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A high anti-cholinergic burden is associated with a history of falls in the previous year in middle-aged women: findings from the Aberdeen Prospective Osteoporosis Screening Study

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Table 1: Participant characteristics by anti-cholinergic burden score in 3,883 middle-aged women of APOSS at second visit.

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Purpose

To examine the cross-sectional association between anti-cholinergic medication burden (ACB) and a history of falls, bone mineral density (BMD), and low trauma fractures in middle-aged women under 65 years of age from the Aberdeen Prospective Osteoporosis Screening Study (APOSS).

Methods

ACB (0= none, 1=possible, ≥2= definite) was calculated from medication use for 3883 Caucasian women (mean age (SD) = 54.3 (2.3) years) attending the second APOSS study visit (1997-2000). Outcomes were examined using logistic regression. Model adjustments were selected a-priori based on expert opinion.

Results

Of 3883 participants, 3293 scored ACB = 0, 328 scored ACB = 1, and 262 scored ACB ≥ 2. High ACB burden (≥2) was associated with increased odds (ACB=0 reference) for falls (fully adjusted OR (95% CI) = 1.81 (1.25-2.62); *P*=0.002), and having low BMD (lowest quintile-20%) at Ward's triangle (3.22 (1.30-7.99); *P*=0.01). A history of falls over the year prior to study visits in participants with ACB score ≥2 was 32 per 100. For ACB categories 1 and 0, a history of falls per 100 was 21 and 22 respectively.

Conclusions

The risk of falling associated with ACB observed in older age may also extend to middle-age women.

Introduction

Medications with anti-cholinergic properties, used to treat a range of common conditions, act by inhibiting the neurotransmitter acetylcholine (ACh), resulting in a relatively high side-effect profile [1-3]. Serious adverse effects of anti-cholinergic medications have been reported, leading to a reduction in overall quality of life [2-4]. A systematic review of 5 randomised controlled trials in 6526 participants with a mean age of 78.7 years showed that anti-cholinergic medication use was associated with decreased mobility and ability to carry out routine daily tasks [1]. In a large community based study of 6343 men and women (mean age = 73.7 years) spanning over 4 years, anti-cholinergic medication use was associated with an increased risk of falling (adjusted odds ratio = 1.6 (1.2–2.1)) during routine daily activities [5].

It is estimated that one in two Caucasian women will suffer a low trauma fracture during their life time. Poor physical function and falling are important risk factors for low trauma fracture [6]. In a meta-analysis of 19 RCTs containing 1577 participants (mean age = 65-83 years, 85% female), decreased physical activity was found to be associated with a reduction in BMD at the lumbar spine and neck of femur (weighted mean difference = 0.011 g/cm2 and 0.016 g/cm2) [7]. BMD measurement with DXA at the femoral neck is predictive of hip fracture, with an increase in risk ratio of 2.88 (95% CI = 2.31-3.59) in women aged 65 years for each SD decrease in BMD [8].

Whether use of medications with anti-cholinergic properties is associated with falls or fractures in middle age has not been examined previously. We postulate that such evidence would provide incentive to reduce anti-cholinergic burden in early life as this could impact healthy ageing. Consequently, the aim of this study was to examine the association between anti-cholinergic medication use and a history of falls in the last year, low trauma fractures, and BMD at fracture prone sites in a cohort of middle-aged women under the age of 65 years.

Methods

Study participants and design

Participants were drawn from the Aberdeen Prospective Osteoporosis Screening Study (APOSS). Briefly, between 1990 and 1993, 7,200 women aged 45-54 years, living within a 32 km radius of the Osteoporosis Research Unit in Aberdeen, North East of Scotland, UK with a catchment population of approximately 500,000 were selected at random from the Community Health Index (a primary care patient register). These women were invited to take part in a screening study for osteoporosis (5, 119 attended), which consisted of a DXA scan of the hip and lumbar spine and completion of an osteoporosis risk factor questionnaire [9]. Between 1997 and 2000, participants who attended the baseline visit were invited for a follow-up visit. Three thousand eight hundred and eighty-three women attended. The ACB Score for each participant was calculated using a detailed self-reported medication list collected during this second visit; prior to the DXA scan, a radiographer asked each participant which medications they were currently taking.

