# Association Between Topical Corticosteroid Use and Type 2 Diabetes in Two European Population-Based Adult Cohorts

*Yuki M.F. Andersen,[1,2,3] Alexander Egeberg,[1,2] Lu Ban,[4,5] Sonia Gran,[4] Hywel C. Williams,[4] Nick A. Francis,[6] Filip K. Knop,[7,8,9] Gunnar H. Gislason,[3] Lone Skov,[1,2,8] and Jacob P. Thyssen[1,2,8]*

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## OBJECTIVE

**Topical corticosteroids (CSs) are commonly used to treat inflammatory skin conditions including eczema and psoriasis. Although topical CS package inserts describe hyperglycemia and glycosuria as adverse drug reactions, it is unclear whether topical CS use in real life is also associated with an increased risk of type 2 diabetes (T2D).**

## RESEARCH DESIGN AND METHODS

**Two matched case-control studies and one cohort study were conducted using routinely collected health care data from Denmark and the U.K. A total of 115,218 and 54,944 adults were identified as case subjects with new-onset T2D in the Danish and U.K. case-control study, respectively. For the Danish cohort study, 2,689,473 adults were included. The main exposure was topical CSs, and the outcome was incident T2D.**

## RESULTS

**Topical CS was significantly associated with T2D in the Danish (adjusted odds ratio [OR] 1.25 [95% CI 1.23–1.28]) and U.K. (adjusted OR 1.27 [95% CI 1.23–1.31]) case-control studies. Individuals who were exposed to topical CSs had significantly increased risk of incident T2D (adjusted hazard ratio 1.27 [95% CI 1.26–1.29]). We observed significant dose-response relationships between T2D and increasing potency of topical CSs in the two Danish studies. The results were consistent across all sensitivity analyses.**

## CONCLUSIONS

**We found a positive association between topical CS prescribing and incident T2D in Danish and U.K. adult populations. Clinicians should be cognizant of possible diabetogenic effects of potent topical CSs.**


Topical corticosteroids (CSs) are widely used to treat chronic inflammatory and pruritic skin conditions such as psoriasis and eczema due their efficacy, moderate costs, and relatively good safety profile (1). However, topical CSs are small molecules that can get absorbed into the skin and ultimately reach the systemic circulation and cause internal exposure (2). According to the Summary of Product Characteristics, systemic toxicity is common, and hyperglycemia and glucosuria are well-established side effects following topical CS use (3). Because most physicians are aware of the numerous serious side effects of prolonged systemic CS use (e.g., type 2 diabetes

*[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark*
*[2]Copenhagen Research Group for Inflammatory Skin (CORGIS), Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark*
*[3]Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark*
*[4]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, U.K.*
*[5]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, U.K.*
*[6]Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, U.K.*
*[7]Clinical Metabolic Physiology, Steno Diabetes Center Copenhagen, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark*
*[8]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*
*[9]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

*Corresponding author: Yuki M.F. Andersen, yuki.maria.fukuda.andersen.01@regionh.dk*

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[T2D]), these are often prescribed with caution and for the shortest amount of time necessary. Topical CSs were initially developed primarily for short-term use, but long-term maintenance therapy is now recommended in many dermatological guidelines (4–9). Concern has previously been raised about similar diabetogenic effects with use of topical CSs, but this risk remains unclear and is therefore not considered by most physicians (10,11).

We performed three large pharmacoepidemiological studies based on data from two European countries to investigate the association between topical CS use and risk of new-onset T2D in adults.

## RESEARCH DESIGN AND METHODS

### Study Design and Setting

Two matched nested case-control studies were conducted in Denmark and the U.K., respectively, in which the outcome was newly diagnosed T2D and the exposure was topical CS use. Furthermore, we performed a cohort study in the Danish population in time-to-event analyses. Data for the Danish studies were extracted from the Danish nationwide health care and administrative registries, which contain information on all hospital contacts, dispensed medication from all pharmacies, as well as social and demographic data on the entire population (12,13). The U.K. study was conducted based on the Clinical Practice Research Datalink (CPRD), a large primary health care database including clinical data from general practitioners (14). Individuals with diabetes-related drugs or diagnostic codes before study start were excluded from all study cohorts to enable identification of new-onset T2D. Patients with polycystic ovary syndrome, pancreatic cancer, and chronic pancreatitis during the entire study period were excluded to avoid misclassification of the outcome variable. The study covariates were selected based on possible confounding effects in terms of the exposure and outcome. As the available data differed in the two data sources, we used proxies as replacements (e.g., missing BMI data in the Danish cohort was replaced by antihypertensive drugs, lipid-lowering drugs, and socioeconomic status to represent the burden of obesity). A detailed description of study design, methodology, and sensitivity analyses is available in the Supplementary Material.

