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Causal association and genetic correlation of frailty with metabolic dysfunction-associated steatotic liver disease: Epidemiological and genetic analyses

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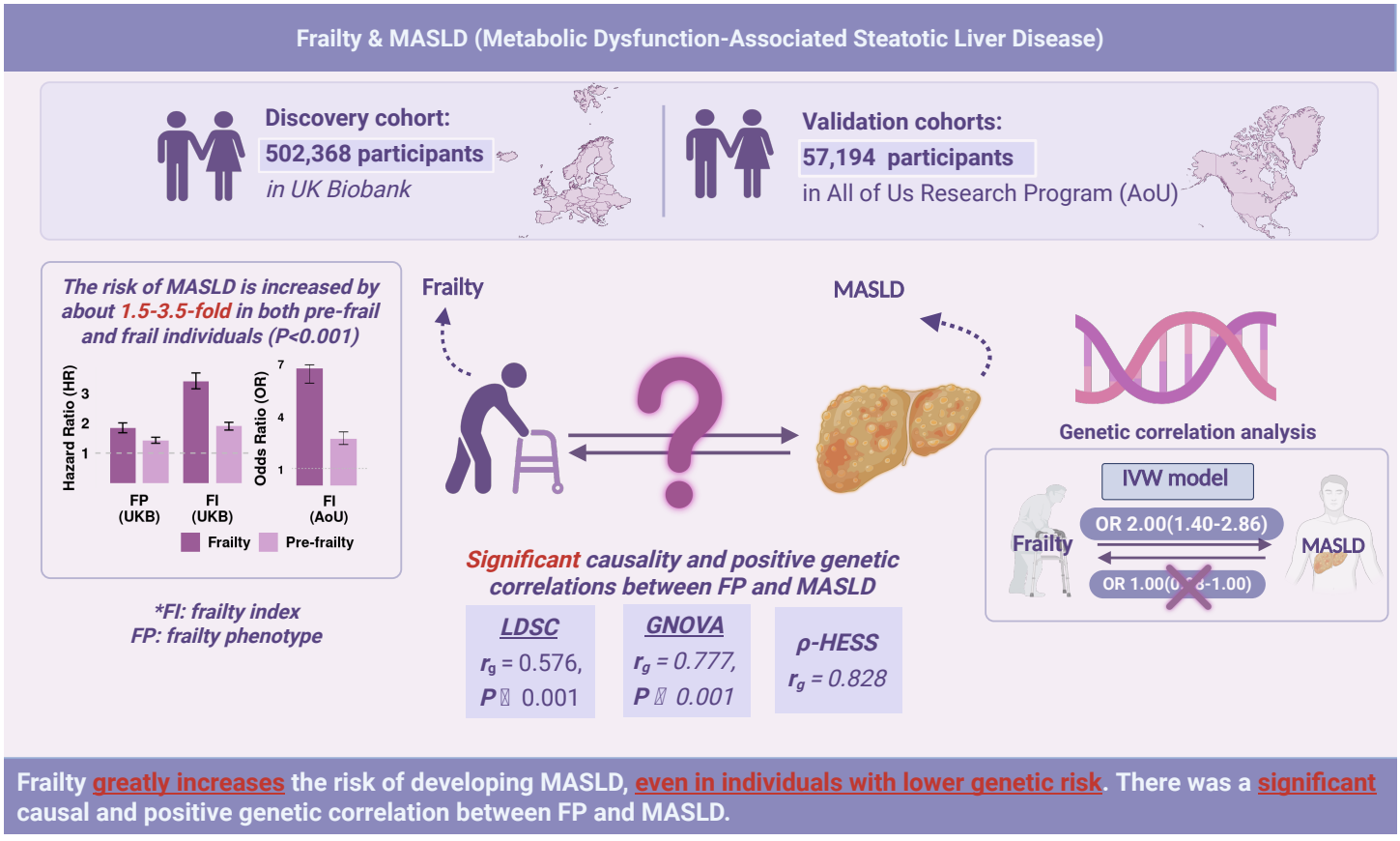
Received: March 9, 2025; Accepted: August 19, 2025; Published Online: August 22, 2025; https://doi.org/10.59717/j.xinn-med.2025.100155

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The risk of metabolic dysfunction-associated fatty liver disease (MASLD) increases significantly with frailty.
- There was a significant causal and positive genetic correlation between frailty and MASLD.
- Early clinical frailty screening can identify high-risk populations for MASLD before liver damage occurs.

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Causal association and genetic correlation of frailty with metabolic dysfunction-associated steatotic liver disease: Epidemiological and genetic analyses

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Citation: Zhang H., Li L., Zhang L., et al. (2025). Causal association and genetic correlation of frailty with metabolic dysfunction-associated steatotic liver disease: Epidemiological and genetic analyses. *The Innovation Medicine* **3**:100155.

Frailty has become a major public health issue, but its association with Metabolic dysfunction-associated steatotic liver disease (MASLD) remains controversial. We conducted an observational study of frailty and MASLD using the frailty index (FI) and frailty phenotype (FP) in the UK Biobank. And the results were validated in the National Health and the All of Us Research Program (AoU) database. We explored the causal relationship and genetic correlation between frailty and MASLD. In the UK population, both pre-frail and frail individuals had increased risks of MASLD in the analyses of FI and FP. Notably, the odds ratios of FI to the occurrence of MASLD were even more significant in our study in the US population. The odds ratios were 2.75 ([95% CI 2.41-3.15]; *P*<0.001) for pre-frailty and 6.88 (95% CI 6.02-7.90; *P*<0.001) for frailty. There was significant causality (OR 2.00; [95% CI 1.40-2.86]; *P*<0.001) and positive genetic correlations (LDSC: *r*g =0.576, *P*<0.001; GNOVA: *r*g =0.777, *P*<0.001; ρ-HESS: *r*g =0.828) between FP and MASLD. Frailty greatly increases the risk of developing MASLD. There was a significant causal and positive genetic correlation between FP and MASLD.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a rapidly growing global health challenge, characterized by pathological hepatic fat accumulation. This condition is intricately linked to obesity, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and insulin resistance; these comorbidities frequently coexist and synergistically exacerbate hepatic steatosis.[1] Current estimates indicate that MASLD affects approximately 38% of adults and 7-14% of children and adolescents worldwide. Alarmingly, projections suggest the adult prevalence could exceed 55% by 2040, imposing an escalating and substantial burden on healthcare systems and economies globally.[2] Critically, the absence of effective, sustainable interventions to halt MASLD progression has cemented its status as a major public health priority.[3]

Frailty an important geriatric syndrome marked by progressive, multisystem physiological decline and heightened vulnerability to stressors is gaining increased recognition, particularly amidst the accelerating global demographic shift towards an aging population.[4]

Previous studies have proposed a potential association between MASLD and frailty. Patients with MASLD demonstrate a significantly higher prevalence of frailty compared to non-MASLD individuals.[5] However, existing research on this relationship faces notable limitations: restricted sample sizes, narrow age ranges, insufficient validation across diverse databases, uncertain generalizability to broader populations, and inadequate exploration of shared genetic underpinnings.[6] Additionally, previous research has shown a potential link between MASLD and common risk factors of frailty, such as age,[7] obesity,[8] and metabolic disorders.[9] Therefore, the association and causality between MASLD and frailty is currently controversial.

