Glucocorticoid treatment

- Population-based studies on utilization and selected adverse effects -

PhD dissertation

Kristina Laugesen

Health

Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital

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Supervisors

Henrik Toft Sørensen, MD, PhD, DMSc, professor (main supervisor)

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Jens Otto Lunde Jørgensen, MD, PhD, DMSc, professor (Co-supervisor)

Department of Internal medicine and Endocrinology, Aarhus University Hospital, Aarhus, Denmark

Irene Petersen, MSc, PhD, professor (Co-supervisor)

Department of Primary Care and Population Health, University College London, London, United Kingdom. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.

Collaborators

Lars Pedersen, MSc, PhD, professor

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Dora Farkas, MSc

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Henrik Støvring, MSc, PhD, DMSc, associate professor

Department of Public Health, Aarhus University, Aarhus, Denmark

Jesper Hallas, MD, DMSc, professor

Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

Anton Pottegård, Master in Clinical Pharmacy, PhD, DMSc, professor

Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

Mogens Vestergaard, MD, PhD, professor

Department of Public Health - Institute of General Medical Practice, Aarhus University, Aarhus, Denmark

Finn Breinholt Larsen, Cand. mag.

Public Health & Health Services Research, Central Denmark Region, Aarhus, Denmark

The assessment committee

Ellen Hauge, MD, PhD, professor (Chairman)

Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

Ian Douglas, BSc, MSc, PhD, professor

Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Mikkel Andreassen, MD, PhD, associate professor

Department of Endocrinology, Department of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark

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Kristina Laugesen, 2019

List of papers

The thesis is based on the following five original studies that are referred to by their Roman numerals (I–V).

I. **Laugesen K**, Jørgensen JOL, Petersen I, Sørensen HT. Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark. Eur J Endocrinol. 2019 Jul 1. pii: EJE-19-0305.R1.

II. **Laugesen K**, Petersen I, Pedersen L, Larsen FB, Jørgensen JOL, Sørensen HT. Prevalence of lifestyle characteristics in glucocorticoid users and non-users: a Danish population-based cross-sectional study. BMJ Open 2019;9:e030780.

III. **Laugesen K**, Støvring H, Hallas J, Pottegård A, Jørgensen JOL, Sørensen HT, Petersen I. Prescription duration and treatment episodes in oral glucocorticoid users: application of the parametric waiting time distribution. Clin Epidemiol 2017;9:591-600.

IV. **Laugesen K**, Petersen I, Sørensen HT, Jørgensen JOL. Clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy: A Danish population-based self-controlled case series analysis. PLoS ONE 2019;*12:* e0212259.

V. **Laugesen K**, Farkas D, Vestergaard M, Jørgensen JOL, Petersen I, Sørensen HT. Glucocorticoid use and risk of suicide: A Danish population-based case-control study. In preparation

Abbreviations

ACTH: Adrenocorticotropic hormone

ATC: Anatomical Therapeutic Chemical classification system of the World Health Organization

BMI: Body mass index

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

CRH: Corticotropin releasing hormone

DAG: Directed Acyclic Graph

DDD: Defined daily dose

HPA: Hypothalamus-pituitary-adrenal

HR: Hazard ratio

ICD: International Classification of Diseases

IRR: Incidence rate ratio

IQR: Interquartile range

PR: Prevalence ratio

Pyar: Person years at risk

SCCS: Self-controlled case series

Contents

1. Introduction

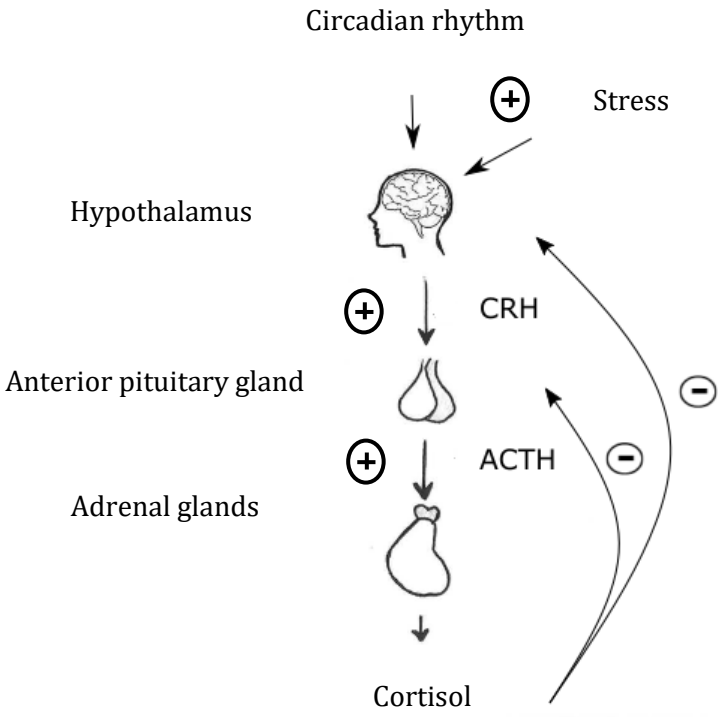
In the 1930s, several steroid hormones were isolated from the adrenal cortex including compound E (cortisone) and F (cortisol).[1] A decade later Hench et al. used cortisone in the treatment of patients with rheumatoid arthritis with significant beneficial effects such as pain relief and improvement in functional capacity.[1] Their discoveries led to the Nobel Prize in physiology and medicine in 1950. However, several adverse effects soon became apparent, including cushingoid appearance, diabetes, osteoporosis, osteonecrosis, cardiovascular adverse effects, cataract, infections, adrenal insufficiency and neuropsychiatric symptoms.[2-8] Still, glucocorticoids are among the most frequently prescribed class of anti-inflammatory medications today. Although glucocorticoid-induced adrenal insufficiency was already recognized as an adverse effect in the 1950s and first revealed as cardiovascular shock[5], clinicians today remain uncertain about the clinical implications in terms of risk and severity of clinical consequences. Prior research has established that biochemically defined adrenal insufficiency following oral glucocorticoid cessation is prevalent (pooled prevalence of ~ 50%).[9] Yet, studies evaluating clinical consequences are limited. Likewise, evidence-based clinical guidelines on how to prevent and manage glucocorticoid-induced adrenal insufficiency are lacking.[10] Neuropsychiatric symptoms are common adverse effects of glucocorticoid treatment (range 1% to 62%).[11 12] Nevertheless, only sparse evidence exists on its potential association with suicide.

To investigate the extent of glucocorticoid use and to fill the gaps in knowledge, we wrote this thesis based on five papers that are referred to by their Roman numerals (I-V). Study I is a drug utilization study. Study II describes prevalence of lifestyle factors according to glucocorticoid use and non-use. Study III examines prescription duration and treatment episodes in oral glucocorticoid users and serves as a method paper that underpins study IV. Study IV examines potential clinical consequences of adrenal insufficiency following oral glucocorticoid cessation. Lastly, study V investigates the association between use of glucocorticoids and risk of suicide.

1.1 The hypothalamic-pituitary-adrenal axis

Cortisol is a steroid hormone synthesized in the adrenal cortex. The synthesis and secretion are regulated by the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1). Cortisol is essential for life and influences a number of physiologic domains including substrate metabolism, cardiovascular function, the inflammatory and immune system and the central nervous system.[13-15] Particularly, cortisol is known for its involvement in the stress-response.[13-15] Cortisol production is in the range of 10 to 20 mg/day under normal conditions, but increases greatly during stress (threatened homeostasis as infection, trauma, operation, starvation etc.). Most physiological effects are mediated by glucocorticoid or mineralocorticoid receptors that regulate gene transcription (activation or repression). An overview of some effects of cortisol in the context of clinical symptoms and signs of adrenal insufficiency is provided in Table 1.[13-15]

Figure 1. **Overview of the hypothalamic-pituitary-adrenal (HPA) axis.**



The hypothalamus secretes corticotropin-releasing hormone (CRH) that stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH promotes synthesis and secretion of cortisol from the adrenal glands. Further, ACTH exerts trophic effects on the adrenal cortex. In turn cortisol exerts negative feedback on CRH and ACTH release.[13 14]

Table 1. An overview of some physiological effects of cortisol in the context of clinical symptoms and signs of adrenal insufficiency.

Physiological system	Effects of cortisol	Potential consequences of insufficient cortisol levels
Substrate metabolism	Stimulates gluconeogenesis, lipolysis and proteolysis and increases peripheral insulin resistance. Exerts permissive effects on the actions of growth hormone, glucagon and catecholamines	Hypoglycemia
The cardiovascular system	Exerts permissive effects on the actions of catecholamines and angiotensin II in order to increase vascular tone, cardiac output and blood pressure	Hypotension Cardiovascular collapse Syncope Dilutional hyponatremia
The renal system	Increases glomerular filtration rate. Increases water clearance by inhibiting vasopressin secretion and counteractioning of vasopressin effects in the kidneys	Dilutional hyponatremia
The immune/inflammatory response	Dampning of the inflammatory/immune response	Overshooting of the inflammatory/immune response

1.2 Glucocorticoid treatment

Synthetic glucocorticoids are structurally and pharmacologically similar to endogenous cortisol, although with modifications. Table 2 provides an overview of systemic glucocorticoids that have been commercially available in Denmark between 1995 to 2015.[16] Systemic glucocorticoids are used for numerous medical conditions owing to their anti-inflammatory and immunosuppressive effects including rheumatic diseases, inflammatory bowel diseases, pulmonary diseases, allergic disorders, skin diseases, certain cancers, and to prevent transplant rejection. Further, hydrocortisone is used as replacement therapy in patients with adrenal insufficiency. Glucocorticoid regimens (generic type, dose, duration and administration) are highly heterogeneous and depend on the indication, the goal of the treatment and clinical treatment guidelines. An overview of some selected treatment indications is provided in Table

3. While, glucocorticoids have beneficial effects and play a pivotal role in the treatment of many diseases, they also have several adverse effects. Among these adverse effects are weight gain, central obesity, buffalo hump, moon face, skin thinning, bruising and striae, osteoporosis, osteonecrosis, myopathy, hyperglycaemia and diabetes, cardiovascular adverse effects, glaucoma, cataract, infections, reproductive dysfunctions, neuropsychiatric symptoms and adrenal insufficiency.[9 11 12 17-26] Locally acting glucocorticoids as inhaled and topical glucocorticoids are also used widespread. Further, they may display similar types of adverse effects as systemic glucocorticoids, although systemic absorption and risk of adverse effects are often lower.[27 28] However, systemic glucocorticoids are the main focus of this thesis.

Table 2. An overview of systemic glucocorticoids sold in Denmark from 1995 to 2015.

Systemic glucocorticoid	Available formulations	Approximate equivalent dose* (mg)	Relative glucocorticoid activity	The biological effective half-life** (hours)
Short-acting				
Hydrocortisone	Oral, injectable	20	1	8-12
Intermediate-acting				
Prednisolone	Oral	5	4	12-36
Prednisone	Oral	5	4	12-36
Methylprednisolone	Oral, injectable	4	5	12-36
Triamcinolone	Injectable	4	5	12-36
Long-acting				
Dexamethasone	Oral, injectable	0.75	30	36-54
Betamethasone	Oral (until 1999) injectable	0.6	30	36-54

* Equivalent anti-inflammatory dose is for oral or intravenous administration. ** The biologic effective half-life is based on the duration of ACTH suppression. Reference: Adapted from Pharmacological use of glucocorticoids. UpToDate.[29]

Table 3. An overview of selected treatment indications for systemic glucocorticoids.

Indications	Examples of glucocorticoid regimens*	Epidemiology
Rheumatic disease		
Polymyalgia rheumatica[30]	Oral prednisolone 15 mg/day with tapering over 52 weeks.	Incidence: 50/100,000/y among people ≥ 50 y of age.
Giant cell arthritis[30]	Oral prednisolone 40-60 mg/day with tapering over 52 weeks.	Incidence: 18-29/100,000/y among people ≥ 50 y of age. 2/1 women.
Rheumatoid arthritis[31]	Intraarticular triamcinolone combined with methotrexate or other DMARDs. Occasionally oral short- or medium-term prednisolone until effect of DMARDs. Rarely long-term use.	Prevalence: 0.7%. 2000 new cases/y 3/4 women. Often onset around 50-70 y of age.
IBD		
Ulcerative colitis[32]	Remission induction. Intravenous methylprednisolone 1-1.5 mg/kg/day for 5 days. Oral prednisolone 1 mg/kg/day for 1 week. Tapering by 5-10 mg/week.	Prevalence: 0.4%. Incidence: 14/100,000/y (increasing). Often onset in young adults.
Crohn´s disease	Remission induction. Intravenous methylprednisolone 1-1.5 mg/kg/day for 5 days. Oral prednisolone 0.5-1 mg/kg/day for 2 weeks. Tapering by 5-10 mg/2. week.	Prevalence: 0.2%. Incidence: 9/100,000/y (increasing). Often onset in young adults.
Pulmonary disease		
COPD[33]	Exacerbation. Oral prednisolone 37.5 mg/day for 5 days. Intravenous methylprednisolone 40-80 mg may be used initially.	Prevalence: 14% among people >35 y of age (increasing).
Asthma[34]	Uncontrolled asthma. Oral prednisolone 37.5-50 mg/day for 7-10 days. Intravenous methylprednisolone 40-80 mg may be used initially. Long-term oral prednisolone 5-10 mg/day may be used in severe asthma.	Prevalence: 3-5% (increasing).
Cancer	Part of chemotherapy for lymphomas[35] Various symptom relief in cancer patients (pain, nausea, cachexia, adverse effects of chemotherapy etc.).[36 37] Often high dose oral prednisolone or injectable methylprednisolone are used.	

*Glucocorticoid treatment regimens may vary; hence these are only examples. Abbreviations: COPD: Chronic obstructive pulmonary disease. DMARDs: Disease-modifying antirheumatic drugs. IBD: Inflammatory bowel disease. Y: Year.

1.3 Literature review

We performed a systematic literature search in PubMed and EMBASE on the topics: glucocorticoid drug utilization, glucocorticoid use and lifestyle, cessation of glucocorticoids and adrenal insufficiency and glucocorticoid use and suicide. A summary of the literature is provided in Table 4-8 and search queries are listed as footnotes. We included papers in English or Danish on clinical trials, observational studies and systematic reviews and meta-analyses. Titles and abstract were reviewed and relevant papers selected for further reading. In addition, we searched reference lists of selected articles.

1.4 Glucocorticoid drug utilization

Drug utilization studies aim to describe the extent, quality and determinants of drug exposure.[38] Hence, they evaluate how medical drugs are used in real world clinical settings. Such studies may include measures of prevalence and incidence as well as a description of patient characteristics, treatment indications and off-label use.[38] Extent and quality of medical drug use are important from public health perspectives as adverse drug effects account for a great burden of disease.[39] Particularly, off-label use, misuse, abuse, medication errors and polypharmacy are of concern. Further, the elderly are particularly prone to develop adverse effects, likely because of age-related changes in pharmacokinetics and pharmacodynamics, comorbidity, and comedication use. At the same time, the elderly are the major consumers of medicine.[40] Seven prior studies have examined the prevalence of systemic glucocorticoid use in the general population (Table 4).[41-47] In these studies, the annual or point prevalence of oral glucocorticoid use was estimated in the range of 0.5% - 17% depending on setting, calendar year and methods [operational definitions of prevalence (annual and point prevalence) and exposure assessment]. Most studies[41 43 45-47] found a higher proportion of women than men (53%-65% women) among glucocorticoid users and an increasing prevalence of use by age. Most common types of glucocorticoid were prednisolone or prednisone and frequent treatment

indications were rheumatic diseases (i.e. polymyalgia rheumatica and rheumatoid arthritis) and respiratory diseases [chronic obstructive pulmonary disease (COPD) and asthma].

Prescribing patterns are affected by numerous factors including demography, trends in underlying medical conditions for which glucocorticoids are prescribed, clinical treatment guidelines and the availability of other treatment options such as disease-modifying drugs. At the time we started our investigations, limited information was available on incident use, frequency of comorbidity and comedications and lifestyle characteristics among glucocorticoid users.

1.5 Glucocorticoid use and lifestyle

Lifestyle may differ between glucocorticoid users and nonusers due to many reasons. Some lifestyle factors, such as smoking, are risk factors for certain glucocorticoid treatment indications like COPD, Crohn´s disease and rheumatoid arthritis and may also impact the disease severity.[48-51] Further, chronic disease may alter your lifestyle. As an example, symptoms like pain and decline in functional capacity can discourage physical activity.[52-54] On the other hand, recommendations from health professionals may encourage a healthier lifestyle. Lastly, excess glucocorticoid is well-known to cause central obesity and increase appetite.[55]

Studies that describe lifestyle among glucocorticoid users are important from several perspectives. First, less healthy lifestyle may interact with glucocorticoid treatment or underlying medical condition in relation to adverse effects and prognosis.[17 56 57] Second, post marketing studies evaluating effectiveness and safety of glucocorticoids are often observational and based on databases and registries. Such studies are sometimes limited by lack of valid information on potential confounding factors, including lifestyle factors.[22 58] One potential way to disentangle this issue of confounding is to compare lifestyle characteristics between glucocorticoid users and non-users to investigate if they differ. Further, unmeasured confounding can be taken into account by a quantitative bias analyses.[59] A bias analysis requires

information on parameters such as the strength of association between the confounder and the outcome and the prevalence of the confounder in the exposed and unexposed groups.[59] Studies that investigate prevalence of lifestyle factors according to glucocorticoid use and non-use can serve as an external source for such bias analyses.[59]

Only two studies have investigated whether prevalence of lifestyle factors differ among glucocorticoid users and non-users (Table 5).[60 61] A Dutch study (n = 140,879) compared lifestyle according to glucocorticoid use and non-use.[61] Of 15,328 glucocorticoid users, 95% were users of locally acting glucocorticoids and 5% of systemic glucocorticoids. The study found no major difference in body mass index (BMI) between glucocorticoid users and non-users, although the prevalence of metabolic syndrome was higher among users. Further, the study found lower prevalence of current smoking and higher prevalence of former smoking in users compared to non-users.[61]

1.6 Glucocorticoid treatment duration

Six prior studies have examined glucocorticoid treatment duration (Table 6).[41-46] Treatment indication was a predictor of duration and patients with rheumatic diseases were treated longer than patients with pulmonary diseases or inflammatory bowel disease (Table 6).[42 44 45]

An issue in many pharmacoepidemiological studies is how to define exposure duration. In some registries, each individual prescription duration is recorded and continuous treatment episodes can then be created. However, information on prescription duration is lacking in many data sources, including the Danish registries.[62] When using the Danish prescription registries, it is therefore necessary to define the duration of single prescriptions. For some medications, clinical reasoning may be used to make this decision, but this approach has limitations. First, clinically defined criteria may poorly reflect actual usage patterns. Second, since glucocorticoid dose and duration are highly heterogeneous, information provided in the Danish registries is not sufficient to support such clinical reasoning. Third, even if duration is recorded (as in some data

sources), it may not coincide with the actual use. Recently, Støvring et al. came up with an alternative approach to estimate duration based on the actual usage pattern. They suggest modelling the time between prescriptions based on the parametric waiting time distribution or the reverse waiting time distribution.[63-66] The reverse waiting time distribution has been successfully validated among warfarin users.[67] The approach showed higher precision and validity compared to methods that assumed a fixed daily dose.

1.7 Adrenal insufficiency following discontinuation of glucocorticoids

1.7.1 Definition of adrenal insufficiency

Adrenal insufficiency is defined as deficient levels of cortisol and is subdivided according to the underlying mechanism.[68 69] Primary adrenal insufficiency denotes adrenal disease and is accompanied by deficient levels of aldosterone. Secondary adrenal insufficiency involves ACTH deficiency due to pituitary or hypothalamic causes (deficient CRH level).[68 69] Treatment with glucocorticoids may cause iatrogenic adrenal insufficiency via feedback suppression of CRH and ACTH as well as adrenal gland atrophy. The diagnosis of adrenal insufficiency is based on biochemically evaluation of the HPA axis. Most commonly used is the 250 µg ACTH stimulation test. The cortisol cut-off value used to define adrenal insufficiency may vary according to assay. As an example, a cut-off value of 420 nM is used in many modern assays.[70]

1.7.2 The clinical presentation of glucocorticoid-induced adrenal insufficiency

The clinical presentation of glucocorticoid-induced adrenal insufficiency is due to glucocorticoid deficiency. Deficient glucocorticoid levels can result in symptoms like fatigue, anorexia, muscle weakness, myalgia, dizziness, gastro intestinal symptoms, weight loss, amenorrhea and neuropsychiatric symptoms or clinical signs like hypotension, cardiovascular collapse, hyponatremia and hypoglycaemia (Table 1). Overt adrenal insufficiency occurs when there is a mismatch between available glucocorticoid (exogenous or endogenous) and the physiological need. During cessation of glucocorticoid treatment, available exogenous glucocorticoid is

diminished and endogenous cortisol production may be compromised. This can lead to overt adrenal insufficiency, especially during stress.

1.7.3 The clinical perspectives of glucocorticoid-induced adrenal insufficiency

We identified 22 studies that investigated adrenal insufficiency following oral glucocorticoid cessation (Table 7)[71-92] in addition to three systematic reviews, including one meta-analysis.[9 93 94] Nine studies[75 78 79 81-84 87 92] included children treated for acute lymphoblastic lymphoma (= 10 to 96), one study (n= 19) included children treated for rheumatic diseases[86] and twelve studies[71-74 76 77 80 85 88-91] included adults with various underlying medical conditions (n= 10 to 150). The studies were heterogeneous with respect to participants, treatment regimens and methods (type of stimulation test, cortisol cut-off limit and assay). Clinical signs and symptoms of adrenal insufficiency were evaluated in seven studies and the prevalence ranged from 0% - 100% (Table 7).[75 79 81 82 86 89 92] It was, however, difficult to distinguish symptoms and signs of adrenal insufficiency from underlying disease and adverse effects of e.g. chemotherapy. In addition, one study found an incidence of 4.5/million/year for hospital admissions coded with treatment-induced adrenal insufficiency among 165,000 glucocorticoid users.[90]

The following can be summarized from prior literature: i) Biochemically defined adrenal insufficiency is prevalent in the first days following oral glucocorticoid cessation (pooled prevalence ~ 50%[9], range 0% -100%). ii) Adrenal insufficiency can persist up to several years after glucocorticoid cessation.[85 86 88 89 91] iii) Adrenal insufficiency is more prevalent after large doses and long-term treatment. However, adrenal insufficiency may occur after low-dose and short-term treatment. iv) Adrenal insufficiency may also occur after tapering of treatment.

Although biochemical adrenal insufficiency following glucocorticoid cessation is prevalent, the clinical implications in terms of risk and severity of clinical consequences are still debated, and no evidence-based clinical guidelines exist regarding how to monitor, prevent and manage glucocorticoid-induced adrenal insufficiency.[10]

1.8 Glucocorticoids, neuropsychiatric symptoms and suicide

Neuropsychiatric symptoms associated with glucocorticoid use span from mood swings to severe depressive symptoms, mania, insomnia and hallucinations.[11 12] According to patients, neuropsychiatric symptoms are among the most distressing adverse effects of glucocorticoids.[95] In spite of this, these adverse effects have received little attention.[11 12 26] A meta-analysis from 1983 reported a weighted average of ~6% (range 1.6% - 50%, n = 2555 persons) for severe neuropsychiatric symptoms and ~28% (range 13% - 62%, n = 935 persons) for mild to moderate symptoms among people treated with glucocorticoids.[11] Symptoms often present early in treatment.[11 12 26] Three studies have investigated the association between glucocorticoid use and suicide (Table 8).[26 96 97] A cohort study (n = 1,597,953) found a 7-fold increased risk of suicide/suicide attempts when comparing people initiating oral glucocorticoids to unexposed people with the same underlying medical condition.[26] They identified younger age and prior suicide attempt as predictors of suicide.[26] A case-control study (n = 3601) found a moderate association [unadjusted odds ratio = 1.33 and 95% confidence interval (CI): 0.88 to 2.00).[96] Lastly, one study using a self-controlled case series (SCCS) design found no association.[97] However, the risk of depression and delirium was increased around the time of cessation compared to 5-3 months before cessation (Table 8).[97]

Cortisol affects mood, behaviour and cognition mediated through both the glucocorticoid and mineralocorticoid receptors in the central nervous system[98 99], but the pathogenesis of the neuropsychiatric adverse effects remains poorly understood.[98 99] Cortisol has a relatively high affinity for the mineralocorticoid receptor compared to many synthetic glucocorticoids, and the combination of excess synthetic glucocorticoid and depleted endogenous cortisol (HPA-axis suppression) may result in imbalanced receptor activation.[98 99] Excess glucocorticoid may also cause dysregulation in the serotonin neurotransmitter system.[98 99] Still, confounding by severity of underlying treatment indications cannot be ruled out in the previous observational studies.[26 96 97]

Table 4. Summary of literature (study I)

Study I: Glucocorticoid drug utilization			
Author, journal, year	**Setting, data sources, period**	**Study population, exposure**	**Results and comments**
Walsh, et al.[41] **-BMJ** **-1996**	-The Nottinghamshire -Eight general practitioners -1991-1995	-n = 65,786 -Continuous (≥ 3 months) oral GC use	-Prevalence 0.5% (303/65,786) during a 4-y period -65% women -Prevalence 1.4% in people ≥ 55 y of age during a 4 y period -Prednisolone most common (97%) -Most frequent indications: RA (23%), PMR (22 %), and pulmonary disease (19%) -14% of GC users received anti-osteoporosis treatment
Van Staa, et al.[42] **-QJM** **-2000**	-England and Wales -The General Practice Research Database -1994-1997	-All adults (≥18 y of age) -Oral GCs	-Point prevalence 0.9% -Equal prevalence in both sexes -Highest prevalence in 70 -79 y of age (2.5%) -Prednisolone most common (91%) -Most frequent indications: Respiratory disease (40%) -4-5.5% of GC users received anti-osteoporosis treatment
Gudbjornsson, et al.[43] **-Ann Rheum Dis** **-2002**	-The Northeast Iceland -1995-1996	-n = 26,664 -Long-term treatment (≥ 3 months) with oral prednisolone	-Point prevalence 0.7% -55% women -Mean age 66 y of age -Most frequent indications: Rheumatic disease (44%), COPD (31%), and IBD (8%)
Chantler, et al.[44] **-Ann Rheum Dis** **-2003**	-Shropshire, UK -41 general practitioners -1997-1998	-n = 62,230 (All ≥ 50 y of age) -Oral GCs	-Annual prevalence 3.2% -Only prednisolone were used -47% of glucocorticoid users received anti-osteoporosis treatment

Study I: Glucocorticoid drug utilization			
Author, journal, year	**Setting, data sources, period**	**Study population, exposure**	**Results and comments**
Fardet, et al.[45] **-Rheumatology** **-2011**	-The UK -THIN database -1989-2008	-Adults (≥18 y of age), n= 4,518,753 -Long-term (≥3 months) oral GC use	-Point prevalence 0.75% -Point prevalence increased from 0.59% in 1989 to 0.79% in 2008 -Highest point prevalence (3%) in women aged 80–90 y -Prednisolone most common (92%) -Most frequent indications: Asthma (19%), PMR/GCA (13%), COPD (13%), RA (4%)
Overman, et al.[46] **-Arthritis Care Res** **-2013**	-The US -The NHANES -1999-2008	-Adults (≥ 20 y of age), n=26,248 -Oral GCs	-Point prevalence 1.2% -53% women -Highest prevalence (2.9%) in ≥80 y of age -Prednisone most common (77%) -40% of glucocorticoid users received anti-osteoporosis treatment
Bénard-Laribière, et al.[47] **-BMJ Open** **-2017**	-France -The French reimbursement database (EGB) -2007-2014	-Adults (≥18 y of age) -Oral GCs	-Annual prevalence 14.7% in 2007 and 17.1% in 2014 -58% women -Highest annual prevalence among women aged 50-59 y (22% in 2014) -Most frequent indications: Obstructive pulmonary disease (21%), cancer (6.4%), rheumatic diseases (1%) -Comedication: Antibiotics (59%), respiratory/otological drugs (50%), analgesics (46%)

Abbreviations: COPD: Chronic obstructive pulmonary disease. GC: Glucocorticoids. GCA: Giant cell arthritis. IBD: Inflammatory bowel disease. PMR: Polymyalgia rheumatica. RA: Rheumatoid arthritis. THIN database: The Health Improvement Network database. The NHANES: The National Health and Nutrition Examination Survey. UC: Ulcerative colitis. UK: United Kingdom. US: United States of America. Y: Years.

Search queries for study I and III: PubMed: **"**Adrenal cortex hormones" [Major] AND ("drug utilization" [Mesh] OR "prevalence" [Mesh] OR "incidence" [Mesh] OR "off-label use" [Mesh] OR "pharmacoepidemiology" [Mesh]). EMBASE: "Corticosteroids" [Emtree as major focus] AND ("drug utilization" [Emtree] OR "prevalence" [Emtree] OR "incidence" [Emtree] OR "off-label use" [Emtree] OR "pharmacoepidemiology" [Emtree]). We only considered studies on use of systemic glucocorticoids in the general population.

Table 5. Summary of literature (study II)

Study II: Glucocorticoid use and lifestyle			
Author, journal, year	**Setting, data sources, period, design**	**Study population, exposure, outcome**	**Results and comments**
Savas, et al.[60] **-Int J Med Sci** **-2017**	-The Netherlands -Obesity Center CGG of the Erasmus Medical Center, Rotterdam. The Lifelines cohort. The NESDA -2011 - 2015 -Cross-sectional	-Obese (n = 274) compared to two control groups of non-obese (n = 235, n = 291) -Recent use of local/systemic GC (≤ 3 months before date of questionnaire)	-27% of obese were recent users of any GC vs. 12% and 15% in the non-obese control groups -2.6% of obese were recent users of systemic GC vs. 0.9% and 2.7% in the non-obese control groups -26% of obese were recent users of local GC vs. 12% and 13% in the non-obese control groups
Savas, et al.[61] **-J Clin Endocrinol Metab** **-2017**	-The Netherlands -The population-based Lifelines cohort study -2006-2013 -Cross-sectional	-n = 140,879 adults (59% women) -Current use of local/systemic GC (≤ 3 months before date of questionnaire)	-Around 5% were current users of systemic GCs and 95% of local GCs -Prevalence of smoking was 18% in current users vs. 21% in non-users in women and 18% vs. 24% in men -Prevalence of alcohol drinking (> 2 drinks/day) was 3.2% in current users vs. 3.0 % in non-users in women and 15 % vs. 16% in men -Prevalence of inactive lifestyle was 6.6% in current users vs. 6.0% in non-users in women and 4.0% vs. 4.2 in men -Mean BMI was 26.7 in current users vs. 25.7 in non-users in women and 26.7 vs. 26.4 in men

Abbreviations: BMI: Body Mass Index measured in kg/m^2. GC: Glucocorticoid. NESDA: The Netherlands study of Depression and Anxiety.

Search queries for study II: PubMed: **"**Adrenal cortex hormones" [Major] AND ("Health Behaviour" [Mesh] OR "Life Style" [Mesh] OR "Body Weights and Measures" [Mesh] OR "Drinking behaviour" [Mesh] OR "Smoking" [Mesh] OR "Tobacco use" [Mesh] OR "Diet" [Mesh] OR "Exercise" [Mesh]). EMBASE: "Corticosteroids" [Emtree as major focus] AND ("health behaviour" [Emtree] OR "Body Mass" [Emtree] OR "Obesity" [Emtree] OR "physical activity, capacity and performance" [Emtree] OR "alcohol" [Emtree] OR "nutrition" [Emtree] OR "tobacco use" [Emtree]).

