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# The temporal association between incident late-life depression and incident dementia

Heser K, Fink A, Reinke C, Wagner M, Doblhammer G. The temporal association between incident late-life depression and incident dementia.

**Objective:** There is an established association between depression and subsequent dementia. The present study examined temporal associations between incident late-life depression and subsequent dementia, also considering age and sex.
**Methods:** We used longitudinal health claims data from the largest German health insurance provider ('Allgemeine Ortskrankenkasse') considering up to 9 follow-up years in piecewise exponential models. ICD-10 codes were used to define incident depression and dementia in individuals ≥65 years ($n$ = 97 110).
**Results:** Incident depression was associated with a higher risk of subsequent dementia (incidence rate ratios (IRR) adjusted for age and sex: IRR = 1.58, 95% CI = 1.51–1.64). The strongest association was found for the shortest interval of 1 quarter (IRR = 2.04, 95% CI = 1.88–2.21), with significant associations up to an interval of roughly 3 years. The association was more pronounced and lasted for more quarters in the younger portion of this study group (ages from 65–74: IRR = 2.00, 95% CI = 1.83–2.18; 75–84: IRR = 1.64, 95% CI = 1.55–1.73; ≥85: IRR = 1.19, 95% CI = 1.08–1.31). It was stronger among men than women (men: IRR = 1.98, 95% CI = 1.84–2.14; women: IRR = 1.44, 95% CI = 1.37–1.51) with no sex-specific temporal association.
**Conclusion:** This large claims data study confirmed that incident late-life depression is associated with a higher risk of dementia within the 3 years following diagnosis. Hence, incident late-life depression should prompt further cognitive examinations and referrals to specialists. This might apply especially to younger seniors and men.

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Key words: depression; dementia; epidemiology

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**Significant outcomes**

- An association between incident late-life depression and a higher risk of subsequent dementia was found.
- The strongest association between incident late-life depression and subsequent dementia risk was found for the shortest interval between both diagnoses.
- A stronger association between incident late-life depression and subsequent dementia risk was found in younger old individuals and in men.

**Limitations**

- Although registry-based data have several strengths, it is also limited to general sociodemographic sample characteristics, for example, without information on neuropsychological performance.
- False diagnoses of incident depression or dementia might explain the short temporal association between both disorders, although we do not consider this likely due to our validation strategy of diagnoses.
- Our results might not be generalizable to members of other public or private health insurance groups.

## Introduction

In aging societies, dementia is an increasingly prevalent condition incurring high societal costs and placing additional burdens on patients and their relatives (1). Depression can be both a risk factor for, and a prodromal feature of dementia (2) in different individuals and samples. Recent meta-analyses have found that, on average, late-life depression or clinically relevant depressive symptoms were associated with a twofold higher risk of incident dementia (3, 4). Importantly, this association seemed to be time-dependent and may be moderated by age and sex. Further elucidation of these moderators could yield clinically useful information, in that incident depression in some patient groups may come along with a higher risk of dementia within close temporal proximity, prompting clinical attention.

Previous research has shown that depressive symptoms at both mid- and late-life were associated with a higher risk of dementia (5), whereas others found a higher risk of subsequent dementia specifically for participants with late-onset depression and elevated late-life depressive symptoms (6, 7). Several studies have suggested a close temporal proximity between late-life or late-onset depression and subsequent dementia (8–12) and intervals of up to 5 years might be particularly relevant (13–15). These results point to a prodromal association between depression and dementia, in which depression can be an early sign of the yet latent and preclinical phase of the dementia process. However, some studies (16, 17) have indicated there may be associations for considerably longer periods between both diagnoses. The patients' age at diagnosis may also affect the temporal association between incident late-life depression and dementia. Only a few studies have addressed this issue so far, with inconsistent results. In a population study with subjects over 75 years of age, Heser et al. (7) found that the risk of subsequent all-cause dementia was higher with increasing age at depression onset. It was insignificant for a recalled depression onset at age 60 and increased to a significant risk with a later onset, for example, at 75 years. Conversely, in a prospective study, Chen et al. (18) found a stronger association between depressive syndromes and dementia in a group of 65- to 74-year-olds with decreasing and non-significant associations for the elder groups. However, these latter results refer to late-life depression in general rather than incident late-life depression. A higher prevalence of depression in women compared with men has often been found (e.g., (19)). It has also been suggested that women have a higher risk of dementia and Alzheimer's disease (AD), but results are less consistent than those for depression and might be driven by women's higher life-expectancy and by geographical differences (20). Sex-specific risk factors of dementia, especially for AD, have recently attracted more interest (20, 21). It is still an open issue whether the association between depression and subsequent dementia differs between men and women. While some studies reported that depression is more strongly associated with a higher risk of dementia in men (13,22–24), others found an association only in women (25, 26), or did not find any sex differences (18, 27).

