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Eight-year nationwide study of the bidirectional association between type 2 diabetes and depression in nearly 8 million German outpatients

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ABSTRACT

Introduction Research linking type 2 diabetes and depression mostly relied on hospital-based diagnoses or prescription data, overlooking many outpatient diagnoses. We aimed to quantify the risks of depression in individuals newly diagnosed with type 2 diabetes, and type 2 diabetes in those newly diagnosed with depression, while exploring potential risk differences depending on age, sex, and follow-up time.

Research design and methods We conducted a matched cohort study using German nationwide outpatient claims data from 2012 to 2022. Participants were individuals newly diagnosed with type 2 diabetes (N=294 642) or depression (N=1 271 537) in 2015, matched in a 1:4 ratio to controls without these conditions by age, sex, and region. The bidirectional risk was evaluated over an 8-year period using mixed-effects Cox proportional hazards models, adjusting for the Charlson Comorbidity Index, urbanicity, and area-level deprivation.

Results New type 2 diabetes diagnosis was associated with higher depression risk over 8 years (N=54 561 with depression, HR=1.23, 99% CI=1.21 to 1.24). Similarly, depression diagnosis was linked to an increased type 2 diabetes risk (N=71 848 with type 2 diabetes, HR=1.15, 99% CI=1.14 to 1.17). The association between depression and type 2 diabetes was stronger in younger age groups, especially under 34 years. Findings held across sex-stratified analyses. Time stratification showed a more pronounced association between type 2 diabetes and depression risk during the earlier follow-up quarters, whereas the risk of developing type 2 diabetes after depression diagnosis remained constant throughout the follow-up period.

Conclusions Our findings confirm a bidirectional link between type 2 diabetes and depression, particularly in younger individuals. As type 2 diabetes and depression are frequent, future research needs to study whether preventive approaches can reduce the risk of developing this comorbidity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have demonstrated a bidirectional relationship between type 2 diabetes and depression, predominantly relying on hospital-based diagnoses or prescription data.

WHAT THIS STUDY ADDS

⇒ This study extends our understanding by confirming the bidirectional association between type 2 diabetes and depression using nationwide outpatient claims data from Germany. Furthermore, it identifies a heightened risk among younger age groups, shedding light on previously underexplored demographic factors.

HOW THIS STUDY MIGHT AFFECT

⇒ The findings underscore the critical need for immediate post-diagnosis preventive strategies targeting both physical and mental health aspects, particularly among younger individuals.

BACKGROUND

Type 2 diabetes and depression, both major causes of disability worldwide,[1] frequently coexist. According to recent epidemiological data, an estimated 529 million people worldwide were living with diabetes in 2021, with type 2 diabetes cases comprising 96% of all diabetes cases.[2] Projections further indicate a rise to 1.3 billion by 2050.[2] Similarly, the global burden of depression remains significant, with approximately 279.6 million people affected in 2019, and these numbers are expected to rise in the coming decades.[3] Longitudinal studies have demonstrated that those with type 2 diabetes are at an elevated risk of developing depression,[4] and reciprocally, those with depression exhibit a greater risk of type 2 diabetes onset.[5] Moreover, individuals affected by both conditions experience increased type 2 diabetes complications,[6] poorer glycemic control, reduced quality of life, heightened healthcare costs,[7] and premature mortality.[8]

However, previous research examining the comorbidity of type 2 diabetes and depression was often limited by relying on survey

data,[4 9] introducing potential reporting biases. Additionally, reliance on hospital-based diagnoses or prescription data poses concerns of selection bias, given that only a fraction of cases are diagnosed within hospital settings, and not all are treated pharmacologically. However, both conditions are frequently encountered in outpatient primary care and specialist practices. Furthermore, many of the previous studies offer a limited temporal perspective, often providing only a few time point comparisons rather than a comprehensive longitudinal view. In contrast, administrative data, as routinely generated within the healthcare system, holds the potential to provide longitudinal data on prevalent health conditions. For instance, the German nationwide Statutory Health Insurance (SHI) physicians' claims data provide longitudinal outpatient care data over extended periods, encapsulating approximately 86% of the German population, an estimate based on 2015 data.[10] These extensive and longitudinal administrative data become particularly valuable when studying the bidirectional link between type 2 diabetes and depression. It allows us to differentiate the risk of developing type 2 diabetes after a depression diagnosis and vice versa over an extended period, encompassing almost the entire German population. Recognizing the value of such data, especially within the context of these highly prevalent diseases, we aimed to address the gaps identified in previous research.