To address the aforementioned knowledge gaps, in this large cohort study leveraged two national cohorts we aimed to investigate whether frailty serves as a risk factor for MASLD. First, we examined the association between frailty and incident MASLD in two large-scale cohorts: the UK Biobank and the All of Us Research Program (AoU). Second, we assessed the causal and genetic correlations between the Frailty Phenotype (FP) and MASLD using Mendelian Randomization (MR), Linkage Disequilibrium Score Regression (LDSC), Genetic Covariance Analyzer (GNOVA), and Heritability Estimation from Summary Statistics (ρ-HESS).

MATERIALS AND METHODS

Observational study

Study design. This study utilized data from two independent prospective cohorts: the UK Biobank and AoU.

UK Biobank cohort: The analysis included 502,368 participants aged 37–73 years who completed baseline assessments with electronic informed consent between 2006 and 2010.[10] Ethical approval was obtained under UK Biobank Project 83339 (NHS National Research Ethics Service 11/NW/0382, 16/NW/0274, and 21/NW/0157).

Individuals were excluded if they had a diagnosis of MASLD at or prior to baseline (n=559), defined using inpatient hospital records (ICD-9 and ICD-10 codes from primary/secondary diagnoses in the HESIN dataset) where the first recorded diagnosis date preceded or coincided with the baseline assessment date, or if they provided no follow-up data (n=1,298). This yielded an initial cohort of 500,511 participants. For frailty assessment using the Frailty Index (FI), participants missing FI calculation data were excluded (n=1,788), resulting in 498,723 participants. For FP analyses, exclusion due to missing FP components (n=31,016; primarily physical performance measures) yielded 469,495 participants (Figure S1).

Within the AoU, an ongoing longitudinal cohort aiming to enroll over 1 million participants and integrating enrollment measurements, surveys, electronic health records (EHR), and integrating enrollment measurements, surveys, electronic health records (EHR), and wearable data, our analysis specifically included participants who possessed a linked Fitbit device and had consented to share both their Fitbit data and EHR data (n= 254,179). From this defined subset, individuals were excluded based on a history of hepatitis (n= 64,060), alcoholic liver disease (n= 5,560), or missing data required for the FI calculation (n= 127,365). Following these exclusions, 57,194 participants remained for preliminary analyses. (In contrast to UK Biobank, exclusions for baseline MASLD or lack of follow-up were not applied

Table 1. Baseline characteristics of participants of Frailty Index (UK Biobank).

		Frailty Index		
	Overall	Non-frailty	Pre-frailty	Frailty
No. of participants, n	498,723	186,335	247,056	65,332
MASLD, n (%)	7,026(1.4)	1,142(0.6)	3,490(1.4)	2,394(3.7)
Age (years), mean (SD)	56.5(8.1)	55.4(8.1)	57.0(8.0)	58.1(7.7)
Sex, n (%)				
Female	271,520(54.4)	94,613(50.8)	138,000(55.9)	38,907(59.6)
Male	227,203(45.6)	91,722(49.2)	109,056(44.1)	26,425(40.4)
Ethnicity, n (%)				
Non-White	26,704(5.4)	9,260(5.0)	13,084(5.3)	4,360(6.7)
White	472,019(94.6)	177,075(95.0)	233,972(94.7)	60,972(93.3)
TDI, n (mean (SD))	-1.3(3.1)	-1.7(2.9)	-1.3(3.1)	-0.2(3.5)
BMI, n (%)				
<18.5kg/m^2	2,623(0.5)	976(0.5)	1,275(0.5)	372(0.6)
18.5–24.9kg/m^2	162,434(32.6)	73,100(39.2)	76,633(31.0)	12,701(19.4)
25.0–29.9kg/m^2	211,895(42.5)	81,498(43.7)	105,996(42.9)	24,401(37.3)
≥30kg/m^2	121,771(24.4)	30,761(16.5)	63,152(25.6)	27,858(42.6)
Education (%)				
Non-university	335,806(67.3)	114,403(61.4)	169,918(68.8)	51,485(78.8)
University	162,917(32.7)	71,932(38.6)	77,138(31.2)	13,847(21.2)
Smoking status, n (%)				
Never	273,072(54.8)	113,269(60.8)	131,049(53.0)	28,754(44.0)
Previous	172,831(34.7)	57,442(30.8)	89,536(36.2)	25,853(39.6)
Current	52,820(10.6)	15,624(8.4)	26,471(10.7)	10,725(16.4)
Alcohol intake frequency, n (%)				
Never	40,207(8.1)	11,019(5.9)	19,517(7.9)	9,671(14.8)
Previous	57,638(11.6)	16,373(8.8)	29,128(11.8)	12,137(18.6)
Current	400,878(80.4)	158,943(85.3)	198,411(80.3)	43,524(66.6)
Living environment score (mean (SD))	18.8(15.3)	17.8(14.6)	18.8(15.3)	21.4(16.7)
Total physical activity, MET-h per week	2,645.2(2,708.7)	2,781.3(2,712.0)	2,614.6(2,698.9)	2,372.7(2,712.3)
Disease				
Cardiopathy, n (%)	27,581(5.5)	3,593(1.9)	14,056(5.7)	9,932(15.2)
Cancer, n (%)	38,523(7.7)	7,244(3.9)	22,390(9.1)	8,889(13.6)
Diabetes, n (%)	169,999(34.1)	58,746(31.5)	84,473(34.2)	26,780(41.0)
Metabolic syndrome, n (%)	26,253(5.3)	1,774(1.0)	14,479(5.9)	10,000(15.3)
Hypertension, n (%)	130,106(26.1)	22,230(11.9)	75,279(30.5)	32,597(49.9)
The use of drugs				
Cholesterol lowering drugs, n (%)	30,988(6.2)	6,563(3.5)	17,838(7.2)	6,587(10.1)
Insulin, n (%)	754(0.2)	122(0.1)	465(0.2)	167(0.3)
Antihypertensive drugs, n (%)	47,272(9.5)	10,683(5.7)	27,828(11.3)	8,761(13.4)

in AoU due to differing study designs and data availability).[11]

Assessment of frailty. The two most commonly used tools, the Frailty Index (FI) and Frailty Phenotype (FP), were utilized to assess frailty.[12] Both FI and FP are effective predictors of diverse adverse outcomes and can reveal shared underlying etiological factors contributing to MASLD. Weight loss, exhaustion, grip strength, physical activity, and walking speed were evaluated as FP indicators according to the Fried and Walston criteria (Table S1).[4] Participants were categorized as frailty (meeting three or more criteria), pre-

