The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2024, **79**(8), glae134
https://doi.org/10.1093/gerona/glae134
Advance access publication 20 May 2024
Original Article

Apolipoprotein ε4 Is Associated With Increased Risk of Fall- and Fracture-Related Hospitalization: The Perth Longitudinal Study of Ageing Women

Jedd Pratt, PhD,[1] Jack Dalla Via, PhD,[2] Craig Sale, PhD,[1] Abadi K. Gebre, PhD,[2,3] Blossom C.M. Stephan, PhD,[4,5] Simon Laws, PhD,[6,7] Kun Zhu, PhD,[8,9] Wai H. Lim, PhD,[2,10] Richard L. Prince, PhD,[2,8] Joshua R. Lewis, PhD,[2,8] and Marc Sim, PhD[2,8,*]

[1]Department of Sport and Exercise Sciences, Manchester Metropolitan University Institute of Sport, Manchester, UK.
[2]Nutrition and Health Innovation Research Institute, School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia.
[3]School of Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Tigray, Ethiopia.
[4]Institute of Mental Health, The University of Nottingham Medical School, Nottingham, UK.
[5]Dementia Centre of Excellence, enAble Institute, Curtin University, Perth, Western Australia, Australia.
[6]Centre for Precision Health, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia.
[7]Collaborative Genomics and Translation Group, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia.
[8]Medical School, The University of Western Australia, Perth, Western Australia, Australia.
[9]Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia.
[10]Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia.

*Address correspondence to: Marc Sim, PhD. E-mail: marc.sim@ecu.edu.au
J.P. and J.D.V. contributed equally to this work and should be considered joint first authors.

Decision Editor: Gustavo Duque, MD, PhD, FRACP, FGSA (Biological Sciences Section)

Abstract

Apolipoprotein ε4 (*APOE ε4*) may be a genetic risk factor for reduced bone mineral density (BMD) and muscle function, which could have implications for fall and fracture risk. We examined the association between *APOE ε4* status and long-term fall- and fracture-related hospitalization risk in older women. A total of 1 276 community-dwelling women from the Perth Longitudinal Study of Aging Women (mean age ± *SD* = 75.2 ± 2.7 years) were included. At baseline, women underwent *APOE* genotyping and detailed phenotyping for covariates including prevalent falls and fractures, as well as health and lifestyle factors. The association between *APOE ε4* and fall-, any fracture-, and hip fracture-related hospitalizations, obtained over 14.5 years from linked health records, was examined using multivariable-adjusted Cox-proportional hazard models. Over 14.5 years, 507 (39.7%) women experienced a fall-related hospitalization and 360 (28.2%) women experienced a fracture-related hospitalization, including 143 (11.2%) attributed to a hip fracture. In multivariable-adjusted models, compared to noncarriers, *APOE ε4* carriers (*n* = 297, 23.3%) had greater risk for a fall- (hazard ratio [HR] 1.48, 95% CI: 1.22–1.81), fracture- (HR 1.28, 95% CI: 1.01–1.63), or hip fracture-related hospitalization (HR 1.83, 95% CI: 1.29–2.61). The estimates remained similar when specific fall and fracture risk factors (fear of falling, plasma 25-hydroxyvitamin D, grip strength, timed up-and-go, hip BMD, vitamin K status, prevalent diabetes, HbA1c, cholesterol, and abbreviated mental test score) were added to the multivariable model. In conclusion, *APOE ε4* is a potential risk factor for fall- and fracture-related hospitalization in community-dwelling older women. Screening for *APOE ε4* could provide clinicians an opportunity to direct higher-risk individuals to appropriate intervention strategies.

Keywords: Women's health, Community-dwelling, Injurious falls, Musculoskeletal

Age-related declines in musculoskeletal health, often considered major risk factors for falls and fractures, are a major public health concern for older populations. Specifically, falls are experienced in about 30% of adults older than 65 years (1). In this age group, falls are the leading cause of injury-related hospitalizations (eg, hip fracture), often resulting in decreased independence and quality of life (2). This is exacerbated by osteoporosis with approximately 1 in 2 women and 1 in 5 men aged >50 years expected to experience an osteoporosis-related fracture (3). Of these, hip fractures are the most clinically relevant as they are strongly linked with increased incidence of morbidity and mortality (4). The burden of falls and fractures is anticipated to increase considerably in coming decades in parallel with societal aging, underscoring the need to identify novel risk factors that may improve the efficacy of current screening practices.

Older women are at a higher risk of falling than men (5,6), likely due to both age-related declines in muscle strength and

Received: March 28 2024; Editorial Decision Date: May 9 2024.

physical function (7,8) and the dramatic deterioration of the structural integrity of bone following menopause (9). The simultaneous presence of impaired muscle and bone health leads older women to have a particular predisposition to sustaining fall-related fractures (5,6). Consequently, increasing attention has been given to the pursuit of biomarkers that may help identify those at high risk of falls and fractures, and ultimately enhance preventative and therapeutic strategies.

Genetic studies indicate that several aspects of bone health, such as bone turnover and bone mineral density (BMD) are highly heritable (10,11). Although recent data suggest that fall risk may also have a genetic component (12), the role of genetics in falls risk remains largely unclear. Therefore, examining the impact of genetic variation on fall and fracture outcomes is a logical avenue for biomarker research. Although a myriad of genes likely contributes to the overall heritability of these phenotypes, one that appears to be particularly promising is the apolipoprotein E (*APOE*) gene. *APOE* has 3 principal alleles, *ε2* (*APOE ε2*), *ε3* (*APOE ε3*), and *ε4* (*APOE ε4*), with the latter being most renowned for its robust association with the risk of dementia, including Alzheimer's disease (13,14). Notably, even preclinical Alzheimer's disease is linked with higher falls risk (15). Interestingly, *APOE ε4* may be a risk factor for poor bone health through its association with dysregulated lipid homeostasis (16), and potentially reduced vitamin K availability (17), an essential nutrient linked to falls and fracture (18,19). Evidence is conflicting, however, as *APOE ε4* has been associated with increased fracture risk and/or poorer BMD (20–22), whereas others have reported no association (23,24). Moreover, despite the role of *APOE ε4* in cognition (14), and the nexus between cognition and physical function (25), the relationship between *APOE ε4* carrier status and fall risk remains unknown. There are also data indicating the *APOE ε4* allele is associated with a more rapid decline in metrics of gait variability (26), which may have further consequences for fall risk.