Data collection

Using the Aging Brain Program's ACB scoring table (as shown in the Supplementary Table) [10], each medication was assigned an ACB score and the total ACB burden was calculated for each participant as described by Myint *et al* [11]. There are multiple ant-cholinergic scoring scales, however, we chose to use the ACB scale because it has previously been shown to describe the association between anti-cholinergic medication use and falls in older adults [3]. In addition to the established anti-cholinergic medications, we also classed Prochlorperazine (or Chlorperazine) and Procyclidine as scoring 3 after consultation with

opinion leaders in the field. Each participants' total score was categorised into one of the three groups depending on the sum of their total ACB score (ACB = 0, ACB = 1, ACB ≥ 2) (see Supplementary Table 1 for the scoring system). Our rationale for using ACB ≥2 category as opposed to ACB≥1 category is based upon the wider literature which has shown that ACB ≥2 is associated with poor outcomes such as mortality [12].

Participants were weighed wearing light clothing and no shoes with scales that were calibrated to 0.05kg (Seca, Hamburg, Germany). Height was measured using a stadiometer (Holtain Ltd, Crymych, UK). Body Mass Index (BMI) was calculated using the formula (BMI= weight (kg)/height $(m)^2$). Physical activity level (PAL) was obtained by questionnaire, which asked about usual activities over the previous year [13]. PAL is defined as the ratio of overall daily energy expenditure to BMR and was calculated from the number of hours in a 24-h period spent doing heavy, moderate, or light activities and the numbers of hours in the same period spent sleeping or resting in bed. These questions were asked separately for workdays and non-work days. Detailed methodology has been previously described [14].

Information on comorbidities was self-reported and collected at baseline by asking about history of osteoporosis, osteoarthritis, rheumatoid arthritis, asthma, kidney disease, thyroid disease, diabetes mellitus, hypertension, myocardial infarction, and stroke. Data were also collected on the use of the following medications: corticosteroids, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics, sex hormones including the oral contraceptive and tamoxifen by asking the question "what prescribed medications have you ever taken?". Participants were asked about smoking status (never, past, or current smoker), and family history of low trauma fractures. Vitamin D status was determined by measuring serum total 25ODH using high-performance liquid chromatography, which is further described by Welsh *et al* [15].

Self-reported falls in the past year and prevalent fractures were captured based on responses to the questions "Have you fallen in the last 12 months?" and "Have you ever fractured a bone?", respectively. BMD DXA measurements were performed using Norland DXA scanners (Cooper Surgical Inc, Trumbull, CT). Scanner calibration was performed daily, and quality assurance checks were made by measuring the manufacturer's phantom at daily intervals and a hologic phantom at weekly intervals. The in vivo precision (CV) at our unit of the XR26 scanner is 1.95% and 2.31% (lumbar spine and femoral neck respectively). These values were determined by duplicate measurements in 8 women aged 49–63 y (mean: 53 y). The majority of participants were scanned using an XR26 but 351 women (11.3%) were scanned using an XR36. There was a small difference (1.258%) in mean BMD when comparing 50 phantom measurements on both machines and a correction factor was used to convert the XR36 values to XR26-equivalent values.

Statistical Analyses

All analyses were performed using Statistical Package for Social Science (SPSS), version 23.0. Descriptive statistics of the full cohort and by ACB category were presented. ANOVA and chi-square test were used respectively to analyse the association between ACB category and measured outcomes. Logistic regression models were constructed to examine the association between ACB as the predictor variable (with ACB score of 0 as the reference category) and dichotomised outcomes. BMD data were dichotomised for logistic regression analyses; lowest 20% vs. remaining 80%. These arbitrary cut off points allow meaningful interpretation of results in terms of the population at risk of detrimental effects from having low BMD and to contextualise results for clinicians [16]. For all logistic regression models, analyses were unadjusted (model A), adjusted for age, BMI, and HRT use (model B), with

further incremental adjustment for menopausal status and PAL (model C), comorbidities (model D), and use of medications (model E). Multiple linear regression analyses were also completed using the same models for our measured BMD sites using continuous BMD values. Collected participant demographics and comorbidities were selected according to an adaptation of the Functional Comorbidity Index proposed by Groll et al [17].

