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Original Article

ORIGINAL ARTICLE

Interaction of general obesity and abdominal obesity with frailty in patients with chronic kidney disease: a nationally representative analysis

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ABSTRACT

Background. General and abdominal obesity are prevalent, with established associations to frailty in the elderly. However, few studies have investigated these associations in patients with chronic kidney disease (CKD), yielding inconsistent results.

Methods. This cross-sectional study analysed data from the National Health and Nutrition Examination Survey (NHANES 2003–2018). Frailty was evaluated by the 36-item frailty index. General obesity was defined as a body mass index (BMI) >30 kg/m^2; abdominal obesity was identified if waist circumference (WC) reached 102 cm in men and 88 cm in women. The associations of general and abdominal obesity with frailty were analysed using weighted multivariate logistic regression and restricted cubic splines. The interaction of general and abdominal obesity with frailty was examined.

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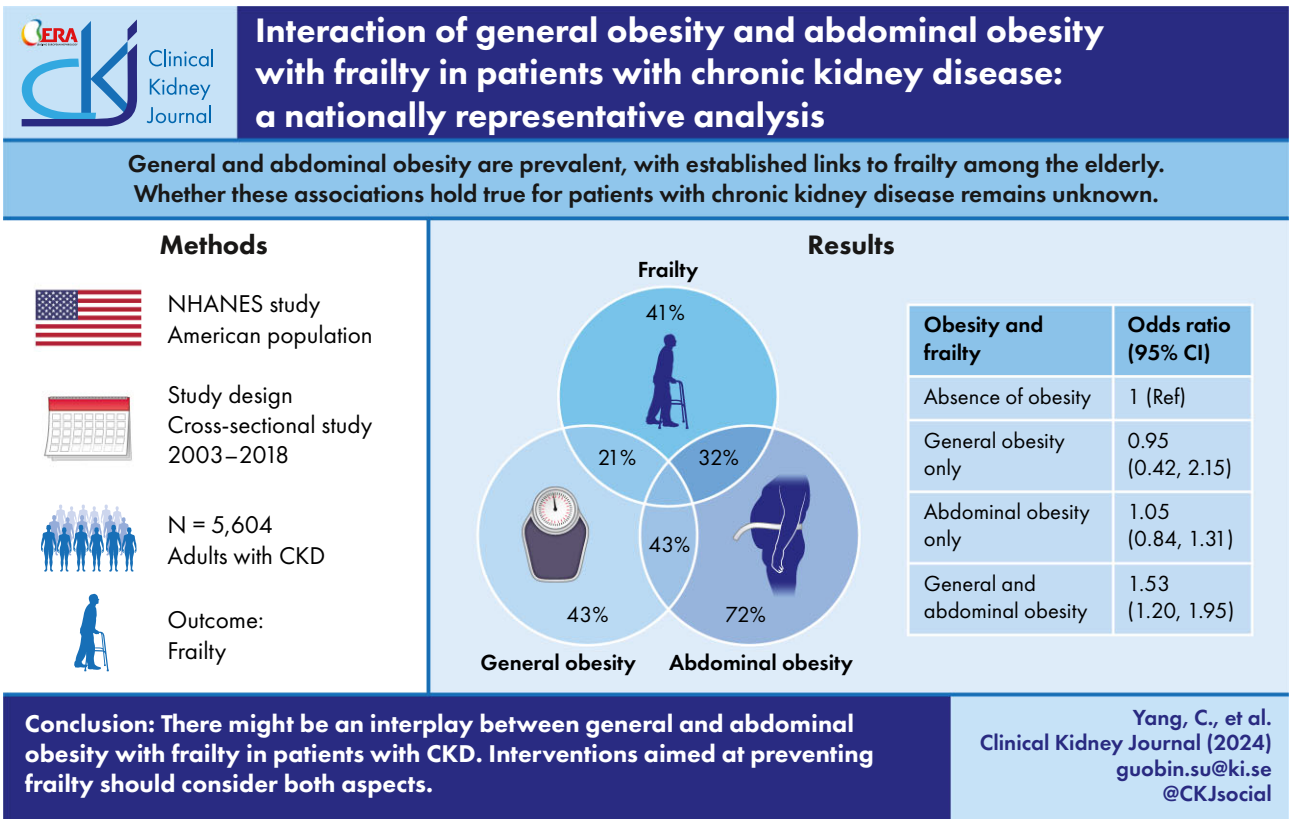
Results. A total of 5604 adult patients (median age 71 years, 42% men) with CKD were included in this analysis, with a median estimated glomerular filtration rate of 57.3 ml/min/1.73 m^2. A total of 21% were frail with general obesity and 32% were frail with abdominal obesity. Neither general nor abdominal obesity alone was associated with frailty. There was an interaction between general and abdominal obesity with frailty. Compared with individuals with normal BMI and WC, those with both general and abdominal obesity, rather than either alone, exhibited significantly increased odds of frailty {odds ratio [OR] 1.53 [95% confidence interval (CI) 1.20–1.95]}. General obesity was associated with being frail only when CKD patients had abdominal obesity [OR 1.59 (95% CI 1.08–2.36)].
Conclusions. There may be an interaction between general and abdominal obesity with frailty in patients with CKD. Interventions aimed at preventing frailty should consider both aspects.

GRAPHICAL ABSTRACT



Keywords: body mass index, chronic kidney disease, frailty, obesity, waist circumference

KEY LEARNING POINTS

What was known:

- Both general obesity, characterized by high body mass index (BMI), and abdominal obesity, characterized by increased waist circumference (WC), were associated with increased risk of frailty in the general elderly population.
- Few studies have explored the relationship between general and abdominal obesity with frailty in patients with chronic kidney disease (CKD), yielding inconsistent outcomes.

This study adds:

- Compared with individuals with normal BMI and WC, those with both general and abdominal obesity, rather than either alone, exhibited significantly increased odds of frailty in patients with CKD.
- There may be an interaction between general and abdominal obesity with frailty in patients with CKD.

Potential impact:

- The study emphasizes the need for a holistic approach in assessing frailty-related risks and tailoring interventions, highlighting the potential additional benefit of weight loss in patients with CKD, especially for those with both general and abdominal obesity.

