scientific reports

Check for updates

OPEN

Effect of low muscle mass on total mortality related to metabolic disease in chronic kidney disease patients

Jong Wook Choi[1,5], Sung Hye Kong[2,5], Yoon Jung Kim[3], Hye Soo Chung[3], Jae Myung Yu[3], Joon-Sung Park[1], Chang Hwa Lee[1], Jung Hwan Park[1], Dong Sun Kim[1], Chang-Myung Oh[4]✉ & Shinje Moon[1]✉

Low muscle mass is a risk factor for mortality in patients with chronic kidney disease (CKD). However, it is not clear to what extent low muscle mass contributes to this risk, either independently or in combination with metabolic abnormalities and frailty. This study used data from the National Health and Nutrition Examination Survey 1999–2006 and 2011–2018. Low muscle mass was defined as Appendicular Skeletal Mass Index < 7 kg/m^2 in men or < 5.5 kg/m^2 in women. The follow-up duration was from the first anthropometric and clinical measurements to death or the last follow-up. This study enrolled 2072 patients with CKD. Low muscle mass was associated with a lower risk of metabolic abnormalities, but was associated with an elevated mortality risk. Conversely, central obesity was associated with a higher likelihood of metabolic abnormalities and frailty, yet showed no significant association with mortality risk. Subsequently conducted mediation analysis indicated that the effect of low muscle mass on mortality was direct, not mediated by frailty and metabolic abnormalities. In spite of the inverse relationship between low muscle mass and metabolic abnormalities, low muscle mass are directly associated with an increased risk of all-cause mortality. Low muscle mass may directly contribute to mortality in patients with CKD, independent of metabolic abnormalities and frailty in these patients.

Sarcopenia is a chronic condition characterized by a progressive decline in skeletal muscle mass and functionality[1]. The prevalence of sarcopenia is estimated to be 10–16% in the elderly worldwide, although it varies depending on the study and definition used[2]. Owing to its association with aging and related diseases, it is of growing concern to clinical researchers[3]. The prevalence of sarcopenia is higher in the geriatric population than in the general population[2]. The prevalence of sarcopenia among community-dwelling Japanese adult males and females is 9.8% and 10.1%, respectively[4]. Among hospitalized geriatric patients, the confirmed prevalence is 22.6%[5]. The prevalence of low muscle mass is higher in older American adult patients with type 2 diabetes mellitus than in those without the disease (27.9% vs. 15.7%)[6]. In a meta-analysis, Xintong et al. found the pooled prevalence of sarcopenia to be 13% (95% confidence interval [95% CI]: 7–17%) in the general population and 35% (95% CI: 28–42%) in patients with cardiovascular disease (CVD)[7].

Chronic kidney disease (CKD) is a state of progressive kidney function loss that ultimately results in the need for renal replacement therapy (dialysis or transplantation)[8,9]. It is a commonly encountered clinical problem in the elderly that can lead to adverse health outcomes such as nutritional imbalance, CVD, mineral bone disease, low muscle mass, poor quality of life, and increased mortality rate[10–12]. Furthermore, CKD, a chronic catabolic condition, leads to chronic inflammation, metabolic acidosis, hormonal dysregulation, negative protein balance, and physical inactivity, all of which contribute to the breakdown of muscle tissue[13]. Low muscle mass is common in all stages of CKD and is strongly linked to negative outcomes such as hospitalization, cardiovascular events,

[1]Department of Internal Medicine, Hanyang University College of Medicine, 222-1 Wangsimni- ro, Seongdong-gu, Seoul 04763, Korea. [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam 13620, Korea. [3]Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul 07441, Korea. [4]Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, 123 Cheomdangwagi-ro, Buk-gu, Gwangju 61005, Korea. [5]Jong Wook Choi and Sung Hye Kong contributed equally to this study as first authors. ✉email: cmoh@gist.ac.kr; sinjei1129@gmail.com

mortality, and diminished quality of life[13,14]. However, the relationship between low muscle mass and clinical outcomes in the early stages of CKD remains complex and not fully understood.

Under this background, we hypothesized that low muscle mass would have a complex relationship with mortality in patients with CKD, depending on the presence or absence of frailty or other metabolic abnormalities. To address these issues, this study explores the associations among low muscle mass, frailty, central obesity, metabolic abnormalities, the risk of cardiovascular disease, and mortality. This study used data from the National Health and Nutrition Examination Survey (NHANES). Additionally, we performed a mediation analysis to assess the direct and indirect effects of frailty-induced low muscle mass on all-cause mortality. Our findings provide valuable insights for the management and prevention of mortality in patients with CKD and low muscle mass.

Results

Baseline characteristics of the participants

The present study enrolled 2072 participants with CKD from the NHANES 1999–2006 and 2011–2018 databases (Fig. 1). The demographic and clinical characteristics of the participants with low and normal muscle mass are summarized in Table 1. The mean age of the participants was 54.2 years in the normal and 64.7 years in the low muscle mass groups, respectively. Females accounted for 53.9% of the participants in the normal muscle mass group and 55.3% in the low muscle mass group.

Participants with low muscle mass demonstrated lower body mass index (BMI, 22.3 ± 3.0 vs. 30.5 ± 6.1, $P < 0.001$) and waist circumference (86.6 ± 11.5 vs. 103.0 ± 15.0, $P < 0.001$) than those with normal muscle mass. Participants with low muscle mass also had lower levels of fasting glucose (116.4 ± 47.9 vs. 133.5 ± 67.2, $P < 0.001$), HbA1c (5.9 ± 1.4 vs. 6.4 ± 1.9, $P < 0.001$), and triglycerides (141.2 ± 87.3 vs. 184.8 ± 190.8, $P < 0.001$) and higher levels of high-density lipoprotein cholesterol (59.3 ± 19.7 vs. 50.6 ± 15.6, $P < 0.001$) than those with normal muscle mass. Consistently, the prevalence of metabolic pathologies, such as diabetes (23.9% vs. 35.0%, $P < 0.001$), central obesity (25.2% vs. 69.9%, $P < 0.001$), and metabolic abnormalities (75.0% vs. 85.6%, $P < 0.001$), was significantly lower in participants with low muscle mass than in those with normal muscle mass. Moreover, participants with low muscle mass were more likely to be frail (frailty index ≥ 0.25: 37.7% vs. 27.9%, $P < 0.001$), have a history of CVD (30.2% vs. 19.0%, $P < 0.001$), and have a higher risk of all-cause mortality (62.9% vs. 30.7%, $P < 0.001$) than their non-sarcopenic counterparts.

