Title

Association between topical corticosteroid use and type 2 diabetes in two European population-based adult cohorts

Running head

Topical corticosteroid use and type 2 diabetes

Manuscript word, table and figure count

3136 words, 4 tables, 2 figures, 1 supplementary figure, 19 supplementary tables

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ABSTRACT

Background
Topical corticosteroids (CS) are commonly used to treat inflammatory skin conditions including eczema and psoriasis. While topical CS package inserts describe hyperglycaemia 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).

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

Results
Topical CS was significantly associated with T2D in the Danish (adjusted OR 1·35; 95% CI 1·33-1·38) and UK (adjusted OR 1·23; 95% CI 1·19-1·27) case-control studies. Individuals who were exposed to topical CS had significantly increased risk of incident T2D (adjusted HR 1·27; 95% CI 1·26-1·29). We observed significant dose-response relationships between T2D and increasing potency of topical CS 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 UK adult populations. Clinicians should be cognizant of possible diabetogenic effects of potent topical CS.

INTRODUCTION

Topical corticosteroids (CS) 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 CS 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 (SmPC), systemic toxicity is common and hyperglycaemia and glucosuria are well-established side effects following topical CS use.[3] Since most physicians are aware of the numerous serious side-effects of prolonged systemic CS use, e.g. type 2 diabetes (T2D), these are often prescribed with caution and for the shortest amount of time necessary. Topical CS were initially developed primarily for short-term use, but long-term maintenance therapy are now recommended in many dermatological guidelines.[4–9] Concern has previously been raised about similar diabetogenic effects with use of topical CS, but this risk remains unclear and is therefore not considered by most physicians.[10,11]

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

METHODS

Study design and setting

Two matched nested case-control studies in Denmark and the United Kingdom (UK), respectively, where 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 healthcare 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 UK 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 as supplementary materials.

The Danish case-control study

The entire Danish population aged ≥18 years from January 1st 2007 through December 31st 2012 served as the source population. All individuals with at least one filled prescription of a non-insulin antidiabetic drug were included as cases on the date of their first such prescription (index date), and matched with the same number of controls without any diabetes, based on age and sex. Cases and controls had the same age on the day they were included. Exposure to topical CS in a period of four 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, where a prescription of a more potent preparation overruled a less potent preparation. The four potency categories were based on WHO's classification of drugs into mild (e.g. hydrocortisone), moderate (e.g. hydrocortisone-17-butyrate), potent (e.g. mometasone furoate), and very potent topical CS (e.g. clobetasol proprionate). Duration of use was classified based on the prescription dates. Long-term use was defined as prescriptions in two consecutive years or more. 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 CS (oral or injections), inhaled corticosteroids (for oral inhalation), antihypertensive drugs, lipid lowering drugs, smoking, alcohol abuse, socioeconomic status, and psoriasis. Psoriasis was

included as a covariate, as topical CS are often used to treat the conditions which is known to be associated with T2D.[15]

The UK case-control study

The source population were individuals aged 26-89 years recorded in the CPRD between January 1st 2007 and December 31st 2015. Patients aged between 30 and 89 with a first diabetes diagnosis (non-specific diabetes or T2D), with no prior prescription of insulin and never coded with type 1 diabetes (T1D), were identified as cases. Cases were matched with the same number of controls with the same age at inclusion, sex and GP practice, who were selected from people without any diagnostic or drug code compatible with any diabetes. Exposure to topical CS was defined as described in the previous paragraph. The covariates in the UK cohort were systemic CS (oral or injections), body mass index (BMI), smoking status, psoriasis, eczema, and orally inhaled CS.