Using German nationwide outpatient claims data, our study addresses three objectives: (1) to assess the risk of incident depression over an 8-year follow-up among individuals newly diagnosed with type 2 diabetes, compared against matched controls without type 2 diabetes, (2) to assess the risk of incident type 2 diabetes among those newly diagnosed with depression over the identical period, compared with matched controls without depression, and (3) to examine potential risk differences depending on age, sex, and follow-up time.

RESEARCH DESIGN AND METHODS

Study design and population

This study used nationwide outpatient claims data from all SHI-accredited physicians (general practitioners and specialists, including those in psychiatric care) and psychotherapists across Germany from 2012 to 2022, collected in accordance with §295 Social Code Book 5. The data set incorporated information on provided medical services per the Uniform Value Scale, diagnoses coded according to the International Classification of Diseases, 10th revision, German modification (ICD-10-GM), and insurees' age, sex, and residential region.

Individuals included needed to have at least one billable contact in 2015 and another in 2012 or earlier. Outpatient diagnoses were associated with a specific calendar quarter (e.g, January–March) since exact diagnosis dates were not available. We estimated the risk of developing comorbidity from 2015 to 2022 in those newly diagnosed in 2015, applying a matched cohort design (figure 1).

Operationalization of type 2 diabetes and depression

Two diagnostic lists were used for type 2 diabetes and depression, the one broad and the other narrow, as shown in online supplemental figure 1. For diabetes, the broad definition encompassed codes E10–E14 of the ICD-10-GM, covering types 1 and 2 diabetes mellitus (DM), malnutrition-related DM, other specified DM, and unspecified DM. The narrow definition, on the other hand, included codes E11–E14, that is, type 2

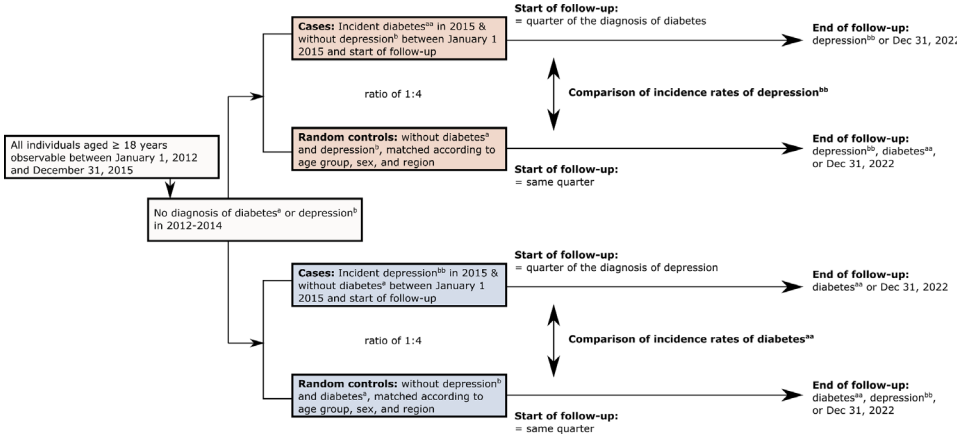

Figure 1 Study design for examining (a) the risk of developing depression over an 8-year follow-up among individuals initially diagnosed with type 2 diabetes, in comparison with matched controls without type 2 diabetes, and (b) conversely, the risk of developing type 2 diabetes in individuals first diagnosed with depression, compared with their matched controls without depression. [a]Diagnosis of diabetes based on broad definition including ICD-10-GM E10–E14 (types 1 and 2 diabetes mellitus, malnutrition-related diabetes mellitus, other specified diabetes mellitus, unspecified diabetes mellitus). [aa]Diagnosis of diabetes based on narrow definition including ICD-10-GM E11–E14 (type 2 diabetes mellitus, malnutrition-related diabetes mellitus, other specified diabetes mellitus, unspecified diabetes mellitus). [b]Diagnosis of depression based on broad definition including ICD-10-GM F32 (depressive episode), F33 (recurrent depressive disorder), and F34.1 (dysthymia). [bb]Diagnosis of depression based on narrow definition including ICD-10-GM F32 (depressive episode) and F34.1 (dysthymia). ICD-10-GM, International Classification of Diseases, 10th revision, German modification.

DM, malnutrition-related DM, other specified DM, and unspecified DM. When considering depression, the broad definition incorporated the ICD-10-GM codes F32 (depressive episode), F33 (recurrent depressive disorder), and F34.1 (dysthymia), while the narrow definition only considered F32 (depressive episode) and F34.1 (dysthymia).