Effects of low muscle mass and central obesity on metabolic disorders

In this study, we applied a comprehensive approach to assess the impact of both low muscle mass and central obesity on metabolic dysfunction using multiple logistic regression analysis (Table 2). In participants with low muscle mass, the risk of metabolic abnormalities (OR, 0.481; 95% CI, 0.314–0.738; $P = 0.001$) was significantly lower than in those with normal muscle mass. Conversely, central obesity was associated with a higher likelihood of diabetes (OR, 2.468; 95% CI, 1.956–3.113, $P < 0.001$), hypertension (OR, 2.680; 95% CI, 2.066–3.475; $P < 0.001$), dyslipidemia (OR 1.518, 95% CI 1.234–1.867, $P < 0.001$), and metabolic abnormalities (OR, 3.728; 95% CI, 2.680–5.186; $P < 0.001$). Furthermore, central obesity was associated with an increased risk of frailty (OR, 1.777; 95% CI, 1.385–2.280; $P < 0.001$). We used PSM to reduce the potential confounding factors between

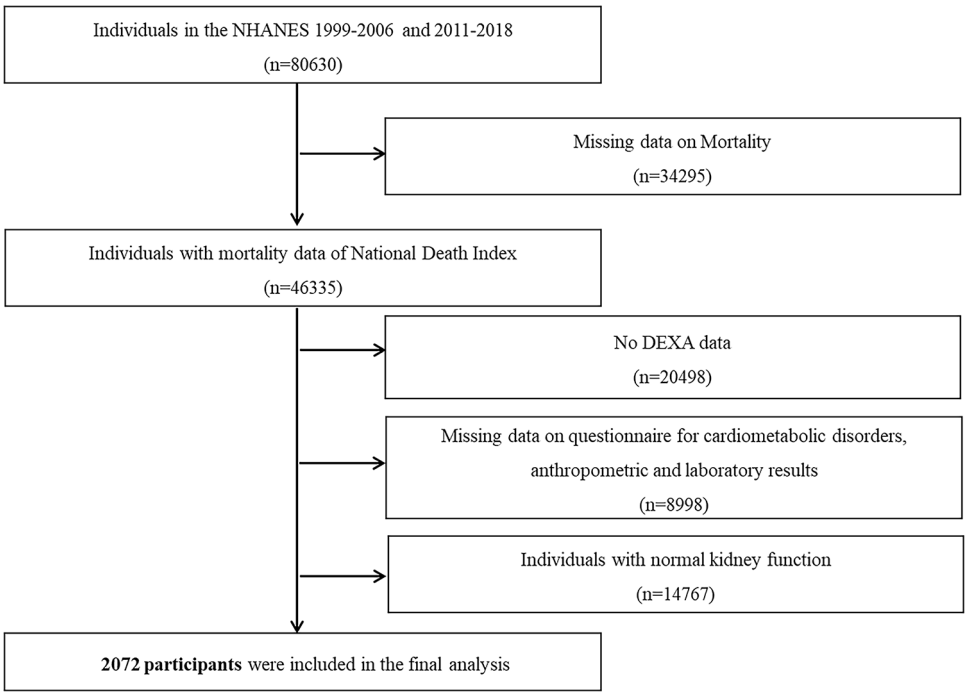

Fig. 1. Flowchart for final selection.

Variables	Normal ($N=1754$)	Low muscle mass (N = 318)	*P* value
Age	54.2 ± 16.8	64.7 ± 18.6	< 0.001
Female sex, n (%)	945 (53.9%)	176 (55.3%)	0.673
Race/ethnicity, n (%)			< 0.001
Hispanic	434 (24.7%)	65 (20.4%)	
Non-Hispanic White	684 (39.0%)	193 (60.7%)	
Non-Hispanic Black	487 (27.8%)	26 (8.2%)	
Other Races	149 (8.5%)	34 (10.7%)	
Smokers, n (%)	818 (46.6%)	172 (54.1%)	0.017
Drinkers, n (%)	1109 (63.2%)	188 (59.1%)	0.184
BMI (kg/m^2)	30.5 ± 6.1	22.3 ± 3.0	< 0.001
Waist circumference (cm)	103.0 ± 15.0	86.6 ± 11.5	< 0.001
Systolic BP, mmHg	134.3 ± 23.3	138.3 ± 27.2	0.019
Diastolic BP, mmHg	73.7 ± 15.2	69.7 ± 16.5	< 0.001
Glucose, mg/dL	133.5 ± 67.2	116.4 ± 47.9	< 0.001
HbA1c, %	6.4 ± 1.9	5.9 ± 1.4	< 0.001
Total cholesterol, mg/dL	205.0 ± 49.9	203.6 ± 46.2	0.642
Triglycerides, mg/dL	184.8 ± 190.8	141.2 ± 87.3	< 0.001
HDL, mg/dL	50.6 ± 15.6	59.3 ± 19.7	< 0.001
eGFR, $mL/min/1.73m^2$	82.6 ± 29.6	76.5 ± 30.8	0.001
Urine Albumin Creatinine Ratio,	263.9 ± 950.5	247.7 ± 958.3	0.782
ASMI	8.03 ± 1.58	5.66 ± 0.78	< 0.001
Previous CVD event, n (%)	333 (19.0%)	96 (30.2%)	< 0.001
Diabetes mellitus, n (%)	614 (35.0%)	76 (23.9%)	< 0.001
Hypertension, n (%)	1241 (70.8%)	225 (70.8%)	1.000
Dyslipidemia, n (%)	1009 (57.5%)	186 (58.5%)	0.796
Central obesity, n (%)	1221 (69.6%)	80 (25.2%)	< 0.001
Metabolic abnormality*, n (%)	1173 (85.6%)	183 (75.0%)	< 0.001
Frailty index	0.19 ± 0.11	0.22 ± 0.13	0.001
Frailty†, n (%)	481 (27.9%)	116 (37.4%)	0.001
Malignancies at baseline survey, n (%)	167 (9.52%)	61 (19.18%)	< 0.001
Risk of CKD progression, n (%)			1.000
Moderate risk	1470 (83.81%)	267 (83.96%)	
High risk	284 (16.19%)	51 (16.04%)	
All-cause death, n (%)	538 (30.7%)	200 (62.9%)	< 0.001
Mean follow up duration, months	112.4 ± 69.1	102.1 ± 63.8	0.013
Median follow up duration, months	93 (IQR 54–175)	91 (IQR 49–150)	0.031

