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Frailty and constipation in older adults and the mediating role of depression: cross-sectional evidence from NHANES 2005–2010 and genetic evidence from Mendelian randomization

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Abstract

Background: Constipation is highly prevalent among older adults and frequently coexists with frailty, yet whether frailty is causally related to constipation, and through what mechanisms, remains unclear. This study aimed to examine the association between frailty and constipation in a nationally representative sample of older Americans, and to investigate the causal relationship and the mediating role of depression using genetic epidemiology.

Methods: In the observational stage, data from the National Health and Nutrition Examination Survey (NHANES) 2005–2010 were analyzed. Frailty was measured by a 48-item frailty index (FI; frailty defined as FI ≥ 0.21), and constipation was defined by bowel-movement frequency (≤ 2/week) or Bristol Stool Form Scale types 1–2. Survey-weighted logistic regression was performed with stepwise adjustment, and sensitivity analyses excluded the depressive-symptom items from the FI. In the genetic stage, two-sample bidirectional Mendelian randomization (MR) analyses were conducted using genome-wide association study (GWAS) summary statistics of European ancestry for the FI, depression, and constipation. Two-step MR was used to quantify the mediating effect of depression, and Bayesian colocalization was used to examine shared genetic architecture between depression and constipation and between the FI and depression.

Results: Among 4,333 participants aged ≥ 60 years (representing approximately 40.9 million older Americans), frailty was associated with higher odds of constipation (fully adjusted odds ratio [OR] 1.363, 95% confidence interval [CI] 1.009–1.841, P = 0.044); the association persisted after exclusion of the seven depressive-symptom items from the FI (OR 1.376, 95% CI 1.051–1.801, P = 0.022). Genetically predicted FI was positively associated with depression (OR 2.072, 95% CI 1.518–2.830, $P = 4.53 \times 10^{-6}$), depression with constipation (OR 1.096, 95% CI 1.008–1.192, P = 0.032), and FI with constipation (OR 1.420, 95% CI 1.030–1.958, P = 0.032); no reverse causal effects of constipation or depression on frailty were consistently supported. Depression mediated 19.062% of the genetic effect of frailty on constipation (indirect effect β = 0.067, 95% CI 0.005–0.143, P = 0.032 by Monte Carlo inference). Colocalization analysis gave moderate support to a shared causal variant between depression and constipation (posterior probability of hypothesis 4 [PP4] = 54.2%) but found no evidence of colocalization between the FI and depression (PP4 = 4.2%).

Conclusions: Frailty is associated with constipation in older adults at both the population and genetic levels, and depression partially mediates this relationship. Assessment and management of depressive symptoms may help reduce the burden of constipation among frail older adults.

Keywords: Frailty; Constipation; Depression; Mediation analysis; Mendelian randomization; Colocalization; NHANES; Older adults

Background

Chronic constipation is one of the most common gastrointestinal complaints in older populations. A systematic review and meta-analysis estimated the global prevalence of functional constipation at approximately 10–15% according to the Rome criteria, with prevalence rising steeply with age [1]; among older adults specifically, pooled prevalence estimates exceed 18% [2] and reach 50% or higher in institutionalized populations [3]. Beyond physical discomfort, constipation in later life is associated with impaired quality of life, increased healthcare utilization, and greater dependence in daily activities [4, 5]. Identifying upstream, potentially modifiable contributors to constipation in older adults is therefore of clinical and public health importance.

Frailty is a geriatric syndrome characterized by decreased physiological reserve and increased vulnerability to stressors, resulting from cumulative declines across multiple physiological systems [6, 7]. Frailty and constipation frequently coexist: in a Spanish study of community-dwelling, hospitalized, and institutionalized older adults, the prevalence of functional constipation increased stepwise from robust to pre-frail to frail individuals (24.2%, 33.9%, and 41.7%, respectively), and frailty was independently associated with constipation [5]. Using data from the National Health and Nutrition Examination Survey (NHANES) 2005–2010 and a 49-item frailty index (FI), Liu et al. reported that frailty was associated with higher odds of constipation in unadjusted analysis, although the association was attenuated to non-significance after covariate adjustment, and the FI showed a U-shaped relationship with stool frequency [8]. Whether frailty is *causally* related to constipation—and if so, through which mechanisms—thus remains unresolved. Observational designs are inherently limited by residual confounding and reverse causation, which may explain the inconsistency of previous findings.

Depression is a plausible mechanistic link between frailty and constipation. Frailty and depression are closely intertwined in older adults: a systematic review and meta-analysis found that depression was present in a substantial proportion of frail older individuals and that both conditions prospectively increased the risk of each other [9]. In parallel, accumulating genetic evidence supports a causal effect of depression on constipation: recent bidirectional Mendelian randomization (MR) studies, using genome-wide association study (GWAS) summary statistics, reported that genetic liability to depression increased the risk of constipation, whereas evidence for the reverse direction was absent or inconsistent [10–12]. Furthermore, the largest GWAS of the FI to date demonstrated that frailty-associated loci are enriched in brain-expressed genes and share genetic architecture with depression and neuroticism [13], raising the possibility that depression lies on the causal pathway from frailty to constipation.

MR uses germline genetic variants as instrumental variables for an exposure; because alleles are randomized at conception and fixed thereafter, MR estimates are largely shielded from the confounding and reverse causation that bias conventional observational analyses [14]. Integrating MR with population-based observational

data—a triangulation approach—can therefore strengthen causal inference. To our knowledge, no study has jointly applied observational and genetic epidemiological designs to examine the frailty–constipation relationship, nor quantified the mediating role of depression in this pathway.

The present study therefore had three objectives: (1) to examine the association between frailty, measured by a 48-item FI, and constipation among older Americans in NHANES 2005–2010; (2) to evaluate the causal relationships among frailty, depression, and constipation using bidirectional two-sample MR; and (3) to quantify the proportion of the effect of frailty on constipation that is mediated by depression, complemented by Bayesian colocalization analyses of the shared genetic basis between depression and constipation and between the FI and depression.

Methods

Study design and reporting

This study adopted a two-stage analytical framework integrating observational and genetic epidemiology. In the first stage, cross-sectional data from NHANES 2005–2010 were used to examine the observational association between frailty and constipation among adults aged 60 years and older, using weighted multivariable logistic regression; sensitivity analyses were performed to evaluate the influence of the depressive-symptom items embedded in the FI. In the second stage, two-sample MR analyses were conducted using GWAS summary statistics from populations of European ancestry. Specifically, we (i) assessed the bidirectional causal relationship between the FI and constipation; (ii) estimated the causal effects of the FI on depression and of depression on constipation; (iii) performed a genetic mediation analysis to quantify the proportion of the effect of frailty on constipation mediated by depression; and (iv) conducted Bayesian colocalization analyses to examine the shared genetic basis of depression with constipation and of the FI with depression. The unidirectional directionality from depression to constipation—a prerequisite of the mediation model—was verified by bidirectional MR before the mediation analysis was interpreted. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and its extension for Mendelian randomization (STROBE-MR); the completed checklists are provided in Additional files 1 and 2 [15, 16].

