

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

For classification of diseases, sign and symptoms, surgical procedures, we used digital records of ICD-10 i.e. the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization (WHO).

For classification of medications, the The Anatomical Therapeutic Chemical (ATC) Classification System was used. It is overseen by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).

**eTable 1. Definition of fracture (prior or incident)**

ICD-codes	Fracture site	Other criteria
S12	Neck	If a fracture diagnosis on the same skeletal site (ICD-10 two digits) was repeated within five months, the latter was discarded since it most likely was a revisit and not a new fracture.
S22	Rib(s), sternum and thoracic spine	
S32	Lumbar spine and pelvis	
S42	Shoulder and upper arm	
S52	Forearm	
S62	Wrist and hand level	
S72	Femur	
S82	Lower leg, including ankle	
S92	Foot, except ankle	
T02	Multiple body regions	
T08	Spine, level unspecified	
T10	Upper limb, level unspecified	
T12	Lower limb, level unspecified	
T142	Unspecified body region	
M485	Collapsed vertebra, not elsewhere classified	

**eTable 2.** Definition of hip fracture, major osteoporotic fracture, vertebral fracture, fall injury, fall injury without fracture and head fracture

Variable	ICD-codes
Hip fracture	S720-S722 (femoral head, neck, trochanter or subtrochanter part of femur) in combination with a code for a surgical procedure starting with NFB or NFJ39-NFJ99 <sup>3</sup>
Major osteoporotic fracture (MOF)	Hip fracture (as defined above), wrist (S525, S526), shoulder (S422) and clinical vertebral fracture (S120, S121, S122, S220, S221, S320, M485)
Vertebral fracture	S120, S121, S122, S220, S221, S320, M485
Fall injury	Injury code (S00-T14) in combination with a code representing a fall (W00-W19)
Fall injury without fracture	Injury codes S00-T14 (except fracture codes S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T142) in combination with a code representing a fall (W00-W19)
Head fracture	S02

**eTable 3.** Definition of adverse effects

<b>Definition</b>	<b>Any of the following ICD-10 codes</b>	<b>Specification</b>
Mild upper GI-symptom	K20	Esophagitis
	K21	Acid reflux
	K30	Dyspepsia
Peptic ulcer	K25	Gastric ulcer
	K26	Duodenal ulcer
	K27	Peptic ulcer, site unspecified
Drug-induced osteonecrosis	M871	
Femoral shaft fracture	S723 in combination with surgical procedure starting with NFB or NFJ39-NFJ99 <sup>3</sup>	If the diagnosis was repeated within five months, the latter was discarded since it most likely was a revisit and not a new fracture.

**eTable 4.** Definition of inflammatory diseases

<b>Definition</b>	<b>ICD-10 codes</b>
Polymyalgia rheumatica	M353
Other systemic connective tissue disorders	M30-M36 (excluding M353)
Non-infective enteritis and colitis	K50-K52
Rheumatoid arthritis	M05-M06

**eTable 5.** Definition of alcohol-related diseases

<b>Definition</b>	<b>ICD-10 codes</b>	<b>Description</b>
Any of the listed diseases	F10	Mental and behavioral disorders due to use of alcohol
	G312	Degeneration of nervous system due to alcohol
	G621	Alcoholic polyneuropathy
	G721	Alcoholic myopathy
	I426	Alcoholic cardiomyopathy
	K292	Alcoholic gastritis
	K70	Alcoholic liver disease
	K852	Alcohol-induced acute pancreatitis
	K860	Alcohol-induced chronic pancreatitis
	T51	Toxic effect of alcohol
	Y912	Severe alcohol intoxication
	Y913	Very severe alcohol intoxication

**eTable 6.** Definition of diseases related to secondary osteoporosis

<b>Definition</b>	<b>ICD-10 codes</b>	<b>Description</b>
Any of the listed diseases	E05	Hyperthyroidism
	E10	Insulin dependent diabetes
	E28-E29	Hypogonadism
	E40-E46	Malnutrition
	K70-K77 (chronic)	Chronic liver disease
	Q780	Osteogenesis imperfecta

**eTable 7.** Definition of previous calcium and vitamin D treatment

<b>Definition</b>	<b>ATC-code</b>	<b>Description</b>
Any previous treatment exceeding 3 months occurring during the last two years prior to the risk assessment	A12AX	Calcium, combinations with vitamin D and/or other drugs



**eTable 8.** Definition of Charlson comorbidity index

Definition	ICD-10 codes	Description	Weight
Weighted sum of the listed codes	F00-F03	Dementia	1
	I20-I25	Ischemic heart diseases	1
	I50	Congestive heart failure	1
	I60-I69	Cerebrovascular diseases	1
	I70-I79	Diseases of arteries, arterioles and capillaries	1
	J43-J46	Chronic pulmonary disease	1
	K70-K77 (chronic)	Chronic liver disease	1
	C00-C76, C80, C97	Tumor without metastasis (<5 years)	2
	C81-C96	Lymphoma or leukemia	2
	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, H360, H360A, H360B, H360X	Diabetes with end organ damage	2
	E10-14 if no diabetic code above	Diabetes without end organ damage	1
	N182-N185	Renal failure moderate or severe	2
	N17-N19, if no renal code above	Other renal failure	1
	G81	Hemiplegia	2
K25-K27	Peptic ulcer disease	2	
C77-C79	Metastatic solid tumor	6	

## **eAppendix. Prednisolone treatment and fracture risk**

The association between prednisolone treatment, according to average daily dose, and fracture risk was investigated. From the sample of 262 307 patients without any osteoporosis medication (alendronate, risedronate, zoledronic acid, denosumab, testosterone, systemic estrogens, strontium ranelate, PTH-analogues, or selective estrogen receptor modulators), 10 332 patients treated with prednisolone were identified (eFigure 1). The patients using prednisolone were divided into groups according to average dose (mg/day): minimal (less than 2.5), low (2.5 or more, less than 5), medium (5 or more, less than 7.5), and high (7.5 or more) and were compared to patients who had not received any glucocorticoid treatment.