Results

The characteristics of the sample by category of total ACB (score 0, score 1, score ≥2) are presented in Table 1. Of 3883 participants, 3293 had ACB score 0, 328 had ACB score 1, and 262 had ACB score ≥2. The mean age (SD) of study participants was 54.3 (± 2.3) years. 3496 of our participants were post-menopausal, of which 1418 were taking HRT. Age and BMI increased with increasing ACB score, whereas PAL decreased with increasing ACB. There was a greater proportion of post-menopausal participants who were currently taking HRT with an ACB score of ≥2 compared to pre- and peri-menopausal participants. There were no differences in the proportion of participants with self-reported osteoporosis, osteoarthritis, thyroid disease, or a family history of fractures across ACB categories. Self-reported comorbidity numbers were highest in participants with ACB score of ≥ 2. Use of steroid tablets, diuretics, and anti-epileptics, were significantly different across ACB score categories (use of corticosteroids and anti-epileptics were highest in participants with ACB score of ≥ 2).

ACB ≥2 was associated with a history of self-reported falls over the last year in univariate (1.71 (1.30-2.25); P = <0.001) and fully adjusted logistic regression models (1.80 (1.25-2.60); P = 0.002) (Table 2). Per 100 population, a history of falls in the last year for participants with ACB score ≥2 was 32. For ACB categories 1 and 0, a history of falls in the last year per 100 was 21 and 22 respectively. Both univariate and multiple variable logistic

regression models showed that ACB score of ≥2 was associated with increased odds for lowest quintile BMD (lowest 20%) at Ward's triangle (OR = 2.81 (1.16-6.79); *P* = 0.022) for fully adjusted model) (Table 3). We found no association between ACB and lowest quintile total hip, trochanter, neck of femur, or lumbar spine BMD. There was no association between ACB and having ever fractured a bone nor having fractured a bone since turning 50 years of age.

Discussion

To the best of our knowledge, this is the first study to investigate the association between anti-cholinergic burden and musculoskeletal health outcomes in middle-aged women under the age of 65. Our study therefore addresses this evidence gap. We found a high ACB score from use of anti-cholinergic medications is associated with an increased likelihood of having fallen in the last year in this age group. We found no association between ACB and BMD except at Ward's triangle. No association was found between ACB score and having ever fractured a bone.

Falls in older people are a global issue; the average health system cost per one fall injury episode for people 65 years and older in Finland and Australia was US$ 3611 and US$ 1049 [18]. Meanwhile in England, falls cost the NHS £2.3 billion per year and are responsible for over 4 million hospital bed days annually [19]. Earlier observational studies examining the association between ACB and falls in older adults show conflicting results [3, 5, 20-22]. Zia and colleagues observed in a cohort of older adults with a mean age of 76.5 years, having an ACB score >1 was associated with falls (OR = 1.8 (1.1-3.0); *P* = 0.01) [3]. Nevertheless, Fraser and colleagues in a 10 year follow up observational study of older adults with a baseline mean age of 71.1 years, observed that when adjusting for potential confounders associated with an increased risk of falling such as diabetes, prostate cancer, osteoarthritis, and Parkinson's

disease, the association between anti-cholinergic medication use and falls was lost (OR = 1.17 (0.97–1.41); *P* = 0.096) [20].

Although one study has already reported an association between anti-cholinergic medication use and a history of falls in post-menopausal women over the age of 65, our study focuses on a younger and relatively healthy cohort of post-menopausal women under 65 years [23]. We therefore extend the evidence base by examining whether such a link exists before older age, whilst being mindful that we cannot draw any conclusions about causality given the observational nature of our study design. Our data show that ACB is associated with higher odds for falling in a group of people previously thought not to be adversely affected to this extent by anti-cholinergic medications. The relatively high ACB threshold associated with a history of falls in our study likely relates to the younger age of our study participants. It has been demonstrated that anti-cholinergic drug use is associated with decreased functional reach in older people, which may result in the reduced ability to actively prevent falling [3].

Both central and peripheral effects of anti-cholinergics may contribute to falls risk [24, 25]. Centrally, anti-cholinergic medications antagonise post-synaptic M1 receptors found in the central nervous system, which may produce abnormalities in perception and attention [26]. Peripherally, anti-cholinergic medications block M3 receptors in the eyes with resultant inability of the pupils to appropriately accommodate to near objects [27]. The combination of perceptual and visual impairment may contribute to the falls risk.