Table 1. Overall characteristics of the participants according to muscle mass. BMI, body mass index; BP, blood pressure; HDL, high density cholesterol; GFR, glomerular filtration rate; ASMI, appendicular skeletal muscle index; CVD, cardiovascular disease; IQR, interquartile range. *Metabolic abnormality was defined as having two or more metabolic syndrome components of the revised NCEP-ATP III criteria, except for central obesity. † ≥ 0.25 of frailty index.

the groups **(Supplementary Table 2).** There were 636 participants with normal and 318 with low muscle mass after PSM. Despite PSM, low muscle mass was associated with a lower likelihood of metabolic abnormalities, and central obesity associated with a higher likelihood of diabetes, hypertension, and other metabolic dysfunctions **(Supplementary Table 3).**

Effects of low muscle mass and central obesity on mortality

In a multiple Cox regression analysis which adjusted for age, sex, race, smoking status, alcohol consumption, history of cancer, hypertension, dyslipidemia, CVD, CKD progression risk, and frailty index, high ASMI was found to be associated with a lower risk of all-cause mortality (HR, 0.831; 95% CI, 0.755–0.916; $P<0.001$), whereas waist circumference was not associated with an increased risk of all-cause mortality (HR, 1.006; 95% CI, 0.998–1.014; $P=0.153$). Further investigation using RCS plots showed a consistent association between ASMI and a reduced risk of all-cause mortality (Fig. 2A). However, waist circumference was associated with a higher risk of all-cause mortality (Fig. 2B).

	Low muscle mass		Central obesity	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Diabetes	0.743 (0.539–1.024)	0.070	2.468 (1.956–3.113)	< 0.001
Hypertension	0.829 (0.572–1.201)	0.321	2.680 (2.066–3.475)	< 0.001
Dyslipidemia	0.939 (0.707–1.247)	0.665	1.518 (1.234–1.867)	< 0.001
CVD events	1.209 (0.873–1.674)	0.253	1.166 (0.897–1.517)	0.251
Metabolic abnormalities	0.481 (0.314–0.738)	0.001	3.728 (2.680–5.186)	< 0.001
Frailty	1.270 (0.925–1.743)	0.139	1.777 (1.385–2.280)	< 0.001
High risk of CKD progression	1.169 (0.808–1.690)	0.407	1.220 (0.929–1.601)	0.153

Table 2. Risk of metabolic disorders and frailty associated with low muscle mass and central obesity. Adjustment for age, gender, race, alcohol, smoking, and history of cancer.

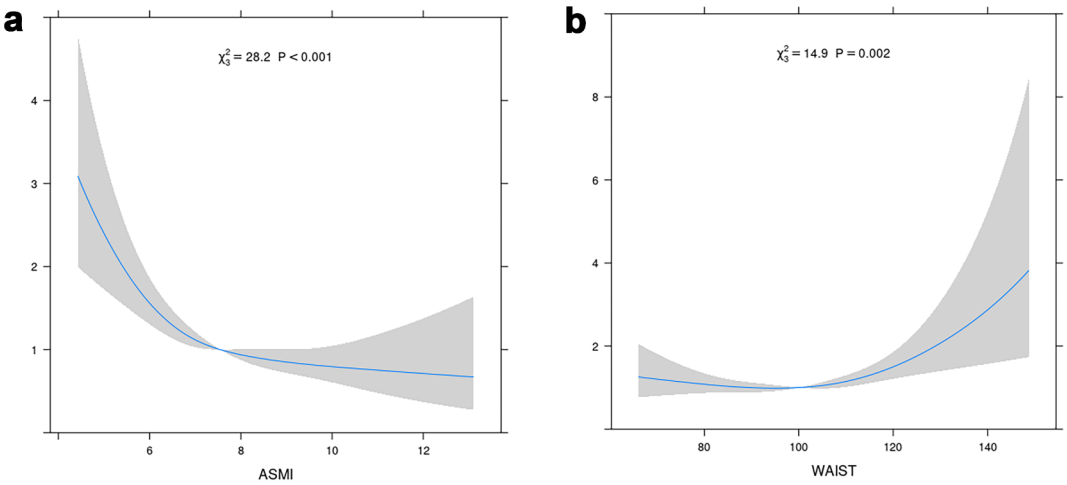

Fig. 2. The hazard ratio for mortality according to (a) Appendicular Skeletal Mass Index (ASMI) and (b) waist circumference. Adjusted for age, sex, race, smoking status, alcohol consumption, history of cancer, DM, hypertension, dyslipidemia, preexistent CVD, risk of CKD progression, and frailty index.

Similar to the Kaplan-Meier curve in Fig. 3A, in the multiple Cox regression analysis, low muscle mass as defined by EWGSOP2 was associated with a higher risk of all-cause mortality (HR, 1.601; 95% CI, 1.324–1.935; $P < 0.001$). Across subgroup analyses categorized by age (20–64 years or above 65 years), sex, and risk of CKD progression, the presence of low muscle mass consistently was associated with a higher risk of mortality in all subgroups (Table 3). In the additional analysis of disease-related mortality, low muscle mass was associated with CVD-related and respiratory disease-related mortalities (Table 4). Conversely, the Kaplan-Meier curve showed no association between central obesity and all-cause mortality (HR, 1.061; 95% CI, 0.894–1.259; $P = 0.499$; Fig. 3B).

Furthermore, after PSM, low muscle mass was associated with a higher risk of all-cause mortality in the multiple Cox regression analysis (HR, 1.819; 95% CI, 1.421–2.328; $P < 0.001$), whereas central obesity was not associated with an increased risk of all-cause mortality (**Supplementary Table 4).**

Effects of low muscle mass on mortality risk according to frailty status and metabolic abnormalities in CKD patients

In the mediation analysis of frailty, the total effect of low muscle mass on all-cause mortality was significant (TE: HR, 1.615: 95% CI, 1.334–1.955; $P < 0.001$). Although low muscle mass significantly affected all-cause mortality (TNDE: HR, 1.593; 95% CI, 1.320–1.922; $P < 0.001$), it was not associated with frailty, which was significantly related to all-cause mortality. Furthermore, low muscle mass did not significantly affect the risk of all-cause mortality through frailty (TNIE: HR, 1.014; 95% CI, 0.978–1.052; $P = 0.449$; Fig. 4A).