### The Danish Case-Control Study

The entire Danish population aged ≥18 years from 1 January 2007 through 31 December 2012 served as the source population. All individuals with at least one filled prescription of a noninsulin antidiabetic drug were included as case subjects on the date of their first such prescription (index date) and matched with the same number of control subjects without any diabetes, based on age and sex. Case and control subjects had the same age on the day they were included. Exposure to topical CSs in a period of 4 years prior to the index date was identified. Topical CS prescriptions during the study period were presented as a binary variable of never/ever exposure prior to the index date. Topical CS exposure was further categorized by potency for each participant, in which a prescription of a more potent preparation overruled a less potent preparation. The four potency categories were based on the World Health Organization's classification of drugs into mild (e.g., hydrocortisone), moderate (e.g., hydrocortisone-17-butyrate), potent (e.g., mometasone furoate), and very potent topical CSs (e.g., clobetasol proprionate). Duration of use was classified based on the prescription dates. Long-term use was defined as prescriptions in ≥2 consecutive years. Current use was defined as a prescription in the year prior to index. In comparative analyses, topical calcineurin inhibitors (an alternative anti-inflammatory topical medication) were used as a negative control. The selected covariates for the Danish study were systemic CSs (oral or injections), inhaled CSs (for oral inhalation), antihypertensive drugs, lipid-lowering drugs, smoking, alcohol abuse, socioeconomic status, and psoriasis. Psoriasis was included as a covariate, as the condition has been repeatedly shown to be associated with T2D (15).

### The U.K. Case-Control Study

The source population were individuals aged 26–89 years recorded in the CPRD between 1 January 2007 and 31 December 2015. Patients aged between 30 and 89 years with a first diabetes diagnosis (nonspecific diabetes or T2D), with no prior prescription of insulin and never coded with type 1 diabetes, were identified as case subjects. Case subjects were matched with the same number of control subjects with the same age at inclusion, sex, and general practicitioner, who were selected from people without any diagnostic or drug code compatible with any diabetes. Exposure to topical CSs was defined as described in the previous paragraph. The covariates in the U.K. cohort were systemic CSs (oral or injections), BMI, smoking status, psoriasis, eczema, and orally inhaled CSs.

### The Danish Cohort Study

The source population was defined as all Danish citizens aged ≥18 years from 1 January 2001 through 31 December 2015. Individuals with any diagnostic code or drug code for any diabetes or any prescriptions of antidiabetic drugs and/or topical CSs before study start were excluded. Topical CS exposure was modeled as a time-varying variable, in which exposure status changed from "unexposed" to "exposed" on the day of the first filled prescription. Similarly, potency of topical CS was modeled as a time-varying exposure variable. The outcome was defined as the first filled prescription of a noninsulin antidiabetic drug. Individuals were followed from study inclusion (1 January 2001 or 18th birthday after this date) and censored at the occurrence of the outcome, migration, death, or 31 December 2015, whichever came first. In sensitivity analyses, we used renal cancer as a neutral outcome. The selected covariates were age, sex, smoking, alcohol abuse, systemic CSs, inhaled CSs, antihypertensive drugs, lipid-lowering drugs, socioeconomic status, and psoriasis.

### Statistical Analysis

Categorical variables were presented as frequencies with percentages and continuous variables as means with SD. Multivariable conditional logistic regression was used to calculate crude and adjusted odds ratios (aORs) modeling T2D as a dichotomous outcome variable in the case-control studies. We adjusted for confounders, as specified previously. Matching variables were not included in the models. Wald and likelihood ratio tests were used to investigate significance. Trend tests were performed for ordered categorical variables. In the cohort study, we applied Cox regression models to estimate crude and adjusted hazard ratios (aHRs). Nelson-Aalen cumulative hazard curves were presented

to illustrate the risk over time. Results were presented with 95% CIs where applicable, and *P* values <0.05 were considered statistically significant. STATA v13.0 (StataCorp, College Station, TX) and SAS v9.4 (SAS Institute, Inc. Cary, NC) were used.

## RESULTS

### The Danish Case-Control Study

A total of 115,218 individuals were identified as case subjects (new-onset T2D) and matched with an identical number of control subjects in the Danish population. The mean (SD) age in the two groups was 61.9 (15.1) years with a slight male predominance (53.8%) (Table 1). The group with T2D had a lower income level and higher prevalence of comorbidities. The prevalence of having at least one claimed topical CS and systemic CS prescriptions during the study period was higher among case subjects (34.2% and 15.5%) than control subjects (26.9% and 11.0%).

Primary analysis showed a significant and positive association between T2D and topical CSs in crude (OR 1.41 [95% CI 1.39–1.44]) and fully adjusted analyses (aOR 1.25 [95% CI 1.23–1.28]) (Table 2). Similarly, T2D was associated with systemic CSs in crude (OR 1.49 [95% CI 1.45–1.53]) and adjusted analyses (aOR 1.28 [95% CI 1.23–1.32]). In analyses of topical CS potency, the association followed a dose-response pattern in which very potent topical CSs showed the strongest association (aOR 1.33 [95% CI 1.27–1.40]) followed by potent (aOR 1.26 [95% CI 1.22–1.29]), moderate (aOR 1.22 [95% CI 1.17–1.27]), and mild (aOR 1.17 [95% CI 1.07–1.28]) topical CSs, with a significant *P* value for trend <0.0001. Analyses of exposure duration and latency showed that current long-term use of topical CS