Given approximately 1 in 4 older women carry the *APOE ε4* allele (27), establishing whether its presence is related to fall- and/or fracture-related hospitalization risk may help uncover a scalable screening strategy for identifying older adults at risk of poor musculoskeletal outcomes. Moreover, *APOE ε4* genotyping can be performed at any stage of adulthood, and could therefore prompt timely preventative strategies. Herein, we examined if the presence of the *APOE ε4* allele increased the long-term risk for fall- and fracture-related hospitalizations in a well-characterized cohort of community-dwelling older women.

Method

Study Population

The study population originated from the Perth Longitudinal Study of Ageing Women (PLSAW), which includes 1 500 community-dwelling women aged 70 years or older recruited using the electoral roll. PLSAW is composed of an initial 5-year, double-blind, randomized controlled trial investigating calcium supplementation for fracture prevention (28), followed by 10 additional years of clinic visits and observation. As PLSAW was completed before the clinical trials registry, it was registered retrospectively in the Australian New Zealand Clinical Trials Registry (ACTRN12615000750583). Of the initial 1 500 women, 224 were excluded because of vitamin D supplementation ($n = 40$), *APOE* genotyping not being available ($n = 159$), and missing covariate or outcome data ($n = 25$; Supplementary Figure 1). A total of 1 276 women were available for analysis. Ethics approval for the initial 5-year trial and the subsequent 10-year follow-up was granted by the Human Research Ethics Committee at the University of Western Australia and the Western Australian Department of Health (ethics number #2009/24). Written informed consent was obtained from all participants, including authorization for future access to Western Australian Department of Health Data.

Baseline Assessments

Height and weight were measured using a wall-mounted stadiometer and digital scales to determine body mass index (BMI, kg/m^2). Smoking history and physical activity were assessed via questionnaire, detailed in Supplementary Material. Previous falls were determined by asking participants if they had fallen in the 3 months prior to the baseline clinical visit. Prevalent fractures were determined at baseline by asking participants the age and location of fractures sustained after the age of 50 years. Only fractures due to minimal trauma, defined as falling from a height of 1 m or less, were considered, excluding fractures of the face, skull, fingers, or toes (28). Detailed methodology for how DXA-derived total hip BMD, abbreviated mental test score (AMTS) (29), diabetes prevalence, timed up-and-go (TUG) performance, grip strength, and fear of falling data were collected is included in Supplementary Material. Participants had blood samples collected at their baseline clinic visit after an overnight fast, which were subsequently stored at −80°C. Detailed description of the measurement methods and coefficient of variation for HbA1c, plasma 25-hydroxyvitamin D2 and D3 (expressed as total 25OHD), cholesterol, and osteocalcin are provided in Supplementary Material.

APOE Genotyping

Genotyping for *APOE* in this cohort has been described previously (22). Genomic DNA was extracted and purified from whole blood samples collected at baseline. A 227 bp region of the *APOE* gene, which spans polymorphic sites at codons 112 and 158 results in several cutting sites for the CFo1 restriction endonuclease (30), was amplified by polymerase chain reaction using oligonucleotide primers (31). Restriction digests were electrophoresed on 20% acrylamide gels, resulting in DNA fragments unique for each isotype and coded *APOE ε2*, *APOE ε3*, and *APOE ε4*, as previously described (31).

Fall- and Fracture-Related Hospitalization

Fall- and fracture-related hospitalization data were obtained from the Western Australia Hospital Morbidity Data Collection (HMDC) using the Western Australian Data Linkage System, providing a complete validated record of every participant's primary diagnosis at hospital discharge using coded data from all hospitals in Western Australia. The HMDC records of all participants were obtained from their baseline visit (1998) and over the next 14.5 years for fall- and fracture-related hospitalization, allowing for ascertainment independent of patient report with the associated problems such as loss to follow-up. Diagnosis codes were defined using the International Classification of Diseases, Injuries, and Causes of Death: Clinical Modification (ICD-9-CM) codes for 1998 to 1999 (32), mapped to the ICD-10 Australian Modification (ICD-10-AM) for 1999 to 2013 (33). Hip and

Table 1. Baseline Characteristics Stratified by *APOE ε4* Presence

Demographics	All Participants	No *APOE ε4*	*APOE ε4*
Number	1 276	979	297
Age, y	75.2 ± 2.7	75.2 ± 2.7	75.0 ± 2.7
Body mass index (BMI), kg/m^2	27.2 ± 4.7	27.2 ± 4.8	27.2 ± 4.4
Randomization			
Placebo, yes (%)	637 (49.9)	498 (50.9)	139 (46.8)
Calcium, yes (%)	639 (50.1)	481 (49.1)	158 (53.2)
Smoker ever, yes (%)	467 (36.6)	359 (36.7)	108 (36.4)
Physical activity, kJ/day	112 (34–202)	110 (29–199)	114 (37–221)
Prevalent fracture from age 50 y, yes (%)	344 (27.0)	272 (27.8)	72 (24.2)
Prevalent falls, yes (%)	152 (11.9)	114 (11.6)	38 (12.8)
Total hip BMD[*], g/cm^2	0.814 ± 0.125	0.817 ± 0.127	0.803 ± 0.117
Timed up-and-go performance[†], s	9.9 ± 3.0	9.9 ± 2.8	10.0 ± 3.6
Grip strength[‡], kg	20.6 ± 4.6	20.6 ± 4.6	20.3 ± 4.6
Fear of falling[§], yes (%)	343 (27.0)	271 (27.8)	72 (24.3)
Prevalent diabetes, yes (%)	78 (6.1)	61 (6.2)	17 (5.7)
HbA1c[‖], %	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.8
Plasma 25OHD[¶]			
<50 nmol/L, yes (%)	330 (28.1)	250 (27.8)	80 (29.0)
50–<75 nmol/L, yes (%)	433 (36.9)	328 (36.5)	105 (38.0)
≥75 nmol/L, yes (%)	412 (35.1)	321 (35.7)	91 (33.0)
Season vitamin D sample taken[¶]			
Winter/Spring, yes (%)	882 (75.1)	670 (74.5)	212 (76.8)
Summer/Autumn, yes (%)	293 (24.9)	229 (25.5)	64 (23.2)
Total cholesterol[#], mg/dL	226 ± 42	**224 ± 41**	**230 ± 46**
ucOC:tOC[‖]	0.49 ± 0.12	0.49 ± 0.12	0.49 ± 0.13
Impaired cognitive function (AMTS < 8), yes (%)[**]	27 (2.1)	**16 (1.6)**	**11 (3.7)**