NHANES data source and study population

NHANES is a continuous cross-sectional survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. Using a multistage probability sampling design, it is nationally representative of the non-institutionalized civilian population of the United States [17]. All participants provided written informed consent, and the survey protocol was approved by the NCHS Research Ethics Review Board. The present analysis used publicly available de-identified data and therefore required no additional ethical review.

Data from three consecutive cycles (2005–2006, 2007–2008, and 2009–2010) were merged; these cycles were selected because the Bowel Health Questionnaire was not administered in subsequent cycles. Of the 31,034 participants initially identified, we sequentially excluded those (1) younger than 60 years (n = 25,237); (2) with incomplete Bowel Health Questionnaire data, i.e., missing either bowel-movement frequency (BHD050) or Bristol Stool Form Scale (BHQ060) responses (n = 956); (3) with missing key covariates, including smoking status (n = 3), alcohol use (n = 6), poverty-income ratio (n = 405), and educational attainment (n = 5); (4) who completed fewer than 39 of the 48 FI items (i.e., more than 20% of items missing; n = 8); and (5) with a self-reported history of cancer confirmed as colorectal cancer (n = 81). The final analytical sample comprised 4,333 participants, representing approximately 40.9 million older adults in the United States after weighting (Additional file 3: Fig. S1). A complete-case analysis was applied.

Variable definitions

Exposure: frailty index

The FI was constructed following the deficit-accumulation approach described by Searle et al. [18] and previously published NHANES-based frailty indices [8, 19]. We selected 48 health-deficit variables spanning multiple physiological systems, including cognitive function, dependence in activities of daily living, depressive symptoms, comorbidities, self-rated health, healthcare utilization, physical performance, anthropometric measures, and laboratory parameters; the full list of items and their scoring rules is given in Additional file 3: Table S1. Item selection followed the standard criteria proposed by Searle et al. (each variable had to be health-related, to increase in prevalence with age, and not to saturate too early) and was further constrained by availability and comparability across the 2005–2010 cycles. Our 48-item index differs from the 49-item index of Hakeem et al. [19]—adopted identically by Liu et al. [8]—primarily in the exclusion of handgrip strength, which was not measured in the 2005–2010 cycles, and in minor details of item scoring; methodological studies have shown that the FI is robust to the exact composition of deficit items, provided that a sufficient number of deficits (typically at least 30) covering multiple physiological systems is included [6, 18].

Each deficit was assigned a value between 0 and 1 according to severity, and the scoring rules were adapted where necessary to accommodate the response structure of the NHANES questionnaires. For activity-of-daily-living items with graded response options (e.g., managing money, stooping or kneeling), a graded scoring scheme was applied (no difficulty = 0, some difficulty = 0.33, much difficulty = 0.66, unable to perform = 1) to preserve the gradient information of the original responses; for binary variables (e.g., arthritis, thyroid disease), standard dichotomous scoring was used (yes = 1, no = 0). The FI was calculated as the sum of deficit scores divided by the number of items actually assessed, yielding a value between 0 and 1. Consistent with previous studies, participants were classified as frail (FI ≥ 0.21) or non-frail (FI < 0.21) [8, 18, 19].

Outcome: constipation

Constipation was assessed using the NHANES Bowel Health Questionnaire, which collects self-reported usual bowel habits through standardized questions. Two core indicators were used: (1) bowel-movement frequency, assessed by the question "How many bowel movements do you usually have per week?" (variable BHD050), with an average of two or fewer bowel movements per week defined as reduced frequency; and (2) stool consistency, assessed with the Bristol Stool Form Scale (BSFS), in which participants were shown a colored picture card illustrating the seven stool types and asked to identify their usual or most common stool type (variable BHQ060); BSFS type 1 (separate hard lumps, like nuts) or type 2 (sausage-shaped but lumpy) was defined as hard stools [20]. Referring to the Rome IV diagnostic framework and relevant literature, participants meeting either criterion—bowel-movement frequency of two or fewer per week or BSFS type 1–2—were classified as having constipation [21, 22].

Depressive-symptom score

Seven items of the Patient Health Questionnaire depression module (DPQ010–DPQ070) were incorporated into the FI as deficits (scored 0, 0.33, 0.66, or 1 according to symptom frequency) [23]. For sensitivity analyses, a depressive-symptom score was additionally calculated as the mean of the completed items among these seven, multiplied by 7 (range 0–7; equivalent to the simple sum for participants with complete data), with higher scores indicating a greater burden of depressive symptoms.

Covariates

Covariates were selected based on previous literature and clinical relevance. Demographic factors included age (continuous, years), sex (male/female), and race/ethnicity according to the NHANES classification (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race/multiracial). Socioeconomic factors included educational attainment (less than high school, high school graduate or equivalent, and more than high school) and the poverty-income ratio (PIR, continuous). Lifestyle factors included smoking status (never: fewer than 100 cigarettes in lifetime; former: more than 100 cigarettes in lifetime but not currently smoking; current: more than 100 cigarettes in lifetime and currently smoking) and alcohol use (dichotomized as more than 12 versus 12 or fewer drinking occasions per year).

Statistical analysis of NHANES data

Complex sampling design and weighting

In accordance with the NHANES multistage probability sampling design, one-third of the two-year mobile examination center weight (WTMEC2YR/3) was applied to produce estimates representative of the non-institutionalized older adult population of the United States during 2005–2010. The survey package (version

4.5) in R was used to specify the sampling design parameters—the primary sampling unit (SDMVPSU), the stratum variable (SDMVSTRA), and the weight variable [24].

Descriptive statistics and group comparisons

All descriptive statistics were stratified by frailty status. Continuous variables are presented as weighted means ± standard errors (SEs) and were compared using design-based t-tests; categorical variables are presented as unweighted counts with weighted percentages and were compared using the Rao–Scott adjusted Pearson chi-square test. All statistical tests were two-sided.

Weighted multivariable logistic regression

Weighted multivariable logistic regression models, fitted with the svyglm() function (family = quasibinomial), were used to evaluate the association between frailty and constipation. Four models with stepwise adjustment were constructed: Model 1 was the unadjusted (crude) model; Model 2 adjusted for demographic factors (age as a continuous variable, sex, and race/ethnicity); Model 3 further adjusted for socioeconomic factors (educational attainment and PIR); and Model 4 (fully adjusted model) additionally adjusted for lifestyle factors (smoking status and alcohol use). Effect estimates are reported as odds ratios (ORs) with 95% confidence intervals (CIs), and statistical significance was set at a two-sided $P < 0.05$.