The Danish cohort study

The source population was defined as all Danish citizens aged ≥18 years from January 1st 2001 through December 31st 2015. Individuals with any diagnostic code or drug code for any diabetes or any prescriptions of antidiabetic drugs and/or topical CS before study start were excluded. Topical CS exposure was modelled as a time-varying variable, where exposure status changed from 'unexposed' to 'exposed' on the day of the first filled prescription. Similarly, potency of topical CS was modelled as a time-varying exposure variable. The outcome was defined as the first filled prescription of a non-insulin antidiabetic drug. Individuals were followed from study inclusion (January 1st 2001 or 18th birthday after this date) and censored at the occurrence of the outcome, migration, death, or December 31, 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 CS, inhaled CS, 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 standards deviations (SD). Multivariable conditional logistic regression was used to calculate crude and adjusted odds ratios (aORs) modelling 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 (HRs). Nelson-Aalen cumulative hazards curves were presented to illustrate the risk over time. Results were presented with 95% confidence intervals (CIs) where applicable, and p-values less than 0·05 were considered statistically significant. STATA v13·0 (StataCorp, College Station, TX, USA) and SAS v9·4 (SAS Institute Inc. Cary, NC, USA) were used.

RESULTS

The Danish case-control study

A total of 115,218 individuals were identified as cases (new onset T2D) and matched with an identical number of controls in the Danish population. The mean age (SD) in the two groups was 61·9 (15·1) years with a slight male predominance (53·8%) (Table 1). The T2D group 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 were higher among cases (34·2% and 15·5%) than controls (26·9% and 11·0%).

Primary analysis showed a significant and positive association between T2D and topical CS 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 CS 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 where very potent topical CS 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 CS, with a significant p-value for trend <0·0001. Analyses of exposure duration and latency showed that current long-term use of topical CS, 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 (Table S1, S2, S3). No association was found between T2D and use of topical calcineurin inhibitors (aOR 0·92; 95% CI 0·84-1·01) (Table S8).

The UK case-control study

In the UK cohort, we identified 54,944 patients with T2D and matched controls, respectively. The fraction of male participants was 56·3% and the mean age (SD) was 62·1 (12·6) in both groups. BMI was higher in patients with T2D compared with controls. The prevalence of current smoking was similar in the two groups. Overall, 38·2% of all cases and 29·5% of controls had at least one prescription of topical CS during the study period. Prescriptions for systemic CS occurred in 21·7% of cases and 14·9% of controls.

Exposure to topical CS was significantly associated with T2D in crude (OR 1·46; 95% CI 1·42-1·50) and adjusted (aOR 1·23; 95% CI 1·19-1·27) analyses (Table 3). The association between T2D and systemic CS use was also significant, and slightly stronger than for topical CS (aOR 1·33; 95% CI 1·27-1·38). 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 CS (aOR 1·27; 95% CI 1·21-1·33) and very potent topical CS (aOR 1·32; 95% CI 1·21-1·44) yielded similar estimates, while moderately potent topical CS (aOR 1·19; 1·11-1·27) and potent topical CS (aOR 1·20; 95% CI 1·14-1·25) were slightly lower. The estimates for current short-term use were strongest (aOR 1·38; 95%CI 1·31-1·45) followed by current long-term use (aOR 1·26; 95% CI 1·19-1·34). Former use of topical CS 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 CS

and T2D became lower than in primary analysis, but remained statistically significant (aOR 1·19; 95% CI 1·14-1·23) (Table S5). The results from the remaining sensitivity analyses are available in supplementary files (Table S4, S6, S7, S8). There was no evidence of effect modification between BMI and topical CS in terms of T2D risk. In comparative analyses, T2D was not associated with topical calcineurin inhibitor use (aOR 1·00; 95% CI 0·79-1·27) (Table S9).

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. 24,808 individuals were excluded due to exclusion diagnoses (PCOS, 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 gender distribution among exposed individuals. Overall, the topical CS exposed group had higher prevalence of comorbidities and co-prescribed 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 1000 person-years among topical CS exposed and unexposed individuals, respectively, yielding an absolute risk difference of 2·17 (2·15-2·19) per 1000 person years (Table 3). In context, the absolute risk difference for systemic CS 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 modelled 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 (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 CS (1·39; 95% CI 1·35-1·42), respectively. When analysing 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 Table S13 and Figure 2. In analyses where renal cancer was modelled as a negative control, no

significant dose-response relationship was observed (Table S18). Furthermore, in a subgroup analysis of participants who had never received treatment with systemic CS, the results remained virtually unchanged (Table S19). In addition, we performed sensitivity analyses where patients were required to have multiple prescriptions of topical CS to be considered exposed, i.e. where 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 (Table S14), while all potencies were significantly associated with T2D risk long-term. Nelson-Aalen cumulative hazards curves showed overall linear curves (Figure 1 and S1).