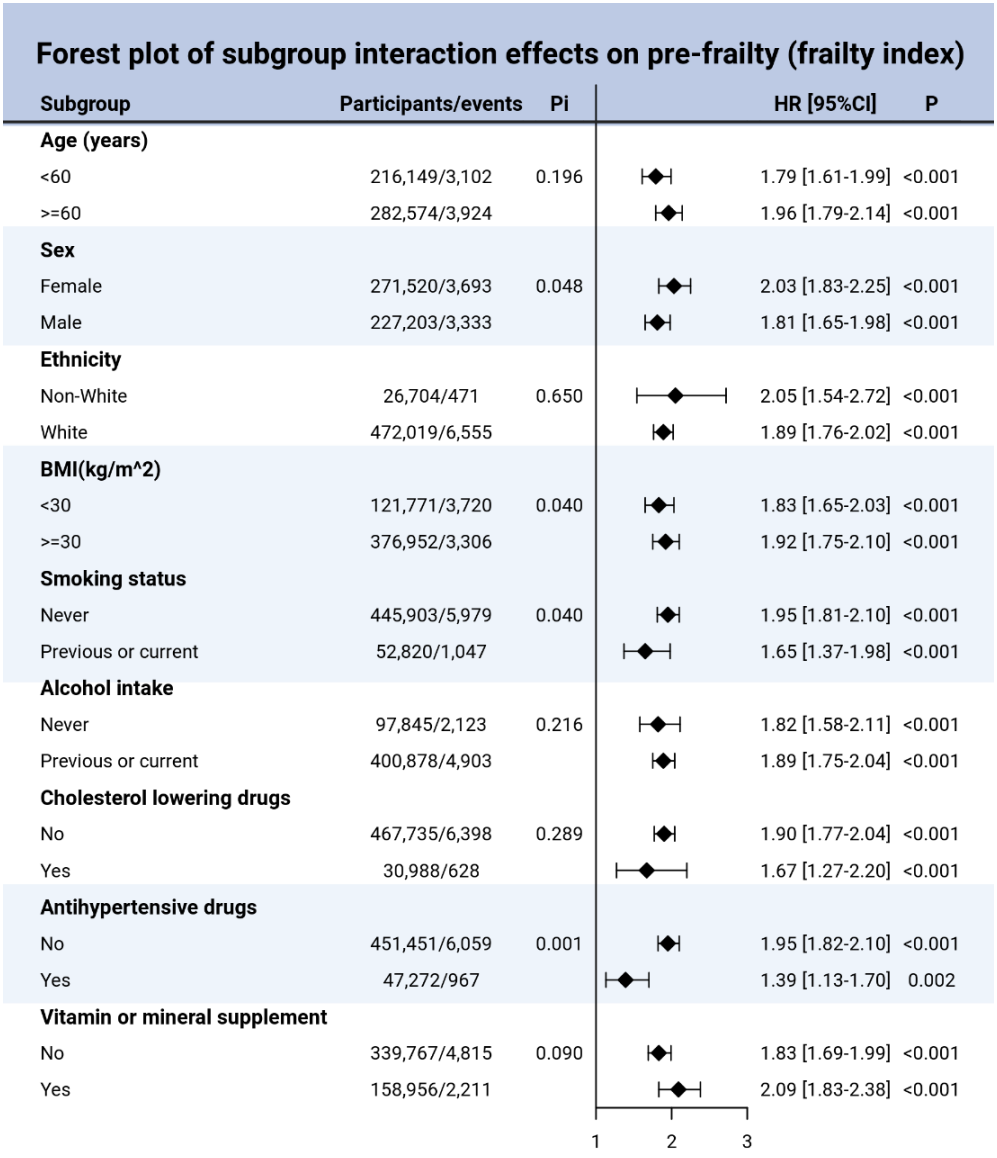


Figure 1. Forest plot of subgroup interaction effects on pre-frailty (frailty index) BMI: body mass index; MetS: Metabolic Syndrome; *Pi*: *P* -value for interaction.

frailty (meeting one or two criteria), and robust (meeting none of the frailty criteria).[4]

Additionally, the FI serves as an established metric for quantifying frailty severity. We selected 49 self-reported deficit items encompassing physiological and mental domains.[13] The FI was calculated as the ratio of present deficits to non-missing items.[14] Based on this score, participants were classified as frailty (≥0.21), pre-frailty (>0.1 to <0.21), and robust (≤0.1).[15]

Furthermore, we opted for the FI criteria established by the AoU cohort for comparative validation. The indicators we chose correspond to indicators from UK Biobank as a way of validating each other. The items included in the FI are listed in Table S2.

Assessment of MASLD. In the UK Biobank cohort, we utilized electronic linkage to hospital admission registries and cancer registries across England, Wales, and Scotland to ascertain follow-up data on liver-related morbidity and mortality. Hospitalized MASLD cases were identified using ICD-10 code K76.0. In the AoU cohort, the combined outpatient and inpatient ICD-10 code K76.0 registry captured MASLD diagnoses across both clinical settings. Additionally, we validated and diagnosed MASLD using MRI-derived proton density fat fraction (MRI-PDFF) values. A PDFF threshold of ≥5.6% was applied for MASLD diagnosis. Disease severity was categorized as: mild (PDFF 5.6%-10%), moderate (PDFF 10%-20%) and severe (PDFF ≥20%).[16]

Covariates. Covariates were selected based on prior epidemiologic evidence and data availability at baseline (Figure S2).[3,7,17-22] Potential confounders included age, sex (male, female), ethnicity (white or non-white), education level (non-university, university), BMI (18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2), socioeconomic status, smoking status (never, current, previous), alcohol intake (never, current, previous), fruit and vegetable intake, living environment score exercise, vitamin and mineral intake, history of cholesterol lowering drugs insulin and antihypertensive medications, hypertension, depression, history of heart disease, vitamin D deficiency, cancer, diabetes and metabolic syndrome. Socioeconomic status was assessed using the Townsend Deprivation Index, which was calculated using the previous national census output area prior to the participant's enrollment in UK Biobank. Education was based on self-report of the highest qualification obtained and was categorized as university or non-university. Covariates were multiply interpolated by chained equations (MICE package in R) and predictive mean matching methods for missing values of covariates.[23]

Furthermore, regarding covariates associated with FI in the AoU cohort, we included sex (male, female), ethnicity (White, Black or African American, Asian, More than one population, Hispanic American, other ethnicity), education (less than high school education, high school diploma or above), BMI (continuous), smoking status (never, some days, everyday), alcohol consumption (never, sometimes, frequent), history of antibiotic use (yes, no) , history of salicylic acid use (yes, no) , history of insulin use (yes, no).

Polygenic risk score (PRS) calculations. Genotypic data from the UK Biobank were acquired using the Affymetrix UK BiLEVE Axiom array, which assayed 825,927 genetic variants followed by genome-wide imputation.[24] MASLD genetic data were sourced from a published study (DOI:10.1186/s12916-019-1364-z)[25] to calculate the polygenic risk score (PRS) for MASLD. In brief, removals of insertions, pseudoautosomal regions, and any minor allele frequencies less than 0.05 were excluded. Genetic variations utilized for weight calculations needed an information (i.e., INFO) score above 0.8. Utilizing a Bayesian methodology, the PRS algorithm was developed by analyzing specific characteristics through meta-analyses, incorporating data from various ancestries and corresponding traits as needed. The value of PRS for each person is determined by adding up the effect size for each genetic variant across the entire genome, and then multiplying it by the allele dosage. PRS compiles data from meta-analyses of genome-wide association studies and subsequently standardizes the results. In our examination of PRS, we classified PRS into low risk (bottom tertile), medium risk (middle tertile), or high risk (top tertile).[26]

Statistical analyses. In the UK Biobank cohort, we examined the association between frailty and incident MASLD using three hierarchical adjustment models: Model 1 adjusted for age, sex, ethnicity, education level, BMI categories, Townsend Deprivation Index, smoking status, alcohol intake, fruit and vegetable intake, living environment score, exercise frequency, and vitamin/mineral supplementation; Model 2 additionally adjusted for comorbidities including depression, cancer, diabetes, metabolic syndrome, and hypertension; Model 3 further adjusted for medication usage (cholesterol-

