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Research Article

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Impact of Depressive Symptom Trajectories on the Risk of Gastrointestinal Disorders: A Longitudinal Prospective Cohort Study Using CHARLS

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Abstract

Background: Depression and gastrointestinal disorders frequently co-occur. However, few studies have systematically explored the long-term effects of depressive symptom trajectories on gastrointestinal disorders. This study aimed to clarify the differential impacts of depressive symptom trajectories on gastrointestinal disorders.

Methods: Using five waves of longitudinal data (2011–2020) from the China Health and Retirement Longitudinal Study, we defined the exposure period for depressive symptom trajectories as 2011–2015 and the outcome period for incident gastrointestinal disorders as 2015–2020. A total of 6108 participants were included. Group-based trajectory modeling identified distinct depressive symptom trajectories. Longitudinal targeted maximum likelihood estimation examined associations between depressive symptom trajectories and the risk of incident gastrointestinal disorders.

Results: Three distinct trajectories were identified: non-depressive (69.0%), low-depressive (25.7%), and high-depressive (5.3%). Cumulative gastrointestinal disease incidence was 6.88%, 10.58%, and 19.14% for the three groups, respectively. Compared with the non-depressive group, both the low-depressive (OR = 1.52, 95% CI: 1.24–1.88, $P < 0.001$) and the high-depressive groups (OR = 3.02, 95% CI: 1.81–

5.04, $P < 0.001$) had significantly increased risks of gastrointestinal disorders. The high-depressive group also showed a significantly higher risk than the low-depressive group (OR = 1.97, 95% CI: 1.40–2.76, $P < 0.001$).

Conclusions: Depressive symptom trajectories were significantly associated with the subsequent gastrointestinal disease risk. Of these, the high-depressive trajectory carries the highest risk. These findings demonstrate the importance of dynamically monitoring depressive symptom trajectories and early interventions for high-risk populations.

Keywords: depressive symptom trajectories, gastrointestinal disorders**,** cohort study, China Health and Retirement Longitudinal Study, longitudinal targeted maximum likelihood estimation

1 Introduction

Gastrointestinal (GI) disorders (excluding tumors and cancers) are among the most prevalent digestive disorders. Their association with depression has attracted growing attention[1, 2], making this a prominent research focus at the interface of gastroenterology and psychiatry. Existing studies have demonstrated complex bidirectional associations between depressive symptoms and GI disorders, including gastroesophageal reflux disease (GERD)[3], inflammatory bowel disease (IBD)[4], and irritable bowel syndrome (IBS)[5]. A case-control study revealed that depression incidence was markedly elevated among participants who were later diagnosed with IBD, occurring several years prior to IBD diagnosis. Moreover, the co-occurrence of

depression and GI symptoms may further raise disease risk[6]. Collectively, these findings indicate that depression may increase the subsequent risk of incident GI disorders, yet causal evidence from longitudinal studies remains limited.

Existing studies investigating the impact of depression on the risk of GI disorders have several limitations. First, limitations in study design. Most prior investigations adopted cross-sectional designs or single-time-point assessments, which can only identify the cross-sectional association between baseline depression and GI disorders and cannot establish a causal relationship between the two conditions[7, 8]. Second, limitations in exposure stratification. Previous investigations typically adopted a binary classification (presence vs. absence) and failed to characterize dynamic depressive symptom trajectories, such as worsening, remission, and stabilization. Accordingly, these studies cannot differentiate long-term risks of GI disorders associated with distinct depressive symptom trajectories[9, 10]. Third, limitations in confounding adjustment. Prior studies have not fully accounted for time-varying confounders such as age, marital status, and smoking status, potentially yielding unstable effect estimates.

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative longitudinal survey of Chinese residents aged ≥ 45 years and their spouses [11]. Two CHARLS-based studies have examined the impact of depression on the risk of incident GI disorders [12, 13]. Nevertheless, both studies have notable

limitations. Gao et al. [12] derived trajectories from 2011–2018 depression scores and ascertained outcomes in 2018, without excluding prevalent GI disorders diagnosed during 2011–2015, causing exposure–outcome overlap and precluding causal inference. Moreover, they used multivariable logistic regression adjusting only for baseline covariates, thus failing to account for time-varying confounding; they directly excluded participants with missing 2013–2018 depression scores, reducing statistical power and risking selection bias; and they did not incorporate the now-available 2020 follow-up wave. Cao et al. [13] demonstrated a dose-dependent association between depressive symptom severity and the risk of incident benign upper gastrointestinal disorders; however, they assessed depressive symptoms only at baseline and stratified them by severity, without characterizing longitudinal trajectories of depressive symptoms, and therefore could not capture the persistence or cumulative burden of depression. Their outcome was ascertained in 2015 (wave 3), yielding a follow-up period of only 4 years, and incident cases reported during follow-up (2011–2015) were not strictly excluded from outcome ascertainment, limiting the temporal separation between exposure measurement and outcome onset. Their multivariable logistic regression likewise adjusted only for baseline covariates, failing to account for time-varying confounding; in addition, approximately 60% of participants with missing key variables were directly excluded and inverse probability weighting was applied to complete-case data, potentially introducing selection bias and reducing statistical power. Accordingly, a longitudinal cohort analysis with strictly non-overlapping exposure and outcome windows and appropriate handling of

time-varying confounding and missing data is needed.

Using five waves of CHARLS longitudinal data from 2011 to 2020, this study investigated the long-term dynamic impacts of depressive symptom trajectories on the risk of incident GI disorders. The findings provide empirical evidence for early warning of depression-associated GI disorders, and support the optimization of integrated physical and mental health management strategies.

2 Methods

2.1 Data source

CHARLS is a nationally representative longitudinal survey of mainland Chinese residents aged 45 years and older. Its national baseline survey was conducted in 2011–2012, with four subsequent regular follow-up questionnaire waves in 2013, 2015, 2018, and 2020. To ensure sample representativeness, the CHARLS baseline covered 150 counties/districts and 450 villages/urban communities across China, enrolling 17708 participants from 10257 households. Face-to-face computer-assisted personal interviewing (CAPI) was adopted in each follow-up wave to maintain the representativeness of middle-aged and older Chinese adults [11].

