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Original Article

ORIGINAL ARTICLE

Chronic kidney disease is associated with incident depression requiring treatment: a retrospective cohort study

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ABSTRACT

Background. Depression is one of the most common psychiatric condition in patients with chronic kidney disease (CKD). It is associated with decreased adherence and quality of life as well as increased risk for dialysis, hospitalization, and mortality. Large population-based analysis evaluating the effect of CKD on the incidence of depression are missing.
Methods. We performed a retrospective cohort study investigating the incidence of depression after CKD diagnosis in a large cohort derived from the IQVIA™ Disease Analyzer database. Patients with CKD were matched to individuals without CKD using the nearest neighbor propensity score matching method. The 10-year cumulative incidence of depression was compared between the cohorts using Kaplan–Meier curves and an univariable conditional Cox regression analysis was performed to assess the association between CKD and depression, as well as antidepressant prescription.
Results. Both cohorts included 165 787 individuals each, either with or without CKD. The 10-year incidence of depression was 24.2% in patients with CKD and 22.2% in patients without CKD ($P < .001$). The incidence of depression followed by an antidepressant prescription was 9.0% in the CKD cohort and 3.5% in the non-CKD cohort ($P < .001$), resulting in a hazard ratio (HR) of 2.63 (95% confidence intervals (CI) 2.51–2.75). This association was strongest in younger patients below 60 years of age (HR 6.03, 95% CI 5.17–7.01).
Conclusion. In this large cohort, CKD is associated with a slightly higher incidence of depression requiring drug treatment. Clinicians caring for patients with CKD, especially younger patients, should be aware of the increased risk.

Keywords: antipsychotics, depression, kidney disease, mood disorders

INTRODUCTION

Chronic kidney disease (CKD) and its complications affect millions of people worldwide, with an estimated prevalence of ~10% and even higher numbers in the elderly [1, 2]. By 2040 CKD might be the fifth most common cause of life years lost globally [3]. Depression is an increasingly common mental health problem in Germany with a 26% rise in prevalence in recent years [4]. Importantly, CKD and depression pose a major societal and economic burden to healthcare systems worldwide [5, 6]. The link and complex interactions between chronic physical illness

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and depression are well established for many diseases [7, 8]. In the setting of CKD, depression is associated with poor outcomes. Dialysis-dependent CKD patients suffering from depression show decreased adherence, increased healthcare utilization, hospitalization, and mortality [9–14]. Non-dialysis-dependent CKD patients suffering from depression show reduced quality of life, more rapid decline of kidney function as well as increased risk for dialysis, hospitalization, and mortality [15–19]. These associations with poor outcomes and the fact that patients recognize psychosocial aspects of living with CKD as most important research priority demands further research on depression in CKD [20].

A meta-analysis of >55 000 patients reported an overall prevalence of ∼25% of depression or depressive symptoms in patients with CKD, included studies were mostly of a cross-sectional design [21, 22]. The prevalence of depressive symptoms varies widely between individual studies, from 25% to almost 100%, with all studies containing a relatively low number of non-dialysis patients [16–18, 21–24]. Another major drawback of a lot of studies is the reliance on self-rating scales in a cross-sectional design, which probably overestimate the prevalence of depression in patients with CKD due to the high burden of somatic symptoms [25, 26]. Currently, longitudinal studies investigating the effect of CKD on developing depression are mostly lacking. In this context, a recent population-based study of 157 398 adults with CKD found an incidence of depression of 8.1% during a median follow-up of 5.1 years [19]. However, this study lacked a control cohort without CKD. To circumvent these limitations and investigate the association of CKD with the incidence of depression, we conducted a population-based retrospective cohort study.

MATERIALS AND METHODS

This study was a retrospective cohort study comparing the incidence of depression in patients with CKD and matched controls without CKD treated in primary care practices in Germany between 2005 and 2022.

