REVIEW ARTICLE

Nagoya J. Med. Sci. **87**. 1–21, 2025
doi:10.18999/nagjms.87.1.1

A systematic review of the relationship between body composition including muscle, fat, bone, and body water and frailty in Asian residents

Kazuaki Hamada[1,2], Tsubasa Mitsutake[1,3], Tomonari Hori[1,4], Yoshitaka Iwamoto[5], Naoki Deguchi[1,6], Takeshi Imura[1,7] and Ryo Tanaka[1]

[1]*Graduate School of Humanities and Social Sciences, Hiroshima University, Higashi-Hiroshima, Japan*
[2]*Wako Orthopedic Clinic, Hiroshima, Japan*
[3]*Clinical Research Center, Saga University Hospital, Saga, Japan*
[4]*Department of Rehabilitation, Fukuyama Rehabilitation Hospital, Fukuyama, Japan*
[5]*Department of Biomechanics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan*
[6]*Research Team for Promoting Independence and Mental Health, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan*
[7]*Department of Rehabilitation, Faculty of Health Sciences, Hiroshima Cosmopolitan University, Hiroshima, Japan*

ABSTRACT

International guidelines suggested that overweight and underweight are risk factors for frailty. However, body composition, which directly affects body weight, was not mentioned as a risk factor. We aimed to investigate whether the body composition, including muscle, fat, bone, and body water, is a risk factor for frailty. MEDLINE, Cumulative Index to Nursing and Allied Health Literature, and Scopus were searched up to June 03, 2022. We included cohort studies or observational studies using a cross-sectional design that reported an association between body composition and frailty. Two reviewers assessed the quality of the included cohort studies. Furthermore, we examined whether body composition as a risk factor for frailty varies depending on the participant's place of residence. Of the 3871 retrieved studies, 77 were ultimately included, 7 of which were cohort studies. The risk-of-bias evaluation in each cohort study showed that all studies had at least one concern. Low lean mass, waist circumference-defined abdominal obesity, and bone mineral density were significantly associated with frailty in the cohort studies. The results of bone mineral density were conflicted in the cross-sectional studies. Considering the participants' place of residence, a significant association between lower-extremity muscle mass and frailty was demonstrated, particularly among Asian residents. Low lean mass and abdominal obesity were likely risk factors for frailty. These results could be useful for developing frailty prevention strategies and could have a positive impact on individual health management. Further, future studies are needed because body composition affecting frailty may differ by race.

Keywords: frailty, risk factors, body composition, Asian residents

Abbreviations:
BMD: bone mineral density
LM: lean mass
WC: waist circumference

Received: June 20, 2024; Accepted: July 31, 2024
Corresponding Author: Tsubasa Mitsutake, RPT, PhD
Clinical Research Center, Saga University Hospital, 5-1-1 Nabeshima, Saga, 849-8501 Japan
Tel: +81-952-34-3400, Fax: +81-952-34-2085, E-mail: ss6308@cc.saga-u.ac.jp

WHR: waist-hip ratio

INTRODUCTION

Frailty is a growing health problem in the aging population worldwide. It was first described by Fried in terms of its physical characteristics (or "phenotype") and is objectively identified as three or more of the following five components: weakness (low grip strength), slowness (slow walking speed), shrinking (unintentional weight loss), exhaustion (self-reported), and low physical activity.[1] These factors inhibit rehabilitation, and frailty can lead to adverse health conditions such as disabilities, hospitalization, and early mortality.[2-4] The demand for long-term health care in frail older adults has also increased, resulting in a heavy burden on the family as well as the society.[5] Thus, identifying the risk factors of frailty is crucial to develop effective prevention strategies.

Frailty is not an essential part of aging, considering that many adults reach advanced ages without developing frailty.[6] Various factors, such as physical inactivity, cardiovascular risk, self-rated health, and alcohol use, have been identified as risk factors for frailty.[7-11] Overweight or obesity, which can be possibly managed on a daily basis, and underweight have also been considered as its risk factors.[12,13]

Body weight changes are influenced by changes in body composition, which includes muscle, fat, bone, and body water. A similar weight loss has a different meaning for muscle mass decrease and fat mass decrease.[14] Muscle mass loss is generally caused by inactivity,[15] and sarcopenia due to decreased muscle mass is related to frailty.[16-19] Physical inactivity can also lead to increased fat and decreased bone mass,[20,21] and obesity and osteoporosis are reportedly associated with frailty.[22,23] Furthermore, extracellular-to-intracellular water ratio has been associated with functional disability,[24] which may result in physical activity decline, one of the elements of frailty. However, few systematic reviews have examined whether body composition, which directly affects body weight, influences the risk of developing frailty. Confirming the influence of body composition on frailty clarifies the body composition that needs more attention. This step could improve the quality of weight management and aid in the development of more effective frailty prevention strategies.

Body composition may be influenced by race. Asians have a lower percentage of fast-twitch fibers than other races.[25-27] Considering that fast-twitch fibers tend to decrease with age, Asians may be more likely to be classified as frail. By examining the impact of body composition on frailty, taking race into account, we can better understand the relationship between frailty and body composition. This may contribute to the development of higher quality frailty measures.

Therefore, this systematic review aimed to investigate whether the body composition, including muscle, fat, bone, and body water, is a risk factor for frailty. Further, we examined the risk separately for participants residing in Asia and for other participants.

MATERIALS AND METHODS

This review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and specific recommendations for systematic reviews.[28] The review protocol is registered in PROSPERO (Registration Number CRD: 42022336355).

Inclusion and exclusion criteria

The inclusion criteria were the following: (1) cohort studies or observational studies using a cross-sectional design that reported an association between frailty and body composition, and (2) studies that assessed either muscle mass, fat, bone, or body water with respect to body composition. In contrast, case reports, reviews, nonhuman studies, and unpublished studies were the exclusion criteria.

Type of exposures

Participants examined in terms of body composition, which included muscle mass, skeletal muscle index, fat mass, body fat distribution, body fat percentage, intra-abdominal fat, muscle fat index, bone mineral density (BMD), and body water, were analyzed in this review. We also included studies reporting risk factors or prevalence of frailty related to body composition. Conversely, we excluded studies using only the body mass index including body weight as the exposure, and those investigating the association between frailty and variables combining body composition with physical function or medical history.

This review confirmed a significant relationship between frailty and body composition for studies dealing with participants residing in Asia and other participants. We examined whether there was a significant difference in the number of studies showing a significant relationship between Asian residency and non-Asian residency by Fisher's exact probability test. For studies that presented results separately for men and women, the results for men and women were counted as a single exposure. We excluded studies that reported the results of correlation analyses. Statistical analyses were performed using JMP Pro version 16 (SAS Institute Inc, Cary, NC, USA), with a significance level of 5%.

Type of outcome

We included studies that quantitatively assessed frailty by using a questionnaire or other methods, such as Cardiovascular Health Study criteria based on the Fried Frailty Phenotype,[1] the Study of Osteoporotic Fractures index,[29] Clinical Frailty Scale,[30,31] and 34-item Frailty Index.[32]

Literature search and study selection

MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus were comprehensively searched, using keywords related to body composition and frailty (Supplementary Table 1). The most recent literature search was performed on June 03, 2022, to check for updated studies.

For preliminary elimination, two reviewers (KH and TH) independently screened all the study titles and abstracts of search results. Subsequently, both researchers independently reviewed the full text of the remaining studies. Any disagreements at either the article screening or the selection stages were resolved through a discussion. If the disagreement persisted, another researcher (TM) was consulted to achieve consensus.

Data extraction

From the included studies, data regarding the study design, setting, participants, exposures, outcome measurements, statistical methods, and results were collected using a data-extraction spreadsheet in Microsoft Excel 365 (Microsoft, Redmond, WA, USA). Two reviewers (KH and TH) discussed and decided on the extracted data, which were confirmed by another researcher (TM).