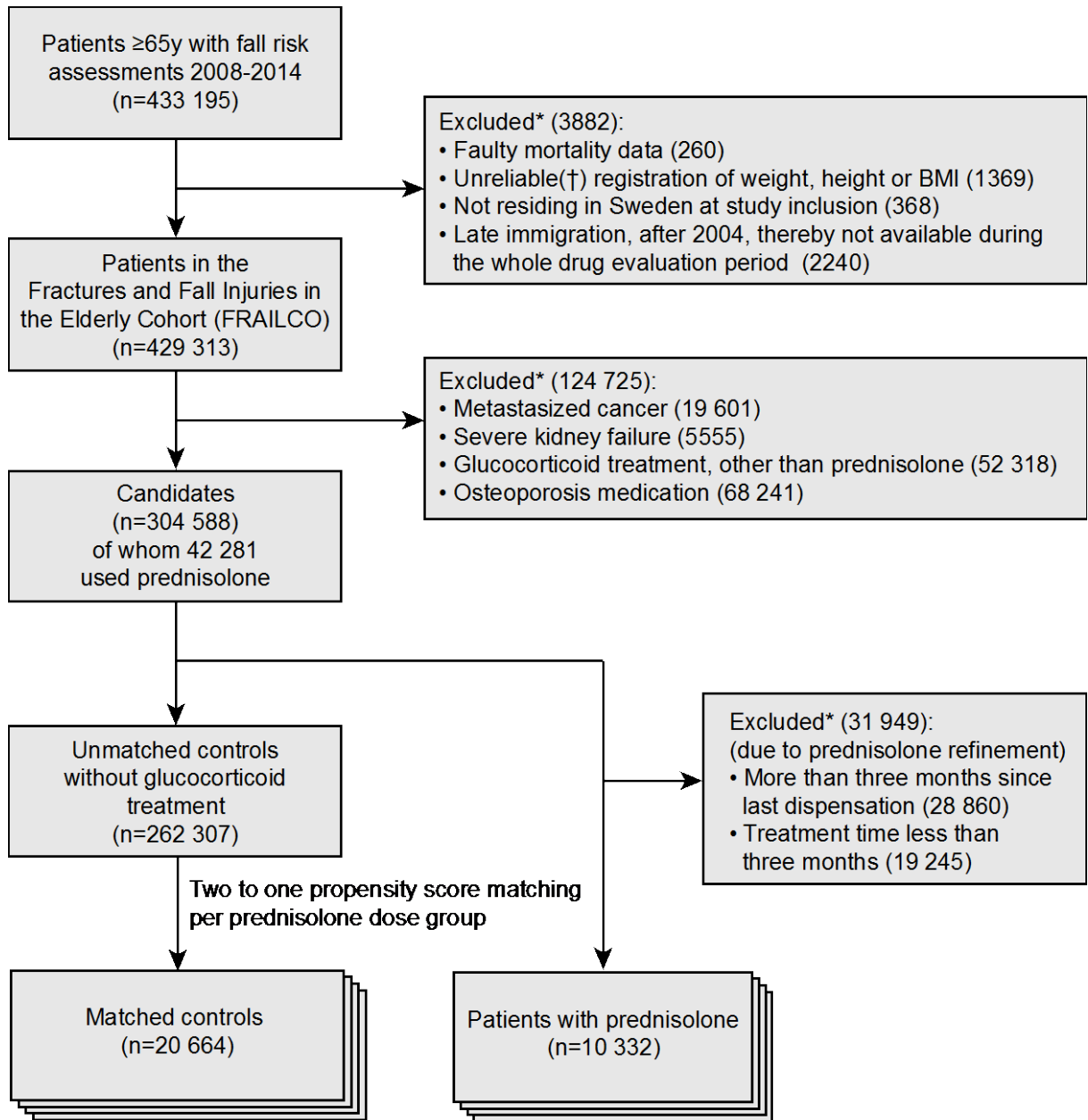
Using propensity score matching by prednisolone dose group, a total of 20 664 patients without prednisolone were selected. Thus, the investigated sample included a total of 30 996 patients. The two-to-one propensity score matching was performed according to age, sex, weight, height, the individual diseases included in the secondary osteoporosis definition (eTable 6), and Charlson comorbidity index (eTable 8, excluding chronic obstructive pulmonary disease), as well as fracture-free time, any previous fracture, number of previous fractures, previous hip fracture, previous vertebral fracture, previous fall injury (eTable 1-2), osteoporosis diagnosis (M80-M81) and alcohol-related diseases (eTable 5).<sup>1,2</sup>

Intergroup differences were evaluated using Fischer's exact test for categorical variables, Chi2-test if multiple categories, and t-tests for continuous variables if normally distributed; if not, the Mann-Whitney U-test. To investigate the association between fracture risk and treatment with prednisolone, a Cox proportional hazards model was used, starting at baseline with follow-up time to fracture and censored for death, emigration or end of study (Dec 31, 2014).

The groups with and without prednisolone were generally well-balanced - apart from secondary osteoporosis being slightly more common in the prednisolone groups (doses more than 2.5 mg/day) - only inflammatory diseases and calcium/vitamin D treatment differed significantly between the groups (eTable 9).

The association between the use of prednisolone and fracture risk was then investigated according to dose group. The incidence of hip fracture, major osteoporotic fracture, as well as any fracture was higher in patients using medium or high prednisolone doses than in untreated patients, in unadjusted and multivariable-adjusted Cox models (eTable 10).

**eFigure 1.** Study population for the association of hip fracture and prednisolone use among patients not receiving osteoporosis medication



\* Each patient may be included in more than one exclusion group

† Accepted values after exclusion of top and bottom 1% of weight, height and BMI

• Weight: 30-176 kg

• Height: 114-197 cm

• BMI: 12.23 – 73.05 kg/m<sup>2</sup>

**eTable 9.** Baseline characteristics of patients not receiving osteoporosis medication with and without prednisolone treatment

