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Diabetes and mental health: from understanding biomedical and social determinants, to promoting wellness in diabetes

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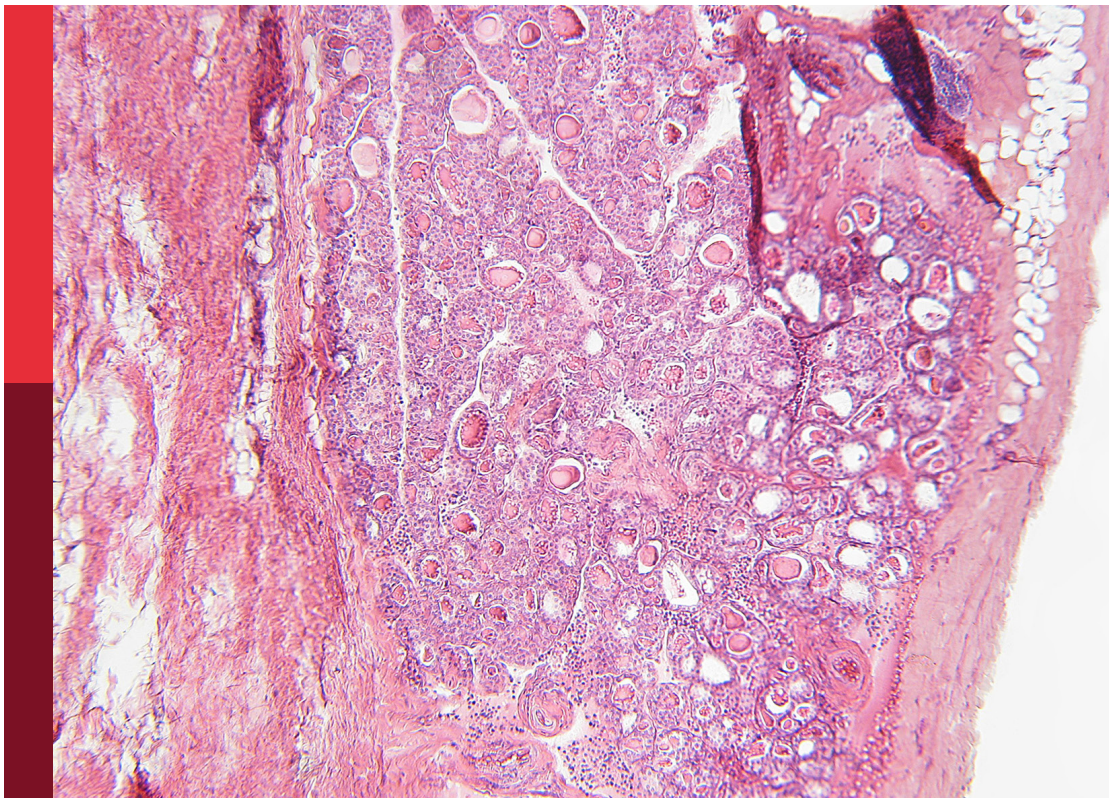

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Diabetes and mental health: from understanding biomedical and social determinants, to promoting wellness in diabetes

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Editorial: Diabetes and mental health: from understanding biomedical and social determinants, to promoting wellness in diabetes

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Editorial on the Research Topic
Diabetes and mental health: from understanding biomedical and social determinants, to promoting wellness in diabetes

Diabetes and mental health disorders are health priorities worldwide, with mounting evidence demonstrating their intertwined connection. In particular, the association between diabetes and depression is frequently reported. Both conditions are highly prevalent, have been on the rise globally, and are main causes of morbidity and mortality (1, 2). Data from clinical and community studies consistently report a complex co-morbidity between diabetes and depression; people with depression have higher rates of type 2 diabetes (3), and conversely, people with diabetes are found to be twice more likely to have depression (4).

The 13 articles included in this Research Topic highlight novel and different facets of the emergence, progression, and outcomes of the diabetes-mental health connection. The articles span investigations of both hypothesized temporal relationships of this co-morbidity, its consequences on management, complications, and well-being, as well as its intersection with other disorders and risk factors.

The work of Sanchez-Carro et al., Huang et al., and Mishra et al., examines the potential role of depression and psychosocial factors in influencing the risk for diabetes and dysglycemia. Investigating metabolic disease development in a prospective Greek cohort (n=755), Sanchez-Carro et al. found that participants with both depression and anxiety had more pronounced inflammation profiles at baseline, and that participants with depression had a higher risk for developing diabetes over the next ten years. Mishra et al. reported that participants with more severe depressive symptoms had higher glycemic variability in a single-center pilot study involving flash glucose monitoring in individuals with depression

and without diabetes. Huang et al., examined diabetes trends in the US from 2005 to 2018 and the contribution of 31 modifiable and non-modifiable risk factors using data from the National Health and Nutrition Examination Survey. Their findings showed increases in diabetes prevalence from 12.2% in 2005-2006 to 17.1% in 2017-2018 and that changes in biological, demographic, anthropometric, psychosocial, and genetic domains accounted for these increasing trends by 46.2%, 41.5%, 35.3%, 21.3%, and 17.3%, respectively. These findings from diverse populations and settings suggest that adverse mental health experiences are associated with higher risk for diabetes and glycemic variability; they also underline that this association spans multiple mental health conditions, psychosocial factors, and health indicators.

In parallel, five studies published in this Research Topic are in support of the hypothesis that diabetes is related to the occurrence of mental health conditions. The cross-sectional study by Yadav et al. on 1125 emerging adults with diabetes, as part of the National Health and Nutrition Examination Survey, found that a major depressive episode was more likely to occur among ethnic minorities and among women. Depression and anxiety were also more common in certain specific settings such as the post-partum period, as demonstrated by Zeng et al. in a sample of 406 women with or without gestational diabetes (GDM). The women with GDM reported higher anxiety 42 days after delivery in a self-reported questionnaire. Similar associations were reported in a meta-analysis by Jin et al., which included 10 studies on women with GDM. Depression was more common among women with GDM as compared to those without GDM across multiple countries and in prospective and retrospective study designs. Furthermore, it was more common in low- and middle-income countries, as compared with high income countries. Together, these findings highlight that depression and anxiety are more prevalent with diabetes among minorities, women, lower socioeconomic status, and specific settings, and underscore that common determinants between both conditions can be psychosocial and socioeconomic/environmental in nature. Other articles suggest that physiologic processes may also play a role. Chamseddine et al., found different associations between mental health and fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) levels depending on the range examined, with only increases in levels in the range consistent with diabetes (≥126 mg/dl and ≥6.5%, respectively) showing patterns of associations with higher depression and anxiety symptoms. This suggests a differential shift in mental health risk in the clinical spectrum of glycemic indicators. In a systematic review and meta-analysis by Shea et al., pooling 31 studies of 2.1 million adults with nonalcoholic fatty liver disease (NAFLD), the presence of depression and anxiety was 26.3% and 37.2% more likely to occur, respectively. NAFLD is a silent clinical condition closely associated with type 2 diabetes and shares its common risk factors such as inflammation, insulin resistance, and genetic predisposition. These findings highlight the importance of early detection and better characterization of processes underlying the transition towards diabetes development and its implications for mental health. Further investigating the co-occurrence of mental health symptoms in the context of diabetes, Zhang et al., present cross-sectional networks of depressive and anxiety symptoms among 1,685 older adults with diabetes (unspecified type) from the 2017–2018 wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). They found that "Feeling blue/depressed", "Nervousness or anxiety", "Uncontrollable worry", "Trouble relaxing", and "Worry too much" were the most central symptoms and might therefore contribute most to the development and maintenance of depression and anxiety, and that symptoms related to "Nervousness or anxiety" and "Everything was an effort" were the strongest nodes to bridge together symptoms of anxiety with symptoms of depression.

In addition to improving our understanding of their emergence and temporal link, data on the progression and implications of diabetes and mental health co-morbidities are critical to guide informed treatment and management strategies. The studies by Yeung et al. and Schmitz et al. investigate downstream complications of this co-morbidity. Using 6-year prospective data from the Hong Kong Diabetes Register (2013–2019), Yeung et al., found that elevated depressive symptoms were associated with incident cardiovascular disease, ischemic heart disease, and all-cause mortality in 4525 Chinese patients with diabetes, accounting for health-related quality of life and self-care factors. The study by Schmitz et al., reported an interaction between depression and high ultra-processed food consumptions in a prospective cohort of middle-aged adults with type 2 diabetes, wherein participants with a combination of elevated depressive symptoms or antidepressant use and high ultra-processed food consumption were at higher risk of new-onset diabetes-related microvascular and macrovascular complications. Both studies document associations of high magnitude (over double the risk of complications), underlining the potentially severe and important sequela of depression-diabetes co-morbidity and its interplay with daily health-related behaviors and other disease processes.

This Research Topic also includes work that examines instruments for assessing psychological barriers to treatment and the impact of newer diabetes management technologies. Improving tools assessing psychological barriers to treatment and diabetes-related distress, depression, and other mental health conditions, and adapting them to different populations and settings, is instrumental for better patient care. The development and psychometric assessment of the Chinese Barriers to Insulin Treatment Questionnaire (BIT-C) by Ma et al. is a good example of the importance of such efforts. The associations between progress in diabetes technology and improvements in mental health and wellbeing was demonstrated by Cyranka et al. who reported improvements in the quality of life and wellbeing of 18 adults with type 1 diabetes approximately one year following a switch from multiple daily injections and self-monitoring of blood glucose to the advanced hybrid closed-loop system. Participants were previously naïve to modern diabetes technologies and improvements included increases in life satisfaction, self-esteem, and well-being, and self-efficacy, and decreases in anxiety.

In conclusion, the articles included in this Research Topic are a collection of efforts from around the world to better understand the

diabetes-mental health connection, its underlying causal pathways, manifestations, and implications for health and treatment outcomes. Together, the articles put forward future research opportunities and directions emphasizing the value of investigating each of these conditions' building blocks and trajectories, with more diversified and at-risk populations, and their interplay with sociodemographic, biological, and health-related factors.

Author contributions

ME: Writing – original draft, Writing – review & editing. SD: Writing – original draft, Writing – review & editing. HA: Writing – review & editing. MN: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Quantifying the contribution of 31 risk factors to the increasing prevalence of diabetes among US adults, 2005–2018

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Introduction: No study has comprehensively quantified the individual and collective contributions of various risk factors to the growing burden of diabetes in the United States.

Methods: This study aimed to determine the extent to which an increase in the prevalence of diabetes was related to concurrent changes in the distribution of diabetes-related risk factors among US adults (aged 20 years or above and not pregnant). Seven cycles of series of cross-sectional National Health and Nutrition Examination Survey data between 2005–2006 and 2017–2018 were included. The exposures were survey cycles and seven domains of risk factors, including genetic, demographic, social determinants of health, lifestyle, obesity, biological, and psychosocial domains. Using Poisson regressions, percent reduction in the β coefficient (the logarithm used to calculate the prevalence ratio for prevalence of diabetes in 2017–2018 vs. 2005–2006) was computed to assess the individual and collective contribution of the 31 prespecified risk factors and seven domains to the growing burden of diabetes.

Results: Of the 16,091 participants included, the unadjusted prevalence of diabetes increased from 12.2% in 2005–2006 to 17.1% in 2017–2018 [prevalence ratio: 1.40 (95% CI, 1.14–1.72)]. Individually, genetic domain [17.3% (95% CI, 5.4%–40.8%)], demographic domain [41.5% (95% CI, 24.4%–76.8%)], obesity domain [35.3% (95% CI, 15.8%–70.2%)], biological domain [46.2% (95% CI, 21.6%–79.1%)], and psychosocial domain [21.3% (95% CI, 9.5%–40.1%)] were significantly associated with a different percent reduction in β. After adjusting for all seven domains, the percent reduction in β was 97.3% (95% CI, 62.7%–164.8%).

Conclusion: The concurrently changing risk factors accounted for the increasing diabetes prevalence. However, the contribution of each risk factor domain varied. Findings may inform planning cost-effective and targeted public health programs for diabetes prevention.

KEYWORDS

trends, prevalence, diabetes, risk factors, contribution

Introduction

Diabetes is a growing health concern as a leading cause of mortality and disability (1). Among US adults, the estimated prevalence of diabetes has increased dramatically in recent decades, reaching 14.7% in 2019 (2). Diabetes posed a colossal economic burden, including $237 billion in direct medical costs and $90 billion in lost productivity in 2017 in the United States (3). Hence, understanding factors contributing to the increasing prevalence of diabetes is critical for devising public health interventions for the prevention of diabetes.

Diabetes is a complex multifactorial disease. The growing prevalence of diabetes likely results from temporal changes in both genetic and more substantially non-genetic factors. The increasing prevalence of diabetes coincides with the changing prevalence of certain risk factors for diabetes among US adults. The prevalence of general and abdominal obesity has continued to increase since 1999 (4–7). Accumulating evidence links psychosocial factors, such as depression, long work hours, and sleep disturbance, with diabetes (8, 9). US adults with psychosocial distress have been a growing population (10, 11). Changes in demographic composition due to birth, death, and migration are in part responsible for the rising prevalence of diabetes (12). Social determinants of health (SDOH) are strong predictors of diabetes, and specific dimensions of SDOH, such as health insurance coverage and food security, levels have changed since 1999 (13, 14). Furthermore, many risk factors of diabetes commonly co-occur within an individual (15). However, no study has comprehensively quantified the individual and collective contribution of various risk factors to the growing burden of diabetes in the United States. The lack of quantitative understanding of major contributing risk factors presents significant challenges for devising cost-effective and targeted public health interventions to reverse the trends in the prevalence of diabetes.

Using data from the National Health and Nutrition Examination Survey (NHANES), the primary objective of this study was to determine the extent to which the increase in the prevalence of diabetes between 2005–2006 and 2017–2018 was related to concurrent changes in the distribution of a wide range of risk factors individually and collectively among US adults.

Materials and methods

Data collection

NHANES, as a multistage, nationally representative survey of the US non-institutionalized civilian population, has been conducted in 2-year cycles since 1999–2000 (16). Data were collected during in-home interviews and study visits at mobile examination centers. Seven cycles between 2005–2006 and 2017–2018 were included because important risk factors reflecting mental health, sleep habits, and disorders were not collected until 2005–2006. Participants aged 20 years or above were included except pregnant women. Written informed consent was obtained from each participant. This study was approved by the Shanghai Jiao Tong University School of Medicine Public Health and Nursing Research Ethics Review Committee.

Definition of diabetes

Consistent with the previous NHANES studies, diabetes was defined as having a self-reported diabetes diagnosis, a fasting plasma glucose level of 126 mg/dl or more, or a hemoglobin A1c level of 6.5% or more (17).

Domains of risk factors for diabetes

Based on the literature review and data accessibility, a range of risk factors were included and categorized into seven domains: genetic, demographic, SDOH, lifestyle, obesity, biological, and psychosocial domains.

Genetic domain

As a proxy for genetic predisposition, family history of diabetes (yes/no) was self-reported through the question "Including living and deceased, were any of your blood relatives, including father, mother, sisters, or brothers, ever told by a health professional that they had diabetes?"

Demographic domain

Demographic variables included age in years, sex (male/female), and race/ethnicity. Race and ethnicity were self-reported based on fix-category questions and categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and other.

SDOH domain

SDOH included marital status, education, income, employment status, country of birth, health insurance type, healthcare access, food security, and number of people living in the household. Marital status was grouped into married, widowed, divorced, separated, never married, and living with a partner. Education level was categorized as less than high school, high school graduate, some college, and college graduate or above. The ratio of family income to poverty was calculated by dividing self-reported family income by the Department of Health and Human Services' poverty guidelines, specific to the family size, appropriate year, and state. Employment status included working at a job or business, with a job or business but not at work, looking for work, and not working at a job or business. Country of birth was recorded as born in the US or elsewhere. Health insurance type was defined as private (including any private health insurance, Medi-Gap, or single service plan), public only (including Medicare, Medicaid, State Children's Health Insurance Program, military healthcare, Indian Health Service, state-sponsored health plan, or other government insurance), and no insurance. Routine place to go for healthcare (yes/no) was used as a surrogate for healthcare access. Food security status was grouped into four categories: full food security, marginal food security, low food security, and very low food security (18). The total number of people in the household was self-reported and used as a continuous variable.

Lifestyle domain

Lifestyle variables included diet quality, physical activity, smoking status and amount, alcohol drinking status and amount, and sleep hours. The Healthy Eating Index 2015 (HEI-2015) was a measure of diet quality according to the 2015–2020 Dietary Guidelines for Americans (19). For physical activity, work-related physical activity was not collected before 2007. This study only included leisure-time physical activity. The minutes spent on the vigorous-intensity physical activity was multiplied by 2 and added to the minutes spent on the moderate-intensity physical activity in a typical week to create weekly minutes of moderate-intensity equivalent physical activity (20). Cigarette smoking status and alcohol consumption status were categorized as never, former, and current (21, 22). Daily cigarettes smoked were calculated using the number of smoking days during the past 30 days and the average number of cigarettes smoked on the smoking days. Daily drinks consumed was calculated using the number of drinking days during the past 12 months and the average number of alcoholic drinks consumed on the drinking days. Sleep hours at night on weekdays or workdays was self-reported and used as a continuous variable.

Obesity domain

Obesity variables included body mass index (BMI) and waist circumference. BMI was computed as weight in kilograms divided by height in meters squared.

Biological domain

Biological variables included systolic blood pressure, serum cholesterol, use of four antihypertensive medications associated with developing diabetes (23), and statin use. Systolic blood pressure was calculated by taking the mean of all available measurements. Total cholesterol and high-density lipoprotein cholesterol levels were measured using standard protocols based on the Centers for Disease Control and Prevention's Lipid Standardization Program. Currently taking prescribed angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers, thiazides, and statins were determined by trained interviewers who documented the product name from the medication containers. Other biological risk factors, including diastolic blood pressure, uric acid, and estimated glomerular filtration rate, were further contained in the alternative biological domain and evaluated separately in a sensitivity analysis because there is evidence that these factors could be bidirectionally associated with diabetes.

Psychosocial domain

Psychosocial variables included working hours, trouble sleeping, and depression symptoms. Hours worked last week was self-reported. Having trouble sleeping (yes/no) was assessed by the response to "Have you ever told a doctor or other health professional that you have trouble sleeping?" The Patient Health Questionnaire-9 was administered to assess the severity of depressive symptoms over the past 2 weeks. It had nine items with four response levels (not at all, several days, more than half the days, nearly every day) scoring from 0 to 3 for each, resulting in a total score of 0 (low depressive symptomatology) to 27 (high depressive symptomatology).

Statistical analysis

Proportions or means were estimated to describe the characteristics of participants, as appropriate for all risk factors. Logistic regressions for categorical risk factors and linear regressions for continuous risk factors were used to compute crude *P*-value for trend from 2005–2006 to 2017–2018 (24).

The previous study revealed a linear trend in prevalence of diabetes between 1999–2000 and 2017–2018 (17). The linear trend between 2005–2006 and 2017–2018 was confirmed in this study. Poisson regressions were used to estimate the prevalence ratio (PR) for prevalence of diabetes comparing 2017–2018 with 2005–2006 (25). The extent to which the increase in prevalence of diabetes between 2005–2006 and 2017–2018 was related to the pre-specified risk factors or risk factor domains was estimated by calculating percent reduction in the β coefficient for the survey cycle (2017–2018 vs. 2005–2006) on the log-scale. Percent reduction in the β coefficient was obtained by contrasting the two models under comparison: $(\beta_{ref} - \beta_{adj})/\beta_{ref} \times 100\%$. β_{ref} was from the base model. β_{adj} was from the model including one or more risk factors or risk factor domains compared with the base model. The 95% confidence intervals (95% CIs) were estimated by performing bootstrap resampling ($n = 200$) (26).

Modeling strategies were described as follows. First, to assess the contribution of individual risk factor domains, the model with adding each of the 31 risk factors was compared with the base model without including any risk factors. Second, to assess the contribution of individual risk factor domains, the model with adding each of the seven risk factor domains was compared with the aforementioned base model. Third, to assess the collective contribution of two or more risk factor domains, each of the seven risk factor domains was sequentially added to the previous model, until all seven domains were included simultaneously. According to the modifiability and etiological proximity of risk factors in regard to diabetes, genetic, demographic, SDOH, lifestyle, obesity, biological, and psychosocial domains were added sequentially. Fourth, to assess the remaining contribution of each risk factor domain, the model excluding one of the seven risk factor domains was compared with the base model. Fifth, to assess the respective contribution of non-modifiable and modifiable risk factors, the model adjusting for non-modifiable risk factor domains (genetic and demographic domains) and modifiable risk factor domains (all other five domains) was compared with the base model. To conservatively account for possible non-linear associations between risk factors and diabetes, a quadratic term was added for all risk factors in continuous form.

Missing data were imputed with multiple imputation by chained equations (27). Considering the convergence issues of logistic regression models, multi-categorical risk factors were converted to binary ones and treated as continuous variables. Instead of the linear regression approach, predictive mean matching was chosen for the estimation, given its advantage of better preserving the original distribution of data (28). The number

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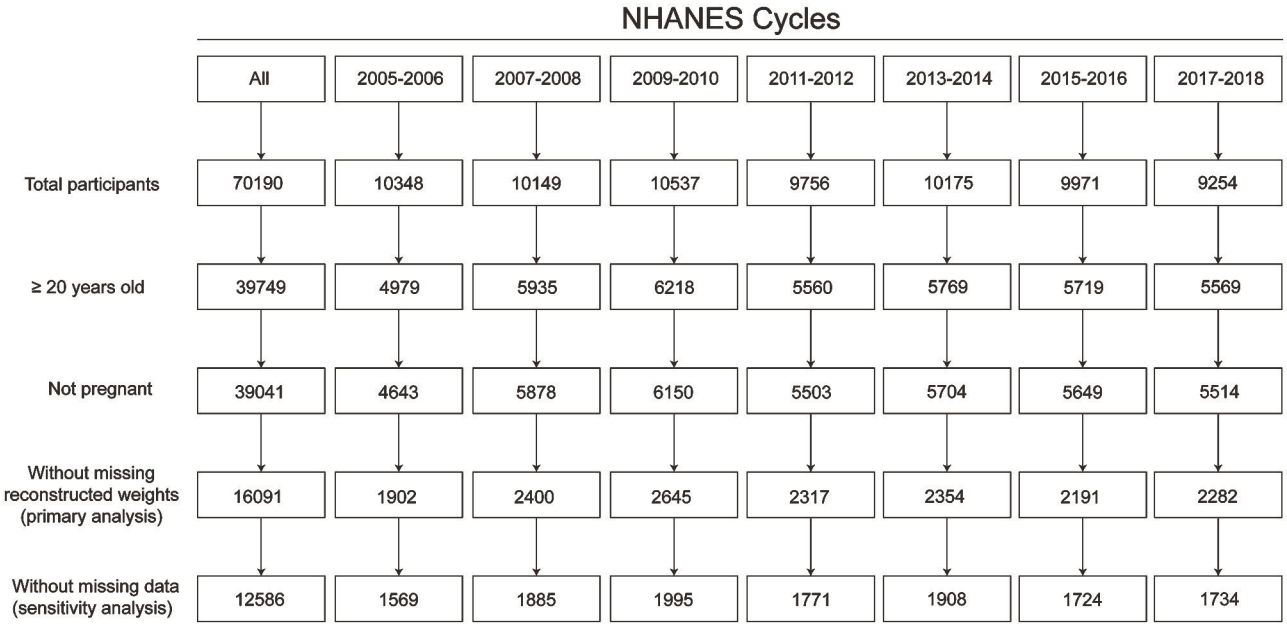

FIGURE 1
Flow chart for sample size. Based on the least-common denominator rule, reconstructed weights incorporating weights from the dietary 2-day sample and fasting subsample were used to ensure the representativeness of the estimates.

of nearest donors in the matching pool was set to be 10 (29). According to the recommendations that the number of imputations should at least equal the highest percentage of the fraction of missing information (FMI), the number of imputed datasets was set to be 10 because the highest FMI percentage of an individual variable was <10% (27). Each model was executed within each of the 10 imputed datasets to obtain 10 sets of estimates, which were then meta-analyzed to produce one pooled estimate. A sensitivity analysis was conducted by performing a complete case analysis to assess the robustness of primary results.

Based on the least-common denominator rule, reconstructed weights incorporating weights from the dietary 2-day sample and fasting subsample were used to ensure the representativeness of the estimates. Design variables were further adjusted to obtain unbiased estimates and standard errors. All analyses were implemented with SAS version 9.4 and STATA version 17.0. A two-tailed *P-value* of <0.05 denoted statistical significance.

Results

Among the 16,091 participants included, 3,505 (21.8%) participants had missing information on the outcome or risk factors of interest (Figure 1). After multiple imputation, the weighted mean age was 48.3 years, 47.8% were men, and 68.5% were non-Hispanic White.

The estimated crude prevalence of diabetes increased significantly from 12.2% (95% CI, 10.1%−14.3%) in 2005–2006 to 17.1% (95% CI, 15.2%−18.9%) in 2017–2018 [crude prevalence ratio (PR): 1.40 (95% CI, 1.14–1.72)].

Crude trends in risk factors

The estimated proportions of participants having a family history of diabetes, having multi-racial backgrounds, looking for work, with marginal, low or very low food security, having public insurance only, never smoking, drinking currently, taking β blockers, taking statins, and having trouble sleeping increased significantly between 2005–2006 and 2017–2018 (all P for trend < 0.05). The estimated proportions of participants having non-Hispanic White background, with an education level of less than high school, with full food security, having private insurance, having no insurance, having routine place to go for healthcare, and smoking currently decreased significantly between 2005–2006 and 2017–2018 (all P for trend < 0.05). The estimated means of participants' age, sleep hours, BMI, waist circumference, systolic blood pressure, and depression score increased significantly from 2005–2006 to 2017–2018 (all P for trend < 0.05). The estimated means of participants' leisure-time physical activity level, daily cigarettes smoked, total cholesterol level, and hours worked during the last week decreased significantly from 2005–2006 to 2017–2018 (all P for trend < 0.05; Table 1).

Contribution of risk factors to the growing prevalence of diabetes

Individually, adjusting for family history of diabetes [17.3% (95% CI, 5.4%−40.8%)], age [25.1% (95% CI, 8.4%−49.5%)], race and ethnicity [5.9% (95% CI, 1.8%−12.6%)], education level [−12.7% (95% CI, −27.3% to −5.8%)], food security

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TABLE 1 Participant characteristics, 2005–2018[a].

Characteristics	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	*P* for trend
No. of participants[b]	1,902	2,400	2,645	2,317	2,354	2,191	2,282	
Genetic domain								
Family history of diabetes[c], %	41.6	38.6	37.5	34.9	38.5	45.1	47.7	0.001
Demographic domain								
Age, years	47.5	47.7	47.7	48.2	48.3	49.2	49.1	0.03
Male, %	47.8	48.2	47.9	47.6	47.5	47.1	48.5	0.94
Race and ethnicity[d], %								
Non-Hispanic White	72.7	72.3	69.1	68.2	66.8	66.6	64.7	0.02
Non-Hispanic Black	10.9	10.7	10.8	11.0	11.4	11.2	11.4	0.75
Hispanic	11.3	12.2	13.4	13.8	14.5	13.5	14.2	0.24
Other	5.1	4.8	6.6	6.9	7.4	8.7	9.6	<0.001
Social determinants of health domain								
Marital status, %								
Married	57.9	58.0	57.2	55.9	58.7	56.5	51.8	0.07
Widowed	5.9	6.5	6.3	5.2	5.9	5.9	5.9	0.65
Divorced	10.1	9.4	9.9	10.5	10.2	9.8	12.8	0.08
Separated	2.5	2.6	1.9	2.2	2.0	2.1	2.4	0.69
Never married	15.0	16.6	17.3	18.0	17.0	16.7	17.4	0.38
Living with partner	8.6	6.9	7.4	8.2	6.1	9.1	9.7	0.32
Education level, %								
Less than high school	15.6	18.2	17.9	16.7	15.1	13.4	10.2	<0.001
High school graduate	26.0	24.9	21.8	19.9	20.4	22.9	27.1	0.93
Some college	32.7	28.3	29.6	31.5	33.0	30.8	32.1	0.52
College graduate or above	25.7	28.7	30.7	31.8	31.6	32.9	30.6	0.13
Employment status, %								
Working at a job or business	63.4	61.4	59.1	59.7	58.4	58.7	59.4	0.07
With a job or business but not at work	3.5	2.7	2.6	1.7	1.5	3.2	2.1	0.15
Looking for work	1.2	1.9	3.9	4.4	2.7	3.3	3.2	0.003
Not working at a job or business	31.9	34.0	34.5	34.2	37.4	34.7	35.2	0.15
Ratio of family income to poverty	3.1	3.1	2.9	2.9	2.9	3.0	3.0	0.31
Born in 50 US states or Washington, DC, %	87.1	86.0	81.3	83.2	83.7	83.5	82.9	0.12
Total number of people in the household	2.9	2.9	3.1	3.0	3.1	3.0	3.0	0.26
Food security[e], %								
Full food security	84.3	82.7	78.5	75.0	76.4	71.9	69.3	<0.001
Marginal food security	7.6	7.0	8.4	9.2	9.4	11.2	11.8	<0.001
Low food security	5.4	6.8	7.6	9.0	8.3	9.7	9.8	<0.001
Very low food security	2.8	3.5	5.5	6.8	6.0	7.2	9.2	<0.001
Health insurance type, %								
Private	67.4	69.5	64.9	61.3	61.7	65.3	60.2	0.01
Public only	14.6	14.3	14.8	19.4	19.9	22.3	26.6	<0.001

(Continued)

TABLE 1 (Continued)

Characteristics	2005–2006	2007–2008	2009–2010	2011–2012	2013–2014	2015–2016	2017–2018	*P* for trend
Uninsured	17.9	16.2	20.2	19.3	18.3	12.3	13.2	0.02
Routine place to go for healthcare, %	86.0	86.7	87.0	86.1	84.2	84.4	81.7	0.004
Lifestyle domain								
Healthy Eating Index 2015 score	52.4	53.4	54.3	55.2	54.3	53.1	51.9	0.46
Leisure-time physical activity[f], min/week	298.3	209.4	197.7	218.1	197.5	202.1	216.1	0.002
Cigarette smoking status, %								
Never	49.1	53.0	55.9	56.3	56.0	54.1	56.6	0.02
Former	25.8	24.5	25.3	23.9	25.2	26.4	25.8	0.63
Current	25.1	22.5	18.8	19.8	18.8	19.5	17.6	0.001
Daily cigarettes smoked	3.9	3.5	2.3	2.4	2.1	2.2	2.0	<0.001
Alcohol consumption status, %								
Never	10.7	11.5	10.8	9.9	12.7	12.4	6.4	0.14
Former	17.6	18.0	15.6	15.4	14.5	14.2	16.4	0.08
Current	71.7	70.5	73.7	74.8	72.9	73.4	77.2	0.02
Daily drinks consumed	0.6	0.4	0.5	0.5	0.4	0.5	0.5	0.25
Sleep hours at night	6.8	6.9	6.9	6.9	6.9	7.7	7.6	<0.001
Obesity domain								
Body mass index[g], kg/m^2	28.9	28.6	29.0	29.0	29.6	29.8	29.7	<0.001
Waist circumference, cm	98.5	98.5	99.2	99.3	100.6	101.7	101.2	<0.001
Biological domain								
Systolic blood pressure, mm Hg	122.7	120.6	119.4	121.3	121.3	123.2	123.3	0.005
Taking angiotensin-converting enzyme inhibitors, %	10.9	12.4	13.3	13.3	14.1	14.6	11.2	0.26
Taking angiotensin II receptor blockers, %	5.8	8.0	6.7	5.4	6.9	8.0	7.5	0.18
Taking β blockers, %	11.2	11.2	11.9	12.2	11.5	12.2	15.4	0.01
Taking thiazides, %	9.2	8.8	9.4	10.3	9.5	8.9	7.8	0.42
Total cholesterol, mg/dl	198.2	196.2	195.3	194.5	189.5	191.5	187.3	<0.001
High-density lipoprotein cholesterol, mg/dl	55.6	52.9	53.9	53.3	53.6	55.7	53.9	0.86
Taking statins, %	14.8	17.5	18.4	19.4	21.4	20.8	20.7	<0.001
Psychosocial domain								
Hours worked last week	26.8	26.0	23.8	23.8	23.7	23.5	23.9	0.002
Depression score[h]	2.5	2.9	3.1	3.0	3.0	3.2	3.2	<0.001
Have trouble sleeping, %	25.0	25.7	25.9	27.6	28.8	30.9	34.3	<0.001

[a]Data are presented as proportions for categorical variables and means for continuous variables.
[b]Unweighted sample size.
[c]Including living and deceased, any blood relatives, including grandparents, parents, sisters, or brothers, were ever told by a health professional that they had diabetes.
[d]Race and ethnicity were determined by self-report in fixed categories.
[e]Adult food security status was measured through the US Household Food Security Survey Module, of which 10 questions for the adults in the household were used to create four response levels, based on the number of affirmative responses to these questions.
[f]The minutes spent on the vigorous-intensity physical activity was multiplied by two and added to the minutes spent on the moderate-intensity physical activity in a typical week to create weekly minutes of moderate-intensity equivalent physical activity.
[g]Body mass index was computed as weight in kilograms divided by height in meters squared.
[h]Patient Health Questionnaire-9 was used to assess the severity of depressive symptoms over the past 2 weeks. The questionnaire has nine items with each having four response levels (not at all, several days, more than half the days, nearly every day) and scoring from 0 to 3. The total score ranges from 0 (low depressive symptomatology) to 27 (high depressive symptomatology).

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TABLE 2 Prevalence ratios for contrasting diabetes prevalence in 2017–2018 vs. 2005–2006 and percent reduction in β estimates according to individual risk factors.

Risk factors	Prevalence ratio (95% CI)	Percent reduction in β (95% CI), %[a]
Base model	1.40 (1.14–1.72)	[Reference]
Individual adjustment for each risk factor		
Family history of diabetes	1.32 (1.10–1.59)	17.3 (5.4 to 40.8)
Age	1.29 (1.07–1.55)	25.1 (8.4 to 49.5)
Sex	1.40 (1.14–1.72)	0.3 (−2.0 to 2.2)
Race and ethnicity	1.37 (1.12–1.69)	5.9 (1.8 to 12.6)
Marital status	1.42 (1.16–1.74)	−3.8 (−16.4 to 5.8)
Education level	1.46 (1.21–1.77)	−12.7 (−27.3 to −5.8)
Employment status	1.35 (1.14–1.61)	9.9 (−1.5 to 22.1)
Ratio of family income to poverty	1.39 (1.13–1.70)	3.0 (−1.6 to 9.2)
Country of birth	1.40 (1.14–1.71)	1.2 (0.1 to 3.5)
Total number of people in the household	1.41 (1.15–1.73)	−2.4 (−9.8 to 4.4)
Food security	1.36 (1.11–1.67)	8.7 (3.3 to 21.0)
Health insurance type	1.28 (1.05–1.57)	25.7 (15.6 to 47.9)
Routine place to go for healthcare	1.44 (1.18–1.76)	−8.5 (−20.7 to −1.5)
Healthy Eating Index 2015 score	1.41 (1.15–1.74)	−2.0 (−6.3 to −0.1)
Leisure-time physical activity	1.33 (1.09–1.62)	16.4 (7.4 to 34.0)
Cigarette smoking	1.42 (1.16–1.74)	−3.7 (−14.0 to 4.1)
Alcohol consumption	1.43 (1.17–1.75)	−6.8 (−21.6 to 3.7)
Sleep hours at night	1.36 (1.11–1.67)	8.7 (−0.1 to 21.0)
Body mass index	1.31 (1.09–1.58)	20.4 (5.6 to 44.0)
Waist circumference	1.25 (1.04–1.50)	33.6 (14.7 to 66.8)
Systolic blood pressure	1.37 (1.15–1.65)	5.6 (−15.8 to 17.2)
Taking angiotensin-converting enzyme inhibitors	1.39 (1.15–1.69)	1.7 (−14.3 to 15.5)
Taking angiotensin II receptor blockers	1.36 (1.13–1.64)	8.8 (−0.6 to 20.5)
Taking β blockers	1.32 (1.09–1.59)	18.5 (4.7 to 37.1)
Taking thiazides	1.42 (1.18–1.72)	−4.9 (−17.5 to 3.5)
Total cholesterol	1.33 (1.08–1.63)	15.9 (8.3 to 31.7)
High-density lipoprotein cholesterol	1.34 (1.09–1.65)	12.9 (1.6 to 28.1)
Taking statins	1.25 (1.03–1.51)	34.6 (17.6 to 61.7)
Hours worked last week	1.36 (1.13–1.63)	9.7 (−0.1 to 21.9)
Depression score	1.36 (1.11–1.67)	9.1 (4.7 to 18.9)
Have trouble sleeping	1.34 (1.09–1.65)	12.4 (6.8 to 22.2)

[a] Percent reduction in the β coefficient, an estimate to quantify the percent contribution of individual risk factors to the increasing prevalence of diabetes comparing 2017–2018 with 2005–2006, was obtained through contrasting the two models under comparison: $(\beta_{ref-}\beta_{adj})/\beta^{*}_{ref}100\%$. β_{ref} was based on the base model which is a crude Poisson model not adjusted for any domains of risk factors. β_{adj} was based on the model including individual risk factors compared with the base model. The 95% confidence intervals (95% CIs) were estimated by performing bootstrap resampling (n = 200). To conservatively account for possible non-linear associations between risk factors and diabetes, a quadratic term was added for all the risk factors in continuous form.

[8.7% (95% CI, 3.3%−21.0%)], health insurance type [25.7% (95% CI, 15.6%−47.9%)], routine place to go for healthcare [−8.5% (95% CI, −20.7% to −1.5%)], HEI-2015 [−2.0% (95% CI, −6.3% to −0.1%)], leisure-time physical activity [16.4% (95% CI, 7.4%−34.0%)], BMI [20.4% (95% CI, 5.6%−44.0%)], waist circumference [33.6% (95% CI, 14.7%−66.8%)], taking β blockers [18.5% (95% CI, 4.7%−37.1%)], total cholesterol [15.9% (95% CI, 8.3%−31.7%)], high-density lipoprotein cholesterol [12.9% (95% CI, 1.6%−28.1%)], statins use [34.6% (95% CI, 17.6%−61.7%)], depression score [9.1% (95% CI, 4.7%−18.9%)], or having trouble sleeping [12.4% (95% CI, 6.8%−22.2%)] was associated with a significant percent reduction in the β coefficient when

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TABLE 3 Prevalence ratios for contrasting diabetes prevalence in 2017–2018 vs. 2005–2006 and percent reduction in β estimates according to individual domains.

Models	Prevalence ratio (95% CI)	Percent reduction in β (95% CI), %[a]
Base model[b]	1.40 (1.14–1.72)	[Reference]
Individual adjustment for each domain		
Base + genetic domain	1.32 (1.10–1.59)	17.3 (5.4 to 40.8)
Base + demographic domain	1.22 (1.02–1.45)	41.5 (24.4 to 76.8)
Base + social determinants of health domain	1.39 (1.17–1.66)	2.0 (−19.1 to 19.4)
Base + lifestyle domain	1.36 (1.12–1.66)	8.0 (−11.4 to 30.3)
Base + obesity domain	1.24 (1.04–1.49)	35.3 (15.8 to 70.2)
Base + biological domain	1.20 (1.02–1.41)	46.2 (21.6 to 79.1)
Base + psychosocial domain	1.30 (1.08–1.57)	21.3 (9.5 to 40.1)
Sequential adjustment for each domain		
Base + genetic domain	1.32 (1.10–1.59)	17.3 (5.4 to 40.8)
Further including demographic domain	1.15 (0.97–1.36)	59.0 (36.2 to 112.4)
Further including social determinants of health domain	1.15 (0.97–1.36)	59.1 (33.4 to 107.7)
Further including lifestyle domain	1.12 (0.95–1.32)	67.2 (38.5 to 129.1)
Further including obesity domain	1.08 (0.93–1.25)	78.3 (49.1 to 150.3)
Further including biological domain	1.01 (0.88–1.17)	95.7 (62.7 to 163.2)
Further including psychosocial domain	1.01 (0.87–1.17)	97.3 (62.7 to 164.8)
Adjustment for all domains but excluding one domain		
Excluding genetic domain	1.03 (0.89–1.20)	90.1 (57.9 to 154.9)
Excluding demographic domain	1.09 (0.95–1.27)	73.4 (42.5 to 124.5)
Excluding social determinants of health domain	1.01 (0.87–1.17)	97.2 (65.6 to 168.4)
Excluding lifestyle domain	1.01 (0.88–1.17)	96.2 (64.0 to 154.9)
Excluding obesity domain	1.03 (0.87–1.21)	92.2 (57.9 to 159.7)
Excluding biological domain	1.06 (0.91–1.24)	81.7 (52.8 to 153.1)
Excluding psychosocial domain	1.01 (0.88–1.17)	95.7 (62.7 to 163.2)
Adjustment for non-modifiable and modifiable domains		
Base + non-modifiable domains	1.15 (0.97–1.36)	59.0 (36.2 to 112.4)
Base + modifiable domains	1.12 (0.96–1.31)	64.7 (40.1 to 110.0)

[a]Percent reduction in the β coefficient, an estimate to quantify the percent contribution of individual and collective domains of risk factors to the increasing prevalence of diabetes comparing 2017–2018 to 2005–2006, was obtained through contrasting the two models under comparison: $(\beta_{ref} - \beta_{adj})/\beta^*_{ref}100\%$. β_{ref} was based on the base model. β_{adj} was based on the model including one or more risk factor domains compared with the base model. The 95% confidence intervals (95% CIs) were estimated by performing bootstrap resampling (n = 200). To conservatively account for possible non-linear associations between risk factors and diabetes, a quadratic term was added for all the risk factors in continuous form.

[b]Base model is the crude Poisson model not adjusted for any domains of risk factors.

comparing prevalence of diabetes between 2017–2018 and 2005–2006 (Table 2).

Contribution of risk factor domains to the growing prevalence of diabetes

Individually, adjusting for biological domain [46.2% (95% CI, 21.6%−79.1%)], demographic domain [41.5% (95% CI, 24.4%−76.8%)], obesity domain [35.3% (95% CI, 15.8%−70.2%)], psychosocial domain [21.3% (95% CI, 9.5%−40.1%)], or genetic domain [17.3% (95% CI, 5.4%−40.8%)] was associated with significant percent reduction in the β coefficient when comparing prevalence of diabetes between 2017–2018 and 2005–2006 (Table 3).

Sequentially, after adjusting for genetic and demographic domains, the percent reduction in the β coefficient was 59.0% (95% CI, 36.2%−112.4%), and the PR for comparing prevalence of diabetes in 2017–2018 with 2005–2006 was no longer significant [PR: 1.15 (95% CI, 0.97–1.36)]. After adjusting for all seven domains of risk factors, the percent reduction in the β coefficient was 97.3% (95% CI, 62.7%−164.8%; Table 3).

When adjusting for all domains but omitting one, the exclusion of demographic domain was associated with the least attenuation in the β coefficient [73.4% (95% CI, 42.5%−124.5%); Table 3]. Percent reduction in the β coefficient was 64.7% (95% CI, 40.1%−110.0%) when adjusting for modifiable domains and 59.0% (95% CI, 36.2%−112.4%) for non-modifiable domains.

Sensitivity analysis

The percent reduction in the β coefficient when adjusting for the alternative biological domain was 36.8% (95% CI, 11.6–68.7%; Supplementary Table S1). Of the 12,586 participants with complete information, the unadjusted prevalence of diabetes increased significantly from 2005–2006 (11.1%) to 2017–2018 [16.1%; PR: 1.46 (95% CI, 1.12–1.90)]. The contribution of a single risk factor was quantified (Supplementary Table S2). Individually, genetic, demographic, obesity, biological, or psychosocial domain was associated with a significant reduction in the β coefficient (Supplementary Table S3). These results were materially similar to the results of primary analysis using imputed data sets.

Discussion

Among US adults, the estimated prevalence of diabetes increased significantly in parallel with concurrent changes in the distribution of a comprehensive set of non-modifiable and modifiable risk factors for diabetes from 2005–2006 to 2017–2018. Ranked by the magnitude of contribution, the increasing prevalence of diabetes was significantly related to biological, demographic, obesity, psychosocial, and genetic domains (ranging from 46% to 17%). After taking into account all seven risk factor domains, the increasing trend in prevalence of diabetes was no longer observed. These findings provide concrete, informative, and targeted data for guiding future public health efforts for the prevention of diabetes.

The demographic domain had a major contribution to the increasing prevalence of diabetes, which primarily resulted from aging and increasing proportion of racial and ethnic minorities. These trends in the demographic composition of the US population likely continue and further contribute to the growing burden of diabetes (12). As this study found that ∼40% of the increase in the diabetes prevalence was related to changing demographic factors, further interventions targeting the aging population and ethnic minorities should be emphasized to effectively address the growing burden of diabetes among US adults.

Family history of diabetes is a well-established strong risk factor for diabetes (30, 31). As a proxy for genetic predisposition, its prevalence was speculated to be relatively stable in short periods. However, an increasing trend in the family history of diabetes was observed in this study, which may in part be driven by aging. Furthermore, the increase in genetically susceptible individuals in the gene pool could be caused by the increase in racial and ethnic minorities (32). The demographic and genetic factors are considered non-modifiable but contributed to a substantial proportion of the growing diabetes burden.

The biological domain accounted for the greatest proportion of the increasing prevalence of diabetes. Biological factors are most proximal to diabetes onset, and risk factors from other domains may directly and indirectly influence biological factors. The prevalence of statin use, the strongest contributor to the rising prevalence of diabetes within the biological domain, increased significantly. Statins are associated with accelerated progression to diabetes via the mechanisms of insulin secretion, insulin resistance, and cellular metabolisms of glucose (33, 34). In addition, the prevalence of taking β blockers, a cardioprotective drug that could worsen glycemic control by increasing insulin resistance and decreasing insulin release (35), also increased significantly, which contributed to the increasing prevalence of diabetes.

Approximately one-third of the increasing prevalence of diabetes was related to elevating BMI and waist circumference; the latter made a greater contribution. BMI and waist circumference increased parallel with a prevalence of diabetes (7, 17). Studies have implied that waist circumference was a stronger predictor for diabetes, especially among persons of low or normal weight compared with BMI (36, 37). Obesity appears to be a mediating factor connecting upstream genetic and lifestyle risk factors and downstream biological risk factors. Therefore, obesity can be a pivotal intervention target from the public health perspective for diabetes prevention (38).

Psychological distress, depression, and sleep disturbance are risk factors for diabetes, especially among the subpopulation with prediabetes and other risk factors (39, 40), but their contribution to diabetes burden has not been well-quantified. The mean depression score and prevalence of trouble sleeping increased significantly among the study population, and both had a significant contribution to the rising prevalence of diabetes. Previous evidence has indicated an increasing prevalence of psychological distress among US adults, especially among young adults (10, 11), of whom the diabetes burden also increased dramatically (17, 41).

SDOH and lifestyle factors are known risk factors for diabetes. The insignificant results for SDOH and lifestyle domains did not translate into that these factors were not important. First, many of these factors, such as diet quality and income, did not change significantly during the study period. Second, the opposite trends in specific risk factors were observed within each domain that contributed negatively to diabetes burden. For example, for the SDOH domain, the contribution by decreased food security level and proportion of the uninsured (i.e., leading to better screening and detection of diabetes) may have been largely counterbalanced by improved education and decreased proportion of people having routine place to go for healthcare.

Non-modifiable factors played an important role in the growing prevalence of diabetes, but modifiable factors from the five domains together accounted for 65% of the increased diabetes prevalence from 2005–2006 to 2017–2018. Through the control of modifiable risk factors, the increasing trend of diabetes can be slowed or even reversed. This analysis precisely identified domains and risk factors of priority for diabetes prevention, which may shed light on the design of effective targeted public health interventions.

Limitations

This study has several limitations. First, causal inference cannot be made with cross-sectional observational data. Findings of this study provide only suggestive evidence on possible contributors for the increasing burden of diabetes. Second, relying on self-reported data may have led to misclassification of diabetes and risk factors. Third, genetic susceptibility was represented by a convenient proxy family history of diabetes, instead of genetic data. Fourth, some risk factors, such as sedentary activity, low birthweight, C-reactive protein, and urinary cadmium, were not considered because they were not available or collected in subsamples or specific cycles only, or had bidirectional or controversial associations with diabetes. Fifth, the grouping method for risk factor domains was somewhat arbitrary. Sixth, this study focused on quantifying the overall contributions of risk factors to the increasing burden of diabetes. Therefore, subgroup analyses by demographic factors were not conducted because changes in these stratification factors themselves were important contributors.

Conclusion

Based on the NHANES data, the increasing trend in prevalence of diabetes among US adults between 2005–2006 and 2017–2018 was related to concurrent changes in the distribution of diabetes-related risk factors. Ranked by the magnitude of contribution, biological, demographic, obesity, psychosocial, and genetic domains of risk factors significantly but differentially accounted for the growing prevalence of diabetes.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Ethics statement

The studies involving human participants were reviewed and approved by Shanghai Jiao Tong University School of Medicine Public Health and Nursing Research Ethics Review Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YH: conceptualization, formal analysis, methodology, writing—original draft, and writing—review and editing. YX: methodology and writing—original draft. YQ: writing—original draft. HW: conceptualization, resources, supervision, and writing—review and editing. VZ: conceptualization, formal analysis, methodology, writing—original draft, resources, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1174632/full#supplementary-material

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Quality of life in the course of a one-year use of an advanced hybrid closed-loop system in adults with type 1 diabetes previously naïve to advanced diabetes technology

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Aim: To evaluate the effect of a one-year use of an advanced hybrid closed-loop (AHCL) system on the quality of life, level of anxiety, and level of self-efficacy in adults with type 1 diabetes (T1D) previously treated with multiple daily injections (MDI) and naïve to advanced diabetes technology

Methods: A total of 18 participants of a previously published 3-month randomized trial (10 men, 8 women; age 40.9 ± 7.6 years) who were switched directly from MDI/BMG to AHCL completed 12 months of MiniMed 780G™system use (a 3-month randomized trial followed by a 9-month follow-up phase). At month 6 of the study, patients were switched from the sensor GS3 (Continuous Glucose Monitoring) system, powered by Guardian™ Sensor 3) to GS4. Quality of life was assessed using the Polish validated version of the 'QoL-Q Diabetes' questionnaire. The level of anxiety was evaluated with the use of the State-Trait Anxiety Inventory (STAI). Self-efficacy was assessed with the General Self-Efficacy Scale (GSES). Results were obtained at baseline and at the end of the study.

Results: Significant increase in QoL was reported in the global score (p=0.02, Cohen d=0.61) and in as many as 11 out of 23 analyzed areas of life: being physically active (p=0.02, Cohen d = 0.71); feeling well (p<.01, Cohen d = 0.73); feeling in control of my body (p<.01, Cohen d = 0.72); looking good (p<.01, Cohen d = 1.07); working (p<.01, Cohen d = 1.12); sleeping (p=0.01, Cohen d = 0.66); eating as I would like (p<.01, Cohen d = 0.79); looking after or being useful to others (p= 0.02, Cohen d = 0.65); being active with pets/animals (p<.01, Cohen d = 0.95); being spontaneous (p=0.02, Cohen d = 0.67); and doing "normal" things (p=0.02, Cohen d = 0.67). Both state (p=0.04, Cohen d = 0.56) and trait (p=0.02, Cohen d = 0.60) anxiety decreased while the general self-

efficacy increased (p=0.03, Cohen d = 0.76). No participant stopped the use of the pump.

Conclusion: Adult patients with T1D previously treated with MDI and naïve to modern technologies experienced significant improvement in their psychological well-being after transitioning to the AHCL system after 12 months of treatment.

KEYWORDS

quality of life, advanced hybrid closed-loop system, diabetes type 1, self-efficacy, anxiety

Introduction

Quality of life (QoL) is a crucial concept in the assessment of individual functioning, general health, and well-being (1). Health-related quality of life (HRQoL) indicates the impact of chronic disease on the health status of the patient (2, 3). HRQoL assessment allows identifying those aspects of patient functioning that require intervention (4). Evaluation of QoL should be a standard procedure in the assessment of the effectiveness of any newly applied treatment, especially in diabetes - a disease that requires a lot of engagement of the patients in all aspects of their life (5). The use of Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) used separately are associated with an improvement in glycemic control. Modern technological advances have integrated CSII with CGM systems, where insulin delivery can now be automated by sensor glucose-driven algorithms (6–9).

The move from patient/healthcare provider-based control of glycemia to algorithm (device) driven therapy is associated with major psychosocial changes. A study with patients from the United Kingdom observed that Hybrid Close Loop (HCL) systems at three months improved glucose control, diabetes management, and quality of life measures such as fear and worry of hypoglycemia in young patients with type 1 diabetes (T1D) and their carers (10). Similar observations concern the improvement of metabolic control and quality of life after introducing MiniMed 780G™in an Australian population of children and adolescents (11, 12). On the other hand, the results of studies on the impact of the MiniMed 780G™Advanced Hybrid Close Loop (AHCL) system on the quality of sleep in a population of adolescents were inconsistent (13, 14). There are also some observations indicating that the MiniMed 780G™ system may be helpful in patients with T1D and comorbid mental health issues, but this field requires further thorough investigation (15).

Recently we published a randomized control study in which we indicated that a population of patients with T1D previously naïve to advanced technology, who decided to undergo transition from multiple daily injections (MDI) and self-monitoring of blood glucose (SMBG) directly to the MiniMed 780G™ AHCL, experienced a significant improvement in selected aspects of quality of life: feeling well, working, eating as I would like, and doing normal things in as short time as 3 months after the transition. In addition, the patients from the AHCL group experienced lower levels of stress, fewer feelings of guilt, and could more easily be in contact with their emotions in stressful situations (16, 17). It was the first such study investigating psychological parameters in a population that has undergone the most extreme transformation from naïve to technology to advanced hybrid closed-loop therapy.

In the current study, we aimed to examine whether the improvement in quality of life in the same group of patients changed or was sustained after 1 year of MiniMed 780G™use and if there were any other significant changes in the psychological parameters of the examined population.

Methods

This was a 9-month observational continuation of the previous 3-month randomized controlled trials (RCT) project, in which we compared the results from the beginning of the study (month 0 with those obtained after 12 months altogether) (8). After the first 3 months of the RCT phase, patients from the AHCL arm continued the follow-up for additional 9 months. The only change in treatment concerned the sensor use – at month 6 the patients were switched from Guardian™ Sensor 3 (GS3) to Guardian™ 4 Sensor (GS4) (calibration-free sensor). The glucose control outcomes were reported by us in a separate research paper (6, 17).

The studied population consisted of 20 T1D technology naïve individuals. After the first 3 months, two male participants withdrew from the study: one due to difficulties in following the protocol and the second due to adhesive issues of infusion sets and sensors during work in high-temperature conditions. A total of 18 patients (10 men, 8 women; age 40.9 ± 7.6 years) completed a 9-month follow-up on a MiniMed 780G™ pump.

The patients filled out a set of questionnaires at the beginning, after 3 months (16), and after 12 months of the study. After the 3 months stage, the control group ended, and the patients from the studied group continued for an observational period of 9 months. The patients had one visit every 3 months during the 9-month follow-up and one more additional visit to change the type of the

sensor from Guardian GS3 to GS4. They did not have additional contact with the clinical team but they were able to get technical support from the company helpline when needed.

For these analyses, we compared the results from the beginning of the study with those observed after a year of study continuation. The following tests were used and considered in the analysis:

State-trait anxiety inventory: this is a tool that allows us to assess anxiety defined as a situational state (State Anxiety X1) of the patient and anxiety measured as a relatively stable personality trait (Trait Anxiety X2). The state anxiety scale assesses the current state of anxiety, nervousness, worry, and tension in a given moment of activation of the autonomic nervous system. The trait anxiety scale assesses the tendency of the patient to react with apprehension and worry in general, and anxiety measured here is understood as a trait of personality. Each subscale consists of 20 items (16, 18). Response for X1 assesses the intensity of current feelings evaluated by answering 1) not at all, 2) somewhat, 3) moderately so, and 4) very much so. Responses for X2 evaluate the frequency of feelings in general: 1) almost never, 2) sometimes, 3) often, and 4) almost always (18)

Generalized self-efficacy scale: a self-report scale measuring self-efficacy. It reflects patients' confidence in the ability to exert control over their own motivation, behavior, and social environment. The construct of perceived self-efficacy reflects the belief that one can perform novel or difficult tasks in various domains of functioning. The scale is a self-administered 10-item tool that requires 4 minutes response time on average. Responses are made on a 4-point scale: 1 = Not at all true, 2 = Hardly true, 3 = Moderately true, and 4 = Exactly true. The results are added to a composite score from 10 to 40. Each item refers to efficient and successful coping from the internal perspective (16, 19).

Quality of life in diabetes questionnaire (20): a tool that assesses the QoL of adults with T1DM. Validation of the Polish version, based on the Mapi Research Trust license, included forward translation by a health professional in clinical psychology and psychiatry, an expert panel analysis of the translation, back translation by a native speaker, and a pilot study on a sample of patients with T1DM. The questionnaire is a self-assessment scale composed of two parts. The first part measures the QoL with diabetes in one out of 23 life areas. In the second part, the patient assesses the importance of each of the 23 aspects of life. The mean value of the global QoL is 138 points and the maximum test result is 345 points. The mean value for a given area is 6, while the maximum for a given area is 15. The higher the result, the better the patient's QoL (16, 21).

To compare two dependent groups, a paired t-test or a non-parametric alternative when appropriate was used. To compare three or more paired groups, an ANOVA or Friedman test was used. Cohen's d-effect size (ES) was used to assess the magnitude of the experimental effect. All statistical analyses were performed with R, version 4.2.2.

Ethical considerations

The study was approved by the bioethics committee (no. 1072.61201.8.2020, dated May 28, 2020, trial registry no. NCT04616391). All patients provided written informed consent to participate in this study. The collected data were stored anonymously on an encrypted disc in the hospital according to recommendations from the bioethics committee. The participants did not receive any financial compensation for participation in the study.

Results

The baseline characteristics of the examined population are presented in Table 1.

The metabolic outcomes of the patients are available in the research paper by Matejko et al. (17) and are presented below in Table 2.

The results obtained after 3 months are presented in Table 3, while a thorough analysis of the results is presented in separate studies (6, 16).

The results obtained with the use of psychological tests are presented in Table 4.

As indicated in Table 4, a statistically significant increase in QoL was reported in the global score (p=0.02) and in as many as 11 out of 23 analyzed areas of life: being physically active (p=0.02), feeling well (p<.01), feeling in control of my body (p<.01), looking good (p<.01), working (p<.01), sleeping (p<.01), eating as I would like (p<01), looking after or being useful to others (p= 0.02), being active with pets/animals (p<01), being spontaneous (p=0.02), and doing "normal" things (p=0.02). Both state (p=0.04) and trait (p=0.02) anxiety decreased while general self-efficacy significantly increased (p=0.03).

There were no domains where a reduction in quality of life was apparent.

Discussion

To the best of our knowledge (17), this is the first long-term follow-up study investigating the psychological well-being of adult people with T1D previously naïve to diabetes technology (treated with MDI and SMBG) who experience a direct switch to the AHCL system with novel calibration-free sensors, and the sustainability of the obtained changes in their quality of life. The aim was to evaluate the effect of a one-year use of an advanced hybrid closed-loop system on the quality of life, level of anxiety, and level of self-efficacy in adults previously treated with multiple daily injections and naïve

TABLE 1 Characteristics of the studied population at baseline (N=18; 10 men, 18 women).

Variable	Mean ± SD
Age [years]	40.9 ± 7.8
Diabetes duration [years]	18.7 ± 11.9
HbA1c at enrolment [%]	7.1 ± 0.9
BMI [kg/m^2]	24.4 ± 3.0

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TABLE 2 Metabolic outcomes, 12 months of follow-up.