We adopted this dual diagnostic approach for two primary reasons. First, our aim was to exclude diagnoses of recurrent depression throughout the observation period, which extended from January 1, 2012 to December 31, 2015. Second, given that the E14 code (unspecified diabetes) often encompasses cases that are fundamentally E11 (type 2 diabetes), relying solely on E11 could lead to systematic bias. This kind of misclassification might also occur when individuals with type 2 diabetes are initially diagnosed under the E12 or E13 codes, potentially causing cases of prevalent type 2 diabetes to be erroneously identified as incident cases. Thus, the broad definition ensured that the cohorts were free from prior diabetes and depression diagnoses, allowing us to infer that all detected cases were most likely incident cases of both conditions. In contrast, the narrow definition specifically targeted the identification of incident cases and outcomes.

For our analyses, we exclusively considered 'assured' diagnoses since outpatient care diagnoses in Germany were accompanied by a compulsory diagnostic modifier, indicating the level of diagnostic certainty (categories: 'assured,' 'suspected,' 'status post,' 'excluded').

Depression cases were grouped into four severity groups: mild (F32.0, F33.0, F34.1), moderate (F32.1, F33.1), severe (F32.2, F32.3, F33.2, F33.3), and unspecified (F32.8, F32.9, F33.8, F33.9). In the case of differing depression diagnoses in the index quarter with regard to severity, we chose the most severe diagnosis for classification.

Additionally, to determine incident cases of type 2 diabetes, it was necessary that at least one specific fee schedule item (Gebührenordnungsposition, GOP) was present, indicating type 2 diabetes-specific diagnostic procedures, or that instructions for self-monitoring of blood glucose were billed in the quarter when the diabetes diagnosis was made. The GOPs in consideration were: 32094 (glycated hemoglobin (HbA1c) test), 32025 or 32057 or 32881 (random blood sugar test and fasting blood sugar test), and 03355 or 13360 (instructions for self-monitoring of blood glucose).

Definition of cases and controls

We defined cases as individuals newly diagnosed with either type 2 diabetes (E11–E14: type 2 diabetes, malnutrition-related DM, other specified DM, unspecified DM) or depression (F32, F34.1: depressive episode, dysthymia) in 2015, excluding those with a prior diagnosis of the other disease at or before the start of follow-up. Controls for each condition were devoid of both conditions from 2012 to their 2015 matching point and were paired 4:1 with cases considering age group (5-year categories), sex, and residential area (spanning 17 regions corresponding to different Associations of SHI Physicians in Germany). Hence, two matching steps were undertaken for each cohort, respectively. Controls who received a diagnosis defining the cases (e.g., receiving a depression diagnosis when being a control for a depression case) and subsequently changed their exposure status were censored at the beginning of the calendar quarter of diagnosis to ensure that the comparison between cases and controls accurately reflects the intended research question, which was to estimate the risk of incident depression over an 8-year follow-up among individuals newly diagnosed with type 2 diabetes, compared against matched controls without type 2 diabetes, and vice versa. Sensitivity analyses, conducted without censoring controls who changed their exposure status during follow-up, showed similar results (see online supplemental tables 6 and 7).

Follow-up and outcomes

Follow-up started at the end of the quarter of diagnosis for both cases and controls (index quarter; for example, March 31 for those diagnosed in the period January 1–March 31) and continued until the occurrence of an outcome or December 31, 2022, whatever came first. The outcome of interest was depression in type 2 diabetes cases and controls (and vice versa). For individuals with an outcome of interest, person-time was counted up to the end date of the quarter the outcome occurred. Controls who received a diagnosis defining the cases (eg, receiving a depression diagnosis when being a control for a depression case) were censored at the beginning of the calendar quarter of diagnosis. Instances of loss to follow-up, which might arise from causes such as death, emigration, or other reasons resulting in an individual's unavailability for continued observation, were not factored into our analyses.

Statistical analysis

We evaluated whether type 2 diabetes was associated with an increased risk of incident depression and vice versa in the 8-year follow-up period by estimating hazard ratios (HRs) using mixed-effects Cox proportional hazards regression. The proportional hazards assumption was checked visually by comparing the Kaplan-Meier survival curves of cases and controls and plotting Schoenfeld residuals against time.

We adjusted for the potential confounding effects of medical comorbidity burden by adding the Charlson Comorbidity Index (CCI; excluding type 2 diabetes and type 2 diabetes with chronic complications) as a covariate in the Cox regression models. Information about the 15 major disease groups were categorized based on the number of diseases (0, 1, and ≥2) registered in the individual 12-month time frame before the index quarter. See online supplemental table 1 for the ICD-10 codes of the variables included in the CCI.

Moreover, the degree of urbanicity of the residential area according to the four-level classification adopted from the Federal Institute for Research on Building, Urban Affairs and Spatial Development (rural areas with low population density, rural areas with population concentrations, urban districts, and big urban municipalities)[11] and area-level deprivation index (least to most deprived, five categories)[12] were added as covariates. Assuming that individuals in a residential area are subject to the same structural living and care conditions (e.g., environment, physician density) that affect health risks in addition to individual factors, we considered the district of residence (N=402) as the smallest available spatial unit as a random effect. For age-depending, sex-depending, and time-depending variations in risk, we conducted stratified analyses.

