Frailty status and risk of irritable bowel syndrome in middle-aged and older adults: A large-scale prospective cohort study

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Summary

Background Frailty is a public health problem for ageing society, however, evidence is lacking regarding its impact on intestinal functions. We aimed to examine prospective relationships of frailty and pre-frailty in middle-aged and older adults with incident irritable bowel syndrome (IBS) in a large-scale population-based cohort.

Methods Participants (aged 37–73 years) free of IBS, coeliac disease, inflammatory bowel disease and any cancer at baseline were included, using data from the UK Biobank (collected 2006–2010, 22 assessment centres). Participants without available primary care data were excluded. Frailty status was assessed using Fried phenotype including five criteria (weight loss, exhaustion, low grip strength, low physical activity, slow walking pace). Participants who met at least three criteria were defined as frail, and those who fulfilled one or two criteria were defined as pre-frail. Primary outcome was incident IBS. Cox proportional hazard model was conducted to examine the associated risk of incident IBS.

Findings Among 176,423 participants (mean age 56.19 years), 7994 (4.5%) and 78,957 (44.8%) were frail and pre-frail at baseline. During a median of 13.2-year follow-up, 4155 cases of incident IBS were identified. Compared with non-frail individuals, those with frail (HR = 1.80, 95% CI: 1.59–2.04) and pre-frail (HR = 1.21, 1.14–1.30) showed significantly higher risk of developing IBS after multivariable adjustment (P_{trend} < 0.001). Specifically, the positive association was not only observed in older adults (HR = 1.69, 1.37–2.08 for frail; 1.24, 1.12–1.39 for pre-frail), but also in middle-aged adults (HR = 1.90, 1.62–2.22 for frail; 1.19, 1.10–1.30 for pre-frail), both with P_{trend} < 0.001. Further sensitivity analysis and subgroup analysis indicated similar results.

Interpretation Frailty and pre-frailty in middle-aged and older adults are associated with increased risk of incident clinical diagnosis of IBS.

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Keywords: Frailty; Irritable bowel syndrome; Cohort study; Geriatric populations

Introduction

Irritable bowel syndrome (IBS), as one of the most common disorders of gut-brain interaction, is estimated to affect around 1 in 10 people globally.[1] It is characterised by recurrent abdominal pain in association with defecation and/or change in bowel habits without any organic lesions.[2] As a chronic condition, IBS results in impaired health-related quality of life and significant healthcare cost to both patients and the whole society.[3,4] Given the rapidly ageing population and increased

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Research in context

Evidence before this study

We searched PubMed, Embase, Cochrane Library, Google Scholar and China National Knowledge Infrastructure for studies published in English and Chinese from inception to September 1st, 2022. We used the search terms "irritable bowel syndrome", "IBS", "gut-brain disorder", "gut-brain axis", "gastrointestinal disorders", "frail", "pre-frail", "older adults" or "middle-aged". Given the rapidly aging population and increased lifespan, the number of older adults with irritable bowel syndrome (IBS) is rising, with a prevalence of 9.7% and 7.5% in middle-aged and older adults, respectively. Frailty is a major public health problem for aging society. Several lines of evidence support a potential link between frailty and IBS due to the shared pathophysiological mechanisms. However, evidence is lacking regarding the impact of frailty on risk of IBS in middle-aged and older adults.

Added value of this study

For the first time, we found that older adults with frail and pre-frail were associated with 1.80 and 1.21-fold higher risk of IBS compared with non-frail. Moreover, middle-aged adults with frail and pre-frail had 1.69 and 1.24-fold excess risk of IBS in comparison to non-frail participants, respectively. An 18% and 21% increased risk was associated with per 1 frailty score change in middle-aged and older adults, respectively.

Implications of all the available evidence

Interventions aimed at improving frailty of middle-aged and older adults may be a potential targeted strategy for the detection, diagnosis and treatment of IBS. Further studies are warranted to confirm our findings in diverse ethnic populations and assess the causality between frailty or pre-frailty and IBS.

lifespan, the number of older adults with IBS is rising, with a prevalence of 9.7% and 7.5% in middle-aged and older adults, respectively.[1] Hence, there is a pressing need to understand geriatric constructs, identify contributing factors and help develop targeted prevention strategies in older adults with IBS.

Frailty is a major public health problem for ageing society, defined as a complex geriatric state of physiological reserve decline and increased vulnerability to adverse health outcomes, which is associated with ageing but independent of age.[5] Approximately 7–20% of older adults are identified as frail, and prevalence in middle-aged adults is similar.[6–8] Intriguing emerging data supports a potential link between frailty and IBS due to the shared plausible mechanisms, including elevated proinflammatory cytokines (i.e., tumor necrosis factor (TNF)-α, interleukin (IL)-6), altered gut microbiota composition, senescence-induced perturbations of gut-brain axis, increased intestinal permeability and impaired gut motility.[9–12] However, to date, there is a considerable lack of epidemiological evidence on whether frailty could increase the risk of IBS in older adults. Additionally, the long-term risk of IBS in middle-aged adults with frailty remains to be answered yet, since identification and intervention of frailty earlier, particularly in middle age, might have great implications on reducing IBS burden.[8]

To address these knowledge gaps, we aimed to examine the prospective association between frailty and risk of incident IBS in middle-aged and older adults from a large long-term follow-up UK cohort.

Methods

Study population

The ongoing large-scale prospective cohort, UK Biobank (UKB), recruited 520,461 participants aged 37–73 years from 22 assessment centres across England, Wales and Scotland between 2006 and 2010. All participants completed baseline questionnaires with anthropometric assessments, and reported medical conditions.[13]

Participants who were free of IBS with available frailty assessment at recruitment were included. Those who had previous cancer, inflammatory bowel disease (IBD) or coeliac disease diagnosis prior to baseline were excluded. All baseline diagnosis were identified through International Classification of Disease-10 (ICD-10) codes (Table S1). Moreover, given that frailty is strongly associated with hospital admission and also that IBS would rarely be the sole reason for an inpatient hospital episode, those with baseline frailty may be considerably more likely to have IBS identified where only hospital data is available. Thus, an additional 218,987 participants without available primary care data were further excluded in order to avoid detection bias. Additionally, 51 participants who withdrew inform content was excluded. Hence, the final analytic cohort included 176,423 participants (Flowchart of participant selection, Fig. 1).