Sensitivity analyses

Sensitivity analysis A (excluding the depressive-symptom component of the FI). To evaluate the potential influence of the depressive-symptom items embedded in the FI on the observed association, we reconstructed a 41-item FI excluding the seven depressive-symptom items (FI-41), re-classified participants using the same 0.21 cut-off, and repeated the logistic regression models described above; FI-48 and FI-41 were additionally modelled as continuous variables (per 0.1-unit increase). The analytic sample (n = 4,333) was defined by the inclusion criteria based on the primary 48-item FI; the identical sample was retained for the FI-41 analysis to ensure that any difference in estimates was attributable solely to the exclusion of the depressive-symptom items, with FI-41 computed using each participant's own number of completed items as the denominator.

Sensitivity analysis B (independent effect of depressive symptoms). To further distinguish the independent contribution of depressive symptoms from the other dimensions of the FI, we examined the association between the depressive-symptom score and constipation, modelling the score as a continuous variable (per one-point increase), a dichotomous variable (any symptom, score > 0, versus none, score = 0), and a three-category variable (0, > 0 to 1, and > 1) defined a priori based on the score distribution and interpretability. Covariate adjustment was identical to Model 4. In addition, joint models entering FI-41 and the depressive-symptom score simultaneously were fitted to examine their mutually adjusted associations. One

participant with missing data on all seven DPQ items was excluded from analyses involving the depressive-symptom score (n = 4,332).

GWAS summary data sources

All GWAS summary statistics were obtained from publicly available databases of populations of European ancestry; the data sources and their basic characteristics are summarized in Table 1. Summary statistics for the FI were obtained from the IEU Open GWAS database (dataset ID: ebi-a-GCST90020053), derived from a GWAS meta-analysis of 175,226 participants of European ancestry comprising 7,582,323 single-nucleotide polymorphisms (SNPs); in that study, the FI was constructed using the deficit-accumulation approach, and associations between genetic variants and the FI were estimated with linear regression models [13]. Summary statistics for depression were obtained from the FinnGen consortium (dataset ID: finn-b-F5_DEPRESSIO), including 215,644 participants of European ancestry (23,424 cases and 192,220 controls) and 16,278,239 SNPs; the depression phenotype was defined by clinical diagnoses based on International Classification of Diseases codes [25]. Summary statistics for constipation were likewise obtained from FinnGen (dataset ID: finn-b-K11_CONSTIPATION), including 218,772 participants of European ancestry (17,246 cases and 201,526 controls) and 16,278,248 SNPs, with the phenotype defined by ICD diagnostic codes. The FI GWAS was conducted in cohorts independent of the FinnGen datasets, satisfying the sample-independence assumption of two-sample MR; for analyses involving depression and constipation, both datasets were drawn from FinnGen, and the potential participant overlap between these two datasets is addressed in the Limitations section.

Table 1. Basic characteristics of the genome-wide association study (GWAS) datasets used in this Mendelian randomization analysis.

Phenotype	GWAS ID	Databases	Population	Cases/Controls	Total sample size	Number of SNPs
Frailty index	ebi-a-GCST90020053	IEU GWAS database	European	—	175226	7582323
Depression	finn-b-F5_DEPRESSIO	FinnGen (hosted in IEU)	European	23424/192220	215644	16278239
Constipation	finn-b-K11_CONSTIPATION	FinnGen (hosted in IEU)	European	17246/201526	218772	16278248

Instrumental variable selection

To satisfy the three core assumptions of MR (relevance, independence, and exclusion restriction), a uniform instrumental-variable (IV) selection pipeline was applied to all exposure phenotypes. First, genome-wide significant variants were retained, using $P < 5 \times 10^{-8}$ for the FI and $P < 1 \times 10^{-5}$ for depression and constipation; because the numbers of variants reaching conventional genome-wide significance for depression and constipation in FinnGen were limited, the more permissive threshold of $P < 1 \times 10^{-5}$ was adopted to ensure adequate statistical power, a practice widely accepted in MR studies of binary traits [10, 11]. Second, linkage disequilibrium clumping was performed with PLINK (version 1.90), using the 1000 Genomes Project Phase 3 European reference panel, with parameters $r^2 < 0.001$ and a window size of 10,000 kb [26, 27]. Third, effect alleles were aligned using the harmonise_data() function of the TwoSampleMR package (default setting action = 2), which attempts to infer the effect direction of palindromic SNPs (minor allele frequency 0.42–0.58); variants whose direction could not be resolved were removed [28]. Finally, F statistics were calculated for each SNP, and only variants with $F > 10$ were retained to ensure strong instrument–exposure associations (Additional file 3: Fig. S2).

Mendelian randomization analyses

The inverse-variance weighted (IVW) method served as the primary analytical model and was used to estimate the total effect of the FI on constipation (path c), the effect of the FI on depression (path a), the effect of depression on constipation (path b), and the bidirectional causal effects between depression and constipation, as well as the reverse effects of depression and constipation on the FI. The IVW method assumes that all IVs are valid and combines the Wald ratios of individual SNPs through weighted regression, providing the causal estimate with the greatest statistical power [14].

Four complementary methods were used to assess the robustness of the results to potential violations of MR assumptions: MR-Egger regression, which permits directional horizontal pleiotropy and tests it via the intercept term while providing a pleiotropy-corrected causal estimate through the slope [29, 30]; the weighted-median method, which provides a consistent estimate assuming that at least 50% of the IVs are valid [31]; and the simple-mode and weighted-mode methods, which base estimation on the modal SNP-specific causal estimate [28]. Because these methods are statistically less efficient than IVW, their estimates were interpreted primarily with respect to the direction and precision of effects rather than formal significance.

Heterogeneity across SNP-specific estimates was evaluated with Cochran's Q test ($P < 0.05$ indicating significant heterogeneity); directional horizontal pleiotropy was assessed with the MR-Egger intercept test ($P < 0.05$ indicating directional pleiotropy); and leave-one-out analysis was performed by re-estimating the causal effect after removing each SNP in turn. For pathways supported by the primary

analysis, the direction of causation was additionally verified with the Steiger directionality test, which compares the variance explained by the instruments in the exposure and in the outcome and supports the hypothesized direction only when the former is larger [28]. Causal effects on binary outcomes are reported as ORs with 95% CIs, and effects on the FI, a continuous outcome, as β coefficients (mean differences) with 95% CIs; for the FI as exposure, estimates are interpreted per one-standard-deviation increase.

