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Original Article

ORIGINAL ARTICLE

Association between frailty and bone health in early-stage chronic kidney disease: a study from the population-based CARTaGENE cohort

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ABSTRACT

Background. Frailty is a clinical syndrome that is particularly prevalent in patients with chronic kidney disease (CKD). We aimed to assess the associations between renal function and the presence of frailty criteria and to assess the association between frailty and bone outcomes.

Methods. We have conducted a retrospective study from a population-based cohort, which represents 1% of people aged 40–69 years in a Canadian province, excluding individuals with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. Frailty was defined with Fried's criteria. Bone density was estimated with quantitative ultrasound at the calcaneus measuring speed of sound (SOS) and broadband ultrasound attenuation (BUA). Time to first fracture event was assessed and analyses were conducted using logistic regressions, multiple linear regressions and Cox models.

Results. Overall, 19 973 individuals were included: mean ± standard deviation age 54.2 ± 7.8 years, women 51.6%, 47.0% CKD stage G2, 3.9% CKD stage G3, 34.8% with at least one frailty criterion. We observed a U-shaped association between eGFR and the odds ratio (OR) of presenting at least one frailty criterion, with a minimum OR around 77 mL/min/1.73 m^2 [per a 10 mL/min/1.73 m^2 increase, respectively, for an eGFR <77 and >77, OR = 0.93, 95% confidence interval (CI) 0.86–1.01 and OR 1.09, 95% CI 1.06–1.13]. After a median follow-up of 5.8 years, there were 837 fracture events. Having at least one frailty criterion was negatively associated with SOS ($\beta = -3.97$, $P < .0001$) and BUA ($\beta = -1.82$, $P < .0001$). Having at least one frailty criterion was associated with a higher fracture risk (hazard ratio 1.23, 95% CI 1.07–1.42).

Conclusion. In conclusion, having at least one frailty criterion was associated with a higher risk of fracture and a lower bone mineral density.

Keywords: bone mineral density, chronic kidney disease, fracture, frailty

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KEY LEARNING POINTS

What was known:

- Frailty is a multisystemic syndrome related to aging which augments an individual's vulnerability to physical stressors and is prevalent in people with advanced chronic kidney disease (CKD).
- Frailty and advanced CKD are associated with alterations in bone microarchitecture and a higher fracture risk.
- The impact of frailty in people with a mildly decreased renal function (early-CKD) is unknown.

This study adds:

- Individuals with mild CKD have a higher risk of being frail or pre-frail.
- In both early-CKD and non-CKD patients, frailty is significantly associated with lower bone mineral density and a higher fracture risk.

Potential impact:

- In the context of a global population aging trend, it is crucial to identify the impact of age-related disease, such as frailty and CKD, on bone health, as it can help to significantly improve patients' quality of life.
- Demonstrating that CKD in its earliest stages, contrary to what has been traditionally thought, is associated with adverse health outcomes, such as fractures, can raise awareness to the necessity of its early management and prevention.

INTRODUCTION

Frailty is a heterogeneous clinical syndrome, mostly observed in the geriatric population. It is characterized by multisystemic pathological aging processes and a lower resilience toward various environmental stressors. Many pathological pathways are thought to lead to frailty, such as inefficient metabolic energy use and production [1–3], chronic inflammation, and impaired immunity [4]. One of the most widely used definition of frailty is the Fried phenotype, which has five criteria: recent weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity [5]. The presence of ≥3 criteria would define a frail individual, while the presence of 1 or 2 criteria is considered as a pre-frailty status and predisposes to the development of frailty later in life [6]. Frailty is associated with poor health outcomes including osteoporosis, fractures and all-cause mortality [7–10].

Chronic kidney disease (CKD) is highly prevalent in the older population worldwide, affecting as much as 13% of the population globally [11, 12]. CKD is classified according to estimated glomerular filtration rate (eGFR). An eGFR <90 mL/min/1.73 m^2 is considered as mildly decreased, an eGFR <60 mL/min/1.73 m^2 as moderately decreased and an eGFR <30 mL/min/1.73 m^2 as severely decreased [13]. CKD is associated with a high morbidity and mortality, notably with an increased fracture risk due to CKD-related mineral and bone disorders (CKD-MBD) [14]. CKD-MBD refer to all the disturbances, affecting bone and mineral metabolism, occurring during CKD from early stages to end stage renal disease such as decreased Klotho expression, high Fibroblast growth factor-23 levels, hyperparathyroidism, vitamin D deficiency or hyperphosphatemia. These anomalies lead to alterations of bone turnover and/or mineralization defects, which are responsible of a reduced bone mineral density (BMD), anomalies of bone microarchitecture, and *in fine*, a decreased bone strength [15].