Ethics

The UKB study was approved by the North West Multicenter Research Ethical Committee e (21/NW/0157), and all participants or their proxy respondents provided written informed consent.[14]

Assessment of baseline frailty

Frailty was assessed by Fried phenotype, one of the most leading conceptual models of quantifying frailty, including five criteria (weight loss, exhaustion, low grip strength, low physical activity, slow walking pace).[7,15]

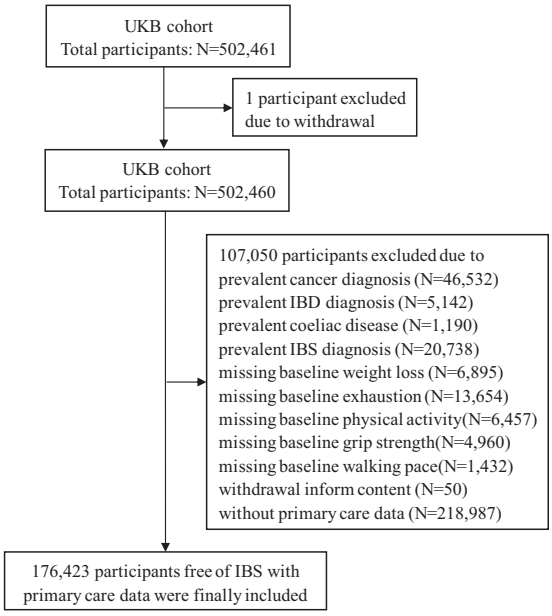

Fig. 1: Flowchart of the study population. IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; UKB: UK Biobank.

Grip strength was measured using Jamar J00105 hydraulic hand dynamometer, and lower value of two hands' measurements was used. Low grip strength was defined according to sex and body-mass index (BMI) adjusted cutoffs.[7] Other four variables included in frailty phenotype were defined based on online touchscreen questionnaire. Question for weight loss ["Compared with one year ago, has your weight changed?"] was asked. Participants' response of "Yes, lost weight" was considered as weight loss, other responses including "No, weigh about the same" and "Yes, gained weight" were considered not. Regarding question for exhaustion ["Over the past two weeks, how often have you felt tired or had little energy?"], participants who selected "More than half the days" or "Nearly every day" were classified as exhaustion, whereas those who selected "Not at all" or "Several days" were considered not. Regarding question for walking pace ["How would you describe your usual walking pace?"], participants who answered "Slow pace" instead of "Steady average pace" or "Brisk pace" were defined as slow walking pace. For measurement of physical activity ["In the last 4 weeks did you spend any time doing the following?"], participants' responses were classified into: none (no physical activity), low (light DIY activity, i.e., pruning, watering lawn), medium (heavy DIY activity, i.e., weeding, lawn mowing, carpentry and digging; walking for pleasure, or other exercises including swimming, cycling, keep fit, bowling) and high (strenuous sports). Then another question ["How many times in the last 4 weeks did you do light DIY?"] was asked. Participants who reported none or light activity with a frequency of once per week or less were considered as low physical activity.

Participants who met at least three criteria were defined as frail (i.e., frailty score 3–5), and those who fulfilled one or two criteria were defined as pre-frail (i.e., frailty score 1–2). Those who met none of the criteria were classified as non-frail as reference group (i.e., frailty score = 0).

Outcome ascertainment

Primary endpoint was incident IBS during follow-up period with censoring date of May 2022. Since all participants included were with available primary care data, incident IBS diagnosis was ascertained through ICD-10 codes (K58, Table S1), with majority based on linkage to primary care using Read codes (J521., J5210, J5211, J5212) in addition to minority based on linkage to hospital admission using ICD-10 codes. However, it has been proved that using Read codes may lead to under identification of IBS.[16]

Covariates

Covariates were selected based on previous epidemiological evidence and data availability at baseline.[6,9,10,15] Potential confounders included age (continuous), sex (male, female), ethnicity (white or nonwhite), BMI (18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2), socioeconomic status, education level, smoking status (never, current, previous), alcohol drinking (never, current, previous), type 2 diabetes (Yes, No), depression (Yes, No) and anxiety (Yes, No). Socioeconomic status was assessed via Townsend deprivation index (quartiles), calculated immediately prior to participant joining UKB using preceding national census output areas. Education was based on self-report of highest qualification achieved and classified as university or non-university.

Statistical analysis

The 13-year cumulative incidence of IBS was calculated via Kaplan–Meier method. Cox proportional hazard model was conducted to examine the association between frailty and incident IBS. The follow-up period started from baseline to date of first IBS diagnosis, or censored at end of study (May 2022), date of death or lost-to-follow-up for participants who did not develop IBS. Considering very small percentage (0.1%–0.9%) of missing values for all covariates, missing indicators were used.

For both frailty status (frail, pre-frail, non-frail) and frailty score (continuous variable), three adjustment models in addition to univariable analysis were performed: (1) model 1, adjusted for age and sex; (2) model 2, additionally adjusted for Townsend deprivation index, education level, ethnicity, BMI, smoking status and

alcohol drinking; (3) model 3, additionally adjusted for type 2 diabetes, depression and anxiety. Tests for trend were performed by assigning median frail score value (0, 1 and 3) of each frailty status and modeling this value as continuous variable, using Wald test to assess statistical significance. Moreover, the association was examined not only in overall population, but also in older (age ≥ 60 years) and middle-aged adults (age < 60 years), in order to assess long-term impact of frailty on IBS risk.

