General Psychiatry

Trajectories of depressive symptoms and risk of cardiovascular disease, cancer and mortality: a prospective cohort study

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ABSTRACT

Background Depressive symptoms are established risk factors for various health outcomes. However, previous studies assessed depressive symptoms at a single time point, neglecting individual variations over time.

Aims To identify depressive symptoms trajectories through repeated measures and examine their associations with cardiovascular disease (CVD), cancer and mortality.

Methods This study included 20 634 UK Biobank participants free of CVD and cancer at baseline with two or more assessments of depressive symptoms during 2006–2016. Group-based trajectory modelling identified depressive symptoms trajectories. Incident CVD, cancer and mortality were followed up until 2021 through linked registries.

Results Six depressive symptoms trajectories were identified: no symptoms (n=6407), mild-stable (n=11 539), moderate-stable (n=2183), severe-decreasing (n=206), moderate-increasing (n=177) and severe-stable (n=122). During a median follow-up of 5.5 years, 1471 CVD cases, 1275 cancer cases and 503 deaths were documented. Compared with the no symptoms trajectory, the mild-stable, moderate-stable and severe-stable trajectories exhibited higher CVD risk, with hazard ratios (HRs) (95% CIs) of 1.19 (1.06 to 1.34), 1.32 (1.08 to 1.34) and 2.99 (1.85 to 4.84), respectively. Moderate-increasing and severe-stable trajectories were associated with higher mortality risks, with HRs (95% CIs) of 2.27 (1.04 to 4.93) and 3.26 (1.55 to 6.88), respectively. However, the severe-decreasing trajectory was not associated with higher risks of adverse outcomes. We did not find significant associations between any trajectory and cancer.

Conclusions Trajectories related to stable and increasing depressive symptoms, but not the trajectory associated with severe depressive symptoms at the initial assessment but decreasing at the follow-up, were associated with higher risks of CVD and mortality. Alleviating severe depressive symptoms at the initial onset may mitigate CVD and mortality risks.

INTRODUCTION

Mental disorders constitute a major contributor to disease and economic burden globally, with depressive disorders accounting for the largest proportion of disability-adjusted

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depressive symptoms have been recognised as risk factors for various physical conditions and mortality. However, previous studies have typically assessed depressive symptoms at a single point in time, neglecting to consider individual variations over time.

⇒ Previous studies have examined the associations between trajectories of depressive symptoms and risk of dementia and CVD, but they have been limited to small samples. In addition, little is known about the associations of depressive symptoms trajectories with the risk of cancer and mortality.

WHAT THIS STUDY ADDS

⇒ In this population-based study, we have identified six distinct depressive symptoms trajectories through repeated measures of Patient Health Questionnaire-4 in the UK Biobank.

⇒ Our findings suggest that different trajectories confer varying risks for CVD, cancer and mortality. Notably, individuals following a severe-stable trajectory exhibited the highest risk, while those on a severe-decreasing trajectory did not show an increased risk for these outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underscore the potential benefits of dynamic monitoring and early interventions targeted at individuals with severe depressive symptoms as an effective approach to mitigate future risks of CVD and mortality.

life-years from mental disorders in 2019.[1] As a long-term psychological condition, a growing body of studies has demonstrated that depressive symptoms are associated with the risk of various physical conditions, such as diabetes,[2] dementia,[3] cancer[4] and cardiovascular disease (CVD),[5] as well as mortality.[6] For instance, a pooled analysis of 563 255 participants found that baseline depressive symptoms, as measured by the Center for Epidemiological Studies-Depression Scale or the Patient Health Questionnaire-2 (PHQ-2),

were associated with a higher risk of CVD incidence.[5] However, previous studies have predominantly focused on assessing depressive symptoms at a single time point, thereby failing to capture the dynamic nature of individual depressive symptoms progression over time.

Depressive symptoms throughout an individual's lifespan are heterogeneous and a chronic form of mental disorders that exhibit dynamic alterations and may present with interindividual variability. Some individuals may experience severe depressive symptoms at the start of the episode that, over time, fully remit; others may have symptoms that progressively worsen, while still others may suffer life-lasting depressive symptoms.[7] Numerous studies have been conducted on the progression of depression to unravel the complex longitudinal course of depressive symptoms in various populations.[8 9] A previous study of 7240 older women with a follow-up of 20 years revealed four distinct patterns of depressive symptoms in the population during follow-up: 27.8% of participants with minimal depressive symptoms, 54.0% with low depressive symptoms, 14.8% with increasing depressive symptoms and 3.4% with a persistently high depressive symptom trajectory.[10] Existing evidence has shown that different trajectories of depressive symptoms confer a differential risk for diabetes, dementia and stroke.[11–13] Nevertheless, the associations between trajectories of depressive symptoms and incident CVD, incident cancer, and mortality remain largely unknown. We hypothesise that the risk of long-term adverse health outcomes would decrease if depressive symptoms were cured or alleviated.

Therefore, using longitudinal data on repeated measures of depressive symptoms from the UK Biobank, our study aimed to identify different trajectories of depressive symptoms and examine their associations with the risk of CVD, cancer and mortality. Additionally, we investigated potential effect modifications by examining whether the impact of depressive symptoms trajectories on CVD, cancer and mortality risk varied across potential risk factors (figure 1).

METHODS
Study design and participants
The UK Biobank cohort comprises over 500 000 participants aged 37–73 years from 22 assessment centres across England, Scotland and Wales who were surveyed at baseline between 2006 and 2010. All participants completed a range of demographic, lifestyle, health and physical assessments and questionnaires.[14] The UK Biobank obtained informed consent from all participants.