Database

This retrospective cohort study is based on data from the Disease Analyzer database (owned by IQVIA). This data source has already been used in several previous studies focusing on depression [27, 28] and CKD [29]. It contains anonymized data on diagnoses, prescriptions, and basic demographic data from computer systems used in the offices of practices [30]. The database contains ∼3000 office-based practices in Germany. The sampling method for the Disease Analyzer database uses statistics from the German Medical Association to determine the panel design according to specialist group, German federal state, community size category, and physician age. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialized practices in Germany [30].

Study population

This study included individuals aged ≥18 years with a CKD diagnosis (ICD-10: N18, N19) in 1293 primary care practices in Germany between January 2005 and December 2022. The date of the CKD diagnosis constituted the index date for the CKD cohort (index date; Fig. 1). For the non-CKD cohort, the index date was that of a randomly selected visit between January 2005 and December 2022 (Fig. 1). Further inclusion criterion was an observation time of at least 12 months before the index date. Patients with schizophrenia (ICD-10: F20-F25), mood (ICD-10: F30-F39), neurotic, stress-related, and somatoforme disorders (ICD-10: F40-F48) documented within 12 months prior to or on the index date were excluded.

After applying similar inclusion criteria, individuals without CKD were matched to CKD patients using nearest neighbor propensity score matching (1:1) based on age, sex, index time (2005–2010, 2011–2016, 2017–2022), average yearly consultation frequency during the follow-up, and Charlson Comorbidity Index (CCI) without CKD. CCI is a weighted index that accounts for the number and severity of comorbidities and includes a wide range of comorbidities (macrovascular diseases; pulmonary diseases; gastrointestinal, liver, and renal diseases; diabetes; tumors; and AIDS) [31].

Standardized mean difference (SMD) was considered to examine the balance of covariate distribution between study cohorts after matching. In this study we allowed a SMD of <0.1 indicating that adequate covariate balance has been achieved [32, 33].

Study outcomes and statistical analyses

The outcome of the study was the diagnoses of depression (ICD-10: F32, F33) within up to 10 years following the index date as function of CKD. In patients with diagnosed depression, prescription of antidepressant (ATC Codes N06A) was also evaluated. Each patient was followed from the index date until the timepoint at which a depression was documented, the last consultation occurred, or the end of the 10-year follow-up period was reached, whichever occurred first.

The 10-year cumulative incidence of depression in the cohort with and without CKD was studied using Kaplan–Meier curves. Finally, an univariable conditional Cox regression analysis was conducted to assess the association between CKD and depression, as well as antidepressant prescription. Results of the Cox regression model have been displayed as hazard ratios (HRs) and 95% confidence intervals (CIs). Regression models were conducted separately for individuals with and without a history of psychiatric diseases as well as separately by age group and sex. For the subpopulation of patients with documented CKD severity stage, regression analyses were conducted for severity stages: stage 1 (ICD-10: N18.1), stage 2 and 3 (ICD-10: N18.2, N18.3), and stages 4 and 5 (ICD-10: N18.4, N18.5). Because of multiple models, a P value of <.001 was considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, USA).

RESULTS

Basic characteristics of the study sample

The present study included 165 787 individuals with CKD and 165 787 individuals without CKD. The characteristics of the study patients are displayed in Table 1. Mean age was 71.6 [standard deviation (SD): 13.1] years, and 48.3% were women. Patients had an appointment with their physician on average 8.8 times per year during the follow-up period. The median CCI was 3.0 for both groups and a history of psychiatric diseases was present in 15.2% and 15.3%.

Due to the matched pairs design, no significant differences were observable between both cohorts in terms of age, sex, visit frequency, CCI, and index period (Table 1).

