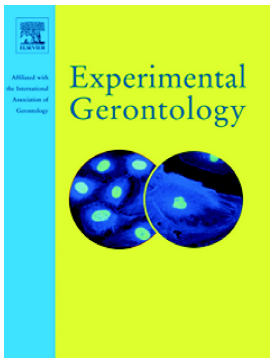

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PII: S0531-5565(25)00282-7

DOI: https://doi.org/10.1016/j.exger.2025.112953

Reference: EXG 112953

To appear in: *Experimental Gerontology*

Received date: 26 August 2025

Revised date: 9 October 2025

Accepted date: 29 October 2025

Please cite this article as: J. Kilaitė, E. Pranckevičienė, V. Ginevičienė, et al., Causal relationships between sarcopenia, frailty, and health outcomes: A systematic review of Mendelian randomization studies, *Experimental Gerontology* (2024), https://doi.org/10.1016/j.exger.2025.112953

Causal Relationships Between Sarcopenia, Frailty, and Health Outcomes: A Systematic Review of Mendelian Randomization Studies

Justina Kilaitė[a, *], Erinija Pranckevičienė[b,c], Valentina Ginevičienė[b], Alina Urnikytė[b], Rūta Dadelienė[d], Asta Mastavičiūtė[a], Ieva Eglė Jamontaitė [d], Vidmantas Alekna[a], Ildus I. Ahmetov[b,e]

[a] Vilnius University, Faculty of Medicine, Institute of Clinical Medicine, Clinic of Internal Diseases and Family Medicine, Vilnius, Lithuania, M. K. Čiurlionio st. 21, LT-03101, Vilnius, Phone: +370 5 239 8700

[b] Vilnius University, Faculty of Medicine, Translational Health Research Institute, Vilnius, Lithuania

[c] Vytautas Magnus University, Faculty of Informatics, Department of Systems Analysis, Kaunas, Lithuania

[d] Vilnius University, Faculty of Medicine, Department of Rehabilitation, Physical and Sports Medicine, Vilnius, Lithuania

[e] Liverpool John Moores University, Liverpool, United Kingdom

* Corresponding author: Justina Kilaitė, justina.kilaite@mf.vu.lt

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Abstract

Background. The development of frailty and sarcopenia is influenced by age-related physiological changes and gene–environment interactions, accelerating musculoskeletal decline and systemic dysfunction in older adults. Mendelian randomization (MR) use genetic variants as instrumental variables to assess causality. This study systematically reviewed two-sample MR studies investigating causal relationships of frailty and sarcopenia-related traits with various health outcomes.

Methods. Following PRISMA guidelines, PubMed and Scopus were searched (last accessed June 27, 2025) using terms including “Mendelian randomization“, “sarcopenia“, “lean mass“ or “fat free mass“, “strength“, “walking pace“, “gait“, and "frailty." Study quality was assessed via STROBE-MR checklist. Extracted data included exposure/outcome details, MR results (odds ratios or beta values with 95% confidence intervals, p-value of the causal association), and instrumental variable sources.

Results. The final analysis included a total of 68 articles on sarcopenia-related traits and 96 on frailty. Gait speed causally affected 25 traits and was affected by 26 traits. Handgrip strength causally affected 20 traits and was affected by 83 traits. Lean mass related phenotypes causally affected 45 traits and were affected by 85 traits. Frailty had a causal effect on 191 traits and was affected by 75 traits. Causal links between 19 groups of disease traits and sarcopenia and frailty were confirmed in observational studies (OS) and MR studies. In the majority of studies, increased muscle strength, lean mass, a faster walking pace, and lower

frailty served as protective factors against the risk of many diseases and were positively associated with cognitive function.

Conclusion. In this systematic review, we identified robust evidence supporting causal associations of both frailty and sarcopenia with a range of health-related outcomes, including sociodemographic and lifestyle factors, respiratory and musculoskeletal disorders, autoimmune disorders, inflammatory bowel disease, changes in gut microbiota, and neurological and vascular conditions.

Study registration

This review was preregistered with PROSPERO (CRD420251110335).

Keywords

Sarcopenia, frailty, mendelian randomization, muscle mass, muscle strength, walking pace

1. Introduction

Frailty and sarcopenia are common geriatric syndromes with major public health implications. Both predict gait disturbances, falls, care dependency, hospitalization, and mortality, reflecting age-related deterioration of musculoskeletal system and depletion of systemic reserves (Ginevičienė et al., 2024). Though most prevalent in older adults, they can also appear earlier in younger adults with multimorbidity or metabolic disorders (Thompson, 2024).

Sarcopenia is a progressive skeletal muscle disorder defined by loss of muscle strength, mass, and physical performance. It drives functional decline, dependence, and higher morbidity and mortality (Sayer and Cruz-Jentoft, 2022).

Frailty is a multidimensional syndrome marked by reduced physiological reserves and resilience across systems, leading to vulnerability to stressors (Doody et al., 2022).

Sarcopenia and frailty increase health care burden through higher hospitalization and mortality risk (Kojima et al., 2018; Xu et al., 2021).

Both conditions lack universal diagnostic criteria. Sarcopenia is usually defined by low muscle strength plus reduced muscle mass and/or performance, but cut-offs vary (Bhasin et al., 2020; Chen et al., 2020; Cruz-Jentoft et al., 2019; Fielding et al., 2011; Studenski et al., 2014; Zanker et al., 2023). Frailty measures are also heterogeneous. It is commonly assessed using either the frailty phenotype or the frailty index (Fried et al., 2001; Rockwood and Mitnitski, 2007).

Sarcopenia and frailty share multifactorial origins: age-related changes, environment, multimorbidity, and genetic factors. Genome-wide studies link variants in inflammatory, hormonal, and structural pathways to sarcopenia-related traits such as grip strength, lean mass, and walking pace (Semenova et al., 2023).

Traditional observational studies, including randomized clinical trials (RCTs), remain central in epidemiology but have important limitations when applied to multifactorial conditions such as sarcopenia and frailty. RCTs face ethical and practical barriers in testing exposures like genetic predisposition, malnutrition, or sedentary behavior, and are often affected by selection bias, limited generalizability, and poor adherence. Observational designs, though more feasible, are vulnerable to confounding, reverse causation, and measurement error, making causal inference difficult. For example, it is challenging to distinguish whether sarcopenia precedes insulin resistance or arises as a consequence (Lovegrove et al., 2024).

To overcome these issues, Mendelian Randomization (MR) uses genetic variants as instrumental variables to infer causal relationships between modifiable risk factors and outcomes. MR minimizes confounding and reverse causation, offering insights into the etiological pathways of frailty and sarcopenia (Ahmetov et al., 2024; Burgess et al., 2023; Richmond and Davey Smith, 2022).

MR can be conducted using individual-level or summary-level genome-wide association study (GWAS) data. For a single variant, causal effect is estimated using the Wald ratio (Lovegrove et al., 2024). More commonly, multiple variants are selected at genome-wide significance ($p < 5\times10^{-8}$). Single-sample MR uses the same cohort for exposure and outcome associations, while two-sample MR separates them, providing greater power and transparency. Widely used software includes TwoSampleMR and MR-PRESSO (Hemani et al., 2018; Verbanck et al., 2018).

Given the expansion of MR research, the aim of this study was to systematically review two-sample MR analyses of frailty and sarcopenia-related traits (e.g., strength, walking pace, lean mass) and the increase/decrease in the risk of various health-related outcomes.

2. Methods

2.1. Literature search and inclusion strategy

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (Liberati et al., 2009) and was also registered on PROSPERO (CRD420251110335). PubMed and Scopus databases were searched for MR studies of interest (last accessed June 27, 2025) using a combination of the search term "Mendelian randomization" combined with “sarcopenia”, and “lean mass”, or “fat free mass”, “strength”, “walking pace”, and “frailty”. MR

studies where participants were aged 18 or older were included. Only open-access full-text original articles written in English from journal sources were queried in the PubMed and Scopus databases, as shown in Table 1.

Table 1. Frailty and sarcopenia-related queries performed in PubMed and Scopus databases.

Trait	**PubMed query**	**Scopus query**
Walking pace	((((((mendelian) AND (randomisation)) OR (mendelian)) AND (randomization)) AND (Sarcopenia)) AND (walking)) AND (pace) Filters: Free full text, English	TITLE-ABS-KEY (mendelian AND randomization) OR TITLE-ABS-KEY (mendelian AND randomisation) AND TITLE-ABS-KEY (sarcopenia) AND TITLE-ABS-KEY (walking AND pace) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (OA , "all")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
Fat free and lean mass	((((((((((mendelian) AND (randomisation)) OR (mendelian)) AND (randomization)) AND (Sarcopenia))) AND (fat free OR lean)) AND (mass) Filters: Free full text, English	TITLE-ABS-KEY (mendelian AND randomization) OR TITLE-ABS-KEY (mendelian AND randomisation) AND TITLE-ABS-KEY (sarcopenia) AND TITLE-ABS-KEY (fat AND free AND mass) OR TITLE-ABS-KEY (lean AND mass) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (OA , "all")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
Strength	((((((((((mendelian) AND (randomisation)) OR (mendelian)) AND (randomization)) AND (Sarcopenia))) AND (strength) Filters: Free full text, English	TITLE-ABS-KEY (mendelian AND randomization) OR TITLE-ABS-KEY (mendelian AND randomisation) AND TITLE-ABS-KEY (sarcopenia) AND TITLE-ABS-KEY (strength) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (OA , "all")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
Frailty	((((((((((mendelian) AND (randomisation)) OR (mendelian)) AND (randomization)) AND (frailty) Filters: Free full text, English	TITLE-ABS-KEY (mendelian AND randomization) OR TITLE-ABS-KEY (mendelian AND randomisation) AND TITLE-ABS-KEY (frailty) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (OA, "all")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))

The frailty and sarcopenia-related studies were selected for further analysis following PRISMA guidelines. Figure 1 presents PRISMA flowchart of study selection (Page et al., 2021).

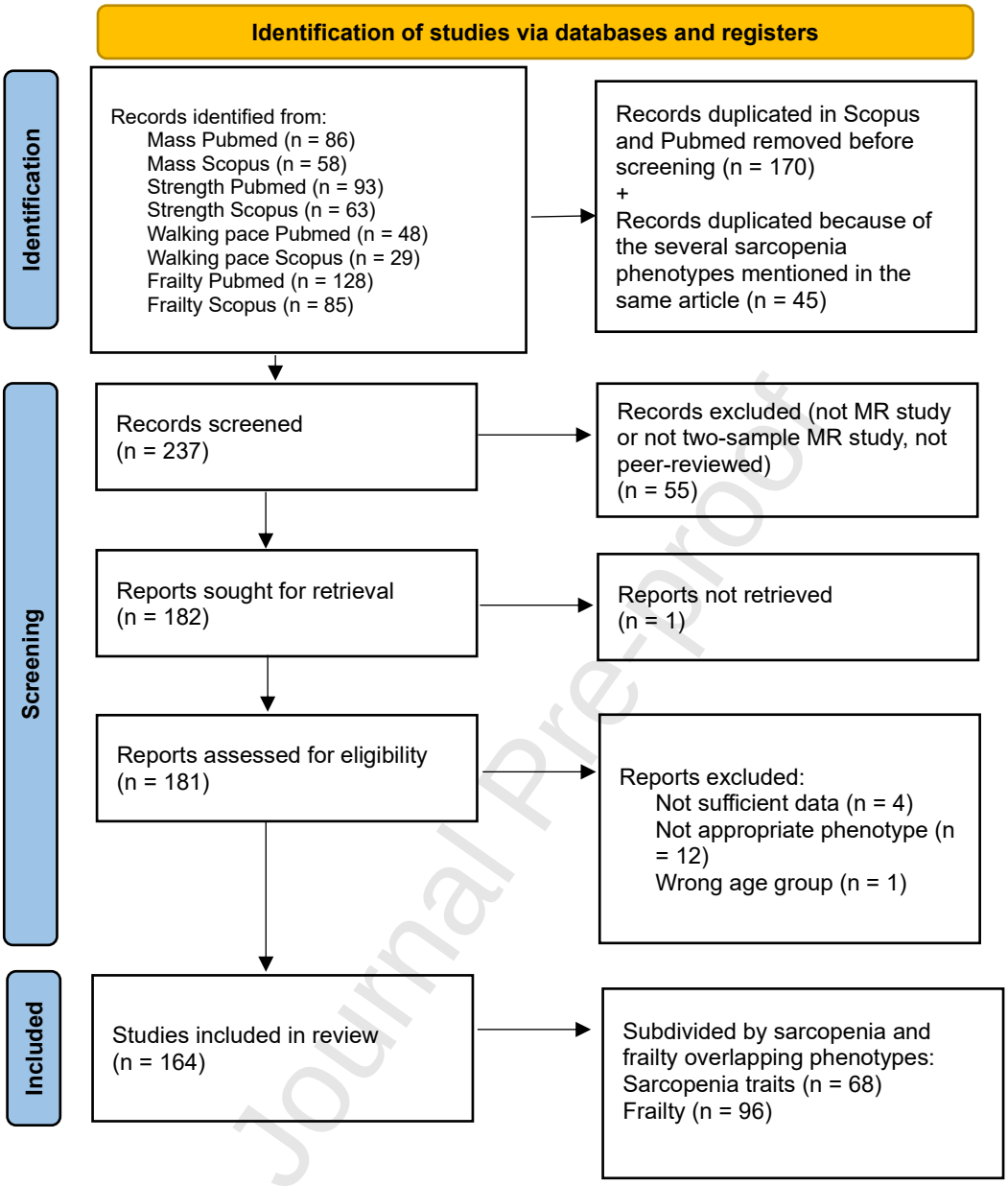

Figure 1. PRISMA flowchart of frailty and sarcopenia-related study selection.

We included two-sample MR studies in which sensitivity analysis at least by two robust methods (MR-Egger, weighted median / mode, MR-PRESSO or other) followed a primary analysis. The PECO strategy (population, exposure, comparison and outcome), was used as a guide for retrieving the relevant articles for this review.

Population (P): Adults presenting with frailty or sarcopenia-related traits.

Exposure (E): A range of health-related traits.

Comparison (C): Adults without frailty or sarcopenia-related traits.

Outcome (O): Evidence from Mendelian randomization studies demonstrating unidirectional and bidirectional causal associations between sarcopenia/frailty and the risk of diseases, disorders, lifestyle factors, and physiological traits associated with their onset and progression, wherein sarcopenia/frailty may act as both an exposure and an outcome.

The studies must have reported how many instrumental variables were used in associations. Each association must have reported Beta value or odds ratio (OR) with 95% confidence intervals and a *p* value.

2.2. Data Extraction

Data extracted from each document included the article reference (first author's family name, publication year, and PMID), the exposure and outcome of interest, the two-sample MR design, and the most essential MR analysis results such as odds ratio (OR), 95% confidence intervals (CIs), beta values with their confidence intervals, and the p-value of the causal association. Six investigators collected the data and removed duplicate articles. Three review authors (EP, JK, RD) independently assessed article eligibility, selected studies for inclusion, and resolved disagreements through discussion with a fourth review author (AU). We categorized the reviewed studies into two groups: (i) the exposures and (ii) the outcomes, focusing on frailty and sarcopenia. Although some articles reported all sarcopenia phenotypes while others reported only one or two, we analyzed each phenotype separately.

2.3. Risk of Bias Assessment and evaluation of robustness

MR studies include biases arising from the genetic instrument (e.g., weak instrument bias, bias due to horizontal pleiotropy, bias due to linkage disequilibrium, bias due to developmental compensation) and biases related to the population from which the data are collected (e.g., bias due to population stratification, assortative mating, dynastic effects, parent of origin effects, and bias due to sample overlap in two-sample MR). Biased estimates can also result from measurement/classification biases, selection biases (including those caused by missing data and collider bias), and reporting biases (Spiga et al., 2023). Evaluation of the quality of evidence reported in each study is achieved by assessing risk of bias through a structured framework such as Strengthening the Reporting of Observational Studies in Epidemiology – Mendelian Randomization (STROBE-MR) (Guan et al., 2024; V W Skrivankova et al., 2021). The risk of bias in each reviewed study was evaluated according to 20 possible STROBE-MR items. This score was then converted to a percentage, and a risk of bias was classified as high (< 80 %), medium (80-90 %), or low (> 90 %) (Guan et al., 2024; Ho et al., 2022). Following the STROBE-MR checklist, we verified that each of the two sample MR studies included in our review provided explicit references to the data sources, an explanation of how instrumental variables were selected to meet MR assumptions, and whether a sensitivity analysis was performed (V W. Skrivankova et al., 2021).

3. Results

A total of 355 articles were found in both PubMed and Scopus databases. After removing duplicate articles, a total of 237 publications were left. Fifty-five articles were excluded based on title and abstract screening. We retrieved 181 full-text articles for further analysis. Following the full text article screening, 17 articles were removed. A total of 164 articles were included in the final analysis.

Extracted data were collated into tables summarizing exposure-outcome associations between frailty and sarcopenia and other traits.

3.1. Bias assessment and overview of findings and quality of published MR studies

Each Mendelian randomization study (68 sarcopenia and 96 frailty studies) was scored based on 20 items in the STROBE-MR checklist (V W. Skrivankova et al., 2021). For each checklist item, a study was assigned a score of 1 if all necessary information required by that item was provided, 0.5 if partial information was provided, and 0 if no information was available. The total score for each study was calculated by summing the individual scores, and a percentage STROBE-MR score was derived by averaging this total across the 20 checklist items. Details of the scoring and quality assessment are available in Supplementary Table S1, "STROBE-MR-checklist." The average percentage score for each checklist item is shown in the sheet "Bias assessment."

The quality threshold suggested in the literature is 75% (Guan et al., 2024; Ho et al., 2022). In this review, we used a higher quality threshold of 80% and considered causal associations reported in the studies as unbiased if they are equal to or above 80%. We identified 27 studies (14 for frailty and 13 for sarcopenia) that scored below 80%.

A significant part of the reviewed studies lacked descriptive data (anthropometric and demographic characteristics); almost all studies were not generalizable (samples of European descent), and they did not properly describe data sharing. Some studies did not clearly explain the assumptions behind instrumental variables in Mendelian randomization studies.

3.2. Data sources of the selected studies

The reviewed MR studies utilized instrumental variables from GWAS, comprising 328 phenotypes from 156 published studies and from GWAS datasets of the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) at the University of Bristol, as well as the United Kingdom (UK) Biobank GWAS pipeline 2. The GWAS by Pei and colleagues was the most used source for instrumental variables (IVs) for appendicular lean mass trait (Pei et al., 2020). The GWAS by Jones and colleagues was the most used source for IVs for hand grip strength (Jones et al., 2021). The GWAS by Atkins and colleagues was most used for frailty traits (Atkins et al., 2021). The MRC–IEU UK Biobank dataset was most used for IVs for the walking pace trait (Elsworth, 2018). Other GWAS studies originated from large consortia: FinnGenn, CARDIoGRAMplusC4D, Chronic Kidney Disease Genetics Consortium, CORtisol NETwork (CORNET), MEGASTROKE consortium, Genetic Factors for Osteoporosis Consortium, Human Metabolome Database, MiBioGen Consortium, Social Science Genetic Association Consortium (SSGAC) and other. Summary of the instrumental variable data sources used in the reviewed MR studies is in Supplementary Table S2 “Data sources”.

3.3. Sarcopenia phenotypes

Sarcopenia phenotypes comprise walking pace, muscle strength expressed through the hand grip strength (HGS), and muscle mass expressed as appendicular lean mass (ALM) and fat-free mass (FFM). Each phenotype will be summarized in turn. Here, we present causally related phenotypes as exposure-outcome relationships in which sarcopenia phenotypes play both exposure and outcome roles.

3.3.1. Walking Pace

Causal relationships between walking pace and other traits were reported in 32 studies of which 16 passed QC thresholds (Supplementary Table S1). In the surveyed MR studies,

walking pace and speed were causally affected by 25 traits and causally affected 26 traits as outcomes (Table 2).

Table 2. Causal associations of walking pace with health-related traits.

