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

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

Several secondary analyses were performed. We as-
essed the effect of doubling the dose of TCSs by using the log2-
transformed cumulative dose of TCSs as a continuous de-
pendent variable. We performed sensitivity analyses limited to
incident users of potent or very potent TCSs (ie, first ever pre-
scription 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 includ-
ing keratinocyte cancers). Additional analyses were per-
formed with exclusion of people with a history of nonkerat-
inocyte cancer before the index date, and analyses restricted
to adults with and without psoriasis. To assess whether an as-
sociation between increased use of potent or very potent TCS
use in psoriasis could be due to the underlying systemic in-
flammation in patients with severe disease, we performed an
analysis limited to patients with psoriasis, wherein these pa-
tients were censored if they received treatment with drugs spec-
ifically used for severe psoriasis (eTable 2 in the Supple-
ment). In addition, we performed analyses limited to people of
Danish origin. Furthermore, we repeated our primary analy-
ses with additional adjustment for previous fractures (not in-
cluding previous MOF because such patients were excluded
at baseline). As a negative outcome, we examined the asso-
ciation 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 tai-
ored analysis that assesses the extent of confounding that
would be necessary to fully explain the observed findings, that

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### Table 1. Baseline Characteristics of the Study Populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TCS exposure group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200-499 g (n = 317 907)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>52.3 (19.8)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>170 546 (53.6)</td>
</tr>
<tr>
<td>Men</td>
<td>147 361 (46.4)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>65 790 (20.7)</td>
</tr>
<tr>
<td>Below average</td>
<td>62 849 (19.8)</td>
</tr>
<tr>
<td>Average</td>
<td>62 287 (19.6)</td>
</tr>
<tr>
<td>Above average</td>
<td>61 659 (19.4)</td>
</tr>
<tr>
<td>Highest</td>
<td>65 322 (20.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>9254 (2.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9344 (2.9)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>21 032 (6.6)</td>
</tr>
<tr>
<td>Statins</td>
<td>24 146 (7.6)</td>
</tr>
<tr>
<td>Thiazides</td>
<td>25 695 (8.1)</td>
</tr>
<tr>
<td>Histamine-receptor</td>
<td>6972 (2.2)</td>
</tr>
<tr>
<td>antagonists</td>
<td></td>
</tr>
<tr>
<td>Psycholeptics</td>
<td>33 470 (10.5)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>762 (0.2)</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>22 170 (7.0)</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>133 (0.04)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Inhaled</td>
<td>9623 (3.0)</td>
</tr>
<tr>
<td>Systemic</td>
<td>24 875 (7.8)</td>
</tr>
</tbody>
</table>

Abbreviation: TCS, topical corticosteroid.

* 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.
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. Moreover, we calculated the exposure needed for 1 additional patient to be harmed (ENH) as 1/unexposed incidence rate × (HR − 1). 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 2000 to 9999 g; and at least 10 000 g, 112.3 (95% CI, 110.5-115.7) per 10 000 person-years. All associations were stronger for cumulative use, with adjusted HRs of 1.06 (95% CI, 1.02-1.09) for exposure to 500 to 999 g, 1.10 (95% CI, 1.05-1.14) for exposure to 1000 to 1999 g, 1.15 (95% CI, 1.10-1.20) for exposure to 2000 to 9999 g, and 1.24 (95% CI, 1.13-1.36) for exposure to at least 10 000 g. Similar dose-dependent increases were seen for the secondary endpoints (Table 2).

