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Association of Potent and Very Potent Topical Corticosteroids and the Risk of Osteoporosis and Major Osteoporotic Fractures

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IMPORTANCE Systemic and inhaled corticosteroids negatively affect bone remodeling and cause osteoporosis and bone fracture when given continuously or in high doses. However, risk of osteoporosis and major osteoporotic fracture (MOF) after application of topical corticosteroids (TCSs) is largely unexplored.

OBJECTIVE To examine the association between cumulative exposure to potent and very potent TCSs and risk of osteoporosis and MOF.

DESIGN, SETTING, AND PARTICIPANTS This nationwide retrospective cohort study included 723 251 Danish adults treated with potent or very potent TCSs from January 1, 2003, to December 31, 2017. Data were obtained from Danish nationwide registries. Filled prescription data were converted in equipotent doses to mometasone furoate (1 mg/g). Data were analyzed from June 1 to August 31, 2019.

EXPOSURES Patients were considered exposed when they had filled prescriptions of cumulative amounts corresponding to the equivalent of at least 500 g of mometasone, using filled prescriptions of 200 to 499 g as the reference group.

MAIN OUTCOMES AND MEASURES The co-primary outcomes were a diagnosis of osteoporosis or MOF. Hazard ratios (HRs) adjusted for age, sex, socioeconomic status, medication use, and comorbidity were calculated with 95% CIs using Cox proportional hazards regression models.

RESULTS A total of 723 251 adults treated with the equivalent of at least 200 g of mometasone were included in the analysis (52.8% women; mean [SD] age, 52.8 [19.2] years). Dose-response associations were found between increased use of potent or very potent TCSs and the risk of osteoporosis and MOF. For example, HRs of MOF were 1.01 (95% CI, 0.99-1.03) for exposure to 500 to 999 g, 1.05 (95% CI, 1.02-1.08) for exposure to 1000 to 1999 g, 1.10 (95% CI, 1.07-1.13) for exposure to 2000 to 9999 g, and 1.27 (95% CI, 1.19-1.35) for exposure to at least 10 000 g. A 3% relative risk increase of osteoporosis and MOF was observed per doubling of the cumulative TCS dose (HR, 1.03 [95% CI, 1.02-1.04] for both). The overall population-attributable risk was 4.3% (95% CI, 2.7%-5.8%) for osteoporosis and 2.7% (95% CI, 1.7%-3.8%) for MOF. The lowest exposure needed for 1 additional patient to be harmed (454 person-years) was observed for MOF with exposure of at least 10 000 g.

CONCLUSIONS AND RELEVANCE These findings demonstrate that use of high cumulative amounts of potent or very potent TCSs was associated with an increased risk of osteoporosis and MOF.

Multimedia

Supplemental content

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Corticosteroids can negatively affect bone remodeling, and their use, either systemic or inhaled, increases the risk of osteoporosis and fracture when given continuously or in high doses.[1-4] Systemic effects are also seen with extreme use of topical corticosteroids (TCSs), which can lead to striae formation, adrenal suppression, and Cushing syndrome as well as Addison crisis after quick withdrawal.[5,6]

Clinical guidelines recommend long-term use of potent TCSs in patients with psoriasis, atopic dermatitis, and other inflammatory diseases[7-11] and even in those with extensive disease affecting large body areas. However, whether such prolonged use of TCSs may increase the risk of osteoporosis and major osteoporotic fracture (MOF) is unknown. Given the widespread use of TCSs, even a small increase in the risk of osteoporosis or MOF would be important from a public health perspective. Moreover, because some patients may consume very large quantities of TCSs per year, the effect of high cumulative use of potent or very potent TCSs on the risk for osteoporosis and MOF needs to be quantified to better support treatment decisions in patients requiring long-term treatment. We therefore examined the association between use of potent or very potent TCSs and the risk of osteoporosis and MOF in adults.

Methods

Study Approvals

This cohort study was approved by the Danish Data Protection Agency and registered at the Capital Region's inventory. This protocol constitutes the necessary legal requirements because Danish law does not require informed consent for observational registry studies using administrative data. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were used for conduct and reporting of this study.[12]

Data Sources

The Danish Civil Registration System[13] enables individual-level cross-linkage of data from nationwide administrative registries.[14] Tax-supported health care ensures equal and unencumbered access to general clinicians and specialists without charge, and the Danish National Patient Registry[14] contains systematically collected data (including diagnoses and treatment/procedures) from all inpatient and outpatient contacts at all Danish hospitals as well as a number of private clinics. The coverage of the Danish National Patient Registry is greater than 99%, and the overall positive predictive value of diagnoses in this registry is greater than 95%.[15] Data on all pharmacy-dispensed medications are recorded in the Danish National Prescription Registry,[16] and data on tax-reported household income are available from the Income Statistics Register.[17]

Study Design

Among Danish individuals 18 years or older who were alive and resident in Denmark from January 1, 2003, to December 31, 2017 (study inclusion period), we identified all who had filled prescriptions of at least 200 g of mometasone furoate (1 mg/g), or

Key Points

Question Does the use of topical corticosteroids cause systemic adverse events such as those seen with use of systemic corticosteroids?

Findings In a cohort study of 723 251 users of potent or very potent topical corticosteroids, use of these drugs was associated with increased risk of osteoporosis and major osteoporotic fracture with a dose-response association for cumulative use.