Notes: AMTS = abbreviated mental test score; BMD = bone mineral density; HbA1c = glycated hemoglobin; 25OHD = plasma 25-hydroxyvitamin D; ucOC:tOC = ratio of undercarboxylated osteocalcin to total osteocalcin. Data expressed as mean ± *SD*, median (interquartile range), or number and (%). Bolded values represent significant differences (p value < .05) between *APOE ε4* categories using independent sample t test, Chi-square test, or Mann–Whitney U test where appropriate.
[*]n = 1 093.
[†]n = 1 274.
[‡]n = 1 265.
[§]n = 1 272.
[‖]n = 1 204.
[¶]n = 1 175.
[#]n = 1 136.
[**]n = 1 275.

fracture-related hospitalizations were identified using ICD-10 codes S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, M80, T02, T08, T10, T12, and T14.2, excluding fractures of the face (S02.2–S02.6), fingers (S62.5–S62.7), and toes (S92.4–S92.5), or those caused by motor vehicle injuries (External Cause of Injury codes V00-V99). Fall-related hospitalizations were identified using ICD-10 codes W01, W05, W06, WO7, W08, W10, W18, and W19.

Statistical Analysis

Kaplan–Meier survival analysis examined the univariate association of *APOE ε4* presence with fall and fracture hospitalizations. Cox-proportional hazards regression models were used to investigate the association between *APOE ε4* presence and fall and fracture outcomes. Two models were run: (1) minimally adjusted: age, treatment code (placebo/calcium) and BMI; and (2) multivariable-adjusted: minimally adjusted model plus smoking history, physical activity, prevalent fracture, and prevalent falls. No violations of the Cox proportional hazards assumptions were detected. All analyses were performed using IBM SPSS (V29, Armonk, NY).

Additional Analyses

We undertook additional analyses where total hip BMD, cognitive impairment (AMTS < 8), TUG, grip strength, fear of falling, prevalent diabetes, HbA1c, plasma 25OHD (and the season the sample was collected), total cholesterol (and the date of lipid testing), and ucOC:tOC (bone-related biomarker of vitamin K status) were individually included as additional covariates in the multivariable-adjusted models, due to their suggested link to fall and fracture outcomes (5,6,18,19,34–37).

Results

Participant baseline characteristics are in Table 1. A total of 297 (23.2%) participants carried the *APOE ε4* allele, and no statistically significant differences in baseline characteristics

were observed between carriers and noncarriers, apart from the number of women with potential cognitive impairment (11 [3.7%] vs 16 [1.6%], respectively) and total cholesterol levels.

APOE ε4 and Fall- and Fracture-Related Hospitalizations

Over 14.5 years, the mean ± *SD* patient follow-up period was 11.0 ± 4.0 years for a fall-related hospitalization (14 028 person years), 11.3 ± 4.0 years for any fracture-related hospitalization (14 470 person years), and 12.2 ± 3.4 years for a hip fracture-related hospitalization (15 604 person years). Across the follow-up, 507 (39.7%) women experienced a fall-related hospitalization, 360 (28.2%) women experienced a fracture-related hospitalization, and 143 (11.2%) women experienced a hip fracture-related hospitalization. Kaplan–Meier survival curves indicated that women carrying the *APOE ε4* allele had a higher falls risk and hip-fracture risk, compared to noncarriers (Figure 1). In multivariable-adjusted models, *APOE ε4* carriers had a 48% greater hazard for a fall-related hospitalization, 28% greater hazard for a fracture-related hospitalization, and 83% greater hazard for a hip fracture-related hospitalization, compared to women without *APOE ε4* (Table 2).

Additional Analyses

The associations between *APOE ε4* presence and falls or fracture outcomes were consistent when impaired cognitive function (AMTS < 8), TUG performance, grip strength, fear of falling, prevalent diabetes, HbA1c, vitamin D status (and season the sample was collected), total cholesterol (and the date of lipid testing), and ucOC:tOC as a biomarker of vitamin K status were each added to the multivariable-adjusted models (Table 3), with the exception that the risk of any fracture hospitalization was slightly attenuated and no longer significant when hip BMD, TUG performance, total cholesterol, or ucOC:tOC were included.

Discussion

This study demonstrates an increased long-term risk of fall- and fracture-related hospitalizations in community-dwelling older women carrying the *APOE ε4* allele. The novel finding is that the *APOE ε4* allele substantially increases the risk of falling. The relevance of *APOE ε4* to fall- and fracture-related hospitalizations may be driven by the robust links between *APOE ε4*, cognitive impairment (14) and cognitive decline with injurious falls (25).

Although there is a paucity of data relating to *APOE ε4* and falls, the *APOE ε4* allele is a reported risk factor for the development of gait impairment, a likely contributor (26). However, the association between *APOE ε4* and fall-related hospitalization risk in the present study withstood adjustment for baseline TUG performance, suggesting the underlying mechanism to be somewhat independent of physical function. Nevertheless, previous data suggest that general measures of gait, such as gait speed do not differ according to *APOE ε4* status, whereas more specific measures of gait, such as stride length and stride time variability, which may be particularly relevant to fall risk, do differ (26,38). Therefore, although TUG performance did not seem to affect the relationship between *APOE ε4* and fall-related hospitalization risk in the present study, future research incorporating sensitive measures of gait is needed to contextualize these findings.