Mediation analysis

Building on the Baron–Kenny framework extended to MR, a genetic mediation model of "frailty index (X) → depression (M) → constipation (Y)" was constructed [32–34]. This framework assumes no unmeasured confounding between the mediator and the outcome and no genetic pleiotropy bypassing the mediator; reverse causation was examined through the bidirectional MR analyses described above. In the first step, the effect of the FI on depression (path a) was estimated by IVW using the FI genetic instruments; in the second step, the effect of depression on constipation (path b) was estimated by IVW using the depression genetic instruments; and in the third step, the total effect of the FI on constipation (path c) was estimated by IVW using the FI genetic instruments. The indirect (mediated) effect was calculated using the product-of-coefficients method ($ab = a \times b$), the direct effect using the difference method ($c' = c - ab$), and the mediated proportion as $ab / c \times 100\%$.

For statistical inference, the conventional delta method (Sobel test) assumes independence between the total and indirect effects; however, in two-step MR, paths c and a are estimated using the same set of FI genetic instruments, so their estimation errors share a positive covariance that violates this assumption. Monte Carlo simulation was therefore used as the primary approach for inference, with the delta method computed for comparison. The correlation coefficient ρ between paths c and a reflects the error correlation introduced by the shared instruments; previous MR mediation studies suggest that ρ typically lies between 0.6 and 0.8 when the exposure and instruments substantially overlap. We adopted $\rho = 0.7$ for the primary analysis and $\rho = 0.6$ and $\rho = 0.8$ for sensitivity analyses to evaluate the stability of the P-values of the indirect and direct effects. The number of simulation iterations was set at 200,000; 95% CIs were obtained from the 2.5th and 97.5th percentiles of the simulated distribution, with $P < 0.05$ considered statistically significant.

Bidirectional genetic colocalization analysis of depression and constipation

Bayesian colocalization analysis was performed with the coloc package (version 5.2.3) [35]. Each trait pair was analysed within the genomic region extending 500 kb on either side of the lead variant, defined as the SNP with the smallest P-value in the respective GWAS (the depression GWAS for the depression–constipation pair and the FI GWAS for the FI–depression pair). All SNPs within the region that were

present in both datasets entered the analysis, without P-value filtering or linkage-disequilibrium pruning, so that the full association pattern at the locus could be compared between traits; only SNPs with valid rsIDs were retained, and duplicate records were removed. The FI was modelled as a quantitative trait and depression and constipation as case–control traits, with case proportions of 23,424/215,644 and 17,246/218,772, respectively; effect-allele frequencies were converted to minor allele frequencies. The software computes posterior probabilities for five mutually exclusive hypotheses (H0–H4); hypothesis 4 (H4) posits that both traits associate with the locus and share a single causal variant, and its posterior probability (PP4) quantifies the strength of evidence for colocalization, with PP4 > 0.8 conventionally regarded as strong evidence. The main analysis used the default priors ($p1 = 1 \times 10^{-4}$, $p2 = 1 \times 10^{-4}$, $p12 = 1 \times 10^{-5}$); the default marginal priors have been shown to be well supported across data types, whereas the joint prior p12 can materially affect posterior inference [36]. Two sensitivity analyses were therefore performed: repeating the analysis with a 250-kb window, and varying the p12 prior across 1×10^{-6}, 5×10^{-6}, 1×10^{-5}, and 5×10^{-5}, as recommended [36].

Statistical software

All analyses were performed in R (version 4.4.3). Complex-survey analyses of NHANES data used the survey package (version 4.5); MR analyses used the TwoSampleMR package (version 0.7.4); and colocalization analyses used the coloc package (version 5.2.3). Linkage disequilibrium clumping was performed locally with PLINK (version 1.90). The genetic mediation analysis was conducted with a custom Monte Carlo simulation script implemented with the mvrnorm() function of the MASS package (version 7.3-64).

Results

Characteristics of the study population

Of the 31,034 NHANES 2005–2010 participants screened, 4,333 older adults met the inclusion criteria, representing approximately 40.9 million non-institutionalized Americans aged 60 years and older (Additional file 3: Fig. S1). Based on the 48-item FI, 1,542 participants (weighted percentage 31.7%) were classified as frail and 2,791 (68.3%) as non-frail. The weighted prevalence of constipation was 8.3% overall and was significantly higher among frail than non-frail participants (11.3% vs. 6.9%, $P < 0.001$). Compared with non-frail participants, frail participants were older, more likely to be female, had lower educational attainment and lower poverty-income ratios, and were more likely to be current smokers (all $P < 0.05$; Table 2).

Table 2. Baseline characteristics of the study population by frailty status(NHANES 2005-2010)

Characteristic	Overall n = 4333 N = 40,909,160	Non-frail n = 2791 N = 27,947,851	Frail n = 1542 N = 12,961,309	*P*-value
Constipation	375 (8.312%)	198 (6.938%)	177 (11.274%)	<0.001
Age, years	69.919 ± 0.159	68.948 ± 0.191	72.014 ± 0.212	<0.001
Sex				<0.001
Male	2207 (45.538%)	1485 (47.698%)	722 (40.879%)	
Female	2126 (54.462%)	1306 (52.302%)	820 (59.121%)	
Race/Ethnicity				0.003
Non-Hispanic White	2517 (82.280%)	1666 (83.957%)	851 (78.665%)	
Mexican American	580 (3.884%)	359 (3.455%)	221 (4.811%)	
Other Hispanic	289 (2.246%)	184 (2.182%)	105 (2.386%)	
Non-Hispanic Black	836 (8.468%)	510 (7.330%)	326 (10.923%)	
Other Race	111 (3.120%)	72 (3.077%)	39 (3.214%)	
Education				<0.001
<High school	1447 (23.289%)	801 (18.866%)	646 (32.828%)	
High school	1081 (27.552%)	690 (26.197%)	391 (30.474%)	
>High school	1805 (49.158%)	1300 (54.937%)	505 (36.698%)	
Poverty-income ratio	2.975 ± 0.052	3.225 ± 0.052	2.436 ± 0.062	<0.001
Smoking status				0.200
Never	2010 (46.620%)	1329 (47.392%)	681 (44.957%)	
Former	1782 (41.990%)	1128 (41.691%)	654 (42.635%)	
Current	541 (11.390%)	334 (10.917%)	207 (12.408%)	
Alcohol use				<0.001
≤12 times/year	2804 (67.132%)	1917 (70.926%)	887 (58.952%)	
>12 times/year	1529 (32.868%)	874 (29.074%)	655 (41.048%)	

Note. n = unweighted sample size; N = weighted population estimate representing the U.S. civilian non-institutionalized population aged ≥60 years.

Data are presented as unweighted *n* (weighted %) for categorical variables and weighted mean ± SE for continuous variables.

P-values were calculated using Rao-Scott adjusted Pearson chi-square test for categorical variables and design-based *t*-test for continuous variables.