Whilst we did not find that ACB relates to fractures, there is overwhelming evidence to suggest that the risk of falling is higher in people that have fallen previously, and that a history of falling is the strongest risk factor for low trauma fractures in older people [28-30]. Additionally, fear of falling is associated with a loss of perception of one's own capabilities, loss of self-confidence and avoidance of activities [31]. In a systematic review of 28 studies, it

has been shown that the greatest risk factor for developing a fear of falling in people aged ≥65 was having fallen at a younger age [31].

Whilst the relationship between anti-cholinergic medication and BMD has been investigated previously, there are limited reports on the association between anti-cholinergic medication use and BMD at Ward's triangle [20]. Ward's triangle is a fracture prone site, due to it being the weakest point on the neck of femur, varying with the individuals' neck of femur shape [32]. However, the literature on Ward's triangle is conflicting primarily due to inconsistency in locating Ward's triangle radiologically and on DXA scans [33]. Our study findings should be replicated using Ward's triangle measured using modern software programmes, where anatomical location can be more accurately identified.

A positive association between extensive use of anti-cholinergic medications and decreased femoral neck BMD has been reported previously although this association was not significant following covariate adjustment [20]. We found no association between ACB and the lowest quintile BMD of the total hip, neck of femur, trochanter and lumbar spine, in both the univariate and multivariate analyses.

Our study benefits from a number of strengths. It was conducted in a well characterised representative cohort of Scottish middle aged women who were selected at random from Community Health Index records. Our focus is on a younger cohort of women with a similar range of functioning, which means that our findings more accurately reflect the effects of ACB in middle age. A detailed and up to date medication list was recorded by a radiographer during participants' visit to the DXA scanner, thus strengthening the accuracy of documentation of medications. We adjusted for a comprehensive range of co-morbidities and medications known to affect our measured outcomes.

We acknowledge some limitations. Given that our study is a cross sectional analysis, we are unable to determine causality. Consequently, a high ACB score may in fact be a marker of ill health and therefore it may be the case that ill health itself is the actual precipitating factor in falls. Information on falls and fractures were self-reported, raising the possibility of recall bias. However, given that our cohort's ages ranged between 50-63 years, their recall ability is likely to have been good overall especially for uncommon and memorable events such as falling in this age group. Our measurement of physical activity level lacked the sensitivity to differentiate between weight bearing activities such as high intensity resistance and impact training which are more closely associated with increased or maintained BMD than simply walking or performing routine daily activities, which was the focus of our measurement tool [34-36]. We did not have information on the duration of medication use nor temporal relationship between ACB and a history of falls, therefore we were unable to rule out the possibility of reverse causality with any degree of confidence. Moreover, we did not have information on the dose nor duration of anti-cholinergic medications being used by participants, therefore we were unable to observe any potential dose dependent or temporal relationship between ACB and a history of falls. We also did not have detailed information of falls such as severity, and impact of the falls. Because there is low to moderate concordance between anti-cholinergic burden scales, it is unclear that ACB is the most appropriate scale to predict our measured outcomes.[37] Future studies should compare the utility of different anticholinergic scales in predicting falls outcome

Nevertheless, we have shown that high ACB scores are associated with a higher likelihood of having fallen in the last year. Per 100 population, we found that a history of falls in middle-aged women with a high ACB score was almost one third (32). Additionally, we found the link between high ACB and low BMD at the Ward's triangle. This finding warrants further investigation as this may provide potential mechanistic link between high

ACB and falls observed in older age. Our findings suggest that the falls risk associated with ACB observed in older age may extend to middle age and high ACB may have potential clinical utility as a novel risk marker in identifying older women with high risk of falls and fractures for targeted intervention strategies.

Contributors

PKM conceived the study. DMR and HMM are PIs of the APOSS study. ADA and JG collected the ACB from records and performed literature review. Data were analysed by ADA under supervision of ADW and PKM. All authors contributed significantly in interpretation of the results. ADA, ADW and PKM drafted the paper and all authors contributed in writing of the paper. PKM is the guarantor.

Conflicts of interest

The authors have nothing to disclose.

Ethics approval

Written informed consent was obtained from all participants. Ethical approval was obtained from the North of Scotland Research Ethics Service. All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments.