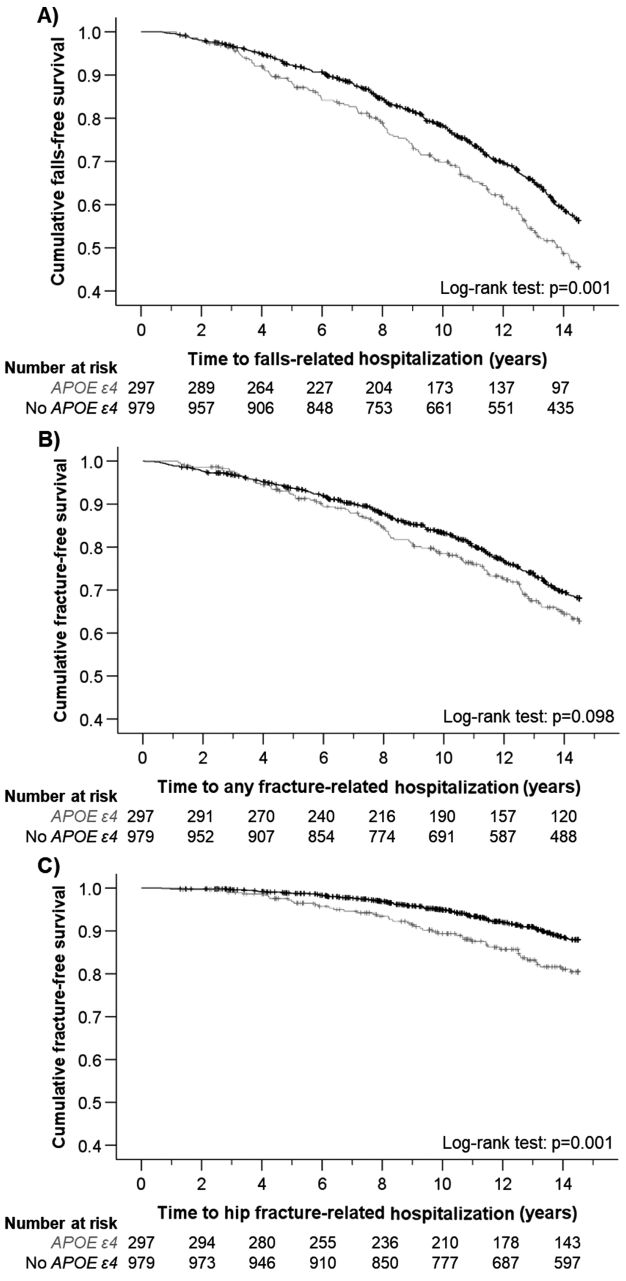

Figure 1. Kaplan–Meier survival curve according to *APOE ε4* status for (A) fall-related hospitalization, (B) any fracture-related hospitalization, and (C) hip fracture-related hospitalization. No *APOE ε4* and *APOE ε4* are represented by black and gray lines, respectively.

Interestingly, decline in cognitive function, rather than physical function, has been reported to have greater prognostic accuracy for injurious falls over long follow-ups (35). Possible mechanisms by which poorer cognition may increase falls risk include poor executive function reducing dual-tasking ability and response inhibition, and delayed reaction speed and poorer attention reducing the ability to react to balance perturbations (39,40). Although the proportion of women in the current study who presented with impaired cognitive function (29) at baseline was slightly higher in APOE ε4 carriers (n = 11, 3.7%) versus noncarriers (n = 16, 1.6%), the prevalence was low overall (n = 27, 2.1%). This is likely

Table 2. Hazard Ratios for Falls and Fracture Risk by *APOE ε4* Presence

	Number of Events (%)	Minimally Adjusted*	Multivariable Adjusted†
		HR (95% CI)	HR (95% CI)
Fall-related hospitalization			
No *APOE ε4*	372/979 (38.0)	**1 (reference)**	**1 (reference)**
APOE ε4	135/297 (45.5)	**1.45 (1.19–1.77)**	**1.48 (1.22–1.81)**
Any fracture-related hospitalization			
No *APOE ε4*	269/979 (27.5)	1 (reference)	**1 (reference)**
APOE ε4	91/297 (30.6)	1.26 (0.99–1.60)	**1.28 (1.01–1.63)**
Hip fracture-related hospitalization			
No *APOE ε4*	97/979 (9.9)	**1 (reference)**	**1 (reference)**
APOE ε4	46/297 (15.5)	**1.84 (1.29–2.61)**	**1.83 (1.29–2.61)**

Notes: n = 1 276. Bolded values represent significant differences. Hazard ratios (95% CI) analyzed using Cox-proportional hazard models. BMI = body mass index; HR = hazard ratio.
*Minimally adjusted = age, treatment code, and BMI.
†Multivariable adjusted = minimally adjusted model plus smoked ever, self-reported prevalent falls, prevalent fractures, and physical activity.

a reflection of women being recruited only if they had a projected survival beyond the 5-year clinical trial. Furthermore, adjustment for AMTS-defined impaired cognition function or the exclusion of these 27 women (data not shown) in our primary analysis did not change the interpretation of our results. In this regard, the low prevalence of impaired cognitive function in our cohort may have precluded an interaction being observed between cognition and fall-related hospitalization risk. Notably, the AMTS alone may not be the optimal tool to screen for cognitive impairment, as some data suggest it may be less sensitive to detect poor cognition, when compared to other screening tools such as the Montreal Cognitive Assessment (41). The AMTS is also a general measure of cognitive function but does not assess individual components of cognition, some of which may be particularly important in predicting falls risk. As such, although in this instance cognitive status did not appear to be a risk factor, future studies incorporating cohorts with diverse ranges in cognitive health and a more comprehensive battery of cognitive assessments to adequately and sensitively assess multiple domains of cognition are needed to contextualize our findings and further elucidate the potential role of cognition in the relationship between *APOE ε4* and falls.