Exposure	Effect	Outcome	OR (95% CI)	P-value significance	Reference PMID
Diseases					
Usual WP	Reduces risk	Crohn's disease	0.467 (0.239-0.914)	0.026	38022582
Usual WP	Reduces risk	Osteoarthritis knee	0.093 (0.055-0.157)	5.29E-19	37731961
Usual WP	Decreases risk	Type 2 diabetes mellitus	0.100 (0.053–0.186)	<0.001	36967750
Usual WP	Protective	Rotator cuff tears	0.46 (0.28, 0.76)	0.003	39534255
Usual WP	Increases	Risk of Attention deficit hyperactivity disorder	2.712 (1.609, 4.571)	<0.001	40143727
Usual WP	Inverse relationship	Obstructive sleep apnea	0.153 (0.092, 0.256)	8.24E-13	40055243
Usual WP	Reduces risk	Risk of ischemic stroke	0.6 (0.394, 0.913)	0.017	38757378
Usual WP	Reduces risk	Gastroesophageal reflux disease	OR = 0.1181, 95% C.I.: 0.0838-0.1666; 0.1184 (0.0819 - 0.1711)	4.10E-34; < 0.0001	38446595;39050602
Usual WP	Lower WP increases risk	Increased risk of diabetes	2.30 (1.14, 4.68)	0.021	37403750
Usual WP	Lower WP increases risk	Hypertension	4.43 (2.68, 7.33)	6.43E-07	37403750
Usual WP	Lower WP increases risk	Coronary heart disease	2.73 (1.84, 4.05); 0.321 (0.191, 0.539)	6.96E-07; 1.728E-05	37403750;37447340
Usual WP	Lower WP increases risk	Myocardial infarction	2.47 (1.63, 3.73)	1.82E-05	37403750
Usual WP	Inverse relationship	Rheumatoid arthritis	0.985 (0.977, 0.993)	5.7E-05	38638121
Usual WP	Inverse relationship	Major depressive disorder	0.673, (0.506, 0.896)	0.007	37800817
Usual WP	Inverse relationship	Breast cancer	0.553 (0.342, 0.895)	0.016	38666335
Usual WP	Inverse relationship	ER breast cancer	0.491 (0.250, 0.965)	0.039	38666335
Walking speed	Inverse relationship	Colorectal cancer	2.8346 (1.0351, 7.7626)	0.0426	39050602
Walking speed	Inverse relationship	NAFLD	0.3961 (0.2111 , 0.7435)	0.0039	39050602
Walking speed	Inverse relationship	Gastroduodenal ulcer	0.9901 (0.9824 - 0.9979)	0.0127	39050602
Walking pace	Inverse relationship	Frailty	0.955 (0.937, 0.974)	0.000	40257716
Usual WP	Increased risk of GDM	Gestational diabetes mellitus	3.3676 (1.8769, 6.0423)	<0.0001	39911357
Biochemical entities					
Walking pace	Increased WP decreases	IGF-1 levels	0.209 (0.051, 0.862)	0.045	39507055
Usual WP	Inverse relationship	Uric acid levels	Beta -0.435(-0.766, -0.103)	0.01	37955003
Usual WP	Influences	High-density lipoprotein cholesterol (HDL-C)	2.98(2.64–3.36)	<0.001	39214262
Usual WP	Influences	Triglycerides (TG)	0.50(0.45–0.56)	<0.001	39214262

Other traits					
Walking pace	Increases	Cognitive performance/function	Beta 0.349 (0.210-0.487); Beta 0.34(SE=0.09); Beta 0.78 (0.53, 1.02); Beta 4.93 (3.06, 6.8)	<0.001; 0.001 <0.001; <0.001	39240885 ; 38555389 ; 40499039
Diseases					
Cardioembolic stroke	Negatively affects	Usual WP	0.989 (0.980, 0.998)	0.013	39450050
GERD	Negatively affects	WP	Beta -0.1329 (−0.1456, -0.1201); 0.147(0.105-0.206)	<0.0001; 8.7E-29	39050602; 38446595
Liver cancer	Negatively affects	WP	Beta -6.3579 (−11.6900, −1.0259)	0.0194;	39050602
Rheumatoid arthritis	Negatively affects	Usual WP	Beta −1.019 (−1.284, −0.754)	6.2E-14	38638121
Biochemical entities					
Homocysteine levels (until increase)	Negative association	Usual WP	Effect = −0.038, SE = 0.011	3.18E-04	36482901
IL1b	Increases	Usual WP	Beta 0.009 SE 0.004	2.58E-02	38556722
IL2	Increases	Usual WP	Beta 0.008 SE 0.003	1.73E-02	38556722
IL8	Increases	Usual WP	Beta 0.005 SE 0.002	2.10E-02	38556722
TNFb	Decreases	Usual WP	Beta -0.004 SE 0.002	1.85E-02	38556722
Glucosamide	Increases	Usual WP	1.26 (1.16, 1.38)	2.55E-07	39764251
Androsterone sulfate	Decreases	WP	Beta -0,025(-0.041, -0.008);	7.91E-03	38622574
MAP3K5	Inverse relationship	WP	0.03 (0.02–0.05)	8.5E-06	38644354
Other traits					
Educational attainment	Increases WP	Usual WP	Beta 0.20 (0.18, 0.22)	< 0.000	39507653
Brain cortical thickness	Increases WP	Usual WP	Beta 0.49 (0.17, 0.81)	0.0026	39507653
Cognitive performance/ function	Positive association	WP	0.073 (0.059, 0.088) ; Beta 0.07(SE 0.01)	0.000, <0.001	39240885, 38555389
Gut microbiota					
family Porphyromonadaceae	Positive relationship	WP	1.05 (1.01, 1.09)	0.027	38995073
family Rikenellaccac	Negative relationship	WP	0.98 (0.97, 1.00)	0.0301	38995073
genus Terrisporobacter	Positive relationship	WP	1.02 (1.00, 1.04)	0.0435	38995073
genus Victivallis	Positive relationship	WP	1.01 (1.00, 1.02)	0.0448	38995073
creatine	Negative relationship	WP	0.95 (0.91, 0.99)	0.0276	38995073
benzoate	Positive relationship	WP	1.10 (1.00, 1.20)	0.04	38995073
carnitine	Negative relationship	WP	0.92 (0.87, 0.99)	0.0155	38995073

malate	Negative relationship	WP	0.93 (0.88, 1.00)	0.038	38995073
manitol	Negative relationship	WP	0.98 (0.97, 1.00)	0.0441	38995073
trans-4-hydroxyproline	Positive relationship	WP	1.11 (1.04, 1.19)	0.0024	38995073

WP – walking pace; ER - Estrogen receptor; NAFLD - Non-alcoholic fatty liver disease; IGF-1 - Insulin-like growth factor 1 ; IL-1b - Interleukin 1 beta; IL-2 - Interleukin 2; IL-8 - Interleukin 8; HDL-C - High-density lipoprotein cholesterol; TG – Triglycerides; TNFb - Tumor necrosis factor beta; GERD - Gastroesophageal reflux disease; MAP3K3 - Mitogen-activated protein kinase kinase kinase 3

Among all diseases affected by walking pace were Crohn's disease, gastroesophageal reflux disease (GERD), rheumatoid arthritis (RA), osteoarthritis, coronary heart disease, hypertension, myocardial infarction, risk of ischemic stroke, risk of diabetes, major depressive disorder, colorectal and breast cancers, nonalcoholic fatty liver disease, gastroduodenal ulcer, frailty, gestational diabetes mellitus, rotator cuff tears, risk of attention deficit hyperactivity disorder and obstructive sleep apnea. An increase in walking pace decreased the risk of T2DM by 90% (Simin Chen et al., 2023). A lower walking pace was causally associated with increased risks of diabetes and hypertension (Ye et al., 2023). The diseases that causally affected walking pace were cardioembolic stroke, liver cancer, GERD and RA.

Walking pace was found to affect IGF-1, uric acid, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels. It was found to be causally associated with cytokines IL1b, IL2, IL8, TNFb2, tumor necrosis factor (TNFb) and androsterone sulfate (Liu et al., 2024). Significant negative associations were found between increased plasma homocysteine (Hcy) levels and walking pace (Yu et al., 2022). Glucosamide, androsterone sulfate and MAP3K5 were found causally affecting usual walking pace (Kang et al., 2024; W. Peng et al., 2024; Yin et al., 2024). Cognitive performance and function have been shown to have a bidirectional association with walking pace, as reported in several independent studies (Liu et al., 2024; C.

Lu et al., 2024; Sha et al., 2025b). Educational attainment and brain cortical thickness were found causally affecting WP (Sha et al., 2025b).

Zhang and colleagues, in their MR analysis, yielded compelling evidence demonstrating a correlation between genetically predicted gut microbiota and metabolites and the risk of sarcopenia (Zhang et al., 2024). The abundance of Porphyromonadaceae, Rikenellaceae, Terrisporobacter, and Victivallis was found to affect the walking pace as well as creatine, benzoate, carnitine, malate, manitol, trans-4-hydroxyproline metabolites.

3.3.2. Muscle strength

Causal relationships between the strength phenotypes and other traits were reported in 38 studies of which 27 passed QC thresholds (Supplementary Table S1).

The strength exposure causally affected 20 traits. The strength phenotypes as outcomes were causally affected by 83 traits (Table 3). The traits associated with the strength phenotypes represent several groups: microbiota, inflammatory cytokines and interleukins, lipid metabolites, serum metabolites, osteoporosis, osteoarthritis and bone density, rheumatoid arthritis, coronary artery disease, gastrointestinal diseases and cancers, and anatomical brain structures.

Table 3. Associations of muscle strength with health-related traits.

Exposure	**Effect**	**Outcome**	**OR (95% CI), Beta**: (95% CI)	**P-value significance**	**Reference PMID**
Diseases					
Left & Right HGS	Protective (high strength reduces risk)	Coronary artery disease	0.737 (0.601 - 0.904); 0.681 (0.558 to 0.832)	3.353E-03; 1.702E-05	37900136
Left & Right HGS	Reduces risk	Myocardial infarction	0.631 (0.515 - 0.765); 0.634 (0.518 - 0.776)	2.575E-06; 9.069E-06	37900136
Low hand grip strength	Causally positive	Gastroesophageal reflux disease (GERD)	1.2358 (1.052-1.451); 1.272 (1.0684 - 1.5145)	0.0099; 0.0069	38446595; 39050602
Low hand grip strength	Negatively correlated	Inflammatory bowel disease	0.76 (0.61-0.94)	0.012	39072277

		(IBD)			
Low hand grip strength; Right & Left HGS	Low strength increases risk;	Crohn's disease	0.76 (0.61-0.94); 16.445 (5.585, 48.422); 10.257 (3.396, 30.983)	0.012; 3.70E-07; 3.60E-05	39072277 ; 38638121
Low hand-grip strength & left HGS	Strong adverse effect	Knee osteoarthritis	1.4569 (1.2007-1.7677)	0.0001	37731961
Right HGS	Inverse association	Small vessel stroke	0.639 (0.437, 0.934)	0.021	39450050
Low HGS (60 years and older)	Increases risk	Obstructive sleep apnea	1.19 (1.003, 1.413)	0.0466	40055243
Low hand-grip strength	Increases risk	Hepatocellular carcinoma	2.287 (1.013–5.164)	0.047	38860158
Right & Left HGS	Increases risk	Gestational diabetes mellitus	1.4194 (1.0773, 1.8701) & 1.6064 (1.2829, 2.0115)	0.0128 & < 0.001	39911357
Right & Left HGS	Protective	Frailty	0.800 (0.737, 0.869) & 0.788 (0.721,0.862)	0.000 & 0.000	40257716
Right & Left HGS	Low strength increases risk	Rheumatoid arthritis	0.993 (0.990, 0.997) & 0.994 (0.990, 0.998)	1.40E-04 & 0.004	38638121
HGS	Positive relationship	Pancreatic cancer	1.7395 (1.1336 - 2.6693)	0.0113	39050602
Biochemical entities					
Grip strength	Negative effect	Platelet-derived growth factor BB	0.756 (0.616, 0.928)	0.007	38820838
HGS	Decreased HGS elevates	IGF-1 levels	1.243 (1.026, 1.505)	0.027	39507055
HGS	Decreased HGS elevates	IGF - 1 R levels	1.454 (1.108, 1.909)	0.007	39507055
Other traits					
Hand grip strength	Increases	Lumbar spine bone mineral density	Beta: 0.288 (0.079 - 0.497)	0.007	36578964
Left & Right HGS	Positive association	Pulmonary function –forced vital capacity (FVC)	1.464 (1.385-1.548); 1.519 (1.418-1.627)	2.83E-41; 8.96E-33	37990169
Left & Right HGS	Positive association	Pulmonary function- Expiratory volume in 1 second (FEV1)	1.419 (1.340-1.502); 1.486 (1.390-1.589)	3.19E-33; 3.19E-31	37990169
HGS	Positive association	Cognitive function	Beta 0.18 (0.08, 0.29)	<0.001	40499039
Diseases					
Hepatocellular carcinoma	Negative association	Grip strength	Beta − 0.0053 (− 0.008 - − 0.0025)	0.0002	38321551
Rheumatoid arthritis	Reduces HGS	Low HGS; Left & Right HGS; Left HGS	1.042 (1.013-1.072); Beta: −2.06 (−2.372, −1.748); Beta: −2.421 (−2.807, −2.035); Beta -0.021 (-0.029, -0.014)	0.0049; 2.8E-38; 1.4E-34; 4.97E-08	37650009; 38638121; 39591827
Systemic lupus erythematosus	Decreases strength	Right HGS	Beta -0.004 (-0.006, -0.002)	0.0004	39591827
Systemic lupus erythematosus	Decreases strength	Left HGS	Beta -0.003 (-0.006, 0)	0.05	39591827

Psoriasis	Decreases strength	Right HGS	Beta -0.004 (-0.008, -0.0001)	0.043	39591827
Irritable bowel disorder	Decreases strength	Left HGS	Beta -0.004 (-0.008, 0.00046)	0.027	39591827
Irritable bowel disorder	Decreases strength	Right HGS	Beta -0.005 (-0.009, -0.001)	0.008	39591827
Akylosing spondylitis	Increases strength	Left HGS	Beta 0.003 (0.00036, 0.005)	0.024	39591827
Akylosing spondylitis	Increases strength	Right HGS	Beta 0.003 (0.000389, 0.005)	0.022	39591827
Gastroesophageal reflux disease	Decreases strength	Grip strength	0.1968 (0.143 - 0.2506)	< 0.0001	39050602
Esophageal cancer	Decreases strength	Grip strength	0.0386 (0.0157 - 0.0616)	0.0009	39050602
Biochemical entities cytokines					
Interleukin-10 (IL-10)	Increases strength	Hand grip strength	1.046 (1.002–1.093); 1.05 (1.01, 1.10)	0.042; 0.028	39122802; 38505750
Interleukin-5 levels		Grip strength	1.028(1.003, 1.055)	0.029	38820838
Interleukin-16 (IL16)	Decreases	Grip strength	0.971 (0.948-0.995)	0.020	38820838
Interleukin-12 (IL12); Interleukin-12p70 levels	Increases	Grip strength	1.003 (1.000-1.066); 1.033 (1.00,1.066)	0.042; 0.049	38505750; 38820838
Vascular endothelial growth factor (VEGF)	Positive association; Increases strength	Grip strength	1.028 (1.003-1.005); 1.02 (1.00, 1.05); 1.056 (1.02453, 1.08956); 1.024 (1.001–1.047)	0.029; 0.042 ; 0.00046; 0.038	38820838; 38505750; 39193020; 39122802
IGF –1 levels	Decreased levels increases HGS , protective	Low HGS; Grip strength;	0.936 (0.892, 0.983); 1.04 (1.02–1.06);	0.008; 1.62E-05	39507055; 38267164
C reactive protein (CRP)	Negative association	Grip strength	0.98 (0.96 - 0.99)	0.022	38267164
Fasting insulin	Positive association	Grip strength	1.09 (1.01–1.17)	0.024	38267164
Plasma cortisol concentration	Negative association	Hand grip strength	Beta: −0.032 (−0.044, −0.02)	0.0003	34850018
SGLT1 inhibition	Negative association	Low HGS	Beta -0.287 (-0.532, -0.041)	0.022	39474649
HP protein	Negative association	Grip strength	0.96 (0.94–0.98)	4.2E-05	38644354
HLA-DRA	Positive association	Grip strength	1.13 (1.07–1.2)	1.8E-05	38644354
MAP3K4	Negative association	Grip strength	0.82 (0.75–0.9)	2.1E-05	38644354
Sterol ester (27:1/16:1) levels	Positive association	total muscle strength	1.050(1.002-1.101)	0.039182214	39285470
Ceramide (d40:2) levels	Positive association	total muscle strength	1.041(1.004-1.080)	0.030985492	39285470
Phosphatidylcholine (16:1_18:2) levels	Positive association	total muscle strength	1.049(1.010-1.089)	0.012315583	39285470

Phosphatidylinositol (16:0_18:2) levels	Negative association	total muscle strength	0.959(0.922-0.997)	0.033873126	39285470
Sphingomyelin (d42:2) levels	Negative association	total muscle strength	0.958(0.919-0.998)	0.040484836	39285470
Triacylglycerol (46:1) levels	Positive association	total muscle strength	1.072(1.011-1.136)	0.019856423	39285470
Triacylglycerol (56:8) levels	Positive association	total muscle strength	1.049(1.000-1.100)	0.04947323	39285470
Sterol ester (27:1/17:0) levels	Positive association	male muscle strength	1.112(1.012-1.221)	0.026422376	39285470
Phosphatidylcholine (16:1_18:2) levels	Positive association	male muscle strength	1.053(1.001-1.107)	0.045084792	39285470
Phosphatidylcholine (O-17:0_15:0) levels	Positive association	male muscle strength	1.108(1.018-1.207)	0.018327491	39285470
Sterol ester (27:1/16:1) levels	Positive association	female muscle strength	1.072(1.006-1.143)	0.031056224	39285470
Phosphatidylcholine (18:0_0:0) levels	Positive association	female muscle strength	1.079(1.015-1.147)	0.014174202	39285470
Phosphatidylcholine (18:1_18:2) levels	Negative association	female muscle strength	0.965(0.935-0.995)	0.023257509	39285470
Phosphatidylcholine (16:1_18:2) levels	Positive association	female muscle strength	1.052(1.005-1.101)	0.029589062	39285470
Phosphatidylethanolamine (18:0_18:2) levels	Negative association	female muscle strength	0.970(0.942-0.999)	0.043839429	39285470
Phosphatidylinositol (16:0_18:2) levels	Negative association	female muscle strength	0.952(0.911-0.994)	0.024480064	39285470
Sphingomyelin (d42:2) levels	Negative association	female muscle strength	0.950(0.913-0.988)	0.010734849	39285470
Triacylglycerol (46:1) levels	Positive association	female muscle strength	1.089(1.014-1.169)	0.018694226	39285470
Triacylglycerol (50:5) levels	Positive association	female muscle strength	1.080(1.011-1.153)	0.021834934	39285470
Triacylglycerol (56:8) levels	Positive association	female muscle strength	1.066(1.012-1.122)	0.016145053	39285470
Microbiota					
Family Bifidobacteriaceae	Positive relationship	Left & Right HGS	Beta: 0.035 (0.011, 0.06); Beta: 0.028 (0.004, 0.052)	0.005; 0.024	37664120
Genus Sellimonas	Positive relationship	Left & Right HGS	Beta: 0.013 (0.005, 0.021); Beta: 0.013 (0.004, 0.022)	0.002; 0.003	37664120
Genus Parabacteroides	Positive relationship	Left & Right HGS	Beta: 0.029 (0.007, 0.051); Beta: 0.03 (0.008, 0.051)	0.011; 0.006	37664120
Genus Bifidobacterium	Positive relationship	Left & Right HGS	Beta: 0.035 (0.013, 0.058); Beta: 0.028 (0.006, 0.05)	< 0.001; 0.012	37664120
Order Bifidobacteriales	Positive relationship	Left & Right HGS	Beta: 0.035 (0.011, 0.06); Beta: 0.028 (0.004, 0.052)	0.005; 0.024	37664120
Class Actinobacteria	Positive relationship	Right HGS	Beta: 0.026 (0.003, 0.05)	0.0002	37664120
Genus Alloprevotella	Positive relationship	Right HGS	Beta: 0.012 (0.002, 0.022)	0.021	37664120

Genus Eisenbergiella	Positive relationship	Right HGS	Beta: 0.012 (0.000, 0.025)	0.049	37664120
Phylum Actinobacteria	Positive relationship	Right HGS	Beta: 0.03 (0.003, 0.056)	0.027	37664120
Genus Paraprevotella	Negative relationship	Right HGS	Beta: -0.014 (−0.023, -0.004)	0.007	37664120
Genus Prevotella9	Negative relationship	Right HGS	Beta: -0.014 (−0.027, 0.000)	0.042	37664120
Genus Eubacterium nodatum group	Positive relationship	Left HGS	Beta: 0.01 (0.002, 0.017)	0.013	37664120
Streptococcaceae	Positive relationship	Grip strength	1.104 (1.006–1.211)	3.72E-02	38995073
Intestinibacter	Positive relationship	Grip strength	1.136 (1.042–1.239)	3.67E-03	38995073
Paraprevotella	Negative relationship	Grip strength	0.932 (0.881–0.986)	1.50E-02	38995073
Ruminococcaceae UCG009	Positive relationship	Grip strength	1.085 (1.004–1.172)	3.95E-02	38995073
Sutterella	Negative relationship	Grip strength	0.85 (0.733–0.986)	3.24E-02	38995073
betaine	Positive relationship	Grip strength	2.473 (1.648–3.711)	1.23E-05	38995073
glycine	Positive relationship	Grip strength	0.752 (0.630–0.897)	1.57E-03	38995073
hippurate	Positive relationship	Grip strength	1.271 (1.026–1.575)	2.83E-02	38995073
p-cresol sulfate	Positive relationship	Grip strength	1.166 (1.003–1.356)	4.62E-02	38995073
pyruvate	Positive relationship	Grip strength	1.302 (1.031–1.645)	2.67E-02	38995073
Behavioral traits					
Educational attainment	Increases strength	Left & Right HGS	Beta 0.042 (0.013, 0.071); Beta 0.05 (0.022, 0.079)	0.0009	39507653
Smoking initiation	Positive association	Grip strength	1.03 (1.01–1.06)	0.01	38267164
Cigarette smoking	Reduces strength	Grip strength	Beta -0.63 (-1.13, -0.13)	0.01	40194871
Alcohol consumption	Reduces strength	Grip strength	Beta -1.15 (-2.09, -0.10)	0.02	40194871
Other traits					
Brain cortical thickness of temporal pole	Positive relationship	Right HGS	Beta: 0.1596 (0.1349, 0.1843)	<0.0001	40014117
Brain cortical thickness of pars triangularis	Positive relationship	Left HGS	Beta: 0.3251 (0.2339, 0.4163)	<0.0001	40014117
Heel-Bone mineral density (BMD)	Increases	Left HGS	0.017 (0.007–0.027)	0.001	35780076
Lumbar spine bone mineral density	Increases	Left & Right HGS	Beta: 0.358; Beta: 0.318	3.97E-04; 0.001	35780076
Reduced glomerular filtration rate adjusted to creatine GFRcrea and to cysteine GFRcys	Inverse association	HGS	0.67 (0.58 - 0.78); 0.5 (0.37 - 0.68)	9.17E-08	38267164
IDP dMRI ProbtrackX OD str l	Found significant impact on	Left HGS	-0.038 (-0.057, -0.01)	9.25E-05	39535371
IDP dMRI TBSS L1 Anterior limb of internal capsule R	Found significant impact on	Left HGS	-0.069 (-0.109, -0.03)	0.000496	39535371
NET100 0160	Found	Left HGS	0.063 (0.03,	0.000162	39535371

	significant impact on		0.095)		
IDP dMRI TBSS OD Posterior limb of internal capsule L	Found significant impact on	Left HGS	-0.059 (-0.091, -0.028)	0.000215	39535371
NET100 1438	Found significant impact on	Left HGS	0.066 (0.034, 0.097)	5.72E-05	39535371
IDP dMRI TBSS L2 Middle cerebellar peduncle	Found significant impact on	Left HGS	0.062 (0.028, 0.097)	0.00044	39535371
volume CC Posterior	Found significant impact on	Left HGS	-0.066 (-0.1, -0.031)	0.000237	39535371

HGS – hand grip strength; IGF-1 - Insulin-like growth factor 1 ; IGF-1 R - Insulin-like growth factor 1 receptor; IL-10 - Interleukin 10; IL-16 - Interleukin 16; IL-12 - Interleukin 12; GERD - Gastroesophageal reflux disease; MAP3K3 - Mitogen-activated protein kinase kinase kinase 3; CRP – C reactive protein; IBD – inflammatory bowel disease; BMD – bone mineral density; FEV1 - Forced expiratory volume in the first second; FVC - Forced vital capacity; HLA-DRA - Major histocompatibility complex, class II, DR alpha; HP -haptoglobin; SGLT-1 - Sodium-glucose cotransporter 1; GFR crea - Glomerular filtration rate adjusted for creatinine; GFRcys - Glomerular filtration rate adjusted for cystatin C

3.3.2.1 Causal associations between muscle strength phenotypes and biochemically active elements, metabolic factors and microbiota.

