RESEARCH: EDUCATIONAL AND PSYCHOLOGICAL ASPECTS

DIABETIC Medicine

Sex-specific impact of major depressive disorder on 12-year change in glycaemic status: Results from a nationwide cohort study of adults without diabetes in Germany

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Abstract

Aims: There is evidence for an increased type 2 diabetes (T2D) risk associated with depression, but its role for diabetes prevention remains unclear. This study aimed to add insight by investigating the impact of major depressive disorder (MDD) on prospective glycaemic changes.

Methods: The study was based on a cohort of $n = 1,766$ adults without diabetes (776 men, 990 women; 18–65 years of age) who participated in the mental health supplement of the German National Health Interview and Examination Survey (GNHIES98-MHS, 1997–1999) and in a follow-up survey (DEGS1, 2008–2011). Glycaemic status was defined as normoglycaemia [HbA1c < 39 mmol/mol (<5.7%)], prediabetes [39 ≤ HbA1c < 48 mmol/mol (5.7–6.4%)] and diabetes [HbA1c ≥ 48 mmol/mol (≥ 6.5%), diagnosed diabetes, or antidiabetic medication], and glycaemic changes categorized as 'remission', 'stability' and 'progression'. Baseline MDD was assessed via a modified German version of the WHO Composite International Diagnostic Interview. Multivariable logistic regressions were applied to analyse the association of MDD with glycaemic changes and incident T2D, adjusting for socio-demographics, lifestyle conditions, chronic diseases, antidepressant use and mental health care.

Results: MDD prevalence was 21.4% for women and 8.9% for men. Among women, MDD was associated with a lower chance for remission (RRR 0.43; 95% CI 0.23, 0.82). Among men, MDD was not significantly related to glycaemic changes. MDD had no significant effect on incident T2D (men: OR 1.58; 0.55, 4.52; women: OR 0.76; 0.37, 1.58).

Conclusions: Findings of the current study highlight the role of depression in T2D prevention, particularly among women.

KEYWORDS
glycaemic status change, HbA1c, longitudinal, major depressive disorder, prediabetes, sex difference, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus is one of the leading causes of years lived with disability worldwide,[1] reflecting a global core health challenge of the 21st century. Furthermore, type 2 diabetes (T2D) represents the most common diabetes type, with a substantially increasing number of cases.[2] Moreover, T2D is linked to depression. Compared to the general population, the prevalence of major depressive disorder (MDD) is remarkably higher among persons with T2D.[3] Based on a meta-analysis, approximately one in four T2D patients shows concurrent depressive symptoms or disorders[4]—whereas only one in ten adults reports depressive symptoms in the general population in Germany.[5]

Given the emotional distress due to living with T2D,[6] it seems not surprising, that people with T2D have a higher risk to develop a MDD compared to people without T2D.[7]

Besides, there is strong evidence for a bi-directional relationship since meta-analyses of longitudinal studies also indicate an increased risk for incident T2D associated with depression, presumably owing to shared common risk factors such as adverse socioeconomic or lifestyle conditions and alterations in metabolic networks.[7–9] However, the evidence is heterogenous and various concepts and definitions of depression have been used, including self-reported depressive symptoms and psychological distress. Furthermore, the use of antidepressant medication was shown to be associated with an increased risk for incident diabetes, which may confound the association between depression and diabetes.[8] Thus, the specific role of clinically relevant MDD regarding T2D risk remains unclear. Moreover, previous studies did not examine the prospective impact of depression on changes in blood glucose levels, also covering prodromal changes from normoglycaemia to prediabetes. In addition, a subgroup meta-analysis indicated that the association of depression and T2D risk may differ between men and women, but only a small number of studies have reported sex-specific estimates, so far.[7]

Therefore, the present study aimed to analyse the impact of clinically relevant MDD on 12-year changes in glycaemic status among adults without diabetes at baseline, based on a nationwide, population-based cohort from Germany. We specifically asked for men and women: 1) Is MDD associated with prospective changes in glycaemic status, including remission and progression? 2) Is MDD associated with the onset of T2D?

2 | METHODS

2.1 | Data basis

Figure 1 shows a participant flow diagram describing the data basis and definition of the study population.

What's new

- Based on a cohort of adults aged 18–65 years without diabetes, major depressive disorder (MDD) at baseline had a sex-specific impact on changes in glycaemic status after 12 years.
- Among women, MDD was associated with a considerably lower chance for remission from prediabetes to normoglycaemia.
- Among men, MDD showed no significant association with remission or progression of glycaemic status over time.
- MDD was not significantly related to incident type 2 diabetes (T2D).
- The sex-specific findings of the current study highlight the role of depression in glycaemic changes and T2D prevention, particularly among women.