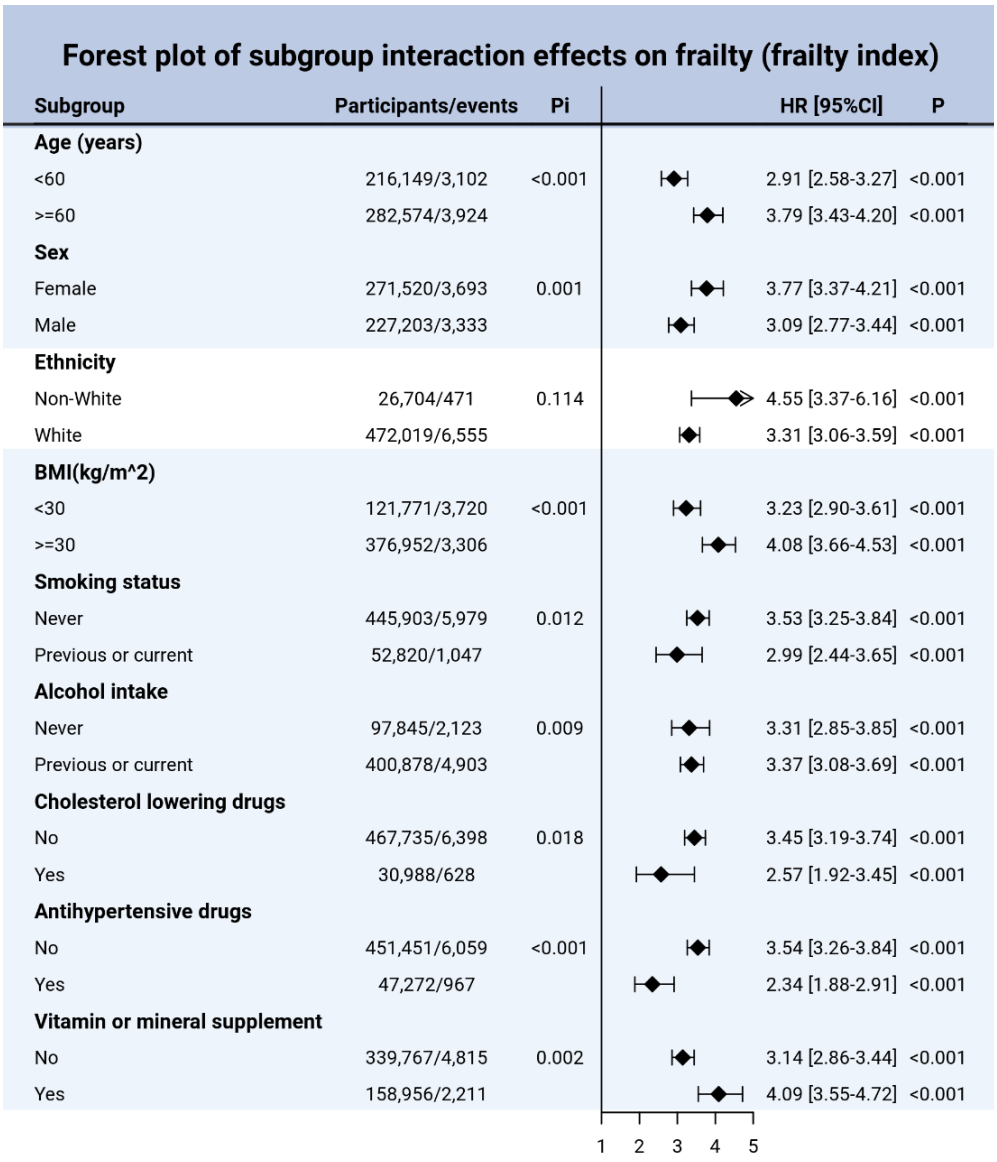


Figure 2. Forest plot of subgroup interaction effects on frailty (frailty index) BMI: body mass index; MetS: Metabolic Syndrome; *Pi*: *P* -value for interaction.

lowering drugs, insulin, and antihypertensive agents). Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. Missing covariate data were handled via multiple imputation by chained equations (MICE package in R) with predictive mean matching. For Frailty Phenotype (FP) analyses, Model 1 and Model 3 covariates were identical to those in the Frailty Index (FI) group. We incorporated interaction terms between each stratification factor and frailty status to assess potential effect modification.

In the UK Biobank cohort, to examine the association between frailty and the incidence of MASLD, we established three adjustment models: (1) Model 1, adjusted based on age, sex, ethnicity, education level, BMI, Townsend Deprivation Index, smoking status, alcohol intake, fruit and vegetable intake, living environment, exercise, and vitamin and mineral intake; (2) Model 2, additionally adjusted for comorbidities; (3) Model 3 had been adjusted by adding medication usage. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional risk models. Multiple imputation by chained equations (MICE packages in R) with predictive mean matching method was used to handle missing values of for the covariates. In the FP group, Model 1 and Model 3 were identical to the FI group. Further variables adjusted for in model 2 included a previous history of depression, cancer, diabetes, metabolic syndrome, and hypertension. Interaction terms were incorporated between each categorization factor and frailty status to assess the possibility of effect modification.

Sensitivity analyses were performed to evaluate the resilience of the findings. Subgroup analyses for the FI were conducted, stratifying by the baseline age (<60 or ≥60 years), gender, BMI (≤30kg/m^2 or >30kg/m^2), ethnicity (white or non-white), smoking status, alcohol intake, cholesterol-lowering medication use, antihypertensive medication use, and vitamin, mineral supplementation, as well as PRS risk subgroups (low, middle, and high). In conducting sensitivity analyses, the initial step was to replicate the results of the main analyses by implementing several exclusion criteria. These criteria included the exclusion of participants with missing covariates, participants taking cholesterol-lowering medication, insulin users, and those taking antihypertensive medications. Additionally, to mitigate the potential risk of reverse causation, individuals who were diagnosed with MASLD within two years after their enrollment were excluded from the study.[25] Additionally, excluding participants with alcoholic fatty liver disease (ALD), we explored the effect of frailty on MASLD. Finally, we utilized MRI-derived proton density fat fraction (PDFF) to further validate the outcomes defined by ICD codes. And, we performed a detailed severity analysis of MASLD using PDFF as the defining criterion.

We used AoU to validate the UK Biobank results. Three adjustment models were developed: (1) Model 1, adjusting for sex and race; (2) Model 2, adjusting for sex, race, education, smoking status, alcohol intake, and BMI at recruitment; and (3) Model 3, adjusting for sex, race, education, smoking status, alcohol intake, BMI, history of antibiotic use, history of salicylic acid use, history of insulin use. Logistic regression was used to estimate ORs and CIs to assess the association between FI and the prevalence of MASLD. In addition, we conducted a stratified analysis of race in AoU.

Causality estimation and genetic correlation. To estimate the genetic predicting causality between frailty and MASLD, we performed MR analysis. Genetic variants are employed as instrumental variables (IVs), providing effective means of deriving tenable causal correlations between exposures and outcomes in MR analysis.[27] The MR analysis is based on 3 key assumptions: independence, relevance, and exclusion restriction.[28] Only SNPs satisfying these three conditions can be used as IVs: (1) P < 5e-7 (significant SNPs); (2) r2 < 0.001 and kb = 10,000 (a longer physical distance and less possibility of linkage disequilibrium); (3) F > 10 (a strong association between the selected IVs and exposure) ($F = \frac{N-k-1}{k} \times \frac{R^2}{1-R^2}$; $R^2 = 2 \times (1 - MAF) \times MAF \times \beta^2$). Four MR methods were used, including MR-Egger, inverse variance weighting (IVW), weighted median (WME), and weighted mode (WM).[29] In addition, the IVW method was employed as the primary method for identifying causal associations between FP and MASLD. Sensitivity analyses such as MR-Egger intercept test, Cochran's Q statistic, and MR-PRESSO were performed to assess the heterogeneity, pleiotropy and potential outliers of MR results.[30]

Additionally, we conducted pairwise global genetic correlation analysis utilizing cross-trait LDSC and genetic covariance analyser (GNOVA).[31] Single nucleotide polymorphisms (SNPs) in the GWAS dataset were found to match the reference panel (INFO score <0.9, minor allele frequency (MAF) <0.01).