One-year follow-up period					
Metrics	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Avg ± SD
Sensor glucose outcomes					
Avg SG (mg/dL)	132.3 ± 7.1	133 ± 9.8	137.6 ± 11.8	136.3 ± 10.2	134.8 ± 9.9
SD of SG (mg/dL)	41.2 ± 5.1	41.3 ± 5.5	41.5 ± 7.0	41.4 ± 7.3	41.4 ± 6.2
GMI (%)	6.5 ± 0.2	6.5 ± 0.2	6.6 ± 0.3	6.6 ± 0.2	6.5 ± 0.2
% of time SG <54 mg/dL	0.4 ± 0.4	0.4 ± 0.5	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.4
% of time SG <70 mg/dL	2.1 ± 1.4	2.1 ± 1.5	1.4 ± 1.3	1.5 ± 1.2	1.7 ± 1.4
% of time SG 70–180 mg/dL	84.8 ± 4.4	84.1 ± 5.3	83.2 ± 6.5	84.0 ± 6.4	84.0 ± 5.6
%of time SG >180 mg/dL	11.4 ± 3.5	12.0 ± 5.0	13.3 ± 5.7	12.3 ± 5.2	12.3 ± 4.9
% of time SG >250 mg/dL	1.4 ± 1.0	1.5 ± 1.1	1.9 ± 1.7	2.0 ± 1.7	1.7 ± 1.4

SG, sensor glucose; SD, standard deviation; GMI, Glucose Management Indicator; N, number; Avg, average.
Values are presented by Mean ± SD (Median).

to advanced diabetes technology. The main focus was the adjustment to the new technology not to the glucose levels, although it was also an important factor connected with the new technology use.

Evaluation of patients' QoL is a well-grounded indicator of the effectiveness of provided healthcare and may be helpful for health professionals and healthcare policymakers in their efforts to improve the well-being of patients (22). In the research paper presenting results after 3 months of transition (16), we reported that the patients experienced a significant increase in four aspects of QoL: feeling well, working, eating as I would like, and doing normal things. This was a substantial change that could be directly associated with a greater level of freedom and safety connected with the change in treatment. However, it became crucial to investigate if changes were not only the result of the initial excitement of the patients, and if the changes could be sustained over time and expanded into other, more specific, aspects of the life of the examined patients. Thus, the 9-month follow-up observation was carried out.

We found that after a year of the study not only were the previously indicated four life areas sustained as much more satisfactory than before the study, but the patients evaluated their quality of life as significantly better in another seven areas: being physically active, feeling in control of my body, looking good, sleeping, looking after or being useful to others, being active with pets/animals, and being spontaneous. An in-depth exploration of those aspects shows that, with time, the patients adjusted to the MiniMed 780G™ pump and more willingly started to experience various life activities, including social relations.

Although there were no radical changes in the food choices of the examined patients, they experienced a greater feeling of freedom in terms of eating. The higher level of freedom in physical activity could be explained by the fact that patients on a hybrid closed loop achieve better glycemic control during their everyday activities (23) and thus they are more willing to undertake various spontaneous activities, such as playing with pets. Patients claimed to feel much more spontaneous than during previous treatment methods. Also worthy of note is that, although the patients started to wear a tethered personal insulin pump (with connecting tubes) and sensors on their body, their subjective assessment of their attractiveness also increased, which can be connected with their general better functioning (24). It is worth mentioning in this respect that even issues of intimacy assessed by asking QoL with regard to enjoying sexual activity showed positive trends (p=0.08).

The observed improvement in sleep quality is consistent with a study on children and young adults with T1D (and their parents) on 780G, but this observation was from a shorter period of time (25, 26). The possible factors contributing to the improvement in the quality of sleep could be fewer hypoglycemia episodes, lower glucose variability, and no need for calibration since the G4S introduction in the course of our follow-up study.

The improvement in the quality of life of the patients undergoing the transition increased not only in the 11 subscales measured but also in the global score of the QoL. This suggests that the patients were not only able to obtain better functioning in selected aspects of their life with diabetes but also that after the 12 months of the study, they achieved generally better life satisfaction, self-esteem, well-being, and meaning of life (2). The improvement in the global indicator of QoL observed in our study can be associated with many component factors found also in other studies (11, 12), such as less exhaustion, more energy, less stress while on AHCL, less thinking about the disease, and better diabetes management, and improved diabetes treatment satisfaction may be a possible consequence of reduced worry and increased trust in AHCL (11). These factors might also result in a decrease in diabetes-related emotional distress and, thus, improvement of QoL (12).

When analyzing the possible sources of such essential change, attention should be paid to the issue of anxiety. Patients with diabetes often struggle with the fear of hypoglycemia (20, 27). One of the ways patients with diabetes deal with this fear is to sustain glucose at slightly elevated levels. This may evoke a fear of

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TABLE 3 Psychological results after a 3-month randomized clinical trial.

Category	3-months randomized clinical trial	
	M	SD
STAI: State-Trait Anxiety Inventory.		
STAI X1 score	32.12	7.84
STAI X1 sten	4.06	2.11
STAI X2 score	37.35	8.59
STAI X2 sten	4.18	2.7
GSES: Generalized Self-Efficacy Scale.		
GSES score	32	4.31
GSES sten	7.31	1.45
QoL-Q Diabetes		
Global QoL score	201.28	55.49
QoL family relationships/friendships	10	3.66
QoL going out or socializing	8.38	2.78
QoL partner/spouse relationship	9.67	4.16
QoL enjoying sexual activity	8.83	3.2
QoL being physically active	8.89	2.83
QoL feeling well[g]	9.83	3.2
QoL feeling in control of my body	8.83	3.38
QoL looking good	7.67	2.59
QoL having holidays	9.22	3.54
QoL working[g]	10.41	3
QoL affording the things I would like	9	3.66
QoL driving	9.06	3.28
QoL practicing my religion	8.27	3.95
QoL sleeping	9.47	3.08
QoL eating as I would like	7	3.41
QoL looking after or being useful to others	8.65	1.97
QoL pets/animals	8.75	3.79
QoL being independent	10.82	3.05
QoL being in control of my life	10.29	3.46
QoL being spontaneous	8.47	4.54
QoL doing a "normal" thing	9.88	3.82
QoL being treated as "normal"	9.29	4.25
QoL having confidence	9.35	3.37

complications, potentially creating a cycle of anxiety (28). Our patients undergoing the transition in treatment after the year of follow-up experienced a significant decrease in both state and trait anxiety. We suggest that, to a high extent, this could be associated with much lower glucose variability, lower time spent below range (<70 mg/dL and 54 mg/dl), and a greater general metabolic safety of the patients. This, in turn, could potentially be one of the major factors resulting in the increase in QoL.

There was a significant increase in the self-efficacy of the patients. Self-efficacy is described as a cognitive process where, through environmental and social influence, individuals learn new behaviors that affect their ability to improve future events (29). Enhancing self-efficacy can improve the clinical outcomes and quality of life for patients living with chronic diseases (29). Self-efficacy is an important factor in the management of self-care among young adults with T1D; which, in turn, can be an important mechanism by which self-efficacy influences HbA1c levels (30). In our analyses, after 12 months of 780 G use, our patients displayed much better self-efficacy. It could be assumed that their better metabolic control gave them a sustained feeling of being able to "grab the disease in required limits" as stated by one of the patients. One can speculate that the treatment diverted cognitive potential from managing glucose and fear of hypoglycemia to expanding patients' capabilities and potentials.

During the study, a new calibration-free GS4 sensor during follow-up was introduced which could be one of the additional factors that contributed to the QoL increase (6), especially in terms of quality of sleep. The patients were not woken up by the need for night calibrations, as it was with S3G, and also they did not have to wake up during the night to check their blood glucose with glucometers, as they did before the 780 G pump usage.

The study has some limitations. One of them is the number of participants and we consider it essential to carry out similar investigations on a greater population. Additionally, the patients had the possibility to discuss their psychological well-being with a clinical psychologist throughout the whole period of the study. Throughout the whole study, only three of the patients asked for such a consultation and they were minor ones, not connected directly with the MiniMed 780G™ pump, but the very fact that the patients felt safe because of such a possibility could have some moderating effect on the quality of life. Another limitation is the lack of continuation of the control group; we observed them only during the 3 months of the initial stage as agreed in the protocol, and later on, the observation included only the studied group on the 780G pump. One of the reasons was the ethical aspect – we did not want to block the patients from the control group from their use of modern technologies for as long as 9 additional months.

Some limitations may also arise from the fact that we did not evaluate the quality of life after the switch from sensor S3G to S4G. However, we could not predict at which moment the impact of the switch could be the isolated factor having an impact on the very complex psychological parameters. We assumed that this was rather an additional factor playing a role in the observed improvement, important especially in terms of the quality of sleep, which we touched upon in the discussion. To assume that this one specific factor was so essential for the whole adaptation to the system could be misleading.

In addition, we did not perform individual profile analyses - in some QoL areas the results may be not uniform over patients, and patients' experiences may diverge over time. However, in this study, we wanted only to show a general trend of change for the whole study group.

Nevertheless, the obtained results show that the transition directly from MDI and SMBG to the MiniMed 780G™ system resulted in

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TABLE 4 Outcomes of anxiety, self-efficacy, and quality of life – comparison of results at the beginning and at the end of the study, 12-month follow-up.

Category	Beginning of the study		End of the study (12 months)		Cohen's d effect size	Absolute difference in mean scores	P value
	M	SD	M	SD			
STAI: State-Trait Anxiety Inventory.							
STAI X1 score	37.5	8.48	33.06	10.25	0.46	4.44	.08
STAI X1 sten	5.12	1.93	3.88	2.53	0.56		**.04**
STAI X2 score	40.44	8.87	36.56	10.27	0.60	3.88	**.02**
STAI X2 sten	4.83	2.62	3.83	2.87	0.60		**.02**
GSES: Generalized Self-Efficacy Scale.							
GSES score	30.4	2.17	31.8	3.16	0.76	1.4	**.03**
GSES sten	6.9	0.88	7.1	0.99	0.32		.42
QoL-Q Diabetes							
Global QoL score	185.41	32.03	209.94	39.73	0.61	24.53	**.02**
QoL family relationships/friendships	9.65	3.24	10.94	2.3	0.35	1.29	.17
QoL going out or socializing	8.5	2.34	10.06	2.08	0.50	1.56	.65
QoL partner/spouse relationship	9.82	3.11	10.76	3.31	0.32	0.94	.20
QoL enjoying sexual activity	8.25	2.38	9.81	3.58	0.46	1.56	.08
QoL being physically active	7.88	2.15	11.06	3.63	0.71	3.72	**.02**
QoL feeling well[g]	7.71	3.14	10.94	2.95	0.73	2.93	**<.01**
QoL feeling in control of my body	7.71	2.39	9.88	3	0.72	2.17	**<.01**
QoL looking good	7.29	2.2	9.47	2.72	1.07	2.18	<.01
QoL having holidays	9.12	3.52	9.94	3.56	0.23	0.82	.36
QoL working[g]	7.29	1.99	9.76	2.56	1.12	2.47	<.01
QoL affording the things I would like	8.65	2.8	9.06	2.82	0.13	0.41	.59
QoL driving	8.53	3.45	8.82	3.7	0.08	0.29	.75
QoL practicing my religion	8.47	4.07	9	4.41	0.16	0.53	.82
QoL sleeping	8.62	2.6	10.31	3.38	0.66	1.69	.01
QoL eating as I would like	5.06	2.62	8	3.97	0.79	2.94	**<.01**
QoL looking after or being useful to others	9	2.28	10.69	2.41	0.65	1.69	.02
QoL pets/animals	7.69	2.02	10.15	3.18	0.95	2.46	<.01
QoL being independent	9.44	3.1	10.62	2.68	0.32	1.18	0.22
QoL being in control of my life	8.94	3.02	10.12	2.36	0.39	1.18	.14
QoL being spontaneous	6.27	2.74	8.67	3.42	0.67	2.4	**.02**
QoL doing a "normal" thing	7.47	3	10.13	3.2	0.67	2.66	**.02**
QoL being treated as "normal"	9.31	2.91	9.88	3.18	0.21	0.57	.41
QoL having confidence	8.88	2.16	10	2.88	0.59	1.12	.05

P<0.05.
Bold values mean statistically significant p-value.

substantial growth in quality of life, sustained over time, much better self-efficacy, and a lower level of anxiety. This, combined with the great improvement in metabolic control, can be considered comprehensive progress in the treatment of patients with type one diabetes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the bioethics committee of Jagiellonian University Medical College (no. 1072.61201.8.2020, date May 28, 2020, trial registry no. NCT04616391). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KC: writing of the paper, selecting the research tools, analyzing the results, participating in the study on each of its stage as a research team member, BM: co-writer of the paper, statistical analyses, leader of the research team, AJ: editing of the text, member of the research team, BK-W: member of the research team, OC: member of the research team, analyzing the results, editing the text, MM: editing the text, participating in creating of the discussion, language correction, TK: senior author, the main researcher and originator of the study. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The psychometric properties of the barriers to insulin treatment questionnaire in Chinese patients with type 2 diabetes mellitus using insulin

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Aim: The objective of this study was to translate the Barriers to Insulin Treatment Questionnaire (BIT) into Chinese and test its psychometric properties in middle-aged and elderly type 2 diabetes mellitus (T2D) patients using insulin in the Han people of urban China.

Methods: We established the Barriers to Insulin Treatment Questionnaire in Chinese (BIT-C). We selected 296 patients with T2D for testing BIT-C's the reliability and validity, of which 120 patients were retested four weeks later. Another 200 patients with T2D were selected to perform the confirmatory factor analysis (CFA).

Results: The final BIT-C consisted of 11 items (BIT-C-11) and four factors. The explained variances of the BIT-C-11 and its four factors were 90.153%, 51.308%, 18.810%, 10.863%, and 9.173%. CFA validated that the four-factor model fit with the data of the BIT-C-11. Standardized factor loadings ranged between 0.77 and 0.90. The Cronbach's α coefficients of the BIT-C-11 and its four factors were 0.903, 0.952, 0.927, 0.938, and 0.917. Correlation analysis was performed between the BIT-C-11 and General Adherence Scale in Chinese (GAS-C) to calculate the criterion-related validity ($r = 0.598$, $p < 0.001$). The correlation coefficient r of the BIT-C-11's test–retest reliability was 0.810 ($p < 0.001$).

Conclusion: The BIT-C-11 has good reliability and validity. It can be used for psychological resistance to insulin therapy studies of middle-aged and elderly patients with T2D using insulin in the Han people of Chinese cities.

KEYWORDS

type 2 diabetes mellitus, barriers to insulin treatment, psychological resistance to insulin therapy, adherence, scale revision, reliability, validity

1 Introduction

If non-insulin medication has failed, type 2 diabetes mellitus (T2D) patients may need insulin injections to control hyperglycemia to recommended levels (1, 2). However, studies in recent years have found poor adherence in patients with T2D who use insulin to treat their diabetes (3, 4).

A 2017 study found that the insulin adherence and persistence of patients with T2D in China are generally poor. Only 53% of patients with T2D persisted with insulin therapy until 12 months. After 1 year of insulin injections, only 30.9% of patients with T2D had a medication possession rate (MPR) ≥0.8 (5). Psychological factors such as negative beliefs about insulin therapy are the most common reasons for these patients' poor adherence to insulin therapy (6, 7). Psychological insulin resistance (PIR) is a barrier for providers and patients in starting and maintaining insulin therapy (8). The patient's psychological resistance to insulin therapy can result in poor glycemic control, damaging their health and burdening their families and society (9, 10). China has many patients with T2D, and many need insulin to control their blood sugar (11, 12). Improving the adherence of these patients with T2D who require long-term insulin therapy is an urgent challenge for the prevention and control of T2D in China. Regarding population health, it may be more effective to focus efforts on those who are least likely to adhere or those with poorly controlled diseases (13). Therefore, there is an urgent need to investigate psychological resistance to insulin therapy in patients with T2D in China. However, no standardized research tools can quantitatively assess psychological resistance to insulin therapy in patients with T2D in China. The Barriers to Insulin Treatment Questionnaire (BIT) is a valuable tool for studying psychological resistance to insulin therapy in patients with T2D, which Petrak et al. (6) developed. This scale has been widely used (14, 15). So, we decided to revise the Barriers to Insulin Treatment Questionnaire in Chinese (BIT-C) and select middle-aged and elderly Chinese patients with T2D who were on insulin therapy as the research objects to evaluate the reliability and validity of the BIT-C.

2 Materials and methods

2.1 Participants

This study has two parts:

Study I: translating the BIT into Chinese and conducting an exploratory factor analysis (EFA) on it;

Study II: confirmatory factor analysis (CFA) of the Chinese version of the BIT.

This study was conducted following the Declaration of Helsinki and was approved by the Shanghai Pudong New Area Mental Health Center (approval number: 2017009). It was conducted from May 2018 to December 2020 in the diabetes wards of several general hospitals in Haicheng City in northeast China.

The inclusion criteria of the study subjects were as follows:

i. Patients who meet the WHO diagnostic criteria for T2D,
ii. currently on insulin therapy,
iii. aged 45–74 years,
iv. Han Chinese who had been continuously residing at the survey site for at least 5 years at the time of the survey,
v. voluntary participation.

Subjects will not be included in our study if they match the following exclusion criteria:

i. those who were seriously ill and unable to complete the study,
ii. those who had a disturbance of consciousness,
iii. those suffering from various severe mental illnesses who cannot complete the study.

2.2 Instruments

2.2.1 General information questionnaire

Demographic and medical data (glycosylated hemoglobin level, insulin use, diabetes duration) were collected by self-report.

2.2.2 BIT

Petrak et al. (6) developed the BIT, which measures psychological resistance to insulin treatment in patients with T2D. The BIT includes 14 items, a total sum score, and the following five factors: Factor 1: fear of injection and self-testing (items 1–3); Factor 2: expectations regarding positive insulin-related outcomes (items 4–6; they were reverse coded); Factor 3: expected hardship from insulin treatment (items 7–9); Factor 4: stigmatization by insulin injections (items 10–12); Factor 5: fear of hypoglycemia (items 13 and 14) (Table 1). The response format of the BIT is a 10-point Likert scale, ranging from "totally disagree" [1] to "totally agree" [10]. The BIT's Cronbach's α for the five subscales ranged from 0.62 to 0.85, and the BIT's α for the total sum score was 0.78 (6). It will be revised in Chinese in this study.

2.2.3 GAS-C

The General Adherence Scale (GAS) was developed by DiMatteo and Hays and is used to assess the general tendency of patients with chronic diseases to adhere to their physicians' recommendations during the past 4 weeks (16, 17). Shi revised the General Adherence Scale in Chinese (GAS-C), which can be applied to the general adherence study of middle-aged and elderly patients with T2D in China. Consistent with the GAS, the GAS-C has five items and is one-dimensional. The Cronbach's α reliability coefficient of the GAS-C was 0.942 (18). In this study, the GAS-C was used to assess the criterion-related validity of the BIT-C.

TABLE 1 Summary of item analysis of the BIT-C-14.

Factors of the BIT	Items of the BIT	R	K/D
1: fear of injection and self-testing	1: I am afraid of the pain when injecting insulin.	0.610**	keep
	2: Besides the pain, I am just afraid of injections.	0.670**	keep
	3: I am afraid of the pain during regular blood-sugar checks.	0.656**	keep
2: expectations regarding positive insulin-related outcomes	4: Insulin works better than pills.	0.173**	**delete**
	5: People who get insulin feel better.	0.246**	**delete**
	6: Insulin can reliably prevent long-term complications due to diabetes.	0.257**	**delete**
3: expected hardship from insulin treatment	7: I just don't have enough time for regular doses of insulin.	0.823**	keep
	8: I can't pay as close attention to my diet as insulin treatment requires.	0.745**	keep
	9: I can't organize my day as carefully as insulin treatment requires.	0.771**	keep
4: stigmatization by insulin injections	10: Injections in public are embarrassing to me. Pills are more discreet.	0.614**	keep
	11: Regular insulin treatment causes feelings of dependence.	0.617**	keep
	12: When people inject insulin, it makes them feel like drug addicts.	0.618**	keep
5: fear of hypoglycemia	13: An insulin overdose can lead to extremely low blood-sugar levels ("hypoglycemia"). I am afraid of the unpleasant accompanying symptoms.	0.564**	keep
	14: An insulin overdose can lead to extremely low blood-sugar levels ("hypoglycemia"). I have concerns about possible permanent damage to my health.	0.589**	keep

**Correlation is significant at the 0.01 level.
BIT, Barriers to Insulin Treatment Questionnaire; BIT-C-14, Chinese version of the BIT questionnaire with 14 items; R, correlation coefficient of each item to the total score of the BIT-C-14; K/D, kept or deleted.

2.3 Translation and adaptation of the scale

After obtaining the developer's permission, we integrated the cross-cultural approach to translate and adapt the BIT into Chinese (19, 20). The translation and adaptation stages of the BIT are as follows:

2.3.1 Forward translation

Two bilingual translators translated the BIT into Chinese separately. One translator is a teacher in the Department of English, and the other is a research group member.

2.3.2 Synthesis of the translations

Team members and two translators analyzed and compared the two drafts resulting from StageI, producing one common translation draft of the BIT.

2.3.3 Back translation

Two other translators with no medical background translated the Chinese BIT draft into English separately to produce two back-translation English BIT scales.

2.3.4 Expert committee review

The expert committees involved two linguists, one epidemiologist, four translators (forward and back translators), and research team members. They analyzed and compared the BIT, two forward translation versions, one common translation draft, and two back-translation BIT to finalize the initial Chinese version of the BIT. After discussion, the expert committee concluded that this initial Chinese version of the BIT is equivalent to the original version of the BIT in terms of semantics, idiomatic expression, experience, and concepts.

2.3.5 Pretesting and cognitive interviews

Fifteen patients with T2D who met the research criteria were asked to fill in the initial Chinese version of the BIT. Patients all filled out the questionnaire without any problems. Next, we conducted a cognitive interview with these patients to examine the comprehensibility of the questionnaire (21). All patients reported that they could understand each questionnaire item without ambiguity.

2.3.6 Establishment of the final Chinese version of the BIT (BIT-C-14)

After discussion, we decided to use the 14-item initial Chinese version of the BIT as the final Chinese version of the BIT (BIT-C-14).

2.4 Data collection

Data were collected the day before the study subjects were discharged from the hospital. Patients who met the subject criteria and agreed to participate in this study were included. Before filling out the questionnaire, subjects were asked to sign an informed consent form. If the subjects have poor eyesight or cannot read or write, the investigator will read the questionnaire aloud and fill out the items according to their true feelings. After the subjects completed the questionnaire, investigators asked if they would

like to participate in the retest. We randomly selected 120 subjects who agreed to be retested. They would be investigated again when they returned to the outpatient clinic for physician follow-up at week 4 after discharge.

2.5 Statistical analysis

We conducted the statistical analysis using SPSS 23.0. The sociodemographic information of the subjects was described by mean and standard deviation, frequency, and percentage. Continuous variables were expressed by mean ± standard deviation (SD). Counts and percentages are used to indicate categorical variables. $p < 0.05$ means a statistically significant difference. AMOS 23.0 was used in the CFA.

2.5.1 Item analysis

Using the homogeneity test to analyze items, those items with a low correlation with the total score on the BIT-C-14 were removed. The removal criteria are the value of the Pearson correlation coefficient $r < 0.4$ or the significant difference test $p \geq 0.05$ (22). If deleting an item may significantly increase the Cronbach's α value of the scale, it means that the item is not homogeneous with the rest of the items, and the item will be removed from the scale (21). For the EFA, those items with communalities <0.2 would be removed (23).

2.5.2 Validity analysis

We analyzed the scale's content validity, construct validity, and criterion-related validity.

Six diabetologists evaluated the scale's content validity based on the item analysis results. They rated the degree of correlation between the content of each item and the evaluation purpose for that item. Content validity was judged by the item-level content validity index (I-CVI) and content validity index (S-CVI/Ave). We would retain those items with I-CVI ≥0.78; if the S-CVI/Ave ≥0.9, the scale-level content validity is acceptable (24, 25). Otherwise, the unqualified items should be deleted or modified and reevaluated until they meet the criteria.

We performed the EFA to test the scale's construct validity. If the Kaiser-Meyer-Olkin measure of sampling adequacy (KMO) ≥0.70 and the difference of the Bartlett's test had statistical significance ($p < 0.05$), the scale was suitable for factor analysis. If an item's measure of sampling adequacy (MSA) is <0.5, the item is unsuitable for factor analysis and will be deleted (26, 27). We chose principal component analysis (PCA) combined with the Varimax orthogonal rotation method to analyze the data. The following criteria were used to determine the number of factors. 1) Kaiser's principle of eigenvalues >1 to extract factors (28). 2) The factor contains at least two items with loadings >0.4 (29). 3) Items with cross-loading >0.75 were deleted (29). The scree test will assist us in judging the results of the PCA. Ultimately, the EFA's results and the original BIT's theoretical structure will guide us in determining the final version of the scale (28). We used the following criteria to assess the goodness of the CFA model: the ratio of chi-square to degrees of freedom (CMIN/df) <5; standardized root mean square residual (SRMR) <0.05; root mean square error of approximation (RMSEA) <0.08; comparative fit index (CFI), the goodness of fit index (GFI), and Tucker–Lewis index (TLI) value >0.9 (30, 31).

We used the GAS-C as a validity criterion to analyze the scale's criterion-related validity. The criterion-related validity is acceptable if the Pearson correlation coefficient $r \geq 0.4$ and is statistically significant (32).

2.5.3 Reliability analysis

We evaluated the scale's reliability. Its internal consistency reliability is appropriate if Cronbach's $\alpha \geq 0.70$ (21). The intraclass correlation coefficient (ICC) between 0.6 and 0.74 is good, and ≥0.75 is excellent (33). We assessed the test–retest reliability also. The Pearson correlation coefficient r of test–retest reliability ≥0.7 is acceptable (34).

2.5.4 Ceiling effect and floor effect

We evaluated the ceiling and floor effects of the data. A ceiling or floor effect exists if more than 15% of respondents achieve an item's maximum or minimum score, meaning a response bias occurred in the data (35).

3 Results

Data from 496 patients with T2D were collected, from whom 296 patients with T2D were randomly selected as subjects for the item analysis, reliability analysis, and validity analysis of the BIT-C-14—the remaining 200 patients with T2D as subjects for the CFA. There were no missing data. Descriptive statistics for participants' socioeconomic, medical, and psychological variables in Study I and Study II are provided in Table 2.

3.1 Item analysis

The Pearson correlation coefficients for the BIT-C-14's items 4–6 with the BIT-C-14's total score were all <0.4. The poor correlation means that these three items are not homogeneous with the remaining 11 items of the BIT-C-14 (22). So, we deleted them and obtained a BIT-C scale with the remaining 11 items (BIT-C-11) (Table 1). No items with communalities were <0.2 (21, 23) (Table 3). Removing an item from the BIT-C-11 would not increase its Cronbach's α value (Table 4). All 11 items in the BIT-C-11 were retained.

3.2 Validity analysis

3.2.1 Content validity

Six diabetologists rated the BIT-C-11's content validity. The I-CVI for all 11 items was 1.0, all higher than 0.78. The S-CVI/Ave was 1.0 higher than 0.9. They all meet the criterion of content validity (24, 25). The BIT-C-11 has good content validity.

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TABLE 2 General characteristics of the participants in samples A and B.

Characteristics	Sample A	Sample B
n	296	200
Age(years)	63.51 ± 7.88	62.05 ± 8.60
Sex		
Male (%)	53.04 (157/296)	52.50 (105/200)
Female (%)	46.96(139/296)	47.50 (95/200)
Education levels(years)	9.45 ± 2.98	9.51 ± 2.81
Duration of diagnosis(month)	87.16 ± 67.92	86.08 ± 64.42
HbA1c		
Mean (SD), %	8.7(1.8)	8.6(1.6)
Mean (SD), mmol/mol	72(20)	70(18)
Total score of the BIT-C-14	70.91 ± 22.86	–
Total score of the GAS **Total score of the BIT-C-11**	19.83 ± 5.05 58.61 + 22.50	- 56.46 + 17.30

Data are means ± SD or percentages.
n, the sample size; HbA1c, hemoglobin A1c; BIT-C-14, Chinese version of the BIT questionnaire with 14 items; GAS, General Adherence Scale; BIT-C-11, Chinese version of the BIT questionnaire with 11 items; Sample A, participants of the exploratory factor analysis; Sample B, participants of the confirmatory factor analysis.

3.2.2 Construct validity

We conducted the EFA on the BIT-C-11 using the PCA combined with the Varimax orthogonal rotation method. The KMO value was equal to 0.830 ≥ 0.7. The difference in the Bartlett's test was statistically significant ($p < 0.01$). The chi-square value was equal to 3,131.231. The results demonstrated that the BIT-C-11 was suitable for factor analysis (24, 36).

Three items in Factor 1 are consistent with the BIT's "fear of injection and self-testing" factor. We named Factor 1 "fear of injection and self-testing" as well. The three items in Factor 2 are consistent with those in the "expected hardship from insulin treatment" factor of the BIT, so we named Factor 2 "expected hardship from insulin treatment." Factor 3 contains the BIT's three items of the "stigmatization by insulin injections" factor. Therefore, we also named Factor 3 "stigmatization by insulin injections." Factor 4 has two items corresponding to the two items in the BIT's "fear of hypoglycemia" factor. We named Factor 4 "fear of hypoglycemia" (Table 3). The scree test also supported extracting four factors (Figure 1).

Results of the first-order CFA confirmed the structure of the BIT-C-11 with a good model fit with CMIN/DF = 1.311 < 5; GFI = 0.954, CFI = 0.961, TLI = 0.944, their values all >0.9; the SRMR = 0.032 < 0.05, and the RMSEA = 0.040 < 0.05. Standardized factor

TABLE 3 Summary of the BIT-C-11's exploratory factor analysis.

Items of the BIT-C-11	Component				MSA	IC
	1	2	3	4		
Factor 1: "fear of injection and self-testing"						
1. I am afraid of the pain when injecting insulin.	0.896				0.872	0.893
2. Besides the pain, I am afraid of injections.	0.905				0.856	0.914
3. I am afraid of the pain during regular blood-sugar checks.	0.922				0.810	0.934
Factor 2: "expected hardship from insulin treatment"						
4. I just don't have enough time for regular doses of insulin.			0.762		0.908	0.841
5. I can't pay as close attention to my diet as insulin treatment requires.			0.889		0.842	0.890
6. I can't organize my day as carefully as insulin treatment requires.			0.874		0.823	0.917
Factor 3: "stigmatization by insulin injections"						
7. Injections in public are embarrassing to me. Pills are more discreet.		0.903			0.857	0.871
8. Regular insulin treatment causes feelings of dependence.		0.913			0.811	0.903
9. When people inject insulin, it makes them feel like drug addicts.		0.922			0.831	0.901
Factor 4: "fear of hypoglycemia"						
10. An insulin overdose can lead to extremely low blood-sugar levels ("hypoglycemia"). I am afraid of the unpleasant accompanying symptoms.				0.921	0.734	0.933
11. An insulin overdose can lead to extremely low blood-sugar levels ("hypoglycemia"). I have concerns about possible permanent damage to my health.				0.885	0.764	0.920
Eigenvalue	5.644	2.069	1.195	1.009		
Variance explained (%)	51.308	18.810	10.863	9.173		
Total variance explained (%)	90.153					

Extraction method: Principal component analysis (Kaiser's eigenvalue >1); Four components extracted; Factor Loadings > 0.40 are reported.
BIT-C-11, Chinese version of the BIT questionnaire with 11 items; MSA, measures of sampling adequacy; IC, item's communalities.

TABLE 4 Reliability of the BIT-C-11.

Item Number	Means ± SD	α
1	5.03 ± 2.59	0.895
2	5.16 ± 2.82	0.893
3	4.92 ± 2.77	0.894
4	4.79 ± 2.95	0.886
5	5.63 ± 2.95	0.893
6	5.16 ± 2.99	0.889
7	5.40 ± 2.89	0.899
8	5.08 ± 2.93	0.897
9	5.10 ± 3.01	0.898
10	6.29 ± 2.84	0.900
11	6.05 ± 2.79	0.897

Cronbach's α = 0.903
CI 0.881–0.916)
test–retest reliability: r = 0.810
BIT-C-11, Chinese version of the BIT questionnaire with 11 items; α, Cronbach's α without item, ICC, intraclass correlation coefficient.

loadings ranged between 0.77 and 0.90 (Figure 2). The second-order CFA of the BIT-C-11 confirmed a good model fit with CMIN/DF = 1.104 < 5; GFI = 0.960, CFI = 0.982, TLI = 0.975; the SRMR = 0.033 < 0.05, and the RMSEA = 0.039 < 0.05. Standardized factor loadings ranged between 0.77 and 0.90 (Figure 3), so creating a total score of the BIT-C-11 is appropriate.

3.2.3 Criterion-related validity

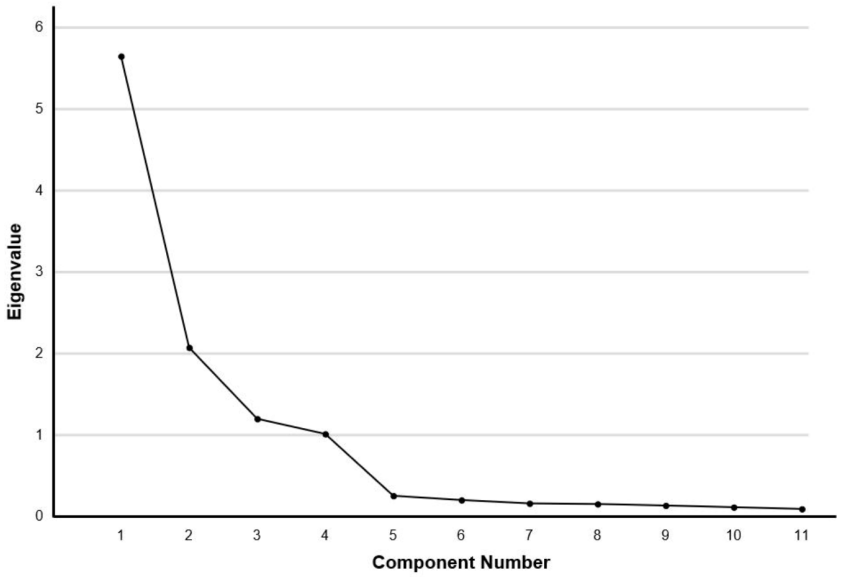
A negative correlation exists between the BIT-C-11 total score and the GAS-C total score, with a Pearson correlation coefficient of 0.598, p < 0.001. The criterion-related validity of the BIT-C-11 is acceptable (32).

3.3 Reliability analysis

The Cronbach's α coefficients of the BIT-C-11 and its four factors were 0.903, 0.952, 0.927, 0.938, and 0.917. They are all >0.7 (p < 0.001). The Cronbach's α values of the BIT-C-11 and its four factors are appropriate (16). The BIT-C-11's ICC was 0.899 (95% CI 0.881–0.916). The ICC values for Factor 1, Factor 2, Factor 3, and Factor 4 were 0.951 (95% CI 0.940–0.960), 0.921 (95% CI 0.897–0.938), 0.937 (95% CI 0.923–0.949), and 0.915 (95% CI 0.893–0.933), respectively. All of which were >0.75 and met Cicchetti's criteria for good (28). The correlation coefficient r of the test–retest reliability of the BIT-C-11, Factor 1, Factor 2, Factor 3, and Factor 4 was 0.810, 0.794, 0.756, 0.778, and 0.757, respectively. They are all >0.4. The test–retest reliability of BIT-C-11 and its four factors is acceptable (34) (Tables 4, 5).

3.4 Ceiling effect and floor effect

There were no subjects who achieved the maximum total score of 110. Two subjects achieved the lowest total score of 11, 0.7% of all people. They were all below the criteria of 15% for both the ceiling and floor effects. No subject response bias was observed in the current study (35).



Notes: four factors have a Kaiser's eigenvalue ≥1; extraction method, principal component analysis.

FIGURE 1
Scree plot.

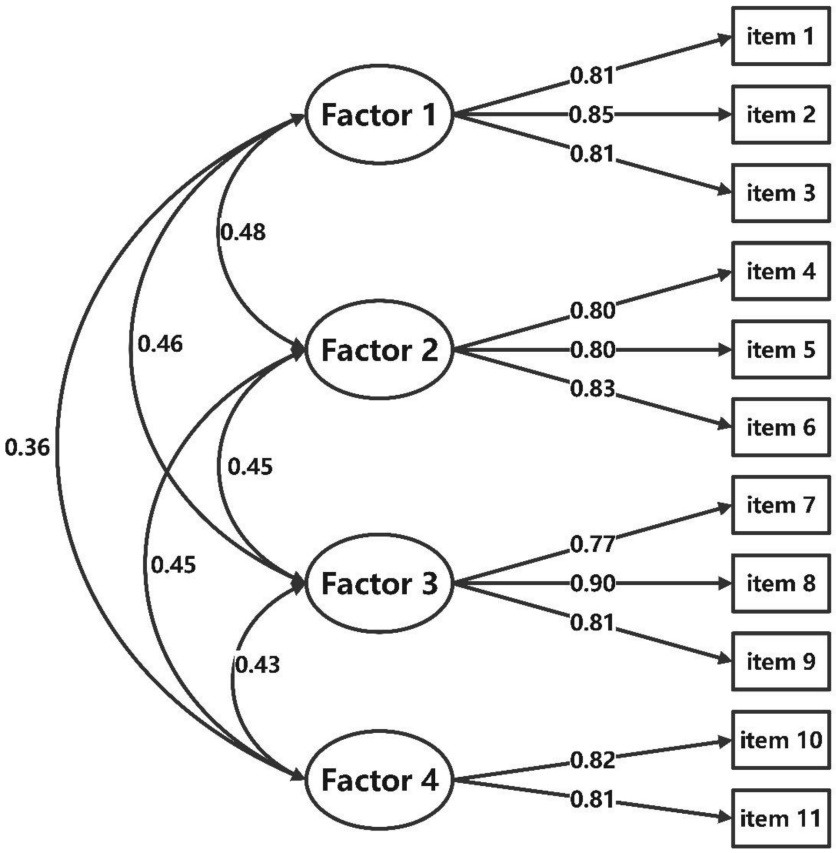


FIGURE 2
Path diagram for BIT-C-11's first-order CFA. BIT-C-11, Chinese version of the BIT questionnaire with 11 items; CFA, confirmatory factor analysis; Factor 1, fear of injection and self-testing factor; Factor 2, expected hardship from insulin treatment factor; Factor 3, stigmatization by insulin injections factor; Factor 4, fear of hypoglycemia factor.

4 Discussion

Chinese patients with T2D generally have poor insulin adherence (5). It is urgent to assess the psychological resistance to insulin therapy in Chinese patients with T2D using a standardized scale. Our revised BIT-C-11 has relatively good psychometric characteristics and can be used to assess the psychological resistance to insulin therapy in middle-aged and elderly Chinese patients with T2D.

It is interesting to note that unlike Petrak's original BIT, which contains five factors, the BIT-C-11 does not include the three reverse score items in the expectations regarding positive insulin-related outcomes factor of the original BIT. The reason for such differences may be due to differences in sample selection.

Petrak et al. (6) selected insulin-naive patients to develop the original BIT, who had no experience of improved health due to using insulin before.

In this study, we selected patients with T2D who were already using insulin as the study subjects. There may be differences in the content of psychological resistance to insulin therapy between patients with T2D treated with insulin and those with T2D not using insulin. Suppose we conduct an in-depth study of patients with T2D psychological resistance to insulin treatment in the future; it might be necessary to classify the study subjects in order to draw more scientific and accurate conclusions.

Another possible explanation is cultural differences. Several studies have suggested cultural differences in psychological insulin resistance, such as, for example, some studies showing ethnic differences in the causes of psychological insulin resistance (37, 38). Among Asian patients with diabetes, especially in China, there is a greater fear of injections and more incredible difficulties in using insulin than Western patients (39, 40). A 2015 study showed that psychosocial factors (rather than the presence of comorbidities) play a more critical role in determining PIR in the Chinese population (41). These studies suggest the influence of cultural differences, but the exact mechanisms are unclear, and more research needs to be done to elucidate them.

Petrak found that patients who opt for oral medications report significantly higher barriers to insulin therapy than those willing to use subcutaneous insulin. The original BIT has an apparent predictive validity for patients' psychological resistance to insulin therapy (6). However, our subjects were patients who already used insulin injections, so we analyzed the BIT-C-11's concurrent validity instead of its predictive validity. The GAS is a commonly used scale to assess general adherence in patients with chronic diseases (17). We found a negative correlation between the BIT-C-11 and the GAS in this study. A correlation coefficient of $0.582 > 0.4$ means that the criterion-related validity of the BIT-C-11 is acceptable (32). It implies that the better the T2D patient's

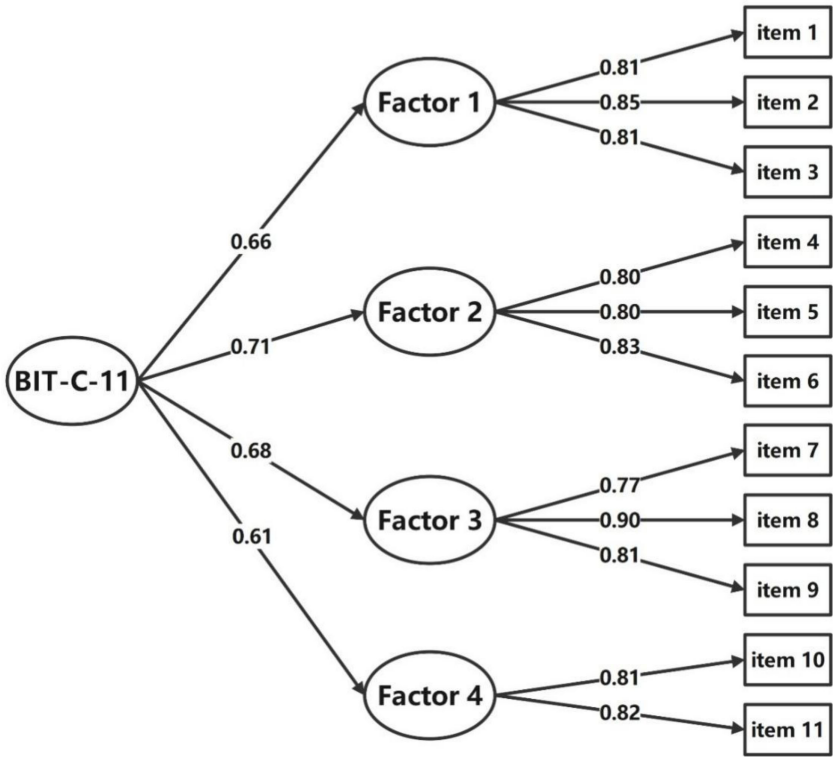


FIGURE 3
Path diagram for BIT-C-11's second-order CFA. BIT-C-11, Chinese version of the BIT questionnaire with 11 items; CFA, confirmatory factor analysis; Factor 1, fear of injection and self-testing factor; Factor 2, expected hardship from insulin treatment factor; Factor 3, stigmatization by insulin injections factor; Factor 4, fear of hypoglycemia factor.

general adherence to his or her physician's recommendations, the lower is his or her psychological resistance to insulin treatment may be. General adherence encompasses many aspects of prevention, treatment, and patient health care. Adherence to insulin treatment is only a part of general adherence, which may explain why the GAS and the BIT-C-11 are related, but the correlation is not too high.

The Cronbach's α value for the BIT-C-11 was 0.903, and the Cronbach's α value in the original BIT was 0.78 (6). Both the original BIT and the BIT-C-11 and their subscales have relatively good internal consistency reliability. Since the subjects of these two studies differed, there was little comparability between their α values.

Petrak et al. (6) did not report the test–retest reliability of the original BIT. The correlation coefficient r of the BIT-C-11's test–retest reliability was 0.810 after 4 weeks, which indicates that the stability of the BIT-C-11 is acceptable (34). Since patients with T2D need to use insulin for a long time, it is possible that some patients' psychological resistance to insulin therapy decreases over time and become more receptive to insulin therapy. However, due to certain specific events, some patients already on insulin therapy may temporarily increase psychological resistance to insulin therapy and may become reluctant to receive insulin therapy for some time. Therefore, unlike personality traits that remain stable over time (42), we speculate that psychological resistance to insulin treatment is a psychological state subject to change by various factors. This changeability might be the basis for our intervention for psychological resistance to insulin treatment in patients with T2D. Further research is needed to identify the factors influencing psychological resistance to insulin therapy and develop specific and effective interventions to address these influences. However, this opinion needs to be supported by more research data in the future.

5 Strengths

The BIT is a valuable research tool to assess patients with T2D's psychological resistance to insulin treatment, but to our knowledge, the BIT-C-11 is the first revised Chinese version of the BIT. The number of subjects in this study met the sample size requirements for a revised scale study. The study's objectives and the inclusion and exclusion criteria of the subjects were clear in this study. There were no missing data in the survey due to the efforts of the investigators. The BIT-C-11 has relatively good reliability and validity, and the CFA verified its structure. All of the above are the strengths of this study.

6 Limitations

Although we have successfully revised the Chinese version of the BIT, the age and ethnic group of the subjects in this study lacked sufficient representation. On the one hand, worldwide, the trend of

TABLE 5 Reliability of the BIT-C-11's factors.

Factors and items of the BIT-C-11	α
Factor 1: fear of injection and self-testing	
1. I am afraid of the pain when injecting insulin.	0.943
2. Besides the pain, I am afraid of injections.	0.930
3. I am afraid of the pain during regular blood-sugar checks.	0.913
Cronbach's α=0.952	
ICC: 0.952 (95% CI 0.940-0.960)	
test-retest reliability: r=0.794	
Factor 2: "expected hardship from insulin treatment"	
4. I just don't have enough time for regular doses of insulin.	0.919
5. I can't pay as close attention to my diet as insulin treatment requires.	0.905
6. I can't organize my day as carefully as insulin treatment requires.	0.859
Cronbach's α=0.927	
ICC: 0.921 (95% CI 0.897-0.938)	
test-retest reliability: r=0.756	
Factor 3: stigmatization by insulin injections	
7. Injections in public are embarrassing to me. Pills are more discreet.	0.925
8. Regular insulin treatment causes feelings of dependence.	0.898
9. When people inject insulin, it makes them feel like drug addicts.	0.905
Cronbach's α=0.938	
ICC: 0.937 (95% CI 0.923-0.949)	
test-retest reliability: r=0.778	
Factor 4: fear of hypoglycemia	
10. An insulin overdose can lead to extremely low blood-sugar levels ("hypoglycemia"). I am afraid of the unpleasant accompanying symptoms.	*
11. An insulin overdose can lead to extremely low blood-sugar levels ("hypoglycemia"). I have concerns about possible permanent damage to my health	*
Cronbach's α=0.917 ICC: 0.915 (95% CI 0.893-0.933) test-retest reliability: r=0.757	

BIT-C-11, Chinese version of the BIT questionnaire with 11 items; α, Cronbach's α without item; *, Not applicable because scale contains only two items.

T2D in the younger population has surpassed that of the middle-aged and older population in recent years. We only selected patients with T2D aged 45–74 years for the study; further validation is needed if the BIT-C-11 is to be used in other age groups. We will further expand the subject's age range to improve these shortcomings in the future.

Due to the study's funding, considering that the BIT contains only 14 items, which is not a large number, we empirically selected 15 patients with T2D who met the study criteria for the pretest and cognitive interviews. Our judgment was not well grounded in theory. It should be noted that sample sizes >30 may be more scientific in pretesting and cognitive interviewing (43).

Another problem is that Factor 4 contains only two items. According to the theory of scale development, each factor should be composed of at least three variables; otherwise, the factor should be discarded or ignored (44). However, considering that "fear of hypoglycemia" is an essential aspect of psychological resistance to insulin therapy, Factor 4 of the BIT-C-11 already has good validity and reliability. We felt that the structure of the Chinese version of the BIT should be consistent with the original BIT, and the "fear of hypoglycemia" factor of the original BIT only has these two items, so we retained Factor 4.

7 Conclusion

We revised the Chinese version of the BIT, which has relatively good reliability and validity. The revised BIT-C-11 is four-dimensional and has a total of 11 items, which can be used to assess the psychological resistance to insulin therapy of middle-aged and elderly urban Han people with T2D who use insulin in China.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Author contributions

MM: conceptualization, methodology, formal analysis, and writing–original draft. XM: methodology, data curation, and writing–original draft. JC: methodology and writing–original draft. FY: methodology and data curation. SM: writing–review and editing. YZ: writing–review and editing. ZS: conceptualization, methodology, writing–original draft, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Exploring the risk of glycemic variability in non-diabetic depressive individuals: a cross-sectional GlyDep pilot study

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Background: Data on the correlation between glycemic variability and depression in nondiabetic patients remain limited. Considering the link between increased glycemic variability and cardiovascular risks, this relationship could be significant in depressed patients.

Methods: In this single-center pilot study, we utilized Flash Glucose Monitoring (Abbott Libre Pro) to study glycemic variability. The CES-D (Center for Epidemiological Studies– Depression) scale was employed to measure depression levels. Based on CES-D scores, patients were classified into two groups: those with scores ≥ 33 and those with scores < 33. We analyzed various glycemic variability indices, including HBGI, CONGA, ADDR, MAGE, MAG, LI, and J-Index, employing the EasyGV version 9.0 software. SPSS (version 28) facilitated the data analysis.

Results: We screened patients with depression visiting the department of psychiatry, FGM was inserted in eligible patients of both the groups which yielded a data of 196 patient-days (98 patient-days for CES-D ≥ 33 and 98 patient-days for CES-D < 33). The glycemic variability indices CONGA (mg/dl), (76.48 ± 11.9 vs. 65.08 ± 7.12) (p = 0.048), MAGE (mg/dl) (262.50 ± 25.65 vs. 227.54 ± 17.72) (p = 0.012), MODD (mg/dl) (18.59 ± 2.77 vs. 13.14 ± 2.39) (p = 0.002), MAG(mg/dl) (92.07 ± 6.24vs. 63.86 ± 9.38) (p = <0.001) were found to be significantly higher in the CES-D ≥ 33 group.

Conclusion: Patients with more severe depressive symptoms, as suggested by CES-D ≥ 33, had higher glycemic variability.

KEYWORDS

depression, glycemic variability, risk of diabetes, FGM, CES-D, glycemic variability indices

1. Introduction

Diabetes mellitus, a global health issue, stands as one of the prevalent non-communicable diseases impacting millions worldwide. Beyond the well-researched complications of neuropathy, nephropathy, retinopathy, and cardiovascular sequelae, there emerges a significant shadow of psychological morbidity, most profoundly depression. This complex relationship is substantiated by recent meta-analyses, such as those conducted by Mezuk et al. (1) and Chireh et al. (2), which indicate that diabetes increases the risk of developing depression by approximately 25% (1, 2). The relationship between diabetes and depression is bidirectional. Diabetes can elevate the risk of developing depression, and similarly, depression can predispose one to diabetes. When they coexist in an individual, it's not just a simple overlap. This confluence exacerbates the progression and complicates the outcomes of both disorders.

Depression, characterized by pervasive mood disturbances, underpins profound implications for metabolic health, particularly glycemic control. A confluence of pathophysiological mechanisms including inflammation, neuroendocrine dysfunction, and alterations in insulin dynamics have been implicated in mediating this association (3). Longitudinal studies further emphasize the chronic impact of depression on glycemic variability (GV), a parameter depicting fluctuations in blood glucose levels that has been linked to microvascular complications and oxidative stress (4).

However, the majority of these studies are conducted in diabetic populations and rely on traditional glucose monitoring systems, which may not accurately capture the day to day spectrum of GV. Recent innovations like the FreeStyle Libre flash glucose monitoring system offer a more nuanced window into these fluctuations, yet there is a paucity of research exploring the depression-GV nexus in non-diabetic individuals using this technology. Observational studies have highlighted the potential connections, but more targeted research is needed (5).

The objective of this research is to fill this research gap through a pilot study examining the relationship between depression severity and GV in non-diabetic individuals, employing the advanced FreeStyle Libre system. This cross-sectional GlyDep Pilot Study seeks to extend the current understanding of this complex interplay by focusing on a population often overlooked in conventional research. By shedding light on the mechanisms at play in non-diabetic individuals, the findings may pave the way for early interventions and personalized therapeutic strategies that account for both mental and metabolic health. By engaging with cutting-edge technology and a novel demographic, this study endeavors to contribute a fresh perspective to the ongoing discourse surrounding depression, GV, and their broader implications for public health (6).

2. Methodology

The present study was conducted in compliance with the ethical principles of the Declaration of Helsinki, and approval for the study was obtained from the Institutional Review Board (approval number: NIMSUR/IEC/2022/211). All study subjects provided informed consent for this observational analysis.

2.1. Design and participants

The present study, called GlyDep, is a primary quantitative exploratory research project aimed at analyzing glycemic variability (GV) in individuals with depressive disorder. Recruitment of participants, aged 18 years and older, diagnosed with depression (ICD-10) was conducted at the Department of Psychiatry, National Institute of Medical Science and Research in Jaipur, India, from April 2022 to November 2022. Diagnosis of incident depression was based on ICD-10 codes F32 (all mild to severe depressive episodes) or F33 (all recurrent depressive disorders) with cognitive behavioral therapy for management of diabetes (7). The study utilized a set of inclusion and exclusion criteria. Inclusion criteria consisted of a proven diagnosis of depression, glycated hemoglobin indices A1c (HbA1c) levels <5.6%, and willingness to give consent for the study. Patients were excluded if they did not meet the clinical diagnosis according to ICD-10, had unstable severe medical conditions such as active malignant diseases, heart failure, or chronic liver diseases, were below 18 years of age, or had HbA1c levels above 5.6%.

2.2. Data collection and recruitment of the study population

2.2.1. Demographic factors

Customized data collection forms were designed and used to collect the study data. Participants' age, gender, marital status, smoking habits, and educational status were documented in the data collection forms. Weight and height were measured as per protocol and the body mass index (BMI) was calculated. The criteria established by the World Health Organization for overweight (23.0 kg/m2) and obesity (25.0 kg/m2) were used to determine BMI status (8). Body composition was assessed with waist and hip measurements, which was obtained from standard measuring tape. Waist-to-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference (9).

2.2.2. Laboratory parameters

The participants lipid profile was assessed, including Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), and Triglycerides (TG), following the guidelines of the American Heart Association (AHA) (10). Additionally, Blood Urea Nitrogen (BUN), Serum Creatinine (SCr), Aspartate Aminotransferase (AST), and Alanine Transaminase (ALT) levels were measured. These particular measurements are integral for monitoring kidney function and liver health, ensuring a comprehensive evaluation of the participants' overall metabolic health.

2.2.3. Glucose assessment

2.2.3.1. HbA1c measurement

HbA1c serves as a sensitive indicator of long-term glycemic control, reflecting average blood glucose levels over a period of approximately 2 to 3 months. In this study, HbA1c levels were measured *via* high-performance liquid chromatography (HPLC) of hemolysates from whole blood (<5.6%) which is a reliable and gold standard technique for HbA1C determination. Glucose levels in fasting serum samples were assessed using glucose oxidase peroxidase and a Siemens Dimension EXL 200 analyzer.

2.2.3.2. Flash glucose monitoring (Freestyle libre Pro)

In this study, the ambulatory glucose profile was calculated using interstitial sensor glucose data obtained from the Freestyle Libre Pro system (Abbott Diabetes Care, Oxon, UK). The system comprised a sensor worn by patients for 2 weeks, which tested interstitial glucose levels at 15-min intervals (11). All study participants were instructed to wear the sensor for the entire two-week period, resulting in a total of 196 patient-days.

Glycemic variability indices, such as mean sensor glucose and its standard deviation (SD), absolute means of daily differences (MODD), continuous overall net glycemic action (CONGA), mean amplitude of glycemic excursion (MAGE), high blood glucose index (HBGI), mean absolute glucose (MAG), liability index (LI), average daily risk ratio (ADRR), and J-Index were among the glycemic variability indices. EasyGV version 9.0 software (University of Oxford, OX2 6GG, United Kingdom) was utilized to compute the above indices using the data collected for 196 patient-days (Review Supplementary Table 1) (12–17).

2.2.4. Measures for depressive symptoms (CES-D)

The Center for Epidemiological Research Depression Scale (CES-D) was devised by the National Institute of Mental Health in the 1970s. Its primary intent was to assess depressive symptomatology in the general population, bridging the gap between clinical diagnosis and population-based assessment. Over the years, it has been adapted for various subpopulations and has become one of the widely accepted tools for screening depression symptoms in epidemiological studies.

Compared to other depression scales, CES-D uniquely incorporates a range of symptoms, capturing diverse domains such as mood, somatic complaints, and interpersonal interactions. This holistic approach ensures a comprehensive understanding of an individual's depressive state. The Center for Epidemiological Research Depression Scale (CES-D) was employed to screen for depression symptoms under the guidance of a designated psychiatrist (18) The CES-D contains 20 items commonly used in screening for depression and depressive symptoms. The CES-D response options were based on recent symptoms and a 4-point Likert scale ranging from "rarely or none of the time" to "most or all of the time." The scale goes from 0 to 60, with a higher score indicating more significant depressive symptoms (19).

Cronbach's alpha was 0.85 in reliability testing (20). Furthermore, significant correlations with other depression measurement scales were observed, supporting the convergent validity of the CES-D, and construct validity was established by differences between psychiatric inpatients and the general population (19).

2.3. Statistical analysis

We used IBM SPSS version 28.0 from Chicago, IL, United States for our statistical analysis. We summarized continuous variables with mean and standard deviation, while categorical variables were presented as frequency and percentage. To compare differences between groups, we used t-tests for continuous variables and Fisher's exact test for categorical variables. Acknowledging our cautious approach toward our small sample's uniqueness and potential data non-normality, we found non-parametric statistical methods to be necessary. Since finding non-diabetic participants posed challenges, we explored alternative methods. Non-parametric tests, known for their reliability with limited data, became suitable choices. We emphasize awareness of assumptions and limitations in both parametric and non-parametric analyses. Furthermore, Microsoft Excel 2015 facilitated data visualization.

3. Results

3.1. Study population

At the psychiatry outpatient department of NIMS hospital, we screened 62 patients for our study. Out of 62 patients with depression, thirty-one patients were found to be eligible for the study. Out of thirty-one, thirteen patients were excluded from the study. The reasons for the exclusion were as follows: (1) difficulty in interviewing patients due to aggressive or irregular behavior ($n = 3$); (2) refusal to use FGMS ($n = 6$); (3) refusal to participate in the study ($n = 4$). Finally, eighteen patients were enrolled, with a loss of follow-up ($n = 4$). The study flow chart is shown in Figure 1.

The study included 14 participants with a total of 196 patient-days. Of 14 participants 10 were males and 4 were females with an average age of 29.53 ± 1.77 years. We made two groups depicting the severity of depression: CES-D scores≥33 (6 males, 1 female) and < 33 (4 males, 3 females). The overall CES-D score was 33.46 ± 7.32 (range: 0–60), 39.71 ± 3.81 for the CES-D ≥ 33 group, and 27.00 ± 2.70 for the CES-D < 33 group. The comparison of the data of patients who had CES-D > 33 to those who had CES-D < 33 is shown in Table 1. Age and HbA1C were significantly higher in the patients with CES-D ≥ 33 (Table 1).

3.2. Distribution of glycemic variability indices

Supplementary Table 2 shows an explanatory version of the measures of glycemic variability, along with their mean and standard deviations. The standard deviation of the blood glucose, a marker of glycemic variability, was higher in CES-D ≥ 33 group (Figures 2A,B).

3.3. Glycemic variability and depression

We compared the glycemic variability indices of the patients who had CES-D ≥ 33 to those who had CES-D < 33. The HbA1c was higher in the patients who had CES-D ≥ 33 (5.52 ± 0.34 vs. 4.82 ± 0.59) ($p = 0.020$) (Table 1).

CONGA (mg/dl) was higher in CES-D ≥ 33 group (76.48 ± 11.9 mg/dL vs. 65.08 ± 7.12 mg/dL) ($p = 0.048$) (Figure 3A). Likewise, HBGI (mg/dl) and MAGE (mg/dl) values were also higher (50.41 ± 5.21 vs. 36.89 ± 4.09) ($p = <0.001$), (262.50 ± 25.65 vs. 227.54 ± 17.72) ($p = 0.012$) respectively (Figures 3B,C) Other glycemic variability indices like J-Index (mg/dl) (4296.49 ± 777.98 vs. 2822.79 ± 526.53) ($p = 0.001$), MODD (mg/dl) (18.59 ± 2.77 vs. 13.14 ± 2.39) ($p = 0.002$), LI(mg/dl) (766.74 ± 266.28vs. 384.41 ± 72.98) ($p = 0.003$), ADDR (mg/dl) (384.14 ± 15.43 vs. 332.71 ± 17.21) ($p = <0.001$) and MAG (mg/dl) (92.07 ± 6.24vs. 63.86 ± 9.38) ($p = <0.001$) were also found to be significantly higher in the CES-D ≥ 33 group (Figures 3D–H).