DISCUSSION

Main findings

We found a positive and significant association between exposure to topical CS and new-onset T2D in two large population-based European adult cohorts. Moreover, a dose-dependent relationship was found between potency of prescribed topical CS and T2D in the two Danish studies. Exposure to systemic CS and topical CS exposure represented a similar excess risk of approximately two more cases of T2D per 1000 persons per year.

Interpretation

These three studies of Danish and UK adults showed that topical CS are very frequently prescribed, highlighting the importance of safety assessments of these drugs. The UK 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 require extensive and prolonged topical CS treatment. Along this line, milder potencies of topical CS were used more frequently in the UK study, whereas higher potencies were used more frequently in the Danish studies. When first developed, topical CS were intended only as short-term therapy, and

their SmPC explicitly state 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 CS 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 CS daily until resolution and then replaced by twice-weekly application as long-term maintenance treatment.[4–9] Interestingly, increased occurrence of T2D have 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 CS.[16,17]

In sensitivity analyses of UK data, we observed that the effect measurements became substantially lower when participants with recent topical CS prescriptions prior to T2D diagnosis were excluded (Table S5), 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 (Table S5), may be less influenced by surveillance bias and represent a more accurate assessment of the true association than the primary analysis of the UK data. In the Danish cohort study, we observed signs of possible surveillance bias after first-time use of potent topical CS in landmark analyses. Potent (but not very potent) topical CS 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 work-up, thereby increasing the chances of detecting already existing T2D. However, in Nelson-Aalen cumulative hazards 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 CS and T2D (OR 1·27; 95% CI 1·10-1·47).[11] However, another UK-based study with data from The Health Improvement Network (THIN) registry found no association.[10] The discrepancies in the results could partially be due to methodological differences. The THIN study was propensity score-matched, based on smoking, BMI and 20 classes of comorbidity and 15 classes of co-prescribed 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 trans-epidermal absorption of topical CS that could influence glucose metabolism. Hyperglycaemia and glucosuria are indeed adverse drug reactions described in patient information leaflets of topical CS.[3,19] Clinical studies have reported adrenal suppression induced by topical CS, suggesting that prolonged and excessive use could impact T2D risk.[20,21] Furthermore, glucosuria and hyperglycaemia have been measured following topical CS application in patients with psoriasis.[22] The molecular weight of topical CS is less than 500 Dalton, 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 over 800 Dalton and its use was not associated with T2D.[23] Furthermore, lesional skin in conditions such as eczema displays a 2-5 fold 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.[20,25–30]

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 cases with T2D, as complete information on clinical measurements such as hyperglycaemia in the studied populations were not available. Due to the prospective data collection, there is virtually no risk of recall bias.[14,31] We controlled for important confounding factors, however, residual confounding cannot be excluded. Furthermore, reverse causality could have influenced our results since patients with pre-diabetes or undiagnosed diabetes could use more topical CS due to increased incidence of dry skin, itch, along with bacterial and fungal infections in turn leading to false-positive associations.[32–34] However, itch is also a symptom of renal cancer, but here we observed no association. Poor treatment adherence and fluctuating symptoms in chronic skin diseases may influence the use of topical CS and it was impossible to estimate the frequency, time, and true amount of applied topical CS per patient. Absorption rates of topical CS 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 CS. Prescriptions from secondary care were unavailable in the UK study, however the vast majority of topical CS 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.

CONCLUSION

In three large population-based studies, use of topical CS in adults was significantly associated with risk of T2D. Clinicians should be cognizant of possible diabetogenic effects of high-potency topical CS and consider other treatment options if possible.

