Stability of individual dementia diagnoses in routine care: Implications for epidemiological studies

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Abstract

Purpose: Epidemiological and health care research frequently rely on diagnoses from routine care, but the intra-individual stability of diagnoses of Alzheimer’s disease (AD), vascular dementia (VD) or other forms of dementia (oD) in patients over time is understudied. More data on the diagnostic stability is needed to appraise epidemiological findings from such studies.

Methods: Using health claims data of the years 2004–2016 from the German Pharmacoepidemiological Research Database, 160 273 patients aged ≥50 with incident dementia were identified and followed for 4 years. According to the incident ICD-10 codes patients were assigned to the categories AD, VD or oD. Changes between categories during follow-up were calculated.

Results: Overall, 18.8% had incident AD (VD: 21.5%, oD: 59.7%). Fifteen thousand eight hundred forty-two patients had only one dementia diagnosis during 4 years (AD: 7.4%, VD: 12.4%, oD: 9.8%). Among those with more than one diagnosis, the incident diagnosis matched the last diagnosis in 65.1% (AD), 53.9% (VD) and 73.8% (oD) of patients. Changes in the diagnostic category were higher in patients with AD (mean: 5.1) than in patients with VD (3.6) or oD (3.3). Patients with stable AD diagnoses during the observation period were younger (median: 76 vs. 79 years) and had less inpatient treatment days (median: 14 days) than patients with changes from an AD diagnosis to another category or from another category to AD (27 days).

Conclusions: While health claims data are feasible for estimating the incidence of dementia in general, the substantial number of changes in dementia diagnoses during the course of the disease warrant caution on the interpretation of epidemiological data on specific dementia types.

Keywords
Alzheimer’s dementia, dementia, epidemiology, GePaRD, health care research, health claims data

Key Points
- How frequently dementia diagnoses in epidemiologic studies change in routine care data, and thus potentially change interpretability of results, is still understudied. We therefore
investigated the intra-individual diagnostic stability of such diagnoses in health claims data over 4 years.

- We found that, depending on the type of dementia, the first and last diagnosis were concordant in between 53.9% and 73.8% of patients – which means that in up to 46.1% of all patients the diagnosis was changed at least once, with a mean number of changes between 3 and 5.
- Although potentially applicable, dementia-specific interpretations of routine care data warrant caution.

**1 | INTRODUCTION**

Dementias rank top among neurodegenerative diseases with an estimated prevalence of 15% beyond the age of 70 years. In addition to the personal burden they also put a substantial burden on society. Patients with dementia have been found to have a markedly increased risk of mortality, with a median survival time of 3–4 years after disease onset as well as an increased risk of institutionalization as compared with age- and sex-matched controls. However, most of these studies have assessed dementia as a group of diseases rather than distinguishing between single entities such as Alzheimer’s disease (AD), vascular dementia (VD) or other dementias (oD). Consequently, the stability of more specific dementia diagnoses in individual patients over time is understudied. Such data would be helpful to appraise findings from other epidemiological studies, which categorize patients on the basis of a single (either prevalent or incident) diagnosis or two successive diagnoses with a short time interval between them. Thus, potential changes in diagnoses during the course of the disease, which could also have an impact on epidemiological estimators, are therefore usually not taken into account. So far, only one study has addressed this issue by assessing the coding practice of dementia in health claims data over time, revealing that 27% of patients with incident dementia diagnoses received two or more different dementia diagnoses within 1 year. Yet, these important findings were limited by a short observation period and a comparably small random sample of patients who were insured by a regional statutory health insurance (SHI) provider. Moreover, a more in-depth characterization of patients with stable and differing dementia diagnoses is still lacking.

Therefore, based on health claims data from a large sample representing 20% of the German population, the present study sought (1) to estimate the proportion of patients with incident diagnosis codes for AD, VD or oD, (2) to analyze changes in these individual diagnoses over time, and (3) to assess characteristics of patients whose dementia diagnoses as reported in claims records changed as compared to patients with stable diagnoses.

