight decline of the pooled prevalence of IPD and secondary parkinsonism from 560 patients per 100,000 persons in 2015 to 530 in 2019 at the national level [4]. This moderate downward trend was mostly driven by a decreasing prevalence in women, as the crude prevalence in women fell by 7.5% from 528 per 100,000 persons in 2015 to 488 in 2019 [4].

The decrease in prevalence may reflect a decline in the annual number of incident cases but other factors such mortality also contribute to prevalence rates. Incidence rates are therefore a better indicator of disease occurrence. Previous German studies reported standardised incidence rates between 192 and 229 new cases in 100,000 persons aged 50 years or older in 2010 [12] and 84.1 new cases per 100,000 persons of all ages in 2015 [7] but did not report trends. European studies that assessed trends in incidence rates over extended time periods during the last decade mostly found stable age and sex standardised rates [13-15]. So far, potential temporal changes in IPD incidence in Germany have not been investigated. Current and reliable epidemiological data on IPD incidence may inform projection of future societal costs and guide health policy decisions with regard to the allocation of resources and may provide clues to change in risk factors.

The aim of this study was to estimate sex and age-specific trends in the incidence of IPD in Germany in the years 2013 to 2019, using nationwide outpatient claims data containing information for all statutory health insurees in Germany (SHI).

Methods

Study design

We used pseudonymized nationwide outpatient claims data according to § 295 and drug prescription data according to § 300 of the German Code of Social Law (Fünftes Sozialgesetzbuch, SGB V) from the years 2010 to 2019, covering roughly 87% of the total German population in the age group 50 years or older in 2019. The different data sources were linked using pseudonymized patient identifiers. The linked dataset contains sociodemographic information such as age, sex and region of residence (Associations of Statutory Health Insurance Physicians, N=17), information on outpatient drug prescriptions and diagnoses coded according to the German modification of the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10-GM). The occurrence of newly diagnosed IPD was assessed in patients 50 years or older, for whom data were present for a minimum period of four years, i.e., in the reporting year and in three or more previous years as

indicated by at least one outpatient visits in both the reporting year and three years before the index year or earlier. The number of patients with at least four years of observation time amounted to 26,008,604 in 2013 and to 31,046,885 in 2019 (fig 1). In Germany, the use of claims data for scientific research is regulated by the Code of Social Law (SGB X). Ethical approval and informed consent are not required as this study used routinely collected pseudonymized data.

Case definition

The population at risk for the occurrence of IPD in each year included all patients without a IPD diagnosis during the preceding three years. For ascertainment of cases the diagnosis code G20 ("Primary Parkinson's syndrome") coded with the additional indicator "confirmed" according to the ICD-10-GM was used. Assigning a diagnostic modifier ("confirmed", "suspected", "excluded", "status post") is mandatory in outpatient care in Germany. To assess the robustness of nation-wide incidence trends three case definitions with varying levels of stringency were defined.

(1) Code of IPD diagnosis with the diagnostic modifier "confirmed" in at least two quarters of a patient-specific time period of four quarters starting with the first quarter of diagnosis, with at least one antiparkinsonian drug prescription (ATC code: N04) during the patient-specific time period used for ascertainment of diagnosis. This primary case definition presents the strictest set of criteria and was used for detailed assessment of annual cumulative incidence by age, sex and region.

(2) Code of IPD diagnosis with the diagnostic modifier "confirmed" in at least two quarters of a patient specific time period of four quarters starting with the first quarter of diagnosis.

(3) At least one code of IPD diagnosis with the diagnostic modifier "confirmed" and at least one antiparkinsonian drug prescription in the same quarter.

Statistical Analysis

For case definitions 1 and 2 a sufficiently long follow-up period was not available for the year 2019. Case numbers for 2019 were estimated based on years with sufficient follow-up (2013 to 2018) using the mean annual positive predictive values (ppv) of a first IPD diagnosis for incident disease according to the respective case definition. Ppv were calculated as the average annual proportion of patients with a first IPD diagnosis that fulfilled the respective case definition. Incident cases in 2019 were extrapolated based on first diagnoses in 2019 using age-group- and sex-specific ppv. The annual cumulative incidence of IPD was assessed per 100,000 insured persons at risk by sex, age group and at the level of the Associations of Statutory Health Insurance Physicians (ASHIP, N=17 regions). IPD incidence was directly age- and sex-standardised using the age and sex structure of all statutorily health insured individuals in the age range 50 years and older in 2013 as reference population [16].