A group of authors tested a causal relationship between 27 lipid metabolites, mainly phosphatidylcholine, phosphatidylethanolamine, ceramide (d40:1 and d40:2), triacylglycerol, sphingomyelin, and sterol ester, which are associated with the risk of sarcopenia (Liu et al., 2024). Ceramide (d40:1), ceramide (d40:2), and sterol ester are risk factors for decreased muscle mass and strength. A positive protective causal relationship between phosphatidylcholine lipid Sphingomyelin (d42:2) and total muscle strength and female muscle strength was shown (Table 3).

Genetic predisposition to increasing levels of interleukin-10 (IL-10), IL-12, and IL-5 was shown to be causally associated with the increased hand grip strength by several studies, while IL-16 decreased strength (Chen et al., 2024; C. Wang et al., 2024; J. Wang et al., 2024). The Insulin-like growth factor 1 (IGF-1) was found bidirectionally causally associated with grip strength, where genetically predicted elevated levels of IGF-1 increase strength and may have a protective effect against sarcopenia (Liu et al., 2024). Strong evidence, supported by four

studies, exists in favour of a positive causal association between Vascular Endothelial Growth Factor (VEGF) and grip strength (Chen et al., 2024; Sun et al., 2024; C. Wang et al., 2024; J. Wang et al., 2024). Diminishing grip strength in sarcopenia increases Platelet-Derived Growth Factor BB (PDGF-BB), which is usually elevated in the context of muscle damage and repair (Chen et al., 2024). Fasting insulin increases grip strength (P. Yan et al., 2024). Evidence supports the negative impact of elevated levels of C reactive protein (CRP) on diminishing handgrip strength (P. Yan et al., 2024). Plasma cortisol concentration also was found causally negatively impacting hand grip strength (Katsuhara et al., 2022). The SGLT1 inhibition, HP protein, HLA-DRA, MAP3K4 were shown causally affecting grip strength (B.-B. Huang et al., 2024; Yin et al., 2024).

Several studies have reported the impacts of gut microbiota species and metabolites on strength (Shuai Chen et al., 2023; Zhang et al., 2024). The 21 gut microbiota-derived metabolites were identified as being associated with the risk of sarcopenia. Suggestive associations of Streptococcaceae, Intestinibacter, Paraprevotella, Ruminococcaceae UCG009, and Sutterella with grip strength were indicated. Another study found that a significant number of microorganisms from the order Bifidobacteriales were associated with increased strength, suggesting that the Family Bifidobacteriaceae and Order Bifidobacteriales are protective factors against sarcopenia.

3.3.2.2 Causal associations between muscle strength phenotypes and diseases.

Genetically predicted higher handgrip strength in sarcopenia reduces the risk of cardiovascular diseases: coronary artery disease, myocardial infarction, and small vessel stroke. Low hand grip strength increases the risk of gastroesophageal reflux disease (GERD), while GERD and esophageal cancer also decrease grip strength (Hu et al., 2024; T. Yang et al., 2024). Low HGS increases risk of inflammatory bowel disease (IBD), Crohn's disease,

obstructive sleep apnea (OSA), and hepatocellular carcinoma (HCC) (Cao et al., 2024; Chen and He, 2024; Sun et al., 2025, 2024). Hand grip strength causally affects gestational diabetes mellitus, frailty, rheumatoid arthritis, pancreatic cancer (Huang et al., 2025; Liu et al., 2025). Left and right hand grip strength has protective effect on coronary artery disease and reduces risk of myocardial infarction while right hand grip strength reduces risk of small vessel stroke (X. Liu et al., 2023; Meng et al., 2024). Strong evidence, supported by three studies, exists that rheumatoid arthritis reduces hand grip strength (Chen and He, 2024; Su et al., 2023; Q. Wang et al., 2025). Inflammatory bowel disease, systemic lupus erythematosus, psoriasis, and hepatocellular carcinoma are associated with reduced hand grip strength. Interestingly, evidence suggests that genetically predicted ankylosing spondylitis has a positive causal effect on increased strength in both hands (Q. Wang et al., 2025). Osteoporosis related bone mineral density in heel bone and lumbar spine bone increases handgrip strength (Ma et al., 2022). On the other hand, low handgrip strength is a risk factor for knee osteoarthritis (L. Zhang et al., 2023).

Hand grip strength affects cognitive function (Sha et al., 2025b). Effects of several brain areas and gene expression in these areas have been reported on hand grip strength (Lei et al., 2025). These effects rely on a very small number of instrumental variables. However, brain cortical thickness in temporal pole and pars triangularis was positively correlated with the right-hand and left-hand grip strength respectively (Zhan et al., 2025). Genetically predicted reduced glomerular filtration rate adjusted to creatine GFRcrea, GFRsys were associated with higher odds of hand grip strength (P. Yan et al., 2024). Positive causal association exists between higher strength and improved pulmonary function (X. Zhao et al., 2023).

3.3.2.3. Behavioural phenotypes and muscle strength.

Recent MR analyses have identified several behavioural phenotypes that exert causal effects on muscle strength, particularly grip strength – a widely used proxy for overall muscular function and a diagnostic criterion for sarcopenia. Educational attainment has been shown to have a positive causal association with grip strength, suggesting that higher levels of education may confer protective effects against age-related muscle decline, potentially through healthier lifestyle choices and improved health literacy (Zhang et al., 2024). In contrast, cigarette smoking and alcohol consumption are causally linked to reduced grip strength, indicating their potential role as modifiable risk factors for sarcopenia (Sha et al., 2025a). Interestingly, the binary phenotype of smoking initiation (i.e., ever smoked vs. never smoked) was also positively associated with grip strength in one study, which may reflect complex gene–environment interactions or compensatory behavioural patterns in certain populations (P. Yan et al., 2024). These findings underscore the importance of behavioural traits in shaping musculoskeletal health and highlight the potential for targeted public health interventions aimed at mitigating sarcopenia risk through behavioural modification and education-based strategies.

3.3.3. Causal associations between muscle mass phenotypes and other traits.

Causal relationships between the muscle mass related phenotypes and other traits were reported in 60 studies, 41 of which passed QC thresholds (Supplementary Table S1). When considered as exposures, muscle mass phenotypes demonstrated causal effects on 45 distinct traits. Conversely, when analysed as outcomes, these phenotypes were found to be causally influenced by 85 traits (Table 4). The phenotypic traits both affected by and causally affecting muscle mass and body composition phenotypes can be broadly categorized into several major biological and clinical domains: gut microbiota, inflammatory cytokines and

interleukins, lipid profiles, cardiovascular diseases, gastrointestinal diseases, various stroke types, anatomical brain structure, bone and joint pathologies, sleep-related disorders and cancer.

Table 4. Associations of mass phenotypes with health-related traits.

Exposure	Effect	Outcome	OR (95% CI)	P-value significance	Reference
Diseases					
ALM	Higher ALM reduces risk	Inflammatory bowel disease (IBD)	0.916 (0.853, 0.984); 0.87 (0.89, 0.95)	0.017; 0.002	38022582; 39072277
ALM	Higher ALM reduces risk	Ulcerative colitis	0.888 (0.813, 0.971); 0.84 (0.76, 0.93); 0.921 (0.852, 0.996)	0.009; 0.029; 0.039	38022582; 39072277; 39591827
ALM	Higher ALM reduces risk	Crohn's disease	0.905 (0.820, 0.999); 0.87 (0.77, 0.99)	0.049; 0.001	38022582; 39072277
ALM	Low ALM increases risk	Knee osteoarthritis	1.15 (1.05, 1.183); 1.104 (1.041, 1.171)	0.0003; 0.001	37731961; 37689698
ALM	Increase in ALM increases risk	Benign prostatic hyperplasia	1.126 (1.032, 1.228)	0.008	38027182
ALM	High ALM has protective effect	Risk of ischemic stroke	0.925 (0.879, 0.974)	0.003	38757378
ALM	High ALM reduces risk	Risk of coronary heart disease	0.835 (0.790, 0.882); 0.848 (0.804, 0.894); 1.20 (1.13, 1.27)	1.00E-10; 8.2E-10 ; 1.39E-10	37447340; 37900136; 37403750
ALM	Increased ALM protective of development	Levodopa induced dyskinesia (Parkinson's)	0.597 (0.440, 0.810)	0.0111	39198455
ALM	Low ALM increases risk	Hypertrophic osteoarthropathy	1.151 (1.071, 1.237)	<0.001	37689698
ALM	Low ALM increases risk	total knee replacement	1.114 (1.007, 1.232)	<0.001	37689698
ALM	Low ALM increases risk	total hip replacement	1.203 (1.099, 1.316)	<0.001	37689698
ALM	High ALM reduces risk	Myocardial infarction	0.810 (0.694, 0.901); 1.18 (1.11, 1.25)	1.27E-13; 4.08E-08	37900136; 37403750
ALM	High ALM reduces risk	Small vessel stroke	0.8 (0.73, 0.89); 1.165 (1.058, 1.284)	< 0.001; 0.002	38762444; 39450050
ALM	High ALM reduces risk	Alzheimer's disease	0.9 (0.85, 0.96); 1.10	0.001; 5.10E-05	38762444; 37403750

			(1.05, 1.15)		
ALM	ALM increases, the risk of HCC decreases	Hepatocellular carcinoma	0.703, (0.524, 0.943)	0.019	38860158
ALM	High ALM reduces risk	Stroke	0.931 (0.89, 0.975); 0.93 (0.89, 0.97)	2.22E-03; 0.002	37900136; 38762444
ALM	Reduced ALM increases risk	Hypertension	0.84 (0.73, 0.96); 1.12 (1.05, 1.20)	0.013; 4.13E-04	38753690; 37403750
ALM	High ALM reduces risk	Cardioembolic stroke	0.790 (0.703, 0.888)	<0.001	39450050
ALM	Protective	Rotator cuff tears	0.895 (0.758, 0.966)	<0.001	39534255
ALM	Increase in ALM predisposes to	Systemic lupus erythematosus	1.184 (1.018, 1.378)	0.029	39591827
ALM; Left & Right leg FFM	Increase in ALM in men predisposes to	Rheumatoid arthritis in males; Rheumatoid arthritis	1.112 (1.012, 1.221); 1.005 (1.003, 1.007); 1.005 (1.001, 1.009)	0.027; 1.90E-04; 2.00E-04	39591827; 38638121
ALM	ALM decrease in women increases risk of psoriasis	Risk of psoriasis in women	0.890 (0.798, 0.993)	0.037	39591827
ALM	Protective ; lower ALM higher risk of T2DM	Diabetes mellitus; risk of T2DM	0.71 (0.54, 0.94); 1.20 (1.10, 1.32)	0.014; 6.42E-05	38753690; 37403750
ALM	Positive relationship	Obstructive sleep apnea	1.133 (1.050, 1.222)	0.001	40055243
ALM	Positive relationship	Gestational diabetes mellitus	1.2182 (1.1397, 1.3021)	<0.0001	39911357
ALM	Negative relationship	GERD	0.8598 (0.8220 - 0.8992); 0.8612 (0.8263, 0.8975)	< 0.0001; 1.00E-12	39050602; 38446595
ALM	Positive relationship	Gastric cancer	1.13 (1.0344 - 1.2343)	0.0067	39050602
ALM	Negative relationship	Colorectal cancer	0.7805 (0.6096 - 0.9992)	0.0493	39050602
ALM	Negative relationship	NAFLD	0.8124 (0.7342 - 0.899); 1.33 (1.08, 1.64)	< 0.0001; 0.006	39050602; 37403750
ALM	Negative relationship	COPD	0.803 (0.680, 0.949)	0.01	37457977
ALM	Positive relationship	FEV1/FVC	1.58 (1.003, 1.115)	0.038	37457977
Biochemical entities					
ALM	Decreases	IGF 1 levels	0.902 (0.877, 0.927)	<0.000	39507055

Whole body fat free mass	Decreases	IGF 1 levels	0.903 (0.859, 0.343)	<0.000	39507055
ALM	Increases	High expression of IGFBP-1	1.314 (1.003, 1.722)	0.047	39507055
ALM	Negative relationship	HDL-C	0.98 (0.97, 0.99); 0.068(0.014)	0.003; <0.001;	39214262; 38595990
ALM	Negative relationship	LDL-C	0.94 (0.93, 0.95); No association	< 0.001;	39214262; 38595990
ALM	Negative relationship	CCL27	0.892 (0.799,0.995)	0.04	38820838
ALM	Positive relationship	NGF	1.143 (1.019, 1.282)	0.022	38820838
ALM	Negative relationship	TNFSF10	0.901 (0.835-0.972)	0.007	38820838
ALM	Negative relationship	VLDL	-0.081(0.017)	<0.001	38595990
ALM	Negative relationship	Triglycerides	0.93(0.91–0.95)	<0.001	39214262
ALM	Negative relationship	Total cholesterol	0.92(0.91–0.93)	<0.001	39214262
Other phenotypes					
ALM	inverse association	Brain cortical thickness of lateral occipital	Beta -0.0079 (-0.0117, -0.0041)	<0.0001	40014117
ALM	Positive relationship	Brain cortical thickness of pars opercularis	Beta 0.008 (0.0042, 0.0117)	<0.0001	40014117
ALM	Low ALM reduces performance	Cognitive performance	Beta 0.049 (0.032, 0.066); Beta 0.07(SE 0.01)	<0.001; <0.001	39240885; 38555389
ALM	Positive realationship	Cognitive function	Beta 0.09 (0.07, 0.12)	<0.001	40499039
Diseases					
Ulcerative colitis	Inverse relationship	ALM	0.994 (0.9876, 0.9998)	0.044	39072277
Crohn’s disease	Negative correlation	ALM	0.993 (0.988, 0.998); 0.989 (0.983, 0.996); 0.991 (0.986, 0.997); Beta: -0.01 (-0.015, -0.005)	0.006; <0.001; 0.002; 0.00031	39072277; 38165870; 38022582; 39591827
Crohn’s disease	Negative correlation	Whole body FFMM; Left & Right leg FFM; Left & Right arm FFM	Beta -0.005(-0.007, -0.003); −0.006 (−0.010, −0.002); −0.006 (−0.010, −0.002); −0.005 (−0.009, −0.001); −0.005 (−0.009, −0.001)	<0.005; 1.80E-04; 2.00E-04; 0.005; 0.001	38638121
IBD	Negative association	ALM	0.990 (0.984, 0.997); 0.988	0.004; 0.001; 6.94E-04	38165807; 38022582; 39591827

			(0.981, 0.995); Beta: -0.010 (-0.015, -0.004)		
Rheumatoid arthritis	Negative association	ALM	0.979 (0.964, 0.995); Beta: -0.019 (-0.032, -0.006)	<0.0001; 4.00E-03	37650009; 39591827
Rheumatoid arthritis	Negative correlation	Whole body FFMM; Left & Right leg FFM; Left & Right arm FFM	−0.829 (−1.125, −0.533); −0.666 (−0.944, −0.388); −0.788 (−1.100, −0.476); −0.63 (−0.899, −0.361); −0.736 (−0.999, −0.473)	3.60E-08; 2.60E-06; 7.20E-07; 4.40E-06; 4.40E-08	38638121
Attention deficit hyperactivity disorder ADHD	intricate relationship absence of clear link	ALM	1.020 (1.012, 1.029)	<0.001	40143727
Psoriasis	Decreases	ALM	Beta -0.012 (-0.17, -0.007)	3.52E-06	39591827
GERD	Negative relationship	ALM	-0.0812 (−0.1224 - -0.04)	0.0001	39050602
Liver cancer	Causal relationship	ALM	9.7125 (1.5 - 17.9247)	0.0204	39050602
Behavioral phenotypes					
Educational attainment	Increases	ALM	Beta 0.25 (0.19, 0.31)	<0.000	39507653
Cigarette smoking	Increases risk	sarcopenia	2.51 (1.26, 5.01)	0.001	40194871
Cigarette smoking	Decreases mass	ALM	Beta -0.22 (-0.44, -0.01)	0.04	40194871
Cognitive performance	Low performance reduces ALM	ALM	0.033 (0.018, 0.048); 0.06(0.02)	< 0.001 ; 0.000	39240885; 38555389
Biochemical entities					
TNF-β	Negative correlation	ALM	0.04255 (0.02838, 0.05672)	3.96E-09	39193020
IGF-1	Positive relationship: elevated levels increases ALM	ALM	1.22 (1.17, 1.27); 1.125 (1.070, 1.182)	1.30E-22; <0.000	38267164; 39507055
Plasma cortisol concentration	Increased cortisol levels decrease ALM	Whole body ALM, ALM	Beta −0.032 (−0.046, −0.017)	0.004	34850018
macrophage colony-stimulating factor	Higher levels associated with higher	ALM	1.01 (1.00, 1.02); 1.01 (1.003, 1.017)	0.003; 0.003	38505750; 39122802

	risk of lower ALM				
IL16	Negative association	Adjusted ALM, ALM	0.991 (0.984, 0.998);0.990 (0.980, 1.00)	1.08E-02; 0.049	38556722; 38820838
Interleukin-1 beta	Positive association	ALM	1.027 *1.011, 1.042)	0.001	38820838
Hepatocyte growth factor	Positive association	ALM	1.020 (1.005, 1.035)	0.009	38820838
Platelet derived growth factor BB	Positive association	Adjusted ALM	1.016 (1.001, 1.030)	3.72E-02	38556722
interferon gamma induced protein 10 IP-10	Inceases ALM	ALM	1.01 (1.00, 1.019); 1.014 (1.003, 1.025)	0.042; 0.01	39122802; 38820838
Pentadecanoate (15:0)	causally linked through sugar, galactose, fructose, mannose and biotin metabolism and carnitine synthesis; Reduces ALM	ALM	Beta -0.25(-0.361, -0.14); 0.78 (0.7–0.87)	8.90E-06; 8.90E-06;	38622574;38415056
1-arachidonoylglycerophosphocholine	Increases	ALM	1.16 (1.09–1.23)	1.75E-06	38415056
Androsterone sulfate	Decreases	ALM	Beta -0.039 (-0.06, -0.018)	2.35E-04	38622574
Elevated IGF-1 levels	Increases	Whole body fat free mass	1.076 (1.047, 1.106)	<0.000	39507055
Glucosamine	Increases	ALM; Whole body fat free mass	1.15 (1.05, 1.25); 1.15 (1.05, 1.25)	1.97E-03; 1.97E-03	39764251
High-density lipoprotein cholesterol (HDL-C),	Inverse relationship	ALM	0.95(0.94–0.96)	<0.001	39214262
Low-density lipoprotein cholesterol (LDL-C),	Inverse relationship	ALM	0.94(0.92–0.96)	<0.001	39214262
Triglycerides (TG)	Inverse relationship	ALM	0.96(0.95–0.98)	<0.001	39214262
Genetically proxied inhibition of PCSK9	Negative relationship	ALM	-0.04 (-0.068, -0.012)	0.005	39254080
Circulating PSCK9 levels	Negative relationship	ALM	-0.019 (-0.033, -0.005)	0.006	39254080
Genetically proxied inhibition of PCSK9 gene expression in the liver	Negative relationship	ALM	-0.013 (-0.035, 0.009)	0.25	39254080
Blood levels of ferritin	Negative relationship	ALM	Beta -0.051 (-0.072, -0.031)	7.33E-07	38649459
Isovalerylcarnitine	Negative relationship	ALM	Beta -0.45 (-0.81, -0.09)	0.015	37764748
Docosapentaenoate	Negative relationship	ALM	Beta -0.45kg (0.08,0.81)	0.016	37764748
Ceramide (d40:1) levels	Positive relationship	total muscle mass	1.015(1.002-1.029)	0.028055338	39285470