Description	No prednisolone (matched)	Prednisolone	No prednisolone (matched)	Prednisolone	No prednisolone (matched)	Prednisolone	No prednisolone (matched)	Prednisolone
		Minimal dose		Low dose		Medium dose		High dose
		<2.5 mg/day		2.5 to <5 mg/day		5 to <7.5 mg/day		≥7.5 mg/day
Number of patients	3476	1738	5036	2518	5980	2990	6172	3086
Average dose, median (IQR), mg/day		1.3 (0.7-1.9)		3.9 (3.1-4.5)		5.8 (5.3-6.6)		10.9 (8.8-14.9)
Treatment time, median (IQR), y		4.9 (2.9-6.3)		5.6 (3.5-6.9)		5.0 (2.7-6.5)		1.6 (0.7-3.9)
Female sex, no. (%)	1838 (52.9)	926 (53.3)	2961 (58.8)	1460 (58.0)	3279 (54.8)	1645 (55.0)	3008 (48.7)	1510 (48.9)
Age, mean (SD), y	79.9 (8.3)	80.2 (8.1)	83.0 (8.0)	82.9 (7.9)	82.6 (8.1)	82.4 (7.8)	80.8 (8.3)	80.7 (7.6)
Weight, mean (SD), kg	72.4 (16.2)	72.2 (17.6)	69.4 (15.6)	69.6 (16.0)	71.2 (16.0)	71.0 (15.5)	74.0 (17.3)	74.3 (16.8)
Height, mean (SD), cm	167.6 (9.8)	167.3 (9.7)	165.8 (9.9)	165.9 (10.0)	166.5 (9.9)	166.5 (9.8)	167.8 (10.0)	168.0 (9.9)
Known fracture-free time, median (IQR), y	25 (9-27)	25 (8-27)	25 (5-26)	25 (5-26)	25 (5-26)	25 (5-26)	25 (6-26)	25 (6-26)
Any previous fracture, no. (%)	1034 (29.7)	515 (29.6)	1681 (33.4)	853 (33.9)	2010 (33.6)	1004 (33.6)	1902 (30.8)	944 (30.6)
Number of previous fractures, no. (%)								
0	2442 (70.3)	1223 (70.4)	3355 (66.6)	1665 (66.1)	3970 (66.4)	1986 (66.4)	4270 (69.2)	2142 (69.4)
1	745 (21.4)	368 (21.2)	1160 (23.0)	594 (23.6)	1382 (23.1)	701 (23.4)	1339 (21.7)	685 (22.2)
2	196 (5.6)	98 (5.6)	338 (6.7)	161 (6.4)	437 (7.3)	197 (6.6)	384 (6.2)	176 (5.7)
≥3	93 (2.7)	49 (2.8)	183 (3.6)	98 (3.9)	191 (3.2)	106 (3.5)	179 (2.9)	83 (2.7)
Previous hip fracture, no. (%)	247 (7.1)	118 (6.8)	550 (10.9)	266 (10.6)	572 (9.6)	276 (9.2)	524 (8.5)	242 (7.8)
Previous vertebral fracture, no. (%)	160 (4.6)	81 (4.7)	263 (5.2)	151 (6.0)	377 (6.3)	195 (6.5)	425 (6.9)	222 (7.2)
Previous fall injury, no. (%)	980 (28.2)	496 (28.5)	1788 (35.5)	907 (36.0)	2145 (35.9)	1073 (35.9)	1996 (32.3)	962 (31.2)
Osteoporosis, no. (%)	134 (3.9)	68 (3.9)	227 (4.5)	120 (4.8)	306 (5.1)	167 (5.6)	330 (5.3)	162 (5.2)
Secondary osteoporosis, no. (%)	173 (5.0)	86 (4.9)	255 (5.1)	160 (6.4)*	340 (5.7)	216 (7.2)†	360 (5.8)	215 (7.0)*
- Insulin dependent diabetes, no. (%)	122 (3.5)	63 (3.6)	243 (4.8)	122 (4.8)	326 (5.5)	172 (5.8)	362 (5.9)	176 (5.7)
- Hyperthyroidism, no. (%)	48 (1.4)	27 (1.6)	68 (1.4)	36 (1.4)	70 (1.2)	33 (1.1)	100 (1.6)	48 (1.6)
- Hypogonadism, no. (%)	5 (0.1)	2 (0.1)	5 (0.1)	3 (0.1)	6 (0.1)	2 (0.1)	1 (0.0)	1 (0.0)
- Malnutrition, no. (%)	16 (0.5)	8 (0.5)	32 (0.6)	13 (0.5)	10 (0.2)	7 (0.2)	26 (0.4)	14 (0.5)
- Osteogenesis imperfecta, no. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.0)	0 (0)
- Chronic liver disease, no. (%)	42 (1.2)	23 (1.3)	63 (1.3)	30 (1.2)	98 (1.6)	44 (1.5)	108 (1.7)	57 (1.8)
Charlson comorbidity index, no. (%):								
0	1261 (36.3)	524 (30.1)†	1736 (34.5)	914 (36.3)*	2078 (34.7)	1103 (36.9)†	2051 (33.2)	1067 (34.6)
1-2	1209 (34.8)	574 (33.0)†	1680 (33.4)	738 (29.3)*	1916 (32.0)	851 (28.5)†	1978 (32.0)	939 (30.4)
≥3	1006 (28.9)	640 (36.8)†	1620 (32.2)	866 (34.4)*	1986 (33.2)	1036 (34.6)†	2143 (34.7)	1080 (35.0)

<u>Charlson comorbidity index components:</u>								
- Ischemic heart diseases, no. (%)	928 (26.7)	468 (26.9)	1411 (28.0)	707 (28.1)	1613 (27.0)	797 (26.7)	1612 (26.1)	803 (26.0)
- Congestive heart failure, no. (%)	874 (25.1)	445 (25.6)	1137 (22.6)	551 (21.9)	1297 (21.7)	657 (22.0)	1384 (22.4)	667 (21.6)
- Cerebrovascular diseases, no. (%)	568 (16.3)	284 (16.3)	876 (17.4)	446 (17.7)	947 (15.8)	494 (16.5)	951 (15.4)	472 (15.3)
- Diseases of arterioles and capillaries, no. (%)	365 (10.5)	177 (10.2)	500 (9.9)	259 (10.3)	712 (11.9)	341 (11.4)	676 (11.0)	323 (10.5)
- Diabetes, no. (%)	488 (14.0)	251 (14.4)	776 (15.4)	384 (15.3)	1006 (16.8)	503 (16.8)	1232 (20.0)	599 (19.4)
- Dementia, no. (%)	194 (5.6)	97 (5.6)	477 (9.5)	232 (9.2)	587 (9.8)	291 (9.7)	558 (9.0)	266 (8.6)
- Chronic liver disease, no. (%)	42 (1.2)	23 (1.3)	63 (1.3)	30 (1.2)	98 (1.6)	44 (1.5)	108 (1.7)	57 (1.8)
- Chronic pulmonary disease, no. (%)	216 (6.2)	639 (36.8)†	317 (6.3)	409 (16.2)†	369 (6.2)	396 (13.2)†	424 (6.9)	340 (11.0)†
- Renal failure, mild, no. (%)	237 (6.8)	122 (7.0)	393 (7.8)	199 (7.9)	499 (8.3)	261 (8.7)	548 (8.9)	259 (8.4)
- Renal failure, moderate or severe, no. (%)	35 (1.0)	17 (1.0)	61 (1.2)	27 (1.1)	59 (1.0)	28 (0.9)	76 (1.2)	38 (1.2)
- Peptic ulcer disease, no. (%)	133 (3.8)	72 (4.1)	290 (5.8)	146 (5.8)	379 (6.3)	174 (5.8)	351 (5.7)	169 (5.5)
- Hemiplegia, no. (%)	39 (1.1)	27 (1.6)	114 (2.3)	50 (2.0)	118 (2.0)	61 (2.0)	116 (1.9)	57 (1.8)
- Tumor without metastasis (<5 years), no. (%)	641 (18.4)	312 (18.0)	987 (19.6)	473 (18.8)	1224 (20.5)	615 (20.6)	1220 (19.8)	605 (19.6)
- Lymphoma or leukemia, no. (%)	86 (2.5)	47 (2.7)	140 (2.8)	66 (2.6)	127 (2.1)	66 (2.2)	372 (6.0)	179 (5.8)
<u>Inflammatory diseases</u>								
Polymyalgia rheumatica, no. (%)	11 (0.3)	129 (7.4)†	22 (0.4)	495 (19.7)†	24 (0.4)	603 (20.2)†	25 (0.4)	706 (22.9)†
Other syst. connective tissue disorders, no. (%)	26 (0.7)	53 (3.0)†	38 (0.8)	125 (5.0)†	37 (0.6)	148 (4.9)†	40 (0.6)	171 (5.5)†
Non-infective enteritis and colitis, no. (%)	70 (2.0)	92 (5.3)†	112 (2.2)	140 (5.6)†	147 (2.5)	141 (4.7)†	142 (2.3)	147 (4.8)†
Rheumatoid arthritis, no. (%)	16 (0.5)	167 (9.6)†	35 (0.7)	504 (20.0)†	41 (0.7)	661 (22.1)†	43 (0.7)	325 (10.5)†
<u>Other characteristics</u>								
Prevalent calcium/vitamin D‡, no. (%)	203 (5.8)	354 (20.4)†	371 (7.4)	1104 (43.8)†	459 (7.7)	1430 (47.8)†	431 (7.0)	1409 (45.7)†
Alcohol related diseases, no. (%)	48 (1.4)	29 (1.7)	28 (0.6)	19 (0.8)	43 (0.7)	22 (0.7)	73 (1.2)	37 (1.2)