Time-to-event curves for cases and controls, that is, developing depression in the diabetes cohort and developing diabetes in the depression cohort, respectively, presented in the online supplemental figure 2 were depicted as inverse of the Kaplan-Meier survival curves. Mathematically, this can be expressed as 1–S(t), where S(t) is the proportion of event-free patients at time t.

The cumulative incidence of newly diagnosed disease in 2015 was assessed as proportion per 1000 persons at risk, that is, without prior diagnosis in the years 2012–2014, by sex and age group.

Data availability

The data analyzed in this study are not publicly available due to the data protection regulations of the German Social Code Book (Fünftes Sozialgesetzbuch, SGB V).

RESULTS

Study population characteristics

From 2012 to 2015, we evaluated 53 207 495 individuals aged ≥18 years. Of these, 16 903 073 were excluded due to a diagnosis of either diabetes or depression between January 1, 2012 and December 31, 2014 (5 411 859 individuals due to diabetes, 9 371 081 due to depression, and 2 120 133 had both diagnoses). Thus, our analysis comprised 36 304 422 patients without prior diagnosis of diabetes or depression.

Within this cohort of 36 304 422 individuals, we identified 294 642 incident type 2 diabetes cases based on the narrow definition and matched 1 178 568 controls in 2015. For incident depression, 1 271 537 cases were identified using the narrow definition, and 5 086 148 controls were matched.

Both cohorts showed balanced age and sex distribution. Minimal variation was noted for area-level deprivation and urbanicity, but a higher medical comorbidity rate was evident in cases versus controls (table 1 and online supplemental table 2 for details).

The average follow-up was 6.6 (SD 1.9) and 6.5 (SD 1.9) years for type 2 diabetes cases and controls, respectively, and 7.2 (SD 1.0) and 6.6 (SD 1.8) years for depression cases and controls, respectively.

Incidence of type 2 diabetes and depression in 2015

Figure 2 illustrates sex-specific and age group-specific incidence for type 2 diabetes (figure 2A) and depression (figure 2B) in 2015. Type 2 diabetes incidence rises until 35–39 years, with men peaking at 65–69 years and women at 75–79 years, followed by subsequent declines. Depression incidence rises until 30–34 years, with subsequent varied patterns: men dip from 55 to 59 to 65–69 years before escalating again up in the oldest age group, while women plateau until 50–54 years, decline until 65–69 years, and then stabilize, consistently higher than men at all ages.

Risk of developing depression after incident type 2 diabetes

Throughout the 8-year follow-up, we identified 54 561 incident depression cases among individuals diagnosed with type 2 diabetes in 2015, and 174 292 incident depression cases within the control group without type 2 diabetes. When adjusting for medical comorbidities, urbanicity, and area-level deprivation as fixed effects, and residential district as random effect, a new diagnosis of type 2 diabetes was associated with a higher risk of depression in the following 8 years, with an adjusted HR of 1.23 (99% CI: 1.21 to 1.24) (online supplemental table 3).

Upon stratifying by age and accounting for the above-listed fixed and random effects, our data indicated a stronger association between younger age and risk of depression, though the age group of ≥90 years displayed an association similar to the middle-aged cohort (figure 3).

When stratified by follow-up time, our data showed a stronger association between earlier follow-up quarters and subsequent depression. Compared with matched controls, the first follow-up quarter was associated with an almost 50% higher risk, which decreased to approximately a 20% increase from the 9th to the 31st quarter (figure 3).

Risk of developing type 2 diabetes after incident depression

We identified 71 848 incident type 2 diabetes cases among individuals diagnosed with depression in 2015, compared with 215 352 within the non-depression control group during the follow-up. Examining the reciprocal association, we found that after adjusting for the same set of fixed and random effects, incident depression in 2015 was associated with an increased risk of type 2 diabetes diagnosis over the following 8 years (adjusted HR 1.15, 99% CI 1.14 to 1.17) (online supplemental table 4). In a subgroup analysis, the depression case group was divided into four severity subcategories, revealing stronger association between the highest level of depression severity and subsequent type 2 diabetes (online supplemental table 5).