Ceramide (d40:2) levels	Positive relationship	total muscle mass	1.015(1.005-1.025)	0.002607166	39285470
Phosphatidylethanolamine (18:1_0:0) levels	Negative relationship	total muscle mass	0.963(0.940-0.987)	0.002697054	39285470
Phosphatidylcholine (16:0_17:1) levels	Positive relationship	total muscle mass	1.024(1.004-1.044)	0.020284237	39285470
Phosphatidylcholine (16:0_20:4) levels	Positive relationship	total muscle mass	1.014(1.002-1.025)	0.018551071	39285470
Phosphatidylcholine (18:0_18:2) levels	Negative relationship	total muscle mass	0.984(0.970-0.999)	0.031895996	39285470
Phosphatidylcholine (O-16:1_20:3) levels	Negative relationship	total muscle mass	0.982(0.970-0.994)	0.00338654	39285470
Phosphatidylinositol (18:0_18:1) levels	Positive relationship	total muscle mass	1.018(1.000-1.036)	0.044893385	39285470
Triacylglycerol (53:3) levels	Negative relationship	total muscle mass	0.977(0.955-1.000)	0.046586578	39285470
Phosphatidylcholine (20:4_0:0) levels	Positive relationship	female muscle mass	1.017(1.001-1.033)	0.040428354	39285470
Phosphatidylethanolamine (18:1_0:0) levels	Negative relationship	female muscle mass	0.971(0.952-0.990)	0.003308281	39285470
Phosphatidylcholine (16:0_18:1) levels	Negative relationship	female muscle mass	0.966(0.939-0.993)	0.014727679	39285470
Phosphatidylcholine (16:0_20:4) levels	Positive relationship	female muscle mass	1.014(1.002-1.027)	0.028037655	39285470
Phosphatidylcholine (17:0_18:1) levels	Negative relationship	female muscle mass	0.971(0.954-0.987)	0.000517944	39285470
Phosphatidylcholine (O-16:1_20:3) levels	Negative relationship	female muscle mass	0.980(0.964-0.997)	0.019240351	39285470
Phosphatidylinositol (18:0_18:1) levels	Positive relationship	female muscle mass	1.021(1.001-1.041)	0.03582864	39285470
Sphingomyelin (d32:1) levels	Positive relationship	female muscle mass	1.014(1.002-1.026)	0.025412404	39285470
Sphingomyelin (d38:1) levels	Positive relationship	female muscle mass	1.016(1.001-1.031)	0.039365849	39285470
Sphingomyelin (d40:2) levels	Positive relationship	female muscle mass	1.020(1.001-1.039)	0.040335365	39285470
Triacylglycerol (52:4) levels	Negative relationship	female muscle mass	0.971(0.949-0.995)	0.01644189	39285470
Sterol ester (27:1/17:1) levels	Negative relationship	male muscle mass	0.966(0.934-0.999)	0.04444191	39285470
Phosphatidylethanolamine (18:1_0:0) levels	Negative relationship	male muscle mass	0.954(0.922-0.987)	0.006474495	39285470
Phosphatidylcholine (16:0_20:2) levels	Negative relationship	male muscle mass	0.977(0.959-0.996)	0.017156395	39285470
Phosphatidylcholine (16:0_22:5) levels	Positive relationship	male muscle mass	1.021(1.004-1.039)	0.018376018	39285470
Phosphatidylcholine (18:0_18:2) levels	Negative relationship	male muscle mass	0.978(0.964-0.993)	0.003804999	39285470
Phosphatidylcholine (18:0_20:3) levels	Negative relationship	male muscle mass	0.967(0.942-0.994)	0.015363781	39285470
Phosphatidylcholine (18:2_18:2) levels	Negative relationship	male muscle mass	0.980(0.962-0.997)	0.025502842	39285470
Phosphatidylcholine (O-18:0_16:1) levels	Negative relationship	male muscle mass	0.961(0.940-0.983)	0.000498807	39285470
Phosphatidylethanolamine (O-16:1_18:2) levels	Positive relationship	male muscle mass	1.023(1.001-1.046)	0.042094782	39285470
Phosphatidylethanolamine (O-18:2_18:1) levels	Negative relationship	male muscle mass	0.983(0.968-0.999)	0.035757298	39285470
Triacylglycerol (49:2) levels	Positive relationship	male muscle mass	1.023(1.001-1.046)	0.041956334	39285470

Triacylglycerol (54:6) levels	Negative relationship	male muscle mass	0.969(0.950-0.988)	0.001249687	39285470
Up regulation HP protein	Positive relationship	Higher ALM	0.012 (0.007–0.018)	1.2E-05	38644354
Down regulation HLA-DRA	Decreased sarcopenia risk	Lower ALM	−0.09 (−0.11 - −0.08)	5.4E-36	38644354
Up regulation MAP3K3	Positive relationship	Higher ALM	0.24 (0.21–0.26)	1.8E-94	38644354
MFGE8 in muscle	Decreased sarcopenia risk	Higher ALM	0.09 (0.06–0.11)	6.1E-13	38644354
COL15A1 in muscle	Decreased sarcopenia risk	Higher ALM	−0.07 (−0.10 - −0.04)	3.4E-07	38644354
MFGE8 in blood	Decreased sarcopenia risk	Higher ALM	Beta -0.05 (-0.06, –0.03)	3.8E-09	38644354
COL15A1 in blood	Decreased sarcopenia risk	Higher ALM	−0.05 (−0.06 - −0.03)	1.6E-07	38644354
AURKA in blood	Inverse relationship	ALM	Beta -0.16 (.0.22, -0.09)	2.1E-06	38644354
AURKA in muscle	Inverse relationship	ALM	Beta 0.03 (0.02, 0.05)	5.3E-05	38644354
Catepsin S	Positive relationship	ALM	1.013 (1.002, 1.023)	0.017	40489878
Catepsin E	Positive relationship	ALM	1.012 (1.002 - 1.022)	0.015	40489878
Catepsin F	Negative association	ALM	0.963 (0.931, 0.997)	0.032	40489878
Catepsin B	Negative association	ALM	0.989 (0.978, 1.000)	0.041	40489878
Anatomical and physiological phenotypes					
Brain cortical thickness of BANKSSTS	Inverse relationship	ALM	Beta -0.434 (-0.6514, -0.2165)	<0.0001	40014117
Brain cortical thickness of frontal pole	Positive relationship	ALM	Beta 0.2981 (0.242, 0.355)	<0.0001	40014117
Brain cortical thickness of rostral anterior cingulate	Positive relationship	ALM	Beta 0.2672 (0.2324, 0.302)	<0.0001	40014117
Brain cortical thickness of temporal pole	Positive relationship	ALM	Beta 0.3778 (0.2478, 0.5078)	<0.0001	40014117
Glomerular filtration rate	Inverse relationship	ALM	0.50 (0.37, 0.68)	8.09E-06	38267164
63 regions of brain	Has significant impact on	Total, female and male muscle mass	(Supplementary table S2)	(Supplementary table S2)	39285470
Gut microbiota					
Gut microbe Lachnospiraceae	Increases	ALM	1.031 (1.011, 1.051)	0.002	38384268
Family Bacteroidaceae	Increases	ALM	Beta: 0.041 (0.010–0.071)	0.008	37664120
Genus Bacteroides	Increases	ALM	Beta: 0.041 (0.010–0.071)	0.008	37664120

Genus Lachnospira	Increases	ALM	Beta: 0.037 (0.000–0.073)	0.049	37664120
Genus Phascolarctobacterium	Increases	ALM	Beta: 0.024 (0.002–0.046)	0.031	37664120
Genus Eubacterium fissicatena group	Decreases	ALM	Beta: -0.017 (−0.034–-0.000)	0.044	37664120
Gut microbial synthesis of the short-chain fatty acid	Descreases	ALM	0.09 (0.002, 0.18)	0.04	34472211
class Bacteroidia	Positive relationship	ALM	1.04 (1.01, 1.08)	0.0237	38995073
Family XIII	Positive relationship	ALM	1.06 (1.02, 1.10)	0.0012	38995073
genus Erysiperotrichaceae UCG003	Negative relationship	ALM	0.91 (0.88, 0.95)	1.71E-05	38995073
genus Eubacterium coprostanoligenes group	Positive relationship	ALM	1.03 (1.00, 1.06)	0.0299	38995073
genus Gordonibacter	Positive relationship	ALM	1.02 (1.00, 1.04)	0.0367	38995073
genus Lachnospiraceae NC2004 group	Positive relationship	ALM	1.04 (1.01, 1.07)	0.0022	38995073
genus Oscillospia	Negative relationship	ALM	0.96 (0.93, 0.99)	0.0129	38995073
genus Phascolarctobacterium	Negative relationship	ALM	0.96 (0.93, 0.99)	0.0076	38995073
genus Ruminococcus2	Negative relationship	ALM	0.97 (0.95, 1.00)	0.0286	38995073
order Bacteroidales	Positive relationship	ALM	1.04 (1.01, 1.08)	0.0237	38995073
phylum Firmicutes	Positive relationship	ALM	1.03 (1.00, 1.07)	0.0437	38995073
phylum Lentisphaerae	Negative relationship	ALM	0.98 (0.97, 1.00)	0.0374	38995073
acetylcarnitine	Negative relationship	ALM	0.44 (0.23,0.83)	0.012	38995073
creatine	Positive relationship	ALM	1.37 (1.02, 1.83)	0.0342	38995073
glycine	Positive relationship	ALM	1.24 (1.06, 1.46)	0.0084	38995073
Ketoleucine	Negative relationship	ALM	0.79 (0.64, 0.97)	0.0249	38995073
lysine	Negative relationship	ALM	0.68 (0.5, 0.91)	0.0095	38995073
proline	Positive relationship	ALM	1.11 (1.02, 1.21)	0.0165	38995073
4-hydroxyhippurate	Positive relationship	ALM	1.07 (1.02, 1.12)	0.0029	38995073
betaine	Negative relationship	ALM	0.74 (0.57, 0.96)	0.0237	38995073
deoxycholate	Negative relationship	ALM	0.93 (0.89, 0.98)	0.0038	38995073
glycodeoxycholate	Negative relationship	ALM	0.97 (0.95, 1.00)	0.0319	38995073
hippurate	Negative relationship	ALM	0.93 (0.87, 0.99)	0.0222	38995073

hyodeoxycholate	Positive relationship	ALM	1.02 (1.00, 1.05)	0.0455	38995073
phenylacetylglutamine	Negative relationship	ALM	0.94 (0.89, 0.99)	0.0263	38995073
stachydrine	Positive relationship	ALM	1.05 (1.01, 1.10)	0.0204	38995073
Actinomycetales	Positive relationship	ALM	1.029 (1.005, 1.053)	0.017	37324750
Actinomycetaceae	Positive relationship	ALM	1.029 (1.005, 1.052)	0.016	37324750
Bacteroidaceae	Positive relationship	ALM	1.041 (1.010, 1.073)	0.008	37324750
Porphyromonadaceae	Positive relationship	ALM	1.036 (1.002, 1.071)	0.037	37324750
Prevotellaceae	Positive relationship	ALM	1.034 (1.007, 1.061)	0.012	37324750
Bacteroides	Positive relationship	ALM	1.041 (1.01, 1.073)	0.008	37324750
Marvinbryantia	Positive relationship	ALM	1.0023 (1.000, 1.046)	0.045	37324750
Phascolarctobacterium	Positive relationship	ALM	1.027 (1.001, 1.054)	0.041	37324750
Eubacterium fissicatena	Negative relationship	ALM	0.983 (0.967, 1.100)	0.044	37324750

ALM - appendicular lean mass; FFMM - fat-free muscle mass; IGF-1 - Insulin-like growth factor 1; IL-16 - Interleukin 16; GERD - Gastroesophageal reflux disease; MAP3K3 - Mitogen-activated protein kinase kinase kinase 3; IBD – inflammatory bowel disease; FEV1 - Forced expiratory volume in the first second; FVC - Forced vital capacity; HLA-DRA - Major histocompatibility complex, class II, DR alpha; HP -haptoglobin; T2DM – type 2 diabetes mellitus; NAFLD – non alcoholic fatty liver disease; COPD – chronic obstructive pulmonary disease; TG – triglycerides; TC – total cholesterol; TNFb – tumor necrosis factor beta; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; CCL27 - chemokine also known as cutaneous T cell-attracting chemokine (CTACK); AURKA - Aurora kinase A, IGFPB-1 - growth factor binding protein 1; NGF - nerve growth factor; TNFSF10 - cytokine that belongs to the tumor necrosis factor (TNF) ligand family; VLDL - very-low-density lipoprotein; MFGE8 - milk fat globule EGF and factor V/VIII domain containing; COL15A1 - collagen type XV alpha 1 chain, SCFA – shot chain fatty acids

Notably, causal effects of ALM on various biochemically active elements are less pronounced compared to multiple biochemical entities causally affecting the mass-related phenotypes.

3.3.3.1. Causal associations between muscle mass related phenotypes and inflammatory cytokines and signaling molecules.

The reduction of appendicular lean mass and whole-body fat-free mass in sarcopenia decreases IGF-1 (Liu et al., 2024). Very strong evidence exists linking an increase in IGF-1 levels to an increase in appendicular lean mass and whole-body fat-free mass (Liu et al., 2024; P. Yan et al., 2024). Elevated levels of growth factor binding proteins 3 and 7 (IGFBP-3 and IGFBP-7) were causally linked to the increase in ALM (Liu et al., 2024). A chemokine CXCL10, also known

as interferon gamma-induced protein 10 IP-10, according to two studies, was causally positively linked to ALM (J. Wang et al., 2024; Chen et al., 2024). Study also showed causal effects of ALM on chemokines: negative on CCL27 and TNFSF10 and positive on NGF (Chen et al., 2024). A negative causal correlation was demonstrated between the inflammatory cytokine TNF-β and appendicular lean mass (Sun et al., 2024). Higher levels of the cytokine macrophage colony-stimulating factor (M-CSF), which plays a role in immune system regulation and bone metabolism, have been causally linked to the increased risk of ALM reduction (C. Wang et al., 2024; J. Wang et al., 2024).

Interleukins have been shown to have causal effects on the muscle mass related phenotypes. Higher levels of IL16 causally linked to the reduction of ALM (Chen et al., 2024; Liu et al., 2024). Increased levels of pro-inflammatory cytokine interleukin-1 beta and hepatocyte growth factor (HGF) have been causally linked to increased ALM as well as platelet-derived growth factor (PDGF BB) (Chen et al., 2024; Liu et al., 2024). Glucosamine, classified as an amino sugar, a naturally derived compound that promotes the synthesis of glycosaminoglycans has been shown causally linked to increase of the ALM and whole-body fat-free mass (Kang et al., 2024). Plasma cortisol concentration was shown to have a negative causal effect on the ALM and whole-body lean mass suggesting a possible negative impact of stress on the mass related phenotypes in sarcopenia (Katsuhara et al., 2022). The up-regulation of HP protein, down-regulation of HLA-DRA, up-regulation of MAP3K3 and expression of MFGE8, COL15A1 and AURKA in muscle and blood were shown to reduce sarcopenia risk (Yin et al., 2024). A study to identify potential therapeutic targets for sarcopenia intervention demonstrated positive influence of cathepsin S and E and negative influence of cathepsin F and B on ALM (Hou et al., 2025).

3.3.3.2. Causal associations between muscle mass related phenotypes and lipid metabolites.

Saturated fatty acid Pentadecanoate (15:0) has been causally linked to the reduced ALM in sarcopenia (W. Peng et al., 2024; Qian et al., 2024). Similarly, anabolic androgenic steroids, androsterone sulfate, and phospholipid metabolite 1-arachidonoylglycerophosphocholine are causally linked to the reduced appendicular lean mass (W. Peng et al., 2024; Qian et al., 2024).

A study that related lipid metabolites to sarcopenia traits found that phosphatidylcholine, phosphatidylethanolamine, ceramide, triacylglycerol, sphingomyelin, and sterol ester were associated with the risk of sarcopenia (Liu et al., 2024). Another similar study reported potential druggable protein targets, including MAP3K3, MFGE8, COL15A1, HP, and HLA-DRA, in sarcopenia (Yin et al., 2024). A causal inverse relationship was described between high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low density lipoprotein (VLDL), triglycerides (TG), and ALM (Kirwan et al., 2024). Same bidirectional associations were shown in a study by Huang and colleagues (H. Huang et al., 2024). Genetically proxied inhibition of PCSK9 and circulating PSCK9 levels, blood levels of ferritin and isovalerylcarnitine, docosapentaenoate affects ALM negatively (Chen et al., 2024; H. Jiang et al., 2024; Sha et al., 2023). Multiple lipid metabolates causally affects ALM (Table 4) among which Phosphatidylcholine levels are more negatively affecting total, male and female muscle mass, Sphingomyelin affects female muscle mass positively (Liu et al., 2024).

3.3.3.3. Causal associations between muscle mass related phenotypes and gut microbiota.

Several studies reported effects of gut microbiota on appendicular lean mass and on sarcopenia (Shuai Chen et al., 2023; Lv et al., 2021; Zhang et al., 2024; J. Zhao et al., 2023). Class Bacteroides were found in all these studies indirectly affecting muscle mass. A

Lachnospiraceae group of anaerobic bacteria that play important roles in the gut microbiome was found causally related to the increase in ALM by two studies suggesting its positive impact on sarcopenia (Shuai Chen et al., 2023; Gao et al., 2024). The genus Phascolarctobacterium was found to increase ALM, while the genus Eubacterium fissicatena decreased ALM (Shuai Chen et al., 2023). In it was shown that gut microbial synthesis of the SCFA butyrate (short-chain fatty acid) decreases ALM (Lv et al., 2021). Study found suggestive associations of 12 intestinal bacteria with appendicular lean mass (Table 4) (Zhang et al., 2024). Study found eight bacterial taxa Actinomycetales, Actinomycetaceae, Bacteroidaceae, Porphyromonadaceae, Prevotellaceae, Bacteroides, Marvinbryantia, Phascolarctobacterium and Eubacterium fissicatena group were associated with ALM (J. Zhao et al., 2023).

3.3.3.4. Causal associations between muscle mass related phenotypes and aging-associated diseases.

MR studies show that appendicular lean mass is causally linked to the risk of gastrointestinal and neurological diseases as well as risks of various types of osteoarthritis, diabetes, and hypertension. Strong evidence exists that higher ALM reduces the risk of inflammatory bowel disease (IBD) and Crohn's disease (Jiao et al., 2023; Sun et al., 2024). Even stronger evidence exists that higher ALM reduces the risk of ulcerative colitis (UC), supported by three studies (Jiao et al., 2023; Sun et al., 2024; Q. Wang et al., 2025). Low ALM has been causally linked to the increased risk of knee osteoarthritis, as demonstrated by observational studies (J. Yang et al., 2023; L. Zhang et al., 2023). Increase of ALM is a protective factor against a risk of many diseases: ischemic stroke, small vessel stroke, stroke in general, cardioembolic stroke, coronary heart disease, myocardial infarction, hypertension, levodopa induced dyskinesia (Parkinson's), Alzheimer's disease, hypertrophic osteoarthropathy, total knee and hip replacement, rotator cuff tears, psoriasis in women (Du et al., 2024; J. He et al., 2023; X.

Liu et al., 2023; Meng et al., 2024; Song et al., 2024; Q. Wang et al., 2025; T. Wang et al., 2024; D. Yang et al., 2024; J. Yang et al., 2023; Ye et al., 2023; Zhu et al., 2024).

On the contrary, an increase of ALM predisposes to systemic lupus erythematosus and rheumatoid arthritis in men and diabetes mellitus (Du et al., 2024; Q. Wang et al., 2025). Appendicular lean mass and fat mass are positively causally linked to obstructive sleep apnea (Sun et al., 2025). Several studies linked an increase in ALM as a protective factor against gastroesophageal reflux disease, gastric cancer, colorectal cancer, nonalcoholic fatty liver disease and chronic obstructive pulmonary disease (Fu and Yang, 2023; Hu et al., 2024; T. Yang et al., 2024). Study found positive relationship between ALM and gestational diabetes mellitus (Huang et al., 2025).

Very strong evidence exists of inflammatory bowel disease and its subtypes, Crohn's disease and ulcerative colitis, causally affecting the decrease of the appendicular lean mass and fat-free muscle mass in sarcopenia (Chen and He, 2024; Jiao et al., 2023; Lin et al., 2023; Sun et al., 2024; Q. Wang et al., 2025). Similarly, very strong evidence exists on rheumatoid arthritis causally affecting a reduction of ALM (Su et al., 2023; Q. Wang et al., 2025). Crohn's disease and rheumatoid arthritis reduces fat free muscle mass in the whole body and limbs (Chen and He, 2024). The found that GERD and liver cancer causally impacts ALM (T. Yang et al., 2024). Intricate relationship exists between attention deficit hyperactivity disorder (ADHD) and ALM in which ADHD increases ALM (Zhao et al., 2025). It has been demonstrated that psoriasis has a causal negative effect on ALM (Q. Wang et al., 2025).