In the mediation analysis of metabolic abnormalities, the total effect of low muscle mass on all-cause mortality was significant (TE: HR, 1.596; 95% CI 1.301–1.960; $P < 0.001$; Fig. 4B). Low muscle mass significantly affected all-cause mortality (TNDE: HR, 1.613; 95% CI, 1.314–1.981; $P < 0.001$). Notably, low muscle mass was associated with a lower likelihood of metabolic abnormalities (OR, 0.475; 95% CI, 0.311–0.724; $P < 0.001$). Furthermore, low muscle mass did not significantly affect the risk of all-cause mortality due to metabolic abnormalities (TNIE:

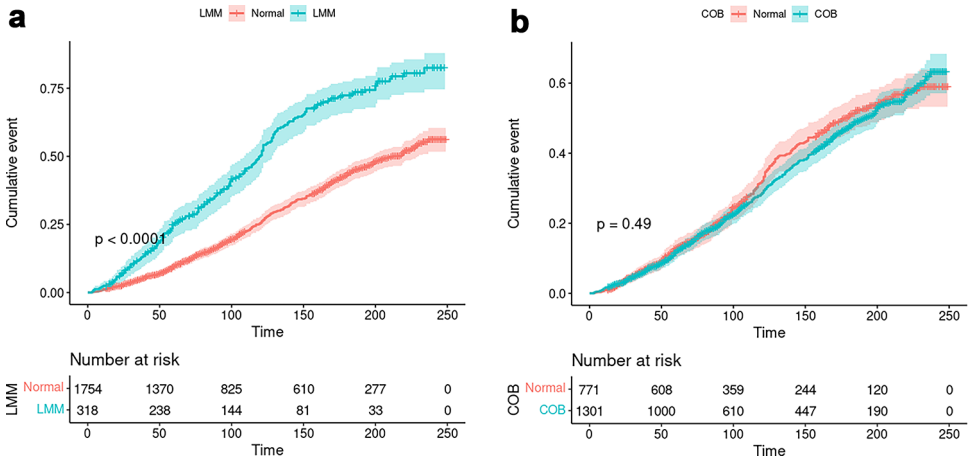

Fig. 3. Kaplan-Meier survival curves of survival data in relation to low muscle mass (LMM) and central obesity (COB).

	Low muscle mass		Central obesity	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Total	1.601 (1.324–1.935)	< 0.001	1.061 (0.894–1.259)	0.499
Subgroup by 3 years after diagnosis.				
During the first 3 years	1.600 (1.049–2.440)	0.029	0.930 (0.626–1.380)	0.718
After a time lag of over 3 years	1.556 (1.282–1.889)	< 0.001	0.914 (0.768–1.080)	0.312
Subgroup by sex				
Men	1.480 (1.135–1.929)	0.004	0.952 (0.759–1.194)	0.672
Women	1.744 (1.315–2.314)	< 0.001	1.239 (0.938–1.638)	0.132
Subgroup by age group				
<65 years	2.494 (1.549–4.015)	< 0.001	1.335 (0.92–1.938)	0.128
≥65 years	1.402 (1.135–1.731)	0.002	1.007 (0.824–1.229)	0.948
Subgroup by the risk of CKD progression				
Moderate risk	1.508 (1.222–1.863)	< 0.001	1.052 (0.867–1.276)	0.610
High risk	2.017 (1.281–3.176)	0.002	1.197 (0.808–1.773)	0.371

Table 3. Cox regression analysis for all-cause mortality risks in patients with CKD. Adjusted for age, sex, race, smoking status, alcohol consumption, history of cancer, DM, hypertension, dyslipidemia, preexistent CVD, risk of CKD progression, and frailty index.

	Low muscle mass		Central obesity	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cancer related mortality	1.116 (0.686–1.818)	0.658	1.074 (0.707–1.629)	0.739
Non-cancer related mortality	1.713 (1.393–2.106)	< 0.001	1.058 (0.877–1.277)	0.556
CVD related mortality	1.653 (1.203–2.271)	0.002	1.175 (0.880–1.568)	0.274
Respiratory disease related mortality	1.980 (1.015–3.863)	0.045	0.666 (0.349–1.273)	0.219
Kidney disease related mortality	0.741 (0.187–2.935)	0.670	0.426 (0.154–1.178)	0.100
Others	1.958 (1.343–2.852)	< 0.001	1.072 (0.762–1.508)	0.690

Table 4. Cox regression analysis for cause specific mortality risks in patients with CKD. Adjusted for age, sex, race, smoking status, alcohol consumption, history of cancer, DM, hypertension, dyslipidemia, preexistent CVD, risk of CKD progression, and frailty index.