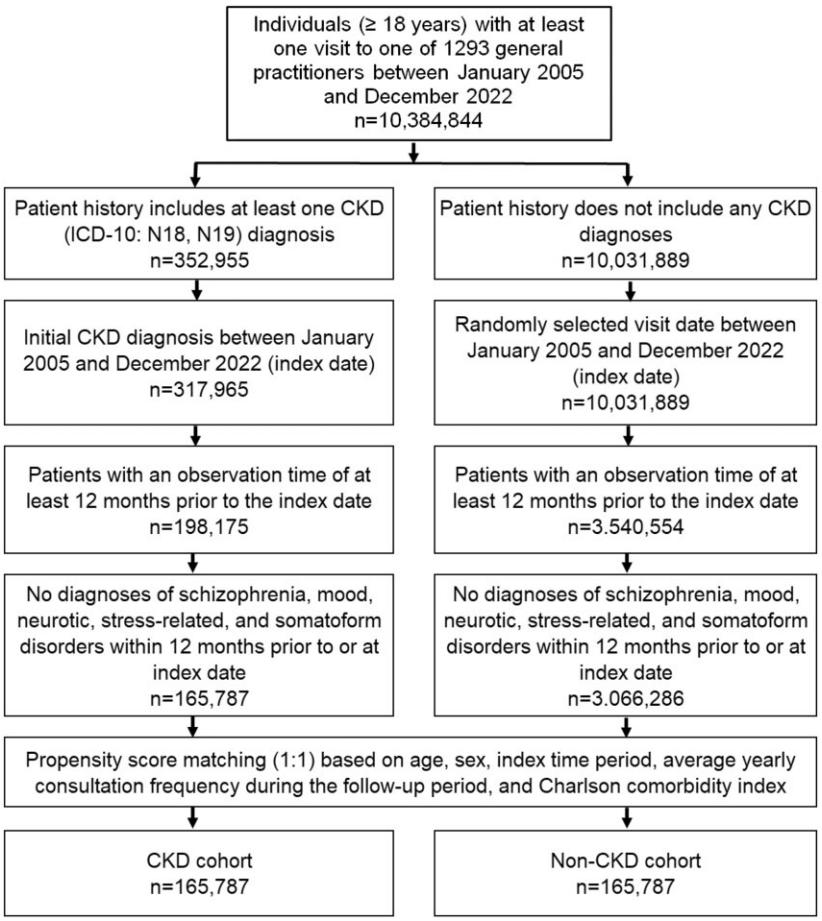

Figure 1: Selection of the study patients.

Among 165 787 CKD patients, CKD stage on the index date was known for 76 666 patients. The most frequent ones were stage 2 (18.2%) and stage 3 (17.9%).

Cumulative incidence of documented depression and antidepressant therapy

The 10-year cumulative incidence of depression was 24.2% in CKD patients and 22.2% in patients without CKD ($P < .001$) (Fig. 2a). A depression diagnosis followed by an antidepressant prescription was observed in 9.0% of the CKD patients and in 3.5% of the patients without CKD ($P < .001$) (Fig. 2b).

Association of CKD with subsequent depression and antidepressant therapy

In the regression analysis, CKD was slightly but significantly associated with an increased risk of a depression diagnosis (HR: 1.11; 95% CI: 1.09–1.13; $P < .001$) and with a slightly stronger association in individuals aged >80 years (HR: 1.20; 95% CI: 1.15–1.26; $P < .001$). The association between CKD and a diagnosis of depression with a subsequent antidepressant prescription was strong (HR: 2.63; 95% CI: 2.51–2.75; $P < .001$), particularly in patients aged ≤60 (HR: 6.03; 95% CI: 5.17–7.02; $P < .001$) (Table 2). When comparing patients of different CKD stages with their matched pairs, the association between CKD and subsequent depression was stronger in stages 4–5 (HR: 1.20) than in stages 1 and 2–3, but these associations did not reach the statistical significance of <.001. The association between different CKD stages and a depression diagnosis with a subsequent antidepressant prescription during follow-up was strong (Table 2).