Acknowledgements:

Funding:

Drs. Thyssen and Andersen are supported by an unrestricted grant from the Lundbeck Foundation. Dr. Andersen was supported by grants from the Aage Bang Foundation and the A.P. Møller Foundation. The guarantor of this study is Yuki Andersen.

Declaration of interests:

Dr. Thyssen has attended advisory boards for Roche and Sanofi-Genzyme and received speaker honorarium from LEO Pharma and Sanofi-Genzyme. Dr. Skov has received speaker honoraria from Abbvie, Pfizer, Janssen-Cilag, and Leo Pharma and is a member of the advisory boards of Abbvie, Pfizer, Janssen-Cilag, Sanofi, Eli Lilly, Celgene and Novartis. Dr. Egeberg has received research funding from Pfizer, Eli Lilly and honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. Prof. Knop has received lecture fees from, participated in advisory boards of, consulted for and/or received research grants from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Novo Nordisk, Sanofi, and Zealand Pharma.

Conflicts of interest:

This research was performed independently through the authors' academic university and hospital affiliations. No potential conflicts of interest relevant to this article were reported.

Author Contributions

Study concept and design: Andersen, Thyssen, Egeberg, Williams, Ratib, Ban and Francis. *Acquisition and analysis of data:* Andersen, Egeberg, Ban and Ratib. *Interpretation of data:* All authors. *Drafting of the manuscript:* Andersen, Egeberg and Thyssen. *Critical revision of the manuscript:* All authors. *Administrative, technical, or material support:* Andersen. *Study supervision:* Egeberg and Thyssen. *Guarantor:* Andersen.

All authors contributed towards the writing of this manuscript. All authors approve the final manuscript and agree to be accountable for all aspects of the work.

References

1. Callen J, Chamlin S, Eichenfield LF, et al. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol*. 2007;156(2):203-221. doi:10.1111/j.1365-2133.2006.07538.x

2. Bos JD, Meinardi MMHM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol*. 2000;9(3):1-5. doi:10.1034/j.1600-0625.2000.009003165.x

3. Elocon Cream - Summary of Product Characteristics (SmPC) - print friendly - (eMC). https://www.medicines.org.uk/emc/product/78/smpc/print. Accessed August 13, 2018.

4. 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 Work Group. *J Am Acad Dermatol*. 2014;71(6):1218-1233. doi:10.1016/j.jaad.2014.08.038

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

6. 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 Dermatology Venereol*. 2012;26(SUPPL. 3):1-10. doi:10.1111/j.1468-3083.2012.04518.x

7. National Clinical Guidelines for Psoriasis, The Danish Health Authority. https://www.sst.dk/da/udgivelser/2016/nkr-psoriasis. Accessed April 10, 2018.

8. English J, Aldridge R, Gawkrodger DJ, et al. Consensus statement on the management of chronic hand eczema. doi:10.1111/j.1365-2230.2009.03649.x

9. 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

10. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. *Diabetes Care*. 2006;29(12):2728-2729. doi:10.2337/dc06-1499

11. van der Linden MW, Penning-van Beest FJA, Nijsten T, Herings RMC. Topical corticosteroids and the risk of diabetes mellitus: a nested case-control study in the Netherlands. *Drug Saf*. 2009;32(6):527-537. http://www.ncbi.nlm.nih.gov/pubmed/19459719. Accessed March 17, 2018.