Table 6. Summary of literature (study III)

Study III: Glucocorticoid treatment duration			
Author, journal, year	**Setting, data sources, period**	**Study population, exposure**	**Results and comments**
Walsh, et al.[41] **-BMJ** **-1996**	-The Nottinghamshire -Eight general practitioners -1995	-n = 65,786 -Continuous (≥ 3 months) oral GC use	-Median duration of continuous treatment 3 y (range 0.3-37 y)
Van Staa, et al.[42] **-QJM** **-2000**	-England and Wales -The General Practice Research Database -1994-1997	-All adults (≥18 y of age) -Oral GCs	-Continued treatment >6 months in 22.1% and >5 y in 4.3% -No difference according to sex -Elderly treated for longer periods -Treatment indication as arthropathies was a predictor of longer treatment duration
Gudbjornsson, et al.[43] **-Ann Rheum Dis** **-2002**	-The Northeast Iceland -1995-1996	-n = 26,664 -Long-term treatment (≥ 3 months) with oral prednisolone	-Average treatment duration 47 months (range of 3–300 months)
Chantler, et al.[44] **-Ann Rheum Dis** **-2003**	-Shropshire, UK -41 general practitioners -1997-1998	-n = 62,230 (All ≥ 50 y of age) -Oral GCs	-Median duration 2 y, with 11% having taken glucocorticoids for <1 y, 67.6% for 1–5 y, and 21.2% for >5 y. Rheumatic diseases had longest treatment duration and COPD shortest
Fardet, et al.[45] **-Rheumatology** **-2011**	-The UK -THIN database -1989-2008	-Adults (≥18 y of age), n = 4,518,753 -Long-term (≥3 months) oral GC use	-Median duration 150 – 926 days (depending on year of initiation, sex and treatment indication) -Long-term prescribing increased in patients with RA, PMR/GCA, however, decreased in COPD, asthma and Crohn´s disease. Incident RA, UC and Crohn´s disease less likely to receive long-term treatment
Overman, et al.[46] **-Arthritis Care Res** **-2013**	-The US -The NHANES -1999-2008	-Adults (≥ 20 y of age), n =26,248 -Oral GCs	-Mean duration 1,606 days -65% usage ≥ 90 days, 42% usage ≥ 2 y and 28.8% usage ≥5 y

Abbreviations: COPD: Chronic obstructive pulmonary disease. GC: Glucocorticoid. GCA: Giant cell arthritis. IBD: Inflammatory bowel disease. PMR: Polymyalgia rheumatica. RA: Rheumatoid arthritis. THIN database: The Health Improvement Network database. The NHANES: The National Health and Nutrition Examination Survey. UC: Ulcerative colitis. UK: United Kingdom. US: United States of America. Y: Years.

Table 7. Summary of literature (study IV)

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Spiegel, et al.[71] -Lancet -1979	-Cohort design	-N = 10 -Mean age 26 y (range 14- 59 y)	-Prednisone -Cancer	-Average dose: 56 mg/day -Duration range 5-20	-ACTH250 -500 nM -RIA	-10 (100%) day 1 -8 (80%) day 2 -5 (50%) day 4 -4 (40%) day 7	-Symptoms or signs of AI not investigated -Treated with chemotherapy
Rodger, et al.[72] -QJ Med -1986	-Cohort design	-N = 21 -Mean age 40 y (range 14-56 y)	-Prednisolone, methylprednisolone -Renal transplant	-Average dose 14.9 mg/day -Duration range 60-4240 (mean 1677)	-ACTH250 -550 nM -RIA	-14 (67%) day 1 -10 (50%) day 91 -6 (29%) day 183	-Symptoms or signs of AI not investigated -Comedication: cyclosporine, azathioprine
Carella, et al.[73] -J Clin Endocrinol Metab -1993	-RCT	-N =10 -Mean age 28 y (range 20-41 y)	-Prednisone -Healthy volunteers	-Average dose 70 mg/day -Duration mean 7	-ACTH250 -500 nM -RIA	-0 day 7 -0 day 14 -0 day 21	-Symptoms or signs of AI not investigated
Henzen, et al.[74] -Lancet -2000	-Cohort design	-N = 75 -Mean age 65 y (range 18-87 y)	-Prednisone, prednisolone, dexamethasone, methylprednisolone -COPD, cancer, neurological disease	-Duration range 5-30	-ACTH1 -500 nM -EIA	-34 (45%) day 1 -34 (45%) day 2 -21 (28%) day 4 -20 (27%) day 6 -13 (17%) day 10 -5 (7%) day 12 -2 (3%) day 14	-Symptoms or signs of AI n investigated

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Felner, et al.[75] -J Pediatr -2000	-Cohort design -Texas	-N = 10 -Mean age 5.3 (range 2-10 y)	-Dexamethasone - ALL	-Duration 28 -0.2 mg/kg per day Abrupt cessation	-ACTH250 -500 nM -CLIA	-10 (100%) day 1 -3 (30%) day 28 -0 (0%) day 56	-All (N = 10) experienced fever, gastrointestinal symptoms, weakness and muscle pain -Treated with chemotherapy
Kuperman, et al.[92] -J Clin Endocrinol Metab -2001	-Cohort design -The Children's Hospital, University of São Paulo, Brazil	-N = 15 -Range 1-12 y of age	-Dexamethasone -ALL	-Duration 42 -6 mg/m2/day -Abrupt cessation	-Ovine CRH -N.r. -FIA	-6 (40%) day 7 -6 (40%) day 14	-1 (7%) had mild symptoms (nausea, malaise) of AI -Treated with chemotherapy
Boots, et al.[76] -Transplant Proc -2002	-RCT	-N = 42 -Mean age 55 y	-Prednisolone -Renal transplant	-Average dose 16.6 mg/day -Duration mean 91	-ACTH250 -550 nM -EIA	-14 (33%) day 1 -11 (26%) day183	-Symptoms or signs of AI not investigated -Comedication with tacrolimus
Nguyen, et al.[77] -Ann Allergy Asthma Immunol. -2003	-Cohort design	-N = 63	-Prednisone -Asthma, bronchitis, allergic dermatitis or urticaria, nasal polyps	-Dose range 10-61 mg/day	-ACTH1 -500 nM -CLIA	-15 (24%) day 2 -10 (16%) day 14 -5 (8%) day 21 -4 (6%) day 28	-Symptoms or signs of AI not investigated

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Petersen, et al.[78] -Med Pediatr Oncol -2003	-Cohort design - The University Hospital, Rigshospitalet, Copenhagen, Denmark	N = 10 (prednisolone) N = 7 (dexamethasone) Median age 5.4 y (range 2-15 y)	-Prednisolone (induction therapy), dexamethasone (reinduction therapy) -ALL	-60 mg/m^2/day in 35 days + 9 tapering days (prednisolone) -10 mg/m^2/day in 21 days +9 tapering days (dexamethasone)	-ACTH250 -500 nM -FIA	Prednisolone: -7 (70%) day 7 -6 (60%) day 21 -4 (40%) day 49 -4 (40%) at 70, 77,77 and 133 days Dexamethasone: -5 (71%) day 7 -4 (57%) day 21 -3 (43%) day 112, 231 and 238 days	-Symptoms or signs of AI not investigated -Treated with chemotherapy and fluconazole (n = 3)
Mahachoklertwattana, et al.[79] -J Pediatr -2004	-Cohort design -Thailand	N = 24 Median age 3.5 y (range 1-14 y)	-Prednisolone, dexamethasone -ALL	40 mg/m^2/day of prednisolone in 28 days following 8mg/m^2/day of dexamethasone in 7 days every 4 weeks Abrupt cessation	-ACTH1 -500 nM -CLIA	-11 (46%) day 14 -9 (38%) day 28 -7 (29%) day 56 -3 (13%) day 84 -3 (13%) day 140	-0 had symptoms or signs of AI -Treated with chemotherapy
Baz-Hecht, et al.[80] -Clin Transplant -2005	-Cohort design -USA	-N = 48 -Mean age 43.3 y (range 16-70 y)	-Prednisone -Kidney/kidney+ pancreas transplant	-Average dose 5 mg/day -Duration mean 546	-ACTH1 -500 nM -N.r.	-4 (8%) day 1 -4 (8%) day 91	-Symptoms or signs of AI not investigated -Treated concomitant with cyclosporine, tacrolimus, azathioprine, mycophenolate

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Rix, et al.[81] -J Pediatr -2005	-Cohort design -Denmark	-N = 24 (2 prednisolone courses) -N = 5 (dexamethasone) -Median age 4.5 y (range 1.8-14.6 y)	-Prednisolone, dexamethasone -ALL	-All received 60 mg/m^2/day of prednisolone in 35 days +9 tapering days - All received 60 mg/m^2/day of prednisolone in 7 days - N = 5 received 10 mg/m^2/day of dexamethasone + 9 days tapering	-ACTH1 -500 nM -CLIA	First prednisolone course: -16/17 (94%) day 1 -8/15 (60%) day 3 -8/17 (47%) day 5 Second prednisolone course: -13/13 (100%) day 2 Dexamethasone: -2/2 (100%) day 1 -3/5 (60%) day 3 -1/5 (20%) day 7	-Clinically manifest AI in N = 3 (12%) with weakness, malaise, gastrointestinal symptoms -Treated with chemotherapy -Inconsistent testing during follow up
Einaudi, et al.[82] -Pediatr Blood Cancer -2008	-RCT -Italy	N = 40 (prednisone) N = 24 (dexamethasone) -Mean age 5 y (range 1 y –12 y)	- Prednisone, dexamethasone -ALL	All received 60 mg/ m2/day of prednisone in 7 days. On day 8 randomized to either 60 mg/ m2/day of prednisone or 10 mg/ m2/day of dexamethasone in 22 days + 9 tapering days	-ACTH1 -500 nM -CLIA	Prednisone: -32 (80%) day 1 -8 (20%) day 7-14 -5 (13%) day 28 -5 (13%) day 42 -0 day 70 Dexamethasone: -20 (83%) day 1 -4 (17%) day 7 -14 -3 (13%) day 28 -3 (13%) day 42 -0 day 70	-18/52 (35%) showed signs or symptoms of AI at day 1 (n=5 vomiting and/or anorexia, n=4 headache or lethargy, n=6 arthralgia/myalgia, n=5 fever, n=2 hypotension), 1/12 (8%) day 7-14, 1/8 (13%) day 28. -No difference between glucocorticoid type -Treated with chemotherapy

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Huber, et al.[86] -Acta Paediatr -2010	-Cohort design -Dep of Paediatrics, Berne, Switzerland.	-N = 19 - median age 9 y (range 2-15 y)	-Prednisone and prednisolone -Rheumatic diseases	1 mg prednisone equivalent/kg/day until stabilization of disease followed by tapering	-ACTH1 -500 nM -CLIA	-6 (32%) day 28 -4 (21%) day 214 -2 (11%) day 610	-0 had symptoms of AI -Treated concomitant with disease modifying drugs and NSAIDs
Vestergaard, et al.[83] -J Pediatr Hematol Oncol -2011	-Cohort design -Denmark	-N = 96 -median age 4.7 y (range: 1.5 - 14.9 y)	-Prednisolone, dexamethasone -ALL	All received 60 mg/m2/day of prednisolone in 36 days + 9 days tapering	-ACTH250 -500 nM -FIA	-64 (67%) within 4 weeks after cessation -AI duration range: 9- 20 weeks	-Symptoms or signs of AI not investigated -Cranial irradiation -Treated with chemotherapy
Kuperman, et al.[84] -Horm Res Paediatr -2012	-RCT -Brazil	-N = 16 (prednisone) -N=13 (dexamethasone) - Median of 5.2 y (range 1.8–15.9)	-Prednisone, dexamethasone -ALL	40 mg/ m2/day of prednisone or 6 mg/ m2/day of dexamethasone in 28 days Abrupt cessation	-ACTH1 -N.r. -FIA	Prednisone: -7/16 (50%) day 7 -5/14 (36%) day 14 -5/15 (36%) day 21 -5/14 (36%) day 28 -3/13 (23%) day 35 -4/14 (29%) day 42 - 5/14 (36%) day 49 -4/15 (27%) day 56 Dexamethasone: -4/10 (40%) day 7 -2/7 (29%) day 14 - 5/13 (38%) day 21 - 1/12 (8%) day 28 -3/13 (23%) day 35 -5/11 (45%) day 42 -3/10 (30%) day 49 -3/12 (25%) day 56	-Symptoms or signs of AI not investigated -No association between infections and AI -Treated with chemotherapy

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Jamilloux Y, et al.[85] -PLoS One -2013	-Cohort design	-N = 150 -Mean age 74 y	-Prednisone -Giant cell arthritis	-Dose range 0.7-5 mg/day -Duration range 152-2166	-ACTH1 -580 nM -RIA	-74 (49%) day 1 -30 (20%) day 365 -15 (10%) day 730 -7 (5%) day 1095	-Symptoms or signs of AI not investigated -Cumulative dose and treatment duration associated with increased risk of AI
Salem, et al.[87] -Hematology -2015	-Cohort design -Children's Hospital, Ain Shams University, Egypt	-N = 20 (prednisone) -N = 20 (dexamethasone)	-Prednisone, dexamethasone -ALL	6 mg/m2 of dexamethasone or 60 mg/m2 prednisone in 28 days + 21 days re-induction Tapering	-ACTH1 -500 nM -CLIA	Prednisone: -5 (25%)- 7(35%) day 14 -0 day 140 Dexamethasone: -9(45%) – 10 (50%) day 28 -0 day 140	-Symptoms and signs of steroid withdrawal syndrome in 50% of prednisone treated and 75% of dexamethasone treated -Treated with chemotherapy and fluconazole
Baek, et al.[88] -Endocrinol Metab (Seoul) -2016	-Cohort design -Gyeongsan Hospital	-N = 34 (With GC-induced AI) -Median age 70 y	- Rheumatic, orthopaedic, chronic lung diseases, cancer	NA	-ACTH250 -500 nM -ECLIA	-14 (41%) did not recover to normal adrenal function within 1 to 2 years (median follow up 500 days)	-Symptoms or signs of AI not investigated
Leong, et al.[89] -Endocr Pract -2018	-Cohort design -Malaya Medical Centre, Malaysia	-N = 33 (With GC-induced AI) -Mean age 64 y	-Dermatologic, rheumatic, renal diseases	-Median duration 2 y	-ACTH250 -500 nM -CLIA	-13 (39%) did not recover to normal adrenal function within median time of 2 y	-5 (15%) presented with symptomatic AI at inclusion -Longer treatment duration was predictor of non-recovery

Study IV: Clinical signs and symptoms of adrenal insufficiency following oral glucocorticoid cessation							
Author, journal, year	**Design, setting**	**Study population**	**Type of oral GC, indication**	**Dose, duration (days)**	**Test, cut-off value, assay**	**Cases (n) of AI according to days after last dose of GC**	**Comments**
Rushworth, et al.[90] -Endocr Pract -2018	-Cross-sectional -All hospitals in New South Wales, Australia	-N = 165,000	-All GCs	NA	NA	N = 345 admitted with treatment-induced AI. Average annual rate of 22.5 admissions/year. Incidence of 4.5/million/year	-Based only on hospital diagnosis codes. No information on test. -No information/ stratification by formulation, duration or dose -Likely incomplete registration of outcome
Karangizi, et al.[91] -BMC Nephrol -2019	-Cohort design -Queen Elizabeth Hospital, Birmingham, UK	-N = 123 -Mean age 52 y	-Prednisolone -Glomerular disease	-Median duration 549 (IQR:275-1068) -Median initial dose 50 mg/day. At time of testing all received ≤ 5 mg/day	-ACTH250 -550 and 450 nM -ECLIA	-57 (46%) day 1 -Mean time of recovery of 265 days and n=15 (45%) had not recovered at latest testing	-Symptoms or signs of AI not investigated -Re-testing was only done every 6 months

Abbreviations: ACTH250: 250 µg Synacthen test. ACTH1: 1 µg Synacthen test. AI: Adrenal insufficiency. ALL: Acute lymphoblastic leukaemia. CLIA: Chemiluminescent immunoassay. CRH: Corticotropin releasing hormone. ECLIA: Electrochemiluminescent immunoassay EIA: Enzyme immunoassay. FIA: Fluoroimmunoassay. GC: Glucocorticoid. IQR: Interquartile range. N: Number. N.r.: Not reported. NSAIDs: Non-steroidal anti-inflammatory drugs. RIA: Radioimmunoassay UK: United Kingdom. RCT: Randomized controlled trial. Y: year.

Search queries for study IV: PubMed: "Adrenal cortex hormones" [Major] AND **"**Adrenal insufficiency**"** [Major]. EMBASE: "Corticosteroids" [Emtree as major focus] AND "Adrenal insufficiency" [Emtree as major focus]. We only considered studies investigating adrenal insufficiency following oral glucocorticoid cessation.

Table 8. Summary of literature (study V)

Study V: Glucocorticoids and suicide			
Author, journal, year	**Setting, data sources, period, design**	**Study population, exposure**	**Results and comments**
Voaklander, et al.[96] **-J Epidemiol Community Health** **-2008**	-British Columbia -Medical registries -1993-2002 -Population-based case-control study	-N = 602 suicide cases (≥ 66 y of age, 72% men) and n = 2999 controls matched by sex and age -GCs	-Unadjusted OR = 1.33 (95% CI: 0.88 to 2.00) -No adjustment -No information on GC administration forms
Fardet, et al.[26] **-Am J Psychiatry** **-2012**	-The UK -THIN database -1990-2008 -Matched cohort design	-N = 372,696 exposed Two comparison cohorts: -N = 1,224,984 matched by sex, age -N = 660,776 matched by sex, age, treatment indication -Initiation of oral GCs	aHRs comparing exposed vs. a comparison cohort matched by sex, age and the same treatment indication: -aHR = 6.89 (95% CI: 4.52–10.5) for suicide/suicide attempt -aHR = 1.83 (95% CI: 1.72–1.94) for depression -aHR = 4.35 (95% CI: 3.67–5.16) for mania -aHR = 5.14 (95% CI: 4.54–5.82) for delirium/confusion/ disorientation -aHR = 1.45 (95% CI: 1.15–1.85) for panic disorder Risk factors: -Younger age -Previous history of suicide attempt
Fardet, et al.[97] **-J Clin Psychiatry** **-2013**	-The UK -THIN database -1990-2008 -SCCS design	-N = 21,995 (62% women, median age 73 y of age) of these 991 were cases. -Cessation of long-term (1-3 y) oral GC treatment	IRR comparing the period of cessation to a reference period (5 to 3 months before cessation): -IRR = 1.13 (95% CI: 1.00-1.28) for depression -IRR = 2.67 (95% CI: 1.96-3.63) delirium/confusion -IRR = 0.62 (95% CI: 0.06-6.92) for suicide/suicide attempt

Abbreviations: aHR: Adjusted hazard ratio. 95% CI: 95% confidence interval. GC: Glucocorticoids. IRR: Incidence rate ratio. OR: Odds ratio. SCCS design: Self-controlled case series design. THIN database: The Health Improvement Network database. Y: Years.

Search queries for study V: PubMed: "Adrenal cortex hormones" [Major] AND **"**Suicide**"** [Major]. EMBASE: "Corticosteroids" [Emtree as major focus] AND "Suicide" [Emtree as major focus].

1.9 Objectives and hypotheses

The overarching aim of this thesis was to examine glucocorticoid drug utilization and to examine two potential severe adverse effects of glucocorticoids, including adrenal insufficiency and suicide. We therefore conducted five studies with the following objectives.

I. To examine the annual prevalence and incidence of systemic glucocorticoid use in Denmark from 1999 to 2014 and to describe use of comedications and morbidity among glucocorticoid users.

II. To investigate whether lifestyle and characteristics related to lifestyle differ according to use of systemic glucocorticoids.

III. To estimate duration of individual prescriptions for oral glucocorticoids and to describe continuous treatment episodes.

IV. To investigate clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy.

V. To investigate the association between glucocorticoid use and suicide.

In study IV, we hypothesized that cessation of oral glucocorticoid increases the risk of diagnoses indicating adrenal insufficiency. In study V, we hypothesized that use of glucocorticoids is associated with increased risk of suicide.

2. Methods

2.1 Setting

Denmark has a population of ~ 5.6 million inhabitants and is administratively divided into five regions (Figure 2). The health care system is organized into primary healthcare (general practitioners) and secondary healthcare (the hospital sector). Except in emergencies, the general practitioners are the first point of contact and act as gate-keepers to secondary healthcare.[100] Denmark provides its entire population with tax-supported healthcare, assuring free-of-charge access irrespective of income and residency. A unique personal civil registration number is assigned to all Danish residents at birth or upon immigration. This number enables valid individual-level linkage of registries and complete follow up.[100 101] Danish registries offer a great opportunity to investigate research questions on the population level and to conduct research that would be impossible or unethical to investigate in clinical trials. All our studies were conducted in Denmark. Studies I, III, IV and V were nationwide, while study II was conducted in Central Denmark Region (Figure 2).

Figure 2. Overview of Denmark divided into 5 regions.

2.2 Data sources

The studies are based on prospectively collected data in population registries or surveys. Table 9 summarizes data sources used in the individual studies (studies I-V). Below, we provide a brief description of the resources that we have used.

The Danish Civil Registration System

Since 1968 the system has kept information on all Danish residents, including the Civil Personal Registration number, sex and date of birth. The Civil Personal Registration number allows valid

individual-level linkage of registries. Migration and vital status are recorded on a daily basis and this permits virtually complete follow up.[101]

The Danish prescription registries

Since 1995 the Danish National Prescription Registry has recorded information on all redeemed prescriptions, including the Civil Registration number, the medication classification code [Anatomical Therapeutic Chemical classification system of the World Health Organization (ATC code)], product code, date of dispensing, package size, tablet strength, and amount [expressed in "defined daily doses" (DDDs)].[62] Prescription duration and indications are not recorded.[62] Further, all drugs used during hospital admissions or supplied directly by hospitals (e.g. chemotherapeutics and immune-modulating therapy) are not recorded in the registries. The Danish National Prescription Registry can only be accessed through closed servers (at Statistic Denmark or The Danish Health Data Authority).[102] If linkage is needed to data outside these servers you may instead use the Danish National Health Service Prescription database.[103]

The Danish National Health Service Prescription database contains information on prescriptions reimbursed by the National Health System since 2004.[103] Variables contained in this registry are the same as in the Danish National Prescription Registry.

MEDSTAT[16 104] provides aggregate statistics on medicine sales in the Danish primary health care sector and in the hospital sector and is considered complete since 1999.[104]

The Danish National Patient Registry

Since 1977 the registry has collected data on patients discharged from all Danish non-psychiatric hospitals. Since 1995, the registry has also included data from psychiatric departments, emergency departments and outpatient contacts. Information includes the civil registration number of the patient, date of admission and discharge, a primary diagnosis and secondary diagnoses classified according to the *International Classification of Diseases* [Eight

Revision (ICD-8) until the end of 1993 and Tenth Revision (ICD-10) thereafter], certain in-hospital drug treatments (e.g. chemotherapeutics and immune-modulating therapy), and surgical procedures among many others.[105]

The survey "Hvordan har du det?" (How Are You?) 2010

The survey is a questionnaire-based public health study with the main incentive to describe health behaviours and self-reported health in the interest of promoting health via targeted prevention and interventions.[106] Between February and May 2010, a random sample of 52,400 people living in Central Denmark Region was invited to the study. In the questionnaire for adults (≥ 25 years of age, 45,373 persons invited) 30,245 persons (67%) filled in the questionnaire. Statistic Denmark has computed post-survey weights to account for non-response.[107]

The Danish Register of Causes of Death

Since 1943 the registry has collected information on all deaths of Danish residents, including date and cause of death (e.g. suicide).[108]

The Danish Cancer Registry

The registry contains information all cancer diagnoses in Denmark since 1943, including date of diagnosis, cancer type and stage.[109]

2.3 Study designs

We conducted two studies using both a cross-sectional and cohort design (I and III), one cross-sectional study (II), one study using both a SCCS design and a cohort design (IV) and one case-control study (V). A summary of methods is provided in Table 9. A brief introduction to the SCCS design is given below.

2.3.1 The self-controlled case series design

The SCCS design[110-112] is based only on cases that act as their own control, i.e. within-person comparison between different periods of time. Thus, the SCCS design evaluates when the event occurs rather than who experience the outcome.[111] The design works best with transient exposures and abrupt onset events. One advantage of the design is that time-invariant confounding is inherently controlled for including unmeasured and unknown confounding. In the SCCS design, an observation period is defined and divided into pre-defined risk periods and a baseline or reference period. An IRR is estimated by comparing incidence rates in risk periods with the incidence rate in the reference period. Contrary to a cohort design, the follow-up time is not stopped at an event. Hence, all time occurring within the observation period (both before and after individuals have experienced the event) is included in the analysis. Importantly, the SCCS design requires certain assumptions to be fulfilled in order to provide valid results.[110-112] First, occurrence of the outcome should not affect subsequent exposures. Second, the outcome should not increase mortality as then the observation period would be censored as a result of the outcome. This event-dependent censoring can lead to bias in the SCCS design. A recommended approach to investigate event-dependent censoring is to investigate whether estimates change when excluding people dying shortly after occurrence of an outcome.[111] Third, recurrent events must be independent as the SCCS design assumes that outcomes arise according to a non-homogeneous Poisson process. This implies that the design is applicable to independent recurrent outcomes. If this does not apply, it is recommended to assess first outcome only.[111]

2.4 Study populations

In study I, we used the entire Danish population as study population (annual population ~ 5.6 million). In study II, we identified all adult responders (≥ 25 years of age) of the "How are you"-survey from 2010.[106] Of 45,373 individuals invited, 30,245 (67%) completed the questionnaire.

In study III, we included 854,429 oral glucocorticoid users. In study IV we included 286,680 persons who discontinued long-term (≥ 3 months) oral glucocorticoid treatment without any prior history of primary or secondary adrenal insufficiency (Appendix 4, Figure 1). In the SCCS design we only included cases. In study V, we identified 14,028 suicide cases and 140,278 population controls using risk-set sampling and matching by birth year and sex. The risk-set sampling from a dynamic cohort provided estimates of IRRs.[113]

2.5 Glucocorticoid exposure

In study I, we used the Danish National Prescription Registry to identify all prescriptions for systemic glucocorticoids during 1999 to 2014.

In study II, we used the Danish National Health Service Prescription database to identify all prescriptions for systemic glucocorticoids and categorized the study population in never users and ever users of systemic glucocorticoids. Ever users were categorized according to timing of exposure (current, recent and former use) and cumulative dose expressed in dose of prednisolone equivalents (< 100 mg, 100 – 499 mg, 500-999 mg, 1000-1999 mg, 2000 – 4999 mg and ≥ 5000 mg). We used the Danish National Health Service Prescription database in order to link prescription data to the "How are you" survey (located outside Statistic Denmark or The Danish Health Data Authority).

In study III, we used the Danish National Prescription Registry to identify all prescriptions for oral glucocorticoids during 1996 to 2014.

In study IV, we assembled continuous oral glucocorticoid treatment episodes. For each person in the study population, we defined an observation period that extended from 3 months before initiation of an oral glucocorticoid to 7 months after the date of the last glucocorticoid prescription (defined as cessation). The observation period was then divided into five risk periods and a reference period according to exposure status (Figure 3).

Figure 3. Pre-defined observation period and risk periods in study V.

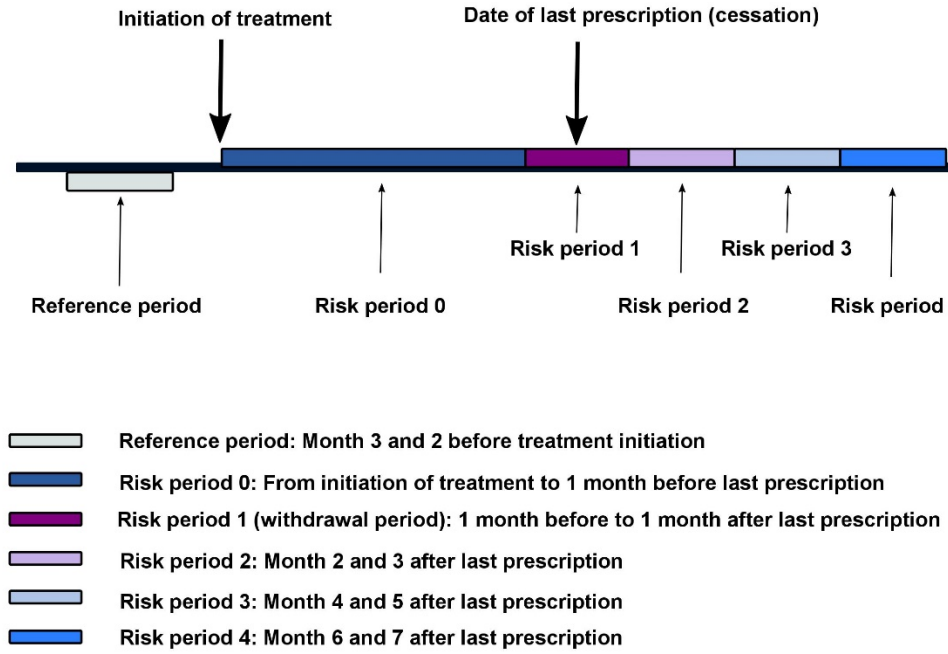


Figure modified from Laugesen K, et al. Clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy: A Danish population-based self-controlled case series analysis. PLoS ONE 2019;12: e0212259.[114]

In study V, we used the Danish National Prescription Registry to identify all prescriptions for oral glucocorticoids. We divided the study population in never users, new users, present users, recent users and former users. We further identified users of injectable and inhaled glucocorticoids as well as glucocorticoids acting on the intestine, considering only exclusive use of each type.

2.6 Outcomes

In study II, we retrieved data on lifestyle and characteristics related to lifestyle such as BMI, participation in regular leisure-time physical activities, diet, smoking, and alcohol intake from the "How are you" survey.[106] BMI was categorized according to WHO criteria, as underweight (BMI <18.5), normal weight (BMI 18.5–24), overweight (BMI 25–29), and obese (BMI ≥30).[115] Questionnaire items on physical activity focused on participation in leisure sports or other

regular exercise (yes/no). To assess diet, the health survey used a scoring system developed by the Research Centre for Prevention and Health, Capital Region of Denmark (Appendix 2). Smoking status was categorized as never, former, or current smoker. Alcohol use was categorized according to the Danish Health and Medicine Authority's recommendations as high-risk consumption [>7/14 (women/men) drinks weekly] or low-risk consumption (≤ 7/14 drinks weekly).

In study IV, we identified clinical indicators of adrenal insufficiency defined as a primary inpatient hospital diagnosis of gastrointestinal symptoms, hypotension, cardiovascular collapse, syncope, hyponatremia, and hypoglycemia in the Danish National Patient Registry. We included only primary inpatient diagnoses to obtain the most accurate date of diagnosis as this is important in the SCCS design. For syncope we also included emergency department visits because medical assessment of syncope usually occurs in the emergency setting. Explicitly, our outcomes were only indicators of adrenal insufficiency and not certain adrenal insufficiency, as the outcome measures were not specific for adrenal insufficiency and we did not have biochemical tests to confirm the diagnosis. To avoid that gastrointestinal symptoms were an indicator of flare up in inflammatory bowel disease rather than adrenal insufficiency, we excluded cases who potentially had inflammatory bowel disease. Further, to avoid that hypoglycemia was caused by insulin or sulfonylurea rather than adrenal insufficiency, we excluded cases of hypoglycemia if it took place in patients treated with these medications.

In study V, we identified all suicides in the Danish Register of Causes of Death.

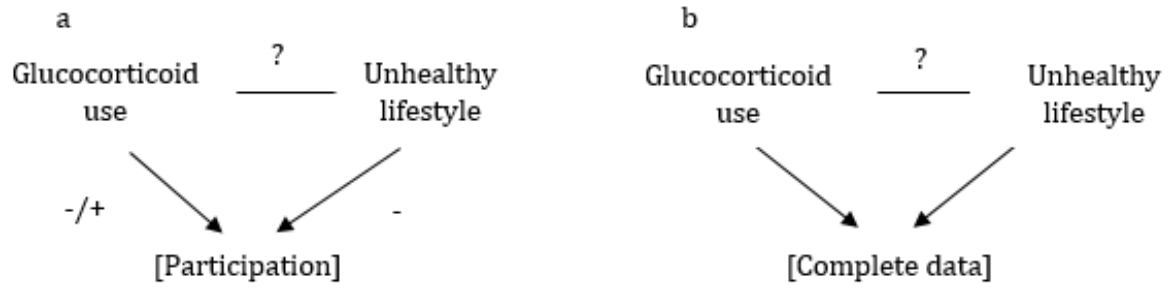
2.7 Statistical analyses

The statistical analyses used for studies I-V are summarized in Table 9 and described in more details in the appendices. Below, we give a brief overview of the statistical analysis in each of the studies.