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Table 1: Participant characteristics of full cohort and by anti-cholinergic burden score in 3883 middle-aged women of APOSS at second visit.

	Full cohort n=3883	ACB score 0 n=3293	ACB score 1 n=328	ACB score ≥2 n=262	*P*
Characteristics					
Age (years)	54.33 (2.27)	54.26 (2.24)	54.63 (2.37)	54.79 (2.36)	**<0.001**
BMI (kg/m2)	26.78 (4.87)	26.51(4.61)	28.08 (5.36)	28.52 (6.55)	**<0.001**
Physical activity (PAL)	1.82 (0.32)	1.84 (0.32)	1.75 (0.31)	1.70 (0.34)	**<0.001**
Menopausal Status					**0.006**
Pre and peri-menopausal	377 (10)	341(10)	20 (6)	16 (6)	
Post-menopausal	3496 (90)	2943 (89)	308 (94)	245 (94)	
Co-morbidities					
Falls during past 12 months	855 (22)	703 (21)	69 (21)	83 (32)	**<0.001**
Ever fractured a bone	1183 (30)	998 (30)	111 (34)	74 (28)	0.30
Osteoporosis	31 (1)	25 (1)	3 (1)	3 (1)	0.77
Osteoarthritis	290 (7)	236 (7)	26 (8)	28 (11)	0.10

Rheumatoid arthritis	54 (1)	36 (1)	10 (3)	8 (3)	**0.001**
Kidney disease	22 (1)	14 (1)	4 (1)	4 (2)	**0.018**
Diabetes	27 (1)	15 (0)	6 (2)	6 (2)	**<0.001**
Hypertension	269 (6)	158 (5)	69 (21)	42 (16)	**<0.001**
Asthma	145 (4)	109 (3)	15 (5)	21 (8)	**<0.001**
Mother has broken their hip	279 (7)	246 (7)	16 (5)	17 (6)	0.21
Thyroid disease	172 (4)	142 (4.3)	18 (5)	12 (5)	0.61
25OHD≤25 nmol/L	3113 (80.2)	1856 (56.4)	179 (54.6)	154 (58.8)	0.10
Medication					
Current HRT user	1080 (28)	911 (28)	87 (27)	82 (31)	0.39
Current smoker	733 (19)	615 (19)	66 (20)	52 (20)	0.75
Medication for osteoporosis	19 (0)	13 (0)	3 (1)	3 (1)	0.13
Calcium supplements	329 (8)	279 (8)	26 (8)	24 (9)	0.86
Steroid tablets	163 (4)	127 (4)	18 (5)	18 (7)	**0.03**
Oral contraceptive	1305 (34)	1122 (34)	110 (34)	73 (28)	0.13
Diuretics	339 (9)	229	73	37	**<0.001**
Anti-epileptics	19 (0)	13 (0)	1 (0)	5 (2)	**0.003**
BMD (g/cm^3)					
Total Hip	2.28 (0.37)	1.54 (0.23)	1.56 (0.23)	1.55 (0.23)	0.09

Ward's Triangle	0.74 (0.16)	0.74 (0.16)	0.75 (0.17)	0.73 (0.18)	0.36
Neck of Femur	0.84 (0.12)	0.84 (0.12)	0.85 (0.12)	0.84 (0.13)	0.19
Trochanter	0.70 (0.12)	0.70 (0.12)	0.72 (0.12)	0.70 (0.13)	0.08
Spine (L2 - L4)	1.01 (0.17)	1.01 (0.17)	1.03 (0.17)	1.03 (0.19)	**0.01**
T-scores					
Neck of Femur	-0.84 (0.76)	-0.84 (0.74)	-0.81 (0.78)	-0.84 (0.93)	0.82
Spine (L2 - L4)	-0.97 (1.48)	-1.00 (1.47)	-0.81 (1.46)	-0.76 (1.66)	**0.005**
Z-scores					
Neck of Femur	-0.37 (0.83)	-0.38 (0.84)	-0.25 (0.82)	-0.33 (0.76)	0.13
Spine (L2 - L4)	0.29 (1.27)	0.27 (1.27)	0.46 (1.21)	0.45 (1.30)	0.08

Values presented are mean (SD) for continuous data and number (%) for categorical data.
P values were generated using a one-way ANOVA test for continuous variables and a chi square test for categorical variables.