Meaning Based on these findings, clinicians may need to consider other corticosteroid-sparing therapeutic options for people requiring potent anti-inflammatory treatment on large body surfaces for prolonged periods to limit the risk of osteoporosis.

the equivalent amount in equipotent doses[18] of other potent or very potent TCSs (hereinafter referred to as mometasone).

Potency of TCSs was determined in accordance with the Anatomical Therapeutic Chemical classification,[19] and potent (eg, mometasone furoate or betamethasone 17 valerate) and very potent (eg, clobetasol propionate) TCSs were included in this study. Person-time exposed to TCSs was divided into the following strata according to cumulative amount of filled prescriptions of potent or very potent TCSs converted in equipotent doses to mometasone furoate (1 mg/g): (1) 200 to 499 g (reference group/unexposed), (2) 500 to 999 g, (3) 1000 to 1999 g, (4) 2000 to 9999 g, and (5) at least 10 000 g. Oral prednisolone equivalents are outlined in eTable 1 in the Supplement. During follow-up, exposure was treated as a time-varying variable. Thus, people would contribute risk time in group 1 until they met the criteria for group 2, and so on. Exposure status at baseline was calculated from the Danish National Prescription Registry[16] from inception (1995) and until cohort entry. The cohort entry was the latter of January 1, 2003, the participant's 18th birthday, or when people had filled the equivalent of at least 200 g of mometasone. People with a prior diagnosis of osteoporosis or an MOF or those who had been treated with any antiresorptive or bone anabolic medication (henceforth referred to as antiosteoporosis medication) before the index date (ie, study start date for the individual patient [eFigure 1 in the Supplement]) were excluded. People were followed up until December 31, 2017; death; migration; or the occurrence of an end point. The study design is outlined in eFigure 1 in the Supplement, and all codes used for the study are available from eTable 2 in the Supplement.

Outcomes

Co-primary end points were a hospital inpatient or outpatient diagnosis of osteoporosis or MOF (defined as a fracture of the hip, distal antebrachium, vertebrae, or humerus according to the World Health Organization's definition[20]). Secondary end points included a diagnosis of a vertebral fracture and a filled prescription of antiosteoporosis medication.

Statistical Analysis

Data were analyzed from June 1 to August 31, 2019. We presented characteristics as means with SDs for continuous, normally distributed variables; medians with interquartile ranges

Table 1. Baseline Characteristics of the Study Populations

Characteristic	TCS exposure group[a]					
	200-499 g (n = 317 907)	500-999 g (n = 186 359)	1000-1999 g (n = 111 203)	2000-9999 g (n = 94 334)	≥10 000 g (n = 13 448)	Total (n = 723 251)
Age, mean (SD), y	52.3 (19.8)	52.3 (19.1)	53.4 (18.7)	54.4 (18.2)	53.3 (17.4)	52.8 (19.2)
Sex						
Women	170 546 (53.6)	99 807 (53.6)	59 545 (53.5)	46 812 (49.6)	5371 (39.9)	382 081 (52.8)
Men	147 361 (46.4)	86 552 (46.4)	51 658 (46.5)	47 522 (50.4)	8077 (60.1)	341 170 (47.2)
Socioeconomic status						
Lowest	65 790 (20.7)	37 295 (20.0)	21 296 (19.2)	17 765 (18.8)	2504 (18.6)	144 650 (20.0)
Below average	62 849 (19.8)	36 561 (19.6)	22 135 (19.9)	20 033 (21.2)	3072 (22.8)	144 650 (20.0)
Average	62 287 (19.6)	37 065 (19.9)	22 713 (20.4)	19 789 (21.0)	2797 (20.8)	144 651 (20.0)
Above average	61 659 (19.4)	37 922 (20.3)	23 051 (20.7)	19 216 (20.4)	2801 (20.8)	144 649 (20.0)
Highest	65 322 (20.5)	37 516 (20.1)	22 008 (19.8)	17 531 (18.6)	2274 (16.9)	144 651 (20.0)
Cancer	9254 (2.9)	4671 (2.5)	2671 (2.4)	2152 (2.3)	237 (1.8)	18 985 (2.6)
Diabetes	9344 (2.9)	5332 (2.9)	3454 (3.1)	3108 (3.3)	491 (3.7)	21 729 (3.0)
Medication						
Proton pump inhibitors	21 032 (6.6)	10 534 (5.7)	5528 (5.0)	4202 (4.5)	459 (3.4)	41 755 (5.8)
Statins	24 146 (7.6)	13 788 (7.4)	8439 (7.6)	6991 (7.4)	850 (6.3)	54 214 (7.5)
Thiazides	25 695 (8.1)	16 725 (9.0)	10 858 (9.8)	10 126 (10.7)	1430 (10.6)	64 834 (9.0)
Histamine-receptor antagonists	6972 (2.2)	5306 (2.8)	3793 (3.4)	3832 (4.1)	618 (4.6)	20 521 (2.8)
Psycholeptics	33 470 (10.5)	20 889 (11.2)	13 281 (11.9)	11 856 (12.6)	1791 (13.3)	81 287 (11.2)
Hormone therapy	762 (0.2)	423 (0.2)	247 (0.2)	200 (0.2)	12 (0.1)	1644 (0.2)
Contraceptives	22 170 (7.0)	14 605 (7.8)	9024 (8.1)	7295 (7.7)	823 (6.1)	53 917 (7.5)
Cyclosporine A	133 (0.04)	160 (0.1)	151 (0.1)	379 (0.4)	210 (1.6)	1033 (0.1)
Corticosteroids						
Inhaled	9623 (3.0)	6405 (3.4)	4255 (3.8)	3888 (4.1)	608 (4.5)	24 779 (3.4)
Systemic	24 875 (7.8)	16 821 (9.0)	11 282 (10.1)	11 055 (11.7)	1648 (12.3)	65 681 (9.1)

Abbreviation: TCS, topical corticosteroid.