INTRODUCTION

Chronic kidney disease (CKD) has become a major public health problem, affecting >9.1% of adults globally [1, 2]. Frailty is characterized by increased vulnerability to stressors due to a decline in physiological reserves and functioning across multiple organ systems [3]. It affects more than one-third of CKD patients [4, 5] and is associated with a spectrum of adverse outcomes, including all-cause mortality [6], cardiovascular events and mortality [7–9] and health-related quality of life [10] in patients with CKD. Obesity, a multifactorial disease in >1.9 billion adults worldwide [11], also poses significant health risks, including cardiovascular disease, type 2 diabetes and hypertension [12]. Among CKD patients, more than two-thirds are either overweight or obese [13]. Given the considerable overlapping prevalence and adverse outcomes of frailty and obesity among patients with CKD, exploring this relationship assumes critical importance.

Previous studies have indicated that both general obesity, characterized by high body mass index (BMI), and abdominal obesity, characterized by increased waist circumference (WC), are associated with an increased risk of frailty in the elderly population [14]. However, this association remains less clear in the context of CKD, with inconsistent results [5, 15]. Unlike the general population, CKD introduces a distinctive set of challenges in these associations, marked by altered metabolic states, dietary restrictions and nutritional imbalances [16, 17]. Considering that BMI fails to distinguish between lean muscle mass and fat mass, obesity defined solely by BMI may not fully capture the nuanced relationship between obesity and frailty [18]. Moreover, patients with end-stage kidney disease or undergoing dialysis who have excess adiposity but also experience sarcopenia, a phenomenon known as sarcopenic obesity, are very unlikely to be classified as obese by BMI alone [19]. This further underscores CKD patients as a unique population to explore the interaction of different types of obesity with frailty. Abdominal obesity, a reliable and prevalent marker of excess visceral fat [20], may elucidate a portion of the intricacy inherent in this relationship [21]. Nevertheless, it is unclear to what extent the interaction of general and abdominal obesity with frailty plays a role in this population.

Therefore, the aims of this study were to examine the associations of general and abdominal obesity with frailty and to evaluate the interactive effects of general and abdominal obesity on frailty risk in CKD patients using a nationally representative population from the USA. We hypothesized that there was an interaction between general and abdominal obesity with frailty in patients with CKD.

MATERIALS AND METHODS

Study design and population

This observational study analysed data from the National Health and Nutrition Examination Survey (NHANES; 2003–2018). NHANES is a complex, multistage and probabilistic sampling design survey conducted annually and released biannually by the National Center for Health Statistics (NCHS) [22]. More details about NHANES survey procedures are available at https://www.cdc.gov/nchs/index.htm. The NHANES protocol was approved by the NCHS ethics review board and written informed consent was obtained from all participants. The current study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline [23].

We included individuals >20 years of age and diagnosed as CKD [defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and/or a urinary albumin:creatinine ratio (UACR) >30 mg/g] [24, 25]. We excluded participants with an eGFR <15 ml/min/1.73 m^2, corresponding to stage 5 CKD, due to the small sample size and the inability to determine if these persons were on maintenance dialysis or not; incomplete data to evaluate frailty [with at least 80% of the data on each frailty index (FI)]; and BMI <18.5 kg/m^2, due to the very small sample size. eGFR was determined by the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26]. We used the NHANES recommended calibrations for serum creatinine correction across time periods if needed. We classified CKD stages using the cut-offs of eGFR recommended by the Kidney Disease: Improving Global Outcomes initiative (Supplementary Table S1) [27].

Data collection

Outcome of interest

Frailty was evaluated at baseline based on a widely adapted, validated 36-item FI from previous NHANES studies, including cognition, dependence, comorbidities, hospital utilization, general health and laboratory data (Supplementary Table S2) [28–30]. The FI score was calculated by the number of deficits present divided by the total deficits considered [31]. Intermediate values were chosen for variables with ordinal, intermediate responses (e.g. 'No difficulty with task', 0; 'Some difficulty', 0.33; 'Much difficulty', 0.67; 'Unable to do', 1). FI scores range from 0 to 1, where a score of 0 represents full health and a higher score indicates a higher level of frailty. Frailty status was defined as an FI value ≥0.25 [32].

General obesity and abdominal obesity

Weight, height and WC were measured by well-trained study personnel at baseline. BMI levels were calculated accordingly and categorized into six groups: 18.5–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight), ≥30.0 kg/m^2 (obesity), 30.0–34.9 kg/m^2 (obese grade 1), 35.0–39.9 kg/m^2 (obese grade 2) and ≥40.0 kg/m^2 (obese grade 3) [33]. General obesity was defined as BMI ≥30 kg/m^2. Abdominal obesity was classified as an absolute WC of ≥102 cm in men and ≥88 cm in women [34].

Covariates

Predefined potential covariates including demographic details (age, sex, race/ethnicity, education level, marital status, working status, alcohol intake and smoking status) and self-reported histories of comorbid conditions (hypertension, diabetes, coronary heart disease and cancer) were obtained via standardized questionnaires at baseline; laboratory tests (eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglycerides, serum iron, white blood cell counts and platelet counts) were also measured at baseline. Detailed information on the assessment of variables and their categories can be found in Supplementary Table S1.

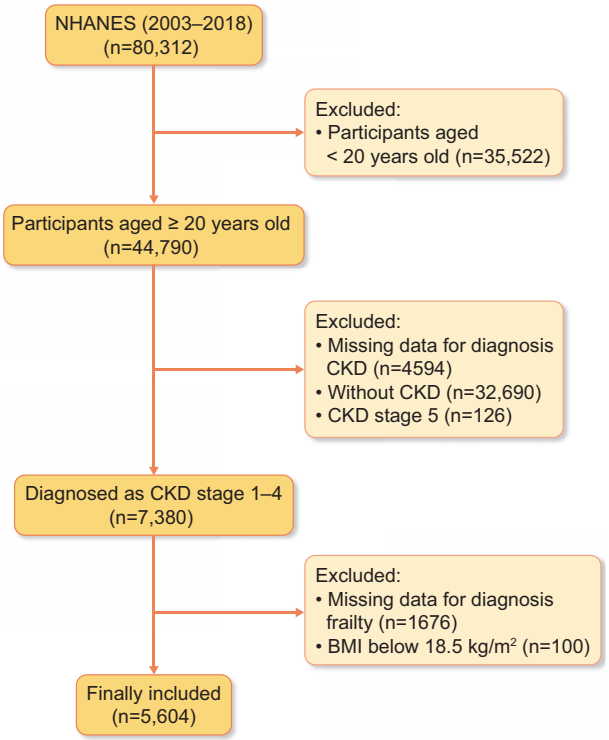
Statistical analysis

Participant characteristics stratified by frailty degree were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables or as number

and percentage for categorical variables. All values were weighted using the sampling weights provided by NHANES for the general US population–based estimates. To avoid potential bias, multiple imputations by chained equations were applied for missing data regarding covariates [35]. Twenty imputations per missing observation were performed.

