Effect of Anticholinergic Medications on Falls, Fracture Risk, and Bone Mineral Density Over a 10-Year Period

Lisa-Ann Fraser, MD, MSc¹, Jonathan D. Adachi, MD², William D. Leslie, MD, MSc³, David Goltzman, MD⁴, Robert Josse, MD⁵, Jerilynn Prior, MD⁶, Stephanie Kaiser, MD⁷, Nancy Kreiger, MPH, PhD⁵, Christopher S. Kovacs, MD⁸, Tassos P. Anastassiades, MD, PhD⁹, and Alexandra Papaioannou, MD, MSc² for the CaMos Research Group

¹Western University, London, ON, Canada

²McMaster University, Hamilton, ON, Canada

³University of Manitoba, Winnipeg, MB, Canada

⁴McGill University, Montréal, QC, Canada

⁵University of Toronto, ON, Canada

⁶University of British Columbia, Vancouver, BC, Canada

⁷Dalhousie University, Halifax, NS, Canada

⁸Memorial University of Newfoundland, St John's, NL, Canada

⁹Queen's University, Kingston, ON, Canada

Abstract

Background—Many medications used in older adults have strong anticholinergic (ACH) properties, which may increase the risk of falls and fractures. Use of these medications was identified in a population-based Canadian cohort.

Objective—To identify the fall and fracture risk associated with ACH medication use.

Methods—Data collection and analysis were conducted at baseline, year 5, and year 10. Cross-sectional analyses were performed to examine associations between ACH medication use and falls. Time-dependent Cox regression was used to examine time to first nontraumatic fracture.

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Corresponding Author: Lisa-Ann Fraser, Division of Endocrinology and Metabolism, St Joseph's Health Care, 268 Grosvenor Street, London, ON N6A 4V2, Canada. LisaAnn.Fraser@sjhc.london.on.ca.

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Finally, change in bone mineral density (BMD) over 10 years was compared in ACH medication users versus nonusers.

Results—Strongly ACH medications were used by 618 of 7753 participants (8.0%) at study baseline, 592 (9.5%) at year 5, and 334 (7.7%) at year 10. Unadjusted ACH medication use was associated with falls at baseline (odds ratio = 1.50; 95% CI = 1.14–1.98; $P = 0.004$), but the association was no longer significant after covariate adjustment. Similar results occurred at years 5 and 10. ACH medication use was associated with increased incident fracture risk before (hazard ratio = 1.22; CI = 1.13–1.32; $P < 0.001$) but not after covariate adjustment. Mean (SD) change in femoral neck BMD T -score over 10 years, in those using ACH medications at both years 0 and 5, was -0.60 (0.63) in ACH users versus -0.49 (0.45) in nonusers ($P = 0.041$), but this was not significant after covariate adjustment.

Conclusions—ACH medications were not found to be independently associated with an increased risk of falling, fractures, or BMD loss. Rather, factors associated with ACH medication use explained the apparent associations.

Keywords

anticholinergic medications; fracture; bone mineral density; falls

Introduction

Many medications used to treat a wide variety of illnesses have strong anticholinergic (ACH) properties. ACH medications have proven efficacy in multiple conditions, such as Parkinson's disease (PD) and overactive bladder, which affect older individuals.^{1,2} There has been increasing concern regarding the use of ACH medications for elderly patients/populations because several studies have linked use to an increased risk of falling.^{3–6} Because ACH medications are used to treat many different conditions, elderly patients, who are already at risk for polypharmacy, may be on multiple ACH medications, thereby increasing the cumulative ACH effect.^{3,7}

ACH medications have also been associated with an increase in fracture risk, although results from different studies have not been consistent.^{8–10} Whether the increased fracture incidence associated with ACH medications is attributable to an increased risk of falling, or other factors, has not yet been determined. A recent study showing excess mortality in men who remained on their ACH medication after suffering a hip fracture has increased the importance of determining the impact of ACH medications on fracture risk.¹¹ Despite this increase in mortality, and the known increase in fall risk, a significant increase in the use of ACH medications has been found in individuals after suffering a hip fracture.¹²

We examined 10 years of prospective data from the Canadian Multicentre Osteoporosis Study (CaMos) to determine if strongly ACH medications are associated with falls, fracture, and/or bone mineral density (BMD) loss.