Age-stratified analysis showed comparable trends to depression risk after incident type 2 diabetes, showing

Table 1 Characteristics of total population, cases and controls of the cohorts

Variable	No (%)				
	Overall*	Diabetes cohort		Depression cohort	
	n=36 304 422	Cases (n=294 642)	Controls (n=1 178 568)	Cases (n=1 271 537)	Controls (n=5 086 148)
Women	19 074 809 (52.5)	131 642 (44.7)	526 568 (44.7)	814 334 (64.0)	3 257 336 (64.0)
Age, median (IQR), years	48 (33–62)	63 (53–74)	63 (52–74)	48 (34–60)	48 (34–60)
Depression severity					
Mild	–	–	–	223 999 (17.6)	–
Moderate	–	–	–	262 971 (20.7)	–
Severe	–	–	–	80 836 (6.4)	–
Unspecified	–	–	–	703 731 (55.3)	–
Charlson Comorbidity Index					
0	25 052 577 (69.0)	155 943 (52.9)	716 345 (60.8)	824 230 (64.8)	3 669 763 (72.2)
1	7 885 189 (21.7)	82 433 (28.0)	299 923 (25.4)	321 063 (25.2)	1 065 529 (20.9)
≥2	3 366 656 (9.3)	56 266 (19.1)	162 300 (13.8)	126 244 (9.9)	350 856 (6.9)
District types					
Big urban municipalities	9 875 378 (27.2)	79 902 (27.1)	305 705 (25.9)	389 379 (30.6)	1 452 198 (28.6)
Urban districts	14 522 091 (40.0)	107 448 (36.5)	446 604 (37.9)	502 067 (39.5)	2 057 184 (40.4)
Rural area with population concentrations	6 508 473 (17.9)	56 134 (19.1)	227 997 (19.3)	208 828 (16.4)	865 517 (17.0)
Rural area with low population density	6 508 473 (14.9)	51 158 (17.4)	198 262 (16.8)	171 263 (13.5)	711 249 (14.0)
Deprivation index					
Lowest	8 517 794 (23.5)	55 509 (18.8)	229 861 (19.5)	308 106 (24.2)	1 243 230 (24.4)
Low	6 828 421 (18.8)	49 205 (16.7)	201 701 (17.1)	245 895 (19.3)	961 348 (18.9)
Middle	7 285 399 (20.1)	55 793 (18.9)	227 480 (19.3)	244 868 (19.3)	1 009 778 (19.9)
High	7 689 509 (21.2)	72 841 (24.7)	291 334 (24.7)	273 568 (21.5)	1 103 747 (21.7)
Highest	5 983 299 (16.5)	61 294 (20.8)	228 192 (19.4)	199 100 (15.7)	768 045 (15.1)

*In the overall observed population, the reference quarter was designated as the first quarter of 2015, which meant that comorbidities were recorded over the four quarters preceding it in 2014.

weaker associations in older age groups, except for the ≥90 years age group (figure 3). Follow-up time-stratified analyses pointed to consistent strength of association over the 8-year span, with the association being more marked in the first quarter (figure 3).

Upon stratifying by sex, we observed only minor differences in the association between depression and type 2 diabetes following a 2015 diagnosis. Among males, the HR was 1.26 (99% CI 1.24 to 1.29), while among females, the HR was 1.20 (99% CI 1.18 to 1.22). When considering the risk of type 2 diabetes following a 2015 depression diagnosis, females exhibited an association with HR of 1.18 (99% CI 1.17 to 1.20), while males had an HR of 1.12 (99% CI 1.11 to 1.14).

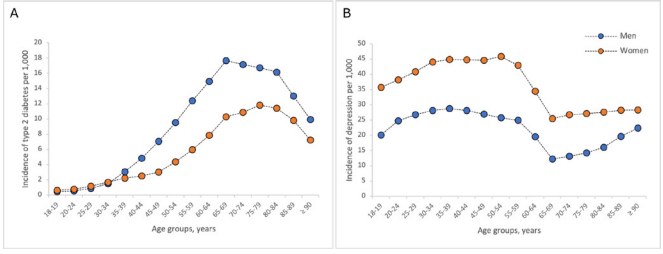

Figure 2 Cumulative incidence of (A) type 2 diabetes and (B) depression in 2015 in men and women, stratified by age groups.

DISCUSSION

In an 8-year nationwide outpatient cohort study examining 294 642 individuals with type 2 diabetes and 1 271 537 individuals with depression, we observed bidirectional associations between type 2 diabetes and depression. Incident type 2 diabetes in 2015 was associated with a 22.7% increased risk of subsequent depression, and a 2015 incident depression diagnosis was associated with a 15.3% increased risk of subsequent type 2 diabetes, both after adjusting for chronic medical conditions, region of residence, and area-level deprivation.