The prevalence of frailty was defined as the number of CKD patients with frailty as the numerator and total study population as the denominator, multiplied by 100 to express it as a percentage. The associations of general obesity and abdominal obesity with frailty were analysed using weighted multivariate logistic regression and results are presented as the odds ratio (OR) and 95% confidence interval (CI). All models were adjusted for available potential covariates, which were identified based on prior research. Model 1 was adjusted for age, sex, race/ethnicity, education level, marital status, working status, alcohol intake and smoking status. Model 2 was further adjusted for eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglycerides, serum iron, white blood cell count and platelet count and the presence of hypertension, diabetes, coronary heart disease and cancer. Model 3 was further adjusted for BMI or WC.

For continuous measures (i.e. BMI and WC), their non-linear associations with frailty were tested using restricted cubic splines (RCS) with four knots set at the 5th, 35th, 65th and 95th percentiles to facilitate comparison against the models with linear terms. Stratified analyses of associations with frailty were also done within prespecified variables, including age (<65 versus ≥65 years), sex, CKD stage (1–2 versus 3–4), presence/absence of diabetes and general obesity or abdominal obesity. The interactive effects of BMI and WC on frailty were examined using an interaction term in weighted multivariate logistic regression analyses. We further explored the new cut-off values for BMI and WC in relation to frailty in patients with CKD if the RCS results indicated a linear relationship between frailty and BMI or WC. A two-sided *P*-value <.05 was considered statistically significant. All statistical analyses were conducted using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).



Abbreviations: BMI: body mass index, CKD: chronic kidney disease

Figure 1: Flow chart of participants selection.

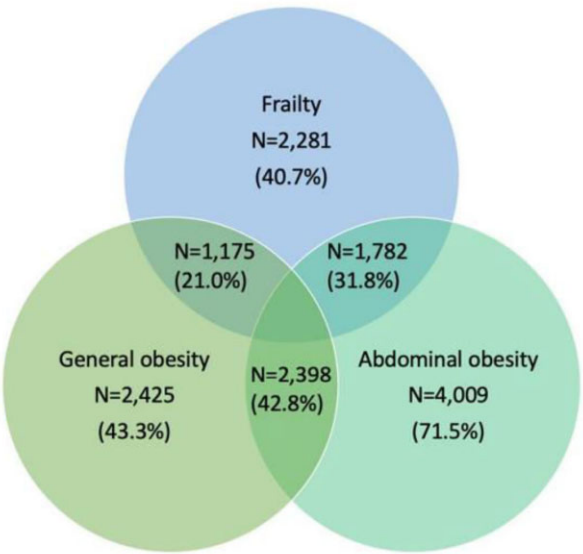


Figure 2: The distribution and overlap of frailty, general obesity and abdominal obesity in CKD patients.

RESULTS

In total, 80 312 participants were extracted from the NHANES database spanning the years 2003–2018. The present analysis ultimately narrowed down the sample to 5604 adult patients with stage 1–4 CKD (Fig. 1). The weighted sample corresponded to 20 811 646 individuals among the general US population, of whom 8 121 494 (40.7%) were deemed to be frail. The median age of participants was 71 years and 42% were men. Nearly three of four individuals were elderly (Supplementary Fig. S1). The median eGFR was 57.3 ml/min/1.73 m^2, with proportions of 15.3%, 23.8%, 56.1% and 4.7% for CKD stages 1–4, respectively. A total of 21% were frail with general obesity and 32% were frail with abdominal obesity (Fig. 2). Overall, the prevalence of frailty tended to increase with age, whereas the prevalence of general and abdominal obesity tended to decrease with age (Supplementary Fig. S2).

Compared with people without frailty, frail participants exhibited a greater likelihood of advanced age, female sex, lower education level, unemployment, smoking, higher BMI and WC and comorbid conditions (Table 1).

General obesity and frailty

Model 1 showed that BMI was associated with an increased risk of frailty (Table 2). This association remained significant in the further adjusted model 2 [OR 1.04 (95% CI 1.03–1.06), $P < .001$]. Upon regarding BMI as a categorical variable, a discernment emerged, wherein the presence of obesity, categorized as grade 2 and grade 3, was associated with a 1.6- and 2.4-fold higher risk of frailty, respectively, in model 2 compared with normal body weight (Table 2). Interestingly, all these associations ceased to maintain statistical significance after the inclusion of WC as an additional covariate adjustment in model 3. By employing RCS

Table 1: Baseline characteristics of weighted sample by frail and non-frail groups