The initial sample of our study comprised 25 564 participants who had data on depressive symptoms in at least two out of the three assessment rounds during the follow-up period: visit 1 (2006–2010), visit 2 (2012–2013) and visit 3 (2014–2016). Subsequently, participants who had a history of CVD or cancer before or at the baseline of this study (n=4174), had missing data on covariates (n=44) or experienced death between the three depressive symptoms assessments (n=38) were excluded. The final analytical cohort consisted of 20 634 participants who were subsequently used to identify trajectories of depressive symptoms and examine associations between these trajectories and the risk of CVD, cancer and
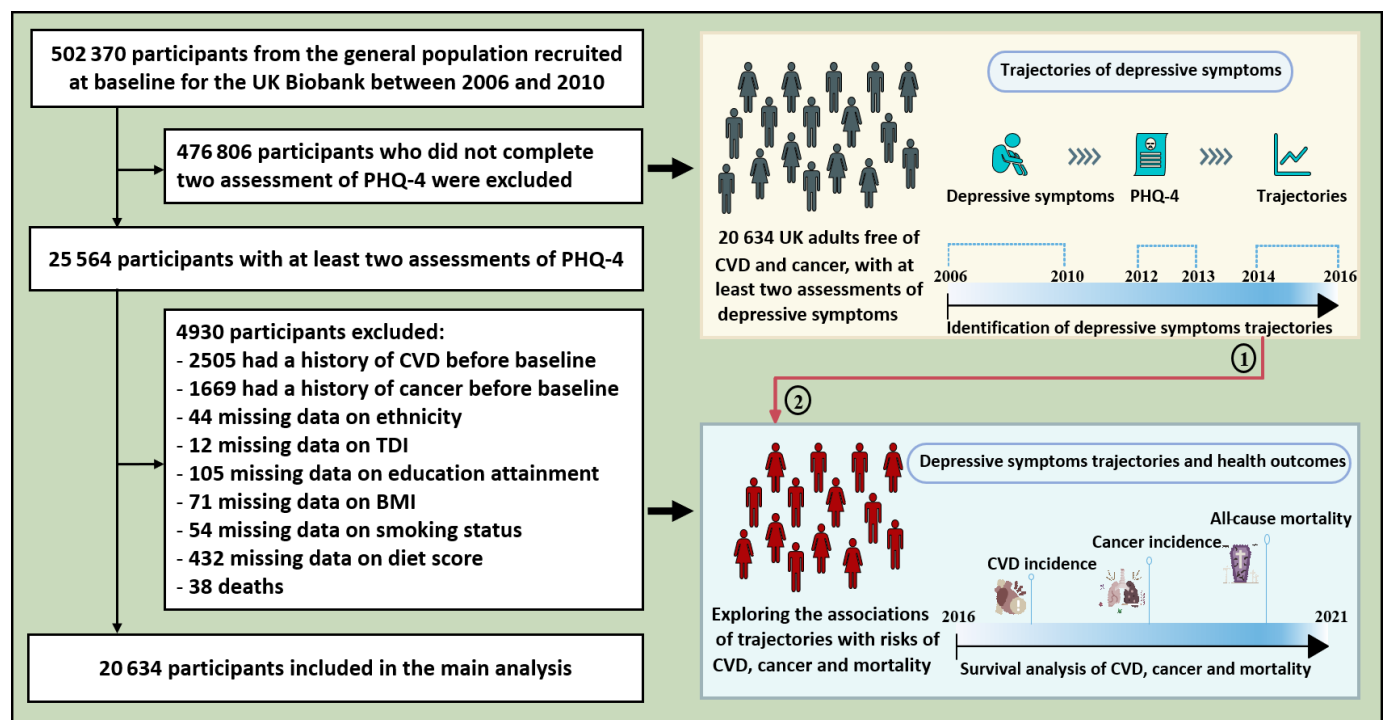

Figure 1 Flowchart of the study design. BMI, body mass index; CVD, cardiovascular disease; PHQ-4, 4-item Patient Health Questionnaire; TDI, Townsend Deprivation Index.

mortality. The timeline and flowchart of the present study are detailed in figure 1.

Assessment of depressive symptoms

Depressive symptoms in the present study were ascertained using the Patient Health Questionnaire-4 (PHQ-4) across three assessment rounds. The PHQ-4 is a validated four-item screening tool for assessing depression and identifying relevant depressive symptoms.[15 16] Participants are asked: 'Over the last 2 weeks, how often have you been bothered by depressed mood/unenthusiasm or disinterest/tenseness or restlessness/tiredness or lethargy?'. Specific questions for PHQ-4 can be found in the following field IDs in the UK Biobank: 2050, 2060, 2070 and 2080. Responses to the four items are scored from 0 (not at all) to 3 (nearly every day), resulting in a total score range of 0–12, with higher scores reflecting more severe symptoms.

Assessment of outcomes

This study classified the primary outcomes of interest, including incident CVD, incident cancer and mortality, using the International Classification of Diseases, 10th Revision (ICD-10). Data on incident CVD events, including ischaemic heart disease (I20-I25), atrial fibrillation (I48), heart failure (I50) and stroke (I60-I61 and I63-I64), were obtained through linked hospital admissions data including the Hospital Episode Statistics-Admitted Patient Care (England), the Scottish Morbidity Records-General/Acute Inpatient and Day Case Admissions (Scotland), and the Patient Episode Database for Wales. Incident cancer events were identified using the ICD-10 codes C00-C99. Information regarding the date and cause of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register (Scotland). The follow-up time began at the date of the third assessment round of depressive symptoms and ended at the occurrence of CVD, cancer, and mortality or the end of the follow-up (30 September 2021), whichever came first. To ensure consistency in follow-up time across all participants, the initiation of follow-up for those lacking data from the third assessment was set on 13 March 2016, which was the end point of the third assessment period in this study.