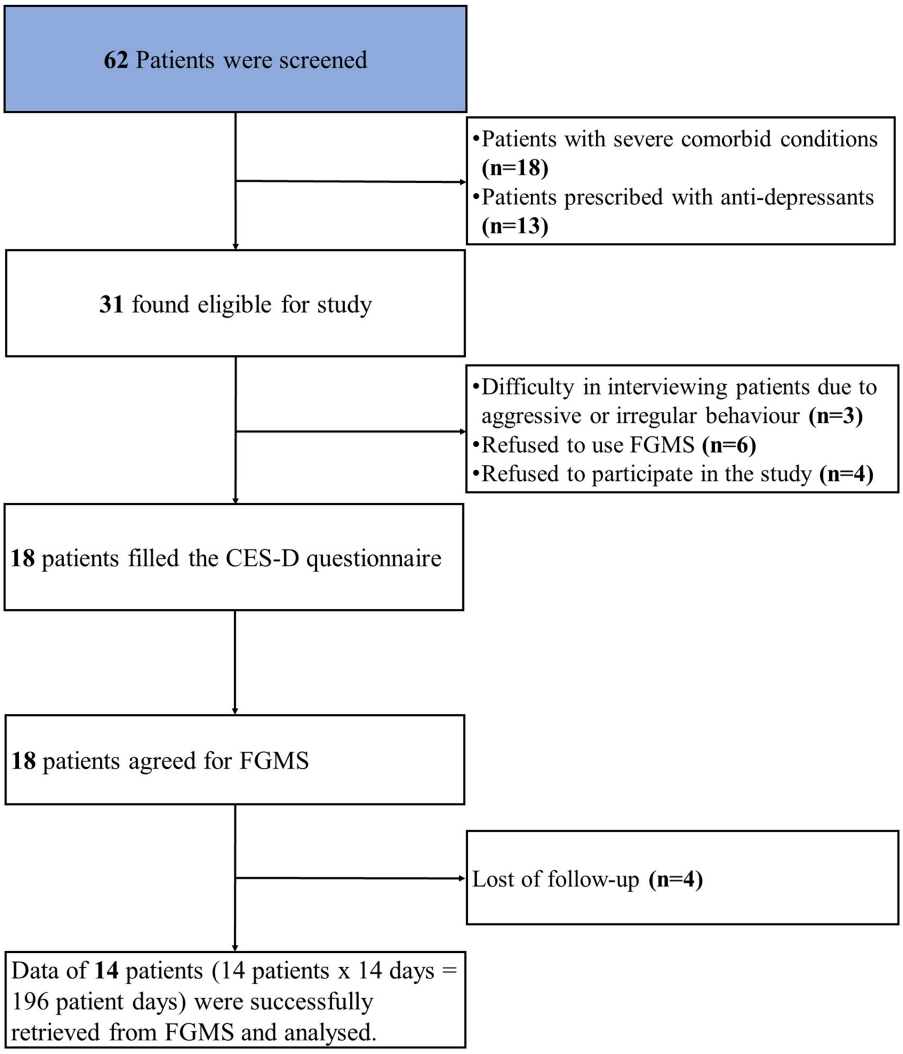

FIGURE 1
Study flow chart showing enrollment and exclusion of the study subjects.

TABLE 1 Baseline comparison of the patients as per the CES-D score, a score used to depict the severity of depression.

Variables	< 33 (*n* = 7)	≥ 33 (*n* = 7)	*p*- value
Age, (years)	24.14 (4.05)	36.42 (4.10)	0.047
Male, *n* (%)	4 (40)	6 (60)	0.559
Married, *n* (%)	4 (40)	6 (60)	0.559
Education status			
Primary school, *n* (%)	0 (0)	1 (14.2)	0.510
Intermediate, *n* (%)	5 (71.42)	4 (57.14)	
Graduate or Post graduate, *n* (%)	2 (28.57)	2 (28.57)	
Smokers, *n* (%)	2 (28.57)	4 (57.14)	0.290
BMI, (kg/m^2)	22.17 (2.56)	23.20 (4.24)	0.594
WHR, mean ± SD	0.91 ± 0.03	0.92 ± 0.03	0.599
HbA1c (%)	4.82 ± 0.59	5.52 ± 0.34	0.020
LDL, (mg/dl), mean ± SD	85.74 ± 21.85	89.42 ± 24.16	0.770
HDL (mg/dl), mean ± SD	45.37 ± 16.41	53.08 ± 14.56	0.371
TG (mg/dl), mean ± SD	143.42 ± 143.76	152.00 ± 72.75	0.890

(Continued)

TABLE 1 (Continued)

Variables	< 33 (*n* = 7)	≥ 33 (*n* = 7)	*p*- value
BUN (mg/dl), mean ± SD	10.82 ± 3.42	10.81 ± 3.38	0.998
SCr (mg/dl), mean ± SD	0.77 ± 0.26	0.85 ± 0.17	0.489
AST (U/L), mean ± SD	42.14 ± 43.73	21.14 ± 7.88	0.235
ALT (U/L), mean ± SD	68.14 ± 71.00	35.14 ± 9.52	0.246

All the data is presented in mean ± standard deviation (SD) or number (*n*) and percentage (%).
BMI, Body Mass Index; WHR, Waist Hip Ratio; HbA1c, Glycated Hemoglobin; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; TG, Triglycerides; BUN, Blood Urea Nitrogen; SCr, Serum Creatinine; AST, Aspartate aminotransferase; ALT, Alanine transaminase; CES-D, Center for Epidemiologic Studies– Depression.

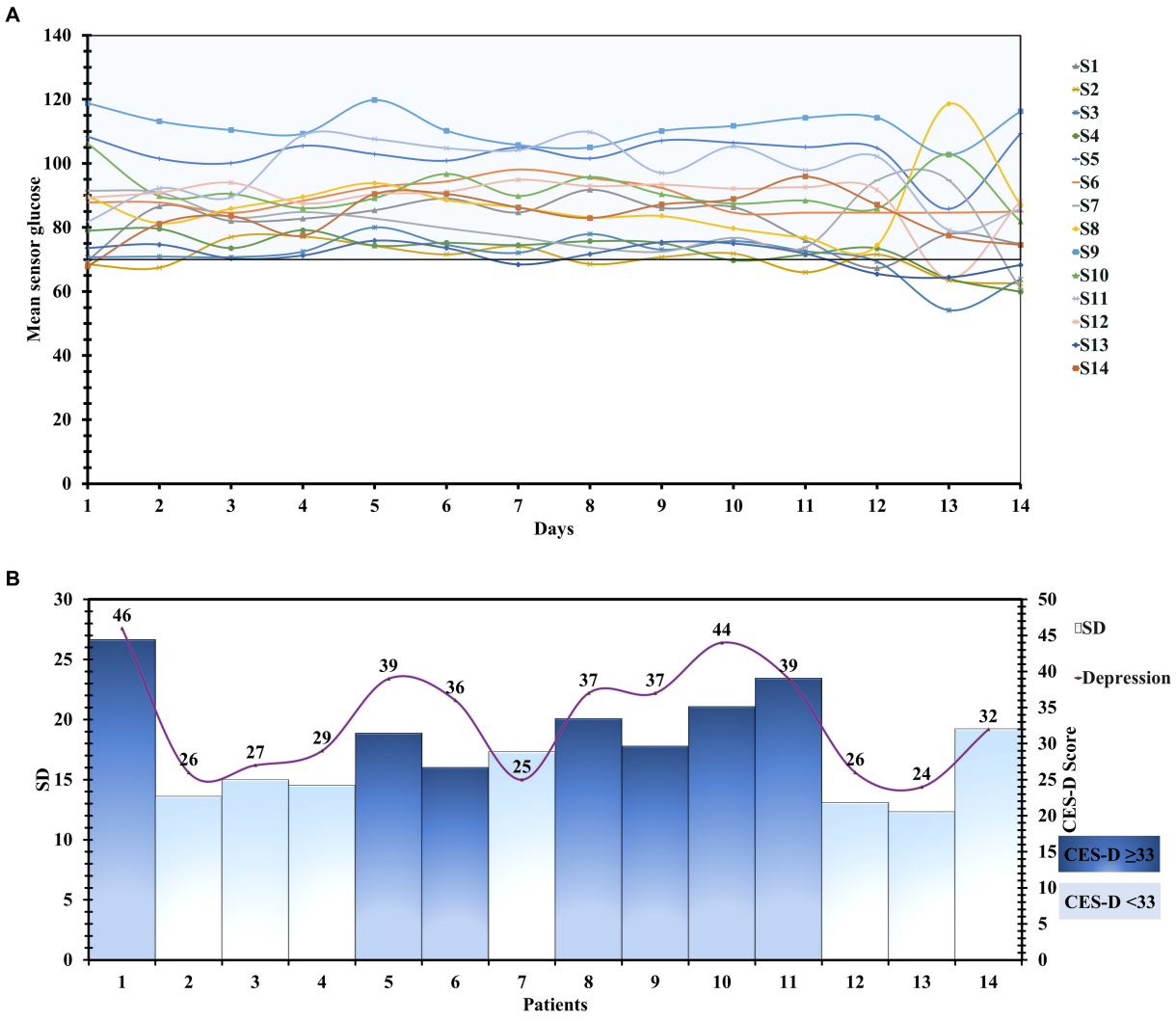

FIGURE 2
(A) Detailed day-wise tracing of the sensor glucose values of 196 patient-days. **(B)** The Mean glucose level and Standard deviation of all the patients with their CES-D scores.

These findings show that glycemic variability was higher in patients with a CES-D score ≥ 33.

4. Discussion

This research endeavors to fill the void of understanding concerning glycemic variability in non-diabetic patients with depression. To assess the patients' glycemic variability, the FGMS was utilized for a period of 2 weeks, which generated an ambulatory glucose profile of 196 patient-days. The glycemic indices were calculated *via* the utilization of EasyGV version 9.0 software. Depression was assessed using the CES-D scale, which has been validated in the Indian population. Patients were assigned to two groups based on their CES-D scores, with scores <33 and scores ≥33. The results of this study reveal that patients with CES-D scores ≥33 exhibited increased glycemic variability.

The etiology of elevated glycemic variability in individuals with depression is multifactorial. In depression, there is an upsurge in stress

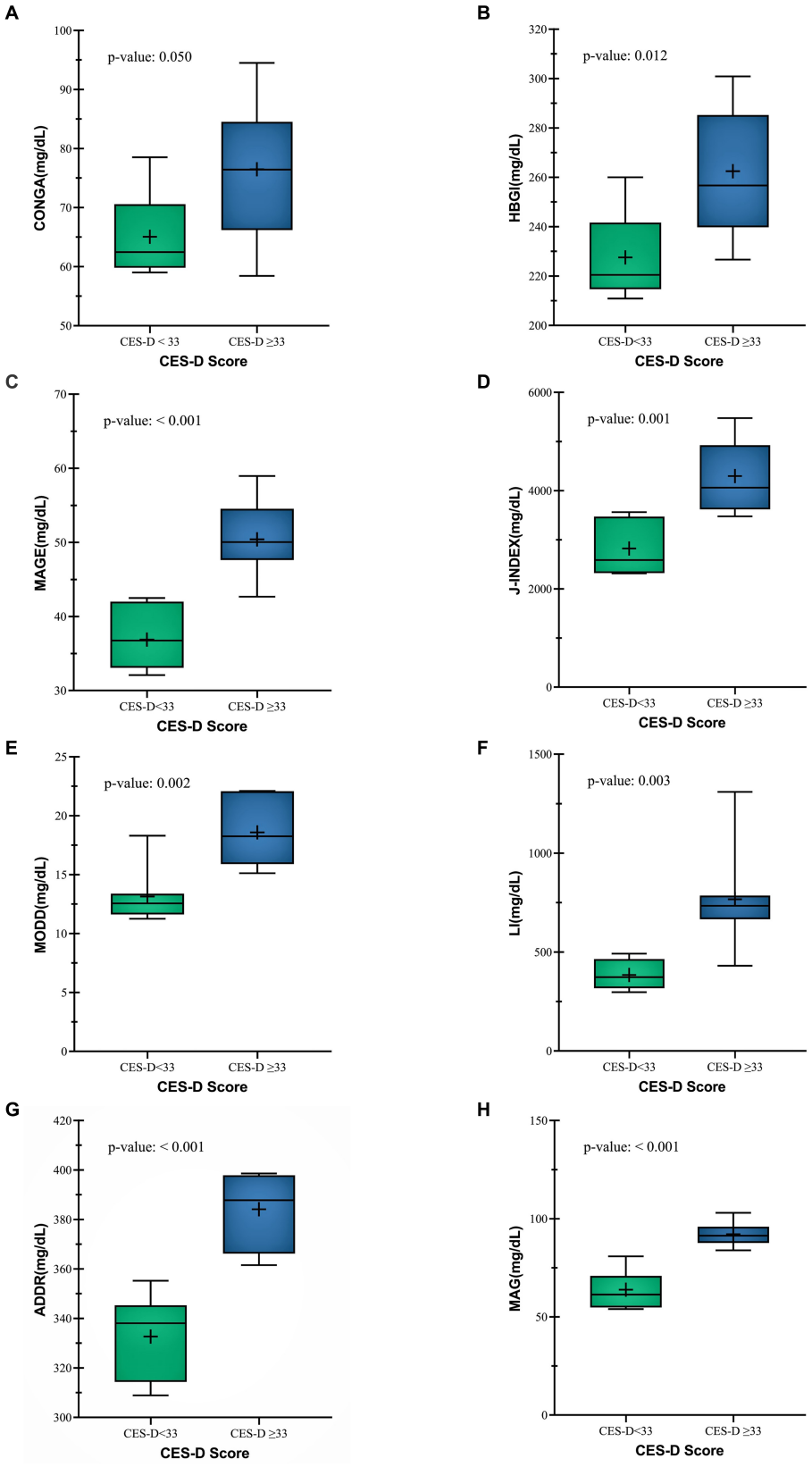

FIGURE 3
Comparison between Glycemic variability indices **(A)** CONGA **(B)** HBGI **(C)** MAGE **(D)** J-INDEX **(E)** MODD **(F)** LI **(G)** ADDR **(H)** MAG of both CES-D groups.

hormones, particularly cortisol, which can be severe enough to result in pseudo- cushing syndrome (21). The elevated cortisol acts on the subcortical area, including the hippocampus and hypothalamus (22). These two areas are crucial for the control of the autonomic nervous system regulation. Autonomic dysfunction, as observed in patients with diabetes, has been linked to elevated glycemic variability. This has been seen in patients with diabetes, who have autonomic dysfunction, and had high glycemic variability (23, 24). The glycemic variability was also found to be associated with incident depression. In a retrospective study from the Korean National Health Insurance Service–National Health Screening Cohort from 2002 to 2007, patients (n-264,480) who have at least three fasting serum glucose were later observed during 2008–2013 (n-198,267), and their hazard ratios (HR) of incident depression were calculated. After adjustment, it was found that the highest glycemic variability was associated with a 9% increased risk of depression (HR, 1.09; 95% CI, 1.02–1.16). The risk of incident depression heightened with increasing GV (p for trend < 0.001) (22). In our pilot study, we tried to explore the glycemic variability in depressive patients. Our pilot study had the objective of exploring glycemic variability among non-diabetic individuals with depression. The heightened glycemic variability observed in patients with CES-D scores ≥33 suggests an elevation in stress hormone levels.

Additionally, there exists a connection between glycemic variability and endothelial dysfunction, which is a precursor to atherosclerosis and cardiovascular incidents. Notably, depression itself is also linked to endothelial dysfunction. The coexistence of both conditions may potentially contribute to an increased risk of cardiovascular events.

In summary, our pilot study illuminates the correlation between glycemic variability and depression in individuals without diabetes. The noted rise in stress hormones among those exhibiting higher CES-D scores highlights the importance of this link. Moreover, the interaction among glycemic variability, endothelial dysfunction, and depression underscores potential repercussions for cardiovascular well-being (25).

4.1. Future recommendations

In this study, our objective is to underscore patient education and awareness initiatives that highlight the link between glycemic variability and depression. Advocating for holistic care includes integrating comprehensive management strategies and interdisciplinary consultations. Expanding this research to a larger, diverse cohort is imperative to bolster the association regarding glycemic variability, particularly in non-diabetic populations. Our recommendation is to enhance robust methodologies by controlling confounders and predictors, encompassing dietary habits, physical activity, medication usage, and lifestyle factors. Embracing these approaches propels progress in patient care and scientific understanding, ultimately enhancing overall well-being.

4.2. Limitations

This pilot research represents a pioneering application of a flash glucose monitoring system to evaluate glycemic variability among patients afflicted with depression, who do not suffer from diabetes. Moreover, the glycemic variability is analyzed relative to the severity of the depression. Nevertheless, certain constraints were observed during the study. The principal restriction was the restricted sample size, which may limit the generalizability of the findings. Additionally, the low screening-to-enrollment ratio was attributed to the social stigma surrounding depression in India, which also served as a significant contributing factor to the attrition of study participants.

5. Conclusion

Patients who have more severe depression (CES-D scores≥33) have high glycemic variability (SD, MAGE, CONGA, and MODD) than the patients who have less severe depression (CES < 33).

Data availability statement

The data collected and/or evaluated in this study are intended for academic research and can be accessed upon suitable request to the corresponding authors.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee, NIMS University Rajasthan, Jaipur (IEC Approval number: NIMSUR/IEC/2022/211) on 26 March 2022 for studies involving humans. The participants provided their written informed consent to participate in this study.

Author contributions

MS: conceptualization, investigation, validation, and writing—original draft. SM: conceptualization, investigation, validation, and writing—original draft. PS: methodology and project administration. DN: conceptualization, validation, resources, writing—original draft, supervision, and funding. SR and AS: investigation, validation, and writing—original draft. PR: investigation, formal analysis, and writing—original draft. HB: investigation, formal analysis, writing, reviewing, and editing. TJ: investigation, writing, reviewing, and editing. BT: conceptualization, resources, writing, reviewing, editing, supervision, and funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1196866/full#supplementary-material

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A correlation analysis on the postpartum anxiety disorder and influencing factors in puerperae with gestational diabetes mellitus

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Objective: The aim of this study is to discuss the postpartum anxiety disorder and influencing factors in puerperae with gestational diabetes mellitus (GDM) to provide a clinical basis for better early identification and intervention of adverse mood.

Methods: Convenient sampling method was adopted to investigate 205 pregnant women as the observation group and 201 normal healthy pregnant women in the same period as the control group. The self-rating anxiety scale (SAS) was used to investigate and observe the respondents, evaluate the postpartum anxiety status of patients with GDM, and analyze the related influencing factors. Statistical analysis of the data was performed using SAS 3.0 software. A proposed $P < 0.05$ was considered as statistically significant.

Results: Patients with GDM had a higher risk than normal maternal anxiety, related to years of education, triglycerides, 1-h postprandial blood glucose, and a history of induced abortion.

Conclusion: GDM can lead to the occurrence of postpartum anxiety, and the poor psychological state is not conducive to the maternal and infant health. Early identification and early intervention can reduce the harm caused by anxiety and promote the progress of maternal and infant health and clinical research.

KEYWORDS

gestational diabetes, postpartum, anxiety, influencing factors, correlation

1 Introduction

As one of the most common complications of pregnancy, gestational diabetes mellitus (GDM) (1) refers to an abnormal glucose metabolism that occurs during pregnancy, excluding the diabetes mellitus preexisting before pregnancy. GDM is associated with various factors like insulin resistance, genetics, changes in diet, and lifestyle during pregnancy (2). According to relevant literature, the prevalence rate of GDM is 14.0% globally (3). The puerperae with GDM are faced with many potential adverse pregnancy outcomes, such as macrosomia, neonatal hypoglycemia, progeny obesity, and type II diabetes, which may lead to an increased risk of mental disorders (4). According to current studies, about 10% to 15% of healthy women suffer from postpartum depression (PPD) after delivery in developed countries (5), whereas the rate was up to 24% in developing countries (6). PPD is often complicated with anxiety (7–12), which usually occurs within 6 months after delivery (13) with an incidence rate 14%–16% (14, 15). Maternal postpartum anxiety may cause some problems compromising the motor development of infant (16) as well as the breastfeeding behavior and breast milk composition (17). Therefore, for patients with GDM, who are at a high risk for mental disorders, early identification of postpartum anxiety is essential. Although current studies have proved that GDM is an important factor leading to postnatal anxiety (18, 19), most of the relevant studies merely focus on PPD, whereas postpartum anxiety and related influencing factors in puerperae with GDM are rarely reported. In this study, the relationship between GDM and postpartum anxiety was first established through a survey, and, also, relevant influencing factors were analyzed. The study results are helpful for early identification of the high-risk factors and early clinical intervention of patients with GDM with postpartum anxiety.

2 Materials and methods

2.1 Subjects

A total of 205 puerperae with GDM treated in the Obstetrics Clinic of The First Affiliated Hospital of Sun Yat-sen University between June 2021 and June 2022 were selected as the observation group, and, for statistical power, 201 healthy pregnant women in the same period were selected as the control group for postpartum anxiety investigation. Sampling method: convenience sampling. Inclusion criteria for the observation group: ① adult puerperae aged 18–49 years old and diagnosed as GDM; ② re-examined 42 days after delivery with the ability to complete the questionnaire independently; ③ without past history of systemic complications like mental disease and nervous system disease; and ④ voluntarily received and cooperated with the survey. Exclusion criteria for the observation group: ① with a history of mental illness before delivery; ② with other pregnancy complications; ③ with endocrine disease, liver or kidney dysfunction, etc.; and ④ with cognitive dysfunction. Inclusion criteria for the control group: ① healthy maternal aged 18–49 years and ② those who voluntarily received and cooperated with the survey. Exclusion criteria for the control group: ① with a history of mental illness before pregnancy; ② with other pregnancy complications; ③ with endocrine disease, liver or kidney dysfunction, etc.; and ④ with cognitive dysfunction.

2.2 Methods

Questionnaire of general information: A self-designed questionnaire of general information (including age, education years, monthly family income, number of children, intervention mode, and etc.) was adopted.

Clinical data: The patients were investigated for weeks of labor, gestational age, number of pregnancies, number of deliveries, history of adverse pregnancy, history of abortion, GDM, body mass index (BMI), Glycosylated hemoglobin (HBA1c), 1-h plasma glucose (1h-PG), triglyceride, and history of diabetes.

Anxiety scale: Self-rating anxiety scale (SAS) (20) formulated by Zung was used for relevant assessment. SAS consists of 20 items, for which Likert 4-grade scoring method was adopted: Scores 1 to 4 represent "never or seldom," "a small amount of time," "considerable time," and "most of or all of the time," respectively, and the total score multiplied by 1.25 was the scale standard score, which was positively correlated with anxiety. If the standard score is ≥50, then there was anxiety disorder. According to relevant literature, the reliability of this scale was 0.82 (20).

2.3 Statistical analysis

Excel 2003 software was used for double entry of questionnaire and SAS 3.0 for statistical analysis of data. Continuous variables were expressed as $x \pm s$, and, Mann-Whitney U-test, a non-parametric test, was used for relevant statistical inference. Categorical variables were described by rate or percentage, and chi-square test was used for relevant analysis. The influencing factors of anxiety were discussed by binary logistic regression analysis and generalized linear mixed model, inspection level $\alpha = 0.05$.

2.4 Ethical statement

This study was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University (approval number: Lunshen (2021)566-1), and all of the patients signed the informed consent form.

3 Results

3.1 General information of puerperae in the observation group and control group

Mann–Whitney U-test was used for continuous variables, and chi-square test was used for categorical variables (see Table 1). There

were 205 subjects in the GDM group and 201 subjects in the healthy control group. There was statistical significance for differences in age, gestational age, 1h-PG, gestational HBA1c, gestational triglyceride, SAS, history of induced abortion, history of diabetes, and blood glucose control. For the differences in age, gestational age, 1h-PG, gestational HBA1c, gestational triglyceride, SAS, and history of induced abortion between the two groups, P = 0.020, and, for the difference in history of diabetes between the two groups, P = 0.010. The mean age, 1h-PG, gestational HBA1c, gestational triglyceride, and SAS of GDM group were higher than that of the control group, whereas the mean gestational age of GDM group was lower than that of the control group. The proportion of induced abortion history and diabetes history of GDM group was higher than that of the control group. As for BMI, education years, employment status, number of pregnancies, number of deliveries, number of children, payment method, monthly family income, and history of spontaneous abortion, there were no differences between the two groups.

3.2 Binary logistic regression analysis on influencing factors of anxiety in puerperae

The binary logistic regression analysis was conducted with whether anxious or not as the dependent variable and general information as the independent variable, and, for categorical variables, the last was taken as the reference category. The results of univariate analysis for anxiety showed that education years, 1h-PG, and GDM were related to anxiety, with education years as a protective factor and with 1h-PG and GDM as risk factors. The Odds Ratio (OR) value for education years was 0.846 (95% CI, 0.732 to 0.977; P = 0.023), that is, with the increase of education years, the risk of anxiety decreased. For 1h-PG, the OR value was 1.227 (95% CI, 1.057 to 1.424; P = 0.007), that is, the risk of anxiety increased with 1h-PG. The OR value for GDM was 15.093 (95% CI, 3.539 to 64.373; P < 0.001), i.e., patients with GDM had an increased risk of anxiety as compared with those without GDM (see Table 2 for details).

3.3 Multiple linear regression analysis on influencing factors of anxiety in puerperae

After adjustment for age, gender, history of diabetes, employment status, number of pregnancies, history of spontaneous abortion or induced abortion, blood glucose control, HBA1c, triglyceride, GDM, normal delivery or not, and newborn weight, the generalized linear mixed model (Figure 1) showed that there was a correlation between educational age and SAS: For every 1 year increase, SAS decreased by 0.487 (95% CI, −0.823 to −0.151; P = 0.005), the risk of anxiety grade (mild *vs*. normal) decreased by 0.243 (95% CI, −0.459 to −0.026; P = 0.028), and the risk of anxiety disorder decreased by 0.252 (95% CI, −0.468 to −0.037; P = 0.022), and, so, it was a protective factor for anxiety.

After adjustment for age, gender, history of diabetes, education years, employment status, number of pregnancies, history of spontaneous abortion or induced abortion, blood glucose controlled or not, HBA1c, triglyceride, normal delivery or not, and neonatal weight, the generalized linear mixed model (Figure 2) showed that GDM was correlated with SAS, and, compared with patients without GDM, patients with GDM had SAS increased by

TABLE 1 Comparison of basic data between the two groups.

Variables	GDM group (n = 205)	Control group (n = 201)	z	P
	Mean ± SD	Mean ± SD		
Age (years)	33.93 ± 3.86	32.42 ± 4.14	**−3.692**	**<0.001**
Gestational age (weeks)	37.79 ± 2.74	38.69 ± 1.31	**−4.503**	**<0.001**
Educational age	15.78 ± 2.62	15.98 ± 2.35	−0.659	0.510
1h-PG	9.19 ± 2.11	7.43 ± 1.05	**−9.188**	**<0.001**
Glycosylated hemoglobin	5.05 ± 0.47	4.83 ± 0.34	**−5.967**	**<0.001**
Triglyceride	2.32 ± 0.94	2.04 ± 1.22	**−3.673**	**<0.001**
SAS	40.05 ± 7.74	35.93 ± 7.20	**−5.205**	**<0.001**
	GDM group	Control group		P
	N (%)	N (%)		
1	59 (28.8)	38 (18.9)	**5.443**	**0.020**
2	146 (71.2)	163 (81.1)		
History of spontaneous abortion				
1	28 (13.7)	28 (13.9)	0.006	0.937
2	177 (86.3)	173 (86.1)		

GDM, gestational diabetes mellitus; 1h-PG, 1-h plasma glucose; SAS, self-rating anxiety scale; P, positive subscore.
Bold values implies statistical significance.

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TABLE 2 Univariate logistic regression analysis of anxiety disorder in the two groups.

Factors	B	S.E.	Wald	Sig.	OR (95% CI)
Age (years)	0.037	0.047	0.627	0.428	1.038 (0.947, 1.137)
Gestational age (weeks)	−0.083	0.058	2.013	0.156	0.921 (0.821, 1.032)
Educational age	−0.167	0.074	5.157	**0.023**	0.846 (0.732, 0.977)
1h-PG	0.205	0.076	7.246	**0.007**	1.227 (1.057, 1.424)
Triglyceride	−0.184	0.265	0.481	0.488	0.832 (0.495, 1.399)
History of Abnormal pregnancy	0.218	0.637	0.117	0.732	1.244 (0.357, 4.337)
History of induced abortion	0.726	0.402	3.268	0.071	2.068 (0.941, 4.546)
History of spontaneous abortion	−0.814	0.747	1.186	0.276	0.443 (0.102, 1.917)
History of diabetes	0.562	0.409	1.886	0.170	1.754 (0.786, 3.914)
GDM	2.714	0.740	13.451	**<0.001**	15.093 (3.539, 64.373)

GDM, gestational diabetes mellitus; 1h-PG, 1-h plasma glucose; Sig., significance test.
Bold values implies statistical significance.

4.275 (95% CI, 1.167 to 7.382; P = 0.007), risk of anxiety grade (mild *vs*. normal) increased by 2.434 (95% CI, 0.044 to 4.823; P = 0.046), and risk of anxiety disorder increased by 2.537 (95% CI, 0.146 to 4.928; P = 0.038), which is a risk factor for anxiety.

After adjustment for age, gender, history of diabetes, education years, employment status, number of pregnancies, history of spontaneous abortion, blood glucose controlled or not, HBA1c, triglyceride, GDM, normal delivery or not, and neonatal weight, there was no correlation between history of induced abortion and SAS (Figure 3), whereas there was a correlation between history of induced abortion and anxiety grade (mild *vs*. normal), and, compared with patients without history of induced abortion, those with history of induced abortion had risk of anxiety grade (mild *vs*. normal) increased by 2.003 (95% CI, 0.043 to 3.963; P = 0.045) and risk of anxiety disorder increased by 2.026 (95% CI, 0.065 to 3.988; P = 0.043), and, so, it was a risk factor for anxiety.

After adjustment for age, gender, history of diabetes, education years, employment status, number of pregnancies, history of

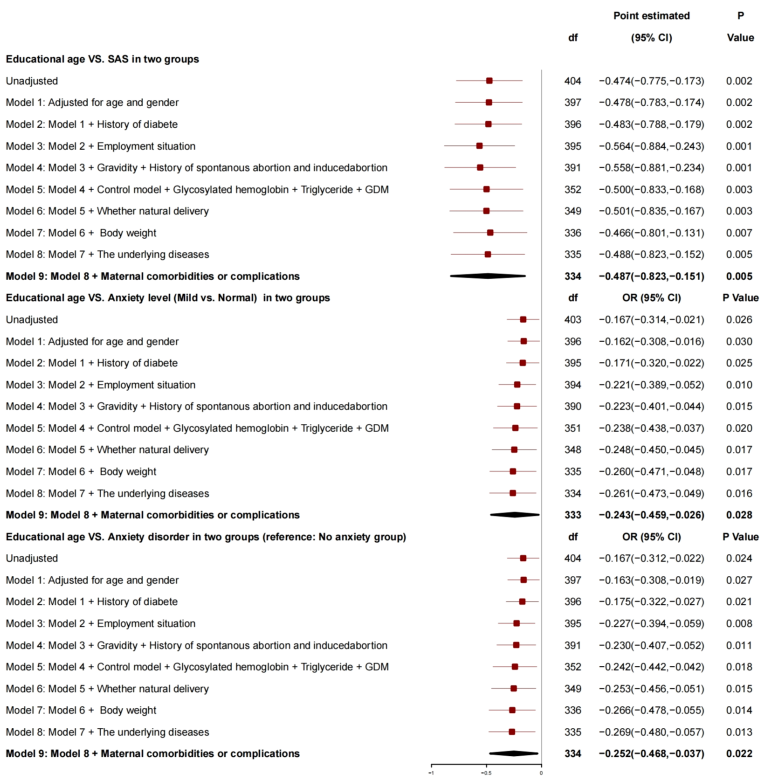

FIGURE 1
Generalized linear mixed model: Educational age and SAS.

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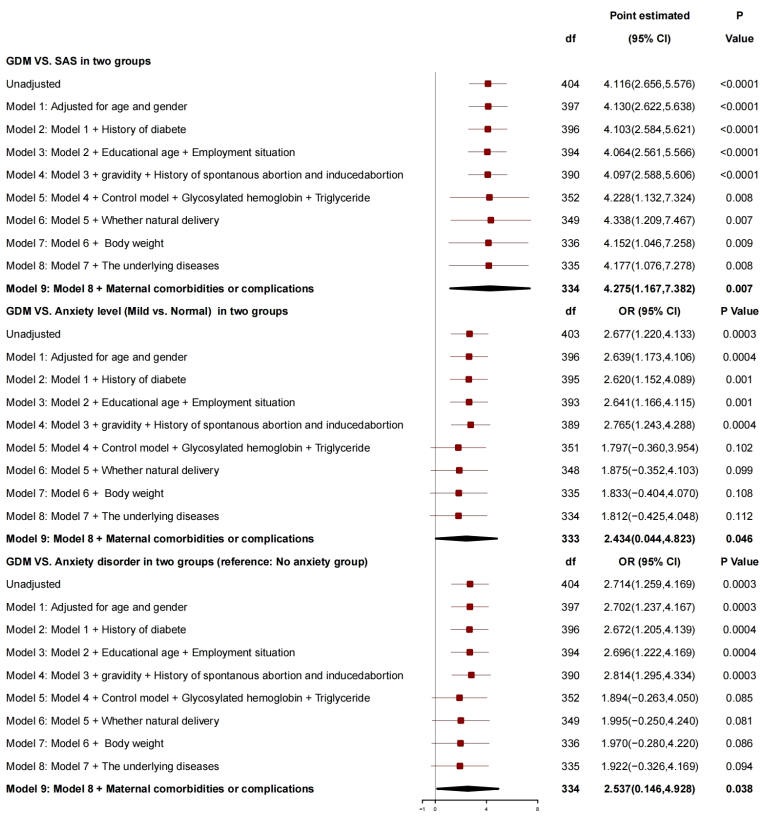

FIGURE 2
Generalized linear mixed model: GDM and SAS.

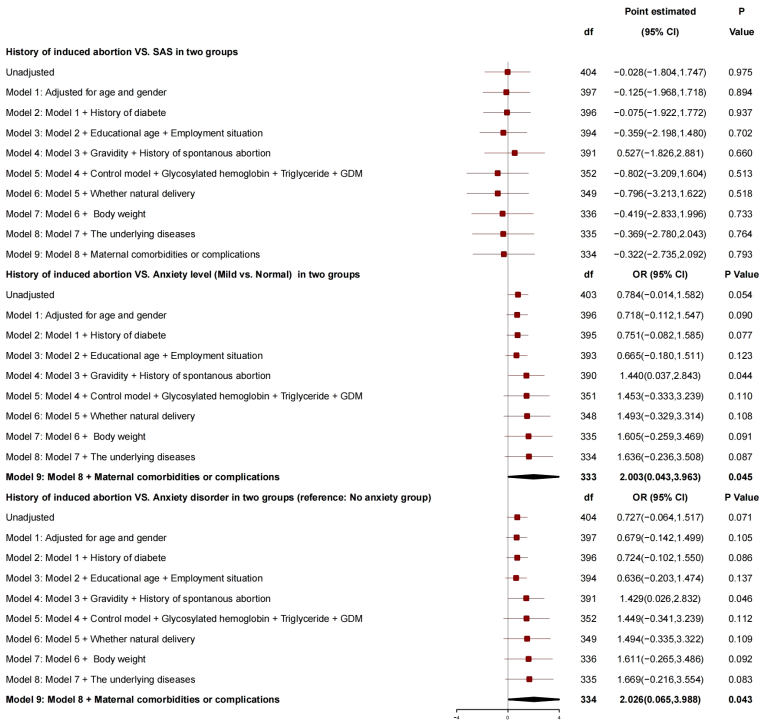

FIGURE 3
Generalized linear mixed model: History of induced abortion and SAS.

spontaneous abortion or induced abortion, blood glucose controlled or not, HBA1c, triglyceride, normal delivery or not, and newborn weight, 1h-PG was correlated with SAS (Figure 4), for every 1-unit increase in 1h-PG, SAS increased by 0.384 (95% CI, 0.001 to 0.767; P = 0.049), risk of anxiety grade (mild *vs.* normal) increased by 0.210 (95% CI, 0.003 to 0.417; P = 0.047), and risk of anxiety disorder increased by 0.222 (95% CI, 0.017 to 0.426; P = 0.034), and, so, it was a risk factor for anxiety.

After adjustment for factors like age, gender, diabetes history, education years, employment status, number of pregnancies, history of spontaneous or induced abortion, blood glucose controlled or not, HBA1c, GDM, normal delivery or not, and newborn weight, the triglyceride had no correlation with SAS (Figure 5), and no correlation with anxiety grade (mild *vs.* normal) but had a correlation with anxiety disorder, and, for every 1-unit increase in triglyceride, the risk of anxiety was reduced by 0.832 (95% CI, −1.653 to −0.011; P = 0.034).

4 Discussion

To our knowledge, this is one of the first studies to find that the postpartum anxiety score of GDM puerperae was 40.05 ± 7.74, which was much higher than that of healthy puerperae (35.93 ± 7.20). The patients' education years and triglyceride were protective factors, whereas GDM, history of induced abortion, and 1h-PG were related to anxiety grade as the risk factors.

Education years were a protective factor for anxiety, and, for every 1-year increase in education years, SAS decreased by 0.487, the risk of anxiety grade (mild *vs.* normal) decreased by 0.243, and the risk of anxiety disorder decreased by 0.252.

Educational age was correlated with SAS as a protective factor for anxiety of puerpera ($p < 0.05$), which was consistent with the results reported by relevant studies from Japan and Nigeria (11, 21, 22). With many years of education and rich knowledge reserve, the patients can understand the process of pregnancy through various scientific ways and a variety of channels, learn the pressure generated during pregnancy, identify their own physical and psychological problems, deal with problems arising in life actively, and thus find a scientific solutions to their own problems (23). At the same time, for the patients, the more the education years, the higher the ability to accept GDM related knowledge, and their anxiety would be reduced with the understanding of GDM. On the contrary, the less the education years, the higher the anxiety grade and risk.

Triglyceride showed no correlation with SAS and anxiety grade, and triglyceride was related to anxiety. For every 1-unit increase in triglyceride, the risk of anxiety disorder decreased by 0.832.

Driven by the increased resistance of insulin, estrogen, progesterone, and placental prolactin, the physiological and basic levels of plasma total cholesterol and triglyceride during pregnancy

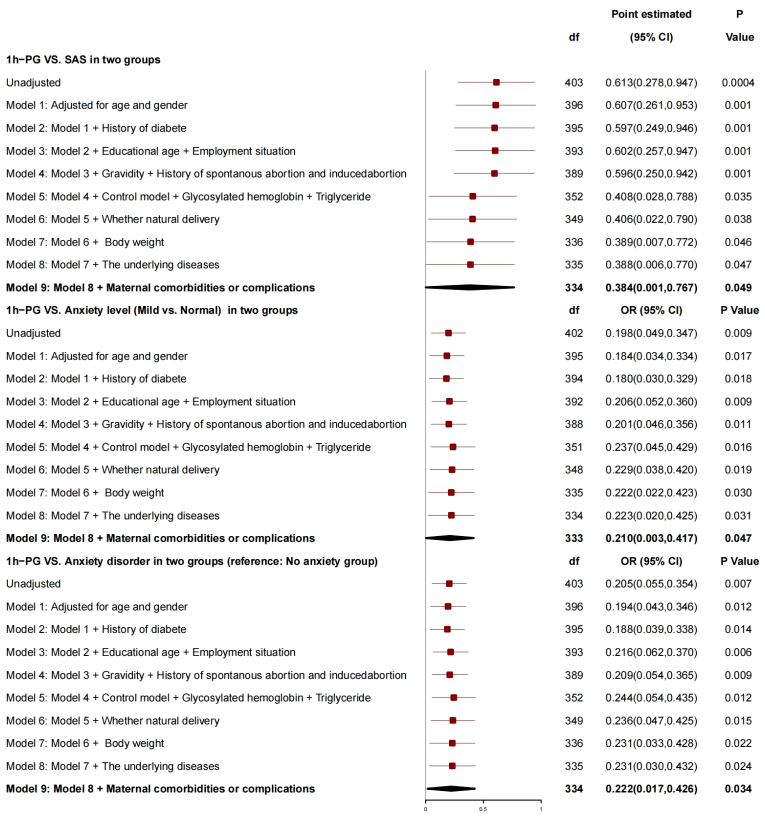

FIGURE 4
Generalized linear mixed model: 1h-PG and SAS.

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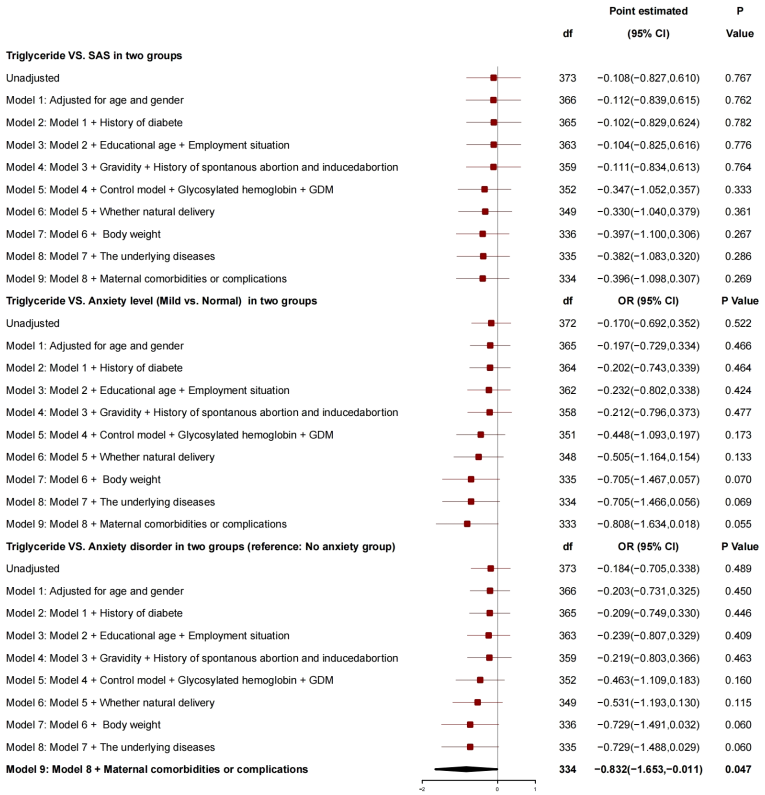

FIGURE 5
Generalized linear mixed model: Triglyceride and SAS.

were increased to guarantee sufficient energy reserves (glucose, amino acids, and lipids) as well as full development and growth of the fetus (24). For the patients in the study group, the triglyceride level was 2.32 ± 0.94, which was higher than the normal level of puerpera and was consistent with the previous study results (25–28), but still at a normal level (29). Although a high triglyceride level significantly increased the risk of GDM as a risk factor for drug-resistant subtype of GDM (30, 31), our study found that, for every 1-unit increase of triglyceride, the risk of anxiety disorder was reduced by 0.832 (95% CI, −1.653 to −0.011; P = 0.034), which was inconsistent with those in previous studies, suggesting that an appropriate increase in the blood lipid level had a protective effect on the anxiety for the patients.

GDM and 1h-PG were correlated with SAS as risk factors for anxiety. Compared with the patients without GDM, those with GDM had SAS increased by 4.275, risk of anxiety grade increased by 2.434, and risk of anxiety disorder increased by 2.537. For every 1-unit increase in 1h-PG, SAS increased by 0.384, and 1h-PG was related to anxiety grade; for every 1-unit increase in 1h-PG, the risk of anxiety grade increased by 0.210, and the risk of anxiety grade increased by 0.222.

1h-PG and GDM were the risk factors for anxiety, and patients with GDM had an increased risk of anxiety disorder as compared with those without GDM. After inclusion of blood glucose–related indicators, including HBA1c, insulin, and Oral Glucose Tolerance Test (OGTT), 1h-PG showed a positive correlation with the anxiety of patients, and the OR value for 1h-PG was 1.227 (95% CI, 1.057 to 1.424; P = 0.007), that is, the risk of anxiety increased with 1h-PG, which was consistent with that in the study of Zhao et al. (32). An analysis of the International Association of Diabetes and Pregnancy Study Groups has clarified the importance of fasting blood glucose plus 1h-PG for the diagnosis of GDM (33). The above results have indicated that 1h-PG is critical for GDM. Therefore, the rise of 1h-PG may cause anxiety in relevant patients. In clinical nursing, we should pay more attention to the health of patients with elevated 1h-PG.

History of induced abortion showed no correlation with SAS. Compared with patient without history of induced abortion, those with history of induced abortion had risk of anxiety grade increased by 2.003, and the risk of anxiety disorder increased by 2.026, and, so, the history of induced abortion was a risk factor for anxiety. This is a significant finding and also the first report on the relationship between history of induced abortion and postpartum anxiety in patients with GDM globally. Induced abortion may lead to a series of problems, including secondary infertility, ectopic pregnancy, spontaneous abortion, premature delivery, low birth weight, and pregnancy or childbirth complications. Therefore, compared with GDM puerperae without history of induced abortion, those with history of induced abortion have a higher level of postpartum anxiety (34) and a higher incidence of anxiety and depression comorbidity. Specifically, 29% of the puerperae might suffer from severe or mild depression and anxiety comorbidity. In this study, 59

patients with GDM had history of induced abortion, accounting for 28.8%, which was 18.9% higher than that of normal puerperae. In future studies, the frequency and reasons of induced abortion may be considered to further explore the relationship between induced abortion and postpartum anxiety in patients with GDM.

There are several limitations to our study that should be considered. First, the study was conducted at one hospital, and the results may not be as widespread. Second, A self-rating scale was used in this study. Although it has passed the internal consistency test, the results are still not so objective. Third, The study results are limited by sample size. In the future, a multicenter study of large sample size will be carried out to include more pregnant women in the survey, so as to obtain more reliable conclusions.

5 Conclusion

For the first time, this study found the status of anxiety in GDM puerperae and the related influencing factors, which are helpful for early identification and early clinical intervention of postpartum anxiety in GDM puerperae, thus reducing relevant hazards and promoting the maternal and child health as well as the progress of relevant clinical studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of the he First Affiliated Hospital of Sun Yat-sen University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors contributed to the study design and data interpretation. FW and JieC were responsible for management and oversight of the study. YY, CL and XZ were responsible for general omnibus data analyses and were keys contributing authors to the manuscript. XY and ZP were responsible for all research interviews and clinical chart reviews associated with this study. SW and JinC provided guidance on the design of primary analyses. CL and MZ assisted with all data collection, analysis, and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effects of elevated emotional symptoms on metabolic disease development: a 10-year follow-up study

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Background: In recent decades, the relationship between emotional disorders (i.e., depression and anxiety) and alterations in physiological functions (i.e., inflammation or metabolism) have been well supported. However, studies on a symptom-based approach have provided mixed results. Our study aims to gain insight into how subclinical statuses, featured by elevated depressive and/or anxious symptoms, may influence immunometabolic alterations in the concurrent relationship; and the development of metabolic diseases at 10-year follow-up: diabetes, hypertension and hypercholesterolemia.

Methods: Data from 758 Greek adults [394 men (aged 41 ± 10 years) and 364 women (aged 37 ± 12 years)] were used. Four groups were created according to the levels of depressive and anxiety symptoms: (1) control group (CG), (2) depressive group (DG), (3) anxiety group (AG) and (4) depressive and anxiety group (DAG). Multi-indicator multi-causes (MIMIC) modeling was used to estimate metabolic function and inflammatory response scores, on a wide selection of blood biomarkers. Finally, a binary logistic regression was carried out to study the influence of symptoms on the development of the aforementioned metabolic diseases on a 10-year follow-up.

Results: Group membership was not associated with metabolic function score. Conversely, DAG membership was related with higher inflammatory response score (B = 0.20, CI_{95} = 0.01, 0.40), with respect to the CG ($p < 0.05$). Both age and sex were significant variables in the calculation of both scores. Regarding disease at 10-year follow-up effect, risk of developing diabetes, hypertension and hypercholesterolemia was associated with age and socioeconomic status. Moreover, DG membership was significant for diabetes risk (OR = 2.08, CI_{95} = 1.00, 4.22) and DAG for hypercholesterolemia (OR = 1.68, CI_{95} = 1.16, 2.43).

Limitations: Data on anti-inflammatory drugs and psychopharmacological medication were not collected in this study.

Conclusions: Elevated symptoms of depression and anxiety accounts for inflammatory alterations at concurrent relationship and a higher risk of 10-year follow-up metabolic diseases.

KEYWORDS

depression, anxiety, inflammation, metabolic syndrome, diabetes, hypertension, hypercholesterolemia

1 Introduction

Emotional disorders (i.e., depression and anxiety) are considered among the top five mental conditions with higher impact, worldwide. In 2015, it is estimated that 4.4% of the world population suffered from a depressive disorder and 3.6% from an anxiety disorder (1). Moreover, comorbidity is quite common between both conditions, observing shared pathophysiological mechanisms and risk factors (2–4). Importantly, emotional disorders may account for large proportion of years of life lived with disability across the lifespan (5, 6).

Emotional disorders may have a critical impact for patients at the individual level, as well as for healthcare provision systems at the socioeconomic level. Further research should be done to improve the understanding of pathophysiological mechanisms to contribute for treatment optimization. In last decades, mounting evidence has stressed the existing relationship between depression and inflammation (7–10). In this line, some depressive endophenotypes (i.e., atypical depression) have been related to evident disturbances in the (pro-)inflammatory response (11–13). Less is known on the relationship between anxiety and inflammation (14). However, existing studies also point to an elevated pro-inflammatory response in patients with an anxiety disorder (10, 15). This inflammation could lead to the occurrence of metabolic diseases comorbid with depression and anxiety, as it seems to have a mediating role in both pathologies, for example, patients with depression are at higher risk of high blood pressure and patients with type 2 were 1.2–2.3 times more likely to have depressive symptoms than the general population (16). The relationship between the two (i.e., emotional disorders and metabolic diseases) seems to be mediated by inflammation. For instance, some evidence stressed a mediating role of NLRP3 inflammatory bodies in hippocampal neuroinflammation and depression-like behavior (16, 17). Thus, the metabolic alteration, would be preceded by an altered inflammatory status.

Unfortunately, studies on comorbid anxiety and depression are scarce. It would be expected to find wider inflammatory alterations in patients with comorbid emotional disorders for several reasons. First, patients with inflammatory diseases have an increased risk of developing both anxiety and depressive disorders (18, 19). Second, both emotional disorders may share some common altered mechanisms. A dysregulation of the hypothalamic pituitary adrenal axis (HPA) is observed in both disorders (20–22), which becomes more evident when they occur together (23).

Dysregulation of the HPA axis, seems to play a role in the immunometabolic alterations observed in patients, such as increased production of cytokines [i.e., Tumor necrosis factor (TNF-α) or interleukin 6 (IL- 6)] (24) and consequent induction of acute phase inflammatory proteins [i.e., and C-reactive protein (CRP) or serum amyloid A (SAA)] (25) and metabolic dysregulation [i.e., stimulation of the release of lipids into the bloodstream, increased triglycerides and decreased cholesterol linked to high-density lipoproteins (HDL-C) or alterations in total cholesterol levels] (26). Moreover, the dysregulation of cortisol secretion may induce alterations in lipid and glucose metabolism that can contribute to metabolic disease development, such as diabetes, hypercholesterolemia or hypertriglyceridemia (27). Evidence is less consistent on the development of cardiovascular conditions and it seems that other mediating pathways (i.e., kynurenine path) may be involved (28).

Although most of the available studies are cross-sectional (8, 9, 14), the longitudinal studies carried out to date seem to relate the presence of emotional disorders with immunometabolic alterations in the short and long term (23, 29–35). Moreover, short-term alterations in the immunometabolic response have also been observed among individuals with subclinical emotional conditions (36–39). Unfortunately, longitudinal studies are scarce on the relationship between subclinical (symptom-based) emotional conditions and metabolic disease development.

The study of subclinical conditions become crucial for prevention to tackle the development of full-blown conditions and mitigate its impact over time. This study aimed to analyze the relationship between subclinical conditions featured by elevated emotional symptoms (i.e., depressive and/or anxious symptoms) and immunometabolic dysregulation at concurrent relationship (diverted levels of immunometabolic markers in plasma) and disease at 10-year follow-up. We hypothesize that participants with elevated levels of both depressive and anxious symptoms would show altered immunometabolic profiles in comparison with people without elevated symptoms. Moreover, it is hypothesized that the presence of comorbid depression-anxiety symptoms would contribute to the development of chronic metabolic diseases (particularly diabetes and hypercholesterolemia) over a 10-year follow-up.

2 Materials and methods

2.1 Study sample

Data from the 10-year follow-up of the ATTICA study (40) were used to satisfy the study aims. The ATTICA study is a population-based cohort focused on examining social,

demographic, lifestyle, clinical and biological characteristics of apparently healthy Greek adults living in the greater metropolitan area of Athens (Greece), on cardiovascular disease incidence, and other health-related conditions. In brief, a baseline survey was carried out during 2001–2002 and a sample of 4056 adults was invited to participate (78% from urban area). This survey relied on a random, multi-stage cluster sampling (considering age and sex distribution of the Attica region in 2001). A total of 3042 individuals (18–89 years old, 49% men) agreed to participate (75% response rate). A follow-up survey was conducted during 2011–2012. Most of participants were enrolled the follow-up survey (n = 2583; 85% response rate).

A randomly selected subsample of the ATTICA cohort completed questionnaires on emotional symptoms. Concretely, a sample of 758 adults was used [394 men (aged 41 ± 10 years) and 364 women (aged 37 ± 12 years)]. Further details on how the subsample was reached and randomization algorithm are provided elsewhere (41). The final sample comprised 615 participants (50.98% women; m = 39.20 years, sd = 10.96). Participants were dropped out because: being older than 65 years at baseline (n = 3), blood sample not available (n = 137) or death at follow-up (n = 3). Significant differences were found between the random subsample initially selected and final sample in analysis, only in terms of family composition at baseline [χ^2 (2) = 8.99, $p < 0.05$, Cramer's $V = 0.10$], with higher proportion of married individuals in the final sample (62.74%) than the one from the drop-out sample (51.75%); and in terms of depressive symptom levels [t (204.66) = 2.09, $p < 0.05$, Cohen's $d = 0.2$], with lower symptoms in the subsample in analysis (m = 35.12, sd = 7.35) in comparison to the drop-out one (m = 36.62, sd = 7.82).

2.2 Demographic, clinical and lifestyle characteristics

Baseline survey included questions about demographic features (i.e., gender, age, marital status, education level and financial status), anthropometric measures [i.e., height, weight, and body mass index (BMI)], history of medical conditions as well as lifestyle habits (i.e., dietary assessment, alcohol consumption, tobacco use and physical activity). The assessment protocol has already been described elsewhere (42).

Depressive symptoms were assessed using the validated Greek translation of the Zung's Self-Rating Depression Scale (ZDRS) (43, 44). ZDRS consists of 20 items covering affective, psychological, and somatic symptoms. To perform the assessment, the patient indicates how often they experience a particular symptom (i.e., 1 = some of the time, 2 = some of the time, 3 = a good part of the time, or 4 = most of the time). The ZDRS total score range is 20–80; with higher values indicating more severe depression symptoms.

Anxiety symptoms were assessed using the validated Greek translation of the Spielberger State Anxiety Inventory (STAI), which is a 20-item self-administered questionnaire (45). The 20 items are scored from 1 to 4 in terms of frequency categories with respect to (never, sometimes, many times, always) and the total scores are obtained by adding the values assigned to each response (46). The total score of the 20-item STAI ranges from 20 to 80 with higher score values being indicative of more severe anxiety symptoms (47).

2.3 Biochemical measurements

All participants were summoned on after 12 h of fasting, to carry out the blood test from 8 to 10 a.m. All the blood samples were collected under the same procedure (in a sitting position and were collected from the antecubital vein) and were carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories.

2.3.1 Metabolic measures

The metabolic indicators were selected according to the National Cholesterol Education Program's Adult Treatment Panel III (revised) report guidelines for metabolic syndrome (MetS) (48). Triglycerides, high density lipoprotein (HDL)-C and blood sugar levels were quantified to know the metabolic state of participants. These biochemical examinations were measured using chromatographic enzymic method in a Technico Automatic Analyzer RA-1000 (Dade Behring Marburg, Germany). In addition, waist circumference, as well as systolic and diastolic blood pressure were measured to determine the metabolic risk factors.

For assessing the validity of the methods details may found elsewhere (41).

2.3.2 Inflammatory measures

The blood samples for the inflammatory biomarkers were taken under the same procedure, at the same time and place as the samples collected for the analysis of metabolic markers. C-Reactive Protein (CRP) and serum amyloid – A (SAA) were assayed by particle-enhanced immunonephelometry (N Latex, Dade-Behring Marburg GmbH, Marburg, Germany) (49). Interleukin-6 (IL-6) levels were quantified with high sensitivity enzyme linked immunoassay (R&D System Europe Ltd., Abingdon, UK) and tumor necrosis factor (TNF)-α was measured with ELISA method (Quantikine HS/human TNF-α immunoassay kit, R&D Systems, Inc., Minneapolis, USA) (49).

2.4 Follow-up examination

The ATTICA Study's investigators performed the 10-year follow-up (median follow-up time 8.41) [see in Georgousopoulou et al. (40)]. During follow-up, the presence or absence of diabetes, hypercholesterolemia and hypertension was determined as follows.

Regarding metabolic diseases, some standard criteria were adopted. First, diabetes diagnosis was determined by fasting blood glucose levels greater than 125 mg/dL or the use of antidiabetic medication. Hypercholesterolemia was defined as total serum cholesterol levels greater than 200 mg/dL or the use of lipid-lowering agents. The presence of hypertension was determined by values greater than or equal to 140/90 mmHg or by being under hypertensive medication. Blood pressure was measured with the participant sitting and resting for at least 30 min, the specialist doctor performed three measurements on the right arm, in a 45° position and leaning on the table with the

aneroid manometric sphygmomanometer (ELKA, Von Schlieben Co., Munich, Germany). The level of systolic blood pressure was determined by the first perception of sound and the diastolic was determined by phase V when the repetitive sounds disappear completely [for more information on how the samples were collected, see (41)].

2.5 Data analysis

Multi-indicator multi-causes (MIMIC) modeling was used to estimate both a metabolic risk score and an inflammatory response score from the biomarkers. MIMIC modeling constitutes a Structural Equation Modeling (SEM) extension to study nested relationships, simultaneously allowing for identifying underlying (latent) factors that are measured by multiple indicators and controlling for other confounding effects (50). Thus, the metabolic risk score was estimated by means of blood (triglycerides, HDL-C, blood sugar, all of them in loglinear scale), cardiovascular (arterial blood pressure) and anthropometric (waist diameter) indicators. Likewise, the inflammatory response score was estimated by using blood indicators (CRP, SAA, IL-6 and TNF-α). Score estimation was conducted controlling for relevant lifestyle covariates (Mediterranean diet adherence, physical activity, smoking and alcohol use). The diagonally weighted least squares (DWLS) methods were used for model estimation, as some binary (e.g., hypertension diagnosis, smoking, alcohol use) and categorical (physical exercise) were included in our analysis. Standard error estimation was based on bootstrapping methods with 1000 samples, that ensures reliable estimates are derived. Fit indexes used to assess goodness-of-fit of MIMIC models were the χ^2 statistic, the root mean square error of approximation index (RMSEA), the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the standardized root mean square residual (SRMR). According to Hu and Bentler (51), adequate model fit is indicated by values of RMSEA < 0.08, CFI ≥ 0.95, TLI ≥ 0.95, and SRMR < 0.08.

For the purposes of our study, sample was categorized into four groups regarding levels of depressive and anxiety symptoms: (1) control group (CG), featured by low levels of depressive and anxiety symptoms; (2) depressive group (DG), comprising individuals with depressive symptom levels overpassing the third quartile of distribution cut-off point and low levels of anxiety symptoms; (3) anxiety group (AG), whose members showed low depressive symptoms but anxiety symptoms overpassing the third quartile of distribution cut-off point; and (4) depressive and anxiety group (DAG), whose members showed elevated levels of both anxiety and depressive symptoms.

Relationship between the metabolic risk and inflammatory scores derived from the MIMIC models (i.e., predicted scores) and study group membership was studied using linear regression. Sex and age were used as covariates. The adjusted R^2 was used as an effect size estimate. Beta coefficients and their CI_{95} was used to explore loading magnitude.