Furthermore, either in overall population, older or middle-aged adults, subgroup analysis was performed to investigate whether the association between frailty and IBS varied by sex, BMI (18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2), alcohol drinking (never, previous, current) and smoking status (never, previous, current). Effect modification was tested by adding interaction terms of each stratified variable and frailty (frailty status or frailty score).

In sensitivity analyses, we excluded participants who had IBS diagnosis within 1 or 2 years after recruitment respectively, in order to avoid detection bias. Secondly, competing risk model by considering lost-to-follow-up and death as competing events were conducted, since those participants might develop IBS thereafter. Thirdly, in order to avoid differential misclassification bias for IBS diagnosis, we also conducted analysis by only considering those incident IBS diagnosed via primary care source (i.e., those incident IBS cases diagnosed through hospital admission or self-report were considered as non-IBS). Additionally, the above sensitivity analyses were conducted for both frailty status (frail, pre-frail, non-frail) and frailty score (continuous variable). Furthermore, since grip strength was the only objective measure of frailty, we also investigated the risk of incident IBS associated with quartiles of baseline grip strength.

All statistical tests were 2-sided, with a P value <0.05 indicating statistical significance. All analyses were conducted using SAS software Version 9.4 and R version 4.0.2 (forestplot, tableone, ggplot2 and survival packages).

Role of the funding sources

The sponsors had no role in the study design, data collection, data analysis, results interpretation and writing of the report.

Results

Baseline characteristics

Among 176,423 participants (mean age 56.19 years), 48.1% were male. Of which, 73,142 (41.5%) and 103,281 (58.5%) were older and middle-aged adults, with mean (SD) age at enrollment 64.05 (2.84) and 50.63 (5.60) years, respectively. Overall, 7994 (4.5%) and 78,957 (44.8%) were frail and pre-frail at baseline. There were 3718 (5.1%) cases of frail and 35,601 (48.7%) of pre-frail in older adults, whereas 4276 (4.1%) cases of frail and 43,356 (42.0%) of pre-frail in middle-aged adults. Participants with frail and pre-frail were more likely to be female, have a lower education level, lower level of socioeconomic deprivation, higher BMI and a higher proportion of prevalent diabetes, depression and anxiety (Table 1, Tables S2 and S3). Baseline characteristics according to frailty status in older and middle-aged adults were listed in Tables S2 and S3, respectively. Median follow-up period was 13.2 years (interquartile range: 12.6–14.1 years).

Frailty and incident IBS risk

During a total of 2,268,525 person-years' follow-up, 4155 incident IBS cases were identified. The 13-year cumulative incidence of IBS was 4.5% (95% CI: 4.1–5.0%) in frail and 2.6% (2.5–2.7%) in pre-frail group versus 2.0% (1.9–2.1%) in non-frail group. Frail (HR = 1.80, 95% CI: 1.59–2.04) and pre-frail (HR = 1.21, 1.14–1.30) were associated with significantly higher risk of developing IBS after multivariable adjustment (P_{trend} < 0.001, Table 2). Moreover, an 20% increased risk was associated with per 1 frailty score change (Table S4).

In older adults, totally 1543 incident IBS developed during 923,945 person-years' follow-up. The 13-year cumulative incidence of IBS was 3.6% (3.0–4.2%) in frail, 2.4% (2.2-2.5%) in pre-frail and 1.8% (1.7–1.9%) in non-frail group. Compared with non-frail individuals, those with frail and pre-frail showed separately 1.69 (1.37–2.08) and 1.24-fold (1.12–1.39) risk of incident IBS (P_{trend} < 0.001, Table 2). Specifically, an 18% excess risk was associated with per 1 frailty score change (HR = 1.18, 1.12–1.25, Table S4).

In middle-aged adults, 2612 IBS cases occurred during 1,344,580 person-years' follow-up. The 13-year cumulative incidence of IBS was 5.3% (4.6-6.0%) in frail, 2.8% (2.6–2.9%) in pre-frail and 2.1% (2.0–2.3%) in non-frail group. Compared with non-frail, both frail (HR = 1.90, 1.62–2.22) and pre-frail (HR = 1.19, 1.10–1.30) were associated with higher risk of IBS (P_{trend} < 0.001, Table 2). Meanwhile, higher risk was also observed with per 1 frailty score change (HR = 1.21, 1.16–1.26, Table S4).

Subgroup analysis

The higher IBS risk associated with frail and pre-frail in overall population, older adults and middle-aged adults, were generally observed across sex, BMI, smoking and alcohol drinking subgroups (Figs. 2 and 3, Figs. S2 and S3). Moreover, significant interactions across sex and frailty status were observed, with higher risk in female for both overall population ($P_{interaction}$ = 0.005) and middle-aged adults ($P_{interaction}$ = 0.029).