Methods

Canadian Multicentre Osteoporosis Study (CaMos)

The CaMos is an ongoing population-based cohort study examining osteoporosis and fracture risk in community-dwelling Canadians (cohort inception period 1995–1997). The study has been described in detail elsewhere.¹³ All women and men older than 50 years who were involved in CaMos were included in the current analyses. The institutional review boards of all sites participating in CaMos approved the study, and informed consent was obtained from all participants.

Study Participants and Methods

Participants were recruited from within 50-km of 1 of 9 study centers across Canada (St John's, Halifax, Québec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary, and Vancouver). A total of 9423 individuals (6539 females and 2884 males) 25 years and older, representing an age-stratified-, sex-, and region-specific sample, were identified from lists of random telephone numbers over an 18-month period. An extensive interviewer-administered questionnaire was performed at baseline (year 0) and at years 5, and 10, in which participant medications were documented in detail. During other years, a 2-page questionnaire was mailed to participants asking about hospitalizations and fractures within the past year and current use of osteoporosis medications. BMD testing was performed at baseline, year 5, and year 10 by dual-energy X-ray absorptiometry using Hologic or GE Lunar machines.

Anticholinergic Medications

We created a list of strongly ACH medications (see the appendix) based on previous studies documenting high ACH burden of these medications.^{14,15} These studies took into account measured serum ACH activity of certain medications as well as documented rates of ACH adverse effects compared with placebo. We included medications rated 2 (strong ACH effect) or 3 (very strong ACH effect) on the Anticholinergic Risk Scale¹⁵ or drugs listed as having an ACH burden classification of 3 ("high effect") by Ancelin et al.¹⁴ All topical or inhaled ACH medications were excluded. ACH medications that are often associated with intermittent "as needed" use were identified, so sensitivity analyses could be performed.

Falls and Fractures

Falls were recorded during the detailed interviews at study baseline, year 5, and year 10. The baseline questionnaire asked about falls over the past month, whereas year 5 and 10 questionnaires documented falls over the preceding year. Previous fractures on the baseline questionnaire were obtained by self-report. Incident clinical fractures were identified by yearly postal questionnaire or at the scheduled interval for reassessment (third, fifth, and tenth year after study entry) and were confirmed by medical or radiographic reports. All clinically recognized nontraumatic fractures (including hip and clinical vertebral and nonvertebral fractures) were included in our analysis. Any fracture associated with trauma or described as a fall from more than standing height was excluded.

Statistical Analysis

All CaMos participants older than 50 years at study baseline were eligible for inclusion in the study. Baseline characteristics known to be associated with fall risk, frailty, fracture risk, or BMD change were recorded. Participants with no baseline BMD were excluded from the BMD analyses. Baseline characteristics are described using mean (standard deviation) for continuous variables and count (percentage) for nominal variables. *P* values for baseline characteristics were calculated using *t* tests for continuous variables and χ^2 statistics for nominal variables. Fisher's exact test was used for nominal variables with low numbers.

Fall risk was examined by cross-sectional analyses at years 0, 5, and 10. Logistic regression modeling was performed to test for an association between strongly ACH medications and falls. Covariates were identified as factors that could affect fall risk and included age, gender, living alone, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, kidney disease, hyperthyroidism, liver disease, breast cancer, prostate cancer, chronic obstructive pulmonary disease (COPD), osteoarthritis, PD, and multiple sclerosis. A sensitivity analysis was performed where ACH medications that are commonly used "as needed" were removed.