[a] People contribute risk-time in the reference group (200-499 g) until they meet the criteria for the next group (500-999 g), and so on. Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

for continuous variables without normal distribution; and frequencies with percentages for categorical variables. We summarized incidence rates per 10 000 person-years and used Cox proportional hazards regression with time-dependent covariates to calculate hazard ratios (HRs). We treated the main exposure variable, cumulative dose category, as a time-dependent variable using the categories described above.

Age, sex, socioeconomic status, medication use, and comorbidity were considered in these models. Age was divided into 5-year bands and updated throughout the study. Socioeconomic status was calculated as an age-standardized index ranging from 0 to 4 based on the mean gross annual income during a 5-year period before the index date. Cancer (excluding keratinocyte cancers), diabetes, and medications that could lead to osteoporosis (listed in Table 1) were treated as time-dependent variables throughout the study.

Several secondary analyses were performed. We assessed the effect of doubling the dose of TCSs by using the log2-transformed cumulative dose of TCSs as a continuous dependent variable. We performed sensitivity analyses limited to incident users of potent or very potent TCSs (ie, first ever prescription after January 1, 2003, and no filled prescriptions from 1995 to 2003). In separate analyses, people were censored when they were prescribed systemic corticosteroids, were pre-

scribed systemic (oral, injection, and/or infusion) or inhaled corticosteroids, or were diagnosed with cancer (not including keratinocyte cancers). Additional analyses were performed with exclusion of people with a history of nonkeratinocyte cancer before the index date, and analyses restricted to adults with and without psoriasis. To assess whether an association between increased use of potent or very potent TCS use in psoriasis could be due to the underlying systemic inflammation in patients with severe disease, we performed an analysis limited to patients with psoriasis, wherein these patients were censored if they received treatment with drugs specifically used for severe psoriasis (eTable 2 in the Supplement). In addition, we performed analyses limited to people of Danish origin. Furthermore, we repeated our primary analyses with additional adjustment for previous fractures (not including previous MOF because such patients were excluded at baseline). As a negative outcome, we examined the association between the use of potent or very potent TCSs and risk of hernia repair surgery. Model assumptions were tested and found to be valid unless otherwise stated. Estimation of the effect of an unmeasured confounder was made according to the rule-out approach.[21] The rule-out approach provides tailored analysis that assesses the extent of confounding that would be necessary to fully explain the observed findings, that

Table 2. Absolute Incidence Rates, Incidence Rate Differences, and Population-Attributable
Risks of the Examined Outcomes

Outcome by TCS exposure group	Follow-up, y	No. of events	Incidence rate per 10 000 person-years (95% CI)	Incidence rate difference per 10 000 person-years (95% CI)	Population-attributable risk, % (95% CI)
Osteoporosis					
200-499 g	2 859 229	10 488	36.7 (36.0 to 37.4)	1 [Reference]	1 [Reference]
500-999 g	1 500 012	6466	43.1 (42.1 to 44.2)	6.4 (6.1 to 6.8)	3.7 (1.3 to 5.0)
1000-1999 g	839 227	4209	50.2 (48.7 to 51.7)	13.5 (12.7 to 14.3)	3.0 (1.7 to 4.3)
2000-9999 g	659 905	3644	55.2 (53.6 to 57.0)	18.5 (17.5 to 19.7)	1.3 (0.8 to 1.8)
≥10 000 g	85 380	501	58.7 (53.8 to 64.1)	22.0 (17.8 to 26.7)	0.4 (0.2 to 0.7)
Major osteoporotic fracture					
200-499 g	2 418 041	22 972	81.6 (80.6 to 82.7)	1 [Reference]	1 [Reference]
500-999 g	1 472 158	13 052	88.7 (87.2 to 90.2)	7.0 (6.6 to 7.5)	0.6 (−0.7 to 1.9)
1000-1999 g	819 781	8246	100.6 (98.4 to 102.8)	19.0 (15.9 to 20.1)	1.7 (0.7 to 2.7)
2000-9999 g	642 266	7261	113.1 (110.5 to 115.7)	31.4 (27.9 to 33.0)	1.3 (0.9 to 1.7)
≥10 000 g	82 565	1010	122.3 (115.0 to 130.1)	40.7 (32.4 to 47.4)	0.5 (0.4 to 0.7)
Osteoporosis medication					
200-499 g	2 832 220	16 706	59.0 (58.1 to 59.9)	1 [Reference]	1 [Reference]
500-999 g	1 481 389	9972	67.3 (66.0 to 68.7)	8.3 (7.9 to 10.6)	0.7 (−0.7 to 2.5)
1000-1999 g	826 322	6350	76.9 (75.0 to 78.8)	17.9 (16.9 to 20.7)	0.7 (−0.4 to 1.7)
2000-9999 g	646 902	5683	87.9 (85.6 to 90.2)	28.9 (27.5 to 32.1)	0.8 (0.4 to 1.3)
≥10 000 g	83 508	775	92.8 (86.5 to 99.6)	33.8 (28.4 to 41.5)	0.3 (0.2 to 0.5)
Vertebral fracture					
200-499 g	2 888 697	2820	9.8 (9.4 to 10.1)	1 [Reference]	1 [Reference]
500-999 g	1 522 451	1650	10.8 (10.3 to 11.4)	1.1 (0.9 to 2.0)	−0.7 (−4.0 to 3.7)[a]
1000-1999 g	854 815	1086	12.7 (12.0 to 13.5)	2.9 (2.7 to 4.1)	1.4 (−1.0 to 4.0)
2000-9999 g	673 823	1026	15.2 (14.3 to 16.2)	5.5 (4.9 to 6.8)	1.6 (0.5 to 2.6)
≥10 000 g	87 518	134	15.3 (12.9 to 18.1)	5.6 (3.5 to 8.7)	0.2 (−0.2 to 0.6)