Characteristic	Total (N = 176,423)	Non-frail (N = 89,472)	Pre-frail (N = 78,957)	Frail (N = 7994)	P value
Age (years)[a]	56.19 ± 8.09	55.49 ± 8.07	56.86 ± 8.07	57.52 ± 7.72	<0.001
Sex					<0.001
Male	84,910 (48.1)	45,621 (51.0)	36,021 (45.6)	3268 (40.9)	
Female	91,513 (51.9)	43,851 (49.0)	42,936 (54.4)	4726 (59.1)	
Ethnicity					<0.001
Non-White	7915 (4.5)	2539 (2.8)	4465 (5.7)	911 (11.4)	
White	168,033 (95.2)	86,716 (96.9)	74,266 (94.1)	7051 (88.2)	
Unknown	475 (0.3)	217 (0.2)	226 (0.3)	32 (0.4)	
Education level					<0.001
Non-university	116,291 (65.9)	54,871 (61.3)	54,916 (69.6)	6504 (81.4)	
University	58,599 (33.2)	34,051 (38.1)	23,206 (29.4)	1342 (16.8)	
Unknown	1533 (0.9)	550 (0.6)	835 (1.1)	148 (1.9)	
Townsend deprivation index					
Mean (SD)	−1.39 (3.00)	−1.79 (2.77)	−1.12 (3.09)	0.42 (3.49)	<0.001
Q1 (≤−3.63)	44,958 (25.5)	25,881 (28.9)	18,043 (22.9)	1034 (12.9)	<0.001
Q2 (−3.63 to −2.12)	44,749 (25.4)	24,285 (27.1)	19,156 (24.3)	1308 (16.4)	
Q3 (−2.12 to 0.58)	44,968 (25.5)	22,388 (25.0)	20,603 (26.1)	1977 (24.7)	
Q4 (>0.58)	41,479 (23.5)	16,795 (18.8)	21,036 (26.6)	3648 (45.6)	
Unknown	269 (0.2)	123 (0.1)	119 (0.2)	27 (0.3)	
Smoking status					<0.001
Never	97,457 (55.2)	51,212 (57.2)	42,609 (54.0)	3636 (45.5)	
Previous	60,073 (34.1)	30,029 (33.6)	27,366 (34.7)	2678 (33.5)	
Current	18,385 (10.4)	8038 (9.0)	8720 (11.0)	1627 (20.4)	
Unknown	508 (0.3)	193 (0.2)	262 (0.3)	53 (0.7)	
Alcohol drinking					<0.001
Never	7234 (4.1)	2506 (2.8)	3888 (4.9)	840 (10.5)	
Previous	5926 (3.4)	2003 (2.2)	3109 (3.9)	814 (10.2)	
Current	163,120 (92.5)	84,928 (94.9)	71,872 (91.0)	6320 (79.1)	
Unknown	143 (0.1)	35 (0.0)	88 (0.1)	20 (0.3)	
BMI					<0.001
<18.5 kg/m^2	764 (0.4)	368 (0.4)	351 (0.4)	45 (0.6)	
18.5–24.9 kg/m^2	53,841 (30.5)	33,173 (37.1)	19,493 (24.7)	1175 (14.7)	
25.0–29.9 kg/m^2	76,639 (43.4)	40,109 (44.8)	34,059 (43.1)	2471 (30.9)	
≥30 kg/m^2	45,179 (25.6)	15,822 (17.7)	25,054 (31.7)	4303 (53.8)	
Frailty indicators					<0.001
Weight loss	27,078 (15.3)	0 (0.0)	23,637 (29.9)	3441 (43.0)	
Exhaustion	21,007 (11.9)	0 (0.0)	15,759 (20.0)	5248 (65.6)	
Low physical activity	15,214 (8.6)	0 (0.0)	10,235 (13.0)	4979 (62.3)	
Slow walking pace	13,169 (7.5)	0 (0.0)	7389 (9.4)	5780 (72.3)	
Low grip strength	48,455 (27.5)	0 (0.0)	41,638 (52.7)	6817 (85.3)	
Diabetes	4981 (2.8)	1168 (1.3)	2836 (3.6)	977 (12.2)	<0.001
Depression	16,368 (9.3)	5902 (6.6)	8686 (11.0)	1780 (22.3)	<0.001
Anxiety	7767 (4.4)	3150 (3.5)	3975 (5.0)	642 (8.0)	<0.001

Note: Numbers are n (%) unless otherwise stated. BMI: body mass index. [a]Displayed as mean ± standard deviation.

Table 1: **Baseline characteristics according to baseline frailty status in the UK Biobank cohort.**

Similarly, consistent subgroup findings associated with per 1 frailty score change were observed (Figs. S3–S5). Significant modification effects by sex were both detected in overall population ($P_{interaction}$ = 0.005) and middle-aged adults ($P_{interaction}$ = 0.008), with greater risk of IBS in female.

Sensitivity analysis

Results of sensitivity analysis by frailty status and frailty score, were all consistent with principal findings either in older adults or in middle-aged adults, when excluding incident IBS cases within 1 year or 2 years after baseline, performing competing risk model, or only

	Non-frail	Pre-frail	Frail	P for trend
Overall population (N = 176,423)				
No. of participants	89,472	78,957	7994	
No. of incident IBS	1776	2029	350	
Follow-up, person-years	1,163,767	1,007,867	96,891	
Follow-up, years				
Median (IQR)	13.3 (12.6–14.1)	13.1 (12.4–14.0)	13.0 (12.1–14.0)	
Hazard ratio for incident IBS (95% CI, P value)				
Unadjusted	Reference	1.31 (1.23–1.39, P < 0.001)	2.31 (2.06–2.59, P < 0.001)	<0.001
Adjusted model 1	Reference	1.29 (1.21–1.37, P < 0.001)	2.22 (1.98–2.49, P < 0.001)	<0.001
Adjusted model 2	Reference	1.26 (1.18–1.34, P < 0.001)	2.04 (1.80–2.30, P < 0.001)	<0.001
Adjusted model 3	Reference	1.21 (1.14–1.30, P < 0.001)	1.80 (1.59–2.04, P < 0.001)	<0.001
Older adults, age ≥60 (N = 73,142)				
No. of participants	33,823	35,601	3718	
No. of incident IBS	596	821	126	
Hazard ratio for incident IBS (95% CI, P value)				
Unadjusted	Reference	1.33 (1.19–1.47, P < 0.001)	2.05 (1.69–2.48, P < 0.001)	<0.001
Adjusted model 1	Reference	1.27 (1.14–1.41, P < 0.001)	1.93 (1.59–2.34, P < 0.001)	<0.001
Adjusted model 2	Reference	1.28 (1.15–1.43, P < 0.001)	1.90 (1.55–2.33, P < 0.001)	<0.001
Adjusted model 3	Reference	1.24 (1.12–1.39, P < 0.001)	1.69 (1.37–2.08, P < 0.001)	<0.001
Middle-aged adults, age <60 (N = 103,281)				
No. of participants	55,649	43,356	4276	
No. of incident IBS	1180	1208	224	
Hazard ratio for incident IBS (95% CI, P value)				
Unadjusted	Reference	1.32 (1.22–1.43, P < 0.001)	2.55 (2.21–2.94, P < 0.001)	<0.001
Adjusted model 1	Reference	1.30 (1.20–1.40, P < 0.001)	2.42 (2.10–2.79, P < 0.001)	<0.001
Adjusted model 2	Reference	1.24 (1.15–1.35, P < 0.001)	2.16 (1.85–2.51, P < 0.001)	<0.001
Adjusted model 3	Reference	1.19 (1.10–1.30, P < 0.001)	1.90 (1.62–2.22, P < 0.001)	<0.001