Assessment of covariates

Based on prior relevant studies,[11] we selected the following variables as covariates: age, sex (female or male), ethnicity (white or others), education (college/university degree or others), the Townsend Deprivation Index (TDI), body mass index (BMI), smoking status (never, former or current), alcohol consumption frequency (never, special occasions only, once to three times a month, once or twice a week, three or four times a week, or daily or almost daily), diet scores (0 to 7), sleep scores (0 to 5), history of hypertension (yes or no), history of diabetes (yes or no) and use of antidepressants (yes or no).

Age, sex and TDI were known before arrival at the assessment centre. TDI is a composite measure of deprivation based on unemployment, non-car ownership, non-cottage ownership and household overcrowding, with higher values indicating lower socioeconomic status.[17] Information on ethnicity, education level, smoking status, alcohol consumption frequency, diet scores and sleep scores was obtained using touch screen questionnaires or verbal interviews. The diet score was constructed to reflect the dietary pattern based on the frequency of consumption of fruits, vegetables, fish, processed meat, unprocessed red meat, whole grains and refined grains, with higher scores indicating a healthier dietary pattern.[18] Sleep scores were generated by incorporating five sleep factors: chronotype, sleep duration, insomnia, snoring and excessive daytime sleepiness. For each sleep factor, we assigned 1 point for a healthy level and 0 points for an unhealthy level. This resulted in a total range score between 0 and 5, with a higher score indicating a healthier sleep pattern. The healthy standards for sleep factors were detailed in our published study.[19] BMI was calculated as the weight in kilograms divided by the square of the height in metres. A history of hypertension and diabetes was obtained from self-reported questionnaires. The initial assessments using touch screen questionnaires or verbal interviews were carried out between 2006 and 2010. Notably, the values of some covariates, including education, BMI, smoking status, alcohol frequency, diet scores and sleep scores, were re-obtained at the time point closest to the third assessment of depressive symptoms. Detailed information is shown in the online supplemental figure 1.

Statistical analysis

This study used the group-based trajectory modelling (GBTM) approach with the Stata 'Traj' plugin to identify distinctive trajectories of depressive symptoms. The GBTM is a semiparametric model capable of classifying participants with similar patterns of depressive symptoms into clusters over time.[20 21] The best-fitting model was estimated using a three-step procedure. First, an appropriate model was selected based on the variable's distribution. As depressive symptoms were treated as a continuous variable in this study, a censored normal model was used to fit the trajectories. Second, the optimal number of trajectories was determined using quadratic polynomial functions. Fitted models with two to seven trajectories were estimated according to the minimum absolute Bayesian Information Criterion while ensuring average posterior probabilities (AvePP) >70% and including at least 100 participants per trajectory. These criteria identified six trajectories as the most suitable model with the ideal number of trajectories. Third, we evaluated the best-fitting trajectory model by determining the proper polynomial order (intercept, linear and quadratic) to specify the optimal shape for each trajectory. In addition to the abovementioned criteria, all model polynomials must meet the criteria for statistical significance (p<0.05). Finally, combining

linear, quadratic, linear, linear, quadratic and linear forms provided the most suitable model for the six-group trajectory.

To enhance interpretability, we assigned labels to each trajectory based on its modelled graphic patterns. Additionally, we visually examined individual participants' trajectories by plotting categorised depressive symptoms values according to the identified trajectory, age and visit to assess the fit of individual trajectories with our final model and patterns of missing data.

Descriptive characteristics were presented as means with standard deviations (SDs) for continuous variables and numbers with percentages for categorical variables by depressive symptoms trajectories. Cox proportional hazards models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the associations between depressive symptoms trajectories and the risk of CVD, cancer and mortality. We implemented three incremental models: model 1 was adjusted for age, sex, ethnicity, TDI, education and BMI. Model 2 was additionally adjusted for smoking status, alcohol consumption frequency, diet scores, sleep scores, history of hypertension and history of diabetes. To evaluate the specific impact of antidepressants on these associations, model 3 was further adjusted for the use of antidepressants. We tested the proportional hazards assumption across all Cox models with Schoenfeld residuals and found no violation. In addition, Kaplan-Meier survival analyses of survival rates for CVD, cancer and mortality were plotted based on groups of depressive symptoms trajectories. Log-rank tests were performed to compare the survival distributions between groups.

Several sensitivity analyses were performed to appraise the robustness of our results. First, to evaluate the robustness of trajectory classification, we recalculated the trajectories using a training data set randomly selected from 50% of our cohort. We then employed the GBTM parameters derived from the training data to calculate the AvePP in the test data set, comprising the other 50% of the cohort. Second, we repeated the main analysis within subgroups to understand whether the associations could be modified by age (≤60 years and >60 years), sex (female and male), BMI ($\leq25\,kg/m^2$ and $>25\,kg/m^2$), education (college/university and others) or TDI (<median value (−2.71) and ≥median value). Third, we performed a landmark analysis excluding participants who experienced events of interest within the initial 2 years of follow-up to minimise the potential reverse causation risks. Fourth, we explored the potential added value of depressive symptoms trajectories compared with baseline scores by introducing the initial PHQ-4 assessment as an additional covariate in our analysis.