Causal links exist between the appendicular lean mass and cancer. Benign prostatic hyperplasia through sarcopenic obesity was causally linked to the ALM, an increase of which can be regarded as a protective factor (Rao et al., 2023). ALM has a protective effect against hepatocellular carcinoma (Cao et al., 2024).

3.3.3.5. Causal associations between muscle mass related and behavioural phenotypes.

Several studies showed that appendicular lean mass is positively associated with cognitive function, and this relationship is bidirectional (Liu et al., 2024; C. Lu et al., 2024; Sha et al., 2025b). Genetically predicted educational attainment is causally bi-directionally positively linked to ALM (Zhang et al., 2024). Cigarette smoking increases the risk of sarcopenia and decreases ALM (Sha et al., 2025b).

3.3.3.6. Causal associations between muscle mass related phenotypes and anatomical–physiological phenotypes.

Glomerular filtration rate was causally inversely linked to the appendicular lean mass, showing a potential link between kidney function and sarcopenia (P. Yan et al., 2024).

Several studies provided evidence of causal links between brain anatomical areas and ALM. ALM is causally linked to brain cortical thickness: the increase of ALM is associated with a reduction of thickness of the lateral occipital area, and its decrease is associated with an increase of thickness of the pars opercularis area (Zhan et al., 2025). Brain cortical thickness of frontal and temporal pole and rostral anterior cingulate have been found to have a positive causal effect on increase of ALM while brain cortical thickness of BANKSSTS (banks of the superior temporal sulcus) had negative effect on ALM (Zhan et al., 2025).

A study by Lei and colleagues described the effects of 160 brain imaging data structures on ALM and other sarcopenia-related traits, as well as twelve to forty-eight gene expression in different brain areas affecting all sarcopenia-related traits (Lei et al., 2025). In this study, the causative relationships relied on just a few instrumental variables.

3.3.3.7. No associations between the sarcopenia related traits and other phenotypes.

No association was confirmed between the walking pace and hepatocellular carcinoma (Cao et al., 2024). No causal relationship was found between walking pace and

ischemic stroke (Song et al., 2024). Neither viral hepatitis nor liver cirrhosis was associated with walking pace (Z. Lu et al., 2024). The inflammatory bowel disease (IBD), ulcerative colitis (UC), had no causal effect on the usual walking pace (Jiao et al., 2023).

MR analyses have not demonstrated causal links between muscle strength and hepatic conditions such as viral hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, or liver cirrhosis (Z. Lu et al., 2024). Low handgrip strength did not causally affect lumbar spine bone density, forearm bone mineral density, and heel mineral bone density (L. Zhang et al., 2023). The causal effect was found only in the other direction, where grip strength was an outcome. A study by Jiao and colleagues did not find a causal relationship between strength phenotypes and IBD and its subtypes, whereas another study by Sun and colleagues has established such a relationship (Jiao et al., 2023; Sun et al., 2024). These two studies employed different data sources for instrumental variables, which may explain the discrepancy between their results. Finally, no causal relationship has been established between cognitive performance and handgrip strength (Liu et al., 2024).

No significant causal association was found between (i) appendicular lean mass and alcohol consumption, large artery stroke or any ischemic stroke (Meng et al., 2024; Sha et al., 2025a); (ii) right and left hand grip strength and rotator cuff tears, obstructive sleep apnea (Sun et al., 2025; D. Yang et al., 2024); (iii) usual walking pace and ischemic stroke subtypes (Meng et al., 2024); (iv) sarcopenia and gestational diabetes mellitus causation of sarcopenia, attention deficit hyperactivity disorder, and alcohol consumption (Huang et al., 2025; Sha et al., 2025a; Zhao et al., 2025). No evidence showed causal effects of ulcerative colitis, systemic lupus erythematosus, psoriasis or multiple sclerosis on sarcopenia-related traits (Chen and He, 2024). No association was found between ALM and LDL (Kirwan et al., 2024). No causal

association in either direction was found between COVID-19 susceptibility, hospitalization, and severity with sarcopenia phenotypes (C. Liu et al., 2023).

3.3.3.8. Subgroup analysis based on STROBE-MR scores of phenotypes related to sarcopenia traits.

Phenotypic relationships that are strongly supported by high-quality studies (STROBE-MR score ≥ 80%) and further reinforced by lower-scoring studies provide sufficient evidence for an association between sarcopenia-related traits and the following conditions: GERD, COPD and lung function, and major depressive disorder.

However, other phenotypic relationships that did not receive additional support reported in lower scoring articles comprise gestational diabetes mellitus (Huang et al., 2025), brain anatomical areas (Lei et al., 2025), signaling catepsin and lipid molecules (Hou et al., 2025; Liu et al., 2024). These relationships need further supporting evidence.

3.4. Frailty

Causal relationships between frailty and other traits were reported in 96 studies, of which 80 passed QC thresholds (Supplementary table S1). Frailty as exposure was causally associated with 191 trait, while frailty as an outcome was causally affected by 75 traits. All associations between frailty and other traits are shown in Table 5.

Table 5. Mendelian randomization associations between frailty and health-related outcomes.

PMID	Exposure	Outcome	Impact	Effect estimate	95% CI	p-value	STROBE-MR score	STROBE-MR % score
Sociodemographic and lifestyle factors								
34431594	Educational attainment (per 1 SD higher)	Frailty index	decreases risk	β = -0.019	(-0.023, -0.015)	7.2E-20	15	75
36765104	Lifetime smoking (genetically predicted)	Frailty in ageing	increases risk	OR = 1.46	(1.37, 1.56)	2.63E-29	16.5	82.5
36765104	Smoking initiation (genetically predicted)	Frailty in ageing	increases risk	OR = 1.23	(1.19, 1.27)	3.21E-39	16.5	82.5

36816044	Alcohol consumption (genetically predicted, drinks/week)	Frailty index	decreases risk	β = -0.090	(-0.151, -0.029)	0.003	14.5	72.5
36816044	Smoking initiation (genetically predicted)	Frailty index	increases risk	β = 0.345	(0.316, 0.374)	1.36E-113	14.5	72.5
37001985	Initiation of smoking (genetic)	Frailty Index	increases risk	β = 0.39	(0.29, 0.49)	5.11E-15	17.5	87.5
38095641	Leisure screen time (per 1 SD)	Frailty Index	increases risk	β 0.19	0.14–0.24	3.54E-15	16.5	82.5
38095641	Moderate-to-vigorous physical activity (per 1 SD)	Frailty Index	decreases risk	β -0.17	-0.32–-0.02	0.03	16.5	82.5
38095641	Smoking initiation (per 1 SD)	Frailty Index	increases risk	β 0.15	0.10–0.21	3.88E-09	16.5	82.5
38368347	Time watching television (per unit higher)	Frailty Index	increases risk	β = 0.26	(0.21, 0.31)	3.98E-25	18	90
38965725	Alcohol intake (overall)	Frailty Index	increases risk	1.16	[1.11, 1.21]	2.52E-10	17	85
38965725	Cereal intake	Frailty Index	decreases risk	0.75	[0.68, 0.83]	8.72E-08	17	85
38965725	Cheese intake	Frailty Index	decreases risk	0.8	[0.75, 0.87]	8.03E-09	17	85
38965725	Coffee intake	Frailty Index	increases risk	1.15	[1.04, 1.28]	0.009	17	85
38965725	Dried fruit intake	Frailty Index	decreases risk	0.73	[0.62, 0.86]	1.46E-04	17	85
38965725	Fresh fruit intake	Frailty Index	decreases risk	0.86	[0.75, 0.99]	0.03	17	85
38965725	Oily fish intake	Frailty Index	decreases risk	0.9	[0.81, 0.99]	0.033	17	85
38965725	Pork intake	Frailty Index	increases risk	1.37	[1.12, 1.67]	2.52E-10	17	85
39071086	Age completed full-time education	Frailty Index	increases risk	β −0.477	−0.634 to −0.319	2.995E-11	19	95
39071086	Average total household income before tax	Frailty Index	increases risk	β −0.321	−0.410 to −0.232	2.810E-12	19	95
39071086	Job involves heavy manual/physical work	Frailty Index	decreases risk	β 0.298	0.113 to 0.484	1.490E-03	19	95
39161855	Accelerometer average acceleration	Frailty	decreases risk	OR 0.99	0.98–0.99	0.01	17	85
39161855	Overall physical activity	Frailty	decreases risk	OR 0.89	0.81–0.98	0.01	17	85

39161855	Sedentary behavior	Frailty	increases risk	OR 0.939	0.885–0.997	0.039	17	85
39461086	Smoking initiation	Frailty Index	increases risk	β 0.899	0.016–0.191	0.02	17	85
39461086	Strenuous sports/other exercise	Frailty Index	decreases risk	β -0.423	-0.692 to -0.154	0.002	17	85
39461086	Television watching	Frailty Index	increases risk	β 0.297	0.249–0.346	1E-10	17	85
Sleeping patterns and disorders								
38368347	Daytime napping (per unit higher)	Frailty Index	increases risk	β = 0.29	(0.18, 0.41)	0.00000268	18	90
38368347	Sleep duration (per unit longer)	Frailty Index	decreases risk	β = -0.18	(-0.26, -0.10)	0.0000604	18	90
38502408	Daytime sleepiness	Frailty (risk)	increases risk	OR = 1.49	(1.25, 1.77)	0.000096	18	90
38502408	Insomnia liability	Frailty (risk)	increases risk	OR = 1.10	(1.03, 1.17)	2.59E-97	18	90
38502408	Long sleep duration	Frailty (risk)	decreases risk	OR = 0.66	(0.37, 1.17)	0.02	18	90
38502408	Short sleep duration	Frailty (risk)	increases risk	OR = 1.30	(1.22, 1.38)	2.23E-17	18	90
38784581	Chronotype (morningness)	Frailty Index	decreases risk	0.975	[0.952, 0.999]	0.041	17.5	87.5
38784581	Daytime napping	Frailty Index	decreases risk	0.804	[0.731, 0.883]	<0.001	17.5	87.5
38784581	Getting up in the morning	Frailty Index	decreases risk	0.866	[0.770, 0.973]	0.015	17.5	87.5
38784581	Insomnia	Frailty Index	increases risk	1.269	[1.128, 1.428]	<0.001	17.5	87.5
38784581	Sleep apnea syndrome	Frailty Index	increases risk	1.053	[1.012, 1.096]	0.012	17.5	87.5
38784581	Sleep duration	Frailty Index	increases risk	1.029	[1.010, 1.048]	0.002	17.5	87.5
38784581	Snoring	Frailty Index	increases risk	1.14	[1.070, 1.215]	<0.001	17.5	87.5
39895115	Frailty index	Insomnia	increases risk	β 0.50	0.25–0.75	1.1E-04	17	85
39895115	Insomnia (genetic liability)	Frailty index	increases risk	β 0.160	0.141–0.179	3.2E-61	17	85
39936043	Frailty Index	Insomnia	increases risk	OR 1.21	1.10–1.32	<0.001	17	85

39936043	Frailty Index	Short sleep duration	increases risk	OR 1.89	1.28–2.79	0.001	17	85
39936043	Frailty Index	Sleep apnea	increases risk	OR 1.21	1.04–1.41	0.015	17	85
39936043	Fried Frailty Score	Insomnia	increases risk	OR 1.28	1.18–1.38	<0.001	17	85
39936043	Fried Frailty Score	Short sleep duration	increases risk	OR 2.65	1.89–3.72	<0.001	17	85
38425786	Frailty	Insomnia	increases risk	OR = 1.14	NR	<0.001	17	85
39936043	Fried Frailty Score	Sleep apnea	increases risk	OR 1.57	1.28–1.94	<0.001	17	85
Biochemical entities								
40344942	Ether-PC (O-16:0_22:5)	Frailty Index	increases risk	1.0264	1.0049–1.0484	0.0158	18	90
40344942	Ether-PC (O-16:1_16:0)	Frailty Index	decreases risk	0.9719	0.9555–0.9886	0.0241	18	90
40344942	Ether-PC (O-18:0_16:1)	Frailty Index	decreases risk	0.9759	0.9575–0.9946	0.0203	18	90
40344942	LPC (16:0_0:0)	Frailty Index	increases risk	1.0172	1.0033–1.0313	0.0167	18	90
40344942	LPC (18:0_0:0)	Frailty Index	increases risk	1.0256	1.0090–1.0424	0.0073	18	90
40344942	PC (16:0_18:3)	Frailty Index	decreases risk	0.9739	0.9547–0.9935	0.0224	18	90
40344942	PC (16:0_20:1)	Frailty Index	decreases risk	0.9603	0.9296–0.9920	0.0175	18	90
40344942	PC (18:0_20:5)	Frailty Index	increases risk	1.0242	1.0106–1.0380	0.0027	18	90
40344942	PC (18:1_20:2)	Frailty Index	decreases risk	0.9833	0.9709–0.9959	0.0192	18	90
34601600	Serum total protein (per g/L higher)	Frailty index	decreases risk	β = -0.153	(-0.251, -0.056)	0.002	14.5	72.5
34684540	Palmitic acid (plasma, multivariable MR)	Frailty index	increases risk	β = 0.288	(0.128, 0.447)	<0.001	15	75
34684540	Stearic acid (plasma, genetically predicted)	Frailty index	increases risk	β = 0.178	(-0.050, 0.307)	0.007	15	75
37184129	Creatinine (per SD), IVW-MR	Frailty index	increases risk	β = 0.38%	(0.10, 0.66)	0.008	19	95
37184129	Glycoprotein acetyls (per SD), IVW-MR	Frailty index	increases risk	β = 0.37%	(0.12, 0.61)	0.004	19	95

37537564	Remnant cholesterol (per 1 mmol/L), IVW	Frailty index	increases risk	β = 0.059	(0.033, 0.085)	1.05E-05	18	90
38322263	Eosinophil count (circulating)	Frailty index	increases risk	β = 0.059	(0.042, 0.078)	5.63E-11	17.5	87.5
38322263	Eosinophil count (multivariable MR)	Frailty index	increases risk	β = 0.063	(0.021, 0.104)	0.003	17.5	87.5
38505750	MIG (CXCL9) level (higher)	Frailty (risk)	increases risk	OR = 1.03	(1.01, 1.05)	<0.0001	16.5	82.5
38505750	TNF-β level (higher)	Frailty (risk)	increases risk	OR = 1.01	(1.00, 1.03)	0.013	16.5	82.5
38535988	Polyunsaturated fatty acids (PUFA)	Frailty Index	increases risk	OR = 1.033	(1.009, 1.057)	NR	17.5	87.5
38542917	IgG glycan GP14	Frailty Index	increases risk	β = 0.026	0.003 to 0.050	0.027	16	80
38542917	IgG glycan GP23 (MVMR)	Frailty Index	decreases risk	β = −0.119	−0.219 to −0.019	0.019	16	80
38781179	Frailty Index (FI)	HDL-C	increases risk	OR 0.92	0.89–0.95	<0.001	16.5	82.5
38781179	Frailty Index (FI)	LDL-C	increases risk	OR 1.04	1.00–1.07	0.039	16.5	82.5
38781179	Frailty Index (FI)	Triglycerides	increases risk	OR 1.06	1.02–1.11	0.005	16.5	82.5
38862035	S.VLDL.L (small VLDL total lipids)	Frailty Index	increases risk	0.83	NR	2.12E-42	13.5	67.5
38862035	Serum triglycerides	Frailty Index	increases risk	0.77	NR	2.47E-22	13.5	67.5
39705437	Frailty index	Carotene level	decreases risk	OR 0.916	0.858–0.979	0.009	15	75
39705437	Frailty index	Iron level	decreases risk	OR 0.921	0.859–0.988	0.022	15	75
39705437	Frailty index	Selenium level	decreases risk	OR 0.622	0.396–0.977	0.039	15	75
39705437	Frailty index	Vitamin C level	decreases risk	OR 0.895	0.837–0.957	0.001	15	75
39705437	Frailty index	Vitamin E level	decreases risk	OR 0.907	0.847–0.971	0.005	15	75
39705437	Vitamin D (serum)	Frailty Index	increases risk	OR 1.096	1.019–1.178	0.014	15	75
40054372	CCL4	Frailty index	decreases risk	OR 0.980	0.961–0.999	0.041	18	90

40054372	CCL8 (MCP-1)	Frailty index	increases risk	OR 1.019	1.001–1.037	0.041	18	90
40054372	CX3CL1 (Fractalkine)	Frailty index	increases risk	OR 1.025	1.001–1.048	0.037	18	90
40054372	CXCL10	Frailty index	decreases risk	OR 0.976	0.959–0.992	0.005	18	90
40054372	FGF-5	Frailty index	decreases risk	OR 0.983	0.970–0.995	0.008	18	90
40054372	IL-33	Frailty index	increases risk	OR 1.029	1.004–1.054	0.021	18	90
40054372	LIF-R	Frailty index	increases risk	OR 1.020	1.001–1.038	0.036	18	90
40054372	TNF-β	Frailty index	decreases risk	OR 0.960	0.929–0.992	0.015	18	90
40448021	Eosinophil counts	Frailty Index	increases risk	OR 1.063	1.039-1.087	0.0000014	18.5	92.5
Gut microbiota								
37990415	Clostridium innocuum (genus)	Frailty Index	increases risk	β 0.023	0.001–0.044	0.036	17	85
38765250	Class Bacteroidia	Frailty Index	decreases risk	β = −0.041	NR	0.014	18	90
38765250	Class Betaproteobacteria	Frailty Index	increases risk	β = 0.049	NR	0.042	18	90
38765250	Genus Allisonella	Frailty Index	increases risk	β = 0.032	NR	0.012	18	90
38765250	Genus Bifidobacterium	Frailty Index	increases risk	β = 0.042	NR	0.013	18	90
38765250	Genus Clostridium innocuum group	Frailty Index	increases risk	β = 0.023	NR	0.036	18	90
38765250	Genus Eubacterium coprostanoligenes group	Frailty Index	increases risk	β = 0.054	NR	0.003	18	90
38765250	Genus Eubacterium ruminantium group	Frailty Index	decreases risk	β = −0.027	NR	0.028	18	90
39113894	Class Bacteroidia (gut microbiota)	Frailty index	decreases risk	OR 0.958	0.924–0.993	0.020	16.5	82.5
39113894	Class Betaproteobacteria (gut microbiota)	Frailty index	increases risk	OR 1.050	1.002–1.101	0.042	16.5	82.5
39113894	Genus Clostridium innocuum group	Frailty index	increases risk	OR 1.023	1.001–1.045	0.036	16.5	82.5
39113894	Genus Eubacterium coprostanoligenes group	Frailty index	increases risk	OR 1.056	1.019–1.094	0.003	16.5	82.5

40074999	Allisonella	Frailty Index	increases risk	OR 1.033	1.005–1.063	0.022	16.5	82.5
40074999	Eubacterium coprostanoligenes	Frailty Index	increases risk	OR 1.037	1.001–1.073	0.042	16.5	82.5
40074999	Flavonifractor	Frailty Index	decreases risk	OR 0.954	0.920–0.990	0.012	16.5	82.5
40074999	Howardella	Frailty Index	increases risk	OR 1.026	1.002–1.050	0.031	16.5	82.5
40074999	Victivallis	Frailty Index	decreases risk	OR 0.984	0.968–1.000	0.049	16.5	82.5
Mental disorders								
37670569	Depression liability	Frailty Index	increases risk	β = 0.143	(0.086, 0.201)	<0.001	17	85
37670569	Frailty Index (genetic)	Depression	increases risk	OR = 1.83	(1.33, 2.52)	<0.001	17	85
37670569	Frailty Phenotype (genetic)	Depression	increases risk	OR = 2.57	(1.54, 4.28)	<0.001	17	85
37729413	Depression liability (PGC)	Frailty Index	increases risk	β = 0.143	(0.086, 0.201)	<0.001	18	90
37729413	Frailty Index (genetic)	Depression	increases risk	OR = 1.860	(1.439, 2.405)	<0.001	18	90
38782943	Genetically predicted physical frailty (per 1-point)	Depression	increases risk	2.55	[1.59, 4.08]	1.01E-04	14.5	72.5
38782943	Physical frailty (frail vs non-frail)	Incident depression	increases risk	3.08	[2.74, 3.47]	<0.001	14.5	72.5
38841572	Frailty index	Delirium	increases risk	1.849	0.027–2.067	0.044	15	75
38911707	Affective disorder	Frailty index	increases risk	1.15	[1.09, 1.21]	3.39E-07	17.5	87.5
38911707	Anxiety	Frailty index	increases risk	1.06	[1.01, 1.11]	2.00E-02	17.5	87.5
38911707	Depression	Frailty index	increases risk	1.14	[1.04, 1.26]	7.99E-03	17.5	87.5
38911707	Frailty index	Affective disorder	increases risk	1.7	[1.28, 2.27]	2.57E-04	17.5	87.5
38911707	Frailty index	Anxiety	increases risk	1.62	[1.13, 2.33]	8.18E-03	17.5	87.5
38911707	Frailty index	Depression	increases risk	1.88	[1.30, 2.71]	8.21E-04	17.5	87.5
38911707	Schizophrenia	Frailty index	increases risk	1.02	[1.01, 1.04]	1.70E-03	17.5	87.5