Antidepressant therapy

Figure 3 shows the proportion of the ten most frequently prescribed antidepressant drugs in cohorts with and without CKD diagnosis. Mirtazapine was prescribed in 25% of CKD and 25% of non-CKD patients following by citalopram (CKD 18%, no CKD 20%), opipramol (CKD 12%, no CKD 12%), amitriptyline (CKD 9%, no CKD 9%), and escitalopram (CKD 7%, no CKD 6%). The distribution of antidepressants did not statistically differ between patents with and without CKD.

DISCUSSION

In this large population-based retrospective cohort study, CKD was associated with a slightly increased risk for incident depression and a strong association between an incident depression diagnoses and subsequent initiation of an antidepressant. This association was particularly pronounced in younger patients below the age of 60 years.

Table 1: Baseline characteristics of the study sample (after propensity score matching).

Variable	Proportion among Individuals with CKD (%) $n = 165\,787$	Proportion among individuals without CKD (%) $n = 165\,787$	SMD
Age (mean, SD)	71.6 (13.1)	71.6 (13.1)	0.02
Age ≤60	30 473 (18.4)	30 506 (18.4)	
Age 61–70	33 806 (20.4)	33 887 (20.5)	
Age 71–80	57 031 (34.4)	57 088 (34.4)	
Age >80	44 477 (26.8)	44 306 (26.7)	
Women	80 009 (48.3)	80 123 (48.3)	0.00
Men	85 778 (51.7)	85 664 (51.7)	
2005–2010	18 815 (11.4)	18.803 (11.4)	
2011–2016	62 654 (37.8)	62 580 (37.8)	0.00
2017–2022	84 318 (50.9)	84 404 (50.9)	
Number of physician visits per year during the follow-up (mean, SD)	8.8 (4.1)	8.8 (4.1)	−0.01
CCI score (mean, SD)	3.0 (2.0)	3.0 (2.0)	0.00
Myocardial infarction	12 057 (7.5)	10 577 (6.6)	
Congestive heart failure	33 219 (20.7)	22 602 (14,1)	
Peripheral vascular diseases	28 364 (17.7)	23 575 (14.7)	
Cerebrovascular diseases	28 268 (17.6)	30 665 (19.1)	
Dementia	10 124 (6.3)	13 779 (8.6)	
Chronic pulmonary disease	46 457 (29.0)	53 495 (33.4)	
Connective tissue disease	7 420 (4.6)	7 694 (4.8)	
Peptic ulcer disease	5 360 (3.3)	5 347 (3.3)	
Liver disease	26 453 (16.5)	24 647 (15.4)	
Diabetes mellitus	65 786 (41.0)	53 273 (33.2)	
Cancer	21 032 (13,1)	20 204 (12.6)	
History of psychiatric diseases	25 379 (15.3)	25 112 (15.2)	−0.01
CKD Stage 1	11 154 (7,0)		
CKD Stage 2	29 237 (18.2)		
CKD Stage 3	28 773 (17.9)		
CKD Stage 4	3 987 (2.5)		
CKD Stage 5	1 377 (0.9)		
CKD with undocumented Stage	85 853 (53.5)		

Proportions of patients in percent given, unless otherwise indicated. CKD: chronic kidney disease; SD: standard deviation.

The 10-year cumulative incidence of a depression diagnosis was 24.2% in CKD patients, which was significantly, but only slightly higher than in controls without CKD. Most CKD patients in our study had stages 1–3. CKD in its early stages is often associated with a low symptom or pill burden and few medical restrictions. Therefore, early stages of CKD are often perceived by patients as not very life impairing. On the other hand, treating physicians might often focus on the somatic symptoms of CKD, rather than the psychosocial aspects, overlooking especially cases of mild depression. Patients themselves might attribute symptoms of depression-like lack of energy, disturbed sleep, or changes in appetite to their diagnosis of CKD rather than acknowledging they might suffer from concomitant depression. All these factors could explain the only marginally higher cumulative incidence of overall depression and higher incidence of depression requiring antidepressant therapy in our analyzed CKD cohort.