In study I, we computed annual prevalence and incidence rates of systemic glucocorticoid use from 1999 to 2014 in the overall population and stratified by sex and age groups. The annual prevalence was calculated as the number of people who redeemed at least one prescription for a systemic glucocorticoid each year divided by the number of people in the population each year (as of 1 January). The incidence rate was calculated as number of initiators (defined as persons who redeemed a prescription for a systemic glucocorticoid without any preceding prescriptions up to 5 years before) divided by time at risk. We used a Poisson model to examine adjusted prevalence and incidence ratios by sex, age group and calendar year. Further, we utilized data on the annual amount (DDD) of conventional disease-modifying drug and biological disease-modifying drug. Finally, we constructed contingency tables on history of comedication use (assessed ≤1 year before first-time use) and morbidity (assessed at any time before first-time use).

In study II, we computed prevalence of lifestyle factors according to glucocorticoid use. Second, we estimated age-adjusted prevalence ratios of lifestyle factors using a Poisson model. All categories of glucocorticoid use were compared to never use. The above analyses were stratified by sex. When estimating prevalence and prevalence ratios, we used post-survey weights computed at Statistic Denmark to account for non-response (response rate 67%).[107] As the frequency of missing data was low (< 5%) we conducted complete-case analyses (i.e. excluded people with missing data from the analyses). In Figure 4, we provide some methodological considerations on potential selection bias related to non-response and the complete-case analysis.

Figure 4. (a) DAG illustrating potential selection bias due to non-response in study II. (b) DAG illustrating potential selection bias due to missing data in study II.



Abbreviation: DAG: Directed Acyclic Graph. [] conditioning.

a) The study population is inherently restricted to responders of the survey. If both exposure and outcome are associated with participation, then you open up a path between the exposure and the outcome by conditioning on the collider participation. Findings from the Danish Health and Morbidity survey indicate that non-respondents are likely less healthy.[116] At the same time, glucocorticoid use may be either negatively or positively associated with participation. To minimize bias due to non-response, we used post-survey weights developed by Statistic Denmark for this particular survey and issue.[107]

b) When analysing data as a complete-case analysis you exclude people with missing data. If both exposure and outcome are associated with complete data, then you open up a path between the exposure and the outcome by conditioning on the collider complete data. However, the frequency of missing data was low (< 5%) and not considered an important issue in our study.

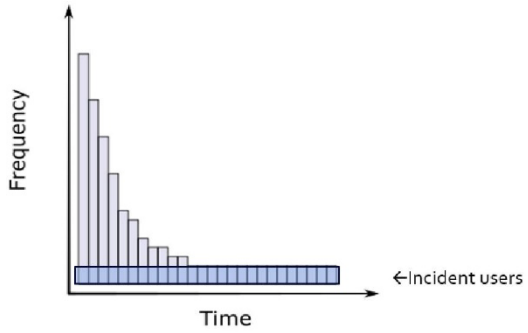
In study III, we estimated the duration of oral glucocorticoid prescriptions by applying the parametric waiting time distribution.[63] In short, this method evaluate the time to the next prescription based on the observed data. This method is based on the maximum likelihood estimation of a parametric 2-component mixture model for the waiting time distribution (Figure 5, page 36). The distribution component for prevalent users estimates the forward recurrence density that is related to the inter-arrival density (distribution of time between subsequent prescription redemptions) for users receiving continued treatment (Figure 5, page 36). The inter-arrival density shows the probability of a new prescription as a function of time.

We estimated the 80th, 90th, 95th, and 99th percentiles for prescription duration each year from 1996 to 2014. The 80th, 90th, 95th, and 99th percentiles of assigned duration corresponded to the time within 80%, 90%, 95% and 99% of users, respectively, redeemed a new prescription. Second, we stratified by age, sex, number of tablets, and the amount dispensed to investigate whether durations varied according to these variables. Third, we assessed length of first continuous treatment episodes. This was done by adding the prescription durations (results from the parametric waiting time distribution stratified by calendar year and number of tablets dispensed) to each prescription and then, for each subject, creating treatment episodes from overlapping prescriptions. To estimate the length of first treatment episodes, we used the Kaplan–Meier function to compute the 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 99th percentiles.

In study IV, we computed incidence rate ratios in a SCCS design comparing each risk period with the reference period by use of a fixed-effect Poisson model conditional on the individual person. We analysed each type of clinical indicator as a distinct case variable. We only considered the first event for each outcome type as recurrent events cannot be assumed independent. Last, we used Cox proportional hazard regression to identify potential risk factors for overt adrenal insufficiency, such as sex, age, treatment duration, cumulative treatment dose, average daily dose and use of antibiotics (as approximation for infection). In the Cox regression, we followed each person from date of last prescription until an event, emigration, death or end of follow up, whichever came first. Use of antibiotics was modelled as a time-varying exposure and a person was considered exposed up to 30 days after a redeemed prescription.

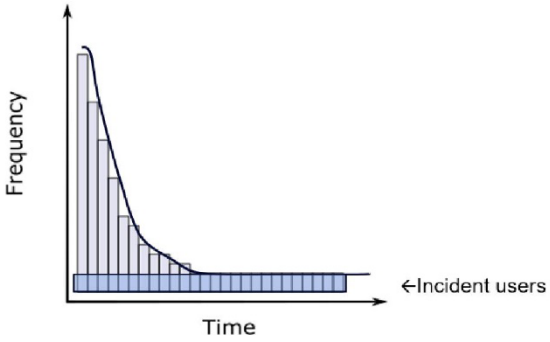
Figure 5. Illustration of the parametric waiting time distribution.

a) The waiting time distribution



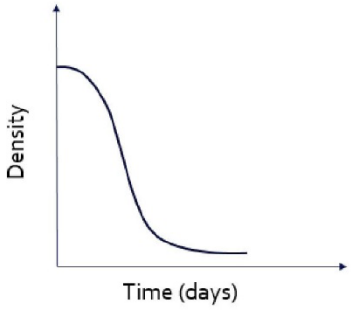
The waiting time distribution is a histogram of when users of a drug appear for the first time within a time-window (e.g. a calendar year)

b) The parametric waiting time distribution



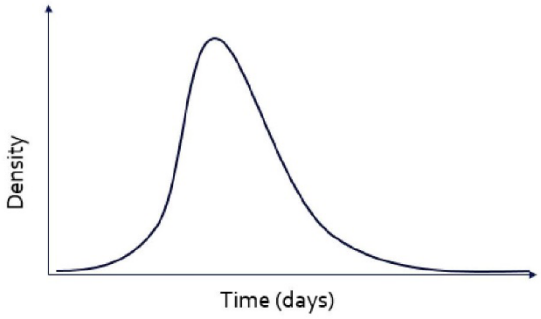
The parametric waiting time distribution is based on a maximum likelihood estimation of a parametric two-component mixture model for the waiting time distribution

c) The forward recurrence density



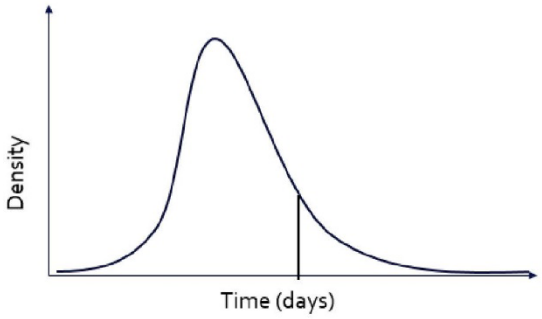
The distribution component for prevalent users estimates the forward recurrence density

d) The inter-arrival density



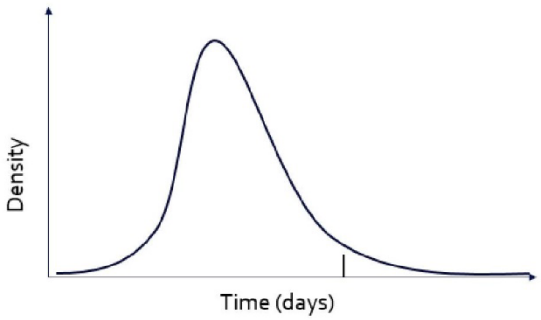
The inter-arrival density for users in continued treatment is the distribution of time between subsequent prescriptions

e) The 80th percentile of the inter-arrival densitv



By using the 80th percentile as prescription duration then 20% of continuous users will mistakenly be classified as having stopped use. This is a specific measure of drug use

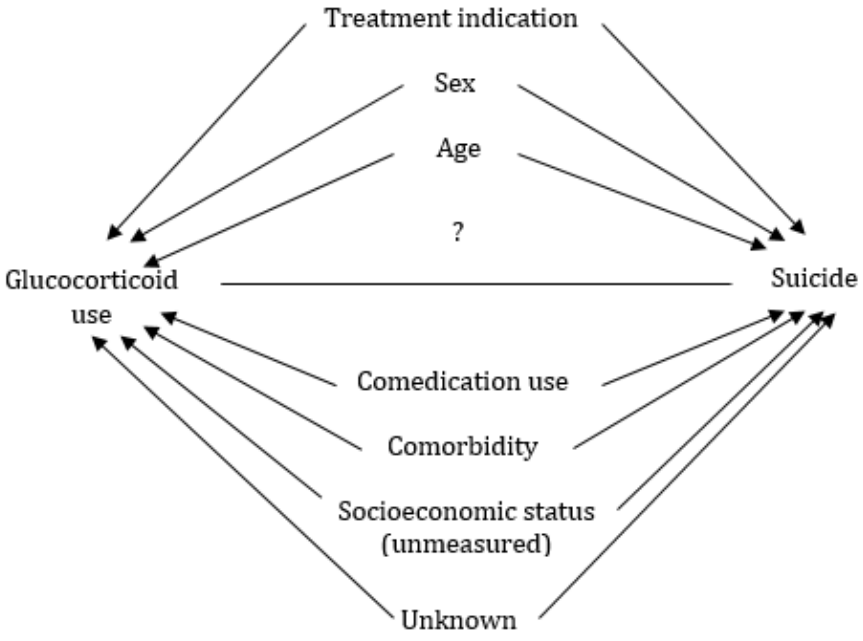
f) The 95th percentile of the inter-arrival density



By using the 95th percentile as prescription duration then 5% of continuous users will mistakenly be classified as having stopped use. This is a sensitive measure of drug use

In study V, we used logistic regression to estimate odds ratios for suicide comparing all categories of glucocorticoid users to never users. As we performed risk-set sampling from a dynamic cohort, the estimated odds ratios provided unbiased estimates of IRRs.[113] We first adjusted for matching factors and second adjusted for matching factors and selected covariates. The analyses were stratified by cancer (any cancer before index date), as we discovered (post-hoc) that cancer was an effect measure modifier. Covariates were included based on the confounding criteria[117] illustrated in the directed acyclic graph (DAG) below (Figure 6). We included covariates as sex, age, treatment indications, comorbidity and comedication use in the fully adjusted models (Figure 6).

Figure 6. DAG illustrating potential confounding in study V.



Abbreviation: DAG: Directed Acyclic Graph. We adjusted for potential confounders as age, sex, treatment indications (obstructive pulmonary disease, rheumatic diseases, skin diseases, renal diseases, inflammatory bowel disease, and other autoimmune diseases), comorbidities (psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorder) and comedication use (opioids, antiepileptic medications). Socioeconomic status was unmeasured. The influence of potential unmeasured/unknown confounding was examined by calculating the E-value[118] as described later in the section "Sensitivity analyses".

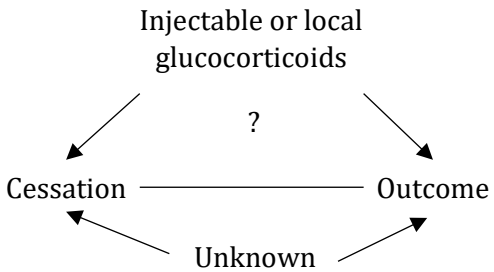
Second, we estimated incidence rate differences by using a back-calculation method.[22 119] We extrapolated the exposure distribution among the controls to the person-years of the general population in order to calculate the suicide incidence rate among users and never users and standardized the difference to the sex and age distribution among suicide cases. Third, we performed a dose-response analysis. The Danish prescription registries do not capture information on daily dose (which is of interest as a risk factor for suicide). Instead, we examined dose of glucocorticoid use near index date by calculating cumulative dose of the latest prescription among new users of oral glucocorticoids (<250, 250-499, 500-999, 1000-1999 and ≥ 2000 mg prednisolone equivalents). Last, we conducted subgroup analyses by age, sex, potential treatment indications and somatic and psychiatric comorbidity.

2.8 Sensitivity analyses

We conducted several sensitivity analyses to ensure robustness of our findings.

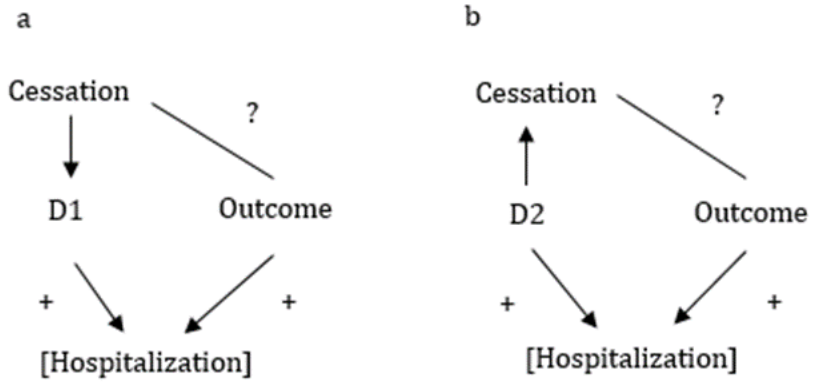
In study IV, we conducted four sensitivity analyses. First, we examined whether our choice of percentile for estimating oral glucocorticoid prescription duration affected our results by applying the 80th and 99th percentile of the inter-arrival density instead of the 95th percentile. Second, we excluded people dying 60 days after an event to investigate potential event-dependent censoring. Third, we excluded people with concomitant use of injection or local glucocorticoids to investigate potential confounding from these formulations. Figure 7 illustrates potential confounding in study IV. Fourth, we included cases based on hospital diagnoses and hospital-based studies may be vulnerable to collider stratification bias through mechanisms described in Figure 8.[120] To investigate this further, we conducted a negative outcome analysis and investigated if hospitalization with erysipelas was associated with cessation of oral glucocorticoids. As we do not expect any association between cessation of treatment and erysipelas in the general population, any findings of an association in hospital-based settings would indicate bias.

Figure 7. DAG illustrating potential confounding in study IV.



Abbreviation: DAG: Directed Acyclic Graph. Injectable and local use of glucocorticoids were controlled for by exclusion (sensitivity analysis). Timestable unknown confounding was controlled for by design. Age was considered constant over the observation period as median treatment duration was 297 days (interquartile range: 179–584 days).

Figure 8. DAG illustrating potential selection bias due to conditioning on hospitalization in study IV.



Abbreviation: DAG: Directed Acyclic Graph. [] conditioning.

Both outcome and exposure (cessation) increase risk of hospitalization. The exposure does not itself lead to hospitalization but via a disease (D). We condition on the collider hospitalization, as only cases based on hospital diagnoses are included in the SCCS design. Hence, we may open up a path between the exposure and outcome. Therefore, a non-existing exposure–outcome association in the general population may become spuriously associated in hospital settings. Examples: a) Cessation of glucocorticoid may cause D1 that leads to hospitalization. D1 may be flare-up in underlying medical condition for which glucocorticoids are prescribed. b) Cessation of glucocorticoid is a consequence of D2. D2 can be cardiovascular disease, diabetes or psychiatric disease that may cause clinicians to stop glucocorticoid treatment. From the rules of signed DAGs, potential bias would lead to an underestimation of the true effects or even inverse the association (The inverse of plus times plus is minus).

In study V, we conducted four sensitivity analyses. First, we stratified by cancer stage (localized/lymph node spread/distant metastatic spread) to investigate potential confounding by cancer severity. Because of limited number of hematological and CNS cancers, we were only able to investigate the effect of cancer stage in solid cancers. Second, we examined the association in a subpopulation of people with a newly cancer diagnosis (≤ 90 days before index date) to investigate potential confounding by timing of cancer diagnosis. Third, the influence of unmeasured confounding (Figure 6) was examined by estimating E-values. The E-value provides the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both glucocorticoid use and suicide to fully explain away our findings.[118] Fourth, cardiovascular diseases, osteoporosis, diabetes and psychiatric diseases may fulfill criteria for both confounding and mediation. To rule out potential bias from including mediators in our models, we performed a sensitivity analyses in which these variables were not adjusted for.

Table 9. Summary of study design, data sources and statistics for all studies.

	Study I	Study II	Study III	Study IV	Study V
Objectives	To examine annual prevalence and incidence of glucocorticoid use and to describe comedications and morbidity	To investigate whether lifestyle differ according to use of glucocorticoids.	To estimate oral glucocorticoid prescription duration and to describe continuous treatment episodes	To investigate clinical indicators of adrenal insufficiency following cessation of oral glucocorticoids	To investigate the association between glucocorticoid use and suicide.
Design	Cross-sectional and cohort design	Cross-sectional	Cross-sectional and cohort design	SCCS design and cohort design	Case-control study
Data sources	CRS, NPR, DNPR, www.medstat.dk	CRS, "How are you"-questionnaire (2010), DNHSPD	CRS, NPR	CRS, NPR, DNPR	RCD, CRS, NPR, DNPR, DCR
Study region, period	Denmark, 1st January 1999 to 31st December 2014	The Central Denmark Region, 1st January 2004 to 31st May 2010	Denmark, 1st January 1996 to 31st December 2014	Denmark, 1st January 1996 to 31st December 2014	Denmark, 1st of January 1995 to 31st December 2015
Study population	The entire Danish population	Adults filling in the "How are you"- questionnaire in 2010 (n = 30,245)	1) All oral glucocorticoid users (n = 854,429) 2) Multiple-prescription users (n = 418,160)	People who discontinued long-term (≥ 3 months) oral glucocorticoid treatment (n= 286,680).	14,028 suicide cases and 140,278 population controls using risk-set sampling and matched by sex and age
Exposure	Systemic glucocorticoids	Systemic glucocorticoids. Never, ever, current, recent and former use. Cumulative dose	Oral glucocorticoids Number of tablets, amount	Discontinuation of long-term (≥ 3 months) oral glucocorticoid treatment.	Glucocorticoids (oral, injectable, inhaled, acting on the intestine). New, present, recent, former and never use. Cumulative dose
Outcomes/cases	NA	BMI, smoking, diet, alcohol intake, physical inactivity	NA	Syncope, hyponatremia, hypotension, cardiovascular collapse, gastro intestinal symptoms, hypoglycemia	Suicide
Covariates	Sex, age	Sex, age, potential COPD (yes/no)	Sex, age	Sex, age, cumulative dose, duration of treatment, average daily dose, antibiotics	Sex, age, treatment indications, somatic, psychiatric morbidities, opioids, antiepileptic medicine
Outcome measures	Annual prevalence and incidence rates, PR and IRR, frequency	Prevalence, PR	80th, 90th, 95th, 99th percentile of the IAD. Median length of continuous treatment episodes	IR, 2-week prevalence, IRR, HR	IRR, IR differences
Statistics	Poisson regression	Poisson regression	The parametric waiting time distribution[30], The Kaplan-Meier estimator	Conditional fixed-effect Poisson regression, Cox proportional hazard regression	Logistic regression
Confounding control	NA	NA	NA	Self-controlled	Matching, adjustment, stratification
Sensitivity analyses	NA	NA	NA	i) Use the 80th and 99th percentile of the IAD as prescription duration ii) Excluding people dying within 60 days after an event. iii) Excluding people with concomitant use of injection or local glucocorticoids iv) Negative outcome analysis	i) Stratification by cancer stage ii) Restriction to a subpopulation with a newly cancer iii) E-values iv) No adjustment for variables that may fulfill both confounding and mediation criteria

Abbreviations: BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. CRS: The Danish Civil Registration System. DCR: The Danish Cancer Registry. DDD: Defined daily dose. DNHSPD: The Danish National Health Service Prescription database. DNPR: The Danish National Patient Registry. GI: gastro intestinal. HR: Hazard ratio. IR: Incidence rates. IRR: incidence rate ratio. IAD: Inter-arrival density. NPR: The Danish National Prescription Registry. PR: prevalence ratio. RCD: Register of Causes of Deaths. SCSS: Self-controlled case series.

3. Results

The main findings from study I-V are presented below and in more detail in the appendices.

3.1 Glucocorticoid drug utilization (Study I)

From 1999 to 2014, we identified 926,314 users of systemic glucocorticoids [54% female, median age 55 years (interquartile range (IQR): 39-69 years of age)]. Prednisolone was the most frequent generic type of systemic glucocorticoid prescribed at initial use (53%), succeeded by betamethasone (25%) and methylprednisolone (14%).[121] The annual prevalence was ~ 3% and the incidence rate was ~ 1.4/100 person years at risk (pyar) each year from 1999 to 2014, and both figures remained constant during this period of time (Figure 9). Women had a higher prevalence of use than men. Among persons aged ≥80 years, prevalence and incidence rates increased from 1999 to 2014 (from 9.7% to 11% and from 3.0/100 pyar to 3.6/100 pyar, respectively) (Figure 9). We found a rise in use of disease-modifying drugs (Appendix 1, Figure 2).[121] Often used comedications were antibiotics (49%), cardiovascular drugs (38%), NSAIDs (37%), agents used to treat COPD/asthma (21%), opioids (19%), non-opioid analgesics (17%) and antidepressants (13%) (Figure 10).[121]

Figure 9. Prevalence (%) and incidence (per 100 person years) of systemic glucocorticoid use, Denmark 1999–2014.

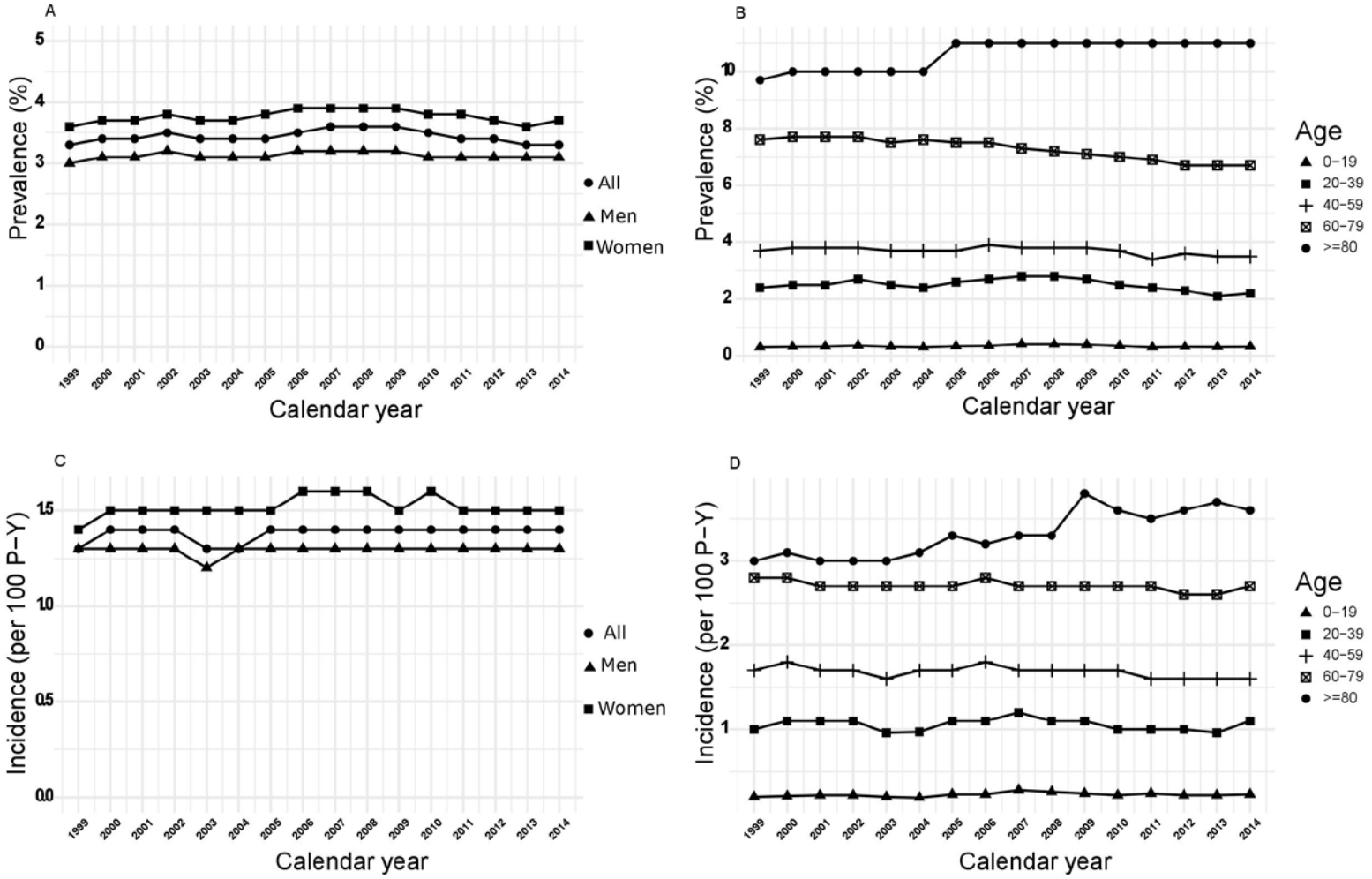
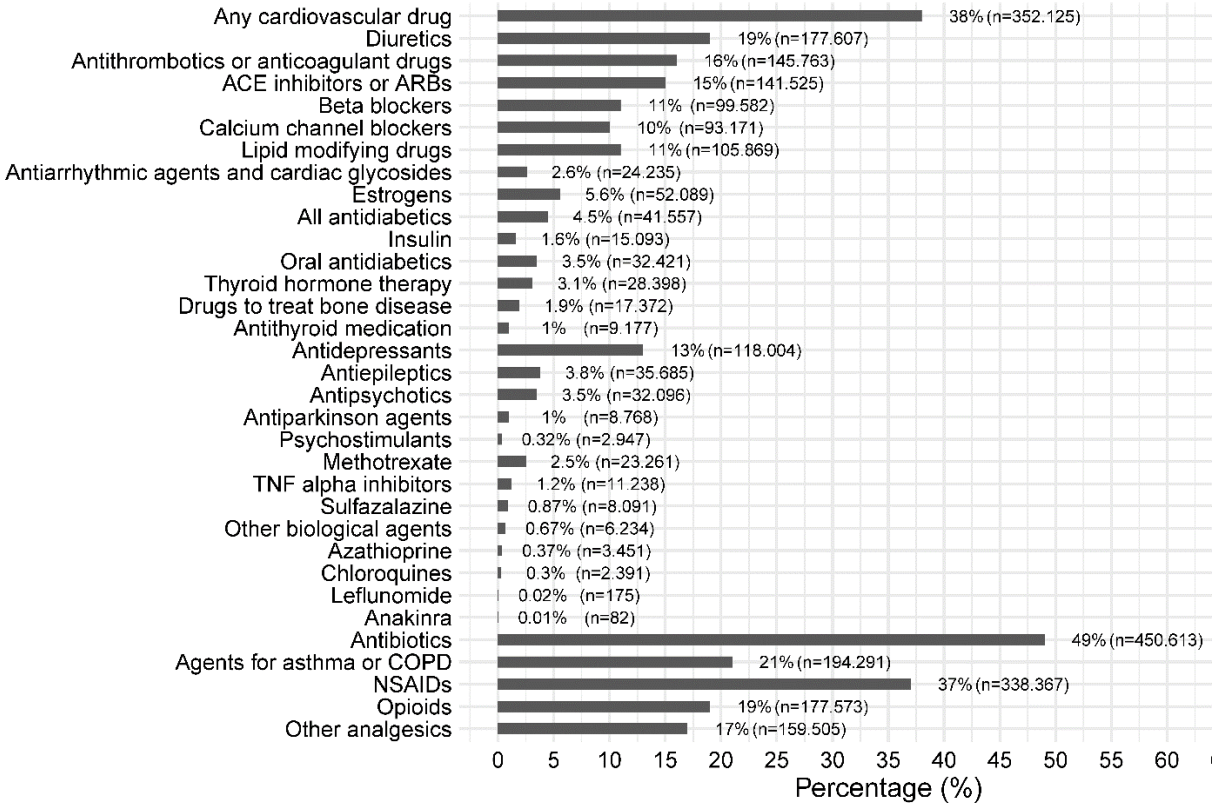


Figure modified from Laugesen K, et al. Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark. Eur J Endocrinol. 2019 Jul 1. pii: EJE-19-0305.R1.[121]

Figure 10. Frequency of comedication use ≤1 year before initial use of a systemic glucocorticoid.



Figures from Laugesen K, et al. Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark. Eur J Endocrinol. 2019 Jul 1. pii: EJE-19-0305.R1.[121]

3.2 Glucocorticoid use and lifestyle (Study II)

The prevalence of less healthy lifestyle among current users of systemic glucocorticoids was 20% - 27% for current smoking, 10% - 15% for unhealthy diet, 59% - 65% for inactive lifestyle, 12% - 21% for high-risk alcohol consumption and 17%-19% for obesity.[122] Overall, a less healthy lifestyle did not differ markedly between glucocorticoid users and never users (Figure 11 and Figure 12). Nevertheless, obesity was more frequent in glucocorticoid users than in never users (Figure 11 and Figure 12). In women, the prevalence of high-risk alcohol consumption was slightly lower and the prevalence of unhealthy diet and no leisure time physical activity slightly higher in users than never users (Figure 11).[122]

Figure 11. Age-adjusted prevalence ratios (aPR) and 95% CI comparing systemic glucocorticoid users to never users in women.

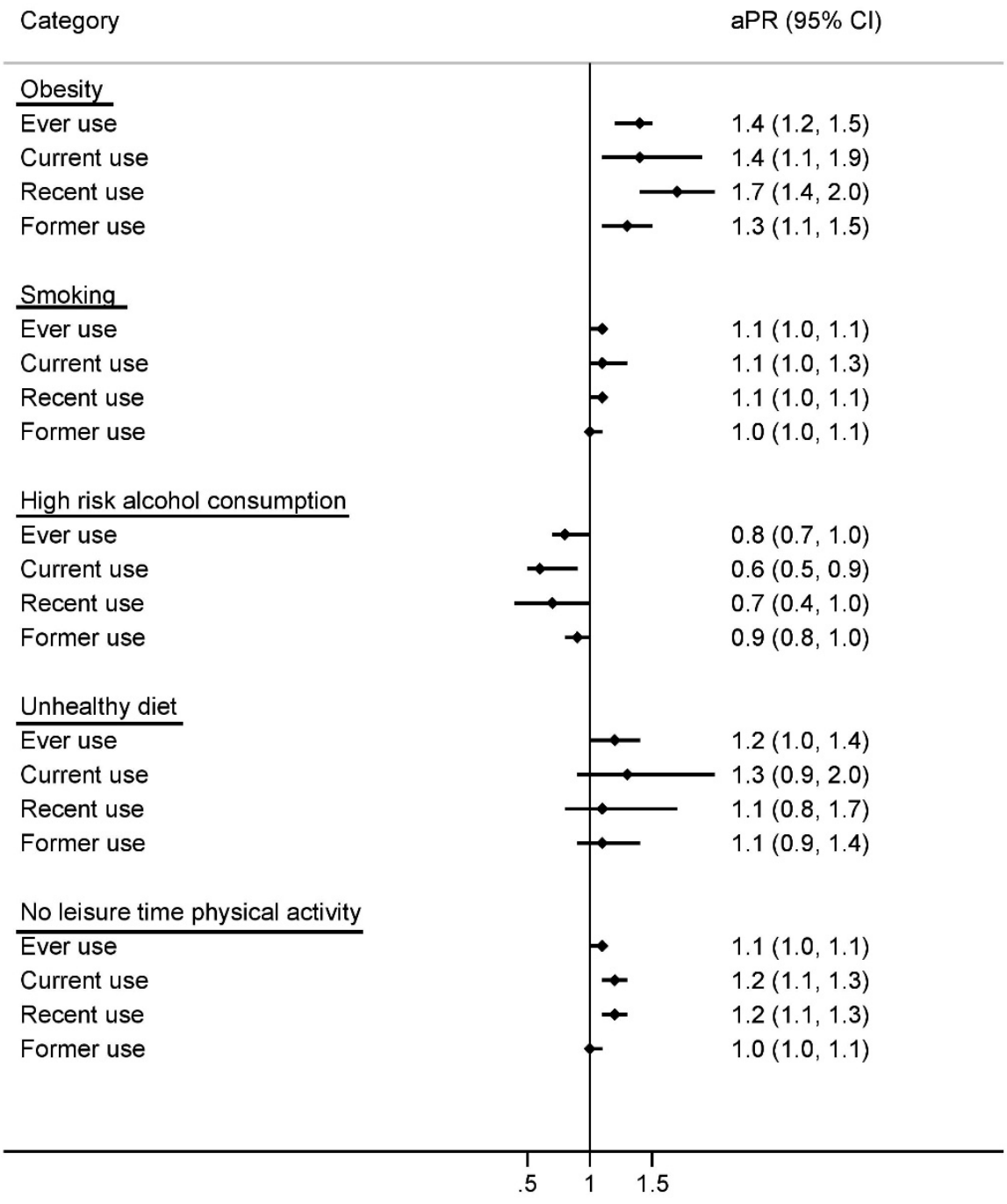


Figure from Laugesen K, et al. Prevalence of lifestyle characteristics in glucocorticoid users and non-users: a Danish population-based cross-sectional study. BMJ Open 2019;9:e030780. doi: 10.1136/bmjopen-2019-030780.[122]

Figure 12. Age-adjusted prevalence ratios (aPR) and 95% CI comparing systemic glucocorticoid users to never users in men.