A prospective analysis of fracture risk was performed using Cox regression. We constructed a time-dependant variable for strongly ACH medication use. A last-value-carried-forward approach was used. Therefore, individuals identifying as using strongly ACH medications at year 0 were coded as ACH users for years 0 to 5. Similarly, those identifying as users at year 5 were considered users for the analysis, from years 5 to 10. This method ensured that ACH drug use preceded any subsequent fracture recorded in CaMos. As a conservative sensitivity analysis, we considered only individuals on ACH medication at year 0 and at year 5 as being ACH users from years 0 to 5 and only those reported to be on strongly ACH medications at year 5 and year 10 as being ACH users from years 5 to 10. Covariates included history of previous nontraumatic fracture, gender, age, bisphosphonate use at any point over the 10-year study, baseline femoral neck BMD *T*-score, diabetes, liver disease, COPD, osteoarthritis, PD, and multiple sclerosis.

Mean change in BMD *T*-score over 10 years was compared in those reporting ACH medication use at baseline and year 5 versus those reporting no ACH medication use at baseline and year 5. An independent *t* test was used to compare the 2 means looking at the change in *T*-score at the femoral neck. Multiple regression analysis was then performed to control for other variables known to be associated with changes in BMD, such as age, gender, BMI, diabetes, hypertension, bisphosphonate use, hyperthyroidism, COPD, and alcohol intake. Study site was also controlled for to compensate for dual-energy X-ray absorptiometry instrument replacements.

All statistics were performed using IBM SPSS version 21 (Armonk, NY).

Results

Study Population

A total of 7753 women and men older than 50 years at study baseline were included in the study. There were 618 participants (8.0%) on strongly ACH medications at study baseline, 592 of 6200 participants (9.5%) at year 5, and 334 of 4345 (7.7%) at year 10. Baseline characteristics of ACH users versus nonusers are shown in Table 1. Mean (SD) age in ACH users was 71.1 (9.5) years, and in nonusers it was 66.7 (9.3) years; $P < 0.001$. The groups were found to be quite different, with ACH users being older, with a lower baseline femoral neck BMD T -score, more likely to live alone, more likely to have a smoking history, and more likely to suffer from a variety of medical conditions, including diabetes, osteoarthritis, hypertension, heart disease, cerebrovascular disease, kidney disease, liver disease, PD, multiple sclerosis, prostate cancer, and COPD.

Falls

ACH medication use was associated with reported falls in the baseline study questionnaire (unadjusted odds ratio [OR] = 1.50, 95% CI = 1.14–1.98, $P = 0.004$). However, after adjusting for potentially confounding variables, the association between ACH medications and falls was lost (OR = 1.25; CI = 0.91–1.72; $P = 0.169$). Diabetes, prostate cancer, osteoarthritis, and PD were all independently associated with an increased risk of a recent fall prior to the baseline visit (Table 2). Similar results occurred in the year 5 questionnaire, with an association between falls and ACH use in the unadjusted analysis (OR = 1.54; CI = 1.29–1.83; $P < 0.001$), but no association after covariate adjustment (OR = 1.17; CI = 0.97–1.41; $P = 0.096$). Older age, diabetes, osteoarthritis, PD, and cerebrovascular disease were all independently associated with increased risk of falling at year 5. This pattern continued with the year 10 analyses, where ACH use was associated with falls in unadjusted analysis (OR = 1.45; CI = 1.16–1.81; $P = 0.001$) but not after covariate adjustment (OR = 1.22; CI = 0.97–1.53; $P = 0.093$). Increasing age, diabetes, and cerebrovascular disease were all associated with falls in the year 10 analysis. All analyses were essentially unchanged in sensitivity analyses with “as needed” medications removed.

Fracture

Over the 10-year study period, 1189 (15.3%) individuals experienced an incident nontraumatic fracture (range: 1 to 9 fractures per person). Hip fracture was the first incident fracture in 159 of these individuals. Of the baseline ACH medication user group, 96 (15.5%) individuals experienced an incident nontraumatic fracture over 10 years, in which the first incident fracture was a hip fracture in 16 participants. In the unadjusted analysis, ACH medication was associated with an increased incidence of fragility fracture over the course of the 10-year study (hazard ratio [HR] = 1.22; CI = 1.13–1.32; $P < 0.001$). However, after covariate adjustment, the association was lost (HR = 0.99; CI = 0.79–1.24; $P = 0.919$). Factors that were associated with an increased risk of incident nontraumatic fractures included increasing age, female gender, lower BMD femoral neck T -score, past history of nontraumatic fracture, bisphosphonate use, PD, and multiple sclerosis (Table 3). When specific fracture types were examined, there was no association between ACH use and incident hip fracture (HR = 1.05; CI = 0.57–1.91; $P = 0.880$) or ACH use and incident