Incidence of related disorders

To assess if possible changes in Incidence of diagnosed IPD over time may have resulted from changes in coding practices by German outpatient physicians for, complementary exploratory analyses were conducted. For this purpose, trends in age- and sex-standardised incidence were compared between single 3-digit ICD-10-GM codes in the disease group extrapyramidal and movement disorders (ICD-code-range: G20-G26). In accordance with case definition 2 used to assess IPD incidence based on the diagnostic code G20, incident cases were counted for each of the six remaining 3-digit-codes.

Thus, patients were included as incident cases per 3-digits ICD codes in the year they received a first diagnosis followed by at least one additional diagnosis in the following three quarters. Annual age- and sex-standardised incidence was calculated for each 3-digits ICD code from 2013 to 2019. Absolute changes in incidence between 2013 and 2019 were compared across 3-digits-code.

Results

The size of the study population ranged from 26 million in 2013 to 31 million in 2019 (fig. 1). In each year, approximately 2% of these SHI-insured patients aged 50 and older were excluded from the population at risk due to a IPD diagnosis in the pre-observation period (fig 1). The absolute number of incident IPD cases in 2013 was 38,168 for case definition 1, 51,101 for case definition 2 and 40,063 for case definition 3 (fig 1). In 2019, the absolute number of incident IPD cases amounted to 34,101, 42,648 and 35,894 for case definitions 1 to 3, respectively (fig 1). Median age of patients with incident IPD according to primary case definition 1 was 77 years in 2013 (inter quartile range, IQR: 72-83) and 78 years (IQR: 71-83) in 2019. In 2013, 51.2% of patients with incident IPD according to primary case definition were male. This percentage increased gradually over the years and amounted to 54.8% in 2019.

[Please insert figure 1 here]

Figure 1. Annual size of the population of patients with observation time of at least 4 years, the population at risk for incident idiopathic Parkinson's disease and absolute numbers of incident cases for three case definitions in the age group 50 years and older from 2013 to 2019.

CD= Case definition

CD1= Code of IPD diagnosis with the diagnostic modifier "confirmed" in at least two quarters of a patient-specific time period of 4 quarters starting with the first quarter of diagnosis, with at least one antiparkinsonian drug prescription (ATC code: N04) during the patient-specific time period used for ascertainment of diagnosis.

CD2= Code of IPD diagnosis with the diagnostic modifier "confirmed" in at least two quarters of a patient specific time period of 4 quarters starting with the first quarter of diagnosis

CD3= At least one code of IPD diagnosis with the diagnostic modifier "confirmed" and at least one antiparkinsonian drug prescription in the same quarter

Using the primary case definition, annual age- and sex-standardised IPD incidence decreased by 23% from 137 (2013) to 106 (2019) new cases per 100,000 persons (fig 2). Regardless of the case definition used, there was a stepwise decline in the annual cumulative incidence over the course of the study (fig 2). Between the years 2013 and 2019, the relative decrease in annual standardised IPD incidence amounted to 28% for case definition 2 and to 23% for case definition 3 (fig 2). In comparison to the primary case definition, the average annual incidence of case definitions 2 and 3) were 29% and 4% higher throughout the observation period, respectively (fig 2).

[Please insert figure 2 here]

Figure 2: Annual age- and sex-standardised cumulative incidence of diagnosed idiopathic Parkinson's disease for three case definitions per 100,000 insured persons aged 50 years and older from 2013 to 2019.

Case definition 1= Code of IPD diagnosis with the diagnostic modifier "confirmed" in at least two quarters of a patient-specific time period of 4 quarters starting with the first quarter of diagnosis, with at least one antiparkinsonian drug prescription (ATC code: N04) during the patient-specific time period used for ascertainment of diagnosis.