Abbreviations: HR, hazard ratio;
TCS, topical corticosteroid.

[a] The adjusted HR was 0.99, thus yielding a negative population-attributable risk.

is, how strong an unmeasured confounder would have to be to move the observed point estimate to the null. This approach thereby allows an unmeasured possible confounder to be ruled out if the model shows that it cannot possibly be strong enough to explain the observed association. We estimated the population-attributable risk according to the formula P × (HR − 1)/[P × (HR − 1) + 1], where P is the prevalence of the exposure.[22] Moreover, we calculated the exposure needed for 1 additional patient to be harmed (ENH) as 1/[unexposed incidence rate × (HR − 1)].[23] All statistical tests were conducted using a level of significance of 2-sided $P < .05$, and HRs were reported with 95% CIs where applicable. All analyses were performed using SAS, version 9.4 (SAS Institute Inc) and STATA, version 15.0 (StataCorp LLC).
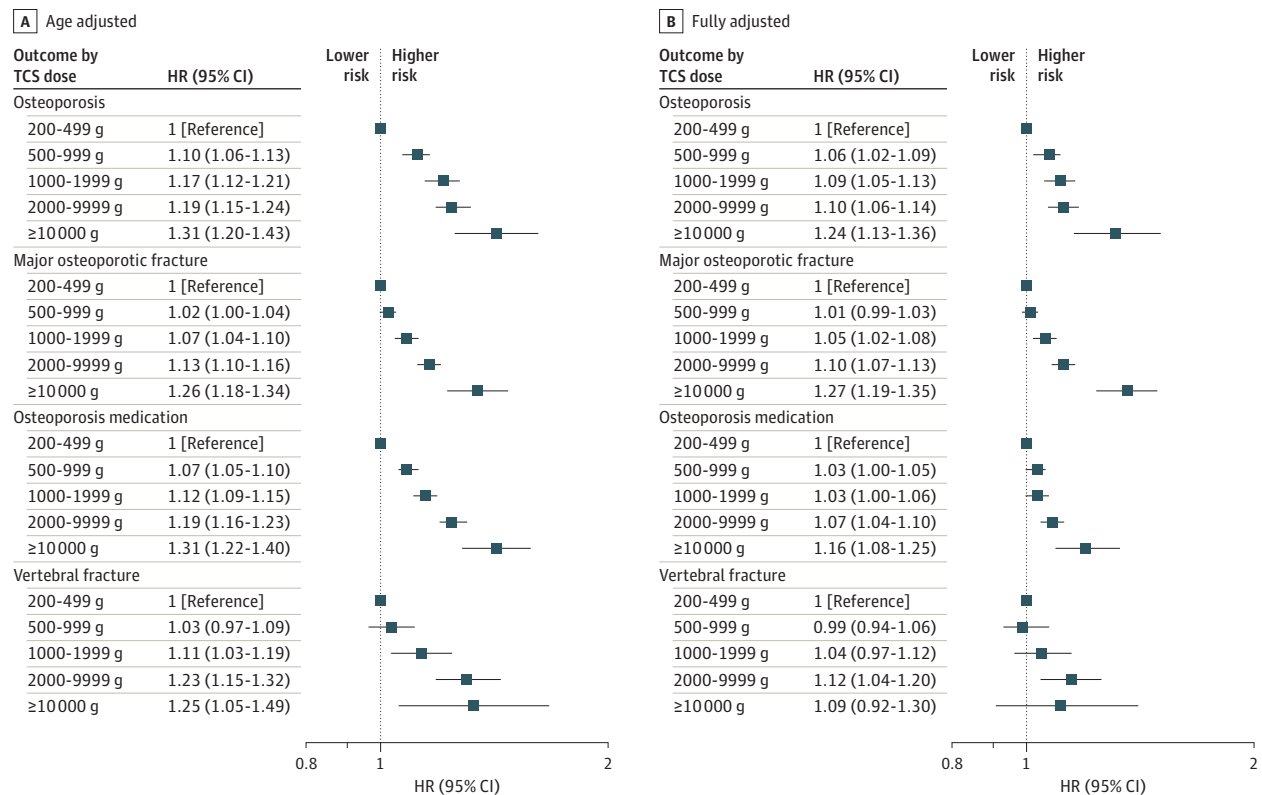
Results

We included a total of 723 251 adults (52.8% women and 47.2% men; mean [SD] age, 52.8 [19.2] years) treated with the equivalent of at least 200 g of mometasone. During the study period, 25.8% (n = 186 359) were categorized as exposed to 500 to 999 g; 15.4% (n = 111 203), to 1000 to 1999 g; 13.0% (n = 94 334), to 2000 to 9999 g; and 1.9% (n = 13 448), to at least 10 000 g (Table 1).