To predict the development of metabolic diseases (i.e., diabetes, hypertension and hypercholesterolemia) over the 10-year follow-up, logistic binary regression was used. Participants with suspected baseline diabetes (glucose level > 126 mg/dL; $n = 15$), hypertension (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90; $n = 172$) or hypercholesterolaemia (total cholesterol level > 240; $n = 57$) were removed from analysis for the 10-year outcome. Taking into account the metabolic risk scores at baseline allows to control the levels of markers associated with metabolic alterations, as an additional adjustment following the exclusion of participants with suspected baseline disease for each outcome of interest.

Invariant (sex), and baseline covariates (age, financial status, emotional group and metabolic score) were considered. The baseline inflammatory response score was considered as a weighting factor for the within-subject heteroscedasticity structure, due to the potential influence on the development of both metabolic conditions and emotional disorders.

The Akaike information criterion (AIC) was used to compare the fit of an unconstrained model (model without covariates), a model with sociodemographic covariates (age and financial status) and a model with all the covariates (full model: age, financial status, emotional group and metabolic score). A better fit was proven by a lower AIC of the full model in comparison to the unconstrained one. In addition, the area under the receiver operating curve (AUC) was used as a classification accuracy estimate. AUC > 0.70 indicates adequate accurate in classification. The odds ratio (*OR*) estimate was used to explore loading magnitude.

All analyses were performed using the R software × 64 3.0.1 (l cmm, ROCR, psych and lmerTest packages).

3 Results

The descriptive statistics are displayed in Table 1, as well as group comparison according to their scores in depressive and anxious symptom scales: CG (61.32% of sample), DG (13.24), AG (11.52%) and DAG (13.90%) (see Table 1).

Regarding the sociodemographic variables, we observed significant differences between the study groups. There was a higher percentage of men with anxiety (62.07%) compared to those in the DG and DAG groups, in which there was a higher percentage of women (68 and 65.71%, respectively). Significant differences were also observed in the variable of years of schooling ($F = 29.17$; $p < 0.01$; $\eta^2_{partial} = 0.04$) and in marital status ($\chi^2 = 17.04$; $p < 0.01$; Cramer's $V = 0.11$). The CG had more years of schooling ($m = 13.51$; $sd = 3.27$) than the rest of the participants, being participants from the DAG those with the lowest number of years of schooling ($m = 11.77$; $sd = 3.54$).

Regarding the emotional symptoms, between-group differences were evident for both the depression ($F = 531.05$; $p < 0.01$; $\eta^2_{partial} = 0.41$) and the anxiety symptoms ($F = 1095.28$; $p < 0.01$; $\eta^2_{partial} = 0.59$). In terms of lifestyle factors, there were significant differences, both in physical exercise and in current alcohol consumption. The DG participants were those who carried out the least level of physical activity compared to the rest of the groups and those who had the least current alcohol consumption.

Finally, data on immunometabolic biomarkers are displayed in Table 1. Significant differences were obtained between the study groups only in CRP levels. The group that had the highest levels of this inflammatory protein was the AG ($m = 2.32$; $sd = 2.9$), followed by DAG ($m = 2.28$; $sd = 3.03$), CG ($m = 1.74$; $sd = 2.21$) and DG ($m = 1.73$; $sd = 2.57$). No significant differences were observed between the groups analyzed for metabolic diseases at follow-up.

TABLE 1 Sociodemographic, clinical and lifestyle factors according to study group (*n* = 755).

	CG (*n* = 463)		DG (*n* = 100)		AG (*n* = 87)		DAG (*n* = 105)		Contrast test	ES
	m/%	*sd*	*m*/%	*sd*	*m*/%	*sd*	*m*/%	*sd*		
Sex (%male)	58.1		32		62.07		34.29		39.63*	0.23
Age (years)	39.54	10.26	36.31	12.25	41.83	10.89	38.31	12.06	0.11	0.01
Formal education (years)	13.51	3.27	13.29	2.92	12.18	3.57	11.77	3.54	29.17**	0.04
Marital status									17.04**	0.11
Never married	31.1		49		28.74		31.43			
Married	63.93		44		62.07		60.95			
Divorced/widowed	4.97		7		9.2		7.62			
Household income									32.78	0.12
1st quartile	16.04		28.28		25.58		34.95			
2nd quartile	26.15		32.32		22.09		28.16			
3rd quartile	36.26		30.3		33.72		24.27			
4th quartile	21.54		9.09		18.6		12.62			
Depression symptoms[1]	31.4	4.61	43.5	3.47	34.33	3.83	46.19	5.68	531.05**	0.41
Anxiety state[2]	34.9	7.96	39.43	6.95	55.13	4.81	58.16	6.56	1095.28**	0.59
Mediterranean diet adherence[3]	26.62	7.09	28.47	9.44	25.78	7.07	28.59	8.61	3.07	0
Physical activity level									14.4*	0.1
Low	31.1		49		28.74		31.43			
Moderate	67.82		51		70.11		66.67			
Intense	1.08		0		1.15		1.9			
Smoking (%yes)	60.69		56		60.92		56.19		1.33	0.04
Alcohol drinking (%yes)	91.79		82		88.51		85.71		10.03*	0.12
Metabolic markers										
Waist circumference (cm)	89.06	15.51	85.39	17.63	91.82	17.36	86.23	17.03	0.81	0
Fasting glucose (mg/dl)	87.87	16.54	89.05	27.4	89.69	15.7	89.45	29.68	0.84	0
Triglycerides (mg/dl)	102.43	63.01	96.36	55.6	111.42	67.41	100.08	70.88	0.01	0
HDL cholesterol (mg/dl)	47.91	12.52	52.96	13.73	46.62	15.17	49.39	13.57	0.64	0
SBP (mmHg)	118.01	16.13	114.99	15.13	119.17	15.54	115.1	19.68	1.43	0
DBP (mmHg)	78.69	11.41	75.65	11.63	80.12	11.92	75.91	11.41	2.39	0
Inflammatory markers										
CRP (mg/l)	1.74	2.21	1.73	2.57	2.32	2.9	2.28	3.03	6*	0.01
IL-6 (mg/dl)	0.31	0.2	0.27	0.25	0.35	0.2	0.31	0.25	0.84	0
SAA	3.63	4.42	4.09	3.16	3.64	4.22	3.56	2.61	0	0
TNF-α (mg/dl)	6.40	2.73	6.22	3.81	6.56	2.78	6.19	3.03	0.17	0
Metabolic diseases at follow-up										
Diabetes (%yes)	4.20		9.26		10.2		4.65		4.18	0.05
Hypercholesterol (%yes)	55.66		56.67		59.32		66.13		2.41	0.04
Hypertension (%yes)	44.37		32.26		52.46		42.86		5.27	0.06

Means (*m*) and standard deviations (*sd*) are displayed for continuous variables. Percentage (%) of cases is displayed for either dichotomous or categorical variables. The contrast test statistic was the *F* statistic for continuous measures and the χ^2 statistic for either dichotomous or categorical variables. The effect size (ES) estimate was the $\eta^2_{partial}$ for continuous measures and the Cramer's *V* statistic for either dichotomous or categorical variables. HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; iL-6, Interleukin 6; SAA, serum amyloid A; TNF-α, tumor necrosis factor α; CG, control group; DG, high depression group; AG, high anxiety group; DAG, high depression and anxiety group.

[1]Measured by the Zung Self-Rating Depression Scale.

[2]Measured by the State-Trait Anxiety Inventory, state form.

[3]Measured by the Mediterranean Diet Adherence Screener test.

*$p < 0.05$; **$p < 0.01$.

3.1 Metabolic and inflammatory profiles

The MIMIC model on the inflammatory score was significant and showed adequate fit indexes (χ^2 = 36.54, *df* = 14, $p < 0.01$; RMSEA = 0.046, CFI = 0.953, TLI = 0.975, SRMR = 0.021). Parameters from the MIMIC model are included in the Supplementary Table 1, as well as correlations between the calculated inflammation score and the inflammatory biomarkers (Supplementary Figure 1). Higher inflammation scores were indicative of elevated inflammation.

In terms of group comparison on the inflammatory score using linear regression, a significant relationship was found between the inflammatory score and the study groups, considering sex and age as covariates ($F_{5,749} = 37.24$, $p < 0.001$, $R^2_{adj} = 0.19$). Inflammation scores according to the study groups are displayed in the Figure 1. Specifically, the DAG group showed a significantly different loading than the CG group ($B = 0.20$, $t = 2.03$, $p < 0.05$). Sex (being a woman) ($B = 0.20$, $t = 2.96$, $p < 0.01$) and age were also significant ($B = 0.04$, $t = 12.24$, $p < 0.001$). Regression coefficients are displayed in Table 2.

The MIMIC model to estimate the metabolic risk score also showed adequate fit indexes (χ^2 = 61.30, *df* = 21, $p < 0.001$; RMSEA = 0.050, CFI = 0.961, TLI = 0.982, SRMR = 0.062). Parameters from the metabolic model are included in the Supplementary Table 2, as well as correlations between the calculated metabolic score and the metabolic biomarkers (Supplementary Figure 1). The higher the metabolic risk score, the higher the risk of metabolic dysregulation.

Regarding the relationship between the metabolic risk profile scores and the study group and covariates, the linear regression ($F_{5,749} = 261.2$, $p < 0.001$, $R^2_{adj} = 0.63$) revealed the significant relationship of the score with sex (being a woman) (being a woman) ($B = 19.26$, $t = 31.12$, $p < 0.01$) and age ($B = 0.31$, $t = 11.11$, $p < 0.01$). No significant relationships were found in terms of study groups (see Table 2 and Figure 1).

3.2 Metabolic diseases 10 years later

The model that showed a better fit for the disease at 10-year follow-up prediction of diabetes was the model that included all covariates (full model) (AIC = 406.05), compared to the model without covariates (AIC = 464.73) and the model that included the sociodemographic variables (AIC = 414.95). This model also showed adequate precision in the classification (AUC = 0.81).

The factors significantly related to the development of diabetes (sample in analysis, $n = 600$) were age ($OR = 1.09$, Wald's $Z = 5.01$, $p < 0.01$) the economic status of the second ($OR = 0.64$, Wald's $Z = -1.99$, $p < 0.05$) third ($OR = 0.35$, Wald's $Z = 3.25$, $p < 0.01$) and fourth quartile ($OR = 0.37$, Wald's $Z = -3.34$, $p < 0.01$), with respect to the participants of the first quartile; DG membership ($OR = 2.08$, Wald's $Z = 2.19$, $p < 0.05$) and the metabolic risk score ($OR = 1.05$, Wald's $Z = 3.06$, $p < 0.01$) (see Table 3).

The full model to predict hypertension development (sample in analysis, $n = 443$) showed a better fit to data (AIC = 647.59), in comparison to the unconstrained model (AIC = 684.39) and the model that included sociodemographic variables (AIC = 658.81). The precision of the full model was considered adequate (AUC = 0.70).

The factors significantly related to the development of hypertension over the follow-up were sex ($OR = 0.06$, Wald's $Z = -2.21$, $p < 0.05$), age ($OR = 1.04$, Wald's $Z = 4.34$, $p < 0.01$) and metabolic risk score ($OR = 1.26$, Wald's $Z = 3.34$, $p < 0.01$) (see Table 3).

The model without covariates (AIC = 1675.01) and the one that included the sociodemographic variables (AIC = 1536.10) showed a worse fit than the full model for hypercholesterolemia (sample in analysis, $n = 558$) (AIC = 1525.33). The full model also showed an adequate precision to predict hypercholesterolemia development (AUC = 0.73).

In Table 3, it can be seen that the variables that were significantly related to the development of hypercholesterolemia in the 10-year follow-up were age ($OR = 1.46$, Wald's $Z = 2.09$, $p < 0.05$), second ($OR = 1.69$, Wald's $Z = 2.51$, $p < 0.05$), third ($OR = 1.74$, Wald's $Z = 2.35$, $p < 0.05$) and fourth financial status quartile membership ($OR = 1.06$, Wald's $Z = 7.68$, $p < 0.01$); DAG membership ($OR = 1.68$, Wald's $Z = 2.55$, $p < 0.01$) and metabolic risk score ($OR = 1.03$, Wald's $Z = 2.90$, $p < 0.01$).

4 Discussion

This study aimed to gain insight into the relationships between subclinical profiles, featured by elevated emotional symptoms (i.e., depression and anxiety symptoms), and immunometabolic alterations. Our study involved a concurrent relationship (i.e., blood inflammatory response and metabolic biomarkers) and disease at 10-year follow-up (i.e., development of chronic metabolic diseases) approach. Individuals with symptoms of anxiety and with symptoms of anxiety and depression had higher CRP levels relative to the control group. However, no differences were observed between the groups (i.e., CG, DG, AG and DAG) in the comparison of the other inflammatory markers (i.e., IL-6, SAA and TNF-α) and metabolic markers (i.e., waist circumference, fasting glucose, triglycerides, HDL cholesterol, SBP and DBP). On the other hand, the DAG group showed higher inflammatory score and was the only group with significant differences with respect to CG. No differences were observed in the metabolic risk profiles between the different groups. At 10-year follow-up, individuals with elevated depressive symptoms had an increased risk of developing diabetes and hypercholesterolemia (in this case when comorbid anxiety systems were present) during the 10-year follow-up.

Our study provided some evidence on the influence of emotional disorders on inflammatory and metabolic function, even from subclinical statuses (i.e., statuses of elevated symptoms, regardless of other criteria to be fulfilled, such as daily interference or functional impairment). The association between inflammation and depression has been supported by studies with clinical samples (15, 25, 52–56). In fact, some emotional symptoms (i.e., anhedonia, hypervigilance, insomnia) may be conceptualized as defensive reactions against (psychological, social) pathogens, leading to increased inflammatory response (57). On the other hand, our study revealed that subclinical profiles of emotional symptoms were not associated with metabolic risk at baseline. Numerous studies have shown significant relationships between metabolic

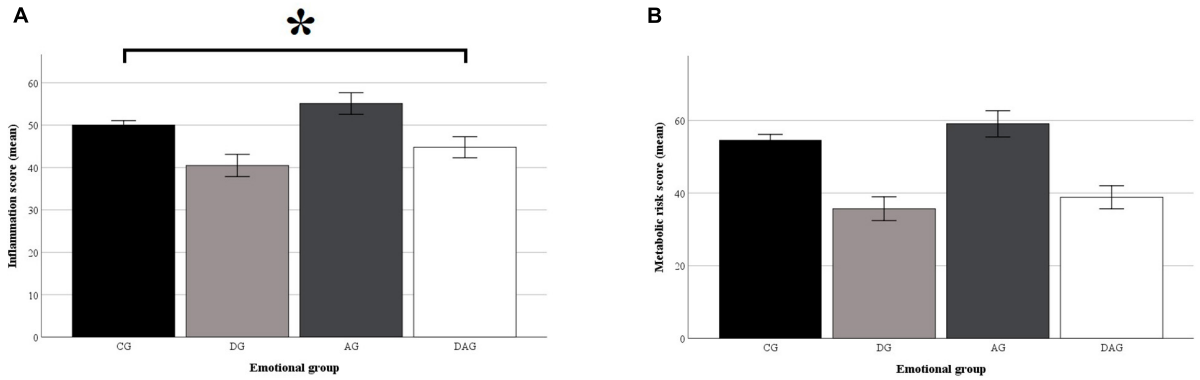

FIGURE 1
Inflammatory and metabolic risk scores according to the study groups. The inflammatory **(A)** and metabolic risk **(B)** scores were calculated using Multiple Indicators Multiple Causes (MIMIC) models. The scores were scaled on a 0–100 scale. For both scores, the higher the score the lower the inflammation/metabolic risk. Both scores were calculated controlling for lifestyle factors (i.e., Mediterranean diet adherence, physical activity and smoking), age and sex at birth. The indicators used for inflammatory score calculation were the C-reactive protein, Interleukin 6, Serum amyloid A, and Tumor necrosis factor α. Indicators used for metabolic risk calculation were waist circumference, blood glucose level, triglycerides, high-density lipoprotein level and hypertension diagnosis. CG, control group; DG, group with elevated depressive symptoms; AG, group with elevated anxiety symptoms; DAG, group with elevated depressive and anxiety symptoms. Whiskers represent the 95% confidence interval of the mean. $*p < 0.05$.

TABLE 2 **Regression loadings to explain inflammatory and metabolic risk score.**

Inflammation profile model	*B*	CI_{95}	*t*-value
Study group (reference = control group)			
DG	0.04	−0,16, 0.24	0.42
AG	0.17	−0.05, 0.39	1.64
DAG	0.20	0.01, 0.40	2.03*
Sex (reference = male)	0.20	0.06, 0.34	2.96**
Age	0.04	0.04, 0.04	12.24***
Metabolic risk profile model	***B***	**CI_{95}**	***t*-value**
Study group (reference = control group)			
DG	0.84	−0.94, 2.62	0.92
AG	1.23	−0.63,3.09	1.30
DAG	0.91	−0.83, 2.65	1.01
Sex (reference = male)	19.26	18.06, 20.46	31.12***
Age	0.31	0.25, 0.37	11.11***

Inflammatory and metabolic risk profile model covariates: marital status, mediterranean diet adherence, physical activity level, smoking and alcohol drinking.
B = Beta coefficient. CI = confidence interval at 95% of Beta coefficient. DG, depressive group; AG, anxiety group; DAG, depressive and anxiety group.
$*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

risk and emotional disorders (58, 59). The relationship between emotional disorders and metabolic risk becomes stronger in the older age, due to the effect of the progressive increase of low-grade systemic inflammation with age (60). We speculate that the statuses of full-blown disorders, qualitatively distinct from normal expression variations in both degree and kind, are needed to mobilize alterations in lipid metabolism. In the studies by van Reedt Dortland et al. (61) and Vogelzangs et al. (62), they followed this line because they found no associations with the dichotomous classification by emotional symptoms, only reporting this association in more severe patients.

Different studies support the association between major depressive disorder and the presence of MetS (12, 32, 59, 63, 64). In addition, depression has been determined as a risk factor for the development of metabolic abnormalities such as obesity and adverse patterns of lipoproteins (12). Regarding the relationship between anxiety and metabolic alterations, it has been less studied (61, 62, 65–68), not always finding positive results due to the heterogeneity of the samples and methodologies used (66–68).

Risky lifestyles, as well as the consumption of psychotropic drugs, have some relevance in the association between MetS and emotional disorders because they can alter metabolic patterns (32, 61). In addition, depression and anxiety are stress-related disorders, by which systemic cortisol action occurs along with alterations in glucocorticoid sensitivity and HPA axis action (32, 64). Derived from the deregulation of the HPA axis, the body is favored to accumulate visceral adipose tissue, an active endocrine organ that produces cytokines and inflammatory hormones (32).

TABLE 3 Logistic binary regression to predict metabolic diseases.

	OR (CI_{95})	*z*-value
Diabetes (n = 600)		
Sex (reference = male)	1.14 (0.57, 2.35)	−0.51
Age	1.09 (1.06, 1.12)	5.01**
Household income(reference = 1st quartile)		
2nd quartile	0.64 (0.3, 1.4)	−1.99*
3rd quartile	0.35 (0.17, 0.77)	−3.25**
4th quartile	0.37 (0.16, 0.86)	−3.34**
Emotional group (reference = CG)		
DG	2.08 (1.00, 4.22)	2.19*
AG	1.32 (0.64, 2.57)	0.97
DAG	0.6 (0.2, 1.49)	−0.22
Metabolic risk score	1.05 (1.02, 1.08)	3.06**
Hypertension (n = 443)		
Sex (reference = male)	0.06 (0.03, 0.1)	−2.21*
Age	1.04 (1.02, 1.05)	4.34**
Household income(reference = 1st quartile)		
2nd quartile	0.79 (0.49, 1.29)	−1.11
3rd quartile	0.6 (0.38, 0.97)	−1.00
4th quartile	0.83 (0.5, 1.39)	−1.53
Emotional group (reference = CG)		
DG	0.94 (0.55, 1.57)	1.57
AG	1.18 (0.78, 1.8)	1.19
DAG	0.98 (0.62, 1.54)	1.26
Metabolic risk score	1.26 (1.22, 1.3)	3.34**
Hypercholesterolemia (n = 558)		
Sex (reference = male)	0.93 (0.65, 1.34)	0.71
Age	1.46 (0.99, 2.16)	2.09*
Household income(reference = 1st quartile)		
2nd quartile	1.69 (1.16, 2.48)	2.51*
3rd quartile	1.74 (1.14, 2.67)	2.35*
4th quartile	1.06 (1.05, 1.07)	7.68**
Emotional group (reference = CG)		
DG	1.16 (0.8, 1.68)	1.01
AG	1.05 (0.74, 1.5)	1.61
DAG	1.68 (1.16, 2.43)	2.55**
Metabolic risk score	1.03 (1.02, 1.05)	2.90**

OR, odds ratio; CI, confidence interval at 95%; CG, control group; DG, depressive group; AG, anxiety group; DAG, depressive and anxiety group.
*$p < 0.05$. **$p < 0.01$.

The greater proinflammatory response activates the release of lipids into the bloodstream, producing a reduction in HDL cholesterol together with an increase in triglycerides (64). This fact, together with the greater production of oxidative stress and dysregulation of the autonomic nervous system derived from the stressed state of the patients, interacts with the glucose homeostasis and insulin resistance, related to the factors that make up MetS (64). All these alterations produced in the organism of people with emotional disorders are those found after the association with MetS.

Patients with depression or anxiety often adopt unhealthy lifestyle habits, such as smoking (69, 70), increased intake of foods high in fat or sugar (71) or sedentary lifestyle (72, 73) that also have a determinant effect on their health status (74). In the sample of our work, we observed significant differences in physical exercise and alcohol intake. On the one hand, the DG group was the one with the highest percentage of individuals who performed little physical activity. Previous studies have shown that patients with depression perform little physical activity, with 88% of them not complying with the recommended guidelines (at least 150 min/week of moderate-intensity aerobic physical activity or 150 min/week of vigorous physical activity) (75, 76). On the other hand, it has been observed that low levels of physical activity are associated with increased risk of depression in the general population (77). In fact, people who exercise regularly show almost 45% less likelihood of having depressive symptoms, being able to be used for the prevention of this disease (78, 79).

Regarding alcohol intake, we observed that the CG subjects were more likely to consume alcohol than the other groups. In contrast, the DG group was the least likely to consume alcohol. Not consuming alcohol was associated with the diagnosis of depression in previous studies (80), and this lower alcohol consumption could be associated with the need for psychopharmacological treatment.

Statuses with comorbid elevated anxiety and depression symptoms may put individuals at higher risk of inflammatory dysregulation due to a greater impact on HPA axis function and subsequent increase of glucocorticoid resistance. In this line, Choi et al. (23) found greater HPA alterations in patients with anxious depression compared to non-anxious depression. The study by Gaspersz et al. (31) revealed an overproduction of cytokines (stimulated by increased lipopolysaccharide response) in patients with comorbid anxiety and depression. In a same vein, Shim et al. (81) observed higher levels of monocytes in patients with major depression and moderate to severe anxiety symptoms compared to the mild-anxiety symptom group. Finally, a reduced number of basophils and elevated fragmented neutrophils have been found in patients with depression who showed higher anxiety symptoms (82). Altogether, these results stress that the statuses featured by higher levels of both anxiety and depression symptoms may boost alterations in the inflammatory response at concurrent relationship.

Regarding the disease at 10-year follow-up effects of subclinical emotional statuses, our results go in line with previous studies on the relationship between the emotional disorders and metabolic disease development (83, 84). More concretely, we found that the status of elevated depression symptoms put individuals at higher risk of diabetes development over the 10-year follow-up. The status of elevated anxiety and depression symptoms was associated with hypercholesterolemia development.

The risk factors for diabetes development were age (i.e., higher age with higher risk), economic status (poorer quartiles), the

status of elevated depression symptoms, and the metabolic risk at baseline. Diabetes is a serious health problem, which may contribute to the development of cardiovascular complications, stroke and subsequent early mortality (85). The total prevalence of diabetes increases significantly in relation to age, reaching figures between 10–15% in the population older than 65 years and up to 20% if we consider only those older than 80 years (86).

Mounting evidence supports the elevated comorbidity between diabetes and major depression (87–91). Our study provides further insight into this relationship, supporting a clear relationship between the status of elevated depression symptoms and diabetes. Despite this, the presence of elevated emotional symptoms of depression and anxiety together was not a risk factor. This could be due to the differences found between both groups in performing physical activity. The DAG group performs a greater amount of moderate and intense physical activity, which could be a protective factor for the development of diabetes. Physical exercise is inversely related to different risk factors for the development of diabetes (92, 93). On the one hand, it improves energy balance and reduces adiposity and, in addition to this, it improves insulin sensitivity and glucose homeostasis, which helps improve the metabolic profile of people who do it and reduce the risk of diabetes (92).

On the other hand, the risk factors for the disease at 10-year follow-up development of hypertension were sex, age and metabolic risk. The statuses of elevated emotional symptoms were not associated with hypertension development. Despite some studies have provided some evidence on the relationship between emotional disorders (mainly depression) and hypertension (94–96), other results have shown opposite findings (97–99), being important to consider confounding factors such as lifestyle or metabolic status of the participants (100). Moreover, some cardiovascular mediating paths (i.e., kynurenine path) may be more independent of emotional factors (28).

Finally, the status of elevated anxiety and depression symptoms was proven to be a risk factor of hypercholesterolemia development. Additional risk factors of hypercholesterolemia development were age, economic status (poorer quartiles), and the metabolic risk at baseline.

Depression has been related with altered lipid metabolism (101), even from a first clinical episode (102). Despite the fact that many studies support this fact (35, 103, 104), the results are contradictory with other studies that have found an inverse relationship between cholesterol and depression (105, 106). These discrepancies may be explained by methodological issues (i.e., different sample selection criteria and assessment protocols).

The longitudinal study by van Reedt Dortland et al. (35) stressed that patients with severe anxiety and depression symptoms were at higher risk of presenting dyslipidemia on a 2-year follow-up. Our results extend the conclusions from the study by van Reedt Dortland et al. (35), by including a longer follow-up and individuals with subclinical statuses of elevated symptoms. We speculate that the individuals with statuses of elevated emotional may show an overproduction of HPA agents and higher glucocorticoid resistance. HPA dysregulation may lead to increased levels of circulating free fatty acids, with subsequent low-density lipoprotein secretion and alterations in lipid metabolism (101).

Our study presents some relevant strengths to be mentioned. Compared to previous studies, our study has a large sample of community people. Moreover, our analytical strategy based on robust protocols (e.g., MIMIC models) controlling for relevant covariates, such as, lifestyle factors and health status. Finally, our study focuses on profiles on symptoms, providing new insight into the development of preventive strategies to prevent from full-blown condition development.

Our study presents some shortcomings to be mentioned. The intake of oral hypoglycemic, antihypertensive or lipid-lowering drugs was not taken into account in the baseline evaluation. Data on anti-inflammatory drugs and psychopharmacological medication were also not collected in this study. In this regard, we adopted a symptom-based approach, highly appropriate on a community basis. However, this study should be seen as a wide picture of how subclinical statuses of emotional disorder may be linked with immunometabolic dysregulation and metabolic diseases. On the other hand, it should be noted that only a baseline assessment of the participants' mental health was carried out. Anxiety and depressive symptoms were not followed up, so the trajectories of the participants' symptoms could not be known. Longitudinal studies are needed to explore how different trajectories of anxiety and depression symptoms influence the subsequent development of metabolic diseases.

5 Conclusion

Depression and anxiety are two of the most prevalent (1) and disabling (5, 6) mental disorders that carry high socioeconomic costs. Therefore, finding the causes of both disorders to reduce or eliminate symptoms is essential in mental health research. With our study, we have been able to demonstrate that both pathologies have concurrent relationship and disease at 10-year follow-up consequences on the health of individuals. We have determined that subjects with comorbid subclinical symptoms of depression and anxiety have concurrent relationship immune system consequences. In addition, these patients have a higher risk of long-term hypercholesterolemia and patients with depression have a higher risk of diabetes. The results therefore suggest the need to follow these patients and propose early healthy lifestyle interventions that can offset this risk by reducing their metabolic risk and thereby reducing the risk of morbidity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The ATTICA study was approved by the Institutional Ethics Committee of Athens Medical School (#017/1.5.2001). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because protocols in the current study did not need a

specific approval from an Ethics Committee as secondary data analysis was performed.

Author contributions

DP and CP designed the study and wrote the protocol. YS-C and AT-L performed the statistical analyses. YS-C managed the literature searches and wrote the first draft of the manuscript, which was supervised by AT-L, PL-G, and JA-M. EG and CV participated in the recruitment, the collection of information, and the creation of databases. All authors contributed to the interpretation and discussion of the results and have approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1148643/full#supplementary-material

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Sociodemographic factors associated with major depressive episodes and suicidal ideation among emerging adults with diabetes in the U.S

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Background: Research focused on disparities related to mental health comorbidities, especially among emerging adults with diabetes, is limited. Identifying associated factors of disparities could inform policy decisions to make diabetes-related interdisciplinary care more accessible for vulnerable groups.

Method: Using data from the National Survey on Drug Use and Health (2015-2019), we examined disparities in presence of major depressive episode (MDE) and suicidal ideation among emerging adults with diabetes. Survey design-adjusted bivariate and multivariable logistic regression models were used for statistical analyses.

Results: The study included 1,125 emerging adults (18-25 years old), with a history of type 1 diabetes (T1D) or type 2 diabetes (T2D). After controlling for sociodemographic and health-related characteristics, we found lower odds of having past-year major MDE for non-Hispanic Black (AOR, 0.42, p=0.032) compared to their non-Hispanic White counterparts. Females were 3.02 times more likely to have past-year MDE than males (AOR, 3.02, p=0.004). The odds of having past-year MDE were 1.96 times higher among individuals who identified as LGB (lesbian, gay, bisexual) (AOR, 1.96, P=0.038). There were no statistically significant disparities in suicidal ideation related to race/ethnicity, sex, education, and family income. However, individuals who identified as LGB had significantly higher likelihood of suicidal ideation than their heterosexual counterparts (AOR, 2.47, P=0.004).

Conclusion: Significant disparities related to MDE and suicidal ideation exist based on race/ethnicity, gender, and sexual orientation. Integration of a mental health professional into the multidisciplinary diabetes care team is critical for effective management of comorbid mental health conditions in younger patients with diabetes.

KEYWORDS

diabetes, disparity, suicidal ideation, mental illness, major depressive episode, LGBTQ

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Highlights

- Higher risk of Major Depressive Episodes (MDE) for women and sexual minority (lesbian, gay, bisexual (LGB)) emerging adults with diabetes.
- LGB emerging adults have an increased risk of suicidal ideation compared to their heterosexual counterparts.
- Among emerging adults, Non-Hispanic Blacks have lower odds of experiencing MDE compared to non-Hispanic Whites.
- Integration of mental health professionals into diabetes care team is crucial for managing comorbid mental health conditions in emerging adults with diabetes.

Introduction

Diabetes is one of the fastest-growing health challenges of the 21st century in the United States (US) and around the world. In 2020, 10.5% of the US population (34.2 million) was estimated to have diabetes (1). Incidence and prevalence of diabetes both type 1 diabetes (T1D) and type 2 diabetes (T2D) is increasing dramatically among adolescents and emerging adults (18-25 years) (2). Diabetes is a challenging condition to live with and mental illness often co-exists with diabetes (3, 4).

Emerging adults with diabetes are particularly at risk as they enter a critical developmental stage in life, often referred to as emerging adulthood (5), characterized by multiple life transitions—from high school to college/workforce, from living with parents to living by themselves, from already established social and peer support system to building new interpersonal relationships in college/workplace (5, 6). These challenges are further complicated by an abrupt change in their professional diabetes care as they enter adulthood, which involves a shift from their pediatric diabetes care provider to an adult diabetes care provider (7). The struggles of these transitions coupled with the relentless demands of day-to-day management of diabetes—diet, insulin, medication schedules, and monitoring blood glucose—may be stressful and burdensome and result in poor prognosis (8, 9).

A meta-analysis by Anderson et al. reported that the prevalence of mental illness among adults with diabetes is 2 times higher than its prevalence among adults without diabetes (10). Early-onset mental illness also increases the risk of significant mental health problems in the later years (11). Mental health comorbidities are also associated with an increased risk of suicide (12) among emerging adults with both T1D and T2D. The association between diabetes and depression, and their co-existence has been studied extensively by researchers among adults (10, 13). However, there are still limited data on the risk of mental health comorbidities among emerging adults with diabetes (3).

Considering the current gap in literature, the objective of this study was to expand the knowledge and understanding of mental health comorbidities and associated factors in this specific demographic of emerging adults with diabetes. This study aimed to identify disparities in past-year prevalence of major depressive episode (MDE) and suicidal ideation among emerging adults with diabetes based on key demographic and socioeconomic determinants using a nationally representative dataset.

Method

Data source and study design

This study used a retrospective cross-sectional study design and data from the 2015 to 2019 National Survey on Drug Use and Health (NSDUH) public use data files. The NSDUH is an annual cross-sectional survey which is representative of the US population. Conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), the NSDUH is one of the primary sources of information about mental health disorders, and other health-related issues among members of the US, including civilian, noninstitutionalized US population aged 12 years and older. The survey collects data from noninstitutionalized residents of all 50 states and the District of Columbia (14).

NSDUH uses a stratified multistage area probability sampling to achieve national representativeness. Household survey interviews are conducted in-person using both computer-assisted personal interviews and audio computer-assisted self-interviewing. Privacy is maintained during the interview to increase the level of comfort and honesty in reporting confidential information about sensitive behaviors related to mental health. Further details about the NSDUH methodology and data structure are available at the SAMHSA website (15). For this analysis, the public-use data files for years 2015-2019 were merged to get stable national estimates. This study was deemed exempt from review by the University of Florida IRB. Study findings were reported by using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Study sample

The sample was drawn from the merged file for years 2015-2019. Data for only emerging adults aged between 18-25 years old with a diabetes diagnosis (both type 1 and type 2) were included in the analysis. Diagnosis of diabetes was derived using the question, "Below is a list of health conditions that you may have had during your lifetime. Please read the list and type in the numbers of all the conditions that a doctor or other health care professional has ever told you that you had: Ever told had diabetes/sugar diabetes." The responses were recorded as Yes/No. Participants with a history of any type of cancer were excluded from the analytic sample. The final study sample included 1,125 individuals of ages 18 to 25 years with a history of diabetes.

Study variables

Past year major depressive episode

MDE was assessed in the NSDUH by an indicator based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th edition (16). MDE was defined as "a period of at least 2 weeks when the respondent experienced a depressed mood or loss of interest or pleasure in daily activities, and other symptoms" (15). A respondent was classified as having MDE, if they reported experiencing at least 5 out of the 9 criteria used to define MDE, where at least one of the criteria is a depressed mood or loss of interest or pleasure in daily activities. Past year MDE was operationalized as dichotomous (Yes/No) variables in the analysis.

Suicidal ideation

Suicidal ideation was assessed with the question: "At any time in the past 12 months, up to and including today, did you seriously think about trying to kill yourself?" Based on their answers to the above question respondents were categorized into 2 groups representing suicidal ideation 1) Suicidal ideation, 2) No suicidal ideation.

Key sociodemographic variables

Self-reported race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), sex (male, female), sexual orientation (lesbian/gay/bisexual, heterosexual), family income (<$20,000, $20,000-$49,999, $50,000-$74,999, $75,000 or more), and education (less than high school, high school, some college) were included as key sociodemographic variables for assessing disparities.

Covariates

Additional demographic characteristics like marital status (married/unmarried), census region (large metro, small metro, non-metro), insurance (yes, no), current school/college enrolment (yes, no), general health status (fair/poor, good, very good/excellent) substance use and alcohol dependence (yes, no), disability status (yes, no), current dorm status (yes, no) and comorbid conditions (yes, no) were included as covariates in the analysis. We chose these covariates given their association with increased risk for suicide or mental health condition based on previous studies (17).

Statistical analysis

For describing the study population, survey-design adjusted descriptive statistics were used. Wald chi-square tests were used to describe differences in the population characteristics by past year prevalence of MDE and suicidal ideation among individuals with a history of diabetes. Proportion of individuals with mental health comorbidities were estimated using survey weights to generate estimates that represented the US civilian noninstitutionalized population. To investigate disparities in mental health comorbidities both bivariate and multivariable logistic regression models were used with key sociodemographic variables as predictors for each outcome measure. All known confounders were included in the models as covariates. All analyses were conducted using SAS 9.4. (SAS Institute, Cary, NC), and statistical significance was determined at $p<0.05$.

Results

Descriptive statistics

The final study sample included 1,125 individuals (weighted sample of 2,620,937 US emerging adults aged 18-25 years old). The baseline characteristics of the study population are presented in Table 1. Out of 1,125 emerging adults with diabetes, majority were female (58%), non-Hispanic White (53%), with a college or higher degree (48%), family income between $20,000 to $49,999 (37%), unmarried (86%), identified as heterosexual (85%), covered by health insurance (85%), had excellent or very good general health (41%), no comorbidities (75%), currently not attending school (60%), not living in college dorm (98%), residing in a large metro area (51%), with no substance abuse disorder (86%), and without any disability (73%).

Disparities related to past year MDE

Lower odds of having past year MDE were estimated for non-Hispanic Black (adjusted odds ratio [AOR], 0.42, 95% CI, 0.19-0.92, p=0.032) compared to their non-Hispanic White counterparts. Females were 3.02 times more likely to have past year MDE than males (AOR, 3.02, 95% CI, 1.45-6.27, p=0.004). The odds of having past year MDE were 1.96 times higher among individuals who identified as LGB (AOR, 1.96, 95% CI, 1.04-3.68, P=0.038) (Table 2).

Disparities related to past year suicidal ideation

There were no statistically significant disparities in suicidal ideation related to race/ethnicity, sex, education, and family income among the study population. Like for MDE, individuals who identified as LGB had significantly higher likelihood of suicidal ideation than their heterosexual counterparts (AOR, 2.47, 95% CI, 1.36-4.47, P=0.004), (Table 3).

Discussion

The purpose of this research was to identify disparities in past-year MDE and suicidal ideation among emerging adults with

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TABLE 1 Baseline characteristics of study population, emerging adults (18-25 years) with diabetes, 2015-2019 NSDUH.

Characteristics	Unweighted population	Weighted population	
	N = 1,125	n = 2,620,937	
	No.	Weighted % (95% CI) [a]	P-value
Sex			
Male	427	41.7 (37.2-46.3)	0.001
Female	698	58.2 (53.6-62.7)	
Race/Ethnicity			
Non-Hispanic White	572	52.5 (47.4-57.6)	<.0001
Non-Hispanic Black	191	17.6 (15.4-19.7)	
Hispanic	242	22.1 (17.5-26.6)	
Other [b]	120	7.69 (5.61-9.77)	
Education			
Less than high School	205	17.6 (15.1-20.0)	<.0001
High school graduate	425	34.5 (30.2-38.8)	
College or higher	495	47.8 (43.9-51.7)	
Family Income			
Less than $20,000	375	29.8 (26.2-33.4)	<.0001
$20,000 to $49,999	424	36.6 (32.8-40.3)	
$50,000 to $74,999	123	10.6 (8.45-12.8)	
$75,000 or More	203	22.8 (19.1-26.5)	
Marital Status			
Married	187	14.3 (11.5-17.1)	<.0001
Unmarried [c]	908	85.6 (82.8-88.4)	
Sexual Identity			
Heterosexual	914	84.7 (82.1-87.2)	<.0001
LGB	191	15.2 (12.7-17.8)	
Health Insurance			
Yes	958	84.7 (81.9-87.5)	<.0001
No	167	15.2 (12.4-18.0)	
General Health			
Excellent/ Very Good	436	41.2 (36.9-45.5)	<.0001
Good	422	35.6 (31.9-39.4)	
Fair/Poor	267	23.0 (20.1-25.9)	
Comorbidities			
No	820	74.8 (71.7-77.9)	<.0001
Yes	305	25.1 (22.0-28.2)	
Current School Enrolment			
No	545	59.9 (55.2-64.7)	<.0001
Yes	321	40.0 (35.2-44.7)	
Dorm Status	<.0001		
No	1093	97.6 (96.4-98.8)	
Yes	32	2.34 (1.15-3.52)	
Census Region			
Large metro	434	50.9 (46.9-54.8)	<.0001
Small metro	439	33.9 (30.2-37.6)	
Non metro	252	15.1 (12.3-17.8)	
Substance Use Disorder [d]			
No	960	86.3 (83.7-88.8)	<.0001
Yes	165	13.6 (11.1-16.2)	
Disability			
No	815	72.9 (69.8-76.0)	<.0001
Yes	310	27.0 (23.9-30.1)	

LGB, lesbian gay bisexual.
[a]Estimates were weighted to be nationally representative using recommended stratification, clustering, and weighting by Substance Abuse and Mental Health Services Administration.
[b]Other includes non-Hispanic Native American/Alaska Native, Native Hawaiians/Other Pacific Islander, non-Hispanic Asian, and more than one races.
[c]Includes widowed, divorced, or separated.
[d]Based on the criteria in the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th edition.

diabetes based on key demographic and socioeconomic factors. Using a nationally representative sample of 1,125 emerging adults, who had a history of diabetes, we found significant disparities in MDE and suicidal outcomes based on race/ethnicity, gender and sexual orientation. Below we discuss these findings in more detail.

Females and participants who identified as LGB were more likely to have past-year MDE. These results are supported by a study that found individuals with diabetes and comorbid depression to be younger, female, and with poor physical health (18). Gender differences in the prevalence of MDE have long been recognized within the general population (18). Possible reasons could be social, biological or psychological in nature such as discrimination based on gender (19), differential biological response to stress (20), differences in exposure to adversities (21). Another explanation of these findings could be the under-reporting of the symptoms of

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TABLE 2 Unadjusted and adjusted analysis of disparities related to Past year MDE among emerging adults (18-25 years) with diabetes.

	Crude Odds Ratio	(95% CI)	P-value	Adjusted [a] Odds Ratio	(95% CI)	P-value
Race/Ethnicity						
Non-Hispanic White	Ref	–	–	Ref	–	–
Non-Hispanic Black	0.58	(0.29-1.14)	0.112	0.42	(0.19-0.92)	0.032
Hispanic	0.59	(0.29-1.20)	0.144	0.59	(0.25-1.33)	0.198
Other	1.21	(0.53-2.75)	0.642	0.81	(0.27-2.33)	0.687
Gender						
Male	Ref	–	–	Ref	–	–
Female	3.00	(1.84-4.86)	<.0001	3.02	(1.45-6.27)	0.004
Education						
Less than High School	Ref	–	–	Ref	–	–
High School Graduate	0.99	(0.53-1.83)	0.966	1.03	(0.45-2.35)	0.936
Some College	1.13	(0.52-2.41)	0.750	1.43	(0.60-3.39)	0.408
Family Income						
Less than $20,000	Ref	–	–	Ref	–	–
$20,000 to $49,999	1.25	(0.69-2.25)	0.450	1.48	(0.75-2.89)	0.248
$50,000 to $74,999	1.08	(0.44-2.62)	0.859	1.92	(0.56-6.48)	0.287
$75,000 or More	0.83	(0.41-1.66)	0.584	0.87	(0.36-2.04)	0.743
Sexual Identity						
Heterosexual	Ref	–	–	Ref	–	–
LGB	2.75	(1.62-4.66)	0.001	1.96	(1.04-3.68)	0.038

LGB, lesbian, gay, bisexual; Ref, reference.
[a]Adjusted model included sex, race/ethnicity, education, family income, marital status, sexual identity, health insurance, general health, comorbidities, current school enrolment, dorm status, census region, substance use disorder, and disability.

depression. Research suggests that males tend to under-report symptoms and severity of depression (22). It has been argued that DSM-5 reflects symptoms of depression in females better than males (23).

It has been found that individuals who identify as LGB are more likely to suffer from poor mental health (24–26). Research suggests that mental health disparities found at younger ages in LGB adults could persist later in the life course (24). The literature recognizes the existence of stigma and minority stress at individual, interpersonal and structural levels, and multiple mechanisms or pathways have been suggested for how stigma and minority stress can cause depressive symptoms among sexual minority individuals (27).

This study also found that non-Hispanic Black population were less likely to experience past-year MDE compared to non-Hispanic White. This finding is consistent with a previous study (28). Researchers speculate that non-Hispanic Blacks benefit from their social ties and coping strategies. For example, Weaver et al. concluded that stressors affect mental health of non-Hispanic Blacks to a lesser extent compared to non-Hispanic Whites (29). However, these assumptions lack empirical support, and reasons for racial/ethnic differences in past-year MDE remain unclear (30). Future research may help explore the factors contributing to lower risk of mental health illnesses among non-Hispanic Black emerging adults with diabetes.

As for suicidal ideation, echoing the existing literature trends, our findings suggest that LGB emerging adults experience increased risk of suicidal ideation relative to their heterosexual counterparts (26). Youth from sexual minority groups are 4 times more likely to attempt suicide as compared to their heterosexual counterparts (31). A recent study done by Roberts et al. included a sample of 64 patients ages 13 to 21 years diagnosed with diabetes, they reported that 9% of the study participants endorsed suicidal ideation (32). Another study reported 9% suicidal ideation rate with 83.4% clinically elevated depressive symptoms among youth and emerging adults (10 to 24 years) with diabetes (33). Within this context, it's imperative to consider the compounded challenges faced by younger (or emerging) adults at the intersection of sexual minority status and diabetes. This suggests that the intersectionality of being both a sexual minority and having diabetes might present distinct mental health vulnerabilities compared to their heterosexual counterparts or those without diabetes. Although

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TABLE 3 Unadjusted and adjusted analysis of disparities related to suicidal ideation among emerging adults (18-25 years) with diabetes.

	Crude Odds Ratio	(95% CI)	P-value	Adjusted [a] Odds Ratio	(95% CI)	P-value
Race/Ethnicity						
Non-Hispanic White	Ref	–	–	Ref	–	–
Non-Hispanic Black	0.60	(0.34-1.06)	0.082	0.63	(0.30-1.31)	0.214
Hispanic	0.57	(0.30-1.08)	0.085	0.76	(0.37-1.53)	0.441
Other	1.15	(0.54-2.39)	0.713	0.98	(0.47-2.01)	0.953
Gender						
Male	Ref	–	–	Ref	–	–
Female	1.35	(0.90-2.00)	0.137	1.66	(0.76-3.59)	0.194
Education						
Less than High School	Ref	–	–	Ref	–	–
High School Graduate	1.06	(0.51-2.18)	0.875	1.14	(0.49-2.64)	0.758
Some College	0.86	(0.46-1.58)	0.626	1.41	(0.66-2.99)	0.359
Family Income						
Less than $20,000	Ref	–	–	Ref	–	–
$20,000 to $49,999	1.21	(0.77-1.91)	0.399	1.41	(0.80-2.46)	0.227
$50,000 to $74,999	0.85	(0.40-1.77)	0.656	1.17	(0.46-2.94)	0.728
$75,000 or More	0.70	(0.38-1.28)	0.245	0.79	(0.41-1.52)	0.481
Sexual Identity						
Heterosexual	Ref	–	–	Ref	–	–
LGB	2.91	(1.80-4.70)	<.0001	2.47	(1.36-4.47)	0.004

LGB, lesbian, gay, bisexual; Ref, reference.
[a]Adjusted model included sex, race/ethnicity, education, family income, marital status, sexual identity, health insurance, general health, comorbidities, current school enrolment, dorm status, census region, substance use disorder, and disability.

reasons for this trend remain unclear, exposure to violence, victimization and higher risk of isolation might lead to heightened levels of hopelessness and increased risk of suicidal ideation (34). Integration of a mental health professional into the multidisciplinary diabetes care team is critical for effective management of comorbid mental health conditions in emerging adults with diabetes. American Diabetes Association (ADA) standards of care specify that, "People with diabetes can benefit from a coordinated multidisciplinary team that includes mental health professionals" (35). Yet, not all diabetes care programs integrate mental health services in their diabetes care, and only 25% to 50% of those with diabetes and comorbid depression get access to treatment (36, 37). Our findings suggest that diabetes care providers and other healthcare professionals, including diabetes educators, should consider screening emerging adults with diabetes for early signs and risk factors of depression and current or past suicidal ideation, particularly LGB females, as part of a comprehensive care plan. Risk-based assessment made at an early stage of life could prevent the development of severe clinical depression among vulnerable individuals later in life. Consistent, widespread interventions to thwart impulsive suicidal behaviors should be established even in the absence of current suicidal thoughts. An inclusive approach supported by empirical evidence should be taken for treatment of depression in LGB emerging adults with diabetes to lower their risk of suicidal behaviors.

Providers who cater to the emerging adult population report having inadequate training and understanding of the unique needs of sexual minorities (38). Trainings and education focused on providing inclusive and quality care to sexual minority emerging adults is crucial and will ultimately help in eliminating disparities and inequities related to mental and physical health disparities. Future studies should demonstrate empirical evidence that supports efficacy of interventions specifically tailored to the unique needs of emerging LGB population. In addition, policy makers should focus on support strategies like awareness, counseling, peer support programs, and destigmatizing efforts while planning public health policies.

This study uses survey data that are representative of diabetes and mental health outcomes in the younger population, including those not necessarily seeing an endocrinologist for diabetes care. However, there are some limitations to this study approach. First, substance use disorder is a known risk factor for MDE and suicidal ideation (39), and it is crucial to fully control for this reverse causation. To address this limitation, all models were adjusted for

substance use disorder. Next, the survey uses diabetes as a broader diagnosis and does not ask the respondents about their specific diabetes type. This is a common limitation of studies that use national survey data and self-reported diagnosis of diabetes, and is also acknowledged as a limitation by CDC and the National Institute of Diabetes and Digestive and Kidney Diseases in their publications (40, 41). Another limitation is that individuals with diabetes and mental illnesses or depressive symptoms are at risk of reciprocal susceptibility and share a high degree of comorbidity (42). Accounting for this reciprocity was not feasible because of the cross-sectional nature of the data. Additionally, the data on most outcomes was based on self-report and are not objectively measured, thus it is difficult to establish the accuracy of the information provided, which may suffer from recall bias or social desirability bias. However, disease incidence and service utilization estimates of NSDUH have been validated against other national data sources, which increases the confidence in the study findings (43). Another constraint of this study is the lack of data pertaining to participants' HbA1C levels and diabetes duration. Consequently, we were unable to incorporate these factors into our analysis of the diabetes-depression relationship. Lastly, there is a possibility of confounding by several unobserved factors that were not controlled for because of the cross-sectional nature of the study.

Conclusion

Despite much effort towards reducing and eliminating disparities related to physical and mental health outcomes, this study provides evidence of prevalent mental health disparities among emerging adults with diabetes. Our findings showed that women and sexual minority emerging adults with a history of diabetes are particularly exposed to higher risk of MDE. Moreover, the results highlight the disadvantages faced by sexual minorities among this specific population in terms of suicidal ideation. This research holds important implications for diabetes care professionals and policy makers to make their practices more favorable for disadvantaged groups who experience disparities and inequities. Further policy efforts are needed to educate, train, and sensitize diabetes care providers towards these prevalent mental health disparities among emerging adults with diabetes and for integration of a mental health professional into the multidisciplinary diabetes care team. These endeavors could ultimately lower the risk of this vulnerable group against development of severe mental health illnesses during later stages in life.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: National Survey on Drug Use and Health 2019 (NSDUH-2019-DS0001) | SAMHDA. https://www.datafiles.samhsa.gov/dataset/national-survey-drug-use-and-health-2019-nsduh-2019-ds0001. Accessed August 31, 2021.

Author contributions

SY: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. Y-RH: Conceptualization, Supervision, Writing – review & editing. SW: Writing – review & editing. NM: Writing – review & editing. MH: Writing – review & editing. AW: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Ultra-processed foods consumption, depression, and the risk of diabetes complications in the CARTaGENE project: a prospective cohort study in Quebec, Canada

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Introduction: This study aimed to assess the association between depression, ultra-processed food consumption (UPFs), and the risk of developing diabetes-specific complications in adults with type 2 diabetes (T2D).

Methods: Baseline data came from the CARTaGENE study, a health survey of adults (40–69 years) in Quebec, Canada. The incidence of T2D complications was examined in N= 683 participants with T2D without complications at baseline by linking survey data with administrative health data. Food and drink consumption was assessed using the Canadian Diet History Questionnaire and categorized by NOVA classification. Participants were categorized into tertiles of UPFs consumption. Depression was defined as having elevated depressive symptoms based on the Patient Health Questionnaire-9 or the use of antidepressant medications. Cox regression models were used to estimate the associations between UPFs, depression, and T2D complications.

Results: In total, 105 individuals developed diabetes-related complications over a 7-year period. Participants with high depressive symptoms and high UPFs consumption had the highest risk for diabetes complications (adjusted hazard ratio (aHR) 2.07, 95% CI: 0.91 – 4.70), compared to participants with low depressive symptoms and low UPFs consumption. Higher risks for diabetes complications were observed when high depressive symptoms and antidepressant use were combined with high UPFs consumption (aHR 2.59, 95% CI: 1.32 – 5.06).

Conclusion: This study indicates that those with co-occurring depression and high UPFs consumption have a greater risk of diabetes complications. Early management and monitoring of both risk factors might be essential to prevent diabetes complications.

KEYWORDS

ultra-processed foods, depressive symptoms, type 2 diabetes complications, interaction, CARTaGENE

1 Introduction

Type 2 diabetes (T2D) is a chronic metabolic condition which requires intensive self-care management (1). Adopting and/or maintaining a healthy diet remains one of the main strategies for the management of T2D and its complications (2). Research has demonstrated that following healthy diets such as the Mediterranean diet (high in olive oil, fruit, nuts, vegetables, and cereals intakes) can reduce the risk of micro-and macrovascular complications among individuals with T2D (3–6).

Recently, in many modern food systems, there has been a nutritional transition characterized by an increase in the consumption of ultra-processed foods (UPFs) as a replacement for fresh foods (7). UPFs are defined as "multi-ingredient industrial formulations" which are characterized by low nutritional quality, high energy density, high saturated and trans fats content, added sugars and salt, and low protein, dietary fiber, and micronutrients (7, 8). Further, UPFs are often designed in a way to encourage eating them in combination (e.g., savory snacks with soft drinks), which can result in excessive caloric intake (7, 8). It has been reported that in higher-income countries, such as the United States and Canada, UPFs can contribute to half of the daily dietary energy intake (9, 10). Higher consumption of UPFs can increase the risk of numerous chronic conditions such as T2D, metabolic syndrome, depression, all-cause mortality, and cardiovascular diseases (9).

Among individuals with T2D, UPFs consumption may increase the risk of developing complications related to T2D. For instance, a recent study found that in individuals with T2D, high consumption of processed foods was associated with poor glycemic control and a greater likelihood of microvascular complications (11). UPFs are associated with elevated levels of glucose (12), which can result in the development of advanced glycation end-products (AGEs). AGEs can activate inflammatory signaling cascades and, consequently, have a crucial role in the pathogenesis of diabetes complications (13).

T2D is a multifactorial disease with psychological complications in addition to physical complications. The risk of developing depressive symptoms is more common in individuals with T2D than in the general population (14). Comorbid depression among individuals with T2D is associated with adverse health outcomes such as micro-and macrovascular complications and higher mortality rates (15). A meta-analysis of longitudinal studies showed that depression was linked with an increased risk of microvascular (HR=1.33; 95% CI: 1.25–1.41) and macrovascular complications (HR=1.38; 95% CI: 1.30–1.47) among adults with T2D (15).

Further, persons with comorbid depression and T2D might have more difficulties following a healthy diet, thereby potentially further increasing the risk of complications (11). Prior research has demonstrated that a history of depression and higher severity of depression was associated with higher emotional and uncontrolled eating, often leading to higher calorie consumption (16). A previous study has also reported an association between depression and high UPFs consumption (17).Consumption of unhealthy foods such as UPFs and high depressive symptoms can independently increase the risk of diabetes-related complications among individuals with T2D (9, 15). It is currently unknown whether high depressive symptoms among individuals with T2D compounds the potential impact of UPFs consumption on the risk of diabetes-related complications. It is possible that depressive symptoms and UPFs consumption may exacerbate the physiological processes, such as systemic inflammation which is risk factor for the T2D and its complications (18–20). Moreover, in a previous study, we found an important interaction between depressive symptoms and UPFs consumption on the risk of developing T2D (21). Adults with both depressive symptoms and high UPFs consumption had a higher risk of developing T2D within a seven-year interval than those without depressive symptoms and with low UPFs consumption (21).

As a next step, we aim to investigate a potential additive interaction between UPFs consumption and depressive symptoms

Abbreviations: UPFs, Ultra-processed food consumption; LUND, Lower/middle tertile of UPFs consumption and low depressive symptoms; LUD, Lower/middle tertile of UPFs consumption and elevated depressive symptoms; HUND, Higher tertile of UPFs consumption and low depressive symptoms; HUD, Higher tertile of UPFs consumption and elevated depressive symptoms; LUNDA, Lower/middle tertile of UPFs consumption and low depressive symptoms and no antidepressant use; LUDA, Lower/middle tertile of UPFs consumption and elevated depressive symptoms or antidepressant use; HUNDA, Higher tertile of UPFs consumption and low depressive symptoms and no antidepressant use; HUDA, Higher tertile of UPFs consumption and elevated depressive symptoms or antidepressant use.

on the incidence of diabetes-related complications in adults with T2D. The combination of depression and consumption of UPFs might not only increase the risk of developing T2D but might also increase the risk of developing diabetes-specific complications in adults with T2D. We, therefore, hypothesized that individuals with T2D with both depressive symptoms and high UPFs consumption at baseline would have a higher risk of developing micro-and macrovascular complications, compared to those without depressive symptoms and with low UPF consumption.

2 Methods

2.1 Study population

The sample was drawn from the baseline CARTaGENE (CaG) (2009–2010) study (22). CaG is a community health survey that gathered detailed information on health, lifestyle, and sociodemographic information, physiological measures, and biological samples from urban areas of Quebec, Canada (22). Participants aged 40–69 years at baseline were randomly recruited from the Régie de l'assurance maladie du Québec (RAMQ), a governmental health insurance database in the Canadian province of Quebec that provides universal health insurance for residents. Details of the study, such as recruitment, enrollment, and data collection methods, are described elsewhere (22). Briefly, the CaG survey design defined by two age groups, gender, and forward sortation area (defined by 3-digit postal codes). Probability proportional to size was used to describe quotas for each stratum. Participants were excluded if they were not registered in the RAMQ database, those residing outside selected regions, individuals in First Nations Reserves or long-term health care facilities or were in prison (22). Various strategies were employed to ensure response rates and minimize attrition, such as (i) utilizing the reputable governmental body RAMQ to handle participant contact and identifying information, (ii) implementing systematic methods for contact, scheduling, and reminders, and (iii) offering a financial compensation of $45 (22). The recruitment process involved a call center at RAMQ to prevent the transfer of identifying information to CaG. Information packages were initially mailed, followed by telephone contact to enroll participants and schedule clinical assessment site interviews. A total of 20, 007 participants provided informed consent to participate in the CaG cohort study and agreed to link their data with the RAMQ database (22). Ethical approval was provided by the Douglas Mental Health University Institute Research Ethics Board and the St. Justine Hospital Research Ethics Board. Follow-up data referring to T2D complication incidence were obtained by linking participants with diagnostic codes from the RAMQ database.

2.2 Depressive symptoms

Depressive symptoms experienced within the past two weeks were measured using the Patient Health Questionnaire-9 (PHQ-9) (23). The PHQ-9 consists of nine questions related to vegetative, emotional, behavioral, and cognitive symptoms of depression. Responses are rated on a 4-point scale ranging from 0 "not at all" to 3 "every day", with a summary score ranging from 0 to 27, with higher scores reflecting greater depressive symptom severity. The PHQ-9 has shown good agreement with a clinical diagnosis of major depressive disorder and good validity and reliability (23). In the present study, elevated depressive symptoms were defined as having a PHQ-9 summary score of 6 and higher, which includes mild to severe depressive symptoms. This cut-off score has been used in previous studies included in the CaG cohort (24, 25). When compared with the fully structured interviews for major depressive disorder, a PHQ-9 cut-off of 6 has a sensitivity of 0.91 and specificity of 0.61 (26).

2.3 Antidepressant use

Participants brought their current medication or reported their current medication at the baseline CaG interview. Medication was classified as an antidepressant based on the medication name (27).

2.4 Dietary intake assessment

Dietary intake in the CaG survey was assessed at baseline using the Canadian-adapted diet history questionnaire II (C-DHQ II) (22). C-DHQ II is a validated food frequency questionnaire (FFQ) which reflects food availability, brand names, nutrition composition, and food fortification in Canada (28, 29).