**2 | METHODS**

**2.1 | Data source**

This study was based on the German Pharmacoepidemiological Research Database (GePaRD) which comprises claims data from four SHI providers in Germany and currently includes information on approximately 25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensations including the anatomical-therapeutic-chemical (ATC) code and outpatient and inpatient services. Diagnoses are coded by physicians, according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision, German Modification (ICD-10-GM). Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented.

**2.2 | Study cohort**

To be eligible for the study cohort, participants had to be 50 years of age or older, had to be insured anytime between 2004 and 2016, and had to be diagnosed with AD (ICD-10 codes F00: “Dementia in Alzheimer disease” or G30: “Alzheimer disease”), VD (F01: “Vascular dementia”) or oD (F02: “Dementia in other diseases classified elsewhere”, F03: “Unspecified dementia”, or F05.1: “Delirium superimposed on dementia”) after at least 1 year without any coded dementia. Moreover, only persons who could be observed for at least 4 years after the incident diagnosis were included.

Participants entered the cohort if they had (a) at least one inpatient dementia diagnosis or (b) at least one outpatient diagnosis coded by a neurologist or (c) one outpatient diagnosis and another in- or outpatient diagnosis of the same dementia category within a time frame of 183 days. Date of cohort entry was the date of incident diagnosis. Persons with more than one incident dementia diagnosis at cohort entry, e.g., those diagnosed with AD and VD on the same day, were assigned to the dementia category according to the following hierarchy: AD > VD > oD, i.e., patients with incident AD and VD on the
same days or incident AD and oD on the same day were assigned to the AD category, patients with incident VD and oD on the same day were assigned to the VD category. Cohort exit was defined by the end of the observation period (i.e., 4 years after cohort entry).

2.3 | Definition of diagnostic stability

Upon cohort entry each patient was assigned to the dementia category AD, VD or oD as described above. A change in dementia category was counted if a patient was coded with a dementia diagnosis following assignment to a different dementia category, e.g., code F00 followed by F01 which corresponds to a change from AD to VD. Correspondingly, multiple diagnoses within the same category were considered as stable. Patients with an incident dementia diagnosis only and no further diagnoses in the observation period were not considered for the assessment of diagnostic stability.

2.4 | Study measures

Dementia as well as selected comorbidities from the Elixhauser measure were defined by the corresponding ICD-10 codes. Treatment with anti-dementia drugs was assessed based on the corresponding ATC codes and was assumed for patients who received at least one prescription of donepezil (ATC-Code N06DA02), galantamine (N06DA04), rivastigmine (N06DA03) or memantine (N06DX01) during their follow-up (2 or 4 years, respectively).

2.5 | Statistical analyses

To assess the stability of dementia diagnoses, the first (at cohort entry) and last available dementia diagnosis during 4 years after cohort entry were considered for each patient. The number of changes between dementia categories was recorded. For each dementia category, absolute numbers and percentages of patients with stable or differing dementia diagnoses were computed. Summary statistics consisted of counts, percentages, means, and quartiles, as appropriate. In order to assess the impact of survival time on the results, all analyses as presented in this manuscript were also conducted with a cohort of patients who could be observed for at least 2 years (see Tables S1 and S2, and Figure S1). Time to first change in dementia category was assessed in Kaplan–Meier curves. All statistical analyses were conducted using SAS statistical software version 9.4.

3 | RESULTS

3.1 | Characteristics of the study sample

Overall, 160 273 participants were included in the 4-year observation cohort (see Table 1). A total of 18.8% of them had an incident diagnosis code for AD, 21.5% had an incident diagnosis code for VD, and 59.7% for oD, respectively.

In all three dementia categories, there were more women than men (range: 62.2%–66.7%). Median age was similar in all dementia categories (range: 77–79 years). Among patients with incident diagnosis codes for AD, 9.8% had at least a diagnosis from another dementia category on the same day and thus were assigned based on the hierarchical rule (for VD: 3.5%). Irrespective of dementia category, the incident diagnosis code was either coded by a neurologist or a GP in more than half of all patients, and the most common comorbidity was essential (primary) hypertension affecting between 61.6% and 69.7% of all patients, followed by disorders of lipoprotein metabolism and other lipemias (39.1%–42.2%). Furthermore, between 24% and 25.2% of patients had diagnosis codes for depression. Overall, patients with incident diagnosis codes for VD suffered from diseases of the circulatory system at baseline more often than those with incident diagnosis codes for AD or oD, respectively. The cohort of the 2-year observation cohort comprised of 310 938 participants and had similar characteristics like participants in the 4-year observation cohort (see Tables S1 and S2 for further details).