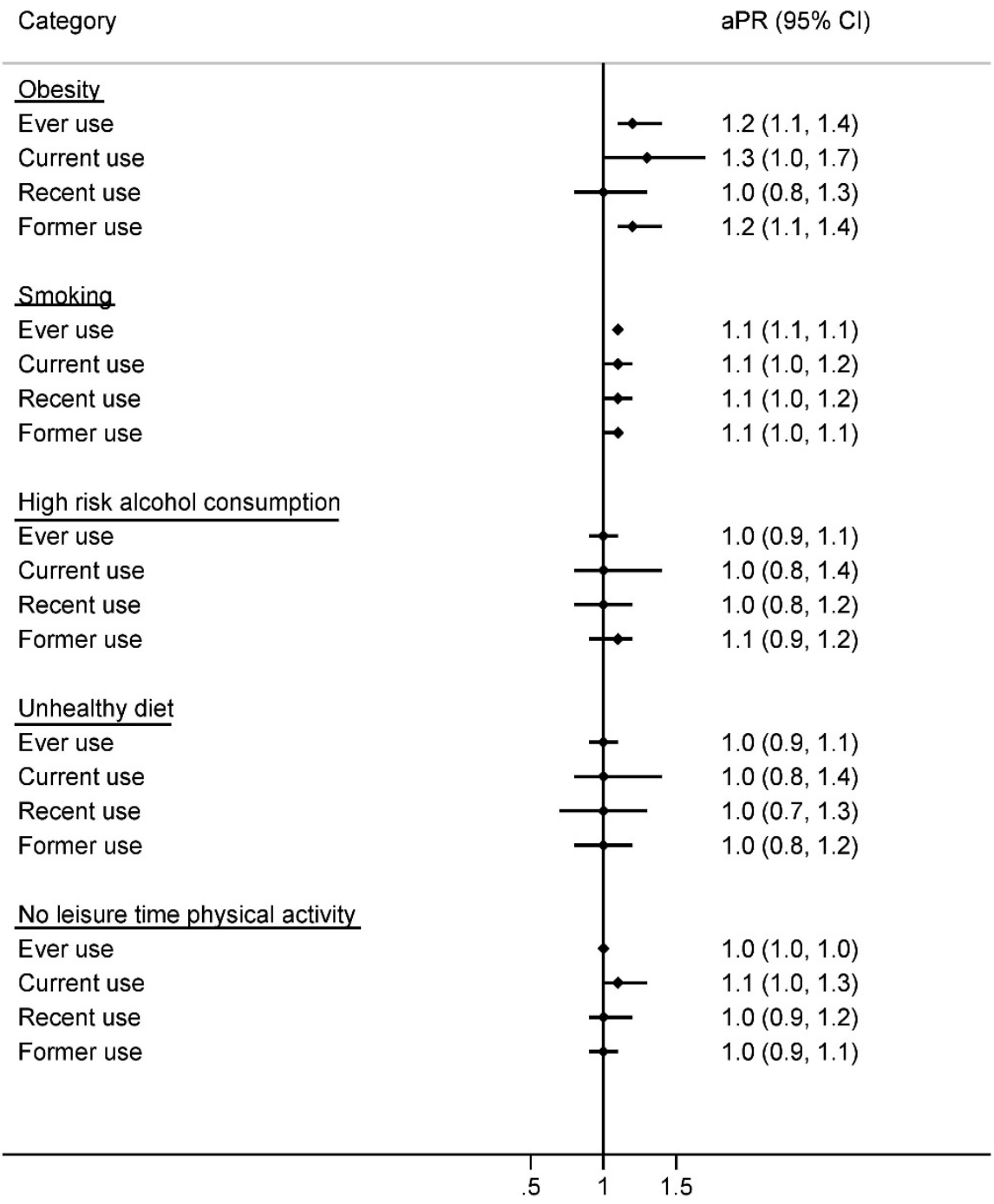


Figure from Laugesen K, et al. Prevalence of lifestyle characteristics in glucocorticoid users and non-users: a Danish population-based cross-sectional study. BMJ Open 2019;9:e030780. doi: 10.1136/bmjopen-2019-030780.[122]

3.3 Glucocorticoid treatment duration (Study III)

During 1996 to 2014, we identified 5,691,985 prescriptions for oral glucocorticoids (n = 854,429 individuals). N = 351,202 (41%) only redeemed one prescription in the entire study period. Prescription durations depended on percentile and number of tablets dispensed and ranged from 87 to 299 days. Not surprisingly, the number of tablets appeared as a predictor of prescription duration. Applying the 80th, 90th, 95th and 99th percentiles of the inter-arrival density as prescription durations presented median treatment lengths of 113, 141, 170, 243 days, respectively.[123]

3.4 Clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy (Study IV)

We identified 286,680 individuals (57% women) who discontinued long-term oral glucocorticoid therapy (≥ 3 months) (Appendix 4, Figure 1). At cessation, median age was 69 years (IQR: 57–78 years). Prednisolone was the most frequent generic type of glucocorticoid used (98%, at last prescription). Median cumulative dose was 3000 mg prednisolone equivalents (IQR: 1125–6500 mg), median treatment length was 297 days (IQR: 179–584 days), and median average daily dose was 6.8 mg prednisolone equivalents per day (IQR: 4.6–12 mg per day).[114]

We found that the incidence rates of hyponatremia, hypotension, gastrointestinal symptoms and hypoglycemia were increased in the withdrawal period compared to the reference period (Table 10). The rates of gastrointestinal symptoms and hypotension remained higher compared to the reference period during the 7 months of follow up, albeit with a declining rate (Table 10). The IRRs for hypoglycemia should be interpreted with caution because of the low number of cases and imprecision in estimates. No cases of cardiovascular collapse were observed in the reference period but, incidence rates and 2-week prevalence in the entire cohort were higher in the withdrawal period than before withdrawal (Appendix 4, Table 2 and Figure 3).[114] We found IRRs close to one in our negative outcome analysis. All sensitivity analyses showed robustness

of results. We identified increasing average daily dose, increasing cumulative dose, use of antibiotics (as approximation for infection) and increasing age as risk factors for overt adrenal insufficiency.[114]

Table 10. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for clinical indicators of adrenal insufficiency by risk period.

	Syncope	Hypo-natremia	Hypotension	Gastrointestinal symptoms	Hypoglycemia
Number of cases	3568	634	295	6332	38
Reference period	1	1	1	1	1
Risk period 0	0.8 (0.7 - 0.9)	0.7 (0.6 - 1.0)	1.5 (0.9 - 2.5)	1.0 (0.9 - 1.1)	0.6 (0.2 - 2.1)
Risk period 1 (withdrawal)	1.1 (0.9 - 1.2)	1.5 (1.1 - 2.0)	2.5 (1.4 - 4.3)	1.7 (1.6 - 1.9)	2.2 (0.7 - 7.3)
Risk period 2	1.0 (0.9 - 1.2)	1.1 (0.7 - 1.5)	2.3 (1.3 - 4.3)	2.0 (1.8 - 2.2)	2.4 (0.6 - 9.5)
Risk period 3	1.0 (0.8 - 1.2)	0.9 (0.6 - 1.4)	2.0 (1.0 - 3.9)	1.5 (1.3 - 1.7)	NA
Risk period 4	0.9 (0.7 - 1.0)	0.7 (0.4 - 1.1)	1.7 (0.8 - 3.6)	1.5 (1.3 - 1.7)	0.9 (0.1 - 8.9)

Reference period: Months 3 and 2 before oral glucocorticoid initiation. Risk period 0: From the date of glucocorticoid initiation to 1 month before redemption of the last prescription. Risk period 1 (withdrawal period): From 1 month before redemption of the last prescription to 1 month after this redemption. Risk period 2: Months 2 to 3 after redemption of the last prescription. Risk period 3: Months 4 to 5 after redemption of the last prescription. Risk period 4: Months 6 to 7 after redemption of the last prescription. Table modified from Laugesen K, et al. Clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy: A Danish population-based self-controlled case series analysis. PLoS ONE 2019;12: e0212259.[114]

3.5. Glucocorticoid use and risk of suicide (Study V)

We identified 14,028 suicide cases and 140,278 population controls (median age 53 years and 72% men). In people with cancer, the risk of suicide was increased 7-fold when comparing new use of oral glucocorticoids to never use (Table 11). The rate difference was 7.6 per 10,000 person years (95% CI: 0 - 17). In people without cancer we found a 2-fold increase (Table 11) and a rate difference of 1.4 per 10,000 person years (95% CI: 0 - 12). We found a dose-response

effect (Appendix 5, Table 4). We found no association between suicide and use of other glucocorticoid administration forms. Our sensitivity analyses showed robustness of our results (Appendix 5, appendix Table 4-7).

Table 11. The association between oral glucocorticoid use and suicide, stratified by cancer (any time before index date).

Exposure	Cases/controls	Adjusted* IRR (95% CIs)	Fully adjusted** IRR (95% CIs)	E-value for point estimate (lower bound of the 95% CI)
Cancer				
Never use (Reference)	707/5865	1	1	
New use	71/68	8.7 (6.2-12)	7.2 (5.0 - 11)	14 (9.5)
Present	152/362	3.6 (2.9-4.4)	2.8 (2.2 - 3.6)	
Recent	51/246	1.8 (1.3-2.5)	1.0 (0.7 - 1.5)	
Former	136/1002	1.2 (1.0-1.5)	0.9 (0.7 - 1.1)	
No Cancer				
Never use (Reference)	8548/91,453	1	1	
New use	60/264	2.5 (1.9-3.3)	2.0 (1.5-2.8)	3.4 (2.4)
Present	280/1521	2.0 (1.8-3.2)	1.5 (1.3-1.8)	
Recent	202/1406	1.6 (1.4-1.9)	1.1 (0.9-1.3)	
Former	735/6586	1.2 (1.1-1.3)	0.9 (0.8-1.0)	

* Conventional logistic regression adjusted for calendar year of index date, age and sex (matching factors).

**Conventional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, skin diseases, renal diseases, inflammatory bowel disease, other autoimmune diseases, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

Abbreviations: IRR: incidence rate ratio. 95% CI: 95% confidence interval.

Table modified from Laugesen K, et al. Glucocorticoid use and risk of suicide: A Danish population-based case control study. In preparation.

4. Discussion

4.1 Main findings

The thesis provides following main findings.

(1) The annual prevalence of systemic glucocorticoid use was ~ 3% and the annual incidence rate was ~1.4/100 pyar in the Danish population each year from 1999 to 2014. The annual prevalence and incidence rates were highest among women and in the elderly. Despite increased use of disease-modifying drugs, both figures stayed nearly stable during 1999 to 2014 in the overall population. Among the elderly (≥ 80 years of age), both prevalence and incidence rates increased.

(2) Less healthy lifestyle and characteristics related to less healthy lifestyle as no leisure time physical activity, unhealthy diet, smoking and high-risk alcohol consumption did not differ extensively among glucocorticoid users and never users. Still, obesity was more prevalent among glucocorticoid users. In women, the prevalence of high-risk alcohol consumption was slightly lower and the prevalence of unhealthy diet and no leisure time physical activity slightly higher in users than never users.

(3) Based on the parametric waiting time distribution, oral glucocorticoid prescription duration ranged from 87 to 299 days, depending on percentile of the inter-arrival distribution and number of tablets dispensed.

(4) Clinical indicators of adrenal insufficiency (hyponatremia, hypotension, gastrointestinal symptoms and hypoglycemia) increased in the glucocorticoid withdrawal period compared to before starting glucocorticoid treatment and remained increased for some clinical indicators (hypotension and gastrointestinal symptoms) during 7 months of follow up. Likely, these findings were attributable to adrenal insufficiency, although not confirmed by biochemical testing. Increasing cumulative dose of oral glucocorticoids, increasing average daily dose, use of

antibiotics (as approximation for infection), and age appeared to predict overt adrenal insufficiency.

(5) New use of oral glucocorticoid was associated with a 7-fold increased risk of suicide compared to never use among people with a history of cancer and a 2-fold increased risk in people without a history of cancer. Other glucocorticoid administration forms as well as former and recent use of oral glucocorticoids were not associated with suicide.

4.2 Comparison with existing literature and perspectives

4.2.1 Glucocorticoid drug utilization

Previous studies from France (2007–2014)[47], the USA (1999–2008)[46], the UK (1989–2008 and 1994-1997)[42 45] and Iceland (1995–1996)[43] have estimated prevalence of glucocorticoid use in the general population in the range of 0.5% to 17% depending on setting, study period and methods (Table 4). Our study is most compatible to the French study[47] as regards exposure assessment and operational definition of prevalence (both measuring annual prevalence). Hence, Denmark seems to prescribe less systemic glucocorticoids than France (annual prevalence of 3% in Denmark vs. 17% in France). Although different operational definitions of prevalence complicate comparison of studies[124], it seems as if prevalence of glucocorticoid use varies across countries. However, as in our study, all previous studies found a higher prevalence of glucocorticoid use in women than in men and a higher prevalence in the elderly.

Frequently reported treatment indications in prior studies were rheumatic diseases (i.e. polymyalgia rheumatica, giant cell arthritis and rheumatoid arthritis) and respiratory diseases (COPD and asthma). In our studies, we were unable to properly identify treatment indications. Despite our findings of increased use of disease-modifying drugs, we found no overall changes in annual prevalence or incidence of systemic glucocorticoid drug use in the general population. Importantly, we were unable to examine prescribing patterns in specific patient groups for which disease-modifying drugs are indicated and often used (i.e. rheumatoid arthritis or

inflammatory bowel disease). Analyses in such patient groups may have revealed a change in prescribing patterns. As example, Fardet et al. found that the prevalence of long-term (≥ 3 months) oral glucocorticoid treatment declined in patients with COPD, asthma, Crohn´s disease and incident rheumatoid arthritis from 1989 to 2008 in the UK. At the same time the prevalence of use increased in prevalent rheumatoid arthritis and polymyalgia rheumatica/giant cell arthritis.[45]

Prescribing of glucocorticoids in the general population is affected by numerous factors such as demography, trends in prevalence of underlying medical conditions, clinical treatment guidelines and the availability of other treatment options. Despite increased use of disease-modifying drugs, current evidence suggests that glucocorticoid use remains widespread, particularly in the elderly. This constitute a concern because of the many adverse effects. Further, the demographic shift towards an aging population is of importance. The elderly are more vulnerable to adverse effects, likely because of age-related changes in pharmacodynamics and pharmacokinetics, comorbidity and comedication use are high. Our findings suggested that the levels of comedication use among systemic glucocorticoid users. Evidence-based clinical guidelines on how to prevent and manage certain glucocorticoid adverse effects exist[17], still adverse effects such as adrenal insufficiency merit more attention, and no evidence-based clinical guidelines exist.[10]

4.2.2 Glucocorticoid use and lifestyle

Our findings are not directly comparable to the Dutch study (where only 5% of glucocorticoid users were users of systemic drugs and the rest were users of locally acting drugs) (Table 5).[61] As regards BMI, the Dutch study found no major difference in BMI between current glucocorticoid users and non-users. However, they found that glucocorticoid use was associated with the metabolic syndrome, especially in women.[61] In our study, glucocorticoid users, both men and women, had a slightly higher prevalence of obesity than never users. Although our study was not designed to investigate glucocorticoid adverse effects, our findings correlate well

with the fact that glucocorticoid excess is associated with central obesity.[55] The Dutch study found similar prevalence of alcohol drinking among current glucocorticoid users and non-users.[61] We found similar results in men; however, female current users had a slightly lower prevalence of high-risk alcohol consumption than never users. Further, the Dutch study found that glucocorticoid users were less likely to be current smokers and more likely to be former smoker compared to non-users.[61] Although, we found no overall difference in smoking status among current glucocorticoid users and never users, we likewise found a higher prevalence of former smoking among current users compared to never users.

Since less healthy lifestyle factors are not or only modestly associated with glucocorticoid use, these factors are unlikely to greatly confound the associations in observational studies of glucocorticoid adverse effects. Further, the slightly higher prevalence of obesity in glucocorticoid users than never users is more likely an effect of glucocorticoid exposure, although, the cross-sectional design does not allow us to address the temporality of the associations. If this is correct, obesity is rather a mediator than a confounder in epidemiological terms (if any).

From a health perspective, prevalence of current smoking (20% - 27%), unhealthy diet (10%-15%), inactive lifestyle (59% - 65%), high-risk alcohol consumption (12% - 21%) and obesity (17%-19%) among current users of systemic glucocorticoids may constitute a concern. Less healthy lifestyle, glucocorticoid use, and some underlying treatment indications are common risk factors of the metabolic syndrome, cardiovascular disease and osteoporosis.

4.2.3 Adrenal insufficiency following discontinuation of glucocorticoid treatment

Former studies (Table 7) have established that biochemically defined adrenal insufficiency is prevalent following cessation of oral glucocorticoid treatment (pooled prevalence ~ 50%, range 0%-100%).[9 71-94] The clinical implications are unclear due to lack of data. Our study shows that the rates of hospitalization with clinical indicators of adrenal insufficiency increased in the

glucocorticoid withdrawal period compared to before starting treatment. The rates were increased 1.7-fold for gastrointestinal symptoms, 2.5-fold for hypotension, 1.5-fold for hyponatremia, and 2.2-fold for hypoglycaemia. Likely, these findings were attributable to adrenal insufficiency. Importantly, our outcomes were only indicators of adrenal insufficiency and not certain adrenal insufficiency, as the outcome measures were not specific for adrenal insufficiency and we did not have biochemical tests to confirm the diagnosis. Further, we were not able to obtain a meaningful estimate of absolute risk due to the data quality of our outcome data and this limitation is discussed later.

Prior studies have shown that adrenal insufficiency can persist longer after glucocorticoid cessation, although the time course for adrenal recovery has not been established.[9 71-94] One study (n = 150) re-tested patients up to 3 years after cessation and found that 5% still had adrenal insufficiency.[85] Our study found that increased rates prevailed for at least 7 months after cessation for some clinical indicators (gastrointestinal symptoms and hypotension).

Current evidence suggests that adrenal insufficiency is more likely after large doses of glucocorticoids and long treatment periods, even though no treatment regimens can be considered safe.[9 93] We investigated potential risk factors and found that increasing average daily dose, cumulative dose and use of antibiotics were predictors of being hospitalized with clinical signs or symptoms of adrenal insufficiency. This is in line with former studies.[9 93 94] In our study, increasing age but not treatment duration appeared as a risk factor. An explanation for age being a risk factor may be altered pharmacokinetics and pharmacodynamics, frailty, greater levels of comorbidity and more frequent use of comedications in the elderly. We were not able to explore potential risk factors such as treatment indication, biomarkers or genetic predispositions.

Overall, our study provides novel clinical data about adrenal insufficiency following glucocorticoid cessation. Still, a substantial number of research questions remain unanswered (please see “Future research directions”).

4.2.4 Glucocorticoid use and risk of suicide

Our study confirms findings from the UK study reporting a 7-fold increased risk of suicide/attempted suicide among oral glucocorticoid users compared to nonusers with the same underlying medical condition.[26] The Canadian case-control study found a more modest association, but this study did not contain information on modes of glucocorticoid administration.[96] In this context, we also found no effect of inhaled glucocorticoids and glucocorticoids acting on the intestines and that may be explained by lower systemic levels compared to oral glucocorticoids.[27 28] Our findings of increased risk of suicide among new users of oral glucocorticoids correlates well with the fact that neuropsychiatric symptoms often present early in treatment cycle, although confounding by disease severity cannot be ruled out.[11 12] We additionally confirmed a dose-response effect as reported in former studies on neuropsychiatric symptoms[12 26]

People with prior/present cancer were in particular risk. We, however, need to investigate these findings further. Glucocorticoid doses may be part of the explanation. The clinical applications of glucocorticoids in cancer are many and comprise use for cytostatic effects (lymphomas) and use for symptom relief as pain, nausea, cachexia and adverse effects of chemotherapy among others.[125] Often high dose treatment regimens are used for these purposes. Further, both younger age and older age were risk factors. This partly confirms the prior UK study that found younger age as a predictor of suicide among oral glucocorticoid users.[26]

Awareness of the association between oral glucocorticoid use and suicide among clinical staff and information to patients and relatives may enhance early intervention and prevention. A special focus should be paid to cancer patients initiating glucocorticoid therapy.

4.3 Methodological considerations

Below, we discuss the internal validity of our findings in terms of selection bias, information bias and confounding.

4.3.1 Selection bias

If the association between the exposure and outcome among participants in a study differs from the association among those eligible, we refer to selection bias.[117] Mechanisms that give rise to selection bias may be how participants enter the study population or loss to follow up after entering the study. Overall, Danish population-based studies have a low risk of selection bias because of a homogeneous demography, a universal and tax-funded health care system and virtually complete follow up of the population.[100] Nevertheless, potential selection bias needs to be discussed in relation to study II (glucocorticoids and lifestyle) and study IV (clinical indicators of adrenal insufficiency following discontinuation of long-term oral glucocorticoids). In study II, we used a survey with a response rate of 67% to identify our study population and non-response could be a potential source of selection bias (Figure 4, page 34). To minimize bias due to non-response we used post-survey weights developed by Statistic Denmark for this particular survey and issue.[107] Another theoretic source of selection bias in study II was missing data (Figure 4, page 34). However, the frequency of missing data was low (< 5%) and not considered an important issue in our study.

In study IV, we included cases based on hospital diagnoses and hospital-based studies may be vulnerable to collider stratification bias (Figure 8, page 39).[120] To investigate this further, we conducted a negative outcome analysis. As expected, we found a null association in this analysis, indicating that this type of bias was not a problem. Further, if collider stratification bias had been an issue in study IV, our findings would probably be conservative estimates of the true effect (Figure 8, page 39). Lastly, individuals only contributed to our SCCS analysis if they were both cases and discontinued glucocorticoid treatment. Therefore, misclassification of exposure

and outcome could affect selection into the study population. Misclassification will be discussed in more details in the section below. Briefly, we did not expect that misclassification of exposure depended on our outcomes of interest or vice versa (Figure 13, page 59). Hence, misclassification would not introduce selection bias.

4.3.2 Data quality and information bias

Information bias may occur when exposure or outcome data are misclassified. Misclassification can be non-differential (misclassification does not depend on other variables) or differential (misclassification does depend on other variables). Bias caused by differential misclassification can exaggerate or underestimate an effect. Whereas, bias introduced by independent non-differential misclassification of a binary exposure/outcome is towards the null.[117]

Below, we will discuss data quality, misclassification and information bias in relation to our studies (Studies I-V).

4.3.2.1 Glucocorticoid use

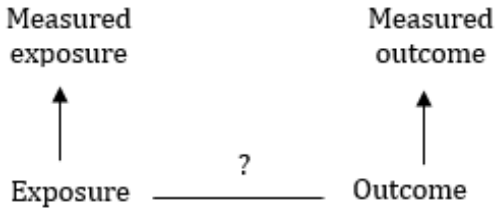
Glucocorticoid use was identified through the Danish prescription registries. These registries are virtually complete in relation to medication dispensed in the primary sector but they lack information on in-hospital treatment. In a prior study we found that 20% of total annual volume of systemic glucocorticoids was used in the hospital sector.[126] As our findings were based on aggregated data, we were unable to examine the corresponding number of users.[126] In addition, information in the Danish prescription registries only reflects prescription redemption and not adherence. Hence, prescription redemption is only an approximation of actual use (studies I-V).

In study I, lack of information on in-hospital treatments might have underestimated annual prevalence and incidence rates of glucocorticoid use.

In study II, true never users might be misclassified as users if they redeemed a glucocorticoid prescription but did not adhere to the treatment. On the other hand, true glucocorticoid users

might be misclassified as never users due to lack of information on in-hospital treatments. Misclassification of glucocorticoid exposure would be independent of the outcomes (less healthy lifestyle), i.e. non-differential (Figure 13). Non-differential misclassification would give bias towards the null when comparing users to never users of glucocorticoids but would lead to unpredictable direction of bias in our cumulative dose estimates.

Figure 13. DAG illustrating independent non-differential misclassification in studies II, IV and V.



Abbreviation: DAG: Directed Acyclic Graph.
Misclassification of the exposure does not depend on the outcome and misclassification of the outcome does not depend on the exposure. Potential misclassification is therefore non-differential.

In study III, unmeasurable exposure time during hospital stays might have affected estimates of prescription duration and length of continuous treatment episodes. As example glucocorticoid treatment might be initiated at the hospital and then continued by prescription redemption at community pharmacies. Thereby, the treatment episode would be estimated to be shorter than the actual true length of treatment episode.

In study IV, we had to assemble continues glucocorticoid treatment episodes. For this purpose we used the parametric waiting time distribution (study III) that has several advantages compared to more traditional ways of assigning prescription duration.[63] The method uses the observed pattern of oral glucocorticoid prescription in our population and does not rely on clinical assumptions or educated guesses. Further, you have information regarding the limit of misclassification on the level of single prescription duration (however, not on the level of continuous treatment episodes). To increase the probability of capturing true discontinuation,

we used the 95th percentile of the inter-arrival density as a measure of prescription duration (stratified by calendar year and number of tablets dispensed). With prescription duration defined by the 95th percentile of the inter-arrival density, only 5% of continuous users will mistakenly be classified as having stopped treatment. On the other hand, use of the 95th percentile is likely to classify a higher proportion of individuals as continued users when, in fact, they had stopped taking the drug. We examined if our choice of percentile for estimating prescription duration affected our results by applying the 80th and 99th percentile instead. This did not change our results substantially. Second, we defined date of glucocorticoid cessation as date of last prescription redemption. We were incapable of determine the precise timing of the last dose, and it is possible that people tapered treatment for weeks after last prescription redemption. In order to manage this inaccuracy, we defined the withdrawal period as a 2-month period surrounding the redemption date of the last prescription. Further, we were not able to explore different tapering schedules. Last, hospital admissions might have concealed true date of cessation because of unmeasurable exposure time. Length of hospital stays were short and therefore unlikely to influence date of cessation substantially. Median length of hospital stays was 1 day (IQR: 1-2 days) for syncope, 4 days (IQR: 1-8 days) for hyponatremia, 1 day (IQR: 1-7 days) for hypotension, 2 days (1-5 days) for gastrointestinal symptoms and 2 days (1-5 days) for hypoglycemia.

In study V, true never users might be misclassified as glucocorticoid users if they redeemed a prescription but did not adhere to the treatment. On the other hand, true glucocorticoid users might be misclassified as never users due to left censoring of the prescription data or lack of information on in-hospital medication use. Misclassification of glucocorticoid exposure would be independent of suicide, hence non-differential (Figure 13, page 59). Non-differential misclassification would give bias towards the null when comparing glucocorticoid users to never users, however, cause unpredictable direction of bias in the cumulative dose estimates.

4.3.2.2 Outcome data

In study II, data on lifestyle were self-reported and prone to misclassification. We expected that misclassification of lifestyle data was independent of glucocorticoid use, hence non-differential (Figure 13, page 59).

In study IV, we identified clinical indicators of adrenal insufficiency through primary hospital diagnoses and several issues should be addressed. First, some of our outcomes are validated (positive predictive value in the range: 92-94); however, syncope, gastrointestinal symptoms and hypoglycemia are not.[105] Second, the outcome measures were only indicators of adrenal insufficiency and not certain adrenal insufficiency, as they were not specific for adrenal insufficiency and we did not have biochemical tests to confirm the diagnosis. To avoid that gastrointestinal symptoms were caused by flare up in inflammatory bowel disease rather than adrenal insufficiency, we excluded cases who had inflammatory bowel disease. Further, to avoid that hypoglycemia was caused by insulin or sulfonylurea rather than adrenal insufficiency, we excluded cases of hypoglycemia if it took place in patients treated with these medications. Despite the above, we did not expect that misclassification of our outcomes varied during the observation period and therefore that any bias would be towards the null (Fig. 13, page 59). Third, we expected incomplete registration of our outcomes both in relation to hospital settings (e.g. not every patient with gastrointestinal symptoms is registered with that diagnosis) and in relation to the general population (e.g. many people with gastrointestinal symptoms are not hospitalized). Because of the quality of our outcome data, we were unable to obtain a meaningful estimate of absolute risk, hence unable to evaluate the clinical impact in terms of risk of adrenal insufficiency caused by glucocorticoid cessation.

In study V, we identified suicides in the Register of Causes of Death.[108] Sudden or unexpected death requires reporting to the police, and the death certificate can be issued only after medicolegal examination according to Danish legislation. Therefore, we expect a high validity of suicide data. Potential misclassification would be non-differential (Figure 13, page 59).

4.3.3 Confounding

Confounding can be a threat to the validity when using observational studies to investigate causal associations. In modern causal terminology, confounding is identified by use of DAGs and arises from open backdoor paths between exposure and outcome.[117] Confounding can be controlled for in the design (randomization, matching, restriction and case-only designs) or in the statistical analyses (stratification, adjustment, standardization, bias analysis or G-methods). Confounding can be divided into residual confounding, unmeasured known confounding and unknown confounding. Residual confounding denotes confounding that has been taken into account, however, not adequately (i.e. because of imprecise measures or misclassification of the variable). An important type of confounding in pharmacoepidemiological studies is confounding by indication. This type of confounding arises from the fact that individuals who are prescribed a medication need the drug for a reason (i.e. they are inherently different from those who are not prescribed the medication). Even if comparison is made within individuals with the same disease, they may differ in disease severity.

In study IV we used the SCCS design that inherently eliminates confounding that is stable over time (e.g. genetics), including potential unmeasured and unknown confounders. Still, the design does not account for time-varying confounders. Knowledge regarding risk factors for adrenal insufficiency is sparse, and prior research has mainly focused on features related directly to the exposure (treatment duration, cumulative dose and daily dose) or stressors. Other routes of glucocorticoid administration (i.e. injection or local) might also cause adrenal insufficiency (Figure 7, page 39). Our sensitivity analysis that excluded people with concomitant use of local or injectable glucocorticoids showed robustness of our results.