### Aims of the study

In sum, while temporal and demographic variables might be interesting moderators of the depression-dementia link, the existing literature does not yet allow researchers and clinicians to draw solid conclusions. Sample sizes have often been small, rendering stratified analyses prone to inconclusive findings. In addition, different age ranges and differences regarding the definition of depression (e.g., symptoms versus diagnosis and incident vs. prevalent depression) limit the integration and interpretation of the data which had been collected. We sought to examine this issue by leveraging a large dataset containing clinician-coded depression and dementia diagnoses. We used registry-based longitudinal health claims data, approximately representative of the German population aged 65 and above. With regard to the existing literature on the prodromal association between depression and dementia, we hypothesized that associations would be stronger for shorter intervals between incident depression and subsequent dementia. In order to better characterize patient groups with incident depression at risk of dementia, we explored whether this temporal association regarding time intervals of quarters between both diagnoses of incident depression and subsequent dementia may be moderated by age of depression incidence and sex. Our results might assist diagnostic and treatment decisions of clinicians regarding different age and sex strata.

## Material and methods

### Study design and sample

We analyzed health claims data from the largest German health insurance provider, the 'Allgemeine Ortskrankenkasse' (AOK). A random sample of 250 000 insured persons born before 1955 was drawn by the data provider in 2004 with a

follow-up through 2015. The data provide information about sex, year, and month of birth and death, in- and outpatient diagnoses coded according to the 10th revision of the International Classification of Diseases (ICD-10), the specialty of physicians, and all medical prescriptions. All medical information was available on a quarterly basis. We included persons who were born before 1940 and excluded persons with dementia or depression diagnoses in 2004 or 2005. Our analysis sample consisted of 97 110 insured persons older than 64 years and included 20 779 dementia cases through the end of 2014 (Fig. 1). This study involved anonymized claims data and fell outside the scope of the Declaration of Helsinki and did not require ethical review.

### Depression diagnosis

We used the following ICD-10 codes for the identification of valid depression diagnoses: depressive episode (F32); recurrent depressive disorder (F33); and dysthymia (F34.1). However, F33 and F34.1 were used only for validation of F32 diagnoses. The validation of depression diagnoses was based on a strategy described in (28). A diagnosis was assumed to be valid if one of the following conditions was met: an inpatient discharge or secondary diagnosis; two outpatient diagnoses in different quarters (within four quarters time); or two outpatient diagnoses by separate physicians in the same quarter. A diagnosis was also assumed to be valid if the person died in the same quarter of the initial depression diagnosis. The severity of depression is classified into broader general categories (mild, moderate, severe, or unknown) which were based on ICD-10 codes (e.g., F32.1). Cases with a depression diagnosis in 2004 or 2005 were excluded from our analyses, as we could not know the time of the first depression incidence. All cases with a valid depression diagnosis after 2005 were considered to be incident cases. We try to approximate incident cases of depression by applying a two-year washout-period, although it is possible that there had been incident cases of depression diagnosed before 2004. Persons remain in the exposed group from the time of first diagnosis onwards; in a sensitivity analysis, we started from the second diagnosis. Remission from depression was not coded.

### Dementia diagnosis

Dementia diagnoses were defined by one of the following ICD-10 codes: dementia in AD (F00), without dementia in AD with early onset (F00.0); vascular dementia (F01); dementia in other diseases classified elsewhere (F02); unspecified

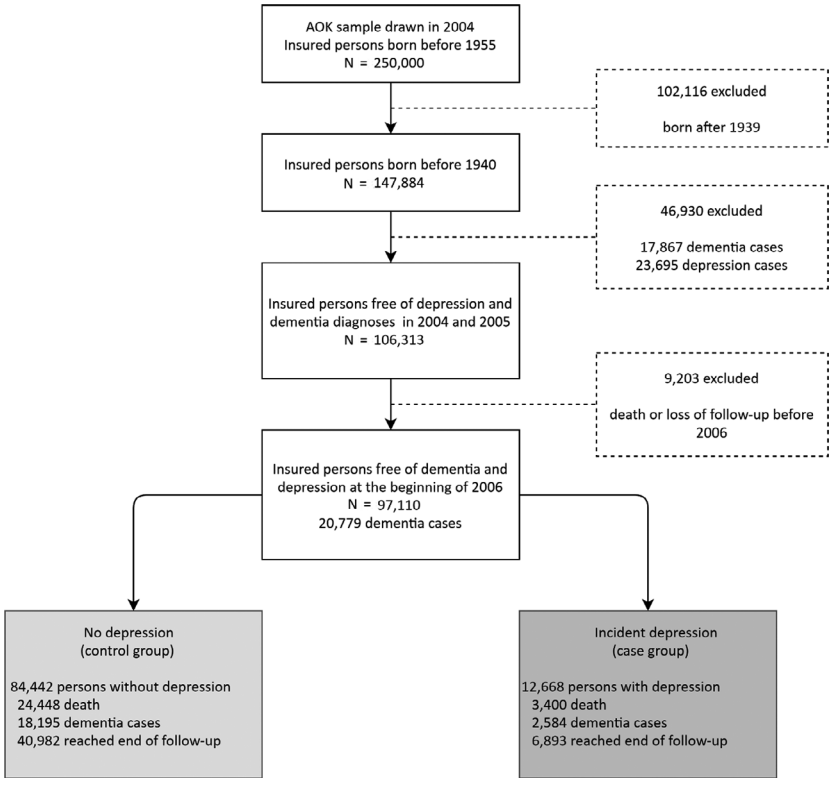


*Fig. 1.* Inclusion of insured subjects in the analyses.

