Constipation preceding depression: a population-based cohort study

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Summary

Background Constipation is generally considered a common physical symptom of depression or a side effect of antidepressant treatments. However, according to the gut-brain axis hypothesis, the association between depression and constipation might be bi-directional. This study investigated the association between premorbid constipation and depression.

Methods We conducted a retrospective cohort study using data from UK Biobank. Individuals free of depression between 2006 and 2010 were included. Constipation status was determined using diagnostic codes from electronic health records or a baseline questionnaire. Data on covariates, including socio-demographic characteristics, lifestyle factors, health conditions, and regular medication use, were also collected through a baseline questionnaire. The primary outcome is incident depression, which was extracted from hospital inpatient admissions, primary care, self-report, and death data from baseline to 2022. The secondary outcome is depressive symptoms, which was assessed by Patient Health Questionnaire–9 (PHQ-9) from an online survey in 2016. Cox proportional hazard regression models were employed to assess the prospective association between constipation and incident depression. Logistic regression models were used to assess its association with depressive symptoms.

Findings Among the 449,459 participants included in the study, 18,596 (4.1%) experienced constipation at baseline, and 18,576 (4.1%) developed depression over a median follow-up period of 12.3 years. Premorbid constipation is associated with a 2.28-fold higher risk of depression. After adjusting the covariates, we found those with constipation still had a 48% higher risk of developing depression (adjusted hazard ratio [aHR] 1.48; 95% CI, 1.41–1.56) than those without constipation. Self-reported and diagnosed constipation were both associated with a higher risk of depression, with the aHR being 1.42 (95% CI: 1.34–1.51) and 1.66 (95% CI: 1.51–1.82), respectively. Participants with constipation were more likely to report depressive symptoms than people without (adjusted odds ratio 2.18; 95% CI, 1.97–2.43). These findings remained consistent in sensitivity analyses.

Interpretation Diagnosed and self-reported constipation are both prospectively associated with an elevated risk of depression. These explorative findings suggest that constipation may be an independent risk factor or a prodromal symptom of depression. Gastroenterologists and primary care physicians should pay more attention to the depressive symptoms of their constipation patients.

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Research in context

Evidence before this study

To evaluate previous evidence, we searched PubMed, Web of Science, and the Cochrane Library databases for studies published in English from database inception to March 30, 2023, that investigated constipation and depression, using the terms: ("constipation", "bowel movement", or "laxative use") and ("depression", "depressive disorders", or "depressive symptoms"). No studies investigated the prospective association between premorbid constipation and later diagnosis of depression. Several cross-sectional studies found people with depression often report experiencing constipation. They suggested this association may be due to the potential gastrointestinal side effects of antidepressant treatments or the gut-brain axis pathway mediated by gut microbiota. A longitudinal study design may provide evidence regarding constipation preceding the diagnosis of depression and clinical implications for early identification of depression.

Added value of this study

To our knowledge, this is the first large-scale cohort study to verify the prospective association between constipation and depression. In this large cohort of 449,459 participants free of depression, individuals with constipation were found to be at a 2.28-fold increased risk of developing depression during a 12-year follow-up. After adjusting sociodemographic characteristics, lifestyle factors, health conditions, and regular medication use, we found those with constipation still had a 48% higher risk of developing depression. Self-reported and diagnosed constipation were both associated with a higher risk of depression. These findings remained consistent in using depressive symptoms as the secondary outcome and several sensitivity analyses.

Implications of all the available evidence

This longitudinal study on premorbid constipation and later onset of depression may complement the previous evidence from cross-sectional studies, suggesting that constipation might be an independent risk factor or prodromal symptom of depression. As diagnosed and self-reported constipation were both associated with a higher risk of depression, gastroenterologists and primary care physicians should pay more attention to the depressive symptoms of their constipation patients.

Introduction

Depression is a leading cause of disability worldwide, with a cross-national lifetime prevalence of 14.6%, affecting the mental and physical health of patients all over the globe.[1,2] Depression often coexists with gastrointestinal disorders,[3,4] which contributes to additional healthcare utilization and social burdens.[5,6] Constipation, as one of the most common functional gastrointestinal disorders,[7] is often reported by people with depression. Two recent large population-based cross-sectional studies showed that 9%–40% of depressive individuals reported having constipation.[8,9] This association may be due to the potential gastrointestinal side effects associated with antidepressant treatments[10] or the gut-brain axis pathway mediated by gut microbiota.[11] A longitudinal study on premorbid constipation and later diagnosis of depression may complement the previous evidence from cross-sectional studies.[12] If this physical symptom happens before the onset of depression, it can also be regarded as a potential prodromal symptom. Together with other known factors, constipation may be useful for early or timely diagnosis of depression.