In our study, we identified a robust relationship between *APOE ε4* status and hip fracture-related hospitalization, with carriers having an 89% greater risk compared to noncarriers. These associations remained unchanged after adjustment for other well-established fall and fracture risk factors, including hip BMD, circulating 25OHD levels, fear of falling, and muscle function measures. Our findings complement previous reports demonstrating *APOE ε4* to be a risk factor for fractures (20,21,42), and for the first time, the relevance of *APOE ε4* to injurious falls risk. Notably, 23.2% of women in our study carried the *APOE ε4* allele, which is similar to other general population estimates of ~25% (43). The high prevalence and concomitant risk of the *APOE ε4* allele support its potential use as a screening tool, with relevance beyond cognitive impairment for which it is most renowned for. Better understanding of the relationship between *APOE ε4*, fall- and fracture-risk may help guide a targeted delivery of strategies to improve musculoskeletal health and reduce the prevalence of injurious falls and fractures among older adults. In this regard, *APOE ε4* screening could help identify older adults at risk of falls and fractures who may benefit from inclusion into therapeutic programs, especially those involving lifestyle intervention (eg, exercise, diet). This approach in early stages of adulthood could assist in supporting musculoskeletal health and minimize declines over time.

The association between *APOE ε4* and bone health is particularly robust in women, with studies having shown associations of *APOE ε4* with BMD and/or fracture risk (20–22,44,45). While total hip BMD did not differ by *APOE ε4* status in the unadjusted analyses presented here, published data from the current cohort shows that women with *APOE ε4* had lower hip BMD and calcaneal ultrasound parameters when adjusted for age, BMI, alcohol consumption, and cigarette smoking, compared to women without *APOE ε4* (22). In that analysis from this cohort, no difference in risk of prevalent or incident clinical fracture was reported over 2 years between women with and without *APOE ε4* (22). This contrasting result may be explained by the longer follow-up in the current analysis, where separation in the Kaplan–Meier curves for falls and fractures was most apparent from approximately 5 years of follow-up. In contrast, the associations shown between *APOE ε4* and bone health in men have been weaker, or absent (24,45,46). Nevertheless, some cross-sectional studies have not shown associations between *APOE ε4* and bone outcomes in females, although small sample size (n = 147) (47) or low *APOE ε4* prevalence (7%) (48) may have influenced results. Notwithstanding such studies, research broadly favors a deleterious effect of *APOE ε4*, particularly in women. Our study adds substantive support, providing evidence over a long follow-up from a well-characterized cohort with verified outcome records and comprehensive adjustment for known risk factors. Future prospective studies are needed, however, to confirm the extent to which sex may mediate the relationship between *APOE ε4*, bone, and functional outcomes.

There are several putative pathways that may underpin the associations between *APOE ε4* status and fractures. First, *APOE ε4* has been linked with dysregulated lipid metabolism and transport, elevated cholesterol, and atherosclerosis risk (16,49), all of which can negatively affect bone health (34,50). Second, there is evidence, although conflicting, that

Table 3. Hazard Ratios for Falls and Fracture Risk by *APOE ε4* Presence

	Fall-Related Hospitalization		Any Fracture-Related Hospitalization		Hip Fracture-Related Hospitalization	
	Number of Events (%)	HR (95% CI)	Number of Events (%)	HR (95% CI)	Number of Events (%)	HR (95% CI)
Multivariable adjusted + total hip BMD[*]						
No *APOE ε4*	318/841 (37.8)	**1 (reference)**	233/841 (27.7)	1 (reference)	87/841 (10.3)	**1 (reference)**
APOE ε4	114/252 (45.2)	**1.44 (1.16–1.79)**	76/252 (30.2)	1.18 (0.91–1.53)	40/252 (15.9)	**1.79 (1.22–2.61)**
Multivariable adjusted + TUG[†]						
No *APOE ε4*	372/978 (38.0)	**1 (reference)**	269/978 (27.5)	1 (reference)	97/978 (9.9)	**1 (reference)**
APOE ε4	134/296 (45.3)	**1.46 (1.20–1.79)**	90/296 (30.4)	1.26 (0.99–1.60)	46/296 (15.5)	**1.85 (1.30–2.63)**
Multivariable adjusted + grip strength[‡]						
No *APOE ε4*	370/975 (37.9)	**1 (reference)**	267/975 (27.4)	**1 (reference)**	96/975 (9.8)	**1 (reference)**
APOE ε4	135/294 (45.9)	**1.46 (1.20–1.78)**	91/294 (31.0)	**1.28 (1.00–1.62)**	46/294 (15.6)	**1.83 (1.29–2.61)**
Multivariable adjusted + fear of falling[§]						
No *APOE ε4*	372/976 (38.1)	**1 (reference)**	269/976 (27.6)	**1 (reference)**	97/976 (9.9)	**1 (reference)**
APOE ε4	135/296 (45.6)	**1.53 (1.25–1.86)**	91/296 (30.7)	**1.30 (1.02–1.65)**	46/296 (15.5)	**1.86 (1.31–2.64)**
Multivariable adjusted + prevalent diabetes[‖]						
No *APOE ε4*	372/979 (38.0)	**1 (reference)**	269/979 (27.5)	**1 (reference)**	97/979 (9.9)	**1 (reference)**
APOE ε4	135/297 (45.5)	**1.50 (1.23–1.83)**	91/297 (30.6)	**1.30 (1.02–1.65)**	46/297 (15.5)	**1.89 (1.32–2.68)**
Multivariable adjusted + HbA1c[¶]						
No *APOE ε4*	343/916 (37.4)	**1 (reference)**	248/916 (27.1)	**1 (reference)**	91/916 (9.9)	**1 (reference)**
APOE ε4	130/288 (45.1)	**1.49 (1.22–1.83)**	89/288 (30.9)	**1.32 (1.03–1.68)**	44/288 (15.3)	**1.85 (1.29–2.66)**
Multivariable adjusted + 25OHD[#]						
No *APOE ε4*	344/899 (38.3)	**1 (reference)**	242/899 (26.9)	**1 (reference)**	88/899 (9.8)	**1 (reference)**
APOE ε4	127/276 (46.0)	**1.49 (1.21–1.82)**	85/276 (30.8)	**1.31 (1.02–1.68)**	43/276 (15.6)	**1.85 (1.28–2.67)**
Multivariable adjusted + total cholesterol[**]						
No *APOE ε4*	330/875 (37.7)	**1 (reference)**	237/875 (27.1)	1 (reference)	88/875 (10.1)	**1 (reference)**
APOE ε4	117/261 (44.8)	**1.50 (1.21–1.86)**	76/261 (29.1)	1.24 (0.95–1.61)	36/261 (13.8)	**1.62 (1.09–2.39)**
Multivariable adjusted + ucOC:tOC[††]						
No *APOE ε4*	353/923 (38.2)	**1 (reference)**	254/923 (27.5)	1 (reference)	95/923 (10.3)	**1 (reference)**
APOE ε4	126/281 (44.8)	**1.43 (1.16–1.75)**	83/281 (29.5)	1.23 (0.96–1.58)	39/281 (13.9)	**1.55 (1.07–2.26)**
Multivariable adjusted + impaired cognitive function[‡‡]						
No *APOE ε4*	372/979 (38.0)	**1 (reference)**	269/979 (27.5)	**1 (reference)**	97/979 (9.9)	**1 (reference)**
APOE ε4	135/296 (45.6)	**1.49 (1.22–1.82)**	91/296 (30.7)	**1.30 (1.02–1.65)**	46/296 (15.5)	**1.85 (1.30–2.63)**