All the analyses were conducted using STATA V.16 statistical software (Stata Corp, College Station, Texas, USA) and R software (V.4.1.3). The statistical significance was set as p<0.05 (two-sided test).

RESULTS

Trajectories of depressive symptoms

A total of 20 634 participants with at least two assessment rounds of depressive symptoms were included in the trajectory analysis, with a median follow-up time of 6.4 years (from visit 1 to visit 3). Based on morphological characteristics, six distinct trajectories of depressive symptoms were identified among the participants: maintaining very low PHQ-4 scores throughout the follow-up (no symptoms; n=6407), maintaining a mildly high score throughout the follow-up (mild-stable; n=11 539), maintaining a moderately high score throughout the follow-up (moderate-stable; n=2183), starting with a high PHQ-4 score that then decreased (severe-decreasing; n=206), starting with a moderately high score that then increased (moderate-increasing; n=177), and consistently maintaining high scores (severe-stable; n=122), respectively (figure 2; online supplemental tables 1,2). Furthermore, we found that the visual assessments of individual patterns in the observed PHQ-4 scores, categorised by the most probable class membership, visit and age, were generally consistent with the model-based descriptions (figure 3). This finding implied that missing data had a negligible impact on the trajectory patterns derived from our models.

Baseline characteristics by trajectories of depressive symptoms

The baseline characteristics of 20 634 participants (53.65% female, mean (SD) age: 56.07 (7.50) years) categorised by determined trajectories of depressive symptoms are shown in table 1. In general, participants within the severe depressive symptoms trajectories exhibited poorer health status and lifestyles compared with those with the no symptom trajectory. For instance, the prevalence rates for smoking, hypertension and diabetes were found to be higher among individuals in the severe-stable trajectory compared with those in the trajectory of no symptoms. Additionally, they displayed lower levels of education attainment, diet scores and sleep scores while exhibiting elevated BMI. Notably, those in the severe-stable trajectory were inclined to be younger and more likely to be female.

Trajectories of depressive symptoms and risk of CVD, cancer and mortality

During a median follow-up of 5.5 years, 1471 cases of CVD, 1275 cases of cancer and 503 cases of death were documented. Based on multivariable-adjusted Cox regression models, the findings revealed that only individuals within specific trajectories exhibited a heightened risk of health outcomes compared with those in the reference group with no symptoms. Specifically, when compared with the trajectory of individuals without symptoms, the HRs (95% CIs) for incident CVD in the trajectories of mild-stable, moderate-stable and severe-stable were 1.19 (1.06 to 1.34), 1.32 (1.08 to 1.61) and 2.99 (1.85 to 4.84), respectively, in the fully adjusted model 3 (table 2). The
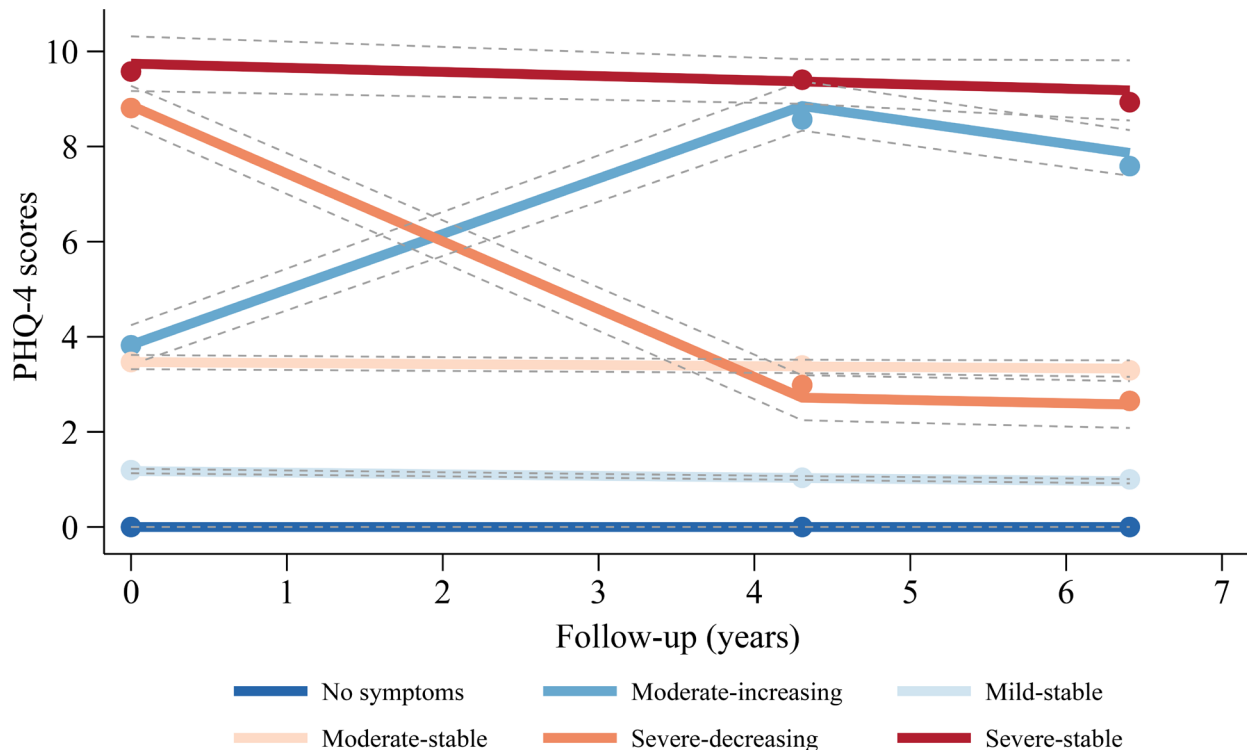
Figure 2 Trajectory of depressive symptoms among 20 634 individuals. The figure shows trajectories of depressive symptoms from 20 634 individuals, with three measures of the Patient Health Questionnaire-4 (PHQ-4), with collection points covering the period 2006–2016. The dotted lines represent confidence bands for the calculated trajectory.

severe-decreasing (HR=1.45, 95% CI 0.85 to 2.48) and moderate-increasing (HR=1.46, 95% CI 0.82 to 2.61) trajectories for CVD outcome did not yield statistically significant results.