3.2 | Diagnostic stability

Of 160 273 patients in the 4-year observation cohort for 15 842 was no further dementia diagnosis coded after their incident diagnosis. The proportion of patients with only one coded diagnosis was higher in patients with incident diagnosis codes for VD (12.4%) and lower in patients with incident diagnosis codes for oD (9.8%) or AD (7.4%), respectively. Thus, 144 431 patients with more than one dementia diagnosis were included in the analyses of diagnostic stability. Figure 1 shows the comparison of the incident and last recorded diagnoses of dementia, stratified by patients with incident diagnosis codes for AD, VD, and oD.

Depending on the incident diagnosis code for dementia, the last available dementia diagnoses matched the incident diagnoses in 73.8% (oD), 65.1% (AD) and 59.9% (VD) of patients. Of patients with incident diagnosis codes for AD or VD, 27.2% and 26.8%, respectively, had a diagnosis code for oD at the end of the observation period. The highest number of changes in diagnosis was found in patients with incident diagnosis code for AD as compared to patients with incident codes for VD or oD. Of patients with AD as incident and last diagnosis, 48.2% did not have changes in diagnosis in between (for VD and oD: 70.1% each, data not shown). Again, these figures were similar to those obtained from the 2-year observation cohort, with a proportion of 68.4% stable AD diagnoses, 67.8% stable VD diagnoses and 78% stable oD diagnoses (see Figure S1 for further details).

Figure 2 displays the time until first change in diagnosis for all three incident dementia categories. The first change occurred most rapidly in patients with incident codes for AD where 30% of patients had a different diagnosis after 350 days.
| TABLE 1 | Baseline sociodemographic and clinical characteristics of the 4-year observation cohort |
|------------------|---------------------------------|---------------------------------|------------------|
|                  | Incident diagnosis code for:    | AD (N = 30 184)                | VD (N = 34 387)  | oD (N = 95 702) |
| Male:Female ratio (%) | 35.6:64.4                      | 37.8:62.2                      | 33.3:66.7        |
| Age at cohort entry, years | 77                             | 78                             | 79               |
| Median             | Q1; Q3                          | 71; 82                         | 71; 83           | 72; 84          |
| Proportion of patients with more than one incident diagnosis code at cohort entry, N (%) | 2967 (9.8)                      | 1221 (3.5)                     | n/a             |
| Specialty of diagnosing physician, N (%) | Neurologist 9406 (31.2) | 6402 (18.6) | 11 922 (12.5) |
|                   | GPb 8139 (27.0)                | 11 133 (32.4)                 | 43 485 (45.4)   |
|                   | Neurosurgeon 7 (0.0)           | 12 (0.0)                      | 34 (0.0)         |
|                   | Psychiatrist 853 (2.8)         | 333 (1.0)                     | 512 (0.5)        |
|                   | Inpatient setting 4975 (16.5)  | 11 219 (32.6)                 | 24 103 (25.2)   |
|                   | Other 6504 (21.5)              | 5113 (14.9)                   | 14 848 (15.5)   |
| Inpatient treatment days | Median 0                       | 0                              | 0               |
|                     | Q1; Q3                          | 0; 0                           | 0; 6            |
| Comorbidities, N (%) | Diseases of the circulatory system: | I10: Essential (primary) hypertension 18 598 (61.6) | 23 985 (69.7) | 61 729 (64.5) |
|                     | I25: Chronic ischemic heart disease 6481 (21.5) | 9398 (27.3) | 22 408 (23.4) |
|                     | I50: Heart failure 3719 (12.3) | 5907 (17.2)                   | 16 162 (16.9)   |
|                     | I67: Other cerebrovascular diseases 3975 (13.2) | 5930 (17.2) | 11 732 (12.3) |
|                     | I83: Varicose veins of lower extremities 4332 (14.3) | 4944 (14.4) | 14 379 (15.0) |
|                     | I64: Stroke, not specified as hemorrhage or infarction 883 (2.9) | 2474 (7.2) | 3874 (4.0) |
|                     | I49: Other cardiac arrhythmias 3455 (11.4) | 4366 (12.7) | 11 209 (11.7) |
|                     | Endocrine, nutritional and metabolic diseases: | E11: Type 2 diabetes mellitus 5658 (18.7) | 8624 (25.1) | 20 122 (21.0) |
|                     | E14: Unspecified diabetes mellitus 3187 (10.6) | 4835 (14.1) | 11 928 (12.5) |
|                     | E78: Disorders of lipoprotein metabolism and other lipemias 12 744 (42.2) | 14 487 (42.1) | 37 425 (39.1) |
|                     | Diseases of the eye and adnexa: | H52: Disorders of refraction and accommodation 8487 (28.1) | 9712 (28.2) | 25 701 (26.9) |
|                     | Diseases of the musculoskeletal system and connective tissue: | M54: Dorsalgia 8754 (29.0) | 10 026 (29.2) | 27 363 (28.6) |
|                     | M17: Osteoarthritis of knee 5094 (16.9) | 6119 (17.8) | 16 891 (17.6) |
|                     | Mental and behavioral disorders: | F32: Depressive episode 7490 (24.8) | 8238 (24.0) | 24 104 (25.2) |
|                     | Diseases of the genitourinary system: | N40: Hyperplasia of prostate 3863 (12.8) | 4517 (13.1) | 11 094 (11.6) |