As the gut-brain pathway has been found to be bidirectional,[13] this suspected prospective association can also be explained in two directions. On the one hand, constipation is possible to be a risk factor of depression. As demonstrated by Koloski's study,[13] those with functional gastrointestinal disorders at baseline had significantly higher levels of depressive symptoms at follow-up. One possible explanation is low-grade intestinal inflammation with mast cell infiltration and activation sets off the release of cytokines and chemokines into the circulation, which may be involved in the pathogenesis of depression.[14,15] On the other hand, depression can also activate the hypothalamic–pituitary–adrenal (HPA) axis and release stress factors,[16] impacting the development of functional gastrointestinal disorders.[17] In this case, constipation might be a physical symptom of depression. No matter which one it is, evidence from this cohort study provides a new longitudinal perspective on the association between constipation and depression. Therefore, the current study aims to examine the association between premorbid constipation and depression by using large-scale cohort study data from the UK Biobank.

Methods

Data source and study population

This study has been conducted using data from UK Biobank (https://www.ukbiobank.ac.uk/). UK Biobank is a large-scale population-based cohort study with more than 500,000 participants aged 37–73 years. Participants were recruited from 22 assessment centers across England, Scotland, and Wales between 2006 and 2010. During the baseline visit, participants completed touchscreen questionnaires, which collected information on demographics, lifestyle factors, and medication usage. Health outcomes were obtained through several online follow-up surveys and were linked records from electronic records from primary care, hospital inpatient, death, and cancer registers. Participants who withdrew from the UK Biobank or had depression before baseline were excluded from the study.

Exposures

Participants with constipation were identified by the following criteria[18] (Supplementary Figure S1): (1) Diagnosed constipation: It was ascertained by using primary care and hospital inpatient records, which contained clinical event records from general practitioners and clinical diagnoses at admissions. Constipation was coded as K590 according to the International Classification of Diseases-10th revision (ICD-10) coding system. (2) Self-reported constipation: Participants were asked about their past and current health conditions and regular laxatives used through a touchscreen questionnaire and a verbal interview at baseline. Regular use was defined by UK Biobank, which referred to consuming laxatives on most days of the week for the last four weeks. If participants reported any regular medication intake, the names of the medications were documented and categorized based on the British National Formulary.[19] Participants who reported constipation and regular use of laxatives are regarded as self-reported constipation patients. For participants with both diagnosed and self-reported constipation, we classified them as patients with diagnosed constipation.

Outcomes

The primary outcome was incident depression (Supplementary Figure S1). The outcome was extracted from the category 'the first occurrences' (category ID: 1712) in the UK Biobank dataset, which maps the clinical codes from hospital inpatient admissions, primary care, self-report, and death data to 3-character ICD-10 codes. The onset date of the depression (ICD-10 code F32.0–9 and F33.0–9)[20,21] was defined as the date of the first diagnosis in all data sources. Follow-up started from recruitment and ended at the time of incident depression, death, loss to follow-up, or Jan 1, 2022, whichever occurred first.

Considering the possibility of under-recording of the primary outcome, depressive symptoms served as the secondary outcome in this study. The information on depressive symptoms was obtained from an online survey collecting follow-up information on mental health in 2016, which included 157,366 participants (Supplementary Figure S1). Depressive symptoms were assessed by Patient Health Questionnaire–9 (PHQ-9), which evaluates symptoms occurring in the last two weeks. The PHQ-9 assigned scores ranging from '0' ('not at all') to '3' ('nearly every day') for each of its nine DSM-IV criteria for depression, and the total scores on the PHQ-9 range from 0 to 27. A cut-off score of ten or above, which has a sensitivity and specificity of 88% in the detection of major depression, was used to identify subjects with depressive symptoms in this study.[22]