It has been reported that patients with severe CKD have a particularly higher risk of developing frailty [16]. Moreover, frailty in dialysis patients is associated with high mortality, cognitive impairment and significantly worse quality of life [17]. However, it remains unclear whether early-stage CKD is also associated with higher prevalence of frailty and how frailty is associated with bone outcomes in this population.

The aim of this study was therefore to assess the association between renal function and the presence of frailty criteria and to assess the association between frailty and bone outcomes in a large population-based cohort including individuals with early CKD.

MATERIALS AND METHODS

Study design and population

This retrospective study was conducted using data from the CARTaGENE cohort. Extensive details about the cohort and its detailed recruitment methods have previously been published [18]. Briefly, participants aged 40–69 years old were randomly selected from the province of Quebec, Canada, to represent approximately 1% of all individuals from this age group. These participants had to be covered under the Quebec public health insurance plan [Régie de l'Assurance Maladie du Québec (RAMQ)]. This cohort was initially created to study the incidence of various chronic diseases in the general population. There were 19 990 participants in the whole cohort. An eGFR of <30 mL/min/1.73 m^2 at recruitment was the only exclusion criteria for this study, as these individuals were considered as having advanced CKD. Detailed health questionnaires on medical history and medication usage, multiple physical measurements and blood samples were obtained by the CARTaGENE nurses at recruitment. This study was authorized by the CHU de Québec-Université Laval research ethics committee (2018–3794) and all authors adhered to the Helsinki Declaration.

Definition of CKD

eGFR, derived from the CKD Epidemiology Collaboration (CKD-EPI) formula, was used to measure renal function. CKD stages were defined according to KDIGO 2024 guidelines [13]. Stage G1 corresponds to a normal filtration (≥90 mL/min/1.73 m^2), G2 corresponds to a mildly decreased filtration (60–89 mL/min/1.73 m^2) and G3 to a moderately decreased filtration (30–59 mL/min/1.73 m^2). Early CKD refers to stages G2 or G3.

Definition of frailty

Frailty was defined with the following criteria, according to Fried phenotype: (i) walking difficulties: the participants reported to have not walked more than 10 min in a row at least 1 day in the last 7 days [19, 20]; (ii) weight loss: the participant has a body mass index (BMI) of <21 kg/m^2 [19, 21]; (iii) tiredness: the participant reported having fatigue or low energy more than 7 days in the last 14 days [20]; (iv) low physical activity: the participant has a score of 1 on the International Physical Activity Questionnaire, which corresponds to a sedentary lifestyle; (v) weakness: the participant has a low grip strength, measured by dynamometer [20]. Grip strength was measured on both sides with a digital hydraulic hand dynamometer (Baseline®). An average of two measures was calculated.

Bone outcomes

We considered two types of bone outcomes: BMD and fractures. BMD was assessed using quantitative ultrasound of the right calcaneus (QUS) at recruitment using Lunar Achilles Express (Aymes Medical/GE LUNAR), measuring speed of sound (SOS) and broadband ultrasound attenuation (BUA) values, both of which are positively correlated with BMD [22, 23]. We considered first fracture event at all sites that occurred after recruitment until 31 December 2016, for analyses [24]. The events were identified through health administrative database using the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition codes (ICD-10), the billing database of *RAMQ*, the Ministry of Health and Social Services (MED-ECHO) and the Institut de la Statistique du Québec [25, 26].

Definition of covariates

We considered as potential confounding variables the following characteristics: hypothyroidism, diabetes, dyslipidemia and hypertension. We considered participants as having these conditions if it was self-reported, if they met diagnostic serum measurements thresholds or if they took medication that were associated with these conditions (Supplementary data, Table S1). Psychotropic medication included antidepressants, hypnotics, neuroleptics and benzodiazepines.