**Table 1—Population characteristics of the three studies**

| | Danish case-control study | | U.K. case-control study | | Danish cohort study | |
|---|---|---|---|---|---|---|
| | Case subjects (T2D), *n* = 115,218 (50%) | Control subjects (no T2D), *n* = 115,218 (50%) | Case subjects (T2D), *n* = 54,944 (50%) | Control subjects (no T2D), *n* = 54,944 (50%) | Exposed (topical CS use), *n* = 1,051,080 (39.1%) | Unexposed (no topical CS use), *n* = 1,638,393 (60.9%) |
| Sex | | | | | | |
| Male | 61,994 (53.8) | 61,994 (53.8) | 30,936 (56.3) | 30,936 (56.3) | 517,929 (49.3) | 917,672 (56.1) |
| Female | 53,224 (46.2) | 53,224 (46.2) | 24,008 (43.7) | 24,008 (43.7) | 533,151 (50.7) | 719,721 (43.9) |
| Age | | | | | | |
| Mean (SD) | 61.9 (15.1) | 61.9 (15.1) | 62.1 (12.6) | 62.1 (12.6) | 46.6 (17.2) | 46.2 (17.9) |
| Median (q25, q75) | 63.8 (52.8, 72.4) | 63.8 (52.8, 72.4) | 63.0 (53, 72) | 63.0 (53, 72) | 45.9 (32.4, 58.8) | 43.9 (31.8, 57.7) |
| BMI (kg/m$^2$) | | | | | | |
| Mean (SD) | NA | NA | 32.3 (5.30) | 27.3 (6.78) | NA | NA |
| Median (q25, q75) | NA | NA | 31.3 (27.7, 35.9) | 26.6 (23.8, 30.0) | NA | NA |
| BMI categories (kg/m$^2$) | NA | NA | | | NA | NA |
| <18.5 | NA | NA | 231 (0.42) | 941 (1.71) | NA | NA |
| 18.5–25 | NA | NA | 5,487 (9.99) | 16,746 (30.5) | NA | NA |
| 25–30 | NA | NA | 16,229 (29.5) | 19,715 (35.9) | NA | NA |
| 30–40 | NA | NA | 25,729 (46.8) | 11,421 (20.8) | NA | NA |
| >40 | NA | NA | 6,623 (12.1) | 1,223 (2.23) | NA | NA |
| Missing | NA | NA | 645 (1.2) | 4,898 (8.9) | NA | NA |
| Smoking | NA | NA | | | NA | NA |
| Current smoker | NA | NA | 9,390 (17.1) | 9,390 (17.0) | NA | NA |
| Nonsmoker | NA | NA | 26,055 (47.4) | 29,085 (52.9) | NA | NA |
| Ex-smoker | NA | NA | 19,370 (35.3) | 15,284 (27.8) | NA | NA |
| Missing | NA | NA | 129 (0.2) | 1,255 (2.3) | NA | NA |
| Alcohol abuse† | 7,829 (6.8) | 5,847 (5.1) | NA | NA | 69,163 (6.6) | 98,493 (6.0) |
| Smoking ever† | 19,089 (16.6) | 12,432 (10.8) | NA | NA | 166,388 (15.8) | 197,109 (12.0) |
| Tax-reported income level | | | NA | NA | | |
| Lowest | 24,637 (21.4) | 21,450 (18.6) | NA | NA | 191,284 (18.2) | 346,614 (21.2) |
| Below average | 26,090 (22.6) | 19,997 (17.4) | NA | NA | 211,975 (20.2) | 325,913 (19.9) |
| Average | 24,555 (21.3) | 21,533 (18.7) | NA | NA | 216,947 (20.6) | 320,948 (19.6) |
| Above average | 21,947 (19.1) | 24,140 (21.0) | NA | NA | 209,019 (19.9) | 328,879 (20.1) |
| Highest | 17,989 (15.6) | 28,098 (24.4) | NA | NA | 221,855 (21.1) | 316,039 (19.3) |
| Eczema* | NA | NA | 9,558 (17.4) | 9,117 (16.6) | NA | NA |
| Psoriasis* | 5,231 (4.5) | 3,869 (3.4) | 2,928 (5.3) | 2,423 (4.4) | 35,848 (3.4) | 7,571 (0.5) |
| Antihypertensive drugs | 35,713 (31.0) | 18,369 (15.9) | NA | NA | 244,615 (23.3) | 271,855 (16.6) |
| Lipid-lowering drugs | 76,048 (66.0) | 25,224 (21.9) | NA | NA | 271,184 (25.8) | 289,418 (17.7) |
| Systemic CSs | 17,868 (15.5) | 12,720 (11.0) | 11,940 (21.7) | 8,163 (14.9) | 284,531 (27.1) | 285,267 (17.4) |
| Inhaled CSs | 7,187 (6.2) | 5,284 (4.6) | 8,127 (14.8) | 5,807 (10.6) | 111,125 (10.6) | 114,162 (7.0) |

Population characteristics are presented as *n* (%) unless otherwise noted. Case subjects were defined as patients with T2D, and control subjects were individuals without T2D. NA, not available; q25, q75, interquartile ranges. *For participants with both diagnoses (*n* = 1,834), the last recorded diagnosis is used. †Based on composite data retrieval algorithm.