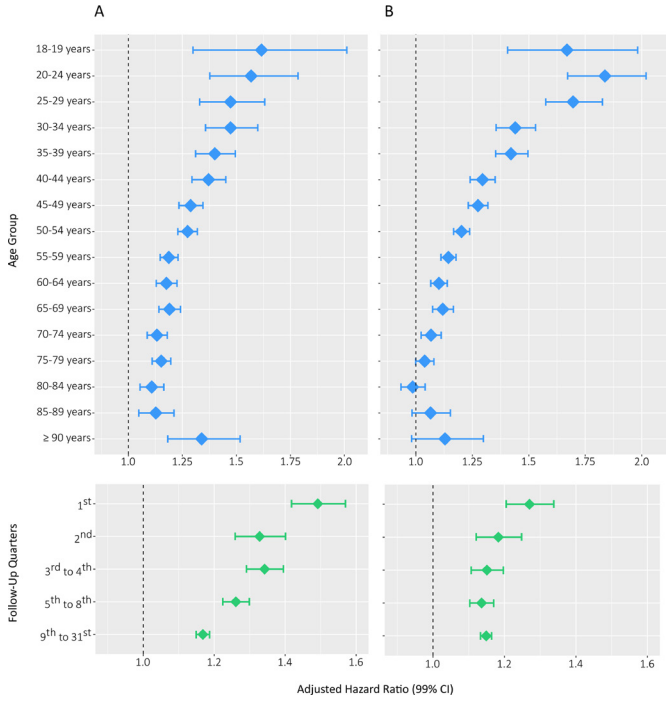

Figure 3 Age group-stratified and follow-up time-stratified adjusted HRs for the risk of developing depression after incident type 2 diabetes (A) and vice versa (B).

Between 2012 and 2014, a substantial number of individuals were diagnosed with a form of diabetes, while approximately double that number had existing depression, highlighting the considerable public health impact of these diseases. After excluding these prevalent cases, our findings regarding the 2015 incidence of depression across age and sex align with, yet are not identical to, previous research.[13 14] Notably, we observed a linear increase until the 30–34 years age group without a distinct peak during adolescence, which is likely attributable to our youngest age group being 18–19 years. A shift toward a midlife peak incidence of depression in the German adult population might be influenced by societal factors and reporting biases among younger individuals. This notion is supported by one of our prior studies, which highlighted an elevated risk of comorbid depression and obesity for middle-aged men and age-specific differences in reporting of depression diagnoses in a representative sample for the German adult population.[15] Additionally, while Pedersen *et al* identified a second peak in the elderly,[13] in our analysis, this peak was discernible only among men, suggesting potential differences in causes of depression in later life.[16] The gender disparity in incidence across several studies necessitates more nuanced, gender-sensitive approaches in depression epidemiology and intervention strategies.

A previous study using Danish registers has shown that individuals with newly diagnosed type 2 diabetes are at increased risk of initiating pharmacological treatment with an antidepressant with an HR of 1.51, while the risk of having a psychiatric hospital contact was not increased to the same extent (HR=1.14).[4] We add to this evidence by showing a 22.7% increased risk of being diagnosed with depression after type 2 diabetes diagnosis in outpatient care, using longitudinal data from approximately 86% of the German population.[10] Both type 2 diabetes and depression, being common in outpatient settings, do not always necessitate medication or inpatient treatment, emphasizing the significance of our findings in an outpatient context. Biological mechanisms, including the disruption of insulin signaling[17] and stress pathway activation,[18] may contribute to higher depression risk following type 2 diabetes. Additionally, the psychological ramifications of chronic disease diagnoses, such as type 2 diabetes, can trigger social and emotional distress, potentially increasing the risk of depression. While factors such as medical comorbidities[19] and environmental influences, such as low socioeconomic status,[20] might confound this relationship, the higher risk of depression remained significant after accounting for these factors.

In contrast to previous research conducted using Danish hospital diagnosis and prescription data,[9] which indicated a stronger association between depression and subsequent type 2 diabetes compared with the association between type 2 diabetes and subsequent depression, our analyses based on German outpatient data suggest a weaker association between type 2 diabetes following depression. Notably, when an alternative definition for type 2 diabetes relying solely on hospital diagnosis was employed, Wimberley *et al* reported an even stronger association between depression and subsequent type 2 diabetes.[9] Since hospital diagnoses tend to capture more severe cases, it raises the possibility that the link between depression and type 2 diabetes may be influenced by disease severity. Indeed, our subgroup analyses also reveal a stronger association between the highest level of depression severity and subsequent type 2 diabetes. These discrepancies, driven by variations in study settings, warrant careful consideration, especially in the context of future targeted interventions aimed at mitigating the burden of this comorbidity. Our findings underscore the importance of prioritizing interventions to prevent depression following the diagnosis of type 2 diabetes, given the multiple distress factors associated with this scenario, including challenges in adhering to medical recommendations, social stigma, and reduced quality of life.[21 22] One potential approach involves reducing barriers in both primary and specialty care settings to facilitate screening for depression and diabetes-related distress, which could positively influence the risk of developing depression and also improve diabetes care.[23] The proposed mechanisms through which depression precipitates type 2 diabetes involve both direct biological effects and indirect influences via health behaviors. Another consideration is the potential diabetogenic effects of certain antidepressant medications.[24] Moreover, individuals newly diagnosed with depression may already exhibit preclinical alterations, such as altered insulin resistance, potential precursors to type 2 diabetes, a phenomenon similarly observed in bipolar disorder.[25]