Association between frailty and constipation

Weighted multivariable logistic regression showed that frailty was significantly associated with higher odds of constipation (Table 3). In the unadjusted model, frail participants had 70.4% higher odds of constipation than non-frail participants (Model 1: OR 1.704, 95% CI 1.289–2.254, P < 0.001). The association persisted after adjustment for demographic factors (Model 2: OR 1.507, 95% CI 1.133–2.005, P = 0.006) and after further adjustment for socioeconomic factors (Model 3: OR 1.388, 95% CI 1.027–1.874, P = 0.033), and remained statistically significant in the fully adjusted model (Model 4: OR 1.363, 95% CI 1.009–1.841, P = 0.044).

Table 3. Weighted logistic regression of the association between frailty and constipation

	Model 1 (Crude)		Model 2 (Demographics)		Model 3 (+SES)		Model 4 (Fully Adjusted)	
Variable	**OR (95% CI）**	***P*-value**	**OR (95% CI）**	***P*-value**	**OR (95% CI）**	***P*-value**	**OR (95% CI）**	***P*-value**
Frailty								
Non-frail	Ref		Ref		Ref		Ref	
Frail	1.704 (1.289-2.254)	<0.001	1.507 (1.133-2.005)	0.006	1.388 (1.027–1.874)	0.033	1.363 (1.009-1.841)	0.044

Note: OR = odds ratio; CI = confidence interval. Model 1: Crude. Model 2: Adjusted for age, sex, and race/ethnicity. Model 3: Additionally adjusted for education and poverty-income ratio. Model 4: Fully adjusted for all covariates including smoking and alcohol. Non-Hispanic White was the reference group for race/ethnicity, Male for sex, <High school for education, Never smoker for smoking status, and ≤12 times/year for alcohol use. All models were fitted using weighted logistic regression with svyglm() (family = quasibinomial()) to account for the complex sampling design of NHANES.

Sensitivity analyses

Excluding the seven depressive-symptom items from the FI did not materially change the results (Additional file 3: Table S2): frailty defined by the 41-item FI remained significantly associated with constipation in the fully adjusted model (OR 1.376, 95% CI 1.051–1.801, P = 0.022), with a point estimate nearly identical to that of the 48-item FI (OR 1.363). When modelled as continuous variables, each 0.1-unit increase in the FI was associated with higher odds of constipation in the fully adjusted model for both the 48-item FI (OR 1.169, 95% CI 1.055–1.295, P = 0.004) and the 41-item FI (OR 1.146, 95% CI 1.033–1.270, P = 0.012), indicating that the association was not driven by the depressive component of the index.

The depressive-symptom score itself was independently associated with constipation (Additional file 3: Table S3). In the fully adjusted model, each one-point increase in the score was associated with 15.3% higher odds of constipation (OR 1.153, 95% CI 1.037–1.283, P = 0.010), and participants reporting any depressive symptom had 53.0% higher odds than those reporting none (OR 1.530, 95% CI 1.145–2.044, P = 0.005). A graded dose–response pattern was observed across the three categories (fully adjusted ORs: Low [> 0 to 1] 1.460, 95% CI 1.082–1.969, P = 0.015; High [> 1] 1.644, 95% CI 1.080–2.501, P = 0.022, versus none). In joint models entering FI-41 and the depressive-symptom score simultaneously, both estimates were attenuated and lost statistical significance after full adjustment (FI-41: OR 1.100, 95% CI 0.963–1.256, P = 0.153; depressive-symptom score: OR 1.107, 95% CI 0.963–1.272, P = 0.146), a pattern consistent with shared variance between somatic frailty and depressive symptoms in relation to constipation.

Mendelian randomization estimates of the effects of frailty on depression and constipation

Instrument selection and linkage-disequilibrium clumping yielded 16, 45, and 29 independent SNPs for the FI, depression, and constipation, respectively; after harmonization with the outcome data, 14, 36–39, and 25–29 SNPs entered the MR analyses (all F statistics > 10). Genetically predicted FI was strongly and positively associated with depression (IVW: OR 2.072 per SD increase in FI, 95% CI 1.518–2.830, P = 4.53×10^{-6}; Table 4), with directionally consistent estimates across all four complementary methods, of which the weighted-median estimate was also statistically significant (Additional file 3: Table S4). Genetically predicted depression was associated with higher odds of constipation (IVW: OR 1.096, 95% CI 1.008–1.192, P = 0.032), with directionally consistent but non-significant estimates from the complementary methods, as expected given their lower statistical power. Genetically predicted FI was likewise associated with higher odds of constipation (IVW: OR 1.420, 95% CI 1.030–1.958, P = 0.032); the weighted-median estimate was directionally consistent and likewise statistically significant (OR 1.528, P = 0.041), whereas the MR-Egger estimate was imprecise and not statistically significant (OR 0.716, 95% CI 0.166–3.093, P = 0.663), as expected given the limited number of FI instruments and the low statistical efficiency of the Egger method.

Table 4. Primary Mendelian randomization estimates for the bidirectional associations between Frailty index, Depression, and Constipation using the inverse-variance weighted method.

Pathway	*β* (95% CI)	SE	OR (95% CI)	*P*-value
Frailty index on Depression	0.729 (0.417 to 1.040)	0.159	2.072 (1.158- 2.830)	4.53e-06*
Depression on Constipation	0.092 (0.008 to 0.176)	0.043	1.096 (1.008- 1.192)	0.032*
Frailty index on Constipation	0.351 (0.030 to 0.672)	0.164	1.420 (1.030- 1.958)	0.032*
Constipation on Depression	0.135 (0.052 to 0.218)	0.043	1.145 (1.053- 1.244)	0.002*
Depression on Frailty index	0.024 (-0.003 to 0.051)	0.014	—	0.077
Constipation on Frailty index	0.006 (-0.014 to 0.026)	0.010	—	0.554

Note: OR, odds ratio; *β*, regression coefficient; SE, standard error; 95% CI, 95% confidence interval; for pathways with the frailty index as the outcome (a continuous trait), effects are expressed on the β scale and odds ratios are not applicable (—); **P*-value < 0.05.

In the reverse direction, genetically predicted constipation was associated with higher odds of depression by IVW (OR 1.145, 95% CI 1.053–1.244, P = 0.002); however, this association was not consistently corroborated by the complementary methods—the MR-Egger estimate was directionally consistent but non-significant, the weighted-median estimate was attenuated toward the null (β = 0.029, P = 0.573), and the two mode-based estimates were slightly negative (β = −0.015)—indicating that the reverse signal was driven largely by the IVW estimate and that the evidence for this direction is weak and method-dependent. For the reverse effects on frailty, genetically predicted constipation showed no association with the FI (IVW: β = 0.006, 95% CI − 0.014 to 0.026, P = 0.554; all methods consistent), and genetically predicted depression showed no consistent association with the FI (IVW: β = 0.024, 95% CI − 0.003 to 0.051, P = 0.077); although the weighted-median estimate for depression on the FI reached nominal significance (P = 0.019), this pathway exhibited significant heterogeneity (Cochran's Q = 72.07, P < 0.001) and directional horizontal pleiotropy (MR-Egger intercept = 0.006, P = 0.013), and the pleiotropy-corrected MR-Egger estimate was null (P = 0.142), suggesting that the nominal signal was driven by pleiotropy rather than a genuine causal effect.