Notes: BMD = bone mineral density; HbA1c = glycated hemoglobin; HR = hazard ratio; TUG = timed up-and-go; 25OHD = plasma 25-hydroxyVitamin D; ucOC:tOC = ratio of undercarboxylated osteocalcin to total osteocalcin. Multivariable adjusted = age, treatment code, BMI, smoked ever, self-reported prevalent falls, prevalent fractures, and physical activity. Bolded values represent significant differences. Hazard ratios (95% CI) analyzed using Cox-proportional hazard models.

[*] n = 1 093.
[†] n = 1 274.
[‡] n = 1 269.
[§] n = 1 272.
[‖] n = 1 276.
[¶] n = 1 204.
[#] Multivariable adjusted plus plasma 25OHD and season 25OHD sample taken (n = 1 175).
[**] Multivariable adjusted plus total cholesterol and date of lipid testing (n = 1 136).
[††] n = 1 204.
[‡‡] Multivariable adjusted plus impaired cognitive function defined as abbreviated mental test score (AMTS) < 8 (n = 1 275).

APOE may affect bone properties through its involvement in transporting vitamin K, an important nutrient involved in the carboxylation of osteocalcin and other bone-related proteins (51). In our study, total cholesterol was higher among women with *APOE ε4* compared to those without, although we showed no difference in the ucOC:tOC ratio, suggesting no difference in vitamin K status. Although the hazard ratios for any fracture were attenuated when either total cholesterol or ucOC:tOC were included in the multivariable models, the associations with hip fracture- and fall-related hospitalizations remained robust and consistent. Thus, the evidence of interactions between *APOE* genotypes, lipid metabolism, and/or vitamin K is conflicting (52,53). Future studies are needed to illuminate the pertinence of their relationship to bone health.

Study strengths include the prospective, population-based study design, the long-term follow-up (14.5 years), and verified fall- and fracture-related hospitalizations being obtained from linked health records, independent of self-report. Additionally, our analyses were adjusted for a panel of relevant covariates that have largely been unaccounted for in previous studies. There are also several limitations. This

was an observational study so causality cannot be established. Considering only older women were included in the study, results should not be generalized to other populations. Nonetheless, older women are arguably the most relevant target population for this work, having the highest predisposition to injurious falls and fractures (5,6), and the proportion of women carrying the *APOE ε4* allele in our study was comparable to other Australian estimates (27). We also cannot rule out the possibility of residual confounding on these results, hence further research is required to explore the potential mechanisms underpinning the relationship between *APOE ε4*, falls, and fractures. Finally, we only included falls and fractures that resulted in hospitalization. Such events have considerable healthcare burden, especially with an aging population, meaning that our data provides an opportunity to examine the most serious falls and fractures that are less frequently reported.

In conclusion, our findings suggest that *APOE ε4* status has value for identifying fall- and fracture-related hospitalization risk in older women. Moreover, considering *APOE ε4* carriers are also at risk of cognitive impairment, the implementation of primary prevention strategies, including exercise, may be particularly beneficial for this cohort. Although *APOE ε4* screening may help guide the deployment of interventions seeking to prevent falls and fractures, many of the corresponding risk factors, such as BMD and muscle strength, are heritable traits that are mediated by a network of genes. Accordingly, the proficiency of genotypic screening would likely be strengthened by including a panel of risk polymorphisms. Further research is therefore needed to (a) identify other prevalent polymorphisms that predispose individuals to falls and fractures and (b) determine the cumulative prognostic power of these polymorphisms, including *APOE ε4*, for fall and fracture risk.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This work was supported by project grants 254627, 303169, and 572604 from the National Health and Medical Research Council of Australia. M.S. is supported by a Royal Perth Hospital Research Foundation Fellowship (RPHRF CAF 00/21) and an Emerging Leader Fellowship from the Western Australian Future Health Research and Innovation Fund. J.R.L. is supported by a National Heart Foundation Future Leader Fellowship (ID: 102817). None of the funding agencies had any role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflict of Interest

None.

Acknowledgments

The authors wish to thank Dr. John Kemp for their insights and suggestions provided. All authors meet ICMJE guidelines for authorship. The authors would also like to thank the staff at the Western Australia Data Linkage Branch, Hospital Morbidity Data Collection, the Australian Coordinating Registry, the State Registries of Births, Deaths and Marriages, the Coroners, the National Coronial Information system, and the Victorian Department of Justice and Community Safety for providing the cause of death unit record file data.