Compared with individuals with no symptom trajectory, the HRs (95% CI) for mortality within the moderate-increasing and severe-stable trajectories were 2.27 (1.04 to 4.93) and 3.26 (1.55 to 6.88), respectively. The trajectory of severe-decreasing, similar to the results of CVD, did not show an increased risk of mortality (HR=0.86, 95% CI 0.27 to 2.73). Additionally, no significant association was observed between trajectories of depressive symptoms and the incidence risk of cancer, with statistically non-significant results across all trajectories. While Kaplan-Meier survival curves demonstrated notable differences in survival rates among individuals in different trajectories for CVD and mortality (p=0.006 for CVD and p=0.032 for mortality by log-rank test), such differences were not evident for cancer (p=0.154) (see online supplemental figures 2–4).

Moreover, we further examined whether the use of antidepressant medications influenced these associations. Comparing models that included antidepressant use with those that did not include it as a covariate, our findings indicated a moderate strengthening of the associations between trajectories of depressive symptoms and CVD, cancer and mortality. The HRs and 95% CIs for the severe-stable trajectory of CVD incidence were 2.99 (1.85 to 4.84) in model 3 and 3.14 (1.95 to 5.05) in model 2,

indicating that adjusting for the use of antidepressants attenuated the associations.

Sensitivity analyses

We performed several sensitivity analyses to confirm the robustness of our primary findings. The results from the training and test data sets reaffirm the presence of six distinct trajectories of depressive symptoms (see online supplemental table 3 and online supplemental figure 5). Subgroup analyses showed that the associations between the severe-stable trajectory and both CVD and mortality were more pronounced among female participants, those aged over 60 years, those with a BMI below 25 kg/m^2, those without a college/university education and those with a TDI less than −2.71, compared with the no symptoms trajectory (see online supplemental table 4). Moreover, the results did not materially change even after excluding participants who experienced outcomes of interest within the first 2 years (see online supplemental table 5) and when accounting for the initial assessment of PHQ-4 scores as an additional covariate (see online supplemental table 6).

DISCUSSION
Main findings

In this large prospective cohort study of the UK Biobank, we have identified six distinct trajectories of depressive symptoms based on three repeated assessments of PHQ-4 scores among 20 634 participants. These trajectories were
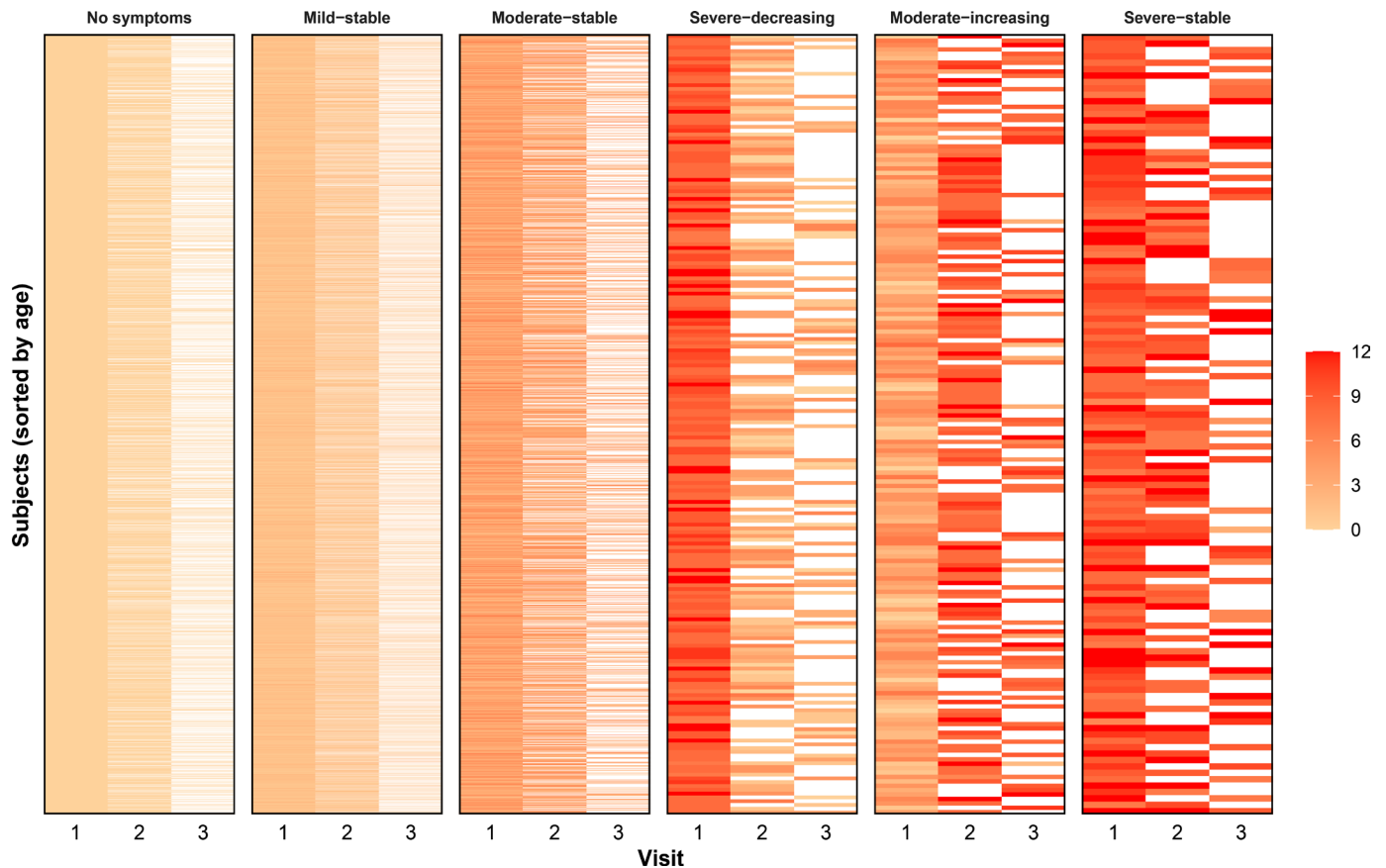
Figure 3 Patient Health Questionnaire-4 scores stratified by follow-up visits for populations with different trajectories. The figure presents the actual scores from three assessments of depressive symptoms for individuals categorised into six distinct trajectories using the group-based trajectory modelling approach. Rows represent individual subjects of the study population, sorted by age in ascending order starting from the top. Colours represent scores of depressive symptoms, darkening with increasing scores, as shown in the colour legend. White spaces represent missing values.

