Apolipoprotein ε4 is associated with increased risk of fall- and fracture-related hospitalisation: the Perth Longitudinal Study of Ageing Women

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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 hospitalisation risk in older women. 1276 community-dwelling women from the Perth Longitudinal Study of Ageing 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* with fall-, any fracture-, and hip fracture-related hospitalisations, obtained over 14.5 years from linked health records, were examined using multivariable-adjusted Cox-proportional hazard models. Over 14.5 years, 507 (39.7%) women experienced a fall-related hospitalisation, 360 (28.2%) women experienced a fracture-related hospitalisation, including 143 (11.2%) attributed to a hip fracture. In multivariable-adjusted models, compared to non-carriers, *APOE ε4* carriers (n=297, 23.3%) had greater risk for a fall- (HR 1.48 95%CI 1.22–1.81), fracture- (HR 1.28, 95%CI 1.01–1.63) or hip fracture-related hospitalisation (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, abbreviated mental test score) were added to the multivariable model. In conclusion, *APOE ε4* is a potential risk factor for fall- and fracture-related hospitalisation 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, Musculoskeletal, Community-dwelling, Injurious falls

INTRODUCTION

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 over 65 years (1). In this age group, falls are the leading cause of injury-related hospitalisations (e.g., 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 ageing, 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 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). While 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 three 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), while 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 one in four older women carry the *APOE ε4* allele *(27)*, establishing whether its presence is related to fall- and/or fracture-related hospitalisation 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 hospitalisations in a well-characterised cohort of community-dwelling older women.

METHODS

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 comprised of an initial five-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 authorisation 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 Text. Previous falls were determined by asking participants if they had fallen in the three 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 one metre 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 the Supplementary Text. 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 (CV) for HbA1c, plasma 25-hydroxyvitamin D2 and D3 (expressed as total 25OHD), cholesterol, and osteocalcin are provided in the Supplementary Text.

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 hospitalisation

Fall- and fracture-related hospitalisation 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 hospitalisation, 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 fracture-related hospitalisations 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 hospitalisations 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 hospitalisations. 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 non-carriers, 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 hospitalisations

Over 14.5 years, the mean ± SD patient follow-up period was 11.0 ± 4.0 years for a fall-related hospitalisation (14,028 person years), 11.3 ± 4.0 years for any fracture-related hospitalisation (14,470 person years), and 12.2 ± 3.4 years for a hip fracture-related hospitalisation (15,604 person years). Across the follow-up, 507 (39.7%) women experienced a fall-related hospitalisation, 360 (28.2%) women experienced a fracture-related hospitalisation, and 143 (11.2%) women experienced a hip fracture-related hospitalisation. Kaplan–Meier survival curves indicated that women carrying the *APOE ε4* allele had a higher falls risk and hip-fracture risk, compared to non-carriers (Figure 1). In multivariable-adjusted models, *APOE ε4* carriers had a 48% greater hazard for a fall-related hospitalisation, 28% greater hazard for a fracture-related hospitalisation, and 83% greater hazard for a hip fracture-related hospitalisation, 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 hospitalisation was slightly attenuated and no longer significant when hip BMD, TUG performance, total cholesterol, or ucOC:tOC was included.

DISCUSSION

This study demonstrates an increased long-term risk of fall- and fracture-related hospitalisations in community-dwelling older women carrying the *APOE ε4* allele. The novel finding is that *APOE ε4* allele substantially increases the risk of falling. The relevance of *APOE ε4* to fall- and fracture-related hospitalisations 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 hospitalisation 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, while 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 hospitalisation

risk in the present study, future research incorporating sensitive measures of gait is needed to contextualise these findings.

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%) vs non-carriers (n=16, 1.6%), the prevalence was low overall (n=27, 2.1%). This is likely 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, nor 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 hospitalisation 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 contextualise our findings and further elucidate the potential role of cognition in the relationship between *APOE ε4* and falls.