Characteristics	Total (N = 5604)	Non-frail (n = 3323)	Frail (n = 2281)	P-value[a]
Age (years), median (IQR)	71 (62–80)	70 (62–78)	73 (64–80)	<.001
Male, n (%)	2747 (42)	1719 (44)	1028 (39)	.014
Race/ethnicity, n (%)				.5
Mexican American	646 (4.7)	397 (4.6)	249 (4.8)	
Non-Hispanic Black	1369 (13)	829 (12)	540 (14)	
Non-Hispanic White	2900 (74)	1681 (74)	1219 (73)	
Other Hispanic	340 (3.2)	202 (3.2)	138 (3.2)	
Other race	349 (5.4)	214 (5.5)	135 (5.3)	
Education level, n (%)				<.001
Less than high school	1972 (25)	1068 (21)	904 (31)	
High school grad/GED or equivalent	1372 (27)	823 (27)	549 (27)	
Some college or AA degree	1398 (28)	825 (28)	573 (28)	
College graduate or above	862 (19)	607 (24)	255 (13)	
Marital status, n (%)				<.001
Never married	383 (6.1)	239 (6.6)	144 (5.3)	
Married	2893 (56)	1826 (58)	1067 (51)	
Separated	2328 (38)	1258 (35)	1070 (44)	
Employed, n (%)	998 (21)	824 (28)	174 (11)	<.001
Alcohol drinker, n (%)	3222 (59)	2010 (63)	1212 (53)	<.001
Smoking status, n (%)				<.001
Never smoker	2579 (47)	1632 (50)	947 (42)	
Former smoker	2147 (38)	1169 (35)	978 (42)	
Current smoker	878 (15)	522 (15)	356 (16)	
BMI (kg/m^2), median (IQR)	28.9 (25.2–33.7)	28.1 (24.8–32.3)	30.3 (26.0–35.9)	<.001
WC (cm), median (IQR)	103.5 (93.5–114.5)	101.3 (92.1–111.3)	106.7 (96.0–119.6)	<.001
Hypertension, n (%)	3992 (70)	2023 (59)	1969 (87)	<.001
Diabetes mellitus, n (%)	1936 (31)	766 (19)	1170 (49)	<.001
Coronary heart disease, n (%)	773 (14)	218 (6.5)	555 (26)	<.001
Cancer, n (%)	1158 (23)	527 (18)	631 (30)	<.001
eGFR (ml/min/1.73 m^2), median (IQR)	57.3 (48.3–78.9)	58.3 (51.3–82.4)	55.0 (43.6–73.0)	<.001
UACR (mg/g), median (IQR)	35.7 (9.6–88.2)	33.6 (8.8–67.8)	42.3(11.6–127.0)	<.001

[a]Continuous variables were analysed using the Kruskal–Wallis test and categorical variables were analysed using the χ^2 test.

Table 2: Association of general and abdominal obesity with frailty in CKD patients

Variables	Participants, n	Cases, n	Model 1 OR (95% CI)	P-value	Model 2 OR (95% CI)	P-value	Model 3 OR (95% CI)	P-value
BMI (kg/m^2)	5604	2281	1.06 (1.05–1.08)	<.001	1.04 (1.03–1.06)	<.001	1.00 (0.97–1.04)	.8
Classification[a]								
Overweight	1827	654	1.07 (0.90–1.28)	.45	1.01 (0.81–1.26)	.91	0.79 (0.61–1.03)	.03
Obesity	2425	1175	2.05 (1.72–2.45)	<.001	1.49 (1.19–1.88)	<.001	0.77 (0.57–1.05)	.09
Obese grade 1	1346	580	1.56 (1.28–1.89)	<.001	1.26 (0.97–1.63)	.09	0.80 (0.57–1.12)	.19
Obese grade 2	611	319	2.47 (1.85–3.30)	<.001	1.64 (1.23–2.19)	<.001	0.85 (0.54–1.35)	.49
Obese grade 3	468	276	3.65 (2.64–5.06)	<.001	2.40 (1.66–3.45)	<.001	0.93 (0.48–1.80)	.83
WC (cm)[b]	5604	2281	1.16 (1.13–1.19)	<.001	1.10 (1.07–1.13)	<.001	1.09 (1.02–1.17)	.01
Abdominal obesity[c]	4009	1782	1.64 (1.38–1.95)	<.001	1.29 (1.05–1.59)	.02	0.92 (0.74–1.14)	.4

Model 1 adjusted for age, sex, race/ethnicity, education level, marital status, working status, alcohol intake and smoking status. Model 2 adjusted for model 1 plus eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglycerides, serum iron, white blood cell count and platelet count, hypertension, diabetes, coronary heart disease and cancer. Model 3 adjusted for Model 2 plus waist circumference or BMI.

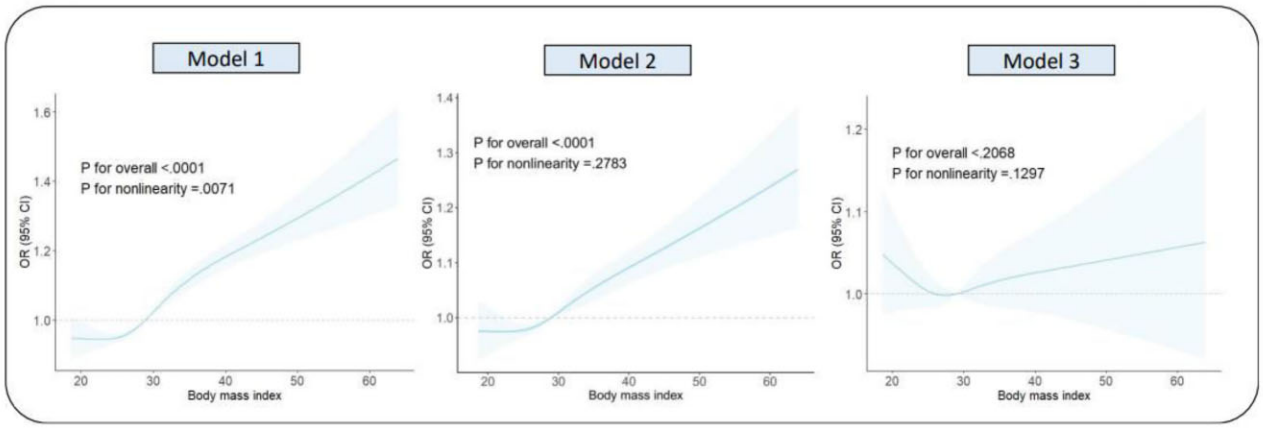
[a]Normal body weight (Reference). BMI levels were categorized as 18.5–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight), ≥30.0 kg/m^2 (obesity), 30.0–34.9 kg/m^2 (obese grade 1), 35.0–39.9 kg/m^2 (obese grade 2) and ≥40.0 kg/m^2 (obese grade 3).

[b]Every 5 cm increase in WC.