2.2 Ethical approval

This study was conducted in accordance with the Declaration of Helsinki. All waves of the CHARLS survey were approved by the Biomedical Ethics Review Committee

of Peking University (approval number: IRB00001052-11015). All participants provided written informed consent prior to field investigation.

2.3 Study participants

Participants enrolled in the 2011–2012 survey wave constituted the baseline cohort and were prospectively followed in 2013, 2015, 2018, and 2020. Participants were excluded if they met any of the following criteria. (1) missing age or sex information (n = 175); (2) baseline age < 45 years (n = 508); (3) missing baseline data on GI disorders (n = 175); (4) missing baseline 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) data (n = 1433); (5) missing follow-up data on GI disease outcomes (n = 8499); (6) prevalent GI disorders at or before 2015 (n = 809). The detailed participant selection flowchart is shown in Figure 1.

2.4 Exposures and outcomes

Data from five survey waves were included in this study: Wave 1 (2011), Wave 2 (2013), Wave 3 (2015), Wave 4 (2018), and Wave 5 (2020). The longitudinal trajectories of depressive symptom scores, assessed across the 2011–2015 exposure period, were defined as the exposure. Incident GI disorders, ascertained throughout the 2015–2020 outcome period (2015 excluded), were defined as the outcomes. This design ensured temporal separation of exposure and outcome windows.

2.5 Assessment of depressive symptoms

Depressive symptoms were assessed using the CES-D-10, which has shown good validity for evaluating depressive symptoms among Chinese adults[14, 15]. The CES-D-10 comprises 10 items measuring the weekly frequency of depressive symptoms, with four ordinal response options: (1) Rarely or none of the time (<1 day); (2) Some or a little of the time (1–2 days); (3) Occasionally or a moderate amount of the time (3–4 days); (4) Most or all of the time (5–7 days). Each item is scored 0, 1, 2, and 3, respectively, yielding a total score ranging from 0 to 30. Higher scores indicate more severe depressive symptoms. In this study, a CES-D-10 score ≥ 10 was defined as the presence of depressive symptoms, whereas a score < 10 indicated no depressive symptoms[14, 16, 17]. Continuous CES-D-10 scores across the exposure period were used to construct depressive symptom trajectories, while the cutoff of 10 was applied to define prevalent depressive symptoms.

2.6 Definition of GI disorders

GI disorders were defined based on self-reported information. Incident GI disorders were ascertained when participants answered "yes" to the survey question: "Have you ever been diagnosed by a doctor with stomach or other digestive disorders (excluding tumors or cancers)?"[18].

2.7 Covariates

Informed by prior population-based studies [19, 20], we selected the following covariates for analysis. Time-invariant covariates were sex, educational attainment,

and residential area. Time-varying covariates included age, marital status, smoking status, alcohol consumption, body mass index (BMI), hypertension, diabetes or elevated blood glucose, heart disease, dyslipidemia, cancer, liver disease, mental disorders, memory-related diseases, global cognitive score, daily physical activity, and sleep quality.

2.8 Statistical analysis

Little's Missing Completely at Random (MCAR) test [21] and Wilcoxon rank-sum tests comparing key covariates between participants with and without complete CES-D-10 data were used to evaluate the missing data mechanism. As the MCAR assumption was rejected and missingness depended on observed rather than unobserved variables, missing data were classified as Missing at Random (MAR); accordingly, multiple imputation by chained equations (MICE) [22] was used for all subsequent analyses. The `mice` R package (version 3.17.0) was used [23], with appropriate imputation models (logistic regression, proportional odds, multinomial logistic regression, and predictive mean matching) selected for each variable type. A random seed (set.seed(123)) was specified, 20 iterations were conducted, and 20 imputed datasets were generated.

Group-based trajectory modeling (GBTM) [24] was applied to identify longitudinal patterns of CES-D-10 scores using measurements from 2011, 2013, and 2015. Linear growth mixture models were fitted via the `hlme` function in the R `lcmm` package

across the 20 imputed datasets, testing 1–4 candidate trajectory groups. Within each imputed dataset, the optimal number of groups was selected by the lowest Bayesian Information Criterion (BIC); the final solution was determined by majority voting across all 20 datasets. Additional selection criteria included the Akaike Information Criterion (AIC), log-likelihood (LL), and classification quality (entropy > 0.7, average posterior probability > 0.7, odds of correct classification > 5), and groups accounting for < 5% of the sample were discarded. After label-switching correction to align group labels across imputed datasets, modal class assignment defined final individual group membership. All information criteria and classification metrics are reported as median (minimum–maximum).

CES-D-10 scores were used to derive trajectory groups and were therefore excluded from baseline comparisons. Educational attainment was dichotomized as junior high school or below versus high school or above. Between-group differences were tested using χ^2 or Fisher's exact tests for binary variables, Wilcoxon rank-sum or Kruskal–Wallis tests for ordinal and non-normally distributed continuous variables, and t-tests or analysis of variance (ANOVA) for normally distributed continuous variables; for variables with missing values, pooled proportions and 95% confidence intervals (CIs) across the 20 imputed datasets were estimated using Rubin's rules. Extreme BMI values were winsorized to 10–60 kg/m². Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), with pooled estimates from the imputed datasets following the same format.