**Table 2—Association between exposure to topical CSs and new-onset T2D in Denmark and U.K.: results of two case-control studies**

| | Danish case-control study | | | | | | | | U.K. case-control study | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Case subjects, *n* (%) | Control subjects, *n* (%) | Crude | | | Adjusted* | | | Case subjects, *n* (%) | Control subjects, *n* (%) | Crude | | | Adjusted† | | |
| | | | OR | 95% CI | *P* value | OR | 95% CI | *P* value | | | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Exposure to topical CSs | 39,364 (34.2) | 31,010 (26.9) | 1.41 | 1.39–1.44 | <0.0001 | 1.25 | 1.23–1.28 | <0.0001 | 21,009 (38.2) | 16,194 (29.5) | 1.46 | 1.42–1.50 | <0.0001 | 1.27 | 1.23–1.31 | <0.0001 |
| Exposure to systemic CSs | 17,868 (15.5) | 12,720 (11.0) | 1.49 | 1.45–1.53 | <0.0001 | 1.28 | 1.23–1.32 | <0.0001 | 11,940 (21.7) | 8,163 (14.9) | 1.59 | 1.54–1.64 | <0.0001 | 1.30 | 1.25–1.35 | <0.0001 |
| Potency | | | | | <0.0001# | | | <0.0001# | | | | | | | | |
| Mild | 1,676 (1.45) | 1,436 (1.25) | 1.30 | 1.21–1.39 | <0.0001 | 1.17 | 1.07–1.28 | <0.0001 | 7,012 (12.8) | 5,354 (9.74) | 1.47 | 1.42–1.53 | <0.0001 | 1.30 | 1.24–1.37 | <0.0001 |
| Moderate | 8,509 (7.39) | 7,145 (6.20) | 1.32 | 1.28–1.37 | <0.0001 | 1.22 | 1.17–1.27 | <0.0001 | 3,352 (6.10) | 2,701 (4.92) | 1.39 | 1.32–1.47 | <0.0001 | 1.22 | 1.14–1.30 | <0.0001 |
| Potent | 21,980 (19.1) | 17,279 (15.0) | 1.42 | 1.39–1.45 | <0.0001 | 1.26 | 1.22–1.29 | <0.0001 | 8,659 (15.8) | 6,720 (12.2) | 1.46 | 1.40–1.51 | <0.0001 | 1.23 | 1.18–1.29 | <0.0001 |
| Very potent | 7,199 (6.25) | 5,150 (4.47) | 1.56 | 1.50–1.62 | <0.0001 | 1.33 | 1.27–1.40 | <0.0001 | 1986 (3.61) | 1,419 (2.58) | 1.58 | 1.47–1.70 | <0.0001 | 1.38 | 1.26–1.49 | <0.0001 |
| Duration/latency | | | | | | | | | | | | | | | | |
| Former short use | 20,443 (17.7) | 17,033 (14.8) | 1.34 | 1.31–1.37 | <0.0001 | 1.20 | 1.17–1.24 | <0.0001 | 4,299 (7.82) | 3,012 (5.48) | 1.30 | 1.26–1.35 | <0.0001 | 1.17 | 1.13–1.22 | <0.0001 |
| Current short use | 9,263 (8.04) | 7,113 (6.17) | 1.45 | 1.40–1.50 | <0.0001 | 1.30 | 1.25–1.36 | <0.0001 | 6,513 (11.85) | 4,441 (8.08) | 1.64 | 1.58–1.71 | <0.0001 | 1.43 | 1.36–1.51 | <0.0001 |
| Former long use | 1,572 (1.36) | 1,225 (1.06) | 1.44 | 1.33–1.55 | <0.0001 | 1.23 | 1.12–1.36 | <0.0001 | 692 (1.26) | 535 (0.97) | 1.46 | 1.30–1.64 | <0.0001 | 1.17 | 1.02–1.34 | 0.021 |
| Current long use | 8,086 (7.02) | 5,639 (4.89) | 1.61 | 1.55–1.66 | <0.0001 | 1.36 | 1.30–1.42 | <0.0001 | 9,505 (17.3) | 8,206 (14.9) | 1.62 | 1.54–1.71 | <0.0001 | 1.31 | 1.23–1.39 | <0.0001 |

Multivariable conditional logistic regression analysis was performed to estimate the association between exposure to topical CSs and T2D. Long-term use of topical CSs was defined as prescriptions in ≥2 consecutive years, and current use was defined as a prescription <1 year prior to index. No exposure was used as the reference. Likelihood ratio tests for categorical variables were <0.001. *Adjusted for systemic CS, socioeconomic status, smoking, alcohol abuse, antihypertensive drugs, lipid-lowering drugs, inhaled CSs, and psoriasis. In analyses in which systemic CS was the main predictor, models were adjusted for topical CSs. †Adjusted for systemic CSs, smoking status, BMI, inhaled CSs, psoriasis, and eczema. In analyses in which systemic CS was the main predictor, models were adjusted for topical CS. Patients with missing smoking status (1.26% of study population) were excluded. Multiple imputations were used for BMI. #*P* value for trend test.

(i.e., 2 consecutive years [aOR 1.36 (95% CI 1.30–1.42)]) and current short-term use (i.e., within past year [aOR 1.30 (95% CI 1.25–1.36)]) were associated with T2D. Estimates for former use were weaker, but still significant. Sensitivity analyses yielded similar results (Supplementary Tables 1–3). No association was found between T2D and use of topical calcineurin inhibitors (aOR 0.92 [95% CI 0.84–1.01]) (Supplementary Table 9).

### The U.K. Case-Control Study

In the U.K. cohort, we identified 54,944 patients with T2D and matched control subjects, respectively. The fraction of male participants was 56.3%, and the mean (SD) age was 62.1 (12.6) years in both groups. BMI was higher in patients with T2D compared with control subjects. The prevalence of current smoking was similar in the two groups. Overall, 38.2% of all case subjects and 29.5% of control subjects had at least one prescription of topical CS during the study period. Prescriptions for systemic CSs occurred in 21.7% of case subjects and 14.9% of control subjects.