Covariates

The following baseline variables were used as the covariates in this study: (1) sociodemographic characteristics, including age, sex, socioeconomic status, ethnicity, education level, and living status; (2) lifestyle factors, including body mass index (BMI), current smoking status, alcohol consumption, physical activities, sleep quality, and healthy diet[23–25]; (3) health conditions, including the chronic diseases, chronic pain, and family history of depression; (4) regular medication use, including opioids, anticholinergic drugs, statins, steroids, calcium channel blockers, and antidiarrheal agents. Socioeconomic status was measured by the Townsend deprivation index, which refers to the material deprivation of the local community an individual belongs to, in reference to the wider society.[26] According to the Townsend deprivation index, socioeconomic status was categorized into low, intermediate, and high. Lifestyle factors were obtained by structured questionnaires, and diet information was collected using the Food Frequency Questionnaires. Diet was categorized into healthy and unhealthy based on recommendations on dietary priorities for cardiometabolic health (Supplementary Table S1). Sleep quality was assessed by five sleep behaviors (sleep duration, chronotype preference, insomnia, snoring, and daytime sleepiness) and was divided into two groups: "good sleep quality" and "poor sleep quality".[25] A healthy diet was defined as meeting at least 4 of 7 dietary components recommendation.[27] Physical activity was categorized according to the World Health Organization's recommendations.[28] As indicated by a previous review, a series of chronic diseases that are commonly comorbid with depression were included as covariates, including cancer, cardiometabolic diseases, neurological diseases, and inflammatory diseases.[29] Some medications that may cause constipation and are also related to depression were considered as covariate.[30–33] Detailed information on covariates is presented in Supplementary Table S1.

Main analyses

All analyses were based on the complete cases. The standardized mean difference was used to denote the magnitude of imbalance in baseline characteristics by constipation and by missing data status.[34] An absolute value of standardized mean difference greater than 0.1 indicated a meaningful imbalance. To estimate the hazard ratio (HR) and 95% confidence interval (CI) for the associations of constipation with incident depression, the Cox proportional hazard models were used. The proportional hazard assumption was tested by Schoenfeld residuals, and the results suggested that the proportional hazard for depression was met (The P value for the test of proportional-hazard assumption was 0.227). Kaplan–Meier analysis was used to calculate the cumulative incidence of depression between the participants with and without constipation, and the log-rank test was used to analyze the differences between the survival curves. Since the information on depressive symptoms was collected by an online survey only in 2016, the logistic regression models were used to estimate the odds ratio (OR) and 95% CI for the associations between constipation and depressive symptoms. To verify whether this association exists in different reporting sources of constipation, we further examined the association between self-reported/diagnosed constipation and depression (depressive symptoms). All analyses were performed using a crude model and three adjusted models: model 1 adjusted for sociodemographic characteristics and lifestyle factors, model 2 additionally adjusted for health conditions, and model 3 additionally adjusted for regular medication use. To investigate whether the constipation–depression association will be different by sociodemographic characteristics, the likelihood ratio test was conducted to compare models with and without an interaction term between the sociodemographic characteristics and the exposure of interest.

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the results. First, we excluded participants who used laxatives and repeated our analysis, as participants might take laxatives for other reasons rather than constipation (e.g., to lose weight) and information bias might occur in this case. Second, an alternative interpretation of the results is the possibility that the increased risk of depression might be mainly associated with laxatives instead of constipation.[35] To examine this possibility, we conducted a head-to-head comparison by dividing patients into the following groups based on laxative types: softening, bulk-forming, osmotic, stimulant, and unknown (laxatives type), and further explored whether regular use of a specific kind of laxative is associated with a higher risk of depression than others. Third, considering that the number of different types of laxatives may indicate the severity of constipation,[36] the association between the number of laxative types and risk of depression was examined.

Reverse causality, the variation of the association between constipation and risk of depression, the potential impact of missing data, and the competing risk analysis were also tested in sensitivity analyses. To avoid potential reverse causality, we excluded participants who developed depression within the first two years or four years and repeated the main analyses. To show the association between self-reported constipation and increased risk of depression in different time intervals, we also considered different intervals after the baseline: (0–1] year, (1–3] years, (3–5] years, and (5–10] years. In addition, to examinate whether the data were missing completely at random, we compared the characteristics of the participants with and without missing data. To assess the potential impact of missing data, the multiple imputations were conducted using chained equations with five imputations. Lastly, to account for the influence of death, a modified Fine and Gray competing risk analysis was used to calculate the sub-distribution HR by treating the death as a competing risk event.

To further explored the association of constipation with the severity of depressive symptoms, we used another validated depression severity cutoff score: a total PHQ-9 score of 0–4 was identified as “no depression”, 5–9 was identified as “mild depression”, 10–14 as “moderate depression”, and ≥15 as “moderately severe to severe”.[37]

Ethics statement

The UK Biobank received ethical approval from the research ethics committee (REC reference for UK Biobank 11/NW/0382), and participants provided written informed consent.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit it for publication.