[c]No abdominal obesity (Reference). Abdominal obesity was classified as a WC ≥102 cm in men and ≥88 cm in women.

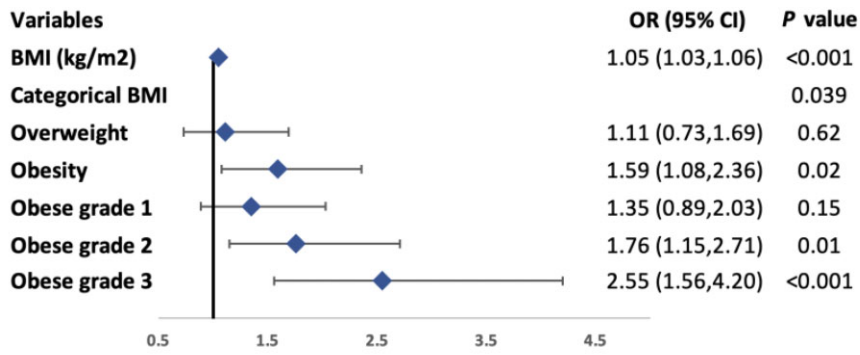
curves, a J-shaped relationship between BMI and frailty was observed (Fig. 3).

Further subgroup analysis based on the presence of abdominal obesity, as defined by WC, revealed that general obesity, general obesity grade 2 and general obesity grade 3 were independently associated with a 1.6-, 1.8- and 2.6-fold higher risk of being frail, respectively, in the abdominal obesity group (Fig. 4). In contrast, no significant relationships between general obesity and frailty were observed among those without abdominal obesity across all multivariate regression models. Additional stratified analyses by age, gender, CKD stage and diabetes similarly failed to reveal associations between general obesity and frailty, except for the relationship observed in the diabetes group (Supplementary Fig. S3).



Model 1 adjusted for age, sex, race/ethnicity, education level, marital status, working status, alcohol intake, and smoking status.
Model 2 adjusted for Model 1 plus eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglyceride, serum iron, white blood cell counts and platelet counts, hypertension, diabetes, coronary heart disease and cancer.
Model 3 adjusted for Model 2 plus waist circumference.
Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval.

Figure 3: RCS plot of the relationship between BMI and frailty in CKD patients.



Adjusted for Model 2: age, sex, race/ethnicity, education level, marital status, employment status, alcohol intake, smoking status, eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglyceride, serum iron, white blood cell counts, platelet counts, hypertension, diabetes, coronary heart disease, and cancer.
Reference: normal weight. BMI levels were categorized as: 18.5–24.9 kg/m² (normal weight), 25.0–29.9 kg/m² (overweight), ≥30.0 kg/m2 (obesity), 30.0–34.9 kg/m² (obese grade 1), 35.0-39.9 kg/m² (obese grade 2) and ≥40.0 kg/m² (obese grade 3).
Abbreviations: BMI: body mass index, OR: odds ratio; 95% CI: 95% confidence interval.
Abdominal obesity was classified as absolute waist circumference of 102 cm or above in men and 88 cm or above in women.

Figure 4: Forest plot of association of general obesity with frailty in 4009 patients with CKD and coexisting abdominal obesity.

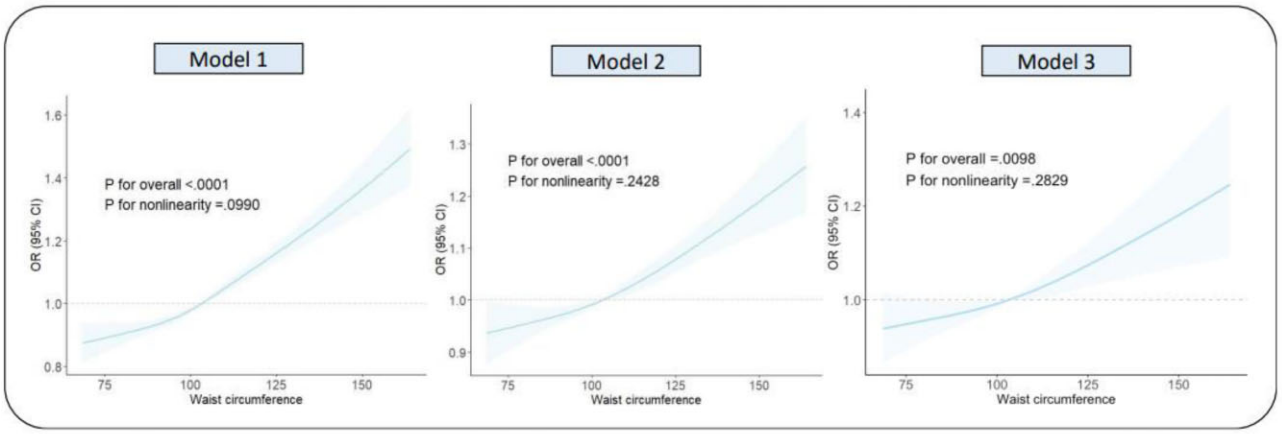
Abdominal obesity and frailty

Likewise, abdominal obesity, as defined by an increased WC cut-off in different genders from the general population, does not appear to be associated with frailty in the fully adjusted model (Table 2). Additional stratified analyses by age, gender, CKD stage and diabetes status also did not reveal associations between abdominal obesity and frailty (Supplementary Fig. S4).

Treating WC as a continuous variable, a considerable association of WC (for every 5-cm increase) with frailty was observed even after adjusting for BMI in fully adjusted model 3 [OR 1.09 (95% CI 1.02–1.17), $P = .01$] (Table 2). By employing RCS modelling, we observed an approximately linear relationship between WC and frailty (Fig. 5). Further subgroup analysis based on gender identified threshold values for WC to prevent frailty at 122 cm for males and 103 cm for females.

Interaction of obesity and abdominal obesity on frailty

Compared with persons with normal BMI and WC, those with both general and abdominal obesity demonstrated a significant association with increased odds of frailty [OR 1.53 (95% CI 1.20–1.95), $P < .001$]. However, patients with either obesity alone or abdominal obesity alone did not have a significant difference in frailty risk (Table 3). The interaction of BMI and abdominal obesity on the FI score is presented in Supplementary Fig. S5.