dementia (F03); delirium superimposed on dementia (F05.1); and AD (G30), without AD with early onset (G30.0). We applied a two-stage validation strategy to overcome the problem of false-positive diagnoses (29). In the first stage, 'verified' outpatient diagnoses as well as inpatient discharge or secondary diagnoses were identified. In the second stage, the diagnoses were confirmed by a simultaneous in- and outpatient diagnosis, by two diagnoses from two different types of physicians in the same quarter, or by co-occurrence over the study period plus the year 2015, which was only used for validation. A diagnosis was also considered to be valid if a person died in the same quarter as the initial dementia diagnosis. If cases validated by co-occurrence over the study period, the time of incident dementia was set to the time of first diagnosis. In a sensitivity analysis, we used time of the second diagnosis. As for depression, all persons with a dementia diagnosis in 2004 or 2005 were excluded. All persons with a valid dementia diagnosis after 2005 were considered to be incident cases.

### Covariates

Covariates were age, sex, and each patient's history of comorbidities, including: mental and behavioral disorders due to psychoactive substance use (F10-F19); schizophrenia, schizotypal, and delusional disorders (F20-F29); hypertensive diseases (I10-I15); diabetes mellitus without type I (E11-E14); cerebrovascular diseases (I60-I69); ischemic heart diseases (I20-I25); injuries to the head (S00-S09); neurotic, stress-related, and somatoform disorders (F40); other anxiety disorders (F41); reaction to severe stress and adjustment disorders (F43); bipolar affective disorder (F31); and atrial fibrillation and flutter (I48). All covariates, with the exception of sex, were considered to be time-varying variables with a value of 1 at time of the first diagnosis in the data.

### Statistical analysis

For analyzing the temporal association of dementia and depression, we assessed the risk of dementia depending on the depression status. We calculated the dementia incidence rate and performed piecewise constant exponential models. Dementia incidence was measured in the 9-year period from the first quarter of 2006 through the last quarter of 2014. Following Hernán et al. (2016) and Emilsson et al. (2018), we considered depression to be a time-varying variable (30, 31). Therefore, we doubled all eligible observations (measured in person-times) and assigned each copy either to the control or to the case group (Fig. 1). For both groups, we defined a time zero of analysis time. For person-times without a depression diagnosis, analysis time started at the beginning of 2006. In the case group, time zero was defined as the time of incident depression diagnosis (middle of the relevant quarter). That means that a person could start in the control group and be censored at time of the first depression diagnosis. This person could then switch to the case group, where his or her analysis time was set to zero again. All persons (in both the control and case groups) were censored at the time of death or at the end of follow-up (end of 2014). Analysis time was measured in months and was split into a maximum of 36-time intervals (quarters) in order to perform piecewise exponential models, which allow a varying baseline hazard. Using the Akaike information criteria to evaluate different functions for the temporal specification, we determined that the natural logarithm of the analysis time best represented our data. The time of dementia diagnosis was set to the middle of the relevant quarter. The time of death was set to the middle of the month of death. We included cases with concurrent onset of depression and dementia in the control group. All analyses were performed using Stata 16.0.

Model 1 was adjusted for age and sex, model 2 additionally for comorbidities. Further, we performed sex- and age-specific models to assess the dementia risk for men and women separately (models 3 and 4) and for the three age groups 65–74 years, 75–84 years, and 85+ years (models 5 to 7). The assignment to one of these age groups was based on the age at time zero for each group. To compare the dementia risk of the control and case group over time, models 8 to 14 replicated models 1 to 7 and estimated additionally the time-related dementia risks by including interaction effects between depression (yes→case group/no→control group) and the analysis time. All models included a time-dummy for the fourth quarter in 2013 and the first quarter of 2014 to consider structural changes in the billing system for physicians ('Chronikerzuschlag'; (32)). This change led to a temporary increase of diagnoses of chronic diseases which do not reflect the epidemiological development in Germany.

## Results

### Descriptive results

Our analyzed sample comprised 97,110 persons with 636 322 person years. The mean follow-up time per subject was 5.82 years. The mean age at

start of observation was 74.7 years (SD = 6.6) for subjects without depression and 78.1 years (SD = 6.1) for subjects at the time of incident depression. Table 1 shows characteristics of the study population and the rate of dementia incidence. There were 12 668 subjects with incident depression (41 384 person years) and 2584 of them subsequently developed dementia (Fig. 1 and Table 1). Incident depression almost doubled the incidence of dementia, and the increase rose with depression severity. Dementia incidence rate was slightly higher in women than in men, and it increased with age and all the comorbidities considered, with the exception of neurotic, stress-related, and somatoform disorders (Table 1).