Statistical analysis

Continuous variables were described as mean and standard deviation or median interquartile range and categorical variables as numbers and percentages. To assess the association between eGFR as a continuous variable and frailty, we developed logistic regression models, accounting for possible confounding variables (Model 1: unadjusted; Model 2: adjusted for age; Model 3: Model 2 + gender, diabetes, smoking, hypertension, presence of active cancer, alcohol, dyslipidemia and hypothyroidism; Model 4: Model 3 + psychotropic medication, vitamin D use and furosemide). We considered the Fried's score as a binary variable, with patients having no Fried criteria being categorized as "non-frail" and patients with $\geq$1 criteria being "pre-frail or frail." In case of a non-linear association, we used cubic splines [27].

We then assessed the association between frailty status (pre-frail or frail vs non-frail) and BMD measured by QUS with multiple linear regressions. Finally, to evaluate the association between frailty as a binary variable (pre-frail or frail vs non-frail) and the risk of fracture at follow-up, we used Cox regression models adjusted for the same confounding variables. Sensitivity analyses were further conducted to evaluate the association between each frailty criteria and fracture risk and the association between frailty (frail vs pre-frail and non-frail) and fracture risk. Main analyses were also stratified according to CKD stages (G1, G2, G3) to assess whether CKD could be an effect modifier in these associations. Individuals who died before any fracture event were censored at the date of death. Analyses for evaluating the association between frailty and the stiffness index were also performed. All analyses were stratified for sex (Supplementary material) and were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). All tests were two-sided and *P*-values $<.05$ were considered statistically significant.

Table 1: Population characteristics.

$n = 19\,973$	Characteristics	Missing data
Demographics		
Age, years	54.2 ± 7.8	0
Sex (women)	10 298 (51.56)	0
Clinical parameters		
Hypertension	7373 (36.91)	0
Active smoking	2908 (14.56)	0
Diabetes	1990 (9.96)	0
BMI, kg/m^2	27.5 ± 5.3	1319
Alcohol consumption, servings per week	1 (0.25–4.50)	150
Menopause	1796 (8.99)	0
Hypothyroidism	2356 (11.85)	98
Dyslipidemia	16 790 (84.06)	0
eGFR, mL/min/1.73 m^2	87.87 ± 14.54	568
CKD stages		
1	9523 (49.07)	568
2	9117 (46.98)	
3	765 (3.94)	
Grip strength, kg	36.15 ± 11.88	2158
Bone parameters		
SOS, m/s	1580 (1556–1608)	1146
BUA, dB/mHz	119.42 ± 14.65	1147
Stiffness index	101.67 (90–114.67)	1142
Medication		
Native vitamin D	4024 (20.15)	0
Psychotropic medication	2859 (14.31)	0
Furosemide	131 (0.66)	0
Fried score		
0	12 997 (65.14)	22
1	5468 (27.41)	22
2	1327 (6.65)	22
3	151 (0.76)	22
4	8 (0.04)	22
5	0 (0.00)	22

Continuous data are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as count (percentage).

RESULTS

Population characteristics

There were 19 973 individuals included in this study (age 54.2 ± 7.8 years, 51.6% women, 36.9% hypertension, 8.0% diabetes); 47.0% were in CKD stage G2 and 3.9% were in CKD stage G3; 34.8% (6954 individuals) had at least one criterion of frailty (pre-frail + frail) and 0.8% (159) were considered frail ($\geq$3 criteria). Detailed population characteristics are presented in Table 1.