labelled as no symptoms, mild-stable, moderate-stable, severe-decreasing, moderate-increasing and severe-stable. We found that trajectories related to stable and increasing depressive symptoms (eg, mild-stable, moderate-stable, moderate-increasing and severe-stable) but not the severe-decreasing trajectory were associated with higher risks of CVD incidence and mortality. Such associations consider potential confounders, including sociodemographic factors, lifestyle behaviours, comorbid conditions and the use of antidepressants.

An examination of the baseline characteristics for all participants across different depressive symptoms trajectories showed that those within the severe-stable trajectory were predominantly younger women. This not only highlights the alarming trend of younger demographics experiencing severe depressive symptoms but also draws attention to the existing gender disparities in the burden of mental health. Our findings were supported by existing literature. Previous epidemiological studies have consistently reported a nearly twofold higher prevalence of depression in women compared with men across all age groups.[22] Another recent survey conducted among the general population in the USA observed an increasing prevalence of depressive symptoms among adolescents and young adults from 2005 to 2014.[23] Moreover, a

prospective cohort study involving 7735 participants in China revealed that women with depression had a higher risk of CVD compared with men,[24] which aligns with the subgroup analysis results obtained in our study. Therefore, it is imperative to prioritise efforts aimed at mitigating the burden of depressive symptoms, particularly among women and younger populations.

Compared with individuals with no symptom trajectory, those with stable depressive symptom trajectories over time, either mild or severe, were all associated with a higher risk of incident CVD and mortality. Interestingly, depressive symptom trajectories that changed over time, such as severe-decreasing and moderate-increasing trajectories, displayed differential associations with health outcomes. In our study, despite having substantially high depressive symptoms during the initial assessment, individuals within the severe-decreasing trajectory did not demonstrate an increased risk for CVD, cancer or mortality. In contrast, individuals within the moderate-increasing trajectory were significantly associated with a higher risk of mortality despite lower depressive symptoms at the initial time in this trajectory than the trajectory of severe-decreasing. This highlighted that experiencing severe depressive symptoms at one point in time may not have a lasting impact on predicting the risk of CVD or

Table 1 Baseline characteristics of study participants by depressive symptom trajectories

Characteristics	Total (n=20 634)	Trajectory of depressive symptoms					
		No symptoms (n=6407)	Mild-stable (n=11 539)	Moderate-stable (n=2183)	Severe-decreasing (n=206)	Moderate-increasing (n=177)	Severe-stable (n=122)
Age, mean (SD), years	56.07 (7.50)	57.77 (7.07)	55.94 (7.46)	52.69 (7.46)	52.89 (7.20)	51.76 (7.08)	51.36 (6.89)
Sex, male, n (%)	9564 (46.35)	3434 (53.60)	5151 (44.64)	800 (36.65)	53 (25.73)	67 (37.85)	59 (48.36)
Ethnicity, white, n (%)	20135 (97.58)	6266 (97.80)	11294 (97.88)	2102 (96.29)	196 (95.15)	163 (92.09)	114 (93.44)
Education, college or university, n (%)	9478 (45.93)	2877 (44.90)	5552 (48.12)	847 (38.80)	90 (43.69)	82 (46.33)	30 (24.59)
TDI, mean (SD)	−2.04 (2.65)	−2.28 (2.49)	−2.07 (2.64)	−1.46 (2.94)	−1.69 (2.87)	−1.14 (3.05)	−0.17 (3.14)
BMI, mean (SD), kg/m^2	26.70 (4.51)	26.27 (4.02)	26.72 (4.52)	27.43 (5.25)	28.38 (5.74)	27.73 (5.46)	29.33 (6.46)
Diet scores, mean (SD)	3.71 (1.45)	3.78 (1.45)	3.70 (1.45)	3.59 (1.43)	3.65 (1.44)	3.43 (1.53)	3.29 (1.62)
Smoking status, n (%)							
Never	12782 (61.95)	4051 (63.23)	7142 (61.89)	1289 (59.05)	130 (63.11)	105 (59.32)	65 (53.28)
Former	6979 (33.82)	2148 (33.53)	3930 (34.06)	736 (33.72)	63 (30.58)	56 (31.64)	46 (37.70)
Current	873 (4.23)	208 (3.25)	467 (4.05)	158 (7.24)	13 (6.31)	16 (9.04)	11 (9.02)
Sleep scores, mean (SD)	3.09 (0.97)	3.32 (0.94)	3.06 (0.96)	2.73 (0.97)	2.79 (0.96)	2.49 (1.01)	2.17 (0.94)
History of hypertension, n (%)	4165 (20.19)	1229 (19.18)	2378 (20.61)	439 (20.11)	48 (23.30)	36 (20.34)	35 (28.69)
History of diabetes, n (%)	504 (2.44)	145 (2.26)	269 (2.33)	67 (3.07)	7 (3.40)	5 (2.82)	11 (9.02)
Antidepressant use, n (%)	1091 (5.29)	95 (1.48)	536 (4.65)	310 (14.20)	57 (27.67)	40 (22.60)	53 (43.44)