12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39:30-33. doi:10.1177/1403494811401482

13. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Heal*. 2011;39(7 Suppl):38-41. doi:10.1177/1403494810394717

14. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836. doi:10.1093/ije/dyv098

15. Gelfand JM, Wan MT. Psoriasis: a novel risk factor for type 2 diabetes. *lancet Diabetes Endocrinol*. 2018;6(12):919-921. doi:10.1016/S2213-8587(18)30127-X

16. Miller IM, Ellervik C, Yazdanyar S, Jemec GBE. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol*. 2013;69(6):1014-1024. doi:10.1016/J.JAAD.2013.06.053

17. Thyssen JP, Halling-Overgaard A-S, Andersen YMF, Gislason G, Skov L, Egeberg A. The association between cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. December 2017. doi:10.1111/bjd.16215

18. Macedo AF, Douglas I, Smeeth L, Forbes H, Ebrahim S. Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice pesearch datalink. *BMC Cardiovasc Disord*. 2014;14(1):85. doi:10.1186/1471-2261-14-85

19. Dermovate ® Cream https://www.medicines.org.uk/emc/PIL.3829.latest.pdf. https://www.medicines.org.uk/emc/PIL.3829.latest.pdf. Accessed October 4, 2017.

20. Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. *Am J Clin Dermatol*. 2002;3(3):141-147. doi:10.2165/00128071-200203030-00001

21. Queille C, Pommarede R, Saurat JH. Efficacy versus systemic effects of six topical steroids in the treatment of atopic dermatitis of childhood. *Pediatr Dermatol*. 1984;1(3):246-253. doi:10.1111/j.1525-1470.1984.tb01124.x

22. Gomez EC, Frost P, RB S, et al. Induction of Glycosuria and Hyperglycemia by Topical Corticosteroid Therapy. *Arch Dermatol*. 1976;112(11):1559. doi:10.1001/archderm.1976.01630350035009

23. Alomar A, Berth-Jones J, Bos JD, et al. The role of topical calcineurin inhibitors in atopic dermatitis: *Br J Dermatol*. 2004;151(s70):3-27. doi:10.1111/j.1365-2133.2004.06269.x

24. Carruthers JA, August PJ, Staughton RC. Observations on the systemic effect of topical clobetasol propionate (Dermovate). *Br Med J*. 1975;4(5990):203-204. doi:10.1136/bmj.4.5990.203

25. Garden JM, Freinkel RK. Systemic Absorption of Topical Steroids. *Arch Dermatol*. 1986;122(9):1007. doi:10.1001/archderm.1986.01660210057018

26. Ohman EM, Rogers S, Meenan FO, McKenna TJ. Adrenal suppression following low-dose topical clobetasol propionate. *J R Soc Med*. 1987;80(7):422-424. doi:10.1177/014107688708000709

27. Carruthers JA, August PJ, Staughton RC. Observations on the systemic effect of topical clobetasol propionate (Dermovate). *Br Med J*. 1975;4(5990):203-204. doi:10.1136/bmj.4.5990.203

28. Lam LH, Sugarman JL. Adrenal Suppression With Chronic Topical Corticosteroid Use in Psoriasis Patients. *J Drugs Dermatol*. 2016;15(8):945-948. http://www.ncbi.nlm.nih.gov/pubmed/27537994. Accessed September 7, 2016.

29. Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*. 2015;100(6):2171-2180. doi:10.1210/jc.2015-1218

30. Böckle BC, Jara D, Nindl W, Aberer W, Sepp NT. Adrenal insufficiency as a result of long-term misuse of topical corticosteroids. *Dermatology*. 2014;228(4):289-293. doi:10.1159/000358427

31. 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

32. Makrantonaki E, Jiang D, Hossini AM, et al. Diabetes mellitus and the skin. *Rev Endocr Metab Disord*. July 2016:1-14. doi:10.1007/s11154-016-9373-0

33. Farshchian M, Farshchian M, Fereydoonnejad M, Yazdanfar A, Kimyai-Asadi A. Cutaneous manifestations of diabetes mellitus: a case series. *Cutis*. 2010;86(1):31-35. http://www.ncbi.nlm.nih.gov/pubmed/21049764. Accessed October 7, 2017.