39542111	Frailty index (genetically predicted)	Bipolar disorder	increases risk	OR 1.60	1.09–2.35	0.017	16	80
39542111	Frailty index (genetically predicted)	Major depressive disorder	increases risk	OR 2.04	1.57–2.63	0.0005	16	80
39542111	Frailty index (genetically predicted)	Schizophrenia	increases risk	OR 1.91	1.22–3.01	0.005	16	80
39542111	Frailty index (genetically predicted)	Suicide/intentional self-harm	increases risk	OR 1.77	1.37–2.31	0.0005	16	80
39710650	Frailty index	Major depressive disorder	increases risk	OR 1.290	1.133–1.469	0.0002	16.5	82.5
39710650	Major depressive disorder (genetic liability)	Frailty index	increases risk	OR 1.211	1.092–1.343	0.0004	16.5	82.5
39710650	Schizophrenia (genetic liability)	Frailty index	increases risk	OR 1.019	1.005–1.033	0.006	16.5	82.5
39856793	Frailty index	Neuroticism	increases risk	OR 1.270	1.173–1.375	<0.001	18	90
39856793	Neuroticism (genetic liability)	Frailty index	increases risk	OR 1.627	1.538–1.722	<0.001	18	90
39895115	Frailty index	Anxiety	increases risk	OR 2.76	1.56–4.90	5.0E-04	17	85
39895115	Frailty index	Major depressive disorder	increases risk	OR 1.86	1.36–2.53	8.1E-05	17	85
39895115	Frailty index	Neuroticism	increases risk	β 0.25	0.11–0.38	3.3E-04	17	85
39895115	Frailty index	Post-traumatic stress disorder	increases risk	OR 2.56	1.69–3.87	9.9E-06	17	85
39895115	Major depressive disorder (genetic liability)	Frailty index	increases risk	β 0.071	0.033–0.110	2.8E-04	17	85
39895115	Neuroticism (genetic liability)	Frailty index	increases risk	β 0.269	0.173–0.365	3.4E-08	17	85
39895115	Suicide attempt (genetic liability)	Frailty index	increases risk	β 0.056	0.029–0.084	3.4E-05	17	85
Diseases and disorders								
36267743	Frailty index (per 1-point higher)	Coronary artery disease	increases risk	OR = 1.46	(1.13, 1.87)	0.003	17.5	87.5
36267743	Frailty index (per 1-point higher)	Heart failure	increases risk	OR = 1.46	(1.24, 1.72)	4.89E-06	17.5	87.5
36267743	Frailty index (per 1-point higher)	Myocardial infarction	increases risk	OR = 1.62	(1.21, 2.17)	0.001	17.5	87.5
37216451	Frailty	Any stroke	increases risk	OR = 1.45	(1.15, 1.84)	0.002	16	80

37216451	Frailty	Intracerebral hemorrhage	increases risk	OR = 6.33	(1.59, 25.27)	0.008	16	80
37216451	Frailty	Ischemic stroke	increases risk	OR = 1.39	(1.07, 1.70)	0.012	16	80
38775917	Any stroke (genetically predicted)	Frailty Index	increases risk	OR = 1.104	1.064 to 1.144	<0.001	17.5	87.5
38775917	Ischemic stroke	Frailty Index	increases risk	OR = 1.081	1.044 to 1.120	<0.001	17.5	87.5
38775917	Large-artery atherosclerotic stroke	Frailty Index	increases risk	OR = 1.037	1.012 to 1.062	0.005	17.5	87.5
38781179	Frailty Index	Atherosclerosis (other)	increases risk	OR 1.17	1.02–1.34	0.026	16.5	82.5
38781179	Frailty Index	Cerebral atherosclerosis	increases risk	OR 1.21	1.01–1.44	0.042	16.5	82.5
38781179	Frailty Index	Coronary atherosclerosis	increases risk	OR 1.20	1.01–1.43	0.041	16.5	82.5
39151487	Atrial fibrillation	Frailty index	increases risk	OR 3.017	1.106–8.232	0.031	16.5	82.5
40024880	Frailty index	Hypertension	increases risk	OR 2.17	1.72–2.74	5.25E-11	17.5	87.5
36090295	Frailty index (per unit higher)	Vestibular disorders	increases risk	OR = 1.00785	(1.00298, 1.01274)	0.001	17.5	87.5
36158533	Frailty index (per unit higher)	Hearing loss	increases risk	OR = 1.090	(1.041, 1.141)	<0.001	17	85
36158533	Hearing loss (genetically predicted)	Frailty index	increases risk	OR = 1.459	(1.117, 1.905)	0.006	17	85
37933558	Frailty index [validation]	Rheumatoid arthritis	increases risk	β 1.25	0.39–2.12	0.00458	16	80
37933558	Rheumatoid arthritis	Frailty index	increases risk	OR 1.01	1.01–1.02	0.0000247	16	80
37933558	Rheumatoid arthritis [validation]	Frailty index	increases risk	OR 1.03	1.02–1.04	3.3E-17	16	80
38162888	Asthma genetic liability	Frailty index	increases risk	OR 2.325	1.958–2.761	6.5275E-22	18	90
38162888	Frailty index	Asthma risk	increases risk	OR 1.088	1.058–1.119	4.81559E-09	18	90
38308830	Crohn's disease genetic liability	Frailty index	increases risk	β 0.012	0.006–0.018	0.0002	17.5	87.5
38308830	Ulcerative colitis genetic liability	Frailty index	increases risk	β 0.014	0.006–0.021	0.001	17.5	87.5

38319411	Frailty index	Inflammatory bowel disease	increases risk	OR = 1.015	(1.005, 1.025)	0.004	18	90
38426414	Frailty index	Psoriasis	increases risk	OR = 2.50	(1.418, 4.408)	0.002	18	90
38994009	Frailty index	Gestational diabetes mellitus	increases risk	3.563	[1.737, 7.309]	<0.001	15.5	77.5
38994009	Gestational diabetes mellitus	Frailty index	increases risk	1.025	[1.009, 1.040]	0.002	15.5	77.5
39050185	Hip or knee osteoarthritis	Frailty index	increases risk	OR 1.082	1.0532–1.1125	1.36E-08	18	90
39133382	Osteoarthritis (FinnGen)	Frailty index	increases risk	OR 1.55	1.16–2.07	0.003	18	90
39133382	Osteoarthritis (UK Biobank)	Frailty index	increases risk	OR 1.03	1.01–1.05	0.007	18	90
39133382	Psoriatic arthritis (FinnGen)	Frailty index	increases risk	OR 4.06	1.03–16.09	0.046	18	90
39133382	Rheumatoid arthritis (FinnGen, adjusted)	Frailty index	increases risk	OR 2.29	1.26–4.18	0.007	18	90
39133382	Rheumatoid arthritis (UK Biobank)	Frailty index	increases risk	OR 1.03	1.01–1.05	0.006	18	90
39257904	Hypothyroidism	Frailty index	increases risk	OR 1.023	1.008–1.038	0.0015	17.5	87.5
39257904	Multiple sclerosis	Frailty index	increases risk	OR 0.984	0.977–0.992	0.0000487	17.5	87.5
39257904	Overall autoimmune disease	Frailty index	increases risk	OR 1.044	1.028–1.061	5.32E-08	17.5	87.5
39257904	Rheumatoid arthritis	Frailty index	increases risk	OR 1.040	1.012–1.069	0.029	17.5	87.5
39257904	Type 1 diabetes	Frailty index	increases risk	OR 1.011	1.004–1.017	0.0012	17.5	87.5
39259375	Frailty index (genetically predicted)	Low back pain	increases risk	OR 1.66	1.17–2.36	0.00492	18	90
39259375	Low back pain (genetic liability)	Frailty index	increases risk	OR 1.13	1.07–1.19	0.0000267	18	90
39300167	Frailty index	Chronic kidney disease	increases risk	OR 2.408	1.135–5.107	0.022	17	85
39300167	Frailty index (genetically predicted)	Chronic kidney disease	increases risk	β 1.270	0.608–1.931	0.0009	17	85
39725839	Asthma (genetic liability)	Frailty index	increases risk	OR 1.092	1.075–1.109	5.00E-28	17.5	87.5

39725839	Asthma (genetic liability) — replication	Frailty index	increases risk	OR 1.073	1.052–1.096	1.41E-11	17.5	87.5
39881812	Frailty index (per 1 SD ↑)	COPD (FinnGen)	increases risk	OR 1.854	1.411–2.434	9.02E-06	18	90
39881812	Frailty index (per 1 SD ↑)	COPD (GBMI)	increases risk	OR 1.784	1.475–2.158	2.40E-09	18	90
40024880	Frailty index	Gout	increases risk	OR 2.45	1.29–4.64	0.006	17.5	87.5
40024880	Frailty index	Hypothyroidism	increases risk	OR 1.96	1.47–2.60	3.47E-06	17.5	87.5
40024880	Frailty index	Type 2 diabetes mellitus	increases risk	OR 1.67	1.24–2.24	6.95E-04	17.5	87.5
40068076	Frailty index	Type 2 diabetes mellitus	increases risk	OR 2.33	1.66–3.26	<0.001	13.5	67.5
40068076	Type 2 diabetes mellitus (genetic liability)	Frailty index	increases risk	OR 1.04	1.02–1.06	<0.001	13.5	67.5
40257716	Hip osteoarthritis (HOA)	Frailty Index	increases risk	OR 1.028	1.007–1.049	0.009	16.5	82.5
40257716	KOA/HOA combined	Frailty Index	increases risk	OR 1.082	1.053–1.113	<0.001	16.5	82.5
38982542	Frailty index	Osteoporosis	increases risk	1.64	[1.19, 2.26]	0.002	19	95
38982542	Osteoporosis genetic liability	Frailty index	increases risk	0.16	[0.101, 0.218]	1.31E-07	19	95
40257716	Knee osteoarthritis	Frailty Index	increases risk	OR 1.086	1.017–1.160	0.014	16.5	82.5
Body composition								
37277933	Overweight (genetic)	Frailty Index	increases risk	β = 0.055	(0.030, 0.079)	<0.0001	17	85
38095641	Birth weight (per 1 SD)	Frailty Index	decreases risk	β -0.05	-0.10–-0.0041	0.03	16.5	82.5
38095641	Body mass index (per 1 SD)	Frailty Index	increases risk	β 0.13	0.08–0.18	0.00000526	16.5	82.5
38095641	Waist circumference (per 1 SD)	Frailty Index	increases risk	β 0.13	0.06–0.20	0.00018	16.5	82.5
38855449	Childhood BMI (per SD)	Frailty Index	increases risk	0.08	[0.046, 0.114]	3.43E-06	17.5	87.5
38855449	Own birth weight (per SD)	Frailty Index	decreases risk	-0.068	[-0.106, -0.030]	3.92E-04	17.5	87.5
40024880	Frailty index	Obesity	increases risk	OR 1.78	1.17–2.70	0.0075	17.5	87.5

40257716	Appendicular lean mass	Frailty Index	increases risk	OR 0.955	0.937–0.974	<0.001	16.5	82.5
40257716	Forearm BMD	Frailty Index	increases risk	OR 0.966	0.936–0.996	0.028	16.5	82.5
40257716	Heel BMD	Frailty Index	increases risk	OR 0.981	0.967–0.995	0.008	16.5	82.5
40257716	Total BMD (45–60)	Frailty Index	increases risk	OR 0.966	0.940–0.993	0.013	16.5	82.5
40257716	Total BMD (>60)	Frailty Index	increases risk	OR 0.974	0.954–0.994	0.011	16.5	82.5
40257716	Ultradistal forearm BMD	Frailty Index	increases risk	OR 0.975	0.953–0.997	0.029	16.5	82.5
Phenotypical traits								
40257716	Grip strength (left hand)	Frailty Index	increases risk	OR 0.788	0.721–0.862	<0.001	16.5	82.5
40257716	Grip strength (right hand)	Frailty Index	increases risk	OR 0.800	0.737–0.869	<0.001	16.5	82.5
40257716	Low grip strength (>60y)	Frailty Index	increases risk	OR 1.168	1.059–1.289	0.002	16.5	82.5
40257716	Walking pace	Frailty Index	increases risk	OR 0.480	0.388–0.593	<0.001	16.5	82.5
39474649	SGLT1 inhibition (genetically proxied)	Frailty index	decreases risk	β -0.290	-0.399 to -0.181	0.0001	13.5	67.5
39474649	SGLT1 inhibition (genetically proxied)	Low grip strength (EWGSOP)	decreases risk	β -0.287	-0.532 to -0.041	0.024	13.5	67.5
39474649	SGLT1 inhibition (genetically proxied)	Low grip strength (FNIH)	decreases risk	β -0.796	-1.216 to -0.376	0.0003	13.5	67.5
38862035	Systolic blood pressure	Frailty index	increases risk	0.44	NR	3.46E-03	13.5	67.5
38862035	Usual walking pace	Frailty index	increases risk	0.19	NR	1.97E-02	13.5	67.5
38297347	FEV1 (per SD higher)	Frailty index	decreases risk	β = -0.08	(-0.11, -0.04)	0.0000203	17.5	87.5
38297347	FEV1/FVC (per SD higher)	Frailty index	decreases risk	β = -0.06	(-0.08, -0.03)	0.00009551	17.5	87.5
38297347	PEF (per SD higher)	Frailty index	decreases risk	β = -0.07	(-0.11, -0.03)	0.00054	17.5	87.5
36729470	Downregulated IL-6 signalling (genetically proxied)	Frailty index	decreases risk	β = -1.89	(-3.39, -0.40)	0.01	17.5	87.5
36939795	LV end-diastolic volume (per SD)	Frailty index	decreases risk	β = -0.079	(-0.117, -0.041)	0.037	18	90

36939795	LV end-systolic volume index (per SD)	Frailty index	increases risk	β = 0.050	(0.031, 0.070)	0.011	18	90
36939795	Left ventricular stroke volume (per SD)	Frailty index	decreases risk	β = -0.132	(-0.160, -0.105)	1.39E-06	18	90
Other traits								
38026367	PM2.5	Frailty index	increases risk	OR 1.33	1.12–1.58	0.001	16.5	82.5
38606010	Age at first birth	Frailty risk	increases risk	OR = 0.93	0.92 to 0.95	0.000	18	90
38606010	Age at first sexual intercourse	Frailty risk	increases risk	OR = 0.74	0.70 to 0.79	0.000	18	90
38606010	Age at menarche	Frailty risk	increases risk	OR = 0.96	0.95 to 0.98	0.000	18	90
No association								
34601600	Serum albumin (per g/L higher)	Frailty index	N/A	β = -0.023	(-0.141, 0.094)	0.694	14.5	72.5
36267743	Frailty index (per 1-point higher)	Atrial fibrillation	N/A	OR = 1.43	(0.93, 1.66)	0.107	17.5	87.5
37201057	Frailty Index (genetic), IVW	Colon cancer	N/A	OR = 0.995	(0.990, 1.001)	0.052	16	80
37732065	Frailty index	Osteoarthritis	N/A	OR 1.69	1.01–2.83	NR	14	70
37933558	Frailty index	Rheumatoid arthritis	N/A	β 0.49	-0.06–1.04	0.08	16	80
38026367	Nitrogen dioxide	Frailty index	N/A	OR 0.98	0.85–1.12	0.73	16.5	82.5
38026367	Nitrogen oxides	Frailty index	N/A	OR 1.15	0.98–1.36	0.09	16.5	82.5
38026367	PM10	Frailty index	N/A	OR 0.91	0.75–1.11	0.36	16.5	82.5
38026367	PM2.5–10	Frailty index	N/A	OR 1.00	0.79–1.28	0.98	16.5	82.5
38095641	Age of smoking initiation	Frailty index	N/A	β -0.23	-0.53–0.08	0.14	16.5	82.5
38095641	Alcoholic drinks per week	Frailty index	N/A	β 0.01	-0.09–0.11	0.89	16.5	82.5
38128266	Asthma genetic liability	Frailty index	N/A	β 0.08	0.06–0.11	NR	18	90
38128266	COPD genetic liability	Frailty index	N/A	β 0.06	0.01–0.10	NR	18	90

38128266	Frailty index	Asthma	N/A	OR 2.10	1.44–3.16	NR	18	90
38128266	Frailty index	COPD	N/A	OR 1.75	1.29–2.36	NR	18	90
38297347	FEV1 (per SD higher)	Frailty index	N/A	β = −0.08	−0.11 - −0.04	2.03E−05	17.5	87.5
38297347	FEV1/FVC ratio (per SD higher)	Frailty index	N/A	β = −0.06	− 0.08 - − 0.03	9.51E−06	17.5	87.5
38297347	FVC (per SD higher)	Frailty index	N/A	β = −0.01	− 0.06 - 0.04	0.681	17.5	87.5
38297347	FVC (per SD higher)	Frailty index	N/A	β = -0.01	(-0.06, 0.04)	0.68	17.5	87.5
38297347	PEF (per SD higher)	Frailty index	N/A	β = −0.07	− 0.10 - − 0.03	4.09E−04	17.5	87.5
38319411	Crohn's disease liability	Frailty (risk)	N/A	OR = 1.018	(1.010, 1.027)	<0.05	18	90
38319411	Ulcerative colitis liability	Frailty (risk)	N/A	OR = 1.016	(1.005, 1.027)	<0.05	18	90
38425786	Insomnia	Frailty	N/A	OR = 1.98	NR	<0.001	17	85
38439017	hs-CRP (genetically predicted higher)	Frailty (risk)	N/A	OR = 1.06	(1.03, 1.08)	<0.05	18	90
38566068	Breakfast skipping	Frailty Index	N/A	β = 0.29	0.12 to 0.45	0.003 (FDR)	18	90
38706793	Alzheimer's disease	Frailty Index	N/A	β −0.01	NR	0.32	16.5	82.5
38706793	Alzheimer's disease	Frailty phenotype	N/A	β −0.03	NR	0.09	16.5	82.5
38706793	Alzheimer’s disease	Frailty Index	N/A	β = -0.01	NR	0.32	16.5	82.5
38706793	Alzheimer’s disease	Frailty Phenotype	N/A	β = -0.03	NR	0.09	16.5	82.5
38706793	Frailty Index	Alzheimer's disease	N/A	β −0.13	NR	0.37	16.5	82.5
38706793	Frailty Index	Alzheimer’s disease	N/A	β = -0.13	NR	0.37	16.5	82.5
38706793	Frailty Phenotype	Alzheimer’s disease	N/A	β = -0.22	NR	0.26	16.5	82.5
38706793	Frailty phenotype	Alzheimer's disease	N/A	β −0.22	NR	0.26	16.5	82.5

38741737	Frailty Index	Allisonella (genus)	N/A	OR 0.96	0.47–1.94	0.903	17.5	87.5
38741737	Frailty Index	Bacteroidia (class)	N/A	OR 0.98	0.75–1.27	0.864	17.5	87.5
38741737	Frailty Index	Betaproteobacteria (class)	N/A	OR 1.14	0.77–1.67	0.515	17.5	87.5
38741737	Frailty Index	Bifidobacterium (genus)	N/A	OR 1.14	0.85–1.54	0.381	17.5	87.5
38741737	Frailty Index	Clostridium innocuum group (genus)	N/A	OR 1.10	0.62–1.93	0.751	17.5	87.5
38741737	Frailty Index	Eubacterium coprostanoligenes group (genus)	N/A	OR 1.05	0.78–1.42	0.743	17.5	87.5
38741737	Frailty Index	Eubacterium ruminantium group (genus)	N/A	OR 0.91	0.55–1.40	0.76	17.5	87.5
38746935	Folate	Frailty risk	N/A	β = 0.029	−0.013, 0.072	0.17	17.5	87.5
38746935	Vitamin B12	Frailty risk	N/A	β = −0.027	−0.041, 0.015	0.37	17.5	87.5
38746935	Vitamin B6	Frailty risk	N/A	β = 0.006	−0.047, 0.061	0.8	17.5	87.5
38746935	Vitamin C	Frailty risk	N/A	β = −0.044	−0.090, 0.001	0.06	17.5	87.5
38746935	Vitamin D	Frailty risk	N/A	β = −0.059	−0.183, −0.065	0.35	17.5	87.5
38746935	Vitamin E	Frailty risk	N/A	β = −0.011	−0.099, 0.075	0.79	17.5	87.5
38781179	Frailty Index	Peripheral artery disease	N/A	OR 1.12	0.99–1.28	0.077	16.5	82.5
38782943	Physical frailty	Incident depression	N/A	1.6	1.53–1.66	NR	14.5	72.5
38855449	Maternal birth weight (per SD)	Frailty index	N/A	-0.033	[-0.076, 0.011]	0.142	17.5	87.5
39010723	*TMPRSS11D*	Frailty index	N/A	OR 1.0280	1.0166–1.0394	0.00	18.5	92.5
39071775	HTT expression	Frailty index	N/A	OR 1.15	1.03–1.30	NR	12.5	62.5
39071775	LRPPRC expression	Frailty index	N/A	OR 0.90	0.85–0.95	NR	12.5	62.5
39103963	Childhood maltreatment	Frailty index	N/A	β 0.31	0.13–0.49	pFDR 0.006	18	90

