

Table S1. The variables in the 48-item frailty index and their respective scoring criteria

Variable	Scoring
Cognition	
1. Experience confusion/memory problems	Yes = 1, No= 0
Dependence	
2. Managing money	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
3. Stooping, crouching, kneeling	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
4. Lifting or carrying	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
5. House chore Difficulty	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
6. Preparing meals	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
7. Standing up from armless chair	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
8. Getting in and out of bed difficulty	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
9. Using fork, knife, drinking from cup	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
10. Dressing yourself	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
11. Standing for long periods difficulty	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
12. Grasp/holding small objects	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
13. Attending social event	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
14. Push or pull large objects	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
15. Walking for a quarter mile difficulty	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
16. Walking up 10 steps difficulty	Difficulty = 1, Much difficulty = 0.66, Some difficulty = 0.33, No Difficulty = 0
Depressive Symptoms	
17. Have little interest in doing things	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0
18. Feeling down, depressed, or hopeless	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0
19. Trouble sleeping or sleeping too much	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0
20. Feeling tired or having little energy	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0
21. Poor appetite or overeating	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0
22. Feeling bad about yourself	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0
23. Trouble concentrating on things	Nearly every day = 1, More than half the days = 0.66, Several days = 0.33, Not at all= 0

Variable	Scoring
Comorbidities	
24. Arthritis	Yes = 1, No = 0
25. Thyroid problems	Yes = 1, No = 0
26. Chronic bronchitis	Yes = 1, No = 0
27. Cancer	Yes = 1, No = 0
28. Congestive heart failure	Yes = 1, No = 0
29. Coronary heart disease	Yes = 1, No = 0
30. Angina	Yes = 1, No = 0
31. Heart attack	Yes = 1, No = 0
32. Stroke	Yes = 1, No = 0
33. Blood pressure	Yes = 1, No = 0
34. Diabetes	Yes = 1, Suspect = 0.5 No = 0
35. weak/failing kidneys	Yes = 1, No = 0
36. Urinary Leakage	A few times a week, Every day and/or night = 1, Less than once a month, A few times a month = 0.5, Never = 0
Hospital Utilization and Access to Care	
37. Self-rated health	Fair, poor = 1, Excellent, Very good, good = 0
38. Health now compared with 1 year ago	Worse =1, About the same, better =0
39. Overnight hospital patient in past year	Yes =1, No =0
40. Frequency of health care use during past year	None =0, 1-3 =0.5, More than 3 =1
41. Number of prescribed medications	None =0, 1-4 =0.5, 5 and more =1
Physical Performance and Anthropometry	
42. Body mass index	<18.5, ≥ 30 = 1; 25-<30 = 0.5; 18.5-25 = 0
Laboratory Values	
43. Glycohemoglobin (%)	0%-5.7% =0, >5.7% =1
44. Red blood cell count (million cells/mL)	MALE: 4.7-6.1 =0, Other =1; FEMALE: 4.2-5.4 =0, Other =1
45. Hemoglobin (g/dL)	MALE: 13.5-18 =0, Other =1; FEMALE: 12-16 =0, Other =1
46. Red cell distribution width (%)	11.6-14.6 =0, Other =1
47. Lymphocyte percent (%)	20-40 =0, Other =1
48. Segmented neutrophils percent (%)	40-80 =0, Other =1

Table S2. Sensitivity analysis A: association between frailty and constipation using alternative frailty index definitions (NHANES 2005–2010, n = 4,333)

Exposure	Model	OR	95% CI	<i>P</i> -value
FI-48, binary (≥ 0.21 vs < 0.21)	1 (crude)	1.704	1.289–2.254	< 0.001
	4 (fully adjusted)	1.363	1.009–1.841	0.044
FI-41, binary (≥ 0.21 vs < 0.21)	1 (crude)	1.713	1.331–2.203	< 0.001
	4 (fully adjusted)	1.376	1.051–1.801	0.022
FI-48, continuous (per 0.1)	1 (crude)	1.294	1.188–1.410	< 0.001
	4 (fully adjusted)	1.169	1.055–1.295	0.004
FI-41, continuous (per 0.1)	1 (crude)	1.256	1.151–1.371	< 0.001
	4 (fully adjusted)	1.146	1.033–1.270	0.012

Note: Model 1: unadjusted. Model 4: adjusted for age, sex, race/ethnicity, educational attainment, poverty-income ratio, smoking status, and alcohol use. For continuous frailty indices, odds ratios are expressed per 0.1-unit increase in the frailty index. Estimates for Models 2 and 3 lay between those of Models 1 and 4 (data not shown). OR, odds ratio; CI, confidence interval; FI, frailty index.

Table S3. Sensitivity analysis B: associations between depressive symptoms and constipation, and joint analysis with the 41-item frailty index (NHANES 2005–2010).