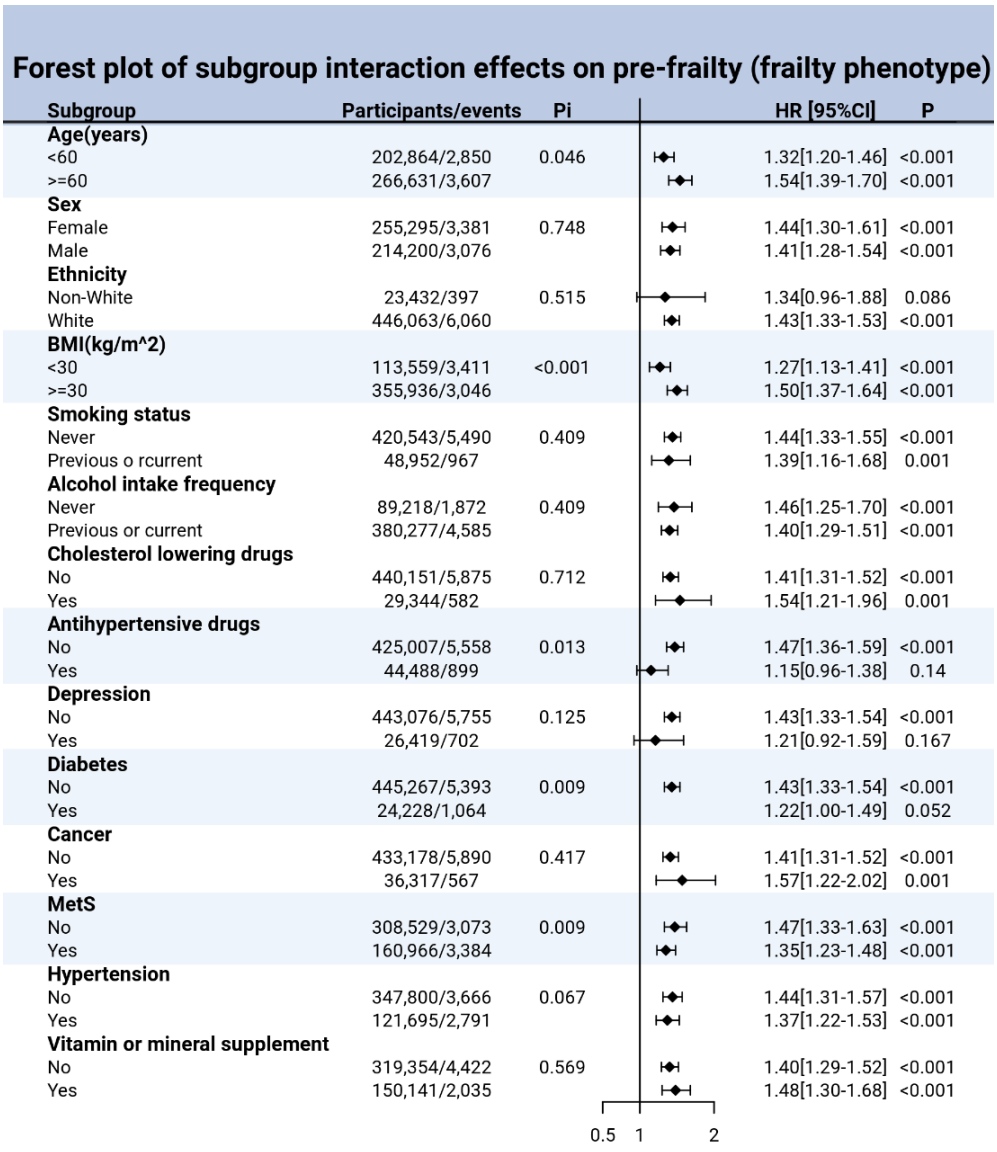


Figure 3. Forest plot of subgroup interaction effects on pre-frailty (frailty phenotype) BMI: body mass index; *Pi*: *P* -value for interaction.

New GWAS statistical summaries were then reformatted using pre-calculated LD scores from the European Population 1000 Genome reference data. Single trait SNP heritabilities (h2) were determined using univariate LDSC.[32] Bivariate LDSC was then used to estimate the genetic correlation between frailty and MASLD (r_g), with $P < 0.05$ considered a significant genetic correlation. To estimate the SNP heritability and genetic correlation between frailty and MASLD, we used the GNOVA as a supplementary technique. The steps for quality control resembled those of LDSC. Using GWAS summary statistics, GNOVA calculates annotation-stratified genetic covariance. Reference data from the European population, provided by the 1000 Genomes Project, was used to perform the calculations.

Moreover, we used ρ-HESS to investigate the genetic correlation in the local genomic region.[32] First, eigenvalues and LD blocks were calculated using the European 1000 Genomes Project. Then, genetic covariates between traits and local SNP heritability for each trait were determined. Local SNP heritability and genetic covariances were used to calculate local genetic correlations.

All analyses were completed in R (version 4.2.3). Statistical significance was set at a two-tailed *P* value of under 0.05.

RESULTS

Baseline characteristics of the study population

The UK Biobank study included 498,723 participants for FI analysis (Table 1). Of these, 73,142 (41.5%) were elderly (≥60 years) and 103,281 (58.5%) middle-aged, with a mean age of 56.5 years; 54.4% were female. At baseline, 65,332 participants (13.1%) were frailty and 247,056 (49.5%) pre-frailty. Compared to robust individuals, pre-frail and frail groups had higher proportions of females, lower educational attainment, reduced income, greater social deprivation, and higher prevalence of diabetes and hypertension. During follow-up, 7,026 incident MASLD cases were identified. Baseline characteristics of FP participants in UK Biobank and AoU participants are presented in Tables S3-S4, respectively.

Risks of frailty and MASLD

Both frailty and pre-frailty were significantly associated with the higher incidence rate of MASLD (*P*<0.001) (Table 2). In Model 1 of FI analysis, the incidence risk of MASLD is relatively high, with pre-frailty (HR 1.93 [95% CI 1.80-2.06]; *P*<0.001) and frailty (HR 3.50 [95% CI 3.24-3.77]; *P*<0.001), respectively. In Model 2, the risk ratios for MASLD were 1.92 ([95% CI 1.80-2.06]; *P*<0.001) for pre-frailty and 3.46 ([95% CI 3.20-3.74]; *P*<0.001) for frailty. In Model 3, the risk ratios for MASLD were 1.90 ([95% CI 1.77-2.03]; *P*<0.001) for pre-frailty and 3.40 ([95% CI 3.15-3.68]; *P*<0.001) for frailty, respectively.