Table 2: Results of logistic regression analysis examining the association between anti-cholinergic burden (reference category = 0) and a history of falls over the previous 12 months

Models	ACB 1			ACB ≥2		
	OR	95% CI	*P*	OR	95% CI	*P*
Falls in the last year						
A	0.95	0.72-1.27	0.72	1.71	1.30-2.25	**<0.001**
B	0.91	0.69-1.21	0.52	1.63	1.24-2.16	**0.001**
C	0.93	0.68-1.28	0.66	1.69	1.24-2.32	**0.001**
D	1.06	0.74-1.51	0.75	1.84	1.28-2.64	**0.001**
E	1.06	0.74-1.52	0.74	1.80	1.25-2.60	**0.002**

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, fractured a bone since turning 50 years of age, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.

Table 3: Results of logistic regression analyses examining association between anti-cholinergic burden (reference category = 0) and hip and spine bone mineral density

Models	ACB 1			ACB ≥2		
	OR	95% CI	*P*	OR	95% CI	*P*
Lowest 20% of total hip BMD						
A	0.94	0.61-1.44	0.76	1.36	0.89-2.07	0.16
B	1.11	0.71-1.75	0.64	1.45	0.92-2.30	0.11
C	0.90	0.53-1.55	0.71	1.19	0.69-2.04	0.53
D	0.97	0.53-1.79	0.92	1.18	0.64-2.20	0.60
E	0.95	0.51-1.77	0.88	1.13	0.60-2.11	0.71
Lowest 20% of Ward's triangle BMD						
A	1.52	0.75-3.08	0.25	3.07	1.66-5.66	**<0.001**
B	1.70	0.82-3.51	0.15	2.81	1.46-5.43	**0.002**
C	1.50	0.62-3.59	0.37	2.77	1.29-5.94	**0.009**
D	1.87	0.70-4.95	0.21	2.86	1.19-6.88	**0.019**
E	1.82	0.68-4.85	0.23	2.81	1.16-6.79	**0.022**
Lowest 20% of neck of femur BMD						
A	0.79	0.34-1.83	0.58	1.40	0.67-2.94	0.37
B	0.96	0.41-2.23	0.92	1.13	0.48-2.67	0.78
C	0.59	0.18-1.92	0.38	0.91	0.32-2.57	0.85
D	0.82	0.25-2.72	0.75	0.80	0.24-2.70	0.72
E	0.79	0.24-2.62	0.70	0.79	0.23-2.69	0.71

Lowest 20% of trochanter BMD						
A	0.73	0.54-1.17	0.24	1.05	0.71-1.56	0.81
B	0.96	0.64-1.45	0.86	1.24	0.81-1.89	0.32
C	0.88	0.55-1.42	0.61	1.21	0.75-1.95	0.43
D	0.95	0.55-1.62	0.84	1.32	0.78-2.27	0.30
E	0.96	0.56-1.66	0.89	1.28	0.74-2.20	0.38
Lowest 20% of spine BMD						
A	0.75	0.54-1.04	0.08	0.99	0.71-1.38	0.95
B	1.13	0.59-1.16	0.27	1.07	0.75-1.52	0.71
C	0.76	0.51-1.13	0.17	0.99	0.66-1.49	0.96
D	0.72	0.45-1.15	0.17	1.03	0.65-1.64	0.90
E	0.72	0.45-1.16	0.18	1.08	0.67-1.73	0.76

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, fallen in the last year, fractured a bone since turning 50 years of age, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.

Supplementary Table 1: Anti-cholinergic burden scoring table.

Medications		
ACB score of 1	ACB score of 2	ACB score of 3
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna	Amoxapine
Alverine	Carbamazepine	Atropine
Aripiprazole	Cyclobenzaprine	Benztropine
Asenapine	Cyproheptadine	Brompheniramine
Atenolol	Loxapine	Carbinoxamine
Bupropion	Meperidine	Chlorpheniramine
Captopril	Methotrimeprazine	Chlorpromazine
Cetirizine	Molindone	Clemastine
Chlorthalidone	Nefopam	Clomipramine
Cimetidine	Oxcarbazepine	Clozapine
Clidinium	Pimozide	Darifenacin
Clorazepate		Desipramine
Codeine		Dicyclomine
Colchicine		Dimenhydrinate
Desloratadine		Diphenhydramine
Diazepam		Doxepin
Digoxin		Doxylamine
Dipyridamole		Fesoterodine
Fentanyl		Flavoxate
Fluvoxamine		Hydroxyzine
Furosemide		Hyoscyamine
Haloperidol		Imipramine
Hydralazine		Meclizine
Hydrocortisone		Methocarbamol
Iloperidone		Nortriptyline
Isosorbide		Olanzapine
Levocetirizine		Orphenadrine