Exposure to topical CSs was significantly associated with T2D in crude (OR 1.46 [95% CI 1.42–1.50]) and adjusted (aOR 1.27 [95% CI 1.23–1.31]) analyses (Table 2). The association between T2D and systemic CS use was also significant and slightly stronger than for topical CSs (aOR 1.30 [95% CI 1.25–1.35]). As opposed to the Danish study, topical CS potency as a categorical variable showed no significant trend in terms of association with T2D. Exposure to mild topical CSs (aOR 1.30 [95% CI 1.24–1.37]) and very potent topical CSs (aOR 1.38 [95% CI 1.26–1.49]) yielded similar estimates, whereas moderately potent topical CSs (aOR 1.22 [95% CI 1.14–1.30]) and potent topical CSs (aOR 1.23 [95% CI 1.18–1.29]) were slightly lower. The estimates for current short-term use were strongest (aOR 1.43 [95% CI 1.36–1.51]) followed by current long-term use (aOR 1.31 [95% CI 1.23–1.39]). Former use of topical CSs showed slightly lower effect measurements. After excluding patients with a first-time prescription within 30 and 90 days, respectively, prior to index date, the effect measurement between topical CSs and T2D became lower than in primary analysis, but remained statistically significant (aOR 1.22 [95% CI 1.14–1.23]) (Supplementary Table 5). The

**Table 3—Incidence rates of T2D per 1,000 person-years in the Danish cohort study**

| | Follow-up time in years | Events | Incidence rate per 1,000 PY | 95% CI |
|---|---|---|---|---|
| No topical CS exposure | 27,051,346 | 96,273 | 3.56 | 3.54–3.58 |
| Any topical CS exposure | 8,172,709 | 46,806 | 5.73 | 5.68–5.78 |
| Mild topical CS | 469,399 | 2062 | 4.39 | 4.21–4.59 |
| Moderate topical CS | 2,382,807 | 11,788 | 4.95 | 4.86–5.04 |
| Potent topical CS | 4,289,682 | 25,887 | 6.03 | 5.96–6.11 |
| Very potent topical CS | 1,030,820 | 7,069 | 6.86 | 6.70–7.02 |
| No systemic CS exposure | 32,469,780 | 124,902 | 3.85 | 3.83–3.87 |
| Any systemic CS exposure | 2,754,275 | 18,177 | 6.60 | 6.50–6.70 |
| No topical CS exposure, by age-groups (years) | | | | |
| <30 | 2,620,134 | 1,578 | 0.60 | 0.57–0.63 |
| 30 | 5,348,455 | 5,221 | 0.98 | 0.95–1.00 |
| 40 | 5,903,227 | 12,334 | 2.09 | 2.05–2.13 |
| 50 | 5,450,538 | 23,183 | 4.25 | 4.20–4.31 |
| 60 | 4,180,552 | 28,475 | 6.81 | 6.73–6.89 |
| 70 | 3,548,438 | 25,482 | 7.18 | 7.09–7.27 |
| Any topical CS exposure, by age-groups (years) | | | | |
| <30 | 464,185 | 661 | 1.42 | 1.32–1.54 |
| 30 | 1,508,550 | 2,712 | 1.80 | 1.73–1.87 |
| 40 | 1,622,123 | 5,622 | 3.47 | 3.38–3.56 |
| 50 | 1,547,443 | 10,325 | 6.67 | 6.54–6.80 |
| 60 | 1,499,321 | 13,796 | 9.20 | 9.05–9.36 |
| 70 | 1,531,089 | 13,690 | 8.94 | 8.80–9.09 |

PY, person-years.

results from the remaining sensitivity analyses are available in Supplementary Tables 4 and 6–8. There was no evidence of effect modification between BMI and topical CSs in terms of T2D risk. In comparative analyses, T2D was not associated with topical calcineurin inhibitor use (aOR 1.00 [95% CI 0.76–1.33]) (Supplementary Table 9).

### The Danish Cohort Study

A total of 4,241,772 individuals served as the source population. We excluded 123,253 individuals with any previous diabetes and 1,404,238 individuals with topical CS prescriptions prior to study start. A total of 24,808 individuals were excluded due to exclusion diagnoses (polycystic ovary syndrome, pancreatic cancer, and pancreatitis), yielding a total study population of 2,689,473 individuals. During the study period, 1,051,080 (39.1%) individuals claimed at least one prescription of topical CS. The mean age (SD) was 46.6 (17.2) years at study inclusion, with a similar sex distribution among exposed individuals. Overall, the topical CS–exposed group had higher prevalence of comorbidities and coprescribed medication compared with unexposed individuals.