Exposure	Model	OR	95% CI	<i>P</i> -value
Depressive-symptom score, per 1-point increase	Model 1 (crude)	1.243	1.133–1.364	<0.001
	Model 4 (fully adjusted)	1.153	1.037–1.283	0.010
Any depressive symptom vs. None	Model 1 (crude)	1.847	1.387–2.460	<0.001
	Model 4 (fully adjusted)	1.530	1.145–2.044	0.005
Low (0–1] vs. None	Model 1 (crude)	1.666	1.253–2.215	<0.001
	Model 4 (fully adjusted)	1.460	1.082–1.969	0.015
High (>1) vs. None	Model 1 (crude)	2.153	1.433–3.237	<0.001
	Model 4 (fully adjusted)	1.644	1.080–2.501	0.022
Joint model: FI-41, per 0.1-unit increase	Model 1 (crude)	1.189	1.056–1.339	0.005
Joint model: depressive-symptom score, per 1-point	Model 1 (crude)	1.151	1.011–1.310	0.034
Joint model: FI-41, per 0.1-unit increase	Model 4 (fully adjusted)	1.100	0.963–1.256	0.153
Joint model: depressive-symptom score, per 1-point	Model 4 (fully adjusted)	1.107	0.963–1.272	0.146

Note: Model 1: unadjusted. Model 4: adjusted for age, sex, race/ethnicity, educational attainment, poverty-income ratio, smoking status, and alcohol use. The depressive-symptom score was calculated as the mean of completed DPQ items (each scored 0, 0.33, 0.66, or 1) multiplied by 7 (range 0–7); odds ratios for the score are expressed per one-point increase, and odds ratios for the 41-item frailty index (FI-41) are expressed per 0.1-unit increase. In joint models, FI-41 and the depressive-symptom score were mutually adjusted. The three-category variable (0, >0 to 1, >1) was defined a priori based on the score distribution and interpretability, not on clinical thresholds. Estimates for Models 2 and 3 lay between those of Models 1 and 4 (data not shown). All analyses incorporated the NHANES complex sampling design and examination weights; one participant with missing data on all seven DPQ items was excluded (*n* = 4,332); OR, odds ratio; CI, confidence interval; FI, frailty index; DPQ, Patient Health Questionnaire depression module.

Table S4. Mendelian randomization analysis results for the bidirectional associations between Frailty index, Depression, and Constipation.

Pathway	Method	nSNP	β (95% CI)	SE	OR (95% CI)	P-value
Frailty index on Depression	Inverse variance weighted	14	0.729 (0.417 to 1.040)	0.159	2.072 (1.518- 2.830)	4.53e-06*
	MR Egger	14	0.790 (-0.679 to 2.259)	0.750	2.204 (0.507- 9.576)	0.313
	Weighted median	14	0.792 (0.392 to 1.193)	0.204	2.209 (1.480- 3.297)	1.05e-04*
	Simple mode	14	0.995 (0.068 to 1.923)	0.473	2.706 (1.070- 6.844)	0.056
	Weighted mode	14	0.864 (-0.161 to 1.889)	0.523	2.372 (0.851- 6.611)	0.123
Depression on Constipation	Inverse variance weighted	36	0.092 (0.008 to 0.176)	0.043	1.096 (1.008- 1.192)	0.032*
	MR Egger	36	0.057 (-0.140 to 0.255)	0.101	1.059 (0.869- 1.290)	0.573
	Weighted median	36	0.069 (-0.052 to 0.189)	0.062	1.071 (0.949- 1.208)	0.265
	Simple mode	36	0.025 (-0.266 to 0.316)	0.149	1.026 (0.766- 1.372)	0.866
	Weighted mode	36	0.032 (-0.273 to 0.338)	0.156	1.033 (0.761- 1.402)	0.838
Frailty index on Constipation	Inverse variance weighted	14	0.351 (0.030 to 0.672)	0.164	1.420 (1.030- 1.958)	0.032*
	MR Egger	14	-0.333 (-1.796 to 1.129)	0.746	0.716 (0.166- 3.093)	0.663
	Weighted median	14	0.424 (0.017 to 0.830)	0.207	1.528 (1.017- 2.294)	0.041*
	Simple mode	14	0.726 (-0.038 to 1.491)	0.390	2.067 (0.963- 4.440)	0.085
	Weighted mode	14	0.621 (-0.376 to 1.618)	0.509	1.861 (0.686- 5.045)	0.244
Constipation on Depression	Inverse variance weighted	29	0.135 (0.052 to 0.218)	0.043	1.145 (1.053- 1.244)	0.002*
	MR Egger	29	0.160 (-0.020 to 0.340)	0.092	1.174 (0.981- 1.405)	0.092
	Weighted median	29	0.029 (-0.073 to 0.131)	0.052	1.030 (0.930- 1.140)	0.573
	Simple mode	29	-0.015 (-0.248 to 0.218)	0.119	0.985 (0.780- 1.243)	0.899
	Weighted mode	29	-0.015 (-0.242 to 0.211)	0.116	0.985 (0.785- 1.235)	0.897
Depression on Frailty index	Inverse variance weighted	39	0.024 (-0.003 to 0.051)	0.014	—	0.077
	MR Egger	39	-0.043 (-0.099 to 0.013)	0.029	—	0.142
	Weighted median	39	0.036 (0.006 to 0.067)	0.016	—	0.019*
	Simple mode	39	0.059 (-0.003 to 0.122)	0.032	—	0.071
	Weighted mode	39	0.049 (-0.020 to 0.119)	0.035	—	0.172
Constipation on Frailty index	Inverse variance weighted	25	0.006 (-0.014 to 0.026)	0.010	—	0.554
	MR Egger	25	0.009 (-0.027 to 0.045)	0.019	—	0.629
	Weighted median	25	0.007 (-0.024 to 0.038)	0.016	—	0.645
	Simple mode	25	-0.005 (-0.124 to 0.115)	0.061	—	0.941
	Weighted mode	25	-0.001 (-0.129 to 0.128)	0.065	—	0.994