Note: Adjusted model 1: Age and sex were adjusted; Adjusted model 2: Townsend deprivation index, education level, ethnicity, BMI, smoking status and alcohol drinking were additionally adjusted; Adjusted model 3: type 2 diabetes, depression and anxiety were additionally adjusted; P for trend was calculated by using median frail score value (0, 1 and 3) of each frailty status. IBS: irritable bowel syndrome; IQR: inter-quartile range.

Table 2: **Risk of IBS associated with baseline frailty status.**

considering those incident IBS diagnosed via primary care source (Table 3, Table S5). Moreover, the increased risk of incident IBS was also observed with lower quartiles of baseline grip strength (Table 4).

Discussion

In this nationwide, population-based prospective cohort with long-term follow-up of nearly 0.2 million adults, we demonstrated for the first time that older adults with frailty and pre-frailty had a 1.80 and 1.21-fold increased risk of IBS occurrence, and an 20% excess risk was associated with per 1 frailty score change. Similar increased IBS risk was detected in middle-aged adults. Furthermore, the positive association was evident in most subgroup analysis. These findings are of considerable value given the rapidly growing burden of geriatric population worldwide and high prevalence of frailty as well as pre-frailty.

Considering the potential adverse impact of frailty and pre-frailty on IBS occurrence, screening frailty may have important implications for the detection, diagnosis and treatment of IBS. Assessment of frailty in older adults might facilitate the early identification of participants at greater risk, which in turn, may benefit from the more accurate targeting of multidimensional interventions and reduce the risk of incident IBS accordingly. To date, several feasible interventions aimed at improving core strength have been proved helpful for both prevention and improvement of frailty in older adults, such as exercise, physical therapy, adequate diet and nutrition interventions.[17,18] Meanwhile, screening pre-frailty may also be helpful given the high prevalence of pre-frailty not only in older adults but also in middle-aged adults.[8,15] Since frailty status is a modifiable process with transitions among being frail, pre-frail and non-frail over time, identifying those with pre-frail early may have more profound public health significance for IBS occurrence.[19] However, causality cannot be inferred from these findings of a potential association between frailty or pre-frailty and IBS. Currently, there is no data suggesting that modifying

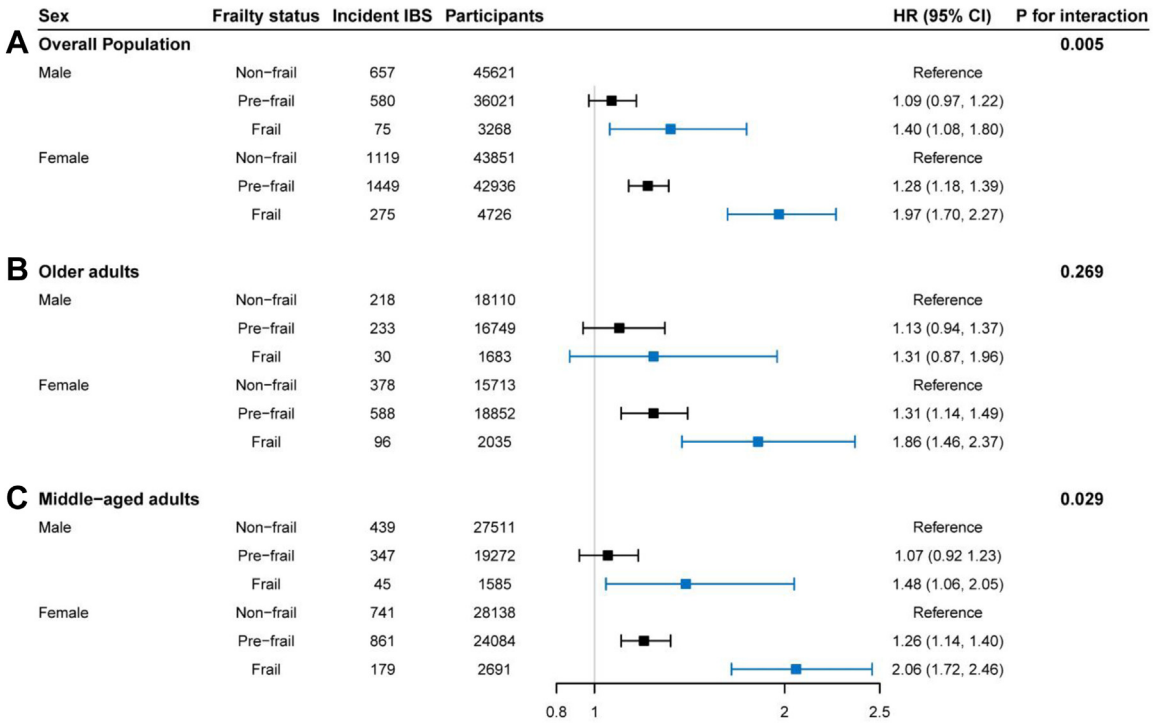

Fig. 2: Association of baseline frailty status with incident IBS by sex. (A). Overall population; (B). Older adults; (C). Middle-aged adults. Note: All HRs were calculated by adjusting age, Townsend deprivation index, education level, ethnicity, BMI, smoking status, alcohol drinking, type 2 diabetes, depression and anxiety. IBS: irritable bowel syndrome; HR: hazard ratio. CI: confidence interval.

frailty or pre-frailty would necessarily reverse or prevent IBS, which remains to be confirmed.