The incidence rates (95% CI) of T2D were 5.73 (5.68–5.78) and 3.56 (3.54–3.58) per 1,000 person-years among topical CS–exposed and unexposed individuals, respectively, yielding an absolute risk difference of 2.17 (2.15–2.19) per 1,000 person-years (Table 3). In context, the absolute risk difference for systemic CSs was 2.67 (2.65–2.69). Cox regression models yielded an age- and sex-adjusted HR of 1.34 (1.32–1.36) and a fully adjusted HR of 1.27 (1.26–1.29) when topical CS was modeled as a binary exposure variable and T2D as outcome (Table 4). We assessed the risk of T2D according to the potency of topical CS exposure and found a dose-response relationship similar to the Danish case-control study results. Adjusted estimates for mild topical CSs (aHR 1.09 [95% CI 1.05–1.14]) was followed by moderate (aHR 1.21 [95% CI 1.18–1.23]), potent (1.30 [95% CI 1.28–1.31]), and very potent topical CSs (1.39 [95% CI 1.35–1.42]), respectively. When analyzing the data according to different age-groups, we found the highest HR for T2D due to topical CS use in the age-group 40–49 years, as seen in Supplementary Table 13 and Fig. 1. In analyses in which renal cancer was modeled as a negative control, no significant dose-response relationship was observed (Supplementary Table 18). Furthermore, in a subgroup analysis of participants who had never received treatment with systemic CSs, the results remained virtually unchanged (Supplementary Table 19). In addition, we performed sensitivity analyses in which patients were required to have multiple prescriptions of topical CSs to be considered exposed (i.e., in which patients only receiving one single prescription of topical CS during the study period were excluded). In such analyses, the effect estimates were comparable to our primary analysis, and all results remained statistically significant (data not shown). In landmark analyses, we observed that potent topical CS was the only significant predictor for T2D within 6 months after first-time exposure (Supplementary Table 14), whereas all potencies were significantly associated with T2D risk long-term. Nelson-Aalen cumulative hazard curves showed overall linear curves (Fig. 2 and Supplementary Fig. 1).

## CONCLUSIONS

### Main Findings

We found a positive and significant association between exposure to topical CSs and new-onset T2D in two large population-based European adult cohorts. Moreover, a dose-dependent relationship was found between potency of prescribed topical CSs and T2D in the two Danish studies. Exposure to systemic CS and topical CS exposure represented a similar excess risk of ~2 more cases of T2D per 1,000 persons per year.

### Interpretation

These three studies of Danish and U.K. adults showed that topical CSs are very frequently prescribed, highlighting the importance of safety assessments of these drugs. The U.K. register contained prescriptions given by general practitioners only, whereas the Danish register also contained prescriptions given by dermatologists who see patients with more chronic and severe disease, which requires extensive and prolonged topical CS treatment. Along this line, milder potencies of topical CSs were used more frequently in the U.K. study, whereas higher potencies were used more frequently in the Danish studies. When first developed, topical CSs were

**Table 4—Cox multivariable regression models of the Danish cohort study**

| Predictor | HR | 95% CI | *P* value |
|---|---|---|---|
| Multivariable model, topical CS exposure | | | |
| Topical CS | 1.27 | 1.26–1.29 | <0.0001 |
| Age | 1.03 | 1.03–1.03 | <0.0001 |
| Sex | 1.50 | 1.49–1.52 | <0.0001 |
| Smoking | 1.40 | 1.39–1.42 | <0.0001 |
| Alcohol | 1.30 | 1.27–1.32 | <0.0001 |
| Psoriasis | 1.28 | 1.23–1.32 | <0.0001 |
| Socioeconomic status | | | |
| Lowest | 0.75 | 0.74–0.77 | <0.0001 |
| Below average | 1.00 | 0.99–1.02 | 0.5431 |
| Average | Reference | | |
| Above average | 0.85 | 0.84–0.86 | <0.0001 |
| Highest | 0.69 | 0.68–0.70 | <0.0001 |
| Antihypertensive drugs | 1.43 | 1.37–1.50 | <0.0001 |
| Lipid-lowering drugs | 1.34 | 1.32–1.37 | <0.0001 |
| Systemic CSs | 1.19 | 1.17–1.21 | <0.0001 |
| Inhaled CSs | 1.13 | 1.11–1.15 | <0.0001 |
| Multivariable model, by topical CS potency | | | |
| Topical CS potency | | | |
| Mild | 1.09 | 1.05–1.14 | <0.0001 |
| Moderate | 1.21 | 1.18–1.23 | <0.0001 |
| Potent | 1.30 | 1.28–1.31 | <0.0001 |
| Very potent | 1.39 | 1.35–1.42 | <0.0001 |
| Age | 1.03 | 1.03–1.03 | <0.0001 |
| Sex | 1.50 | 1.49–1.52 | <0.0001 |
| Smoking | 1.41 | 1.39–1.42 | <0.0001 |
| Alcohol | 1.30 | 1.27–1.32 | <0.0001 |
| Psoriasis | 1.25 | 1.21–1.29 | <0.0001 |
| Socioeconomic status | | | |
| Lowest | 0.75 | 0.74–0.77 | <0.0001 |
| Below average | 1.01 | 0.99–1.02 | 0.4800 |
| Average | Ref· | | |
| Above average | 0.85 | 0.84–0.86 | <0.0001 |
| Highest | 0.69 | 0.68–0.70 | <0.0001 |
| Antihypertensive drugs | 1.43 | 1.37–1.49 | <0.0001 |
| Lipid-lowering drugs | 1.34 | 1.31–1.37 | <0.0001 |
| Systemic CSs | 1.19 | 1.75–1.21 | <0.0001 |
| Inhaled CSs | 1.13 | 1.11–1.15 | <0.0001 |

intended only as short-term therapy, and their Summary of Product Characteristics explicitly states that "systemic toxicity is common especially following long continued use on large areas of damaged skin, in flexures and with polythene occlusion" (3). Typically, dermatologists use potent or very potent topical CSs in patients with extensive and moderate-to-severe inflammatory skin diseases such as psoriasis, eczema, lichen planus, and bullous pemphigoid and for long periods, as these are chronic diseases. Accordingly, Danish and international guidelines for eczema and psoriasis treatment include recommendations of using moderately potent topical CSs daily until resolution and then replacing that with twice-weekly application as long-term maintenance treatment (4–9). Interestingly, increased occurrence of T2D has been reported in patients with psoriasis and atopic dermatitis in some but not all studies, which in part could be explained by the chronic and widespread use of topical CSs (16,17).