Note: nSNP, number of instrumental single nucleotide polymorphisms; β , regression coefficient; SE, standard error; OR, odds ratio; 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-values for MR-Egger were derived from a t-distribution with nsnp-2 degrees of freedom, and those for the mode-based estimators from a t-distribution with nsnp - 1 degrees of freedom, as implemented in TwoSampleMR; consequently, mode-based P-values may not correspond exactly to normal-approximation confidence intervals; *P-value < 0.05.

Table S5. Steiger directionality tests for the Mendelian randomization pathways.

Pathway	SNP r^2 (exposure)	SNP r^2 (outcome)	Correct causal direction	Steiger P
Frailty index → Depression	0.0032	0.0004	TRUE	7.1×10^{-30}
Depression → Constipation	0.0088	0.0007	TRUE	4.2×10^{-112}
Frailty index → Constipation	0.0032	0.0002	TRUE	1.5×10^{-38}
Constipation → Depression	0.0069	0.0005	TRUE	1.4×10^{-91}

Note: SNP r^2 denotes the proportion of variance in the trait explained by the instrumental variables. P values are from Steiger's test comparing the SNP–exposure and SNP–outcome correlations. For the continuous frailty index, correlations were derived from effect estimates and standard errors (get_r_from_bsen; $N = 175,226$). For binary traits, correlations were derived using get_r_from_lor with case/control sample sizes of 23,424/192,220 for depression and 17,246/201,526 for constipation; allele frequencies were taken from the harmonised data where exposure-specific frequencies were unavailable.

Table S6. Bayesian colocalization results for the depression–constipation and frailty index–depression trait pairs.

Trait pair	Locus (lead variant)	Window	nSNP	PP.H0	PP.H1	PP.H2	PP.H3	PP.H4
Depression–Constipation	chr11: 43,918,222 (rs187821300)	±500 kb	5,555	0.004	0.329	0.002	0.124	0.542
Depression–Constipation	chr11: 43,918,222 (rs187821300)	±250 kb	3,045	0.004	0.347	0.001	0.075	0.572
Frailty index–Depression	chr6: 32,652,620 (rs9275160)	±500 kb	8,123	<0.001	0.709	<0.001	0.249	0.042
Frailty index–Depression	chr6: 32,652,620 (rs9275160)	±250 kb	4,319	<0.001	0.845	<0.001	0.105	0.050

Prior sensitivity analysis: PP.H4 under different values of the joint prior p12 (±500-kb window).

Trait pair	p12 = 1×10^{-6}	p12 = 5×10^{-6}	p12 = 1×10^{-5} (default)	p12 = 5×10^{-5}
Depression–Constipation	0.106	0.372	0.542	0.855
Frailty index–Depression	0.004	0.021	0.042	0.180

Note: Analyses included all SNPs within the indicated window of the lead variant, without P-value filtering or linkage-disequilibrium pruning. H0, no association with either trait; H1, association with the first trait only; H2, association with the second trait only; H3, association with both traits but distinct causal variants; H4, association with both traits and a shared causal variant. PP, posterior probability. The main analysis used the default priors ($p_1 = 1 \times 10^{-4}$, $p_2 = 1 \times 10^{-4}$, $p_{12} = 1 \times 10^{-5}$). nSNP, number of shared SNPs in the region.