References

1. Ganz DA, Latham NK. Prevention of falls in community-dwelling older adults. *N Engl J Med*. 2020;382:734–743. https://doi.org/10.1056/NEJMcp1903252
2. Montero-Odasso M, Van Der Velde N, Martin FC, et al.; Task Force on Global Guidelines for Falls in Older Adults. World guidelines for falls prevention and management for older adults: a global initiative. *Age Ageing*. 2022;51:afac205. https://doi.org/10.1093/ageing/afac205
3. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos*. 2013;8:136. https://doi.org/10.1007/s11657-013-0136-1
4. Dyer SM, Crotty M, Fairhall N, et al.; Fragility Fracture Network (FFN) Rehabilitation Research Special Interest Group. A critical review of the long-term disability outcomes following hip fracture. *BMC Geriatr*. 2016;16:158. https://doi.org/10.1186/s12877-016-0332-0
5. Stevens JA, Sogolow ED. Gender differences for non-fatal unintentional fall related injuries among older adults. *Inj Prev*. 2005;11:115–119. https://doi.org/10.1136/ip.2004.005835
6. Chang VC, Do MT. Risk factors for falls among seniors: implications of gender. *Am J Epidemiol*. 2015;181:521–531. https://doi.org/10.1093/aje/kwu268
7. Yeung SSY, Reijnierse EM, Pham VK, et al. Sarcopenia and its association with falls and fractures in older adults: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. 2019;10:485–500. https://doi.org/10.1002/jcsm.12411
8. Sim M, Prince R, Scott D, et al. Utility of four sarcopenia criteria for the prediction of falls-related hospitalization in older Australian women. *Osteoporos Int*. 2019;30:167–176. https://doi.org/10.1007/s00198-018-4755-7
9. Farlay D, Bala Y, Rizzo S, et al. Bone remodeling and bone matrix quality before and after menopause in healthy women. *Bone*. 2019;128:115030. https://doi.org/10.1016/j.bone.2019.08.003
10. Hunter D, De Lange M, Snieder H, et al. Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. *J Bone Miner Res*. 2001;16:371–378. https://doi.org/10.1359/jbmr.2001.16.2.371
11. Makovey J, Nguyen TV, Naganathan V, Wark JD, Sambrook PN. Genetic effects on bone loss in peri-and postmenopausal women: a Longitudinal Twin Study. *J Bone Miner Res*. 2007;22:1773–1780. https://doi.org/10.1359/jbmr.070708
12. Trajanoska K, Day F, Medina-Gomez C, Uitterlinden AG, Perry J, Rivadeneira F. Genetic basis of falling risk susceptibility. *Calcif Tissue Int*. 2018;102:S34. https://doi.org/10.1007/s00223-018-0418-0
13. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat Rev Neurol*. 2019;15:501–518. https://doi.org/10.1038/s41582-019-0228-7
14. Gharbi-Meliani A, Dugravot A, Sabia S, et al. The association of APOE ε4 with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. *Alzheimers Res Ther*. 2021;13:5. https://doi.org/10.1186/s13195-020-00740-0