In study V, we used matching, adjustment and stratification to limit measured known confounding (Figure 6, page 37). Still, we cannot rule out residual confounding from e.g. incomplete registration of treatment indications or morbidity in the Danish National Patient Registry. Despite our adjusting for treatment indications, the most important limitation of study

V was potential confounding by indication or confounding due to the severity of the underlying medical conditions. Our sensitivity analyses showed robustness of our results towards confounding by cancer severity (stage) and timing, although the association between oral glucocorticoid use and suicide was more pronounced among individuals with lymph node spread and metastatic spread than among individuals with localized cancer. As regards unmeasured confounding (known or unknown), the association between the confounder and glucocorticoid use and the association between the confounder and suicide needed to be minimum 14 and 3.4 on the risk ratio scale, respectively, to fully explain our findings (Table 11). As example, socioeconomic status was a potential unmeasured known confounder (Figure 6, page 37). Yet, the large E-values made it unlikely that our findings could be explained by such confounding. Especially, given the effect sizes of the association between socioeconomic and suicide found in Danish settings (Unemployed vs. employed: adjusted odds ratio = 1.24 and 95% CI: 1.12-1.37; disability pensioner vs. employed: adjusted odds ratio = 1.42 and 95% CI: 1.32-1.53; lowest quartile vs. highest quartile income level: adjusted odds ratio = 2.66 and 95% CI: 2.46-2.88).[127] Given our results in study II, we did not consider lifestyle as a strong source of confounding.

4.4 Future research directions

Glucocorticoid drug utilization

Current evidence suggests that glucocorticoid use remains widespread, especially in the elderly. This constitutes a challenge because of the many adverse effects. In addition, the demographic shift towards an aging population is of concern, as elderly are more vulnerable to adverse effects and at the same time are the major consumers of medicine. More research and evidence-based clinical guidelines on how to prevent and manage glucocorticoid adverse effects are needed. Future research may focus on predictive factors for beneficial and adverse effects of glucocorticoids in order to guide optimal treatment for the individual patient or on the development of drugs that optimize the risk-benefit ratio of glucocorticoids. An example of the

latter is the selective glucocorticoid receptor agonists that have not yet been approved for the market.[128] The selective glucocorticoid receptor agonists are designed to favour anti-inflammatory and immunosuppressive effects but with less adverse effects by favouring transrepression vs. transactivation. Still, it is unknown if transrepression alone provide an adequate anti-inflammatory response. Further, the exact mechanisms behind many adverse effects remain poorly understood. Emerging research from both the pharmaceutical industry and academia may affect glucocorticoid drug utilization in the future; however, the time perspectives are most likely extensive.

Glucocorticoid-induced adrenal insufficiency

This thesis provides novel data about clinical consequences of glucocorticoid cessation, but several questions still need to be addressed. First, absolute risk estimates of biochemical and overt adrenal insufficiency need to be assessed in relation to different treatment regimens (generic glucocorticoid type, cumulative and average daily dose and treatment duration) and tapering schedules. Second, patient characteristics such as age, sex, genetics, biomarkers, treatment indication, comorbidity, comedication use and lifestyle may be relevant to study in the context of risk factors and interaction. Future research may involve establishment of a large cohort and biobank of patients treated with glucocorticoids with collection of information from clinical examinations, questionnaires, biochemical testing and biological samples. Such a cohort could serve as a strong resource for cohort studies, genomic studies and for recruiting patients to large-scale clinical trials. Further, from a socioeconomic perspective, it would be relevant to establish a prediction score to guide which patients should be monitored for adrenal insufficiency.

Glucocorticoid use and suicide

We added new knowledge to the potential association between glucocorticoid use and suicide. Still, more studies are needed in order to ensure unbiased observed effects. A way to strengthen

the evidence is to apply different methodological approaches or to conduct studies in other settings. Nevertheless, confounding by indication or disease severity is difficult to eliminate in observational studies, and a randomized controlled trial would be poorly suited to this research question.

5. Conclusion

- Use of systemic glucocorticoids is prevalent in the Danish general population (~ 3%), and annual prevalence and incidence remain constant in the total population. The persistent widespread use underscores the need for more research in order to establish evidence-based clinical guidelines on how to manage glucocorticoid adverse effects.
- Less healthy lifestyle did not differ markedly among glucocorticoid users and never users, although the prevalence of obesity was slightly higher among glucocorticoid users than never users. These findings suggest that lifestyle may not confound observational studies on glucocorticoids to a great extent.
- Based on the parametric waiting time distribution, oral glucocorticoid prescription duration depended on percentile of the inter-arrival distribution and number of tablets dispensed. These findings provide a framework for observational studies on glucocorticoids.
- Oral glucocorticoid cessation was associated with increased risk of outcomes indicative of adrenal insufficiency. This emphasizes the need for more research to evaluate the clinical impact of glucocorticoid-induced adrenal insufficiency.
- Oral glucocorticoid use was associated with a 7-fold increased risk of suicide compared to never use among people with prior/present cancer and a 2-fold increased risk in people without cancer. Although confounding cannot be ruled out, awareness of this association may enhance early intervention and prevention.

6. English summary

Glucocorticoids are used widely and associated with adverse effects, including adrenal insufficiency and neuropsychiatric symptoms. Biochemically assessed adrenal insufficiency following oral glucocorticoid cessation is prevalent (prevalence ~ 50%). Still, the clinical importance is questioned and studies that evaluate clinical signs and symptoms of adrenal insufficiency are limited. Neuropsychiatric symptoms are common adverse effects of glucocorticoids (1% to 62%). Nevertheless, only sparse evidence exists on a potential association with suicide. In this thesis we conducted five Danish registry-based observational studies with the following aims: to quantify glucocorticoid use, to describe user characteristics, to investigate clinical consequences of adrenal insufficiency and to examine the association between glucocorticoid use and suicide.

We conducted a drug utilization study **(study I)** and found an annual prevalence of systemic glucocorticoid use of ~ 3% and an annual incidence rate of ~1.4/100 person years at risk in the Danish population each year from 1999 to 2014. Both prevalence and incidence rates were highest among women and the elderly. Despite increased use of disease-modifying drugs, all figures remained stable during 1999 to 2014 in the total population. The frequent use of systemic glucocorticoids underscores the need for more research in order to establish evidence-based clinical guidelines on how to monitor and handle glucocorticoid adverse effects.
In **study II**, we identified 30,245 responders of a health survey from 2010. We quantified and compared prevalence of lifestyle factors in systemic glucocorticoid users and never users. The prevalence of less healthy lifestyle among current users of glucocorticoids was 20% (women)-27% (men) for current smoking, 10% - 15% for unhealthy diet, 59% - 65% for inactive lifestyle, 12% - 21% for high-risk alcohol consumption and 17% - 19% for obesity. Less healthy lifestyle did not differ markedly between users and never users. Glucocorticoid users had a slightly higher prevalence of obesity than never users (1.4-fold higher in women and 1.2-fold higher in

men). This study provides information that can be used to quantify potential uncontrolled confounding by lifestyle in observational studies of glucocorticoids.

Study III was a method paper underpinning study IV. Prescription duration is not recorded in the Danish prescription registries. We therefore used the parametric waiting time distribution to estimate oral glucocorticoid prescription duration among 854,429 users identified between 1996 and 2014. Prescription duration depended on the percentile of the inter-arrival distribution and number of tablets dispensed (range: 87 to 299 days). This study provides a framework for observational studies on glucocorticoids.

In **study IV**, we identified 286,680 individuals who discontinued long-term oral glucocorticoid therapy (≥ 3 months). We investigated clinical indicators of adrenal insufficiency (gastrointestinal symptoms, hypotension, cardiovascular collapse, syncope, hyponatremia, and hypoglycemia) during and following oral glucocorticoid cessation in a self-controlled case series design. The rates of clinical indicators increased up to 2.5-fold in the glucocorticoid withdrawal period compared to before starting treatment and remained increased for some indicators (hypotension and gastrointestinal symptoms) during 7 months of follow up. Likely, these findings were attributable to adrenal insufficiency, although not confirmed by biochemical testing. Cumulative glucocorticoid dose, average daily dose, use of antibiotics (as approximation for infection), and age appeared to predict clinical symptoms and signs of adrenal insufficiency. Still, more research is needed to evaluate the clinical importance.

In **study V**, we conducted a population based matched case-control study and identified 14,028 suicide cases and 140,278 population controls. New use of oral glucocorticoids was associated with a 7-fold increased risk of suicide compared to never use in people with cancer (any time before index date) and a 2-fold increase in people without cancer. Awareness of this association may enhance early intervention and prevention.

7. Dansk resume

Glukokortikoider anvendes hyppigt og er også associeret med alvorlige bivirkninger, herunder iatrogen binyrebarkinsufficiens og neuropsykiatriske symptomer. Biokemisk defineret binyrebarkinsufficiens efter behandling med orale glukokortikoider forekommer hyppigt (prævalens ~ 50%). Den kliniske betydning er dog stadig omdiskuteret og antallet af studier, der undersøger symptomer og kliniske fund associeret med binyrebarkinssuficiens, er begrænsede. Neuropsykiatriske symptomer associeret med behandling er hyppige (1%- 62%). Alligevel eksisterer der kun sparsom evidens vedrørende en mulig association med selvmord. Denne afhandling er skrevet på baggrund af fem danske observationelle register-baserede studier med formålene at kvantificere forbruget af glukokortikoider og beskrive glukokortikoidbrugere, at undersøge kliniske konsekvenser af binyrebarkinsufficiens samt undersøge om behandling med glukokortikoider er associeret til selvmord.

I **studie I** fandt vi en årlig prævalens af systemisk glukokortikoidbrugere på ~ 3% og en årlig incidensrate på ~1.4/100 personår i den danske befolkning hvert år fra 1999 til 2014. Både prævalens og incidenrate var højest blandt kvinder og hos ældre. Selvom forbruget af sygdomsmodificerende behandling er steget, er glukokortikoidforbruget forblevet på samme niveau siden 1999. Dette understreger vigtigheden af at få etableret evidens-baserede kliniske guidelines ift. forebygning, monitorering og håndtering af glukokortikoidbivirkninger.

I **studie II** identificerede vi 30,245 personer, der havde besvaret et spørgeskema om sundhed i 2010. Vi beregnede og sammenlignede prævalens af usund livstil blandt glukokortikoidbrugere og ikke-brugere. Prævalens heraf blandt glukokortikoidbrugere var 20% (kvinder) – 27% (mænd) for rygning, 10%-15% for usund kost, 59%-65% for inaktiv livsstil, 12%-21% for høj-risiko alkoholindtagelse og 17%-19% for fedme. Usund livsstil varierede ikke væsentlig mellem glukokortikoidbrugere og ikke-brugere. Glukokortikoidbrugere have en lidt højere prævalens af

fedme end ikke-brugere (1.4 gange højere blandt kvinder og 1.2 gange højere blandt mænd). Dette studie bidrager til at kvantificere confounding fra livsstil i obsevationelle studier .

Studie III var et metodestudie, der dannede grundlag for studie IV. Receptvarighed er ikke registreret i de danske receptregistre. Vi brugte derfor den parametriske ventetidsfordeling til at estimere receptvarighed på orale glukokortikoider blandt 854,429 personer identificeret mellem 1996 og 2014. Receptvarigheden afhang af percentil for inter-arrival density og antal tabletter (87-299 dage). Studiet danner et grundlag for fremtidige observationelle studier vedrørende glukokortikoider.

I **studie IV** identificerede vi 286,680 personer, der ophørte med langtidbehandling (≥ 3 måneder) med orale glukokortikoider. Vi undersøgte kliniske indikatorer for binyrebarkinsufficiens (gastrointestinale symptomer, hypotension, kardiovaskulært kollaps, synkope, hyponatriæmi og hypoglykæmi) under behandling og efter ophør af behandling i et self-controlled case series design. Raterne for de kliniske indikatorer var forøget op til 2.5 gange i aftrapningsperioden sammelignet med før behandlingsstart og forblev forøget for nogle af de kliniske indikatorer (hypotension og gastrointestinal symptoms) igennem 7 måneders follow up. Dette skyldes antageligvis binyrebarkinsufficiens, omend vi ikke havde mulighed for at verificere det ved stimulationstest. Brug af antibiotika (som indikator for infektion), kummuleret glukokortikoiddosis, gennemsnitlig dagelige dosis samt alder var risikofaktorer for kliniske manifest binyrebarkinsufficiens. Der er behov for mere forskning på området for at undersøge de kliniske implikationer af iatrogen binyrebarkinsufficiens.

Studie V var et populations-baseret case-kontrol studie med 14,028 cases (selvmord) og 140,278 kontroller. Orale glukokortikoider var associeret med 7-gange højere risiko for selvmord blandt personer med cancer og en 2-gange højere risiko for selvmord i personer uden cancer sammelignet med ikke-brugere. Kendskab til denne association øger måske muligheden for tidlig intervention og forebyggelse.

8. References

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9. List of appendices

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Appendix I

Paper I

Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark

Kristina Laugesen[1], Jens Otto Lunde Jørgensen[2], Irene Petersen[1,3] and **Henrik Toft Sørensen[1]**

[1]Department of Clinical Epidemiology, [2]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus N, Denmark, and [3]Department of Primary Care and Population Health, University College London, London, UK

Correspondence should be addressed to K Laugesen
Email
Kristina.laugesen@clin.au.dk

Abstract

Objective: Glucocorticoid treatment of inflammatory disorders is associated with significant adverse effects related to glucocorticoid excess as well as adrenal insufficiency. This necessitates awareness of its use. We therefore investigated trends in systemic glucocorticoid use as well as morbidity and comedications among users.
Design: Cross-sectional drug utilisation study.
Methods: We conducted a population-based study of 926,314 users of systemic glucocorticoids (oral and injectable formulations) from 1999 to 2014 using Danish nationwide registries. We computed annual prevalence and incidence of systemic glucocorticoid use and prevalence of comedications and morbidity. Further, we assessed the annual amount of disease-modifying drug use.
Results: Of the 926,314 users of systemic glucocorticoids, 54% were female and median age at first-time use was 55 years. The annual prevalence was ≈ 3%, while the incidence was ≈ 1.4/100 person years (p-y). Both figures remained constant from 1999 to 2014. In the elderly, the annual prevalence was 6.7–7.7% (60–79 years of age) and 9.7–11% (≥80 years of age). Incidence increased among persons aged ≥80 years from 3.0/100 p-y in 1999 to 3.6/100 p-y in 2014. Concomitantly, the annual amount of for example methotrexate, azathioprine and tumour necrosis factor (TNF)-alpha agents increased and new biological agents emerged. The most frequent comedications were antibiotics (49%), cardiovascular drugs (38%) and NSAIDs (37%).
Conclusions: Our findings confirm a widespread use of systemic glucocorticoids, especially in the elderly, which prevails despite increased use of disease-modifying drugs. The continuously prevalent use of glucocorticoid use constitutes a challenge for the endocrine community.

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Introduction

Synthetic glucocorticoids are potent anti-inflammatory drugs introduced into clinical practice in the 1950s to treat rheumatoid arthritis (RA) (1). Since then, glucocorticoids have proven useful in the treatment of numerous conditions, including other rheumatic diseases, asthma, chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (2, 3, 4, 5, 6).

Serious adverse effects, however, are associated with glucocorticoid use, including features of iatrogenic Cushing's syndrome, diabetes (7) and osteoporosis (8). Moreover, glucocorticoid use and discontinuation increases the risk of adrenal insufficiency (9, 10). In addition, studies have reported increased risk of cardiovascular diseases and venous thromboembolism (11, 12, 13, 14) as well as neuropsychiatric symptoms and disorders (15).

Several studies from Western countries have estimated the prevalence of glucocorticoid use to range between

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0.5% and 17% depending on calendar year, setting and methodology (16, 17, 18, 19, 20, 21, 22).

Updated and population-based data on glucocorticoid utilisation and knowledge on comedication use and morbidity remain important. Therefore, we examined annual prevalence and incidence of systemic glucocorticoid use (oral and injectable formulations) and described the prevalence of comedications and morbidity among users.

Materials and methods

Setting

Denmark provides its entire population with tax-supported healthcare, guaranteeing access to primary and secondary care free-of-charge. A unique personal civil registration number is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous individual-level linkage of relevant registries (23).

Systemic glucocorticoids, disease-modifying drugs and comedications

We used the Danish National Prescription Registry to identify all persons in the Danish population who redeemed prescriptions for systemic glucocorticoids (oral and injectable formulations) between 1 January 1999 and 31 December 2014 (24). The Danish National Prescription Registry records information on all prescriptions redeemed in Denmark on an individual level, including the civil registration number of the patient, the medication classification code (Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization) and date of dispensing (24). A limitation of the Danish National Prescription Registry is that medication provided directly by the hospital sector, which includes most disease-modifying drugs for the treatment of the underlying conditions, is not captured. We therefore used Medstat (http://www.medstat.dk/en) to retrieve information on annual amount of conventional disease-modifying drug and biological disease-modifying drug use in the primary health care sector and in the hospital sector. The publicly available Medstat website provides aggregated Medstat statistics that are complete from 1999 onwards and allows for extraction of annual amount used (primary healthcare and hospital sector separately and in a combined total) (25). The amount is expressed in defined daily doses (DDDs) developed by WHO and defined as the assumed average maintenance daily dose of a drug used for its main indication in adults (https://www.whocc.no/ddd/definition_and_general_considera/). Methotrexate and rituximab are not expressed in DDD but in grams (active substance). Codes for systemic glucocorticoids, disease-modifying drugs and comedications are provided in Supplementary Tables 1 and 2 (see section on supplementary data given at the end of this article).

Morbidity

Information on morbidity leading to hospital contacts (hospitalisations and outpatient clinic visits) was obtained from the Danish National Patient Registry (DNPR) (26). The DNPR has captured information on all inpatient stays at Danish public hospitals since 1977 and on all outpatient clinic and emergency room visits at public hospitals since 1995. Data recorded in the DNPR include the patient's civil registration number, dates of admission and discharge or outpatient visits, and up to 20 discharge diagnoses for each contact, classified according to the Eighth Revision of the International Classification of Diseases (ICD-8) until 1994 and the Tenth Revision (IDC-10) thereafter (26). We assessed patients' history of hospital contacts for pulmonary, cardiovascular, gastrointestinal, endocrine, neurological, rheumatic, renal and dermatological disease, as well as for cancer (Supplementary Table 3 for ICD codes).

Statistical analyses

We first described systemic glucocorticoid users at the time of initial use, including sex, age and generic type of systemic glucocorticoid.

Second, we computed annual prevalence and incidence of systemic glucocorticoid users from 1999 to 2014 in the overall population and stratified by sex and age group (0–19, 20–39, 40–59, 60–79 and ≥80 years). Annual prevalence was defined as the number of persons who redeemed at least one prescription for a systemic glucocorticoid each year divided by the number of people in the population on January 1st of each year. The incidence was calculated as number of initiators (defined as persons who redeemed a prescription for a systemic glucocorticoid without any preceding prescriptions up to 5 years before) divided by person time at risk. We used a Poisson regression model to examine the prevalence and incidence ratios by sex, age group and calendar year. When comparing age groups, we adjusted for sex and calendar year;

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Table 1 Sex and age distribution of persons at first time use of systemic glucocorticoid and type of glucocorticoid prescription redeemed initially, Denmark 1999–2014.

	Number of persons (%)
Total	926,314 (100)
Sex	
Female	498,021 (54)
Male	427,793 (46)
Missing	500 (0.05)
Age (years)	
0–19	38,875 (4.2)
20–39	191,034 (21)
40–59	305,634 (33)
60–79	302,759 (33)
≥80	87,511 (9.5)
Missing	501 (0.05)
Type of glucocorticoid	
Prednisolone	487,333 (53)
Hydrocortisone	3163 (0.34)
Dexamethasone	2042 (0.20)
Betamethasone	231,090 (25)
Prednisone	42,684 (4.6)
Triamcinolone	28,214 (3.1)
Methylprednisolone	131,788 (14)

when comparing sex, we adjusted for age group and calendar year, and when comparing calendar years, we adjusted for sex and age group. Third, we utilised data on the annual amount (DDD) of conventional disease-modifying drug and biological disease-modifying drug used in the primary sector and hospital sector combined.

Finally, we constructed contingency tables based on history of comedication use and morbidity in the cohort. We assessed comedications ≤1 year before first-time use of a systemic glucocorticoid and morbidity at any time before first-time use.

All statistical analyses were conducted using SAS, version 9.4.

Results

We identified 926,314 users (54% female) of systemic glucocorticoids. Median age at first-time use was 55 years (interquartile range: 39–69 years) (Table 1). The most frequent generic type of systemic

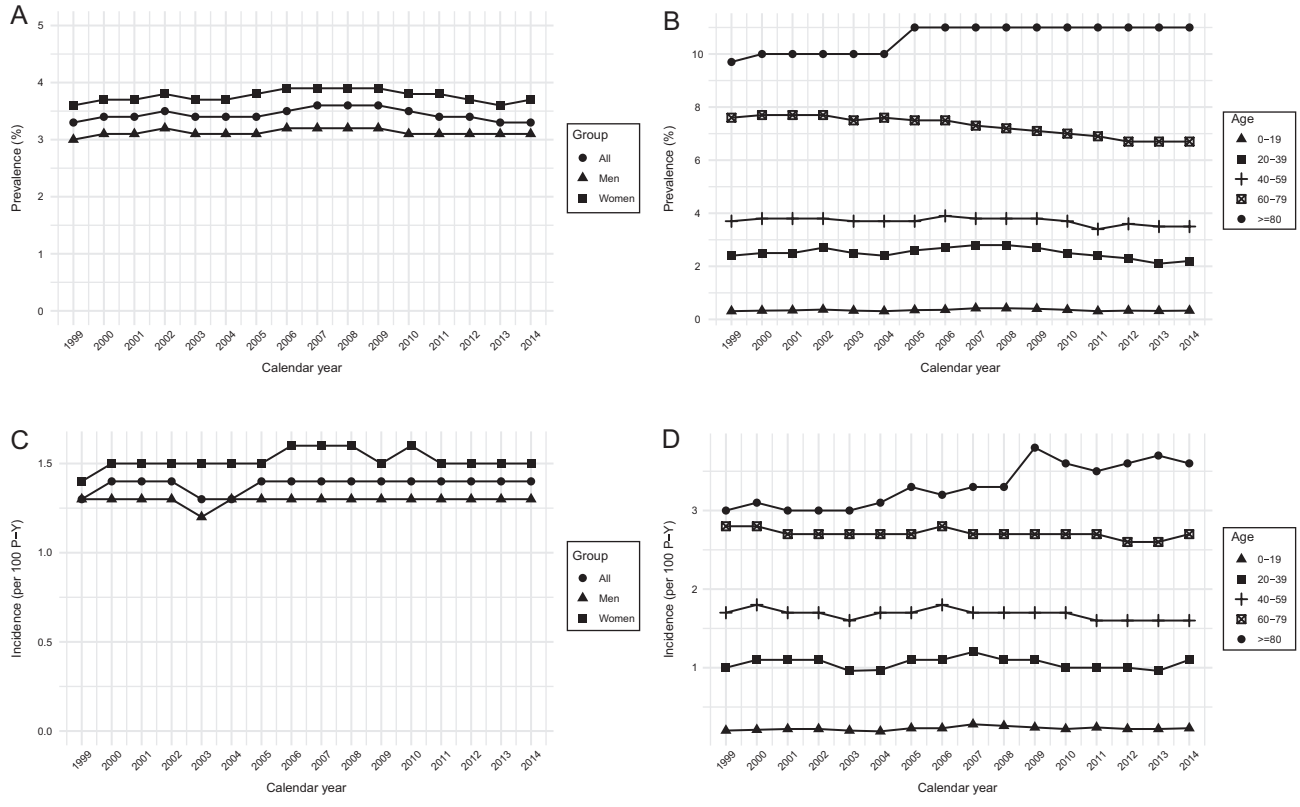

Figure 1
Prevalence (%) and incidence (per 100 person years) of systemic glucocorticoid use, Denmark 1999–2014. (A) Prevalence (%) in the overall population and stratified by sex, (B) prevalence stratified by age group, (C) incidence (per 100 person years) in the overall population and stratified by sex and (D) incidence (per 100 person years) stratified by age group.

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Table 2 Prevalence ratios and incidence ratios (with 95% confidence intervals (CIs)) of systemic glucocorticoid use according to age, sex and calendar year, modelled using a multivariable Poisson regression.

	Adjusted† prevalence ratio with 95% CI	Adjusted† incidence ratios with 95% CI
Sex		
Men	1 (ref)	1 (ref)
Women	1.10 (1.10–1.11)	1.10 (1.10–1.11)
Age (years)		
0–19	1 (ref)	1 (ref)
20–39	7.09 (7.04–7.15)	4.65 (4.60–4.70)
40–59	10.5 (10.5–10.6)	7.37 (7.30–7.44)
60–79	20.5 (20.3–0.36)	11.9 (11.8–12.0)
≥80	29.7 (29.5–30.0)	14.3 (14.1–14.5)
Calendar year		
1999	1 (ref)	1 (ref)
2000	1.03 (1.03–1.04)	1.04 (1.03–1.05)
2001	1.03 (1.03–1.04)	1.02 (1.01–1.03)
2002	1.05 (1.04–1.06)	1.02 (1.01–1.03)
2003	1.01 (1.00–1.01)	0.96 (0.95–0.97)
2004	1.01 (1.01–1.02)	0.98 (0.97–0.99)
2005	1.03 (1.02–1.03)	1.02 (1.01–1.04)
2006	1.05 (1.04–1.06)	1.04 (1.03–1.05)
2007	1.05 (1.04–1.06)	1.04 (1.03–1.05)
2008	1.04 (1.04–1.05)	1.04 (1.03–1.05)
2009	1.03 (1.03–1.04)	1.02 (1.01–1.03)
2010	1.00 (1.00–1.01)	1.02 (1.01–1.03)
2011	0.99 (0.98–0.99)	1.01 (1.00–1.02)
2012	0.96 (0.95–0.97)	0.98 (0.97–0.99)
2013	0.94 (0.94–0.95)	0.97 (0.96–0.98)
2014	0.94 (0.94–0.95)	1.00 (1.00–1.03)

†When comparing age groups, we adjusted for sex and calendar year; when comparing sex, we adjusted for age group and calendar year and when comparing calendar years, we adjusted for sex and age group.

glucocorticoid prescribed was prednisolone (53%), followed by betamethasone (25%) and methylprednisolone (14%) (Table 1).

Systemic glucocorticoid and disease-modifying drug use

The prevalence of systemic glucocorticoid use was approximately 3% each year (Fig. 1A). From 1999 to 2014 we observed a 6% decrease in annual prevalence (adjusted prevalence ratio: 0.94 (95% CI: 0.94–0.95) (Table 2)) The incidence remained constant at 1.4/100 p-y from 1999 to 2014 (Fig. 1C) (adjusted incidence ratio of 1.00 (95% CI: 1.00–1.03) (Table 2)) Prevalence and incidence were higher in women than in men (Fig. 1). Among the elderly population, the prevalence was 6.7–7.7% and the incidence was 2.6/100 p-y–2.8/100 p-y in the 60- to 79-year age group, and the prevalence was

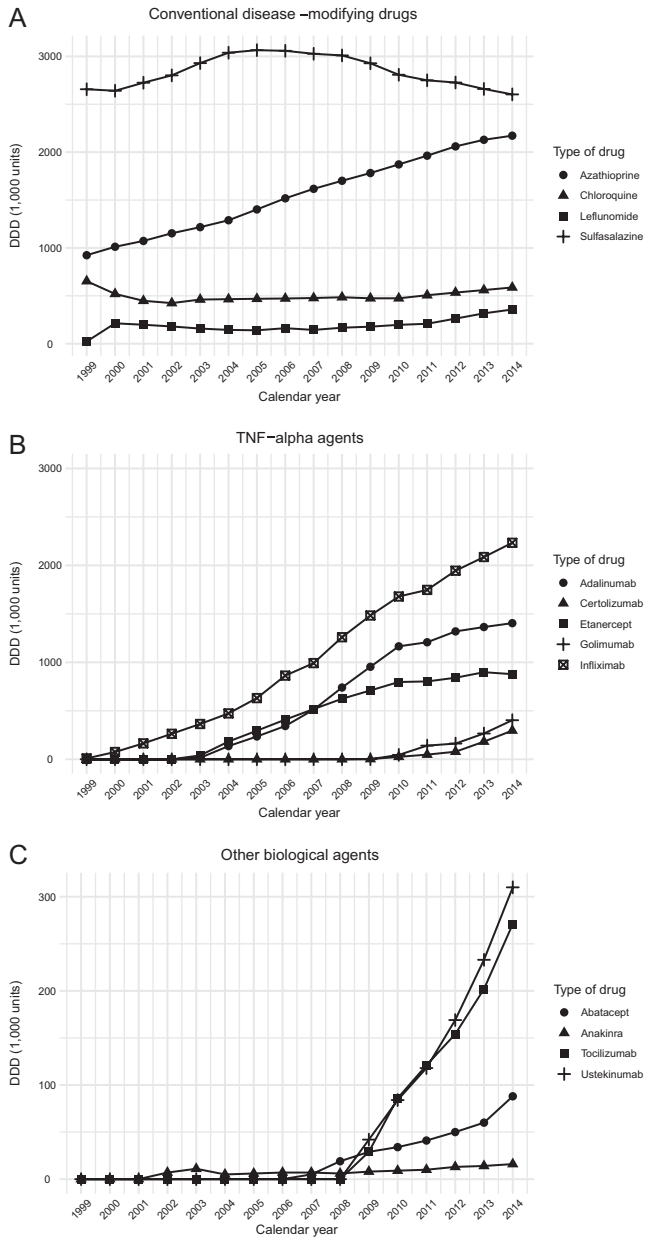

Figure 2
Amount of annual disease-modifying drugs use expressed in defined daily dose (DDD), Denmark 1999–2014.
(A) Conventional disease-modifying drugs. (B) Tumour necrosis factor (TNF)-alpha agents. (C) Other biological agents. Methotrexate and rituximab are not expressed in DDD but grams (active substance). Use of methotrexate increased from 2007 g in 1999 to 6225 g in 2014. Use of rituximab increases from 1000 g in 2004 to 10,000 g in 2014.

9.7–11% and the incidence was 3.0/100 p-y–3.6/100 p-y among persons aged ≥80 years (Fig. 1). The incidence increased slightly among persons aged ≥80 (Fig. 1D).

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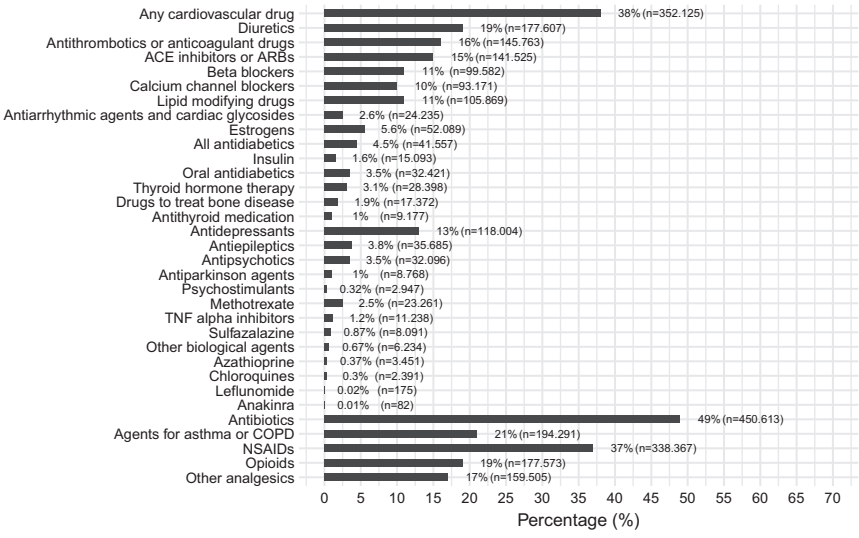

Figure 3
Frequency of comedication use assessed ≤1 year before initial use of a systemic glucocorticoid.

From 1999 to 2014, we observed an increase in use of disease-modifying drugs to treat the underlying inflammatory diseases, including methotrexate, azathioprine, tumour necrosis factor (TNF)-alpha agents (Fig. 2), and rituximab, abatacept, tocilizumab and ustekinumab (Fig. 2C).