Table 1. Characteristics of the study population and dementia incidence rate per 1000 person years with 95% confidence intervals

| | | | Dementia incidence rate per 1000 person years | | |
|---|---|---|---|---|---|
| Variable | Person years | Cases with dementia | Rate | 95% Confidence interval | |
| Depression | | | | | |
| No | 594 938 | 18 195 | 30.58 | 30.14 | 31.03 |
| Yes | 41 384 | 2584 | 62.44 | 60.08 | 64.89 |
| Severity of depression | | | | | |
| Unknown | 24 861 | 1809 | 72.77 | 69.49 | 76.20 |
| Mild | 3991 | 347 | 86.94 | 78.26 | 96.59 |
| Moderate | 7612 | 751 | 98.66 | 91.85 | 105.97 |
| Severe | 5030 | 567 | 112.73 | 103.82 | 122.40 |
| Sex | | | | | |
| Male | 262 952 | 7618 | 28.97 | 28.33 | 29.63 |
| Female | 373 371 | 13 161 | 35.25 | 34.65 | 35.86 |
| Age group at start of observation | | | | | |
| 65-74 | 386 055 | 6156 | 15.95 | 15.55 | 16.35 |
| 75-84 | 216 258 | 10 722 | 49.58 | 48.65 | 50.53 |
| 85+ | 34 010 | 3901 | 114.70 | 111.16 | 118.36 |
| Mental & behavioral disorders due to psychoactive substance use | | | | | |
| No | 617 183 | 19 462 | 31.53 | 31.09 | 31.98 |
| Yes | 19 139 | 1317 | 68.81 | 65.19 | 72.63 |
| Schizophrenia | | | | | |
| No | 628 241 | 19 770 | 31.47 | 31.03 | 31.91 |
| Yes | 8081 | 1009 | 124.86 | 117.39 | 132.81 |
| Hypertensive diseases | | | | | |
| No | 110 456 | 2044 | 18.51 | 17.72 | 19.32 |
| Yes | 525 866 | 18 735 | 35.63 | 35.12 | 36.14 |
| Diabetes without type I | | | | | |
| No | 402 467 | 10 933 | 27.16 | 26.66 | 27.68 |
| Yes | 233 855 | 9846 | 42.10 | 41.28 | 42.94 |
| Cerebrovascular diseases | | | | | |
| No | 480 089 | 10 534 | 21.94 | 21.53 | 22.36 |
| Yes | 156 234 | 10 245 | 65.57 | 64.32 | 66.86 |
| Ischemic heart diseases | | | | | |
| No | 366 959 | 9138 | 24.90 | 24.40 | 25.42 |
| Yes | 269 363 | 11 641 | 43.22 | 42.44 | 44.01 |
| Injuries to the head | | | | | |
| No | 564 148 | 15 985 | 28.33 | 27.90 | 28.78 |
| Yes | 72 174 | 4794 | 66.42 | 64.57 | 68.33 |
| Neurotic, stress-related disorders | | | | | |
| No | 623 767 | 20 371 | 32.66 | 32.21 | 33.11 |
| Yes | 12 555 | 408 | 32.50 | 29.49 | 35.81 |
| Other anxiety disorders | | | | | |
| No | 598 295 | 19 068 | 31.87 | 31.42 | 32.33 |
| Yes | 38 027 | 1711 | 44.99 | 42.91 | 47.18 |
| Reaction to severe stress, and adjustment disorders | | | | | |
| No | 587 021 | 18 833 | 32.08 | 31.63 | 32.54 |
| Yes | 49 302 | 1946 | 39.47 | 37.76 | 41.26 |
| Bipolar affective disorder | | | | | |
| No | 635 464 | 20 701 | 32.58 | 32.14 | 33.02 |
| Yes | 859 | 78 | 90.85 | 72.77 | 113.42 |
| Atrial fibrillation and flutter | | | | | |
| No | 530 131 | 14 194 | 26.77 | 26.34 | 27.22 |
| Yes | 106 191 | 6585 | 62.01 | 60.53 | 63.53 |
| Total | 636 322 | 20 779 | 32.65 | 32.21 | 33.10 |

*Source:* AOK data 2004–2015, own calculations.

### Model results

Table 2 shows the estimated incidence rate ratios (IRR) of the piecewise exponential models to assess the risk of dementia depending on an incident depression diagnosis. Incident depression increased the subsequent risk of dementia by a factor of 1.58 ($P < 0.01$, model 1). Controlling for comorbidities attenuated some of this effect (IRR = 1.11, $P < 0.01$, model 2). Men with incident depression had a 1.98-fold ($P < 0.01$, model 3), and women with incident depression had a 1.44-fold ($P < 0.01$, model 4) higher risk of subsequent dementia. In the age group 65–74, an incident depression diagnosis increased the risk of dementia by a factor of 2 ($P < 0.01$, model 5), persons aged 75–84 years had a 1.64-fold ($P < 0.01$, model 6) higher risk, and persons aged 85 years or above had a 1.19-fold ($P < 0.01$, model 7) higher risk. We confirmed the effect of depression on dementia using Cox models in a sensitivity analysis. However, since Cox regression does not permit us to estimate the temporal association of depression and dementia, we continue with piecewise exponential models.