15. Stark SL, Roe CM, Grant EA, et al. Preclinical Alzheimer disease and risk of falls. *Neurology*. 2013;81:437–443. https://doi.org/10.1212/WNL.0b013e31829d8599
16. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA*. 2007;298:1300–1311. https://doi.org/10.1001/jama.298.11.1300
17. Saupe J, Shearer MJ, Kohlmeier M. Phylloquinone transport and its influence on gamma-carboxyglutamate residues of osteocalcin in patients on maintenance hemodialysis. *Am J Clin Nutr*. 1993;58:204–208. https://doi.org/10.1093/ajcn/58.2.204
18. Sim M, Smith C, Bondonno NP, et al. Higher dietary vitamin K intake is associated with better physical function and lower long-term injurious falls risk in community-dwelling older women. *J Nutr Health Aging*. 2023;27:38–45. https://doi.org/10.1007/s12603-022-1866-9
19. Sim M, Strydom A, Blekkenhorst LC, et al. Dietary Vitamin K1 intake is associated with lower long-term fracture-related hospitalization risk: the Perth longitudinal study of ageing women. *Food Funct*. 2022;13:10642–10650. https://doi.org/10.1039/d2fo02494b
20. Cauley JA, Zmuda JM, Yaffe K, et al. Apolipoprotein E polymorphism: a new genetic marker of hip fracture risk—the Study of Osteoporotic Fractures. *J Bone Miner Res*. 1999;14:1175–1181. https://doi.org/10.1359/jbmr.1999.14.7.1175
21. Souza LS, Rochette NF, Pedrosa DF, et al. Role of APOE gene in bone mineral density and incidence of bone fractures in Brazilian postmenopausal women. *J Clin Densitom*. 2018;21:227–235. https://doi.org/10.1016/j.jocd.2017.03.005
22. Dick IM, Devine A, Marangou A, et al. Apolipoprotein E4 is associated with reduced calcaneal quantitative ultrasound measurements and bone mineral density in elderly women. *Bone*. 2002;31:497–502. https://doi.org/10.1016/s8756-3282(02)00851-7
23. Schoofs MW, van der Klift M, Hofman A, et al. ApoE gene polymorphisms, BMD, and fracture risk in elderly men and women: the Rotterdam study. *J Bone Miner Res*. 2004;19:1490–1496. https://doi.org/10.1359/JBMR.040605
24. von Mühlen DG, Barrett-Connor E, Schneider DL, Morin PA, Parry P. Osteoporosis and apolipoprotein E genotype in older adults: the Rancho Bernardo study. *Osteoporos Int*. 2001;12:332–335. https://doi.org/10.1007/s001980170124
25. Trevisan C, Ripamonti E, Grande G, et al. The association between injurious falls and older adults' cognitive function: the role of depressive mood and physical performance. *J Gerontol A Biol Sci Med Sci*. 2021;76:1699–1706. https://doi.org/10.1093/gerona/glab061
26. Sakurai R, Montero-Odasso M. Apolipoprotein E4 allele and gait performance in mild cognitive impairment: results from the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*. 2017;72:1676–1682. https://doi.org/10.1093/gerona/glx075
27. Fowler C, Rainey-Smith SR, Bird S, et al.; the AIBL investigators. Fifteen years of the Australian imaging, biomarkers and lifestyle (AIBL) Study: progress and observations from 2,359 older adults spanning the spectrum from cognitive normality to Alzheimer's disease. *J Alzheimers Dis Rep* 2021;5:443–468. https://doi.org/10.3233/ADR-210005
28. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med*. 2006;166:869–875. https://doi.org/10.1001/archinte.166.8.869
29. Jitapunkul S, Pillay I, Ebrahim S. The abbreviated mental test: its use and validity. *Age Ageing*. 1991;20:332–336. https://doi.org/10.1093/ageing/20.5.332
30. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet*. 1991;337:1158–1159. https://doi.org/10.1016/0140-6736(91)92823-k
31. Martins RN, Clarnette R, Fisher C, et al. ApoE genotypes in Australia: roles in early and late onset Alzheimer's disease and Down's syndrome. *Neuroreport*. 1995;6:1513–1516.
32. World Health Organization & International Conference for the Ninth Revision of the International Classification of Diseases. *Manual of the international statistical classification of diseases, injuries, and causes of death: based on the recommendations of the ninth revision conference, 1975, and adopted by the twenty-ninth World Health Assembly*. World Health Organization; 1975.
33. World Health Organization. *ICD-10: international statistical classification of diseases and related health problems*. World Health Organization; 2004.
34. Ghorabi S, Shab-Bidar S, Sadeghi O, Nasiri M, Khatibi SR, Djafarian K. Lipid profile and risk of bone fracture: a systematic review and meta-analysis of Observational Studies. *Endocr Res*. 2019;44:168–184. https://doi.org/10.1080/07435800.2019.1625057
35. Welmer AK, Rizzuto D, Laukka EJ, Johnell K, Fratiglioni L. Cognitive and physical function in relation to the risk of injurious falls in older adults: a Population-Based Study. *J Gerontol A Biol Sci Med Sci*. 2017;72:669–675. https://doi.org/10.1093/gerona/glw141
36. Vilaca T, Schini M, Harnan S, et al. The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: a systematic review and meta-analysis update. *Bone*. 2020;137:115457. https://doi.org/10.1016/j.bone.2020.115457
37. Yang Y, Hu X, Zhang Q, Zou R. Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis. *Age Ageing*. 2016;45:761–767. https://doi.org/10.1093/ageing/afw140
38. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil*. 2001;82:1050–1056. https://doi.org/10.1053/apmr.2001.24893
39. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci*. 2010;65:1086–1092. https://doi.org/10.1093/gerona/glq077
40. Mirelman A, Herman T, Brozgol M, et al. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS One*. 2012;7:e40297. https://doi.org/10.1371/journal.pone.0040297
41. Emery A, Wells J, Klaus SP, Mather M, Pessoa A, Pendlebury ST. Underestimation of cognitive impairment in older inpatients by the abbreviated mental test score versus the Montreal cognitive assessment: cross-sectional observational study. *Dement Geriatr Cogn Dis Extra*. 2020;10:205–215. https://doi.org/10.1159/000509357
42. Johnston JM, Cauley JA, Ganguli M. APOE 4 and hip fracture risk in a community-based study of older adults. *J Am Geriatr Soc*. 1999;47:1342–1345. https://doi.org/10.1111/j.1532-5415.1999.tb07436.x
43. Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a "thrifty" allele? *Ann Hum Genet*. 1999;63:301–310. https://doi.org/10.1046/j.1469-1809.1999.6340301.x
44. Salamone LM, Cauley JA, Zmuda J, et al. Apolipoprotein E gene polymorphism and bone loss: estrogen status modifies the influence of apolipoprotein E on bone loss. *J Bone Miner Res*. 2000;15:308–314. https://doi.org/10.1359/jbmr.2000.15.2.308
45. Peter I, Crosier MD, Yoshida M, et al. Associations of APOE gene polymorphisms with bone mineral density and fracture risk: a meta-analysis. *Osteoporos Int*. 2011;22:1199–1209. https://doi.org/10.1007/s00198-010-1311-5
46. Booth SL, Tucker KL, Chen H, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr*. 2000;71:1201–1208. https://doi.org/10.1093/ajcn/71.5.1201
47. Efstathiadou Z, Koukoulis G, Stakias N, Challa A, Tsatsoulis A. Apolipoprotein E polymorphism is not associated with spinal bone mineral density in peri- and postmenopausal Greek women. *Maturitas*. 2004;48:259–264. https://doi.org/10.1016/j.maturitas.2004.01.008
48. Wong SY, Lau EM, Li M, Chung T, Sham A, Woo J. The prevalence of Apo E4 genotype and its relationship to bone mineral density in Hong Kong Chinese. *J Bone Miner Metab*. 2005;23:261–265. https://doi.org/10.1007/s00774-004-0593-0

49. Garcia AR, Finch C, Gatz M, et al. APOE4 is associated with elevated blood lipids and lower levels of innate immune biomarkers in a tropical Amerindian subsistence population. *Elife*. 2021;10:e68231. https://doi.org/10.7554/eLife.68231
50. Barzilay JI, Buzkova P, Cauley JA, Robbins JA, Fink HA, Mukamal KJ. The associations of subclinical atherosclerotic cardiovascular disease with hip fracture risk and bone mineral density in elderly adults. *Osteoporos Int*. 2018;29:2219–2230. https://doi.org/10.1007/s00198-018-4611-9
51. Stafford DW. The vitamin K cycle. *J Thromb Haemost*. 2005;3:1873–1878. https://doi.org/10.1111/j.1538-7836.2005.01419.x
52. Pilkey RM, Morton AR, Boffa MB, et al. Subclinical vitamin K deficiency in hemodialysis patients. *Am J Kidney Dis*. 2007;49:432–439. https://doi.org/10.1053/j.ajkd.2006.11.041
53. Apalset EM, Gjesdal CG, Eide GE, Tell GS. Intake of vitamin K1 and K2 and risk of hip fractures: the Hordaland Health Study. *Bone*. 2011;49:990–995. https://doi.org/10.1016/j.bone.2011.07.035