We applied Longitudinal Targeted Maximum Likelihood Estimation (LTMLE) [25] to estimate the causal association between depressive trajectory classes (A, derived from 2011–2015 CES-D-10 scores) and incident GI disorders (Y, ascertained in 2018–2020), following the longitudinal structure $Z \rightarrow A \rightarrow L_1 \rightarrow L_2 \rightarrow L_3 \rightarrow Y$, where L_1–L_3 are time-varying covariates measured in 2011, 2013, and 2015. The full covariate set (time-invariant Z and time-varying L_t) is specified in Section 2.7; age was adjusted only at baseline owing to perfect multicollinearity across repeated surveys. G-computation was first conducted via backward recursive logistic generalized linear models:

$$Q_3 = E\,[Y \mid A, Z, L_1, L_2, L_3]$$

$$Q_2 = E\,[Q_3 \mid A, Z, L_1, L_2]$$

$$Q_1 = E\,[Q_2 \mid A, Z, L_1]$$

We further implemented a targeted maximum likelihood updating step to ensure valid causal inference with asymptotic properties. The one-parameter fluctuation function was applied:

$$\text{Logit}\,(Q_1^*\,(A, L)) = \text{Logit}\,(Q_1\,(A, L)) + \varepsilon \times H\,(A, L)$$

where ε is the fluctuation parameter and $H\,(A, L)$ denotes the clever covariate. We used a simplified weighting form: $H\,(A, L) = A/g(A|Z) - (1-A)/(1-g(A|Z))$, with the propensity score $g(A|Z)$ estimated from time-invariant covariates Z and truncated at 0.01–0.99 to avoid extreme weights. Counterfactual event rates (E_1 for A=1, E_0 for A=0) were predicted from the updated estimator Q_1^*, variance was estimated using the

LTMLE influence function, and odds ratios (ORs) with 95% CIs were calculated. All analyses were conducted on the 20 imputed datasets, with final estimates pooled on the log scale according to Rubin's rules.

We conducted a series of sensitivity analyses (detailed in Section 3.4): (1) excluding participants with missing CES-D-10 scores in any of the three waves (412 excluded; final n = 5696); (2) restricting the outcome to incident GI disorders ascertained in 2018 only; (3) limiting the outcome to new 2020 cases, excluding 2018 cases; (4) adjusting only for time-invariant covariates; (5) adjusting only for time-varying covariates; (6) performing a crude unadjusted analysis; (7) tightening propensity-score truncation from 0.01–0.99 to 0.05–0.95; and (8) replacing LTMLE with conventional logistic regression on the imputed datasets. All analyses retained the identical longitudinal framework and used the same 20 imputed datasets.

3 Results

3.1 Trajectories of depressive symptom scores

GBTM was performed to identify distinct trajectories of depressive symptom scores across three survey waves (2011, 2013, and 2015). Trajectory models with one to four classes were separately fitted for model comparison (Additional file 1). Based on the minimum BIC principle, the 3-class model was optimal for 17 out of 20 multiply imputed datasets. By contrast, the 4-class model produced lower BIC values in only three datasets and showed unstable classification performance (Additional file 2).

Therefore, the 3-class trajectory solution was ultimately selected as the optimal model.

The three identified depressive symptom trajectory classes exhibited distinct longitudinal patterns and were defined as the non-depressive, low-depressive, and high-depressive groups (Figure 2, Additional file 3). The non-depressive group (n = 4215, 69.0%) showed persistently low CES-D-10 scores ranging from 4.55 to 4.88 across the study period. The low-depressive group (n = 1569, 25.7%) presented stable CES-D-10 scores (10.65–12.04). The high-depressive group (n = 324, 5.3%) displayed consistently elevated CES-D-10 scores (18.73–18.98). All three trajectory groups achieved satisfactory classification quality, satisfying the predefined criteria of average posterior probability (AvePP) > 0.7 and odds of correct classification (OCC) > 5 (Additional file 4).

3.2 Comparison of participants' baseline characteristics across depressive symptom trajectory groups

Table 1 summarizes the baseline characteristics of participants across the non-depressive, low-depressive, and high-depressive trajectory groups. Statistically significant intergroup differences ($P < 0.05$) were detected for age, sex, residential location type, marital status, smoking status, alcohol consumption, hypertension, heart disease, emotional and mental disorders, memory-related diseases, global cognitive score, educational attainment, and sleep quality. No significant differences ($P > 0.05$)

were observed for BMI, daily physical activity, diabetes or elevated blood glucose, dyslipidemia, cancer, and liver disease.

Compared with the non-depressive group, the low-depressive group exhibited a higher proportion of female sex (60.9% vs. 46.3%), rural residence (87.8% vs. 78.7%), hypertension (26.4% vs. 22.9%), heart disease (10.2% vs. 7.3%), and emotional and mental disorders (1.6% vs. 0.4%). In addition, participants in the low-depressive group were less likely to have a high school or higher education (6.4% vs. 14.6%), be married (82.5% vs. 88.5%), and report smoking status (27.7% vs. 33.2%) and alcohol consumption (27.5% vs. 38.0%). This group also presented older age (58.73 ± 8.50 vs 57.96 ± 8.76) and lower global cognitive scores (12.43 ± 5.68 vs 15.14 ± 5.67). These disparities were further amplified in the high-depressive group.

Compared with the non-depressive group, participants with high depressive symptoms had markedly higher proportions of female sex (74.1% vs. 46.3%), rural residence (92.3% vs. 78.7%), hypertension (31.1% vs. 22.9%), heart disease (13.0% vs. 7.3%), emotional and mental disorders (2.2% vs. 0.4%), and memory-related diseases (3.7% vs. 0.8%). Meanwhile, they showed lower rates of high school or higher educational attainment (4.3% vs. 14.6%), being married (79.0% vs. 88.5%), smoking (24.4% vs. 33.2%), and alcohol consumption (23.1% vs. 38.0%), accompanied by older age (59.63 ± 8.16 vs. 57.96 ± 8.76 years) and poorer cognitive performance (11.24 ± 5.35 vs. 15.14 ± 5.67).

Of note, a clear dose–response gradient was observed across escalating depressive symptom burden. With increasing depression severity, the proportions of female participants and rural residents gradually increased, alongside advancing age and higher prevalence of hypertension, heart disease, emotional and mental disorders, memory-related diseases, and poor sleep quality. In contrast, educational attainment, marital prevalence, smoking and alcohol consumption rates, and global cognitive function scores declined progressively across trajectory groups.