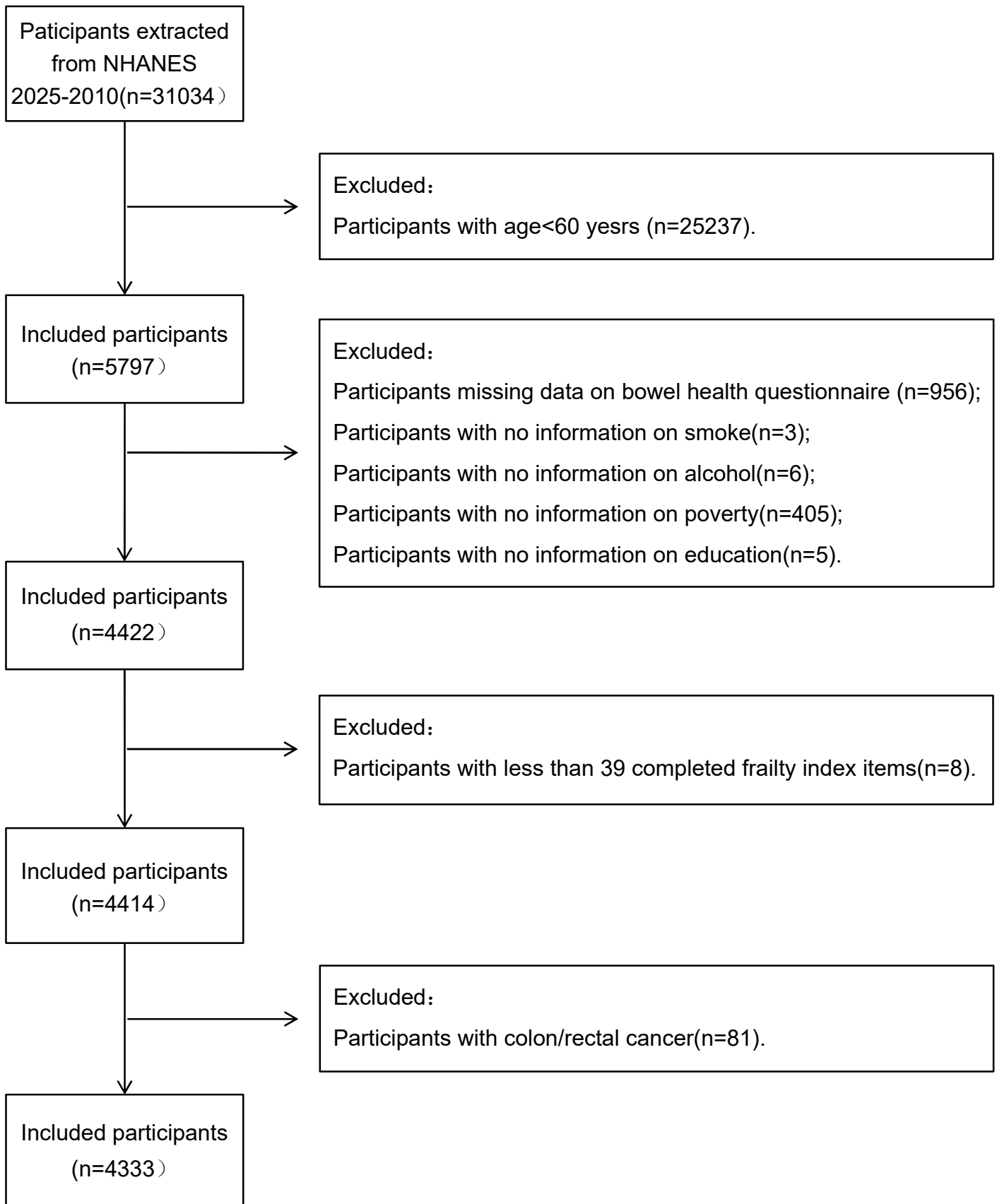


Figure S1. Flowchart of the sample selection from NHANES 2005-2010

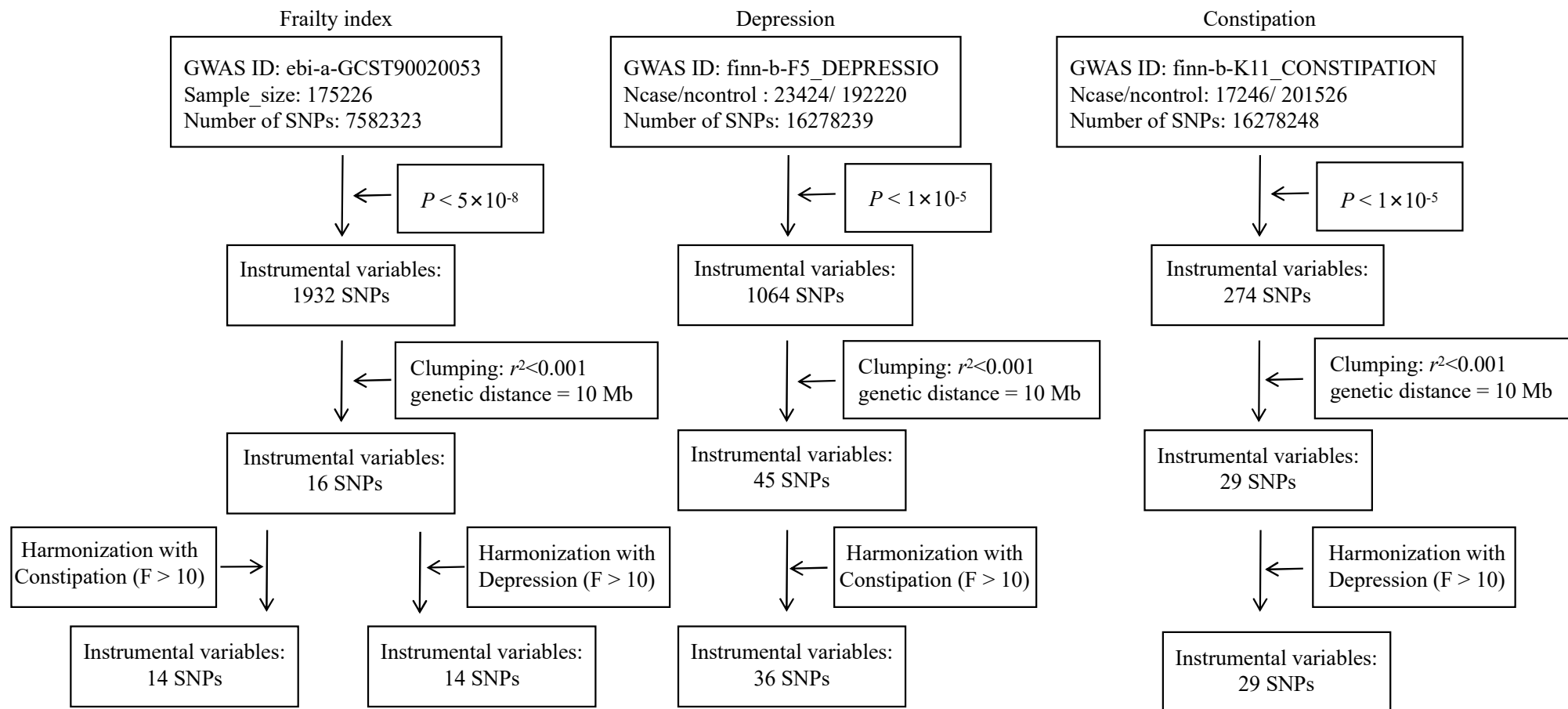


Figure S2. Flowchart of SNP screening and inclusion for Mendelian randomization analysis.