Risk-of-bias evaluation in individual studies

To evaluate the risk of bias in each study, two researchers (YI and KH) independently applied the Cochrane risk-of-bias instrument to assess the risk of bias in cohort studies. The articles were evaluated using the predetermined criteria.[33]

RESULTS

Study selection

Figure 1 presents the literature search results. Using the computer-aided search strategy, we identified 3871 studies, including 991 duplicates. The primary screening of the titles and abstracts revealed 126 articles that were potentially eligible or for which no clear judgment could be made. In the secondary screening (full-text review), 77 eligible articles were found.[34-110]

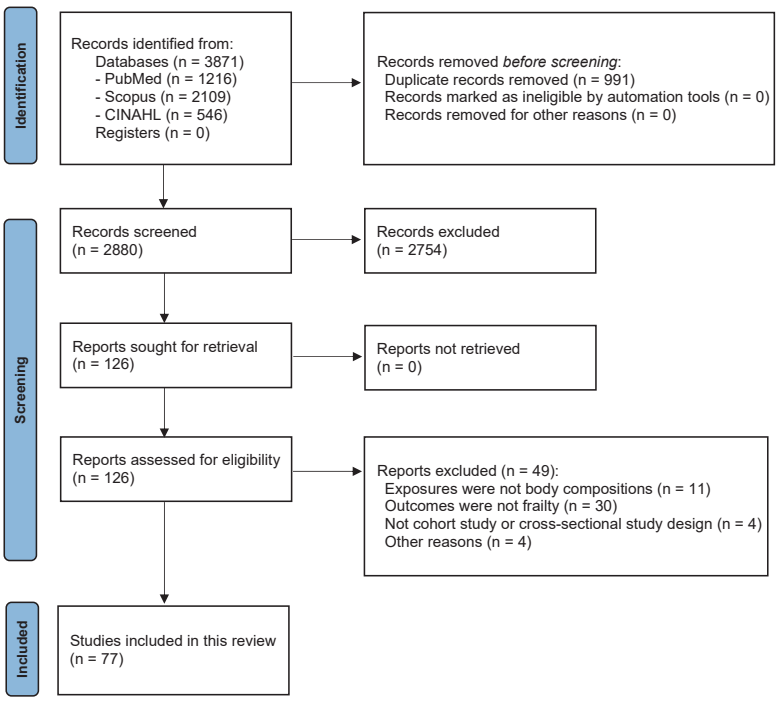

Fig. 1 Flow diagram of the study selection process

Study characteristics

Table 1 and Supplementary Table 2 summarize the features of the 77 studies included in the final analysis. Among these studies, 7 were cohort studies,[60,61,76,80,86,92,108] and 70 were cross-sectional studies.[34-59,62-75,77-79,81-85,87-91,93-107,109,110] The sample sizes ranged from 20 to 7753, and the participants' average or median age ranged from 48.6 to 83.4 years.

Furthermore, 54, 47, 17, and 6 studies reported exposures related to muscles,[35,37-41,44,47,48,50-52,55,56,58,59,62-64,67-75,77,78,80-82,85-88,90,91,93-100,102-106,108,109] fat,[34-36,38,40-46,49,50,53,54,56-63,68,71-79,82,84,86,88,91-93,96,98,101,103-105,110] bone,[35,40,47,50,58,62,65,66,78,89,92,97,102,104,106-108] and body water,[38,71,75,78,83,85] respectively. We found three studies constructing a predictive model of frailty combined with body composition as one independent

variable.[86,102,106] One study also constructed a predictive model of frailty combined with body composition and reported its accuracy without the odds ratio of each independent variable.[108]

For assessing frailty, 53 studies used the Fried Frailty Phenotype or Cardiovascular Health Study criteria,[34-37,40-43,46,47,49-52,54-57,59-61,63,66-68,71,73-80,83,85-89,91,93-97,101-104,106,107,109] 3 used the Study of Osteoporotic Fractures index,[62,86,100] 3 used Clinical Frailty Scale,[38,58,95] and 3 used Frailty Index.[66,76,110] The 19 remaining studies reported different frailty-related outcomes[39,44,45,48,53,64,65,69,70,72,81,82,84,90,92,98,99,105,108] (Table 1 and Supplementary Table 2).

Muscle-related exposures

Table 2 and Supplementary Table 3 summarize the studies' main results regarding exposures related to different body compositions.

Concerning muscle-related exposures, we found 51 cross-sectional studies[35,37-41,44,47,48,50-52,55,56,58,59,62-64,67-75,77,78,81,82,85,87,88,90,91,93-100,102-106,109] and 3 cohort studies.[80,86,108] One cohort study reported low lean mass (LM), which was regarded as a categorical variable with cut-off values (appendicular lean mass/body mass index < 0.789) and was significantly associated with onset of frailty.[86] Similarly, lower appendicular lean mass index was reported to be a significant risk factor for frailty during a long follow up period in the other study.[108] In the other study assessed the influence of arm muscle area, calf circumference, and appendicular skeletal muscle mass index for onset of pre-frailty with univariate analysis, and did not show a significant association.[80] This study had a short follow-up period of one year.

Of the 51 cross-sectional studies, 31 conducted multivariate analyses.[35,37-41,44,52,55,56,59,67,70-72,74,77,81,82,85,87,88,93,94,98,99,102,103,105,106,109] Ten studies reported skeletal muscle mass index[35,37,41,59,70,82,87,88,98,99]; among them, 9 analyzed without separating men and women,[35,37,41,59,70,82,87,88,99] with 6 showing significant negative associations with frailty.[35,37,41,59,88,99] The only one study conducting an analysis by sex showed that only men demonstrated a significant negative association with frailty.[98] Moreover, 6 studies reported skeletal muscle mass[38,39,44,88,93,105]; among them, 4 analyzed without separating men and women,[38,44,88,105] with 3 showing significant negative associations with frailty.[38,44,88] Of the two studies that were analyzed by sex,[39,93] one showed that both sexes were negatively associated with frailty[93]; the other study showed a significant association with frailty in men only.[39] Furthermore, three studies reported LM[63,106,109]; two of them regarded LM as a categorical variable with a cut-off value (<0.512 for women and <0.789 for men, appendicular lean mass/height^2 ≤ 5.45 kg/m^2 for women and ≤ 7.26 kg/m^2 for men, respectively) and showed significant negative associations with frailty.[106,109] One of these three studies considered LM as a continuous variable and did not show a significant association with frailty.[63] In addition, five studies evaluated the lower-extremity muscles (calf circumference[52,56,59,94] and thigh muscle cross-sectional area[44]), and all showed significant negative associations with frailty. Moreover, five studies reported upper-extremity muscles (mid-arm circumference,[55,72,88] mid-arm muscle circumference,[74] mid-arm muscle area,[72] and pectoralis muscle area[67]). However, only 3 of these five studies showed significant negative associations with frailty,[55,67,74] and 1 reported a significant association in a limited number of participants.[72] Each of the 12 remaining exposures was reported in a single study,[40,59,70,71,77,81,87,93,102,103] with 8 revealing significant associations with frailty.[40,59,70,77,87,93,103]

The percentage of studies that found a significant association between muscle-related exposure factors and frailty is presented in Figure 2, separately for studies with Asian residents and studies with non-Asian residents. The studies of Asian residents indicated a higher proportion of studies reporting a significant difference in lower extremity muscle mass (p=0.015).

Table 1 Characteristics of included studies (Cohort studies)

Authors	Follow up (years)	Population	Sample size (n)	Age Age (SD) or Age [IQR]	Sex Male n (%)	BMI BMI (SD) or [IQR]	Exposures related to body compositions	Frailty evaluation
Bouillon et al,[61] 2013	Mean 10.5 years	London-based British civil servants aged 35 to 55 years from 1985 to 1988.	Not frail: 1616 Pre frail/Frail: 1091	Not frail: 54.6 (5.6) Pre frail/Frail: 55.6 (6.2)	Not frail: 1228 (76.0) Pre frail/Frail: 724 (66.4)	Not frail <25: 730 25–30: 700 30≥: 186 Pre frail/Frail <25: 469 25–30: 445 30≥: 177	• WC	Fried frailty phenotype
García-Esquinas et al,[60] 2015	Mean 3.5 years	Noninstitutionalized individuals aged 60 years and older in Spain.	Diabetes+: 346 Diabetes-: 1404	Diabetes+: 69.4 (6.4) Diabetes-: 68.4 (6.3)	Diabetes+: 204 (59.0) Diabetes-: 647 (46.1)	Not available	• Abdominal obesity (WC >102 cm in men and WC >88 cm in women)	Fried frailty phenotype
Gajic-Veljanoski et al,[92] 2018	After 10 years	The Canadian Multicentre Osteoporosis Study participants aged 50 years and older in Canada	Men: 2187 Women: 5566	Men: 66.3 (9.5) Women: 66.8 (9.3)	Men: 2187 (28)	Men: 27.2 (4.0) Women: 27.0 (5.1)	• Femoral neck BMD by DXA	CaMos Frailty Index
Hirani et al,[86] 2017	After 2 years and 5 years	Men aged 70 years and over in Australia	Baseline: 1685	Baseline: 76.9 (5.5)	Baseline: 1685 (100%)	Baseline: 27.8 (4.0)	• Obesity alone (fat mass >30.0%) • Low LM alone (ALM/BMI <0.789) • Sarcopenic obesity (low LM = ALM/BMI <0.789 and fat mass >30.0%)	Fried frailty phenotype and the study of osteoporotic fractur frailty index
Tembo et al,[108] 2021	Mean 15 years	Men were aged over 18 years in Australia	Non-frail: 239 Frail: 48	Non-frail: 58 [54–65] Frail: 62 [55–71]	Non-frail: 239 (100) Frail: 48 (100)	Non-frail: 27.5 (3.6) Frail: 28.0 (4.1)	• Femoral neck BMD by DXA • ALMI by BIA	Modified Fried frailty phenotype