\* p-value <0.05. † p-value <0.01.

‡ Data regarding prevalent calcium and vitamin D treatment was retrieved from the Prescribed Drug Register and defined as any treatment length exceeding three months during the last two years before baseline.

Abbreviations used: IQR=Interquartile range, SD=Standard Deviation, Syst.=Systemic

**eTable 10.** Fracture risks associated with prednisolone treatment in older patients without osteoporosis medication

Description	No prednisolone (matched)	Prednisolone	No prednisolone (matched)	Prednisolone	No prednisolone (matched)	Prednisolone	No prednisolone (matched)	Prednisolone
		Minimal dose <2.5 mg/day		Low dose 2.5 to <5 mg/day		Medium dose 5 to <7.5 mg/day		High dose ≥7.5 mg/day
Number of patients	3476	1738	5036	2518	5980	2990	6172	3086
Time at risk, median (IQR), d	512 (222-869)	413 (161-766)†	510 (223-863)	435 (167-803)†	508 (225-892)	451 (182-827)†	504 (225-907)	420 (145-819)†
<b>Hip fractures</b>								
No. (%)	104 (3.0)	49 (2.8)	213 (4.2)	94 (3.7)	246 (4.1)	130 (4.3)	213 (3.5)	121 (3.9)
Per 1000 person-years (95%CI)	19 (16-23)	21 (16-27)	27 (24-31)	26 (21-32)	26 (23-29)	30 (25-35)	22 (19-25)	28 (23-33)*
Per 1000 person-years difference (95%CI)	Reference	1.7 (-5.2 – 8.5)	Reference	-0.7 (-7.1 – 5.7)	Reference	3.8 (-2.2 – 9.9)	Reference	6.4 (0.7-12.2)*
<b>Prednisolone (yes/no) HR (95% CI)</b>								
Unadjusted	Reference	1.07 (0.76-1.50)	Reference	0.96 (0.76-1.23)	Reference	1.14 (0.92-1.40)	Reference	1.28 (1.03-1.60)*
Adjusted for age, sex, weight, height	Reference	1.06 (0.75-1.49)	Reference	0.98 (0.77-1.25)	Reference	1.18 (0.96-1.47)	Reference	1.38 (1.10-1.72)*
Multivariable adjustment‡	Reference	1.02 (0.71-1.46)	Reference	1.10 (0.84-1.45)	Reference	1.33 (1.04-1.69)*	Reference	1.49 (1.16-1.92)†
<b>Major Osteoporotic Fractures (MOF)</b>								
No. (%)	145 (4.2)	71 (4.1)	273 (5.4)	125 (5.0)	321 (5.4)	182 (6.1)	290 (4.7)	165 (5.3)
Per 1000 person-years (95%CI)	27 (23-31)	30 (24-38)	35 (31-39)	35 (30-42)	34 (31-38)	42 (37-49)*	30 (26-33)	39 (33-45)†
Per 1000 person-years difference (95%CI)	Reference	3.4 (-4.8 – 11.7)	Reference	0.4 (-7.0 – 7.9)	Reference	8.1 (0.9-15.2)*	Reference	9.1 (2.3 – 15.9)†
<b>Prednisolone (yes/no) HR (95% CI)</b>								
Unadjusted	Reference	1.11 (0.83-1.47)	Reference	1.00 (0.81-1.23)	Reference	1.22 (1.02-1.47)*	Reference	1.29 (1.06-1.56)*
Adjusted for age, sex, weight, height	Reference	1.09 (0.82-1.45)	Reference	1.02 (0.82-1.26)	Reference	1.26 (1.05-1.51)*	Reference	1.35 (1.12-1.64)†

Multivariable adjustment <sup>‡</sup>	Reference	1.07 (0.79-1.44)	Reference	1.10 (0.86-1.40)	Reference	1.31 (1.05-1.62)*	Reference	1.45 (1.16-1.80)†
<b>Any fracture</b>								
No. (%)	271 (7.8)	131 (7.5)	457 (9.1)	232 (9.2)	537 (9.0)	313 (10.5)*	511 (8.3)	284 (9.2)
Per 1000 person-years (95%CI)	52 (46-58)	57 (48-68)	61 (56-67)	68 (60-77)	59 (55-65)	75 (68-84)†	54 (49-59)	69 (61-77)†
Per 1000 person-years difference (95%CI)	Reference	5.8 (-6.0 – 17.0)	Reference	6.9 (-3.5 – 17.2)	Reference	16.1 (6.3-25.8)†	Reference	14.7 (5.5-24.0)†
<u>Prednisolone (yes/no) HR (95% CI)</u>								
Unadjusted	Reference	1.07 (0.87-1.32)	Reference	1.09 (0.93-1.28)	Reference	1.25 (1.09-1.44)†	Reference	1.23 (1.07-1.43)*
Adjusted for age, sex, weight, height	Reference	1.05 (0.86-1.30)	Reference	1.11 (0.95-1.30)	Reference	1.29 (1.12-1.48)†	Reference	1.28 (1.11-1.48)†
Multivariable adjustment <sup>‡</sup>	Reference	1.06 (0.85-1.32)	Reference	1.14 (0.95-1.37)	Reference	1.27 (1.07-1.49)*	Reference	1.34 (1.14-1.59)†

\* p-value <0.05. † p-value <0.01

‡ multivariable adjustment = age, sex, weight, height, known fracture-free time, previous fracture, number of previous fractures, previous hip fracture, previous vertebral fracture, previous fall injury, osteoporosis, secondary osteoporosis, Charlson comorbidity index, rheumatoid arthritis, previous calcium and vitamin D treatment and alcohol related diseases.