In Model 1 of FP analysis, compared to pre-frailty (HR 1.48 [95% CI 1.38-1.58]; *P*<0.001), frailty individuals (HR 2.10 [95% CI 1.92-2.30]; *P*<0.001) had higher risks of MASLD. In Model 2, the risk ratios for MASLD were 1.43 (95% CI 1.33-1.53; *P*<0.001) for pre-frailty and 1.84 (95% CI 1.69-2.02; *P*<0.001) for frailty. In Model 3, the risk ratios for MASLD were 1.42 (95% CI 1.33-1.53; *P*<0.001) for pre-frailty and 1.84 (95% CI 1.68-2.01; *P*<0.001) for frailty.

Sensitivity analysis

The results for most of the subgroups of pre-frailty and frailty showed significant correlations (Figures 1-4). In the pre-frailty analyses of the FI group, a significant interaction was observed between different sexes (*P* interaction = 0.048) and frailty status. In addition, significant interactions with pre-frailty were also found for BMI (*P* interaction = 0.040), smoking status (*P* interaction = 0.040), and antihypertensive medications (*P* interaction = 0.001). For frail populations of the FI group, the risk of MASLD was significantly increased in all subgroups, with female, high BMI populations having a higher risk of developing the disease. In the FP group of pre-frail individuals, the results showed significant correlations between subgroups except for ethnicity, depression, and diabetes, where there was a significant interaction between antihypertensive drugs and diabetes. Among frail patients of the FP group, age, BMI, cholesterol lowering drugs, antihypertensive drugs, and metabolic syndrome had a relatively significant impact on the incidence of MASLD, and they all had a significant interaction. The results of the remaining sensitivity analyses are in Tables S5-S8.

Polygenic risk score (PRS) results

We used PRS to explore the association between PRS for MASLD and frailty for the risk of MASLD incidence in the UK Biobank. Results demon-

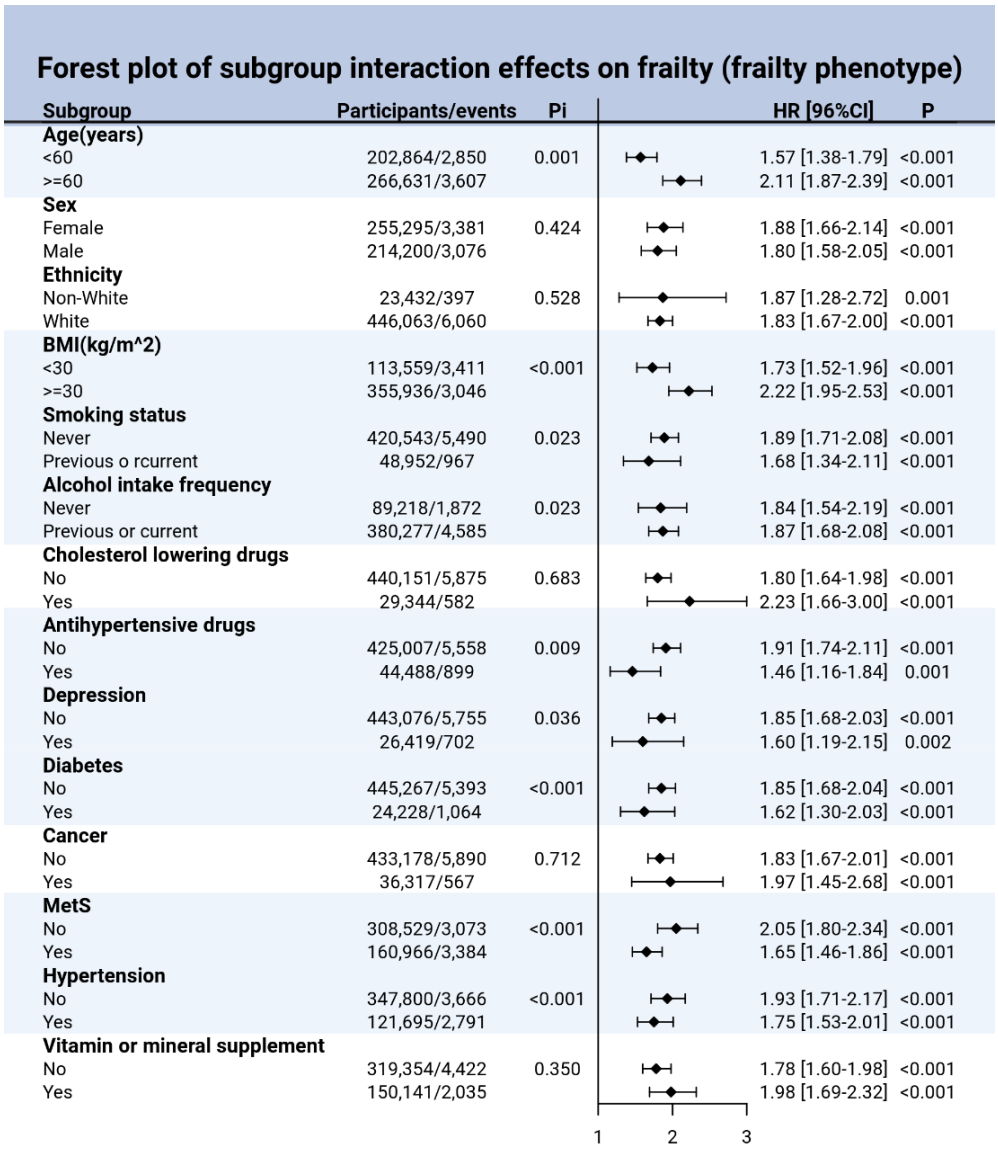


Figure 4. Forest plot of subgroup interaction effects on frailty (frailty phenotype) BMI: body mass index; *Pi*: *P* -value for interaction.

strated differential MASLD risk across genetic susceptibility strata. For the FP group, frailty status conferred elevated MASLD risk even in individuals with low genetic susceptibility (pre-frailty HR 1.29 [95% CI 1.13-1.48], P<0.001; frailty HR 1.72 [95% CI 1.45-2.04], P<0.001). For the FI group, frailty was associated with the greatest increase in the risk ratio for MASLD incidence in subjects with low MASLD susceptibility (pre-frailty HR 2.11 [95% CI 1.84-2.43], P<0.001; frailty HR 3.64 [95% CI 3.11-4.25], P<0.001) (Table 3). This highlights that frail individuals with low genetic susceptibility remain at significant MASLD risk, establishing frailty as an independent risk factor irrespective of genetic background.

AoU: logistic analysis results of FI

Similarly, significant associations between FI and MASLD were observed in the AoU cohort. In Model 1, compared to pre-frailty (OR 3.36 [95% CI 2.95-3.85]; *P*<0.001), frailty individuals (OR 10.64 [95% CI 9.36-12.15]; *P*<0.001) exhibited substantially higher MASLD risk. In Model 2, the odds ratios for MASLD were 2.91 (95% CI 2.55-3.33; *P*<0.001) for pre-frailty and 7.97 (95% CI 7.01-9.09; *P*<0.001) for frailty. In Model 3, the odds ratios for MASLD were 2.75 ([95% CI 2.41-3.15]; *P*<0.001) for pre-frailty and 6.88 (95% CI 6.02-7.90; *P*<0.001) for frailty (Table 2).