doi:10.18999/nagjms.87.1.1

Thompson et al,[76] 2018	Mean 4.5years	Community-dwelling adults aged over 65years living in the North West of Adelaide in South Australia	Frailty phenotype categories Non-frail: 233 Pre-frail: 357 Frail: 106 Frailty Index (34-item) categories Non-frail: 175 Pre-frail: 219 Frail: 302	65–74 years/ ≥75 years Fraily pheno-type categories Non-frail: 171/62 Pre-frail: 234/123 Frail: 37/69 Frailty Index (34-item) categories Non-frail: 129/46 Pre-frail: 152/67 Frail: 161/141	Frailty phenotype categories Non-frail: 127 (35.7) Pre-frail: 179 (50.5) Frail: 47 (13.8) Frailty Index (34-item) categories Non-frail: 98 (27.3) Pre-frail: 115 (33.2) Frail: 140 (39.5)	Not available	• Obesity (WC men >102 cm and women >88 cm)	Fried frailty phenotype 34-item frailty index
Uno et al,[80] 2021	Mean 1-year period	Residents aged 60 years or older in Japan	Men: 106 Women: 123	Men: 69.8 (4.2) Women: 68.8 (4.1)	Men: 106	Men: 23.1 (2.4) Women: 21.8 (2.5)	• Arm muscle area (Calculated from arm circumference and triceps skinfold) • CC • ASMI by BIA	Fried frailty phenotype

n: number
SD: standard deviation
IQR: interquartile range
BMI: body mass index
WC: waist circumference
CC: calf circumference
LM: lean mass
ALM: appendicular lean mass
BMD: bone mineral density
DXA: dual-energy X-ray absorptiometry
ASMI: appendicular skeletal muscle mass index
BIA: bioelectrical impedance analysis

doi:10.18999/nagjms.87.1.1

Table 2 Main results of included studies (Cohort studies)

Authors	Analysis	Main results of the association between body compositions and frailty
Bouillon et al,[61] 2013	Logistic regression analyses were carried out to examine the associations between individual risk factors for diabetes and subsequent frailty. In these analyses, frailty status was dichotomized (frail/prefrail versus non−frail) owing to the low number of frail participants. Covariates are shown on the right.	WC (cm) was not significantly associated with frailty (Men <94/women <80: reference. Men 94–102/women 80–88: aOR=0.99 [95% CI: 0.79, 1.25]. Men ≥102/women: ≥88: aOR=1.25 [95% CI: 0.91, 1.71]) adjusting for age, sex, family history of diabetes, BMI, systolic/diastolic blood pressure, antihypertensive and corticoid treatments, smoking status, physical activity, daily consumption of fruits and vegetables, fasting glucose, HDL−cholesterol, and triglycerides.
García-Esquinas et al,[60] 2015	Logistic regression model was carried out to evaluate the association of cardiometabolic biomarkers with risk of frailty adjusting for age, sex, and educational level.	Abdominal obesity was significantly associated with frailty (aOR=2.64 [95% CI: 1.61, 4.33]).
Gajic-Veljanoski et al,[92] 2018	Generalized estimating equations models with an autoregressive correlation structure was used to analyze repeated measurements and associations between rates of change in frailty over time and predictors. All models were adjusted for a statistically significant age-time interaction. The modifying effects of sex (p=0.0005), prevalent hip (p=0.006) and clinical vertebral fractures (p=0.03) were confirmed, the following five models were developed: one for each sex for the whole sample (women, n=5566; men, n=2187), one for each sex for the sample without prior fractures (women, n=4348; men, n=1814), and one for the participants with prior fractures (n=1574) as the rate of change was not significantly different between women and men with prior fractures (p=0.62).	In case of changes in the CFI per 5-year period in adults aged 50+ years with prior low-trauma fracture, baseline BMD T-scores were significant predictor (p=0.02). Baseline BMD T-scores were not significant predictors in the following four models: one for each sex for the whole sample, one for each sex for the sample without prior fractures.
Hirani et al,[86] 2017	To study the longitudinal associations between measures of body composition (continuous and categorical) and outcomes between baseline, 2-year follow-up and 5-year follow-up, generalized estimating equation analyses was used. The model was used in continuous analysis for ALM adjusted BMI, fat percentage and their interaction. This analysis was also used in categorical analysis (neither obese nor low muscle mass [referent variable]), obese only, low muscle mass only and sarcopenic obesity.	Low LM and sarcopenic obesity were significantly associated with frailty (aOR=2.12 [95% CI: 1.42, 3.18], p<0.0001, aOR=2.00, 95% CI: 1.42, 2.82, p<0.0001, respectively). Obesity alone was not significantly associated with frailty (p=0.94).
Tembo et al,[108] 2021	Binary logistic regression models and model-based AUC were constructed to investigate and quantify the best predictors for frailty. A referent model was constructed using age, weight, fat mass index, Charlson comorbidity index, social economic status, smoking, alcohol and physical activity, after which musculoskeletal parameters (including BMD and ALM index) were added. Model 1: Referent model plus BMD, ALM index, muscle strength (hip flexors), interleukin-6, and total antioxidant capacity. Model 2: Referent model plus BMD, ALM index, muscle strength (hip abductors), interleukin-6, and total antioxidant capacity.	Model 1: ALM index and BMD were significant risk factors for frailty (aOR=0.503 [95%CI: 0.275, 0.921], aOR=0.079 [95%CI: 0.0008, 7.745], respectively). Model 2: ALM index and BMD were significant risk factors for frailty (aOR=0.467 [95%CI: 0.306, 0.713], aOR=2.72 [95%CI: 0.165, 45.067], respectively).

doi:10.18999/nagjms.87.1.1

Thompson et al,[76] 2018	The model contained significant covariates and confounders associated with frailty state transitions that were included in the final multivariate analysis. Covariates included: sex, age group (65–74 years and ≥75 years), the presence of multimorbidity (≥2 chronic conditions), obesity (waist circumference men >102 cm, women >88 cm), polypharmacy (≥5medications) and living arrangements (alone or with others). As the length of time between the baseline and follow-up clinics varied for each participant, time between clinics was also included as a covariate.	• Improved at follow up Obese individuals those who were pre-frail at baseline were significantly less likely to improve according to both frailty phenotype and frailty index (aOR=0.37 [95% CI: 0.20, 0.68], p=0.001, aOR=0.25 [95% CI: 0.09, 0.74], p=0.013, respectively). Obesity was not significantly associated with improvement according to both frailty phenotype and frailty index in those who were frail at baseline. • Worse at follow up Obesity was significantly associated with worsening according to frailty index in those who were non-frail at baseline (aOR=2.24 [95% CI: 1.06–4.76], p=0.035). Obese individuals those who were pre-frail at baseline were significantly less likely to worsen for the frailty phenotype (aOR=0.54 [95% CI: 0.30–0.97], p=0.038). Obesity was not significantly associated with worsening according to both frailty phenotype and frailty index in those who were frail at baseline.
Uno et al,[80] 2021	The baseline characteristics of those who showed prefrailty at the 1-year follow-up were compared with those of the individuals who had retained their robust statuses by paired t-test. In this comparison, the participants were stratified in terms of sex.	There were not significant differences in arm muscle area, CC, and ASMI at baseline between prefrail and robust group at 1-year follow up in men and women.

ALM: appendicular lean mass
aOR: adjusted odds ratio
ASMI: appendicular skeletal muscle index
AUC: area under the receiver operative characteristic curves
BMD: bone mineral density
BMI: body mass index
CC: calf circumference
CFI: Canadian Multicentre Osteoporosis Study Frailty Index
HDL: high-density lipoprotein
LM: lean mass
WC: waist circumstance

doi:10.18999/nagjms.87.1.1

Table 3 Risk of bias evaluation of included studies in the systematic review (Cohort studies)

	García-Esquinas et al,[60] 2015	Bouillon et al,[61] 2013	Thompson et al,[76] 2018	Uno et al,[80] 2021	Hirani et al,[86] 2017	Gajic-Veljanoski et al,[92] 2018	Tembo et al,[108] 2021
1. Was selection of exposed and non-exposed cohorts drawn from the same population?	PY	PY	PY	PY	PY	PY	PY
2. Can we be confident in the assessment of exposure?	PN	PN	PN	DY	PN	PN	PN
3. Can we be confident that the outcome of interest was not present at start of study?	DY	DN	DY	DY	DN	DN	PY
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	PY	PN	PN	PY	PY	PY	PY
5. Can we be confident in the assessment of the presence or absence of prognostic factors?	PN	PN	PN	PY	PN	PN	PN
6. Can we be confident in the assessment of outcome?	DY	DY	DY	DY	DY	PN	DY
7. Was the follow up of cohorts adequate?	DY	PN	PY	PY	DN	DY	DN
8. Were cointerventions similar between groups?	PN	PN	PN	PN	PN	PN	PN

DN: definitely no (high risk of bias)
DY: definitely yes (low risk of bias)
PN: probably no
PY: probably yes