Although the exact biological mechanisms for positive association of frailty with incident IBS remain elusive, recent evidence suggests the complex interplay between frailty and inflammation along with cellular senescence may play important roles.[20–22] Previous studies have demonstrated the upregulation of the proinflammatory cytokines (i.e., TNF-α, IL-6) in older adults both with frailty and pre-frailty, which are associated with impaired intestinal epithelial barrier, and may accordingly facilitate the development of IBS symptoms.[20–22] Another plausible explanation might be the occurrence of impaired intestinal permeability accompanied by ageing and frailty. Increasing evidence indicated the important alternations of tight junction proteins (i.e., elevated zonulin and claudin-2, decreased ZO-1 and occluding) associated with frailty, which in turn, may lead to disturbed epithelial permeability and further susceptibility of IBS.[9,23] Despite these recent promising advances, data are still very limited and more investigation is needed to further clarify related underlying mechanisms.

In addition, intriguing emerging evidence suggests that the alternation of gut microbiota composition associated with frailty and pre-frailty may also be linked to the development of IBS.[9,12,24–26] It has been reported an inverse association between frailty and α-diversity of gut microbiota in older adults, with lower abundance of lactobacilli and *Faecalibacterium prausnitzii* in individuals with high frailty score.[9,24,25] Moreover, similar microbial alternations associated with frailty were also examined in middle-aged individuals.[26] As the common gut microbiota in healthy adults, lactobacilli and *F. prausnitzii* have been proved playing pivotal role on the maintenance of intestinal barrier integrity and balance of the intestinal immune response.[27] As a result, these microbial alternations may be involved in the long-term pathogenesis of IBS via the adverse impact on intestinal permeability, intestinal motility and visceral hypersensitivity. Besides, frailty-related dysfunction of gut-brain axis may also contribute to the onset of IBS via complex interaction between gut microbiota and central, autonomic along with enteric nervous systems, since IBS has been considered as one of the common gut-brain disorders.[9,28] Nevertheless, further clarification is yet to be made regarding the potential role of gut microbiota alternations and gut-brain axis dysfunction in the relationship between frailty and IBS occurrence.

One worthy to be noted, given the inaccuracies in coding of IBS relying on routinely collected data and the well-established relationship between frailty and healthcare utilization, participants with frailty are likely to be more frequent users of healthcare in general, and