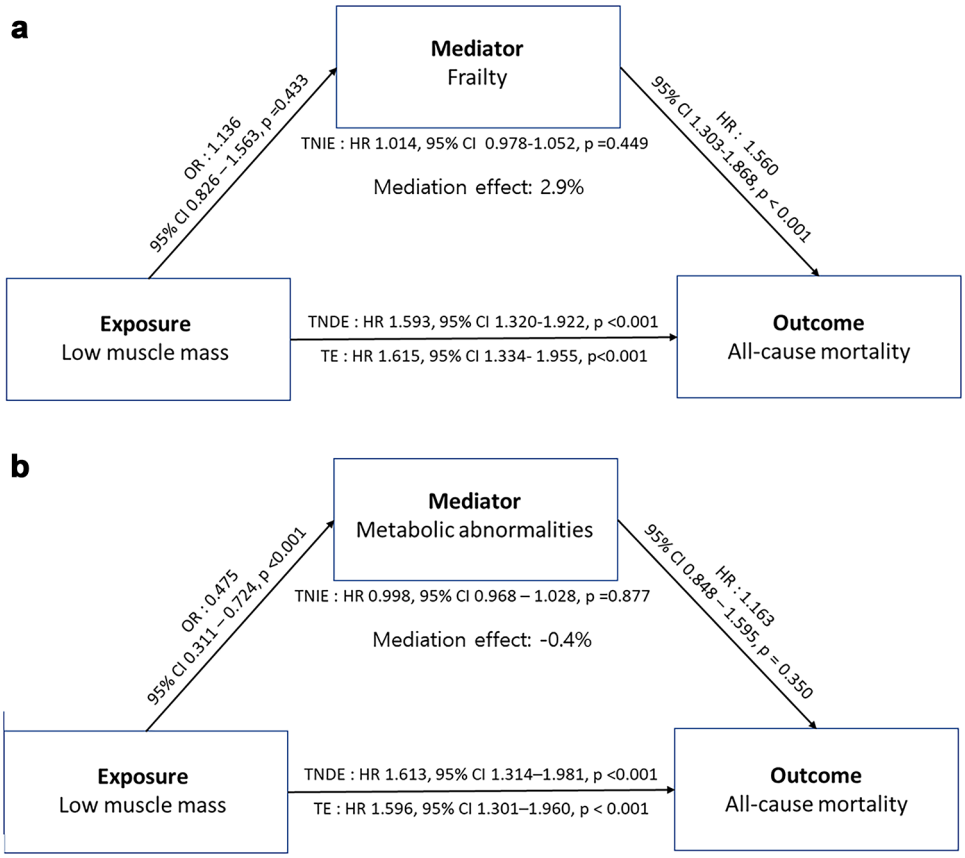

Fig. 4. Mediation Analysis of the effect of low muscle mass through frailty and metabolic abnormalities in patients with CKD on all-cause mortality.

HR, 0.998; 95% CI, 0.968–1.028; $P=0.877$). These results suggest that low muscle mass directly affects all-cause mortality; however, this effect is not mediated by frailty or metabolic abnormalities.

Central obesity did not directly affect mortality (**Supplementary Fig. 1**). In the mediation analysis of frailty, the direct effect of central obesity on all-cause mortality was insignificant (TNDE: HR, 1.088; 95% CI, 0.914–1.296; $P=0.344$). Nonetheless, central obesity increased the risk of frailty (OR, 1.741; 95% CI, 1.351–2.242; $P<0.001$). Consequently, frailty significantly increased the risk of all-cause mortality (HR, 1.615; 95% CI, 1.266–2.060; $P<0.001$). Furthermore, central obesity indirectly affected the risk of all-cause mortality through frailty (TNIE: HR, 1.060; 95% CI, 1.020–1.101; $P=0.002$; **Supplementary Fig. 1A**).

In the mediation analysis of metabolic abnormalities, the direct effect of central obesity on all-cause mortality was not significant (TNDE: HR: 1.196, 95% CI: 0.987–1.449; $P=0.068$). Although central obesity increased the risk of metabolic abnormalities (OR: 3.631; 95% CI, 2.610–5.052: $P<0.001$), it did not have a significant indirect effect on the risk of all-cause mortality through metabolic abnormalities (TNIE: HR 1.017, 95% CI 0.991–1.043, $P=0.204$; **Supplementary Fig. 1B**). These findings indicated that central obesity does not directly affect all-cause mortality. Instead, it indirectly increased mortality risk by mediating frailty rather than metabolic abnormalities.

Discussion

This study investigated the association between low muscle mass and all-cause mortality in patients with CKD. This nationwide study pioneered the investigation of the association between low skeletal muscle mass and mortality risk in patients with CKD, uniquely incorporating the influences of frailty, central obesity, and metabolic disease. Unlike previous research, it assessed the direct and indirect effects of low muscle mass on mortality through mediation analysis[14,15].

The baseline characteristics of the study cohort showed significant differences between the participants with normal and low muscle masses. Specifically, participants with low muscle mass were older, had a lower BMI, and a decreased waist circumference compared to participants with normal muscle mass. To address the potential confounding factors, we employed PSM, which resulted in well-matched cohorts of participants with normal and low muscle mass. Even after PSM, the persistence of a protective effect against diabetes and metabolic abnormalities in the presence of low muscle mass underscores its distinct role in maintaining metabolic homeostasis. Notably, low muscle mass was associated with an increased risk of frailty, reinforcing its independent impact. Conversely, central obesity, even after PSM, was associated with an elevated risk of diabetes, hypertension, and other metabolic disorders.

Our findings regarding the positive association between CKD and low muscle mass are consistent with current literature[11,16,17]. An observational cohort study consisting of 123 patients with CKD and 57 healthy individuals revealed that sarcopenia was significantly associated with increased CKD progression and mortality in the CKD group[11]. In this cohort, the relative ASMI was significantly decreased as CKD progressed ($Z = -3.253$, $P = 0.001$)[11]. In a cross-sectional study of 11,625 participants using the Korea National Health and Nutrition Examination Survey, the prevalence of sarcopenia was higher in elderly adults (normal and CKD stages 1, 2, and 3–5:2.6%, 5.6%, and 18.1% in men and 5.3%, 7.1%, and 12.6% in women, respectively; $P < 0.001$) than younger ones[18]. Additionally, eGFR and sarcopenia were significantly correlated in both men and women ($r = 0.173$ in men and 0.043 in women; $P < 0.001$)[18]. This may be attributed to the uremic environments induced by CKD, potentially intensifying the imbalance between muscle growth and breakdown, rendering them more susceptible to breakdown[19].

Consistent with previous studies related to sarcopenia in the general population[20,21], despite their metabolic advantages, the low muscle mass group demonstrated a higher prevalence of frailty and elevated all-cause mortality rates in patients with CKD among adults in the US. Survival analysis through Kaplan-Meier curves also revealed that low muscle mass was significantly associated with high all-cause mortality, while central obesity did not. This trend persisted even after PSM, with low muscle mass independently related to the risk of all-cause mortality. This finding is consistent with a report by Thomas et al., which analyzed the association between sarcopenia and mortality in an elderly population (46% male, aged 62.8 years) from a UK Biobank study and found that participants with CKD and sarcopenia had a higher mortality risk than normal ones[14]. Patients with CKD and sarcopenia had a lower 10-year survival than those without sarcopenia (0.85 vs. 0.89)[14]. A recent meta-analysis by Ribeiro et al. reported that low muscle strength (15 studies; HR, 1.99; 95% CI, 1.65–2.41), low muscle mass (20 studies; HR, 1.51; 95% CI, 1.36–1.68), and low physical performance (5 studies; HR, 2.09; 95% CI, 1.68–2.59) were associated with higher mortality in patients with CKD[17]. Recently, muscle loss in patients with CKD has been attributed to several negative outcomes, including reduced quality of life, depression, protein-energy wasting, increased risk of fractures, cardiovascular disease, and increased hospitalizations, which lead to higher mortality rates[22–24].