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

<table>
<thead>
<tr>
<th>Outcome by TCS exposure group</th>
<th>Follow-up, y</th>
<th>No. of events</th>
<th>Incidence rate per 10 000 person-years (95% CI)</th>
<th>Incidence rate difference per 10 000 person-years (95% CI)</th>
<th>Population-attributable risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteoporosis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>200-499 g</td>
<td>2 859 229</td>
<td>10 488</td>
<td>36.7 (36.0 to 37.4)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>500-999 g</td>
<td>1 500 012</td>
<td>6466</td>
<td>43.1 (42.1 to 44.2)</td>
<td>6.4 (6.1 to 6.8)</td>
<td>3.7 (1.3 to 5.0)</td>
</tr>
<tr>
<td>1000-1999 g</td>
<td>839 227</td>
<td>4209</td>
<td>50.2 (48.7 to 51.7)</td>
<td>11.5 (12.7 to 14.3)</td>
<td>3.0 (1.7 to 4.3)</td>
</tr>
<tr>
<td>2000-9999 g</td>
<td>659 905</td>
<td>3644</td>
<td>55.2 (53.6 to 57.0)</td>
<td>18.5 (17.5 to 19.7)</td>
<td>1.3 (0.8 to 1.8)</td>
</tr>
<tr>
<td>≥10 000 g</td>
<td>85 380</td>
<td>501</td>
<td>58.7 (53.8 to 64.1)</td>
<td>22.0 (17.8 to 26.7)</td>
<td>0.4 (0.2 to 0.7)</td>
</tr>
<tr>
<td><strong>Major osteoporotic fracture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-499 g</td>
<td>2 418 041</td>
<td>22 972</td>
<td>81.6 (80.6 to 82.7)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>500-999 g</td>
<td>1 472 158</td>
<td>13 052</td>
<td>88.7 (87.2 to 90.2)</td>
<td>7.0 (6.6 to 7.5)</td>
<td>0.6 (0.7 to 1.9)</td>
</tr>
<tr>
<td>1000-1999 g</td>
<td>819 781</td>
<td>8246</td>
<td>100.6 (98.4 to 102.8)</td>
<td>19.0 (15.9 to 20.1)</td>
<td>1.7 (0.7 to 2.7)</td>
</tr>
<tr>
<td>2000-9999 g</td>
<td>642 266</td>
<td>7261</td>
<td>113.1 (110.5 to 115.7)</td>
<td>31.4 (27.9 to 33.0)</td>
<td>1.3 (0.9 to 1.7)</td>
</tr>
<tr>
<td>≥10 000 g</td>
<td>82 565</td>
<td>1010</td>
<td>122.3 (115.0 to 130.1)</td>
<td>40.7 (32.4 to 47.4)</td>
<td>0.5 (0.4 to 0.6)</td>
</tr>
<tr>
<td><strong>Osteoporosis medication</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-499 g</td>
<td>2 832 220</td>
<td>16 706</td>
<td>59.0 (58.1 to 59.9)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>500-999 g</td>
<td>1 481 389</td>
<td>9972</td>
<td>67.3 (66.0 to 68.7)</td>
<td>8.3 (7.9 to 10.6)</td>
<td>0.7 (0.7 to 2.5)</td>
</tr>
<tr>
<td>1000-1999 g</td>
<td>826 322</td>
<td>6350</td>
<td>76.9 (75.0 to 78.8)</td>
<td>17.9 (16.9 to 20.7)</td>
<td>0.7 (0.4 to 1.7)</td>
</tr>
<tr>
<td>2000-9999 g</td>
<td>646 902</td>
<td>5683</td>
<td>87.9 (85.6 to 90.2)</td>
<td>28.9 (27.5 to 32.1)</td>
<td>0.8 (0.4 to 1.3)</td>
</tr>
<tr>
<td>≥10 000 g</td>
<td>83 508</td>
<td>775</td>
<td>92.8 (86.5 to 99.6)</td>
<td>33.8 (28.4 to 41.5)</td>
<td>0.3 (0.2 to 0.5)</td>
</tr>
<tr>
<td><strong>Vertebral fracture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200-499 g</td>
<td>2 888 697</td>
<td>2820</td>
<td>9.8 (9.4 to 10.1)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>500-999 g</td>
<td>1 522 451</td>
<td>1650</td>
<td>10.8 (10.3 to 11.4)</td>
<td>1.1 (0.9 to 2.0)</td>
<td>−0.7 (−4.0 to 3.7)*</td>
</tr>
<tr>
<td>1000-1999 g</td>
<td>854 815</td>
<td>1086</td>
<td>12.7 (12.0 to 13.5)</td>
<td>2.9 (2.7 to 4.1)</td>
<td>1.4 (1.0 to 4.0)</td>
</tr>
<tr>
<td>2000-9999 g</td>
<td>673 823</td>
<td>1026</td>
<td>15.2 (14.3 to 16.2)</td>
<td>5.5 (4.9 to 6.8)</td>
<td>1.6 (0.5 to 2.6)</td>
</tr>
<tr>
<td>≥10 000 g</td>
<td>87 518</td>
<td>134</td>
<td>15.3 (12.9 to 18.1)</td>
<td>5.6 (3.5 to 8.7)</td>
<td>0.2 (−0.2 to 0.6)</td>
</tr>
</tbody>
</table>

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

* The adjusted HR was 0.99, thus yielding a negative population-attributable risk.
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% CI, 1.09-1.41) for people without psoriasis. Restricting analyses to patients with psoriasis that was not severe yielded virtually identical HRs (Tables 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 study18 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 Denmark24 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 other 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 absorption29) 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 a 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,²⁴ 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 TCSs.
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Association of Topical Corticosteroids and Risk of Osteoporosis and Major Osteoporotic Fractures

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