The incidence rate of osteoporosis among patients treated with the equivalent of 200 to 499 g of mometasone was 36.7

(95% CI, 36.0-37.4) per 10 000 person-years; 500 to 999 g, 43.1 (95% CI, 42.1-44.2) per 10 000 person-years; 1000 to 1999 g, 50.2 (95% CI, 48.7-51.7) per 10 000 person-years; 2000 to 9999 g, 55.2 (95% CI, 53.6-57.0) per 10 000 person-years; and at least 10 000 g, 58.7 (95% CI, 53.8-64.1) per 10 000 person-years. For MOF, incidence rates were 81.6 (95% CI, 80.6-82.7) per 10 000 person-years for 200 to 499 g; 88.7 (95% CI, 87.2-90.2) per 10 000 person-years for 500 to 999 g; 100.6 (95% CI, 98.4-102.8) per 10 000 person-years for 1000 to 1999 g; 113.1 (95% CI, 110.5-115.7) per 10 000 person-years for 2000 to 9999 g; and 122.3 (95% CI, 115.0-130.1) per 10 000 person-years for at least 10 000 g. Similar dose-dependent increases were seen for the secondary end points (Table 2). In fully adjusted (age, sex, socioeconomic status, medication use, and comorbidity) analyses, we found significant associations between exposure (any exposure ≥500 g vs 200-499 g) to potent or very potent TCSs and the risk of osteoporosis (HR, 1.08; 95% CI, 1.05-1.11) and MOF (HR, 1.05; 95% CI, 1.03-1.07). Effect estimates for association with osteoporosis were stronger with increasing cumulative use, with adjusted HRs of 1.06 (95% CI, 1.02-1.09) for exposure to 500 to 999 g, 1.09 (95% CI, 1.05-1.13) for exposure to 1000 to 1999 g, 1.10 (95% CI, 1.06-1.14) for exposure to 2000 to 9999 g, and 1.24 (95% CI, 1.13-1.36) for exposure to at least 10 000 g. For MOF, HRs were 1.01 (95% CI, 0.99-1.03) for exposure to 500 to 999 g, 1.05 (95% CI, 1.02-1.08) for exposure to 1000 to 1999 g, 1.10 (95% CI, 1.07-1.13) for exposure to 2000 to 9999 g, and 1.27 (95% CI, 1.19-1.35) for exposure to at

Figure. Association Between Use of Potent and Very Potent Topical Corticosteroids (TCSs) and the Risk of Osteoporotic Outcomes

A Age adjusted

Outcome by TCS dose	HR (95% CI)
Osteoporosis	
200-499 g	1 [Reference]
500-999 g	1.10 (1.06-1.13)
1000-1999 g	1.17 (1.12-1.21)
2000-9999 g	1.19 (1.15-1.24)
≥10 000 g	1.31 (1.20-1.43)
Major osteoporotic fracture	
200-499 g	1 [Reference]
500-999 g	1.02 (1.00-1.04)
1000-1999 g	1.07 (1.04-1.10)
2000-9999 g	1.13 (1.10-1.16)
≥10 000 g	1.26 (1.18-1.34)
Osteoporosis medication	
200-499 g	1 [Reference]
500-999 g	1.07 (1.05-1.10)
1000-1999 g	1.12 (1.09-1.15)
2000-9999 g	1.19 (1.16-1.23)
≥10 000 g	1.31 (1.22-1.40)
Vertebral fracture	
200-499 g	1 [Reference]
500-999 g	1.03 (0.97-1.09)
1000-1999 g	1.11 (1.03-1.19)
2000-9999 g	1.23 (1.15-1.32)
≥10 000 g	1.25 (1.05-1.49)

B Fully adjusted

Outcome by TCS dose	HR (95% CI)
Osteoporosis	
200-499 g	1 [Reference]
500-999 g	1.06 (1.02-1.09)
1000-1999 g	1.09 (1.05-1.13)
2000-9999 g	1.10 (1.06-1.14)
≥10 000 g	1.24 (1.13-1.36)
Major osteoporotic fracture	
200-499 g	1 [Reference]
500-999 g	1.01 (0.99-1.03)
1000-1999 g	1.05 (1.02-1.08)
2000-9999 g	1.10 (1.07-1.13)
≥10 000 g	1.27 (1.19-1.35)
Osteoporosis medication	
200-499 g	1 [Reference]
500-999 g	1.03 (1.00-1.05)
1000-1999 g	1.03 (1.00-1.06)
2000-9999 g	1.07 (1.04-1.10)
≥10 000 g	1.16 (1.08-1.25)
Vertebral fracture	
200-499 g	1 [Reference]
500-999 g	0.99 (0.94-1.06)
1000-1999 g	1.04 (0.97-1.12)
2000-9999 g	1.12 (1.04-1.20)
≥10 000 g	1.09 (0.92-1.30)

The fully adjusted models are adjusted for age, sex, socioeconomic status, cancer, diabetes, and use of proton pump inhibitors, statins, thiazide diuretics, histamine-receptor antagonists, psycholeptics, hormone therapy, contraceptives, cyclosporine A, systemic corticosteroids, and inhaled corticosteroids. HR indicates hazard ratio.

least 10 000 g (**Figure**). Similar findings were seen for the secondary end points (Figure). We saw comparable estimates when stratified by sex and when limiting analyses to people of Danish origin (eTables 3 and 4 in the Supplement). A 3% increase in the relative risk of osteoporosis and MOF was observed per doubling of the TCS dose (HR, 1.03 [95% CI, 1.02-1.04] for both). Similar findings were seen for osteoporosis medication (HR, 1.02 [95% CI, 1.01-1.04]) and vertebral fracture (HR, 1.03 [95% CI, 1.01-1.04]).