Data basis was a cohort study of adults aged 18–65 years and without diagnosed or unknown diabetes at baseline who participated in the mental health supplement of the 'German National Health Interview and Examination Survey 1998' (GNHIES98-MHS) in 1997–1999 and within the examination part of the 'German Health Interview and Examination Survey for Adults' (DEGS1) in 2008–2011. Both national health surveys targeted non-institutionalized adults residing in Germany; design and methods have previously been described in detail.[10–12] In brief, a two-stage stratified cluster sampling procedure was used in GNHIES98 to select participants aged 18–79 years ($n = 7,124$). Overall, 87.6% ($n = 4,181$) of GNHIES98 participants aged 18–65 years also took part in the mental health supplement GNHIES98-MHS, among them $n = 3,783$ participants without diagnosed or unknown diabetes. The subsequent DEGS1 ($n = 8,151$) combined a nationally representative survey ($n = 4,192$, 18–79 years of age) and a longitudinal follow-up of former GNHIES98 participants ($n = 3,959$, 18–91 years), including $n = 2,452$ GNHIES98-MHS participants without diagnosed or unknown diabetes. Among them, $n = 1,891$ also took part in the DEGS1 examination part.

For this study, we excluded persons with missing information for defining glycaemic status changes between baseline and follow-up ($n = 21$), with missing information for any covariables ($n = 88$), and individuals with incident type 1 or gestational diabetes at follow-up ($n = 16$). The final study sample was $n = 1,766$ (men: $n = 776$; women: $n = 990$).

GNHIES98 and DEGS1 were conducted according to the Federal and State Commissioners for Data Protection
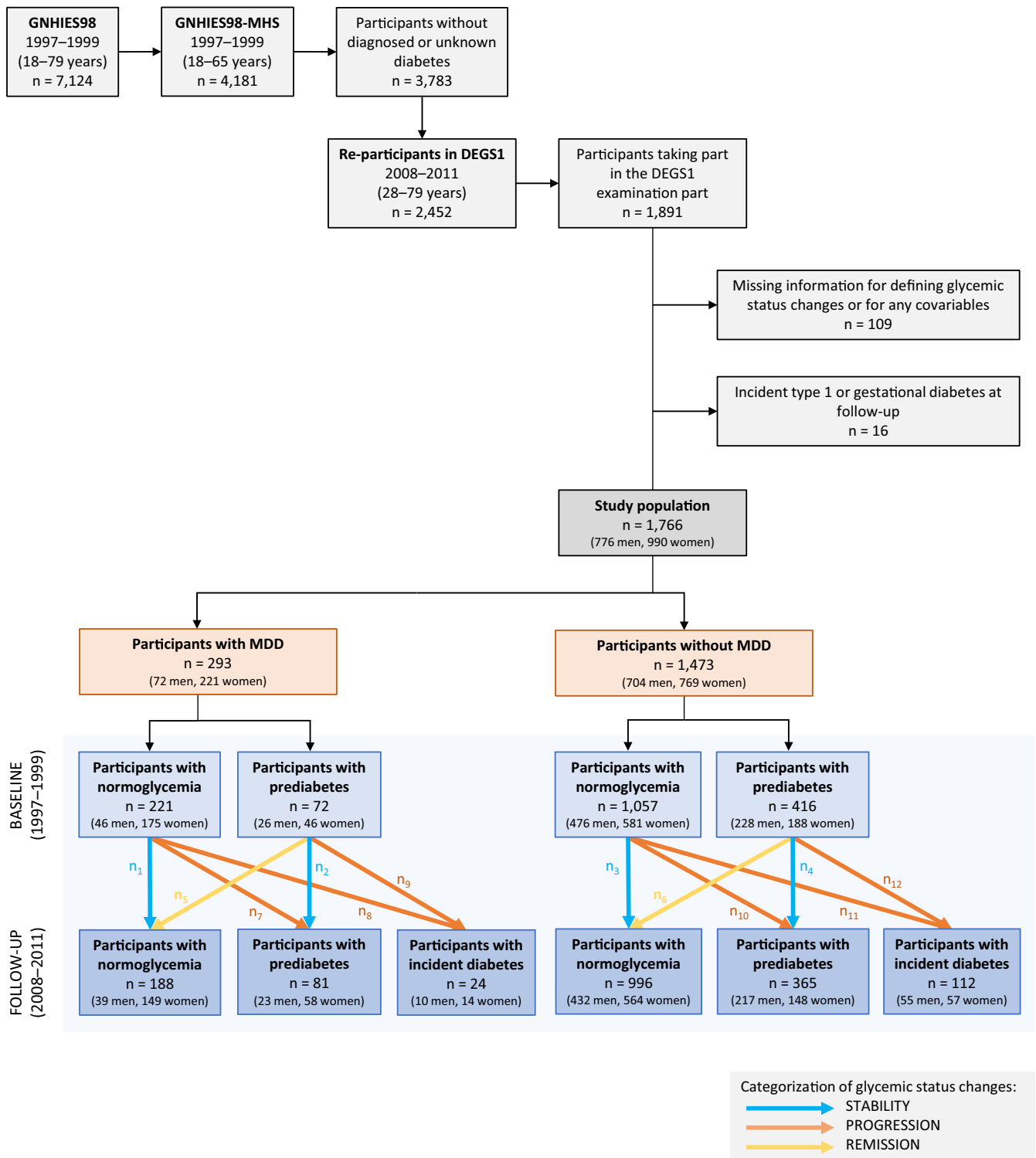
FIGURE 1 Participant flow diagram describing the definition of the study population (n = 1,766) and glycaemic status changes between baseline (GNHIES98-MHS) and follow-up (DEGS1). Frequencies of itemized changes: n_1 = 162 (29 men, 133 women), n_2 = 28 (10 men, 18 women), n_3 = 812 (340 men, 472 women), n_4 = 153 (99 men, 54 women), n_5 = 26 (10 men, 16 women), n_6 = 184 (92 men, 92 women), n_7 = 53 (13 men, 40 women), n_8 = 6 (4 men, 2 women), n_9 = 18 (6 men, 12 women), n_{10} = 212 (118 men, 94 women), n_{11} = 33 (18 men, 15 women), n_{12} = 79 (37 men, 42 women). GNHIES98-MHS: German National Health Interview and Examination Survey 1998, mental health supplement; DEGS1: German Health Interview and Examination Survey for Adults; MDD: major depressive disorder [Colour figure can be viewed at wileyonlinelibrary.com