Case definition 2= Code of IPD diagnosis with the diagnostic modifier "confirmed" in at least two quarters of a patient specific time period of 4 quarters starting with the first quarter of diagnosis

Case definition 3= At least one code of IPD diagnosis with the diagnostic modifier "confirmed" and at least one antiparkinsonian drug prescription in the same quarter

Over time, decreases in incidence of IPD according to the primary case definition were observed in all age groups for both women and men (fig 3). Relative reductions between 2013 and 2019 varied from 19% (50-54 years) to 41% (≥90 years) in women and from 16% (75-79 years) to 29% (≥90 years) in men (fig 3). In 2019, relative risk (RR) of incident IPD in men compared to women was lowest in the age group 50-54 years (RR= 1.6) and highest in the age group ≥=90 years (RR=1.9, data not shown).
In 2019, age- and sex-standardised IPD incidence varied regionally by a factor of 1.5 between Baden-Wuerttemberg, the region with the lowest incidence (87 new cases per 100,000 persons), and Saarland, the region with the highest incidence (127) (fig 4). Between 2013 and 2019 IPD incidence decreased in all German regions and the majority of regions showed a gradually decreasing trend (fig 4).

[Please insert figure 3 here]

Figure 3. Annual cumulative incidence of diagnosed idiopathic Parkinson's disease per 100,000 persons by age group and sex in 2013 and 2019.

New cases were defined as IPD diagnoses in at least two quarters coded with the diagnostic modifier "confirmed" in a patient specific time period of 4 quarters starting with the first quarter with a diagnosis in the reporting year plus at least one antiparkinsonian drug prescription (ATC code: N04) during the patient individual time period used for ascertainment of diagnoses

[Please insert figure 4 here]

Figure 4: Annual age- and sex-standardised cumulative incidence of diagnosed idiopathic Parkinson's disease per 100,000 persons at the level of regional Association of Statutory Health Insurance Physicians (N=17 regions) from 2013 to 2019.

New cases were defined as IPD diagnoses in at least two quarters coded with the diagnostic modifier "confirmed" in a patient specific time period of 4 quarters starting with the first quarter with a diagnosis in the reporting year plus at least one antiparkinsonian drug prescription (ATC code: N04) during the patient individual time period used for ascertainment of diagnoses.

BB, Brandenburg; BE, Berlin; BW, Baden-Wuerttemberg; BY, Bavaria; HB, Bremen; HE, Hesse; HH, Hamburg; MV, Mecklenburg-Western Pomerania; NI, Lower Saxony; NO, North Rhine; RP, Rhineland-Palatinate; SH, Schleswig-Holstein; SL, Saarland; SN, Saxony; ST, Saxony-Anhalt; TH, Thuringia; WL, Westphalia-Lippe

Figure 5 depicts annual age- and sex-standardised Incidence of diagnosed IPD for each 3-digit ICD-10-GM code in the disease group extrapyramidal and movement disorders. The annual incidence for the 3-digit code G20 is the cumulative incidence of diagnosed idiopathic Parkinson's disease according to case definition 2 shown in figure 2. Standardised cumulative incidence per 3-digit code in 2019 varied between 0.45 (G26) and 310 (G25) cases per 100,000 persons (fig 5). By far the strongest absolute risk decrease was observed for G20, which showed a reduction by 51 newly diagnosed cases per 100,000 persons in 2019 in contrast to 2013. Only the 3-digit ICD code G23 showed an absolute increase of the

standardised incidence from 2013 to 2019, amounting to four additional newly diagnosed cases per 100,000 persons (fig 5).

[Please insert figure 5 here]

Figure 5: A) Annual age- and sex-standardised cumulative diagnosis incidence of 3-digits ICD-10-GM codes in the disease group extrapyramidal and movement disorders (ICD-code-range: G20-G26) per 100,000 insured persons aged 50 years and older from 2013 to 2019 and B) corresponding absolute differences of standardised cumulative incidence per 100,000 persons between the years 2013 and 2019.

G20 – Primary Parkinson's syndrome, G21 - Secondary parkinsonism, G22 - Parkinsonism in diseases classified elsewhere, G24 – Dystonia, G25 – Other extrapyramidal and movement disorders, G26 - Extrapyramidal and movement disorders in diseases classified elsewhere

New cases per 3-digits ICD code were defined as diagnoses in at least two quarters coded with the diagnostic modifier "confirmed" in a patient specific time period of 4 quarters starting with the first quarter with a diagnosis in the reporting year.