Causality estimation and genetic correlation

We performed MR analyses to estimate the causal association between FP and MASLD. When FP was used as the exposure, a total of 43 IVs were selected based on 3 hypotheses. Then, using the MR-PRESSO method, 9 aberrant SNPs were excluded and 34 SNPs remained. Recalculations showed that FP was causally associated with an increased risk of MASLD (OR 2.00 [95% CI 1.40-2.86], *P*<0.001). There was no causal association between MASLD and increased risk of FP (OR 1.00 [95% CI 0.98-1.00], *P*=0.982) when MASLD was the exposure. Sensitivity analyses showed robust estimates (Figure 5).

The results of LDSC showed a significant global genetic correlation between frailty and MASLD (r_g =0.576, *P*<0.001). Similar to LDSC results, GNOVA also demonstrated a positive genetic correlation between frailty and MASLD (r_g =0.777, *P*<0.001). Additionally, we used ρ-HESS to evaluate the local genetic correlation. And the results of ρ-HESS showed a positive local genetic correlation between frailty and MASLD (r_g =0.828) (Figure 5).

DISCUSSION

In this large prospective UK Biobank cohort study, frailty demonstrated a significant association with MASLD, independent of socio-demographic factors, lifestyle behaviors, comorbidities, and genetic susceptibility. These findings were validated in the AoU cohort. Notably, the association between frailty status and MASLD risk exhibited significant heterogeneity across genetic susceptibility strata and stratified populations. Genetic analyses further established causal effects and robust genetic correlations between the FP and MASLD.

Emerging evidence suggests a potential association between frailty and the etiology of cirrhosis.[33] Additionally, an Australian cross-sectional study of 16,703 individuals aged ≥70 years supports an association between frailty and MASLD.[34] However, three critical limitations persist in prior research: first, existing studies could not establish causal relationships between frailty and MASLD or investigate underlying genetic correlations; second, study populations predominantly comprised hospitalized patients with advanced MASLD, overlooking those with mild disease; finally, previous work lacked validation across diverse databases to assess generalizability. Our study directly addresses these knowledge gaps through robust causal inference, comprehensive disease spectrum representation, and multi-cohort validation.

We examined the influence of genetic susceptibility on the frailty-MASLD association. Notably, significantly elevated MASLD risk persisted with increasing frailty even among individuals with low genetic risk. Our finding emphasizes the fact that even frail people with low genetic susceptibility are also at risk for MASLD, meaning that frailty is an independent risk factor for MASLD regardless of genetic background.

Our study is the first investigation to establish both causal and genetic correlations between frailty and MASLD. MR analyses confirmed a causal relationship between the FP and MASLD. By minimizing confounding through genetic randomization, this approach provided robust evidence for causal inference. Additionally, significant global genetic correlation between FP and MASLD was demonstrated in LDSC and GNOVA results. This indicates that FP and MASLD share substantial genetic variation across the genome. Such concordance enhances the reliability of our findings and confirms a robust

Table 2. Association between frailty and risk of MASLD.

	Pre-frailty		Frailty	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Frailty Index in UK Biobank				
Model1	1.93(1.80-2.06)	<0.001	3.50(3.24-3.77)	<0.001
Model2	1.92(1.80-2.06)	<0.001	3.46(3.20-3.74)	<0.001
Model3	1.90(1.77-2.03)	<0.001	3.40(3.15-3.68)	<0.001
Frailty Phenotype in UK Biobank				
Model1	1.48(1.38-1.58)	<0.001	2.10(1.92-2.30)	<0.001
Model2	1.43(1.33-1.53)	<0.001	1.84(1.69-2.02)	<0.001
Model3	1.42(1.33-1.53)	<0.001	1.84(1.68-2.01)	<0.001
Frailty Index in AoU				
Model 1	3.36 (2.95-3.85)	<0.001	10.64 (9.36-12.15)	<0.001
Model 2	2.91(2.55-3.33)	<0.001	7.97 (7.01-9.09)	<0.001
Model 3	2.75 (2.41-3.15)	<0.001	6.88 (6.02-7.90)	<0.001

UK Biobank: 1.FI Model1: Adjusted for age at recruitment, sex, TDindex, education, smoking status, ethnicity, alcohol status, BMI, vegetable intake, fruit intake, exercise, Vitamin and mineral intake. 2.FI Model2: Additional history of vitamin D deficiency, history of heart disease added to FI model1. 3.FI Model3: Additional history of cholesterol-lowering medications, insulin, and antihypertensive medications were added to the FI model2. 4.FP Model1: Adjusted for age at recruitment, sex, TDindex, education, smoking status, ethnicity, alcohol status, BMI, vegetable intake, fruit intake, exercise, Vitamin and mineral intake. 5.FP Model2: Compared to FP Model1, history of heart disease, history of vitamin D deficiency, history of cancer, history of anxiety, history of depression, history of metabolic syndrome, history of hypertension were added. 6.FP Model3: Compared to FP Model2, history of cholesterol-lowering medications, insulin, and antihypertensive medications were added AoU 1. Model 1: Adjusted for age at recruitment, sex, ethnicity. 2. Model 2: Adjusted for age at recruitment, sex, ethnicity, education, smoking status, alcohol intake, BMI. 3. Model 3: Adjusted for age at recruitment, sex, ethnicity, education, smoking status, alcohol intake, BMI and medication use. BMI: Body mass index.

Table 3. Association between frailty and risk of MASLD in UK Biobank, stratified by polygenic risk status.

	Low genetic risk (n=136,716)		Medium genetic risk (n=136,716)		High genetic risk (n=136,716)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Frailty index						
Robust	1 (ref)	..	1 (ref)	..	1 (ref)	..
Pre-frailty	2.11(1.84-2.43)	<0.001	1.94(1.70-2.21)	<0.001	1.66(1.47-1.88)	<0.001
Frailty	3.64(3.11-4.25)	<0.001	3.41(2.94-3.96)	<0.001	3.05(2.65-3.52)	<0.001
	Low genetic risk (n=129,568)		Medium genetic risk (n=129,568)		High genetic risk (n=129,568)	
Frailty phenotype						
Robust	1 (ref)	..	1 (ref)	..	1 (ref)	..
Pre-frailty	1.29(1.13-1.48)	<0.001	1.54(1.34-1.76)	<0.001	1.39(1.22-1.58)	<0.001
Frailty	1.72(1.45-2.04)	<0.001	1.86(1.56-2.22)	<0.001	1.70(1.44-2.01)	<0.001

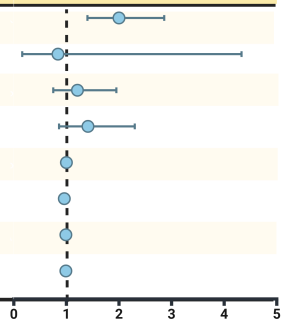
1.Frailty index: Models were adjusted for age, sex, Townsend deprivation index, education, smoking status, ethnicity, alcohol status, BMI, vegetable intake, fruit intake, exercise, vitamin and mineral intake, history of vitamin D deficiency, history of heart disease, history of cholesterol-lowering medications, insulin, and antihypertensive medications. 2.Frailty phenotype: Models were adjusted for age, sex, Townsend deprivation index, education, smoking status, ethnicity, alcohol status, BMI, vegetable intake, fruit intake, exercise, vitamin and mineral intake, history of heart disease, history of vitamin D deficiency, history of cancer, history of anxiety, history of depression, history of metabolic syndrome, history of hypertension, history of cholesterol-lowering medications, insulin, and antihypertensive medications.

genetic link between FP and MASLD. Furthermore, our ρ-HESS results provide additional support for this genetic association. These findings not only address inherent limitations of observational studies (including potential confounding and reverse causation) but also establish evidence for a causal relationship between frailty and elevated MASLD risk.