guidelines. DEGS1 was approved by the local ethics committee at Charité – Universitätsmedizin Berlin in October 2008 (No: EA2/047/08). The implementation of the surveys conformed to the principles of the Helsinki Declaration. Participants provided written informed consent prior to participation.

2.2 | Glycaemic changes

Diagnosed diabetes was defined as self-reported physician-diagnosed diabetes in standardized computer-aided personal interview (CAPI) or as taking any anti-diabetic medication (Anatomical Therapeutic Chemical (ATC) Code A10) within the 7 days preceding the interview. Using HbA1c measurements, participants without diagnosed diabetes were categorized into normoglycaemia [< 39 mmol/mol (<5.7%)], prediabetes [39 ≤ HbA1c < 48 mmol/mol (5.7–6.4%)] and unknown diabetes [≥48 mmol/mol (≥6.5%)] according to previous definitions using recommendations of the American Diabetes Association.[13] For this study, diagnosed and unknown diabetes at follow-up were summarized as 'diabetes'. HbA1c was assessed from venous blood samples drawn in both surveys, using a Diamant high-performance liquid chromatography (HPLC) analyzer (Bio-Rad Laboratories, Munich, Germany) in GNHIES98, and an immunoturbidimetric method (ARCHITECT ci8200; Abbott, Wiesbaden, Germany) in DEGS1. Both methods were traceable to the National Glycohemoglobin Standardization Program and the comparability of methods was carefully assessed in a metabolically healthy subset of study participants aged 18–39 years as previously shown.[13,14]

Glycaemic changes over time were categorized into 're-mission' (from prediabetes to normoglycaemia), 'stability' (unchanged normoglycaemic or prediabetic status) and 'progression' (from normoglycaemia to prediabetes or diabetes, or from prediabetes to diabetes).

2.3 | MDD assessment

Lifetime MDD ('yes' vs. 'no') was assessed by clinically trained interviewers at baseline in the GNHIES98-MHS and according to diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),[15] using a modified German version of the WHO Composite International Diagnostic Interview (DIA-X/M-CIDI),[16] a standardized and fully-structured clinical face-to-face interview. DSM-IV criteria for MDD diagnosis require at least five of nine symptoms persisting nearly every day for a minimum of 2 weeks, accompanied by clinically significant distress and impairment. Depressive mood and/or decreased interest/pleasure should be present. MDD exclusion criteria are lifetime (hypo)manic episodes and depressive symptoms due to direct physiological effects of a substance, a general medical condition or attributable to grief.

2.4 | Covariables

All covariables described below were assessed at baseline.

Standardized self-administered questionnaires were used to collect information on sex, age, educational level (categorized as 'low', 'medium' vs. 'high' according to the Comparative Analysis of Social Mobility in Industrial Nations criteria, CASMIN) and living alone (being the only person living in the household, 'yes' vs. 'no').

Social support was categorized into 'low' (up to three persons) versus 'high' (at least four persons), based on a question of the Oslo-3 Social Support Scale ("How many people are so close to you that you can count on them if you have serious personal problems?").[17]

The German Diabetes Risk Score (GDRS)[18] was used to estimate the predicted 5-year risk of T2D, based on self-reported information on age, smoking, physical activity, prevalent hypertension, family history of diabetes, intake of coffee, wholegrain and red meat, as well as standardized measures of body height and waist circumference, as previously described.[19]

Comorbid conditions were assessed via CAPI. Calculating the number of self-reported physician-diagnosed chronic diseases other than diabetes (categorized into 'no', 'one' vs. 'at least two'), we considered the following conditions: a lifetime history of cancer, myocardial infarction, stroke, chronic heart failure, osteoarthritis, osteoporosis, Parkinson's disease, and cirrhosis of the liver as well as asthma, rheumatoid arthritis, gout, hepatitis, gastric-duodenal ulcer, epilepsy, hypertension and dyslipidaemia within the past 12 months.