**eTable 11.** General health, nutrition and liquid intake among patients receiving medium and high-dose prednisolone with and without alendronate treatment

Description	No alendronate	Alendronate	<i>p</i> -value
<u>General condition</u>			
Good - no. (%)	600 (33.3)	624 (34.6)	
Fairly good - no. (%)	976 (54.2)	962 (53.4)	
Bad - no. (%)	193 (10.7)	187 (10.4)	
Very bad - no. (%)	25 (1.4)	21 (1.2)	
Missing value - no. (%)	8 (0.4)	8 (0.4)	
Total - no. (%)	1802 (100)	1802 (100)	0.91
<u>Nutrition</u>			
normal portion - no. (%)	1100 (61.0)	1126 (62.5)	
$\frac{3}{4}$ portion - no. (%)	332 (18.4)	302 (16.8)	
$\frac{1}{2}$ portion - no. (%)	254 (14.1)	277 (15.4)	
< $\frac{1}{2}$ portion - no. (%)	108 (6.0)	89 (4.9)	
Missing value - no. (%)	8 (0.4)	8 (0.4)	
Total - no. (%)	1802 (100)	1802 (100)	0.34
<u>Liquid intake</u>			
>1000 ml - no. (%)	1030 (57.2)	1074 (59.6)	
700-1000 ml - no. (%)	589 (32.7)	563 (31.2)	
500-700 ml - no. (%)	144 (8.0)	129 (7.2)	
<500 ml - no. (%)	31 (1.7)	28 (1.6)	
Missing value - no. (%)	8 (0.4)	8 (0.4)	
Total - no. (%)	1802 (100)	1802 (100)	0.65

General condition, food intake, and liquid intake were characterized using the validated RAPS and Norton scales,<sup>4</sup> which were assessed at baseline.



**eTable 12.** Fracture risk and alendronate treatment analyzed according to gender (medium or high dose prednisolone)

Description	Women			Men		
	No alendronate	Alendronate	<i>p</i> -value	No alendronate	Alendronate	<i>p</i> -value
N=	1248	1276		554	526	
Time at risk, median (IQR), d	517 (210-882)	535 (247-870)	0.29	411 (124-808)	438 (192-810)	0.23
<b>Hip fractures</b>						
No. (%)	62 (5.0)	24 (1.9)	<0.001	11 (2.0)	3 (0.6)	0.06
Per 1000 person-years	32.3 (25.2-41.4)	11.6 (7.8-17.4)	<0.001	14.4 (8.0-25.9)	3.9 (1.3-12.1)	0.05
Per 1000 person-years difference	Reference	-20.7 (-29.9 -- 11.4)	<0.001	Reference	-10.5 (-20.0 -- 0.9)	0.03
<u>Alendronate treatment (yes/no) HR (95% CI)</u>						
Unadjusted	Reference	0.36 (0.23-0.58)	<0.001	Reference	0.27 (0.08-0.98)	0.05
Adjusted for age, weight, height	Reference	0.38 (0.23-0.60)	<0.001	Reference	0.24 (0.07-0.87)	0.03
Multivariable adjustment*	Reference	0.36 (0.23-0.58)	<0.001	Reference	0.22 (0.06-0.84)	0.03
<b>Major Osteoporotic Fractures (MOF)</b>						
No. (%)	91 (7.3)	51 (4.0)	<0.001	15 (2.7)	8 (1.5)	0.21
Per 1000 person-years	48.4 (39.4-59.4)	25.2 (19.2-33.2)	<0.001	19.7 (11.9-32.6)	10.5 (5.2-20.9)	0.15
Per 1000 person-years difference	Reference	-23.1 (-35.2 -- 11.0)	<0.001	Reference	-9.2 (-21.5 -- 3.1)	0.14
<u>Alendronate treatment (yes/no) HR (95% CI)</u>						
Unadjusted	Reference	0.53 (0.38-0.75)	<0.001	Reference	0.54 (0.23-1.27)	0.16
Adjusted for age, weight, height	Reference	0.54 (0.38-0.76)	<0.001	Reference	0.48 (0.20-1.14)	0.10
Multivariable adjustment*	Reference	0.53 (0.37-0.74)	<0.001	Reference	0.49 (0.20-1.20)	0.12

<b>Any fracture</b>						
No. (%)	157 (12.6)	102 (8.0)	<0.001	29 (5.2)	16 (3.0)	0.09
Per 1000 person-years	87.9 (75.1-102.7)	52.1 (42.9-63.2)	<0.001	38.7 (26.9-55.7)	21.1 (12.9-34.5)	0.05
Per 1000 person-years difference	Reference	-35.8 (-52.8 – -18.7)	<0.001	Reference	-17.6 (-35.0 – -0.1)	0.05
<u>Alendronate treatment (yes/no) HR (95% CI)</u>						
Unadjusted	Reference	0.60 (0.47-0.77)	<0.001	Reference	0.56 (0.30-1.02)	0.06
Adjusted for age, weight, height	Reference	0.61 (0.47-0.78)	<0.001	Reference	0.48 (0.26-0.89)	0.02
Multivariable adjustment*	Reference	0.59 (0.46-0.75)	<0.001	Reference	0.54 (0.29-1.01)	0.06
<b>Non-vertebral fracture</b>						
No. (%)	142 (11.4)	89 (7.0)	<0.001	27 (4.9)	13 (2.5)	0.05
Per 1000 person-years	78.6 (66.7-92.6)	44.9 (37.5-56.5)	<0.001	35.9 (24.6-52.4)	17.1 (9.9-29.4)	0.03
Per 1000 person-years difference	Reference	-33.7 (-49.6 – -17.8)	<0.001	Reference	-18.9 (-35.3 – -2.4)	0.02
<u>Alendronate treatment (yes/no) HR (95% CI)</u>						
Unadjusted	Reference	0.58 (0.45-0.76)	<0.001	Reference	0.48 (0.25-0.94)	0.06
Adjusted for age, weight, height	Reference	0.58 (0.45-0.76)	<0.001	Reference	0.41 (0.21-0.80)	0.009
Multivariable adjustment*	Reference	0.56 (0.43-0.74)	<0.001	Reference	0.47 (0.24-0.94)	0.03

\* Multivariable adjustment = age, weight, height, known fracture-free time, previous fracture, number of previous fractures, previous hip fracture, previous vertebral fracture, previous fall injury, osteoporosis, secondary osteoporosis, Charlson comorbidity index, rheumatoid arthritis, previous calcium and vitamin D treatment and alcohol-related diseases.