Several potential mechanisms may explain the frailty-MASLD association. Primarily, frailty reduces physical activity, promoting adipose accumulation that elevates MASLD risk.[35,36] Concurrently, frailty correlates with metabolic disorders (e.g., insulin resistance) that contribute to hepatic steatosis.[37] Studies demonstrate elevated pro-inflammatory factors in frail individuals, while interactions among hepatocytes, macrophages, and hepatic stellate cells within hepatic inflammatory and oxidative stress environments represent key pathogenetic mechanisms for.[38] Thus, MASLD and frailty exhibit intrinsic links through amplified inflammatory responses and oxidative stress. Moreover,

(A) Mendelian randomization analysis links genetic frailty with MASLD risk

Outcome	Exposure	Method	OR (95% CI)	P-value	SNPs
MASLD	FP	IVW	2.00 (1.40 – 2.86)	<0.001	34
MASLD	FP	MR-Egger	0.84 (0.16 – 4.33)	0.839	34
MASLD	FP	Weighted Mode	1.21 (0.75 – 1.95)	0.441	34
MASLD	FP	Weighted Median	1.41 (0.86 – 2.30)	0.171	34
FP	MASLD	IVW	1.00 (0.98 – 1.02)	0.982	9
FP	MASLD	MR-Egger	0.96 (0.92 – 1.00)	0.113	9
FP	MASLD	Weighted Mode	0.99 (0.97 – 1.00)	0.156	9
FP	MASLD	Weighted Median	0.99 (0.97 – 1.00)	0.102	9



(B) Heritability and genetic correlation between frailty and MASLD

Trait	Method	Frailty	MASLD
Heritability (h^2)	LDSC	0.110	0.010
Heritability (h^2)	GNOVA	0.120	0.011
Heritability (h^2)	ρ-HESS	0.190	0.007
Genetic Correlation, *rg,P*	LDSC	0.576, 845E-24	
Genetic Correlation, *rg,P*	GNOVA	0.777,4.27E-83	
Genetic Correlation, *rg,P*	ρ-HESS	0.828	

Figure 5. The results of genetic analysis of frailty and MASLD (A) Mendelian randomization analysis links genetic frailty with MASLD risk (1) Scatter plot of SNPs potential effects on frailty vs MASLD, with the slope of each line corresponding to estimated MASLD effect method. (2) Funnel plot from genetically predicted frailty on MASLD. (3) MR results for the relationship between frailty and MASLD. MASLD: Metabolic dysfunction-associated steatotic liver disease; IVW: inverse variance weighted; OR: odds ratio; CI: Confidence Interval; SNPs: single nucleotide polymorphisms. (B) Heritability and genetic correlation between frailty and MASLD LDSC: linkage disequilibrium score regression; GNOVA: genetic covariance analyser. ρ-HESS: heritability estimator from summary statistics; MASLD: Metabolic dysfunction-associated steatotic liver disease.

frailty may induce chronic inflammation and intestinal dysbiosis, further exacerbating MASLD. Additionally, frailty associates with impaired mitochondrial function and heightened oxidative stress—established pathogenic factors in MASLD.[39]

While cross-sectional studies have reported associations between frailty and MASLD,[40] our study provides the first longitudinal evidence demonstrating that frailty precedes and predicts MASLD onset, independent of genetic susceptibility. This extends prior observations of a 1.8-fold frailty risk in MASLD patients (Zhang et al., OR=1.82) by establishing a bidirectional temporal relationship through integrated observational and genetic analyses. Mechanistically, shared pathophysiology likely involves frailty-associated chronic inflammation (e.g., elevated IL-6/TNF-α activating hepatic JNK/NF-κB pathways) and mitochondrial dysfunction-parallel to findings in skeletal muscle of frail individuals.[41] Clinically, integrating frailty assessments (e.g., Fried Phenotype) into hepatology practice may enable early identification of high-risk populations, particularly when combined with genetic stratification. Emerging interventions such as resistance training[42] and senolytics (NCT04553133)[43] could concurrently target both conditions, representing a transformative approach to MASLD prevention in aging cohorts.

Strength and limitation

This investigation possesses several key innovations and strengths. First, by integrating analyses from both the UK Biobank and AoU cohorts representing the UK and US populations, we enhanced the generalizability and robustness of findings through cross-population validation. Second, incorporating polygenic risk scores enabled exploration of frailty-genetic susceptibility interactions, offering novel insights into MASLD's multifactorial etiology. Third, application of MR and genetic correlation analyses provided causal evidence overcoming key constraints of observational studies, yielding more comprehensive genetic epidemiological insights. Finally, extensive adjustment for covariates, complemented by sensitivity and subgroup analyses, confirmed result robustness.

Several limitations merit acknowledgment. First, the absence of liver biopsy (gold-standard for MASLD diagnosis) in population-based cohorts may affect diagnostic precision. Second, frailty assessment relied on self-reported measures, introducing potential measurement bias. Third, despite comprehensive covariate adjustment, residual confounding remains possible, though mitigated through MR approaches.

CONCLUSION

In conclusion, integrated observational and genetic analyses establish significant association, causality, and genetic correlation between frailty and incident MASLD risk. Critically, frail individuals with low genetic susceptibility retain substantial MASLD risk. Mendelian randomization and genetic correlation analyses further delineate causal pathways and shared genetic architecture, underscoring the imperative for early frailty assessment in MASLD prevention and clinical management.

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FUNDING AND ACKNOWLEDGMENTS

This work is supported by the National Natural Science Foundation of China Regional Innovation and Development Joint Foundation (U23A20408), the National Natural Science Foundation of China (82171698, 81300279, 81741067, 82170561, 82273727), the Program for High-level Foreign Expert Introduction of China (G2022030047L), the Natural Science Foundation for Distinguished Young Scholars of Guangdong Province (2021B1515020003), the Guangdong Basic and Applied Basic Research Foundation (2022A1515012081), Guangzhou Basic and Applied Basic Research Scheme-Project for Pilot Voyage (2024A04J6573), the Climbing Program of Introduced Talents and High-level Hospital Construction Project of Guangdong Provincial People's Hospital (DFJH201803, KJ012019099, KJ012021143, KY012021183, the Science and Technology Program of Guangzhou (No. 202201011046) and the Foreign Distinguished Teacher Program of Guangdong Science and Technology Department (KD0120220129), and in part by VA Clinical Merit and ASGE clinical research funds (FWL). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

HZ, LYL, WHS, and LJZ contributed equally to this work. HC, JQX, CYD and FWL are senior and corresponding authors who also contributed equally to this study. HZ, LYL, LJZ, WHS and ZL contributed to data extraction, data analyses, and manuscript drafting. YYM, WTH, RJZ, DLL, MJM and YJW contributed to manuscript drafting. HC, JQX, CYD and FWL contributed to study design, data interpretation, and final approval of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

The UK Biobank database received ethical clearance from the North West Multi-Center Research Ethics Committee, indicated by approval numbers: 11/NW/0382, 16/NW/0274, and 21/NW/0157. All participants gave written informed consent before enrolment in the study, which was conducted in 395 accordance with the principles of the Declaration of Helsinki.

DATA AND CODE AVAILABILITY

The UK Biobank data are available on application to the UK Biobank (http://www.ukbiobank.ac.uk/register-apply).

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2025.100155.