Information on antidepressant medication use (past 7 days) was recorded by trained health professionals via computer-assisted brown bag review of all medications—prescribed and Over-The-Counter (OTC) products. Universal product codes on the original medication containers were coded according to the ATC classification system. An ATC code N06A was considered as 'antidepressants' (including herbal antidepressants).

Self-reported utilization of health services (past 12 months) was assessed for several outpatient medical and therapeutic services via self-administered questionnaire. Mental health care use was defined as using a psychiatrist, neurologist or psychotherapist at least once during the past year ('yes' vs. 'no').

2.5 | Statistical analysis

Percentages, means and 95% confidence intervals (95% CIs) were calculated to describe the study participants' characteristics. All analyses were performed separately for men and women. Significance of differences was evaluated for each of the 10 variables based on Rao-Scott Chi-Square test (for categorial variables) or Adjusted Wald test (for continuous variables), using a significance level of 0.005 due to Bonferroni correction for multiple testing (calculated by dividing the conventional significance level by the number of variables: 0.05/10). The mean difference of HbA1c measurements (follow-up minus baseline) is only reported for participants without self-reported diagnosed diabetes at follow-up (740 men and 933 women), since accompanied antidiabetic treatment may affect blood glucose levels.

The impact of MDD on prospective glycaemic changes was evaluated based on multinomial logistic regression analyses (reported as risk rate ratio [RRR], which can be interpreted as odds ratio [OR], with 95% CI; reference category: 'stability'), adjusted for potential confounders at baseline, derived from the literature and available data in the survey: sex, educational status, living alone, social support, chronic conditions, 5-year T2D risk (including age), antidepressant medication and mental health care use—as well as the interaction of sex with MDD. As a result, we conducted sex-stratified analyses and added the considered covariables consecutively: Model 1 adjusted for age. Model 2 adjusted for age, educational status, living alone, social support and chronic conditions. Model 3 additionally accounted for the 5-year T2D risk (including age) without considering age separately anymore. Model 4 additionally adjusted for antidepressant medication and mental health care use.

In addition, the association of baseline MDD with incident T2D was evaluated based on sex-stratified multivariable logistic regression analyses (reported as OR with 95% CI), using MDD and consecutively added covariables (see Model 1 – 4) as independent variables.

A conventional significance level of 5% was considered statistically significant (two-sided tests). All statistical tests were performed with Stata SE 17.0 and its survey design procedures, using cohort-specific weighting factors adjusting for the demographic-geographic population structure and re-participation probabilities. The re-participation probability of GNHIES98-MHS participants without diabetes in the examination part of DEGS1 was derived from a generalized linear mixed model including the independent variables age at the time of GNHIES98-MHS (six categories) and at the time of DEGS1 (eight categories) as well as education (three categories), income (three categories), smoking (yes or no), migration background (yes or no) and 12-month MDD (yes or no) at the time of GNHIES98-MHS.

3 | RESULTS

3.1 | Study population and descriptive results

Figure 1 shows the GNHIES98-MHS-cohort and itemized glycaemic status changes between baseline and follow-up, depending on initial MDD status. Among 1,766 study participants, a total number of n = 293 participants aged 18–65 years was diagnosed with lifetime MDD at baseline (72 men, 221 women). Thus, lifetime MDD prevalence was 15.1% (men: 8.9%, women: 21.4%; p-value for sex difference <0.001). After a mean follow-up period of 11.9 years (range: 9.6–14.1 years), 69.5% of the participants with baseline MDD showed stability of their initial glycaemic status (men: 59%, women: 73.9%), 23% progressed to prediabetes or diabetes (men: 27%, women: 21.3%) and 7.5% showed remission from prediabetes to normoglycaemia (men: 14%, women: 4.8%). Among participants without MDD, 67.1% showed stability (men: 66.3%, women: 68.1%), 22.4% progressed (men: 21.6%, women: 23.3%) and 10.5% remitted (men: 12.1%, women: 8.6%). The proportion of incident cases of diagnosed or unknown T2D after 12 years was 5.9% among persons with baseline MDD (men: 7.7%; women: 5.2%) and 7.1% among individuals without MDD (men: 6.4%; women: 7.9%). Excluding participants with diagnosed diabetes at follow-up (36 men and 57 women), the mean difference of HbA1c measurements was 0.19% for participants with MDD (men: 0.19%, women: 0.19%) and 0.14% for participants without MDD (men: 0.16%, women: 0.12%).

Baseline characteristics of the study population are displayed in Table 1 for men and women with and without MDD. After applying a Bonferroni correction, the following significant sex differences were observed: Among women, there was a lower proportion of prediabetes ($p < 0.001$), a higher mean age ($p < 0.001$), a lower HbA1c mean value ($p < 0.001$), a higher antidepressant application frequency ($p < 0.001$), and a higher mental health care utilization rate ($p = 0.002$) compared to men. No significant differences of baseline characteristics were observed with regard to MDD status, except that participants with MDD reported mental health care use more often than participants without MDD (men: $p = 0.002$, women: $p < 0.001$).