Model 1 adjusted for age, sex, race/ethnicity, education level, marital status, working status, alcohol intake, and smoking status.
Model 2 adjusted for Model 1 plus eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglyceride, serum iron, white blood cell counts and platelet counts, hypertension, diabetes, coronary heart disease and cancer.
Model 3 adjusted for Model 2 plus body mass index.
Abbreviations: OR: odds ratio; 95% CI: 95% confidence interval.

Figure 5: RCS plot of the association between WC and frailty in CKD patients.

Table 3: Interactive effects of general and abdominal obesity on frailty risk in CKD patients

	Abdominal obesity absent, OR (95% CI)	Abdominal obesity present[a], OR (95% CI)
General obesity absent	1 (Reference)($n = 1568$)	1.05 (0.84–1.31)($n = 1611$)
General obesity present[b]	0.95 (0.42–2.15)($n = 27$)	1.53 (1.20–1.95)($n = 2398$)

Adjusted for age, sex, race/ethnicity, education level, marital status, employment status, alcohol intake, smoking status, eGFR, UACR, total calcium, serum phosphorus, serum potassium, serum sodium, total cholesterol, triglycerides, serum iron, white blood cell count, platelet count, hypertension, diabetes, coronary heart disease and cancer.
[a]Abdominal obesity was classified as a WC of ≥102 cm in men and ≥88 cm in women.
[b]General obesity was defined as BMI >30 kg/m^2.

DISCUSSION

In this nationally representative analysis involving 5604 patients with CKD, we identified an interactive effect between general and abdominal obesity on frailty. Neither general obesity nor abdominal obesity in isolation demonstrated an association with frailty. These findings offer valuable insights into the complex relationship between obesity and frailty in patients with CKD. The considerable prevalence of frailty and its potential link to adverse outcomes underscore the significance of understanding the factors contributing to frailty within this specific population.

The observed association of general obesity, assessed by BMI, and abdominal obesity, as measured by WC, with frailty in patients with CKD does not align with the findings in a prior systematic review that focused on the elderly population, despite nearly three-fourths of the participants in the current study comprised older people [14]. This discrepancy may be attributed to several factors. Previous studies exploring the relationship between obesity and frailty predominantly focused on older people in the general population and seldom investigated patients with CKD. CKD introduces a range of disease-specific characteristics that distinguish this population from the general elderly. Second, CKD is characterized by altered metabolic states, involving disturbances in glucose and lipid metabolism, leading to insulin resistance [36–38]. Insulin resistance not only affects energy metabolism, but also may mediate the impact of obesity on frailty by influencing nutrient availability for muscle function [39, 40]. Moreover, hormonal dysregulation, including alterations in insulin-like growth factor-1 and adipokines, also underscores the intricate interplay between CKD-induced metabolic alterations, obesity and frailty [36]. Third, individuals with CKD commonly encounter dietary restrictions and nutritional imbalances, often related to managing electrolyte and fluid balance, which can affect nutritional status and muscle mass, thereby affecting the relationship between obesity and frailty [16, 17]. Finally, CKD is often accompanied by a higher burden of comorbid conditions, such as hypertension, diabetes and cardiovascular disease, which can also contribute to frailty and may interact with obesity in unique ways [41]. These findings lend support to the possibility that existing evidence from the general population cannot be extrapolated to patients with CKD. Furthermore, a recent systematic review that enrolled a total of 3294 patients with CKD identified an association between BMI and a reduced risk of frailty [5]. However, the multivariate models employed in the majority of studies included in this systematic review failed to concurrently account for both BMI and WC. This oversight tends to isolate the effects of each obesity metric without accounting for potential interactions.

The current study found that there was an interaction between general and abdominal obesity and frailty in patients with CKD, aligning with findings from a prior study that highlighted the association of the interplay between BMI and WC with prognosis in the same population [42]. Additionally, a previous multicentre longitudinal study that found frailty was associated with increased mortality risk specifically among CKD patients with general or abdominal obesity, rather than those without, also indirectly supports our research findings [43]. This association can be explained for the following reasons. On the one hand, the coexistence of general and abdominal obesity may have a synergistic impact on muscle function in CKD patients. General obesity, defined solely by BMI, may not comprehensively reflect the relationship between obesity and frailty, as BMI does not distinguish between lean muscle mass and fat mass [18]. General obesity, characterized by excessive overall body fat, and abdominal obesity, with a focus on visceral fat, could collectively contribute to greater strain on skeletal muscles [44]. Additionally, in CKD, where there is already a propensity for muscle wasting and weakness, the additive effects of obesity may further reduce muscle strength and functionality, which is generally considered as a core component of frailty [45]. On the other hand, obesity, particularly abdominal obesity, is linked to chronic inflammation, as adipose tissue in the abdominal region tends to release more inflammatory cytokines [46]. In CKD, inflammation is a significant contributor to disease progression and complications [1]. The conjunction of general and abdominal obesity may exacerbate inflammatory responses, creating a pro-inflammatory environment that further contributes to frailty. Prior research primarily investigated the relationship between either BMI or WC alone and frailty, with limited exploration of the interaction between the two, and mainly focused on elderly people. The current study addresses these gaps by explicitly examining the interaction between general and abdominal obesity and frailty in patients with CKD. This finding may contribute to the development of more personalized management approaches for CKD, particularly for individuals with general or abdominal obesity, and enhance our understanding of the mechanisms underlying the association between obesity and frailty.

Frailty has been confirmed to be associated with several adverse outcomes, including all-cause mortality, cardiovascular events and hospitalization in patients with CKD [6, 7]. Thus, studies aiming to investigate possible modifiable risk factors for frailty are of great significance in this population. However, although the National Institutes of Health employed threshold values of WC ($\geq$88 cm in female and $\geq$102 cm in male) for abdominal obesity in the general population, it is crucial to establish an appropriate WC range for people with lifestyle-related diseases, such as coronary heart disease and CKD [34]. This study observed an approximately linear relationship between WC and frailty, suggesting threshold values of WC to be associated with frailty in CKD patients are 103 cm for females and 122 cm for males. This implies that the WC range to be associated with frailty in this population may be considerably higher (by +17% for women and +20% for men) than that for the general population. This, in turn, may explain the difference in the relationship between abdominal obesity and frailty observed in this study compared with the general population. Furthermore, we also found a significant association between BMI and frailty in subgroup analyses based on the presence of abdominal obesity. This also implies that there may be an interaction between general and abdominal obesity and frailty in patients with CKD. Therefore, further studies aiming to explore the relationship between obesity and frailty in patients with CKD should account for the impact of both BMI and WC. If BMI is unavailable, new cut-offs of WC for abdominal obesity should be considered.