Most previously published studies followed a cross-sectional design and only reported the prevalence of depression at a given point in time. Only few studies report the incidence of depression after the diagnosis of CKD. A recent study of 157 398 individuals with CKD reported an incidence of depression of 8.1% during a median follow-up of 5.1 years [19]. The study also established depression as a possible risk factor for poor outcomes in CKD, such as hospitalization, CKD progression and all-cause mortality but lacked a comparison cohort without CKD. The overall lower incidence of depression diagnoses compared to our current study might be explained by the shorter follow-up time. However, it has to be acknowledged that the incidence of depression with a subsequent antidepressant prescription was much lower in our study, highlighting that one has to keep in mind that there is a difference between the incidence of mild or more severe cases of depression.

Although depression is well coded in the Disease Analyzer, its severity, ranging from mild to severe, is not. To separate mild depression from moderate to severe depression, the incidence of depression with a consecutive antidepressant prescription was analyzed. As per guideline recommendations, mild depression is often managed by active surveillance and supplemental treatment, whereas moderate to severe depression should be treated with an antidepressant [34, 35]. Unfortunately, the Disease Analyzer does also not contain information on how depression was diagnosed or whether other medical specialties such as psychiatrists or psychologists were consulted.

Our study adds to the body of existing literature by demonstrating that CKD is strongly associated with the occurrence of more severe depression forms. Of note, we found a particularly strong association in younger patients aged ≤60 (HR: 6.03). This is an interesting finding given that in the setting of chronic disease older age usually seems to be associated with a higher risk of depression [8]. This could show that a diagnosis of CKD might be an incisive experience especially for younger patients. CKD

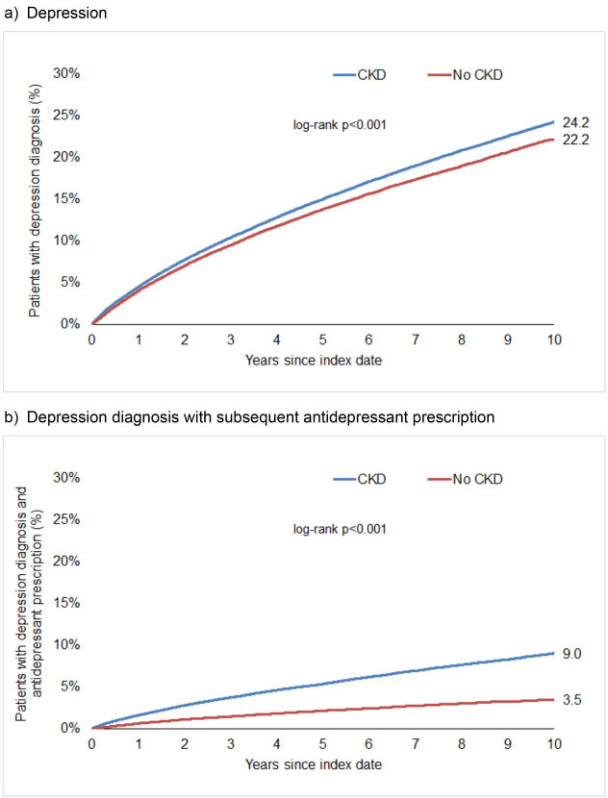

Figure 2: Cumulative incidence of depression diagnosis in individuals with and without CKD. (**a**) Depression. (**b**) Depression diagnosis with subsequent antidepressant prescription.

usually means permanent medication use and living with the eventuality of the need for renal replacement therapy. This could explain a stronger impact on psychosocial cognition and social roles in younger individuals.

Additionally, we found no gender effect, which is surprising regarding the incidence of depression. In studies analyzing the general population, women have a ~2-fold increased risk for depression [36]. The association of CKD with the incidence of depression diagnosis independent of gender suggests that CKD itself might increase the risk of depression beyond the baseline risk in the general population equalizing the usual gender differences.