clinical vertebral fracture (HR = 0.83; CI = 0.40–1.73; $P = 0.620$). The results remained nonsignificant on sensitivity analysis using the more conservative definition of ACH use (adjusted HR = 1.05; CI = 0.72–1.53; $P = 0.815$).

Bone Mineral Density

In the group of participants who reported being on ACH medications at study baseline and at year 5 ($n = 194$), the mean change in BMD T -score at the femoral neck over the 10-year study was greater than the mean change over 10 years in the group not on ACH medications (Mean [SD] = -0.60 [0.63] vs -0.49 [0.45]; $P = 0.041$). However, after controlling for other covariates known to affect BMD, including bisphosphonate use, there was no significant association between ACH use and BMD change ($P = 0.086$).

Discussion

In this large, population-based cohort of Canadians older than 50 years, we found that the use of strongly ACH medications appeared to be associated with an increased risk of falling and nontraumatic fractures in unadjusted analyses; however, after adjusting for confounding variables, there was no significant association. Similarly, an accelerated decline in femoral neck BMD was seen in ACH medication users, but this decline was accounted for by factors other than the ACH use, and after covariate adjustment, no significant association was seen.

In unadjusted analyses, ACH medication use was associated with a history of falls. There was a consistent association identified in the baseline, year 5, and year 10 analyses (OR = 1.50, 1.54, and 1.45, respectively). This is consistent with previous studies showing an increased risk of falling with ACH medications. Risk of falling in the geriatric inpatient psychiatric patient population has been examined previously in several small studies, and use of ACH medications has been identified as one, of several, significant risk factors.^{4,6} Similarly, in a large community-based study of men and women older than 65 years, medications with ACH properties were found to be associated with fall risk (OR = 1.6; CI = 1.2–2.1).⁵ Unlike the present study, however, these previous studies did not control for underlying medical conditions.

ACH medications are known to cause dizziness and lightheadedness and, therefore, the association between ACH medication use and falls seems logical.¹⁶ Declines in instrumental activities of daily living and other measures of performance status have been associated with increasing ACH drug burden.¹⁷ However, we found that after adjusting for cofactors, the link between ACH medication use and falls was no longer present. Medical conditions that increase the likelihood of falling or frailty were identified as important risk factors for falls. Diabetes was consistently associated with an increased history of falls (OR = 1.53 at year 0, 1.25 at year 5, and 1.48 at year 10) in our study. This link has been documented previously and may be a result of diabetes-associated neuropathy and/or hypoglycemia from diabetes treatment, particularly insulin therapy.^{18,19} Similarly, we found osteoarthritis to be associated with an increased history of falls. Fall risk factors, including impaired muscle performance and balance and mobility problems, have been identified in those with hip and knee osteoarthritis in the past.²⁰ Cerebrovascular disease has also been reported previously

to be associated with increased fall and fracture risk, particularly in those left with visual and cognitive deficits.^{21,22}