Attributable and Absolute Risk Estimates

The population-attributable risk of any exposure (ie, ≥500 g) compared with nonexposed individuals (ie, 200-499 g) was 4.3% (95% CI, 2.7%-5.8%) for osteoporosis, 2.7% (95% CI, 1.7%-3.8%) for MOF, 2.2% (95% CI, 1.1%-3.3%) for use of osteoporosis medication, and 2.2% (95% CI, −0.6% to 4.8%) for vertebral fractures. Estimates for the different quantities of TCS use are described in Table 2. Overall, the ENH was high but decreased with increasing cumulative use. For people exposed to 500 to 999 g, the ENH for osteoporosis was 4544 person-years; 1000 to 1999 g, 3029 person-years; 2000 to 9999 g, 2726 person-years; and at least 10 000 g, 1136 person-years. Similarly, for MOF, the ENH was 12 250 person-years for people exposed to 500 to 999 g; 2450 person-years for people exposed to 1000 to 1999 g; 1225 person-years for people exposed to

2000 to 9999 g; and 454 person-years for people exposed to at least 10 000 g.

Sensitivity Analyses

Across all sensitivity analyses, we generally observed similar findings (eTables 3 and 4 in the Supplement). Limiting analysis of osteoporosis to incident users (ie, people filling their first-ever potent or very potent TCS prescription after January 1, 2003) yielded adjusted HRs of 1.11 (95% CI, 1.03-1.19) among people treated with 500 to 999 g; 1.20 (95% CI, 1.10-1.32) among people treated with 1000 to 1999 g; 1.18 (95% CI, 1.06-1.32) among people treated with 2000 to 9999 g; and 1.48 (95% CI, 1.08-2.04) among people treated with at least 10 000 g for association with osteoporosis. Results for analysis of patients with psoriasis were very similar to those of patients without psoriasis. For example, use of at least 10 000 g yielded adjusted HRs of 1.19 (95% CI, 1.04-1.37) for people with psoriasis and 1.24 (95%, 1.09-1.41) for people without psoriasis. Restricting analyses to patients with psoriasis that was not severe yielded virtually identical HRs (eTables 3 and 4 in the Supplement). Moreover, analyses with additional adjustment for previous fractures, with exclusion of people with prevalent cancer, with censoring when people developed first-time cancer, and with censoring when people were prescribed their first-ever oral injection, infusion, or in-

haled corticosteroid were also consistent with our main analyses (eTables 3 and 4 in the Supplement). In post hoc analyses, stratification into presumed premenopausal and postmenopausal age groups showed that younger women (aged <50 years) had slightly higher risk estimates associated with TCS use than older women (eTables 3 and 4 in the Supplement). In analysis of hernia repair surgery (negative outcome), there was no increased risk associated with TCS use regardless of cumulative dose (eTable 5 in the Supplement).

Unmeasured Confounding
Assuming a 20% prevalence of an unmeasured confounder in the entire population, that is, a prevalence exceeding that of an osteoporosis risk factor such as underweight (body mass index [calculated as weight in kilograms divided by height in meters squared] <18.5) or heavy smoking (20 cigarettes/d), and a prevalence of the exposure (high use, ie, ≥10 000 g of mometasone) of 1.9% (13 448 of 723 251), we found that an unmeasured confounder would have to be very strongly associated with the outcome and, importantly, be very unevenly distributed between groups with a very strong association with high use of potent or very potent TCSs (eFigure 2 in the Supplement). For example, the unmeasured confounding factor would have to increase the risk of MOF by a factor of 3 and simultaneously increase the risk of exposure to high use of potent or very potent TCSs by a factor of 2.5 for adjustment to nullify the observed association in our study.

Discussion

Main Findings
This study shows that use of potent and very potent TCSs is associated with increased risk of osteoporosis and MOF, with a dose-response effect for cumulative use. We found a population-attributable risk for TCSs of as much as 4.3%, and our results remained consistent across a wide range of sensitivity analyses as well as after adjustment for potential confounding factors. However, the absolute risk to the average TCS user was low.

Interpretation
Although prolonged, high-dose systemic corticosteroid use causes bone loss and increased fracture risk, this area has been largely unexplored for TCS use. Previously, a Danish case-control study[18] of 20 035 patients with distal antebrachium fracture and 60 030 age- and sex-matched controls found an odds ratio of 1.15 (95% CI, 0.78-1.68) for prior exposure to high-dose TCSs (equivalent to ≥7.5 mg/d of oral prednisolone, assuming 100% systemic absorption). However, the study only included data collected in a 4-year period (1996-2000) and did not perform exposure-time analyses or assess the association with osteoporosis or MOF as a whole. High-potency TCSs are used frequently and in high quantities for chronic skin diseases, such as atopic dermatitis and psoriasis, each of which affect 3% to 8% of adults in Denmark[24] and other countries.[25] We found somewhat stronger risk associated with TCS use in women presumed to be premenopausal (aged <50 years), al-

beit that older women had an increased risk as well, suggesting that the relative effect of TCS use on osteoporosis risk may be greater in younger women.