Due to the design of our study, we are unable to delineate pathophysiologic reasons for the association between CKD and the incidence of more severe stages of depression. However, we hypothesize that an important reason might be the huge burden of somatic symptoms associated with kidney diseases in general and the psychosocial aspects of living with a chronic, incurable disease [25, 26].

Causative, depression and CKD are both associated with persistent low-grade inflammation [37, 38], which leads to altered metabolism of neurotransmitters [39]. Uremic toxins, accumulating with diminishing kidney function, are known to cause chronic low-grade inflammation [40]. In patients with kidney disease and depression higher levels of inflammatory markers such as Interleukin-6 and lower levels of serum albumin have been found when compared to patients with CKD without depression [41, 42]. Additionally, animal models of uremia show an altered neurotransmitter milieu, impairment of synaptic plasticity as well as depression-like behavior [43, 44]. Given that there are many different uremic compounds accumulating in the body with worsening of kidney function, it is hard to differentiate which one causes inflammation and psychological symptoms of depression. Additionally, vitamin D deficiency, which is a common complication of CKD, has been shown to be an independent predictor for concomitant depression, raising the question whether this is due to inherent functions of vitamin D or just confounding [45]. Unfortunately, this cannot be analyzed in our current study due to the fact that vitamin D is sold over the counter in Germany and is therefore not sufficiently captured in the database. The same applies to anemia which is a common complication of CKD [46, 47], and has been shown to be associated with depression especially in the elderly population [48].

The major strengths of this study are its large sample size, which is highly representative of the German population treated in primary care. This resulted in thorough and robust propensity score matching. Therefore, this study may serve as an initial step for further well-structured and thoroughly planned research focusing on extra-renal symptoms and improving quality of life in patients with CKD.

Table 2: Association between CKD and subsequent depression diagnosis in patients followed in primary care practices in Germany stratified by subgroups (univariable Cox regression models).

Patients group	Depression diagnosis	Depression diagnosis and subsequent antidepressant prescription
	HR (95% CI)	HR (95% CI)
Total	1.11 (1.09–1.13)*	2.63 (2.51–2.75)*
Age ≤60	1.03 (0.09–1.07)	6.03 (5.17–7.02)*
Age 61–70	1.12 (1.07–1.17)*	3.13 (2.78–3.52)*
Age 71–80	1.09 (1.06–1.13)*	2.12 (1.97–2.27)*
Age >80	1.20 (1.15–1.26)*	2.19 (2.01–2.38)*
Women	1.12 (1.09–1.15)**	2.66 (2.50–2.82)*
Men	1.10 (1.06–1.13)*	2.58 (2.40–2.78)*
No history of psychiatric disease	1.14 (1.11–1.17)*	2.83 (2.66–3.00)*
History of psychiatric disease	1.08 (1.04–1.11)*	2.37 (2.20–2.56)*
CKD Stage 1	1.07 (0.99–1.16)	3.08 (2.52–3.76)*
CKD Stage 2,3	1.04 (1.00–1.07)	2.43 (2.25–2.63)*
CKD Stage 4,5	1.20 (1.04–1.37)	2.66 (2.00–3.52)*