Recent Mendelian randomization studies also pointed to a causal relationship between depression and type 2 diabetes, with approximately 36.5% of this effect being channeled through body mass index.[26] This suggests that obesity could be a shared underlying factor linking depression and type 2 diabetes.

In our analysis of both directions of association, age stratification highlighted differential risks across age groups. Younger individuals were more susceptible to developing the comorbidity than their middle-aged or elderly counterparts. However, the ≥90 years age group stood out as an exception. This deviation may be influenced by survivorship bias, indicating those reaching such advanced ages might possess unique health or genetic profiles not typical of the wider population, altering perceived risk dynamics. Moreover, there is an increased risk of misclassification among the elderly due to potential non-capture of depressive episodes predating the pre-observational period. Intriguingly, our analyses consistently highlight a heightened risk in younger individuals, which may be potentially attributed to unique challenges they face, particularly when considering health disparities in relation to their same-aged peers. Early onset of type 2 diabetes or depression in younger ages might also flag a group with an unusually high medical burden, especially because younger individuals tend to seek medical consultations less frequently, resulting in fewer diagnoses.[15 27] Lastly, the age trends we observed may be shaped by our methodological choices. Specifically, we excluded those with existing depression or diabetes between 2012 and 2014. Consequently, elderly individuals newly diagnosed with depression or type 2 diabetes at a more advanced age may not carry a heightened risk of the other condition compared with their controls, representing a selectively 'healthier' cohort, having reached advanced ages without either condition, suggesting an inherent resilience.

The immediate quarter following incident type 2 diabetes or depression diagnosis emerged as the most vulnerable period, possibly due to detection bias from temporarily increased medical attention. Distinctively, while depression risks decreased over time following type 2 diabetes, the risk of type 2 diabetes following depression remained consistently elevated, potentially reflecting the distinct nature of diabetes, which might take longer to manifest, whereas depression could be more immediately triggered.

Through sex-stratified analyses, we observed minimal divergence between sexes. Previous findings of higher comorbidity rates in women parallel our observation of elevated type 2 diabetes risk following depression in women.[28 29] Notably, hormonal fluctuations during the perimenopausal phase have been linked to elevated depression rates in longitudinal studies involving premenopausal women.[30] Additionally, the perimenopausal period is associated with weight gain and the onset of metabolic diseases.[31] These biological factors could potentially contribute to the observed disparities. Furthermore, variations in mental healthcare utilization by gender, with women being more likely to access healthcare services, may also influence comorbidity risk differently between men and women.[32] Meanwhile, psychosocial factors and medical factors, such as obesity and alcohol use,[33] might differentially influence the risk of depression for men and women following type 2 diabetes diagnosis, thereby meriting further exploration.

One of the limitations of our study is the inherent assumption that individuals without a specified outcome or exposure diagnosis survive until the end of follow-up. Differential mortality rates between cases and controls, attributed to their distinct disease exposures, could pose competing risks. This becomes increasingly relevant given the heightened mortality often associated with type 2 diabetes, predominantly due to cardiovascular comorbidities.[34] While age-matching addresses this to a degree, the lack of mortality data likely biases our results. However, this might lead to a more cautious interpretation of the association, rather than overestimating it. In other words, our study may underestimate the impact of type 2 diabetes on the risk of developing depression due to the unaccounted deaths among individuals with diabetes who might have developed depression had they survived. Additionally, factors such as individuals leaving SHI, migrating to other countries, or not using medical healthcare services would result in a loss to follow-up. Unfortunately, we cannot account for these reasons as the claims data lack such information. Consequently, our analyses may carry a bias and cannot be generalized to individuals who did not seek statutory healthcare during the observational period. Another limitation lies in the reliance on accurate diagnosis and precise data input by healthcare professionals and/or administrators.