For the association with osteoporosis, we found a population-attributable risk of 4.3%. From a public health perspective, this finding indicates that as many as 4.3% of osteoporosis cases in our population could have been prevented if other therapies had been used instead of high-potency TCSs in their current quantities. The lowest ENH was 454 person-years (observed for MOF in patients using ≥10 000 g of mometasone), whereas lower cumulative use had a much higher ENH (eg, 2450 person-years for 500-999 g), suggesting that the risk for the individual patient may be limited. For context, however, with very high use (ie, ≥40 mg/d [median, 60 mg/d] for ≤30 days) of oral prednisolone, the fracture-associated ENH is 115 person-years.[26] Although dosage consideration is crucial when prescribing all types of medication, TCSs are normally prescribed with little thought regarding the applied quantity per skin surface area. With recent studies showing significantly increased risk of type 2 diabetes in individuals exposed to TCSs,[27,28] more detailed risk assessment appears to be needed. Alternative topical and systemic therapies could be considered for inflammatory skin conditions (perhaps in particular those displaying increased skin absorption[29]) that would otherwise require large quantities or prolonged treatment with high-potency TCSs, although the benefit of such interventions, strictly speaking, has not been demonstrated for TCS users. Alternatively, if long-term or high-dose treatment with a potent or a very potent TCS is needed, the clinicians may want to consider lowering the threshold for bone mineral density screening by dual energy x-ray absorptiometry scanning and prescription of prophylactic treatment for osteoporosis.

Strengths and Limitations
Important strengths of the study include the robust dose-response association that was confirmed across several sensitivity analyses. Use of nationwide registries allows analysis of large number of patients while reducing selection bias owing to, for example, sex, age, or socioeconomic status. Owing to a very high level of completeness and the prospective registration of respective codes in these registries, recall bias and bias caused by nonresponse are minimal.

We lacked data on underweight and smoking; however, we found comparable estimates among people with and without psoriasis (a condition strongly associated with obesity and smoking). In addition, it is unlikely that the association is exclusively owing to systemic low-grade inflammation in the underlying skin disease because limiting our analyses to patients with psoriasis without severe disease yielded virtually identical results compared with our primary model. Furthermore, we found that an unmeasured confounder would have to be highly prevalent and carry a considerable risk to remove the observed association. Indeed, the estimated magnitude of a confounder that could nullify our results exceeded the effects and distribution of any measured confounder, including that of systemic corticosteroids, rendering its existence unlikely. In addition, it is noteworthy that our study is

nested among users of potent or very potent TCSs. To the extent that such users share mutual characteristics, confounding will be substantially mitigated. Table 1 shows most characteristics to be well balanced at baseline.

Surveillance bias is a concern in observational register-based studies; however, when analyzing our negative outcome, we did not find evidence of surveillance bias being present. Furthermore, our end point of MOF is unlikely to be affected by surveillance. The *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes for osteoporosis have not been formally validated in the National Patient Register; however, because we found similar results when the end point was changed to first prescription of antiosteoporosis medication, this finding suggests that our results were not affected by misclassification of the end point in a major way. Moreover, it is important to keep in mind that the formula for calculating the population-attributable risk assumes that there is no confounding in the models.

It is notable that our sensitivity analyses using an incident (new user) design produced greater magnitude of the association with the study outcomes compared with our primary analyses. This outcome is likely owing to the fact that prevalent user designs may not capture events associated with treatment duration or that occur early after the exposure, and it is therefore quite possible that the true effect of TCS exposure is even higher than what was seen in our main analyses. We excluded people with a negligible exposure to TCSs (<200 g) and used the lowest exposure (200-499 g) as the reference category; this approach considerably reduces heterogeneity because patients with negligible TCS use will represent a very dissimilar group of patients. Importantly, there would not only be considerable differences within the group of sporadic users of TCSs (eg, a patient using only 10 g of a TCS combined with an antifungal agent to treat a superficial fungal infection will look much different than a patient using 150 g of TCSs for several years to treat genital lichen sclerosus), but these patients would also be markedly different compared with the long-term users of potent TCSs in terms of sex distribution, comorbidity profile, and overall lifestyle habits. Indeed, such patients would differ markedly from our exposed population to

an extent wherein it is likely that significant residual confounding would persist even after possible adjustments. However, because such patients were excluded from our study, our unexposed control group consisted of patients treated with 200 to 499 g of potent or very potent TCSs (ie, the equivalent of 80-200 mg of oral prednisolone assuming 5% absorption), which may also have led to a slight underestimation of the true effect of TCSs. We lacked data on the anatomical locations where the TCSs were applied. Patients with skin diseases will use different classes and amounts of TCSs, both over time and in different body regions. There is as much as a 42-fold difference in skin penetration in different anatomical regions,[30] and the penetration of TCSs depends to a large extent on the molecule. Moreover, use of TCSs as ointments can have a reservoir effect that might prolong bioavailability and thus systemic effects, yet our results did not distinguish between ointments and creams, and although we demonstrated significant dose-response associations between osteoporosis and cumulative amount of filled prescriptions for TCSs, the actual applied and absorbed amounts remain unknown. However, any bias related to such potential misclassification of exposure would arguably draw the results toward the null, suggesting that the true effect of TCSs exposure may be even higher.