*a*Patients were assigned to a dementia category following the hierarchy AD > VD > oD.

*b*General practitioner.

*c*ICD-10 codes.

Abbreviations: AD, Alzheimer’s disease; oD, other dementias; VD, vascular dementia.
The same proportion was reached after 506 days in the VD subgroup and after 733 days in patients with incident diagnosis codes for oD.

Table 2 compares patients without a change in the incident AD diagnosis or with changes to or from AD during the 4-year observation period.

FIGURE 1  Comparison of incident and last recorded diagnosis of dementia in the 4-year observation cohort

FIGURE 2  Time (in days) until first change in diagnosis in patients with incident diagnosis codes for Alzheimer's disease (AD), vascular dementia (VD) or other dementias (oD)
The sex distribution was similar in all three groups. As compared to patients with any changes in diagnosis, patients with stable AD diagnoses were younger, had less inpatient treatment days, and less often consulted a neurologist. The distribution of comorbidities was similar across all patient groups with essential primary hypertension, disorders of lipoprotein metabolism and other lipidemias, and disorders of refraction and accommodation as the most common comorbidities while stroke, not specified as hemorrhage or infarction, other cardiac arrhythmias, and unspecified diabetes mellitus accounted for the lowest proportions.

4 | DISCUSSION

We investigated the proportion and stability of incident dementia diagnoses and factors associated with diagnostic (non-)stability in a 4-year observation cohort (and in a 2-year observation cohort in a sensitivity analysis, respectively) of incident dementia patients based on German health claims data. Several noteworthy findings have emerged from our analyses.

4.1 | Proportions of dementia diagnoses

One in five patients was diagnosed first with AD or VD while more than half of all patients were initially diagnosed with oD. These proportions are substantially lower than the 60%-70% of AD cases among all dementia cases repeatedly reported in the literature. In fact, findings from the Rotterdam study which were derived from a small community-based sample in the early 1990s, suggested AD to account for approximately 72%, VD for 16%, and oD for 12% of all dementia cases. However, these figures should be interpreted with caution, as they have been hardly replicated. Indeed, depending on the setting and methodology, AD proportions comparable to ours or even significantly lower have also been reported. Based on a survey among German outpatient neurologists, Lohmann et al. reported a proportion of 25%-40% of AD in all incident dementia diagnoses. Albrecht et al. recently published findings from an administrative claims-based case–control study on prediction models for dementia, reporting only 10% incident AD diagnoses. Kaduszkiewicz et al. who investigated diagnostic coding of dementias in German health claims data found even smaller proportions of AD (8%) and VD (14%) in their sample—most likely due to a stricter case definition which required a diagnosis in each quarter of the year under study. Our data add to their findings by using a larger and more representative cohort, a longer observation period, and by comparing differing vs. stable diagnoses which to our knowledge has not been investigated so far. Nevertheless, it must be explicitly stated that just as from the results of the Rotterdam Study, no “etiological truth” should be derived from our data as well. Both in routine care – as mapped by real world data – and in clinical epidemiological studies, the accuracy of a diagnosis depends on the individual clinical expertise as well as the framework conditions under which the diagnosis is made. This is particularly true for dementia diseases, whose accurate determination does not usually have different consequences for disease prognosis, treatment options, or billing terms.