34. Sakai S, Kikuchi K, Satoh J, Tagami H, Inoue S. Functional properties of the stratum corneum in patients with diabetes mellitus: similarities to senile xerosis. *Br J Dermatol*. 2005;153(2):319-323. doi:10.1111/j.1365-2133.2005.06756.x

Table 1. Population characteristics of the three studies

	Danish case-control study		UK case-control study		Danish cohort study	
	Cases (T2D)	**Controls (no T2D)**	**Cases (T2D)**	**Controls (no T2D)**	**Exposed (topical CS use)**	**Unexposed (no topical CS use)**
	n=115,218 (50)	n=115,218 (50)	n=54,944 (50)	n=54,944 (50)	n=1,051,080 (39·1)	n=1,638,393 (60·9)
Gender						
Male (%)	61994 (53·8)	61994 (53·8)	30936 (56·3)	30936 (56·3)	517929 (49·3)	917672 (56·1)
Female (%)	53224 (46·2)	53224 (46·2)	24008 (43·7)	24008 (43·7)	533151 (50·7)	719721 (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						
Mean (SD)	n/a	n/a	32·3 (5·30)	27·3 (6·78)	n/a	n/a
Median (q25, q75)	n/a	n/a	31·3 (27·7, 35·9)	26·6 (23·8, 30·0)	n/a	n/a
BMI categories						
<18·5	n/a	n/a	231 (0·42)	941 (1·71)	n/a	n/a
18·5-25	n/a	n/a	5487 (9·99)	16746 (30·5)	n/a	n/a
25-30	n/a	n/a	16229 (29·5)	19715 (35·9)	n/a	n/a
30-40	n/a	n/a	25729 (46·8)	11421 (20·8)	n/a	n/a
>40	n/a	n/a	6623 (12·1)	1223 (2·23)	n/a	n/a
Missing	n/a	n/a	645 (1·2)	4898 (8·9)	n/a	n/a
Smoking						
Current smoker	n/a	n/a	9390 (17·1)	9390 (17·0)	n/a	n/a
Non-smoker	n/a	n/a	26055 (47·4)	29085 (52·9)	n/a	n/a
Ex- smoker	n/a	n/a	19370 (35·3)	15284 (27·8)	n/a	n/a
Missing	n/a	n/a	129 (0·2)	1255 (2·3)	n/a	n/a
Alcohol abuse[¤]	7829 (6·8)	5847 (5·1)	n/a	n/a	69163 (6·6)	98493 (6·0)
Tobacco use[¤]	19089 (16·6)	12432 (10·8)	n/a	n/a	166388 (15·8)	197109 (12·0)
Tax reported income level						
Lowest	24637 (21·4)	21450 (18·6)	n/a	n/a	191284 (18·2)	346614 (21·2)

Below average	26090 (22·6)	19997 (17·4)	n/a	n/a	211975 (20·2)	325913 (19·9)
Average	24555 (21·3)	21533 (18·7)	n/a	n/a	216947 (20·6)	320948 (19·6)
Above average	21,947 (19·1)	24140 (21·0)	n/a	n/a	209019 (19·9)	328879 (20·1)
Highest	17989 (15·6)	28098 (24·4)	n/a	n/a	221855 (21·1)	316039 (19·3)
Eczema *	n/a	n/a	9558 (17·4)	9117 (16·6)	n/a	n/a
Psoriasis *	5231 (4·5)	3869 (3·4)	2928 (5·3)	2423 (4·4)	35848 (3·4)	7571 (0·5)
Anti-hypertensive drugs	35,713 (31·0)	18,369 (15·9)	n/a	n/a	244615 (23·3)	271855 (16·6)
Lipid-lowering drugs	76,048 (66·0)	25,224 (21·9)	n/a	n/a	271184 (25·8)	289418 (17·7)
Systemic corticosteroids	17,868 (15·5)	12,720 (11·0)	11940 (21·7)	8163 (14·9)	284531 (27·1)	285267 (17·4)
Inhaled corticosteroids	7,187 (6·2)	5,284 (4·6)	8127 (14·8)	5807 (10·6%)	111125 (10·6)	114162 (7·0)

Population characteristics presented as n (%) if not otherwise specified. Cases were defined as patients with type 2 diabetes and controls were individuals without. The column of exposed
BMI, body mass index; CS, topical corticosteroids; SD, standard deviation; T2D, type 2 diabetes; q25, q75, interquartile ranges
* For participants with both diagnoses (n=1834), the last recorded diagnosis is used
¤ Based on composite data retrieval algorithm

Table 2. Association between exposure to topical corticosteroids and new onset type 2 diabetes in Denmark and UK, results of two case-control studies.