39614164	Frailty index	ARDS	N/A	OR 0.96	0.14–6.88	0.97	17	85
39614164	Fried frailty score (FFS ≥3)	ARDS	N/A	OR 1.95	0.14–28.16	0.62	17	85
39716054	APOB	Frailty index	N/A	OR 1.053	1.037–1.069	FDR< 0.05	17	85
39716054	BIRC2	Frailty index	N/A	OR 0.978	0.967–0.990	FDR< 0.05	17	85
39716054	CYP3A4	Frailty index	N/A	OR 1.098	1.068–1.128	FDR< 0.05	17	85
39716054	PSME1	Frailty index	N/A	OR 0.936	0.909–0.965	FDR< 0.05	17	85
40035195	Glucokinase activation	Frailty index	N/A	β −0.161	−0.282 to −0.040	0.011 (FDR)	17	85
39154868	Frailty index	IGF-1 (female)	N/A	β −0.66	−1.13 to −0.19	0.01	17.5	87.5
39154868	Frailty index	SHBG (all-sex)	N/A	β −4.36	−7.40 to −1.31	0.01	17.5	87.5
39154868	Frailty index	SHBG (female)	N/A	β −5.49	−9.67 to −1.32	0.01	17.5	87.5
39154868	Frailty index	SHBG (male)	N/A	β −3.10	−5.64 to −0.56	0.02	17.5	87.5
39154868	Frailty phenotype	IGF-1 (all-sex)	N/A	β −1.48	−2.63 to −0.33	0.01	17.5	87.5
39154868	Frailty phenotype	IGF-1 (female)	N/A	β −1.63	−2.85 to −0.41	0.01	17.5	87.5
39154868	Frailty phenotype	IGF-1 (male)	N/A	β −1.29	−2.49 to −0.10	0.03	17.5	87.5
39154868	Frailty phenotype	SHBG (all-sex)	N/A	β −7.01	−11.40 to −2.62	0.00	17.5	87.5
39154868	Frailty phenotype	SHBG (female)	N/A	β −10.14	−16.16 to −4.13	0.00	17.5	87.5
39154868	Frailty phenotype	SHBG (male)	N/A	β −3.46	−6.69 to −0.23	0.04	17.5	87.5
38271334	Forearm FA-BMD	Frailty Index	N/A	β = −0.035	−0.066 to −0.004	0.028	16.5	82.5
38271334	Forearm FA-BMD	Frailty Index	N/A	β -0.035	-0.066–-0.004	0.028	16.5	82.5
38271334	Heel e-BMD	Frailty Index	N/A	β = −0.020	−0.038 to −0.002	0.029	16.5	82.5

38271334	Heel e-BMD	Frailty Index	N/A	β - 0.020	-0.038–-0.002	0.029	16.5	82.5

N/A – not applicable; NR – not reported; SD – standard deviation; Ether-PC – ether-phosphatidylcholines; LPC – lysophosphatidylcholines; PC – phosphatidylcholine; MIG - Monokine induced by interferon-γ; TNFβ – Tumor necrosis factor beta; IgG - Immunoglobulin G; GP – glycan peak; S.VLDL.L – small very low density lipoprotein total lipids; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; CCL4 - CC motif chemokine 4; CCL8 - Monocyte chemoattractant protein-2; CXCL10 - C-X-C motif chemokine 10 (also known as IP-10 and small-inducible cytokine B10); CX3CL1 – fractalkine; FGF-5 - fibroblast growth factor 5; IL-33 - Interleukin 33; LIF-R - leukemia inhibitory factor receptor; KOA – knee ostoerthritis; HOA – hip osteoarthritis; BMI - body mass index; BMD - bone mineral density; SGLT-1 - sodium-glucose cotransporter 1; FEV1 - forced expiratory volume in the first second; FVC - forced vital capacity; PEF - peak expiratory flow; IL-6 - Interleukin 6; LV – left ventricle; PM – particulate matter; COPD -chronic obstructive pulmonary disease; hs-CRP – high sensitivity C-reactive protein; HTT – Huntigtin; LRPPRC - leucine-rich pentatricopeptide repeat-containing protein; APOB - apolipoprotein B; BIRC2 - baculoviral IAP repeat containing 2; CYP3A4 - cytochrome P450 family 3 subfamily A member 4; PSME1 - proteasome activator subunit 1; IGF-1 - insulin-like growth factor 1; SHBG – sex hormone biding globulin.

3.4.1. Causal association between frailty and sociodemographic and lifestyle factors.

Several studies have confirmed that higher education level and higher average income are associated with reduced risk of frailty (Atkins et al., 2021; J. Huang et al., 2024). Additionally, research has shown that social isolation and occupations involving physical labor are associated with an increased risk of frailty (J. Huang et al., 2024). In addition, sedentary lifestyle patterns, such as leisure screen time and watching television, were associated with an increased risk of frailty, while physical activity was linked to a reduced risk of frailty (Chen et al., 2024; Gu et al., 2023; C. Li et al., 2024). Additionally, the intake of cereal, cheese, fruit, and oily fish was associated with a reduced risk of frailty (Yingye Tu et al., 2024). However, alcohol, coffee, and pork intake as well as breakfast skipping were associated with increased risk of frailty (Yingye Tu et al., 2024; Z. Zhang et al., 2024b). A group of studies also confirmed that a younger age of smoking initiation, a longer lifetime of smoking, and a higher count of cigarettes smoked per day were causally associated with increased risk of frailty (Gu et al., 2023; Guo et al., 2023; W. Liu et al., 2023; Lv et al., 2023).

Several studies have examined the relationship between frailty and sleep patterns. It was found that there is a bidirectional association between insomnia and frailty (Che et al., 2025; Deng et al., 2024; Z.-X. Lu et al., 2024; Zhou et al., 2025). Additionally, frailty and daytime

napping had a bidirectional association with each other (Deng et al., 2024; Z.-X. Lu et al., 2024). Short sleep duration was also associated with an increased risk of frailty (Che et al., 2025; Z.-X. Lu et al., 2024). Finally, sleep apnea and frailty were found to be bidirectionally associated (Deng et al., 2024).

3.4.2. Causal association between frailty and blood biomarkers.

One study revealed that higher levels of glycoprotein acetyls were associated with an increased risk of frailty (Mak et al., 2023). Additionally, it was found that glucokinase activation was related to a lower risk of frailty (Hua et al., 2025). Another study found that higher levels of high-sensitivity C-reactive protein (CRP) were associated with a higher risk of frailty (Luo et al., 2024). In addition, a higher level of CRP was associated with frailty (Zheng et al., 2024). Additionally, high levels of TNF-β and monokine induced by interferon-γ (MIG) were associated with a higher risk of frailty (C. Wang et al., 2024). Furthermore, it was revealed that higher levels of fractalkine (CX3CL1), interleukin-33 (IL-33), leukemia inhibitory factor receptor (LIF-R) and monocyte chemoattractant protein-1 (CCL8) were related to higher risk of frailty, while were CC motif chemokine 4 (CCL4), C-X-C motif chemokine 10 (CXCL10), fibroblast growth factor 5 (FGF-5), and TNF-beta (TNFB) levels were negatively associated with the risk of frailty (Wen et al., 2025). Additionally, one study found that downregulation of interleukin-6 (IL-6) signaling is associated with a reduced risk of frailty (Mourtzi et al., 2023).

A higher eosinophil count was associated with increased risk of frailty (Guo et al., 2024). In another study, the relationship between eosinophil count and frailty was bidirectional (Chen et al., 2025). In the same study, the percentage of eosinophils among white blood cells, the percentage of eosinophils among granulocytes, the sum of eosinophil and basophil counts, and the percentage of neutrophils among granulocytes were associated with frailty (Chen et al., 2025).

3.4.3. Causal association between frailty and lipid profiles.

It was found that saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids increased the risk of frailty (Chen et al., 2024). Additionally, higher remnant cholesterol levels were associated with a higher risk of frailty (Hu et al., 2023). One study found that lowering low-density lipoprotein cholesterol (LDL-C) levels was associated with lower frailty scores (Wang et al., 2019). Phosphatidylcholine (PC) and lysophosphatidylcholine (LPC) species such as: PC (18:0_20:5), LPC (18:0_0:0), LPC (16:0_0:0), and ether-PC (O-16:0_22:5) were associated with increased risk of frailty, while PC(18:1_20:2), PC(16:0_18:3), PC(16:0_20:1), ether-PC (O-18:0_16:1), and ether-PC (O-16:1_16:0) were related to decreased risk of frailty (Han et al., 2025). Frailty was associated with higher levels of triglycerides and lower levels of LDL-C (Xu et al., 2024).

3.4.4. Causal association between frailty and gut microbiota.

Some studies have analyzed the impact of gut microbiota on frailty. It was found that some bacteria types, such as Bacteroidia, E. ruminantium, Akkermansia, Butyrivibrio, Catenibacterium, Christensenellaceae R-7 group, Defluviitaleaceae UCG-011 and Bifidobacterium are associated with increased risk of frailty (Bo et al., 2024; Cui et al., 2023; Z. Wang et al., 2024; Yao et al., 2024). To add, it was confirmed that there is a bidirectional association between frailty and Butyrivibrio species (Bo et al., 2024). On the other hand, such species as Betaproteobacteria, C. innocuum, E. coprostanoligenes, Allisonella, Howardella and Ruminococcus were confirmed to reduce the risk of frailty (Bo et al., 2024; Cui et al., 2023; Z. Wang et al., 2024; Yan et al., 2025; Yao et al., 2024).

3.4.5. Causal association between frailty and cardiovascular / cerebrovascular systems disorders.

Atrial fibrillation was associated with increased risk of frailty (Chen et al., 2024). One study found that higher stroke volume, a cardiac function parameter, is associated with a reduced risk of frailty (Zhang et al., 2022). Also, peripheral arterial disease was causally associated with increased risk of frailty (Xu et al., 2024). In the same study, it was found that a bidirectional association exists between frailty and coronary arteriosclerosis. Li and colleagues reported that frailty increased the risk of such diseases: coronary artery disease, myocardial infarction, and heart failure (Li et al., 2022). In addition, frailty was related to an increased risk of hypertension (H. Wang et al., 2025). Furthermore, Renedo and colleagues have reported that frailty increases the risk of any type of stroke, ischemic stroke, and intracerebral hemorrhage (Renedo et al., 2023). In addition, it was revealed that both frailty and cerebral atherosclerosis increase the risk of each other (Xu et al., 2024).

3.4.6. Causal association between frailty and mental disorders.

Five studies have identified a bidirectional association between frailty and depression (major depressive disorder) (Deng et al., 2023; Ma et al., 2024; Sun et al., 2024; Xiao et al., 2025; Zhou et al., 2025; Zhu et al., 2023). Also, a bidirectional causal relationship was found between frailty and anxiety, affective disorder, and obsessive-compulsive disorder (Ma et al., 2024). Moreover, mania and schizophrenia were associated with increased risk of frailty (Ma et al., 2024). Two studies have reported a bidirectional association between frailty and neuroticism (Xing et al., 2025; Zhou et al., 2025). In addition, frailty and suicide attempts increased the risk of each other (Xiao et al., 2025; Zhou et al., 2025). It was found that frailty increased the risk of bipolar disorder and schizophrenia (Sun et al., 2024; Xiao et al., 2025, 2023).

3.4.7. Causal association between frailty and the musculoskeletal system.

Several studies have reported that body composition parameters, such as being overweight, body weight, birth weight, body fat mass, body fat percentage, childhood BMI, BMI, and waist circumference, are associated with increased risk of frailty (Z. Chen et al., 2023; Cui et al., 2024; Gu et al., 2023). Also, bidirectional causal associations were found between frailty and osteoporosis as well as rheumatoid arthritis (S. Li et al., 2024; Que et al., 2024). One study found that osteoarthritis of the hip or knee increased the risk of frailty (J. Zhou et al., 2024a). Moreover, it was revealed that total bone mineral density (BMD), forearm BMD, ultradistal forearm BMD, heel-BMD, increased grip strength, and increased appendicular lean mass were associated with reduced risk of frailty, while low grip strength, knee osteoarthritis, and hip osteoarthritis were associated with increased risk of frailty (Liu et al., 2025). Furthermore, it was found that frailty increased the risk of osteoarthritis and psoriatic arthritis (Weichu Sun et al., 2024). In addition, one study reported that frailty increased the risk of obesity and gout (H. Wang et al., 2025).

3.4.8. Causal association between frailty and other traits.

It was revealed that lung function parameters, such as forced expiratory volume in the first second (FEV1), ratio of FEV1 on forced vital capacity (FVC) (FEV1/FVC), and peak expiratory flow (PEF), were negatively associated with frailty (R. Zhou et al., 2024). Multiple bidirectional associations were found between frailty and asthma, as well as chronic obstructive pulmonary disease (COPD) (Cheng et al., 2025; Ma et al., 2023; Qu et al., 2024).

Furthermore, frailty was associated with increased risk of chronic kidney disease in one study (Chen et al., 2024). Also, it was found that levels of blood urea nitrogen, estimated glomerular filtration rate (cystatin c), and estimated glomerular filtration rate (creatinine) were negatively related to frailty risk, while chronic kidney disease and renal failure were associated with a higher risk of frailty (Zheng et al., 2024).

Notably, one study found that hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, multiple sclerosis, and overall autoimmune disease were associated with increased risk of frailty (J. Zhou et al., 2024b). Also, another study confirmed the association between hypothyroidism and frailty (H. Wang et al., 2025).

It was found that type 2 diabetes mellitus increased the risk of frailty (H. Wang et al., 2025). A bidirectional association was found between frailty and psoriasis, hearing loss, and lower back pain (Lei et al., 2024; Liu et al., 2022, 2024). Childhood maltreatment was related to a higher risk of frailty (Z. Zhang et al., 2024a). It was found that 5 proteins, including BIRC2 and PSME1, are associated with reduced risk of frailty, while 49 proteins, including APOB and CYP3A4, were related to an increased risk of frailty (Chen et al., 2024). Two studies have shown that Crohn's disease and ulcerative colitis are causally associated with increased risk of frailty (J. Feng et al., 2024; P. Wang et al., 2024). One study revealed that age at menarche, age at first birth, and age at first sexual intercourse were related to reduced risk of frailty (Fan et al., 2024). Additionally, particulate matter with a diameter of less than 2.5 micrometers (PM2.5) was found to be associated with an increased risk of frailty in one study (Xiao et al., 2023).

3.4.9. Phenotypes without established causal associations with frailty.

No causal relationship has been identified between frailty and acute respiratory distress syndrome (ARDS) (Chen et al., 2024). Similarly, one study found no association between frailty and bone mineral density across various anatomical sites (Shen et al., 2024). A variety of metabolites were used to assess the relationship with frailty, but no significant results were found (Qian et al., 2024). Furthermore, no association was found between frailty and several neurological and neurodegenerative disorders, including Alzheimer’s disease, vascular dementia, Parkinson's disease, amyotrophic lateral sclerosis, vestibular schwannomas, or vestibular disorders (Enduru et al., 2024; Imahori et al., 2024; Xiao et al.,

2022; Z. Zhang et al., 2023). No causal associations were observed between frailty and colorectal cancer, nor with key biochemical markers such as Immunoglobulin G (IgG) N-Glycosylation, sex hormone-binding globulin, or insulin-like growth factor-1 (IGF-1) levels (Fan et al., 2024; Gao et al., 2023; Sun et al., 2024). Additionally, vitamin levels did not exhibit any causal relationship with frailty in the examined datasets (Kuribanjiang et al., 2024). One study also reported no evidence of a causal link between frailty and multiple sclerosis (Jeong et al., 2024).

These null findings underscore the complexity of frailty as a multidimensional phenotype and highlight the need for further research using refined instruments and larger datasets to clarify potential biological pathways.

3.4.10. Subgroup analysis based on STROBE-MR scores of phenotypes related to frailty.

Additional supportive evidence is need for the following associations: vitamin D was associated with increased risk of frailty and, also that frailty was negative associated with other micronutrients (Wen et al., 2024); frailty and gestational diabetes mellitus have bidirectional association (Li and Xiong, 2024); systolic blood pressure (Yihan Chen et al., 2024); delirium (Chen et al., 2024); alcohol consumption (Lv et al., 2023); serum total protein (Tomata et al., 2022).

Associations that are supported by lower-quality studies but have been found in high-scoring studies as well provide ample evidence for an association between frailty and the following conditions: type 2 diabetes mellitus (Gao et al., 2025); lipid profile and walking pace (Yihan Chen et al., 2024; Tomata et al., 2021); depression (R. Jiang et al., 2024); smoking (Lv et al., 2023); education attainment (Atkins et al., 2021).

4. Discussion

In this systematic review, we synthesized current knowledge from two-sample Mendelian randomization (MR) studies on frailty and sarcopenia in relation to health-related outcomes (Figure 2 and 3). Out of 164 included studies, most were of good quality. We compared MR results with observational evidence to identify reliable associations and underlying mechanisms (Table 6).

Figure 2. Health related outcomes that are affected by sarcopenia (and sarcopenia related traits: walking pace, muscle mass, muscle strength) and frailty.

Figure 3. Health related outcomes that affect sarcopenia and frailty. Arrows with black arrowheads show health-related outcomes that increase the risk of sarcopenia and frailty. Arrows with empty arrowheads show health-related outcomes that decrease the risk of sarcopenia and frailty.

Table 6. Comparison of knowledge from observational and Mendelian randomization studies about associations between frailty and sarcopenia and different disorders.

Disease or abnormality group	**Sarcopenia**	**Frailty**	**Observational studies (OS) or systematic reviews of OS**	**Confirmation of association in OS**	**Confirmation of association in MR studies**
Neurodegenerative diseases (e.g. Alzheimer's, Parkinson's)	Cognitive performance and function, Levodopa induced dyskinesia (Parkinson's), Alzheimer's disease	Alzheimer's disease, vascular dementia, Parkinson's disease, amyotrophic lateral sclerosis	(Amini et al., 2024; Gotaro Kojima et al., 2017; McMillan et al., 2021; Ponsoni et al., 2023)	Confirmed	Lower muscle mass is associated with the risk of Alzheimer's and Parkinson's diseases. Cognitive performance positively correlated with walking pace. No association with frailty.
Inflammatory bowel disease (e.g. Ulcerative colitis, Chron's disease)	Inflammatory bowel disease (IBD), Crohn's disease (CD), Ulcerative colitis (UC)	Crohn's disease, ulcerative colitis	(Carbery et al., 2025; Y. Zhang et al., 2023)	Confirmed	Confirmed
Gut microbiota	Bifidobacteriacea, Sellimonas, Parabacteroides, Bifidobacterium, Bifidobacteriales, Actinobacteria, Alloprevotella, Eisenbergiella, Phylum	Bacteroidia, E. ruminantium, Akkermansia, Butyrivibrio, Catenibacterium, Christensenellaceae	(Rashidah et al., 2022; M. Wang et al., 2024)	Confirmed	Confirmed