In our study, we identify a robust relationship between *APOE ε4* status and hip fracture-related hospitalisation, with carriers having an 89% greater risk compared to non-carriers. 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, supports its potential use as a screening tool, with relevance beyond cognitive impairment for which it is most renowned for. Better understanding 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 programmes, especially those involving lifestyle intervention (e.g., exercise, diet). This approach in early stages of adulthood could assist in supporting musculoskeletal health and minimise 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 two 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 five 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 favours a deleterious effect of *APOE ε4*, particularly in women. Our study adds substantive support, providing evidence over a long follow-up from a well-characterised 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 *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 was attenuated when either total cholesterol or ucOC:tOC were included in the multivariable models, the associations with hip fracture-and fall-related hospitalisations 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 hospitalisations 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 generalised 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 hospitalisation. Such events have considerable health care burden, especially with an ageing 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 hospitalisation 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.

Conflicts of interest: None

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Table 1. Baseline characteristics stratified by *APOE ε4* presence.

Demographics	**All participants**	**No *APOE ε4***	***APOE ε4***
Number	1276	979	297
Age, years	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
Randomisation			
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 years, 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 [a], g/cm^2	0.814 ± 0.125	0.817 ± 0.127	0.803 ± 0.117
Timed up-and-go performance [b], sec	9.9 ± 3.0	9.9 ± 2.8	10.0 ± 3.6
Grip strength [c], kg	20.6 ± 4.6	20.6 ± 4.6	20.3 ± 4.6
Fear of falling [d], yes (%)	343 (27.0)	271 (27.8)	72 (24.3)
Prevalent diabetes, yes (%)	78 (6.1)	61 (6.2)	17 (5.7)
HbA1c [e], %	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.8

Plasma 25OHD [f]			
<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 [f]			
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 [g], mg/dL	226 ± 42	**224 ± 41**	**230 ± 46**
ucOC:tOC [e]	0.49 ± 0.12	0.49 ± 0.12	0.49 ± 0.13
Impaired cognitive function (AMTS<8), yes (%) [h]	27 (2.1)	**16 (1.6)**	**11 (3.7)**

Data expressed as mean ± SD, median (interquartile range), or number and (%). Bolded values represent significant differences (p value < 0.05) between *APOE ε4* categories using independent sample t-test, Chi-square test, or Mann-Whitney U test where appropriate. AMTS = Abbreviated mental test score, BMD = bone mineral density, HbA1c = glycated haemoglobin, 25OHD = plasma 25-hydroxyvitamin D, ucOC:tOC = ratio of undercarboxylated osteocalcin to total osteocalcin. [a] n = 1093, [b] n = 1274, [c] n = 1265, [d] n = 1272, [e] n = 1204, [f] n = 1175, [g] n = 1136, [h] n = 1275.

Table 2. Hazard ratios (HR) for falls and fracture risk by *APOE ε4* presence.

	Number of events (%)	Minimally adjusted [a] HR (95%CI)	Multivariable adjusted [b] HR (95%CI)
Fall-related hospitalisation			
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 hospitalisation			
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 hospitalisation			
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)**

n = 1276. Bolded values represent significant differences. Hazard ratios (95% CI) analysed using Cox-proportional hazard models. HR = hazard ratio. [a] Minimally adjusted = age, treatment code and BMI. [b] Multivariable adjusted = minimally adjusted model plus smoked ever, self-reported prevalent falls, prevalent fractures, and physical activity.

Table 3. Hazard ratios for falls and fracture risk by *APOE ε4* presence.

	Fall-related hospitalisation		Any fracture-related hospitalisation		Hip fracture-related hospitalisation	
	Number of events (%)	**HR (95%CI)**	**Number of events (%)**	**HR (95%CI)**	**Number of events (%)**	**HR (95%CI)**
Multivariable adjusted + total hip BMD [a]						
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 [b]						
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 [c]						
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 [d]						
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 [e]						
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 [f]						
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 [g]						
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 [h]						
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 [i]						
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 [j]						
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)**

Bolded values represent significant differences. Hazard ratios (95% CI) analysed using Cox-proportional hazard models. HR = hazard ratio, BMD = bone mineral density, TUG = timed up-and-go, HbA1c = glycated haemoglobin, 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. [a] n = 1093, [b] n = 1274, [c] n = 1269, [d] n = 1272, [e] n = 1276, [f] n = 1204. [g] Multivariable adjusted plus plasma 25OHD and season 25OHD sample taken (n = 1175), [h]

Multivariable adjusted plus total cholesterol and date of lipid testing (n = 1136), [i] n = 1204, [j] Multivariable adjusted plus impaired cognitive function defined as abbreviated mental test score (AMTS) <8 (n = 1275).

Figure caption:

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

Figure 1