Use of comedications

Prescription drugs redeemed most frequently ≤1 year prior to initial use of a systemic glucocorticoid were: antibiotics (450,613 persons (49%)), agents used to treat cardiovascular conditions (352,125 persons (38%)), NSAIDs (338,367 persons (37%)), agents used to treat asthma/COPD (194,290 persons (21%)), opioids (177,573 persons (19%)), non-opioid analgesics (159,505 persons (17%)) and antidepressants (117,666 persons (13%)) (Fig. 3).

Morbidity

Assessment of morbidity leading to hospital contacts at any time prior to first-time use of a systemic glucocorticoids showed that cardiovascular and pulmonary diseases and cancer were prevalent: 172,400 (19%) had cardiovascular disease including hypertension in 90,721 persons (9.8%), ischaemic heart disease in 22,825 persons (2.5%), peripheral artery disease (PAD) present in 17,043 persons (1.8%) and stroke present in 39,095 persons (4.2%). 158,658 persons (17%) had a pulmonary disease, with COPD present in 58,114 persons (6.3%). As well, 122,629 persons (13%) had a recorded cancer diagnosis (Fig. 4).

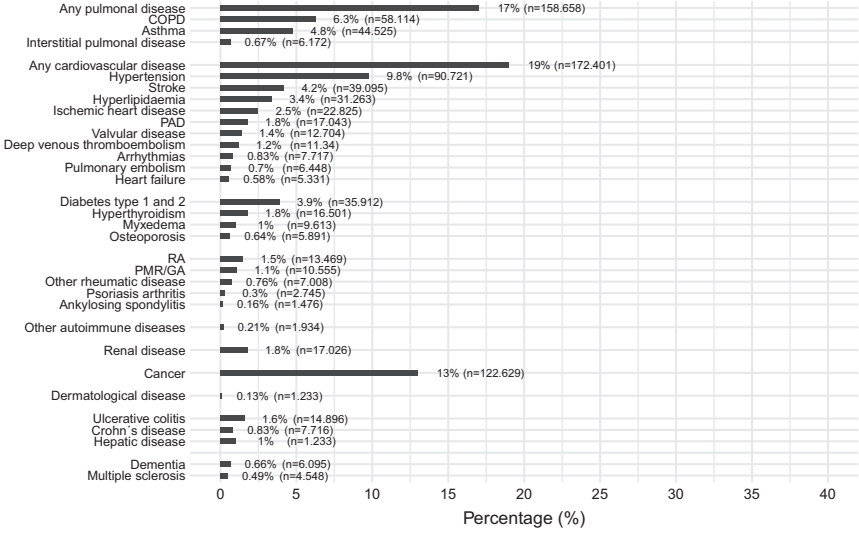

Figure 4
Frequency of morbidity assessed any time before initial use of a systemic glucocorticoid. COPD, chronic pulmonary disease. PAD, peripheral artery disease; PMR/GCA, polymyalgia rheumatica/giant cell arthritis; RA, rheumatoid arthritis.

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Discussion

In this 15-year nationwide study, we found a high (≈3%) annual prevalence and incidence (≈1.4/100 p-y) of systemic glucocorticoid use. Glucocorticoid use was more prevalent in the elderly, with prevalence reaching 11% in persons aged ≥80 years and a slightly increase in incidence from 1999 to 2014. As expected, the prevalence of comedication and morbidity was high prior to glucocorticoid use.

Prior studies from the United Kingdom (UK) (1989–2008), the United States of America (USA) (1999–2008), Iceland (1995–1996), Denmark (1999–2015) and France (2007–2014) have estimated the prevalence of glucocorticoid use to range between 0.5 and 17% depending on calendar year, setting and methodology (16, 17, 18, 19, 20, 21, 22). The study from the USA (20) and the UK (19) reported prevalence of oral glucocorticoid use at approximately 1%, and this lower figure may partly be explained by methodological differences. First, our study investigated all systemic glucocorticoids (oral and injectable formulations) as opposed to only oral glucocorticoids (19, 20). Second, we estimated the annual prevalence while previous studies estimated point prevalence (19, 20). Third, the UK study investigated long-term use (≥3 months) (19). The study from France reported an annual prevalence of 17% (22). Altogether, glucocorticoid use seems to vary across countries. Compared to the prior Danish study (21), which lacked individual-level data, this current study added important information on incidence use, comedication and morbidity.

Despite improved awareness of adverse effects and increased use of more targeted treatments, glucocorticoid use remains a mainstay of therapy of many inflammatory diseases. Therefore, the clinical challenge of how to manage and prevent adverse effects of glucocorticoids continues. This involves for example prevention and treatment of glucocorticoid-induced osteoporosis, glucocorticoid-induced hyperglycaemia and diabetes and guidelines about the assessment and management of adrenal insufficiency during and after glucocorticoid treatment (8, 11, 13, 14, 21). This challenge may increase as incident use among elderly increases. In addition, several clinical concerns arise when morbidity and comedication use is high. Concomitant use of NSAIDs and glucocorticoids increases risk of gastrointestinal haemorrhage (37% in our study) (27) and prior/current psychiatric disease increases risk of psychiatric adverse effects (13% are taking antidepressants prior to glucocorticoid initiation) (15). Also, special caution is mandated in patients with incipient and overt diabetes (4.5% are taking oral antidiabetics or insulin prior to glucocorticoid initiation) (7).

We conducted a population-based nationwide study with complete data on medication use, but our study also has limitations. First, data on the use of systemic glucocorticoids and comedications relied on redeemed prescription as an approximation of use, without evaluation of adherence. Second, when patients are treated in hospital setting, pharmacological treatment is so far not retrievable at an individual level in our national registries. Third, we were able to capture morbidity only in hospital settings (inpatient and outpatient clinics), excluding primary health care. In addition, we were not able to identify the indication for glucocorticoid treatment. Moreover, the validity of discharge diagnoses recorded in the DNPR is heterogeneous (26). Finally, we did not compare medication use and morbidity among systemic glucocorticoid users to people not treated with glucocorticoids.

In conclusion, our findings suggest a continuously widespread use of systemic glucocorticoids, especially in the elderly. This calls for a more comprehensive approach to prevent complications to glucocorticoid therapy, including the risk of adrenal insufficiency, which should be spearheaded by the endocrine community.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-19-0305.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement
K L, I P, J O L J and H T S made primary contributions to conception of the study and wrote the manuscript. K L performed statistical analyses. K L, I P, J O L J and H T S contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript. H T S is the guarantor for this study.

Ethics approval
This study was approved by the Danish Data Protection Agency (record number: 2016-051-000001, serial number 448).

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Supplementary Table 1. Anatomical Therapeutic Chemical classification system of the World Health Organization (ATC codes) for systemic glucocorticoids.

Drug	ATC code
Systemic glucocorticoids	H02AB
Methylprednisolone	H02AB04
Prednisolone	H02AB06
Hydrocortisone	H02AB09
Dexamethasone	H02AB02
Prednisone	H02AB07
Triamcinolone	H02AB08
Betamethasone	H02AB01

Supplementary Table 2. Comedications. Anatomical Therapeutic Chemical classification system of the World Health Organization (ATC codes) and Nordic Medico-Statistical Committee's Classification of Surgical Procedures (NCSP).

Drug	ATC code/NCSP code
Any cardiovascular drug	C
Diuretics	C03
Antithrombotics/anticoagulant drugs	B01
ACE inhibitors and ARBs	C09
Beta blockers	C07
Calcium channel blockers	C08
Antiarrhytmic agents and cardiac glycosides	C01A, C01B
Estrogens	G03C
Antidiabetics	A10
Insulin	A10A
Oral antidiabetics	A10B
Thyroid hormone medication	H03A
Antithyroid medication	H03B
Antibiotics	J01
Azathioprine	L04AX01
Sulfazalazine	A07EC01
Leflunomid	L04AA13
Methotrexate	L01BA01, L04AX03, BWHA115
Etanercept	L04AB01, BOHJ18A2
Adalimumab	L04AB04, BOHJ18A3
Certolizumab	L04AB05, BOHJ18A5
Golimumab	L04AB06, BOHJ18A4
Infliximab	L04AB02, BOHJ18A1
Rituximab	L01XC02, BOHJ11
Abatacept	L04AA24, BOHJ18C1
Ustekinumab	L04AC05, BOHJ18B3
Tocilizumab	L04AC07, BOHJ18B2
Anakinra	L04AC03, BOHJ18B1
Chloroquine	P01BA02
Non-steroidal anti-inflammatory drugs	M01A
Drugs to treat bone disease	M05
Opioids	N02A
Other analgesics	N02B
Antiepileptics	N03
Antiparkinson agents	N04
Antipsychotics	N05A
Antidepressants	N06A
Psychostimulants	N06B
Asthma/COPD	R03

Supplementary Table 3. Morbidity. *Eighth Revision* of the *International Classification of Diseases* (ICD-8) until 1994 and the *Tenth Revision* (IDC-10) codes.

Disease	ICD-10	ICD-8
Pulmonary diseases		
Asthma	DJ45, DJ46	493
Chronic obstructive pulmonary disease	DJ41, DJ42, DJ43, DJ44	491, 492
Interstitial lung disease	DJ60-DJ70, DJ82, DJ84	515, 516, 517
Other respiratory diseases (respiratory insufficiency, pulmonary infections, pulmonary oedema, pleural disease)	DJ09, DJ10, DJ11,D J13, DJ14, DJ15, DJ16, DJ17, DJ18, DJ20, DJ21, DJ22, DJ 40, DJ47, DJ81, DJ85, DJ 90-94, DJ96	470, 471, 472, 480, 481, 482, 483, 484, 485, 486, 490, 510, 511, 512, 513, 514, 518, 519
Cardiovascular diseases		
Ischaemic heart disease	DI20, DJ21, DI25	410, 411, 412, 413, 414
Arrhythmias	DI47-DI49	427.90 -97
Heart failure	DI500-3, DI508, DI509, DI110, DI130, DI32, DI420, DI426-9	427.09-427.11, 427.19, 428.99, 782.49
Valvular diseases	DI05-06, DI34-35, DI390, DI391, DI511A	394, 395
Stroke	DI60, DI61, DI63, DI64, DG45.9	430, 431, 433-435
Hypertension and hypertensive heart disease	DI10, DI11, DI12, DI13, DI14, DI15	400, 401, 402, 403, 404
Peripheral artery disease	DI70	440.20-29, 445
Hyperlipidaemia	DE78.0	27200
Pulmonary embolism	DI26	450.99
Deep venous thrombosis	DI80.1-3	451.00
Endocrine diseases		
Diabetes, types 1 and 2	DE10 DE11	249 250
Hyperthyroidism	DE05	242
Myxedema	DE02 DE03	244
Osteoporosis	DM80-M82	72309
Rheumatic diseases		
Polymyalgia rheumatica/ Giant cell arthritis	DM315, DM316, DM35.3	446.30, 446.31, 446.39
Rheumatoid arthritis	DM05, DM06	712.19, 712.29, 712.39, 712.59
Psoriasis arthritis	DM07.0-M07.3	696.09
Ankylosing spondylitis	DM45	712.49
Other rheumatic diseases	DL94.0, L94.1 (Sclerodermia)	734.00, 734.02, 734.03, 734.04
	DM35.1 (mixed connective disease)	734.08, 734.09 (Sclerodermia)
	DM34.0-9 (LE), DM32, DG73.7C,	695.49 (LE), 734.19 (SLE) 716.09,
	DN08.5A, DN16.4B (SLE), DM33	716.19
	(polymyositis/dermatomyositis).	(polymyositis/dermatomyositis),
	DM35.0, G73.7A (Sjögren's	734.90 (Sjögren's syndrome)

	syndrome)	446.29 (Wegener´s granulomatosis)
	DM30.0 (Polyarteritis nodosa)	287.09 (Schonlein henochs purpura)
	DM31.3 (Wegener´s granulomatosis)	446.09 (Vasculitis/arteritis)
	DD69.0B, DM31.0B (Schonlein henochs purpura)	
	DI77.6, DL95 (Vasculitis/arteritis)	
Gastrointestinal diseases		
Crohn's disease	DK50	563.01, 563.02, 563.09
Colitis ulcerosa	DK51	563.19
Hepatic diseases	DK70.1-9, DK71, DK72, DK73, DK74, DK75, DB18	571, 573
Cancer	C00-97	140-209
Dermatological diseases	L10.0, L10.2, L10.4, L12.0, L13.0,	694 , 693.00, 693.08, 693.09, 684.00
Pemphigus / pemphigoid dermatitis herpetiformis	L00, L51.2, L11, L13,14	
Bullous disorders		
Renal diseases	N00, N01, N03, N04, N05 N06, N07, N08, N11, N14, N15, N16, N18, N19, N26, N27, I12. I13, I15.0, I15.1, E10.2, E11.2, E14.2, Q61.1-Q61.4	249.02, 250.02, 403, 404, 580-584, 590.09, 593.20, 753.10-753.19
Other autoimmune diseases	DD59.0	283.90
	DD59.1 (autoimmune hemolytic anemia)	283.91 (autoimmune hemolytic anemia)
	DD69.3 (Idiopathic thrombocytopenic purpura)	287.10 (Idiopathic thrombocytopenic purpura)
	DK75.4 (autoimmune hepatitis)	571.93 (autoimmune hepatitis)
Neurological diseases		
Multiple sclerosis	DG35	340
Dementia	DF00, DF01, DF02, DF03, DF05.1, DF1x.73 (DF10.73-DF19.73).	094.19, 290.09 – 290.11, 290.18-290.19, 292.09
	DG23.1, DG31.0, DG31.1, DG31.8B, DG31.8E, DG30	293.09, 293.19

Paper II

Appendix II

BMJ Open

Prevalence of lifestyle characteristics in glucocorticoid users and non-users: a Danish population-based cross-sectional study

Kristina Laugesen ,[1] Irene Petersen,[1,2] Lars Pedersen,[1] Finn Breinholt Larsen,[3] Jens Otto Lunde Jørgensen,[4] Henrik T Toft Sørensen[1]

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[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[2]Department of Primary Care and Population Health, University College London Medical School, London, UK
[3]Public Health and Quality Improvement, Aarhus, Denmark
[4]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Correspondence to
Ms Kristina Laugesen;
kristina.laugesen@clin.au.dk

ABSTRACT

Objectives Lifestyle may affect observed associations between glucocorticoid use and adverse events. This study aimed to investigate whether lifestyle differ according to use of systemic glucocorticoids.

Design Population-based cross-sectional study.

Setting The Central Denmark Region.

Participants 30 245 adults (≥25 years of age) who participated in a questionnaire-based public health survey in 2010.

Outcome measures Systemic glucocorticoid use was categorised as never use, current use (prescription redemption ≤90 days before completing the questionnaire), recent use (prescription redemption 91–365 days before completing the questionnaire), former use (prescription redemption >365 days before completing the questionnaire) and according to cumulative dose expressed in prednisolone equivalents (<100, 100–499, 500–999, 1000–1999, 2000–4999, ≥5000 mg). We computed the prevalence of lifestyle factors (body mass index, smoking, alcohol intake, physical activity and dietary habits) according to glucocorticoid use. We then estimated age-adjusted prevalence ratios (aPRs) and 95% CIs, comparing the categories of glucocorticoid users versus never users. All analyses were stratified by sex.

Results Of the 30 245 participants (53% women, median age 53 years), 563 (1.9%) were current users, 885 (2.9%) were recent users, 3054 (10%) were former users and 25 743 (85%) were never users. Ever users of glucocorticoids had a slightly higher prevalence of obesity than never users (18% vs 14%, aPR=1.4, 95% CI 1.2 to 1.5 in women and 17% vs 15%, aPR=1.2, 95% CI 1.1 to 1.4 in men). In women, ever users of glucocorticoids had a slightly lower prevalence of high-risk alcohol consumption compared with never users (17% vs 20%, aPR=0.8, 95% CI 0.7 to 1.0). Smoking, diet and physical activity did not differ substantially according to use of glucocorticoids.

Conclusion Our study provides a framework for quantifying potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids.

Strengths and limitations of this study

- ► Lifestyle may confound the observed associations between glucocorticoid use and adverse events in observational studies.
- ► This large population-based study may guide assessment of the association between lifestyle and glucocorticoid use when data on lifestyle factors are not available.
- ► The response rate to the questionnaire was 67% and it is possible that the respondents had a different health profile than non-respondents. To minimise bias due to non-response, we used a weighting method developed for this particular survey.
- ► Information on lifestyle factors was based on self-reported data, which can be prone to misclassification.
- ► As this study had a cross-sectional design, it was unable to evaluate whether lifestyle predicts glucocorticoid use or vice versa.

BACKGROUND

Since their introduction in the 1950s, glucocorticoids have been prescribed to treat numerous inflammatory conditions and are widely used with annual prevalence of 3% in Denmark.[1 2] However, glucocorticoids also are associated with several adverse events, including truncal obesity, hypertension, dyslipidaemia,[3] cardiac disease,[4–7] venous thromboembolism,[6] diabetes mellitus,[8] psychiatric illnesses[9] and osteoporosis.[10]

Lifestyle factors, including smoking, alcohol consumption, physical inactivity and obesity, are well-described risk factors for many adverse events associated with glucocorticoids.[11–14] Moreover, prior studies have found that unhealthy lifestyle is abundant in populations with diseases frequently treated with glucocorticoids, for example, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease and rheumatoid arthritis, and also associated with severity of disease development.[15–21] Thus, lifestyle factors potentially can confound observed associations between glucocorticoid exposure and adverse events. Pharmacosurveillance of glucocorticoids is often performed

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Table 1 Prevalence of lifestyle factors according to glucocorticoid use in women and men

	Ever use	Current use	Recent use	Former use	Never use	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Women						
All	2460 (100)	301 (100)	489 (100)	1670 (100)	13 485 (100)	15 945 (100)
Median age (range), years	61 (25–98)	66 (26–94)	58 (25–98)	58 (25–98)	52 (25–101)	53 (25–101)
Body mass Index						
<18.5	58 (2.7)	17 (5.4)	15 (3.9)	26 (1.8)	310 (2.6)	368 (2.6)
18.5–24	1113 (45)	126 (38)	218 (44)	769 (46)	7203 (54)	8316 (52)
25–29	717 (28)	89 (31)	120 (23)	508 (29)	3718 (27)	4435 (27)
≥30	444 (18)	50 (17)	105 (22)	289 (17)	1862 (14)	2306 (14)
Missing	128 (6.3)	19 (8.2)	31 (7.3)	78 (5.6)	392 (3.3)	520 (3.8)
Smoking						
Current	552 (22)	66 (20)	112 (22)	374 (22)	2744 (21)	3296 (21)
Former	765 (30)	111 (35)	148 (30)	506 (29)	3913 (28)	4678 (28)
Never	1047 (44)	107 (40)	206 (42)	734 (45)	6535 (49)	7582 (48)
Missing	96 (4.2)	17 (4.6)	23 (5.3)	56 (3.9)	293 (2.4)	389 (2.7)
Diet						
Unhealthy	191 (7.9)	29 (9.7)	36 (7.6)	126 (7.7)	852 (6.8)	1043 (7.0)
Reasonably healthy	1425 (58)	181 (62)	280 (57)	964 (57)	8021 (60)	9446 (59)
Healthy	730 (29)	72 (22)	143 (27)	515 (31)	4234 (30)	4964 (30)
Missing	114 (5.2)	19 (5.5)	30 (7.6)	65 (4.4)	378 (3.2)	492 (3.5)
Alcohol intake						
Low-risk consumption	1832 (76)	231 (80)	376 (77)	340 (74)	10 146 (75)	11 978 (75)
High-risk consumption	458 (17)	43 (12)	75 (13)	1225 (18)	2730 (20)	3188 (19)
Missing	170 (7.9)	27 (8.1)	38 (9.2)	105 (7.5)	609 (4.7)	779 (5.2)
Participation in regular leisure time physical activity						
No	1179 (49)	171 (59)	245 (53)	763 (46)	5853 (44)	7032 (45)
Yes	1209 (48)	121 (39)	228 (44)	860 (50)	7354 (54)	8563 (53)
Missing	72 (3.2)	9 (2.3)	16 (3.2)	47 (3.3)	278 (2.3)	350 (2.4)
Men						
All	2042 (100)	262 (100)	396 (100)	1384 (100)	12 258 (100)	14 300 (100)
Median age (range), years	61 (25–98)	65 (28–94)	57 (25–88)	59 (25–100)	53 (25–99)	54 (25–100)
Body mass Index						
<18.5	21 (1.3)	6 (4.0)	6 (1.8)	9 (5.3)	40 (0.04)	61 (0.6)
18.5–24	644 (33)	88 (34)	128 (34)	428 (32)	4572 (39)	5216 (38)
25–29	959 (46)	116 (41)	188 (46)	655 (47)	5566 (44)	6525 (44)
≥30	365 (17)	47 (19)	65 (14)	253 (18)	1864 (15)	2229 (15)
Missing	53 (2.8)	5 (2.2)	9 (3.5)	39 (2.6)	216 (1.7)	269 (1.9)
Smoking						
Current	518 (27)	64 (27)	98 (26)	356 (27)	3072 (27)	3590 (27)
Former	843 (38)	126 (43)	157 (36)	560 (38)	4022 (30)	4865 (31)

Continued

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Table 1 Continued

	Ever use	Current use	Recent use	Former use	Never use	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Never	630 (32)	67 (27)	132 (35)	431 (32)	4968 (42)	5598 (41)
Missing	51 (2.8)	5 (2.2)	9 (3.2)	37 (2.8)	196 (1.6)	247 (1.8)
Diet						
Unhealthy	310 (15)	47 (15)	63 (15)	200 (15)	1906 (16)	2216 (16)
Reasonably healthy	1301 (64)	159 (62)	253 (65)	889 (64)	7874 (64)	9175 (64)
Healthy	342 (15)	38 (13)	68 (16)	236 (15)	2069 (17)	2411 (16)
Missing	89 (5.1)	18 (9.3)	12 (3.2)	59 (4.9)	409 (3.4)	498 (3.6)
Alcohol intake						
Low-risk consumption	1489 (72)	184 (70)	293 (73)	1012 (72)	9231 (75)	10720 (75)
High-risk consumption	443 (22)	62 (21)	81 (19)	300 (22)	2588 (21)	3031 (21)
Missing	110 (6.7)	16 (8.7)	22 (7.6)	72 (6.0)	439 (3.5)	549 (4.0)
Participation in regular leisure time physical activity						
No	1128 (54)	82 (65)	214 (52)	739 (52)	6265 (50)	7393 (51)
Yes	874 (44)	175 (32)	171 (45)	621 (46)	5791 (48)	6665 (48)
Missing	40 (2.2)	5 (2.6)	11 (2.7)	24 (2.0)	202 (1.6)	242 (1.7)

Percentages are weighted. Never use: persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire. Ever use: at least one redemption of a prescription for a systemic glucocorticoid before completing the questionnaire. Current use: redemption of a prescription for a systemic glucocorticoid ≤90 days before completing the questionnaire. Recent use: redemption of a prescription for a systemic glucocorticoid 91–365 days before completing the questionnaire. Former use: redemption of a prescription for a systemic glucocorticoid >365 days before completing the questionnaire.

using observational studies, in which control of such confounders is important. However, many data sources used for surveillance lack data on lifestyle. This has been acknowledged as a limitation in prior studies.[6 22]

To quantify the amount of potential uncontrolled confounding by lifestyle factors in observational studies of systemic glucocorticoids, we used data from a population-based health survey and conducted a cross-sectional study to examine prevalence of lifestyle factors according to glucocorticoid use.

METHODS

Setting

Denmark provides tax-supported health services to all residents with access to primary and secondary care free of charge. A unique central personal registration number is assigned to all Danish residents at birth or immigration, permitting accurate and unambiguous linkage of relevant registries at the individual level.[23] Denmark is administratively divided into five regions. We conducted this study in the Central Denmark Region, with a population of 1.2 million inhabitants.

Study population

The study population was identified through responses to the survey, 'Hvordan har du det?' (How Are You?), a questionnaire-based public health study conducted by DEFACTUM (formerly Centre for Public Health and Quality Improvement).[24] The main incentive of the survey was to map health and health behaviours among citizens in order to promote better health through targeted prevention and intervention by Danish health authorities. Yet, data are available for research also. Between February and May 2010, a random sample of 52 400 people (7026 in the 16–24 year age group and 45 373 in the ≥25 year age group) living in the Central Denmark Region was invited to participate in the study. The current study only included adults (≥25 years of age) who completed the study's detailed questionnaire (30 245 persons, 67% of those invited). The questionnaire was sent by post and had to be returned by mail in reply enveloped (postage was prepaid). Up to three reminders were sent if people did not answer. The first 1000 people answering the questionnaire were promised two tickets for the cinema. In addition, participants were able to win lottery gifts.

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Lifestyle data

Lifestyle-related items included in the questionnaire were body mass index (BMI), participation in regular leisure-time physical activities, diet, smoking status and alcohol intake. BMI was calculated as self-reported weight in kilograms divided by self-reported height in metres, squared. BMI was categorised according to WHO criteria, as underweight (BMI <18.5), normal weight (BMI 18.5–24), overweight (BMI 25–29) and obese (BMI ≥30).[25] Questionnaire items on physical activity focused on participation in leisure sports or other regular exercise (yes/no). To assess diet, the health survey used a scoring system developed by the Research Centre for Prevention and Health, Capital Region of Denmark. Thirty different questions were included on intake of fruit, vegetables, fish and fat. The scoring system was used to summarise responses into categories of 'healthy' (high amount of fruit, vegetables, fish and low amounts of saturated fat), 'reasonably healthy' (median high intake of fruit, vegetables, fish and saturated fat), or 'unhealthy' (low amount of fruit, vegetables, and fish, and high amount of saturated fat). Smoking status was categorised as never, former or current (daily or occasional). We categorised alcohol use according to the Danish Health and Medicine Authority's recommendations, that is, high-risk consumption (>7/14 (women/men) drinks weekly) or low-risk consumption (≤7/14 drinks weekly).

Data on medication use

Use of systemic glucocorticoids was identified through the Danish National Health Service Prescription Database (DNHSPD). The DNHSPD contains information on prescriptions reimbursed by the National Health System since 2004.[26] Use of systemic glucocorticoids was defined as never use (persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire) and ever use of systemic glucocorticoids. Ever use was categorised further according to timing of exposure and cumulative dose expressed in dose of prednisolone equivalents. Timing of exposure was classified as current use (redemption of a prescription for a systemic glucocorticoid ≤90 days before completing the questionnaire), current new use (first-ever redemption of a prescription ≤90 days before completing the questionnaire), current continuing use (first-ever prescription redemption more than 90 days before completing the questionnaire, but most recent prescription ≤90 days), recent use (redemption of a prescription for a systemic glucocorticoid 91–365 days before completing the questionnaire) and former use (redemption of a prescription for a systemic glucocorticoid >365 days before completing the questionnaire). The cumulative dose expressed in prednisolone equivalents was divided in <100 mg, 100–499 mg, 500–999 mg, 1000–1999 mg, 2000–4999 mg and ≥5000 mg. (See online supplementary table 1 for codes used in the Anatomical Therapeutic Chemical classification system of WHO and online supplementary table 2 for calculation of prednisolone equivalent doses.)

Statistical analyses

First, prevalence of lifestyle factors was computed according to glucocorticoid use.

Second, adjusted prevalence ratios (aPRs) and 95% CIs were estimated using a Poisson regression model. All categories of systemic glucocorticoid use (ever use, current use, current new use, current continuing use, recent use and former use as well as categories of cumulative dose of prednisolone equivalents) were compared with the reference of never use. The prevalence ratios (PRs) were adjusted for age (10 year age groups). All analyses were stratified by sex.

In supplementary analyses, PRs were estimated stratified by age group (25–44, 45–64, ≥65 years of age) and by potential COPD (yes/no). Based on history of medication use, potential COPD was defined as at least two redeemed prescriptions after age 40 (and none before) for a long-acting beta2 agonist (LABA), a long-acting muscarinic receptor antagonist (LAMA) or an inhaled corticosteroid (or combinations thereof).

In estimating prevalence and PRs, postsurvey weights computed at Statistic Denmark were used to account for survey design and non-response.[27]

All statistical analyses were conducted using Stata software (Release V.12, StataCorp LP).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

In total, 30 245 persons completed the study questionnaire (53% women), and median age was 53 years. Of these, 563 (1.9%) were current users of glucocorticoids, 885 (2.9%) were recent users, 3054 (10%) were former users and 25 743 (85%) were never users. The prevalence of demographics and lifestyle factors according to glucocorticoid use is presented in table 1 and in the online supplementary table 3.

Body mass index

In women, ever users of glucocorticoids were slightly more obese than never users (18% vs 14%; aPR 1.4 (95% CI 1.2 to 1.5); see table 1 and figure 1) with the highest prevalence in current continuing users (21%) and recent users (22%; see table 1, online supplementary table 3 and table 4). Also, male ever users were slightly more obese than never users (17% vs 15%; aPR 1.2 (95% CI 1.1 to 1.4); see table 1 and figure 2). In addition, prevalence of obesity increased with greater cumulative glucocorticoid dose in both sexes (figures 3 and 4).

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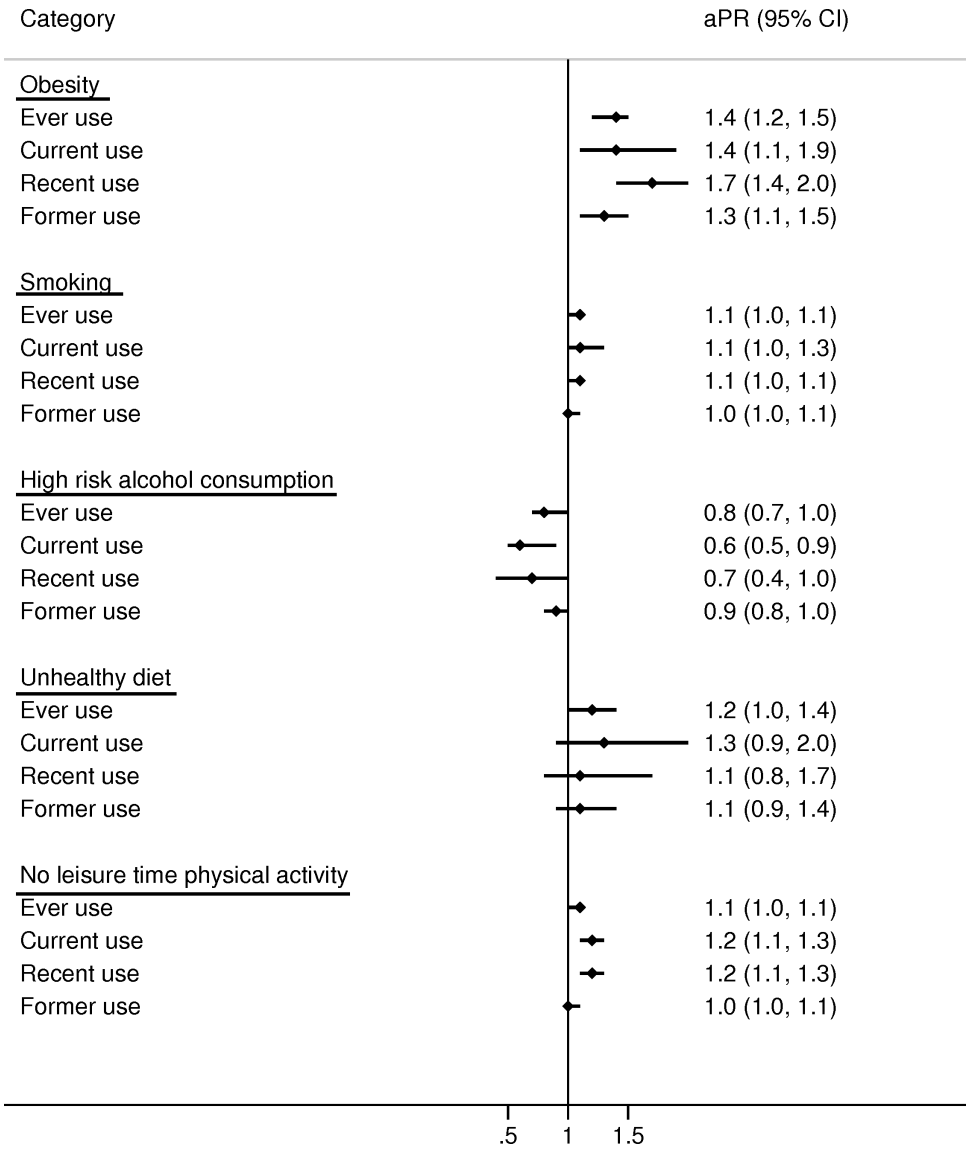

Figure 1 Age-adjusted prevalence ratios (aPRs) and 95% CIs for lifestyle factors comparing glucocorticoid users to never users in women. Never use: persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire. Ever use: at least one redemption of a prescription for a systemic glucocorticoid before completing the questionnaire. Current use: redemption of a prescription for a systemic glucocorticoid ≤90 days before completing the questionnaire. Recent use: redemption of a prescription for a systemic glucocorticoid 91–365 days before completing the questionnaire. Former use: redemption of a prescription for a systemic glucocorticoid >365 days before completing the questionnaire.