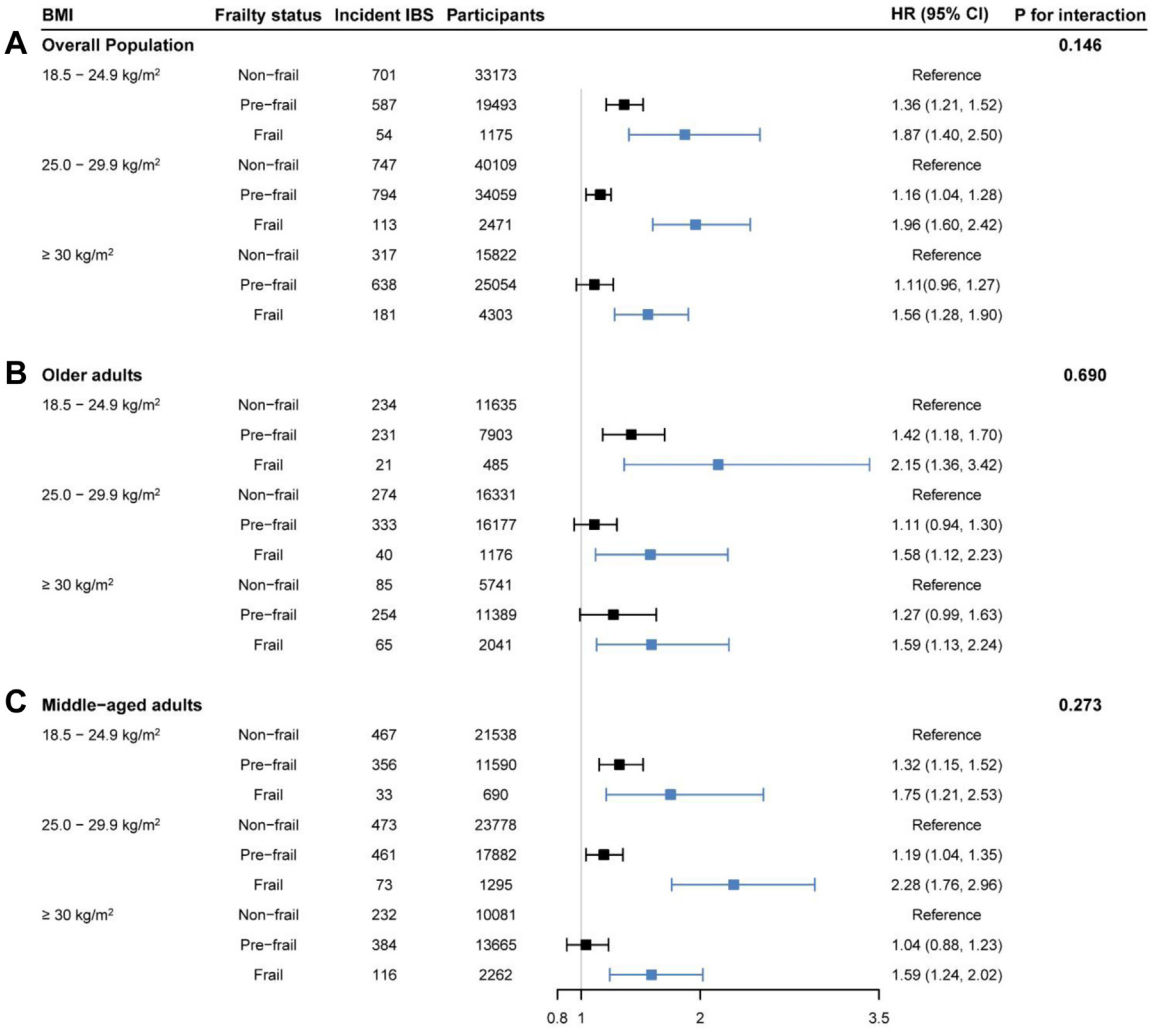

Fig. 3: Association of baseline frailty status with incident IBS by BMI. (A). Overall population; (B). Older adults; C. Middle-aged adults. Note: All HRs were calculated by adjusting age, sex, Townsend deprivation index, education level, ethnicity, smoking status, alcohol drinking, type 2 diabetes, depression and anxiety. CI: confidence interval; HR: hazard ratio; IBS: irritable bowel syndrome.

therefore potentially more likely to have IBS diagnoses coded.[15,29,30] Thus, it may further lead to differential misclassification bias, which would favor the findings in the direction of positive association. However, considering the under-identification of IBS in primary care as well as detection bias particularly in hospital admission data, risk estimates may prone to be conservative if we only considered those diagnosed via primary care source as incident IBS.[16] Since such sensitivity analysis still confirmed this positive association, our findings seemed more convincing. Nonetheless, further prospective studies are needed to confirm the findings.

The major novelty of the current study is to highlight the long-term risk of incident IBS associated with frailty in middle-aged and older adults for the first time, based on the well-designed longitudinal cohort. The large sample size of 103,281 middle-aged adults and 73,142 older adults allowed substantial subgroup analysis by sex, BMI, smoking and alcohol drinking available with sufficient statistical power, and the results were all consistent. Furthermore, many important lifestyle and psychological confounders, including sex, alcohol, smoking, socioeconomic status, type 2 diabetes, depression and anxiety, were thoroughly adjusted. Additionally, rigorous sensitivity analyses by accounting for protopathic bias and misclassification bias, and further assessment of frailty in different approaches (i.e., frailty status, frailty score) were conducted, verifying robustness of principal results.

Potential limitations also need to be considered. Firstly, frailty phenotype was assessed through the adapted Fried criteria, based on a mix of self-reported

Frailty status	No. of IBS	No. of participants	HR (95% CI)	P value	P for trend
Overall population					
Sensitivity analysis 1: excluding IBS participants diagnosed within 1 year after baseline (N = 175,914)					
Non-frail	1571	89,267	Reference		<0.001
Pre-frail	1769	78,697	1.19 (1.11–1.28)	<0.001	
Frail	306	7950	1.78 (1.56–2.04)	<0.001	
Sensitivity analysis 2: excluding IBS participants diagnosed within 2 years after baseline (N = 175,430)					
Non-frail	1346	89,042	Reference		<0.001
Pre-frail	1546	78,474	1.22 (1.13–1.31)	<0.001	
Frail	270	7914	1.83 (1.59–2.11)	<0.001	
Sensitivity analysis 3: competing risk model (N = 176,423, No. of competing events = 10,118)					
Non-frail	1776	89,472	Reference		<0.001
Pre-frail	2029	78,957	1.21 (1.13–1.29)	<0.001	
Frail	350	7994	1.76 (1.55–2.00)	<0.001	
Sensitivity analysis 4: only considered those diagnosed with IBS through primary care as incident IBS (N = 176,423)					
Non-frail	1207	89,472	Reference		<0.001
Pre-frail	1298	78,957	1.16 (1.07–1.26)	<0.001	
Frail	187	7994	1.46 (1.24–1.72)	<0.001	
Older adults, age ≥60					
Sensitivity analysis 1: excluding IBS participants diagnosed within 1 year after baseline (N = 72,972)					
Non-frail	532	33,759	Reference		<0.001
Pre-frail	729	35,509	1.24 (1.10–1.39)	<0.001	
Frail	112	3704	1.69 (1.36–2.10)	<0.001	
Sensitivity analysis 2: excluding IBS participants diagnosed within 2 years after baseline (N = 72,780)					
Non-frail	452	33,679	Reference		<0.001
Pre-frail	634	35,414	1.28 (1.13–1.45)	<0.001	
Frail	95	3687	1.73 (1.36–2.19)	<0.001	
Sensitivity analysis 3: competing risk model (N = 73,142, No. of competing events = 7168)					
Non-frail	596	33,823	Reference		<0.001
Pre-frail	821	35,601	1.24 (1.11–1.38)	<0.001	
Frail	126	3718	1.62 (1.32–2.00)	<0.001	
Sensitivity analysis 4: only considered those diagnosed with IBS through primary care as incident IBS (N = 73,142)					
Non-frail	371	33,823	Reference		<0.001
Pre-frail	501	35,601	1.22 (1.06–1.40)	0.005	
Frail	72	3718	1.53 (1.17–2.00)	0.002	
Middle-aged adults, age <60					
Sensitivity analysis 1: excluding IBS participants diagnosed within 1 year after baseline (N = 102,942)					
Non-frail	1039	55,508	Reference		<0.001
Pre-frail	1040	43,188	1.17 (1.07–1.27)	0.001	
Frail	194	4246	1.87 (1.59–2.21)	<0.001	
Sensitivity analysis 2: excluding IBS participants diagnosed within 2 years after baseline (N = 102,650)					
Non-frail	894	55,363	Reference		<0.001
Pre-frail	912	43,060	1.18 (1.07–1.30)	0.001	
Frail	175	4227	1.93 (1.62–2.30)	<0.001	