*The annual standardised incidence of the 3-digits ICD-10-GM code G20 equates to the incidence of diagnosed idiopathic Parkinson's disease according to case definition 2 depicted in figure 2.

Discussion

The present study is first to examine trends in IPD incidence over an extended time period in the German SHI population, covering about 87% of the total population in 2019. Between 2013 and 2019, the age- and sex-standardised IPD incidence in patients at age 50 years and older decreased by 23% to 28%, depending on the case definition used. The decline in incidence was seen in both sexes, in all age groups 50 years and older and in almost all German regions.

In agreement with these observed decreasing trend in IPD incidence, Bohlken et al. found a declining number of newly diagnosed IPD patients between 2010 and 2019 using a panel of about 2,500 German SHI-physicians' practices [17]. In the UK, Schrag et al also found a subtle decline in incidence of PD between 2006 and 2016 although this was not consistently different to the baseline year [15]. Compared to findings from other international studies, the decreasing IPD risk found in Germany is however an unexpected finding. The clear decline in incidence of IPD found in this large, representative study, contributes information to a controversial area. Globally, crude IPD incidence is expected to increase further due to population aging. Furthermore, Savica et al. showed a substantial increase in the age-standardised IPD incidence among men in a US cohort study from 38.8 cases per 100,000 person-years in the decade 1976-1985 to 56.0 in the decade 1996-2005 [18]. Analysis of data from the Global Burden of Disease studies indicate that the majority of countries exhibited an increasing trend in IPD incidence between the years 1990 and 2019, even when standardised for populations' age structure and regardless of the industrial development stage [19]. However, this examination of long-term trends is based on a comparison of cross-sectional estimates for the years 1990 and 2019 [20] and does not allow conclusions about the time-dependent dynamics of the IPD incidence in recent years.

Few European studies have investigated trends in IPD incidence over a comparably recent observation period as the present study. Of these, the majority found stable values of IPD incidence over time [13-15]. Canonico et al. examined the incidence of IPD in French women aged 40 years and older in a cohort study from 1998 to 2018 and found a stagnating incidence rate over the period from 2002 to 2018 [13]. Brakedal et al. examined pharmaceutical sales data from individuals 30 years of age and older from

2004 to 2017 in Norway [14]. No general time-trend in the incidence of PD was observed and the average annual incidence in females and males amounted to 23 and 30 cases per 100,000 person-years, respectively [14]. Okunoye et al. conducted a population based study of electronic health records of UK residents 50 years of age and older to assess IPD incidence trends between the years 2006 to 2016 using different case definitions [15]. The observed annual incidence rate showed a stable or moderately declining trend over time, depending on the case definition used [15]. To our knowledge, a clearly decreasing trend in IPD incidence in Europe has previously only been shown in the Rotterdam study, a Dutch cohort study among residents 50 years or older [21]. In this study a sharp decline of the age- and sex-adjusted IPD incidence was observed in study participants with a study entry in the year 2000 in contrast to those with a study entry in 1990 (Rate Ratio: 0.39, 95-%-CI: 0.19-0.72). An assessment of suspected risk factors on the individual level yielded no obvious explanation for the observed trend [21]. Previous studies outside of Europe commonly reported stable [22,23] or increasing trends [18,24,25] in age standardised IPD incidence rates. This increase in incidence of IPD may at least in part be due to changes in diagnostic recognition of a condition that is still often underdiagnosed. Some studies also found decreases in IPD incidence over time [26,27]. Wong et al. analyzed administrative health data of people 20 years or older for the years 1996 to 2014 from Ontario, Canada. They recorded a decrease in the age standardised incidence of 13% over 18 years [26]. Hugh-Jones et al. examined inpatient hospital data from 1999 to 2012 from Louisiana, USA [27,28]. They reported a RR of PD of 0.66 for Louisiana residents with a cohort entry in the years 2006-2012 compared to those with study entry in the years 1999-2005 [27,28]. In Louisiana, Hugh-Jones et al. observed associations of the decreasing trend in IPD risk and temporal changes in quantity and quality of agricultural utilisation of pesticides. Positive associations of PD risk and rural living, farming and pesticide use have been reported frequently [29,30]. Also in Germany, a rural-urban gradient in PD prevalence was recently reported [4]. Future studies should investigate changes in the use of agroindustrial pesticides in Germany as potential explanatory factor for the observed changes in IPD risk