BMI, body mass index; TDI, Townsend Deprivation Index.

Table 2 Association between depressive symptom trajectories and risk of cardiovascular disease, cancer and mortality

Outcomes	Trajectory of depressive symptoms, HRs (95% CIs)					
	No symptoms	Mild-stable	Moderate-stable	Severe-decreasing	Moderate-increasing	Severe-stable
CVD incidence						
Case/N	448/6407	839/11 539	139/2183	14/206	12/177	19/122
Model 1	1 (Reference)	1.23 (1.09 to 1.38)	1.43 (1.18 to 1.74)	1.59 (0.93 to 2.71)	1.63 (0.92 to 2.90)	3.71 (2.33 to 5.90)
Model 2	1 (Reference)	1.19 (1.06 to 1.34)	1.34 (1.10 to 1.64)	1.50 (0.88 to 2.57)	1.52 (0.85 to 2.71)	3.14 (1.95 to 5.05)
Model 3	1 (Reference)	1.19 (1.06 to 1.34)	1.32 (1.08 to 1.61)	1.45 (0.85 to 2.48)	1.46 (0.82 to 2.61)	2.99 (1.85 to 4.84)
Cancer incidence						
Case/N	424/6407	702/11 539	129/2 183	9/206	8/177	3/122
Model 1	1 (Reference)	1.03 (0.91 to 1.16)	1.23 (1.01 to 1.51)	0.92 (0.48 to 1.79)	0.98 (0.49 to 1.98)	0.49 (0.16 to 1.54)
Model 2	1 (Reference)	1.02 (0.90 to 1.16)	1.23 (1.00 to 1.51)	0.91 (0.47 to 1.76)	0.96 (0.47 to 1.94)	0.49 (0.16 to 1.54)
Model 3	1 (Reference)	1.02 (0.90 to 1.15)	1.22 (0.99 to 1.50)	0.89 (0.46 to 1.74)	0.95 (0.47 to 1.92)	0.48 (0.15 to 1.52)
Mortality						
Case/N	164/6407	272/11 539	49/2 183	3/206	7/177	8/122
Model 1	1 (Reference)	1.10 (0.90 to 1.34)	1.43 (1.03 to 1.98)	0.98 (0.31 to 3.09)	2.77 (1.29 to 5.92)	4.05 (1.97 to 8.31)
Model 2	1 (Reference)	1.07 (0.88 to 1.30)	1.30 (0.93 to 1.82)	0.90 (0.29 to 2.83)	2.37 (1.10 to 5.12)	3.47 (1.67 to 7.22)
Model 3	1 (Reference)	1.06 (0.87 to 1.30)	1.27 (0.91 to 1.78)	0.86 (0.27 to 2.73)	2.27 (1.04 to 4.93)	3.26 (1.55 to 6.88)

Cases/N = number of outcome cases/number of total individuals at risk per trajectory.
Model 1 was adjusted for age, sex, ethnicity, Townsend Deprivation Index, education and BMI.
Model 2 was additionally adjusted for smoke status, alcohol frequency, diet scores, sleep scores, history of hypertension and history of diabetes.
Model 3 was further adjusted for the use of antidepressants.
BMI, body mass index; CVD, cardiovascular disease; HR, hazard ratio.