	Danish case-control study								UK case-control study							
			Crude			Adjusted*					Crude			Adjusted ¤		
	Cases, n (%)	Controls, n(%)	OR	95% CI	p-value	OR	95% CI	p-value	Cases, n (%)	Controls, n(%)	OR	95% CI	p-value	OR	95% CI	p-value
Exposure to topical CS	39364 (34·2)	31010 (26·9)	1·41	1·39-1·44	<0·0001	1·25	1·23-1·28	<0·0001	21009 (38·2)	16194 (29·5)	1·46	1·42-1·50	<0·0001	1·27	1·23-1·31	<0·0001
Exposure to systemic CS	17868 (15·5)	12720 (11·0)	1·49	1·45-1·53	<0·0001	1·28	1·23-1·32	<0·0001	11940 (21·7)	8163 (14·9)	1·59	1·54-1·64	<0·0001	1·30	1·25-1·35	<0·0001
Potency					<0·0001 #			<0·0001 #								
Mild	1676 (1·45)	1436 (1·25)	1·30	1·21-1·39	<0·0001	1·17	1·07-1·28	<0·0001	7012 (12·8)	5354 (9·74)	1·47	1·42-1·53	<0·0001	1·30	1·24-1·37	<0·0001
Moderate	8509 (7·39)	7145 (6·20)	1·32	1·28-1·37	<0·0001	1·22	1·17-1·27	<0·0001	3352 (6·10)	2701 (4·92)	1·39	1·32-1·47	<0·0001	1·22	1·14-1·30	<0·0001
Potent	21980 (19·1)	17279 (15·0)	1·42	1·39-1·45	<0·0001	1·26	1·22-1·29	<0·0001	8659 (15·8)	6720 (12·2)	1·46	1·40-1·51	<0·0001	1·23	1·18-1·29	<0·0001
Very potent	7199 (6·25)	5150 (4·47)	1·56	1·50-1·62	<0·0001	1·33	1·27-1·40	<0·0001	1986 (3·61)	1419 (2·58)	1·58	1·47-1·70	<0·0001	1·38	1·26-1·49	<0·0001
Duration/ latency																
Former short use	20443 (17·7)	17033 (14·8)	1·34	1·31-1·37	<0·0001	1·20	1·17-1·24	<0·0001	4299 (7·82)	3012 (5·48)	1·30	1·26-1·35	<0·0001	1·17	1·13-1·22	<0·0001
Current short use	9263 (8·04)	7113 (6·17)	1·45	1·40-1·50	<0·0001	1·30	1·25-1·36	<0·0001	6513 (11·85)	4441 (8·08)	1·64	1·58-1·71	<0·0001	1·43	1·36-1·51	<0·0001
Former long use	1572 (1·36)	1225 (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	8086 (7·02)	5639 (4·89)	1·61	1·55-1·66	<0·0001	1·36	1·30-1·42	<0·0001	9505 (17·3)	8206 (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 CS and type 2 diabetes.
Long term use of topical CS was defined as prescriptions in two consecutive years or more, and current use was defined as a prescription less than one 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, anti-hypertensive drugs, lipid-lowering drugs, inhaled corticosteroids, and psoriasis. In analyses where systemic CS was the main predictor models were adjusted for topical CS.
¤ Adjusted for systemic CS, smoking status, body mass index, inhaled corticosteroids, psoriasis, and eczema. In analyses where 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 body mass index.
p-value for trend test
CI, confidence interval; CS, corticosteroids; OR, odds ratio; systemic CS, systemic corticosteroids.