When defining case definitions for the ascertainment of incident disease in claims data, a trade-off inevitably arises between the intention to comprehensively record all patients with emerging diseases while excluding false positive cases [31]. In the context of IPD, it is important to note that due to a lack of definitive diagnostic tests, diagnoses are mostly made clinically, which is associated with an increased potential for diagnostic inaccuracies. For instance, the additional requirement for a Parkinson's disease-specific drug therapy in addition to diagnostic codes applied in our own study increases the ppv, but may lead to underreporting of mild cases with no compelling indication for drug therapy yet [32]. The same applies to patients who refuse drug therapy at the onset of disease or who discontinue medication shortly after initiation of therapy, e. g. due to side effects. Nevertheless, in the present study all case definitions, which featured varying levels of stringency, point to a decline in IPD incidence. It is worth highlighting that all age groups in both sexes between 2013 and 2019 showed relevant incidence reductions ranging from 16% (men, 75-79 years) to 41% (women, ≥90 years). Consistent with the trend at the national level, a unified pattern of a gradual reduction in incidence was mirrored in almost all regions and emphasizes the nationwide character of the observed trend.

Due to a lack of definitive diagnostic tests for IPD it is conceivable, that the diagnosis of IPD and related disorders exhibits an increased likelihood of changes over time concerning physician´s diagnostic coding practices, which may affect Incidence of diagnosed IPD using administrative data. We analysed if changes in trends in diagnosis incidence of related disorders occurred contemporaneous to the decreasing Incidence of diagnosed IPD by assessing incidence of 3-digit ICD-10-GM codes in the disease group extrapyramidal and movement disorders. There was no indication of an obvious diagnosis shift as the 3-digit ICD code G20 showed by far the strongest absolute incidence reduction between 2013

and 2019 and only the code G23 exhbited a slight absolute increase in incidence. This study has limitations. IPD incidence was estimated based on diagnoses documented by SHI-physicians as justification for the provision of medical services and the prescription of drugs. Patients with IPD onset without an outpatient visit were not captured in the dataset. Furthermore, the data did not contain information on inpatient diagnoses. Our study used an uniform disease-free interval of three years for the estimation of annual IPD incidence. A former study showed an inverse relationship of the degree of overestimation of disease incidence and the length of disease-free intervals applied [33]. IPD is a chronic disease with a usually high need for outpatient services. Hence, we assume that the degree of overestimation of annual IPD incidence due to false ascertainment of prevalent patients as incident cases to be moderate and most likely independent of time over the study period. A further limitation of the data arises from the fact that a proportion of patients are cared for under selective contracts in IPD networks, which are concluded directly between health insurance funds and service providers. These care data are not included in the SHI claims data used.

Conclusion

Incidence of diagnosed IPD in German residents over 50 years of age or older displayed a clear declining trend. This trend was robust to variable criteria of different case definitions. Further research is required to elucidate underlying factors of this trend and to inform future preventional strategies.

Author contributions

JHO conceived the study and was primarily responsible for study design and data analysis. LD was involved in further developing the study design and statistical analysis and wrote the manuscript's first draft. AS, CK, JBAE, JBO, JHE, JHO, JS and MKA critically reviewed the manuscript and were involved in interpretation of results. MKA visualised the results. JHO and JB supervised the project. All authors read and approved the final version of the manuscript and gave final consent for publication.

Conflict of interest

The authors reported no financial interests or potential conflicts of interest related to this study.