Results

Baseline characteristics

A total of 449,459 participants with complete data were included in the main analysis (Fig. 1); 53.5% of participants were female, and 90.5% were white. The average age of participants was 56.6 ± 8.1 years. Constipation was more likely to present in females, individuals with lower socio-economic status, and individuals with lower education. Compared with individuals without constipation, individuals with constipation were more likely to report less alcohol consumption, engage in fewer physical activities, have poor sleep, and have more comorbidities. A detailed description of participants' baseline characteristics is demonstrated in Table 1.

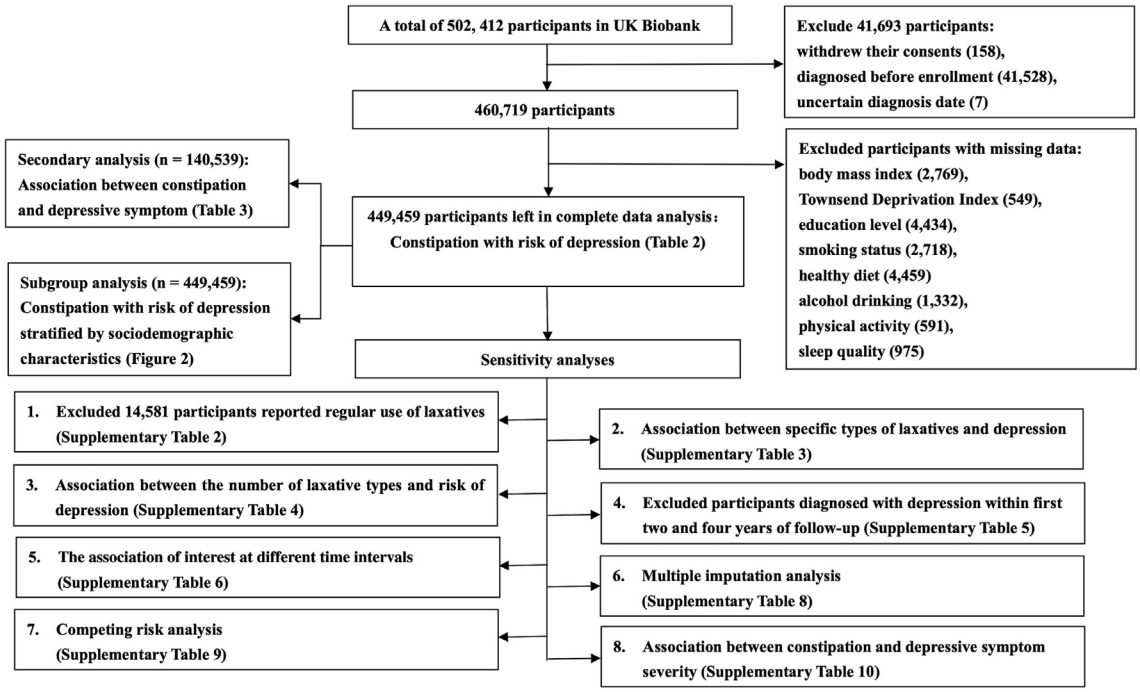

Fig. 1: Flow chart of the study.

Association between constipation and depression

At baseline, 18 569 (4.1%) participants had constipation, and a total of 18,576 (4.1%) participants were diagnosed with depression during a median follow-up of 12.3 years. Individuals with constipation had more than two times increased risk of depression than people without (Supplementary Figure S2), and the unadjusted HR for the association between constipation and depression was 2.28 (95% CI: 2.16–2.40). In the fully adjusted model, the HR for the association between constipation and depression was 1.48 (95% CI: 1.41–1.56). This association persisted among the individuals with self-reported and diagnosed constipation with adjusted HRs of 1.42 (95% CI: 1.34–1.51) and 1.66 (95% CI: 1.51–1.82) (Table 2). Similar results were found in the association between constipation and depressive symptoms. Participants with constipation were more likely to report depressive symptoms than people without (Table 3), and the adjusted odds ratio was 2.18 (95% CI: 1.97–2.43). The corresponding sensitivity analysis showed stronger associations between constipation and more severe depressive symptoms (Supplementary Table S10).

In the subgroup analyses stratified by sociodemographic variables (Fig. 2), the associations between constipation and the risk of depression were generally consistent across most covariates except for gender. The fully adjusted HR of depression in association with constipation was higher among males (1.74, 95% CI: 1.57–1.93) compared to females (1.41, 95% CI: 1.33–1.50).