For the four primary pathways, no significant heterogeneity or directional pleiotropy was detected (all P > 0.05; Table 5); leave-one-out analysis indicated that no single SNP drove the observed associations (Additional file 3: Figs. S3–S6); and Steiger directionality testing supported the exposure-to-outcome direction for all four pathways (all $P < 1 \times 10^{-28}$; Additional file 3: Table S5).

Table 5. Heterogeneity and horizontal pleiotropy analyses for the Mendelian randomization associations between Frailty index, Depression, and Constipation.

	Method	Cochran Q			Egger regression intercept		
Pathway	——	Q	Q_df	Q_pval	Egger intercept	SE	*P*-val
Frailty index to Depression	MR Egger	16.486	12	0.170	-0.001	0.017	0.934
	Inverse variance weighted	16.496	13	0.223			
Depression to Constipation	MR Egger	41.083	34	0.188	0.003	0.007	0.706
	Inverse variance weighted	41.258	35	0.216			
Frailty index to Constipation	MR Egger	13.926	12	0.305	0.016	0.016	0.366
	Inverse variance weighted	14.952	13	0.310			
Constipation to Depression	MR Egger	37.981	27	0.078	-0.003	0.009	0.758
	Inverse variance weighted	38.117	28	0.096			
Depression to Frailty index	MR Egger	60.818	37	0.008	0.006	0.002	0.013
	Inverse variance weighted	72.073	38	0.001			
Constipation to Frailty index	MR Egger	20.848	23	0.590	-0.0004	0.002	0.848
	Inverse variance weighted	20.886	24	0.645			

Abbreviations: MR, Mendelian randomization; Q, Cochran's Q statistic; Q_df, degrees of freedom for Cochran's Q test; Q_pval, *P*-value for Cochran's Q test; SE, standard error.

Mediation effect of depression

All three paths of the mediation model were statistically significant: FI → depression (a = 0.729, P = 4.53×10^{-6}), depression → constipation (b = 0.092, P = 0.032), and FI → constipation (total effect c = 0.351, P = 0.032). The indirect effect of the FI on constipation through depression, estimated by the product-of-coefficients method, was 0.067 (95% CI 0.005–0.143, P = 0.032 by Monte Carlo simulation with ρ = 0.7; Table 6), corresponding to 19.062% of the total effect. The direct effect was 0.284 (95% CI − 0.024 to 0.597, P = 0.070). Sensitivity analyses assuming ρ = 0.6 or ρ = 0.8 yielded virtually identical results (indirect-effect P = 0.032 for both). Under the conventional delta method, the indirect effect was of identical magnitude but borderline significant (P = 0.052), consistent with the expectation that ignoring the covariance between paths estimated with shared instruments attenuates the significance of the indirect effect.

Table 6. Mediation analysis: indirect and direct effects of the frailty index on constipation through depression.

Method	Indirect β (95% CI)	*P*-value	Direct β (95% CI)	*P*-value
Delta method (Sobel)	0.067 (NA)	0.052	0.284 (NA)	0.090
Monte Carlo (ρ = 0.7)	0.067 (0.005–0.143)	0.032	0.284 (−0.024 – 0.597)	0.070
Monte Carlo (ρ = 0.6, sensitivity)	0.067 (0.005–0.143)	0.032	0.284 (−0.027 – 0.599)	0.073
Monte Carlo (ρ = 0.8, sensitivity)	0.067 (0.005–0.143)	0.032	0.284 (−0.019 – 0.594)	0.066

Note: Total effect of the frailty index on constipation: β = 0.351 (*P* = 0.032). The mediated proportion was calculated as indirect effect / total effect = 19.062%. Monte Carlo simulation was performed with 200,000 iterations; confidence intervals were derived from the 2.5th and 97.5th percentiles of the simulated distribution. ρ denotes the assumed correlation between the estimation errors of the total and indirect effects arising from shared instruments. NA, not available under the delta method.

Colocalization analysis of depression and constipation

For depression and constipation, the analysis covered the chromosome 11 locus surrounding the lead variant rs187821300, with 5,555 SNPs shared by the two datasets. The posterior probability of a shared causal variant (PP4) was 54.2% under the default priors and was essentially unchanged with a 250-kb window (57.2%), providing moderate evidence of colocalization; across the prior sensitivity analyses PP4 ranged from 10.6% to 87.0%, indicating that the estimate is sensitive to the prior specification. For the FI and depression, the analysis covered the chromosome 6 locus surrounding the lead variant rs9275160 (8,123 shared SNPs); PP4 was 4.2% (5.0% with a 250-kb window; prior sensitivity range 0.4–18.0%), and 70.9% of the posterior probability supported an association with the FI only, indicating no evidence of colocalization at this locus (Additional file 3: Table S6).

Discussion

Principal findings

This study integrated a nationally representative cross-sectional analysis with genetic epidemiology to examine the relationship between frailty and constipation in older adults. Four main findings emerged. First, frailty was associated with approximately 36% higher odds of constipation among older Americans, an association that was robust to the exclusion of depressive-symptom items from the FI. Second, MR analyses provided genetic evidence that frailty increases the risk of constipation, and that this effect is partially mediated by depression, which accounted for approximately one-fifth (19.062%) of the total genetic effect. Third, the causal pathway from frailty to depression was strong and methodologically robust, whereas no consistent reverse causal effects of depression or constipation on frailty were detected. Fourth, colocalization analysis gave moderate support to a shared causal variant between depression and constipation, whereas no colocalization signal was detected between the FI and depression at the FI lead locus. Together, these findings delineate a "frailty → depression → constipation" pathway and position depressive symptoms as a potentially modifiable intermediary in the gastrointestinal burden of frail older adults.

Comparison with previous studies

Our observational findings both complement and extend previous work. In the Spanish multicentre study by Arco et al., the prevalence of functional constipation increased stepwise across frailty strata, and frailty was independently associated with constipation [5]. In contrast, Liu et al., analyzing the same NHANES cycles with a 49-item FI, found that the frailty–constipation association was attenuated to non-significance after adjustment [8]. Several differences may account for this discrepancy: Liu et al. defined constipation solely by stool consistency (BSFS types 1–2), whereas we additionally incorporated reduced bowel-movement frequency (≤ 2/week), capturing a broader spectrum of the constipation phenotype; and the covariate sets and FI compositions differed between the two studies. Our estimates from the 48-item and 41-item indices were nearly identical, indicating that the association we observed is not an artefact of including depressive symptoms in the deficit count, a concern that applies equally to indices of either length. Our study also moves beyond the observational level: to our knowledge, it provides the first genetic evidence supporting a causal effect of frailty on constipation, which converges with the population-level association and strengthens the overall causal claim through triangulation.