Ethics approval and informed consent

The use of claims data for scientific research is regulated by the German Code of Social Law (Fünftes Sozialgesetzbuch, SGB V). An ethical approval and informed consent are not required as this study used routinely collected anonymized data. The research was conducted in accordance with the Helsinki Declaration (in its current revised form: 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
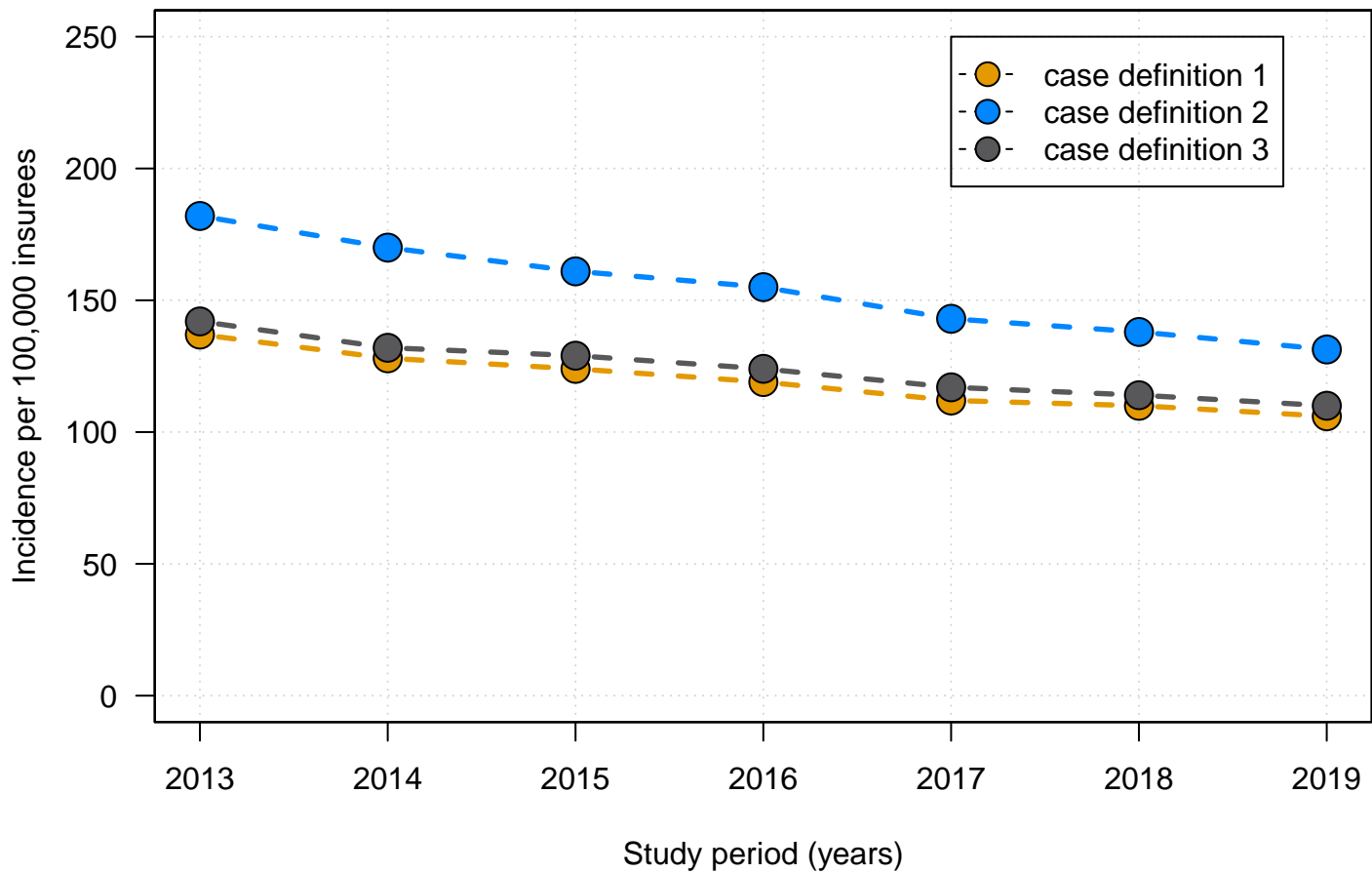
Availability of data and materials