A broader perspective, as depicted by Lindekilde *et al*,[35] suggests an array of psychiatric disorders, beyond depression, as potential risk factors for incident type 2 diabetes. Furthermore, it has been reported that antidepressant medication may mediate the relationship between depression and type 2 diabetes.[24] Our study, however, did not incorporate data on the relationship between type 2 diabetes and other psychiatric disorders or medication, limiting the scope of our findings. We did not have access to diabetes biomarkers like HbA1c. Nonetheless, we employed two distinct diagnostic lists based on ICD-10-GM codes to delineate cases and controls. This approach served a dual purpose—it not only ensured the exclusion of individuals with prior diabetes and depression diagnoses within our cohorts, allowing us to confidently identify all detected cases as incident cases to the highest degree possible, but also facilitated the differentiation between type 1 and type 2 diabetes cases. In the context of diabetes, the broader definition encompassed ICD-10-GM codes for all types of diabetes, while the narrower definition included only type 2 DM, malnutrition-related DM, other specified DM, and unspecified DM. Given that adult type 1 diabetes cases constituted a mere 0.3% of the total 9.7% diabetes prevalence in Germany in 2010, as indicated

by data from both inpatient and outpatient sectors,[36] the likelihood of misclassifying individuals with type 1 diabetes as type 2 diabetes cases using the narrow definition remains low. Additionally, although we made efforts to control for potential confounding factors, the possibility of unmeasured or residual confounding (e.g., individual lifestyle factors) cannot be entirely ruled out in observational studies of this nature.

While we acknowledge the potential for bias due to not adjusting for the matching factors age and sex in our Cox proportional hazards model, we mitigated this limitation through stratified analyses by age group and sex. These stratifications allowed us to explore risk within subgroups stratified by these key demographic variables, providing valuable insights into the associations under study. The third matching factor (residential area) was taken into account by including the district of residence as random effect.

Our study design aimed to estimate the risk of developing type 2 diabetes following the initial diagnosis of depression, irrespective of the course of the depressive illness, including whether it was episodic or chronic. Consequently, individuals without depression at baseline were censored from the control group of the depression cohort if they subsequently developed depression during the follow-up period, but individuals in the depression group were not similarly excluded if their depression resolved during the follow-up. This approach was chosen to focus on the association between incident depression and type 2 diabetes, but we acknowledge that it may be perceived as inconsistent with the treatment of individuals in the depression group. Moreover, our results might not be representative of those experiencing recurrent depressive episodes, particularly in the context of age-stratified analyses. Additionally, there is potential for misclassification, where individuals diagnosed with depression before our pre-observational period might inadvertently be labeled as incident cases. Given that our study used only outpatient claims data, the results may not generalize to inpatient treatments typically involving more severe manifestations.

While our use of a matched cohort study design and adjustments for covariates enhanced the internal validity of our findings, it is important to acknowledge that this approach may have reduced statistical power due to a smaller sample size. Nevertheless, given the enormity of the data set including almost the entire German adult population, practical feasibility and computational resources played a significant role in our methodology selection. Matching more controls or including the entire data set would have posed substantial computational challenges without necessarily substantially enhancing statistical power. Our primary limitation lies in the availability of additional data rather than the sample size itself. Lastly, we did not consider time-dependent variables and this may have influenced the trajectories of depression and type 2 diabetes over the observed span.

CONCLUSIONS

In summary, our study, based on extensive German nationwide outpatient claims data spanning an 8-year follow-up period following a 3-year pre-observational phase, offers a comprehensive insight into the bidirectional relationship between type 2 diabetes and depression, particularly across diverse demographic subgroups. Our analysis revealed that incident type 2 diabetes in 2015 was associated with a 22.7% increased risk of subsequent depression, while an incident depression diagnosis in the same year was linked to a 15.3% elevated risk of subsequent type 2 diabetes. These associations persisted even after adjustments for chronic medical conditions, region of residence, and area-level deprivation. In light of the evidence presented here and recent research demonstrating the potential for improved outcomes through early detection and management of this prevalent comorbidity, our study underscores the pressing need for immediate post-diagnosis preventive strategies and the integration of medical and mental healthcare. This emphasis is particularly critical in the context of younger populations who appear to be more vulnerable. For example, the antidepressant bupropion has exhibited promise in enhancing glycemic control and insulin sensitivity,[37] while collaborative care or integrative care models that combine cognitive–behavioral therapy with lifestyle counseling have demonstrated effectiveness not only in reducing depressive symptoms but also in fostering positive lifestyle changes and improving glycemic outcomes.[38 39] Continued development and implementation of early intervention models that seamlessly integrate both medical and mental healthcare are essential. These models are instrumental in addressing the intricate health needs of individuals with the comorbidity of type 2 diabetes and depression.

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Patient consent for publication Not applicable.

Ethics approval This study used outpatient claims data from the 17 regional Associations of Statutory Health Insurance Physicians in Germany. In Germany, the use of claims data for scientific research is regulated by the Code of Social Law (SGB X). Ethical approval and informed consent are not required as this study used routinely collected anonymized data.

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