Sensitivity analyses

After excluding participants who regularly use laxatives, the estimate of the constipation–depression association was similar to the primary result (Supplementary Table S2), indicating that information bias is not a major issue in the current study. Among the patients with constipation, no matter whichever laxatives were used, the HRs of their associations with depression were similar, and their 95% CI highly overlapped. Therefore, it might be constipation, not a specific kind of laxative, that is associated with depression (Supplementary Table S3). Additionally, the risk of depression increased with the number of laxative types (Supplementary Table S4). As using two or more types of laxatives usually reflects severe constipation, this dose-response relationship further supports the association between constipation and depression.

To examine the potential reverse causality, we excluded cases from the first two years and four years, and similar findings were found (Supplementary Table S5). As the proportional hazard assumption was met, similar HRs were found in different time intervals (Supplementary Table S6). The data were not missing completely at random. There were differences in sociodemographic characteristics, lifestyle factors, and health conditions between the participants with and

	Total (N = 449 459)	Constipation		SMD[a]
		Yes (n = 18 596)	No (n = 430 863)	
Mean (SD) baseline age (years)	56.6 (8.1)	58.5 (7.8)	56.5 (8.1)	0.25
Women	240,345 (53.5%)	13,651 (73.4%)	226,694 (52.6%)	0.44
Non-white	42,619 (9.5%)	1944 (10.5%)	40,675 (9.4%)	0.03
University degree or higher	147,281 (32.8%)	4420 (23.8%)	142,861 (33.2%)	0.20
Socio-economic status:				
Low	85,641 (19.1%)	4454 (24.0%)	81,187 (18.8%)	0.12
Moderate	271,742 (60.5%)	10,755 (57.8%)	260,987 (60.6%)	
High	92,076 (20.5%)	3387 (18.2%)	88,689 (20.6%)	
Living alone	79,747 (17.7%)	3843 (20.7%)	75,904 (17.6%)	0.08
Smoking status:				0.06
Never	248,968 (55.4%)	9689 (52.1%)	239,279 (55.5%)	
Former	155,683 (34.6%)	6920 (37.2%)	148,763 (34.5%)	
Current	44,808 (10.0%)	1987 (10.7%)	42,821 (9.9%)	
Alcohol consumption:				0.26
Less than once a week	133,945 (29.8%)	7705 (41.4%)	126,240 (29.3%)	
Physical activities:				0.17
Low	174,185 (38.8%)	8750 (47.1%)	165,435 (38.4%)	
Moderate	141,597 (31.5%)	5229 (28.1%)	136,368 (31.6%)	
High	133,677 (29.7%)	4617 (24.8%)	129,060 (30.0%)	
Body mass index				0.02
Underweight	2314 (0.5%)	144 (0.8%)	2170 (0.5%)	
Normal weight	148,206 (33.0%)	6197 (33.3%)	142,009 (33.0%)	
Overweight	192,122 (42.7%)	7367 (39.6%)	184,755 (42.9%)	
Obese	106,817 (23.8%)	4888 (26.3%)	101,929 (23.7%)	
Healthy diet	233,051 (51.9%)	10,329 (55.5%)	222,722 (51.7%)	0.08
Poor sleep	298,987 (66.5%)	13,483 (72.5%)	285,504 (66.3%)	0.14
Cancer	41,357 (9.2%)	2657 (14.3%)	38,700 (9.0%)	0.17
Cardiometabolic diseases	129,647 (28.8%)	6772 (36.4%)	122,875 (28.5%)	0.17
Neurological diseases	12,635 (2.8%)	1103 (5.9%)	11,532 (2.7%)	0.16
Inflammatory diseases	30,967 (6.9%)	2829 (15.2%)	28,138 (6.5%)	0.28
Chronic pain	184,164 (41.0%)	10,757 (57.8%)	173,407 (40.2%)	0.36
Family history of depression	52,662 (11.7%)	2752 (14.8%)	49,910 (11.6%)	0.10
Anticholinergic drugs	14,837 (3.3%)	2196 (11.8%)	12,641 (2.9%)	0.34
Calcium channel blocker drugs	27,429 (6.1%)	1579 (8.5%)	25,850 (6.0%)	0.09
Opioid	11,950 (2.7%)	1661 (8.9%)	10,289 (2.4%)	0.29
Statin	70,057 (15.6%)	4039 (21.7%)	66,018 (15.3%)	0.17
Steroids	16,474 (3.7%)	1284 (6.9%)	15,190 (3.5%)	0.15

[a]Abbreviation: SMD, standardized mean difference (shown as an absolute value).