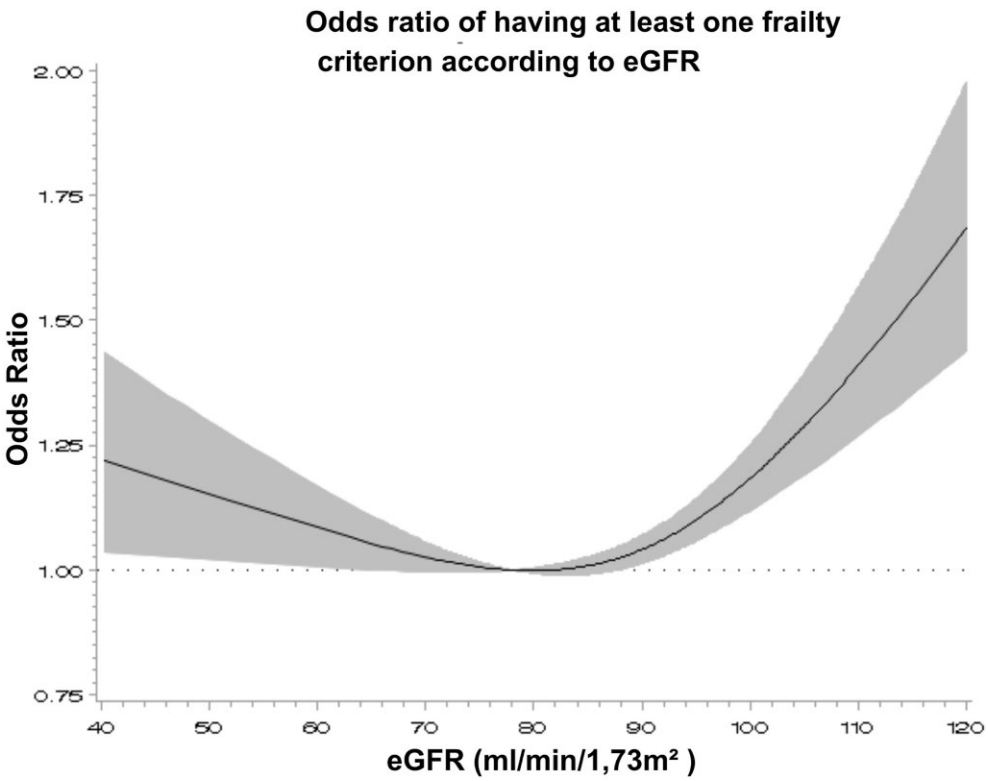

Figure 1: Restricted cubic splines model of the odds ratio of frailty criteria according to eGFR adjusted for possible confounding variable according to Model 3 (age, gender, diabetes, smoking, hypertension, presence of active cancer, alcohol, dyslipidemia and hypothyroidism). 95% CIs are represented in gray. $n = 19\,973$.

Association between eGFR and frailty

Our models suggested a non-linear association between eGFR and frailty. Indeed, we observed a U-shaped association between eGFR and the odds ratio (OR) of presenting frailty criteria (Fig. 1), with a minimum OR situated around 77 mL/min/1.73 m^2. Indeed, in individuals with an eGFR <77 mL/min/1.73 m^2, the association between eGFR and the odds of being pre-frail or frail (vs non frail) was not statistically significant [OR 0.93, 95% confidence interval (CI) 0.86–1.01 per 10 mL/min/1.73 m^2 increase]. In contrast, in individuals with an eGFR above 77 mL/min/1.73 m^2, eGFR was positively associated with the odds of being pre-frail or frail (OR 1.09, 95% CI 1.06–1.13 per 10 mL/min/1.73 m^2 increase, Table 2).

Association between frailty and QUS and impact of CKD

In adjusted multiple linear regression analyses, being frail or pre-frail (vs non frail) was inversely associated with SOS values ($\beta = -3.97$, $P < .0001$, $R^2 = 0.04$). In stratified analyses, the same association was observed in multivariable models for G1 and G2 groups, but not in the G3 group ($\beta = -4.13$, $P < .0001$, $R^2 = 0.05$ in G1 and $\beta = -3.4$, $P = .0011$, $R^2 = 0.04$ in G2, Table 3).

We obtained similar results when assessing the association between frailty and BUA. In adjusted multiple linear regression analyses, frailty or pre-frailty was inversely associated with BUA values ($\beta = -1.82$, $P < .0001$, $R^2 = 0.07$). In stratified analyses, the same association was observed in multivariable models for G1 and G2 groups, but not in the G3 group ($\beta = -2.27$, $P = .0001$, $R^2 = 0.07$ in G1 and $\beta = -1.24$, $P = .0002$, $R^2 = 0.08$ in G2, Table 4). Similar associations were found when assessing the association between frailty and the stiffness index. (Supplementary data, Table S2).

Table 2: eGFR is associated with Frailty status (pre-frail and frail vs non-frail).