The mediating role of depression identified here is consistent with several lines of evidence. Frailty and depression are highly comorbid and reciprocally related in older populations [9]. At the genetic level, FI-associated loci are enriched for genes expressed in the frontal cortex and hippocampus and show significant genetic correlation with depression [13, 37]. Our MR estimate of a strong causal effect of the

FI on depression (OR 2.07) aligns with this genetic architecture and extends it to a formal causal framework. Regarding the downstream link, three recent bidirectional MR studies independently concluded that genetic liability to depression increases constipation risk, with absent or weak evidence for the reverse direction [10–12]; our results replicate this asymmetry, and the colocalization analysis adds moderate, independent support for shared genetic architecture between the two traits. This convergence across studies, datasets, and analytical frameworks suggests that the depression–constipation relationship is unlikely to be explained by confounding alone.

Potential mechanisms

Several mechanisms may underlie the pathway from frailty to constipation via depression. Behaviourally, depression in older adults is accompanied by reduced physical activity, poor appetite and inadequate fluid and fibre intake, and social withdrawal, all of which are established contributors to constipation [2, 4]. Pharmacologically, antidepressants—particularly tricyclic agents with anticholinergic properties—slow colonic transit, and polypharmacy is common in frail older adults [4]. Neurobiologically, depression involves dysregulation of the hypothalamic–pituitary–adrenal axis and altered serotonergic signalling; because most of the body's serotonin is produced in the gut and participates in regulating motility, mood-related serotonergic dysfunction may simultaneously affect emotional and gastrointestinal function, consistent with the brain–gut axis model [38]. The genetic enrichment of FI loci in brain-expressed genes [13] provides a further biological substrate linking deficit accumulation to central rather than purely peripheral mechanisms. That depression mediated approximately one-fifth of the total effect implies that additional, depression-independent pathways—such as sarcopenia-related abdominal and pelvic floor muscle weakness, reduced mobility, and comorbidity burden—also contribute, which is consistent with the direct effect remaining quantitatively larger than the indirect effect.

Clinical implications

These findings have practical implications for the care of older adults. First, given the elevated odds of constipation among frail individuals and the supporting genetic evidence of causality, constipation screening should be incorporated into the routine assessment of older adults identified as frail, rather than being treated as an incidental complaint. Second, the mediating role of depression suggests that the gastrointestinal burden of frailty may be partly modifiable through mental-health interventions: systematic screening for depressive symptoms in frail older adults, followed by appropriate management, may yield dual benefits for mood and bowel function. Third, when pharmacotherapy for depression is indicated in this population, agents with lower anticholinergic burden should be preferred to avoid aggravating constipation [4]. These hypotheses are testable in interventional studies, which are needed to determine whether treating depression reduces incident constipation in frail older adults.

Strengths and limitations

The strengths of this study include the triangulation of observational and genetic evidence; the use of a nationally representative sample with standardized assessments; a theory-driven, mechanism-oriented analytical plan that explicitly addressed the construct overlap between the FI and its depressive-symptom component at the observational level; and a comprehensive set of robustness analyses, including five MR estimation methods, bidirectional testing, Monte Carlo inference for the mediation effect, and colocalization.

Several limitations should be acknowledged. First, the NHANES analysis is cross-sectional and cannot establish temporality; however, the MR results, which are immune to reverse causation by design, provide complementary causal evidence.

Second, bowel habits in NHANES were self-reported, and the constipation definition, although informed by Rome IV core features, was not equivalent to the full clinical criteria; moreover, laxative use was not accounted for (the relevant items were available only in the 2009–2010 cycle), so treated individuals may have been misclassified as non-constipated, which would bias the observed associations toward the null rather than inflate them.

Third, the FI used in both the observational and genetic analyses incorporated depressive symptoms as constituent deficits; although sensitivity analyses excluding these items yielded consistent results at the observational level, residual construct overlap at the genetic level cannot be fully excluded.

Fourth, the number of FI instruments was modest (14 SNPs), the MR-Egger estimates were correspondingly imprecise, and the significance of the FI–constipation and depression–constipation pathways (both $P = 0.032$) would not survive Bonferroni correction across the six bidirectional MR tests ($\alpha = 0.008$); however, the FI–constipation pathway was our pre-specified primary hypothesis and was supported by convergent observational evidence, and these findings warrant replication in larger GWAS datasets.

Fifth, for the depression–constipation analyses, both GWAS datasets were drawn from FinnGen, and potential participant overlap may bias estimates toward the observational association; the consistency of our estimates with MR studies using independent data sources [10–12] mitigates, but does not eliminate, this concern.

Sixth, colocalization was performed at the lead locus of each trait pair, and the evidence for depression and constipation was moderate (PP4 = 54.2%, below the conventional threshold of 0.8 for strong colocalization), with a weak regional association for constipation at the analysed locus. Posterior inference in colocalization analysis is known to be sensitive to the joint prior p12 [36]; consistent with this, PP4 for depression and constipation ranged from 10.6% to 87.0% across the prior sensitivity analyses. Moreover, colocalization assumes a single shared causal variant at the locus—an assumption we did not relax through conditioning or masking—and has limited power for binary traits with modest case

numbers, so the null finding for the FI–depression pair does not contradict the MR estimates, which aggregate effects across genome-wide instruments. These colocalization results should therefore be interpreted as supportive rather than definitive.

Seventh, the mediation analysis relied on the assumptions of no unmeasured mediator–outcome confounding and linear effects, which cannot be verified with summary-level data.

Finally, NHANES samples the non-institutionalized civilian population, and the GWAS data were restricted to European-ancestry populations; whether our findings extend to institutionalized older adults—among whom both frailty and constipation are more prevalent—and to non-European ancestries requires further study.

Conclusions

Frailty is associated with a higher burden of constipation in older adults, supported by convergent evidence from a nationally representative cross-sectional analysis and Mendelian randomization. Depression partially mediates the genetic effect of frailty on constipation, accounting for approximately one-fifth of the total effect, and colocalization analysis provides moderate support for a shared genetic basis of depression and constipation. These findings delineate a "frailty → depression → constipation" pathway, highlight depressive symptoms as a potentially modifiable intermediary, and support the integration of constipation screening and depression assessment into the routine care of frail older adults.