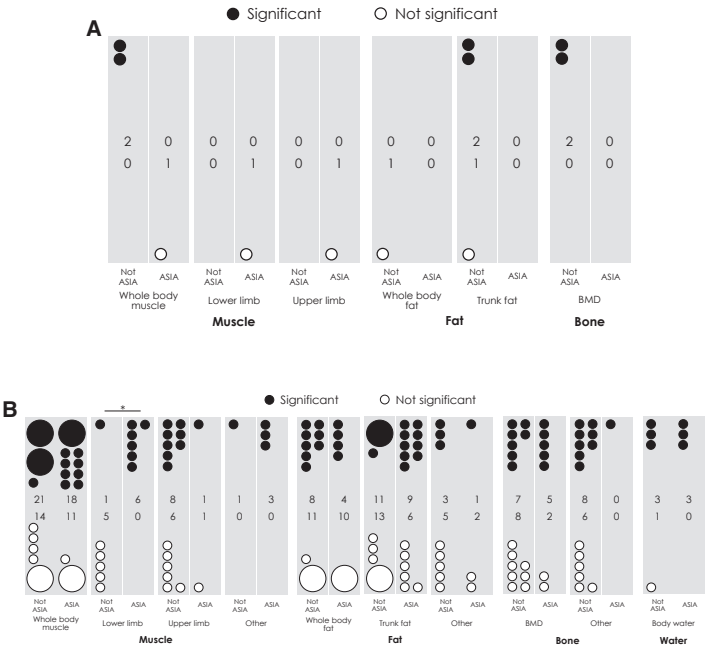

Fig. 2 The number of studies that found a significant association between body compositions and frailty in Asian and other residents

Fig. 2A: Cohort studies.
Fig. 2B: Cross-sectional studies.
BMD: bone mineral density
*: $p < 0.05$

Fat-related exposures

We found 4 cohort studies[60,61,76,86] and 43 cross-sectional studies.[34-36,38,40-46,49,50,53,54,56-59,62,63,68,71-75,77-79,82,84,88,91-93,96,98,101,103-105,110] Of the 4 cohort studies, 3 reported waist circumference (WC).[60,61,76] Among these 3 studies, 2 defined obesity by WC with cut-off values[60,76] (>102 cm for men, >88 cm for women), with 1 showing a significant positive association with onset of frailty.[60] In the other study, obesity was significantly positively associated with worsening frailty index in those who were non-frail at baseline.[76] One of the three studies, which included non-frail and pre-frail participants at baseline, did not show a significant association between WC and frailty.[61] Furthermore, one of the four cohort studies reported body fat percentage, which also did not show a significant association with frailty.[86]

Of the 43 cross-sectional studies, 25 conducted multivariate analyses.[34-36,38,40,41,44-46,49,53,56,58,59,71,72,77,82,84,88,91,93,103,105,110] Thirteen studies reported WC,[35,36,38,40,41,45,46,49,56,59,71,88,110] with six regarding WC as a categorical variable and showed significant positive associations with frailty.[35,36,38,45,49,110] We also found 7 studies that considered WC as a continuous variable,[40,41,46,56,59,71,88] with 3 showing significant positive associations with frailty.[40,59,71] Five studies reported body fat percentage,[53,82,91,103,105] and three of them analyzed by sex.[82,103,105] In these three studies, one showed a significant positive association with frailty only in men,[82] whereas the others did not report any significant associations.[103,105] The two remaining studies did not analyze by sex and showed no significant associations with frailty.[53,91] Four studies reported fat mass,[38,71,88,105] with three showing significant positive associations with frailty.[38,71,88] Three studies reported waist-hip ratio

(WHR),[49,84,93] with two treating WHR as a continuous variable and showing significant positive associations with frailty.[84,93] The other study considered WHR as a categorical variable and did not show a significant association.[49] Moreover, two studies reported visceral adipose tissue, and both showed significant positive associations with frailty.[34,35] Two studies reported visceral fat area,[44,58] with one treating visceral fat area as a continuous variable and showing a significant positive association with frailty.[44] Each of the five remaining exposures was reported in a single study,[59,72,77,103] with two reporting significant positive associations with frailty[59,77] and one reporting a significant positive association when the number of participants was limited.[103]

The percentage of studies that found a significant association between fat-related exposure factors and frailty is presented in Figure 2, separately for studies of Asian and non-Asian residents. There were no statistical differences between participant's place of residence and the percentage of studies showing a significant relationship between fat-related exposures and frailty.

Bone-related exposures

We found 2 cohort study[92,108] and 15 cross-sectional studies.[35,40,47,50,58,62,65,66,78,89,97,102,104,106,107] One cohort study reported BMD T-score and showed a significant negative association with onset of frailty when participants had prior low trauma fractures.[92] The other also reported that BMD was a significant risk factor for frailty.[108]

Of the 15 cross-sectional studies, 7 conducted multivariate analyses.[35,40,65,89,102,106,107] Among these 7 studies, 4 reported hip BMD,[35,40,65,107] with three showing significant negative associations with frailty,[35,40,65] and 3 reported BMD-defined osteoporosis[89,102,106] in which all did not show significant differences. In addition, two studies reported lumbar BMD,[40,65] and one of them reported a significant negative association with frailty.[65] One study assessed broadband ultrasound attenuation, speed of sound, and stiffness index, but only the stiffness index in men was significantly negatively associated with frailty.[107]

The percentage of studies that found a significant association between bone-related exposure factors and frailty is presented in Figure 2, separately for Asian and non-Asian residents. There were no statistical differences between participant's place of residence and the percentage of studies showing a significant relationship between bone-related exposures and frailty.

Body water-related exposures

We found 6 cross-sectional studies[38,71,75,78,83,85] in which 2 conducted multivariate analyses.[71,85] In these 2 studies, 1 reported the extracellular water-intracellular water ratio,[71] and the other reported the intracellular water-LM ratio.[85] Both studies showed significant associations with frailty (extracellular water-intracellular water ratio; positive association and intracellular water-LM ratio; negative association.).

The percentage of studies that found a significant association between body-water-related exposure factors and frailty is presented in Figure 2, separately for studies of Asian and non-Asian residents. There were no statistical differences between participant's place of residence and the percentage of studies showing a significant relationship between body water-related exposures and frailty.

Other exposures

We found 1 cohort study[86] and 2 cross-sectional studies.[102,106] One cohort study reported obesity plus low LM and showed a significant positive association with frailty.[86]

Two cross-sectional studies conducted multivariate analyses.[102,106] One study reported BMD plus LM,[102] and the other reported osteoporosis plus LM.[106] Both showed significant positive associations.[102,106]

All these studies were conducted on non-Asian residents.

Risk-of-bias assessment

Table 3 summarizes the risk-of-bias evaluation of the included studies. In brief, one study had one item rated as probably no or definitely no.[80] Another study had three items rated as probably no or definitely no.[60] With similar rules, 6,[61] 5[86,92], and 4[76,108] items rated as probably no or definitely no were found in 1, 2, and 2 studies, respectively.

DISCUSSION

This study aimed to investigate whether the body composition, including muscle, fat, bone, and body water, is a risk factor for frailty. We found 77 studies that met our criteria. Among them, seven cohort studies suggested that low LM, WC-abdominal obesity, and BMD were significant risk factors for frailty. Conversely, body fat percentage-defined obesity was not significantly associated with frailty. The sample sizes ranged from 20 to 7753, and the participants' average or median age ranged from 48.6 to 83.4 years. Fried Frailty Phenotype or Cardiovascular Health Study criteria were used as the outcomes of frailty in 53 studies. The reports ranged from small-group reports to large-data analyses, and frailty has been reported in older adults and young individuals. The risk-of-bias evaluation in each study according to the Cochrane risk-of-bias instrument showed that all studies had at least one concern. Focusing on Asian residents, there was a significant association between lower extremity muscle mass and frailty.

International guidelines about frailty diagnosis and management suggested overweight or underweight as one of the risk factors for frailty; currently, body composition, which directly affects body weight, has not been mentioned as a risk factor.[111] Sarcopenia was reported to be associated with frailty,[16-19] but it is not a concept consisting solely of body composition. In the present study, we showed the relationship between body composition and frailty.

In the studies reporting muscle-related exposures, two out of three cohort studies showed a significant association between LM and onset of frailty.[86,108] The other study did not show significant association between muscle related exposures and pre-frailty.[80] This difference could be partly explained by follow-up period and the difference of exposures. The latter study had a shorter follow-up period of one year than the former studies, and the muscle related exposure was different between former and latter studies. Of the cross-sectional studies using multivariate analyses, the largest number (10) reported skeletal muscle mass index.[35,37,41,59,70,82,87,88,98,99] Although more than half of these studies showed significant negative associations with frailty, the results remained inconsistent. The differences in these results were difficult to explain, owing to the dissimilarities in participants or outcomes. Four studies evaluated the lower-extremity muscles (calf circumference[56,59,94] and thigh muscle cross-sectional area[44]) and consistently showed significant negative associations with frailty. Regarding the upper-extremity muscles (mid-arm circumference,[55,72,88] mid-arm muscle circumference,[74] mid-arm muscle area,[72] and pectoralis muscle area[67]), the results were conflicted. The lower-extremity muscle mass significantly positively correlated with physical activity,[112] and physical activity is one of the components of frailty.[1] Thus, muscle atrophy in the lower extremities would have a more direct effect on frailty than that in the upper extremities.