	OR	95% CI
eGFR <77 mL/min/1.73 m^2, $n = 5004$		
Model 1[a]	**0.89**	**0.83–0.96**
Model 2[a]	**0.89**	**0.83–0.96**
Model 3[b]	0.93	0.86–1.01
Model 4[b]	0.94	0.86–1.02
eGFR >77 mL/min/1.73 m^2, $n = 14\,969$		
Model 1[c]	**1.11**	**1.08–1.15**
Model 2[c]	**1.13**	**1.09–1.17**
Model 3[d]	**1.09**	**1.06–1.13**
Model 4[d]	**1.10**	**1.06–1.14**

Results are presented for an eGFR increase of 10 mL/min/1.73 m^2.
Results with $P < .05$ are highlighted in bold.
Model 1: unadjusted; Model 2: adjusted for age; Model 3: Model 2 + gender, diabetes, smoking, hypertension, presence of active cancer, alcohol, dyslipidemia and hypothyroidism; Model 4: model 3 + psychotropic medication, vitamin D use, furosemide.
[a] $n = 4433$.
[b] $n = 4384$.
[c] $n = 14\,956$.
[d] $n = 14\,782$.

Association between frailty and fracture risk, and impact of CKD

After a median follow-up of 5.8 ± 0.8 years, there were 837 first fracture events and 261 deaths. The presence of at least one frailty criterion was associated with a higher risk of fractures at follow up [hazard ratio (HR) 1.23, 95% CI 1.07–1.42]. In stratified

Table 3: Having at least one frailty criterion is associated with speed of sound in G1 and G2 groups.

	R^2	β (95% CI)	P
All cohort, $n = 18\,818$			
Model 1	**0.0023**	**−4.36 (−5.65; −3.07)**	**<.0001**
Model 2[a]	**0.0281**	**−4.47 (−5.74; −3.19)**	**<.0001**
Model 3[b]	**0.0393**	**−3.97 (−5.26; −2.68)**	**<.0001**
G1, $n = 9009$			
Model 1	**0.0021**	**−4.04 (−5.80; −2.28)**	**<.0001**
Model 2[c]	**0.0346**	**−4.18 (−5.91; −2.44)**	**<.0001**
Model 3[d]	**0.0472**	**−4.13 (−5.88; −2.37)**	**<.0001**
G2, $n = 8596$			
Model 1	**0.0019**	**−4.39 (−6.43; −2.34)**	**<.0001**
Model 2[e]	**0.0259**	**−4.22 (−6.24; −2.20)**	**<.0001**
Model 3[f]	**0.0372**	**−3.4 (−5.44; −1.36)**	**.001**
G3, $n = 708$			
Model 1	**0.0074**	**−7.9 (−14.08; −1.72)**	**.01**
Model 2[g]	**0.0237**	**−7.3 (−13.44; −1.16)**	**.02**
Model 3[h]	0.0450	−5.33 (−11.57; 0.90)	.09

Results with $P < .05$ are highlighted in bold.
Model 1: unadjusted; Model 2: adjusted for age; Model 3: Model 2 + gender, diabetes, smoking, hypertension, presence of active cancer, alcohol, dyslipidemia and hypothyroidism.
[a]$n = 18\,818$.
[b]$n = 18\,587$.
[c]$n = 9009$.
[d]$n = 8900$.
[e]$n = 8596$.
[f]$n = 8512$.
[g]$n = 708$.
[h]$n = 700$.

Table 4: Having at least one frailty criterion is associated with lower broadband ultrasound attenuation in G1 and G2 groups.

	R^2	β (95% CI)	P
All cohort, $n = 18\,818$			
Model 1	**0.0067**	**−2.53 (−2.97; −2.09)**	**<.0001**
Model 2[a]	**0.272**	**−2.56 (−3.00; −2.13)**	**<.0001**
Model 3[b]	**0.07**	**−1.82 (−2.25; −1.39)**	**<.0001**
G1, $n = 9009$			
Model 1	**0.0085**	**−2.8 (−3.43; −2.18)**	**<.0001**
Model 2[c]	**0.0328**	**−2.85 (−3.47; −2.23)**	**<.0001**
Model 3[d]	**0.07**	**−2.27 (−2.89; −1.66)**	**<.0001**
G2, $n = 8596$			
Model 1	**0.0047**	**−2.16 (−2.82; −1.50)**	**<.0001**
Model 2[e]	**0.0324**	**−2.1 (−2.75; −1.45)**	**<.0001**
Model 3[f]	**0.08**	**−1.24 (−1.88; −0.60)**	**.0002**
G3, $n = 708$			
Model 1	0.0036	−1.95 (−4.35; 0.45)	.11
Model 2[g]	0.005	−1.84 (−4.24; 0.56)	.13
Model 3[h]	0.08	−0.67 (−3.04; 1.70)	.58

Results with $P < .05$ are highlighted in bold.
Model 1: unadjusted; Model 2: adjusted for age; Model 3: Model 2 + gender, diabetes, smoking, hypertension, presence of active cancer, alcohol, dyslipidemia and hypothyroidism.
[a]$n = 18\,818$.
[b]$n = 18\,587$.
[c]$n = 9009$.
[d]$n = 8900$.
[e]$n = 8596$.
[f]$n = 8512$.
[g]$n = 708$.
[h]$n = 700$.