Loperamide		Oxybutynin
Loratadine		Paroxetine
Metoprolol		Perphenazine
Morphine		Promethazine
Nifedipine		Propantheline
Paliperidone		Propiverine
Prednisone		Quetiapine
Quinidine		Scopolamine
Ranitidine		Solifenacin
Risperidone		Thioridazine
Theophylline		Tolterodine
Trazodone		Trifluoperazine
Triamterene		Trihexyphenidyl
Venlafaxine		Trimipramine
Warfarin		Trospium

ACB score of 1 = Evidence from in vitro data that chemical entity has antagonist activity at muscarinic receptor.

ACB score of 2 = Evidence from literature, prescriber's information, or expert opinion of clinical anti-cholinergic effect.

ACB score of 3 = Evidence from literature, expert opinion, or prescribers' information that medication may cause delirium.

Supplementary Table 2: Results of logistic regression analysis examining the association between anti-cholinergic burden (reference category = 0) and a history of falls over the previous 12 months.

Models	ACB ≥1		
	OR	95% CI	*P*
Falls in the last year			
A	1.29	1.05-1.58	**0.014**
B	1.23	1.00-1.51	0.05
C	1.27	1.00-1.60	**0.048**
D	1.42	1.09-1.86	**0.010**
E	1.41	1.08-1.85	**0.013**

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, fractured a bone since turning 50 years of age, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.

Supplementary Table 3: Results of logistic regression analyses examining association between anti-cholinergic burden (reference category = 0) and hip and spine bone mineral density.

Models	ACB ≥1		
	OR	95% CI	*P*
Lowest 20% of total hip BMD			
A	1.13	0.82-1.55	0.46
B	1.30	0.92-1.80	0.14
C	1.04	0.70-1.54	0.85
D	1.07	0.68-1.69	0.77
E	1.04	0.66-1.64	0.88
Lowest 20% of Ward's triangle BMD			
A	2.42	1.46-4.02	**0.001**
B	2.44	1.44-4.15	**0.001**
C	2.27	1.22-4.23	**0.009**
D	2.62	1.29-5.34	**0.008**
E	2.56	1.25-5.23	**0.010**
Lowest 20% of neck of femur BMD			
A	1.06	0.60-1.90	0.84
B	1.04	0.56-1.95	0.90
C	0.73	0.33-1.62	0.43
D	0.80	0.33-1.93	0.62
E	0.78	0.32-1.88	0.58

Lowest 20% of trochanter BMD			
A	0.90	0.67-1.20	0.46
B	1.09	0.80-1.48	0.58
C	1.03	0.73-1.46	0.86
D	1.12	0.76-1.67	0.57
E	1.11	0.75-1.66	0.60
Lowest 20% of spine BMD			
A	0.84	0.66-1.07	0.16
B	0.93	0.72-1.19	0.55
C	0.86	0.65-1.16	0.32
D	0.84	0.60-1.18	0.32
E	0.86	0.61-1.22	0.40

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, fallen in the last year, fractured a bone since turning 50 years of age, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.

Supplementary Table 4: Results of multiple linear regression analyses examining association between anti-cholinergic burden (reference category = 0) and hip and spine bone mineral density (N =3883).