Table 1: **Baseline characteristics of the study population.**

	No. of case/ no. of participants (%)	Hazard ratio (95% CI)			
		Crude model	Model 1[b]	Model 2[c]	Model 3[d]
No constipation	16,981/430,863 (3.9%)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Constipation	1595/18,569 (8.6%)	2.28 (2.16–2.40)[a]	1.90 (1.81–2.01)[a]	1.66 (1.58–1.75)[a]	1.48 (1.41–1.56)[a]
Self-reported constipation	1137/13,540 (8.4%)	2.22 (2.09–2.36)[a]	1.84 (1.73–1.96)[a]	1.60 (1.51–1.71)[a]	1.42 (1.34–1.51)[a]
Diagnosed constipation	458/5056 (9.1%)	2.44 (2.22–2.67)[a]	2.08 (1.89–2.28)[a]	1.82 (1.66–2.00)[a]	1.66 (1.51–1.82)[a]

[a]$P < 0.001$. [b]Adjusted for sociodemographic variables and lifestyle factors: age, sex, ethnicity, education, living alone, socio-economic status, smoking status, alcohol consumption, physical activities, sleep quality, healthy diet score, and body mass index. [c]Additionally adjusted for medical conditions: cancer, cardiometabolic diseases, neurological diseases, inflammatory diseases, chronic pain, and family history of depression. [d]Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, and steroids.

Table 2: **Association between constipation and risk of depression.**

	No. of case/ no. of participants (%)	Odds ratio (95% CI)			
		Crude model	Model 1[b]	Model 2[c]	Model 3[d]
No constipation	5946/135,916 (4.4%)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Constipation	443/4523 (9.8%)	2.37 (2.14–2.63)[a]	2.39 (2.15–2.65)[a]	2.30 (2.07–2.56)[a]	2.18 (1.97–2.43)[a]
Self-reported constipation	333/3274 (10.2%)	2.47 (2.20–2.78)[a]	2.53 (2.25–2.85)[a]	2.44 (2.16–2.75)[a]	2.32 (2.06–2.61)[a]
Diagnosed constipation	110/1249 (8.8%)	2.11 (1.73–2.57)[a]	2.04 (1.67–2.49)[a]	1.98 (1.61–2.42)[a]	1.87 (1.52–2.29)[a]

[a]P < 0.001. [b]Adjusted for sociodemographic variables and lifestyle factors: age, sex, ethnicity, education, living alone, socio-economic status, smoking status, alcohol consumption, physical activities, sleep quality, healthy diet score, and body mass index. [c]Additionally adjusted for medical conditions: cancer, cardiometabolic diseases, neurological diseases, inflammatory diseases, chronic pain, and family history of depression. [d]Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, and steroids.