Baseline characteristics depending on participants' glycaemic status are provided as supporting information (see Table S1). After applying a Bonferroni correction, participants with prediabetes had a higher HbA1c mean value

TABLE 1 Baseline characteristics of the study population

	Men			Women		
	With MDD (n = 72)	Without MDD (n = 704)	Total (n = 776)	With MDD (n = 221)	Without MDD (n = 769)	Total (n = 990)
Total, % (95% CI)	8.9 (6.9, 11.5)	91.1 (88.5, 93.1)	100	21.4 (18.4, 24.9)	78.6 (75.1, 81.6)	100
Glycaemic status, % (95% CI)						
Normoglycaemia	67.3 (52.4, 79.4)	69.8 (64.6, 74.4)	69.5 (64.6, 74.1)	80.8 (73.1, 86.8)	80.2 (76.5, 83.4)	80.3 (76.8, 83.4)
Prediabetes	32.7 (20.6, 47.6)	30.2 (25.6, 35.4)	30.5 (25.9, 35.4)	19.2 (13.2, 26.9)	19.8 (16.6, 23.5)	19.7 (16.6, 23.2)
HbA1c in %, mean (95% CI)	5.5 (5.3, 5.6)	5.4 (5.3, 5.4)	5.4 (5.4, 5.5)	5.3 (5.2, 5.3)	5.3 (5.3, 5.4)	5.3 (5.3, 5.3)
Age (years), mean (95% CI)	39.6 (36.0, 43.2)	39.2 (37.9, 40.5)	39.2 (38.0, 40.4)	42.3 (40.4, 44.3)	41.9 (40.6, 43.1)	42.0 (40.9, 43.1)
Educational level, % (95% CI)						
low	45.7 (30.9, 61.3)	43.7 (38.6, 49.0)	43.9 (38.8, 49.1)	40.4 (33.0, 48.2)	44.1 (39.0, 49.3)	43.3 (38.7, 48.0)
medium	45.7 (32.2, 59.8)	41.3 (36.5, 46.2)	41.6 (36.9, 46.5)	47.3 (40.4, 54.3)	46.4 (41.5, 51.2)	46.5 (42.4, 50.7)
high	8.7 (4.5, 16.2)	15.0 (12.2, 18.3)	14.5 (11.8, 17.5)	12.4 (8.1, 18.5)	9.6 (7.1, 12.8)	10.2 (7.9, 13.0)
Living alone, % (95% CI)						
no	25.5 (13.9, 42.0)	28.2 (23.4, 33.6)	28.0 (23.3, 33.2)	24.3 (17.6, 32.6)	20.8 (16.7, 25.7)	21.6 (17.8, 25.9)
yes	74.5 (58.0, 86.1)	71.8 (66.4, 76.6)	72.0 (66.8, 76.7)	75.7 (67.5, 82.4)	79.2 (74.3, 83.4)	78.4 (74.1, 82.2)
Social support, % (95% CI)						
low	30.3 (19.0, 44.6)	35.1 (30.9, 39.8)	34.7 (30.6, 39.1)	40.5 (32.7, 48.9)	34.0 (29.6, 38.7)	35.4 (31.4, 39.6)
high	69.7 (55.4, 81.0)	64.9 (60.2, 69.3)	65.3 (61.0, 69.5)	59.5 (51.1, 67.3)	66.0 (61.3, 70.4)	64.6 (60.4, 68.6)
Chronic somatic conditions, % (95% CI)						
no	55.4 (40.0, 69.8)	57.3 (52.4, 62.0)	57.1 (52.5, 61.6)	47.0 (38.6, 55.5)	58.0 (53.4, 62.5)	55.6 (51.5, 59.7)
1	33.1 (20.7, 48.4)	29.4 (25.2, 33.9)	29.7 (25.7, 34.0)	32.0 (23.9, 41.3)	24.8 (21.2, 28.8)	26.4 (23.1, 29.9)
≥ 2	11.6 (6.2, 20.5)	13.4 (10.7, 16.5)	13.2 (10.9, 15.9)	21.1 (14.6, 29.4)	17.2 (14.1, 20.7)	18.0 (15.0, 21.5)
5-year T2D risk in %, mean (95% CI)	2.3 (1.6, 2.9)	2.7 (2.4, 3.1)	2.7 (2.4, 3.0)	1.5 (1.2, 1.8)	2.2 (1.6, 2.7)	2.0 (1.6, 2.4)
Antidepressant medication use, % (95% CI)						
no	97.6 (93.0, 99.2)	98.4 (96.7, 99.2)	98.3 (96.8, 99.1)	93.4 (89.4, 96.0)	94.0 (91.7, 95.7)	93.9 (92.0, 95.4)
yes	2.4 (0.8, 6.9)	1.6 (0.8, 3.3)	1.7 (0.9, 3.2)	6.6 (4.0, 10.6)	6.0 (4.3, 8.3)	6.1 (4.6, 8.0)
Mental health care use, % (95% CI)						
no	87.1 (76.7, 93.2)	96.3 (94.4, 97.6)	95.5 (93.7, 96.8)	84.5 (78.3, 89.2)	93.0 (90.5, 95.0)	91.2 (88.6, 93.3)
yes	12.9 (6.8, 23.3)	3.7 (2.4, 5.6)	4.5 (3.2, 6.3)	15.5 (10.8, 21.7)	7.0 (5.0, 9.6)	8.8 (6.7, 11.4)