Models	ACB 1			ACB ≥2		
	B	SE	*P*	B	SE	*P*
Total hip BMD						
A	0.03	0.02	0.11	<0.01	0.02	0.87
B	0.01	0.02	0.78	-0.04	0.02	0.12
C	0.01	0.02	0.78	-0.03	0.03	0.31
D	0.01	0.03	0.63	-0.04	0.03	0.20
E	0.01	0.03	0.57	-0.03	0.03	0.37
Ward's triangle BMD						
A	0.01	0.01	0.32	-0.01	0.01	0.26
B	<0.01	0.01	0.80	-0.02	0.01	**0.042**
C	<0.01	0.01	0.87	-0.02	0.01	0.14
D	<0.01	0.01	0.99	-0.02	0.01	0.07
E	<0.01	0.01	0.93	-0.02	0.01	0.23
Neck of femur BMD						
A	0.01	0.01	0.14	0.01	0.01	0.33
B	<0.01	0.01	0.83	<0.01	0.01	0.94
C	<0.01	0.01	0.70	<0.01	0.01	0.85
D	0.01	0.01	0.46	<0.01	0.01	0.80
E	0.01	0.01	0.43	<0.01	0.01	0.76
Trochanter BMD						
A	0.02	0.01	**0.027**	<0.01	0.01	0.60

B	<0.01	0.01	0.78	-0.01	0.01	**0.049**
C	<0.01	0.01	0.81	-0.01	0.001	0.19
D	0.01	0.01	0.47	-0.02	0.01	0.08
E	0.01	0.01	0.41	-0.01	0.001	0.13
Spine BMD						
A	0.02	0.01	0.06	0.02	0.01	**0.031**
B	0.01	0.01	0.44	0.01	0.01	0.39
C	0.01	0.01	0.58	0.02	0.01	0.22
D	0.01	0.01	0.51	0.01	0.01	0.33
E	0.01	0.01	0.52	0.01	0.01	0.35

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, fallen in the last year, fractured a bone since turning 50 years of age, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.

Supplementary Table 5: Results of multiple linear regression analyses examining association between anti-cholinergic burden (reference category = 0) and T-scores of lumbar spine and neck of femur (N =3870).

Models	ACB 1			ACB ≥2		
	B	SE	*P*	B	SE	*P*
T-score of lumbar spine						
A	0.17	0.09	**0.044**	0.22	0.10	**0.019**
B	0.07	0.08	0.37	0.10	0.09	0.28
C	0.06	0.09	0.49	0.15	0.10	0.15
D	0.08	0.11	0.45	0.14	0.12	0.23
E	0.08	0.11	0.45	0.14	0.12	0.25
T-score neck of femur						
A	0.03	0.04	0.53	<-0.01	0.05	0.98
B	-0.01	0.04	0.78	-0.04	0.05	0.41
C	-0.01	0.05	0.77	-0.01	0.05	0.87
D	-0.02	0.05	0.77	-0.05	0.06	0.43
E	-0.01	0.05	0.85	-0.03	0.06	0.66

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, fallen in the last year, fractured a bone since turning 50 years of age, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.

Supplementary Table 6: Results of multiple linear regression analyses examining association between anti-cholinergic burden (reference category = 0) and Z-scores of lumbar spine and neck of femur (N =1864).

Models	ACB 1			ACB ≥2		
	B	SE	*P*	B	SE	*P*
Z-score of lumbar spine						
A	0.18	0.11	0.09	0.16	0.13	0.19
B	0.10	0.10	0.33	<0.01	0.12	0.98
C	0.08	0.12	0.50	0.06	0.13	0.68
D	0.10	0.14	0.46	0.07	0.16	0.66
E	0.09	0.14	0.53	0.09	0.17	0.59
Z-score neck of femur						
A	0.13	0.07	0.06	0.05	0.08	0.57
B	0.06	0.07	0.37	-0.05	0.08	0.53
C	0.08	0.07	0.29	-0.06	0.09	0.49
D	0.12	0.09	0.17	-0.01	0.10	0.94
E	0.12	0.09	0.17	0.02	0.11	0.86

Model A: Unadjusted.
Model B: Adjusted for age, BMI and current hormone replacement therapy.
Model C: Model B additionally adjusted for menopausal status and physical activity level.
Model D: Model C additionally adjusted for history of comorbidities: osteoporosis, osteoarthritis, rheumatoid arthritis, kidney disease, thyroid disease, diabetes mellitus, current smoker, hypertension, stroke, fallen in the last year, fractured a bone since turning 50 years of age, mother has broken their hip, 25OHD ≤25 nmol/L.
Model E: Model D additionally adjusted for other medications taken; corticosteroids, oral contraceptive, calcium supplements, osteoporosis medication, anti-epileptic medication, diuretics.