Frequency of consumption and portion sizes are defined for most of the food items in FFQ. Daily consumption of each FFQ food item was computed based on one of four units of time, depending on which answer choice was selected: year, month, week, or day (30). To calculate the daily consumption of each FFQ item, consumption frequency of the items was first converted into daily equivalents such never = 0; 1-6 times per year = 0.01; 7-11 times per year = 0.02; 1 time per month = 0.03; 2-3 times per month = 0.07; 1 time per week = 0.14; 2 times per week = 0.29; 3-4 times per week = 0.48; 5-6 times per week = 0.74; 1 time per day = 1; 2 or more times per day = 3, as specified by the C-DHQII database (30). Secondly, portions of consumed food items were converted into grams by using the nutrient database for the C-DHQII (30). Portions are sex-specific and based on the percentiles of intake reported in the Canadian Community Health Survey (CCHS) – Cycle 2.2 Nutrition (28, 29). The consumed amount for every food item was then calculated by multiplying the frequency per day and grams of consumption. In the present analysis, food items without portion size and items such as vitamins, minerals, or herbal supplements were excluded. Further, items of the C-DHQ II with missing information were filled in with zero imputation, based on the assumption that non-response to the items may be because those items were not consumed by the participants (31).

Every C-DHQ II reported food and beverage item was categorized into one of the four NOVA classification groups.

NOVA is not an acronym, but a classification system that groups foods according to the nature, extent, and purpose of the industrial processing (7). Foods were classified into four different groups: 1) unprocessed or minimally processed foods which includes fruit and vegetables, grains (cereals), fresh or pasteurized milk products, seeds without oil and salt, legumes, meat, and fish; 2) processed culinary ingredients such as salt, sugar, vegetable oil, and butter; 3) processed foods, such as canned vegetables and fruits, cheeses, and freshly made bread; and 4) ultra-processed foods and drinks (UPFs) that were prepared mostly or entirely from substances derived from foods, derived from food constituents, or produced in the laboratories from food substrates or other organic sources. Examples of products are ready-to-eat meals, carbonated drinks, biscuits, processed meat, and sugared milk and fruit drinks (7).

To estimate the frequency of consumption of UPFs (grams/day), we summed the amount consumed (grams/day) of each food and beverage item classified in the fourth category of the NOVA classification (a total of 30 foods and seven beverage items). Next, we divided the sample into tertiles according to the total consumption of UPFs (grams/day). Low and middle tertiles were merged as one group for analysis (21).

2.5 Incidence of T2DM complications

The study outcomes included micro-and macrovascular diabetes complications. Complications were assessed using diagnostic codes in the RAMQ billing database. Diagnostic codes were based on the World Health Organization's International Classification of Diseases, 9th or 10th edition (ICD-9 and ICD-10, respectively). Codes for micro-and macrovascular diabetes complications in ICD-9 and ICD-10 were based on prior literature and can be found in Supplementary Table 1. For the main analysis, micro-and macrovascular complications were combined. Participants were followed for up to seven years using administrative data from the date of their CARTaGENE baseline assessment. The date of the first diagnosis for micro-and macrovascular diabetes complications was recorded. Observational time was calculated from the day of baseline assessment to the day of complication onset, the date of death, or the study end date of December 31, 2016.

2.6 Confounders

Potential confounders include sociodemographic characteristics (age, sex, annual household income, education, and self-reported ethnicity (white was compared with others groups for analysis), behavioral factors including alcohol consumption, defined as whether participants consume alcohol daily or not, smoking ("currently smokes daily or occasionally", "past smoker", or has "never smoked"), physical activity (five or more-day moderate activity in a week or three or more vigorous in a week), and body mass index (BMI, continuous) (15).

2.7 Statistical analysis

2.7.1 Inclusion criteria

Only CaG participants with information on the nutrition component, depressive symptoms and diabetes status at baseline were included (n = 7,011) (21). Furthermore, the sample was restricted to participants with diabetes and without diabetes complications at baseline (n = 881). Diabetes was self-reported based on a diagnosis made by a physician on a positive response to the following question: 'Has a doctor ever told you that you had diabetes?' or HbA1c levels equal to or above 6.5 during the CAG baseline assessment. We excluded all participants who reported implausible energy intakes <800 or >4000 kcal/d in men and <500 or >3500 kcal/d in women (n = 52) as reported in previous research (32). Implausible reporting, particularly underreporting, is a commonly recognized limitation of dietary assessment methods; participants tend to underestimate their total energy intakes and underreport intakes of foods that are deemed unhealthy or socially undesirable, such as foods that are high in fat and refined carbohydrates (32). Further, we excluded participants whose response rates were less than 50% on the UPFs items (n = 146). A total of N = 683 participants were included for the analyses (Figure 1). Moreover, we performed two sensitivity analyses, first with a 40% response rate on UPFs items (sample size n = 814) and second with a 60% response rate on the UPFs items (sample size n = 561) to test the robustness of the study.

Cox proportional hazards models were conducted to examine the univariate associations between UPFs consumption, depressive symptoms, and antidepressant use with diabetes complications incidence. Micro-and macrovascular complications were combined for the analysis due to small sample size. However, they were also examined separately in secondary analysis.

To evaluate the potential additive interaction on the incidence of diabetes complications, four groups were defined based on the presence/absence of depressive symptoms and low/high intake of UPFs. The groups were: 1) lower/middle tertile of UPFs consumption and low depressive symptoms (LUND as the reference group), 2) lower/middle tertile of UPFs consumption and elevated depressive symptoms (LUD), 3) higher tertile of UPFs consumption and low depressive symptoms (HUND), and 4) higher tertile of UPFs consumption and elevated depressive symptoms (HUD).

Further, an additional analysis was performed combining depressive symptoms with antidepressant medications as an indicator for depression. Similarly to our primary analyses, four groups were created: 1) lower/middle tertile of UPFs consumption and low depressive symptoms and no antidepressant use (LUNDA as the reference group), 2) lower/middle tertile of UPFs consumption and elevated depressive symptoms or antidepressant use (LUDA), 3) higher tertile of UPFs consumption and low depressive symptoms and no antidepressant use (HUNDA), and 4) higher tertile of UPFs consumption and elevated depressive symptoms or antidepressant use (HUDA). All Cox regression analyses were performed in unadjusted models, in models

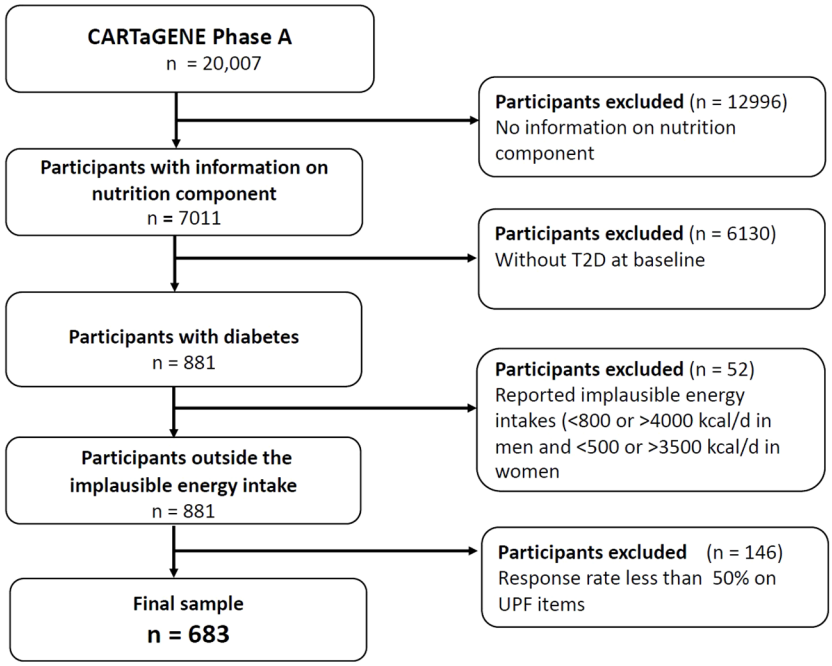

FIGURE 1
Flow diagram of the final sample for the analysis.

adjusted for age and sex only, and in fully adjusted models for all the confounders described above. Hazard ratios [HRs] with 95% confidence intervals are reported. Missing information on the covariates was imputed using the fully conditional specification with discriminant or logistic methods using PROC MI procedure in SAS. Cox regression analyses were conducted using SPSS software.

3 Results

The main food group contributors to UPFs intake are shown in Table 1. Overall, mean (SD) consumption of the UPFs was 276.9 (SD 421.0) g/d, and mean consumption in lower, middle, and highest tertiles was 71.5 (2 SD 3.6) g/d, 154.2 (SD 29.8) g/d, and 604.0 (SD 605.3) g/d, respectively.

Table 2 displays the characteristics of the sample. The baseline data reveals a mean age of 55.5 years (SD = 7.5), with 52.6% being female and 93.3% identifying as white. A total of 105 (15.4%) individuals developed diabetes-related complications during the observation period. Using the categorical classifications for groups based on UPFs and PHQ-9 scores, there were 395 (57.0%) participants in LUND group (reference group); 60 (8.9%) participants in LUD group; 191 (28.8%) participants in HUND group; and 37 (5.3%) participants in HUD group. Participants in the HUD group exhibited a higher percentage of lower-income levels and a lower percentage of postsecondary education compared to the other group. Additionally, individuals in the HUD group were more likely to be daily or occasional smokers and physically inactive compared to the other group. Moreover, the HUD group had a higher mean intake of UPFs 615.2 (478.2) g/d, and a higher BMI 31.0 (6.2) as compared to the other groups.

Table 3 describes the results of three univariate Cox regression analyses examining UPFs, depressive symptoms, and antidepressant use. Participants in the highest tertile of UPFs consumption had the greatest hazard ratios for developing complications in the fully adjusted model (HR=1.56, 95% CI: 0.92-2.62); however, the CI were overlapping with the one. Similarly, the CI overlapped with one in a fully adjusted model for depressive symptoms (PHQ-9>= 6) and for antidepressant use with HRs of 1.45 (95% CI: 0.84- 2.51) and 1.61 (95% CI: 0.86 – 3.00) respectively.

Table 4 shows results obtained from the additive interaction analysis, with the reference category in model 1 set as the LUND group. In HUD group, 24.3% of individuals developed complications. In the age and sex-adjusted model, the HUD group had a 2.4-fold increased risk of developing complications as compared to the LUD and HUND group. However, in the fully adjusted model, HUD group HR was 2.07 (95% CI: 0.91 – 5.06), and CI overlapped with one.

Further in model 2, when elevated depressive symptoms and antidepressant medication were combined as indicators for depression, 28.6% of individuals developed T2D complications. And similarly greater risk for T2D complications was found in the HUDA group in the model adjusted for age and sex (2.82, 95% CI: 1.53-5.18). Moreover, in a fully adjusted model, the HR was 2.59 (95% CI: 1.32-5.06).

We also performed separate analyses for microvascular complications. The results are not presented in the tables because

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TABLE 1 Contribution of each food group to the total amount of ultra-processed foods consumed in the CARTaGENE study cohort (*n=683*).

Food groups (n= 37)	Contribution to total ultra-processed foods intake (%) *	Daily amount consumed mean g/d (SD)
Beverages (n=7)		
Dairy beverages	4.2	11.6 (38.8)
Soft/isotonic drinks	51.2	141.8 (384.3)
Fruit drinks	3.1	8.5 (54.4)
Solid Foods (n = 30)		
Processed meat	4.8	13.3 (30.9)
Fast food and ready to eat	10.8	29.9 (32.9)
Breakfast cereals	3.7	10.3 (16.2)
Cookies, biscuits, muffins, and cake	10.4	28.7 (40.0)
Potato chips and salty snacks	3.0	8.2 (9.7)
Confectionery and chocolate	2.0	5.4 (9.5)
Ketchup, salad dressing and similar	3.9	10.7 (13.5)
Ice-cream	1.9	5.3 (9.8)
Jelly and jams products	1.2	3.2 (6.6)
Total	100	276.9 (421.0)

*Contribution (%) of each food group/beverage to the total consumption of ultra-processed food was calculated by dividing the amount (g/d) of each food group by the total amount of ultra-processed foods (g/d) multiplied by 100.

of the small sample size. For micro complications, there were 37 individuals in group HUD, and out of these individuals, only 8 individuals developed the micro complication with an adjusted HR of 2.64 (95% CI: 1.06 – 6.54) (Supplementary Table 2).

Moreover, two sensitivity analysis showed similar results, suggesting that participants in the depressive symptoms and UPFs consumption groups had higher hazard ratios for developing diabetes complications than those with either condition alone (Supplementary Tables 3, 4).

4 Discussion

In this prospective study, we examined the associations between UPFs consumption, depressive symptoms, and the risk of developing T2D complications among middle-aged adults by linking survey data with administrative data. We found that individuals with depressive symptoms and higher consumption of UPFs at baseline had a higher risk of developing T2D related micro-and macro complications in a model adjusted for sex and age as compared to those with neither condition, and this risk estimate was higher than those with depressive symptoms only and those with high UPF consumption only. Further, when depressive symptoms and higher consumption of the UPFs group were controlled for additional confounders in the fully adjusted model, the HRs were lowered and included 1.00 in the CI. However, when depressive symptoms and antidepressant medication use were combined as indicators for depression, then the combination of both resulted in the CI that did not include 1.00 in the fully adjusted model. These results suggest an interaction between depression and UPFs consumption in relation to an increased risk of diabetes-related complications.

To our knowledge no study in the past directly investigated this interaction. One study has reported that T2D individuals with food addiction, which is associated with UPFs consumption (33), had a greater prevalence of diabetes retinopathy, neuropathy, nephropathy, and depressive symptoms compared to those without food addictions (11).

There are several pathways in which depression or depressive symptoms may be associated with an increased risk of developing diabetes complications. One of the potential pathways by which depression among T2D individuals might increase the risk of diabetes-related complications is through suboptimal diabetes management (14, 15). It has been reported that individuals with T2D and high depressive symptoms tend to have lower adherence to medication, diet, and exercise than individuals with T2D alone (15). In addition, depression can be accompanied by behavioral changes, such as reduced self-care and medication adherence, increased intake of high-calorie food, smoking, reduced physical activity, and increased sedentary behaviors (15). These behaviors might have more detrimental effects in the context of diabetes, possibly resulting in poor glycemic control, which, in turn, may be associated with an increased risk of complications (15).

Diabetes with comorbid depressive symptoms is associated with increased hypothalamic–pituitary–adrenal axis and sympathetic nervous system activation (14). Further, increased insulin resistance and high concentration of inflammatory markers may lead to complications in individuals with comorbid diabetes and depression (14, 18). Depressive symptoms and UPFs are also independently associated with inflammatory markers such as C-reactive protein, tumor necrosis factor-α, interleukin-1, and interleukin-6 levels (18, 19). UPFs often occur within high obesogenic environments and have higher glycemic loads (18, 19). These diets may induce hyperglycemia, which is associated with increased pro-inflammatory cytokines, including IL-6 and TNF-α, leading to insulin resistance by disruptions in insulin signalling and subsequently might increase the risk of the diabetes complications (13). Besides the nutritional aspects of UPFs, recent concern has emerged on changes in microbiota induced by non-nutritive components, mainly by flavors, emulsifiers, and thickeners, which may provoke gut dysbiosis and initiate inflammation in the gut (34). However, more research is needed to better understand the relative effects of UPFs on diabetes related complication incidence.

Furthermore, antidepressants use is one of the standard treatments for depressive disorders (35). However, certain antidepressants can increase the risk of body weight and poor

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TABLE 2 Baseline characteristics of the study sample.

	LUND (n = 395)	LUD (n = 60)	HUND (n = 191)	HUD (n = 37)	Total (n = 683)
Age, mean (SD)	56.2 (7.5)	55.2 (7.5)	54.5 (7.5)	53.7 (5.9)	55.5 (7.5)
Sex n (%)					
Male	163 (41.3)	18 (30.0)	122 (63.9)	21 (56.8)	324 (47.4)
Female	232 (58.7)	42 (70.0)	69 (36.1)	16 (43.2)	359 (52.6)
Household income n (%)					
Lower income level (<49,999 $)	123 (31.1)	23 (38.3)	55 (28.9)	20 (54.1)	221 (32.4)
Middle income level (50,000 – 149,999 $)	231 (58.5)	33 (55.0)	117 (61.9)	15 (40.5)	396 (58.0)
High income level (>150,000 $)	41 (10.4)	4 (6.7)	19 (9.9)	2 (5.4)	66 (9.7)
Postsecondary education n (%)					
No	89 (22.5)	19 (31.7)	51 (26.7)	15 (40.5)	174 (25.5)
Yes	306 (77.5)	41 (68.3)	140 (73.3)	22 (59.5)	509 (74.5)
Born in Canada n (%)					
No	43 (10.9)	14 (23.3)	11 (5.8)	2 (5.4)	70 (10.2)
Yes	352 (89.1)	46 (76.7)	180 (94.2)	35 (94.6)	613 (89.8)
Ethnicity n (%)					
Other	25 (6.3)	10 (16.7)	6 (3.1)	5 (10.9)	60 (6.7)
White	370 (93.7)	50 (83.3)	185 (96.9)	32 (86.5)	637 (93.3)
Marital status n (%)					
Married/partner	270 (68.4)	38 (63.3)	128 (67.0)	26 (70.3)	462 (67.6)
Single	53 (13.4)	9 (15.0)	31 (16.2)	7 (18.9)	100 (14.6)
Divorced/separated/widowed	72 (18.5)	13 (21.7)	32 (16.8)	4 (10.8)	121 (17.7)
Daily alcohol consumption n (%)					
No	342 (86.6)	55 (91.7)	179 (93.7)	35 (94.6)	611 (89.5)
Yes	53 (13.4)	5 (8.3)	12 (6.3)	2 (5.4)	72 (10.5)
Smoking status n (%)					
Daily and occasional	45 (11.4)	11 (18.3)	38 (19.9)	8 (21.6)	102 (14.9)
Past smoking	184 (46.6)	19 (31.7)	82 (42.9)	16 (43.2)	301 (44.1)
Never smoking	166 (42.0)	30 (50.0)	71 (37.2)	13 (35.1)	280 (41.0)
Physical activity n (%)					
Yes	152 (38.5)	17 (28.3)	83 (43.5)	9 (24.3)	261 (38.2)
No	243 (61.5)	43 (71.7)	108 (56.5)	28 (75.7)	422 (61.8)
UPF consumption grams/day, mean (SD)	112.0 (49.7)	118.7 (46.8)	601.8 (628.0)	615.2 (478.2)	276.9 (421.0)
BMI, mean (SD)	27.8 (5.4)	29.0 (6.6)	29.8 (5.9)	31.0 (6.2)	28.6 (5.9)
Diabetes complication n (%)	52 (13.2)	10 (16.7)	34 (17.8)	9 (24.3)	105 (15.4)

Results reported as mean ± SD for continuous data and n (%) for categorical data.

LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; UPFs, Ultra-processed foods.

TABLE 3 Results of Cox regression for UPFs consumption and depression assessed using PHQ9 and antidepressant for incident T2D complications.

Groups	N	Unadjusted Model, HR (95% CI)	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI) *
Model 1: UPFs consumption univariate association				
Lower tertile of UPFs consumption	227	Reference	Reference	Reference
Middle tertile of UPFs consumption	228	0.99 (0.60 -1.63)	1.08 (0.65 -1.79)	1.15 (0.69 – 1.93)
Higher tertile of UPFs consumption	228	1.32 (0.83– 2.21)	1.54 (0.95 -2.50)	1.56 (0.92 - 2.62)
Model 2: Depression univariate association				
PHQ-9 summary score (< 6) Low	586	Reference	Reference	Reference
PHQ-9 summary score (>= 6) High	97	1.57 (0.95 -2.59)	1.63 (0.98 – 2.71)	1.45 (0.84 – 2.51)
Model 3: Antidepressant use univariate association				
Anti-depressant use NO	625	Reference	Reference	Reference
Antidepressant use YES	58	1.54 (0.86- 2.78)	1.57 (0.87 – 2.81)	1.61 (0.86 – 3.00)

UPFs, Ultra-processed foods; PHQ-9, Patient Health Questionnaire-9.
*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.

glycemic control (35), which might lead to diabetes-related complications (36). Our study shows that; when antidepressant use and depressive symptoms were combined with high UPFs consumption, the risk of diabetes complications was higher than the depressive symptoms combined with high UPFs consumption.

4.1 Strengths and limitation

Strengths of this study include its prospective design, the use of two different measures for depression, the combined use of survey data with administrative health data, and adjustment for potential confounders. Further, two sensitivity analyses using two

TABLE 4 Results of Cox regression for UPFs consumption and depression assessed using PHQ9 and antidepressant joint association for incident T2D complications.

Model 1 UPFs consumption lower & middle tertile combined and depressive symptoms joint association					
Groups	N	Incident complications (N)	Unadjusted	Age- and Sex-Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI)
LUND	395	52	Reference	Reference	Reference
LUD	60	10	1.49 (0.75- 2.94)	1.48 (0.75 – 2.94)	1.39 (0.69- 2.80)
HUND	191	34	1.29 (0.83 -2.00)	1.40 (0.90 – 2.20)	1.41 (0.88 - 2.25)
HUD	37	9	2.07 (1.02 – 4.20)	2.43 (1.18 – 4.99)	2.07 (0.91 – 4.70)
Model 2 UPFs consumption lower & middle tertile combined and depressive symptoms/Antidepressant use joint association					
LUNDA	367	49	Reference	Reference	Reference
LUDA	88	13	1.30 (0.70 - 2.42)	1.29 (0.70 - 2.40)	1.30 (0.69 – 2.45)
HUNDA	179	29	1.16 (0.73 -1.84)	1.25 (0.78 - 2.01	1.27 (0.78 – 2.09)
HUDA	49	14	2.37 (1.30 – 4.30)	2.82 (1.53 – 5.18)	2.59 (1.32 – 5.06)

*Fully adjusted model is adjusted for the following variables: age, sex, household income, education, ethnicity, born in Canada, smoking status, physical activity, daily alcohol consumption and BMI.
LUND, lower/middle tertile of ultra-processed foods consumption and low depressive symptoms; LUD, lower/middle tertile of ultra-processed foods consumption and high depressive symptoms; HUND, higher tertile of ultra-processed foods consumption and low depressive symptoms; HUD, higher tertile of ultra-processed foods consumption and high depressive symptoms; LUNDA, lower and middle tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant use; LUDA, lower and middle tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant use; HUNDA, higher tertile of ultra-processed foods consumption and low depressive symptoms and no antidepressant; HUDA, higher tertile of ultra-processed foods consumption and high depressive symptoms or antidepressant.

different response rates on UPFs consumption were conducted to assess the robustness of the study findings. Acknowledging that the data is 13 years old, we also acknowledge the general challenge of low response rates to food frequency questionnaires in epidemiological studies focusing on nutrition and health outcomes. Despite the age of the data, this study plays a crucial role in addressing a gap in the literature. By examining the combined impact of depression and UPF consumption, two significant modifiable risk factors, it provides valuable insights into how they jointly influence the risk of diabetes related complications.

There are also various limitations that should be noted. First, the C-DHQ II used in this study was designed to evaluate the intake of major food groups, energy, and macronutrients, not specifically to collect data about the NOVA classification of UPFs consumption. Further, there is also limitation related to NOVA classification. Because of its complex and multidimensional definition of levels of food processing, there is a potential for introducing ambiguity and variations in interpretation related to UPF (37). Assessment of the diet intake was self-reported and only measured at the baseline; therefore, it might be possible that participants change their intake of ultra-processed foods during the follow-up. Participants of the CaG study were volunteers in a nutrition component, and thus it may be possible that these individuals were more interested in nutritional issues and healthy lifestyles than the general population. And it might be possible that their consumption of UPFs may be lower compared to the general population, which may underestimate the risk investigated in our study. Depressive symptoms were assessed at baseline only. The PHQ-9 is a self-report scale that measures symptoms of depression experienced in the past two weeks and does not consider the history and treatment of depression. Given that depressive symptoms were not measured during the follow-up, symptoms may vary and change over time. Further, another important limitation is that our analysis does not eliminate the possibility that part of this association stems from a shared pathophysiological factor — specifically, the impact of UPF consumption on both diabetes progression/complications and the onset of depression (9). Moreover, there is also limitation with administrative data. In Canada administrative hospital data are produced by health professionals who review, abstract, and code information from inpatient charts following hospital discharge. One of issue with the administrative data is the undercoding of diabetes and its related complications by physicians which can lead to an incomplete representation of the true prevalence (38).

The individual group sizes were small, and therefore studies with large sample size are needed to replicate the findings. CaG participants were mostly white participants (93.3%) and metropolitan; as a result, generalization of our findings should be made with caution.

4.2 Conclusion

To conclude, our study suggests that individuals with co-occurring depression and high UPF consumption may represent a group at risk of developing T2D complications. Thus, this group possibly be benefit from greater monitoring and preventive care. However, future research is needed to disentangle the mechanisms linking depression and UPF consumption to T2D complications. In addition, further research is required to replicate these findings in large samples with longer follow-up periods.

Data availability statement

Publicly available datasets were analyzed in this study. Data can be obtained from the Cartagene cohort study.

Ethics statement

The studies involving humans were approved by Douglas Research Ethics Board, Montreal, QC Canada. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NS: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. AS: Conceptualization, Formal Analysis, Methodology, Writing – original draft. AB: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. SD: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. HR-Q: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1273433/full#supplementary-material

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Network analysis of depressive and anxiety symptoms in older Chinese adults with diabetes mellitus

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Background: The move away from investigating mental disorders as whole using sum scores to the analysis of symptom-level interactions using network analysis has provided new insights into comorbidities. The current study explored the dynamic interactions between depressive and anxiety symptoms in older Chinese adults with diabetes mellitus (DM) and identified central and bridge symptoms in the depression-anxiety network to provide potential targets for prevention and intervention for depression and anxiety.

Methods: This study used a cross-sectional design with data from the 2017–2018 wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). A regularized partial correlation network for depressive and anxiety symptoms was estimated based on self-reported scales completed by 1685 older adults with DM aged 65 years or older. Depressive and anxiety symptoms were assessed using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) and the Seven-Item Generalized Anxiety Disorder Scale (GAD-7), respectively. Expected influence (EI) and bridge expected influence (BEI) indices were calculated for each symptom.

Results: According to cutoff scores indicating the presence of depression and anxiety, the prevalences of depression and anxiety in our sample were 52.9% and 12.8%, respectively. The comorbidity rate of depression and anxiety was 11.5%. The six edges with the strongest regularized partial correlations were between symptoms from the same disorder. "Feeling blue/depressed", "Nervousness or anxiety", "Uncontrollable worry", "Trouble relaxing", and "Worry too much" had the highest EI values. "Nervousness or anxiety" and "Everything was an effort" exhibited the highest BEI values.

Conclusion: Central and bridge symptoms were highlighted in this study. Targeting these symptoms may be effective in preventing the comorbidity of depressive and anxiety symptoms and facilitate interventions in older Chinese adults with DM who are at risk for or currently have depressive and anxiety symptoms.

KEYWORDS

depression, anxiety, network analysis, people with diabetes, older adults

1 Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia and caused by both genetic and environmental factors (1). The number of adults with DM worldwide is increasing rapidly, and according to the International Diabetes Federation (IDF) report, this number has currently reached 537 million and is expected to increase to 643 million by 2030 (2). China has the largest number of people with diabetes in the world, with about 140 million in 2021 (3). With the increasingly serious problem of population aging in China, the proportion of people over 65 years with diabetes is increasing, and older adults have become the primary demographic of people with diabetes (4). Furthermore, according to the guideline for the management of diabetes mellitus in older people in China (2021 edition), type 2 diabetes mellitus (T2DM) is predominant in the over 65-year-old Chinese population with diabetes, while type 1 diabetes mellitus (T1DM) occurs in the minority (5). In this study, however, diabetes refers to both type 1 and type 2 diabetes.

DM is a chronic non-communicable disease that seriously threatens mental health. The incidence of depression and anxiety disorders (assessed by the Composite International Diagnostic Interview) in people with diabetes is much higher than in the population at large over time, and is 60% higher for major depressive disorder and 123% for general anxiety disorder (6). In particular, the complex condition of older adults, the decline in their physical function and immune systems, long-term monitoring of blood glucose and diet control, and the increased economic pressure resulting from long-term drug treatment, together increase the susceptibility of older adults with DM to comorbid depression and anxiety (7, 8). DM interacts bidirectionally with depression and anxiety. On the one hand, as mentioned above, DM increases the prevalence of depression and anxiety; on the other hand, depression and anxiety can be independent risk factors for the occurrence and development of DM and are known to predict the incidence of later DM (9, 10).

The comorbidity of depression and anxiety is also common in older adults with diabetes. It has been reported that approximately 30% of those with major depressive disorder (MDD) and roughly 50% of those with general anxiety disorder (GAD) meet the criteria for a dual MDD/GAD diagnosis in a sample of people with diabetes with mean age of 57.8 years (6). In the general population, the presence of either depression or anxiety often increases the risk of developing the other (11), and the comorbidity of depression and anxiety results in more severe symptoms, fewer effective treatments are available, and the prognosis is poorer than for either disorder alone (12). Furthermore, people with diabetes with depression and anxiety also have an increased risk of diabetes complications, have a poor prognosis, poor blood glucose control and have lower quality of life (13–15). Therefore, the comorbidity of depression and anxiety in older adults with DM is an important research topic.

Most prior studies on comorbid depression and anxiety have been based on the assumption that anxiety and depression are holistic psychopathological constructs and have generally studied them at a disorder level, using the total score of the corresponding measurement scale to evaluate the severity of each disorder. However, such an approach ignores the interactions between individual symptoms (i.e., items of the measurement scales) and masks the heterogeneity of the various symptoms (16, 17). The pervasive use of sum-scores (i.e., summing the scores for each item) has hampered progress in key research fields such as the search for more effective intervention targets for anxiety and depression (18). Therefore, to better understand the comorbidity of depression and anxiety in older adults with DM and identify possible targets for interventions, we need to adopt a more fine-grained research methodology such as the analysis of individual symptoms and their interactions. Notably, in this study, unless otherwise stated, the term "symptom" refers to items from the scales rather than clinical diagnoses.

Network analysis is an emerging, data-driven approach that provides a new perspective for understanding psychopathology and comorbidity. It permits the structure of mental disorders and the interactions between individual symptoms to be investigated and visualized (19–21). Network analysis is based on the assumption that psychiatric disorders emerge from active interactions between various symptoms, and different symptoms may actively reinforce or inhibit other symptoms, rather than simply viewing symptoms as reflecting underlying latent variables (20, 21). The high comorbidity between depression and anxiety means that the specific symptoms of one psychiatric disorder will increase the risk of developing the other. It is both reasonable and feasible, therefore, to regard them as a complex network comprising the interactions of different symptoms (22, 23). Network analysis helps identify relatively important relationships between the individual symptoms of anxiety and depression. A centrality index can be calculated to quantify the influence of individual symptoms in the network, and determine critical central symptoms that are more likely to activate other symptoms and play major roles in the onset and/or maintenance of the mental disorder (24). Network analysis also calculates a bridge centrality index to identify important bridge symptoms that can facilitate the contagion of one disorder to another, leading to the development and maintenance of comorbidity (25).

Prior studies have used network analysis to explore comorbid symptom networks of anxiety and depression in different populations, such as people with epilepsy (26, 27), older people with functional impairment (28), nursing students (29, 30), people with MDD (31), and people with anxiety disorders (32, 33). However, the results of those studies have been inconsistent. One study based on network analysis examined diabetes distress and depressive and anxiety symptoms in middle-aged Canadians, and findings revealed strong connections between the anxiety symptom of "trouble relaxing" and the depressive symptom of "sleep

Abbreviations: DM, diabetes mellitus; CLHLS, Chinese Longitudinal Healthy Longevity Survey; EI, expected influence; BEI, bridge expected influence; IDF, International Diabetes Federation; MDD, major depressive disorder; GAD, general anxiety disorder; CESD-10, 10-item Center for Epidemiologic Studies Depression Scale; GAD-7, Seven-Item Generalized Anxiety Disorder Scale; GGM, Gaussian graphical model; LASSO, least absolute shrinkage and selection operator; EBIC, extended Bayesian information criterion; CI, confidence interval; CS, correlation stability.

problems," as well as between the anxiety symptom of "restless" and the depressive symptom of "psychomotor agitation/retardation" (34). However, to date, depressive and anxiety symptoms in older Chinese adults with DM have not been studied using network analysis. Thus, despite the high prevalence of comorbid depression and anxiety in older adults with diabetes, which seriously affects their mental health and quality of life, these comorbid psychiatric disorders have not received due attention. Considering the data-driven nature of network analysis, the examination of different study populations with various symptoms of depression and anxiety can lead to heterogeneous results. Additionally, the features of symptoms are influenced by sociocultural factors, which can result in variations across countries. For example, culture impacts the experience of depression symptoms and depression is highly stigmatized in some cultures (35), while traditional Chinese social and cultural factors have been reported to potentially serve as protective factors against depression (36). Hence, findings based on other samples are not necessarily applicable to older Chinese adults with DM, and studies are warranted to investigate the comorbidity of depression and anxiety in this population.

The current study is the first to use network analysis to construct a symptom-level network of depression and anxiety in older Chinese adults with DM. We aimed to explore the dynamic interrelationships between depressive and anxiety symptoms. We also aimed to identify central symptoms and bridge symptoms to identify potential targets for the prevention and intervention of anxiety and depression in older Chinese adults with DM.

2 Materials and methods

2.1 Study design and participants

This study used a cross-sectional design based on data from the 2017–2018 wave of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). The CLHLS is a nationally representative, population-based, ongoing survey focusing on older adults in mainland China. Following the baseline survey in 1998, the CLHLS has conducted seven waves of serial follow-up surveys in 2000, 2002, 2005, 2008–2009, 2011–2012, 2014, and 2017–2018. Due to the need for a representative sample, the CLHLS adopted a multi-stage disproportionate and targeted random sampling method (37). The participants were older adults (aged 65 years and above) and their children (aged 35–64 years) selected from about half of the counties and cities in 23 provinces, municipalities, and autonomous regions across China. More details about the CLHLS can be found elsewhere (38–40). The 2017–2018 wave of the CLHLS included 15,874 older adults aged 65 years and over (41). Following the example of previous studies (42, 43), older adults were defined in this study as those aged more than 65 years old. The inclusion criteria for this study were (1): validated age ≥ 65 (2), DM diagnosed by a hospital, and (3) complete data for all depressive and anxiety items. Participants with missing values or answers of "not able to answer", "don't know", or "not applicable" in any scale items of interest were excluded. We focused on the general population of older adults with DM with a full range of symptom severity levels of depression and anxiety, such as ranging from "not depressed" to "severely depressed" rather than a clinical sample with formal diagnoses of depression and/or anxiety. Therefore, there were no other eligibility requirements for participants in this study. Finally, a total of 1685 older adults were included in the current study. The gender distribution of the included participants did not differ significantly from those excluded. However, there was a significant difference in age between included participants versus those excluded ($p < 0.001$). All methods were carried out in accordance with the Declaration of Helsinki and with relevant guidelines and regulations. Written informed consent was obtained from all participants included in this study. The ethical approvals of the CLHLS study were obtained from the Biomedical Ethics Committee, Peking University (IRB00001052–13074) and the Institutional Review Board, Duke University (Pro00062871). The CLHLS dataset used in this study is open, public, and free.

2.2 Measures

2.2.1 10-item center for epidemiologic studies depression scale

The CESD-10 is a self-report scale used to measure how often each symptom of depression occurred during the past week and has been validated in Chinese older adults (44, 45). It comprises 10 items, each of which is rated using a 4-point Likert-type scale ranging from 0 = *never* to 3 = *always* (46). The total score on the CESD-10 can range from 0 to 30, with higher scores representing more severe symptoms of depression. In accordance with previous studies (45–47), a cutoff score of 10 was used to indicate the possible presence of depression. The Cronbach's α coefficient of this scale was 0.79 in the current study, indicating good internal consistency.

2.2.2 Seven-item generalized anxiety disorder scale

The GAD-7 is a reliable self-report scale used to assess the frequency of the most important diagnostic symptoms of GAD over the previous two weeks (48). It comprises seven items, each of which is rated using a 4-point Likert-type scale ranging from 0 = *not at all* to 3 = *nearly every day*. The total score for the GAD-7 can range from 0 to 21 with higher scores indicating more severe anxiety symptoms. Cutoff scores of 5, 10, and 15 represent mild, moderate, and severe levels of anxiety (48, 49). The Cronbach's α coefficient of the GAD-7 was 0.91 in our sample, indicating excellent internal consistency.

2.3 Statistical analysis

2.3.1 Network estimation

The program RStudio (version 4.3.1) was used to construct the network structure and calculate the expected influence (EI) and bridge expected influence (BEI) of each node. The R package *qgraph* was used to build and visualize the depression-anxiety network (50). The network was estimated via the Gaussian graphical model (GGM), which is an undirected network (51). According to a

tutorial (52), we constructed the network based on Spearman correlations instead of polychoric correlations because of the ordinal nature of item scores, possibly skewed data distribution, and low frequency cross tables leading to biased polychoric correlations, as in previous studies (53, 54). In the constructed network, nodes represented symptoms and were divided into the depression community and the anxiety community; each edge represented the partial correlation between two nodes, with the confounding effects of all other nodes in the network eliminated by statistical controls (55). To regularize the network, a combination of least absolute shrinkage and selection operator (LASSO) and the extended Bayesian information criterion (EBIC) was adopted to shrink all the edges and attenuate small correlations to zero (52, 56, 57). We set the EBIC hyperparameter to 0.5 to determine the optimal network model, thereby creating a sparse and interpretable network (52, 56).

2.3.2 Centrality and bridge centrality estimation

The R packages *qgraph* and *networktools* were used to calculate the centrality index (i.e., EI) and bridge centrality index (i.e., BEI) of each node to determine important central and bridge nodes, respectively (25, 50). The EI index was chosen because it outperforms other centrality indices when networks contain both positive and negative edges (58, 59). Node EI is the sum of non-absolute weights of all edges directly connected to a given node (58). Compared with other centrality measures such as node strength, the sum of the absolute value of its connections with other nodes in the network, EI can distinguish between positive and negative edges, and the signs of edge weights are important when assessing the nature and strength of a node's cumulative influence within the network (e.g., the overall role of activating or remission effect on other nodes) (58). A higher EI value indicates the node is more positively associated with other nodes and exerts more influence on the entire network. Node BEI is the sum of the non-absolute weights of all edges directly linking a given node to nodes in another community, differing from bridge strength which sums the absolute values of the weights, and thus this index is the better option for networks containing both negative and positive edges (25). A higher BEI value suggests the node might contribute more to comorbidity and presents a higher risk of contagion from the current community to another community.

2.3.3 Network accuracy and stability estimation

R package *bootnet* was used to estimate the robustness of the network by testing the accuracy of edge weights and the stability of the centrality and bridge centrality indices (55), to ensure the accuracy and replicability of the network analysis. The accuracy of the edge weights was assessed by computing 95% confidence intervals (CIs) using non-parametric bootstrapping (1000 bootstrapped samples); the narrower the 95% CI for each edge weight, the more accurate the edge weight estimation (60). The bootstrapped difference tests ($\alpha = 0.05$, 1000 bootstrapped samples) were conducted to evaluate the differences between the edge weights of node pairs based on 95% CIs, with two edges being statistically different if zero was not included in the CI of the difference between the two edges (60, 61). The stabilities of EI and BEI were assessed by case-dropping bootstrapping (1000 bootstrapped samples) (55). We quantified stability using the correlation stability coefficient (CS-coefficient). The CS-coefficient should not be less than 0.25 and should preferably be greater than 0.5, which represents ideal stability (55). Subsequently, the differences between two node EIs or two node BEIs were also tested by bootstrapped difference tests ($\alpha = 0.05$, 1000 bootstrapped samples) based on 95% CIs. Similarly, the two EIs or two BEIs were considered significantly different if zero was not included (55, 60).

3 Results

3.1 Descriptive statistics

The mean age of the included participants (N = 1,685) was 80.53 ± 9.98 years (mean ± standard deviation, range = 65–109 years); of whom 748 (44.4%) were male, 758 (45.0%) were registered urban residents, 648 (38.5%) resided in the city area, 872 (51.8%) were married and living with their spouses, 957 (56.8%) slept less than 7 h each day, 1092 (64.8%) were using antidiabetic medications, and 232 (13.8%) perceived diabetes to affect daily life rather seriously. The average years of education was 4.96 with the means of all non-missing values used to impute the missing values. The demographic characteristics of the sample are shown in Table 1. The prevalences of depression (defined as CESD-10 total score ≥ 10) and anxiety (defined as GAD-7 total score ≥ 5) in the present sample were 52.9% and 12.8%, respectively. Additionally,

TABLE 1 Demographic characteristics of the sample (N = 1,685).

Variable	Mean (SD) or n (%)
Age (years)	80.53 (9.98)
Sex	
Male	748 (44.4%)
Female	937 (55.6%)
Hukou	
Registered urban residents	758 (45.0%)
Registered rural residents	924 (54.8%)
Missing	3 (0.2%)
Current residence region	
City	648 (38.5%)
Town	465 (27.6%)
Rural	572 (33.9%)
Education (years)	4.96 (4.69)
Ethnicity	
Han	1475 (87.5%)
Hui	13 (0.8%)

(Continued)

TABLE 1 Continued

Variable	Mean (SD) or n (%)
Zhuang	30 (1.8%)
Yao	1 (0.1%)
Man	6 (0.4%)
Others	4 (0.2%)
Missing	156 (9.3%)
Current marital status	
Currently married and living with spouse	872 (51.8%)
Separated	27 (1.6%)
Divorced	7 (0.4%)
Widowed	754 (44.7%)
Never married	11 (0.7%)
Missing	14 (0.8%)
Sleep duration each day	
≤7 h	957 (56.8%)
≥8 h	718 (42.6%)
Missing	10 (0.6%)
Smoking or not at present	
Yes	204 (12.1%)
No	1466 (87%)
Missing	15 (0.9%)
Drinking or not at present	
Yes	189 (11.2%)
No	1467 (87.1%)
Missing	29 (1.7%)
Exercising or not at present?	
Yes	675 (40%)
No	987 (58.6%)
Missing	23 (1.4%)
Whether to use the antidiabetic medications	
Yes	1092 (64.8%)
No	570 (33.8%)
Missing	23 (1.4%)
Whether diabetes affects daily life	
Rather serious	232 (13.8%)
More or less	715 (42.4%)
No	712 (42.3%)
Missing	26 (1.5%)

the comorbidity rate of depression and anxiety was 11.5%. Table 2 shows the abbreviations, mean scores, standard deviations, EIs (raw values), and BEIs (raw values) for each symptom of depression and anxiety in the present network.

3.2 Network structure

Figure 1 shows the network structure of depression and anxiety symptoms. The network comprised 17 nodes and was estimated with 62.5% (85 of 136) non-zero edges. All edges had positive weights. The six strongest edges that exhibited relatively strong regularized partial correlations were identified. Four of these were in the depression community, those being the edges between CESD2 "Difficulty with concentrating" and CESD4 "Everything was an effort" (weight = 0.26), between CSED8 "Loneliness" and CSED9 "Inability to get going" (weight = 0.30), between CSED1 "Feeling bothered" and CSED3 "Feeling blue/depressed" (weight = 0.33), and between CSED5 "Hopelessness" and CSED7 "Lack of happiness" (weight = 0.39). The other two were in the anxiety community, those being the edges between GAD2 "Uncontrollable worry" and GAD3 "Worry too much" (weight = 0.29) and between GAD5 "Restlessness" and GAD6 "Easily annoyed/irritated" (weight = 0.30). Although weaker, there were several edges linking depression nodes and anxiety nodes, hereafter referred to as bridge edges. Notably, we enumerated these bridge edges based on the relative size of edge weights rather than using a cutoff value or statistical comparisons using bootstrapped difference tests. GAD1 "Nervousness or anxiety" was positively connected to: CESD10 "Sleep disturbances" (weight = 0.10), CESD3 "Feeling blue/depressed", CESD4 "Everything was an effort", CESD5 "Hopelessness", and CESD6 "Feeling nervous/fearful" (weights = 0.05 from CESD3 to CESD6). CESD4 "Everything was an effort" was also positively associated with GAD3 "Worry too much" (weight = 0.06). Supplementary Table 1 gives all the edge weights within the depression-anxiety network.

3.3 Central symptoms and bridge symptoms

Figure 2 shows the EI indices of each node to assess their relative importance in the network. The five nodes with the highest EIs were CESD3 "Feeling blue/depressed" (EI = 1.12), GAD1 "Nervousness or anxiety" (EI = 1.05), GAD2 "Uncontrollable worry" (EI = 1.05), GAD4 "Trouble relaxing" (EI = 1.04), and GAD3 "Worry too much" (EI = 1.02), indicating that those were the most influential symptoms. Figure 3 shows the raw BEI values of each node. The node GAD1 "Nervousness or anxiety" and the node CESD4 "Everything was an effort" had the highest BEI values overall (BEI = 0.38 and 0.13, respectively), with the node GAD1 "Nervousness or anxiety" having the highest BEI by far. This indicates that these two nodes represent critical bridge symptoms.

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TABLE 2 Abbreviations, mean scores, standard deviations, EIs (raw values), and BEIs (raw values) for each symptom in the depression-anxiety network.

Symptoms	Abb	M	SD	EI	BEI
Depression symptoms (CESD-10)					
Feeling bothered	CESD1	0.79	0.58	0.90	0.05
Difficulty with concentrating	CESD2	1.02	0.70	0.68	0.06
Feeling blue/depressed	CESD3	0.73	0.58	1.12	0.09
Everything was an effort	CESD4	1.06	0.73	0.85	0.13
Hopelessness	CESD5	1.29	0.88	0.66	0.05
Feeling nervous/fearful	CESD6	0.65	0.60	0.84	0.08
Lack of happiness	CESD7	1.45	0.92	0.71	0.02
Loneliness	CESD8	0.64	0.65	0.92	0.04
Inability to get going	CESD9	0.50	0.60	0.90	0.10
Sleep disturbances	CESD10	1.36	0.77	0.39	0.13
Anxiety symptoms (GAD-7)					
Nervousness or anxiety	GAD1	0.32	0.56	1.05	0.38
Uncontrollable worry	GAD2	0.23	0.51	1.05	0.05
Worry too much	GAD3	0.28	0.54	1.02	0.11
Trouble relaxing	GAD4	0.20	0.47	1.04	0.09
Restlessness	GAD5	0.16	0.42	0.92	0.01
Easily annoyed/irritated	GAD6	0.20	0.47	0.89	0.09
Afraid something terrible might happen	GAD7	0.12	0.38	0.65	0.03

Abb, abbreviation; M, mean; SD, standard deviation; EI, expected influence; BEI, bridge expected influence; CESD-10, 10-item Center for Epidemiologic Studies Depression Scale; GAD-7, seven-item Generalized Anxiety Disorder scale.

3.4 Network accuracy and stability

As shown in Supplementary Figure 1, the bootstrapped 95% CI was narrow, suggesting that the estimation of edge weights was accurate and stable. Supplementary Figure 2 presents the bootstrapped difference test results for the edge weights, indicating that the weights of the six strongest edges were significantly higher than those of 88.1% - 98.8% of the other nodes. The CS-coefficients of EI and BEI were both 0.75, suggesting that the estimations of EI and BEI were both adequately stable (see Figures 4, 5). The bootstrapped difference test for node EIs showed that the EI values of the five central nodes were significantly higher than those of 68.8% - 75% of the other nodes (see Supplementary Figure 3). Supplementary Figure 4 illustrates the bootstrapped difference test for node BEIs, indicating that the BEI values of the two bridge nodes were significantly higher than those of 56.3% - 100% of other nodes.

4 Discussion

To the best of our knowledge, this is the first study to use network analysis to investigate symptom-level interactions between depression and anxiety in a group of older Chinese adults with DM. We found some important connections between individual symptoms. We also identified several influential central and bridge symptoms. These findings may facilitate our understanding of the dynamic interplay of individual symptoms in depression and anxiety, shed light on the pathological mechanisms that underly the development and maintenance of comorbid depression and anxiety, and provide better insights into potential intervention and treatment strategies.

The strongest edges appeared within each mental disorder community rather than in connections between the depressive and anxiety symptom communities. This is consistent with many previous studies that have used network analysis to examine the comorbidity of depression and anxiety and found that the strongest edges were between symptoms from the same disorder (26, 29, 31, 62–65), although they have used different assessment tools. The majority of previous studies have used the nine-item Patient Health Questionnaire (PHQ-9) and the GAD-7 to assess depressive and anxiety symptoms, respectively (26, 29, 62–65), except for Park and Kim's study which used the Beck Depression Inventory and Beck Anxiety Inventory (31). The results of the present study identified four strong connections within the depressive community. Our findings are partly consistent with a prior study that used network analysis to examine insomnia and depressive symptoms (measured by the CESD-10), with the strong edges identified within the depression community of symptoms, i.e., "Loneliness"-"Inability to get going", "Feeling bothered"-"Feeling blue/depressed", and

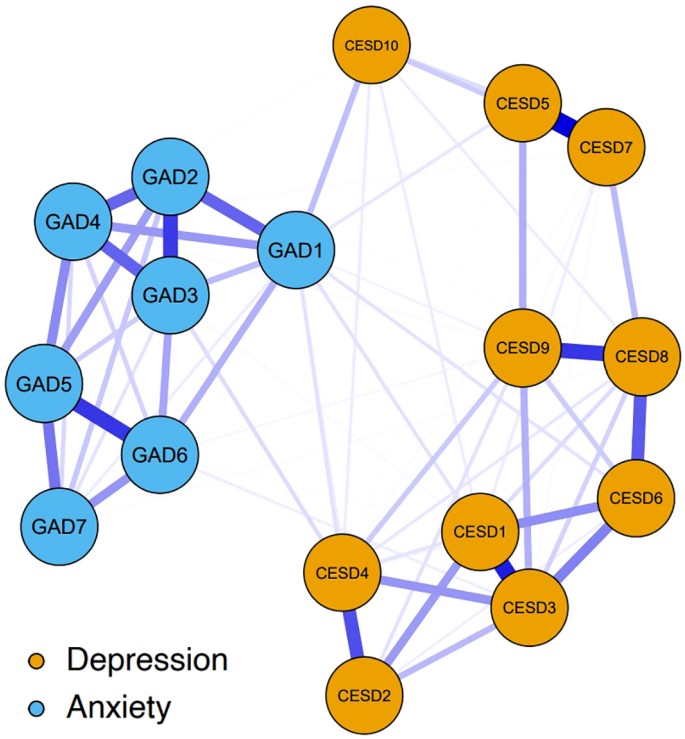

FIGURE 1
The network structure of depression and anxiety symptoms. The yellow nodes denote the depression symptoms (10-item Center for Epidemiologic Studies Depression Scale, CESD-10); the blue nodes denote the anxiety symptoms (seven-item Generalized Anxiety Disorder scale, GAD-7). The specific meanings of each node are shown in Table 1. Blue edges represent positive relations, with thicker and more saturated edges denoting stronger connections between symptom nodes. Nodes with stronger connections are closer to each other. The weights of the edges are provided in Supplementary Table 1.

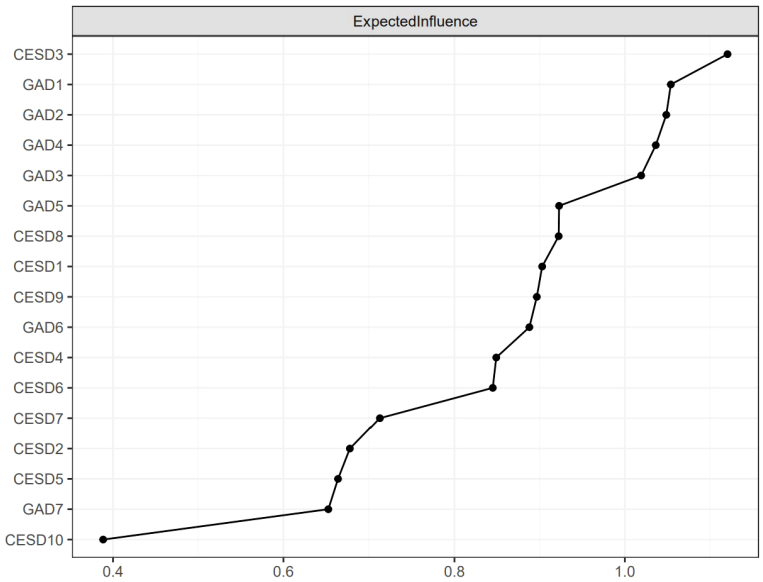

FIGURE 2
The raw values of EI for each node in the present network. The specific meanings of each node are shown in Table 1.

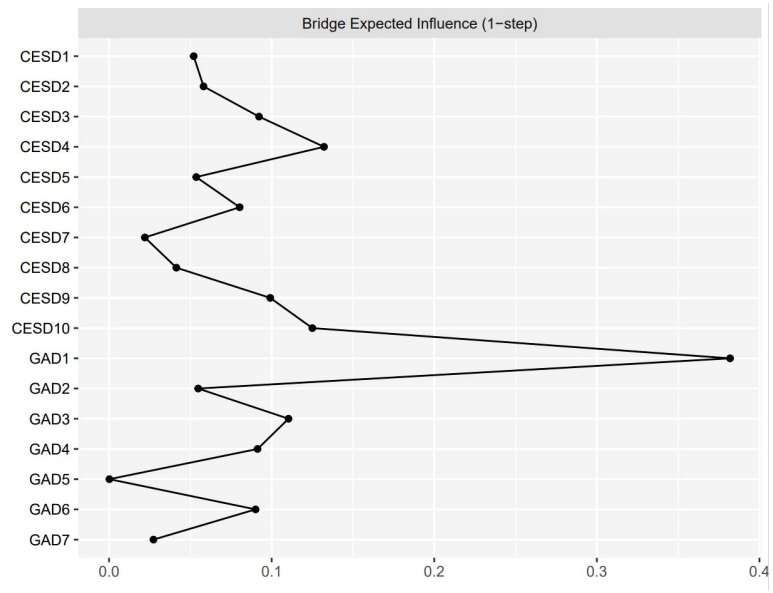

FIGURE 3
The raw values of BEI for each node in the present network. The specific meanings of each node are shown in Table 1.

"Hopelessness"-"Lack of happiness" (66). Additionally, within the anxiety community, the finding that strong edges existed between GAD2 "Uncontrollable worry" and GAD3 "Worry too much" and between GAD5 "Restlessness" and GAD6 "Easily annoyed/irritated" is consistent with prior network analysis studies of comorbid depressive and anxiety symptoms assessed using the PHQ-9 and GAD-7, respectively (29, 62, 64). Together, these findings that the strongest edges existing within each community were expected because, from a theoretical perspective, the associated symptoms from the same community (e.g., depressive symptoms) interact closely with each other to induce mental disorders (e.g., depression) (20).

According to the network theory of psychopathology, EI may be a crucial way to identify influential central symptoms. Nodes with high EI are thought to be critical central symptoms that contribute to the development and maintenance of mental disorders (20, 58). By activating other symptoms in the network, these central symptoms are thought to trigger and maintain the other symptoms and, by extension, the psychopathological networks. The results of this study showed that CESD-3 "Feeling blue/

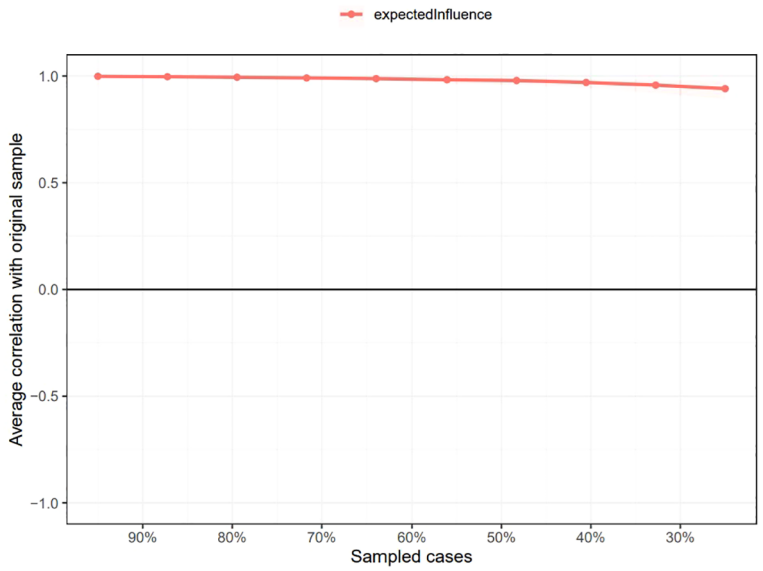

FIGURE 4
Stability of node expected influences in the network. The red bar represents the average correlation between node expected influences in the full sample and subsample with the red area depicting the 2.5th to the 97.5th quantile.

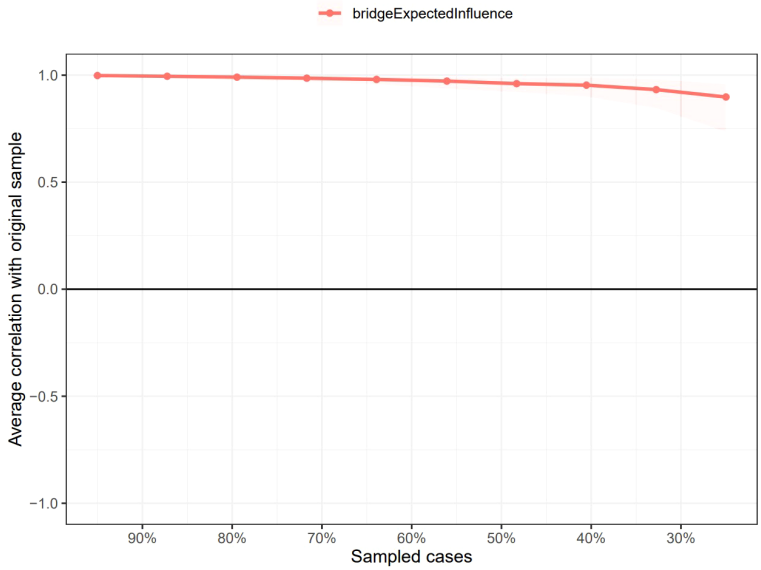

FIGURE 5
Stability of node bridge expected influences in the network. The red bar represents the average correlation between node bridge expected influences in the full sample and subsample with the red area depicting the 2.5th to the 97.5th quantile.

depressed" was the symptom highest in EI, indicating its central role in the depression-anxiety network for Chinese older adults with DM. Similarly, "Depressed or sad mood" was found to be a central symptom, as has been previously reported in network analyses of depressive and anxiety symptoms in adolescents (67), psychiatric samples (mood, anxiety, personality, and psychotic disorders) (62), nursing students (30), and people diagnosed with both depression and anxiety disorders (68). The majority of these studies used PHQ-9 and GAD-7 to measure depressive and anxiety symptoms, respectively (62, 67, 68), except for Bai et al.'s study which used two-item PHQ and GAD-7 (30). Our findings are also consistent with other network analysis studies of individuals with elevated depressive symptoms and shift workers (with depressive symptoms assessed using the Inventory of Depressive Symptomatology and CESD-10, respectively) that reported that feeling depressed was one of the central symptoms (17, 66). Therefore, the central symptom of "Feeling blue/depressed" may be consistent across different populations; nonetheless, it should be examined further. Additionally, depressed or sad mood has been reported to be important for the prediction of MDD and increases the incidence of MDD (69), which is in line with our finding. Furthermore, prior studies have revealed that DM is associated with an increased risk of incident depressed mood in 70-to 79-year-old adults with DM (70). These lines of evidence support our finding that "Feeling blue/depressed" is critical to the development and maintenance of the depression-anxiety network in older adults with DM.