**eTable 13.** Fracture risk and alendronate treatment analyzed according to daily dose of prednisolone

Description	Medium dose (5.0 to <7.5 mg/day)		p-value	High dose (≥7.5 mg/day)		p-value
	No alendronate	Alendronate		No alendronate	Alendronate	
N=	865	696		937	1106	
Time at risk, median (IQR), d	479 (196-891)	486 (224-862)	0.78	463 (181-845)	506 (231-846)	0.05
<b>Hip fractures</b>						
No. (%)	36 (4.2)	15 (2.2)	0.03	37 (3.9)	12 (1.1)	<0.001
Per 1000 person-years	27.4 (19.8-38.0)	13.8 (8.3-22.9)	0.03	26.9 (19.5-37.2)	6.9 (3.9-12.1)	<0.001
Per 1000 person-years difference	Reference	-13.6 (-25.0 – -2.2)	0.02	Reference	-20.1 (-29.6 – -10.6)	<0.001
<b>Alendronate treatment (yes/no) HR (95% CI)</b>						
Unadjusted	Reference	0.51 (0.28-0.93)	0.03	Reference	0.26 (0.13-0.49)	<0.001
Adjusted for age, sex, weight, height	Reference	0.50 (0.28-0.92)	0.03	Reference	0.25 (0.13-0.49)	<0.001
Multivariable adjustment*	Reference	0.45 (0.24-0.83)	0.01	Reference	0.26 (0.13-0.50)	<0.001
30 months ARR (%) - multivariable adjustment*	Reference	3.0 (1.2-5.2)	0.01	Reference	4.7 (3.0-6.3)	<0.001
30 months NNT - multivariable adjustment*	Reference	33 (19-83)	0.01	Reference	21 (16-33)	<0.001
<b>Major Osteoporotic Fractures (MOF)</b>						
No. (%)	54 (6.2)	33 (4.7)	0.22	52 (5.5)	26 (2.4)	<0.001
Per 1000 person-years	41.8 (32.0-54.6)	31.2 (22.2-43.9)	0.18	38.4 (29.3-50.4)	15.1 (10.3-22.1)	<0.001
Per 1000 person-years difference	Reference	-10.7 (-26.1 – 4.8)	0.18	Reference	-23.4 (35.3 – -11.4)	<0.001
<b>Alendronate treatment (yes/no) HR (95% CI)</b>						
Unadjusted	Reference	0.75 (0.49-1.16)	0.20	Reference	0.40 (0.25-0.64)	<0.001
Adjusted for age, sex, weight, height	Reference	0.74 (0.48-1.14)	0.18	Reference	0.39 (0.24-0.63)	<0.001
Multivariable adjustment*	Reference	0.68 (0.44-1.06)	0.09	Reference	0.40 (0.25-0.64)	<0.001
30 months ARR (%) - multivariable adjustment*				Reference	4.7 (2.8-6.7)	<0.001
30 months NNT - multivariable adjustment*				Reference	21 (15-36)	<0.001

<b>Any fracture</b>						
No. (%)	101 (11.7)	65 (9.3)	0.14	85 (9.1)	53 (4.8)	<0.001
Per 1000 person-years	82.1 (67.6-99.8)	63.1 (49.5-80.5)	0.10	65.0 (52.6-80.4)	31.4 (24.0-41.1)	<0.001
Per 1000 person-years difference	Reference	-19.0 (-41.2 – 3.2)	0.09	Reference	-33.6 (-49.8 – -17.4)	<0.001
<b>Alendronate treatment (yes/no) HR (95% CI)</b>						
Unadjusted	Reference	0.77 (0.57-1.06)	0.11	Reference	0.49 (0.35-0.69)	<0.001
Adjusted for age, sex, weight, height	Reference	0.75 (0.55-1.03)	0.07	Reference	0.48 (0.34-0.68)	<0.001
Multivariable adjustment*	Reference	0.69 (0.50-0.95)	0.02	Reference	0.48 (0.34-0.68)	<0.001
30 months ARR - multivariable adjustment*	Reference	4.8 (1.3-8.2)	0.02	Reference	6.1 (3.7-8.6)	<0.001
30 months NNT - multivariable adjustment*	Reference	21 (12-76)	0.02	Reference	16 (12-27)	<0.001
<b>Non-vertebral fracture</b>						
No. (%)	94 (10.9)	58 (8.3)	0.10	75 (8.0)	44 (4.0)	<0.001
Per 1000 person-years	75.9 (62.0-92.9)	55.6 (43.0-71.9)	0.06	56.8 (45.3-71.2)	25.9 (19.3-34.8)	<0.001
Per 1000 person-years difference	Reference	-20.4 (-41.3 – 0.6)	0.06	Reference	-30.9 (-45.9 – -16.0)	<0.001
<b>Alendronate treatment (yes/no) HR (95% CI)</b>						
Unadjusted	Reference	0.74 (0.53-1.02)	0.07	Reference	0.46 (0.32-0.67)	<0.001
Adjusted for age, sex, weight, height	Reference	0.72 (0.52-1.00)	0.05	Reference	0.45 (0.31-0.66)	<0.001
Multivariable adjustment*	Reference	0.66 (0.47-0.92)	0.01	Reference	0.45 (0.31-0.66)	<0.001
30 months ARR - multivariable adjustment*	Reference	4.6 (1.3-7.9)	0.02	Reference	5.9 (3.6-8.2)	<0.001
30 months NNT - multivariable adjustment*	Reference	22 (13-77)	0.02	Reference	17(12-28)	<0.001

\* Multivariable adjustment = age, sex, weight, height, known fracture-free time, previous fracture, number of previous fractures, previous hip fracture, previous vertebral fracture, previous fall injury, osteoporosis, secondary osteoporosis, Charlson comorbidity index, rheumatoid arthritis, previous calcium and vitamin D treatment and alcohol-related diseases.

**eTable 14.** Other outcomes in older patients using prednisolone, with and without alendronate

<b>Description</b>	<b>No alendronate</b>	<b>Alendronate</b>	<b><i>p</i>-value</b>
Number of patients	1802	1802	
<b>Death</b>			
No. (%)	698 (38.7)	642 (35.6)	0.05
Per 1000 person-years (95% CI)	252.9 (234.8-272.4)	224.0 (207.3-242.0)	0.03
Per 1000 person-years difference (95% CI)	Reference	-28.9 (-54.5 – -3.4)	0.03
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	0.89 (0.80-0.99)	0.03
Adjusted for age, sex, weight, height	Reference	0.89 (0.80-0.99)	0.03
Adjusted for age, sex, weight, height and Charlson Comorbidity Index	Reference	0.88 (0.79-0.98)	0.02
<b>Fall injury without fracture</b>			
No. (%)	99 (5.5)	118 (6.5)	0.21
Per 1000 person-years (95% CI)	37.1 (30.5-45.2)	43.0 (35.9-51.5)	0.28
Per 1000 person-years difference (95% CI)	Reference	5.9 (-4.8 – 16.5)	0.28
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	1.16 (0.89-1.51)	0.28
Adjusted for age, sex, weight, height	Reference	1.17 (0.89-1.52)	0.26
Adjusted for age, sex, weight, height, previous fall injury and Charlson Comorbidity Index	Reference	1.17 (0.89-1.53)	0.26
<b>Mild upper gastrointestinal symptoms (UGI)</b>			
No. (%)	35 (1.9)	44 (2.4)	0.36
Per 1000 person-years (95% CI)	12.9 (9.3-18.0)	15.6 (11.6-21.0)	0.40