mortality during follow-up. This finding also implied that if we could implement timely interventions for populations who have exhibited severe depressive symptoms by assisting in the alleviation of their severity, it has the potential to protect and prevent those with severe depressive symptoms at the initial time from developing CVD or cancer or an untimely death. However, most existing evidence relied on a single measurement of depressive symptoms when investigating associations of depressive symptoms with disease onset risk, which may potentially obscure the true magnitude of the association between long-term depressive symptoms and the risk of disease. For instance, a meta-analysis of community-based cohort studies using a single assessment of depressive symptoms found that late-life depression was associated with a significant risk of all-cause dementia (HR=1.85, 95% CI 1.67 to 2.04, p<0.001).[3] Nevertheless, in a prospective cohort study of 3325 dementia-free participants, five unique depressive symptoms trajectories were identified after a 10-year follow-up and only individuals within the increasing trajectory had an elevated dementia risk (HR=1.42, 95% CI 1.04 to 1.94, p=0.024), indicating that the risk of dementia varied with different courses of depressive symptoms.[11] Moreover, another prospective cohort study involving 2488 older adults of both black and white ethnicity (mean age, 74.0 years) identified three distinct depressive symptoms trajectories based on repeated assessments from baseline to year 5. The findings revealed that individuals following the high and increasing depressive symptoms had a significantly higher risk of dementia (HR=1.94, 95% CI 1.30 to 2.90).[12] The findings from these studies suggest that the predictive value of disease incidence may be better captured by examining trajectories of depressive symptoms rather than assessing depressive symptoms at a single time point. In the current study, we used repeat measures to evaluate depressive symptoms trajectories and investigate their associations with CVD, cancer and mortality. Our findings have significant implications for improving timely surveillance and intervention of depressive symptoms within the population by public health systems.

Due to variations in baseline characteristics and management settings, the trajectory of depression across an individual's lifespan exhibits significant heterogeneity, particularly concerning episode duration, lifetime episode frequency and pattern of occurrence.[25] Several previous observational studies have reported that older adults may experience a dynamic and changeable course of depressive symptoms.[10] For example, one study that encompassed 392 participants aged >65 years was conducted to track their depressive symptoms for 2 years. This study identified six distinct trajectory clusters that followed clinically intuitive patterns,[26] revealing that depression is not simply a static state but a complex process that changes over time.

Therefore, using repeated data to measure depressive symptoms over time and examine their associations with the risk of diseases may provide more accurate evidence

than from a single observation of depression. To the best of our knowledge, this was the first study to use the GBTM approach to assess the trajectories of depressive symptoms of individuals over time in the UK Biobank and to provide novel insights into understanding how different trajectories of depressive symptoms can influence the risk of CVD, cancer and mortality over time. Our findings highlight the importance of dynamic monitoring and early interventions aimed at mitigating depressive symptoms as a valuable strategy for preventing the future development of CVD and risk reduction in mortality.

Previous studies have suggested several potential mechanisms by which depressive symptoms are associated with CVD and mortality. Biologically, depression has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system and inflammatory pathways, which may promote atherosclerosis, endothelial dysfunction, platelet aggregation, arrhythmia and myocardial infarction.[25 27] Socially, depression is associated with loneliness, low social support and fewer health-promoting resources.[28 29] In addition, participants with severe depressive symptoms were more likely to have unhealthy lifestyles, such as smoking, heavy drinking, poor sleep quality and poor dietary habits. Taken together, these mechanisms likely interact to produce worse effects, which may be involved in the pathways from depression to CVD and mortality. In this study, we found that participants in the stable and increasing trajectories of depressive symptoms were associated with higher risks of CVD and mortality but not in the decreasing trajectory of depressive symptoms. However, whether the mechanisms driving the associations between depressive symptoms and CVD, cancer or mortality differ according to the different trajectories of depressive symptoms that individuals experience over time is still unclear and needs to be clarified in the future.

Limitations

The current study possesses several notable strengths. It capitalises on a substantial sample size, enabling a robust analysis of the trajectory of depressive symptoms. We used the GBTM approach to capture the life course of depressive symptoms, allowing for an examination of the average, variability and direction of variability to investigate the heterogeneity in trajectories among individuals. Furthermore, meticulous control over covariates and comprehensive sensitivity analyses have significantly bolstered the reliability of our findings.

Nonetheless, it is important to acknowledge several limitations in the current study. First, our reliance on self-reported PHQ-4 for assessing depressive symptoms may introduce information bias. However, previous studies have validated a high sensitivity and specificity of the PHQ-4 in screening mental disorders, thereby minimising such potential bias.[16] Second, because our trajectory modelling included individuals with data from at least two out of three visits for depressive symptoms, missing data could potentially affect our ability to

detect actual effects, causing biased results. However, given the observed symptom patterns (figure 3) and the universally high posterior probabilities of class membership (see online supplemental table 2), we do not have strong evidence regarding the influence of missing data. Third, the statistical power may have been limited due to the assignment of relatively small populations within the trajectory of severe-decreasing (n=206), moderate-increasing (n=177) and severe-stable (n=122), which could explain why no significant associations were found with CVD or cancer. Fourth, the limited number of time points for trajectory analysis could potentially impact the reliability of classification. Future research should conduct trajectory analysis with data sets with more time points to assess depressive symptoms. Fifth, like other observational studies, we cannot entirely rule out the possibility of reverse causality and the impact of unmeasured confounders despite adjusting for a series of potential confounders within this study. Nonetheless, we found that the results of the landmark analysis remained consistent with the primary analysis, which can minimise the possibility of reverse causation. Sixth, it should be noted that our data were obtained from the UK Biobank, which may not provide a fully representative sample due to its overrepresentation of white British participants residing in less socioeconomically deprived areas who maintain healthier lifestyles than the general population in the UK.[30] Therefore, caution must be exercised when generalising these findings to other populations.

Implications

In summary, we have identified six distinct depressive symptoms trajectories through repeated measures of the PHQ-4 in the UK Biobank. Our findings suggest that different trajectories confer varying risks for CVD, cancer and mortality. Notably, individuals following a severe-stable trajectory exhibited the highest risk, while those on a severe-decreasing trajectory did not show an increased risk for these outcomes. These results underscore the potential benefits of dynamic monitoring and early interventions targeted at individuals with severe depressive symptoms as an effective approach to mitigate future risks of CVD and mortality.

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