The symptom GAD2 "Uncontrollable worry" was another predominant central symptom (the second highest in EI overall) that emerged in the depression-anxiety network, suggesting that it may also contribute to the activation of other symptoms and the maintenance of the depression-anxiety network in older adults with DM. This is consistent with prior studies that have identified "Uncontrollable worry" as a central node in the network of depression and anxiety symptoms (measured by the PHQ-9 and GAD-7, respectively) in different populations (college students, patients diagnosed with both depression and an anxiety disorder, clinicians) based on strength centrality (65), strength and EI centrality (68), or EI centrality (64), respectively. In addition, we also found that GAD1 "Nervousness or anxiety", GAD4 "Trouble relaxing", and GAD3 "Worry too much" were high in EI and were thus identified as central symptoms. These findings are partially consistent with prior studies that have shown that "Trouble relaxing" (or "Unable to relax") and "Excessive worry" (or "Too much worry") had high centrality indices for the populations studied (27, 62, 64, 65, 68). The aforementioned studies all used the PHQ-9 and the GAD-7 to assess depressive and anxiety symptoms except for Gauld et al. (27) who used the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and the GAD-7. However, GAD1 "Nervousness or anxiety" was not found to be a central symptom in prior studies. This inconsistency may be the result of the use of different study samples, e.g., older adults with DM in our study versus a psychiatric sample in Beard et al.'s study (62), people with epilepsy in Gauld et al.'s study (27), and people with both depression and an anxiety disorder in Kaiser et al.'s study (68). The characteristics of older adults with DM differ from those of individuals with neurological or psychiatric disorders. Serious diabetes complications such as macrovascular complications (e.g., cardiovascular disease) and microvascular complications (e.g., kidney disease and diabetic retinopathy and neuropathy) (71), as well as diabetes-related distress such as hypoglycemia induced by insulin treatment (72, 73), are all intractable problems for people with DM. In particular, the potential pathophysiology of DM in older adults is worse because of the adverse effects of aging on metabolic regulation; aging effects can interact with diabetes to accelerate the progression of diabetic complications (74). Additionally, older adults are more susceptible to hypoglycemia

and its consequences such as falls and consequent fractures, cardiovascular events, and mortality (75–77). Therefore, older adults with DM can be prone to feel nervous, anxious, or on edge (i.e., GAD1 "Nervousness or anxiety"). This distinguishes them from other populations and warrants further validation in future studies.

People with comorbid depressive and anxiety symptoms tend to respond poorly to treatment, have a longer duration of illness, and experience poor prognoses (12). The results of this study found GAD1 "Nervousness or anxiety" and CESD4 "Everything was an effort" to be critical bridge symptoms, indicating their roles in the development and maintenance of concurrent depression and anxiety in older adults with DM. Bridge symptoms could facilitate the spread of activation of one mental disorder to another, thereby contributing to contagion between disorders, and providing a new perspective for explaining comorbidity (25). GAD1 "Nervousness or anxiety" was identified as the bridge symptom, indicating the role of anxiety in the development of depression. This finding is consistent with prior research that has found "Nervousness" to be the bridge symptom between depression and anxiety for nursing students (30, 78). Our results showed that GAD1 "Nervousness or anxiety" was positively linked to many anxiety symptoms, such as CESD10 "Sleep disturbances" and CESD3 "Feeling blue/depressed". This is consistent with prior studies that showed that the edges between "Nervousness or anxiety" and "sad mood" and between "Nervousness or anxiety" and "Sleep difficulties" are bridge pathways between depression and anxiety (symptoms measured using the PHQ-9 and GAD-7, respectively) (28, 62). Similarly, we found the influential bridge symptom within the depression community to be CESD4 "Everything was an effort", suggesting it has an important role in contagion from depression to anxiety. Specifically, CESD4 "Everything was an effort" had relatively strong and positive associations with GAD1 "Nervousness or anxiety" and GAD3 "Worry too much". Our findings indicated that feeling that everything was an effort might increase the risk of anxiety symptoms such as nervousness/anxiety and worrying too much. However, no previous studies have reported finding that "Everything was an effort" was the bridge symptom, consequently, a direct comparison cannot be made, and hence this issue is worthy of further study. Although we adopted a cross-sectional design and thus causality cannot be inferred from our study, our findings provide preliminary insights into the hallmark bridge symptoms facilitating the comorbidity of depression and anxiety. Moreover, our findings are in accordance with prior longitudinal studies that demonstrated that anxiety and depression are reciprocal risk factors for one another: that is to say, anxiety symptoms can lead to depressive symptoms and vice versa (11, 79–82).

The prominent central and bridge symptoms that were identified in the depression-anxiety network have potential clinical implications. According to the theory of psychopathological network, interventions targeting important central symptoms may have the greatest effect in destroying the overall network and reducing the severity of the network as a whole, facilitating intervention and treatment (19, 58). This study thus provides guidance for intervention strategies and suggests that targeting the symptoms "Feeling blue/depressed", "Nervousness or anxiety", "Uncontrollable worry", "Trouble relaxing", and "Worry too much" may be conducive to the prevention and treatment of depression and anxiety. Similarly, deactivating important bridge symptoms can disrupt the connections between comorbid mental disorders and prevent the contagion of one disorder to another, thereby reducing comorbidity (25). Based on the results of the present study, the bridge symptoms "Nervousness or anxiety" and "Everything was an effort" are recommended as intervention targets for the prevention and reduction of comorbid depression and anxiety disorders. Cognitive behavior therapy (CBT) is an effective treatment that is commonly used in the prevention of and intervention for depressive and anxiety symptoms in people with DM (83–85). Our findings indicate that CBT strategies (e.g., cognitive restructuring and behavioral activation) focusing on the central symptoms and bridge symptoms may be of benefit for the prevention and treatment of depression and anxiety and reduce their comorbidity in older adults with DM, although this needs further empirical research.

The strengths of this study include its large sample size, the representative study sample, and the utilization of network analysis to visualize depressive and anxiety symptom structures in older Chinese adults with DM with stable results. However, this study also has several limitations that should be noted. First, due to the cross-sectional design of our study, we could not infer the direction of causality between depression and anxiety. For insights into the temporal relationships, longitudinal research is needed. Second, the depressive and anxiety symptoms were measured using self-report scales, which may induce recall bias and remind us to interpret the results cautiously. Third, the findings may have limited generalizability as our sample focused on older Chinese adults with DM, and it is not known how generalizable our findings are to other populations. The applicability of our results to other populations with DM or older adults with clinically diagnosed depression and/or anxiety also requires replication. Fourth, the network did not include covariates or confounders such as diabetes complications, individuals' personality traits, and biological factors which should be considered in future studies. Fifth, the type of diabetes was not considered since it was not recorded in the CLHLS dataset we used. Although type 2 diabetes was predominant among the older adults, future studies should examine whether the type of diabetes has an effect on the network structure. Finally, the network structure constructed in this study only reflects group effects, meaning that it cannot capture idiographic individual-level processes of depression and anxiety.

5 Conclusion

This study presents the first application of symptom-level network analysis to investigate the depressive and anxiety symptoms of older Chinese adults with DM. The results revealed that "Feeling blue/depressed", "Nervousness or anxiety", "Uncontrollable worry", "Trouble relaxing", and "Worry too much" were the most central symptoms and that "Nervousness or

anxiety" and "Everything was an effort" were the key bridge symptoms within the depression-anxiety network. These identified symptoms may be potentially effective targets for the prevention of depression and anxiety among at-risk older adults with DM and inform treatment strategies for those who have depression and anxiety.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://opendata.pku.edu.cn/dataset.xhtml?persistentId=doi:10.18170/DVN/WBO7LK.

Ethics statement

The studies involving humans were approved by Biomedical Ethics Committee, Peking University (IRB00001052–13074), and the Institutional Review Board, Duke University (Pro00062871). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YZ: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. YC: Formal analysis, Writing – original draft. YL: Writing – original draft. HL: Data curation, Software, Writing – review & editing. HH: Methodology, Visualization, Writing – review & editing. JS: Formal analysis, Investigation, Visualization, Writing – original draft. ZG: Data curation, Formal analysis, Resources, Writing – original draft. DM: Formal analysis, Funding acquisition, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1328857/full#supplementary-material

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Gestational diabetes and risk of perinatal depression in low- and middle-income countries: a meta-analysis

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Background: The relationship between gestational diabetes (GDM) and the risk of depression has been thoroughly investigated in high-income countries on their financial basis, while it is largely unexplored in low- and middle- income countries. This meta-analysis aims to assess how GDM influences the risk of perinatal depression by searching multiple electronic databases for studies measuring the odds ratios between them in low- and middle-income countries.

Methods: Two independent reviewers searched multiple electronic databases for studies that investigated GDM and perinatal mental disorders on August 31, 2023. Pooled odds ratios (ORs) and confidence intervals (CIs) were calculated using the random effect model. Subgroup analyses were further conducted based on the type of study design and country income level.

Results: In total, 16 observational studies met the inclusion criteria. Only the number of studies on depression (n=10) satisfied the conditions to conduct a meta-analysis, showing the relationship between mental illness and GDM has been overlooked in low- and middle-income countries. Evidence shows an elevated risk of perinatal depression in women with GDM (pooled OR 1.92; 95% CI 1.24, 2.97; 10 studies). The increased risk of perinatal depression in patients with GDM was not significantly different between cross-sectional and prospective design. Country income level is a significant factor that adversely influences the risk of perinatal depression in GDM patients.

Conclusion: Our findings suggested that women with GDM are vulnerable to perinatal depressive symptoms, and a deeper understanding of potential risk factors and mechanisms may help inform strategies aimed at prevention of exposure to these complications during pregnancy.

KEYWORDS

mental disorders, gestational diabetes, meta-analysis, pregnancy, perinatal depression, developing countries

1 Introduction

Gestational diabetes (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy and can affect up to 25% of women during pregnancy globally (1). As one of the most common pregnancy complications, GDM is related to both short- and long-term adverse health outcomes in women and their offspring. Women with GDM are more likely to have gestational hypertension, preeclampsia, emergency Caesarean delivery, and type 2 diabetes mellitus (2–4). Besides, increasing evidence also suggested the close relationship between GDM and the risk of mental disorders, with a predominant focus on the attention drawn to its association with depression (5–7). For instance, a recent meta-analysis in 10 cohort studies with a total population of 2,000,002 identified a significantly increased risk of developing postpartum depressive symptoms in women with GDM (8). The risk of depression in women with GDM is worth emphasizing, as physical health and mental health are tightly connected. When mental health problems coexist with physical health problems, health outcomes, disability, and costs tend to be much worse (9, 10).

However, the relationship between GDM and the risk of perinatal depression in low- and middle-income countries has only recently become the subject of interest. Accumulating evidence shows both the risks of physical and mental health vary based on income levels (11, 12). Moreover, high-income countries tend to have more healthcare budgets and distribute greater proportions of budgets on mental health treatment than low- and middle-income countries. Therefore, previous findings based on high-income countries were insufficient to guide disease treatment in low- and middle- income countries.

Recent research found a mental health-based "poverty trap": poverty results in poor physical health and early-life conditions, which in turn leads to depression and anxiety disorders that could adversely affect individuals' childhood development, productivity, women's empowerment, as well as economic decision-making, and eventually reinforces poverty (9). Hence, understanding the link between physical and mental health, as well as how they interact with income, is an important next step for low- and middle-income countries. It not only allows countries to optimize the distribution of their healthcare budgets, but also reinforces them to escape the poverty trap and enhance economic gains. Therefore, the primary aim of this meta-analysis is to systematically investigate the association between GDM and the risk of perinatal depression in low- and middle-income countries; by doing this, we want to emphasize the importance of caring for depression among the GDM population, especially in low- and middle-income countries.

2 Material and methods

2.1 Literature search

Two investigators independently (YJ and CW) searched databases of Medline, EMBASE, Pubmed, Web of Science, and PsycINFO from inception until August 31, 2023. Search terms such as "gestational diabetes mellitus" and "mental disorders" were adapted from previous systematic reviews in the area (13–15). The complete list of the search terms used is presented in the Supplementary File. Forward and backward citation was also undertaken.

2.2 Study selection

Inclusion criteria were confined to peer-reviewed studies published in English or with sufficiently detailed English abstracts to extract relevant information, measuring both GDM and perinatal mental disorders. Perinatal mental disorders included depression, anxiety, psychotic or eating disorders diagnosed at antenatal (between conception and delivery) or postpartum (up to 1 year following delivery) period, as there were plausible mechanisms for an association between these disorders and GDM. The study type is either cohort (prospective or retrospective) or cross-sectional.

Exclusion criteria included studies conducted in countries classified as high-income by the World Bank. Additionally, studies from high-income regions of Hong Kong, Taiwan, and Macau were excluded from the analysis due to their distinct economic and healthcare conditions compared to mainland China. Furthermore, studies in which mental disorders were diagnosed prior to the onset of GDM were excluded. Finally, studies that did not report unadjusted odds ratios for the relationship between GDM and mental disorders, or did not

provide sufficient data for the calculation of odds ratios, were excluded from the meta-analysis.

Following de-duplication, titles and abstracts were screened, followed by full-text screening by two independent reviewers. In total, 16 studies met the study's inclusion criteria.

2.3 Data extraction

Data extraction was conducted by two independent reviewers (YJ and CW) and the following data were extracted: the last name of the first author, year of publication, country, sample size, study design, diagnostic criteria of exposure and outcome, the timing of outcome assessment (antepartum vs. postpartum), significant risk factors (BMI, age, occupation, etc.), and unadjusted odds ratios with corresponding 95% confidence intervals (CIs).

2.4 Risk of bias assessment

The quality of the selection, comparability, and outcome of the included studies was assessed using a pre-piloted modified Newcastle-Ottawa scale (16) (Supplementary Table S1). Two independent reviewers (YJ and CW) performed the quality assessment and scored the included studies. Scores for selection bias and measurement bias were of particular interest as most of the studies were of observational design. A study with a score of zero in any of the evaluation domains was categorized as high risk of bias. Otherwise studies were categorized as low to moderate risk (17, 18). A lower risk of bias indicates higher quality.

2.5 Data synthesis

Unadjusted ORs with 95% CIs were used as measures of the association as studies were adjusted for different covariates. If ORs for at least three studies were available for one mental disorder, a meta-analysis was performed (19). DerSimonian-Laird random effects model (20) was the most commonly used method in meta-analysis because it is especially useful for providing an overall effect estimate and characterizing the heterogeneity of effects across a series of studies. When the proportion of total variation in study estimates that is due to heterogeneity (denoting as I^2), it was decided a-priori such as 90% would preclude meta-analysis as this represents substantial heterogeneity (21). To evaluate the influence of each study, we conduct a sensitivity analysis by omitting each study individually and recalculating the pooled unadjusted ORs for the rest of the studies. All analyses were performed using STATA version 17 (22).

Subgroup analysis was performed for factors that could potentially impact the relationship between GDM and the risk of perinatal mental disorders. Potential factors include study type (prospective or cross-sectional studies), country income level, the timing of diagnostic (symptoms measured in antepartum or postpartum period) and mental disorder type. If ORs for at least three studies were available for each subgroup, a subgroup meta-analysis was additionally performed.

3 Results

3.1 Study characteristics

As shown in Figure 1, we identified 1316 studies from five different electronic databases. During the initial screening by title and abstract, the majority of the articles were excluded for being conducted in high-income countries or intervention studies without baseline data.

Among the 16 studies included, 10 studies were eligible for meta-analysis, and 6 studies were only used for prevalence and risk factors analysis due to lack of unadjusted ORs. The characteristics of the included studies were summarized in Table 1.

The most prevalent study design was prospective cohort (N=10) and 8 studies were cross-sectional. All of the studies were performed in low- or middle-income countries and 7 studies were from China. Diagnostic criteria for GDM include the International Classification of Diseases (ICD), oral glucose tolerance test, medical records, and self-report. Assessments for depressive symptoms or depression were based on the Edinburgh Postnatal Depression Scale (EDPS), the ICD, the Montogomery and Asberg Depression Rating Scale (MADRS), the Zung Self-Rating Depression Scale (SDS), The Beck Depression Inventory (BDI), and self-report. Assessment for anxiety symptoms or anxiety were based on the Self-Rating Anxiety Scale (SAS), the ICD, and MINI structured interview.

It is worth mentioning that in our original planned analysis, we intended to examine the relationship between GDM and a comprehensive range of perinatal mental disorders, encompassing depression, anxiety, psychotic, and eating disorders. However, the search results suggest current studies from low- and middle-income countries can only be found sufficient when they pertain to either depression or anxiety. Furthermore, among these perinatal mental disorders, only the quantity of literature on depression fulfilled the criteria for meta-analysis. Therefore, this study will primarily concentrate on examining the risk associated with perinatal depression in patients with GDM.

3.2 Risk of depression in patients with GDM

Out of 16 included studies, 10 studies measured diagnoses or symptoms of depression and were eligible for meta-analysis (23–32). Their respective characteristics and relevant findings were presented in Table 2.

The unadjusted ORs varied from 0.83 to 5.90 across studies (Figure 2). Among the 10 studies, 8 studies found a significant increase in risk of depression, while 2 studies reported no association. Pooling together, women with GDM compared with the control group had a notably increased risk of developing perinatal depressive symptoms (pooled unadjusted OR= 1.92, 95% CI 1.24, 2.97). There was a high degree of heterogeneity across studies (I^2 = 80.87%, P for heterogeneity = 0.00).

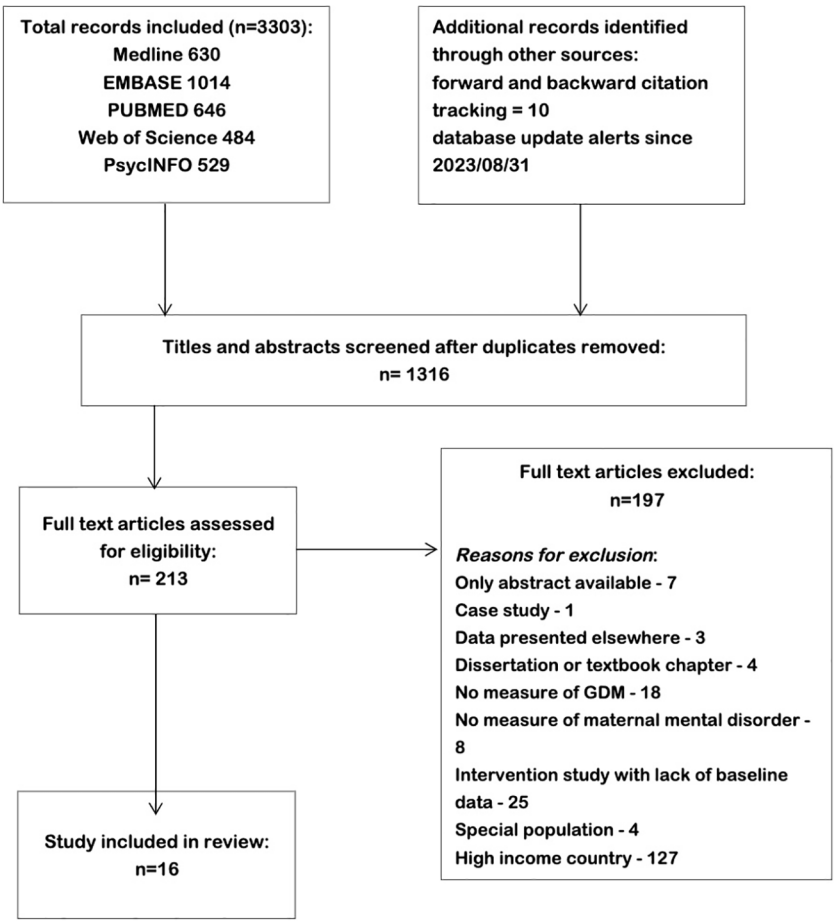

FIGURE 1
Study selection process for meta-analysis of studies on Gestational diabetes and risk of perinatal mental disorders in low- and middle-income countries.

The following 6 studies were not included in the meta-analysis for having no unadjusted ORs available as effect estimates. Dame et al. reported the proportion of women with antenatal depression among GDM women (proportion = 31%) (34). Mak et al. found that the 3 months postpartum EPDS score was significantly higher in women with GDM than those without GDM (EPDS in GDM group=2.1, EPDS in control group=1.5, p-value <0.001) (35). Chen et al. and Peng et al. provided GDM prevalence and treated depression as exposure (36, 37). Dai et al. aggregated depression, anxiety and obsessive-compulsive disorders into one measure and reports the prevalence of GDM in psychiatric and healthy control group (prevalence in psychiatric group = 20.7%, prevalence in healthy control group=6.1%) (38). Lastly, Levy-Shiff et al. found no association between GDM and depressive symptoms in second trimester (BDI score in GDM group=6.70, BDI score in control group=6.59, p-value=0.42) (39).

3.3 Study type influence in risk of depression in patients with GDM

In this section, we investigated the impact of study type on the reported results of the relationship between GDM and the risk of perinatal depression, as a prior study observed significant variations in associations across different study types (8), by performing a subgroup analysis. In the subgroup analysis, only the difference between cross-sectional and prospective studies was analyzed (Figure 3), as there were not enough retrospective studies presented. The pooled unadjusted ORs for cross-sectional and prospective study design were 1.34 (95% CI 0.90,1.99) and 2.36 (95% CI 1.22, 4.57) respectively. Cross-sectional studies had lower estimates than prospective studies, but the difference in pooled unadjusted ORs across different study design was not substantial (P for group difference = 0.15). There was no evidence of heterogeneity in cross-sectional cohort studies (I^2 = 45.36%, P for heterogeneity = 0.16), and a high degree of heterogeneity in prospective cohort studies (I^2 = 85.20%, P for heterogeneity = 0.00). Sensitivity analysis did not identify studies that had substantial influences on the overall effect estimate, with pooled unadjusted ORs ranging from 1.66 to 2.14.

3.4 Income influences in risk of depression in patients with GDM

In this section, we proceeded to conduct a subgroup analysis based on income levels (Figure 4). Specifically, the studies were divided into subgroups of lower-middle-income and upper-middle-

TABLE 1 Characteristics of included studies.

Disorder	Depression	Anxiety
Total N (2 studies measures both depression and anxiety)	14	4
Study Design		
Cross-sectional	6	2
Prospective cohort	8	2
Income Category		
Low-income	1	0
Lower-middle-income	2	2
Upper-middle-income	11	2
Country		
Bangladesh	1	0
Brazil	1	0
China	6	1
India	1	1
Iraq	1	1
Peru	1	0
Sri Lanka	0	1
Turkey	2	0
Ethiopia	1	0

income, according to the World Bank's yearly classification of national income level. That means the studies conducted in a same country, mainly China in our analysis, would be grouped differently due to the income level at their publication year. As a major result, the association between GDM and depression was found to be remarkably influenced by income levels of studied countries (P for group difference = 0.00). The pooled unadjusted ORs for studies performed in lower-middle- and upper-middle-income countries were 3.32 (95% CI 2.07, 5.31) and 1.34 (95% CI 0.89. 2.03), respectively. There was no evidence of heterogeneity in studies from lower-middle-income countries (I^2 = 42.18%, P for heterogeneity = 0.16), and a notable degree of heterogeneity in studies from upper-middle-income countries (I^2= 67.41%, P for heterogeneity = 0.01). Besides, we found that the risk of depression in women with GDM is significantly higher in lower-middle-income countries compared to that in upper-middle-income countries, suggesting country income level is a significant factor that adversely influences the risk of perinatal depression in middle-income countries. It is unfortunate that data from low-income countries were insufficient to take part in this subgroup analysis, which could have made the analysis result more comprehensive.

4 Discussion

4.1 Main findings

Our meta-analysis differed from previous literature with an emphasis on studies conducted in low- and middle-income

TABLE 2 Summary of data provided by each study.

Author and year	Country	Study design and sample size	GDM measure	Mental disorder measure	Risk factors	Quality	Unadjusted OR(95%CI)	Type
Atlaw et al., 2022 (24)	Ethiopia	Prospective cohort, N=432 women GDM- 68	fasting capillary blood glucose between 92 and 125 mg/dL	The Edinburgh Postnatal Depression Scale	GDM: 1,3,5	Low to moderate risk of bias	[a]5.9 (3.04, 11.48)	Antenatal depression
Boggaram et al., 2017 (33)	India	Cross-sectional, N=100 women GDM- 11	Not specified	MINI structured interview during pregnancy (unknown if MINI ICD10 or DSM-IV) for anxiety disorders		High risk of bias	[c]3.33 (0.75,14.87)	Antenatal anxiety
Hassan et al., 2017 (23)	Iraq	Prospective cohort, N=100 GDM- 50	OGTT	BDI ≥ 20 at 24-36 weeks gestation		High risk of bias	Depression [a]4.45 (1.68,11.81) Anxiety [a]1.64 (0.74,3.66)	Antenatal depression or anxiety

(Continued)

TABLE 2 Continued

Author and year	Country	Study design and sample size	GDM measure	Mental disorder measure	Risk factors	Quality	Unadjusted OR(95%CI)	Type
Isik and Cetisli., 2022 (25)	Turkey	Cross-sectional study, N=237 women GDM- 104	Based on medical records	EPDS ≥12	GDM: 1,4,7,9	Low to moderate risk	Antenatal [b]1.46 (0.85, 2.50) Postpartum [b]1.35 (0.68, 2.66)	Antenatal and Postpartum depression
Keskin et al., 2015 (27)	Turkey	Prospective cohort, N=89 women GDM- 44	OGTT	Antepartum BDI (unknown what version) ≥17 after GDM diagnosis	GDM: 2	High risk of bias	[a]1.19 (0.41,3.43)	Antenatal depression
Larrabure-Torrealva et al., 2018 (29)	Peru	Cross-sectional study, N=1300 women GDM- 205	OGTT	Patient Health Questionnaire-9	GDM: 1,2,5	High risk of bias	[a]1.52 (1.09–2.12)	Antenatal depression
Li et al., 2022 (31)	China	Retrospective cohort, N=1043 women GDM - 313	OGTT	Edinburgh Postnatal Depression Scale (EPDS) ≥ 9	GDM: 1,2,3,5,7,8	Low to moderate risk of bias	1st trimester: [a]0.65(0.44–0.94) 2nd trimester: [a]0.86(0.49–1.53)	Antenatal depression
Natasha et al., 2015 (28)	Bangladesh	Prospective cohort, N=748 women GDM - 382	Plasma Glucose found ≥7.0 (WHO) or ≥5.3 mmol/L at Fasting, and ≥8.6 mmol/L at 2 h after 75 gm Glucose intake (ACOG), (which ever detected first)	Montogomery and Asberg Depression Rating Scale (MADRS)	GDM: 1,4,6	Low to moderate risk of bias	[a]3.02 (2.01, 4.53)	Antenatal depression
Singh et al.,2023 (32)	India	Prospective cohort, N=347 women GDM- 48	Seventy-five grams of glucose was given in 300 ml of water irrespective of fasting stage and blood glucose was measured by glucometer using reagent strips after two hours. The blood glucose level of ≥140 mg/dl after two hours of glucose load was taken as cut off for diagnosis of GDM.	EPDS ≥12	Depression: 1, 3, 4	Low to moderate risk of bias	[b]1.71(0.70,4.19)	Postpartum depression
Song et al, 2004 (26)	China	Prospective cohort, N=104 women GDM- 50	OGTT	SDS (Zung Self-rating depression scale) during pregnancy ≥41		High risk of bias	[a]3.53 (1.04,11.93)	Antenatal depression
Tang, Yi et al, 2020 (30)	China	Prospective cohort, N=1426 women GDM- 533	OGTT	self-rating anxiety scale, SAS≥50 as anxiety and self-rating depression scale,SDS ≥53 as depression		Low to moderate risk of bias	Anxiety: [b]1.22 (0.82, 1.81) Depression: [b]0.83(0.58,1.20)	Antenatal anxiety and depression

GDM, gestational diabetes; OR, odds ratio; OGTT, oral glucose tolerance test.
Risk factors: 1, age; 2, BMI; 3, occupation; 4, educational level; 5, family history of diabetes; 6, history of hypertension; 7, parity; 8, gravidity; 9, social support.
[a]Estimate given in paper.
[b]Derived from data in paper.
[c]Data provided by study author.

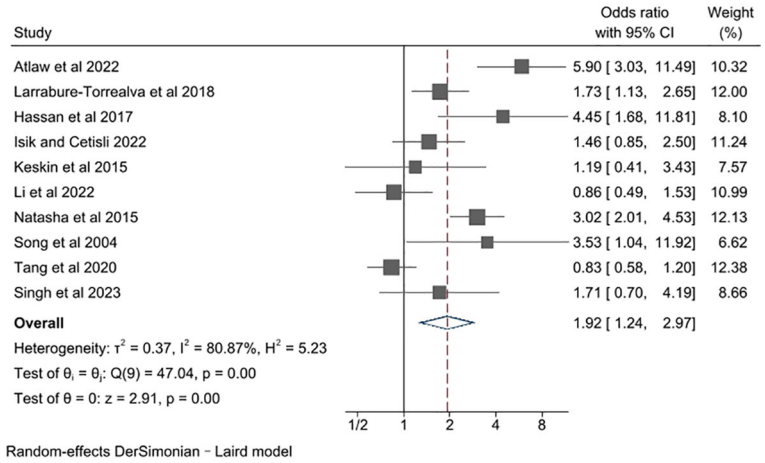

FIGURE 2
Meta-analysis of studies examining the association between gestational diabetes and risk of perinatal depression.

countries. Pooled unadjusted ORs for risk of perinatal depression was 1.92 (95% CI 1.24, 2.97), indicating that women with GDM have elevated risk of depression than those without GDM. This finding was in accordance with past researches in high income countries (8, 40). Furthermore, the pooled unadjusted ORs was substantially higher in studies conducted in lower-middle-countries than that in upper-middle-income countries, which supports our hypothesis that poverty exposes women to adverse mental and physical conditions. Among the included studies, one study (23) in Iraq and another study in Ethiopia (24) have notably higher unadjusted ORs (OR=4.45, 95% CI 1.68, 11.81 and OR=5.90, 95% CI 3.03, 11.49) compared to other studies in the same country income category. We speculated the elevated risk of depression was linked to constant armed conflicts in the regions. Moreover, it should be pointed out that the number of studies in anxiety disorder and other mental illness did not meet our standard to conduct meta-analysis, leaving opportunities for future research in low- and middle-income countries.

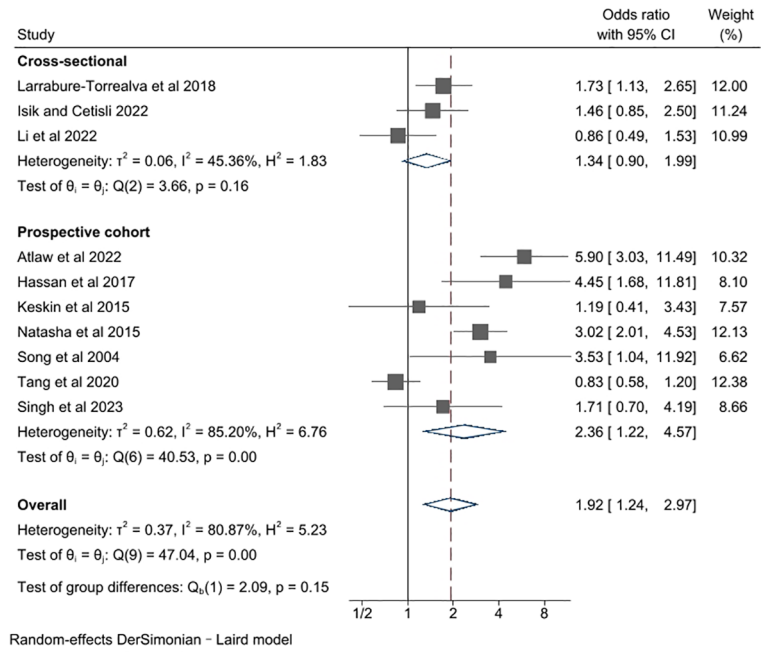

FIGURE 3
Subgroup meta-analysis of studies examining the association between gestational diabetes and risk of perinatal depression according to study design type.

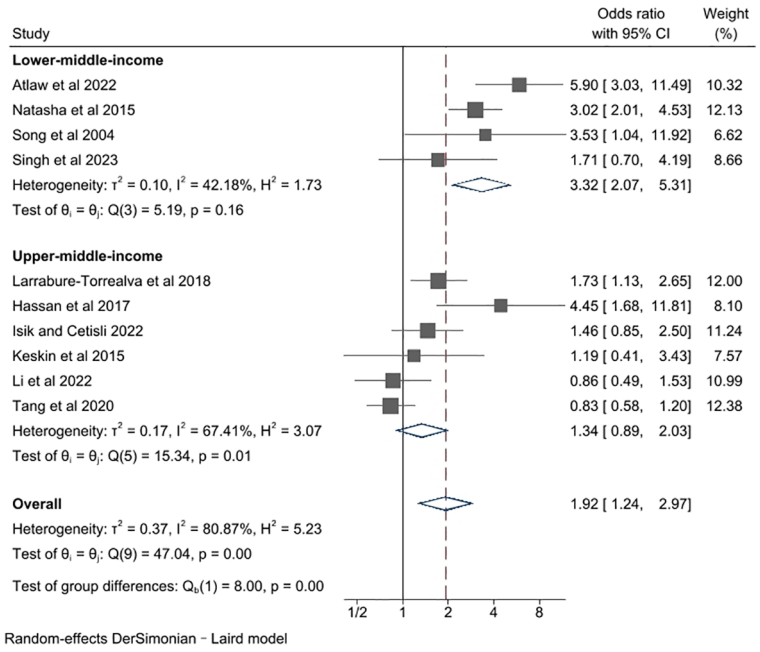

FIGURE 4
Subgroup meta-analysis of studies examining the association between gestational diabetes and risk of perinatal depression according to country income level.

4.2 Potential mechanisms

The mechanism underlying the relationship between GDM and the risk of perinatal depression is unclear. Previous literature on type 2 diabetes speculated that perinatal depression resulted from biochemical changes directly due to GDM or from the psychological factors related to GDM or its treatment (41). There is also evidence suggesting that diabetes and depression may share common biological risk factors. For example, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in people with either diabetes or depression (42, 43). Women with GDM are more prone to experience increased inflammation and adipokine concentration, which are also related to depression as well (44, 45). The event of having GDM itself could also result in depressive mood. In addition, we found that GDM and mental disorders shared several common risk factors, including age, education level, and occupation. Women with elder maternal age or unemployed women and housewives are more likely to have GDM and mental disorders (Table 2). Besides, a number of studies found that depressive symptoms were related to difficulties in adaption to diabetic complications and adverse obstetric outcome, including caesarean delivery and preterm delivery (46, 47). Moreover, insufficient nutritional support is also speculated to be associated with mental illness and GDM (48, 49). Studies have indicated a consistent correlation between lower income levels and inferior diet quality. (50, 51). Compared to individuals with higher income, those with lower income consume fewer fruits and vegetables, a greater amount of sugar-sweetened beverages, and have a lower overall diet quality (52, 53). Based on the theory of social causation, the condition of poverty could cause depression through financial stress, decreased social capital and inferior diet (54).

4.3 Strengths and limitations

To our knowledge, this is the first study that has thoroughly reviewed the literature in low- and middle-income countries and meta-analyzed the risk of perinatal depression in women with GDM. Since effect estimate and symptoms of depression may vary across subgroups, our meta-analysis was also grouped by study design and country income level.

Most of the included studies only provided unadjusted ORs, which may inflate the estimates for risk of depression. A few studies indicated that BMI and ethnicity may moderate the impact of perinatal depression, but information related to these confounders were often missing from studies (55, 56). Furthermore, previous literature found that obesity, level of glycemic control and GDM management strategies (insulin vs. diet intervention) may also have an impact on depression (57–59). Despite acknowledging the potential moderating effect of these variables on perinatal depression, the lack of detailed reporting hindered our ability to conduct a robust subgroup analysis.

Nearly half of the studies were identified as high risk of bias. Studies at high risk of bias mostly lack information regarding sample selection process or GDM diagnostic criteria. There was a high degree of heterogeneity among included studies. The source of heterogeneity came from both depression and GDM. Moreover, the screening tools of perinatal depression and GDM varied across studies. For depression evaluation, there were multiple assessment tools

including EPDS, BDI, and Patient Health Questionnaire-9, and there is a lack of consensus on the optimal cut-off point in the literature. For instance, the cut-offs for EPDS were 9, 10, and 12 in three included studies. The screening time of postpartum depression include 1-month, 3-months, and 6-months postpartum. Previous studies also have contradictory results regarding 6-months depressive scores (35, 60). For GDM diagnosis, two studies used self-reported data, which may add to the risk of information bias.

4.4 Implications

A future potential and urgent area for research is the investigation of relationships between GDM and the risk of mental disorders other than depression in low- and middle-income countries. Current studies in less common mental disorders, such as eating disorders and bipolar disorder, were mostly performed in high-income countries. Current studies independently found that the prevalence of GDM and mental disorders was both higher in resource-constrained countries (61, 62), but the relationship between them are still relatively unexplored. Research in resource-constrained countries is speculated to have an important impact, as we found in this study on depression that the severity of mental disorders could be significantly negatively correlated to country income level. The research would also be important from both social and healthcare contexts because mental health problems can cause adverse consequences for women, their infants, and even the larger families. Addressing barriers in nutrition education and counselling, diet intervention, antenatal and postpartum care services, as well as emotional support services may contribute to improve health outcomes of pregnant women in low- and middle-income countries. During future investigations, we also emphasize a greater understanding of the underlying mechanism between GDM and depression, for it is essential for interventions to reduce not only the risk of depression but also other complications.

5 Conclusion

In this study, we performed a meta-analysis to examine the risk of perinatal depression among individuals diagnosed with GDM in low- and middle-income countries. We searched for studies on various mental disorders, but only identified sufficient research on depression that met the criteria for inclusion in our meta-analysis. This finding underscores the limited amount of research available on perinatal mental disorders in low- and middle-income countries and emphasizes the urgent need for further studies in this area.

Focusing specifically on perinatal depression, we found a significant increase in the likelihood of experiencing depressive symptoms in individuals with GDM. This finding emphasizes the importance of managing GDM, as doing so can help reduce adverse obstetric outcomes. Additionally, we found that the risk of depression in women with GDM is significantly higher in lower-middle-income countries compared to that in upper-middle-income countries, indicating country income level is a significant factor that adversely impacts the risk of depression in middle-income countries. The implications of this study are particularly relevant for low- and middle-income countries, as depression can directly impact individuals' economic decision-making and productivity, potentially leading to increased poverty. Therefore, addressing perinatal mental health issues, especially in the context of GDM, is crucial for improving overall well-being and socio-economic outcomes. A deeper understanding of the relation and mechanisms between GDM and depression may help to identify the risk of depression at an early stage and reduce obstetric complications.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

YJ: Writing – original draft, Writing – review & editing, Data curation, Formal analysis. CW: Data curation, Writing – review & editing. WC: Writing – review & editing. JL: Writing – review & editing. HJ: Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1331415/full#supplementary-material

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Associations of comorbid depression with cardiovascular-renal events and all-cause mortality accounting for patient reported outcomes in individuals with type 2 diabetes: a 6-year prospective analysis of the Hong Kong Diabetes Register

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Background: Psychosocial status and patient reported outcomes (PRO) [depression and health-related quality-of-life (HRQoL)] are major health determinants. We investigated the association between depression and clinical outcomes in Chinese patients with type 2 diabetes (T2D), adjusted for PRO.

Methods: Using prospective data from Hong Kong Diabetes Register (2013-2019), we estimated the hazard-ratio (HR, 95%CI) of depression (validated Patient Health Questionnaire 9 (PHQ-9) score≥7) with incident cardiovascular disease (CVD), ischemic heart disease (IHD), chronic kidney disease (CKD: eGFR<60 ml/min/1.73m^2) and all-cause mortality in 4525 Chinese patients with T2D adjusted for patient characteristics, renal function, medications, self-care and HRQoL domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression measured by EQ-5D-3L) in linear-regression models.

Results: In this cohort without prior events [mean ± SD age:55.7 ± 10.6, 43.7% women, median (IQR) disease duration of 7.0 (2.0-13.0) years, HbA1c, 7.2% (6.6%-8.20%), 26.4% insulin-treated], 537(11.9%) patients had depressive symptoms and 1923 (42.5%) patients had some problems with HRQoL at baseline. After 5.6(IQR: 4.4-6.2) years, 141 patients (3.1%) died, 533(11.8%) developed CKD and 164(3.6%) developed CVD. In a fully-adjusted model (model 4) including self-care and HRQoL, the aHR of depression was 1.99 (95% confidence interval CI):1.25-3.18) for CVD, 2.29 (1.25-4.21) for IHD.

Depression was associated with all-cause mortality in models 1-3 adjusted for demographics, clinical characteristics and self-care, but was attenuated after adjusting for HRQoL (model 4- 1.54; 95%CI: 0.91-2.60), though HR still indicated same direction with important magnitude. Patients who reported having regular exercise (3-4 times per week) had reduced aHR of CKD [0.61 (0.41–0.89)]. Item 4 of PHQ-9 (feeling tired, little energy) was independently associated with all-cause mortality with aHR of 1.66 (1.30-2.12).

Conclusion: Depression exhibits significant association with CVD, IHD, and all-cause mortality in patients with diabetes, adjusting for their HRQoL and health behaviors. Despite the association between depression and all-cause mortality attenuated after adjusting for HRQoL, the effect size remains substantial. The feeling of tiredness or having little energy, as assessed by item Q4 of the PHQ-9 questionnaire, was found to be significantly associated with an increased risk of all-cause mortality after covariate adjustments. Our findings emphasize the importance of incorporating psychiatric evaluations into holistic diabetes management.

KEYWORDS

depression, cardiovascular-renal events, mortality, patient reported outcomes, health related quality of life

1 Introduction

Type 2 diabetes (T2D) is a chronic disease requiring self-care and discipline to prevent complications and premature death (1, 2). Rapid socio-economical changes in China were paralleled by a rise in T2D prevalence from 1% in 1980 to 10% in 2021 (2). Depression and diabetes (3) frequently coexist, with most of the data coming from Europeans. In the last 30 years, mental illness, especially depression, has become prevalent across Asia (4). In 2013, amongst 0.5 million Chinese participating in the China Kadoorie Biobank Project, those with major depression had 1.75 times (95%CI: 1.47–2.08) increased risk of prevalent T2D (5). In a Hong Kong clinic-based register, we reported that 18% of patients with T2D had depression (Patient health questionnaire 9 (PHQ-9) score of ≥7), which was associated with poor glycaemic control and hypoglycaemia (6), in part due to poor treatment adherence (7).

From a biological perspective, neurohormonal dysregulation associated with depression may worsen cardiovascular risk factors (8). There are multiple clinical studies that reported patients with T2D and co-morbid depression have elevated risk in experiencing CVD morbidity and mortality (9–11). In our previous study, we reported that using a diagnosis of depression registered by psychiatrist, Hong Kong Chinese patients with T2D who received specialist care for depression had more than 2 times increased risk of premature mortality and cardiovascular disease (CVD) than those without depression (12). Against a backdrop of growing burden of diabetes and depression, the Lancet Commission Report on Diabetes (1) and American Diabetes Association/European Association for Study of Diabetes (ADA/EASD) practice guidelines (13) highlighted the importance of evaluating psychosocial needs and patient-reported outcomes (PRO) including depressive symptoms, health-related quality of life (HRQoL), self-care and their inter-relationships in influencing clinical outcomes to inform practice and policies. There is paucity in evidence that establish association between depression, cardiovascular-renal outcomes and mortality that consider the influence of PROs such as HRQoL and health behaviours of patients with diabetes.

In this study, utilizing the Hong Kong Diabetes Register (HKDR) with detailed documentation of clinical profiles including PRO during structured assessment, we examined prospectively the association of depression with all-cause mortality, CVD and CKD and their associations with PRO including self-care and HRQoL in patients with T2D.

2 Materials and methods

2.1 Patients

The HKDR was established in 1995 at the Diabetes and Endocrine Centre, Prince of Wales Hospital (PWH), as a research-driven quality improvement program using structured clinical assessment (14). Using a unique identifier, HKDR was linked to a territory-wide electronic medical record system with hospitalization data and death registry for epidemiological analysis. In the present analysis, we included patients diagnosed with T2D aged ≥18 years and excluded patients with Type 1

diabetes (T1D) in the HKDR. The latter was defined by acute presentation with ketosis or requirement of continuous insulin treatment within 1 year of diagnosis, adapted from a definition of T1D in Caucasians (15). Hospitalization data was captured using international classification of disease codes (ICD-9) and causes of death by ICD-10 (14) (Supplementary Table 1). In 2007, we included EuroQol-5 Dimension 3 Levels (EQ5D-3L) to measure HRQoL (16) and in 2013, we included Chinese-validated PHQ-9 to measure depression (6). By 2019, 6818 patients had completed both PHQ-9 and EQ5D-3L. Amongst them, we excluded 2293 patients with (1) history of CVD [stroke, peripheral vascular disease (PVD), ischaemic heart disease (IHD)] (n=1436) and/or (2) CKD defined as estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m^2 (n=1181) and/or (3) incomplete responses to the PHQ-9 questionnaire (n=112). We analysed clinical outcomes in the remaining 4525 patients with T2D, of whom 4429 (97.9%) had completed all items of EQ5D-3L.

2.2 Baseline clinical assessment

All participants of the HKDR underwent protocol-driven assessment by trained nurses (history taking, physical examination including eye and feet and laboratory investigations including blood and urine tests) directed by case report forms. The data included sociodemographic factors, years of education, occupation, medical history, current drug use and self-care [adherence to a balanced diet, regular exercise, self-monitoring of blood glucose (SMBG), medication adherence] were documented. Physical examination included measurements of blood pressure, body weight, height, waist and hip circumference (14). After an overnight fast, blood was drawn for measurement of glycated haemoglobin (HbA1c), plasma glucose, lipid profile (total cholesterol, triglyceride, high-density cholesterol (HDL-C) and calculated low-density lipoprotein cholesterol (LDL-C) and random spot urine sample was used to measure urinary albumin-to-creatinine ratio (ACR). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to derive estimated glomerular filtration rate (eGFR) (17).

2.3 Psychological assessment

The PHQ-9 was derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for major depression. Based on a 2-week recall period, the questionnaire consists of 9 items with a score range of 0 (not at all) to 3 (nearly every day) for each item with a total score range of 0-27. In Hong Kong Chinese patients with T2D, using semi-structured interview as reference test, our group validated a cut-off score of 7 to detect depression with optimal sensitivity and specificity (6) versus a cut-off value of 10 in most European studies (6).

PHQ-9 items Q1 (little interest or pleasure in doing things) and Q2 (feeling down, depressed or hopeless) had been validated as a short screening tool (PHQ-2) (18). Amongst PHQ-9 items, Q3-5 (trouble sleeping, low energy and appetite) enquire about somatic symptoms while Q6-9 items (feeling bad about yourself, trouble concentrating, moving or speaking slowly, suicidal ideation) assess non-somatic symptoms (19). EQ-5D-3L evaluates five health domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression (20), rated on three levels: 1 (no problem), 2 (some problems) to 3 (extreme problems). The traditional Chinese versions of PHQ-9 (6) and EQ-5D-3L (21) were used in this study.

All patients gave written informed consent for anonymized data to be analysed for publication and research purpose (22). The study was approved by the Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

2.4 Statistical analysis

We analysed patients enrolled in the HKDR who had completed both PHQ9 and EQ-5D-3L questionnaires since 13th March 2013 as part of a continuous quality improvement program. We censored these patients on the first CVD, CKD, death event or 31st December 2019, whichever came first. Longitudinal data on patient clinical outcomes were extracted from electronic patient medical records.

Continuous variables were expressed as mean ± standard deviation (SD), or median (inter-quartile range, IQR), and categorical variables, number (percentage). Between-group comparisons were analyzed by Chi-square test for categorical data, Wilcoxon two-sample test for continuous variables and Mann-Witney test for skewed data. Statistical analysis was performed using Statistical Package for Social Science (version 27.0). We compared the frequency of depression in patients with CVD (n=1436) or CKD (n=1181) at baseline. In the remaining patients with complete data (n=4429) for analysis, we used Kaplan–Meier estimator to demonstrate the survival probabilities of incident CVD and CKD and all-cause mortality in both depressed and non-depressed groups. Cox proportional hazards regression model was constructed to obtain hazard ratios (HRs, 95% confidence intervals [CI]) for: 1) all-cause mortality, 2) any incident CVD (stroke, PVD IHD), 3) IHD only, and 4) CKD, fitted to four models. Model 1 included age, gender, education, occupation, smoking status, duration of diabetes, body mass index (BMI), systolic and diastolic blood pressure, HbA1c and lipid profiles (LDL-C, HDL-C, triglycerides). Model 2 included variables in Model 1 plus Ln (urine ACR+1), eGFR, use of lipid-lowering drugs, angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), other anti-hypertensive drugs and anti-diabetic drugs. Model 3 included variables in Model 2 plus frequency of self-reported adherence to balanced diet (never/no/occasional/yes), vigorous exercise corresponding to brisk walking > 30 minutes (no regular physical activity/1-3 times per week/3-4 times per week/5 times per week/>5 times per week), SMBG (yes/no), medication adherence level (1-100%) in the past 3 months and whether they had regular follow-up visits in past year. Model 4 included variables in Model 3 plus mean scores of EQ-5D-3L domains (excluding anxiety/

depression) to adjust for baseline HRQoL. For CKD outcome, models 1 to 4 excluded Ln (urine ACR+1) and eGFR. In sensitivity analysis, we compared HRs of PHQ-2 versus PHQ-9 as well as independent risk associations of each item of PHQ-9 with clinical outcomes.

To examine the association between each individual item in the PHQ-9 questionnaire and all-cause mortality, all-CVD outcomes (including IHD, PVD and stroke), and CKD, hazard ratios were calculated and adjusted for all covariates in model 4. All regressions on each PHQ-9 item were adjusted for other PHQ-9 items.

In sensitivity analysis, we compared HRs of PHQ-2 versus PHQ-9 as well as independent risk associations of each item of PHQ-9 with clinical outcomes. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (23).

3 Results

3.1 Baseline characteristics

Supplementary Figure 1 shows the flow chart of patient recruitment. Amongst 6818 Chinese patients with T2D enrolled in the HKDR with both PHQ-9 and EQ-5D-3L-5D data, 1436 patients had prior CVD (21%) and 1181 (17%) had CKD. In these patients with prior events, the prevalence of depression was 15.4% (15.6% for CVD and 17.0% for CKD). After excluding these patients with prior events, in the prospective cohort (n=4525), 537 patients (11.9%) had depressive symptoms based on PHQ-9≥7. Patients with depression were more likely to be women, younger, unemployed and had lower education attainment than the non-depressed group. They were less likely to perform regular exercise and more likely to forget or self-adjust medications. Patients with depression had higher serum triglyceride, HbA1c, ACR and eGFR, and were more likely to be treated with insulin. Overall, 5.33% of patients reported at least some problems in mobility, 1.46% for self-care, 4.66% for usual activities, 35.6% for pain/discomfort and 19.1% for anxiety/depression. The depressed group had more severe problems in all EQ-5D-3L domains (Table 1). For PHQ-9 items, 10% of patients reported somatic symptoms (Q3-5) for at least 7 days during the last 14 days, as compared to 5% for anhedonia (Q1), 3% for negative moods (Q2) and 3% for non-somatic (Q6-9) complaints (Supplementary Table 2). The majority of patients with T2D and co-morbid depression rated experiencing sleeping problems in Q3 (n= 330, 61.4%) and tired and lack of energy in Q4 (n = 299, 55.7%) on somatic complaints in more than half the days in the past 2 weeks.

During a median follow-up period of 5.6 (IQR: 4.4-6.2) years, 141 patients (3.1%) died, 533 (11.8%) developed CKD and 164 (3.6%) developed CVD. In the latter group, 95 (57.9%) had IHD, 75 (45.7%) had other cardiovascular events (stroke: n=67, PVD: n= 8). The depressed group had a higher cumulative incidence of any CVD [5.8% versus 3.3%, p=0.005], IHD [3.7% versus 1.9%, p=0.005], all-cause mortality [4.8% versus 2.9% p=0.014] and CKD [13.8% versus 11.5%, p=0.125] than non-depressed group (Figure 1).

3.2 PHQ-9 items and clinical outcomes

Depression was significantly associated with increased CVD and IHD, where HR remained consistent in all 4 models after adjustment for demographics and clinical characteristics (model 1 – CVD: 1.97; 95%CI: 1.32–2.96, IHD: 2.41; 95%CI: 1.44-4.04), renal function (model 2– CVD: 1.86; 95%CI:1.24–2.80, IHD: 2.37; 95%CI: 1.41-3.99), medication use (model 3– CVD: 2.04; 95%CI: 1.32–3.16, IHD: 2.83; 95%CI: 1.62-4.94), and self-care (model 4– CVD: 1.99; 95%CI:1.25–3.18, IHD: 2.29; 95%CI: 1.25-4.21). Depression was associated with all-cause mortality in models 1-3 (model 1- 1.97; 95%CI: 1.27-3.06, model 2- 1.94; 95%CI: 1.24-3.03, model 3- 1.77; 95%CI: 1.09-2.88) but was rendered non-significant after adjusting for HRQoL (model 4- 1.54; 95%CI: 0.91-2.60), though HR still indicated same direction with important magnitude (Table 2).

Detailed results of models 1 to 4 for all clinical outcomes (CVD, CKD, IHD and all-cause mortality) are shown in Supplementary Tables 3–6. In the final models, smoking, high HbA1c and lipid values were consistently associated with these adverse outcomes with physical activity and non-use of insulin associated with better outcomes. Although CKD was not associated with depression, patients who reported having regular exercise (3-4 times per week) had reduced risk of CKD (HR: 0.61, 95%CI: 0.41–0.89) (model 4). In the sensitivity analysis, HR of depression with all clinical outcomes were comparable using PHQ-2 (≥3) or PHQ-9 (≥7) scores to define depression (Supplementary Tables 7-10).

Amongst the nine items of PHQ-9 questionnaire, only Q4 (feeling tired or having little energy) was associated with all-cause mortality (HR:1.66, 95%CI: 1.30–2.12) after adjustment for covariates (Table 3).

4 Discussion

Despite the growing burden of depression and T2D, their inter-relationships with PRO such as HRQoL and health behaviors on clinical outcomes had not been fully explored. In this ongoing clinic-based diabetes register set up for quality improvement purpose, 1 in 5 Chinese patients with T2D had either CVD or CKD at enrolment. Amongst these patients, 15% had depressive symptoms highlighting the importance of including PRO in patients with diabetes at high risk of multiple morbidities. In the remaining patients without complications, 11.9% had depression who were more likely to be women, had younger age and treated with insulin. They also had suboptimal control of risk factors, health behaviors and treatment adherence and worse HRQoL than those without depression.

Our results align with that reported in the UK and US diabetes population (24), which suggest a higher prevalence of depression among younger patients diagnosed with diabetes, particularly those with young-onset diabetes, compared to those with late-onset diabetes. Younger individuals with diabetes may face unique challenges and psychosocial burdens that contribute to a higher risk of depression in these regions. In contrast, depression prevalence increased with age in a study conducted in South

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TABLE 1 Baseline clinical profiles, patient reported outcomes and clinical events in Chinese patients with type 2 diabetes in the Hong Kong Diabetes Register (2013-2019) stratified by depression defined as PHQ-9 score ≥7.

	No depression (*n* = 3988)		Depression (*n* = 537)		P-value
	Mean or Frequency	SD or %	Mean or Frequency	SD or %	
Demographics					
Age (years)	55.9	10.6	54.4	10.6	**0.001**
Gender (Male)	2287	57.3%	259	47.3%	**<0.001**
Occupation status					**<0.001**
Employed	2215	55.5%	247	46.0%	
Unemployed	1770	44.4%	290	54.0%	
Highest education attained					**0.016**
Primary school, illiterate or others	913	22.9%	148	27.6%	
Middle school	1855	46.5%	259	48.2%	
Higher school	384	9.6%	44	8.2%	
College or above	815	20.4%	86	16.0%	
Clinical risk factors					
Duration of diabetes (years)	8.6	7.5	9.2	7.8	0.064
Body mass index (kg/m^2)	26.2	4.74	26.5	4.9	0.172
Systolic blood pressure (mmHg)	130	17.1	130	18.6	0.940
Diastolic blood pressure (mmHg)	75.1	10.8	75.5	11.3	0.364
Self-care and patient-reported outcomes					
Use of tobacco					0.155
Non-smoker	2883	72.3%	394	73.4%	
Current smoker	472	11.8%	74	13.8%	
Ex-smoker	630	15.8%	68	12.7%	
Missing	3	0.1%	1	0.2%	
Regular physical activity in last 3 months					**<0.001**
No regular physical activity	1464	36.7%	265	49.3%	
1-3 times per week	829	20.8%	95	17.7%	
3-4 times per week	337	8.4%	41	7.6%	
5 times per week	175	4.4%	11	2.0%	
>5 times per week	1140	28.6%	124	23.1%	
Missing	3	0.1%	1	0.2%	
Adherence to a balanced diet in last 3 months					0.396
Never	85	2.1%	16	3.0%	
No	286	7.2%	48	8.9%	
Occasional	1670	41.9%	219	40.8%	
Yes	1936	48.5%	252	46.9%	
Missing	11	0.3%	2	0.4%	
Self-monitoring of blood glucose	2942	73.8%	400	74.5%	0.091

(Continued)

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TABLE 1 Continued

	No depression (*n* = 3988)		Depression (*n* = 537)		P-value
	Mean or Frequency	SD or %	Mean or Frequency	SD or %	
Self-care and patient-reported outcomes					
Missing	288	7.2%	50	9.3%	
Having regular follow-up	3820	95.8%	521	97.0%	0.383
Missing	1	0.0%	0	0%	
EQ-5D-3L domains[a]					
Mobility					**<0.001**
No problems in walking about	3785	96.3%	427	80.7%	
Some problems in walking about	137	3.5%	100	18.9%	
Confined to bed	2	0.1%	2	0.4%	
Missing	64	1.6%	8	1.5%	
Self-care					**<0.001**
No problems with self-care	3884	99.1%	498	94.1%	
Some problems washing or dressing myself	34	0.9%	28	5.3%	
Unable to wash or dress myself	2	0.1%	2	0.4%	
Missing	68	1.7%	8	1.5%	
Usual activities					**<0.001**
No problems with performing my usual activities	3812	97.1%	430	81.3%	
Some problems with performing my usual activities	109	2.8%	93	17.6%	
Unable to perform my usual activities	3	0.1%	6	1.1%	
Missing	64	1.6%	8	1.5%	
Pain/discomfort					**<0.001**
No pain or discomfort	2655	67.8%	180	34.0%	
Moderate pain or discomfort	1218	31.1%	310	58.6%	
Extreme pain or discomfort	44	1.1%	39	7.4%	
Missing	71	1.8%	8	1.5%	
Anxiety/depression					**<0.001**
Not anxious or depressed	3405	87.1%	169	32.0%	
Moderately anxious or depressed	498	12.7%	330	62.5%	
Extremely anxious or depressed	6	0.2%	29	5.5%	
Missing	79	2.0%	9	1.7%	
Medication adherence					**<0.001**
Self-rated medication adherence score (0-100%)	92.4	12.2	88.5	16.8	
Missing	218	5.5%	29	5.4%	
Use of medications					
Lipid lowering drugs	2272	57%	308	57.4%	0.866
Antihypertensive drugs including ACEIs or ARBs	2524	63.3%	351	65.4%	0.349

(Continued)

TABLE 1 Continued

	No depression (*n* = 3988)		Depression (*n* = 537)		P-value
	Mean or Frequency	SD or %	Mean or Frequency	SD or %	
Use of medications					
Insulin	1011	25.4%	183	34.1%	**<0.001**
Oral anti-diabetic drugs	3505	87.9%	477	88.8%	0.530
Laboratory results					
HbA1c (%)	7.6	1.5	7.9	1.8	**0.005**
LDL-cholesterol (mmol/L)	2.4	0.7	2.4	0.8	0.097
HDL-cholesterol (mmol/L)	1.3	0.4	1.3	0.4	0.237
Triglyceride (mmol/L)	1.6	1.1	1.7	1.7	**0.014**
Spot urine albumin creatinine ratio (mg/mmol) [c]	1.2	0.5-3.9	1.5	0.6-6.5	**<0.001**
eGFR (mL/min, 1.73m^2)[b]	92.7	14.7	94.1	15.6	**0.028**
Clinical outcomes					
Follow up duration [c]	5.6	4.5-6.2	5.4	4.3-6.1	0.408
All-cause mortality	115	2.9%	26	4.8%	**0.014**
All cardiovascular outcomes	133	3.3%	31	5.8%	**0.005**
Ischaemic heart disease	75	1.9%	20	3.7%	**0.005**
Chronic kidney disease	459	11.5%	74	13.8%	0.125

[a]EQ5D-3L items were rated on the following scale: 1-no problem, 2-some problems to 3-extreme problems.
[b]eGFR = glomerular filtration rate from CKD-EPI equation.
[c]Median and Interquartile range.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Bold values represent p<0.05.