4.2 | Stability of dementia diagnoses

Up to 40% of all patients had at least two different dementia diagnoses during the 4-year observation period with a mean of three to five changes, potentially indicating that for a proportion of patients etiological determination is not finished shortly after the incident diagnosis. A small but distinctive fraction of patients were only diagnosed once with dementia during the 4 years, which happened to be more likely for patients with incident diagnosis codes for VD than for those with incident codes for AD or oD. Like Kaduszkiewicz et al., we did not find higher rates of changes in diagnosis in patients with incident diagnosis codes for oD (in the sense of a specification of an initially unclear diagnosis). Moreover, these patients had the slowest rates of changes in diagnosis of all three dementia categories. This would not be expected if the oD diagnosis would be only an initial diagnosis more precisely defined in the further course of the disease (through additional diagnostics, etc.). The reasons for this remain unclear, since the diagnostic process can hardly, if at all, be mapped in health claims data. However, most dementia diagnoses do not substantially differ regarding the prognosis and treatment for the patient or the billing specifications for the physician, as previously mentioned, which may have influenced the coding behavior as seen. It should be noted here that the diagnosis of delirium superimposed on dementia (F05.1) was deliberately assigned to the group “oD”, although a differentiation of dementia subtype is not implied by this code. However, the inclusion of F05.1 seemed necessary to allow comparability of our data with previous studies based on health claims data. We consider the risk of bias low because this diagnosis accounts for only a fraction (~2%) of all patients within the oD category. Thus, the increased complexity of analyses of diagnosis changes by considering another separate category would have been disproportionate to the scientific benefit.