Of particular interest is the strong association found between PD and falls (OR = 4.06; CI = 1.72–9.56; $P = 0.001$) at year 0. Several strongly ACH medications are used in PD. Patients with PD have issues with postural instability, gait abnormalities, postural orthostasis, and dementia, which independently increase their baseline risk of falling.^{23,24} These findings suggest the possibility that the underlying medical condition for which ACH medications are used is more important in terms of causing falls than the ACH medication itself. Another interpretation is that ACH medications are more likely to induce falls only when used in a vulnerable population with certain medical conditions, with a high underlying fall risk to begin with. PD patients have cholinergic loss, which is postulated to be associated with the nonmotor symptoms seen in the condition, including dementia, attention impairment, and visuospatial and executive control problems.²⁵ In a small, randomized control trial where PD patients were assigned to donepezil (a central cholinesterase inhibitor—causing cholinergic augmentation) or placebo, those on donepezil experienced half the number of falls compared with the placebo group over 6 weeks, thereby lending support to the idea that decreasing acetylcholine (with ACHs) is detrimental to fall risk in PD patients.²⁶ However, cholinesterase inhibitors have been linked with an increase in hip fracture in a large observational study; therefore, the association between acetylcholine levels and falls/fractures remains unclear.²⁷

In addition to the above-mentioned conditions, we also found increasing age and prostate cancer, conditions associated with increased frailty, to be associated with increased falls.^{28,29}

We did not identify ACH medication use as an independent risk factor for incident nontraumatic fracture over the 10-year study period. Other studies have shown mixed results, with some identifying a link between ACH medication use and fracture risk and others showing no association.^{10,27} Our study had the strength of controlling for multiple important covariates that are known to affect fracture risk, such as BMD and bisphosphonate use. Indeed, we found lower BMD *T*-scores to be strongly associated with fracture risk (<0.001). Bisphosphonate use at any point over the 10-year study was associated with a higher fracture risk, likely because many individuals were started on bisphosphonate therapy in response to sustaining a fragility fracture (confounding by indication). We found both PD and multiple sclerosis, 2 conditions where ACH medication use is common, to be associated with an increased risk of incident fracture. These findings are supported by other studies showing increased fracture risk in these populations.³⁰

We examined the change in BMD at the femoral neck over 10 years in ACH users and nonusers. To our knowledge, no other study to date has looked at the impact of ACH medications on BMD scores. Similar to our fall and fracture results, we found an association between ACH medication use and BMD decline in the unadjusted analysis, but after covariate adjustment, the association was nonsignificant.

There are several important strengths to our study, including the large population-based sample that consisted of both men and women, the long follow-up period of 10 years, and

the longitudinal BMD analysis. We have detailed fracture data for the full 10 years of follow-up making it unlikely that any important fall-related fractures were missed. Our ability to control for a wide range of cofactors was a particular strength because results were strongly affected, and the study conclusions would have been different had we not been able to control for this large number of important cofactors.

There are, however, several limitations to the current analysis. The list of ACH medications used may not capture newer highly ACH medications in use since the original studies of these medications was performed. We only had full medication data at 3 time points over the 10-year study (years 0, 5, and 10), which limited our ability to accurately define ACH use and assess cumulative exposure. To overcome this, we used 2 different definitions of ACH medication use. Both these definitions were conservative in order to ensure that ACH use was recorded prior to any reported fracture. The last-value-carried-forward method used for the time-dependant Cox regression analysis does not account for individuals who started strongly ACH medications during the 5-year period between visits that provided detailed medication lists. This would affect our results by diluting an effect of ACH use on fractures, and therefore, it is possible that an association may still be present, even though it was not detected. Similarly, fall data were collected only for the period immediately prior to baseline (year 0), year 5, and year 10 visits; therefore, we had to perform 3 separate cross-sectional analyses at each of these time points, as opposed to a single longitudinal analysis. Finally, like most studies measuring falls, data were collected based on self-report and, therefore, are subject to recall bias.

In summary, we initially found a statistically significant association between ACH medication use and falls, fractures, and BMD loss. However, this association was lost after correction for important confounding variables. These results imply that ACH medication use itself may not cause falls, fractures, or BMD loss but may be a marker for conditions that predispose to these outcomes. Comorbid conditions and markers of frailty accounted for the increase in falls, fractures, and BMD decline seen in those taking ACH medications in our study.