Sarcopenia primarily affects elderly people; therefore, most studies have focused on investigating its clinical effects in these participants group[14,25,26]. However, the onset of sarcopenia may be associated with non-age-related conditions[27], as revealed in our study. We found that the effect of low muscle mass on mortality risk was worse in participants aged < 65 years than in those older. This underscores the importance of muscle status assessment and consistent muscle training from a young age.

Further examination of mortality risk through mediation analysis revealed direct and indirect associations between low muscle mass and mortality. We found that low muscle mass directly affected mortality independent of frailty or metabolic abnormalities in patients with CKD. Notably, central obesity did not directly affect mortality in patients with CKD. Similar findings have been reported in several CKD cohorts in recent studies[25]. A 1 kg/m^2 increase in BMI in patients undergoing hemodialysis was linked to a 3% and 4% reduction in cardiovascular and all-cause mortality, respectively[25,28]. In preterminal CKD patients, the mortality risks without renal replacement therapy in overweight, mildly obese, and moderately obese males were 0.65, 0.60, and 0.77, respectively, compared with patients with a normal BMI[28]. Although obesity is a risk factor for CKD, survival benefits have been observed in advanced CKD patients[29]. Individuals with a higher BMI demonstrated lower mortality rates than those with normal BMI in the CKD cohort, which is consistent with the concept of the 'obesity paradox'[28,29]. However, the underlying mechanisms remain unclear.

This study had a few limitations. First, in our mediation analysis, low muscle mass had a frailty-independent effect on mortality in patients with CKD. In contrast, frailty is a well-known independent risk factor for mortality in patients with CKD[30]. This could be because both sarcopenia and frailty are prevalent, and many patients overlap in the CKD population[31]. To overcome this limitation, large population-based cohort studies should be performed using frailty and sarcopenia as independent risk factors for mortality in patients with CKD. Secondly, we could not elucidate the mechanism underlying the effects of low muscle mass on mortality in this analysis. Further prospective studies investigating biomarkers reflecting aging, inflammation, and muscle and renal dysfunction are needed to elucidate the complex role of low muscle mass in the mortality of patients with CKD.

Our comprehensive assessment of the effects of low muscle mass and central obesity on metabolic dysfunction and mortality highlights important findings. The risks for diabetes and metabolic abnormalities were significantly lower in participants with low muscle mass than in those with normal muscle mass. In contrast, central obesity substantially increased the risk of frailty, diabetes, dyslipidemia, and metabolic abnormalities; however, it did not have a direct effect on mortality.

In conclusion, our study sheds light on the independent roles of low muscle mass and central obesity in metabolic dysfunction and mortality in patients with CKD. Although low muscle mass was associated with a lower likelihood of metabolic abnormalities, it exerts a direct influence on mortality. Central obesity, however, influenced mortality indirectly through its impact on frailty. These findings provide valuable insights into the complex interplay between several factors in CKD, thus paving the way for targeted interventions to improve patient outcomes.

Methods

Study population

This study utilized data from the NHANES, a comprehensive cross-sectional survey of the United States population covering various aspects, including health, nutritional, medical, dental, and physical aspects. The baseline data used in this study spanning four NHANES cycles (1999–2006 and 2011–2018) were linked to mortality data obtained from the National Death Index for the longitudinal analysis.

Measurements of kidney function and muscle mass

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) and urinary albumin-to-creatinine ratio (ACR) were calculated to assess kidney function. The eGFR was calculated based on the CKD Epidemiology Collaboration (CKD-EPI) equation. The ACR was calculated as the albumin level in spot urine (mg/dL) divided by the creatinine level in spot urine (g/dL). To assess total and regional body composition, whole-body dual X-ray absorptiometry was performed using a Hologic QDR 4500 A fan-beam X-ray bone densitometer (Hologic Inc., Marlborough, MA, USA) in NHANES 1999–2006, and Hologic Discovery model A densitometers in NHANES 2011–2018.

Definitions

Metabolic parameters

Central obesity and metabolic abnormality were defined according to the National Cholesterol Education Program-Adult Treatment Panel III criteria (NCEP-ATP III criteria): Central obesity was defined as a waist circumference greater than 102 cm in men and greater than 88 cm in women and metabolic abnormalities were defined as the presence of two or more of the metabolic risk factors, including impaired fasting glucose (fasting blood glucose level ≥ 100 mg/dL or diagnosed diabetes), high blood pressure (BP) (systolic BP > 130 mmHg and/or diastolic BP > 85 mmHg or a diagnosed of hypertension), triglyceride level ≥ 150 mg/dL, and a high-density lipoprotein cholesterol level < 40 mg/dL in men and < 50 mg/dL in women. The Appendicular Skeletal Mass Index (ASMI) was calculated by dividing the appendicular skeletal mass by the square of the individual's height in meters (m). Low muscle mass was defined as ASMI < 7 kg/m^2 in men and < 5.5 kg/m^2 in women, based on the criteria set by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2).

Outcomes

Data on all-cause and cardiovascular mortality and follow-up duration were collected from linked mortality data of the National Center for Health Statistics up to December 31, 2019.

Covariates

Baseline covariates included age, sex, race/ethnicity, smoking status, alcohol consumption, history of cancer, metabolic disorders (dyslipidemia, hypertension, diabetes, and CVD), CKD progression risk, and frailty index. Demographic information such as age, sex, race/ethnicity, smoking status, alcohol consumption, and history of cancer was collected using a questionnaire. Hypertension was defined as systolic and diastolic blood pressures > 140 mmHg and > 90 mmHg or the use of hypertensive medications. Similarly, diabetes was defined based on fasting blood glucose levels > 126 mg/dL, random blood glucose levels > 200 mg/dL, HbA1c levels > 6.5%, or the use of antidiabetic medications. Dyslipidemia was characterized by fasting total cholesterol levels ≥ 240 mg/dL or the use of lipid-lowering treatments. A structured questionnaire was used to investigate preexisting CVD events. participants were classified as having CVD if they had a history of one or more of the following conditions: angina pectoris, coronary heart disease, myocardial infarction, congestive heart failure, or cerebrovascular disease. As per the 2022 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[32], the risk of CKD progression was categorized as follows: moderately increased risk group was defined as eGFR of 45–59 mL/min/1.73 m^2 with ACR < 30 mg/g or eGFR > 60 mL/min/1.73 m^2 with ACR of 30–299 mg/g; High-risk group was defined as eGFR < 45 mL/min/1.73 m^2, ACR ≥ 300 mg/g, or eGFR < 60 mL/min/1.73 m^2 with ACR ≥ 30 mg/g. The frailty index, constructed from 46 variables, was included in the analysis for individuals with data on ≥ 40 items (**Supplementary Table 1**)[18,33]. It was calculated as the the number of deficits present divided by the number of deficits measured. Frailty was defined as a frailty index > 0.25.