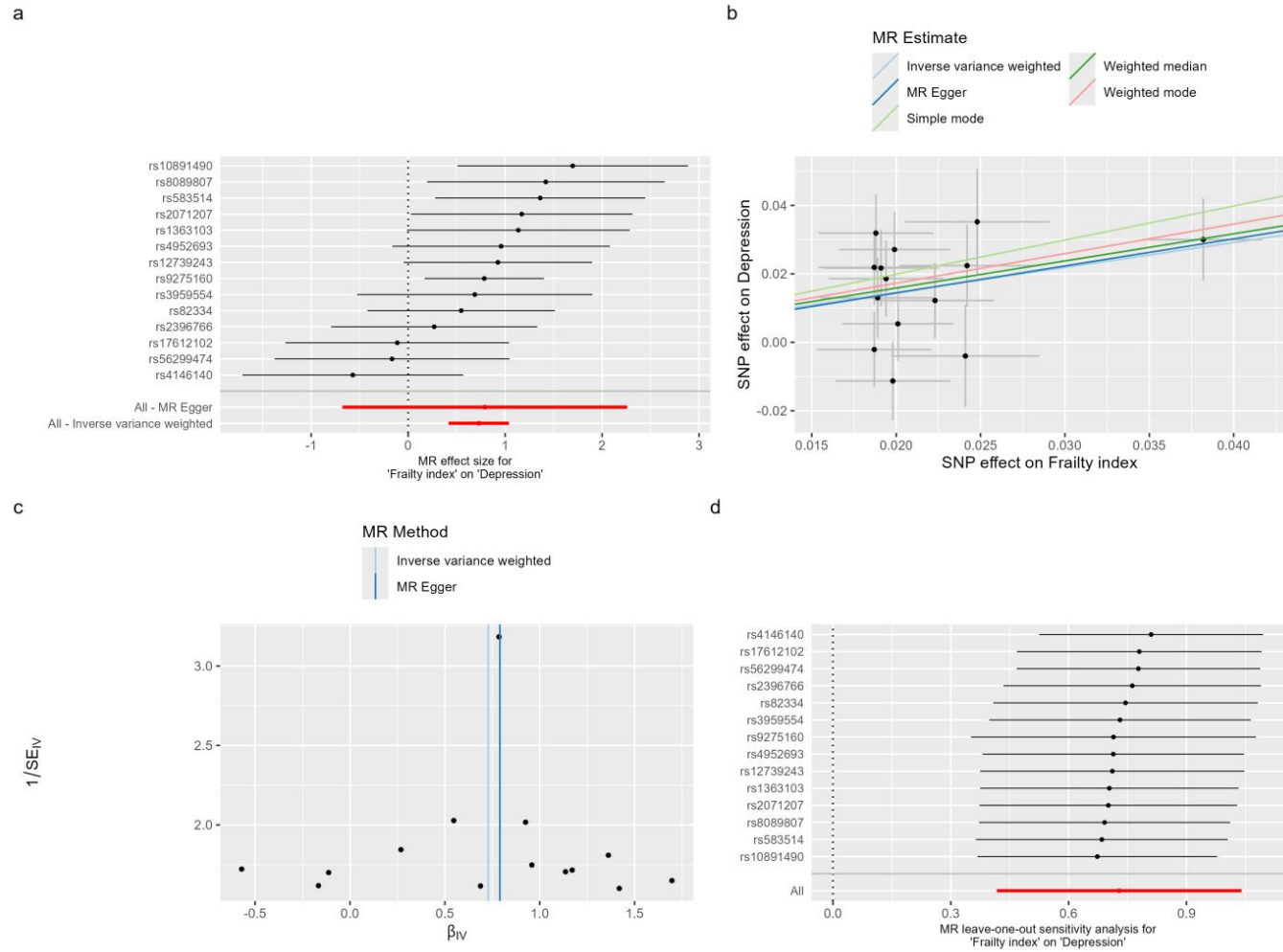


Figure S3. Mendelian randomization diagnostics for the effect of the Frailty index on Depression. (a) Forest plot: points represent SNP-specific estimates and horizontal lines represent 95% confidence intervals; the bottom rows show the overall inverse-variance-weighted and MR-Egger estimates. (b) Scatter plot of SNP effects on the Frailty index (x-axis) and on Depression (y-axis); lines represent the fitted slopes of the five MR methods. (c) Funnel plot of SNP-specific estimates against their precision, used to assess directional horizontal pleiotropy. (d) Leave-one-out analysis: each point represents the inverse-variance-weighted estimate after removing the indicated SNP; the bottom row (All) shows the overall estimate.