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Appendix. List of Medications With Strongly Anticholinergic Effects

Drug	Therapeutic Class	Baseline Users
Alprazolam	Benzodiazepine	42
Amantadine hydrochloride	Antiviral/Antiparkinsonian	0
Amitriptyline	Tricyclic antidepressant (TCA)	113
Baclofen ^a	Muscle relaxant	4
Benztropine mesylate	Parkinsonism	3
Cetirizine	Antihistamine	0
Chlorpromazine	Antipsychotic	5
Cimetidine	H ₂ -antagonist	53
Clomipramine	TCA	8
Clorazepate	Benzodiazepine	3
Colchicine ^a	Anti-hyperuricemic	17

Drug	Therapeutic Class	Baseline Users
Cyclobenzaprine hydrochloride ^a	Muscle relaxant	7
Cyproheptadine hydrochloride ^a	Antihistamine	1
Dicyclomine hydrochloride	Antispasmodic	3
Digoxin	Antiarrhythmic	169
Diphenhydramine hydrochloride ^a	Antihistamine	2
Fluphenazine hydrochloride	Antipsychotic	0
Furosemide	Diuretic	164
Hydroxyzine	Anxiolytic/Antihistamine	13
Imipramine	TCA	17
Loperamide hydrochloride ^a	Antidiarrheal	11
Maprotiline	Tetracyclic antidepressant	1
Nortriptyline	TCA	6
Olanzapine	Antipsychotic	0
Oxybutynin	Antispasmodic	20
Perphenazine	Antipsychotic	3
Prochlorperazine ^a	Antiemetic	0
Promethazine	Neuroleptic/Antihistamine	0
Pseudoephedrine ^a	Decongestant	0
Thioridazine	Antipsychotic	5
Tizanidine hydrochloride	Muscle relaxant	0
Trifluoperazine hydrochloride	Antipsychotic	5
Trihexyphenidyl	Antiparkinsonian	0
Trimipramine	TCA	19

^aMedications often taken intermittently “as needed.”

Table 1

Characteristics of Strongly ACH Medication Users and Nonusers Older Than 50 Years in CaMos at Baseline.

Characteristic	Baseline ACH User (n = 618)	ACH Nonuser (n = 7135)	P Value
Age, mean (SD), years	71.1 (9.5)	66.7 (9.3)	<0.001
Female gender (%)	462 (74.8)	5104 (71.5)	0.088
BMI, mean (SD)	27.5 (5.3)	27.0 (4.7)	0.031
Living alone (%)	252 (40.8)	2321 (32.5)	<0.001
Femoral neck BMD <i>T</i> -score, mean (SD)	−1.34 (1.02)	−1.23 (0.98)	0.015
Bisphosphonate use (%)	7 (1.1)	96 (1.3)	0.854
Reporting fall(s) in the past month (%)	56 (9.1)	445 (6.2)	0.006
Previous nontraumatic fracture (%)	167 (27.0)	1966 (27.6)	0.776
Smoker ^a (%)	268 (46.3)	2261 (33.0)	<0.001
Alcohol, mean (SD), drinks per week	2.17 (5.23)	2.95 (5.91)	0.002
Diabetes (%)	95 (15.4)	511 (7.2)	<0.001
Hyperthyroidism (%)	19 (3.1)	164 (2.3)	0.223
Osteoarthritis (%)	268 (46.3)	2261 (33.0)	<0.001
Hypertension (%)	293 (47.6)	2232 (31.4)	<0.001
Previous myocardial infarction (%)	132 (21.6)	445 (6.3)	<0.001
Previous stroke or TIA (%)	74 (12)	280 (3.9)	<0.001
Kidney disease (%)	19 (3.1)	106 (1.5)	0.003
Liver disease (%)	25 (4.1)	167 (2.3)	0.009
Parkinson's disease (%)	7 (1.1)	27 (0.4)	0.016
Multiple sclerosis (%)	6 (1.0)	14 (0.2)	0.004
Breast cancer (%)	26 (4.2)	238 (3.3)	0.252
Prostate cancer (%)	14 (2.3)	75 (1.1)	0.007
COPD (%)	89 (14.1)	595 (8.30)	<0.001

Abbreviations: ACH, anticholinergic; SD, standard deviation; BMI, body mass index; BMD, bone mineral density; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

^a Ever use daily for >6 months.