Smoking

Glucocorticoid ever users had a similar prevalence of smoking as never users of glucocorticoids in both women (aPR 1.1 (95% CI 1.0 to 1.1)) and men (aPR 1.1 (95% CI 1.1 to 1.1); figures 1 and 2). These findings were consistent across all categories of glucocorticoid users (figures 1–4) and when stratifying on potential COPD (online supplementary table 5).

Alcohol intake

In women, the prevalence of high-risk alcohol consumption was somewhat lower in ever users of glucocorticoids than never users (17% vs 20%; aPR=0.8 (95% CI 0.7 to 1.0); see table 1 and figure 1). For men, there was no difference (aPR 1.0 (95% CI 0.9 to 1.1); see table 1 and figure 2).

Physical activity

Physical activity did not differ substantially according to use of glucocorticoids in either women (aPR 1.1 (95% CI 1.0 to 1.1)) or men (aPR 1.0 (95% CI 1.0 to 1.0); see figures 1 and 2) although greater cumulative dose of glucocorticoid use was slightly associated with less physical activity (figures 3 and 4).

The PRs did not differ substantially by age group (online supplementary table 6 and online supplementary table 7).

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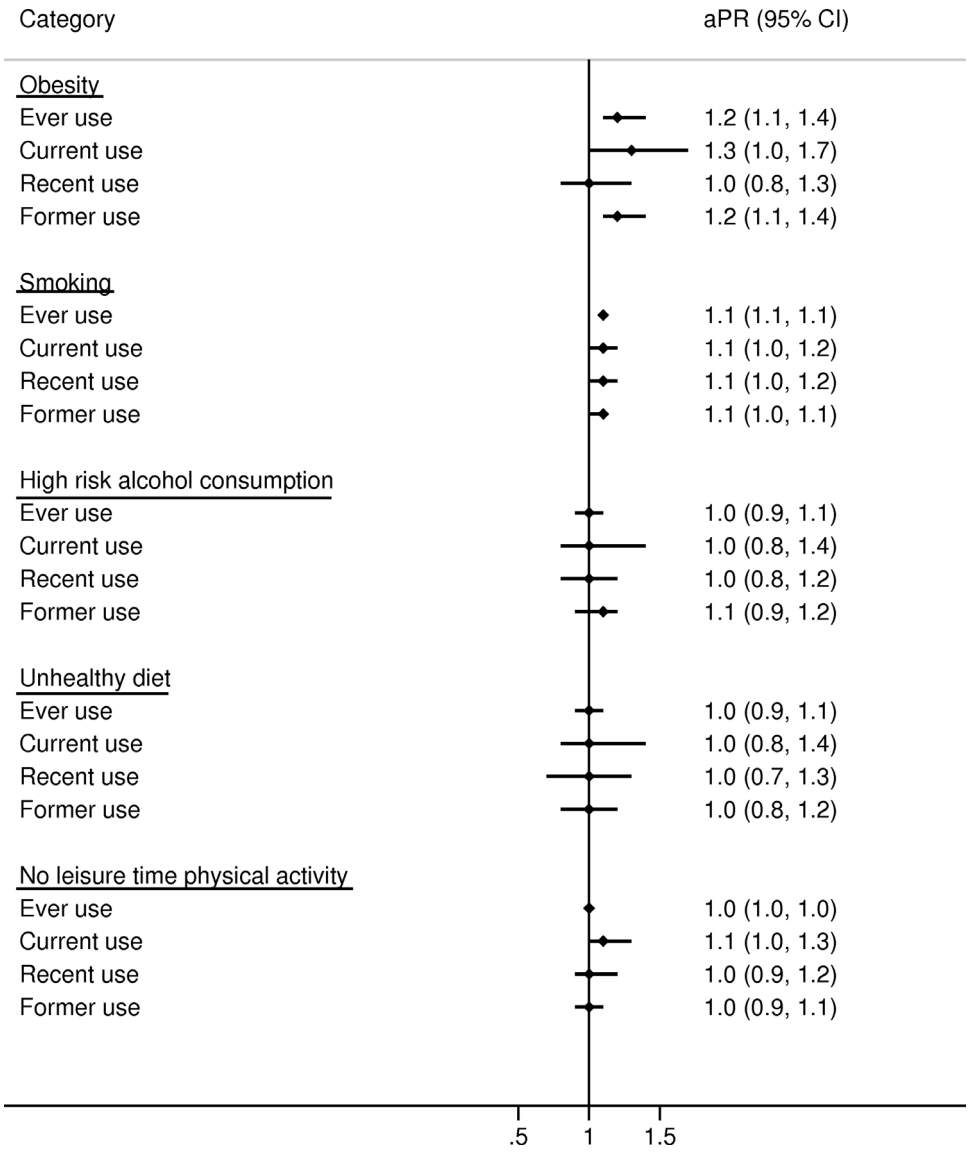

Figure 2 Age-adjusted prevalence ratios (aPRs) and 95% CIs for lifestyle factors comparing glucocorticoid users to never users in men. Never use: persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire. Ever use: at least one redemption of a prescription for a systemic glucocorticoid before completing the questionnaire. Current use: redemption of a prescription for a systemic glucocorticoid ≤90 days before completing the questionnaire. Recent use: redemption of a prescription for a systemic glucocorticoid 91–365 days before completing the questionnaire. Former use: redemption of a prescription for a systemic glucocorticoid >365 days before completing the questionnaire.

DISCUSSION

This population-based study found that users of systemic glucocorticoids had a slightly higher prevalence of obesity than never users. In women, the prevalence of obesity was 1.4-fold higher and in men 1.2-fold higher. In women, the prevalence of high-risk alcohol consumption was 0.8-fold lower in users of glucocorticoids than never users. This finding did not apply for men. Smoking habits, diet and physical activity did not differ substantially according to use of systemic glucocorticoids.

Data on lifestyle among glucocorticoid users are sparse, although truncal obesity is a well-known feature of glucocorticoid excess.[3 28] In addition, one study reported higher prevalence of glucocorticoid use in obese versus non-obese people[29] and one study found that overweight and obesity were risk factors of self-reported arthritis.[19] In contrast, the prevalence of overweight and obesity was lower in people with inflammatory bowel disease than healthy controls.[20] While arthritis and inflammatory bowel disease are potential indications for glucocorticoid treatment, these populations do not compare directly to our study population. Due to the cross-sectional design of our study, we were not able to investigate if glucocorticoid use predicted obesity or vice versa and the study did not aim to investigate adverse effects of glucocorticoids. Nevertheless, we found higher prevalence of obesity in current continuing users of glucocorticoids compared with current new users and increasing prevalence of

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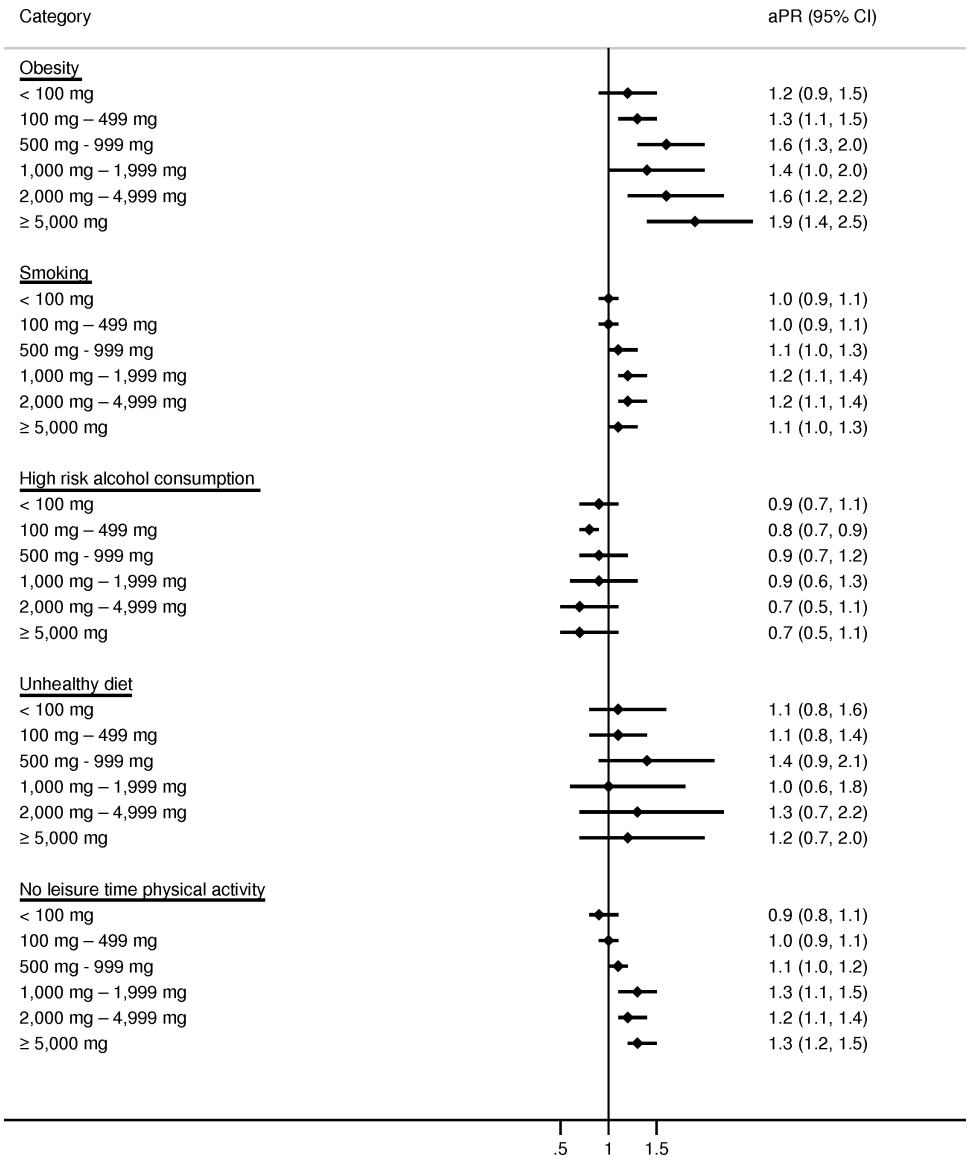

Figure 3 Age-adjusted prevalence ratios (aPRs) and 95% CIs for lifestyle factors comparing cumulative glucocorticoid dose (in grams of prednisolone equivalents) to never users in women.

obesity with increasing cumulative glucocorticoid dose. These results may indicate that glucocorticoid use precedes obesity. Physical activity has been reported to be low in some patient groups ordinarily treated with glucocorticoids; one study found that more than 60% of adults with arthritis do not comply with physical activity recommendations.[21] The reasons why the majority of persons with arthritis did not meet physical activity recommendations were not investigated, but authors discussed if it may be related to arthritis-specific barriers to physical activity such as fear of making their arthritis worse, fatigue or pain.[21] In our study, we found no major difference in physical activity according to glucocorticoid use, although greater cumulative dose of glucocorticoid was slightly associated with less physical activity.

While we conducted a large population-based cohort study with detailed information on lifestyle factors, its limitations must be considered. First, the response rate to the questionnaire was 67%. We cannot be sure if persons who completed the health survey had a different health profile than those who declined. To minimise such bias, we used a weighting method developed by Statistic Denmark for this particular survey.[27] Second, persons who completed the questionnaire might have answered incorrectly. Third, redeemed prescriptions may be an imperfect measure of actual drug intake and its timing. Also, the prescription database only covers prescriptions from 2004 on, which may have led to misclassification of glucocorticoid use. We were not able to predict direction of bias due to potential misclassification of glucocorticoid use or lifestyle factors. Fourth, we did not stratify on socioeconomic status and were not able to identify treatment indication. The algorithm used to define people as having potential COPD may be imperfect. In particular, certain persons identified as having COPD actually have asthma. To address this issue, redeemed prescriptions for

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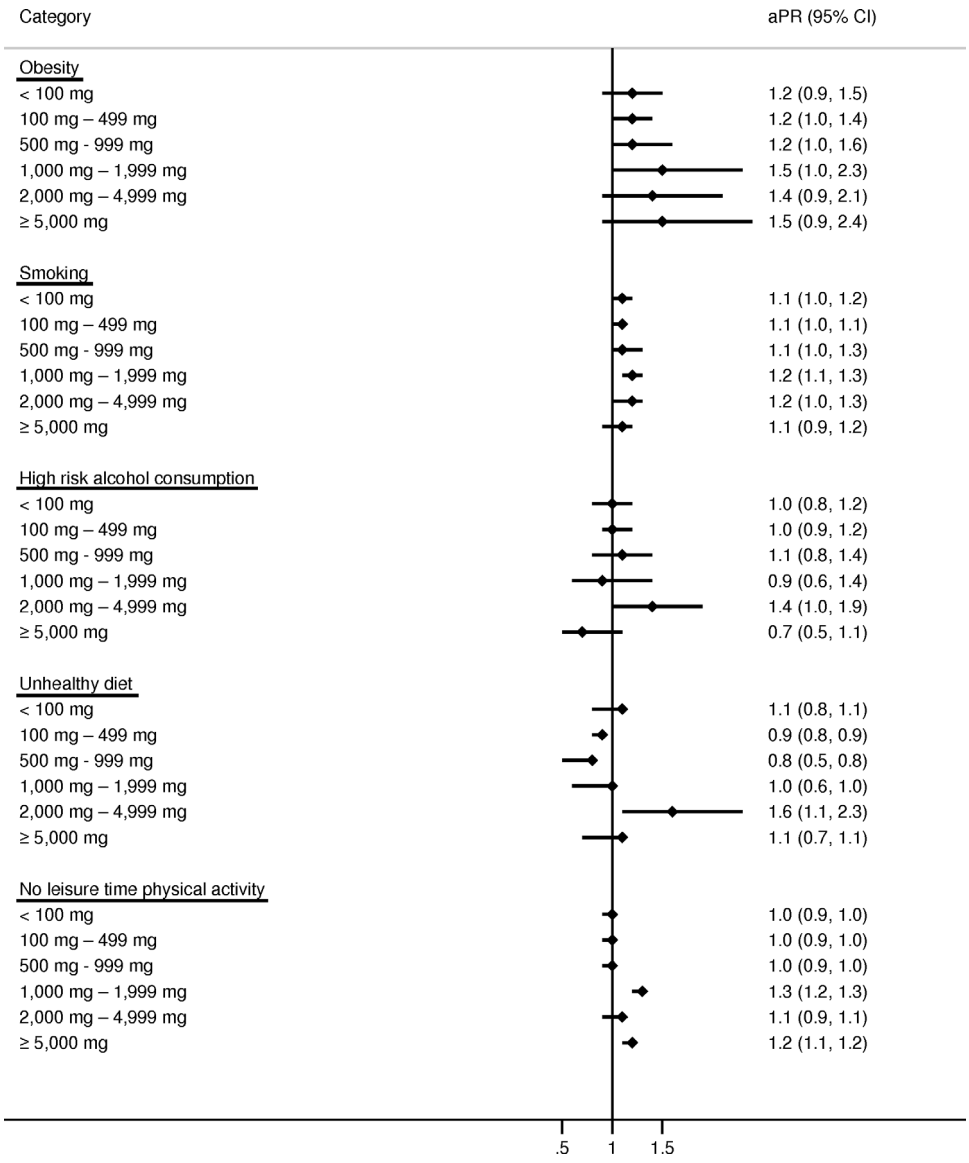

Figure 4 Age-adjusted prevalence ratios (aPRs) and 95% CIs for lifestyle factors comparing cumulative glucocorticoid dose (in grams of prednisolone equivalents) to never users in men.

LABA or LAMA before age 40 were an exclusion criterion, as asthma onset most often occurs in childhood or adolescence, whereas COPD onset is later in life. Last, as this study had a cross-sectional design, it was unable to evaluate whether lifestyle predicts glucocorticoid use or vice versa. Still, the study did not aim or was designed to evaluate adverse effects of glucocorticoids.

Our study has important implications for quantifying the amount of potential uncontrolled confounding by lifestyle factors in observational studies of systemic glucocorticoids. Results from this study may guide assessment of the association between lifestyle and glucocorticoid use and can, for example, be used in a bias analysis when data on lifestyle factors are not available.[6 7 30] Yet, it must be acknowledged that any assessment should not be based solely on associations found in this study. Directed acyclic graphs could be applied to ensure that recorded lifestyle factors are not mediators or colliders.[31]

In conclusion, glucocorticoid users had a slightly higher prevalence of obesity and female glucocorticoid users had a slightly lower prevalence of high-risk alcohol consumption compared with never users. Smoking habits, diet and physical activity did not differ substantially according to use of glucocorticoids. Our study provides a framework for quantifying potential uncontrolled confounding by lifestyle factors in studies of systemic glucocorticoids.

Contributors All authors made primary contributions to the concept of the study and wrote the manuscript. KL performed statistical analyses. All authors contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript.

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Competing interests None declared.

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Patient consent for publication Not required.

Ethics approval This study was approved by the Danish Data Protection Agency (Record number: 2016-051-000001, serial number 448). For this type of study, approval from ethics committee and formal consent is not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

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ORCID iD

Kristina Laugesen http://orcid.org/0000-0001-7971-8223

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SUPPLEMENTARY

Supplementary Table 1. Anatomical Therapeutic Classification (ATC) codes

Medication	ATC codes
Systemic glucocorticoids	H02AB
Betamethasone	H02AB01
Dexamethasone	H02AB02
Methylprednisolone	H02AB04
Prednisolone	H02AB06
Prednisone	H02AB07
Triamcinolone	H02AB08
Hydrocortisone	H02AB09
Inhaled medications	
Salmeterol	R03AC12
Formeterol	R03AC13
Indacaterol	R03AC18
Olodaterol	R03AC19
Tiotropium	R03BB04
Aclidinium	R03BB05
Glycopyrronium	R03BB06
Umeclidinium	R03BB07
Salmeterol and fluticasone	R03AK06
Formeterol and budesonide	R03AK07
Formeterol and beclomethasone	R03AK08
Vilanterol and fluticasone	R03AK10
Formeterol and fluticasone	R03AK11
Beclomethasone	R03BA01
Budesonide	R03BA02
Flunisolide	R03BA03
Fluticasone	R03BA05
Mometasone	R03BA07
Ciclisonide	R03BA08
Vilanterol and umeclidinium	R03AL03
Indaceterol and glycopyrronium	R03AL04
Formeterol and aclidinium	R03AL05
Olodaterol and tiotropium	R03AL06
Beclomethasone	R03BA01
Budesonide	R03BA02
Flunisolide	R03BA03
Fluticasone	R03BA05
Momentasone	R03BA07
Ciclosonide	R03BA08

Supplementary Table 2. Equivalency table presenting systemic glucocorticoids and corresponding prednisolone conversion factors.

	Equivalent glucocorticoid dose	Prednisolone conversion factor
Cortisone	25	0.2
Cortisol	20	0.25
Methylprednisolone	4	1.25
Prednisolone	5	1
Prednisone	5	1
Triamcinolone	4	1.25
Dexamethasone	0.75	6.67
Betamethasone	0.6	8.33

Cumulative dose calculation:

The cumulative dose was calculated by multiplying the number of pills/injections, dose per pill/injection, and prednisolone conversion factor for each prescription and then adding them up across all prescriptions.

Supplementary Table 3. Prevalence of lifestyle factors according to current new use and current continuing use of glucocorticoid in women and men. Percentages are weighted

	Women		Men	
	Current new use	Current continuing use	Current new use	Current continuing use
	N (%)	N (%)	N (%)	N (%)
All	78 (100)	223 (100)	77 (100)	185 (100)
Median age (range), years	59 (26-88)	67 (28-94)	59 (28-92)	68 (32-94)
Body Mass Index				
< 18.5	<5 (-)	14 (6.3)	<5 (-)	5 (4.8)
18.5-24	42 (51)	84 (34)	23 (25)	65 (37)
25-29	21 (30)	68 (31)	35 (50)	81 (38)
≥30	8 (8.2)	42 (21)	17 (20)	30 (18)
Missing	<5 (-)	15 (8.1)	<5 (-)	<5 (-)
Smoking				
Current	20 (25)	46 (18)	22 (32)	42 (25)
Former	26 (31)	85 (37)	39 (47)	87 (42)
Never	30 (43)	77 (39)	15 (20)	52 (30)
Missing	<5 (-)	15 (5.8)	<5 (-)	<5 (2.5)
Diet				
Unhealthy	< 5 (-)	25 (11)	16 (18)	31 (14)
Reasonably healthy	49 (63)	132 (62)	51 (71)	108 (58)
Healthy	22 (28)	50 (20)	8 (7.4)	30 (16)
Missing	< 5 (-)	16 (5.9)	<5 (-)	16 (12)
Alcohol intake				
Low risk consumption	65 (86)	166 (77)	55 (71)	129 (70)
High risk consumption	12 (13)	31 (12)	18 (19)	44 (22)
Missing	<5 (-)	26 (11)	<5 (-)	12 (8.0)
Participation in regular leisure time physical activity				
No	38 (46)	133 (63)	50 (65)	125 (65)
Yes	39 (53)	82 (34)	26 (33)	56 (32)
Missing	<5 (-)	<5 (-)	<5 (-)	<5 (-)

Current new use: First-ever redemption of a prescription ≤ 90 days before completing the questionnaire. Current continuing use: First-ever prescription redemption more than 90 days before completing the questionnaire, but most recent prescription ≤ 90 days.

Supplementary Table 4. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users, stratified by sex.

	aPR (95% CI)	
Category	**Women**	**Men**
Obesity		
Current new use	0.7 (0.3 to 1.4)	1.4 (0.9 to 2.3)
Current continuing use	1.7 (1.2 to 1.6)	1.4 (1.0 to 1.3)
Ever smoking		
Current new use	1.1 (0.9 to 1.4)	1.3 (1.1 to 1.4)
Current continuing use	1.1 (1.0 to 1.1)	1.0 (1.0 to 1.1)
High risk alcohol consumption		
Current new use	0.6 (0.9 to 1.0)	0.9 (0.8 to 1.4)
Current continuing use	0.6 (0.3 to 1.0)	1.1 (0.9 to 1.2)
Unhealthy diet		
Current new use	0.6 (0.2 to 1.9)	1.1 (0.7 to 1.9)
Current continuing use	1.5 (0.9 to 2.4)	1.0 (0.9 to 1.1)
No participation in regular leisure time physical activity		
Current new use	0.9 (0.7 to 1.3)	1.2 (1.0 to 1.4)
Current continuing use	1.3 (1.0 to 1.1)	1.1 (1.0 to 1.3)

Current new use: First-ever redemption of a prescription ≤ 90 days before completing the questionnaire. Current continuing use: First-ever prescription redemption more than 90 days before completing the questionnaire, but most recent prescription ≤ 90 days.

Supplementary Table 5. Age- and sex- adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users, stratified by potential chronic obstructive pulmonary disease (COPD).

Characteristics	aPR (95% CI)	
	Potential COPD	**No COPD**
Obesity		
Ever	1.1 (0.9-1.3)	1.3 (1.2-1.4)
Current	1.0 (0.7-1.5)	1.2 (1.0-1.6)
Recent	1.0 (0.7-1.4)	1.3 (1.1-1.6)
Former	1.0 (0.8-1.4)	1.2 (1.1-1.4)
Smoking		
Ever	1.1 (1.0-1.1)	1.0 (1.0-1.1)
Current	1.1 (0.9-1.2)	1.1 (1.0-1.2)
Recent	1.1 (1.0-1.3)	1.1 (1.0-1.1)
Former	1.0 (1.0-1.1)	1.0 (1.0-1.1)
High risk alcohol consumption		
Ever	0.9 (0.7-1.1)	0.9 (0.9-1.0)
Current	1.0 (0.7-1.5)	0.8 (0.6-1.0)
Recent	0.6 (0.4-1.0)	0.9 (0.7-1.0)
Former	0.9 (0.7-1.2)	1.0 (0.9-1.1)
Unhealthy diet		
Ever	1.1 (0.8-1.6)	1.0 (0.9-1.1)
Current	1.6 (1.0-2.5)	0.9 (0.6-1.2)
Recent	1.3 (0.8-2.0)	1.0 (0.7-1.2)
Former	0.8 (0.6-1.3)	1.0 (0.9-1.2)
No leisure time physical activity		
Ever	1.1 (1.0-1.2)	1.0 (1.0-1.1)
Current	1.2 (1.1-1.4)	1.1 (1.0-1.2)
Recent	1.2 (1.0-1.3)	1.1 (1.0-1.2)
Former	1.1 (1.0-1.2)	1.0 (0.9-1.0)

Potential COPD was defined as at least two prescriptions for a long-acting beta2 agonist (LABA), a long-acting muscarinic receptor antagonist (LAMA), or an inhaled corticosteroid (ICS) (or combination thereof) after age 40, and no prescriptions for these agents redeemed at or before age 40.

Supplementary Table 6. Prevalence ratios (PRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in women, stratified by age group.

Category	PR (95% CI)			
	25-44 years of age	45 to 64 years of age	≥65 years of age	All
Obesity				
Ever	1.40 (1.13-1.72)	1.41 (1.21-1.65)	1.33 (1.07-1.65)	1.37 (1.23-1.52)
Current	1.37 (0.41-2.78)	1.56 (1.01-2.39)	1.32 (0.87-2.03)	1.33 (1.00-1.77)
Recent	1.86 (1.32-2.63)	1.95 (1.49-2.54)	1.72 (0.65-1.91)	1.66 (1.36-2.02)
Former	1.28 (0.99-1.65)	1.24 (1.03-1.49)	1.42 (1.10-1.84)	1.29 (1.13-1.47)
Smoking				
Ever	0.98 (0.87-1.10)	1.10 (1.03-1.17)	1.06 (0.96-1.16)	1.09 (1.04-1.14)
Current	1.34 (0.97-1.86)	1.19 (1.02-1.40)	1.14 (0.86-1.26)	1.16 (1.03-1.31)
Recent	0.89 (0.84-1.12)	1.08 (0.95-1.22)	1.26 (1.07-1.47)	1.11 (1.01-1.23)
Former	0.97 (0.85-1.12)	1.09 (1.02-1.17)	1.00 (0.89-1.12)	1.07 (1.01-1.13)
High risk alcohol consumption				
Ever	0.74 (0.56-0.98)	0.90 (0.80-1.03)	0.71 (0.57-0.89)	0.86 (0.78-0.96)
Current	0.47 (0.10-2.20)	0.76 (0.48-1.22)	0.53 (0.31-0.90)	0.65 (0.46-0.92)
Recent	0.78 (0.45-1.37)	0.69 (0.51-0.94)	0.58 (0.33-1.02)	0.71 (0.56-0.91)
Former	0.75 (0.54-1.04)	0.98 (0.85-1.13)	0.82 (0.64-1.06)	0.95 (0.84-1.07)
Unhealthy diet				
Ever	1.18 (0.86-1.63)	1.10 (0.79-1.44)	1.28 (0.95-1.72)	1.18 (0.99-1.41)
Current	0.61 (0.19-1.97)	1.55 (0.77-3.12)	1.48 (0.85-2.55)	1.45 (0.96-2.20)
Recent	1.11 (0.55-2.26)	1.21 (0.65-2.24)	1.22 (0.65-2.28)	1.17 (0.81-1.70)
Former	1.26 (0.88-1.80)	0.96 (0.67-1.38)	1.23 (0.86-1.76)	1.14 (0.92-1.40)
No leisure time physical activity				
Ever	0.98 (0.87-1.11)	1.13 (1.04-1.21)	1.11 (1.03-1.21)	1.12 (1.07-1.18)
Current	1.43 (1.05-1.96)	1.32 (1.09-1.58)	1.16 (1.00-1.36)	1.33 (1.19-1.49)
Recent	1.12 (0.81-1.29)	1.18 (1.01-1.19)	1.28 (1.11-1.47)	1.20 (1.09-1.33)
Former	0.93 (0.81-1.08)	1.09 (0.99-1.19)	1.05 (0.95-1.17)	1.06 (1.00-1.13)

Never use: Persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire. Ever use At least one redemption of a prescription for a systemic glucocorticoid before completing the questionnaire. Current use: Redemption of a prescription for a systemic glucocorticoid ≤ 90 days before completing the questionnaire. Recent use: Redemption of a prescription for a systemic glucocorticoid 91-365 days before completing the questionnaire. Former use: Redemption of a prescription for a systemic glucocorticoid > 365 days before completing the questionnaire.

Supplementary Table 7. Prevalence ratios (PRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in men, stratified by age group.

Category	PR (95% CI)			
	25-44 years of age	45 to 64 years of age	≥65 years of age	All
Obesity				
Ever	1.13 (0.80-1.33)	1.30 (1.11-1.52)	1.22 (0.96-1.54)	1.19 (1.05-1.34)
Current	1.12 (0.41-2.54)	1.29 (0.84-1.98)	1.46 (0.94-2.27)	1.27 (0.95-1.71)
Recent	0.83 (0.50-1.38)	1.23 (0.85-1.79)	0.91 (0.51-1.62)	0.99 (0.75-1.29)
Former	1.12 (0.83-1.51)	1.32 (1.10-1.59)	1.22 (0.92-1.62)	1.23 (1.07-1.42)
Smoking				
Ever	1.12 (1.00-1.25)	1.11 (1.06-1.18)	1.08 (1.02-1.14)	1.17 (1.12-1.22)
Current	1.47 (1.12-1.91)	1.15 (0.99-1.33)	1.02 (0.90-1.15)	1.26 (1.16-1.38)
Recent	1.16 (0.95-1.41)	1.05 (0.93-1.19)	1.11 (0.99-1.24)	1.12 (1.02-1.22)
Former	1.05 (0.92-1.21)	1.13 (1.06-1.20)	1.09 (1.03-1.16)	1.17 (1.11-1.22)
High risk alcohol consumption				
Ever	1.16 (0.92-1.47)	0.95 (0.82-1.10)	1.04 (0.86-1.26)	1.06 (0.96-1.18)
Current	1.16 (0.54-2.51)	1.19 (0.84-1.69)	0.79 (0.51-1.22)	1.06 (0.82-1.38)
Recent	1.16 (0.76-1.77)	0.67 (0.46-0.97)	1.22 (0.85-1.77)	0.97 (0.77-1.22)
Former	1.17 (0.88-1.55)	0.98 (0.83-1.16)	1.08 (0.86-1.36)	1.10 (0.96-1.24)
Unhealthy diet				
Ever	1.00 (0.79-1.27)	1.02 (0.83-1.24)	0.93 (0.72-1.19)	0.97 (0.85-1.11)
Current	1.22 (1.07-1.69)	1.04 (0.61-1.77)	1.41 (0.94-2.11)	1.01 (0.73-1.38)
Recent	1.25 (0.85-1.84)	0.69 (0.41-1.19)	0.73 (0.43-1.24)	0.96 (0.72-1.27)
Former	0.98 (0.74-1.31)	1.09 (0.88-1.37)	0.82 (0.59-1.15)	0.97 (0.83-1.13)
No leisure time physical activity				
Ever	1.02 (0.90-1.16)	1.03 (0.96-1.10)	1.06 (0.98-1.14)	1.09 (1.03-1.14)
Current	1.17 (0.79-1.73)	1.21 (1.04-1.42)	1.18 (1.04-1.34)	1.31 (1.19-1.45)
Recent	1.10 (0.87-1.37)	0.97 (0.82-1.15)	1.07 (0.91-1.25)	1.05 (0.94-1.18)
Former	0.96 (0.82-1.13)	1.01 (0.93-1.10)	1.01 (0.92-1.11)	1.05 (0.98-1.12)

Never use: Persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire. Ever use At least one redemption of a prescription for a systemic glucocorticoid before completing the questionnaire. Current use: Redemption of a prescription for a systemic glucocorticoid ≤ 90 days before completing the questionnaire. Recent use: Redemption of a prescription for a systemic glucocorticoid 91-365 days before completing the questionnaire. Former use: Redemption of a prescription for a systemic glucocorticoid > 365 days before completing the questionnaire.