3.3 Comparison of GI disease risks across depressive symptom trajectory groups

LTMLE was used to estimate the associations between the non-depressive, low-depressive, and high-depressive trajectories and the risk of incident GI disorders over 2015–2020, with cases diagnosed in 2015 excluded. During this follow-up window, the observed cumulative incidence of GI disorders was 6.88%, 10.58%, and 19.14% for the non-depressive, low-depressive, and high-depressive groups, respectively (Table 2). Relative to the non-depressive group, both the low-depressive group (OR = 1.52, 95% CI: 1.24–1.88, $P < 0.001$) and high-depressive group (OR = 3.02, 95% CI: 1.81–5.04, $P < 0.001$) had significantly elevated risks of incident GI disorders. Furthermore, the high-depressive group showed a significantly higher disease risk than the low-depressive group (OR = 1.97, 95% CI: 1.40–2.76, $P < 0.001$) (Table 3).

3.4 Sensitivity analyses

Sensitivity analyses were performed to further test the stability of the main findings (Figure 3a–c, Additional file 5):

(1) After excluding participants with missing CES-D-10 scores at any of the three follow-up waves from 2011 to 2015 (n = 5696; 412 participants excluded), the results were consistent with the main analysis, suggesting that multiple imputation for the exposure variable (CES-D-10) did not affect the stability of conclusions.

(2) When the outcome was restricted to incident GI disorders reported at Wave 4 (2018), the OR was 1.72 for low-depressive versus non-depressive group, 3.53 for high-depressive versus non-depressive group, and 1.95 for high-depressive versus low-depressive group. The effect estimates remained consistent with the main analysis, demonstrating that the association between depressive symptom trajectories and GI disease risk was insensitive to the choice of outcome time window.

(3) We restricted the outcome to incident GI disorders reported at Wave 5 (2020), the OR was 1.39 for the low-depressive versus non-depressive group, 2.57 for the high-depressive versus non-depressive group, and 1.91 for the high-depressive versus low-depressive group. The effect estimates also remained consistent with the main analysis, indicating that the association between depressive symptom trajectories and GI disease risk was robust to the choice of outcome time window.

(4) When adjusting only for time-invariant covariates, the results were nearly identical to those of the main analysis: low-depressive group versus non-depressive group, OR = 1.52; high-depressive group versus non-depressive group, OR = 3.02; high-depressive group versus low-depressive group, OR = 1.97. The findings were consistent with the main analysis, suggesting that time-varying confounding exerted no substantial impact on the study conclusions.

(5) When adjusting only for time-varying covariates, the results were nearly identical to those of the main analysis: low-depressive group versus non-depressive group, OR = 1.51; high-depressive group versus non-depressive group, OR = 3.02; high-depressive group versus low-depressive group, OR = 1.84. The findings were consistent with the main analysis, suggesting that time-invariant confounding exerted no substantial impact on the study conclusions.

(6) In the crude analysis without covariate adjustment, the OR was 1.60 for the low-depressive versus non-depressive group, 3.20 for the high-depressive versus non-depressive group, and 2.00 for the high-depressive versus low-depressive group. All ORs were slightly higher than those in the main analysis. The effect estimates decreased slightly after confounding adjustment, indicating that covariate adjustment in the main analysis controlled confounding without markedly attenuating the true association.

(7) When the propensity score truncation range was tightened from 0.01–0.99 to 0.05–0.95, the OR was 1.52 for the low-depressive versus non-depressive group, 3.02 for the high-depressive versus non-depressive group, and 1.97 for the high-depressive versus low-depressive group. The results remained nearly unchanged from the main analysis. The stable estimates indicated that model specification and extreme propensity scores did not materially affect our conclusions.

(8) After switching to multiple imputation logistic regression, the OR was 1.43 for the low-depressive versus non-depressive group, 2.61 for the high-depressive versus non-depressive group, and 1.80 for the high-depressive versus low-depressive group. The ORs decreased slightly but remained statistically significant. Consistent conclusions were obtained using both approaches, suggesting that the main findings were not dependent on a specific statistical method.

Across all sensitivity analyses, the ORs for all comparisons were greater than 1 with consistent direction of effects. The effect estimates remained stable across sensitivity analyses, supporting the robustness of the main analysis conclusions.

4 Discussion

Using longitudinal data from the CHARLS database, this study identified three distinct dynamic trajectories of depressive symptoms from 2011 to 2015 via GBTM:

the non-depressive trajectory (non-depressive group), low-depressive trajectory (low-depressive group), and high-depressive trajectory (high-depressive group). LTMLE was subsequently applied to compare the risk of incident GI disorders across participants with the three depressive trajectories. The results demonstrated that compared with the non-depressive group, participants in the low-depressive group (OR = 1.52, 95% CI: 1.24–1.88) and high-depressive group (OR = 3.02, 95% CI: 1.81–5.04) had significantly increased risks of incident GI disorders. Furthermore, the high-depressive group exhibited a significantly higher risk of incident GI disorders than the low-depressive group (OR = 1.97, 95% CI: 1.40–2.76). To our knowledge, this is the first national cohort study to adopt the LTMLE framework to examine the causal effect of depressive trajectories on incident GI disorders among middle-aged and older Chinese adults (≥ 45 years), with a complete separation between the exposure period (2011–2015) and outcome period (2015–2020). This study addresses limitations of prior investigations, which mostly relied on cross-sectional designs or single-time-point assessments of depression[7, 8, 13]. Although Gao et al.[12] adopted a trajectory-based design, their exposure and outcome windows overlapped, which limited causal interpretation.