In studies reporting fat-related exposures, four were cohort studies.[60,61,76,86] Abdominal obesity defined by WC was significantly positively associated with frailty,[60,76] but that defined by body fat percentage showed no significant association.[86] One cohort study reported a conflict result as WC was not significantly associated with frailty.[61] This difference may partly be explained by

participants' characteristics at baseline. This previous study may meet the criteria for pre-frailty at baseline due to the low physical activity of more than half of the participants. WC could affect frailty depending on the physical status of the measurement.[61] Eighteen cross-sectional studies reported abdominal obesity–related exposures (WC, WHR, visceral fat area, and visceral adipose tissue).[34-36,38,40,41,44-46,49,56,58,59,71,84,88,93,110] All studies treating WC as a categorical variable, such as WC associated with abdominal obesity, showed significant associations with frailty,[35,36,38,45,49,110] whereas the results in studies treating WC as a continuous variable were conflicting.[40,41,46,56,59,71,88] WHR and visceral fat area treated as continuous variables showed significant associations with frailty.[44,84,93] All two studies reported that visceral adipose tissue showed significant positive associations with frailty.[34,35] Interestingly, almost all studies reporting body fat percentage showed no significant association,[53,91,103,105] suggesting that abdominal obesity, including visceral fat, is more likely to be associated with frailty than total body fat. This finding is consistent with that of previous studies reporting the association between metabolic syndromes, including abdominal obesity, and frailty.[113-115] Abdominal obesity is positively related to frailty even when adjusted for comorbidities.[35,38,71,76,110] In the previous studies, metabolic syndromes were associated with low physical activity,[114] unintentional weight loss,[114] and low grip strength.[113] In addition, WC and metabolic syndrome are associated with mobility decline.[116,117] According to five components of frailty, namely, weakness (low grip strength), slowness (slow walking speed), shrinking (unintentional weight loss), exhaustion (self-reported), and low physical activity,[1] abdominal obesity is considered as a risk factor for frailty.

In the studies reporting bone-related exposures, two cohort studies showed significant negative associations between BMD and onset of frailty.[92,108] One cohort study revealed a significant association between BMD T-score and frailty in participants with prior low trauma fractures.[92] Considering the conflicting results of cross-sectional studies, further study is needed. In the studies reporting body water-related exposures, no cohort study was found. Cross-sectional studies with multivariate analyses showed consistent associations with frailty,[71,85] although the reports were few. Further research is needed to make definitive conclusions.

Of the studies that examined the association between the combined variable of body composition and frailty, only one reported an adjusted odds ratio, and it was a cohort study.[86] Obesity combined with low LM was significantly positively associated with frailty, consistent with the abovementioned results. The previous cohort study also mentioned an association between frailty and sarcopenic obesity.[118]

Considering the relationship between body composition and frailty by dividing the subjects' residence into Asian and non-Asian, a higher percentage of articles showed a significant association with frailty among those living in Asia with respect to lower limb muscle mass. In sarcopenia, which conceptually overlaps with the physical aspects of frailty, unique Asian criteria have been established.[119] The percentage of muscle fibers by race differs significantly. Asians, including Japanese people, have the lowest percentage of fast twitch muscle fibers compared to other racial groups.[25-27] Since fast-twitch fibers tend to decrease with age, Asians, who structurally have fewer fast-twitch fibers, may be more likely to be assessed as frail as they age. However, there are no studies on risk factors for frailty by race, and further validation is needed.

This review indicates that low LM, particularly the muscle mass of the lower extremities, and abdominal obesity were likely risk factors for frailty. These results not only could be useful for healthcare providers to develop frailty prevention strategies but could also have a positive impact on the way people manage themselves. On the individual level, given that WC is easy to measure, people may need to focus on WC, as well as body weight, for preventing frailty. Moreover, this study could be a basis for implementing Lifestyle Health Checkups and Health Guidance in Japan.[120] This strategy could help prevent and early detect lifestyle-related diseases,

focusing on abdominal obesity. It could also be beneficial for preventing frailty on the national level. In addition, body composition assessments are included in malnutrition diagnosis. Based on the findings of this study, these prevention strategies could be useful not only for frailty but also for malnutrition.

This systematic review has several limitations. First, some relevant studies might be missed because our search strategy used selected words and databases. Second, most of the studies were cross-sectional studies, and only a few were cohort studies. Further studies with high-quality evidence are needed. Third, considering the heterogeneity of the participants, analysis method, and outcomes for frailty, we did not consider quantitative analyses. Nonetheless, to our knowledge, this study is the first to consolidate evidence on body composition's influence on frailty in various participants. The present results still need to be verified by high-quality studies, with definitive conclusions regarding the influence of body composition on frailty.

Low LM and abdominal obesity were likely risk factors for frailty. Regarding muscles, lower-extremity muscles may be more associated with frailty than the upper-extremity muscles. The bone-related results were inconsistent, and no studies had high-quality evidence with respect to body water. Further verification is needed because body composition affecting frailty may differ by race.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

This work was supported by Ministry of Health, Labour and Welfare (MHLW) FA Program Grant Number 22FA1003.

SUPPLEMENTARY DATA

Supplementary Table 1, 2, and 3 are not shown in this paper due to data volume. They can be shared upon request to the authors.

REFERENCES

1 Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156. doi:10.1093/gerona/56.3.m146
2 Hoogendijk EO, Muntinga ME, van Leeuwen KM, et al. Self-perceived met and unmet care needs of frail older adults in primary care. *Arch Gerontol Geriatr*. 2014;58(1):37–42. doi:10.1016/j.archger.2013.09.001
3 Chode S, Malmstrom TK, Miller DK, Morley JE. Frailty, Diabetes, and Mortality in Middle-Aged African Americans. *J Nutr Health Aging*. 2016;20(8):854–859. doi:10.1007/s12603-016-0801-3
4 Vermeiren S, Vella-Azzopardi R, Beckwée D, et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. *J Am Med Dir Assoc*. 2016;17(12):1163.e1–1163.e17. doi:10.1016/j.jamda.2016.09.010
5 Bock JO, König HH, Brenner H, et al. Associations of frailty with health care costs--results of the ESTHER cohort study. *BMC Health Serv Res*. 2016;16:128. doi:10.1186/s12913-016-1360-3
6 Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–762. doi:10.1016/S0140-6736(12)62167-9
7 Savela SL, Koistinen P, Stenholm S, et al. Leisure-time physical activity in midlife is related to old age