Table 3: **Associations between constipation and depressive symptoms.**

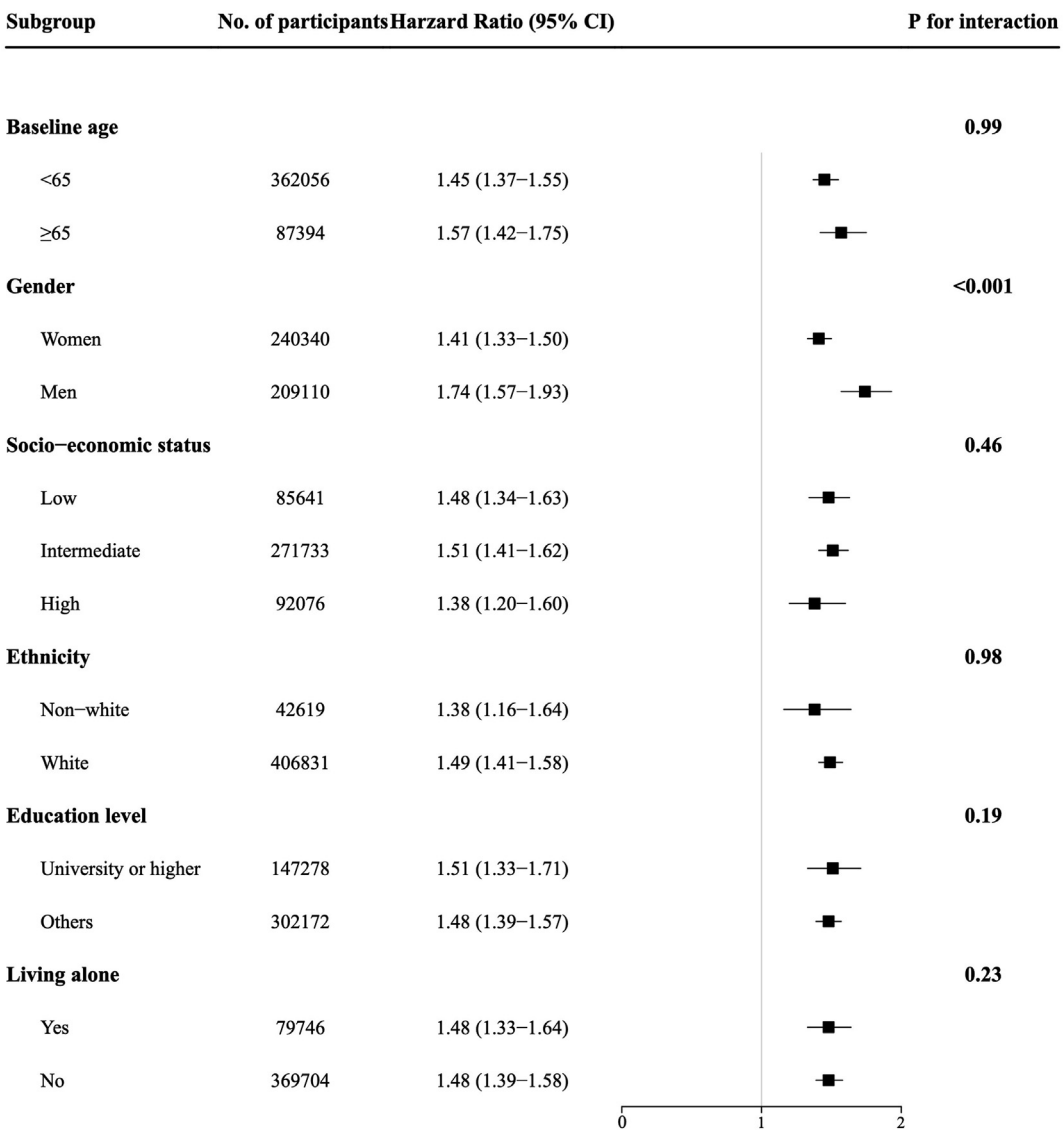

Fig. 2: Subgroup analysis, association between constipation and the risk of depression stratified by sociodemographic characteristics.

without missing data (Supplementary Table S7). The results of multiple imputations show the average relative variance increases were small (0.004), and the HRs after multiple imputations were also similar to the primary results, suggesting that missing data were not likely to distort the association (Supplementary Table S8). The competing risk analysis showed a similar finding to the main result, indicating that death before potential depression occurrence has less influence on the association (Supplementary Table S9).

Discussion

This is the first large-scale cohort study to verify the prospective association between constipation and depression. Individuals with constipation are found to be at a 2.28-fold increased risk of developing depression during a 12-year follow-up. After adjusting sociodemographic characteristics, lifestyle factors, medical conditions, and regular medication use, we found those with constipation still had a 48% higher risk of developing depression. Regardless of self-report or diagnosis of constipation, such constipation–depression association exists. Findings were robust to different alternative outcome and various sensitivity analyses.

Consistent with the results of previous cross-sectional studies,[8,9] this study found an association between constipation and depression. More importantly, this study also found that constipation occurs before depression, offering evidence of the association between constipation and drug-free depression, as antidepressants usually induce constipation, and this possibility cannot be ruled out in cross-sectional studies.[10] Additionally, this study found that men with constipation are at a greater risk of depression than women with constipation in this study. This finding is consistent with the results from the cross-sectional studies.[38,39] Such longitudinal evidence suggests that constipation might be a risk factor or prodromal symptom depression, offering epidemiological evidence for the bidirectional gut-brain pathway assumptions. Future studies need to determine whether treatment of constipation can lower the risk of depression or further clarify whether constipation occurs during the prodromal phase of depression.[40] If constipation exists in the early stage of depression, it may also be a new prodromal somatic complaint of depression in addition to sleep disturbances, fatigue, change of appetite, and pain.[12] However, no matter it is a risk factor or prodromal symptom, both diagnosed or self-reported constipation can be used to assess patients' risk of depression by gastroenterologists and primary care physicians in the future.

This study found an association between two diseases: constipation and depression. One may argue that this association might be caused by admission rate bias or Berkson's bias, as the participants with constipation were more likely to seek medical services, and thus they have a greater chance of being diagnosed with depression. Underreporting of diagnoses of constipation and depression was also a reasonable concern of this study, since most of these data were obtained from participants' health-related records, in which constipation and depression are commonly underdiagnosed.[41] If the patterns of underdiagnosed depression were different between those with and without constipation, this selection bias may cause a false association between constipation and depression. In this study, we adopted two strategies to examine these potential biases. First, we considered those who regularly use laxatives at baseline as self-reported constipation patients. As the questions about regular laxative intake were supposed to be answered by all the UK biobank participants, it complemented the underreporting of constipation cases from health-related records. Second, we included a secondary outcome, depressive symptoms, in this study. The information on depressive symptoms was obtained from all the 157,366 participants that were included in an online mental health survey in 2016. An analysis based on this group of people with completed information on depressive symptoms yielded similar results (Table 3). Therefore, the admission rate bias and selection bias of under-recording of depression were unlikely to be a major issue of this study.