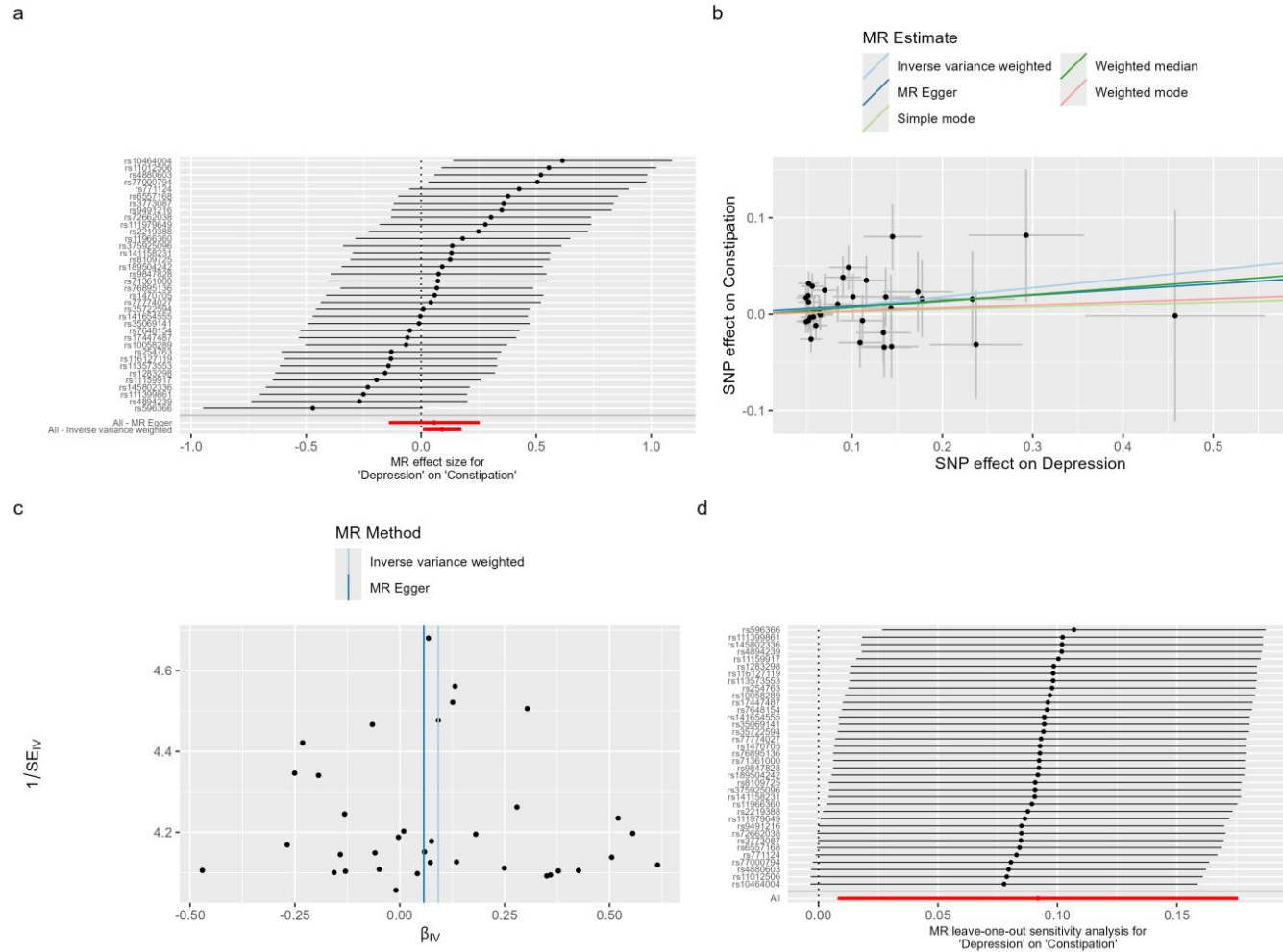


Figure S4. Mendelian randomization diagnostics for the effect of the Depression on Constipation. (a) Forest plot: points represent SNP-specific estimates and horizontal lines represent 95% confidence intervals; the bottom rows show the overall inverse-variance-weighted and MR-Egger estimates. (b) Scatter plot of SNP effects on the Depression (x-axis) and on Constipation (y-axis); lines represent the fitted slopes of the five MR methods. (c) Funnel plot of SNP-specific estimates against their precision, used to assess directional horizontal pleiotropy. (d) Leave-one-out analysis: each point represents the inverse-variance-weighted estimate after removing the indicated SNP; the bottom row (All) shows the overall estimate.