Conclusions

Use of potent or very potent TCSs was independently associated with increased risk of osteoporosis and MOF. Use of these drugs is very common, and we found an estimated population-attributable risk of as much as 4.3%. Importantly, however, the absolute risk for the individual average user of TCSs remains low. For people requiring potent treatment on large body surfaces for prolonged periods, other corticosteroid-sparing treatments for inflammatory dermatoses may be considered, although the benefit of such intervention, strictly speaking, has not been demonstrated for TCS users. Alternatively, earlier evaluation of and prophylaxis for osteoporosis and prophylactic therapy may be considered in patients with extensive use of potent and very potent TCS.

REFERENCES

1. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)*. 2000;39(12):1383-1389. doi:10.1093/rheumatology/39.12.1383

2. Gonzalez AV, Coulombe J, Ernst P, Suissa S. Long-term use of inhaled corticosteroids in COPD and the risk of fracture. *Chest*. 2018;153(2):321-328. doi:10.1016/j.chest.2017.07.002

3. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, Van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum*. 2007;56(1):208-214. doi:10.1002/art.22294

4. Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet*. 2000;355(9213):1399-1403. doi:10.1016/S0140-6736(00)02138-3

5. Hepburn DJ, Aeling JL, Weston WL. A reappraisal of topical steroid potency. *Pediatr Dermatol*. 1996;13(3):239-245. doi:10.1111/j.1525-1470.1996.tb01211.x

6. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol*. 2006;54(1):1-15. doi:10.1016/j.jaad.2005.01.010

7. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 4: prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014;71(6):1218-1233. doi:10.1016/j.jaad.2014.08.038

8. Wollenberg A, Oranje A, Deleuran M, et al; European Task Force on Atopic Dermatitis/EADV Eczema Task Force. ETFAD/EADV Eczema Task Force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol*. 2016;30(5):729-747. doi:10.1111/jdv.13599

9. Paul C, Gallini A, Archier E, et al. Evidence-based recommendations on topical treatment and phototherapy of psoriasis: systematic review and expert opinion of a panel of dermatologists. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 3):1-10. doi:10.1111/j.1468-3083.2012.04518.x

10. English J, Aldridge R, Gawkrodger DJ, et al. Consensus statement on the management of chronic hand eczema. *Clin Exp Dermatol*. 2009;34(7):761-769. doi:10.1111/j.1365-2230.2009.03649.x

11. Menné T, Johansen JD, Sommerlund M, Veien NK; Danish Contact Dermatitis Group. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis*. 2011;65(1):3-12. doi:10.1111/j.1600-0536.2011.01915.x

12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457. doi:10.1016/S0140-6736(07)61602-X

13. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

14. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

15. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83. doi:10.1186/1471-2288-11-83

16. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije3/dyw213

17. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39(7)(suppl):103-105. doi:10.1177/1403494811405098

18. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with systemic and topical corticosteroids. *J Intern Med*. 2005;257(4):374-384. doi:10.1111/j.1365-2796.2005.01467.x

19. WHO Collaborating Centre for Drug Statistics Methodology. *ATC Classification Index With DDDs and Guidelines for ATC Classification and DDD Assignment*; Norwegian Institute of Public Health. 2006.

20. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int*. 2005;16(suppl 2):S3-S7. doi:10.1007/s00198-004-1702-6

21. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15(5):291-303. doi:10.1002/pds.1200

22. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88(1):15-19. doi:10.2105/AJPH.88.1.15

23. Hallas J, Christensen RD, Stürmer T, Pottegård A. Measures of "exposure needed for one additional patient to be harmed" in population-based case-control studies. *Pharmacoepidemiol Drug Saf*. 2014;23(8):868-874. doi:10.1002/pds.3635

24. Egeberg A, Andersen YMF, Thyssen JP. Prevalence and characteristics of psoriasis in Denmark: findings from the Danish skin cohort. *BMJ Open*. 2019;9(3):e028116. doi:10.1136/bmjopen-2018-028116

25. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy*. 2018;73(6):1284-1293. doi:10.1111/all.13401

26. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. 2017;357:j1415. doi:10.1136/bmj.j1415

27. Andersen YMF, Egeberg A, Ban L, et al. Association between topical corticosteroid use and type 2 diabetes in two European population-based adult cohorts. *Diabetes Care*. 2019;42(6):1095-1103. doi:10.2337/dc18-2158

28. Andersen YMF, Egeberg A, Gislason GH, Skov L, Knop FK, Thyssen JP. Adult atopic dermatitis and the risk of type 2 diabetes. *J Allergy Clin Immunol*. 2017;139(3):1057-1059. doi:10.1016/j.jaci.2016.08.049

29. Halling-Overgaard AS, Kezic S, Jakasa I, Engebretsen KA, Maibach H, Thyssen JP. Skin absorption through atopic dermatitis skin: a systematic review. *Br J Dermatol*. 2017;177(1):84-106. doi:10.1111/bjd.15065

30. Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of 14C cortisol in man. *J Invest Dermatol*. 1967;48(2):181-183. doi:10.1038/jid.1967.29