Importantly, the high-depressive group had the highest risk of GI disorders, whereas the non-depressive group had the lowest risk, indicating that a greater depression burden corresponds to higher GI disease risk. The observed event rates increased in a graded manner (6.88% for the non-depressive group, 10.58% for the low-depressive

group, and 19.14% for the high-depressive group), which is consistent with findings from previous studies demonstrating a graded association between depression burden and GI disease risk[12, 13]. This finding suggests a dose–response relationship between depression burden and GI disease risk. Even participants in the low-depressive group, who had relatively low depressive symptom scores, exhibited a significantly higher risk of GI disorders than the non-depressive group ($P < 0.001$). This indicates that subclinical depressive symptoms may still be associated with an increased risk of GI disorders [26]. Defining risk solely by a binary classification of "depression yes/no" may underestimate the disease burden among middle-aged and older adults[27]. In addition, Zheng et al.[10] conducted a three-stage study among approximately 458000 participants from the UK Biobank using Cox proportional hazards models, Mendelian randomization analysis, and machine learning prediction models. Their study found that depression was associated with elevated risk of six GI disorders including esophagitis, further supporting depression as a modifiable risk factor for GI disorders.

Multiple biological mechanisms may underlie the association between depression and GI disorders, involving crosstalk among the nervous, endocrine, immune, and gut microbiome systems[28-30]. First, persistent depressive states can activate the hypothalamic–pituitary–adrenal axis, leading to elevated cortisol levels and increased sympathetic nerve activity, which in turn impairs the integrity of the GI mucosal barrier and promotes inflammatory responses[31]. Second, inflammatory depression

can activate inflammatory pathways via gut dysbiosis, resulting in intestinal mucosal inflammation and intestinal barrier injury. Meanwhile, gut dysbiosis can mediate peripheral and central neuroinflammation, forming a bidirectional vicious cycle between depression and intestinal damage[32]. Finally, abnormal metabolism of monoamine neurotransmitters such as serotonin during depression may affect GI motility and secretory function through the enteric nervous system[31]. Notably, these mechanisms are self-reinforcing: depression exacerbates intestinal inflammation and microbial imbalance, whereas GI disorders can worsen depressive symptoms through neuroendocrine and immune pathways[2]. Mendelian randomization studies have also confirmed causal associations between depression and multiple GI disorders, including GERD, esophageal ulcer, gastric ulcer, IBS, and acute appendicitis[33-35]. Nevertheless, some studies have failed to identify a significant causal association between depression and digestive disorders[36]. Such heterogeneity may stem from differences in disease definitions, selection of genetic instruments, and statistical power. This further highlights the necessity of conducting causal inference studies based on longitudinal cohorts with strictly non-overlapping exposure and outcome time windows.

A series of sensitivity analyses was performed in this study to further verify the robustness and reliability of the findings. After excluding participants with missing CES-D-10 scores at any of the three follow-up waves (n = 5696), the results remained consistent with the main analysis. Restricting outcomes to events reported at Wave 4

(2018) or Wave 5 (2020) also yielded findings consistent with the main analysis. Similar results were observed when only time-invariant covariates, only time-varying covariates, or no covariates were adjusted, as well as after tightening the propensity score truncation range. When multiple imputation logistic regression was adopted, the OR values decreased slightly but remained statistically significant. Collectively, these findings indicate that the main results of this study were not dependent on strategies for missing data handling, definitions of outcome time points, covariate adjustment schemes, or the choice of statistical models. This provides multi-dimensional robust evidence for the causal effect estimates of depressive trajectories on GI disease risk.

The strengths of this study are mainly reflected in the following aspects: (1) Rigorous outcome definition: the exposure period (2011–2015) and outcome period (2015–2020, excluding events in 2015) were completely non-overlapping. Participants with prevalent GI disorders at baseline or any follow-up during the exposure period were excluded to minimize reverse causation and bias mediated by disease status. (2) Dynamic trajectory analysis: GBTM was used to identify depressive trajectories. Model selection was based on BIC, AIC, log-likelihood, entropy, average posterior probability, and odds of correct classification. The classification stability was validated across 20 imputed datasets (17 out of 20 supported the three-class model), balancing statistical power and clinical interpretability. (3) Causal inference method: LTMLE was applied to perform doubly robust adjustment for time-invariant and time-varying confounding, which is more robust to model misspecification than

conventional multivariable regression[25]. (4) Missing data handling: the missing data mechanism was first assessed, followed by MICE to address missing values. Imputation was implemented throughout trajectory identification and effect estimation. Analyses were performed on all 6108 enrolled participants, avoiding selection bias and loss of statistical power caused by direct deletion of participants with missing depressive symptom scores.

The findings of this study carry important implications for clinical practice and public health. First, early warning and stratified management: even participants in the low-depressive group with relatively low depressive symptom scores require close monitoring of GI health, while those in the high-depressive group should receive priority interventions. Dynamic assessment of depressive trajectories is recommended as a routine component of health management for middle-aged and older adults, with special attention paid to high-risk groups including women, rural residents, participants with low educational attainment, and people with sleep disturbances [17]. Second, optimization of integrated mind-body care strategies: for participants following a high-depressive trajectory, psychological interventions and GI health management should be coordinated. Reducing depression burden may indirectly lower the burden of GI disorders[29, 31]. Third, social support and lifestyle interventions: strengthening health education and early screening targeting women, rural populations, and people with low education levels, together with promotion of physical activity, improved sleep quality, and balanced diets, may serve as important

public health strategies to reduce the burden of depression-related GI disorders[17, 37]. Notably, the prevalence of depressive comorbidity among patients with organic upper GI disorders undergoing gastroscopy is markedly higher than that in the general population, yet the detection rate of depressive comorbidity by gastroenterologists is only 3.92%[38]. This highlights the necessity of integrating depression screening into the diagnostic and therapeutic pathway for GI disorders to achieve interdisciplinary mind-body collaborative care. Regarding lifestyle interventions, existing research has reported that higher intake of dietary live microorganisms among patients with GI disorders is associated with a reduced risk of depressive symptoms[39]. Diet can modulate both GI and mental health via the gut–brain axis[40], suggesting that intervention strategies centered on dietary optimization may confer dual physical and mental benefits.