Stability of AD diagnoses during the 4-year observation period was associated with younger age at first dementia diagnosis and substantially fewer inpatient treatment days as compared to patients with changes either from or to AD during that time. The lower number of inpatient treatment days can be potentially explained by the fact that some patients might already have been nursing home residents who received their diagnoses during an in-house check-up by visiting physicians and were not transferred to inpatient facilities for further examinations. However, this could not be verified as the identification of nursing-home residents in health claims data is complex and requires resources that could not be allocated for this study. There is a considerable number of patients who appears to not be seen by specialists after the incident diagnosis. Merely half of all patients consulted neurologists and less than 20% saw psychiatrists during the observation period. In fact, our results suggest that GPs remain the
| TABLE 2 Characteristics of AD patients from the 4-year observation cohort with and without changes in diagnosis during follow-up |
|----------------------------------------------------------|
| **No change (AD = AD)** | **Change to AD** | **Change from AD** |
| (N = 18 201) | (N = 17 868) | (N = 9760) |
| Male:Female ratio (%) | 36.4:63.6 | 32.2:67.8 | 33.3:66.7 |
| Age at cohort entry, years | | | |
| Median | 76 | 79 | 79 |
| Q1: Q3 | 71; 82 | 73; 84 | 73; 83 |
| ≥1 specialized medical care visit(s), N (%) | | | |
| Neurologist | 9482 (52.1) | 9374 (52.5) | 5500 (56.3) |
| GP* | 18 060 (99.2) | 17 796 (99.6) | 9716 (99.5) |
| Neurosurgeon | 698 (3.8) | 502 (2.8) | 302 (3.1) |
| Psychiatrist | 3258 (17.9) | 3655 (20.5) | 1722 (17.6) |
| Inpatient treatment days | | | |
| Median | 14 | 27 | 27 |
| Q1; Q3 | 2; 38 | 8; 54 | 9; 55 |
| Treatment with anti-dementia drugs, N (%) | | | |
| Donepezil | 5026 (27.6) | 5053 (28.3) | 2503 (25.6) |
| Galantamine | 2703 (14.8) | 2407 (13.5) | 1331 (13.6) |
| Rivastigmine | 2919 (16.0) | 3156 (17.7) | 1627 (16.7) |
| Memantine | 4601 (25.3) | 4953 (27.7) | 2430 (24.9) |
| None | 7242 (39.8) | 6298 (35.2) | 3915 (40.1) |
| Any | 10 959 (60.2) | 11 570 (64.7) | 5845 (59.9) |
| Comorbidities, N (%)b | | | |
| Diseases of the circulatory system: | | | |
| I10: Essential (primary) hypertension | 14 593 (80.2) | 15 154 (84.8) | 8242 (84.4) |
| I25: Chronic ischemic heart disease | 5965 (32.8) | 6515 (36.5) | 3527 (36.1) |
| I50: Heart failure | 5502 (30.2) | 6839 (38.3) | 3803 (39.0) |
| I67: Other cerebrovascular diseases | 5525 (30.4) | 6411 (35.9) | 3511 (36.0) |
| I83: Varicose veins of lower extremities | 4529 (24.9) | 4665 (26.1) | 2449 (25.1) |
| I64: Stroke, not specified as hemorrhage or infarction | 1343 (7.4) | 1696 (9.5) | 980 (10.0) |
| I49: Other cardiac arrhythmias | 4009 (22.0) | 4036 (22.6) | 2230 (22.9) |
| Endocrine, nutritional and metabolic diseases: | | | |
| E11: Type 2 diabetes mellitus | 5195 (28.5) | 5539 (31.0) | 2947 (30.2) |
| E14: Unspecified diabetes mellitus | 3499 (19.2) | 3548 (19.9) | 1946 (19.9) |
| E78: Disorders of lipoprotein metabolism and other lipemias | 10 526 (57.8) | 10 388 (58.1) | 5627 (57.6) |
| Diseases of the eye and adnexa | | | |
| H52: Disorders of refraction and accommodation | 10 392 (57.1) | 9245 (51.7) | 5198 (53.3) |
| Diseases of the musculoskeletal system and connective tissue: | | | |
| M54: Dorsalgia | 9743 (53.5) | 9092 (50.9) | 4935 (50.6) |
| M17:Osteoarthritis of knee | 5340 (29.3) | 5159 (28.9) | 2759 (28.3) |
| Mental and behavioral disorders: | | | |
| F32: Depressive episode | 8660 (47.5) | 8936 (50.0) | 4826 (49.4) |
| Diseases of the genitourinary system: | | | |
| N40: Hyperplasia of prostate | 3878 (21.3) | 3370 (18.9) | 1964 (20.1) |

*General practitioner.

bICD-10 codes.

Abbreviation: AD, Alzheimer’s disease.
main medical contact for patients after diagnosis. While this is not generally ruled out by established guidelines, it is also not specifically recommended, especially in the presence of neuropsychiatric comorbidities, which are common in dementia. Again this could also hint at some patients already living in nursing homes where routine examinations are usually conducted by GPs rather than specialists. It is interesting though to note that the specialist treatment rates are similarly low for patients with and without changes in diagnosis. This suggests that consulting a specialist does not lead more often to alterations (also in terms of corrections) of incident diagnoses.

### 4.3 Implications and limitations

In summary, the results of our analyses show that in well over half of all dementia patients, the incident diagnosis remains stable and is confirmed during the course of the disease, possibly multiple times. Conversely, it can be concluded that in up to 40% of patients the diagnosis is revised during the course of the disease, again possibly multiple times. This implies that results from epidemiological studies in which patients are explicitly assigned to specific dementia categories based on diagnoses from routine care should be interpreted with caution, as those diagnoses are likely to still be subject to change. To our knowledge this is the first study to quantify the extent of this variability.