(Table 3 continues on next page)

Frailty status	No. of IBS	No. of participants	HR (95% CI)	P value	P for trend
(Continued from previous page)					
Sensitivity analysis 3: competing risk model (N = 103,281, No. of competing events = 2950)					
Non-frail	1180	55,649	Reference		<0.001
Pre-frail	1208	43,356	1.19 (1.10–1.30)	<0.001	
Frail	224	4276	1.88 (1.60–2.20)	<0.001	
Sensitivity analysis 4: only considered those diagnosed with IBS through primary care as incident IBS (N = 103,281)					
Non-frail	836	55,649	Reference		<0.001
Pre-frail	797	43,356	1.13 (1.02–1.25)	0.017	
Frail	115	4276	1.44 (1.17–1.77)	0.001	

Note: All HRs were calculated by adjusting the following covariates: age, sex, Townsend deprivation index, education level, ethnicity, BMI, smoking status, alcohol drinking, type 2 diabetes, depression and anxiety. P for trend was calculated by using median frail score value of (0, 1 and 3) of each frailty status. CI: confidence interval; HR: hazard ratio; IBS: irritable bowel syndrome.

Table 3: **Sensitivity analysis regarding risk of IBS associated with baseline frailty status.**

(i.e., exhaustion, walking pace, weight loss and physical activity) and objective (i.e., grip strength) measurements.[7] Thus, it might lead to potential measurement error in the ascertainment of frailty due to some subjective symptoms, particularly for those middle-aged adults. However, it has been proved as a valid measure of frailty phenotype in the UK Biobank.[15] Moreover, our sensitivity analysis also demonstrated the inverse association between incident IBS and quartiles of baseline grip strength (i.e., the objective measure of frailty), making the results more convincing. Secondly, frailty is a dynamic process with transitions between frail, pre-frail and non-frail over time. However, the current study only measured it once at baseline, making the investigation of long-term incident IBS risk associated with longitudinal variation of frailty unavailable. Thirdly, although participants without available primary care data were excluded, the use of hospital admission data to identify minority of incident IBS cases may still bias the results as hospital admission may be a prerequisite for outcome (incident IBS) identification. Hence, risk estimates would be attenuated and toward to the null if we only considered those diagnosed via primary care source as incident IBS. Nevertheless, results of such sensitivity analysis still indicated the increased risk of IBS associated with frailty, which

Baseline grip strength	No. of IBS	No. of participants	HR (95% CI)	P value	P for trend
Overall population (N = 176,423)					<0.001
Q1 (grip ≤ 21 kg)	1512	45,787	Reference		
Q2 (21 kg < grip ≤ 28 kg)	1209	45,880	0.84 (0.78–0.91)	<0.001	
Q3 (28 kg < grip ≤ 38 kg)	844	45,929	0.76 (0.69, 0.85)	<0.001	
Q4 (grip > 38 kg)	590	38,827	0.74 (0.65, 0.85)	<0.001	
Older adults, age ≥60 (N = 73,142)					0.009
Q1 (grip ≤ 21 kg)	678	22,780	Reference		
Q2 (21 kg < grip ≤ 28 kg)	382	15,694	0.90 (0.79–1.02)	0.108	
Q3 (28 kg < grip ≤ 38 kg)	302	19,471	0.81 (0.68, 0.97)	0.020	
Q4 (grip > 38 kg)	181	15,197	0.73 (0.58, 0.91)	0.006	
Middle-aged adults, age <60 (N = 103,281)					<0.001
Q1 (grip ≤ 21 kg)	766	20,778	Reference		
Q2 (21 kg < grip ≤ 28 kg)	688	22,927	0.84 (0.76–0.92)	<0.001	
Q3 (28 kg < grip ≤ 38 kg)	641	29,254	0.75 (0.66, 0.85)	<0.001	
Q4 (grip > 38 kg)	517	30,322	0.72 (0.61, 0.85)	<0.001	

Note: All HRs were calculated by adjusting the following covariates: age, sex, Townsend deprivation index, education level, ethnicity, BMI, smoking status, alcohol drinking, type 2 diabetes, depression and anxiety. P for trend was calculated by using median baseline grip strength value (18, 25, 34 and 44 kg) of each quartile group. CI: confidence interval; HR: hazard ratio; IBS: irritable bowel syndrome.

Table 4: **Sensitivity analysis regarding risk of IBS associated with quartiles of baseline grip strength.**

instead supported our positive associations. Fourthly, residual confounders might still exist as some potential covariates, either unmeasured or unknown, may confound the relationship between frailty and IBS, although we have carefully controlled for numerous potential confounders, such as psychological elements. Finally, since our study was conducted in UK general population with most White ethnicity, it is unclear whether our results can be generalised to other populations or other ethnicities. Future long-term follow-up cohort studies in different populations with diverse ethnicities are warranted to confirm our findings.

In summary, frailty and pre-frailty in middle-aged and older adults were significantly associated with increased risk of incident clinical diagnosis of IBS. Relevant guidelines should incorporate these findings into disease management pathways, which might have implications for reducing IBS burden in addition to providing novel and interesting insights for future studies. Further prospective studies in diverse ethnic populations are warranted to confirm our findings and elucidate the underlying mechanisms.

Contributors

S.W. and S.Zhu. designed the study. S.W. drafted the manuscript. S.W. and Q.Z. accessed and verified the underlying data. Z.Y. and S.L. revised the manuscript. S.W., Z.Y., Q.Z., S.Zhang, S.L. and S.Zhu. interpreted the results, incorporated comments for the co-authors and finalised the manuscript. All authors approved the final version of the paper.

Data sharing statement

All data relevant to the study were acquired from the UK Biobank Resource under application number 74444. No additional data available.

Declaration of interests

The authors declare no conflict of interest.

Acknowledgements

This research has been conducted using the UK Biobank Resource under application number [74444].

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101807.

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