Note: The final study sample comprised n = 1,766 adults aged 18–65 years without diabetes at baseline who participated in the mental health supplement of the 'German National Health Interview and Examination Survey 1998' (GNHIES98-MHS) in 1997–1999 and re-participated an average of 12 years later in the examination part of the 'German Health Interview and Examination Survey for Adults' (DEGS1) in 2008–2011, after excluding persons with incident type1 diabetes or gestational diabetes at follow-up (n = 16), with missing information for defining glycaemic status at baseline or follow-up (n = 21), and with missing information for any covariables (n = 88). MDD: major depressive disorder; 95% CI: 95% confidence interval.

TABLE 2 Impact of lifetime major depressive disorder (MDD) at baseline on glycaemic changes at follow-up

	Men						Women					
	Remission (n = 102)		Stability (n = 478)	Progression (n = 196)		Remission (n = 108)		Stability (n = 677)	Progression (n = 205)	
	RRR (95% CI)	p-value	RRR	RRR (95% CI)	p-value	RRR (95% CI)	p-value	RRR	RRR (95% CI)	p-value
Model 1	1.30 (0.51, 3.30)	0.574	1.0 (ref)	1.42 (0.73, 2.79)	0.300	**0.50 (0.27, 0.90)**	**0.022**	1.0 (ref)	0.82 (0.49, 1.37)	0.444
Model 2	1.28 (0.51, 3.20)	0.602	1.0 (ref)	1.51 (0.82, 2.80)	0.184	**0.44 (0.24, 0.82)**	**0.011**	1.0 (ref)	0.80 (0.47, 1.37)	0.415
Model 3	1.31 (0.53, 3.23)	0.554	1.0 (ref)	1.62 (0.89, 2.97)	0.115	**0.45 (0.24, 0.84)**	**0.012**	1.0 (ref)	0.88 (0.52, 1.49)	0.630
Model 4	1.48 (0.60, 3.70)	0.394	1.0 (ref)	1.80 (0.97, 3.33)	0.063	**0.43 (0.23, 0.82)**	**0.011**	1.0 (ref)	0.90 (0.53, 1.55)	0.708

Note: Relative Risk Ratios (RRR) with 95% confidence intervals (95% CI) and p-values from multinomial logistic regression. Bold type indicates significant differences (local significance level α = 0.05). Model 1: adjusted for age; Model 2: adjusted for age, educational status, living alone, social support, chronic somatic conditions; Model 3: see Model 2, additionally adjusted for antidepressant medication and mental health care use; all covariables at baseline.

(men: $p < 0.001$, women: $p < 0.001$), a higher mean age (men: $p < 0.001$, women: $p < 0.001$), a higher occurrence of chronic somatic conditions (men: $p = 0.005$, women: $p < 0.001$), and a higher 5-year T2D risk (men: $p < 0.001$, women: $p < 0.001$) compared to participants with normo-glycaemia. Furthermore, the proportion of living alone differed depending on glycaemic status (men: $p = 0.001$, women: $p = 0.005$), as well as the educational level among women ($p = 0.001$).

3.2 | Association between MDD and glycaemic changes

In the overall study population, MDD had no effect on remission (RRR = 0.80; 95% CI: 0.43, 1.49; $p = 0.482$) or progression (RRR = 1.08; 95% CI: 0.70, 1.66; $p = 0.732$) of glycaemic status over time (fully adjusted model, ref.: stability), but there was a significant interaction effect of sex and MDD on remission (p-value for interaction = 0.049) and a tendency for an interaction effect of sex and MDD on progression (p-value for interaction = 0.082). Table 2 shows the results from multinomial logistic regression analyses for men and women.

Among women, baseline MDD was associated with a lower chance for remission, irrespective of covariates (model 4: RRR = 0.43; 95% CI: 0.23, 0.82; $p = 0.011$). There were no significant associations between MDD and progression (model 4: RRR = 0.90; 95% CI 0.53, 1.55; $p = 0.708$).

Among men, there were no significant associations of MDD with remission (model 4: RRR = 1.48; 95% CI 0.60, 3.70; $p = 0.394$) or progression (model 4: RRR = 1.80; 95% CI: 0.97, 3.33; $p = 0.063$).