Our study has several strengths. To the best of our knowledge, this is the first study to explore the association between obesity and risk of frailty defined by a well-established scale in patients with non-dialysis CKD through a multidimensional assessment of WC and BMI using a large representative database of the US population, while adjusting for the main potential confounders. However, the following limitations should be considered when interpreting the results. First, the NHANES only provided a single measurement of serum creatinine and urine albuminuria, which may introduce bias in diagnosing CKD. Second, several variables, including medical history and healthcare access, relied on self-reported observations, introducing the possibility of recall and response biases. Third, while associations between obesity and frailty are likely bidirectional, with factors such as limited physical activity and a sedentary lifestyle contributing to general and abdominal obesity, we did not explore these relationships. Fourth, residual confounding is a concern. Some potential contributing factors of frailty, such as medications and sarcopenia, were not assessed by this study and could confound observed associations between obesity and frailty. Finally, this study focused on patients with early-stage CKD. Caution should be exercised when generalizing this result to those with end-stage kidney disease or undergoing dialysis, as well as in other contexts. Therefore, future studies should employ a prospective design to explore the relationship between general and abdominal obesity and frailty in patients undergoing dialysis.

CONCLUSION

This nationally representative study highlights the intricate interplay between general and abdominal obesity and frailty in patients with CKD. We uniquely explore the combined impact of these obesity types, emphasizing the advantages of this bimodal evaluation over unimodal approaches. Additionally, our findings indirectly underscore the potential benefits of weight loss in reducing frailty risk among CKD patients. This highlights the importance of a comprehensive approach to assessing frailty-related risks and tailoring interventions accordingly.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

C.Y. and G.S. contributed to the study conception. C.Y., X.Q., R.D., A.X., Q.C., Y.L., L.S., J.Q., J.Z. and Z.Y. contributed to data acquisition. C.Y. conducted the data analysis and was responsible for writing the first draft of the manuscript. G.S. reviewed the first draft of the manuscript. G.B., B.L., X.L., C.M. and F.L. critically reviewed the manuscript. All authors read and approved the final version of the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and agreed to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work are answered.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the National Health and Nutrition Examination Survey (https://www.cdc.gov/nchs/nhanes/index.htm).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Kalantar-Zadeh K, Jafar TH, Nitsch D *et al*. Chronic kidney disease. *Lancet* 2021;**398**:786–802. https://doi.org/10.1016/S0140-6736(21)00519-5
2. Matsushita K, Ballew SH, Wang AYM *et al*. Epidemiology and risk of cardiovascular disease in populations with chronic kidney disease. *Nat Rev Nephrol* 2022;**18**:696–707. https://doi.org/10.1038/s41581-022-00616-6
3. Evans NR, Todd OM, Minhas JS *et al*. Frailty and cerebrovascular disease: concepts and clinical implications for stroke medicine. *Int J Stroke* 2022;**17**:251–9. https://doi.org/10.1177/17474930211034331
4. Pérez-Sáez MJ, Arias-Cabrales CE, Dávalos-Yerovi V *et al*. Frailty among chronic kidney disease patients on the kidney transplant waiting list: the sex-frailty paradox. *Clin Kidney J* 2022;**15**:109–118. https://doi.org/10.1093/ckj/sfab133
5. Li BH, Sang N, Zhang MY *et al*. The prevalence and influencing factors of frailty in patients with chronic kidney disease: a systematic review and meta-analysis. *Int Urol Nephrol* 2024;**56**:767–79. https://doi.org/10.1007/s11255-023-03739-2
6. Mei F, Gao Q, Chen F *et al*. Frailty as a predictor of negative health outcomes in chronic kidney disease: a systematic review and meta-analysis. *J Am Med Dir Assoc* 2021;**22**:535–43. https://doi.org/10.1016/j.jamda.2020.09.033
7. Hannan M, Chen J, Hsu J *et al*. Frailty and cardiovascular outcomes in adults with CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2024;**83**:208–15. https://doi.org/10.1053/j.ajkd.2023.06.009
8. Wilkinson TJ, Miksza J, Zaccardi F *et al*. Associations between frailty trajectories and cardiovascular, renal, and mortality outcomes in chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2022;**13**:2426–35. https://doi.org/10.1002/jcsm.13047
9. Alfaadhel TA, Soroka SD, Kiberd BA *et al*. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol* 2015;**10**:832–40. https://doi.org/10.2215/CJN.07760814
10. Nixon AC, Bampouras TM, Pendleton N *et al*. Frailty is independently associated with worse health-related quality of life in chronic kidney disease: a secondary analysis of the Frailty Assessment in Chronic Kidney Disease study. *Clin Kidney J* 2020;**13**:85–94. https://doi.org/10.1093/ckj/sfz038
11. World Health Organization. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [accessed 5 October 2023].
12. Powell-Wiley TM, Poirier P, Burke LE *et al*. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2021;**143**:e984–1. https://doi.org/10.1161/CIR.0000000000000973
13. Flegal KM, Carroll MD, Ogden CL *et al*. Prevalence and trends in obesity among US adults (1999–2008). *JAMA* 2010;**303**:235–41. https://doi.org/10.1001/jama.2009.2014
14. Yuan L, Chang M, Wang J. Abdominal obesity, body mass index and the risk of frailty in community-dwelling older adults: a systematic review and meta-analysis. *Age Ageing* 2021;**50**:1118–28. https://doi.org/10.1093/ageing/afab039
15. Yang C, Xiao C, Zeng J *et al*. Prevalence and associated factors of frailty in patients with chronic kidney disease: a cross-sectional analysis of PEAKING study. *Int Urol Nephrol* 2023;**6**:751–8. https://doi.org/10.1007/s11255-023-03720-z
16. MacLaughlin HL, Friedman AN, Ikizler TA. Nutrition in kidney disease: core curriculum 2022. *Am J Kidney Dis* 2022;**79**:437–49. https://doi.org/10.1053/j.ajkd.2021.05.024
17. Fouque D, Pelletier S, Mafra D *et al*. Nutrition and chronic kidney disease. *Kidney Int* 2011;**80**:348–57. https://doi.org/10.1038/ki.2011.118
18. Gray DS, Fujioka K. Use of relative weight and Body Mass Index for the determination of adiposity. *J Clin Epidemiol* 1991;**44**:545–50. https://doi.org/10.1016/0895-4356(91)90218-X
19. Androga L, Sharma D, Amodu A *et al*. Sarcopenia, obesity, and mortality in US adults with and without chronic kidney disease. *Kidney Int Rep* 2017;**2**:201–11. https://doi.org/10.1016/j.ekir.2016.10.008
20. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;**444**:881–7. https://doi.org/10.1038/nature05488
21. Kim HY, Kim JK, Shin GG *et al*. Association between abdominal obesity and cardiovascular risk factors in adults with normal body mass index: based on the Sixth Korea National Health and Nutrition Examination Survey. *J Obes Metab Syndr* 2019;**28**:262–70. https://doi.org/10.7570/jomes.2019.28.4.262
22. Akinbami LJ, Chen TC, Davy O *et al*. National Health and Nutrition Examination Survey, 2017–March 2020 prepandemic file: sample design, estimation, and analytic guidelines. *Vital Health Stat 1* 2022;**190**:1–36.
23. von Elm, E, Altman DG, Egger M *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X