The datasets analysed during the current study are not publicly available due to data protection regulations by the German Code of Social Law (Fünftes Sozialgesetzbuch, SGB V).
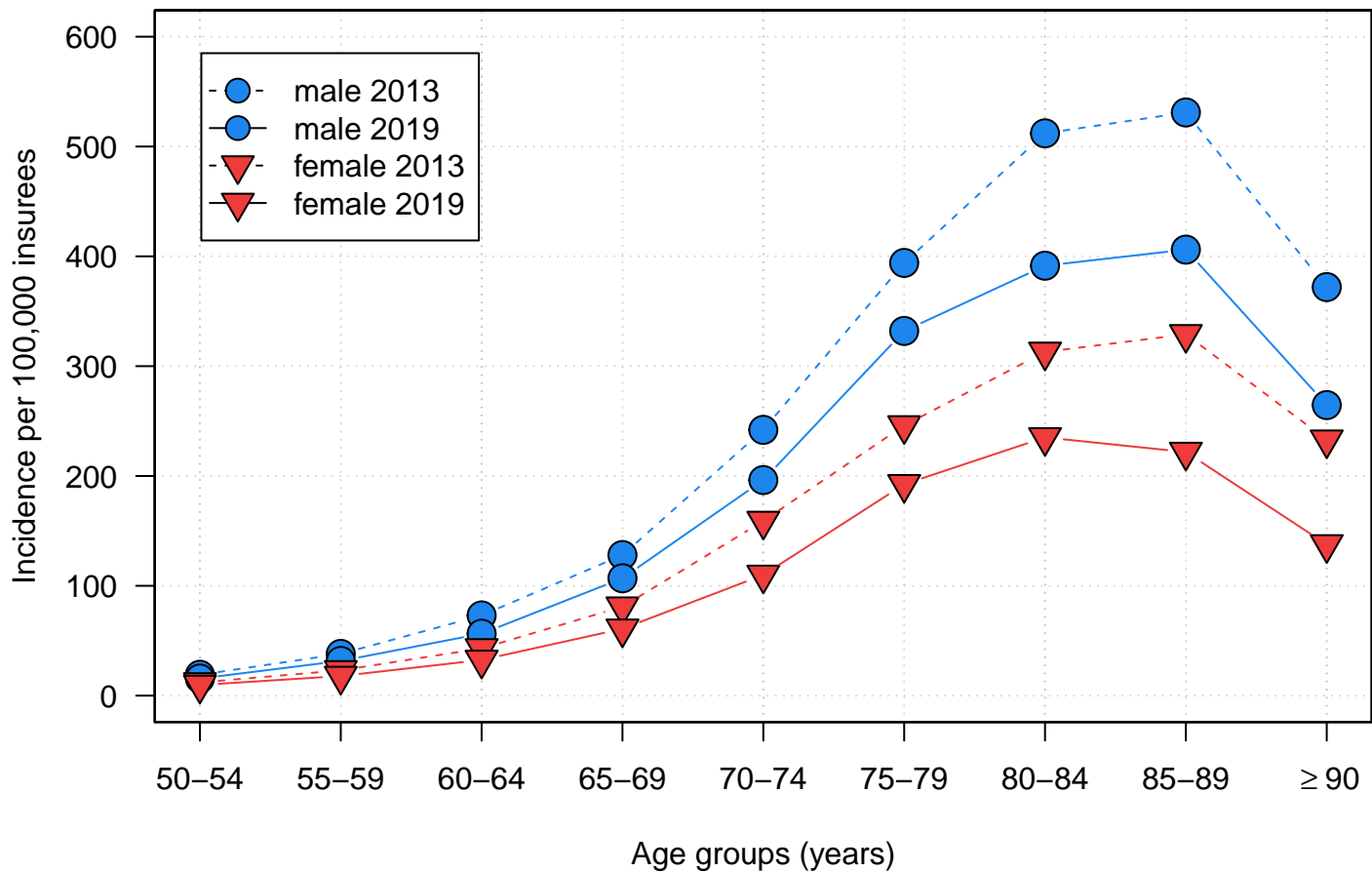
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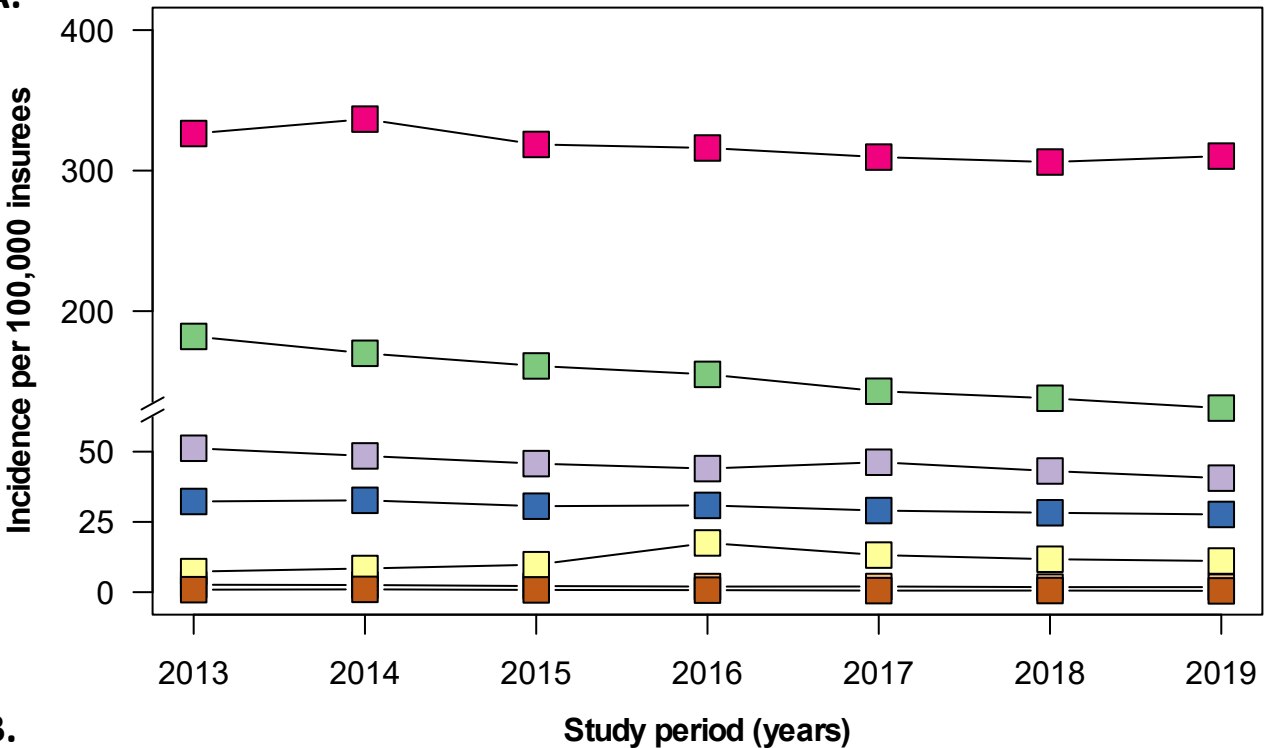
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	2013	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Patients with observation time of ≥4 years, N	26,008,604	27,706,643	28,982,697	29,695,661	30,225,461	30,712,055	31,046,885
Population at risk, n	25,630,941	27,295,754	28,544,166	29,243,309	29,760,786	30,241,805	30,575,726
Incident cases, n	CD1: 38,168 CD2: 51,101 CD3: 40,063	CD1: 37,422 CD2: 50,354 CD3: 39,165	CD1: 37,641 CD2: 49,456 CD3: 39,611	CD1: 36,842 CD2: 48,331 CD3: 38,736	CD1: 35,160 CD2: 45,405 CD3: 37,169	CD1: 34,863 CD2: 44,001 CD3: 36,707	CD1: 34,101 CD2: 42,648 CD3: 35,894

A.

B.

- ■ G20* (parkinson disease)
- ■ G21 (secondary parkinsonism)
- ■ G22 (parkinsonism in other diseases)
- ■ G23 (other degenerative diseases of basal ganglia)
- ■ G24 (dystonia)
- ■ G25 (other extrapyramidal and movement disorders)
- ■ G26 (extrapyramidal and movement disorders in other diseases)