3.3 | Association between MDD and T2D incidence

Table 3 shows the impact of MDD on incident T2D for men and women. For both sexes, MDD had no significant effect on incident T2D (men: OR = 1.58; 95% CI: 0.55, 4.52; $p = 0.389$; women: OR = 0.76; 95% CI: 0.37, 1.58; $p = 0.457$; see model 4).

4 | DISCUSSION

4.1 | Key findings

Based on a prospective population-based study, we examined the association of MDD with glycaemic changes and incident T2D after 12 years among adults without diabetes

TABLE 3 Impact of lifetime major depressive disorder (MDD) at baseline on incident type 2 diabetes (T2D) at follow-up

	Men (n = 776)		Women (n = 990)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Model 1	1.37 (0.52, 3.61)	0.517	0.66 (0.33, 1.32)	0.241
Model 2	1.25 (0.45, 3.47)	0.668	0.60 (0.29, 1.26)	0.174
Model 3	1.47 (0.53, 4.08)	0.456	0.74 (0.35, 1.56)	0.431
Model 4	1.58 (0.55, 4.52)	0.389	0.76 (0.37, 1.58)	0.457

Note: At follow-up, n = 65 men and n = 71 women showed incident T2D. Odds Ratios (OR) with 95% confidence intervals (95% CI) and p-values from logistic regression. Model 1: adjusted for age; Model 2: adjusted for age, educational status, living alone, social support, chronic somatic conditions; Model 3: adjusted for educational status, living alone, social support, chronic somatic conditions and 5-year T2D risk; Model 4: see Model 3, additionally adjusted for antidepressant medication and mental health care use; all covariables at baseline.

in Germany. Overall, we found no significant effect of MDD on remission or progression over time, but there was a sex-specific impact on glycaemic changes: Women with versus without MDD showed a remarkably lower chance for remission from prediabetes to normoglycaemia, irrespective whether covariables were considered or not. Among men, baseline MDD was not significantly related to glycaemic changes. For both sexes, MDD showed no significant association with incident T2D.

4.2 | Surrounding evidence

Overall, previous meta-analyses of prospective data revealed relative risks for incident T2D associated with depression ranging from 1.26 to 1.60, but findings largely vary between studies.[7-9] When considering only clinically relevant interview-defined MDD as within our study, one longitudinal analysis indicated a pronounced T2D risk (RR = 2.23).[20] Furthermore, studies controlling for unknown diabetes at baseline showed a slightly higher T2D risk associated with depression (RR = 1.54),[9] whereas studies using physiological examinations or clinical records for T2D assessment at follow-up showed smaller effects compared to studies focusing on self-reported diabetes, solely.[7] Moreover, also the age range of studies may be crucial, since a subgroup meta-analyses indicated a higher T2D risk associated with depression for persons aged less than 50 years (RR = 1.96) compared to persons ≥50 years (RR = 1.50).[7]

Based on a subgroup meta-analysis it was already suggested, that the association of depression and incident T2D varies by sex, with a presumably more pronounced T2D risk among men (RR = 1.57) compared to women (RR = 1.26).[7] Thus, our results may partly correspond to previous findings, since effect sizes and courses of associations among men also indicate an aggravation of glycaemic status and an increased T2D risk associated with MDD over time—and low statistical power may account for the

lacking significance of findings within this specific subgroup (see strengths and limitations). However, MDD had no impact on glycaemic status progression or on incident T2D among women within our study—albeit the outlined analysis indicated that the association may be weaker compared to men, but still apparent.[7] Nevertheless, three of the included studies revealed an association between depression and incident T2D among men, solely, and further research on sex differences is still needed.

Finally, by focusing on changes in blood glucose levels over time, our findings reveal an entirely different role of depression between men and women. Thus, depression among women may not provoke an aggravation of glycaemic status over time (as suggested for men), but account for the maintenance of a pre-existing elevated T2D risk instead (as indicated by a lower chance for remission from prediabetes to normoglycaemia)—and therefore, contribute to a higher T2D risk in a particular manner.

4.3 | Explanatory approaches

Several explanations for the observed sex-specific impact of MDD on glycaemic changes come into question:

First, sex differences in mental health literacy and mental health care utilization may have contributed to the sex-specific impact of MDD on glycaemic changes. Previous research already showed an increased T2D risk associated with untreated depression.[8] Unfortunately, our covariables on antidepressant and mental health care use covered only a short period, and information on MDD treatment status or history was not available. However, an additional analysis clearly indicates further pre-existing sex differences regarding mental health care as proxy, since the proportion of women with MDD also reporting any lifetime clinician-diagnosed mental disorder at baseline was almost two-fold compared to men with MDD (34.3% vs. 18.0%, *p* = 0.026). This corresponds to previous findings, showing that service utilization owing to mental

health problems is particularly low in men.[21] Based on a systematic review of literature, conformity to traditional male gender roles has an impact on (expression of) symptoms, attitudes to mental health care, help-seeking behavior and symptom management.[22] Furthermore, men's depression is more likely to be undetected by practitioners due to clinical bias.[23] Since GNHIES98, the gender gap in help-seeking for mental disorders even extended in Germany[21]—whereas the psychosocial burden of MDD particularly increased among men.[24] In conclusion, an inferior mental health care (utilization) among men most certainly contributes to a particular impact of depression on unfavourable glycaemic changes over time, as reflected by a more pronounced T2D risk among men versus women with MDD.[7]