*P < .001

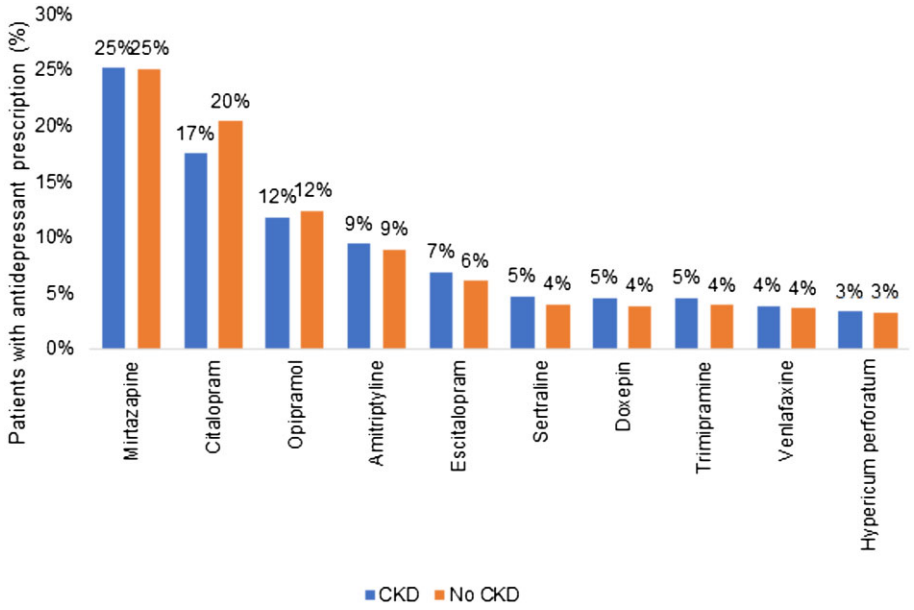

Figure 3: Proportions of different antidepressant drugs prescribed in patients with and without CKD.

However, there are also limitations that have to be acknowledged. The study relies on ICD-10 codes for diagnoses, which are used for the calculation of reimbursement of the underlying practices. This could lead to miscoding or undercoding of diagnosis due to missing financial incentives. This might in turn result in a falsely high or low incidence of depression but should affect both cohorts equally. On the other hand, it could lead to patients with CKD in the non-CKD cohort, therefore underestimating the effect of CKD on the incidence of depression. Due to the nature of these databases, patients with a coded diagnosis of a disease usually actually suffer from that disease [49]. Since prescriptions of medications require a diagnosis as indication, the findings regarding the diagnosis of depression followed by an antidepressant prescription are likely to be valid. Another limitation that has to be mentioned is that the database does not contain information on the way depression was diagnosed. Additionally, the database has no information on the relief of depressive symptoms or effectiveness of treatment.

The Disease Analyzer database does not include laboratory values for every patient and therefore we are also unable to track progression of kidney disease. This also means we cannot account for differences between early CKD, progression and the initiation of renal replacement therapy. Additionally, etiologies of CKD, e.g. diabetic or hypertensive nephropathy, are not sufficiently coded. Due to the long observation period and the missing data on the progression of kidney disease, we cannot account for progression to end stage kidney disease needing dialysis or transplantation and at which point in time this happened. Therefore, we cannot delineate the effect of rapid progression on depression risk in CKD. Moreover, the database does not contain data on hospitalizations, possibly confounding the outcome. However, we matched for contacts with the respective physician, which might decrease the risk for this potential bias.

In conclusion, this study demonstrates a robust association between CKD and an incident depression diagnosis with subsequent initiation of an antidepressant in German patients treated in primary care. Clinicians caring for patients with CKD should be aware of the slightly increased risk in these patients. However, our findings argue against strict screening protocols for the detection of depression in all patients with CKD. Despite this, some awareness should be raised for younger patients, given that depression risk was highest in this subgroup.

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AUTHORS’ CONTRIBUTIONS

A.K., K.K., and C.L. designed the study. K.K. performed statistical analyses and generated figures and tables. A.K., K.K., and C.L. wrote the manuscript. P.C.C., E.M.S., and J.W.M. provided intellectual input and revised the manuscript. All authors agreed to the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly due to ethical restrictions but are available on reasonable request from K.K.

CONFLICT OF INTEREST STATEMENT

Karel Kostev is an employee of IQVIA. IQVIA has no influence on the preparation or subject matter of this paper. The other authors have no conflicts of interest regarding this tpaper.

ETHICAL STATEMENT

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments. The Disease Analyzer database, used for analysis, contains anonymized electronic patient records. Patient data were analyzed in aggregated form without individual data being available. An individual consent form was not obtained following national and European legislation.

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