The main limitations of this study are as follows: (1) Self-report bias: the diagnosis of GI disorders relied on participants' self-reports, which may introduce recall bias. Future studies may combine clinical diagnoses and medical insurance claims data for further validation. (2) Residual confounding: although LTMLE was used to adjust for time-invariant and time-varying confounders, observational studies cannot completely rule out the effects of unmeasured confounding, such as genetic susceptibility and gut microbiota composition. (3) Limited mechanistic evidence: this study did not incorporate biomarkers (e.g., gut microbiota and cytokines), so it cannot directly elucidate the specific molecular pathways underlying the gut–brain axis. Future

research may employ metabolomics, metagenomics, and other techniques to explore the biological basis through which depressive trajectories affect GI disorders. (4) Restricted follow-up duration: follow-up ended in 2020; longer follow-up is required to investigate long-term impacts. (5) Generalizability concerns: this study was conducted among middle-aged and older Chinese adults. Caution should be exercised when extrapolating the findings to populations of other age groups, cultural backgrounds, or healthcare systems.

5 Conclusion

Based on longitudinal cohort data from middle-aged and older Chinese adults (≥ 45 years), this study revealed that depressive symptom trajectories were significantly associated with subsequent risk of incident GI disorders. The risk was highest in the high-depressive trajectory group, and the risk was also significantly elevated in the low-depressive trajectory group. The findings highlight the importance of dynamically monitoring the progression of depressive symptoms. Future studies should further integrate multi-omics data and intervention research to deepen the understanding of the interplay between depression and GI disorders, and promote the innovation and development of integrated mind-body care strategies.

Abbreviations

GI Gastrointestinal

CES-D-10 10-item Center for Epidemiologic Studies Depression Scale

CHARLS China Health and Retirement Longitudinal Study

LTMLE Longitudinal Targeted Maximum Likelihood Estimation

GBTM Group-Based Trajectory Modeling

BIC Bayesian Information Criterion

AIC Akaike Information Criterion

LL log-likelihood

MAR Missing at Random

MICE Multiple Imputation by Chained Equations

CAPI Computer-Assisted Personal Interviewing

GERD Gastroesophageal Reflux Disease

IBD Inflammatory Bowel Disease

IBS Irritable Bowel Syndrome

BMI Body Mass Index

OR Odds Ratio

AvePP average posterior probability

OCC odds of correct classification

CI confidence interval

SD standard deviation

IQR interquartile range

MCAR Missing Completely at Random

ANOVA analysis of variance

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Authors' contributions

Yuejin Ji: Conceptualization, Data curation, Software, Formal analysis, Methodology, Writing - original draft, Writing - review and editing. **Hongxiao Li**: Data curation, Software, Formal analysis, Validation, Writing - original draft. **Guoliang Dai**: Methodology, Supervision, Writing - review and editing. **Wenzheng Ju**: Conceptualization, Supervision, Writing - review and editing.

Competing interests

The authors report no conflicts of interest.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. All waves of the CHARLS survey were approved by the Biomedical Ethics Review Committee of Peking University (approval number: IRB00001052-11015). All participants provided written informed consent prior to field investigation.

Consent for publication

Not applicable.

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Availability of data and materials

Data are available from the CHARLS official website (https://charls.pku.edu.cn) upon registration and approval.

Additional files

Additional file 1: Model fit indices for candidate trajectory models across 20 multiply imputed datasets. Description: Number of parameters and median (range) values of log-likelihood, AIC, BIC, and entropy for one- to four-class group-based trajectory models across the 20 imputed datasets. File format: .xlsx

Additional file 2: Detailed model fit statistics for candidate trajectory models in each imputed dataset. Description: BIC, AIC, log-likelihood, number of parameters, entropy, group number, group size, and group proportion for each candidate trajectory model (one to four classes) in each of the 20 imputed datasets. File format: .xlsx

Additional file 3: Trajectory group assignment for each participant across 20 imputed datasets. Description: Individual-level trajectory group assignments (non-depressive, low-depressive, or high-depressive) for each of the 6108 participants in each of the 20 imputed datasets. File format: .xlsx

Additional file 4: Classification quality indices for the three trajectory groups.

Description: Number of participants and median (range) values of AvePP, OCC, and group proportion for each trajectory group across the 17 imputed datasets in which the 3-class model was selected. File format: .xlsx

Additional file 5: Effect estimates of the main analysis and eight sensitivity analyses. Description: ORs with 95% CIs, *P* values, and standardized event rates (E_1 and E_0) for the main LTMLE analysis and each of the eight sensitivity analyses. File format: .xlsx

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Table 1. Baseline characteristics of included study participants

Variable	Non-depressive group (n = 4215)	Low-depressive group (n = 1569)	High-depressive group (n = 324)	P
Age (years)	57.96±8.76	58.73±8.50	59.63±8.16	< 0.001
Female	1952 (46.3)	956 (60.9)	240 (74.1)	< 0.001
BMI (kg/m²)	23.93±4.17	23.69±4.31	23.45±4.31	0.072
Married	3730 (88.5)	1294 (82.5)	256 (79.0)	< 0.001
High school education or above	615 (14.6)	100 (6.4)	14 (4.3)	< 0.001
Rural residence	3317 (78.7)	1377 (87.8)	299 (92.3)	< 0.001
Smoking	1399 (33.2)	434 (27.7)	79 (24.4)	< 0.001
Alcohol consumption	1603 (38.0)	432 (27.5)	75 (23.1)	< 0.001
Hypertension	965 (22.9)	414 (26.4)	100 (31.1)	< 0.001
Diabetes or elevated blood glucose	216 (5.1)	96 (6.1)	21 (6.5)	0.24
Dyslipidemia	345 (8.2)	138 (8.8)	40 (11.8)	0.09
Cancer	30 (0.7)	10 (0.6)	1 (0.3)	0.952