### Temporal association of depression and dementia

Figures 2 and 3 show the predicted incidence rates of the total interaction effect concerning the dementia risk of depressed and non-depressed persons for each time interval of the analysis time (adjusted for age and sex for all, adjusted for age in sex-specific models, adjusted for age and sex in age-specific models). In the first quarter after an incident depression diagnosis, the risk of dementia was 2.04-fold (calculation in supplementary material, see Table S1 and formula below) compared to the first quarter after study entry of persons without depression (Table 2, model 8; Fig. 2, all). This excess risk decreased with increasing follow-up time. After 11 quarters (about 3 years), depressed and non-depressed persons did not differ significantly regarding their dementia risk. After 20

Table 2. Results of regression models representing risk of subsequent dementia depending on incident depression diagnosis

| | Model 1† (no comorb.) | Model 2‡ (with comorb.) | Model 3§ (male) | Model 4§ (female) | Model 5† (65–74 years) | Model 6† (75–84 years) | Model 7† (85 + years) |
|---|---|---|---|---|---|---|---|
| Variable | IRR (95% CI) | IRR (95% CI) | IRR (95% CI) | IRR (95% CI) | IRR (95% CI) | IRR (95% CI) | IRR (95% CI) |
| Depression | 1.58 (1.51–1.64) | 1.11 (1.07–1.17) | 1.98 (1.84–2.14) | 1.44 (1.37–1.51) | 2.00 (1.83–2.18) | 1.64 (1.55–1.73) | 1.19 (1.08–1.31) |
| | Model 8† (no comorb.) | Model 9‡ (with comorb.) | Model 10§ (male) | Model 11§ (female) | Model 12† (65–74 years) | Model 13† (75–84 years) | Model 14† (85 + years) |
| Depression | 2.04 (1.88–2.21) | 1.38 (1.27–1.49) | 2.61 (2.27–3.01) | 1.82 (1.65–2.01) | 3.84 (3.17–4.64) | 2.30 (2.06–2.56) | 1.34 (1.14–1.57) |
| Ln(Time) | 0.84 (0.82–0.86) | 0.76 (0.74–0.77) | 0.88 (0.84–0.91) | 0.83 (0.81–0.85) | 0.90 (0.84–0.96) | 0.86 (0.83–0.89) | 0.83 (0.78–0.88) |
| Depression × Ln(Time) | 0.79 (0.74–0.84) | 0.82 (0.77–0.88) | 0.77 (0.68–0.86) | 0.80 (0.74–0.87) | 0.61 (−0.53 to 0.69) | 0.73 (0.67–0.80) | 0.87 (0.75–1.02) |

95% CI, 95% Confidence interval; IRR, Incidence Rate Ratio; comorb, comorbidity.
Source: AOK data 2004–2015, own calculations.
All p-values are ≤ 0.05 (with the exception of Depression × Ln(Time) in model 14).
†Controlled for age and sex.
‡Controlled for age, sex, and comorbidities.
§Controlled for age.

quarters, both groups had the same dementia risk. In the first quarter, depressed men had a 2.61-fold higher dementia risk compared with non-depressed men (Fig. 2, male). After 13 quarters, depressed and non-depressed men did not differ significantly. Depressed women started with a 1.82-fold higher dementia risk. Depressed and non-depressed women did not differ significantly regarding their dementia risk after 8 quarters of follow-up (Fig. 2, female).

Persons aged 65–74 years with a diagnosis of depression had a 3.84-fold higher dementia risk compared to non-depressed persons of the same age group (Fig. 3, 65–74). After 9 quarters, the two groups did not differ significantly. Depressed persons aged 75–84 years had a 2.3-fold higher dementia risk and after 8 quarters did not significantly differ from non-depressed persons of this age group (Fig. 3, 75–84). Depressed persons aged 85 years and above had only a 1.34-fold higher