In sensitivity analyses of U.K. data, we observed that the effect measurements became substantially lower when participants with recent topical CS prescriptions prior to T2D diagnosis were excluded (Supplementary Table 5), suggesting possible surveillance bias. Similar indications of surveillance bias were observed in another CPRD study that investigated statin use and the risk of T2D (18). Therefore, our analysis, which excluded people with a recent topical CS prescription prior to diagnosis of T2D (Supplementary Table 5), may be less influenced by surveillance bias and represent a more accurate assessment of the true association than the primary analysis of the U.K. data. In the Danish cohort study, we observed signs of possible surveillance bias after first-time use of potent topical CSs in landmark analyses. Potent (but not very potent) topical CSs are typically used as the first-line treatment of unspecified inflammatory skin rash on the body, and blood samples may be a part of the initial diagnostic workup, thereby increasing the chances of detecting already existing T2D. However, in Nelson-Aalen cumulative hazard curves, we observed that the risk of T2D was constant over time and not isolated immediately after the first-time exposure. Indeed, this finding was corroborated by our landmark analyses, suggesting that the findings cannot be explained solely by surveillance bias. We performed comparative analyses with topical calcineurin inhibitor use in both cohorts and found no association with T2D. Furthermore, we did not observe an increased risk of renal cancer following topical CS use in time-to-event analysis, a condition that is associated with itch and therefore may be treated with topical CS. This supports the notion that the results indicate a true association between topical CS and T2D and are not driven by bias alone.

Our findings are in accordance with a large Dutch study that showed a significant association between topical CSs and T2D (OR 1.27 [95% CI 1.10–1.47]) (11). However, another U.K.-based study with data from The Health Improvement Network registry found no association (10). The discrepancies in the results could partially be due to methodological differences. The Health Improvement Network study was propensity score matched, based on smoking, BMI, 20 classes of comorbidity, and 15 classes of coprescribed medication—possibly a more conservative approach that would tend to underestimate a true effect. From a mechanistic perspective, the observed association may be explained by transepidermal absorption of topical CSs that could influence glucose metabolism. Hyperglycemia and glucosuria are indeed adverse drug reactions described in patient information leaflets of topical CSs (3,19). Clinical studies have reported adrenal suppression induced by topical CSs, suggesting that prolonged and excessive use could impact T2D risk (20,21). Furthermore, glucosuria and hyperglycemia have been measured following topical CS application in patients