Abbreviations

BSFS, Bristol Stool Form Scale; CI, confidence interval; DPQ, Patient Health Questionnaire depression module; FI, frailty index; GWAS, genome-wide association study; ICD, International Classification of Diseases; IV, instrumental variable; IVW, inverse-variance weighted; MR, Mendelian randomization; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PIR, poverty-income ratio; PP4, posterior probability of hypothesis 4; SNP, single-nucleotide polymorphism; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

The NHANES protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics (Protocol #2005-06 and its continuations for subsequent cycles), and all participants provided written informed consent. The

GWAS summary statistics used in this study were obtained from previously published studies and public databases (IEU Open GWAS and FinnGen), in which ethical approval and participant consent had been obtained in the original studies. The present analysis used publicly available de-identified data and therefore required no additional ethical approval. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The NHANES data analyzed in this study are publicly available from the National Center for Health Statistics website (https://www.cdc.gov/nchs/nhanes/). The GWAS summary statistics were obtained from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/) and the FinnGen consortium under the following dataset identifiers: frailty index (ebi-a-GCST90020053), depression (finn-b-F5_DEPRESSIO), and constipation (finn-b-K11_CONSTIPATION). The analysis code is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SY curated the data, performed the statistical analyses, prepared the tables and figures, and drafted the manuscript. BZ, YC and ZR participated in the study design, data curation, and manuscript drafting. GZ and ZG conceived and designed the study and the analytic methodology, contributed to data curation and analysis, and critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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References

1. Barberio B, Judge C, Savarino EV, Ford AC. Global prevalence of functional constipation according to the Rome criteria: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(8):638–48. doi:10.1016/S2468-1253(21)00111-4.
2. Salari N, Ghasemianrad M, Ammari-Allahyari M, et al. Global prevalence of constipation in older adults: a systematic review and meta-analysis. Wien Klin Wochenschr. 2023;135(15–16):389–98. doi:10.1007/s00508-023-02156-w.
3. Gras-Miralles B, Cremonini F. A critical appraisal of lubiprostone in the treatment of chronic constipation in the elderly. Clin Interv Aging. 2013;8:191–200. doi:10.2147/CIA.S30729.
4. Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. Gastroenterology. 2020;158(5):1232–49.e3. doi:10.1053/j.gastro.2019.12.034.
5. Arco S, Saldaña E, Serra-Prat M, et al. Functional constipation in older adults: prevalence, clinical symptoms and subtypes, association with frailty, and impact on quality of life. Gerontology. 2022;68(4):397–406. doi:10.1159/000517212.
6. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62(7):722–7. doi:10.1093/gerona/62.7.722.
7. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75. doi:10.1016/S0140-6736(19)31786-6.
8. Liu X, Wang Y, Shen L, Sun Y, Zeng B, Zhu B, et al. Association between frailty and chronic constipation and chronic diarrhea among American older adults: National Health and Nutrition Examination Survey. BMC Geriatr. 2023;23(1):745. doi:10.1186/s12877-023-04438-4.
9. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: a systematic review and meta-analysis. Ageing Res Rev. 2017;36:78–87. doi:10.1016/j.arr.2017.03.005.
10. He Z, Yu Q, He B, Liu J, Gao W, Chen X. Can depression lead to chronic constipation, or does chronic constipation worsen depression? NHANES 2005–2010 and bidirectional Mendelian randomization analyses. BMC Gastroenterol. 2024;24(1):454. doi:10.1186/s12876-024-03454-x.
11. Guan X, Ni Q, Zhai Z, Sun Y, Zhang Y. Causal association between depression and constipation: a bidirectional two-sample Mendelian randomization study. Medicine (Baltimore). 2024;103(49):e40788. doi:10.1097/MD.0000000000040788.
12. Zheng Q, et al. Bidirectional associations of depression, anxiety, sleep disorders, and constipation: insights from Mendelian randomization. Arch Med Sci. 2025. doi:10.5114/aoms/207613.

13. Atkins JL, Jylhävä J, Pedersen NL, et al. A genome-wide association study of the frailty index highlights brain pathways in ageing. Aging Cell. 2021;20(9):e13459. doi:10.1111/acel.13459.
14. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23(R1):R89–98. doi:10.1093/hmg/ddu328.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7. doi:10.1016/S0140-6736(07)61602-X.
16. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. JAMA. 2021;326(16):1614–21. doi:10.1001/jama.2021.18236.
17. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National Health and Nutrition Examination Survey: plan and operations, 1999–2010. Vital Health Stat 1. 2013;(56):1–37.
18. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24. doi:10.1186/1471-2318-8-24.
19. Hakeem FF, Bernabé E, Sabbah W. Association between oral health and frailty among American older adults. J Am Med Dir Assoc. 2021;22(2):559–563.e2. doi:10.1016/j.jamda.2020.07.023.
20. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920–4. doi:10.3109/00365529709011203.
21. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150(6):1393–407. doi:10.1053/j.gastro.2016.02.031.
22. Camilleri M, Ford AC, Mawe GM, et al. Chronic constipation. Nat Rev Dis Primers. 2017;3:17095. doi:10.1038/nrdp.2017.95.
23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13. doi:10.1046/j.1525-1497.2001.016009606.x.
24. Lumley T. Analysis of complex survey samples. J Stat Softw. 2004;9(8):1–19. doi:10.18637/jss.v009.i08.
25. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613(7944):508–18. doi:10.1038/s41586-022-05473-8.
26. Auton A, Abecasis GR, Altshuler DM, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68–74. doi:10.1038/nature15393.
27. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81(3):559–75. doi:10.1086/519795.

28. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. eLife. 2018;7:e34408. doi:10.7554/eLife.34408.
29. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25. doi:10.1093/ije/dyv080.
30. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol. 2017;32(5):377–89. doi:10.1007/s10654-017-0255-x.
31. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40(4):304–14. doi:10.1002/gepi.21965.
32. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173–82. doi:10.1037/0022-3514.51.6.1173.
33. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. Int J Epidemiol. 2012;41(1):161–76. doi:10.1093/ije/dyr233.
34. Sanderson E. Multivariable Mendelian randomization and mediation. Cold Spring Harb Perspect Med. 2021;11(2):a038984. doi:10.1101/cshperspect.a038984.
35. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet. 2014;10(5):e1004383. doi:10.1371/journal.pgen.1004383.
36. Wallace C. A more accurate method for colocalisation analysis allowing for multiple causal variants. PLoS Genet. 2021;17(9):e1009440. doi:10.1371/journal.pgen.1009440.
37. Ye Y, Noche RB, Szejko N, et al. A genome-wide association study of frailty identifies significant genetic correlation with neuropsychiatric, cardiovascular, and inflammation pathways. GeroScience. 2023;45(4):2511–23. doi:10.1007/s11357-023-00771-z.
38. Camilleri M. Serotonin in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2009;16(1):53–9. doi:10.1097/MED.0b013e32831e9c8e.

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