Second, a reduced utilization of (preventive) physical health care as well as an inferior medical compliance in persons with MDD presumably affects the respective risk to develop cardiometabolic diseases.[25] Here, also men with MDD may particularly be disadvantaged, since women generally show higher utilization of outpatient medical services[26] and preventive services,[27] and determinants of physical health care utilization seem to be sex- and gender-role-specific.[28] Correspondingly, men with MDD show a two-fold risk for hospital admissions, whereas there is no such association among women with MDD.[29]

Third, our findings may reflect sex differences of further T2D risk factors among persons with MDD, particularly with regard to lifestyle conditions. As previously shown, the association of health behaviors (including smoking, alcohol consumption, sports, weight maintenance and consumption of fruits and vegetables) with diagnosed depression was specific to women.[30] Consequently, unfavourable health behaviours may account for the lower chance for remission from prediabetes to normoglycaemia among women with MDD within our study. Applying the GDRS, we accounted for major known behavior-related risk factors of T2D (summarized as 5-year T2D risk), including smoking, physical activity, intake of coffee, wholegrain and red meat, as well as waist circumference. Thus, our results seem to strengthen previous findings indicating that the association of depression with incident T2D is not modified by any of the known diabetes risk factors including sociodemographic variables, health behaviour, body mass index and social relations.[31] Nevertheless, particularly physical activity is well-known to improve mental and physical health status in patients with MDD,[32] and a potential preventive impact of lifestyle modification on T2D risk has rarely been examined in people with MDD, yet.[25] In addition, previous trend analyses revealed an increasing relevancy of significant weight or appetite change for women with MDD since GNHIES98[24]—which possibly also indicates unfavourable

changes in health behaviours among women with MDD. However, we had no information on health behaviours in between surveys.

4.4 | Strengths and limitations

Based on a nationwide cohort study, the current study provides information about the impact of MDD on glycaemic changes and incident T2D for the general adult population in Germany, for the first time. To date, longitudinal data on glycaemic changes associated with depression also covering prediabetes have been lacking. Furthermore, only clinically relevant MDD was considered as depression, assessed on a high-quality diagnostic level. Moreover, analyses considered potential covariates and confounding factors. To ensure representativeness, cohort-specific weighting factors have been used.

The following limitations should be kept in mind when interpreting the results of this study:

First, the small number of persons with baseline MDD resulted in low statistical power for detecting changes over time, particularly among men.

Second, potential selection biases cannot be ruled out. An underestimation of MDD may have been caused by the selective non-response of less healthy participants and the exclusion of institutionalized individuals. Thus, particularly severe depression may have been underrepresented—presumably also leading to an underestimation of the examined associations. Furthermore, willingness and ability to re-participate in DEGS1 might have varied by the mental and physical health of the former GNHIES98-MHS participants. Although cohort-specific weighting factors accounted for re-participation probabilities, an additional selection bias may have occurred.

Third, further potential biases of our study include regression to the mean and an underestimation of MDD among men due to measurement bias.[23]

Furthermore, unmeasured confounding cannot be ruled out—although we adjusted for a broad variety of potential risk factors. Notably, it was not possible to consider ethnicity or migrant status as a covariable, although HbA1c levels possibly vary between European whites and other ethnic groups. However, a previous subgroup meta-analysis showed similar T2D risks associated with MDD for studies primarily focusing on whites (RR = 1.65) in comparison to studies including a minimum of 10% African Americans (RR = 1.79).[7]

Finally, our definition of glycaemic changes may have masked potential differences of associations with MDD between persons with 'normoglycaemia' versus 'prediabetes' at baseline, since a prospective cohort study previously reported a remarkable synergistic effect of depressive

symptoms and prediabetes on newly diagnosed T2D.[33] Likewise, associations may vary between persons with 'diagnosed' versus 'unknown' diabetes at follow-up. In addition, our definition of glycaemic changes was based on only two points of observation without any information on the dynamic of glycaemic changes in between surveys.

5 | CONCLUSION

The findings of the current population-based prospective study highlight the role of clinically relevant MDD in glycaemic changes and T2D prevention. This applies particularly to women, since women with versus without MDD showed a remarkably lower chance for remission from prediabetes to normoglycaemia over time—and thus, likelier maintained their pre-existing elevated T2D risk. In clinical practice, an early detection and adequate treatment of depression may be crucial, as well as the continuous monitoring of the glycaemic status of depressed persons. Finally, our findings emphasize the importance of evaluating sex differences when examining associations of depression with T2D and its underlying mechanisms. Here, future research should also consider further sex-specifics as potential confounders, especially with regard to mental and physical health care utilization and health-related behaviours.

CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

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