Per 1000 person-years difference (95% CI)	Reference	2.7 (-3.6 – 9.0)	0.40
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	1.22 (0.78-1.90)	0.38
Adjusted for age, sex, weight, height	Reference	1.24 (0.79-1.93)	0.35
Adjusted for age, sex, weight, height, Charlson comorbidity index, previous proton pump inhibitors and previous mild UGI	Reference	1.25 (0.80-1.95)	0.33
<b>Peptic ulcer</b>			
No. (%)	31 (1.7)	31 (1.7)	1.00
Per 1000 person-years (95% CI)	11.4 (8.0-16.2)	10.9 (7.7-15.5)	0.86
Per 1000 person-years difference (95% CI)	Reference	-0.5 (-6.1-5.1)	0.86
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	0.96 (0.58-1.58)	0.86
Adjusted for age, sex, weight, height	Reference	0.96 (0.58-1.58)	0.87
Adjusted for age, sex, weight, height, Charlson comorbidity index, previous proton pump inhibitors and previous ulcer	Reference	0.91 (0.55-1.51)	0.73

**eTable 15.** Fracture risk in older patients receiving prednisolone with and without alendronate treatment – unmatched analysis

Description	No alendronate (unmatched)	Alendronate	<i>p</i> -value
N=	6076	1802	
Time at risk, median (IQR), d	435 (166-825)	498 (228-851)	0.11
<b>Hip fractures</b>			
No. (%)	251 (4.1)	27 (1.5)	<0.001
Per 1000 person-years	28.8 (25.5-32.6)	9.5 (6.5-13.9)	<0.001
Per 1000 person-years difference	Reference	-19.3 (-24.4 – -14.2)	<0.001
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	0.33 (0.22-0.49)	<0.001
Adjusted for age, sex, weight, height	Reference	0.36 (0.24-0.53)	<0.001
Multivariable adjustment*	Reference	0.38 (0.25-0.57)	<0.001
30 months ARR (%) - multivariable adjustment*	Reference	3.4 (2.5-4.3)	<0.001
30 months NNT - multivariable adjustment*	Reference	29 (23-39)	<0.001
<u>Alendronate treatment time (years)</u>			
HR per year (95% CI), multivariable adjustment*	Reference	0.83 (0.74-0.92)	0.001
<u>Alendronate medication possession ratio</u>			
HR per 10% medication possession ratio (95% CI), multivariable adjustment*	Reference	0.90 (0.86-0.94)	<0.001
<b>Major Osteoporotic Fractures (MOF)</b>			
No. (%)	347 (5.7)	59 (3.3)	0.001
Per 1000 person-years	40.4 (36.4-44.9)	21.2 (16.4-27.4)	<0.001
Per 1000 person-years difference	Reference	-19.2 (-26.1 – -12.3)	<0.001

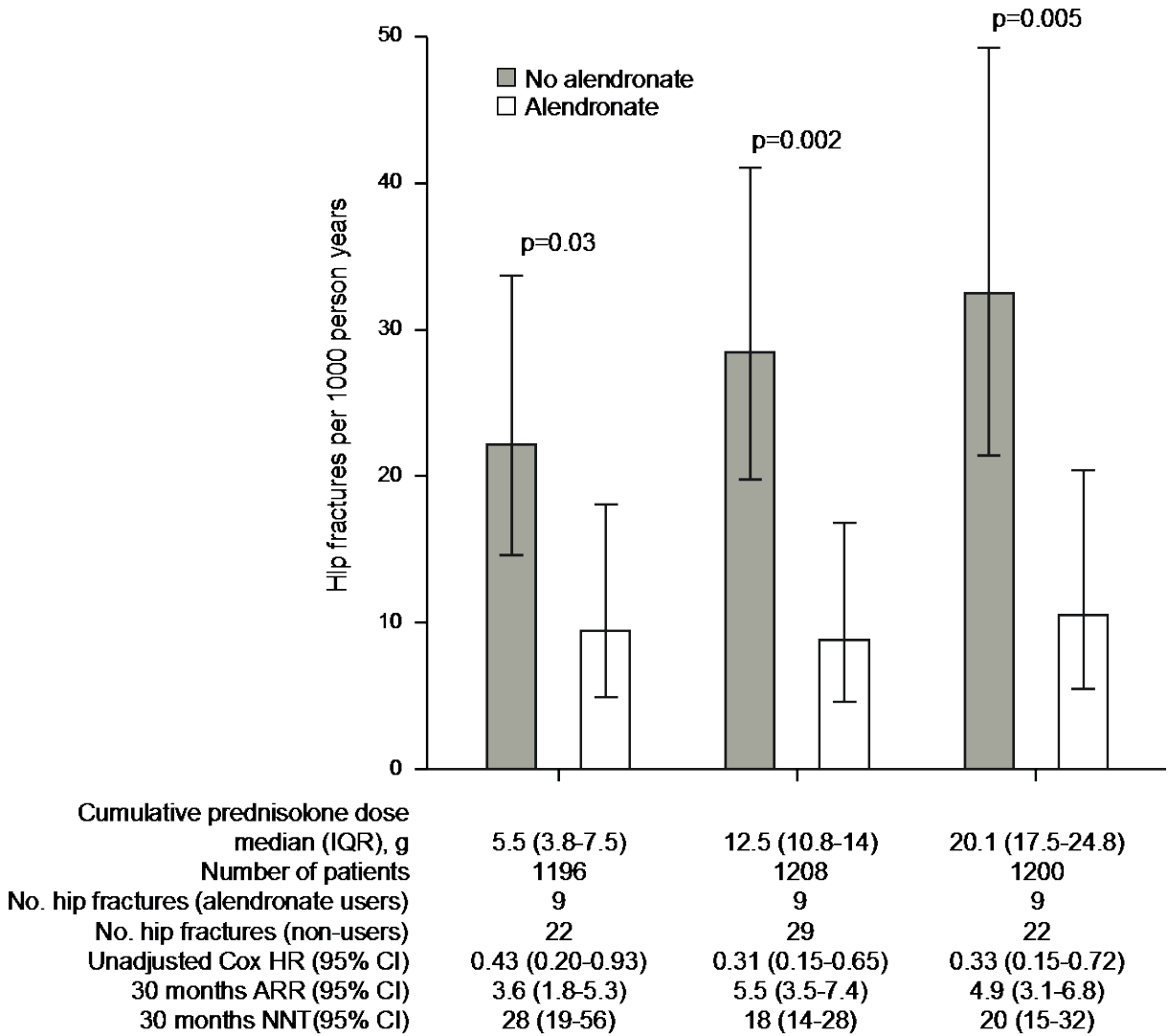
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	0.53 (0.40-0.70)	<0.001
Adjusted for age, sex, weight, height	Reference	0.53 (0.40-0.71)	<0.001
Multivariable adjustment*	Reference	0.54 (0.40-0.73)	<0.001
<u>30 month ARR (%) - multivariable adjustment*</u>			
Reference	Reference	3.6 (2.5-4.8)	<0.001
<u>30 month NNT - multivariable adjustment*</u>			
Reference	Reference	28 (21-41)	<0.001
<u>Alendronate treatment time (years)</u>			
HR per year (95% CI), multivariable adjustment*	Reference	0.90 (0.84-0.97)	0.002
<u>Alendronate medication possession ratio</u>			
HR per 10% medication possession ratio (95% CI), multivariable adjustment*	Reference	0.93 (0.90-0.96)	<0.001
<b>Any fracture</b>			
No. (%)	597 (9.8)	118 (6.5)	<0.001
Per 1000 person-years	72.0 (66.5-78.0)	43.4 (36.3-52.0)	<0.001
Per 1000 person-years difference	Reference	-28.6 (-38.3 – -18.8)	<0.001
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	0.61 (0.50-0.75)	<0.001
Adjusted for age, sex, weight, height	Reference	0.61 (0.50-0.74)	<0.001
Multivariable adjustment*	Reference	0.60 (0.49-0.74)	<0.001
<u>30 month ARR (%) - multivariable adjustment*</u>			
Reference	Reference	5.5 (3.9-7.0)	<0.001
<u>30 month NNT - multivariable adjustment*</u>			
Reference	Reference	18 (14-26)	<0.001
<u>Alendronate treatment time (years)</u>			
HR per year (95% CI), multivariable adjustment*	Reference	0.93 (0.89-0.98)	0.007
<u>Alendronate medication possession ratio</u>			
HR per 10% medication possession ratio (95% CI), multivariable adjustment*	Reference	0.94 (0.92-0.97)	<0.001