Liver disease		82 (1.9)	39 (2.5)	9 (2.8)	0.318
Heart disease		307 (7.3)	160 (10.2)	42 (13.0)	< 0.001
Emotional and mental disorders		16 (0.4)	25 (1.6)	7 (2.2)	< 0.001
Memory-related diseases		34 (0.8)	21 (1.3)	12 (3.7)	< 0.001
Cognitive score		15.14±5.67	12.43±5.68	11.24±5.35	< 0.001
Daily physical activity		55.92±102.58	59.22±106.91	56.66±108.02	0.561
Sleep quality	<1 d	2761 (65.5)	559 (35.6)	65 (20.1)	< 0.001
	1-2 d	666 (15.8)	276 (17.6)	34 (10.5)	
	3-4 d	388 (9.2)	315 (20.1)	74 (22.8)	
	5-7 d	400 (9.5)	419 (26.7)	151 (46.6)	

Table 2. Incidence of GI disorders across three depression trajectory groups during 2015–2020

Group	Cases in 2018	Cases in 2020	Total cases*	Total participants	Observed event rate
Non-depressive group	105	198	290	4215	6.88%
Low-depressive group	72	110	166	1569	10.58%
High-depressive group	29	35	62	324	19.14%

*A case was defined as incident GI disease reported at either Wave 4 (2018) or Wave 5 (2020). Therefore, the total number of cases does not equal the sum of cases from the two waves due to overlapping participants who reported disease at both waves: 13 in the non-depressive group, 16 in the low-depressive group, and 2 in the high-depressive group.

Table 3. LTMLE analysis of GI disease risks across different depression symptom trajectory groups

Comparison	Standardized event rate *		*OR* (95% CI)	*P*
	E_1	E_0		
Low vs Non-depressive	10.2%	7.0%	1.52 (1.24–1.88)	<0.001
High vs Non-depressive	18.5%	7.0%	3.02 (1.81–5.04)	<0.001
High vs Low-depressive	19.1%	10.7%	1.97 (1.40–2.76)	<0.001

*E_1 denotes the Standardized event rate for the comparison group and E_0 for the reference group. Standardization for each contrast was performed to the population composition of the corresponding sub-sample, so E0 and E1 for the same group may slightly differ across different contrasts.

Figure Legends

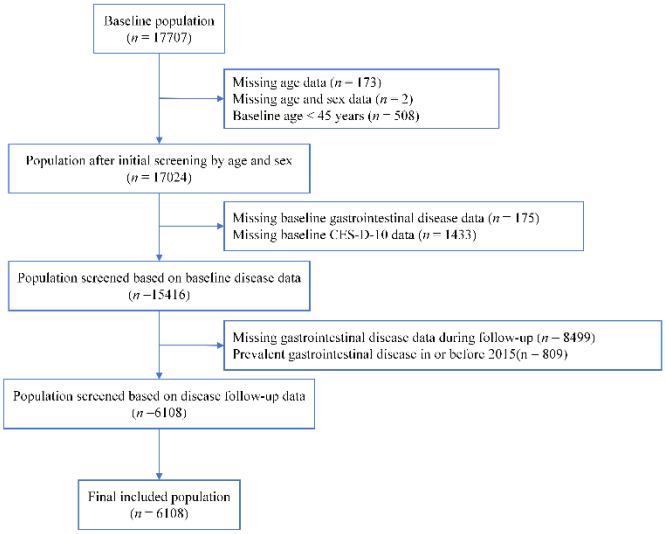


Figure 1. Flowchart of participant selection.

The CHARLS baseline recruited 17708 participants. After dataset merging, the analytic sample comprised 17707 participants.