frailty. *J Gerontol A Biol Sci Med Sci*. 2013;68(11):1433–1438. doi:10.1093/gerona/glt029
8 Strandberg TE, Sirola J, Pitkälä KH, Tilvis RS, Strandberg AY, Stenholm S. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. *Int J Obes (Lond)*. 2012;36(9):1153–1157. doi:10.1038/ijo.2012.83
9 Huohvanainen E, Strandberg AY, Stenholm S, Pitkälä KH, Tilvis RS, Strandberg TE. Association of Self-Rated Health in Midlife With Mortality and Old Age Frailty: A 26-Year Follow-Up of Initially Healthy Men. *J Gerontol A Biol Sci Med Sci*. 2016;71(7):923–928. doi:10.1093/gerona/glv311
10 Strandberg AY, Trygg T, Pitkälä KH, Strandberg TE. Alcohol consumption in midlife and old age and risk of frailty: Alcohol paradox in a 30-year follow-up study. *Age Ageing*. 2018;47(2):248–254. doi:10.1093/ageing/afx165
11 Atkins JL, Delgado J, Pilling LC, et al. Impact of Low Cardiovascular Risk Profiles on Geriatric Outcomes: Evidence From 421,000 Participants in Two Cohorts. *J Gerontol A Biol Sci Med Sci*. 2019;74(3):350–357. doi:10.1093/gerona/gly083
12 Strandberg TE, Stenholm S, Strandberg AY, Salomaa V V, Pitkälä KH, Tilvis RS. The "obesity paradox," frailty, disability, and mortality in older men: a prospective, longitudinal cohort study. *Am J Epidemiol*. 2013;178(9):1452–1460. doi:10.1093/aje/kwt157
13 Stenholm S, Strandberg TE, Pitkälä K, Sainio P, Heliövaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. *J Gerontol A Biol Sci Med Sci*. 2014;69(1):73–78. doi:10.1093/gerona/glt052
14 Willoughby D, Hewlings S, Kalman D. Body Composition Changes in Weight Loss: Strategies and Supplementation for Maintaining Lean Body Mass, a Brief Review. *Nutrients*. 2018;10(12):1876. doi:10.3390/nu10121876
15 Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. *Am J Clin Nutr*. 2010;91(4):1123S-1127S. doi:10.3945/ajcn.2010.28608A
16 Reijnierse EM, Trappenburg MC, Blauw GJ, et al. Common Ground? The Concordance of Sarcopenia and Frailty Definitions. *J Am Med Dir Assoc*. 2016;17(4):371.e7–371.e12. doi:10.1016/j.jamda.2016.01.013
17 Davies B, García F, Ara I, Artalejo FR, Rodriguez-Mañas L, Walter S. Relationship Between Sarcopenia and Frailty in the Toledo Study of Healthy Aging: A Population Based Cross-Sectional Study. *J Am Med Dir Assoc*. 2018;19(4):282–286. doi:10.1016/j.jamda.2017.09.014
18 Nishiguchi S, Yamada M, Fukutani N, et al. Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults. *J Am Med Dir Assoc*. 2015;16(2):120–124. doi:10.1016/j.jamda.2014.07.010
19 Mijnarends DM, Schols JM, Meijers JM, et al. Instruments to assess sarcopenia and physical frailty in older people living in a community (care) setting: similarities and discrepancies. *J Am Med Dir Assoc*. 2015;16(4):301–308. doi:10.1016/j.jamda.2014.11.011
20 Slentz CA, Aiken LB, Houmard JA, et al. Inactivity, exercise, and visceral fat. STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol (1985)*. 2005;99(4):1613–1618. doi:10.1152/japplphysiol.00124.2005
21 Carter MI, Hinton PS. Physical activity and bone health. *Mo Med*. 2014;111(1):59–64.
22 García-Esquinas E, José García-García F, León-Muñoz LM, et al. Obesity, fat distribution, and risk of frailty in two population-based cohorts of older adults in Spain. *Obesity (Silver Spring)*. 2015;23(4):847–855. doi:10.1002/oby.21013
23 Li G, Thabane L, Papaioannou A, Ioannidis G, Levine MA, Adachi JD. An overview of osteoporosis and frailty in the elderly. *BMC Musculoskelet Disord*. 2017;18(1):46. doi:10.1186/s12891-017-1403-x
24 Taniguchi M, Ikezoe T, Kamitani T, et al. Extracellular-to-intracellular water ratios are associated with functional disability levels in patients with knee osteoarthritis: results from the Nagahama Study. *Clin Rheumatol*. 2021;40(7):2889–2896. doi:10.1007/s10067-021-05591-0
25 Kumagai H, Tobina T, Ichinoseki-Sekine N, et al. Role of selected polymorphisms in determining muscle fiber composition in Japanese men and women. *J Appl Physiol (1985)*. 2018;124(5):1377–1384. doi:10.1152/japplphysiol.00953.2017
26 Nielsen J, Christensen DL. Glucose intolerance in the West African Diaspora: a skeletal muscle fibre type distribution hypothesis. *Acta Physiol (Oxf)*. 2011;202(4):605–616. doi:10.1111/j.1748-1716.2011.02272.x
27 Ama PF, Simoneau JA, Boulay MR, Serresse O, Thériault G, Bouchard C. Skeletal muscle characteristics in sedentary black and Caucasian males. *J Appl Physiol (1985)*. 1986;61(5):1758–1761. doi:10.1152/jappl.1986.61.5.1758
28 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

29 Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med*. 2008;168(4):382–389. doi:10.1001/archinternmed.2007.113

30 Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–495. doi:10.1503/cmaj.050051

31 Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392–397. doi:10.1016/j.jamda.2013.03.022

32 Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323–336. doi:10.1100/tsw.2001.58

33 Imura T, Mitsutake T, Iwamoto Y, Tanaka R. A systematic review of the usefulness of magnetic resonance imaging in predicting the gait ability of stroke patients. *Sci Rep*. 2021;11(1):14338. doi:10.1038/s41598-021-93717-4

34 Anderson MR, Kolaitis NA, Gao Y, et al. A nonlinear relationship between visceral adipose tissue and frailty in adult lung transplant candidates. *Am J Transplant*. 2019;19(11):3155–3161. doi:10.1111/ajt.15525

35 Hawkins KL, Zhang L, Ng DK, et al. Abdominal obesity, sarcopenia, and osteoporosis are associated with frailty in men living with and without HIV. *AIDS*. 2018;32(10):1257–1266. doi:10.1097/QAD.0000000000001829

36 Palomo I, Giacaman RA, León S, et al. Analysis of the characteristics and components for the frailty syndrome in older adults from central Chile. The PIEI-ES study. *Arch Gerontol Geriatr*. 2019;80:70–75. doi:10.1016/j.archger.2018.10.004

37 Kołodziej M, Sebastjan A, Ignasiak Z. Appendicular skeletal muscle mass and quality estimated by bioelectrical impedance analysis in the assessment of frailty syndrome risk in older individuals. *Aging Clin Exp Res*. 2022;34(9):2081–2088. doi:10.1007/s40520-021-01879-y

38 Xu L, Zhang J, Shen S, et al. Association Between Body Composition and Frailty in Elder Inpatients. *Clin Interv Aging*. 2020;15:313–320. doi:10.2147/CIA.S243211

39 Bahat G, Kilic C, Ilhan B, Karan MA, Cruz-Jentoft A. Association of different bioimpedanciometry estimations of muscle mass with functional measures. *Geriatr Gerontol Int*. 2019;19(7):593–597. doi:10.1111/ggi.13668

40 Liu LK, Lee WJ, Chen LY, et al. Association between Frailty, Osteoporosis, Falls and Hip Fractures among Community-Dwelling People Aged 50 Years and Older in Taiwan: Results from I-Lan Longitudinal Aging Study. *PLoS One*. 2015;10(9):e0136968. doi:10.1371/journal.pone.0136968

41 Hwang AC, Liu LK, Lee WJ, et al. Association of Frailty and Cardiometabolic Risk Among Community-Dwelling Middle-Aged and Older People: Results from the I-Lan Longitudinal Aging Study. *Rejuvenation Res*. 2015;18(6):564–572. doi:10.1089/rej.2015.1699

42 Bastos-Barbosa RG, Ferriolli E, Coelho EB, Moriguti JC, Nobre F, Lima NK. Association of Frailty Syndrome in the Elderly With Higher Blood Pressure and Other Cardiovascular Risk Factors. *Am J Hypertens*. 2012;25(11):1156–1161. doi:10.1038/ajh.2012.99

43 Crow RS, Lohman MC, Titus AJ, et al. Association of Obesity and Frailty in Older Adults: NHANES 1999–2004. *J Nutr Health Aging*. 2019;23(2):138–144. doi:10.1007/s12603-018-1138-x

44 Tabara Y, Kohara K, Ochi M, et al. Association of office-based frailty score with hypertensive end organ damage in the J-SHIPP cross-sectional study. *Int J Cardiol*. 2016;216:25–31. doi:10.1016/j.ijcard.2016.04.135

45 Song X, Zhang W, Hallensleben C, et al. Associations Between Obesity and Multidimensional Frailty in Older Chinese People with Hypertension. *Clin Interv Aging*. 2020;15:811–820. doi:10.2147/CIA.S234815

46 Wang Y, Han HR, Yang W, et al. Associations between risk factors for cardiovascular diseases and frailty among community-dwelling older adults in Lanzhou, China. *Int J Nurs Sci*. 2021;8(2):168–174. doi:10.1016/j.ijnss.2021.03.008

47 Laskou F, Fuggle NR, Patel HP, Jameson K, Cooper C, Dennison E. Associations of osteoporosis and sarcopenia with frailty and multimorbidity among participants of the Hertfordshire Cohort Study. *J Cachexia Sarcopenia Muscle*. 2022;13(1):220–229. doi:10.1002/jcsm.12870

48 Makizako H, Kubozono T, Kiyama R, et al. Associations of social frailty with loss of muscle mass and muscle weakness among community-dwelling older adults. *Geriatr Gerontol Int*. 2019;19(1):76–80. doi:10.1111/ggi.13571

49 Ferriolli E, Pessanha FPADS, Moreira VG, Dias RC, Neri AL, Lourenço RA. Body composition and frailty profiles in Brazilian older people: Frailty in Brazilian Older People Study-FIBRA-BR. *Arch Gerontol Geriatr*. 2017;71:99–104. doi:10.1016/j.archger.2017.03.008

50 Falsarella G, Gasparotto LP, Barcelos CC, et al. Body composition as a frailty marker for the elderly community. *Clin Interv Aging*. 2015;10:1661–1666. doi:10.2147/CIA.S84632

51 Miyazaki S, Iino N, Koda R, Narita I, Kaneko Y. Brain-derived neurotrophic factor is associated with sarcopenia and frailty in Japanese hemodialysis patients. *Geriatr Gerontol Int*. 2021;21(1):27–33. doi:10.1111/ggi.14089

52 Kim M, Jeong MJ, Yoo J, Song DY, Won CW. Calf Circumference as a Screening Tool for Cognitive Frailty in Community-Dwelling Older Adults: The Korean Frailty and Aging Cohort Study (KFACS). *J Clin Med*. 2018;7(10):332. doi:10.3390/jcm7100332

53 Nadruz W Jr, Kitzman D, Windham BG, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. *J Gerontol A Biol Sci Med Sci*. 2017;72(7):958–964. doi:10.1093/gerona/glw199

54 Tavares DM, Colamego CG, Pegorari MS, Ferreira PC, Dias FA, Bolina AF. Cardiovascular risk factors associated with frailty syndrome among hospitalized elderly people: a cross-sectional study. *Sao Paulo Med J*. 2016;134(5):393–399. doi:10.1590/1516-3180.2016.0028010616