India (25). This discrepancy could be attributed to region-specific trends and characteristics. In a separate study investigating age- and sex-specific hospital bed-day rates in a territory-wide cohort, we observed bimodal distribution associated with type 2 diabetes but not in those without. While the overall rate of hospital bed-days increased with age, among individuals diagnosed with T2D before the age of 40, 38.4% of hospital bed-days were attributed to mental health disorders (26). This highlights the severity of the issue and underscores the need for more comprehensive screening, interventions, and support services targeting mental health problems in young individuals with diabetes.

After 6 years of observations, patients with depression were 2 times more likely to develop CVD, mainly due to IHD, and all-cause death. These risk associations remained significant after adjusting for demographic and cardiometabolic risk factors, medications, self-care and HRQoL, albeit with some attenuation after adjusting for HRQoL. Exploratory analysis suggested that good self-care was associated with reduced risk of CKD. For the first time, we found that a single item Q4 (tiredness, low energy) in PHQ-9 was independently associated with all-cause mortality, suggesting that patients with failure to concentrate, excessive tiredness, motor retardation or restlessness required further evaluation of psychosocial-behavioural health. In support of professional practice guidelines (13), our results confirmed the importance of collecting PROs such as PHQ-9, EQ-5D-3L and psychosocial-behavioral factors for prognostication and providing holistic care to improve outcomes (1).

4.1 Associations of depression with CVD and all-cause mortality adjusting for HRQoL

In this study, young patients and women had higher prevalence of depression than their counterparts. Given the close associations between depression and clinical outcomes, our observations accorded with the higher incidence of all-cause and cardiovascular events in Asian women than men with diabetes (27). In agreement with other researchers, we also found that depression was associated with smoking, hypertension, poor metabolic control, albuminuria (28), suboptimal self-care (29) and drug non-adherence (30) which contributed to increased risk for CVD. In other studies, adherence to diet and exercise, SMBG (31) and foot care (32) were associated with reduced morbidity and mortality in patients with T2D. The introduction of risk assessment and education program at PWH had closed some care gaps as evidenced by similar use of ACEi/ARB and statin as well as similar frequency of SMBG between the depressed and non-depressed

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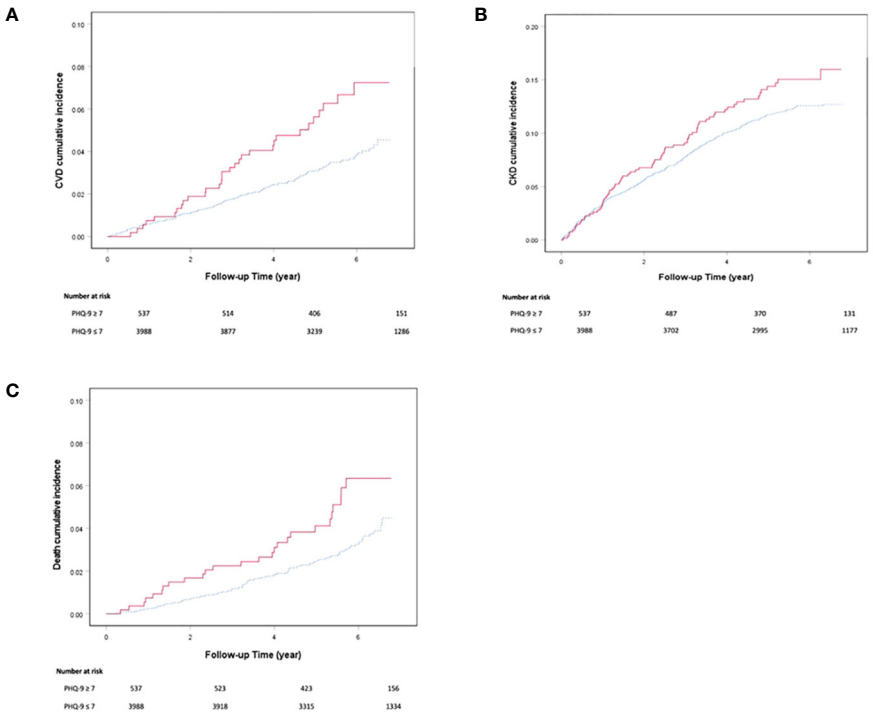

FIGURE 1
Cumulative incidence of **(A)** cardiovascular disease, **(B)** chronic kidney disease and **(C)** all-cause mortality derived from Kaplan-Meier analysis in Chinese patients with type 2 diabetes with or without depression defined by PHQ-9 score ≥ 7. The red solid line denotes patients with depression and the blue dotted line denotes patients without depression.

groups. However, depressed patients remained more likely to be treated with insulin, had higher HbA1c, worse lipid profiles, heavier albuminuria and reported poorer drug adherence and physical inactivity than the non-depressed group calling for more personalized treatment in these patients.

Compared with the non-depressed group, patients with depression were less likely to have balanced diet by 2.6% and regular exercise by 12.6%. In line with reports from European patients (33), after adjusting for these confounders including socioeconomic status represented by level of education and occupation, depression was associated with 2 times increased risk of CVD, notably IHD. These findings concurred with our previous report of 2 times increased risk of CVD in Chinese patients with T2D diagnosed with depression who received specialist care (12). In the current cohort, associations of depression based on PHQ-9 and CVD was attenuated after adjusting for HRQoL, albeit remained significant. Depression was also associated with 2 times increased risk of all-cause death, which was rendered non-significant after HRQoL adjustment.

On the other hand, we did not find an association between depression and CKD in both unadjusted and adjusted models. In another Chinese cohort, 37.8% had depression which was associated with CKD stages in a graded manner (34). Chinese adults with normal kidney function and severe depressive symptoms had 39% higher risk of rapid decline in kidney function than those without depression (35). Using PHQ-9≥10 to define depression, other researchers had reported an adjusted odds ratio of 1.36 (95% CI: 1.04-1.77) for microalbuminuria in patients with T2D (36). In this study, we excluded patients with CKD (eGFR<60 ml/min/1.73m^2) at baseline, 17% of whom had depression. In the remaining patients without or with early CKD, longer follow-up will be needed to evaluate its association with depression and deterioration of renal function.

The magnitude of association between depression, CVD, IHD and all-cause mortality is consistent even after accounting for the influence of HRQoL and PROs, suggests that this relationship holds true across diverse patient populations with diabetes, regardless of their quality of life, lifestyle and self-management practices. These findings highlight the potential impact of mental health conditions on the development of cardiovascular complications in all patients with diabetes, denoting the importance to develop evidence-based policies and prevention interventions that address not only the acute health conditions of patients with diabetes, but also provide comprehensive support for their psychiatric well-being.

The complex nature of diabetes is evident, as studies have demonstrated strong intercorrelations and impacts among its physical, and psychosocial components (37, 38). This complements our previous study results which modelled that individuals diagnosed with T2D before the age of 40 may accrue an average of 100 inpatient bed days when they reach 75 years old, with approximately one-third of hospitalizations attributed to mental illness (39). Considering the 2023 pricing of public hospital psychiatric bed day cost at $300 USD in Hong Kong (40), and extrapolating the modelled results to the territory-wide cohort of 21,000 patients diagnosed with diabetes before the age of 40 (39), it is projected that an estimated total of $210 million USD

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TABLE 2 Incidence and hazard ratios (95% confidence interval) of depression defined by PHQ-9 score ≥7 for clinical outcomes in Chinese patients with type 2 diabetes.

Clinical outcomes	Depression (n = 537)	P-value
All-cause mortality (n=141)		
Unadjusted	1.75 (1.14-2.68)	**0.010**
Model 1	1.97 (1.27-3.06)	**0.003**
Model 2	1.94 (1.24-3.03)	**0.004**
Model 3	1.77 (1.09-2.88)	**0.022**
Model 4	1.54 (0.91-2.60)	0.108
All cardiovascular disease [a] (n=164)		
Unadjusted	1.80 (1.22-2.67)	**0.003**
Model 1	1.97 (1.32-2.96)	**0.001**
Model 2	1.86 (1.24-2.80)	**0.003**
Model 3	2.04 (1.32-3.16)	**0.001**
Model 4	1.99 (1.25-3.18)	**0.004**
Ischaemic heart disease (n=95)		
Unadjusted	2.06 (1.26-3.38)	**0.004**
Model 1	2.41 (1.44-4.04)	**<0.001**
Model 2	2.37 (1.41-3.99)	**0.001**
Model 3	2.83 (1.62-4.94)	**<0.001**
Model 4	2.29 (1.25-4.21)	**0.008**
Chronic kidney disease (n=533) [b]		
Unadjusted	1.24 (0.97-1.58)	0.087
Model 1	1.24 (0.96-1.61)	0.100
Model 2	1.22 (0.95-1.58)	0.125
Model 3	1.14 (0.87-1.51)	0.344
Model 4	1.04 (0.77-1.40)	0.820

Model 1: Adjusted for age, gender, occupation status, highest education attained, smoking status, duration of diabetes, BMI, systolic and diastolic blood pressure, HbA1c, lipid profile (LDL cholesterol, HDL cholesterol, triglycerides).
Model 2: Model 1 + adjusted for Ln(ACR+1), eGFR, use of lipid lowering drugs, ACEI or ARB, other anti-hypertensive drugs, anti-diabetic drugs and insulin.
Model 3: Model 2 + adjusted for adherence to balanced diet, physical activity, level of medication adherence and self-monitoring of blood glucose in last 3 months and regular follow up in last 1 year.
Model 4: Model 3 + adjusted for ED-5D-3L Q1-Q4 (excluding Q5 on anxiety/depression)
[a]Including IHD, stroke and PVD.
[b]Models 1-4 for CKD outcome (eGFR<60 ml/min/1.73m^2), Ln(urine ACR+1) and eGFR were excluded as covariates.
Bold values represent p<0.05.

may be spent on long-term mental illness-related hospitalizations in patients YOD over the next 35 years in Hong Kong. It is important to note that this estimation excludes potential costs associated with comorbid depression, such as cardiovascular disease (CVD) and mortality, in patients with diabetes. Another study conducted in Singapore identified one of the highest healthcare utilization clusters was characterized by a high prevalence of depression in women under the age of 65 with short-to-moderate disease duration (41). These findings emphasize the need for a holistic approach to diabetes management that takes into account the multifaceted aspects of the disease.

4.2 Association of PHQ-9 Q4 (lack of energy) with all-cause mortality in patients with T2D

In this cohort, 11.9% of patients had depressive symptoms and the majority had not been diagnosed. Depressive symptomatology can be heterogeneous with diverse cultural norms, perceptions and interpretations. International practice guidelines suggested screening for depression in patients with diabetes, especially in those with poor glycaemic control (13). However, in busy clinic settings, routine administration of PHQ-9 could be challenging, calling for a simple but robust screening tool to identify patients with comorbid T2D and depression.

In Hong Kong, we reported higher discriminatory power with PHQ-9 than Center for Epidemiological Studies Depression (CES-D) scale for depression screening (19). The latter puts more emphasis on the affective component of depression. The optimal cutoff value to detect depressive symptoms varied between populations and settings. For example, the optimal cut-off score for PHQ-9 in outpatient population with diabetes was 9 in Malawi (sensitivity: 64%, specificity: 94%) (42), 12 in Netherlands (sensitivity: 75.7%, specificity: 80.0%) (43) and 7 in Poland (sensitivity 90.62%; specificity 90.22%) (44). Before we introduced PHQ9 in our routine service, 99 randomly selected patients enrolled in the register were interviewed by psychiatrists using the Mini International Neuropsychiatric Interview as the golden standard (19). Utilizing receiver operating characteristic (ROC) analysis, the area under the curve (AUC) was 0.85(95%CI:0.76–0.94) with a cutoff score of ≥7 yielding an optimal balance between sensitivity (82.6%) and specificity (73.7%). By contrast the widely accepted score of 10 had comparable specificity (84.2%) but poor sensitivity (56.5%). When the categorical algorithm was used to define major depressive disorder based on 1) 5 of 9 items including item 1 (anhedonia) or 2 (depressed mood) being endorsed as "more than half the days" or "nearly every day" or 2) Item 9 (suicidal ideation) regardless of duration, the sensitivity was 39.1% and specificity, 96.1% (19).

In this study, Chinese patients with T2D were more likely to report somatic symptoms with Q4 in PHQ-9 (feeling tired or having little energy) being independently associated with 57% increased risk of all-cause mortality. Other researchers had reported a correlation coefficient of 0.50 between Q4 and four items in Fatigue Questionnaire (45). Patients with diabetes who reported fatigue were 10.37 times more likely to have depression than those without symptoms of fatigue (46, 47). The robust associations of all-cause mortality with Q4 of PHQ-9, at least in Chinese patients with T2D, called for routine enquiry of physical activity and energy level to identify patients at risk of depression. Apart from using the overall PHQ-9 score to screen for depression, a high score for Q4 should alert healthcare providers to conduct comprehensive assessment of mental health for psychosocial interventions.

TABLE 3 Hazard ratios (95% confidence interval) of questions from PHQ-9 for clinical outcomes in Chinese patients with type 2 diabetes.

PHQ9 Items	All-cause mortality	P-value	All CVD outcomes [a]	p-value	CKD [b]	P-value
Q1: Little interest or pleasure in doing things						
	0.79 (0.56-1.11)	0.165	1.31 (0.95-1.80)	0.100	1.11 (0.93-1.34)	0.254
Q2: Feeling down, depressed or hopeless						
	1.01 (0.63-1.61)	0.970	0.85 (0.54-1.34)	0.494	1.11 (0.85-1.44)	0.450
Q3: Trouble falling or staying asleep, or sleeping too much						
	0.95 (0.75-1.20)	0.678	1.17 (0.95-1.46)	0.147	1.03 (0.91-1.17)	0.611
Q4: Feeling tired or having little energy						
	1.66 (1.30-2.12)	**<0.001**	1.09 (0.84-1.42)	0.500	1.05 (0.90-1.22)	0.542
Q5: Poor appetite or overeating						
	1.05 (0.11-1.42)	0.771	0.99 (0.74-1.34)	0.954	1.02 (0.86-1.22)	0.824
Q6: Feeling bad about yourself — or that you are a failure or have let yourself or your family down						
	1.08 (0.73-1.60)	0.699	1.04 (0.71-1.53)	0.826	0.90 (0.71-1.14)	0.370
Q7: Trouble concentrating on things, such as reading the newspaper or watching television						
	0.94 (0.69-1.28)	0.696	0.99 (0.72-1.35)	0.935	1.07 (0.90-1.26)	0.436
Q8: Moving or speaking so slowly that other people could have noticed, or so fidgety or restless that you have been moving a lot more than usual						
	1.10 (0.77-1.57)	0.604	0.87 (0.56-1.33)	0.505	0.95 (0.74-1.21)	0.655
Q9: Thoughts that you would be better off dead, or thoughts of hurting yourself in some way						
	1.72 (0.92-3.23)	0.089	1.70 (0.91-3.17)	0.094	0.60 (0.33-1.10)	0.098

Adjusted for age, gender, occupation status, highest education attained, smoking status, duration of diabetes, BMI, systolic and diastolic blood pressure, HbA1c, lipid profile (LDL-cholesterol, HDL-cholesterol, triglycerides), Ln(ACR+1), eGFR, use of lipid lowering drugs, ACEI or ARB, other anti-hypertensive drugs, anti-diabetic drugs and insulin, adherence to balanced diet, physical activity, level of medication adherence and self-monitoring of blood glucose in last 3 months and regular follow up in last 1 year, ED-5D-3L: Q1-Q4 (excluding Q5 on anxiety/depression). All regressions on each PHQ-9 item were adjusted for other PHQ-9 items.

[a]Including IHD, PVD and stroke.

[b]CKD outcome (eGFR<60 ml/min/1.73m^2): Ln(urine ACR+1) and eGFR were excluded as covariates.

Bold values represent p<0.05.

In a recent network analysis study conducted in Canada, involving 1,796 middle-aged patients with diabetes (48), findings indicate that early targeted intervention on behavioral activation and cognitive restructuring that address "failure" (item 6 in PHQ-9),"uncontrollable worry, "excessive worrying" and "difficulty relaxing" [item 2-4 in Diabetes Distress Scale (DSS-17)] may potentially prevent the development of future comorbid mental conditions in individuals with type 2 diabetes (48). In our current study, we reported that the majority of our patients with T2D and comorbid depression (PHQ-9 ≥7) scored high on somatic problems such as "sleeping difficulties" (item 3) and "lack of energy" (item 4) in PHQ-9. The inclusion of network analysis in future investigations on depression in Chinese patients with diabetes holds significant potential to contribute valuable insights into the complex dynamics and interactions among symptoms and domains of depression. This approach has the capacity to enhance our ability to precisely identify and characterize different subtypes of depression in this population for designing effective targeted interventions.

4.3 Study implications

The myriad of complications associated with diabetes, use of long-term medication, necessity for regular follow-up visits, and demand for lifestyle changes may adversely impact an individual's lifestyles, perspectives and emotions. These factors can be modified by sociodemographic factors such as education, poverty and personal relationships in family or work. All these dimensions can interact in a complex manner to influence quality of life which in turn can feed back on these psychosocial-behavioral dimensions. Apart from influencing self-care, these perceptions and emotions may be associated with biological changes (8). There are now growing interests on the associations of gene-environment interactions with depression and health behaviors in diabetes with inconclusive results (49). In a recent Chinese study, dietary intake, alcohol drinking and smoking, physical activity, and socioeconomic status were reported to interact with genetic variants to modulate the risks of impaired fasting glucose and impaired glucose tolerance (50). In this light, despite the many technological

advances in the field of diabetes, such as medications and monitoring tools, there remain considerable care gaps with high complications rates calling for better understanding of genetic factors and PROs and clinical outcomes to improve physical, mental and behavioral health (1, 51).

Dysregulation of neurohormonal and immune systems may underlie the clustering of subphenotypes including cardiovascular-renal complications (52). In randomized controlled trials, multicomponent care including use of medications and anti-depressants, lifestyle modification and psychosocial support improved depression, PRO and cardiometabolic risk factors in patients with T2D and depression (53). In a secondary analysis of the Look Ahead Study, obese patients with T2D receiving intensive lifestyle intervention had reduced incidence of depression and CKD than the control group (54, 55). Our group also reported benefits of peer support using telephone counselling in reducing hospitalizations in patients with T2D especially in those with negative emotions (56). Other community- and family-based interventions including use of lifestyle intervention and digital technologies also improved QoL in patients with diabetes (57). Taken together, there is a need to integrate PHQ-9 questionnaire into routine diabetes screening and assessment to detect these high risk individuals early for personalized care in order to improve their physical, social and mental health.

5 Strengths and limitations

The comprehensiveness of data collection including biomedical-psychosocial-behavioural factors, HRQoL and clinical outcomes is a major strength of the study, albeit not without limitations. Our cohort was recruited in an ambulatory clinic setting catering patients with more complex and specialized healthcare needs, thus may restrict the broader applicability of our findings to a primary care context. Furthermore, in this quality improvement program, patients with PHQ-9 score >10 were referred to an on-call endocrinologist and psychiatrist while patients with score of 9-10 received counselling from trained nurses. The absence of a comprehensive psychiatric evaluation for all patients may limit our ability to accurately determine the true prevalence of depression in this population. Health behaviors such as adherence to medication, diet and physical activity in last 3 months were subject to recall bias. Despite their frequent coexistence, diabetes and depression can independently have negative impacts on clinical outcomes. In this diabetes register, we did not have patients without T2D and could not test the mediation effects of depression-alone, T2D-alone and co-morbid depression and T2D on clinical outcomes compared to those with neither condition.

It is important to note that our study is designed to demonstrate the risk associations between clinical outcomes and baseline depression and PROs. Therefore, conclusions cannot be drawn regarding the temporal changes of depression and PROs over time. Furthermore, we acknowledge that as many as 64% of patients with depression might have comorbid mental disorders (58) which could confound our results. However, due to the pragmatic nature of the register, we did not capture full details of other mental illness in these patients. In this context, randomized controlled trials had confirmed the benefits of multidisciplinary care on physical and mental health in patients with T2D and depression (53), in support of identifying these patients early for intervention. The attenuation of risk association between depression and clinical outcomes by HRQoL suggested that other social, environmental and behavioral factors might be important which calls for more systemic data collection to inform interventions beyond healthcare. To unravel these complex inter-relationships, advanced methodology such as structural equation modelling will be needed to quantify the causal effects of these factors to inform practice and policies (59).

6 Conclusions

In conclusion, the association between depression, CVD and IHD remains significant across all patients with diabetes, regardless of their HRQoL and health behaviours. Despite the association between depression and all-cause mortality being attenuated after adjusting for HRQoL, the effect size and direction of association remained substantial. Our findings highlight the importance of holistic diabetes management with comprehensive support for mental well-being. Given the complex nature of diabetes, including PROs such as PHQ-9, EQ-5D-3L and health behaviors can further increase the value of a regular structured assessment program for identifying high risk patients for holistic management. In Chinese patients with T2D and depression, somatic complaints were common with lack of energy captured by item 4 in PHQ-9 being independently associated with all-cause mortality. In busy clinic settings, patients who reported physical inactivity or low energy level warrant further evaluation of emotional health for early intervention.

Data availability statement

The datasets presented in this article are not readily available because Due to legal restrictions, patient-level data cannot be made publicly available. Aggregate data may be available upon reasonable request. Requests to access the datasets should be directed to jchan@cuhk.edu.hk.

Ethics statement

This study involving humans was approved by The Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committe. This study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants.

Author contributions

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Conflict of interest

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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1284799/full#supplementary-material

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Non-alcoholic fatty liver disease and coexisting depression, anxiety and/or stress in adults: a systematic review and meta-analysis

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Background: Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease, affecting 25-30% of the general population globally. The condition is even more prevalent in individuals with obesity and is frequently linked to the metabolic syndrome. Given the known associations between the metabolic syndrome and common mental health issues, it is likely that such a relationship also exists between NAFLD and mental health problems. However, studies in this field remain limited. Accordingly, the aim of this systematic review and meta-analysis was to explore the prevalence of one or more common mental health conditions (i.e., depression, anxiety, and/or stress) in adults with NAFLD.

Methods: PubMed, EBSCOhost, ProQuest, Ovid, Web of Science, and Scopus were searched in order to identify studies reporting the prevalence of depression, anxiety, and/or stress among adults with NAFLD. A random-effects model was utilized to calculate the pooled prevalence and confidence intervals for depression, anxiety and stress.

Results: In total, 31 studies were eligible for inclusion, involving 2,126,593 adults with NAFLD. Meta-analyses yielded a pooled prevalence of 26.3% (95% CI: 19.2 to 34) for depression, 37.2% (95% CI: 21.6 to 54.3%) for anxiety, and 51.4% (95% CI: 5.5 to 95.8%) for stress among adults with NAFLD.

Conclusion: The present findings suggest a high prevalence of mental health morbidity among adults with NAFLD. Given the related public health impact, this finding should prompt further research to investigate such associations and elucidate potential associations between NAFLD and mental health morbidity, exploring potential shared underlying pathophysiologic mechanisms.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42021288934.

KEYWORDS

non-alcoholic fatty liver disease, NAFLD, NASH, mental health, depression, anxiety, stress

Introduction

Non-alcoholic fatty liver disease (NAFLD) develops as a result of excess accumulation of fat in hepatocytes, which is unrelated to excess alcohol intake, and extends from simple steatosis to non-alcoholic steatohepatitis (NASH) with or without fibrosis that may lead to liver failure and even hepatocellular carcinoma (1–3). NAFLD currently constitutes the most prevalent chronic liver disease worldwide with prevalence rates of up to 25-30% among the general adult population (1–3). Furthermore, NAFLD is frequently linked to the metabolic syndrome which represents a cluster of interrelated cardio-metabolic conditions associated with central obesity, and obesity-related insulin resistance [i.e., type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia] (4). Indeed, it is reported that approximately 85% of individuals with NAFLD exhibit at least one element of the metabolic syndrome (5), with the prevalence of NAFLD among individuals with obesity reaching 70-90% (2, 3, 6). In addition, it is reported that future generations are at risk of a 'second wave' of metabolic liver disease, in the form of NAFLD, owing to potential early-onset as an impact of weight issues during childhood (7).

Owing to these associations with obesity and the metabolic syndrome, NAFLD is often referred to as the hepatic manifestation of metabolic syndrome (8–11). Of note, to highlight these links and to more accurately describe the pathophysiology of NAFLD, renaming this condition to metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD) has been recently proposed (12, 13). Indeed, as reported by the European Association for the Study of the Liver (14), the term 'MASLD' is reflective of patients with hepatic steatosis who experience more than one of five cardiometabolic risk factors, and thus is considered to be less stigmatizing and a preferred nomenclature as opposed to the term 'NAFLD'. Taking into account these newer proposed terms for NAFLD, it is noteworthy that, in addition to introducing the new nomenclatures of MAFLD and MASLD in the scientific literature, the definitions of these nosologies are also redefined based on specific diagnostic criteria for each term (15–18). As such, whereas the diagnosis of NAFLD requires the exclusion of alternative etiologies of steatosis/steatohepatitis (e.g., alcoholic or viral hepatitis), the diagnosis of both MAFLD and MASLD acknowledges that in such patients a combination of dysmetabolic and other (e.g. alcohol-related) pathophysiologic components may contribute to the underlying hepatic nosology (15–18). Accordingly, these conditions are diagnosed based primarily on the presence of metabolic dysfunction rather than on the exclusion of other causes of steatosis/steatohepatitis. Thus, MAFLD is defined as steatosis which is detected - either by imaging or blood biomarkers/scores or histology - in the presence of at least either obesity, and/or T2DM, or at least two out of seven predefined dysmetabolic risk abnormalities (relating to waist circumference, blood pressure, plasma triglycerides, plasma HDL-cholesterol, plasma high-sensitivity C-reactive protein, prediabetes, and the homeostatic model assessment for insulin resistance score) in those adults who are lean (normal weight by ethnic-specific BMI criteria) and do not have T2DM (15, 16, 18). Similarly, MASLD is defined as the presence of steatotic liver disease combined with at least one of five predefined cardio-metabolic criteria relating to BMI, fasting plasma glucose levels, blood pressure, plasma triglycerides, and plasma HDL-cholesterol (17). From these definitions, it is evident that, despite the significant overlap (>95% of adult patients previously diagnosed as having NAFLD also fulfil the MASLD diagnostic criteria) (19), the terms NAFLD, MAFLD and MASLD cannot always be applied interchangeably, whilst there are also concerns regarding whether the clinical evidence accumulated for NAFLD can be directly extrapolated to MAFLD and MASLD (20). Indeed, following the introduction of the term MASLD, researchers have called for more flexible editorial conduct regarding the proposed MASLD nomenclature, since these three nosologies/terms are defined differently and, thus, accurate distinction between NAFLD, MAFLD, and MASLD is important for the accuracy of the relevant scientific literature (20). To address issues relating to the different definitions of NAFLD, MAFLD and MASLD, in the present systematic review the NAFLD terminology has been retained since

the accumulated evidence of interest has been primarily accumulated under the NAFLD nomenclature/definition.

NAFLD often remains asymptomatic for a lengthy duration, hence representing a 'silent epidemic' (21). However, NAFLD constitutes a significant risk factor for cardiovascular disease (CVD), which is reported as the most common cause of mortality in this patient population (21, 22). In parallel to the data highlighting NAFLD as an evolving epidemic, growing evidence also suggests direct associations between common mental health issues, such as depression, anxiety and chronic stress, and the metabolic syndrome (23, 24). Based on the strong overlap between NAFLD and the metabolic syndrome, it seems likely that such associations may also be observed in individuals with NAFLD, potentially with shared underlying mechanisms that create a feed-forward vicious cycle between NAFLD and such mental health morbidity (12). However, further research is required to fully clarify the complete spectrum of such potential associations. Furthermore, it is plausible that certain features associated with NAFLD, such as lack of awareness regarding the condition, fatigue, and perceived stigma (13, 25–27), may result in feelings of isolation and loneliness (28), which, in turn, may have a further impact on mental health and have been reported to be associated with cardio-metabolic disorders linked to NAFLD, including obesity, T2DM, metabolic syndrome, and CVD (29, 30).

In this context, research addressing potential mental health issues in individuals with NAFLD warrants attention. However, despite previous systematic reviews which have investigated links between psychological health and NAFLD and associations with depression (31–33), such issues remain relatively under-recognized in clinical practice. Indeed, a systematic review by Macavie et al. (32) draws attention to depression and anxiety as the most relevant emotional factors among individuals with NAFLD/NASH, suggesting that such conditions may be regarded as cognitive-behavioral in nature with lifestyle modification representing the most effective management (32). Furthermore, additional systematic reviews - albeit with a low number (up to ten) of included eligible studies (31, 33) - have demonstrated an association between NAFLD and depression.

Given the limited but growing data in this field, the present systematic review and meta-analysis aimed to explore the prevalence of one or more common mental health conditions of interest (i.e., depression, and/or anxiety, and/or stress) in adults with NAFLD, and to identify relevant gaps and weaknesses within the existing literature.

Methodology

Search strategy and study selection

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (34), and was registered with the International Prospective Register of Systematic Reviews (PROSPERO Reference Number: CRD42021288934).

Inclusion criteria were any study (observational or interventional) published as a scientific paper reporting the prevalence of at least one of the three mental health conditions of interest (i.e., depression, anxiety, or chronic psychological stress) in adults (male and female) aged over 18 years with a diagnosis of NAFLD.

A search was conducted in relation to NAFLD and mental health utilizing the PubMed, EBSCOhost, ProQuest, Ovid, Web of Science, and Scopus databases. The search terms applied for the PubMed database included the following: ((metabolic associated fatty liver disease[Title/Abstract] OR MAFLD OR metabolic dysfunction associated fatty liver disease[Title/Abstract] OR NAFLD[MeSH Terms] OR NAFLD OR non-alcoholic fatty liver disease[Title/Abstract] OR non-alcoholic steatohepatitis[Title/Abstract] OR NASH)) AND ((mental health [MeSH Terms] OR mental health[Title/Abstract] OR "mental health" OR "mental well-being" OR "mental wellbeing" OR depression[MeSH Terms] OR depression[Title/Abstract] OR major depressive disorder [MeSH Terms] or major depressive disorder[Title/Abstract] OR major depression[Title/Abstract] OR MDD OR anxiety[MeSH Terms] OR anxiety[Title/Abstract] OR generalized anxiety disorder[MeSH Terms] OR generalized anxiety disorder[Title/Abstract] OR generalized anxiety disorder[Title/Abstract] OR stress, psychologic[MeSH Terms] OR disorder, mood[MeSH Terms] OR distress[Title/Abstract])). This search string was applied and adapted to the syntax of all of the utilized databases (Supplementary Table 1).

The searches were conducted by LL and the results of the searches were imported into Covidence systematic review software V2.0 (Veritas Health Innovation, Melbourne, Australia). Following removal of duplicates, title and abstract screening was completed by SS, LL and CK. No publication date restriction was adopted for the timeframe of the search strategy (no publication date restriction up to 2022). Full-text screening was performed by SS and LL, with any disputes being resolved by the inclusion of a third reviewer (CK).

Data extraction and quality assessment

Data (including country, year, study design, number of participants, mental health measures, NAFLD diagnosis, gender, and age) were independently extracted by two reviewers (SS, LL), with the outcome of interest being the prevalence of depression, anxiety, and/or stress. Any disagreements or possible input errors were checked and resolved via discussion between the two reviewers.

Risk of bias assessment was performed by SS and LL using the Covidence systematic review software V2.0 which utilizes a standard template based on the Cochrane Risk of Bias version 1 tool. The assessment criteria were amended within Covidence to reflect risk of bias assessment for non-randomized studies (RoBaNS) (35). Any disputes were settled by a third reviewer (CK). The categories assessed were selection of participants, confounding variables, exposure measurements, selective outcome reporting, incomplete outcome data, and other sources of bias. Author judgement for risk of bias was rated as high, low, or unclear for each category (Supplementary Figure 1).

Statistical analysis

The Freeman-Tukey variant of the arcsine square root transformation was applied in order to normalize the raw prevalence estimates obtained from each included study; an approach commonly used for the pooling of proportions (36). For the performed meta-analyses, the DerSimonian-Laird random-effects model was utilized; a methodology frequently adopted in anticipation of discrepancies in population demographics, research techniques, and study environments (37). The heterogeneity amongst studies was evaluated by examining the forest plots, and by applying the chi-squared test for heterogeneity, setting a statistical significance level of $P \leq 0.10$, as well as the use of the I^2 statistic, with a 50% value indicative of moderate heterogeneity (38), and a 75-100% value representing considerable heterogeneity (39).

Subsequent to the primary analyses, additional subgroup analyses were also conducted, differentiated by the types of validated instruments used to deduce prevalence estimates. The potential for reporting bias was examined using a funnel plot, a graphical tool typically used to assess the presence of publication bias in systematic reviews (40). The robustness of the meta-analysis results were evaluated using a leave-one-study-out sensitivity analysis (41). In addition, to assess the influence of individual studies on the overall meta-analysis results and their contribution to heterogeneity, we utilized Baujat plots. This graphical tool plots the contribution of each study to the overall heterogeneity against its influence on the overall result (42).

Results

A total of 1470 studies were identified from the performed database searches and were then imported to Covidence where 81 duplicates were removed, thus resulting in 1389 studies for title and abstract screening. Following title and abstract screening, 1305 studies were considered irrelevant, leading to an initial total of 84 studies going forward for full text review. During full text review, 53 studies were excluded with reasons (Figure 1), resulting in a total of 31 studies eligible for inclusion.

For the 31 studies included in this systematic review, NAFLD was defined by various means including liver biopsy, ultrasonography/evidence of ultrasound, hepatic steatosis index, pathology and/or radiologic testing, computed tomography, magnetic resonance imaging, and self-reported physician diagnosis (Table 1). From the 31 included studies, 18 studies (58%) measured only depression (44, 49–53, 57, 58, 61–70), one study measured only anxiety (55), 10 studies (32%) measured depression and anxiety (43, 45–48, 56, 60, 71–73), one study measured only stress (54), and one study measured stress and anxiety (59). In these studies, the mental health conditions of interest were identified by validated measures (including DSM-IV and ICD-10) in 17 studies (44, 46, 48, 49, 53, 54, 56–59, 63, 65–68, 70, 73), self-reported in six studies (43, 47, 55, 61, 62, 69), or identified by other diagnosis (e.g., medical history) in eight studies (45, 50–52, 60, 64, 71, 72). Characteristics of the included studies are presented in Table 1.

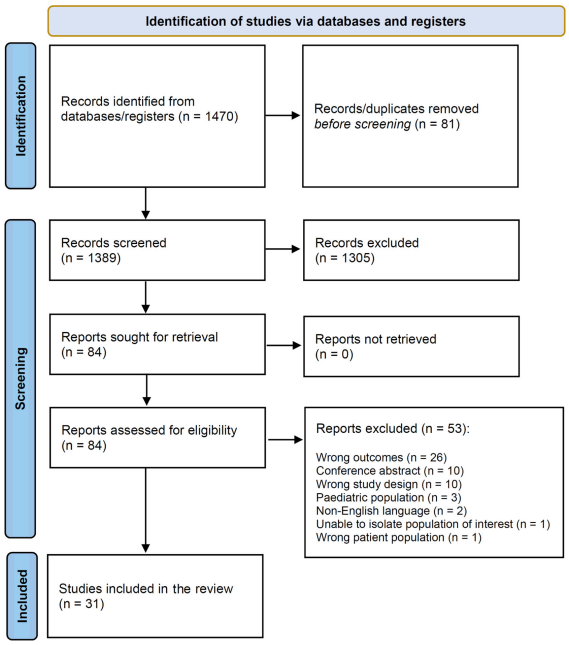

FIGURE 1
PRISMA flow chart for the present systematic review.

TABLE 1 Study characteristics of the 31 eligible studies on non-alcoholic fatty liver disease (NAFLD) and coexisting depression, anxiety and/or stress in adults which are included in the present systematic review.

Study (year)	Country	Study Design	Participant Characteristics	Mental Health Assessment Method	NAFLD Diagnosis	Summarized Main Study Findings
Balp et al. (2019) (43)	European	Cross-Sectional	Total sample: n = 184 (male: 57.1%) Age: 54.5 (13.1) years Depression: n = 57 Anxiety: n = 59	Self-Reported	Self-reported physician diagnosis	Depression and anxiety diagnosis was greater in the NASH cohort, compared to the matched general population, with a significant burden to HRQoL.
Canivet et al. (2020) (44)	France	Prospective cohort study	Total sample: n =388* (female: 81%) Age: 40 (30-50) *A sub-sample of 183 patients were selected from the initial sample of 388 and were tested for depression. Depression: n = 62 (BDI) 83 (HADS)	BDI HADS	Liver Biopsy	Participants with severe obesity had more severe BED and depression compared to lean individuals, independent of NAFLD severity.
Castellanos-Fernández et al. (2021) (45)	Cuba	Cross-Sectional	Total sample: n = 221 (female: 67.9%) Age: 54 (11.3) years Depression: n = 86 Anxiety: n = 124	Other diagnosis (e.g. medical history)	Liver biopsy or imaging	Fatigue, anxiety, depression and abdominal pain represented the strongest independent predictors of HRQoL among participants.
Choi et al. (2021) (46)	South Korea	Retrospective Cross-Sectional	Total sample: n = 7,846 (male: 78.63%) Age: 50.5 (10) years Depression: n = 335 State Anxiety: n = 541 Trait Anxiety: n = 162	BDI STAI	Ultrasonography	NAFLD was significantly and independently associated with depression. Steatosis stage had significant associations with both state anxiety and trait anxiety in women.
Doward et al. (2021) (47)	USA	Qualitative	Total sample: n = 43 (female: 66.65%) Age: 53.25 (10.2) years Depression: n = 13 Anxiety: n = 8	Self-Reported	Liver biopsy or phenotypic diagnosis	Depression was one of the most frequently reported comorbidities (>25% mentioned feeling depressed and anxious due to NASH).
Elwing et al. (2006) (48)	USA	Case-control study	Total sample: n = 36 (female: 58.3% Age: 48.8 (2.01) years Depression: n = 20 Anxiety: n = 18	DSM-IV	Liver Biopsy	Lifetime rates of major depressive disorder and general anxiety disorder were significantly increased in patients with NASH, and were associated with advanced histological hepatic abnormalities.
Fillipovic, Markovic & Duric (2018) (49)	Serbia	Case-control study	Total sample: n = 40 (male: 55%) Age: 47.88 (6.07) years Depression: n = 33	HAM-D	Abdominal ultrasound	Patients with NAFLD had a higher risk of depression compared to those without.
Forlano et al. (2021) (50)	UK	Service Evaluation Project	Total sample: n = 81 (female: 61.73%) Age (with BEDs): 52 (45-57.5) years Age (without BEDs): 59 (49-63) years Depression: n = 15	Other Diagnosis e.g. Medical History	Not reported	Participants with BED experienced more frequent depression than those without.
Glass et al. (2021) (51)	USA	Intervention Study	Total sample: n = 248 (female: 54%) Age: 53.5 (44-62) years Depression: n = 100	Other Diagnosis e.g. Medical History	Ultrasound, computed tomography, or magnetic resonance imaging	Depression was independently associated with high-risk behaviors (e.g. unhealthy diet and sedentary behavior) among people with NAFLD.

(Continued)

TABLE 1 Continued

Study (year)	Country	Study Design	Participant Characteristics	Mental Health Assessment Method	NAFLD Diagnosis	Summarized Main Study Findings
Huang et al. (2021) (52)	China	Cross-Sectional	Total sample: n = 5,181 (male: 65.8%) Age: 43.8 (13.3) years Depression: n = 135	Other Diagnosis e.g. Medical History	Ultrasound, computed tomography, and magnetic resonance imaging in 24 months or liver biopsies in 36 months.	Depression, and factors such as disease severity, CVD and diabetes, influenced HRQoL based on the CLDQ-NAFLD.
Jung et al. (2019) (53)	South Korea	Cross-sectional	Total sample: n = 31,635 (male: 77.38%) Age: 41.25 (7.15) years Depression: n = 2,870	CES-D	Abdominal ultrasound	NAFLD, both in terms of presence and severity was associated with depressive symptoms.
Kang et al. (2020) (54)	South Korea	Cross-Sectional	Total sample: n = 47,538 (male: 76.6%) Age: 42 (9.1) years Stress: n = 36,555	PSI	Ultrasound	Perceived stress levels were associated with the NAFLD prevalence, even after controlling for behavioral metabolic, & socioeconomic, factors (stronger association in men, and in participants with obesity).
Khoonsari et al. (2017) (55)	Iran	Cross-Sectional	Total sample: n = 206 (male: 52.9%) Age: 41.2 (8.3) years Anxiety: n = 181	Self-Reported	Ultrasonography	Anxiety and gastrointestinal problems were common in patients with NAFLD.
Labenz et al. (2020) (56)	Germany	Retrospective cohort study	Total sample: n = 19,871 (male: 57.5%) Age: 58.5 (14.2) years Depression: n = 4,173 Anxiety: n = 1,590	ICD-10	Not specified	NAFLD was identified as an independent risk factor for depression and anxiety.
Lee & Park (2021) (57)	Korea	Cross-Sectional	Total sample: n = 4,688 (female 61.6%) Age: 48.25 (0.75) years Depression: n = 422	PHQ-9	Hepatic steatosis index	Adults with depression had a higher risk of NAFLD, with depression also being associated to insulin resistance.
Lee et al. (2013) (58)	USA	Cross-Sectional	Total sample: n = 497 (female: 55%) Age: 49.62 (0.72) years Depression: n = 148	PHQ-9	NAFLD defined by the absence of any other causes of CLD	Depression was not found to be independently associated with NAFLD at a population level after controlling for other confounding factors.
Magalhaes et al. (2020) (59)	Brazil	Case-control study	Total sample: n = 26 (female: 89.1%) Age: 37 (8.9) years Anxiety: n = 21 Stress: n = 6	HAM-A LSSI	Ultrasonography	Findings did not identify significant associations between NAFLD and anxiety or stress, although all participants with NAFLD had some level of anxiety. No significant association between NAFLD and stress was identified.
Moon et al. (2021) (60)	USA	Prospective cohort study	Total sample: n = 3,474 (female: 58.9%) Age: 56.9 (12.96) years Depression: n = 1,333 Anxiety: n = 925	Other Diagnosis e.g. Medical History	Liver biopsy and/or pragmatic case definitions	Opioid use was identified in 1 out of 5 patients with NAFLD and was more common in those with depression, anxiety, and severe liver disease.
Patel et al. (2017) (61)	Australia	Prospective cohort study	Total sample: n = 95 (male: 61%) Age: 59.6 (9.4) years Depression: n = 42	Self-Reported	Ultrasound	Adults with NAFLD and T2DM had at least two other chronic conditions, with the most common being metabolic syndrome and self-reported depression.
Patel et al. (2017) (62)	Australia	Cross-Sectional	Total sample: n = 151 (male: 63.6%) Age: 60.7 (10.3) years Depression: n = 72	Self-Reported	Ultrasound	Self-reported depression was highly prevalent and more common in those with moderate alcohol consumption.
Sayiner et al. (2020) (63)	USA	Cross-sectional	Total sample: n = 1,980,950 (female: 54.7%) Age: 70 (11.11) years Depression: n = 188,307	ICD-10	ICD-9/ICD-10 Codes	Depression was among the most common extra-hepatic diseases identified.

(Continued)

TABLE 1 Continued

Study (year)	Country	Study Design	Participant Characteristics	Mental Health Assessment Method	NAFLD Diagnosis	Summarized Main Study Findings
Shaheen et al. (2021) (64)	United Kingdom	Retrospective cohort study	Total sample: n = 19,053 (female: 54.7%) Age: 54.1 (12.7) years Depression: n = 3,061	Other Diagnosis e.g. Medical History	Read Codes	No significant difference in liver disease progression among patients with NAFLD and ALD in relation to major depressive disorder.
Surdea-Blaga & Dumitraşcu (2011) (65)	Romania	Cross-Sectional	Total sample: n = 63 (female: 60.3%) Median Age: 46.4/50.1 years (men/women) Depression: n = 36	BDI	Abdominal Ultrasound	No significant relationship between depression/anxiety and NAFLD. Anxiety and depression are common in the studied region.
Takahashi et al. (2017) (66)	Japan	Retrospective cohort study	Total sample: n = 24 (female: 100%) Age: 54 (47-61) years Depression: n = 1	CES-D	Ultrasonography	Potential association between decreased brain activity and NAFLD, regardless of depression.
Tomeno et al. (2015) (67)	Japan	Retrospective cohort study	Total sample: n = 258 (male: 53.1%) Age: 48.6 (13.25) years Depression: n = 32	DSM-IV	Liver biopsy	The comorbid state of MDD was associated with more severe histological steatosis and worse treatment outcomes in NAFLD.
Tutunchi et al. (2021) (68)	Iran	Case-control study	Total sample: n = 95 (female: 56.8%) Age: 48.8 (5.9) years Depression: n = 44	BDI	Ultrasonography	Higher prevalence of depression in those with NAFLD, compared to those without NAFLD.
Weinstein et al. (2011) (69)	USA	Cross-Sectional	Total sample: n = 184 (female: 69.4%) Age: 46.7 (11.2) years Depression: n = 50	Self-Reported	Pathology and/or radiologic testing	Patients with NAFLD and HCV had higher depression prevalence compared to individuals with HBV and the depression rates among the general population.
Yang et al. (2021) (70)	USA	Cross-Sectional	Total sample: n = 595 (female: 53.2%) Age: 59.9 (0.7) years Depression: n = 65	PHQ-9	Liver steatosis in the absence of possible secondary causes of fatty liver.	Depression was an independent predictor for MAFLD risk, with a positive relationship between depression and MAFLD in middle-aged and older adults.
Younossi et al. (2019) (71)	USA	Cross-Sectional	Total sample: n = 1,338 (female: 53.1%) Age: 57 (8.9) years Depression: n = 339 Anxiety: n = 260	Other Diagnosis e.g. Medical History	Histologic evidence	NASH was associated with significant impairment on patient reported outcomes and well-being.
Younossi et al. (2020) (72)	USA	Cross-Sectional	Total sample: n = 1,222 (female: 56.7%) Mean Age: 57.8 years Depression: n = 272 Anxiety: n = 335	Other Diagnosis e.g. Medical History	Liver biopsy	Depression or a nervous system disorder were associated with fatigue and increased likelihood to report pruritus.
Youssef et al. (2013) (73)	USA	Cross Sectional	Total sample: n = 567 (female: 67%) Age: 48 (1.1) years Depression: n = 80 Anxiety: n = 143	HADS	Histological diagnosis of NAFLD	Subclinical and clinical depression was noted in 53% and 14% of patients, respectively. Increased severe depression symptoms were associated with a greater likelihood of severe hepatocyte ballooning.

ALD, Alcoholic Liver Disease; BDI, Beck Depression Inventory; BED, binge eating disorder; BMI, Body Mass Index; CES-D, Centre for Epidemiological Studies-Depression; CLDQ, Chronic Liver Disease Questionnaire; CVD, Cardiovascular Disease; DSM-IV, Diagnostic and Statistical Manual of Mental Health Disorders; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HBV, Hepatitis B; HCV, Hepatitis C; HRQoL, Health-Related Quality of Life; ICD, International Classification of Diseases; LSSI, Lipp's Stress Symptoms Inventory; MAFLD, Metabolic Dysfunction-Associated Fatty Liver Disease; NAFLD, non-alcoholic fatty liver disease; PHQ-9, Patient Health Questionnaire; PSI, perceived stress inventory; STAI, State-Trait Anxiety Inventory; T2DM, Type 2 Diabetes Mellitus. Age is reported as mean (Standard Deviation or range), or median (Interquartile Range) based on available data reported by each study.

Assessment of risk of bias

Judgements regarding risk of bias are presented in Figure 2, whilst further information is available in Supplementary Figure 1.

Selection bias was identified in 13 studies (42%). The main support for judgement was that for these studies, patients had been recruited from a single center and therefore findings may not be representative of the general patient population with NAFLD.

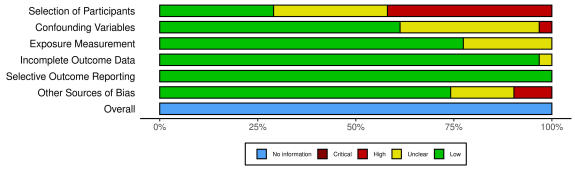

FIGURE 2
Risk of bias assessment of the included studies.

Selection bias was judged to be low for nine studies (29%) and unclear for nine studies (29%). For confounding factors, 19 studies (61%) were judged to have a low risk of bias, since these had been controlled for within analyses. The remaining studies were judged as having an unclear risk for 11 studies (35.4%) and high risk for one study (3.2%). Risk of bias was judged as low for intervention (exposure) measurement for 24 (77.4%) studies, with the remaining seven studies (22.5%) judged as unclear owing to the use of self-report measures. Low risk of bias was also reported for incomplete outcome data in 30 (96.7%) studies, with one study identified as unclear. Selective outcome reporting was judged as being low risk of bias for all included studies. When other sources of bias were assessed, 22 studies were judged as low risk (70%), five studies (16.1%) were judged as unclear, whilst four (12.9%) studies were rated as having a high risk of bias.

Depression

In total, 28 of the included studies measured depression, with the total number of participants amounting to 2,079,270. Validated instruments were used to measure depression in 15 studies (44, 46, 49, 53, 56–59, 63, 65–68, 70, 73), while self-report and other diagnosis (e.g., medical history) were used in five (43, 47, 61, 62, 69) and eight studies (45, 50–52, 60, 64, 71, 72), respectively. Of these studies, 11 were from the USA (47, 48, 51, 58, 60, 63, 69–73), resulting in a total of 1,989,154 participants from this geographical region. However, the majority of USA participants were recruited for one particular study involving 1,980,950 individuals (63).

It should be noted that one study (44) had utilized both the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS) to measure depression, but we included only the data from the BDI within the primary analysis for pooled prevalence of depression, as this had gleaned a higher prevalence when the authors reported mild depression in addition to moderate to severe. When the data were analyzed by sub-groups, on the basis of individual validated measures, both the BDI and HADS were included.

The pooled prevalence of depression for all studies yielded an estimate of 26.3% (95% CI: 19.2 to 34%) (Figure 3). The I^2 statistic was 100%, indicating a considerable degree of heterogeneity among the studies. The funnel plot for examination of publication bias is shown in Supplementary Figure 2. We found evidence of publication bias as indicated by the asymmetrical funnel plot of studies' precision against prevalence estimates (in logarithmic scale). However, the results of leave-one-study-out sensitivity analyses showed that no study had undue influence on the pooled depression prevalence as presented in Supplementary Figure 3A. The Baujat plot highlighted the study by Sayiner et al. (63) as a significant contributor to the overall heterogeneity and influence on the meta-analysis results (Supplementary Figure 3B). The large sample size of this study (63) in relation to the total combined sample size of all studies contributes significantly to the heterogeneity (I^2 = 100%) of the meta-analysis. Another study by Fillipovic et al. (49) appears to have a minimal influence on the overall meta-analysis result when compared to its contribution to heterogeneity. This suggests that while the study adds to the variability within the meta-analysis, its effect size or weight does not substantially alter the combined effect estimate of depression prevalence.

As presented in Figure 3, the pooled estimate tended to be higher among studies that used self-reported tools (36.0%, 95% CI: 27.8 to 44.5%), followed by studies that used validated measures (24.8%, 95% CI: 13.7 to 37.8%), and studies that used other diagnosis such as medical history (24%, 95% CI: 14.3 to 35.3%).

Figure 4 presents the results of the meta-analysis stratified by validated tools/measures. The pooled prevalence estimate was highest among studies that used the Hospital Anxiety and Depression Scale (HADS), followed by the Beck Depression Inventory (BDI), the Centre for Epidemiological Studies-Depression (CES-D) scale, and the Patient Health Questionnaire-9 (PHQ-9).

Anxiety

Of the studies reporting depression, ten additionally measured anxiety, resulting in a total of 12 studies measuring anxiety (43, 45–48, 55, 56, 59, 60, 71–73), with the corresponding total number of participants amounting to 35,034. Validated instruments were used to measure anxiety in four studies (Table 1), utilizing the DSM-IV (48), ICD-10 (56), the Hamilton Anxiety Rating Scale (59) and the Hospital Anxiety and Depression Scale (73). Self-report and other diagnosis (e.g., medical history) were used in three (43, 47, 55) and four studies (45, 60, 71, 72), respectively. A further study (46), utilized a validated instrument to measure both state and trait anxiety. To separate the two domains, this study was not incorporated into the primary analysis for pooled prevalence of anxiety and was included in the additional sub-group analyses only.

Six of these studies originated from the USA (47, 48, 60, 71–73), with a total of 7,127 participants. However, the largest number of participants (n = 19,871) was from a study originating from Germany (56).

The pooled prevalence of anxiety yielded an estimate of 37.2% (95% CI: 21.6 to 54.3%) (Figure 5). As with depression, the I^2 statistic was 100%, indicating considerable heterogeneity between the studies. The funnel plot for the examination of publication bias is presented in Supplementary Figure 4. We found evidence of publication bias as indicated by the asymmetrical funnel plot of studies' precision against prevalence estimates (in logarithmic scale). However, the results of the leave-one-study-out sensitivity analyses showed that no study had undue influence on the pooled anxiety prevalence (Supplementary Figure 5).

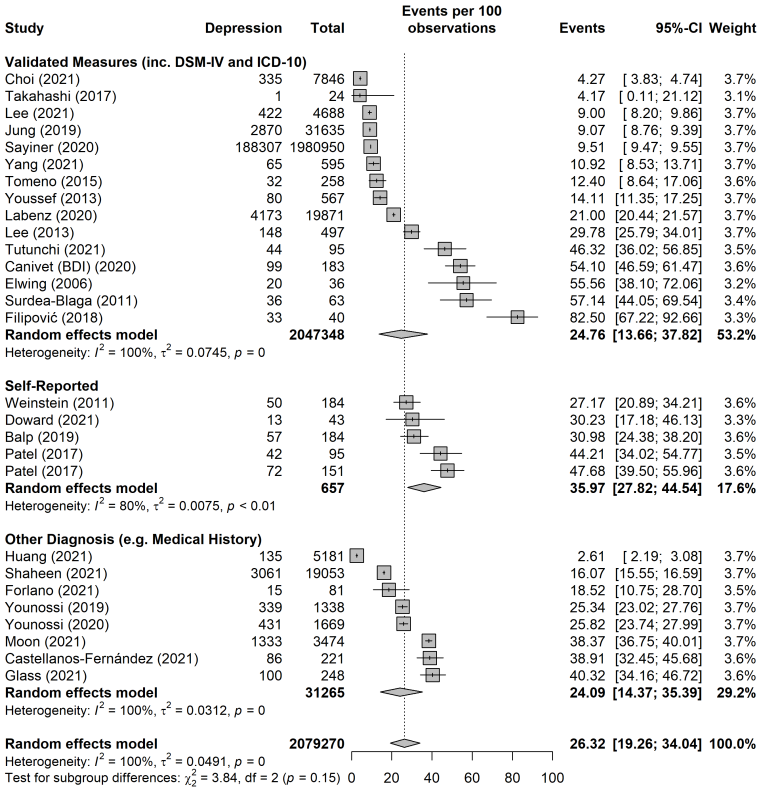

FIGURE 3
Pooled prevalence of depression, split into subgroups by method of diagnosis, i.e. validated measures (including DSM-IV and ICD-10), self-report, and other diagnosis (e.g. medical history).

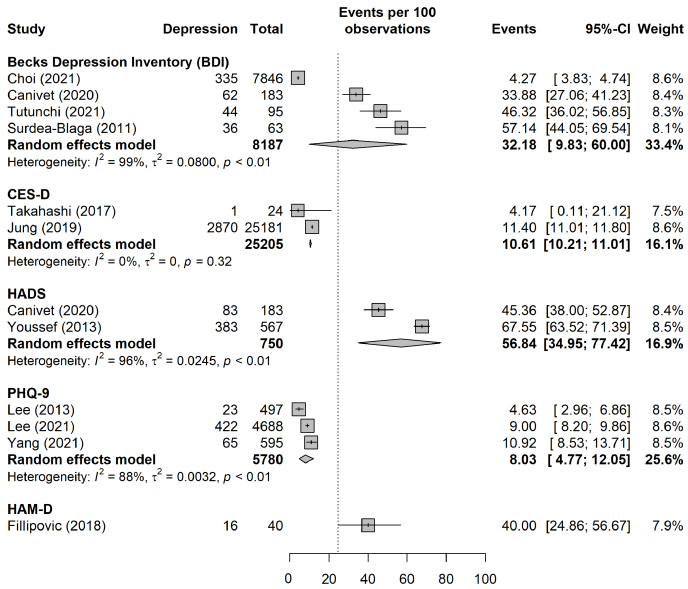

FIGURE 4
Pooled prevalence of depression, by validated tools/measures. In the sub-group analysis, only data for moderate to severe depression were included for the purpose of consistency across studies.

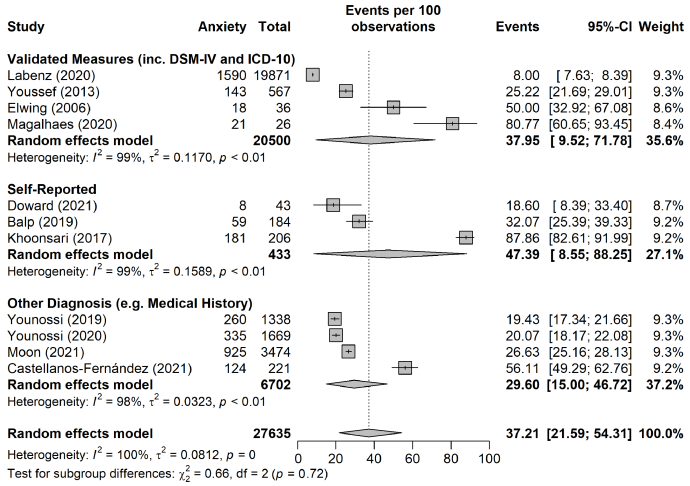

FIGURE 5
Pooled prevalence of anxiety broken down into subgroups by method of diagnosis, namely validated tool/measure (including DSM-IV and ICD-10), self-report, and other diagnosis (e.g. medical history).

As presented in Figure 5, the pooled estimate tended to be higher among studies that used self-reported tools (47.4%, 95% CI: 8.5 to 88.2%), followed by studies that used validated measures (38.0%, 95% CI: 9.5 to 71.8%), and studies that used another method for diagnosis such as medical history (29.6%, 95% CI: 15.0 to 46.7).

Stress

One of the included studies also measured stress in addition to anxiety (59). In total, only two of the included studies investigated stress in association with NAFLD (54, 59), involving a total of 47,564 participants. However, one of these studies (54), conducted in South Korea, included 47,538 participants. Both studies utilized validated instruments to measure stress. One study used the Perceived Stress Inventory to measure stress (54), whilst the other utilized the Lipp's Stress Symptoms Inventory (59) (Table 1).

The pooled prevalence of stress (Figure 6) yielded an estimate of 51.4% (95% CI: 5.5 to 95.8%). The I^2 statistic was 97%, indicating a considerable degree of heterogeneity between the studies.

Discussion

The present systematic review and meta-analysis presents novel data on the prevalence of depression, anxiety, and/or stress in adults living with NAFLD, whilst comprehensively summarizing the relevant literature. When we meta-analyzed data from 28 studies, a high prevalence of depression was revealed among this patient population (26.3%; 95% CI: 19.2 to 34%). A higher pooled prevalence estimate of 37.2% (95% CI: 21.6 to 54.3%) was noted for anxiety in patients with NAFLD, whilst stress appears to affect one in two patients with NAFLD (51.4%; 95% CI: 5.5 to 95.8%). To our knowledge, this is the largest meta-analysis of available data on the prevalence rates of depression, and/or anxiety, and/or stress among adults with NAFLD, documenting even higher mental health comorbidity in this patient population than previously reported (33). As discussed in the following sections, this apparently high overlap between NAFLD and these common mental health problems constitutes a significant health issue which merits further attention both in the context of the clinical care of these patients and for targeted research in this field.

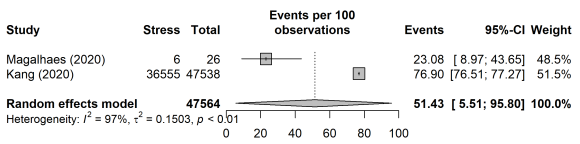

FIGURE 6
Pooled prevalence of stress.