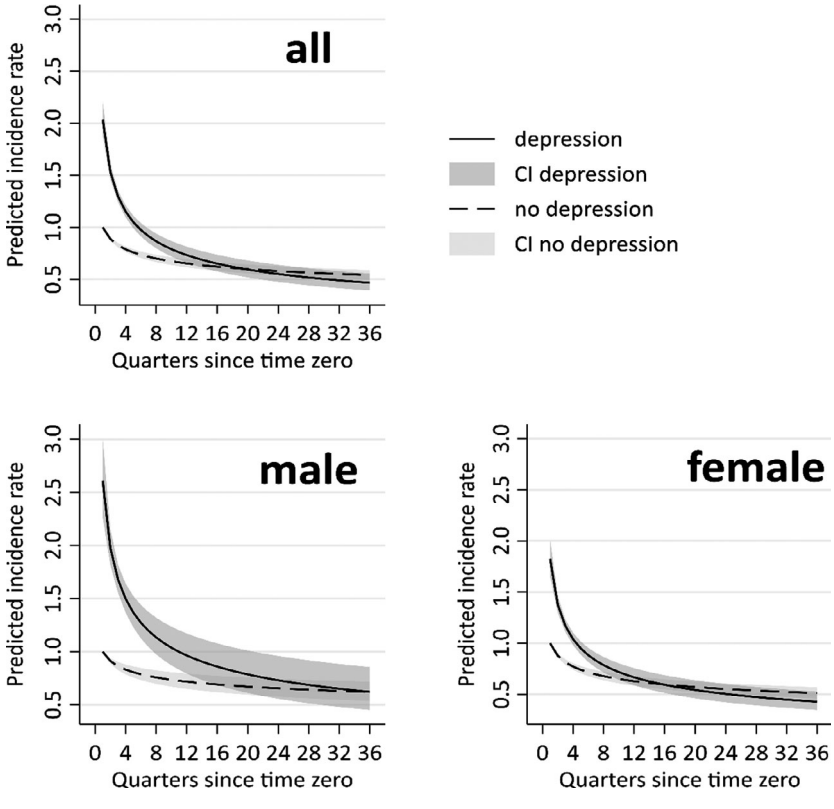


*Fig. 2.* Predicted incidence rates with 95% confidence intervals for dementia risk of persons with and without depression dependent on time since time zero for the total study population (all), men (male), and women (female). *Source:* AOK data 2004–2015, own calculations.

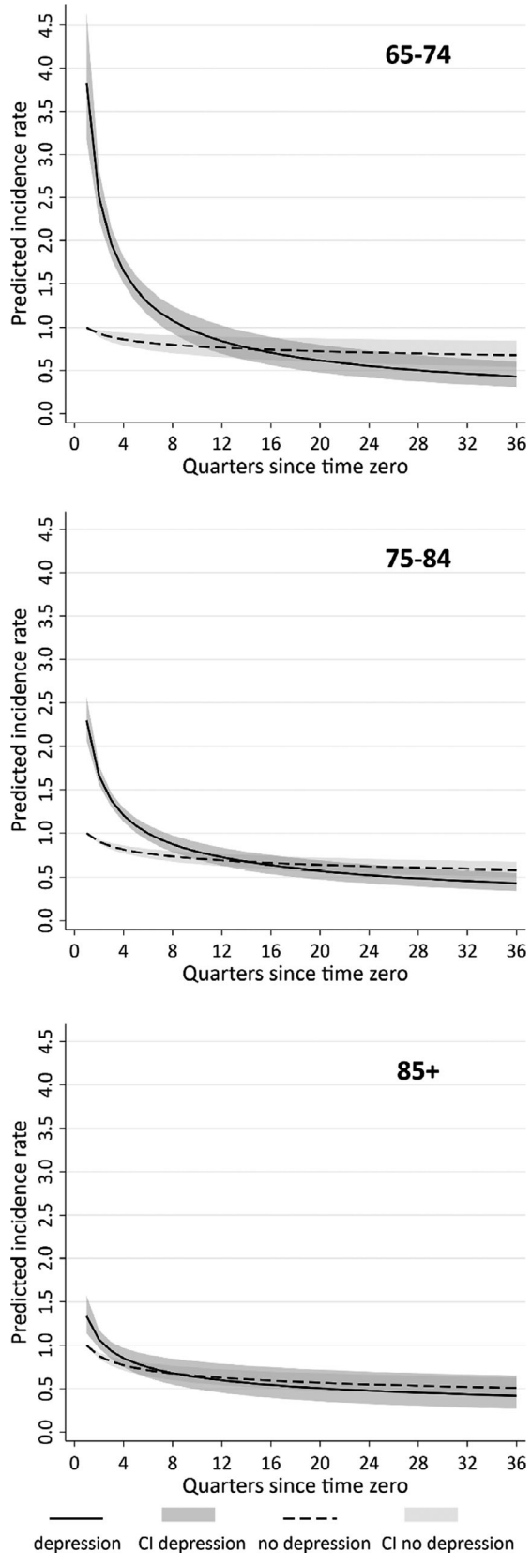


*Fig. 3.* Predicted incidence rates with 95% confidence intervals for dementia risk of persons with and without depression dependent on time since time zero by age groups (65–74, 75–84, 85+). *Source:* AOK data 2004–2015, own calculations.

dementia risk and did not significantly differ after 3 quarters (Fig. 3, 85+).

Adjustment for comorbidities attenuates some but not all of the duration effect.