24. Zeng X, Zeng Q, Zhou L *et al*. Prevalence of chronic kidney disease among US adults with hypertension, 1999 to 2018. *Hypertension* 2023;**80**:2149–58. https://doi.org/10.1161/HYPERTENSIONAHA.123.21482
25. Murphy D, McCulloch CE, Lin F *et al*. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016;**165**:473–81. https://doi.org/10.7326/M16-0273
26. Inker LA, Eneanya ND, Coresh J *et al*. New creatinine- and cystatin C–based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. https://doi.org/10.1056/NEJMoa2102953
27. Inker LA, Astor BC, Fox CH *et al*. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014;**63**:713–35. https://doi.org/10.1053/j.ajkd.2014.01.416
28. Jayanama K, Theou O, Blodgett JM *et al*. Frailty, nutrition-related parameters, and mortality across the adult age spectrum. *BMC Med* 2018;**16**:188. https://doi.org/10.1186/s12916-018-1176-6
29. Jayanama K, Theou O, Godin J *et al*. Relationship of body mass index with frailty and all-cause mortality among middle-aged and older adults. *BMC Med* 2022;**20**:404. https://doi.org/10.1186/s12916-022-02596-7
30. Blodgett JM, Theou O, Howlett SE *et al*. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. *GeroScience* 2017;**39**:447–55. https://doi.org/10.1007/s11357-017-9993-7
31. Searle SD, Mitnitski A, Gahbauer EA *et al*. A standard procedure for creating a frailty index. *BMC Geriatr* 2008;**8**:24. https://doi.org/10.1186/1471-2318-8-24
32. Li C, Ma Y, Yang C *et al*. Association of cystatin C kidney function measures with long-term deficit-accumulation frailty trajectories and physical function decline. *JAMA Netw Open* 2022;**5**:e2234. https://doi.org/10.1001/jamanetworkopen.2022.34208
33. U.S. Department of Health and Human Services. Classification of overweight and obesity by BMI, waist circumference, and associated disease risks. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm [accessed 5 October 2023].
34. Ross R, Neeland IJ, Yamashita S *et al*. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol* 2020;**16**:177–89. https://doi.org/10.1038/s41574-019-0310-7
35. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. https://doi.org/10.1002/sim.4067
36. Zoccali C, Vanholder R, Massy ZA *et al*. The systemic nature of CKD. *Nat Rev Nephrol* 2017;**13**:344–58. https://doi.org/10.1038/nrneph.2017.52
37. Spoto B, Pisano A, Zoccali C. Insulin resistance in chronic kidney disease: a systematic review. *Am J Physiol Renal Physiol* 2016;**311**:F1087–108. https://doi.org/10.1152/ajprenal.00340.2016
38. Kobayashi S, Maesato K, Moriya H *et al*. Insulin resistance in patients with chronic kidney disease. *Am J Kidney Dis* 2005;**45**:275–80. https://doi.org/10.1053/j.ajkd.2004.09.034
39. Garibotto G, Sofia A, Russo R *et al*. Insulin sensitivity of muscle protein metabolism is altered in patients with chronic kidney disease and metabolic acidosis. *Kidney Int* 2015;**88**:1419–26. https://doi.org/10.1038/ki.2015.247
40. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. *Lancet Diabetes Endocrinol* 2018;**6**:743–52.
41. Tonelli M, Wiebe N, Guthrie B *et al*. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. *Kidney Int* 2015;**88**:859–66. https://doi.org/10.1038/ki.2015.228
42. Kramer H, Shoham D, McClure LA *et al*. Association of waist circumference and body mass index with all-cause mortality in CKD: the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis* 2011;**58**:177–85. https://doi.org/10.1053/j.ajkd.2011.02.390
43. 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**:346–54. https://doi.org/10.1093/ndt/gfy124
44. Kramer H, Tuttle KR, Leehey D *et al*. Obesity management in adults with CKD. *Am J Kidney Dis* 2009;**53**:151–665. https://doi.org/10.1053/j.ajkd.2008.10.003
45. Clegg A, Young J, Iliffe S *et al*. Frailty in elderly people. *Lancet* 2013;**381**:752–62. https://doi.org/10.1016/S0140-6736(12)62167-9
46. Zoccali C, Mallamaci F, Tripepi G. Adipose tissue as a source of inflammatory cytokines in health and disease: focus on end-stage renal disease. *Kidney Int* 2003;**63**(Suppl 84):S65–8. https://doi.org/10.1046/j.1523-1755.63.s84.50.x

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