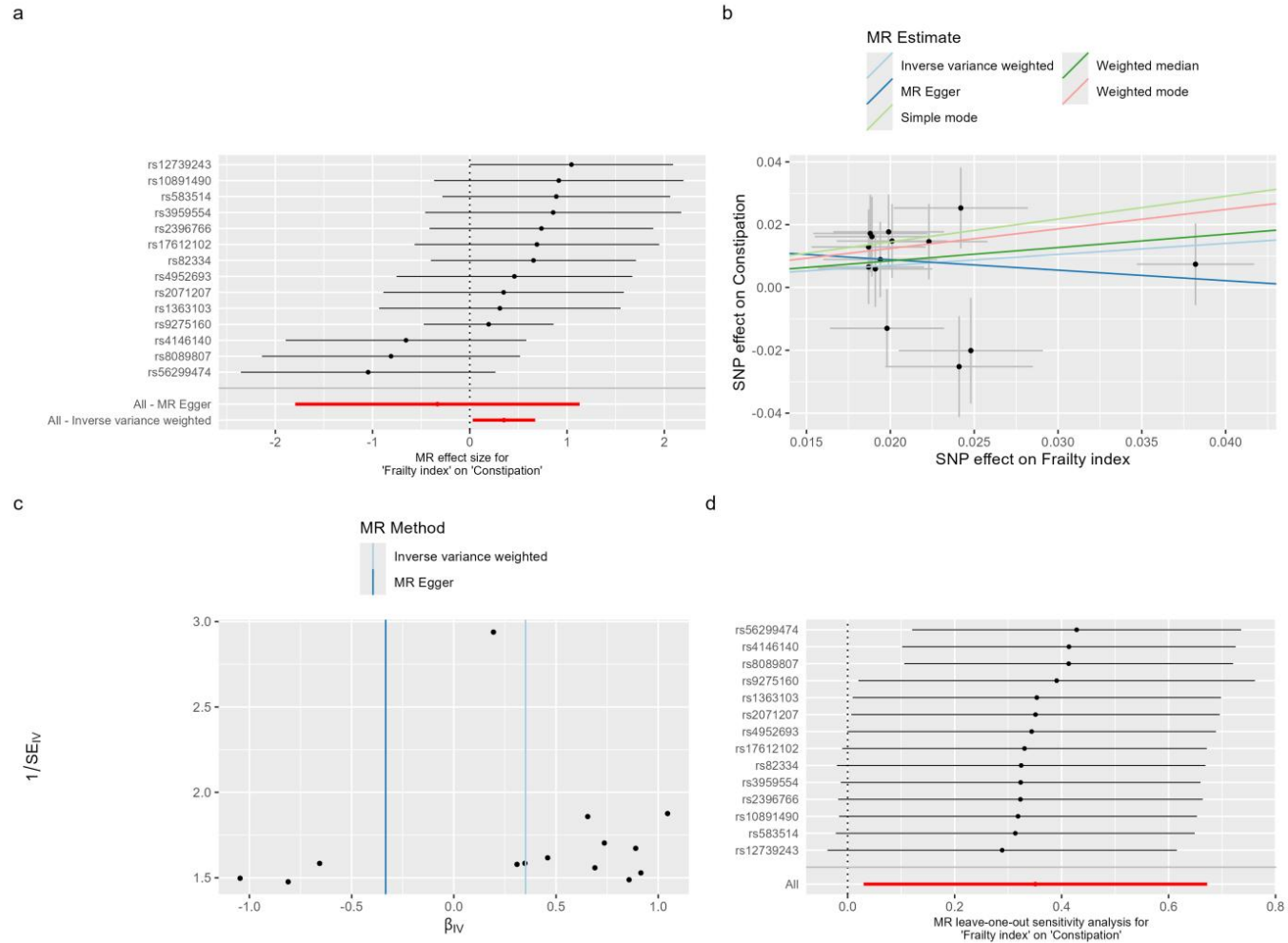


Figure S5. Mendelian randomization diagnostics for the effect of the Frailty index on Constipation. (a) Forest plot: points represent SNP-specific estimates and horizontal lines represent 95% confidence intervals; the bottom rows show the overall inverse-variance-weighted and MR-Egger estimates. (b) Scatter plot of SNP effects on the Frailty index (x-axis) and on Constipation (y-axis); lines represent the fitted slopes of the five MR methods. (c) Funnel plot of SNP-specific estimates against their precision, used to assess directional horizontal pleiotropy. (d) Leave-one-out analysis: each point represents the inverse-variance-weighted estimate after removing the indicated SNP; the bottom row (All) shows the overall estimate.