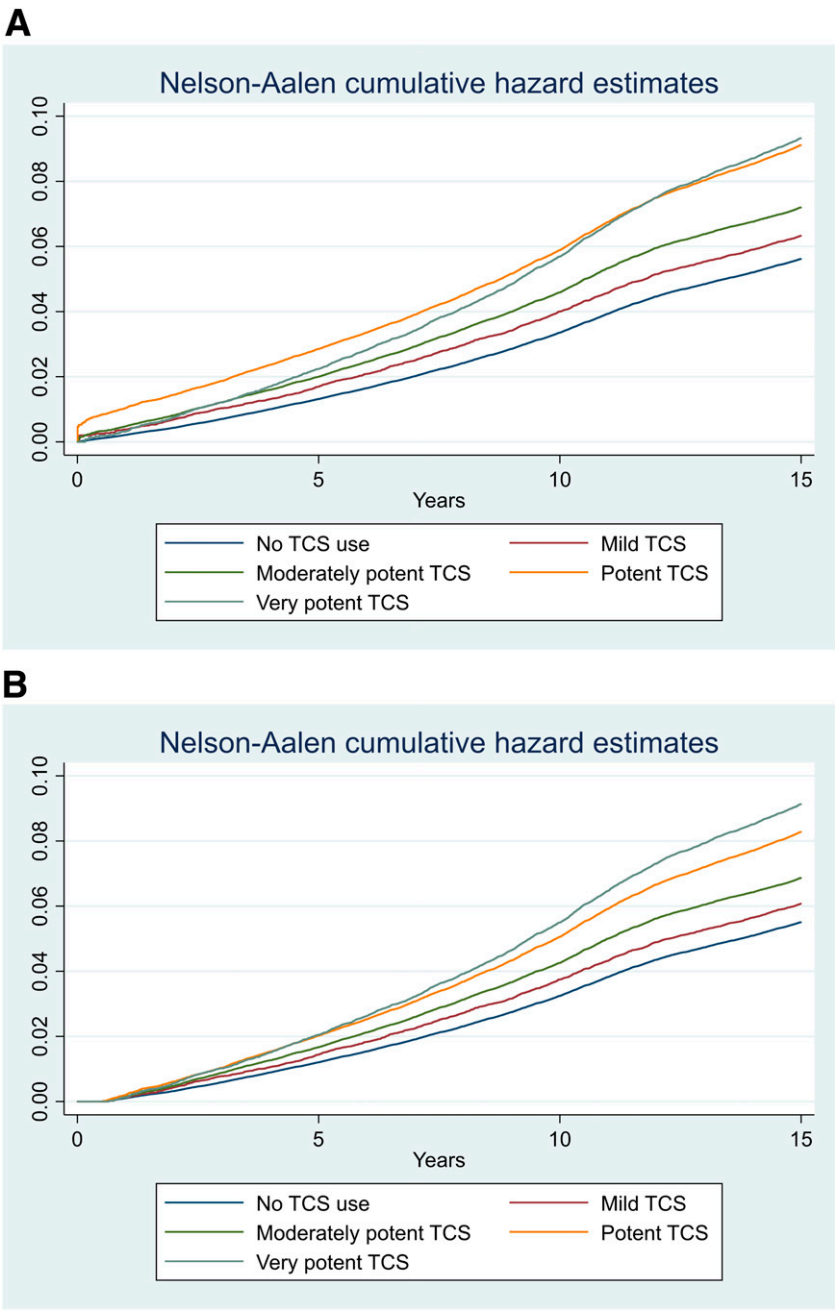


**Figure 1**—Nelson-Aalen cumulative hazard curves of the risk of T2D by topical CS (TCS) potency. *A*: Cumulative hazard curves overall, in which TCS is modeled as a categorical exposure by potency. *B*: Cumulative hazard curves in landmark analysis, 6 months after initial exposure, in which TCS is modeled as a categorical exposure by potency.

with psoriasis (22). The molecular weight of topical CS is <500 Da (i.e., the pragmatic upper limit for a molecule to penetrate the epidermal barrier) (2). In contrast, the molecular weight of topical calcineurin inhibitors is >800 Da, and its use was not associated with T2D (23). Furthermore, lesional skin in conditions such as eczema displays a two- to fivefold higher absorption rate compared with intact skin, indicating that patients with chronic severe skin conditions may be at higher risk of systemic adverse effects (24). No large studies have, to our knowledge, examined glucose levels or insulin resistance in patients treated with topical CS; however, a number of smaller exposure studies have suggested systemic metabolic changes following topical CS exposure, including suppression of the hypothalamic-pituitary-adrenal axis (20,25–29).

### Strengths and Limitations

We found similar results in two large data sets from two countries. The Danish cohort study confirmed the association in time-to-event analysis securing the chronology between the exposure and outcome. The Danish registries and the CPRD are recognized for their high data quality and representativeness. Despite the high quality, some misclassification of the variables may have occurred, due to limited validation studies. Importantly, in the current study, we used drug prescription codes to identify case subjects with T2D, as complete information on clinical measurements such as hyperglycemia in the studied populations was not available. Due to the prospective data collection, there is virtually no risk of recall bias (14,30). We controlled for important confounding factors; however, residual confounding cannot be excluded. Furthermore, reverse causality could have influenced our results because patients with prediabetes or undiagnosed diabetes could use more topical CSs due to increased incidence of dry skin and itch, along with bacterial and fungal infections, in turn leading to false-positive associations (31–33). However, itch is also a symptom of renal cancer, but in this study, we observed no association. Poor treatment adherence and fluctuating symptoms in chronic skin diseases may influence the use of topical CSs, and it was impossible to estimate the frequency, time, and true amount of applied topical CSs per patient. Absorption rates of topical CSs are influenced by the anatomical regions of the skin; however, this information was unavailable. Although we used topical calcineurin inhibitors as a control marker, these drugs are usually not first-line treatment, and their indications are more restricted than topical CSs. Prescriptions from secondary care were unavailable in the U.K. study; however, the vast majority of topical CSs are prescribed in primary care, and sensitivity analyses indicated that the lack of such data did not bias the results substantially. Importantly, these studies were limited to adults.

### Conclusions

In three large population-based studies, use of topical CSs in adults was significantly associated with risk of T2D. Clinicians should be cognizant of possible

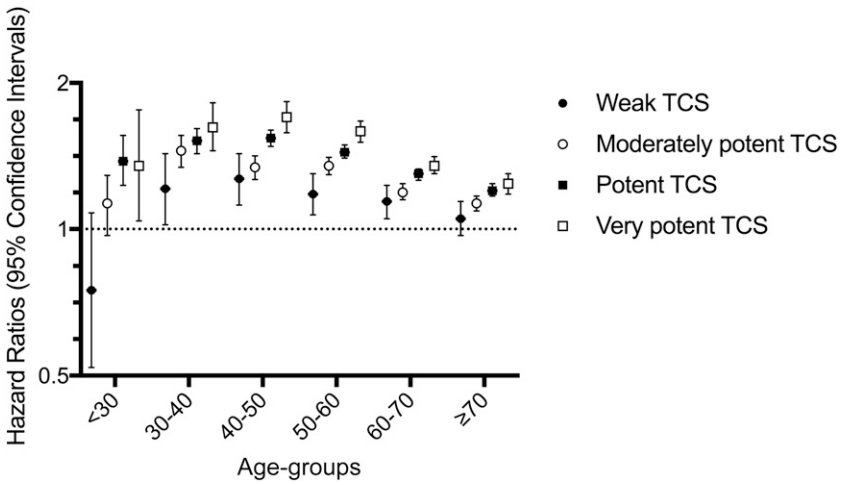


**Figure 2**—Forest plot of HRs for T2D according to potency in different age-groups. TCS, topical CS.

diabetogenic effects of high-potency topical CSs and consider other treatment options if possible.

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