Table 3. Incidence rates of type 2 diabetes per 1000 person-years in the Danish cohort study

	Follow-up time in years	Events	Incidence rate per 1000 PY	95% CI
No topical CS exposure	27051346	96273	3·56	3·54-3·58
Any topical CS exposure	8172709	46806	5·73	5·68-5·78
Mild topical CS	469399	2062	4·39	4·21-4·59
Moderate topical CS	2382807	11788	4·95	4·86-5·04
Potent topical CS	4289682	25887	6·03	5·96-6·11
Very potent topical CS	1030820	7069	6·86	6·70-7·02
No systemic CS exposure				
Any systemic CS exposure	2754275	18177	6·60	6·50-6·70
No topical CS exposure, by age-groups				
<30	2620134	1578	0·60	0·57-0·63
30	5348455	5221	0·98	0·95-1·00
40	5903227	12334	2·09	2·05-2·13
50	5450538	23183	4·25	4·20-4·31
60	4180552	28475	6·81	6·73-6·89
70	3548438	25482	7·18	7·09-7·27
Any topical CS exposure, by age-groups				
<30	464185	661	1·42	1·32-1·54
30	1508550	2712	1·80	1·73-1·87
40	1622123	5622	3·47	3·38-3·56
50	1547443	10325	6·67	6·54-6·80
60	1499321	13796	9·20	9·05-9·36
70	1531089	13690	8·94	8·80-9·09

CI, confidence interval; CS, corticosteroids; PY, person-years.

Table 4. Cox multivariable regression models of the Danish cohort study

Multivariable model, topical CS exposure				Multivariable model, by topical CS potency			
Predictor	**HR**	**95% CI**	**P-value**	**Predictor**	**HR**	**95% CI**	**P-value**
				Topical CS potency			
Topical CS	1·27	1·26-1·29	<0·0001	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	**Age**	1·03	1·03-1·03	<0·0001
Sex	1·50	1·49-1·52	<0·0001	**Sex**	1·50	1·49-1·52	<0·0001
Smoking	1·40	1·39-1·42	<0·0001	**Smoking**	1·41	1·39-1·42	<0·0001
Alcohol	1·30	1·27-1·32	<0·0001	**Alcohol**	1·30	1·27-1·32	<0·0001
Psoriasis	1·28	1·23-1·32	<0·0001	**Psoriasis**	1·25	1·21-1·29	<0·0001
Socio-economic status				**Socio-economic status**			
Lowest	0·75	0·74-0·77	<0·0001	Lowest	0·75	0·74-0·77	<0·0001
Below average	1·00	0·99-1·02	0·5431	Below average	1·01	0·99-1·02	0·4800
Average	Ref·			Average	Ref·		
Above average	0·85	0·84-0·86	<0·0001	Above average	0·85	0·84-0·86	<0·0001
Highest	0·69	0·68-0·70	<0·0001	Highest	0·69	0·68-0·70	<0·0001
Anti-hypertensive drugs	1·43	1·37-1·50	<0·0001	**Anti-hypertensive drugs**	1·43	1·37-1·49	<0·0001
Lipid-lowering drugs	1·34	1·32-1·37	<0·0001	**Lipid-lowering drugs**	1·34	1·31-1·37	<0·0001
Systemic corticosteroids	1·19	1·17-1·21	<0·0001	**Systemic corticosteroids**	1·19	1·75-1·21	<0·0001
Inhaled corticosteroids	1·13	1·11-1·15	<0·0001	**Inhaled corticosteroids**	1·13	1·11-1·15	<0·0001

CI, confidence interval; CS, corticosteroids; HR, hazard ratio.

Figure 1. Nelson-Aalen cumulative hazards curves of the risk of type 2 diabetes by topical corticosteroid potency

Figure legend: CS, corticosteroids.

A. Cumulative hazards curves overall, where topical CS is modelled as a categorical exposure by potency
B. Cumulative hazards curves in land-mark analysis, after 6 months after initial exposure, where topical CS is modelled as a categorical exposure by potency.

Figure 2. Forest plot of hazard ratios for type 2 diabetes according to potency in different age-groups.

Figure legend: CS, corticosteroids