Table 5: Having at least one frailty criterion is associated with an increased risk of fracture in G2 and G3.

	Hazard ratio	95% CI
All cohort, $n = 856$ events/19 951		
Model 1	**1.31**	**1.14–1.50**
Model 2[a]	**1.32**	**1.15–1.51**
Model 3[b]	**1.23**	**1.07–1.42**
Model 4[b]	**1.20**	**1.05–1.39**
G1, $n = 378$ events/9514		
Model 1	1.14	0.93–1.40
Model 2[c]	1.14	0.93–1.41
Model 3[d]	1.07	0.87–1.32
Model 4[d]	1.04	0.84–1.30
G2, $n = 400$ events/9111		
Model 1	**1.41**	**1.16–1.72**
Model 2[e]	**1.41**	**1.15–1.72**
Model 3[f]	**1.34**	**1.09–1.64**
Model 4[f]	**1.32**	**1.08–1.63**
G3, $n = 49$ events/764		
Model 1	**2.44**	**1.38–4.29**
Model 2[g]	**2.50**	**1.42–4.40**
Model 3[h]	**2.40**	**1.35–4.29**
Model 4[h]	**2.32**	**1.30–4.15**

Results with $P < .05$ are highlighted in bold.
Model 1: unadjusted; Model 2: adjusted for age; Model 3: Model 2 + gender, diabetes, smoking, hypertension, presence of active cancer, alcohol, dyslipidemia and hypothyroidism; Model 4: Model 3 + psychotropic medication, vitamin D use, furosemide.
[a]$n = 856$ events/19 951.
[b]$n = 837$ events/19 689.
[c]$n = 378$ events/9514.
[d]$n = 372$ events/9396.
[e]$n = 400$ events/9111.
[f]$n = 390$ events/9015.
[g]49 events/764.
[h]49 events/755.

analyses according to CKD stage, this association was mainly present in CKD stages G2 and G3 (HR 1.34, 95% CI 1.09–1.64 in G2 and HR 2.40, 95% CI 1.35–4.29 in G3 vs HR 1.07, 95% CI 0.87–1.32 in stage G1, Table 5). When stratified by sex, results remained significant in women and in G3 men (Supplementary material). The presence of frailty (≥3 Fried criteria present, $n = 159$) was not significantly associated with a higher risk of fracture during follow-up in our cohort. (Supplementary data, Table S3).

In sensitivity analyses, all Fried criteria, except reported walking difficulties, were individually associated with a higher fracture risk during follow-up in our cohort (Supplementary data, Table S4).

DISCUSSION

In a large population-based Canadian cohort including individuals with normal to moderately decreased renal function, we observed a U-shaped association between eGFR and the odds of having at least one frailty criterion. Furthermore, we observed that frailty or pre-frailty were associated with a lower BMD and a higher fracture risk mainly in individuals with CKD stages G2 and G3.

It is well recognized that patients undergoing dialysis [16] have a higher prevalence of frailty than the general population [28]. To our knowledge, the non-linear relationship between eGFR and frailty risk has rarely been reported in individuals with early CKD. A previous study showed that lower eGFR, measured

by cystatin C, was associated with a higher risk of frailty. It was also reported that an eGFR between 76 and 89 mL/min/1.73 m^2 was associated with a significantly lower risk of frailty compared with an eGFR ≥90 mL/min/1.73 m^2, similar to our findings [29]. One possible explanation for this U-shaped association might be that creatinine, as a product of creatine kinase and protein metabolism, is directly associated to muscle mass [30, 31]. Elderly individuals and frail individuals typically have lower muscle mass. Indeed, frailty criteria, such as low grip strength, low BMI or a sedentary lifestyle, are correlated with low muscle mass. In short, individuals with pre-frailty and frailty might have lower muscle mass, which leads to lower serum creatinine and a higher eGFR calculation with the CKD-EPI formula. This could lead and contribute to the finding of increased risk of frailty with higher eGFR in our study [32]. However, a higher eGFR could also result from renal hyperfiltration, which can be pathological. Indeed, it has been reported that a high eGFR is associated with metabolic syndrome, hypertension, adverse cardiovascular outcomes and increased all-cause mortality [33–36].