## Discussion

Using a large claims data sample from the largest German health insurer, we clearly confirmed that a new diagnosis of depression in old age is associated with a higher risk of incident dementia within the subsequent 3 years, but this association ceases thereafter. This temporal association was particularly strong between ages 65 and 74 and became weaker with advancing age; above age 85 it was only present up to three quarters after the depression diagnosis. To our knowledge, this is the first study that has shown significant differences in the pattern of the temporal association between incident late-life depression and subsequent dementia in different age groups and for both sexes.

The 2.04-fold risk observed for receiving a subsequent dementia diagnosis within the next quarter, which leveled off but remained significant for about 3 years, confirms results from a previous registry-based study: Tapiainen et al. (15) found that the association between hospital-discharge diagnoses of 'depression and other mood disorders' and subsequent risk of AD weakened when the time period between both diagnoses increased from 0 years (OR about 1.7) to 7 years (OR about 1.1). Our data confirm and extend this finding to the general population, including persons with a diagnosis of depression who were not hospitalized. A marked temporal decay of the association between any newly diagnosed mood disorder and any organic disorder was also reported by Plana-Ripoll et al. (33), with strong associations particularly in the first 6 months. Prospective epidemiological studies have shown an increase of depressive symptoms as early as a decade before dementia, reaching a threshold of 'clinically relevant depression' about 4 years before (cf. (12)). Another population-based study found only an association between the increasing depressive symptoms trajectory and subsequent dementia risk compared to the constantly low depressive symptom trajectory, whereas the decreasing, remitting, and constantly high depressive symptoms trajectories were not significantly associated with incident dementia risk over a 10-year follow-up (34). Methodological characteristics of registry-based and epidemiological studies might contribute to the temporal association between depression and dementia. As we used clinical diagnoses, cases of depression and dementia are presumably more

severe or characterized by a later disease stage than those identified by screening scales or diagnostic interviews in epidemiological studies (35, 36). Additionally, not all subjects who score above a depression screener cut-off receive a depression diagnosis in the healthcare setting. However, those diagnosed with depression in health care are probably more likely to be treated and monitored. This results in relatively earlier detection of dementia, for example, when treatment is not effective and additional problems are reported during follow-up visits. It is therefore plausible that registry and health claims data show a rather close temporal coupling of depression and dementia within a time span of up to 3 years. Together with the epidemiological literature, these data support the assumption that late-life depression can be a prodrome of dementia, which also does not exclude consideration of mid-life depression as a risk factor. Early detection and treatment of depression in the elderly, for example, with selective serotonin reuptake inhibitors (SSRIs), might have a positive effect on cognitive deterioration and incident dementia (37), although well-conducted randomized clinical trials are needed for further examination.

In our study, adjusting for a wide range of mental and physical comorbidities attenuated, but did not eliminate, the association. The attenuation is plausible considering interrelationships of both depression and dementia with vascular diseases (2) or other comorbidities, suggesting that common mechanisms may give rise to incident depression and dementia.

Incident depression and subsequent dementia were most strongly associated in the age group of 65 to 74, with steadily decreasing but still significant associations in the 75 to 84 and 85+ year-old groups. This is in line with the results of Chen et al. (18), who found a stronger association between prevalent depressive syndromes and incident dementia in the age group 65–74. We were also able to show that with increasing age the temporal association between depression and dementia was reduced from about 3 years to 3 quarters. Several reasons may contribute to this age-dependency. First, there might be a possible bias due to referral and treatment, which could lead to different likelihoods of being diagnosed and treated in case of depression. For example, depression being diagnosed and treated might be more likely in women or in the younger elderly, leading to the underestimation of the association between depression and dementia in the other groups. In older age groups, incident depression may arise more often in the context of loss experiences, multi-morbidity, and increasing disability compared with younger ages (38). In contrast, younger patients with an incipient neurodegenerative disorder may perceive the increasing cognitive impairment as being particularly abnormal, giving rise to depression, which is diagnosed well before the threshold of dementia is reached (e.g., (39)). Finally, due to the high incidence of dementia in very old subjects, older patients presenting with depressive symptoms may have been screened for cognitive impairment more often, and a dementia diagnosis might have been reached without a delay.

We found that depression was a stronger predictor for subsequent dementia in men, which is in line with prior smaller studies (e.g., (23, 24)). In addition, we were able to show that the weakening of the association over time was similar for both sexes, despite higher male susceptibility. The higher base rate of depression in women might partially explain this finding, as women are affected by depression about twice as often as men (19). Furthermore, there may be sex-dependent reporting biases, that is, a higher reluctance to report depressive symptoms among males (24), so that men who receive a depression diagnosis might be more severely affected. As depression severity is related to dementia risk (e.g., (18)), an effect which can be seen also in our data (Table 1), such reporting biases regarding depressive symptoms may also impact the association of depression diagnosis and dementia.