Table 2

Factors Associated With Falls at Baseline, Year 5, and Year 10.

Variable	Baseline (n = 7753)				Year 5 (n = 6200)				Year 10 (n = 4345)			
	Odds Ratio	95% CI	P Value		Odds Ratio	95% CI	P Value		Odds Ratio	95% CI	P Value	
ACH medication use	1.25	0.91–1.72	0.169		1.17	0.97–1.41	0.096		1.22	0.97–1.53	0.093	
Age (per year increase)	1.00	0.99–1.01	0.479		1.01	1.00–1.02	<0.001		1.01	1.01–1.02	<0.001	
Female gender	1.07	0.86–1.33	0.565		1.13	1.00–1.28	0.055		1.15	1.00–1.33	0.051	
Diabetes mellitus	1.53	1.13–2.08	0.005		1.23	1.03–1.48	0.024		1.48	1.09–2.00	0.013	
Hypertension	1.01	0.83–1.24	0.915		1.00	0.89–1.12	0.953		0.87	0.69–1.09	0.234	
Myocardial infarction	1.15	0.82–1.60	0.434		0.92	0.75–1.13	0.432		1.04	0.72–1.50	0.848	
Stroke/TIA	1.29	0.86–1.92	0.221		1.40	1.12–1.73	0.003		1.55	1.12–2.15	0.008	
Kidney disease	1.10	0.55–2.20	0.797		1.27	0.86–1.89	0.233		1.22	0.49–3.04	0.678	
Living alone	1.22	1.00–1.50	0.054		1.12	1.00–1.27	0.057		1.04	0.91–1.19	0.588	
Hyperthyroidism	0.87	0.45–1.65	0.655		0.95	0.71–1.26	0.710		1.07	0.38–3.03	0.904	
Liver disease	1.10	0.63–1.92	0.738		1.17	0.84–1.65	0.353		0.93	0.32–2.67	0.873	
Breast cancer	1.08	0.66–1.80	0.769		1.03	0.78–1.34	0.856		1.32	0.86–2.02	0.211	
Prostate cancer	2.19	1.09–4.40	0.028		0.86	0.54–1.36	0.517		0.85	0.40–1.81	0.668	
COPD	1.18	0.87–1.60	0.295		1.09	0.87–1.37	0.445		1.24	0.73–2.11	0.430	
Osteoarthritis	1.28	1.05–1.56	0.013		1.38	1.23–1.54	<0.001		1.16	0.90–1.50	0.253	
Parkinson's disease	4.06	1.72–9.56	0.001		1.99	1.00–3.96	0.050		1.63	0.64–4.18	0.311	
Multiple sclerosis	0.79	0.104–5.96	0.818		2.50	0.88–6.84	0.085		N/A ^a			

Abbreviations: ACH, anticholinergic; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease.

^aNo year 10 participant had multiple sclerosis.

Table 3

Factors Associated With Incident Nontraumatic Fracture Over 10 Years (n = 6424).

Variable	Hazard Ratio	95% CI	P Value
ACH medication use	0.99	0.79–1.24	0.919
Female gender	1.52	1.28–1.81	<0.001
Previous nontraumatic fracture	1.58	1.39–1.81	<0.001
Diabetes	1.21	0.94–1.56	0.140
Age (years)			
60–69	0.91	0.76–1.10	0.323
70–79	1.35	1.12–1.62	0.001
80–89	1.52	1.16–2.10	0.003
90	1.67	0.53–5.26	0.379
Femoral neck T-score (per SD increase)	0.73	0.67–0.79	<0.001
Liver disease	1.40	0.98–2.00	0.065
COPD	1.14	0.92–1.41	0.229
Osteoarthritis	0.11	0.98–1.28	0.105
Parkinson's disease	5.68	3.03–10.64	<0.001
Multiple sclerosis	3.16	1.01–9.82	0.047
Bisphosphonate use	1.51	1.31–1.73	<0.001

Abbreviations: ACH, anticholinergic; COPD, chronic obstructive pulmonary disease.