Regarding bone outcomes, it is now well described in the literature that frailty is associated with a higher risk of falls [37]. This contributes to the higher fracture risk observed in frail and pre-frail individuals. Furthermore, bone adapts to the mechanical demands to which it is exposed. Therefore, weight-bearing activities and activities that require sustained muscle contractions, such as cycling or resistance training, have been associated with higher bone mass [38]. In contrast, sarcopenia, low physical activity and a sedentary lifestyle are criteria of frailty and have all been associated with a higher prevalence of osteoporosis [39, 40]. Others have found a lower endurance of skeletal muscles in frail people compared with non-frail individuals. Indeed, it is hypothesized that skeletal muscle mitochondrial function becomes impaired with age, accelerates with frailty and is associated with low walking speed and muscle weakness [2, 3]. This dysfunction also leads to sarcopenia in pre-frail and frail individuals [41], which is strongly associated with fractures [42]. Malnutrition is also commonly observed in both frail patients and CKD patients [43, 44], and various nutritional deficiencies, such as vitamin D deficiencies [45], can lead to osteoporosis or other adverse bone outcomes [46]. This could partly explain our findings that pre-frail and frail individuals with CKD have a particularly high fracture risk.

In addition, as mentioned earlier, early CKD status promotes an inflammatory state and oxidative stress, which is also frequently observed in frail individuals, leading to increased osteoclastic activity, bone resorption and fractures rate [9, 10, 47]. We and others have previously shown that early stages of CKD are associated with bone architecture alterations [25, 48, 49]. The results of our study showed that pre-frailty or frailty was inversely associated with BMD, suggesting that frailty independently impacts bone microarchitecture. It is thus probable that CKD and frailty may have synergetic or additive effects on bone alterations. Still, the variation in QUS parameters associated with frailty is modest and may not necessarily be translated into clinical meanings.

Our results demonstrated no association between frailty and fracture risk when frailty was defined as the presence of ≥3 Fried criteria, as opposed to the presence of ≥1 Fried criterion. Nevertheless, we believe that these analyses lack statistical power due to the very limited number of individuals who meet this definition in our relatively young cohort.

Our study has several strengths. First, we used a large cohort (over 19 900) of participants that is highly representative of the middle-aged Quebec's population. We also used both quantitative and clinical indicators of bone health. We further performed restricted cubic splines to assess the non-linear relationships between variables of interest. We conducted multiple sensitivity analyses with various CKD status strata. To our knowledge, this is the largest study to assess the impact of frailty on bone health in early-CKD individuals.

Our study also has limitations. Indeed, there are potential self-report biases from our data, most notably in variables where participants were surveyed on highly subjective topics, such as tiredness or level of physical activity. Also, while it has been correlated with BMD [50], QUS is not widely used in clinical settings and DEXA (dual-energy X-ray absorptiometry) scan remains the gold standard for the diagnosis of osteoporosis. As mentioned earlier, our population is also relatively young (mean age 54.2 years) and frailty is a syndrome that is mostly found in the geriatric population. As a result, most of the participants are either pre-frail or not frail. Few have sufficient criteria to be considered as frail. Therefore, our results might only be applicable to community-dwelling pre-frail middle-aged individuals. In addition, GFR was estimated with serum creatinine, which, as discussed above, is dependent on external factors such as muscle mass. In some individuals, the estimation of GFR may be less accurate. Finally, we have not been able to discriminate between fractures following a high-force traumatic event and pathological fractures. Some events may not have been related to the frailty status of the individual.

CONCLUSION

In this large population-based cohort study, we have observed a U-shaped association between eGFR and the risk of frailty. We also observed that having at least one frailty criterion was associated with an increased risk of fractures, particularly in early-CKD individuals. A better understanding of the causes and consequences of frailty in early-CKD is crucial to prevent future complications in these vulnerable populations.

SUPPLEMENTARY DATA

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

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AUTHORS' CONTRIBUTIONS

A.D. and K.-A.K. carried out the analyses. A.D. wrote the manuscript with support from C.V., K.-A.K. and F.M.-W. F.M.-W. supervised the project and conceived the original idea.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

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