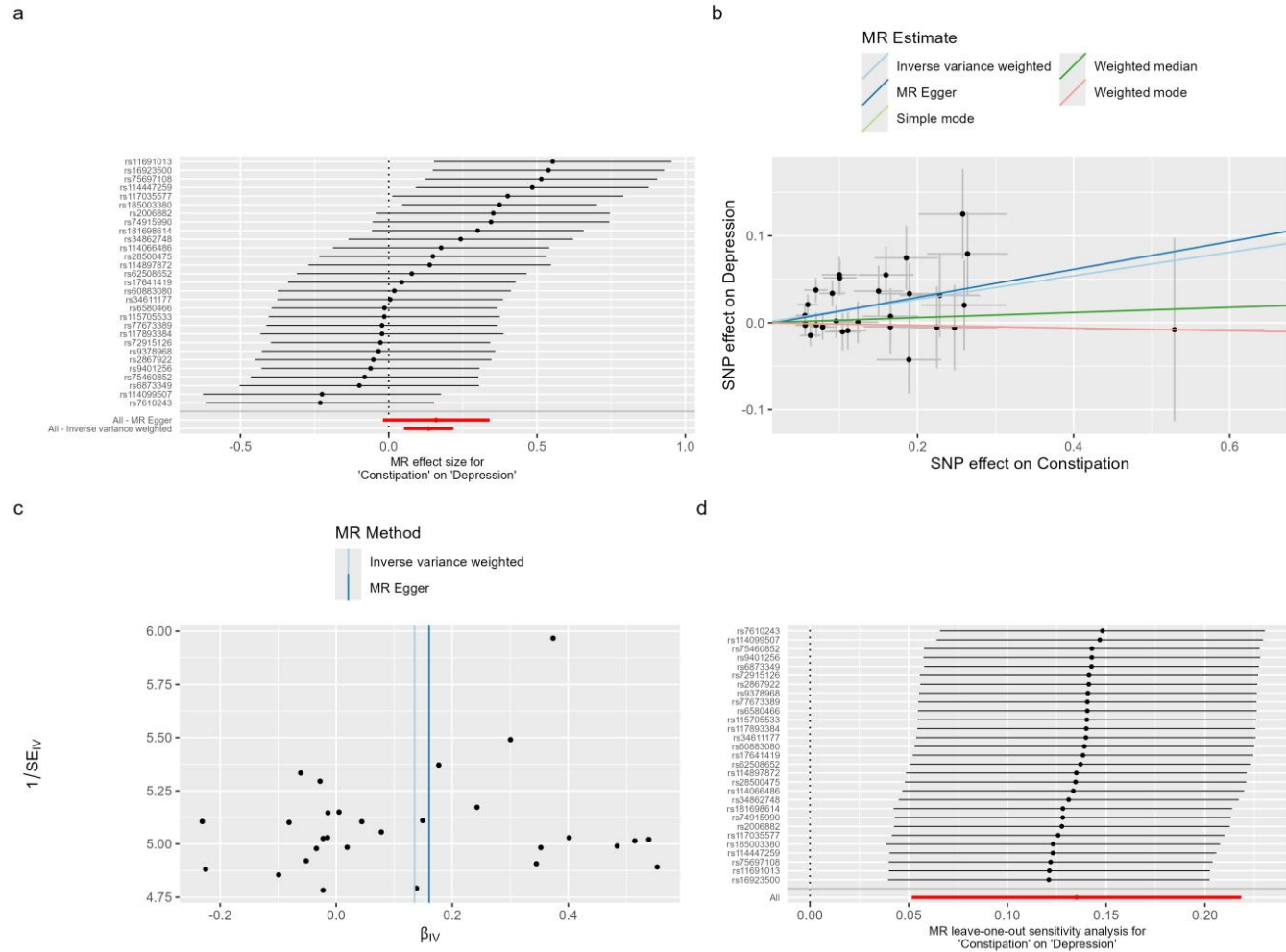


Figure S6. Mendelian randomization diagnostics for the effect of the Constipation on Depression. (a) Forest plot: points represent SNP-specific estimates and horizontal lines represent 95% confidence intervals; the bottom rows show the overall inverse-variance-weighted and MR-Egger estimates. (b) Scatter plot of SNP effects on the Constipation (x-axis) and on Depression (y-axis); lines represent the fitted slopes of the five MR methods. (c) Funnel plot of SNP-specific estimates against their precision, used to assess directional horizontal pleiotropy. (d) Leave-one-out analysis: each point represents the inverse-variance-weighted estimate after removing the indicated SNP; the bottom row (All) shows the overall estimate.