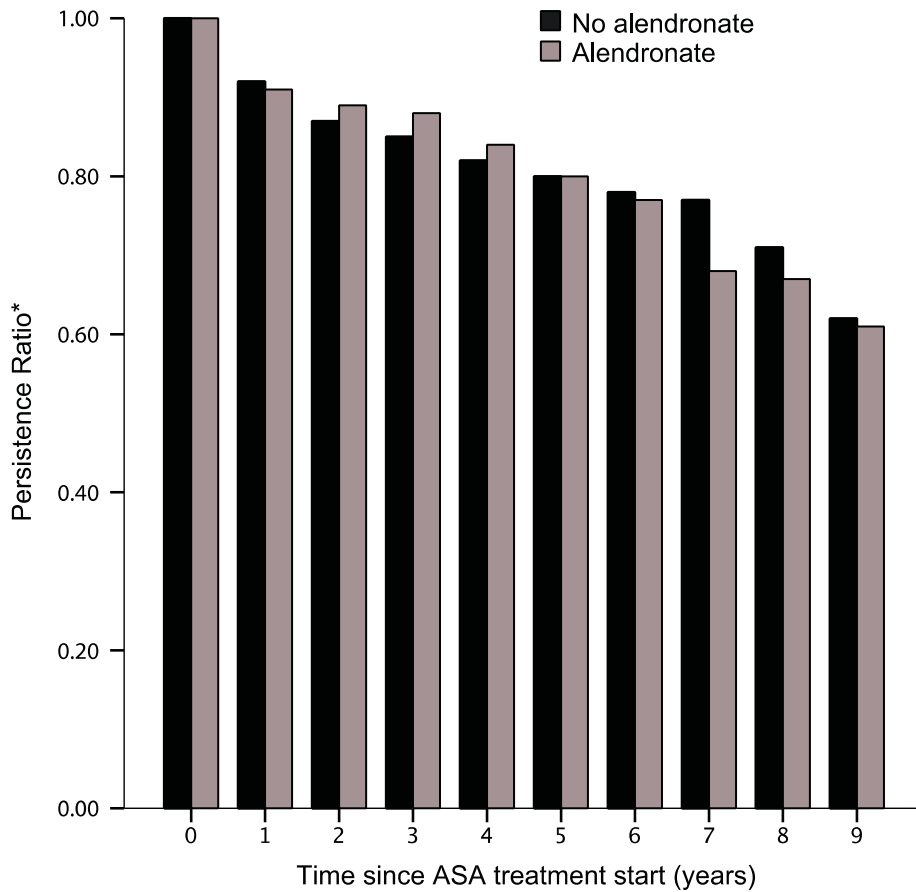
<b>Non-vertebral fracture</b>			
No. (%)	546 (9.0)	102 (5.7)	<0.001
Per 1000 person-years	65.4 (60.1-71.1)	37.2 (30.6-45.1)	<0.001
Per 1000 person-years difference	Reference	-28.2 (-37.3 – -19.1)	<0.001
<u>Alendronate treatment (yes/no) HR (95% CI)</u>			
Unadjusted	Reference	0.58 (0.47-0.71)	<0.001
Adjusted for age, sex, weight, height	Reference	0.57 (0.46-0.71)	<0.001
Multivariable adjustment*	Reference	0.58 (0.46-0.73)	<0.001
30 month ARR (%) - multivariable adjustment*	Reference	4.1 (2.8-5.4)	<0.001
30 month NNT - multivariable adjustment*	Reference	25 (19-36)	<0.001
<u>Alendronate treatment time (years)</u>			
HR per year (95% CI), multivariable adjustment*	Reference	0.93 (0.88-0.98)	0.008
<u>Alendronate medication possession ratio</u>			
HR per 10% medication possession ratio (95% CI), multivariable adjustment*	Reference	0.94 (0.92-0.96)	<0.001

\* Multivariable adjustment = age, sex, weight, height, known fracture-free time, previous fracture, number of previous fractures, previous hip fracture, previous vertebral fracture, previous fall injury, osteoporosis, secondary osteoporosis, Charlson comorbidity index, rheumatoid arthritis, previous calcium and vitamin D treatment and alcohol-related diseases.

**eFigure 2.** Hip fracture incidence per tertiles of cumulative prednisolone dose in elderly patients treated with alendronate or not



**eFigure 3.** Persistence analysis of acetylsalicylic acid (ASA) as function of years since ASA start



Sample size:

No alendronate	928	865	801	724	652	576	436	271	127	21
Alendronate	912	855	790	736	663	567	440	268	135	23

The number of acetylsalicylic acid (ASA) users were 928 (51%) among the those not using alendronate and 912 (51%) among those currently using alendronate. ASA persistence is shown for the two groups.

\* Persistence Ratio = For each set of columns, the number of patients still under ASA treatment after x years divided by the total number of patients who initiated treatment x years ago or longer. Drug evaluation period is from 2005 to baseline (2008-2014)

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