	Actinobacteria, Paraprevotella, Prevotella9, Eubacterium nodatum group, Lachnospiraceae, Bacteroidaceae, Bacteroides, Lachnospira, Phascolarctobacterium, Eubacterium fissicatena group, Porphyromonadaceae, Rikenellaceae, Terrisporobacter, Victivallis Streptococcaceae, Intestinibacter, Ruminococcaceae UCG009	R-7 group, Defluviitaleaceae UCG-011, Bifidobacterium, Betaproteobacteria, C. innocuum, E. coprostanoligenes, Allisonella, Howardella, Ruminococcus			
Joint and musculoskeletal disorders (e.g. osteoarthritis, rotator cuff tear)	Osteoarthritis, Hypertrophic osteoarthropathy Knee osteoarthritis, Ankylosing spondylitis, Rotator cuff tears, Total knee and hip replacement, Bone mineral density in heel and lumbar spine bone	Osteoarthritis, psoriatic osteoarthritis	(Cook et al., 2022; P. Peng et al., 2024)	Confirmed	Confirmed
Autoimmune diseases (e.g. Rheumatoid arthritis, hypo-/hyper-thyrodism, psoriasis, SLE)	Rheumatoid arthritis, SLE, Psoriasis	Rheumatoid arthritis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, multiple, overall autoimmune disease, psoriasis	(R.-C. Gao et al., 2022; Li et al., 2021)	Did not confirm for psoriasis and sarcopenia. Mixed results for hypothyroidism and frailty	Confirmed for rheumatoid arthritis, psoriasis. Autoimmune thyroid diseases are not evaluated in sarcopenia. SLE not evaluated in frailty.
Blood biomarkers (chronic inflammation, signaling metabolites and hormones)	Platelet-derived growth factor BB (PDGF-BB), IGF-1 levels, IGF - 1 R levels, IGFPB-3 and IGFPB-7 levels, IL-10, IL-5, IL-16, IL-12; Interleukin-12p70, VEGF, CRP, fasting insulin, plasma cortisol concentration, Homocysteine levels, IL1b, IL2 , IL8, TNFb, TNFb2, Glucosamine, Androsterone sulfate, Cytokine macrophage colony-stimulating factor M-CSF, Hepatocyte growth factor (HGF), IP-10 also known as chemokine CXCL10	IL-6, glycoprotein acetyls, high-sensitivity CRP, CRP, TNF-β, MIG, CX3CL1, IL-33, LIF-R , CCL8, CCL4, CXCL10, FGF-5, eosinophil count, the eosinophil percentage of white blood cells, the eosinophil percentage of granulocytes, the sum of eosinophil and basophil counts, the neutrophil percentage of granulocytes, proteins	(Bano et al., 2017; Picca et al., 2022; Soysal et al., 2016)	Confirmed	Confirmed
Sociodemographic factors	Educational attainment	Education level; Average income; Social isolation; Occupations with	(Gao et al., 2021; Hanlon et al., 2018)	Confirmed	Confirmed in frailty, muscle mass, and

		physical labor; childhood maltreatment			strength. Not evaluated in WP.
Lifestyle and behaviour factors (e.g. physical activity, smoking, drinking)	Smoking initiation, Cigarette smoking, Alcohol consumption	Leisure screen time; watching television; physical inactivity; Intake of cereal, cheese, fruit, and oily fish; alcohol, coffee, and pork intake; breakfast skipping; age of smoking initiation; lifetime of smoking; count of cigarettes smoked per day	(Amiri and Behnezhad, 2019; Lee et al., 2018; Mo et al., 2023; Soltani et al., 2024; Steffl et al., 2016, 2015; Zhao et al., 2022)	Confirmed for smoking, physical activity	Confirmed smoking. Confirmed for physical activity in frailty.
Lipid profiles / Lipoproteins	High-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), Triglycerides (TG), Pentadecanoate (15:0), 1-arachidonoylglycerophosphocholine, lipid metabolites: phosphatidylcholine, phosphatidylethanolamine, ceramide (d40:1 and d40:2), triacylglycerol, sphingomyelin (d42:2), sterol ester.	Saturated fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid, remnant cholesterol, LDL-C; phosphatidylcholine (PC) and lysophosphatidylcholine (LPC) species such as: PC (18:0_20:5), LPC (18:0_0:0), LPC (16:0_0:0), and ether-PC (O-16:0_22:5), PC(18:1_20:2), PC(16:0_18:3), PC(16:0_20:1), ether-PC (O-18:0_16:1), and ether-PC (O-16:1_16:0); triglycerides	(Hwang et al., 2015; Jiang et al., 2023; Yin et al., 2023)	Mixed results	Confirmed, but not evaluated in WP
Neoplasms	Hepatocellular carcinoma, Liver cancer, Colorectal cancer, Breast and ovarian cancers, Benign prostatic hyperplasia	Colorectal cancer	(Haiducu et al., 2021; Handforth et al., 2015; Komici et al., 2022; Wang et al., 2020)	Confirmed	Confirmed in sarcopenia. Not evaluated in frailty.
Cardiovascular diseases	Coronary artery disease, Myocardial infarction, Risk of coronary heart disease, Hypertension	Atrial fibrillation, stroke volume, peripheral arterial disease, coronary arterosclerosis, coronary artery disease, myocardial infarction, heart failure, hypertension	(K. Gao et al., 2022; Liperoti et al., 2021; Zuo et al., 2023)	Confirmed	Confirmed, but not evaluated in muscle strength
Kidney diseases	Glomerular filtration rate (GFR)	CKD, blood urea nitrogen, estimated	(Dalrymple et al., 2013;	Confirmed	Confirmed in frailty.

		glomerular filtration rate (cystatin c), estimated glomerular filtration rate (creatinine), renal failure	P. He et al., 2023; C. Wang et al., 2023)		Muscle mass was related to GFR. Not evaluated in muscle strength, WP.
Diabetes	Type 2 DM	Type 2 DM	(Chung et al., 2021; Y Liu et al., 2024; Lyu et al., 2023; Qiao et al., 2021; Veronese et al., 2019)	Confirmed	Confirmed, but not evaluated in muscle strength
Lung function and diseases	COPD Pulmonary function FEV1 and FVC	Asthma, COPD, FEV1, FEV1/FVC, PEF	(G.-Y. Feng et al., 2024; Singer et al., 2018; H. Wang et al., 2023; Weber et al., 2023)	Confirmed	Confirmed in frailty.
Gastrointestinal diseases (e.g. liver cirrhosis, NAFLD, hepatitis)	Gastroesophageal reflux disease (GERD), Irritable bowel disorder	Not evaluated	(Bhanji et al., 2019; Cai et al., 2020; He et al., 2025; Zhong et al., 2025)	Confirmed	No association with sarcopenia. Not evaluated in frailty.
Cerebrovascular diseases (e.g. stroke)	Small vessel stroke, Cardioembolic stroke, Risk of ischemic stroke, Risk of stroke	any type of stroke, ischemic stroke, intracerebral hemorrhage, cerebral atherosclerosis	(Fang et al., 2023; Palmer et al., 2019)	Confirmed	Confirmed
Sleep Initiation and Maintenance Disorders (e.g. insomnia, sleeping patterns, obstructive sleep apnea)	Obstructive sleep apnea	Insomnia, daytime napping, short sleep duration, obstructive sleep apnea	(Li et al., 2023; Moreno-Tamayo et al., 2020; Nagaura et al., 2020; Shibuki et al., 2023; Souza et al., 2025; Zhu et al., 2022)	Confirmed	Confirmed in frailty. Only sleep apnea was assessed in muscle strength and muscle mass. Not evaluated in WP
Mental disorders (e.g. schizophrenia, bipolar disorder, affective disorder, OCD, ADHD, depression, anxiety)	Risk of Attention deficit hyperactivity disorder, Major depressive disorder	Depression, anxiety, affective disorder, obsessive-compulsive disorder, mania, schizophrenia, neuroticism, suicide attempts, bipolar disorder	(Bulbul et al., 2021; Demichelis et al., 2023; Yunyun Liu et al., 2024; Pearson et al., 2022; C. Yang et al., 2023)	Confirmed	Confirmed in frailty. Only ADHD was assessed in muscle mass and WP. Not assessed in muscle strength.

Body constitution (e.g. BMI, waist circumference, body composition) and anatomical structures	Brain cortical thickness	Being overweight, obesity, body weight, birth weight, body fat mass, body fat percentage, childhood BMI, BMI, waist circumference, appendicular lean mass	(Jayanama et al., 2022; Xu et al., 2020)	Confirmed	Confirmed for frailty, muscle strength. Not evaluated in muscle mass and WP. Brain cortical thickness was associated with muscle strength and mass.
Hearing disorders	Not evaluated	Hearing loss	(Tian et al., 2021; Zhang, 2024)	Confirmed	Confirmed
Back pain	Ankylosing spondylitis	Back pain	(Ceolin et al., 2024; Hu et al., 2025; Qing et al., 2024; Rocha et al., 2023)	Confirmed	Confirmed in frailty.
Osteoporosis	Lumbar spine BMD, Heel-BMD, Lumbar spine BMD	Osteoporosis, total BMD, forearm BMD, ultradistal forearm BMD, Heel-BMD,	(Yoshimura et al., 2018, 2017)	Confirmed	Confirmed in frailty, WP and muscle mass. Not evaluated in muscle strength.

OS - Observational Studies, SLE - Systemic lupus erythematosus OCD - Obsessive compulsive disorder, ADHD - Attention deficit hyperactivity disorder, WP – Walking pace, CKD - Chronic kidney disease, COPD - Chronic obstructive pulmonary disease , DM - Diabetes mellitus, GFR - Glomerular filtration rate, NAFLD - Non-alcoholic fatty liver disease, BMI - Body mass index, UC – ulcerative colitis, CD - Crohn's disease, IBD - Inflammatory bowel disease, BMD – Bone mineral density, CRP – C-reactive protein, PDGF-BB - Platelet-derived growth factor, IGF-1 - Inulin-like growth factor 1, IGFPB-3 Insulin-like growth factor binding protein 3, IGFPB-7 - Insulin-like growth factor binding protein 7, IL-10 – Interleukin 10, IL-5 – Interleukin 5, IL-16 – Interleukin 16, IL-12 – Interleukin 12, VEGF - Vascular endothelial growth factor, IL1b – Interleukin 1b, IL2 – Interleukin 2 , IL8 – Interleukin 8, TNFb – Tumor necrosis factor-beta, M-CSF - Macrophage colony-stimulating factor, HGF - Hepatocyte growth factor, CXCL10 - Interferon gamma-induced protein 10

Muscle mass was associated with neurodegenerative diseases such as Alzheimer's and Parkinson's (T. Wang et al., 2024; Zhu et al., 2024). Walking pace was linked to cognitive performance, with slower gait predicting decline (Liu et al., 2024). Inflammatory bowel disease (IBD) was causally related to frailty and sarcopenia, consistent with observational findings (Carbery et al., 2025; Y. Zhang et al., 2023). Chronic inflammation and cytokine activity (e.g., TNF-α, IL-6) likely mediate these effects (Nishikawa et al., 2021).

Gut microbiota were reliably associated with frailty traits (Rashidah et al., 2022; M. Wang et al., 2024). Beneficial bacteria enhance muscle health via short-chain fatty acids, while dysbiosis promotes inflammation and sarcopenia (Kang et al., 2021; Ticinesi et al., 2019). Joint diseases, particularly osteoarthritis, were linked to frailty and sarcopenia in MR and observational research (J. Yang et al., 2023; L. Zhang et al., 2023; J. Zhou et al., 2024a). Shared cytokine activity and signaling pathways (e.g., Wnt/β-catenin) could explain these overlaps (Greco et al., 2019; J. Yang et al., 2024).

Several blood biomarkers were associated with sarcopenia and frailty, including IGF-1, PDGF-BB, IL-16, cortisol, and CRP (Bano et al., 2017; Picca et al., 2022). Socioeconomic and lifestyle factors were also influential: higher education/income reduced risk, while smoking increased it (Hanlon et al., 2018; Sha et al., 2025a). Physical activity protected against frailty, partly through mTOR and IGF-1 pathways (Chen et al., 2024; Ziaaldini et al., 2017).

Sarcopenia traits were associated with several cancers in MR and observational data, including liver, colorectal, breast, ovarian, lung, and gastrointestinal (Endo et al., 2024; Haiducu et al., 2021). Mechanisms include chronic inflammation, cytokine-driven muscle loss, and cachexia (Williams et al., 2021). Cardiovascular diseases (CHD, hypertension, MI) were linked to sarcopenia and frailty (K. Gao et al., 2022; Zuo et al., 2023). Shared mechanisms include insulin resistance, inflammation, and endothelial dysfunction (Loh et al., 2022).

Chronic kidney disease (CKD) and reduced kidney function correlated with frailty (Dalrymple et al., 2013; C. Wang et al., 2023). Diabetes was associated with frailty, walking pace, and muscle mass, via insulin resistance and impaired mTOR signaling (Cleasby et al., 2016; Veronese et al., 2019). Respiratory conditions (asthma, COPD) showed bidirectional associations with frailty (J. Feng et al., 2024; Weber et al., 2023). Mechanisms included

inflammation, oxidative stress, and IGF-1/Akt/mTOR pathway involvement (W. Wang et al., 2024).

Stroke was causally linked to frailty and sarcopenia (Palmer et al., 2019). Key contributors include malnutrition, mobility loss, and metabolic disturbances (Chon et al., 2024). Sleep disorders (insomnia, apnea, short sleep) were associated with frailty (Souza et al., 2025; Z. Yan et al., 2024). Depression, anxiety, schizophrenia, and suicidal behaviour also showed causal associations (Bulbul et al., 2021; Demichelis et al., 2023). Shared pathways involve inflammation, inactivity, and social isolation (Vaughan et al., 2015). Osteoporosis was consistently related to frailty, likely via endocrine changes, malnutrition, and inactivity (Gielen et al., 2023; Yoshimura et al., 2017).

5. Challenges, Future Perspectives, and Conclusions

Limitations of MR studies included lack of descriptive data, European-only samples, limited instrumental variables, and use of prior MR instead of GWAS sources. Our review was stringent, excluding weaker evidence and restricting databases. Moreover, the term “sarcopenia” was not used directly in search strategies. In addition, we only included results from two databases, which could have limited our search results

Despite limitations, robust evidence supports causal associations between frailty, sarcopenia, and diverse group of disorders. Both sarcopenia and frailty were linked to sociodemographic and lifestyle factors, respiratory and joint diseases, gut microbiota, IBD, stroke, and cancer. These findings underscore the systemic role of frailty and sarcopenia as contributors to chronic disease. Integrating genetic epidemiology with clinical data highlights pathways for prevention and intervention.

Glossary

ADHD	Attention deficit hyperactivity disorder
ALM	Appendicular lean mass
APOB	Apolipoprotein B
ARDS	Acute respiratory distress syndrome
AURKA	Aurora kinase A
BANKSSTS	Banks of the superior temporal sulcus
BIRC2	Baculoviral IAP repeat containing 2
BMD	Bone mineral density
BMI	Body mass index
CCL4	CC motif chemokine 4
CCL8	Monocyte chemoattractant protein-2
CCL27	Chemokine also known as cutaneous T cell-attracting chemokine (CTACK)
CD	Crohn's disease
CI	Confidence interval
CKD	Chronic kidney disease
COL15A1	Collagen type XV alpha 1 chain
COPD	Chronic obstructive pulmonary disease
CRP	C reactive protein
CXCL10	C-X-C motif chemokine 10 (also known as IP-10 and small-inducible cytokine B10)
CX3CL1	Fractalkine
CYP3A4	Cytochrome P450 family 3 subfamily A member 4
DM	Diabetes mellitus
Ether-PC	Ether-phosphatidylcholines
ER	Estrogen receptor
FEV1	Forced expiratory volume in the first second
FFM	Fat-free mass
FGF-5	Fibroblast growth factor 5
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GP	Glycan peak
GWAS	Genome-wide association study
HCC	Hepatocellular carcinoma
Hcy	Homocysteine
HDL-C	High-density lipoprotein cholesterol
HP	Haptoglobin
HGF	Hepatocyte growth factor
HGS	Hand grip strength
HLA-DRA	Major histocompatibility complex, class II, DR alpha
HOA	Hip osteoarthritis
hs-CRP	High sensitivity C-reactive protein
HTT	Huntigtin
IBD	Inflammatory bowel disease
IGF-1	Insulin-like growth factor 1

IGFPB-3	Growth factor binding protein 3
IGFPB-7	Growth factor binding protein 7
IgG	Immunoglobulin G
IL-1b	Interleukin 1 beta
IL-2	Interleukin 2
IL-8	Interleukin 8
IL-6	Interleukin 6
IL-10	Interleukin 10
IL-12	Interleukin 12
IL-5	Interleukin 5
IL-16	Interleukin 16
IL-33	Interleukin 33
IP-10	Interferon gamma induced protein 10
IV	Instrumental variable
KOA	Knee ostoerthritis
LDL-C	Low-density lipoprotein cholesterol
LIF-R	Leukemia inhibitory factor receptor
LPC	Lysophosphatidylcholine
LRPPRC	Leucine-rich pentatricopeptide repeat-containing protein
LV	Left ventricle
MAP3K3	Mitogen-activated protein kinase kinase kinase 3
M-CSF	Macrophage colony-stimulating factor
MFGE8	Milk fat globule EGF and factor V/VIII domain containing
MIG	Monokine induced by interferon-γ
MR	Mendelian randomization
MRC-IEU	Medical Research Council Integrative Epidemiology Unit
NGF	Nerve growth factor - neurotrophic factor and neuropeptide
NAFLD	Non-alcoholic fatty liver disease
OCD	Obsessive compulsive disorder
OR	Odds ratio
OS	Observational studies
OSA	Obstructive sleep apnea
PC	Phosphatidylcholine
PDGF-BB	Platelet-derived growth factor BB
PEF	Peak expiratory flow
PM	Particulate matter
PRISMA	Preferred reporting items for systematic reviews
PSCK9	Enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) encoded by the PCSK9 gene
PSME1	Proteasome activator subunit 1
RA	Rheumatoid arthritis
RCT	Randomized control trials
SGLT-1	Sodium-glucose cotransporter 1
SHBG	Sex hormone biding globulin
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism

STROBE-MR Strengthening the reporting of observational studies in epidemiology – mendelian randomization
S.VLDL.L Small very low density lipoprotein total lipids
PM Particle matter
QC Quality control
TG Triglycerides
TNFb Tumor necrosis factor beta
TNFSF10 Cytokine that belongs to the tumor necrosis factor (TNF) ligand family
TNFb2 Tumor necrosis factor beta 2
T2DM Type 2 diabettes mellitus
UC Ulcerative colitis
VEGF Vascular endothelial growth factor
VLDL Very-low-density lipoprotein
WHO World health organization
WP Walking pace

Additional files

1. Supplementary table S1 STROBE-MR checklist.xlsx: Quality scores of the reviewed articles (frailty n=96 and sarcopenia, n=68 phenotypes) according to the 20 items from the STROBE-MR checklist.
2. Supplementary table S2 Data sources.xlsx: Summary of sources of instrumental variables for exposure and outcome phenotypes used in the reviewed mendelian randomization studies.

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding sources

This work in part was funded by Research Council of Lithuania (agreement No S-MIP-22-36) as part of the project “Genome, epigenome and telomere length features of sarcopenia and frailty” (GEPITEL).

Authors' contributions

IIA and VA conceived and planned the study. AU created the search strategy and downloaded article identifiers. EP, JK, RD, VG, AU, AM extracted articles and removed duplicates. EP, JK, RD independently assessed article eligibility. EP, JK, RD, AU selected studies for inclusion and resolved disagreements by discussion. EP and JK filled in STROBE-MR checklist. JK, EP, AM, AU, RD, VG extracted data of sarcopenia/frailty and health outcomes as exposure and outcome associations (odds ratio or beta value), instrumental variable data sources and p values. All authors filled in the tables of exposure/outcome associations. AU summarized walking pace phenotype associations. VG and RD summarized muscle strength related phenotype associations. EP and AM summarized muscle mass related phenotype associations. JK and IEJ summarized frailty phenotype associations. IIA and VA coordinated and managed the systematic review data collection and resolved disagreements. All authors participated in writing and editing the manuscript. JK and EP were major contributors in writing the manuscript and contributed to this work equally. All authors read and approved the final manuscript.

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Figure 2

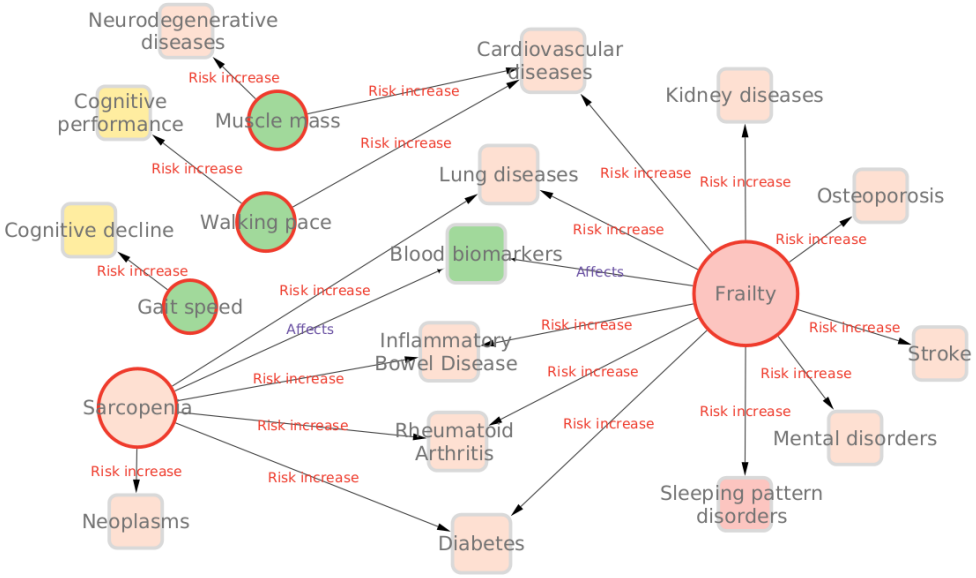
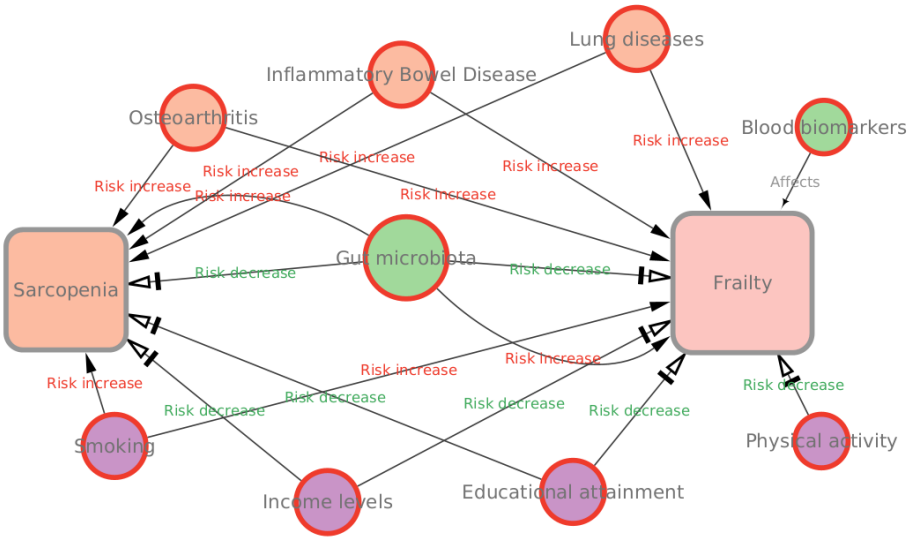


Figure 3



Highlights

- Evidence causally links frailty and sarcopenia to many health outcomes.
- Causal links between 19 disease traits, sarcopenia, and frailty were confirmed in both observational and Mendelian randomization studies.
- Increased muscle strength or mass, a faster gait speed, and lower frailty reduced the risk of many diseases.