Given the association between constipation and depression might be confounded by sociodemographic characteristics,[42] unhealthy lifestyle factors,[23] health conditions,[43] and medication use, we adjusted these factors, and the association persisted. It suggested that constipation was a potential independent risk factor for depression. After excluding participants who developed depression within the first two years or four years, the relationship still existed (Supplementary Table S5). Moreover, we found a dose-response relationship between the number of different types of laxatives and depression, indicating that the severity of constipation is associated with the risk of depression (Supplementary Table S4). We used to consider constipation only as a symptom of depression, but the above evidence suggested that constipation may also be an independent risk factor of depression.

Considering the brain-gut pathway might be bidirectional, constipation may also be a potential prodromal symptom of depression.[12] The underlying mechanism is the dysregulation of the HPA axis.[16] Clinically, depression is associated with dysregulation of the HPA axis, and activation of the HPA axis will release stress factors, such as corticotropin-releasing factor (CRF),[17] which has effects on gastrointestinal function and thus leads to constipation. It is possible the above process also happens in the prodromal stage of depression. If constipation is a potential prodromal symptom of depression, it can be observed several years before diagnosis of depression (Supplementary Table S6). Compared with participants with mild or

moderate depressive symptoms, participants with severe depressive symptoms were more likely to be diagnosed with clinical depression.[44] Therefore, the activation of the stress pathways and the dysregulation of the HPA axis may be more serious among them, which partly explains the stronger associations between constipation and moderately severe to severe depressive symptoms (Supplementary Table S10).

Given this study was not a pre-registered analysis, the findings of the current study are explorative. Future research is still needed to clarify the mechanism of the association between constipation and depression. Some limitations need to be noted when interpreting the results of this study. First, like other studies,[18,36] constipation was defined as either having laxative use or having a diagnosis for constipation, which is not exactly the gold standard measurement.[7] However, to verify the stability of the results, we used different classifications of exposure to repeat the main analysis (e.g., by applying different reporting sources of constipation, by using the number of different types of laxatives to represent the severity) and the results were consistent. Second, constipation is a transient symptom; we did not consider the participant developed constipation during follow-up, and thus, we might have underestimated the HRs and ORs of their association. We were also unable to assess the impact of the duration of constipation on depression since this information was not available in the UK biobank. Third, there might be some unknown confounding variables in the constipation–depression association, and residual confounding may still exist. Fourth, it is important to note that a small number of depression cases in our study were on self-reported (5.2%). However, the majority were diagnosed by a medical professional. Fifth, it should be cautious when generalizing this finding to other populations since the selection bias might occur in the UK Biobank cohort. It has been reported that participants of UK Biobank are from less deprived areas, and over 90% of participants are white.[45] Both the racial and socioeconomic deprivation factors are associated with depression,[26,46] and they may be disproportionately affected by depression. Last, although we conducted several analyses to evaluate the potential selection bias of underreporting of constipation and depression, selection bias may still exist.

Premorbid constipation is associated with a 2.28-fold higher risk of depression. After adjusting sociodemographic characteristics, lifestyle factors, health conditions, and medication use, we found those with constipation still had a 48% higher risk of developing depression. The prospective association between constipation and depression suggests that constipation might be an independent risk factor or prodromal symptom of depression. As diagnosed and self-reported constipation were both associated with a higher risk of depression, gastroenterologists and primary care physicians should pay more attention to the depressive symptoms of their constipation patients.

Contributors

FS, ZY, and JT conceptualized the study. FS, ZY, SC, HL, and XY provided critical methodological input. QY and SW curated the data and contributed to the formal analysis with the guidance of SF. QY, SW, and SF wrote the first draft, and the other authors made critical revisions to the manuscript. FS, ZY, HL, BL, PY, XY, and JT contributed to the clinical interpretation. FS, QY, and SW have accessed and verified the data. All authors had final responsibility for the decision to submit for publication; reviewed and edited the later version of the manuscript; and approved the final version of the manuscript.

Data sharing statement

All raw and derived data in this study are available from the UK Biobank (http://www.ukbiobank.ac.uk/).

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102371.

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