55 Bekić S, Babič F, Filipčić I, Trtica Majnarić L. Clustering of Mental and Physical Comorbidity and the Risk of Frailty in Patients Aged 60 Years or More in Primary Care. *Med Sci Monit*. 2019;25:6820–6835. doi:10.12659/MSM.915063

56 Kim H, Awata S, Watanabe Y, et al. Cognitive frailty in community-dwelling older Japanese people: Prevalence and its association with falls. *Geriatr Gerontol Int*. 2019;19(7):647–653. doi:10.1111/ggi.13685

57 Buch A, Carmeli E, Shefer G, et al. Cognitive impairment and the association between frailty and functional deficits are linked to abdominal obesity in the elderly. *Maturitas*. 2018;114:46–53. doi:10.1016/j.maturitas.2018.05.009

58 Laur O, Weaver MJ, Bridge C, et al. Computed tomography-based body composition profile as a screening tool for geriatric frailty detection. *Skeletal Radiol*. 2022;51(7):1371–1380. doi:10.1007/s00256-021-03951-0

59 Tanaka S, Ando K, Kobayashi K, et al. Declining neck circumference is an anthropometric marker related to frailty in middle-aged and elderly women. *Mod Rheumatol*. 2020;30(3):598–603. doi:10.1080/14397595.2019.1627023

60 García-Esquinas E, Graciani A, Guallar-Castillón P, López-García E, Rodríguez-Mañas L, Rodríguez-Artalejo F. Diabetes and Risk of Frailty and Its Potential Mechanisms: A Prospective Cohort Study of Older Adults. *J Am Med Dir Assoc*. 2015;16(9):748–754. doi:10.1016/j.jamda.2015.04.008

61 Bouillon K, Kivimäki M, Hamer M, et al. Diabetes Risk Factors, Diabetes Risk Algorithms, and the Prediction of Future Frailty: The Whitehall II Prospective Cohort Study. *J Am Med Dir Assoc*. 2013;14(11):851.e1–851.e6. doi:10.1016/j.jamda.2013.08.016

62 Mohamad MI, Khater MS. Evaluation of insulin like growth factor-1 (IGF-1) level and its impact on muscle and bone mineral density in frail elderly male. *Arch Gerontol Geriatr*. 2015;60(1):124–127. doi:10.1016/j.archger.2014.08.011

63 Serra-Prat M, Papiol M, Vico J, Palomera E, Sist X, Cabré M. Factors associated with frailty in community-dwelling elderly population. A cross-sectional study. *Eur Geriatr Med*. 2016;7(6):531–537. doi:10.1016/j.eurger.2016.09.005

64 Van Roie E, Verschueren SM, Boonen S, et al. Force-Velocity Characteristics of the Knee Extensors: An Indication of the Risk for Physical Frailty in Elderly Women. *Arch Phys Med Rehabil*. 2011;92(11):1827–1832. doi:10.1016/j.apmr.2011.05.022

65 Chao CT, Huang JW, Chan DC; Cohort of Geriatric Nephrology in NTUH (COGENT) study group. Frail phenotype might herald bone health worsening among end-stage renal disease patients. *PeerJ*. 2017;5:e3542. doi:10.7717/peerj.3542

66 Cook MJ, Oldroyd A, Pye SR, et al. Frailty and bone health in European men. *Age Ageing*. 2017;46(4):635–641. doi:10.1093/ageing/afw205

67 Sheth JS, Xia M, Murray S, et al. Frailty and geriatric conditions in older patients with idiopathic pulmonary fibrosis. *Respir Med*. 2019;148:6–12. doi:10.1016/j.rmed.2019.01.008

68 Houssein M, Inkaya AÇ, Balci C, et al. Frailty and sarcopenia among Turkish people aged 40 and above living with HIV. *HIV Med*. 2022;23(10):1061–1068. doi:10.1111/hiv.13311

69 Anani S, Goldhaber G, Brom A, et al. Frailty and Sarcopenia Assessment upon Hospital Admission to Internal Medicine Predicts Length of Hospital Stay and Re-Admission: A Prospective Study of 980 Patients. *J Clin Med*. 2020;9(8):2659. doi:10.3390/jcm9082659

70 Williams GR, Deal AM, Muss HB, et al. Frailty and skeletal muscle in older adults with cancer. *J Geriatr Oncol*. 2018;9(1):68–73. doi:10.1016/j.jgo.2017.08.002

71 Noori N, Sharma Parpia A, Lakhani R, Janes S, Goldstein MB. Frailty and the Quality of Life in Hemodialysis Patients: The Importance of Waist Circumference. *J Ren Nutr*. 2018;28(2):101–109. doi:10.1053/j.jrn.2017.07.007

72 Skladany L, Molcan P, Vnencakova J, et al. Frailty in Nonalcoholic Fatty Liver Cirrhosis: A Comparison with Alcoholic Cirrhosis, Risk Patterns, and Impact on Prognosis. *Can J Gastroenterol Hepatol*. 2021;2021:5576531. doi:10.1155/2021/5576531

73 Alabadi B, Civera M, De la Rosa A, Martinez-Hervas S, Gomez-Cabrera MC, Real JT. Frailty Is Associated with Oxidative Stress in Older Patients with Type 2 Diabetes. *Nutrients*. 2021;13(11):3983. doi:10.3390/nu13113983

74 Valdiviesso R, Azevedo LF, Moreira E, et al. Frailty phenotype and associated nutritional factors in a sample of Portuguese outpatients with heart failure. *Nutr Metab Cardiovasc Dis*. 2021;31(8):2391–2397. doi:10.1016/j.numecd.2021.03.028

75 Batko-Szwaczka A, Dudzińska-Griszek J, Hornik B, et al. Frailty Phenotype: Evidence of Both Physical and Mental Health Components in Community-Dwelling Early-Old Adults. *Clin Interv Aging*. 2020;15:141–150. doi:10.2147/CIA.S238521

76 Thompson MQ, Theou O, Adams RJ, Tucker GR, Visvanathan R. Frailty state transitions and associated factors in South Australian older adults. *Geriatr Gerontol Int*. 2018;18(11):1549–1555. doi:10.1111/ggi.13522

77 Cesari M, Leeuwenburgh C, Lauretani F, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. *Am J Clin Nutr*. 2006;83(5):1142–1148. doi:10.1093/ajcn/83.5.1142

78 São Romão Preto L, Dias Conceição MDC, Figueiredo TM, Pereira Mata MA, Barreira Preto PM, Mateo Aguilar E. Fragilidad, composición corporal y estado nutricional en ancianos no institucionalizados. Article in English, Spanish. *Enferm Clin*. 2017;27(6):339–345. doi:10.1016/j.enfcli.2017.06.004

79 Fitzpatrick J, Sozio SM, Jaar BG, et al. Frailty, body composition and the risk of mortality in incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study. *Nephrol Dial Transplant*. 2019;34(2):346–354. doi:10.1093/ndt/gfy124

80 Uno C, Okada K, Matsushita E, Satake S, Kuzuya M. Friendship-related social isolation is a potential risk factor for the transition from robust to prefrailty among healthy older adults: a 1-year follow-up study. *Eur Geriatr Med*. 2021;12(2):285–293. doi:10.1007/s41999-020-00422-y

81 Reeve TE 4th, Ur R, Craven TE, et al. Grip strength measurement for frailty assessment in patients with vascular disease and associations with comorbidity, cardiac risk, and sarcopenia. *J Vasc Surg*. 2018;67(5):1512–1520. doi:10.1016/j.jvs.2017.08.078

82 Choe YR, Jeong JR, Kim YP. Grip strength mediates the relationship between muscle mass and frailty. *J Cachexia Sarcopenia Muscle*. 2020;11(2):441–451. doi:10.1002/jcsm.12510

83 Tanaka S, Ando K, Kobayashi K, et al. Higher extracellular water-to-total body water ratio more strongly reflects the locomotive syndrome risk and frailty than sarcopenia. *Arch Gerontol Geriatr*. 2020;88:104042. doi:10.1016/j.archger.2020.104042

84 Kooij KW, Wit FW, Schouten J, et al. HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls. *AIDS*. 2016;30(2):241–250. doi:10.1097/QAD.0000000000000910

85 Serra-Prat M, Lorenzo I, Palomera E, Yébenes JC, Campins L, Cabré M. Intracellular Water Content in Lean Mass is Associated with Muscle Strength, Functional Capacity, and Frailty in Community-Dwelling Elderly Individuals. A Cross-Sectional Study. *Nutrients*. 2019;11(3):661. doi:10.3390/nu11030661

86 Hirani V, Naganathan V, Blyth F, et al. Longitudinal associations between body composition, sarcopenic obesity and outcomes of frailty, disability, institutionalisation and mortality in community-dwelling older men: The Concord Health and Ageing in Men Project. *Age Ageing*. 2017;46(3):413–420. doi:10.1093/ageing/afw214