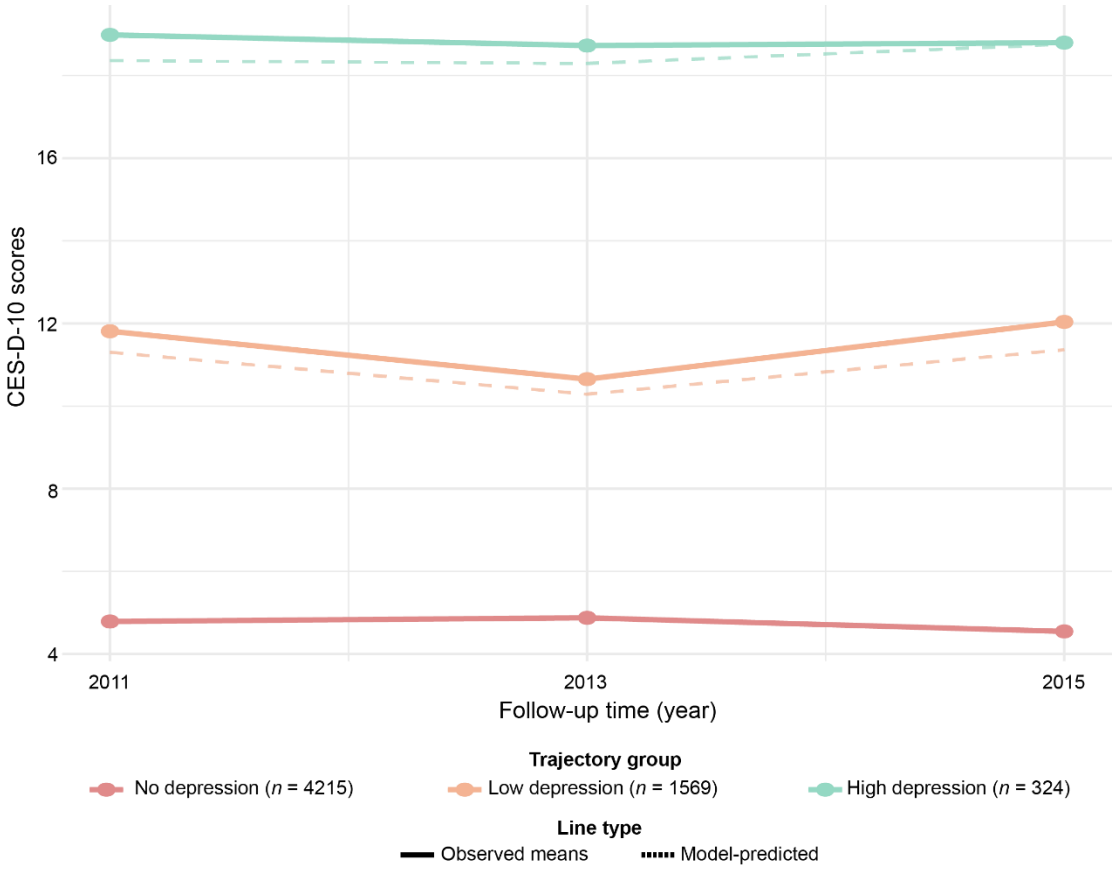


Figure 2. Three-class trajectory model of depressive symptoms assessed by CES-D-10 across 2011, 2013, and 2015.

Solid lines represent observed means; dashed lines represent model-predicted means.

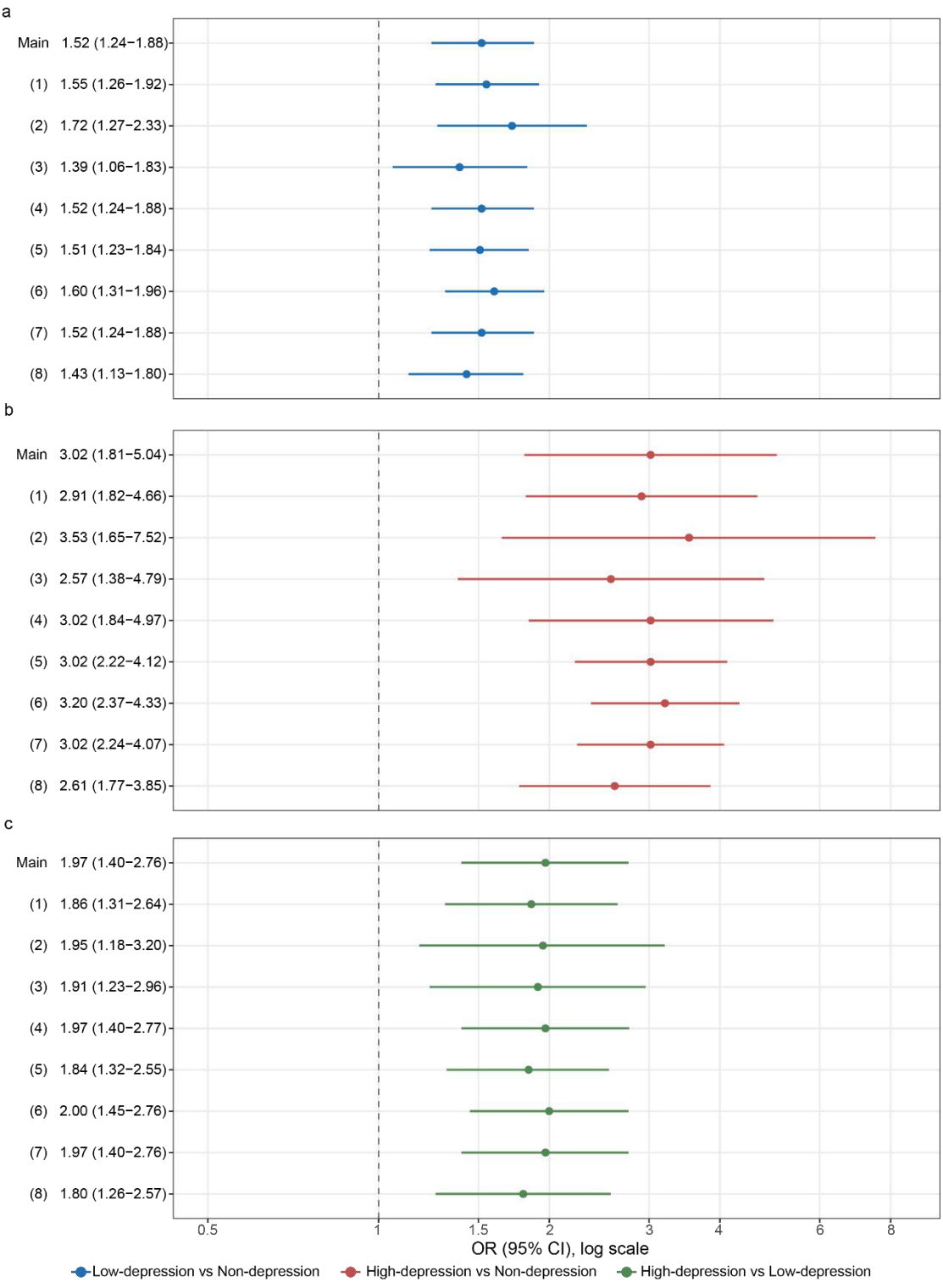


Figure 3. Sensitivity analyses of the associations between different depressive symptom trajectories and GI disease risk.

a: Low vs non-depressive group; b: High vs non-depressive group; c: High vs low-

depressive group. ORs and 95% CIs were pooled across 20 imputed datasets according to Rubin's rules. Main: LTMLE adjusted for all covariates (time-invariant covariates Z and time-varying covariates L_t). (1) Excluding participants with missing CES-D-10 scores at any of the three follow-up waves; (2) Outcome defined as incident GI disorders reported at Wave 4 (2018); (3) Outcome defined as incident GI disorders reported at Wave 5 (2020), excluding participants with prevalent disease at Wave 4 (2018); (4) Adjustment for time-invariant covariates only; (5) Adjustment for time-varying covariates only; (6) Crude analysis without covariate adjustment; (7) Propensity score truncation range tightened to 0.05–0.95; (8) Multiple imputation logistic regression. Standardized event rates were not reported for (6) and (8).

Supplementary Files

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