In addition to the previously mentioned limitations, some further restrictions should be kept in mind when interpreting our data. Our data originate from a large sample of persons covered by SHI and, in addition, they correspond very well with the results of a German field study in the same study period with regard to age and gender distribution as well as treatment status. Nonetheless, distortions in our study cohort cannot be ruled out. It was a prerequisite that members of the cohort could be observed for at least 4 years. While this is in line with previously reported mean survival times, patients who met these requirements could have been more vital or less morbid than dementia patients with a shorter minimum survival time. We tried to minimize this bias by additionally computing all figures and tables based on a cohort of minimum 2-years survivors and found no substantial differences as compared to the cohort of minimum 4-years survivors. However, this might not have prevented distortions completely and further studies in this regard should consider shorter or longer timeframes or should be based on an open time frame, which could not be realized in our study due to logistic and methodological reasons.

Another limitation of our results lies in the inpatient data. For technical reasons, in health claims data the specialty of a physician in the inpatient sector cannot be determined, i.e., inpatient dementia diagnoses could in principle have been made by any specialist. If inpatient dementia diagnoses by a specialist other than a neurologist were to be less valid, this would represent a weakness in our database. Similarly, in inpatient data primary diagnoses and secondary diagnoses are usually distinguished. Again, it would in principle be possible (but not mandatory) that secondary diagnoses might be less valid than primary diagnoses. To account for the epidemiological nature of our study and to avoid underestimation of dementia incidence, both types of diagnoses were considered. However, for technical reasons, it is not possible to distinguish retrospectively how many of the inpatient diagnoses were attributable to primary and secondary diagnoses. This should be taken into account in future research projects to better estimate possible biases.

Furthermore, although we were able to provide important information on the number of changes in diagnosis per patient during the observation periods, we could not assess the quality of those changes in patients with more than two diagnoses. We had to limit our analyses to the comparison of the incident and last available diagnosis due to technical and logistical reasons. Therefore, sequences of diagnoses with matching first and last dementia category are considered “stable” even if other diagnoses from other dementia categories were coded in between. Similarly, while AD and VD were unambiguous categories, oD comprised several codes, including those for “dementia in other diseases”, “unspecified dementia”, and “delirium superimposed on dementia”. Thus, although “unspecified dementia” is by far the most common diagnosis among oD, it is theoretically possible that patients with oD as incident and last diagnostic category in fact did have differing diagnoses within this category without this being apparent in the analyses. More comprehensive analyses that could analyze diagnostic changes between first and last dementia diagnosis would have required a different study design and resources which were not available for this study. Thus, more data on the full diagnostic path throughout the course of dementias is needed and should be addressed in future research. This also applies to the use of medications other than antidementia drugs in dementia patients. Recently published studies suggest a difference in the use of e.g., analgetics between dementia patients and persons without dementia or even identified the use of benzodiazepines as a potential risk factor for dementia. However, a more in-depth consideration of medication could not be implemented in our research project due to budgetary reasons and should therefore be considered in future studies. To sum up, our study demonstrates that while health claims data are feasible for estimating the incidence of dementia in general, the substantial number of changes in dementia diagnoses during the course of the disease warrant caution on the interpretation of epidemiological data on specific dementia types.

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CONFLICT OF INTEREST
OR, MB and IL are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry.

AUTHOR CONTRIBUTIONS
Oliver Riedel wrote the first draft of the manuscript. Malte Braitmaier conducted all statistical analyses. Malte Braitmaier and Ingo Langner assisted with the interpretation of data. All authors revised the first draft of the manuscript.

DATA AVAILABILITY STATEMENT
As we are not the owners of the data we are not legally entitled to grant access to the data of the German Pharmacoepidemiological Research Database. In accordance with German data protection regulations, access to the data is granted only to employees of the Leibniz Institute for Prevention Research and Epidemiology – BIPS on the BIPS premises and in the context of approved research projects. Third parties may only access the data in cooperation with BIPS and after signing an agreement for guest researchers at BIPS.

ETHICS STATEMENT
In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Patient consent was not required for this study.

PRIOR POSTINGS AND PRESENTATIONS
Not applicable.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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