87 Lin CS, Liu LK, Lee WJ, et al. Low masseter muscle mass is associated with frailty in community-dwelling older adults: I-Lan Longitudinal Aging Study. *Exp Gerontol*. 2022;163:111777. doi:10.1016/j.exger.2022.111777

88 Norazman CW, Adznam SN, Jamaluddin R. Malnutrition as Key Predictor of Physical Frailty among Malaysian Older Adults. *Nutrients*. 2020;12(6):1713. doi:10.3390/nu12061713

89 Chew J, Yeo A, Yew S, et al. Nutrition Mediates the Relationship between Osteosarcopenia and Frailty: A Pathway Analysis. *Nutrients*. 2020;12(10):2957. doi:10.3390/nu12102957

90 Güngör Başaran AY, Akal Yıldız E. Nutrition Status, Muscle Mass, and Frailty in Older People: A Cross-Sectional Study Conducted in Cyprus. *J Am Nutr Assoc*. 2022;41(3):318–324. doi:10.1080/07315724.2021.1884142

91 Pérez-Ros P, Vila-Candel R, López-Hernández L, Martínez-Arnau FM. Nutritional Status and Risk Factors for Frailty in Community-Dwelling Older People: A Cross-Sectional Study. *Nutrients*. 2020;12(4):1041. doi:10.3390/nu12041041

92 Gajic-Veljanoski O, Papaioannou A, Kennedy C, et al. Osteoporotic fractures and obesity affect frailty pro-

gression: a longitudinal analysis of the Canadian multicentre osteoporosis study. *BMC Geriatr*. 2018;18(1):4. doi:10.1186/s12877-017-0692-0

93 Lee JS, Auyeung TW, Leung J, Kwok T, Leung PC, Woo J. Physical frailty in older adults is associated with metabolic and atherosclerotic risk factors and cognitive impairment independent of muscle mass. *J Nutr Health Aging*. 2011;15(10):857–862. doi:10.1007/s12603-011-0134-1

94 Ninomiya K, Takahira N, Ikeda T, Suzuki K, Sato R, Hirakawa K. Prevalence of frailty and associated factors among community-dwelling older adults after total hip arthroplasty. *Hip Int*. 2023;33(3):397–403. doi:10.1177/11207000211048180

95 Hernández-Luis R, Martín-Ponce E, Monereo-Muñoz M, et al. Prognostic value of physical function tests and muscle mass in elderly hospitalized patients. A prospective observational study. *Geriatr Gerontol Int*. 2018;18(1):57–64. doi:10.1111/ggi.13138

96 Jyväkorpi SK, Lindström M, Suominen MH, et al. Relationship between frailty, nutrition, body composition, quality of life, and gender in institutionalized older people. *Aging Clin Exp Res*. 2022;34(6):1357–1363. doi:10.1007/s40520-022-02077-0

97 Saeki C, Kanai T, Nakano M, et al. Relationship between Osteosarcopenia and Frailty in Patients with Chronic Liver Disease. *J Clin Med*. 2020;9(8):2381. doi:10.3390/jcm9082381

98 Feng H, Wang X, Mao L, et al. Relationship between sarcopenia/myosteatosis and frailty in hospitalized patients with cirrhosis: a sex-stratified analysis. *Ther Adv Chronic Dis*. 2021;12:204062232110269. doi:10.1177/20406223211026996

99 Meerkerk CDA, Chargi N, de Jong PA, van den Bos F, de Bree R. Sarcopenia measured with handgrip strength and skeletal muscle mass to assess frailty in older patients with head and neck cancer. *J Geriatr Oncol*. 2021;12(3):434–440. doi:10.1016/j.jgo.2020.10.002

100 Chou HH, Lai TJ, Yen CH, Chang PS, Pan JC, Lin PT. Sarcopenic Obesity Tendency and Nutritional Status Is Related to the Risk of Sarcopenia, Frailty, Depression and Quality of Life in Patients with Dementia. *Int J Environ Res Public Health*. 2022;19(5):2492. doi:10.3390/ijerph19052492

101 Buch A, Keinan-Boker L, Kis O, et al. Severe central obesity or diabetes can replace weight loss in the detection of frailty in obese younger elderly; a preliminary study. *Clin Interv Aging*. 2018;13:1907–1918. doi:10.2147/CIA.S176446

102 Frisoli A Jr, Chaves PH, Ingham SJ, Fried LP. Severe osteopenia and osteoporosis, sarcopenia, and frailty status in community-dwelling older women: Results from the Women's Health and Aging Study (WHAS) II. *Bone*. 2011;48(4):952–957. doi:10.1016/j.bone.2010.12.025

103 Soh Y, Won CW. Sex differences in association between body composition and frailty or physical performance in community-dwelling older adults. *Medicine (Baltimore)*. 2021;100(4):e24400. doi:10.1097/MD.0000000000024400

104 Wysham KD, Shoback DM, Andrews JS, Katz PP. Sex differences in frailty and its association with low bone mineral density in rheumatoid arthritis. *Bone Rep*. 2020;12:100284. doi:10.1016/j.bonr.2020.100284

105 Nishimura A, Harashima S, Hosoda K, Arai H, Inagaki N. Sex-related differences in frailty factors in older persons with type 2 diabetes: a cross-sectional study. *Ther Adv Endocrinol Metab*. 2019;10:204201881983330. doi:10.1177/2042018819833304

106 Frisoli A Jr, Paes AT, Borges J, et al. The association between low lean mass and osteoporosis increases the risk of weakness, poor physical performance and frailty in Brazilian older adults: data from SARCOS study. *Eur J Clin Nutr*. 2021;75(3):446–455. doi:10.1038/s41430-020-00753-w

107 Tembo MC, Mohebbi M, Holloway-Kew KL, et al. The contribution of musculoskeletal factors to physical frailty: a cross-sectional study. *BMC Musculoskelet Disord*. 2021;22(1):921. doi:10.1186/s12891-021-04795-4

108 Tembo MC, Mohebbi M, Holloway-Kew KL, et al. The Predictability of Frailty Associated with Musculoskeletal Deficits: A Longitudinal Study. *Calcif Tissue Int*. 2021;109(5):525–533. doi:10.1007/s00223-021-00865-w

109 Fougère B, Sourdet S, Lilamand M, et al. Untangling the overlap between frailty and low lean mass: Data from Toulouse frailty day hospital. *Arch Gerontol Geriatr*. 2018;75:209–213. doi:10.1016/j.archger.2017.12.013

110 Liao Q, Zheng Z, Xiu S, Chan P. Waist circumference is a better predictor of risk for frailty than BMI in the community-dwelling elderly in Beijing. *Aging Clin Exp Res*. 2018;30(11):1319–1325. doi:10.1007/s40520-018-0933-x

111 Dent E, Morley JE, Cruz-Jentoft AJ, et al. Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. *J Nutr Health Aging*. 2019;23(9):771–787. doi:10.1007/s12603-019-1273-z

112 Park H, Park S, Shephard RJ, Aoyagi Y. Yearlong physical activity and sarcopenia in older adults: the

Nakanojo Study. *Eur J Appl Physiol*. 2010;109(5):953–961. doi:10.1007/s00421-010-1424-8
113 Pérez-Tasigchana RF, León-Muñoz LM, Lopez-Garcia E, et al. Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study. *Age Ageing*. 2017;46(5):807–812. doi:10.1093/ageing/afx023
114 Saifuddin Ekram ARM, Espinoza SE, Ernst ME, et al. The Association between Metabolic Syndrome, Frailty and Disability-Free Survival in Healthy Community-dwelling Older Adults. *J Nutr Health Aging*. 2023;27(1):1–9. doi:10.1007/s12603-022-1860-2
115 McCarthy K, Laird E, O'Halloran AM, Fallon P, Ortuño RR, Kenny RA. Association between metabolic syndrome and risk of both prevalent and incident frailty in older adults: Findings from The Irish Longitudinal Study on Ageing (TILDA). *Exp Gerontol*. 2023;172:112056. doi:10.1016/j.exger.2022.112056
116 Blazer DG, Hybels CF, Fillenbaum GG. Metabolic syndrome predicts mobility decline in a community-based sample of older adults. *J Am Geriatr Soc*. 2006;54(3):502–506. doi:10.1111/j.1532-5415.2005.00607.x
117 Carriere I, Pérès K, Ancelin ML, et al. Metabolic syndrome and disability: findings from the prospective three-city study. *J Gerontol A Biol Sci Med Sci*. 2014;69(1):79–86. doi:10.1093/gerona/glt101
118 Yang M, Hu M, Zhang Y, et al. Sarcopenic obesity is associated with frailty among community-dwelling older adults: findings from the WCHAT study. *BMC Geriatr*. 2022;22(1):863. doi:10.1186/s12877-022-03617-z
119 Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc*. 2020;21(3):300–307.e2. doi:10.1016/j.jamda.2019.12.012
120 Kohro T, Furui Y, Mitsutake N, et al. The Japanese national health screening and intervention program aimed at preventing worsening of the metabolic syndrome. *Int Heart J*. 2008;49(2):193–203. doi:10.1536/ihj.49.193