Ethical considerations

The study protocol was approved by the Institutional Review Board of Kangnam Sacred Heart Hospital (IRB No. HKS 2020-01-020). The NHANES procedures were authorized by the National Center for Health Statistics Research Ethics Review Board, and the participants provided written informed consent (NCHS IRB/ERB Protocol Numbers: 1999–2004, Protocol #98 − 12, and 2005 − 206, Protocol #2005-06). All methods were performed in accordance with the Declaration of Helsinki.

Statistical analysis

Continuous variables were presented as means with standard deviations, while categorical variables were presented as frequencies and percentages. Multiple Cox regression analyses were performed to determine the hazard ratios (HRs) for mortality, adjusting for various confounding variables. The graphical association between the HR and obesity parameters was assessed using restricted cubic spline (RCS) plots. To address demographic, clinical, and laboratory heterogeneity based on muscle mass status, propensity score matching (PSM) was conducted. The matching variables included age, sex, race/ethnicity, current smoking status, alcohol consumption, and cancer history. Using the R software package "MatchIt", 1:2 matching was performed according to muscle mass status using the nearest neighbor method with a caliber of 0.25[34]. Causal mediation analysis was performed using the package "Regmedint" developed by Yoshida et al. to investigate the direct and indirect effect of low muscle mass on mortality[35]. The total effect (TE), total natural indirect effect (TNIE), total natural direct effect (TNDE), and cumulative effect of low muscle mass and central obesity on mortality were calculated. Statistical analyses were performed using IBM SPSS version 24.0 and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Statistical significance was set at $P < 0.05$.

Data availability

The data for this study are available through the corresponding author upon reasonable request.

Received: 28 May 2024; Accepted: 23 September 2024
Published online: 01 October 2024