Depression

Depression is a highly prevalent disorder worldwide, constituting a leading cause of years lived with disability and affecting over a quarter of a billion people (74). The findings of this systematic review suggest that depression is present in approximately one out of four (~26.3%) patients with NAFLD. This prevalence of depression is even higher than the one reported in a previous meta-analysis (33), which included 10 studies with an 18.21% pooled prevalence of depression in patients with NAFLD. This may, at least in part, be reflective of the larger number of studies and the larger sample size included in our systematic review.

Notably, in the larger study included in the present systematic review, involving 1,980,950 Medicare beneficiaries, depression was reported to be one of the most common extra-hepatic diseases identified in people with NAFLD (63). Depression was further reported as a contributing factor to impaired health-related quality of life (45, 52), whilst there are data supporting an independent

association of depression with high-risk behaviors, such as sedentariness and unhealthy diet among individuals with NAFLD (51). Another included study reported similarities between both men and women regarding a significant association between NAFLD and the incidence of depression, independently of other confounders such as diabetes, CVD, asthma, sex and age (56). In addition, a further retrospective cross-sectional study conducted by Choi et al. (46), involving 7,846 participants, identified an independent association of NAFLD with the risk for depression after controlling for other factors including diabetes and age.

Regarding more severe forms of NAFLD, studies investigating rates of depression in patients with NASH identified a higher frequency of depression among this patient group (43, 47, 48). Additional evidence from included studies suggests an association of depression with NAFLD progression/severity, with the study by Tomeno et al. (67) showing that major depressive disorder was associated with more severe histological hepatic steatosis and worse treatment outcomes in patients with NAFLD. Furthermore, both major depressive disorder and general anxiety disorder have been identified as being significantly increased in patients with NASH, and associated with increased advanced liver histological abnormalities (48). An association of increased symptoms of depression with a greater likelihood of severe hepatocyte ballooning has also been reported by Youssef et al. (73).

Contrary to the above, one study reported that depression was not found to be independently associated with NAFLD at a population level after controlling for other confounding factors, such as diabetes and obesity (58). Likewise, in a study conducted in Romania, authors reported that they were unable to detect a relationship between NAFLD and depression and anxiety, highlighting that symptoms of depression and anxiety are common in this particular region (65).

Anxiety

A total of 12 studies included in the present systematic review measured anxiety, resulting in a pooled prevalence rate of ~37.2%. Thus, as with depression, our findings indicate that anxiety appears to be a very common mental health problem among patients with NAFLD, which has a potential impact on the overall health-related quality of life (43, 45, 47, 55). Notably, one study indicated that general anxiety disorder is significantly increased in patients with NASH and is associated with advanced liver histological abnormalities (48).

Furthermore, the study by Choi et al. (46) explored the presence of both state anxiety and trait anxiety among a NAFLD population, demonstrating that, although NAFLD in itself was not significantly associated with anxiety, associations with state and trait anxiety did emerge depending on the stage of steatosis. These associations remained consistent after adjusting for factors such as age, body mass index (BMI), diabetes, and smoking, but were evident only in females. However, a study by Magalhaes et al. (59) did not identify significant associations between NAFLD and anxiety, although all participants with NAFLD had some level of anxiety.

Stress

Growing evidence suggests an association between chronic psychosocial stress and an increase in the prevalence of various cardio-metabolic diseases, such as obesity, T2DM, CVD and hypertension (75, 76). Despite this emerging importance of chronic stress as a potential factor associated with metabolic syndrome and NAFLD, there is a paucity of studies which have explored such a relationship. Indeed, the present systematic review identified only two eligible studies which investigated chronic stress in relation to NAFLD, gleaning a pooled prevalence of ~51.4%. Interestingly, of these two studies, the large cross-sectional study conducted in South Korea (54) identified a positive independent association between increased prevalence of NAFLD and perceived stress, suggesting a probable relationship between the two. Contrarily, the small study by Magalhaes et al. (59), which sought to identify an association between NAFLD and occupational stress among 26 healthcare professionals employed at a community hospital in Brazil, failed to confirm a significant relationship between stress and the presence of NAFLD, although the authors suggest that such an association should continue to be explored. Accordingly, caution should be adopted when interpreting these findings since data are drawn from only two studies. However, this (both the existing data and the absence of more such data) should clearly prompt further research into the potential links between NAFLD and chronic stress.

Comparison with other population groups and general population data

Certain studies included within this review investigated the prevalence of mental health problems in patients with NAFLD compared with other population groups (48, 49, 68–70). For example, the study by Elwing et al. (48) identified a higher rate of depression and anxiety in patients with NASH compared to a matched control group without liver disease. Furthermore, Fillipovic et al. (49) demonstrated greater risk of cognitive impairment and depression in patients with NAFLD compared to those without, whilst Weinstein et al. (69) reported a higher prevalence of depression in individuals with NAFLD in comparison with patients with another liver disease, namely those with a hepatitis B virus infection.

In terms of comparisons with general population data, data suggest a lifetime prevalence estimate for depression of 14.6% and an average 12-month prevalence estimate of 5.5% for adults in high-income countries (77). It is further estimated that generalized anxiety disorder has a lifetime prevalence of between 1-7% in Europe and around 7.8% in the USA, although it is suggested that generalized anxiety disorder is often underdiagnosed (78). Therefore, based on even the lower corresponding estimates from the present systematic review, it appears that the prevalence of depression and anxiety among patients with NAFLD is likely to be considerably higher when compared to the general population.

Depression is a key health issue of concern globally, which has significantly worsened after the COVID-19 pandemic, with the

WHO reporting that the prevalence of depression and anxiety increased by 25% within the first year of this pandemic (79). Furthermore, depression is reported to be a common co-existing problem among patients with chronic disorders (80). For example, a large prospective cohort study conducted in Spain, identified that around 20% of patients with diabetes suffered from depression, and that this was associated with a number of diabetes related outcomes and complications (81). A further systematic review revealed a 28% prevalence of anxiety in patients with diabetes, with those with pre-existing anxiety at higher risk of developing diabetes (19%) (82). Likewise, stress is reported as a trigger for the onset of both type 1 and type 2 diabetes, with the combination of chronic stress and obesity leading to metabolic failure and increasing diabetes risk in such individuals (83). Depression, anxiety and chronic psychological stress are also reported as being common in people with CVD, with a recent systematic review revealing a prevalence of depression at 31.3%, and anxiety and stress at 32.9% and 57.7%, respectively, among this population (84). Moreover, a systematic review and meta-analysis by Mejarah et al. (83), revealed a high prevalence of depression among cancer patients, with the highest prevalence being identified among those with colorectal cancer (32%) (83), whilst a 13.8% prevalence of anxiety among patients with cancer has also been reported (85).

Thus, our present findings suggest that the prevalence rates of these common mental health problems in patients with NALFD may be similar to those documented for other chronic disorders; however, this seems to have received less attention and awareness among the NAFLD population in comparison to other patient groups.

Diagnosis of NAFLD/measurement of mental health

Among the studies included in this review, a range of methods were used to diagnose NAFLD. In general, liver biopsy continues to be considered the gold standard for the diagnosis of NAFLD and NASH, as it allows the histologic assessment of hepatic steatosis, inflammation, and fibrosis. However, liver biopsy is an invasive strategy which is costly, not always feasible, and carries a risk of complications (e.g., bleeding). As such, many patients are currently diagnosed via non-invasive methods (e.g., ultrasound and other imaging methods), with liver biopsy more commonly reserved for use where there is diagnostic uncertainty (86, 87). This also explains the range of NAFLD diagnostic methods utilized in the studies included in this systematic review (Table 1).

Regarding assessment of the mental health problems of interest, a number of the included studies involved the use of well-established validated tools/methods, whilst others utilized self-report or other means, such as medical records. Of interest, for studies where depression and anxiety were self-reported, a higher prevalence of these conditions was evident - a finding that was also noted in a previous systematic review (33). This may be due to problems regarding patient recall of physician diagnosis, but might also reflect the possibility that generic validated tools may not capture depression and anxiety among this specific NAFLD patient group. To our knowledge, there are no mental health measures validated specifically for NAFLD patients. Likewise, as far as we are aware, the tools that are currently in widespread use for measuring common mental health problems have not been specifically validated for use among this patient group.

It is important to note that in some of the studies included in this review, mental health was not the primary outcome. For example, two of our included studies had a focus on binge eating disorder (BED), with the primary aim being to assess if BED related to obesity was associated with the severity of NAFLD in one study (44), and to assess risk factors for the presence of BED among patients with NAFLD together with the impact of BED on body mass composition in another study (50). Additionally, Patel et al. (61) sought to describe the number and type of chronic conditions and medications taken by patients with diabetes and NAFLD and to identify characteristics that may impact on liver disease severity, whilst another study by Patel et al. (62) aimed to examine the association between lifetime alcohol consumption and significant liver disease in patients with diabetes and NAFLD (62). Therefore, the assessment of mental health might be seen as a secondary objective of these studies, and, thus, care should be taken when interpreting these findings, since the relevant mental health issues identified might be due to other causes beyond NAFLD itself. However, it should be noted that when these studies were omitted during the performed leave-one-out sensitivity analysis, their omission had no significant effect on the overall pooled prevalence of depression.

Potential underlying mechanisms

The present systematic review specifically looked at the prevalence of one or more common mental health issues (i.e., depression, anxiety and stress) in adults with NAFLD, thus the included studies offered evidence predominantly on this research question. However, growing broader data suggest that a bi-directional pathophysiologic association between NAFLD and depression might be in existence (31), whilst it is also plausible that a feed-forward vicious cycle exists between these common mental health conditions and NAFLD, whereby such mental health morbidity may promote NAFLD, and *vice versa* (12). Thus, it is important to consider the potential underlying mechanisms that may link NAFLD with these common mental health problems. Indeed, some of the studies included in this review also refer to such potential underlying mechanisms, including insulin resistance, inflammation, and the activity of the hypothalamic-pituitary-adrenal axis (HPA) axis (46, 54, 56, 73). For example, when exploring the association between depression and NAFLD, one of the studies included within this systematic review suggests that insulin resistance appears to play an important role in modulating the link between depression and NAFLD risk (57). Moreover, the potential involvement of the serotonin pathway, and the gut microbiome have also been discussed in the context of underlying mechanisms linking NALFD and these mental health problems (12,

46). Finally, brain insulin resistance, neuro-inflammation and cerebrovascular changes are also considered as part of the NAFLD-related pathophysiology which may affect the central nervous system in these patients and could contribute to the development of depression and anxiety (88). Of note, a Mendelian randomization study by Lin et al. showed that NAFLD causally affects the brain cortical structure, revealing an association between NAFLD (NAFLD activity score and fibrosis stages) and cortical structures (reduced global surface area and changes in the cortical structures of several brain gyri as assessed by MRI) which may contribute to disease/dysfunction of the central nervous system (89). These findings further support the notion of a liver-brain axis and suggest that MRI scans could be introduced in the routine care offered to patients with NAFLD in order to promptly diagnose potential neuropsychiatric comorbidity (89).

It is important to highlight that there could be many other factors that may contribute to the mental health and well-being of patients with NAFLD, including symptoms of fatigue which may impact on quality of life and the high risk of significant complications, as well as the lack of awareness of the condition and perceived stigmatization (28). Furthermore, it is reported that NAFLD patients with depression are at a greater risk of adverse outcomes, such as stroke, CVD and cancer-related mortality compared to those without depression (90). Similarly, anxiety has been shown to be associated with a number of health issues including CVD, hypertension and gastrointestinal issues (91), and increased levels of anxiety among NAFLD patients might also lead to further physical complications. Anxiety may also impair quality of life both in terms of physical and mental health and in association with everyday functioning (92), and this is highly likely to be the case with NAFLD patients.

Overall, NAFLD is a complex condition and may further be associated with various socioeconomic factors and unmet needs, which could in turn lead to mood imbalances and feelings of social isolation and loneliness, representing a further substantial risk to overall health and quality of life (28). Interestingly, chronic loneliness is reported as being associated with both mental health problems and metabolic disorders, potentially acting as a chronic stressor leading to HPA axis overactivity which may contribute to the development of both mental health and metabolic problems that, in turn, may also lead to feelings of social isolation (93).

Limitations

This systematic review and meta-analysis has certain limitations. Firstly, because a number of the included studies were cross-sectional in design, it is not possible to determine causality. In addition, our analysis included some studies wherein mental health issues were not representative of the intended primary study outcomes. Also, high heterogeneity was documented throughout the analysis, which is potentially due to the cross-sectional nature of many of the included studies, different methods used for diagnosing NAFLD and measuring mental health, and differences across country of study origin, and sample size. High levels of heterogeneity have also been identified in previous reviews of this nature (31, 33). It is possible that high heterogeneity is a common feature in meta-analyses of observational studies, due to high risk of bias and because not all included studies may be answering the same research question (94). In terms of risk of bias judgement for the studies included in our review, risk of bias was judged highest for the selection bias domain, since 13 of the included studies involved patients recruited from a single center. These centers were predominantly either liver clinics or centers specializing in gastroenterology or hepatology, implying that the corresponding findings may not be representative of the general population of patients with NAFLD. In addition, in the present systematic review we included only papers which were published in the English language, whilst we did not include unpublished studies. Hence, it is likely that there may be additional relevant studies which are currently unpublished or have been published in languages other than English. Furthermore, it was not possible to explore potential ethnicity related differences in the context of this systematic review since ethnic specific data were not consistently reported by the included studies. It would be of interest if future research could further investigate differences in the prevalence, disease management, and associations of NAFLD and mental health problems across different ethnic groups. Finally, it was not possible to further analyse potential differences depending on the exact stage of NAFLD and whether steatosis/steatohepatitis and/or comorbid conditions are present or not, since the included studies did not consistently report such detailed data as well.

Concluding remarks

Given that the prevalence rates of both NAFLD and mental health problems are expected to continue to increase globally, a further growth in the patient group presenting with such comorbid chronic problems should be expected in the following years. Thus, it is important for the clinical practice to ascertain the exact degree of mental health comorbidity among the NAFLD patient population in order to prioritize and/or tailor relevant treatment interventions. The present systematic review and meta-analysis presents such up-to-date data on the apparently high prevalence of depression, anxiety, and stress among adults with NAFLD, and comprehensively summarizes the existing relevant literature. Our findings show markedly high pooled prevalence rates of these mental health disorders in adults with NAFLD, indicating a plausible underlying pathophysiological link, however, the present work does not draw conclusions on such an association. Thus, additional research is required to elucidate the potential pathophysiological links between these common mental health disorders and NAFLD, and to further identify the exact risk of developing stress, anxiety and depression disorders in this patient population. Indeed, our present work further highlights such gaps/weaknesses which remain within the relevant literature, including the need to understand potential bi-directional links between NAFLD and mental health problems. Therefore, whilst clinical practice should acknowledge the apparently high prevalence rates of depression, anxiety, and stress among adults with NAFLD and accordingly offer

tailored care to these patients, research efforts should also be directed on elucidating potential underlying mechanisms shared between these common chronic health problems which could result in developing novel treatment options for such patients.

Data availability statement

Information for existing publicly accessible datasets is contained within the article.

Author contributions

SS: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. CL: Conceptualization, Visualization, Writing – review & editing. CK: Formal analysis, Visualization, Writing – review & editing. LL: Visualization, Writing – review & editing. OU: Formal analysis, Visualization, Writing – review & editing. AD: Formal analysis, Visualization, Writing – review & editing. LA: Supervision, Visualization, Writing – review & editing. SC: Visualization, Writing – review & editing. HR: Conceptualization, Supervision, Visualization, Writing – review & editing. IK: Conceptualization, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

Author LA was employed by company iPrescribe Exercise Digital Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1357664/full#supplementary-material

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Glycemic indicators and mental health symptoms: results from the greater Beirut area cardiovascular cohort

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Introduction: Depression and anxiety present high and complex comorbidity with diabetes. One proposed explanation is that glycemic dysregulations and diabetes-related processes can influence mental health risk. We examined the associations of concurrent and prior glycemic indicators (Hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) levels) with depression and anxiety symptoms in a community-based sample of middle-aged Lebanese adults.

Methods: Data come from the Greater Beirut Area Cardiovascular Cohort (GBACC), with baseline and 5-year assessments of sociodemographic, lifestyle, and biological factors (n=198). Depression (Patient Health Questionnaire-9) and anxiety (General Anxiety Disorder-7) symptoms were assessed at follow-up. We investigated associations between glycemic indicators and continuous mental health scores using first linear and then piecewise regression models.

Results: Adjusted piecewise regression models showed different associations with mental outcomes across glycemic indicators in the diabetic/clinical compared to the non-diabetic range: Among participants with <126 mg/dl baseline FBG, higher FBG levels in this range were significantly associated with lower depressive (beta=-0.12, 95%CI= [-0.207, -0.032]) and anxiety symptoms (beta=-0.099, 95%CI= [-0.186, -0.012]). In contrast, among participants with baseline FBG levels ≥126 mg/dl, higher FBG levels were significantly associated with higher anxiety symptoms (beta=0.055; 95%CI= 0.008, 0.102). Higher baseline FBG levels in the ≥126 mg/dl range showed a not statistically significant trend for higher depressive symptoms. Although not significant, baseline HbA1c levels showed similar patterns with negative associations with mental health symptoms in the <6.5% range.

Discussion: Results show that FBG levels were associated with poorer mental health symptoms only in the clinical/diabetic range, and not in the normal range. Associations were observed with baseline glycemic indicators, highlighting

potentially early and prolonged associations with mental health. Findings highlight the importance of clinical changes in glycemic indicators for mental health and motivate further research into the transition toward adverse associations between diabetes and mental health.

KEYWORDS

fasting blood glucose (FBG), HbA1c - hemoglobin A1C, depressive symptoms, anxiety symptoms, mental health, community-based sample, glycemic indicators, diabetes

1 Introduction

Mental health disorders are a growing public health priority, affecting up to one billion people globally (1). Depression was the second and anxiety eighth leading cause of healthy life years lost to disability according to the Global Burden of Disease (GBD) in 2019 (2). This burden was largely exacerbated during the COVID-19 pandemic, with a 2020 Lancet review, reporting prevalence increase of 27.6% and 25.6% for major depressive and anxiety disorders respectively (3).

These worldwide prevalence and burden trends call for an improved understanding of the development of mental health disorders and for better recognition of specific higher-risk subgroups and trajectories. While the exact mechanisms underlying depression and anxiety remain unclear, accumulated data indicate that the risk of depression and anxiety is multifaceted and includes genetic, socioeconomic, environmental, lifestyle, and biological factors (4). Importantly, mental health disorders show high patterns of co-morbidity with other chronic disorders, underlining potential common biological and physiological processes. One consistently reported co-morbidity is that between depression and type II diabetes mellitus (T2DM), a common and serious chronic disease, ranked as the eighth leading cause of death and disability worldwide (2). According to the International Diabetes Federation (IDF), 425 million people had diabetes in 2017 and this number is anticipated to climb to 629 million by 2045 (5).

Both epidemiological and clinical studies show a higher prevalence of depression among people with diabetes; estimates from meta-analyses indicate that depression is twice more common in diabetic compared to non-diabetic populations (6–8). Moreover, data suggest that the course of depression among people with diabetes is more severe and complicated, due to underdiagnosis, under-treatment, and higher relapse occurrences (7, 9). Although less studied, data also suggest a link between diabetes and anxiety disorders, whereby patients with diabetes were reported to be 1.5 times more likely to develop severe anxiety than persons without diabetes (10–12), This suggests that diabetes-mental health links go beyond a specific disorder, further warranting a better understanding of how diabetes and its processes may impact mental health.

In parallel, several studies indicate that people with depression have an increased risk of T2DM (13). Combined, current evidence suggests a complex bi-directional relationship between depression and diabetes (14, 15), which is predominantly explained by three hypotheses: that shared common risk factors increase risk of both disorders simultaneously; that diabetes is a risk factor for depression; and that depression and stressful experiences may lead to diabetes (13, 16). One approach to better delineate this complex comorbidity is to investigate the more direct links between mental health symptoms and the biological building blocks of diabetes (10). However, studies investigating the links between depression and glycemic indicators have yielded mixed findings and have important limitations. First, most prior research consists of cross-sectional studies and do not include repeated assessments of glycemic indicators to investigate their timing and change in relation to mental health symptoms. Second, existing longitudinal studies have predominantly focused on patients with diabetes, where extreme changes in diabetes indicators may have already occurred, limiting the investigations of the relation of mental health symptoms across the non-diabetic to diabetic ranges. For instance, in a recent meta-analysis summarizing longitudinal studies, a bidirectional relationship has been reported between depressive symptoms and Hemoglobin A1c (HbA1c), with higher baseline HbA1c levels being associated with increased risk of probable depression; and higher baseline depressive symptoms associated with subsequent higher levels of HbA1c (17). Similar evidence is observed for anxiety symptoms, with studies reporting positive correlations between HbA1c, fasting blood glucose (FBG) levels and anxiety symptoms (18, 19). While these studies provide evidence for a link between depression and biological diabetes indicators, they are conducted in type 1, type 2, and mixed diabetic populations, and there is increasing interest and need for investigating how these relationships occur in the normal-to-pathological range of glycemic indicators (i.e., across the non-diabetic to diabetic range and in both people with and without diabetes) (17, 20–22). Reports of a positive association between pre-diabetic FBG/HbA1c levels and depressive symptoms (22) further highlight the need for investigating earlier associations with mental health illnesses across the spectrum of FBG/HbA1c variations -i.e., before the shift to more extreme and clinical ranges have occurred -

to better assess relationships of glycemic deregulations and diabetes-related processes with depression and anxiety. For that, investigations in middle-aged adults can provide an added advantage to explore a time window where diabetes risk is changing (20).

This study aimed to examine the relationship of previous, concurrent, as well as changes in glycemic indicators (FBG and HbA1c) over five years with depression and anxiety symptoms in a community-based sample of middle-aged Lebanese adults.

2 Materials and methods

2.1 Study design and sample

This study was based on data from the Greater Beirut Area Cardiovascular Cohort study. Details of the study are described elsewhere (23, 24). Briefly, at baseline (2014), a sample of 501 adults were enrolled in the study following multistage probability sampling across the Greater Beirut area. Participants aged 18 and above and living in the Greater Beirut area were eligible to participate; pregnant women, dialysis patients, subjects with intellectual inability to understand the study and to provide informed consent were excluded (25, 26). Baseline data collection consisted of face-to-face interviews, anthropometric measurements, and extensive data on blood markers of cardiac and metabolic disorders. At the five-year follow-up (2019), participants were invited to participate in the second study wave. All participants who had consented at baseline to be re-contacted and who provided contact information (n=486) were called to participate in the follow-up, except for 8 subject who were no longer eligible to participate in the study; 198 completed the study follow-up examination. Of the 478 who were eligible to partake in the follow-up study, 36.1% were not successfully reached because of wrong phone numbers and 17.9% did not answer; 17.5% were too busy, 15.7% were not interested, 8.9% were too ill, and 3.9% had moved/traveled. A cohort flowchart is included in Supplementary Figure S1. Both study waves were approved by the Institutional Review Board at the American University of Beirut and all participants provided written consent at both study examinations.

2.2 Data collection

At baseline and follow-up, data on sociodemographic, socioeconomic, and lifestyle factors and medical history were collected through face-to-face interviews with trained data collectors; anthropometric and blood samples were also collected, through similar protocols at baseline and follow-up.

2.2.1 Depression and anxiety symptoms

Data on mental health were only collected at the follow-up wave. Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) (27). The scale includes 9 self-reported items that assess the presence and severity of major depressive disorders based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria in the past two weeks; each item is ranked in frequency on a 4-point Likert scale, with the total scores ranging from 0 to 27 (28) and higher score indicating higher depressive symptoms. The scale has been shown to have high internal consistency (Cronbach's alpha between .86 and .88) (29) and high test reliability (Cronbach's alpha between .84 and .95) (28, 30).

Anxiety symptoms were assessed using the Generalized Anxiety Disorder -7 (GAD-7) scale, a reliable and valid instrument widely used for assessing presence and severity of anxiety symptoms (31). The GAD-7 includes seven items, based on DSM-IV criteria (28), with each item's frequency of occurrence over the past two weeks ranked on a 4-point Likert scale. Total scores range from 0 to 21, with higher scores indicating higher anxiety symptoms. The GAD-7 exhibits excellent internal consistency (Cronbach's alpha between .89 and .92) (30–32).

Both scales were adapted and validated in Lebanon and Arab speaking communities (28) and the validated versions were used for data collection. We analyzed depressive and anxiety symptoms continuously (total scores of each the PHQ-9 and GAD-7 scales) as well as categorically, comparing those with elevated symptoms and those without using validated cut-offs [scores of 10 and more for each scale (12)].

2.2.2 Glycemic indicators

The two main exposure variables of interest were fasting blood glucose (FBG) and glycosylated hemoglobin A1C (HbA1c), and we were interested in the baseline and follow-up values of these indicators, as well as their baseline to 5-year change measured as

$$(\text{Value at baseline}) - (\text{Value at the 5–year follow-up}).$$

Glycemic indicators were based on blood draws collected at both the baseline and follow-up examination. Blood draws were split into two ethylenediaminetetraacetic acid tubes, one frozen for future studies and the other refrigerated and saved for HbA1c measurement within one week. The remaining blood was centrifuged with serum split into several 1 mL Eppendorf tubes, the one dedicated for FBG analysis was refrigerated and sent to be assayed immediately (on same day). HbA1c assessments were performed using the HPLC (Bio-Rad) and FBG assessments using the Enzymatic method (Cobas 6000, Roche). The same glycemic definitions were used at baseline at follow-up, according to the American Diabetes Association (ADA) guidelines: Diabetic FBG levels were considered as those equal and above 126 mg/dl; diabetic HbA1c levels were considered at 6.5% or higher. Presence of probable diabetes was defined as the presence of self-reported diabetes, taking diabetes medications, and/or either FBG≥126 mg/dl or HbA1c≥6.5% (48mmol/mol). Information on family history of diabetes was self-reported and categorized into presence of family history of diabetes (if any one of participant's mother, father, or siblings had diabetes) versus no family history of diabetes.

2.2.3 Covariates

The following covariates were selected to be accounted for in the analysis, based on an extensive literature review of the factors that are consistently associated with anxiety, depression and diabetes and that can be on common causal pathways for these conditions. Sociodemographic covariates included age (continuous variable), sex (men/women), and educational attainment (higher educational level including secondary/technical/university degree versus lower including no education/primary or intermediate school). Health characteristics included BMI (kg/m^2), current smoking status (yes/no) (33), and physical activity (low, moderate and high) according to the International Physical Activity Questionnaire (IPAQ) scoring cut-offs (34). Participants self-reported whether they have been ever told by a doctor or healthcare professional that they have high blood pressure (hypertension: yes/no) at both study visits. We also considered the following self-reported medical conditions that are potentially relevant for both mental health disorders and diabetes: presence (yes/no) of dyslipidemia, coronary heart disease (CHD), cancer, thyroid, and stroke; a composite score was generated summarizing the number of metabolic conditions and chronic diseases (ranging from 0 to 4, with higher values indicating more conditions/comorbidities), to facilitate analysis as the prevalence of some disorders was low in the sample. The baseline (2014) values of the covariates were used for analyses involving baseline assessments of FBG and HbA1c, and follow-up (2019) values were used in analyses of follow-up FBG and HbA1c levels.

2.3 Statistical data analysis

Sample characteristics, mental health symptoms, and glycemic indicators (HbA1c and FBG) were described using mean and standard deviations for continuous variables and frequency distributions for categorical variables. We first investigated the correlation between the main exposures (HbA1c and FBG) at both study waves using Pearson correlations; similarly, we investigated the overlap in elevated depression and anxiety symptoms (using chi-square tests) and the correlation between continuous depression and anxiety scores using Pearson correlations.

For the main relationships of interest (glycemic indicators and mental health), we first investigated bivariate relationships between each of the baseline and follow-up FBG and HbA1c levels as well as the 5-year change in these levels with each of the depression and anxiety symptoms at follow-up (both continually and categorically (i.e., elevated symptoms yes/no), using linear and logistic regression analyses, respectively). We also investigated whether probable diabetes status at baseline and follow-up were related with depression and anxiety symptoms.

We investigated graphically the association of baseline and follow-up FBG and HbA1c levels with depressive and anxiety symptoms, using Locally Weighted Scatterplot Smoothing (Lowess) plots, which identified ranges across each of the HbA1c and FBG levels that showed differential relationships with mental health symptoms. As detailed in the results, relationships of FBG and HbA1c with mental health symptoms were different in the non-diabetic and diabetic ranges (below and above HbA1c of 6.5; below and above FBG of 126). Accordingly, we used segmented linear piecewise regression, a type of analysis that is efficient for scenarios of different patterns of associations specific ranges of the predictor variables; this method thus allowed to partition the glycemic indicators' levels into two intervals (the non-diabetic and diabetic/clinical ranges), based on the ranges identified in the Lowess plots. We conducted adjusted piecewise regression models sequentially, first adjusting for age, sex, educational levels, BMI, smoking status, and hypertension; then, we further adjusted for number of medical conditions (dyslipidemia and number of chronic diseases), family history of diabetes, and physical activity. Analyses were performed for each glycemic indicator (FBG and HbA1c) and for each of the baseline and follow-up values of these predictors, aiming to assessing both cross-sectional association with mental health symptoms (follow-up data) and relationship of prior levels of these indicators (baseline) with mental health symptoms 5 years later. We used the covariates values that correspond to the year of the primary predictor in the model (e.g., baseline covariate values for baseline FBG levels). Regression coefficients (betas) and 95% confidence intervals were reported. The threshold for statistical significance was 5%. For each outcome, same analysis was repeated for the binary outcome classification (elevated symptoms yes/no) using logistic regression models (Supplementary Table S1) and results were concordant. Data analysis were performed using STATA 13.

3 Results

3.1 Sample characteristics

At five-year follow-up, mean age was 51.5 years (SD=13.38); 64.14% of the sample were women and 36.22% had higher educational attainment (Table 1). Average BMI was 30.43 kg/m^2 (± 5.90) compared to 30.00 (± 5.85) kg/m^2 at baseline. Current smoking and low physical activity were prevalent at both baseline and follow-up. Regarding medical history, 59.09% of participants had no chronic diseases at baseline while 45.45% reported no chronic diseases at follow-up; the most frequent diseases and conditions were dyslipidemia and hypertension and their prevalence increased at follow-up; presence of cancer and stroke history was stable over the 5 years with low prevalence of 2.53% and 1% respectively at both years (Table 1).

At baseline, 21.27% of the sample had diabetes and the prevalence increased to 30.30% at the five-year follow-up. This was accompanied with increases in FBG and HbA1c levels: Average FBG and HbA1c levels at follow-up were 117.62 mg/dl (± 39.76) and 5.95% (± 1.31%), compared to 109.08 mg/dl (± 29.52) and 5.9% (± 1.15%) at baseline, respectively.

With regards to mental health symptoms, 32.3% and 26.8% of participants had elevated depression and anxiety symptoms respectively. Average depression symptoms score was 7.16 (±5.68) and average anxiety symptoms score was 6.57 (± 5.55). Depression and anxiety scores were highly correlated (ρ = 0.69); 20.71% of the total sample had co-morbid elevated depression and anxiety symptoms. Most participants with elevated depression symptoms

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TABLE 1 Characteristics at baseline and follow-up of the Greater Beirut Area Cardiovascular Cohort sample (n=198).

		Baseline		5-years follow-up	
		n (%) or Mean ± SD	Missing n	n (%) or Mean± SD	Missing n
Age		46.96 ± 3.31	0	51.56 ± 13.38	0
Sex	Female	127 (64.14)	0	–	0
Educational level	Higher	59 (29.95)	0	71 (36.22)	2
Glycemic and diabetes indicators					
FBG (mg/dl)		109.08 ± 29.52	0	117.62 ± 39.76	3
HbA1c (%)		5.90 ± 1.15	0	5.95 ± 1.31	3
Diabetes[¥]	Yes	43 (21.27)	0	60 (30.30)	0
Family history of diabetes	Yes	107 (54.04)	0		
Lifestyle and health characteristics					
BMI (kg/m^2)		30.00 ± 5.85	0	30.43 ± 5.90	1
Current smoking		78 (39.39)	0	80 (40.40)	0
Hypertension		38 (19.19)	0	72 (35.35)	0
Dyslipidemia		51 (25.76)	0	81 (40.91)	0
Coronary heart disease		17 (8.59)	0	30 (15.15)	0
Stroke		2 (1.01)	0	2 (1.01)	0
Cancer		5 (2.53)	0	5 (2.53)	0
Thyroid disease		24 (12.12)	0	27 (13.64)	0
Number of medical conditions[€]	None	117 (59.09)	0	90 (45.45)	0
	One	66 (33.33)	0	74 (37.37)	0
	Two	13 (6.57)	0	31 (15.66)	0
	Three	1 (0.51)	0	3 (1.52)	0
	Four	1 (0.51)	0	0	0
Physical activity levels	Low	92 (46.46)	0	104 (52.79)	1
	Moderate	73 (36.87)		70 (35.53)	
	High	33 (16.67)		23 (11.68)	
Mental health outcomes					
Elevated depressive symptoms	Yes	–	–	64 (32.3%)	0
Total depression scores		–	–	7.16 ± 5.68	0
Elevated anxiety symptoms	Yes	–	–	53 (26.8%)	0
Total anxiety scores		–	–	6.57 ± 5.55	0

[¥]Presence of diabetes is defined as FBG ≥ 126 or HbA1c ≥ 6.5 and/or self-reported diabetes and/or taking diabetic medication.
[€]Medical conditions include the presence of any of: Dyslipidemia, coronary heart disease, stroke, cancer, thyroid disease.
FBG, Fasting Blood Glucose; HbA1c, Hemoglobin A1c; BMI, Body Mass Index.

had co-morbid elevated anxiety symptoms (64.06%), and the majority of participants with elevated anxiety symptoms had co-morbid elevated depression symptoms (77.36%).

Bivariate associations between covariates of interest and total depression and anxiety scores (PHQ-9 and GAD-7 scores) are presented in Supplementary Table S2: Women had significantly higher depression and anxiety scores; higher education level was associated with significantly higher depression scores and with close-to-statistical significance higher anxiety scores. Baseline hypertension was associated with higher depressive symptoms (p=0.06); having a higher number of medical conditions at baseline and follow-up was associated with significantly higher depressive symptoms; anxiety scores were also higher with each additional condition at follow-up (p value=0.076).

3.2 Correlations among glycemic indicators

HbA1c and FBG levels showed positive, strong, and significant correlation at both study waves: at baseline (ρ = 0.81) and five-year follow-up (ρ = 0.84). Baseline HbA1c levels were strongly correlated with follow-up HbA1c levels (ρ = 0.79); baseline FBG levels were highly correlated with five-year follow-up FBG levels (ρ = 0.69) (Table 2).

3.3 Glycemic indicators and depressive and anxiety symptoms

Unadjusted linear regression analyses (Table 3) showed that baseline glycemic indicators were related to both mental health outcomes: higher baseline FBG levels were associated with higher depressive and anxiety symptoms (beta=0.024, 95% CI= [-0.002, 0.051], p-value=0.072 and beta=0.035, 95% CI= [0.009, 0.060], p-value=0.009, respectively); higher baseline HbA1c levels also showed a trend of positive association with depressive symptoms but without reaching statistical significance (beta=0.532, 95% CI = [-0.158, 1.223], p-value=0.130). Baseline diabetes status was associated with higher depression scores (beta=2.110, 95% CI= [0.195, 4.026], p-value=0.031) and with a trend for higher anxiety symptoms (beta=1.647, 95% CI = [-0.223, 3.52], p-value=0.08).

5-year follow-up FBG and HbA1c levels were not associated with concurrent depressive symptoms (p-value>0.33) or anxiety symptoms (p-values>0.47). Change in HbA1c and FBG levels was also not significantly related to mental health symptoms.

Figures 1, 2 represent Lowess plots of the association of baseline and follow-up FBG (Figure 1) and HbA1c (Figure 2) levels with depression and anxiety symptoms. The FBG plots (Figure 1) suggest a change in the association, wherein a positive association is observed in the range of FBG>126 whereas below 126 associations have a negative trend, and this is observed for both baseline and follow-up FBG values and for both depression and anxiety symptoms. A similar trend is observed for HBA1c values, wherein above 6.5% HbA1c values, a positive linear trend between HbA1c and mental health symptoms is more apparent, whereas below 6.5%, the association either follows a plateau or no clear patterns of association.

Given that these trends were observed for both glycemic indicators and for both outcomes, we conducted segmented piecewise regressions separating the ranges of <126 and ≥126 for FBG and <6.5 and ≥6.5 for HbA1c (Table 4). Significant associations were observed between baseline FBG levels and mental health symptoms: In the <126 (non-diabetic) FBG range,

TABLE 2 Correlation of fasting blood glucose (FBG) levels and Hemoglobin A1c (HbA1c) levels at baseline and five-year follow-up in the Greater Beirut Area Cardiovascular Cohort sample (n=198).

Glycemic indicators	Study wave	FBG Baseline	FBG 5-year follow-up	HbA1c Baseline	HbA1c 5-year follow-up
FBG	Baseline	1			
FBG	5-year follow-up	0.69**	1		
HbA1c	Baseline	0.81**	0.67**	1	
HbA1c	5-year follow-up	0.71**	0.84**	0.79**	1

**p-value <0.05.

TABLE 3 Unadjusted linear regression models of baseline and five-year follow-up glycemic indicators and mental health symptoms.

		Depression symptoms (PHQ-9 scores)			Anxiety symptoms (GAD-7 scores)		
		beta	95% CI	P-value	beta	95% CI	P-value
FBG	Baseline	0.024	[-0.002 0.051]	0.072	0.035**	[0.009 0.060]	0.009
	5-year follow-up	0.009	[-0.009 0.029]	0.329	0.007	[-0.012 0.027]	0.473
HbA1c	Baseline	0.532	[-0.158 1.223]	0.130	0.460	[-0.214 1.135]	0.180
	5-year follow-up	0.126	[-0.490 0.742]	0.687	0.135	[-0.467 0.738]	0.661
Change in FBG[¶]		-0.008	[-0.036 0.018]	0.535	-0.024	[-0.051 0.003]	0.084
Change in HbA1c[¶]		-0.702	[-1.690 0.286]	0.163	-0.538	[-1.507 0.430]	0.274
Diabetes, yes	Baseline	2.110**	[0.195 4.026]	0.031	1.647	[-0.223 3.520]	0.085
	5-year follow-up	0.509	[-1.228 2.247]	0.564	-0.556	[-2.251 1.139]	0.519

[¶]Value at 5-year follow-up – Value at baseline
**p-value <0.05.
FBG, Fasting Blood Glucose; HbA1c, Hemoglobin A1c; PHQ-9, Patient Health Questionnaire 9; GAD-7, Generalized Anxiety Disorder 7.

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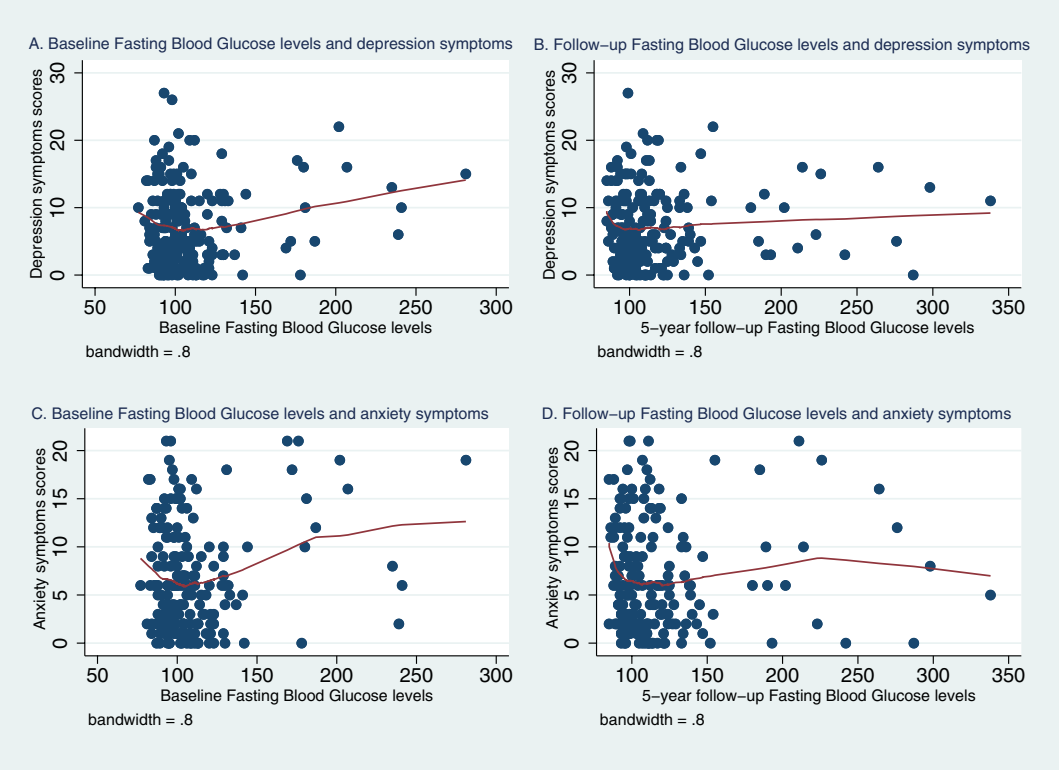

FIGURE 1
Lowess plots of the relationship of depression and anxiety symptoms with baseline and 5-year follow-up fasting blood glucose (FBG) levels. **(A)** Baseline Fasting Blood Glucose level and depression symptoms. **(B)** Follow–up Fasting Blood Glucose levels and depression symptoms. **(C)** Baseline Fasting Blood Glucose levels and anxiety symptoms. **(D)** Follow–up Fasting Blood Glucose levels and anxiety symptoms.

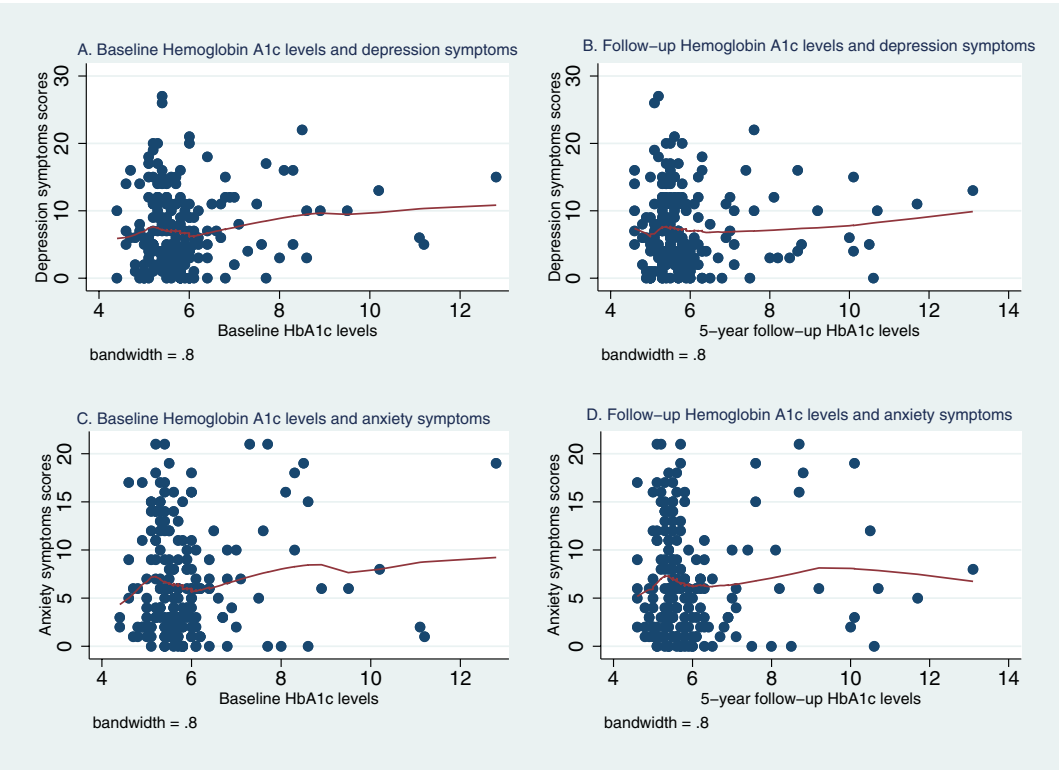

FIGURE 2
Lowess plots of the relationship of depression and anxiety symptoms with baseline and 5-year follow-up Hemoglobin A1c (HbA1c) levels. **(A)** Baseline Hemoglobin A1c levels and depression symptoms. **(B)** Follow–up Hemoglobin A1c levels and depression symptoms. **(C)** Baseline Hemoglobin A1c levels and anxiety symptoms. **(D)** Follow–up Hemoglobin A1c levels and anxiety symptoms.

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TABLE 4 Piecewise regression analysis of baseline and 5-year follow-up fasting blood glucose (FBG) and Hemoglobin A1c (HbA1c) levels and depression and anxiety symptoms.

Model	Glycemic Indicators		Depression symptoms (PHQ-9 scores)				Anxiety symptoms (GAD-7 scores)			
		Glycemic indicator range	beta	95% CI		p-value	beta	95% CI		p-value
Unadjusted Model 1	**FBG Baseline**	< 126	-0.093**	[-.0177	-0.009]	0.030	-0.095**	[-.1763	-.0147]	0.021
		≥126	0.038	[-0.011	0.087]	0.126	0.054**	[0.007	0.101]	0.026
	FBG 5-year Follow-up	< 126	-0.017	[-0.101	0.066]	0.684	-0.048	[-0.131	0.035]	0.255
		≥126	0.013	[-0.019	0.045]	0.436	0.018	[-0.014	0.050]	0.268
	HbA1c Baseline	< 6.5	-1.436	[-3.477	0.604]	0.167	-1.526	[-3.520	0.467]	0.133
		≥6.5	0.429	[-0.911	1.770]	0.528	0.488	[-0.821	1.798]	0.463
	HbA1c 5-year Follow-up	< 6.5	-0.989	[-3.204	1.226]	0.380	-1.617	[-3.773	0.538]	0.141
		≥6.5	0.525	[-0.688	1.738]	0.395	0.587	[-0.593	1.769]	0.328
Adjusted Model 2 ¶	**FBG Baseline**	< 126	-0.111**	[-0.199	-0.023]	0.013	-0.092**	[-0.179	-.0005]	0.038
		≥126	0.039	[-0.008	0.087]	0.103	0.055**	[0.008	0.102]	0.022
	FBG 5-year Follow-up	< 126	-0.025	[-0.113	0.063]	0.569	-0.041	[-0.130	0.046]	0.354
		≥126	0.014	[-0.017	0.045]	0.378	0.017	[-0.014	0.049]	0.274
	HbA1c Baseline	< 6.5	-2.062*	[-4.243	0.119]	0.064	-1.456	[-3.650	0.737]	0.192
		≥6.5	0.447	[-0.837	1.732]	0.493	0.519	[-0.773	1.811]	0.429
	HbA1c 5-year Follow-up	< 6.5	-2.089*	[-4.430	0.251]	0.080	-1.974*	[-4.296	0.348]	0.095
		≥6.5	0.469	[-0.703	1.642]	0.431	0.486	[-0.677	1.649]	0.411
Adjusted Model 3 ¥	**FBG Baseline**	< 126	-0.120**	[-0.207	-0.032]	0.008	-0.099**	[-0.186	-0.012]	0.026
		≥126	0.041*	[-0.006	0.088]	0.087	0.055**	[0.008	0.102]	0.021
	FBG 5-year Follow-up	< 126	-0.020	[-.1086	0.067]	0.647	-0.031	[-0.121	0.058]	0.494
		≥126	0.009	[-.0218	0.041]	0.543	0.013	[-0.018	0.045]	0.409
	HbA1c Baseline	< 6.5	-1.91*	[-4.120	0.293]	0.089	-1.269	[-3.496	0.956]	0.262
		≥6.5	0.517	[-0.769	1.804]	0.429	0.536	[-0.762	1.834]	0.416
	HbA1c 5-year Follow-up	< 6.5	-1.940	[-4.311	0.430]	0.108	-1.833	[-4.258	0.590]	0.137
		≥6.5	0.297	[-0.860	1.456]	0.613	0.302	[-0.882	1.486]	0.615

*p-value <0.10.
** p-value <0.05.
¶adjusted for age, sex, educational attainment, smoking, body mass index, and hypertension.
¥adjusted for age, sex, educational attainment, smoking, body mass index, hypertension, family history of diabetes, count of chronic diseases, and physical activity.

higher baseline FBG levels were associated with lower depressive (beta=-0.093, 95%CI= [-0.0177, -0.009], p=0.03), and anxiety symptoms (beta=-0.095, 95%CI=[-0.1763, -0.0147]; p=0.02). In the diabetic ≥ 126 FBG range, higher baseline FBG levels were significantly associated with higher anxiety symptoms (beta=0.054; 95%CI= [0.007, 0.101]; p=0.026). Higher baseline FBG levels in the ≥126 range showed a non-significant trend for higher depressive symptoms (Table 4).

Similar conclusions were observed in models adjusted for age and sex and following further adjustment for educational attainment, BMI, current smoking, hypertension, family history of diabetes, number of medical conditions, and physical activity (Table 4). FBG levels at follow-up were not associated with concurrent mental health symptoms.

With regards to HbA1c, there was a similar trend for baseline HbA1c levels, with negative associations with mental health symptoms in the below 6.5 range and positive association in the ≥6.5 range; however, they did not reach statistical significance. Following adjustments for lifestyle and health indicators, the negative association between baseline HbA1c and depressive symptoms (beta= -1.91, 95%CI= [-4.21, 0.293]; p= 0.089) and between concurrent HBA1c levels and both depression (beta= -1.940, 95%CI= [-4.311,0.430]; p=0.108) and

anxiety symptoms (beta= -1.833, 95%CI= [-4.528,0.590]; p= 0.137) in the below 6.5 range were more apparent (Table 4).

4 Discussion

4.1 Main findings

The current study aimed to assess the relationship of glycemic indicators with depression and anxiety scores in a community-based sample of middle-aged adults. In our sample, the prevalence of mental health problems was elevated with 32% of respondents having elevated depression and 26% having elevated anxiety symptoms; estimates from previous Ministry of Public Health reports (prevalence of 10-20% prior to the pandemic) also highlight the importance of and need for research on mental health in Lebanon (35). Our study revealed novel findings regarding the association of glycemic indicators and mental health. One important finding is that the association between FBG levels and mental health symptoms was differential across the non-diabetic to diabetic range of glycemic indicators, wherein only increases in FBG levels in the 126 and above range were associated with worsening depression and anxiety scores. Conversely increases in FBG levels, if they were in the below 126 range, were not associated with worst mental health scores and were related to lower mental health symptoms. A similar trend was observed for HbA1c levels, but it was close to statistical significance, with HbA1c levels in the below 6.5 range showing associations with lower mental health scores. This finding highlights a risk specific to reaching the diabetic range and worsening of glycemic indicators in the diabetic range for mental health outcomes. Another key finding was the association between baseline glycemic indicators with mental health symptoms, suggesting longer-term associations and indicating the value of early detection and management for diabetes and co-morbidities.

The finding of associations of FBG levels in the ≥126 range with poorer mental health outcomes are in line with other findings. According to a study conducted in New York that included 249 participants, a sample size that is close to ours, patients with diabetes showed a positive and significant correlation between FBG levels and PHQ-9 depression scores (36). Another study conducted in an Indian health care center among patients with diabetes also showed agreement with our result, where anxiety symptoms were positively associated with FBG (37). We note that very limited number of studies investigates FBG levels and most studies focused on HbA1c. Given the importance of both of these indicators in the context of diabetes, our study investigated both. We also note that associations of HbA1c with mental health outcomes followed the same trend of negative relationships with mental health scores in the non-clinical/diabetic HbA1c ranges (with close-to-statistical significance associations between baseline HbA1c <6.5 and lower mental health symptoms at baseline and follow-up (p ranging from 0.064 to 0.089 in models 2 and 3). In contrast, and unlike FBG levels, changes in HbA1c levels in the clinical/diabetic range were not associated with mental health symptoms. This could be explained in several ways. It is possible that the study's sample size was limited in detecting some associations (despite the consistent pattern of associations for both HbA1c and FBG, at both times points, and with both outcomes), and that larger samples are needed to confirm the lack of association with mental health in the HbA1c clinical/diabetic range. It is possible that HbA1C, which reflects a 3-month average glucose, may lump fasting and post prandial glucose levels and capture different aspects than FBG levels. FBG levels in the non-diabetes state provide a more granular reflection of internal processes preceding the onset of diabetes, such as increased gluconeogenesis and insulin resistance, more so than the post prandial glucose which reflects beta cell function. It is also possible that increases in HbA1c levels within the diabetic range do not carry important consequences for mental health. Some studies found that HbA1c levels are associated with depression (15, 38–41) and anxiety (37) in people with diabetes whereas other studies found no association (42–44). A study among 514 participants in Iran did not find an association between poor glycemic control (high HbA1c values) and depression in people with diabetes (OR = 1.11, 95% CI = [0.87-1.57]) (45). While most of these studies are cross-sectional, other longitudinal studies also found no association. One longitudinal study over 5 years among 3762 patients with diabetes and another 3-year longitudinal study that aimed – as a secondary purpose – to investigate the relation between glycemic control and depression among adolescents showed that the relationship between depression and HbA1c was not significant after adjustment for confounders (17, 43, 46). Our results are in line with these findings, however the observed pattern of associations in our study emphasize that future studies will benefit from exploring the non-diabetic to diabetic ranges of HbA1c to better delineate particularities of this relationship.

In sum, our results show that increases in FBG and HbA1c levels were not linked to poorer mental health, as long as the glycemic values did not reach the clinical diabetes threshold. These findings can have important public health and clinical implications, as they suggest that it is not the gradual/cumulative increase in glycemic indicators' values that is problematic in itself but rather it is entering the disease/pathological range. Further, these associations were observed directly with glycemic indicators (irrespective of diabetes status or treatment), suggesting that non-diabetic FBG and HbA1c levels (either naturally or controlled) may not impact mental health negatively. While our sample size limited thorough investigations of diabetes medication, we note that adjustment for diabetes medication did not change conclusions. Depression and anxiety have been linked to poorer glycemic control, adherence to treatment regimens, and dietary habits (38, 47, 48) further highlighting the need for future studies with larger samples and repeated assessments of both glycemic measures and mental health outcomes that can help assess their complex relationship and interplay through the role of adherence and success of treatment.

Another important finding of this study are the associations of the baseline diabetes-related measures with mental health scores, which were more apparent than associations with the 5-year follow-up diabetes-related measures, assessed at same time as the mental health scores. Changes in FBG and HbA1c levels were not related to

mental health symptoms, which could be explained by the differential associations at different time points and across the diabetic and non-diabetic ranges. We also found that, similarly to FBG levels, diabetes status at baseline was associated with mental health outcomes. This could suggest a delayed or cumulative response between glycemic indicators and mental health outcomes, and that the relationship of higher glycemic levels and mental health may not appear instantly. This is in line with the nature of diabetes, a chronic disease involving complex interactions between multiple factors and consequences on several biological processes. Further, diabetes duration was associated with risk of depression in previous studies (48, 49). We note that patterns of associations were consistent at both baseline and follow-up and that HbA1c 5-year follow-up values in the non-diabetic range showed close to significance associations. We also note that values of both HBA1C and FBG were correlated across time, highlighting the stability of these indicators and raising the question of why some relationships will be observed at a specific time-point. Our analysis was limited by the one measurement of mental health and the absence of assessments at baseline, so we cannot exclude reverse causality and that higher previous glycemic indicators might have been observed among people with a prior mental health problem.

4.2 Strengths and limitations

To the best of our knowledge, this is the first study that address the relationship of mental health conditions across the normal to clinical range of glycemic indicators in a community sample. Prior studies were limited to specific samples with existing comorbidities (people with cardiovascular problems, diabetes 1 and 2, hypertensive, dialysis patients). In addition, this study is a cohort study with repeated assessments of glycemic indicators using rigorous and standardized data collection methods, whereas most previous studies relied on a one-time assessment of glycemic measures. Moreover, the time interval of 5 years between the two study waves allowed assessment of glycemic indicators and their relationships with mental health over a longer-term period. Our study was limited by the high drop-out rate, wherein 303 participants in the baseline wave were lost to follow-up. However, there was no major difference between the responders and non-responders (23). It is also important to note that the primary cause for loss to follow-up was due to the inability to contact because of the change in their contact information. This suggests that, despite the reduction in sample size, the follow-up sample was still representative of the baseline sample and that the drop-out did not cause major systematic differences and selection bias. The drop in sample size may have hindered the detection of smaller magnitude associations and the performance of some sub-group analysis (e.g., controlled diabetes versus uncontrolled diabetes). Furthermore, the study sample remains a selective sample recruited from the capital and its surroundings, and thus it is not representative of the general population in Lebanon. Another important limitation is that the study included only one follow-up wave and importantly one assessment of mental health at the follow-up visit. This hindered the assessment of temporal relationships between glycemic indicators and mental health symptoms. The one-time assessment of mental health also makes it difficult to rule out reverse causality and the scenario that baseline mental health may have impacted baseline and subsequent glycemic markers, as discussed above. At the same time, the lack of cross-sectional association of mental health with glycemic indicators and presence of diabetes at follow-up suggests that it is possible that mental health at baseline may be similarly unrelated to baseline glycemic indicators; and, that the associations of FBG and diabetes with mental health might be more delayed and prolonged in time. Longitudinal studies with several repeated assessments of both glycemic and mental health measures are needed to better describe their temporal and longitudinal associations and to identify shifts to the clinical range and earlier associations. Another limitation concerns potential measurement error in assessing mental health given their subjective nature. Moreover, most of the other chronic diseases were self-reported, and thus limited in capturing undiagnosed or unknown prior occurrences of disease and residual confounding. Finally, stress and traumatic exposures (whether previous such as war exposures or exposure to current hardships) were not assessed in the study and; these exposures are prevalent in the Lebanese context and may influence both mental health and the occurrence of chronic diseases.

5 Conclusion

In summary, results from this community-based sample showed that adverse associations with higher glycemic levels and poorer mental health were not observed in the normal range of these indicators, but rather only in the clinical/diabetic range of FBG. Moreover, this association was observed with prior and not concurrent glycemic levels strengthening the rationale for longitudinal investigations of the relationship between glycemic indicators and mental health symptoms that can help identify temporal and earlier associations and their timing with regards to clinical/diabetic changes in glycemic indicators. A better understanding of the complex co-morbidity between diabetes and mental health disorders can have significant implications for these highly prevalent and burdensome conditions, particularly for improving their prevention, management, and consequences. Advancing this knowledge can aid in developing two-dimension strategies for managing diabetes and mental health simultaneously, which can be particularly important in low-resourced settings such as Lebanon. Our work also puts forward important questions regarding the clinical course of glycemic indicators, as only the clinical range was associated with depression and anxiety symptoms, advocating for prioritizing medical and lifestyle interventions for diabetes and glycemic control to better improve the consequences and mental health co-morbidities for patients with diabetes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Both study waves were approved by the Institutional Review Board at the American University of Beirut and all participants provided written consent at both study examinations.

Author contributions

ZC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing, Software. MN: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing. HT: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. LN: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. ME: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1347092/full#supplementary-material

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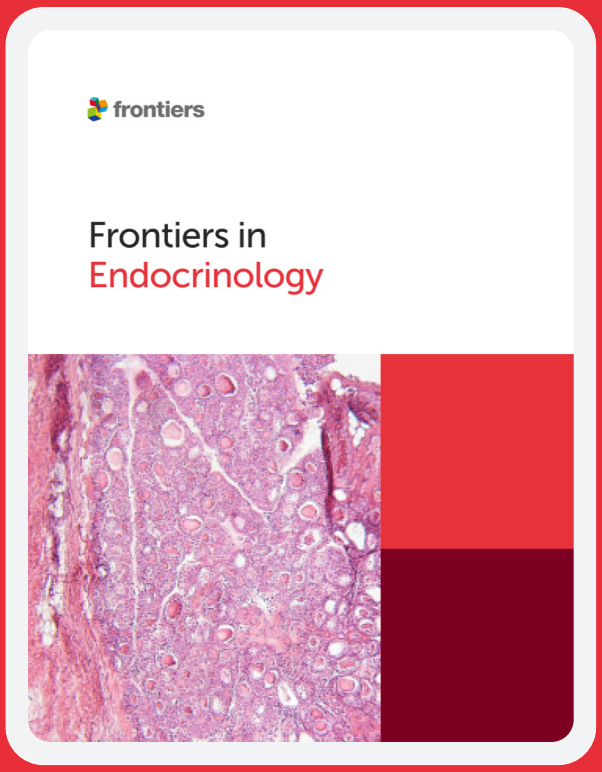

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