The temporal effect is additive to the age and sex effects described above, resulting in effects for specific subgroups which might also become useful for clinical use. For example, a new diagnosis of depression in the younger senior group (65–74 years) confers about a 3.8-fold risk of incident dementia in the next quarter, and a roughly 2.6-fold risk for men. Another study also found a stronger short-term temporal proximity between depressive symptoms and dementia in men (13), regarding a follow-up time of 0 to 5 years. Thus, any incident late-life depression in younger seniors and in men might serve as a clinical signal for incipient dementia, triggering low-cost cognitive screening for cognitive impairment. However, as depression was also significantly associated with a higher risk of subsequent dementia in women and in older seniors, these groups should not be dismissed. Our data also suggest that a depression diagnosis made longer than 3 years ago is not related to a higher risk of dementia.

The strengths of our study include the large study population and a prospective observation period of about 9 years. Furthermore, the data contained information extracted from both

outpatient and institutionalized populations, which is important when assessing age-related diseases such as dementia. All of these strengths also favor the generalizability of our results. Due to the nature of claims data, positive sample selection bias, reporting bias, and recall bias are less relevant compared with other study designs. Established strategies to validate depression and dementia diagnoses were applied, and we used a time-varying exposure definition in order to prevent immortal time bias (40).

This study is not without limitations. Firstly, as the association between depression and subsequent dementia was strongest for short time intervals, false diagnoses may explain our findings (i.e., true dementia cases initially misdiagnosed as false-depression cases). However, our validation strategy of diagnoses included a confirmation of the diagnoses by a secondary physician, which reduced the probability of misdiagnosis. Secondly, although we introduced a two-year washout-period to exclude prevalent cases of depression, undetected prevalent cases may still bias our results. Thirdly, individuals who receive one diagnosis may have a higher probability of receiving a second diagnosis due to the fact that they are being treated and are in contact with the healthcare system. Related to this point is that our validation procedure sets the incidence of the disease to the time of the first diagnosis, which may introduce an immortal time bias. In a sensitivity analysis, we used the second diagnosis as the incidence of the disease and found that the risk of dementia in subsequence of depression was even higher than in our original model while the pattern over time remained nearly unchanged (results in supplementary material, see Table S2). Fourthly, medical claims data include only the medical histories of those persons who sought medical attention, which lowers the generalizability of our findings. Furthermore, our results might not be applicable to patients with private insurance or who are covered by a smaller health insurance provider, as we used data from only one public insurer in Germany. Studies have shown that the AOK's proportion of persons with a low socio-economic status is higher on average, which may lead to higher morbidity rates compared to other public insurers and also compared to private insurers, which are not included here (41). Unfortunately, our registry-based data do not contain any information on educational attainment, socio-economic status, or lifestyle variables, such as smoking and physical activity, all of which relate to depression and dementia and therefore might confound results. We tried to capture this bias by including several comorbidities which are in turn associated with a person's socio-economic status, although we have to admit that this correction cannot fully address the lack of confounder variables such as smoking and socio-economic status. In addition, we can assume that the relative associations between depression and dementia also apply to the total population. Patients with early-stage dementia may have been undiagnosed in our study. Finally, the data do not allow us to distinguish between dementia subtypes with high accuracy.

We provide a detailed analysis of the association between depression and subsequent dementia in old age. While most cases of incident depression in the elderly are not followed by dementia in the next decade, a clinically relevant incident depression, as noticed and diagnosed by healthcare professionals in daily routine, can be a prodrome of dementia and signal an increased dementia risk in the near future. Such a diagnosis should prompt diagnostic scrutiny and monitoring for cognitive and functional impairment. This is particularly true for the younger elderly population, where the prevalence of dementia is still low. Whether immediate and successful treatment of late-life depression can reduce the risk of dementia is an important field of future research.

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#### Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Kathrin Heser and Michael Wagner received financial support from the German Federal Ministry of Education and Research as part of the study 'Healthy Aging: Gender specific trajectories into latest life' (AgeDifferent.de; funding program 'Gesund – ein Leben lang', grant numbers 01GL1714A, 01GL1714B, 01GL1714C, 01GL1714D); Constantin Reinke and Gabriele Doblhammer received financial support from the German Research Foundation (Funding program 'Research Grants' https://gepris.dfg.de/ project number 386913674); Constantin Reinke received personal fees from Heidelberg Engineering

GmbH outside the submitted work; Gabriele Doblhammer received personal fees from Eli Lilly and Company outside the submitted work; there were no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years; and there were no other relationships or activities that could appear to have influenced the submitted work.

## Data availability statement

The Scientific Research Institute of the AOK (WIdO) imposes strict rules on sharing health claims data as these are classified according to ethical restrictions due to privacy concerns. Anonymized data are available to researchers and institutions upon request. In order to request access to the health claims data of the AOK, please contact the WIdO directly (http://www.wido.de/, mail: wido@wido.bv.aok.de).

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Parameter estimates (b) of regression models representing risk of subsequent dementia depending on incident depression diagnosis.
**Table S2.** Results of regression models representing risk of subsequent dementia depending on incident depression diagnosis using the alternative validation.