References

1. Santilli, V., Bernetti, A., Mangone, M. & Paoloni, M. Clinical definition of Sarcopenia. *Clin. Cases Min. Bone Metab.* **11**, 177–180 (2014).
2. Yuan, S. & Larsson, S. C. Epidemiology of Sarcopenia: prevalence, risk factors, and consequences. *Metabolism*. **144**, 155533. https://doi.org/10.1016/j.metabol.2023.155533 (2023).
3. Cruz-Jentoft, A. J., Sayer, A. A. & Sarcopenia *Lancet* **393**, 2636–2646 https://doi.org/10.1016/s0140-6736(19)31138-9 (2019).
4. Makizako, H., Nakai, Y., Tomioka, K. & Taniguchi, Y. Prevalence of Sarcopenia defined using the Asia Working Group for Sarcopenia criteria in Japanese community-dwelling older adults: a systematic review and meta-analysis. *Phys. Ther. Res.* **22**, 53–57. https://doi.org/10.1298/ptr.R0005 (2019).
5. Bertschi, D., Kiss, C. M., Beerli, N. & Kressig, R. W. Sarcopenia in hospitalized geriatric patients: insights into prevalence and associated parameters using new EWGSOP2 guidelines. *Eur. J. Clin. Nutr.* **75**, 653–660. https://doi.org/10.1038/s41430-020-00780-7 (2021).
6. Dai, S. et al. Higher risk of Sarcopenia in older adults with type 2 diabetes: NHANES 1999–2018. *Obes. Facts*. **16**, 237–248. https://doi.org/10.1159/000530241 (2023).
7. Zuo, X. et al. Sarcopenia and cardiovascular diseases: a systematic review and meta-analysis. *J. Cachexia Sarcopenia Muscle*. **14**, 1183–1198. https://doi.org/10.1002/jcsm.13221 (2023).
8. Kalantar-Zadeh, K., Jafar, T. H., Nitsch, D., Neuen, B. L. & Perkovic, V. Chronic kidney disease. *Lancet*. **398**, 786–802. https://doi.org/10.1016/s0140-6736(21)00519-5 (2021).
9. Levey, A. S. et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). *Kidney Int.* **67**, 2089–2100. https://doi.org/10.1111/j.1523-1755.2005.00365.x (2005).
10. Mallappallil, M., Friedman, E. A., Delano, B. G., McFarlane, S. I. & Salifu, M. O. Chronic kidney disease in the elderly: evaluation and management. *Clin. Pract. (Lond)*. **11**, 525–535. https://doi.org/10.2217/cpr.14.46 (2014).
11. Yu, M. D. et al. Relationship between chronic kidney disease and sarcopenia. *Sci. Rep.* **11**, 20523. https://doi.org/10.1038/s41598-021-99592-3 (2021).
12. Khairallah, P. & Nickolas, T. L. Management of osteoporosis in CKD. *Clin. J. Am. Soc. Nephrol.* **13**, 962–969. https://doi.org/10.2215/cjn.11031017 (2018).
13. Wang, K. et al. Chronic kidney disease-induced muscle atrophy: molecular mechanisms and promising therapies. *Biochem. Pharmacol.* **208**, 115407. https://doi.org/10.1016/j.bcp.2022.115407 (2023).
14. Wilkinson, T. J. et al. Association of Sarcopenia with mortality and end-stage renal disease in those with chronic kidney disease: a UK Biobank study. *J. Cachexia Sarcopenia Muscle*. **12**, 586–598. https://doi.org/10.1002/jcsm.12705 (2021).
15. Androga, L., Sharma, D., Amodu, A. & Abramowitz, M. K. Sarcopenia, obesity, and mortality in US adults with and without chronic kidney disease. *Kidney Int. Rep.* **2**, 201–211. https://doi.org/10.1016/j.ekir.2016.10.008 (2017).
16. Moon, S. J., Kim, T. H., Yoon, S. Y., Chung, J. H. & Hwang, H. J. Relationship between stage of chronic kidney Disease and Sarcopenia in Korean aged 40 years and older using the Korea National Health and Nutrition Examination Surveys (KNHANES IV-2, 3, and V-1, 2), 2008–2011. *PLoS One*. **10**, e0130740. https://doi.org/10.1371/journal.pone.0130740 (2015).
17. Ribeiro, H. S. et al. Association between Sarcopenia and clinical outcomes in chronic kidney disease patients: a systematic review and meta-analysis. *Clin. Nutr.* **41**, 1131–1140. https://doi.org/10.1016/j.clnu.2022.03.025 (2022).
18. Blodgett, J. M., Rockwood, K. & Theou, O. Changes in the severity and lethality of age-related health deficit accumulation in the USA between 1999 and 2018: a population-based cohort study. *Lancet Healthy Longev.* **2**, e96–e104. https://doi.org/10.1016/s2666-7568(20)30059-3 (2021).
19. Fahal, I. H. Uraemic sarcopenia: aetiology and implications. *Nephrol. Dial Transpl.* **29**, 1655–1665. https://doi.org/10.1093/ndt/gft070 (2014).
20. Xu, J., Wan, C. S., Ktoris, K., Reijnierse, E. M. & Maier, A. B. Sarcopenia is Associated with mortality in adults: a systematic review and Meta-analysis. *Gerontology*. **68**, 361–376. https://doi.org/10.1159/000517099 (2022).
21. Brown, J. C., Harhay, M. O. & Harhay, M. N. Sarcopenia and mortality among a population-based sample of community-dwelling older adults. *J. Cachexia Sarcopenia Muscle*. **7**, 290–298. https://doi.org/10.1002/jcsm.12073 (2016).
22. Carrero, J. J. et al. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. *Kidney Int.* **90**, 53–66. https://doi.org/10.1016/j.kint.2016.02.025 (2016).
23. Giglio, J. et al. Muscle mass assessment by computed tomography in chronic kidney disease patients: agreement with surrogate methods. *Eur. J. Clin. Nutr.* **73**, 46–53. https://doi.org/10.1038/s41430-018-0130-1 (2019).
24. Noori, N. et al. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* **5**, 2258–2268. https://doi.org/10.2215/cjn.02080310 (2010).
25. Ladhani, M., Craig, J. C., Irving, M., Clayton, P. A. & Wong, G. Obesity and the risk of cardiovascular and all-cause mortality in chronic kidney disease: a systematic review and meta-analysis. *Nephrol. Dial Transpl.* **32**, 439–449. https://doi.org/10.1093/ndt/gfw075 (2017).
26. Papadopoulou, S. K. Sarcopenia: a Contemporary Health Problem among older adult populations. *Nutrients*. **12.** https://doi.org/10.3390/nu12051293 (2020).
27. Jung, H. N., Jung, C. H. & Hwang, Y. C. Sarcopenia in youth. *Metabolism*. **144**, 155557. https://doi.org/10.1016/j.metabol.2023.155557 (2023).
28. Wang, Z. et al. BMI and its association with death and the initiation of renal replacement therapy (RRT) in a cohort of patients with chronic kidney disease (CKD). *BMC Nephrol.* **20**, 329. https://doi.org/10.1186/s12882-019-1513-9 (2019).
29. Kalantar-Zadeh, K. et al. The obesity Paradox in kidney disease: how to reconcile it with obesity management. *Kidney Int. Rep.* **2**, 271–281. https://doi.org/10.1016/j.ekir.2017.01.009 (2017).
30. Zhang, Q., Ma, Y., Lin, F., Zhao, J. & Xiong, J. Frailty and mortality among patients with chronic kidney disease and end-stage renal disease: a systematic review and meta-analysis. *Int. Urol. Nephrol.* **52**, 363–370. https://doi.org/10.1007/s11255-019-02369-x (2020).
31. Wong, L., Duque, G. & McMahon, L. P. Sarcopenia and Frailty: challenges in Mainstream Nephrology Practice. *Kidney Int. Rep.* **6**, 2554–2564. https://doi.org/10.1016/j.ekir.2021.05.039 (2021).
32. Navaneethan, S. D. et al. Diabetes management in chronic kidney disease: Synopsis of the KDIGO 2022 clinical practice Guideline Update. *Ann. Intern. Med.* **176**, 381–387. https://doi.org/10.7326/m22-2904 (2023).
33. Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M. & Rockwood, K. A standard procedure for creating a frailty index. *BMC Geriatr.* **8**, 24. https://doi.org/10.1186/1471-2318-8-24 (2008).
34. Ho, D., Imai, K., King, G., Stuart, E. A. & MatchIt Nonparametric preprocessing for Parametric Causal Inference. *J. Stat. Softw.* **42**, 1–28. https://doi.org/10.18637/jss.v042.i08 (2011).
35. Li, Y. et al. Effect measure modification by covariates in Mediation: extending regression-based Causal Mediation Analysis. *Epidemiology*. **34**, 661–672. https://doi.org/10.1097/ede.0000000000001643 (2023).

Author contributions

Conceptualization: Shinje MoonData curation: Jong Wook Choi, Sung Hye KongFormal analysis: Jong Wook Choi, Shinje MoonFunding acquisition: Sung Hye Kong, Chang-Myung OhInvestigation: Jong Wook Choi, Yoon Jung Kim, Hye Soo Chung, Jae Myung YuMethodology: Jong Wook Choi, Sung Hye Kong, Joon-Sung Park, Chang Hwa Lee, Jung Hwan Park, Dong Sun Kim Project administration: Chang-Myung Oh, Shinje MoonResources: Chang-Myung Oh, Shinje MoonSupervision: Chang-Myung Oh, Shinje MoonVisualization: Jong Wook Choi, Shinje MoonWriting – original draft: Jong Wook Choi, Sung Hye KongWriting – review & editing: Chang-Myung Oh, Shinje Moon.

Funding

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (2020R1C1C1004999 to C.-M.O., 2021R1A2C2003410 to S.H.K.), and National Research Council of Science & Technology (NST) grant by the Korean government (MSIT) (No. CAP23021-000 to C.-M.O.).

Declarations

Competing interests

The authors declare no competing interests.

Ethics committee approval

The study protocol was approved by the Institutional Review Board (IRB) of Gwangju Institute of Science and Technology (#20221201-BR-69-02-02). All the NHANES procedures in the United States were authorized by the National Center for Health Statistics Research Ethics Review Board (Protocol Numbers: 1999–2004, Protocol #98 – 12, and 2005 – 206, Protocol #2005-06). All the participants provided written informed consent.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-73903-w.

Correspondence and requests for materials should be addressed to C.-M.O. or S.M.