Appendix III

Paper III

Clinical Epidemiology

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ORIGINAL RESEARCH

Prescription duration and treatment episodes in oral glucocorticoid users: application of the parametric waiting time distribution

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Kristina Laugesen[1]
Henrik Støvring[2]
Jesper Hallas[3]
Anton Pottegård[3]
Jens Otto Lunde Jørgensen[4]
Henrik Toft Sørensen[1]
Irene Petersen[1,5]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, [2]Department of Public Health, Aarhus University, Aarhus, [3]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, [4]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; [5]Department of Primary Care and Population Health, University College London, London, UK

Purpose: Glucocorticoids are widely used medications. In many pharmacoepidemiological studies, duration of individual prescriptions and definition of treatment episodes are important issues. However, many data sources lack this information. We aimed to estimate duration of individual prescriptions for oral glucocorticoids and to describe continuous treatment episodes using the parametric waiting time distribution.

Methods: We used Danish nationwide registries to identify all prescriptions for oral glucocorticoids during 1996–2014. We applied the parametric waiting time distribution to estimate duration of individual prescriptions each year by estimating the 80th, 90th, 95th and 99th percentiles for the interarrival distribution. These corresponded to the time since last prescription during which 80%, 90%, 95% and 99% of users presented a new prescription for redemption. We used the Kaplan–Meier survival function to estimate length of first continuous treatment episodes by assigning estimated prescription duration to each prescription and thereby create treatment episodes from overlapping prescriptions.

Results: We identified 5,691,985 prescriptions issued to 854,429 individuals of whom 351,202 (41%) only redeemed 1 prescription in the whole study period. The 80th percentile for prescription duration ranged from 87 to 120 days, the 90th percentile from 116 to 150 days, the 95th percentile from 147 to 181 days, and the 99th percentile from 228 to 259 days during 1996–2014. Based on the 80th, 90th, 95th and 99th percentiles of prescription duration, the median length of continuous treatment was 113, 141, 170 and 243 days, respectively.

Conclusion: Our method and results may provide an important framework for future pharmacoepidemiological studies. The choice of which percentile of the interarrival distribution to apply as prescription duration has an impact on the level of misclassification. Use of the 80th percentile provides a measure of drug exposure that is specific, while the 99th percentile provides a sensitive measure.

Keywords: glucocorticoids, pharmacoepidemiology, prescription duration, parametric waiting time distribution

Background

Prescription registries offer huge potential for studying benefits and adverse effects of drugs. An important issue in many pharmacoepidemiological studies is timing of administration, duration of individual prescriptions, and definition of treatment episodes. Many prescription data sources, including the Danish, provide information only on the date of prescription redemption together with some information on the amount of medication dispensed.[1] Thus, it is often necessary to make assumptions

Correspondence: Kristina Laugesen
Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43–45, 8200 Aarhus N, Denmark
Tel +45 8 716 8063
Email Kristina.laugesen@clin.au.dk

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about the duration of single prescriptions when conducting pharmacoepidemiological research. Information on drug exposure must be handled cautiously to achieve meaningful results and to avoid false conclusions and it is well known that assigning treatment periods in pharmacoepidemiological studies is a source of bias.[2,3]

For some medications, clinical input may be used to guide the estimation of duration of individual prescriptions and to define treatment episodes. However, there is little consensus on how best to do this, and externally defined criteria may poorly reflect actual usage patterns.[3] Støvring et al recently suggested that estimates be based instead on observed usage patterns using the parametric waiting time distribution (WTD).[4] This method allows estimation of the time point at which a given proportion of users receiving continued treatment will have redeemed their next prescription, that is, the "inter-arrival time". The method's primary advantage is in assigning duration exposure to prescriptions based only on observed prescription redemption patterns.

Glucocorticoids are effective agents for treatment of, for example, rheumatic diseases, COPD as well as other autoimmune diseases.[5] Annual prevalence of systemic glucocorticoid use is up to 3% in the Danish population[6] and prevalence of long-term oral use (≥3 months) in the UK population has been estimated to 1%.[7] Importantly, dosing regimens, treatment duration, and choice of glucocorticoid subtype vary substantially by treatment indication.[8]

To provide a framework for future pharmacoepidemiological studies on oral glucocorticoids, we aimed to use the parametric WTD to estimate duration of individual oral glucocorticoid prescriptions and length of continuous treatment episodes.

Methods

Setting

We used Danish national registries. Denmark provides its entire population with tax-supported health care, guaranteeing cost-free access to health care. A unique central personal registration number (the civil registration number) is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous individual-level linkage of health and administrative registries.[9]

Oral glucocorticoids

Oral glucocorticoids are available only by prescription in Denmark. We used the Danish National Prescription Registry[1] to identify all persons in the Danish population who redeemed prescriptions for oral glucocorticoids between January 1, 1996 and December 31, 2014. The Danish National Prescription Registry records information on the customer's civil registration number, the medication classification code (Anatomical Therapeutic Chemical classification system of the World Health Organization), date of dispensing, the number of packages dispensed, the number of tablets in a package, tablet strength, and amount dispensed, expressed according to "defined daily doses" (DDDs) developed by WHO. A DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.[10] ATC codes for glucocorticoids are provided in Table S1.

Statistical analyses

We first counted the total number of prescriptions redeemed for oral glucocorticoids during the study period, and the total number of individuals who redeemed these prescriptions. We described the cohort according to sex and age at first prescription. We tallied the total number of prescriptions and total DDDs redeemed for all oral glucocorticoids and for individual glucocorticoid substances.

Second, we estimated the duration of individual prescriptions by applying the parametric WTD. This method is based on the maximum likelihood estimation of a parametric 2-component mixture model for the WTD.[4] The distribution component for prevalent users estimates the forward recurrence density, which is related to the inter-arrival density (distribution of time between subsequent prescription redemptions) for users receiving continued treatment. The inter-arrival density directly shows the probability of the appearance of a new prescription as a function of time. We estimated the 80th, 90th, 95th, and 99th percentiles for prescription duration (days) for oral glucocorticoid users each year from 1996 to 2014. The 80th, 90th, 95th, and 99th percentiles of assigned prescription duration in days corresponded to the time within which 80%, 90%, 95% and 99% of users, respectively, presented a new prescription. We applied the Log-Normal model in estimating the forward recurrence density.[4] The parametric WTD relies on separation of users into 2 categories: prevalent users and incident users. To assess whether this method would work, we visually inspected the empirical WTD to discern if there was a distinct uniform tail toward the end of the observation window and a smoothly declining section in the beginning. We stratified subanalyses by sex, and age groups (0–19, 20–39, 40–79, ≥80 years of age), the number of tablets dispensed, and the amount (DDD) dispensed to investigate whether individual prescription durations differed according to these variables. The number of tablets dispensed was calculated as the number of tablets

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in a package times the number of packages dispensed and categorized as 10–30, 50–60, 100 and ≥200. The amount dispensed was calculated as the amount in a package times the number of packages dispensed and categorized as ≤25 DDD, 50–70 DDD, 100–150 DDD and 200–250 DDD.

Third, using each percentile estimated by the parametric WTD (80th, 90th, 95th, and 99th), we estimated length of first continuous treatment episodes. This was accomplished by adding the estimated prescription duration (results from the parametric WTD stratified by calendar year) to each prescription and then, for each subject, creating treatment episodes from overlapping prescriptions (i.e., periods with assumed continuous drug treatment). To estimate the length of first treatment episodes, we used the Kaplan–Meier survival function to ascertain the first, fifth, tenth, twenty-fifth, fiftieth, seventy-fifth, 90th, 95th and 99th percentiles (treating emigration as censoring and death as event).

Fourth, we excluded sporadic prescriptions to obtain a cohort of multiple-prescription use. For each prescription, we searched for prior or forthcoming prescriptions in the time interval defined by the 99th percentile as estimated by the WTD. If no prior or forthcoming prescriptions appeared in this time interval, we excluded the prescription, as this was regarded as a sporadic prescription. We described this cohort as we did above for the full cohort.

Statistical analyses were conducted using Stata 14. The study was approved by the Danish Data Protection Agency (Record number: 2016-051-000001, serial number 448).

Results

During the study period, 5,691,985 prescriptions for oral glucocorticoids (335,161,216 DDDs) were redeemed by 854,429 individuals (56% female). Median age at first prescription redemption was 60 years (Table 1). The number of persons who redeemed only 1 prescription during the study period was 351,202 (41% of the study population). Prednisolone was the most frequent subtype of oral glucocorticoid redeemed (4,662,315 prescriptions [82% of total prescriptions] and 269,275,861 DDDs [80% of total DDDs]) (Table 2). When excluding sporadic prescriptions (i.e., multiple-prescription use), 4,719,061 prescriptions (275,597,541 DDDs) were issued to 418,160 persons (56% female) and median age was 66 years (Table 1).

When we applied the parametric WTD, the 80th percentile for prescription duration estimated for each year ranged from 87 to 120 days; the 90th percentile ranged from 116 to 150 days, the 95th percentile from 147 to 181 days, and the 99th percentile from 228 to 259 days (Figure 1). Stratifying by sex did not change these estimates substantially (Figure 2). When we stratified by age group, the percentiles for 2 groups (40–79 years of age and ≥80 years of age) were similar to those for overall population (Figure 2). When we inspected the empirical WTD for the younger age groups, no clear separation of prevalent and incident users appeared. Thus, we did not perform analyses separately for these. When we stratified by the number of tablets, the 80th percentile ranged from 87 to 107 days in the category of 50–60 tablets, 89–120 for 100 tablets and 121–171 for ≥200 tablets (Figure 3). When we stratified by the amount, the 80th percentile ranged from 90 to 118 days for 50–70 DDD, 120–176 for 100–150 DDD and 96–132 for 200–250 DDD (Table S2). The empirical WTD in the categories of 10–30 tablets and ≤25 DDD showed no clear separation of prevalent and incident users. Thus, we did not perform analyses separately for these. When restricting to the cohort of multiple-prescription use, estimates of the 80th, 90th, 95th, and 99th percentiles of prescription duration did not change substantially (Table S3).

When we applied the estimated durations of individual prescriptions to the full cohort, length of first treatment episodes varied depending on selection of percentiles. Applying the 80th percentile yielded a median episode length of 113 days (interquartile range [IQR]: 103–142 days). In contrast, applying the 90th, 95th and 99th percentiles yielded median episode lengths of 141 days (IQR: 132–184 days), 170 days (IQR: 160–224 days), and 243 days (IQR: 232–325 days), respectively (Table S4). In the multiple-prescription cohort,

Table 1 Sex and age distribution among all oral glucocorticoid use and multiple-prescription use, Denmark, January 1, 1996 – December 31, 2014

Characteristics	Number (%)	
	All use	Multiple-prescription use
Total number of users	854,429	418,160
Sex		
Female	477,633 (56)	235,643 (56)
Male	376,327 (44)	182,369 (44)
Missing	469 (<0.001)	148 (0.04)
Age (years) at first redeemed prescription		
Median age	60	66
0–19	30,084 (3.5)	8170 (2.0)
20–39	136,914 (16)	41,992 (10)
40–59	242,769 (28)	97,343 (23)
60–79	334,333 (39)	198,367 (47)
≥80	109,858 (13)	72,140 (17)
Missing	471 (0.06)	148 (0.04)

Table 2 Number of prescriptions and DDDs redeemed by all oral glucocorticoid use and multiple-prescription use by medication subtype, Denmark, January 1, 1996–December 31, 2014

Glucocorticoid substance	Number of prescriptions (%)		DDD (%)	
	All use	Multiple-prescription use	All use	Multiple-prescription use
Total	5,691,985 (100)	4,719,061 (100)	335,161,216 (100)	275,597,541 (100)
Betamethasone	1069 (0.02)	872 (0.02)	36,800 (0.01)	30,200 (0.01)
Dexamethasone	6942 (0.12)	2927 (0.06)	115,796 (0.03)	87,380 (0.03)
Methylprednisolone	98,176 (1.7)	70,337 (1.5)	10,875,877 (3.2)	8,235,906 (3.0)
Prednisolone	4,662,315 (82)	3,813,628 (81)	269,275,861 (80)	218,693,311 (79)
Prednisone	786,599 (14)	699,486 (15)	45,159,744 (13)	39,210,258 (14)
Hydrocortisone	136,882 (2.4)	131,811 (2.8)	9,697,138 (3)	9,340,486 (3.4)

Abbreviation: DDDs, defined daily doses.

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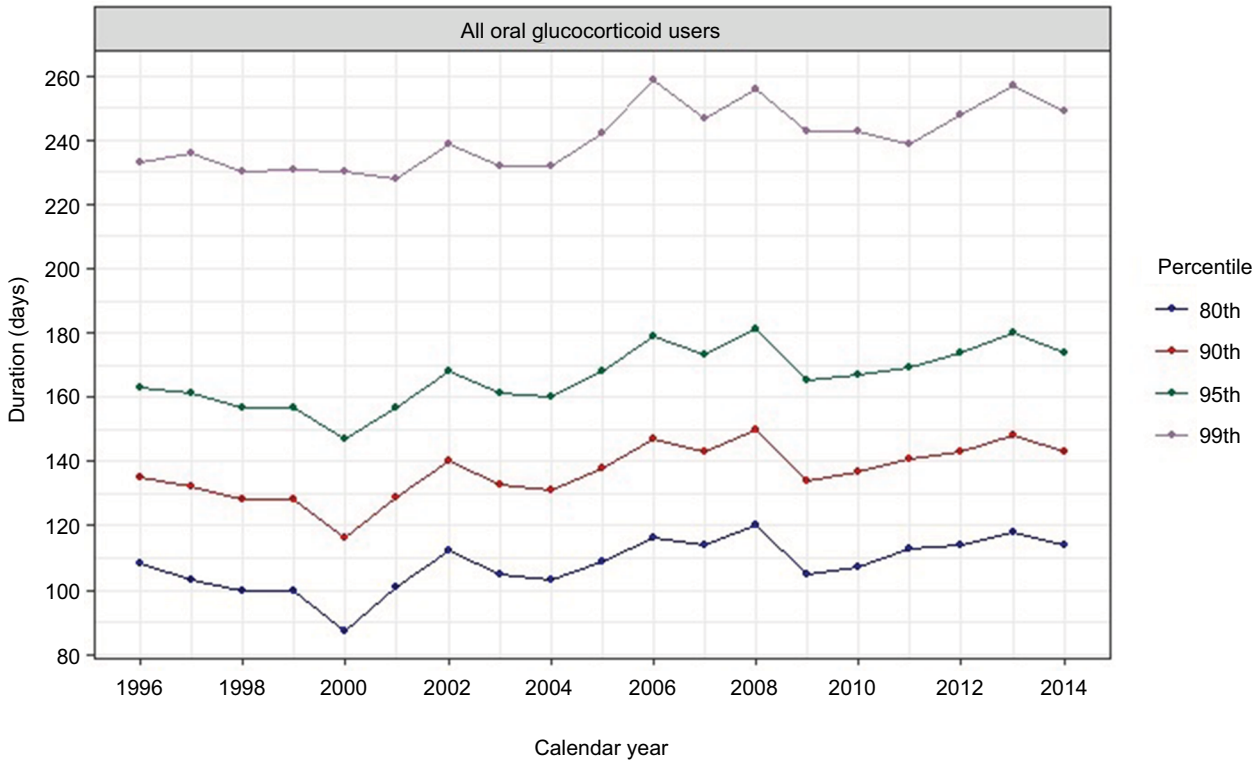

Figure 1 Estimated 80th, 90th, 95th and 99th percentiles for prescription duration (days) in users of oral glucocorticoids, based on the parametric waiting time distribution.

the 80th percentile yielded median episode length of 152 days (IQR: 109–252 days). Applying the 90th, 95th and 99th percentiles yielded median episode lengths of 200 days (IQR: 141–359 days), 248 days (IQR: 173–460 days), and 364 days (IQR: 255–691 days), respectively (Table S4).

Discussion

In this nationwide study, we estimated the duration of single prescriptions among users of oral glucocorticoids and described continuous treatment episodes using the parametric WTD. People who only redeemed 1 prescription in the whole study period accounted for 41% of the population. Prescription duration ranged from 87 to 299 days depending on choice of percentile, calendar year as well as number of tablets and amount dispensed. Application of the 80th, 90th, 95th and 99th percentiles yielded median lengths of first continuous treatment episodes of 113, 141, 170 and 243 days, respectively.

This study can provide important information for future studies of glucocorticoids. As well, the study provides a valuable framework for determining duration of prescribing episodes in pharmacoepidemiological studies. Prescription

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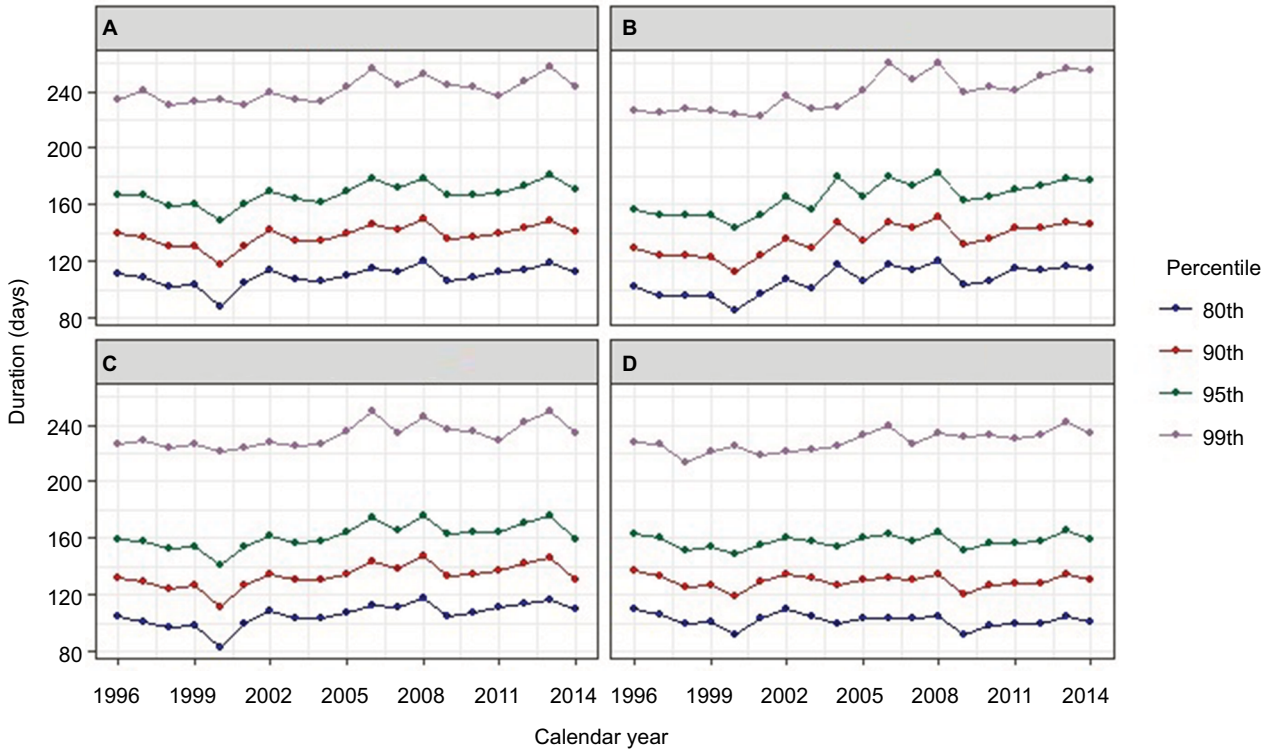

Figure 2 Estimated 80th, 90th, 95th and 99th percentiles for prescription duration (days) in users of oral glucocorticoids using the parametric waiting time distribution, stratified by sex and age group.
Note: (**A**) Women, (**B**) men, (**C**) age group 40–79 years of age, (**D**) age group ≥80 years of age.

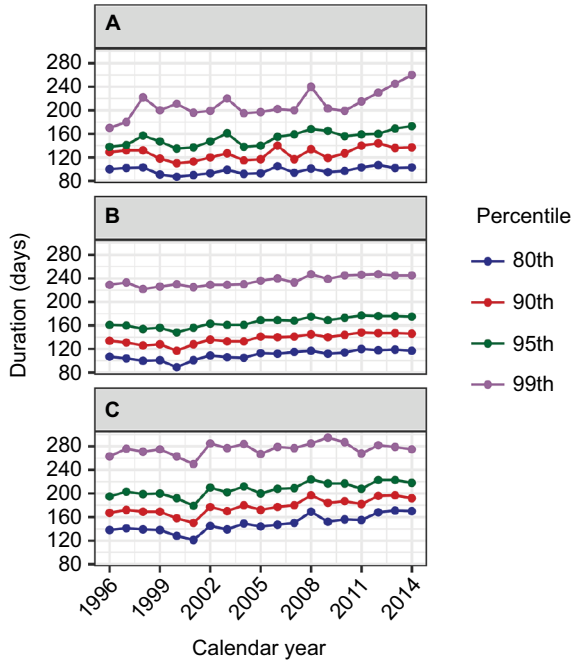

Figure 3 Estimated 80th, 90th, 95th and 99th percentiles for prescription duration (days) in users of oral glucocorticoids using the parametric waiting time distribution, stratified by number of tablets dispensed (number of tablets in a package × number of packages dispensed).
Note: (**A**) 50–60 tablets, (**B**) 100 tablets, (**C**) ≥200 tablets.

registries offer huge potential for studying benefits and adverse effects of drugs. However, information on drug exposure must be handled cautiously to achieve meaningful results and to avoid false conclusions. It is well known that assigning treatment periods in pharmacoepidemiological studies is a source of bias.[2,3] Decisions about duration of single prescriptions and overall length of treatment are often not based on evidence. For example, duration of a single prescription is often assumed to be 3 months; a grace period of, for example, 3 weeks is often added for subsequent prescriptions to be considered a part of the same treatment episode. Such decisions clearly cause some degree of misclassification. Use of the parametric WTD to estimate a percentile of the inter-arrival density among continued users can be viewed as putting a limit on their misclassification. For example, with prescription duration defined on the basis of the 95th percentile, only 5% of continuous users will mistakenly be classified as having stopped use. When the 99th percentile is chosen, only 1% of continued users will be classified mistakenly as having stopped use. On the other hand, use of the 99th percentile is likely to classify a higher proportion of individuals as continued users when, in fact,

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they have stopped. In our study, the 80th percentiles were 87–120 days, whereas the 99th percentiles were 228 to 259 days. Intermittent users of oral glucocorticoids (e.g., COPD patient) may explain the high values of the 99th percentiles. The higher percentiles (e.g., the 99th) of the interarrival distribution are probably not a realistic estimate of prescription duration in our population but rather a measure of time since last prescription in the group of intermittent users. Notably, we found median length of continuous treatment episodes close to duration of individual prescriptions, which can be explained by the high proportion (41%) of people who only redeemed 1 prescription in the whole study.

The method used in this study cannot account for individual covariates that might be predictive of the length of the interval between 2 consecutive prescriptions. These include the number of tablets dispensed, the amount dispensed, frequency of daily intake, the administered dose, patient characteristics and any hospitalizations. However, we performed stratified analyses by the number of tablets as well as amount dispensed. A larger number of tablets yielded longer intervals between consecutive prescriptions, whereas when stratifying on amount the category of 100–150 DDD yielded longer intervals than the category of 200–250 DDD. The longer intervals found in the 100–150 DDD category compared with the 200–250 DDD category were explained by a larger number of tablets dispensed in the 100–150 DDD category than in the 200–250 category. For glucocorticoids, number of tablets dispensed may be a more logic predictor of time interval between consecutive prescriptions than amount dispensed. First, amount reflects a mixture of tablet strength and number of tablets in a package. Second, DDD does not correlate well with prescribed daily dose for glucocorticoids. In addition, we stratified by patient characteristics such as sex and age group and this did not change the estimates appreciably. Other relevant patient characteristics to consider could be treatment indication and disease severity; however, we were not able to identify these. Furthermore, the WTD requires reliable separation of current users into 2 categories: prevalent and incident users. Intermittent use may make the method less reliable. When there is substantial intermittent use, the parametric WTD approach becomes more sensitive to choice of parametric distribution, as it is difficult to separate the uniform distribution for incidence from a slowly declining forward recurrence density for prevalence. We investigated this issue by visually inspecting the empirical WTD, to see if there was a distinct uniform tail toward the end of the observation window and a smoothly declining section in the beginning. This was confirmed graphically. In addition, the Log-Normal distribution chosen in our analyses is highly robust in handling this issue.[4]

Conclusion

In conclusion, we estimated the duration of single prescriptions among users of oral glucocorticoids and described continuous treatment episodes using the parametric WTD. The choice of which percentile of the interarrival density to apply as prescription duration has an impact on the level of misclassification. Use of the 80th percentile provides a measure of drug exposure that is specific, while the 99th percentile provides a sensitive measure. In a population with intermittent users, as in oral glucocorticoid users, the higher percentiles (e.g., the 99th) are probably not a realistic estimate of prescription duration but rather a measure of time since last prescription in the group of intermittent users.

Author contributions

KL, HS, AP, JH, JOLJ, HTS, and IP made primary contributions to writing the manuscript. All authors contributed to the study conception, study design and interpretation of the results. KL performed statistical analyses. KL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 ATC codes for glucocorticoids

Oral glucocorticoids	ATC code
Betamethasone	H02AB01
Dexamethasone	H02AB02
Methylprednisolone	H02AB04
Prednisolone	H02AB06
Prednisone	H02AB07
Hydrocortisone	H02AB09

Abbreviation: ATC, Anatomical Therapeutic Classification.

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Table S2 Estimated 80th, 90th, 95th and 99th percentiles for prescription duration (days) in users of oral glucocorticoids using the parametric waiting time distribution, stratified by amount dispensed (amount in a package × number of packages)

Calendar year	Amount											
	50–70 DDD				100–150 DDD				200–250 DDD			
	80th percentile	90th percentile	95th percentile	99th percentile	80th percentile	90th percentile	95th percentile	99th percentile	80th percentile	90th percentile	95th percentile	99th percentile
1996	105	131	158	225	134	163	191	259	120	155	180	250
1997	104	131	160	230	137	168	194	270	113	140	168	236
1998	99	126	152	219	138	169	198	269	106	120	142	205
1999	99	126	154	224	133	163	193	266	107	133	159	221
2000	90	117	148	230	120	152	180	263	96	117	136	192
2001	101	128	157	227	127	157	177	250	100	137	156	200
2002	109	136	163	228	144	175	206	282	116	145	173	242
2003	106	133	160	228	139	169	199	270	104	130	153	213
2004	105	132	160	229	142	173	204	278	113	139	163	220
2005	113	140	167	230	166	194	220	278	113	142	171	241
2006	110	140	168	230	156	186	216	286	125	153	181	247
2007	116	144	172	230	176	206	234	299	112	133	152	197
2008	116	145	175	244	163	191	218	280	113	140	167	234
2009	109	136	163	230	143	177	210	290	111	140	169	240
2010	111	139	167	236	153	184	216	288	129	148	188	263
2011	113	140	165	226	159	187	214	276	108	145	157	225
2012	116	144	172	239	172	199	225	282	121	148	174	235
2013	118	146	174	242	163	189	214	271	121	148	174	241
2014	114	142	170	237	171	200	226	276	132	159	187	255

Abbreviation: DDD, defined daily doses.

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Table S3 Estimated 80th, 90th, 95th, and 99th percentiles for prescription duration (days) in multiple-prescription use of oral glucocorticoids using the parametric waiting time distribution, by calendar year

Calendar year	80th percentile	90th percentile	95th percentile	99th percentile
1996	102	128	154	220
1997	102	130	159	232
1998	98	125	152	222
1999	100	127	156	229
2000	86	114	145	227
2001	99	126	155	226
2002	106	133	161	229
2003	103	131	159	230
2004	102	130	159	232
2005	104	133	162	236
2006	107	136	166	242
2007	107	136	164	236
2008	120	150	181	256
2009	102	132	163	241
2010	105	136	167	246
2011	107	136	165	238
2012	109	139	169	244
2013	110	141	172	251
2014	126	162	200	295

Table S4 Duration (days) of first oral glucocorticoid continous treatment episodes among all use and multiple-prescription use estimated by the Kaplan–Meier survival function and presented as 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 99th percentiles

Kaplan–Meier estimated percentiles, duration (days)	Parametric WTD estimated percentiles of duration of treatment episodes			
	80th percentile	90th percentile	95th percentile	99th percentile
All use				
1st percentile	9	9	9	9
5th percentile	43	43	43	43
10th percentile	87	116	121	121
25th percentile (Q1)	103	132	160	232
50th percentile (Median)	113	141	170	243
75th percentile (Q3)	142	184	224	325
90th percentile	301	429	544	808
95th percentile	499	777	1029	1593
99th percentile	1298	2149	2999	4545
Multiple-prescription use				
1st percentile	28	28	28	28
5th percentile	73	73	73	73
10th percentile	99	124	140	140
25th percentile (Q1)	109	141	173	255
50th percentile (median)	152	200	248	364
75th percentile (Q3)	252	359	460	691
90th percentile	484	783	1058	1664
95th percentile	749	1264	1758	2760
99th percentile	1739	3002	4127	6047

Abbreviation: WTD, waiting time distribution.

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Paper IV

PLOS ONE

RESEARCH ARTICLE

Clinical indicators of adrenal insufficiency following discontinuation of oral glucocorticoid therapy: A Danish population-based self-controlled case series analysis

Kristina Laugesen[1]*, Irene Petersen[1,2], Henrik Toft Sørensen[1], Jens Otto Lunde Jørgensen[3]

1 Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, **2** Department of Primary Care and Population Health, University College London, London, United Kingdom, **3** Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

* Kristina.laugesen@clin.au.dk

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Data Availability Statement: According to Danish legislation, the authors' own approvals to use the Danish data sources for the current study do not allow them to distribute or make patient data directly available to other parties. Up-to-date information on data access is available online (http://sundhedsdatastyrelsen.dk/da/forskerservice). Access to data from the Danish Health Data Authority requires approval from the Danish Data Protection Agency (https://www.datatilsynet.dk/english/the-danish-data-protection-

Abstract

Background

Biochemical adrenal insufficiency induced by glucocorticoid treatment is prevalent, but data on the clinical implications are sparse. We investigated clinical consequences of glucocorticoid-induced adrenal insufficiency after oral glucocorticoid cessation.

Methods

We conducted a Danish population-based self-controlled case series utilizing medical registries. In this design each individual serves as their own control allowing event rates to be compared as a function of time and treatment. Clinical indicators of adrenal insufficiency were defined as diagnoses of gastrointestinal symptoms, hypotension, cardiovascular collapse, syncope, hyponatremia, and hypoglycaemia. We included 286,680 persons who discontinued long-term ($\geq$ 3 months) oral glucocorticoid treatment. We defined five risk periods and a reference period (before treatment): period 0 (on treatment), withdrawal period (1 month before and after cessation), followed by three consecutive 2 month-risk periods after withdrawal (periods 2–4).

Results

Median age at cessation was 69 years and 57% were female. Median treatment duration was 297 days and median cumulative dose was 3000 mg prednisolone equivalents. The incidence rates of hypotension, gastrointestinal symptoms, hypoglycemia and hyponatremia were increased in the withdrawal period compared to before treatment started (reference period). Incidence rate ratios comparing the withdrawal period with the reference period were 2.5 [95% confidence interval (CI): 1.4–4.3] for hypotension, 1.7 (95% CI: 1.6–1.9) for gastrointestinal symptoms, 2.2 (95% CI: 0.7–7.3) for hypoglycemia, and 1.5 (95% CI: 1.1–2.0) for hyponatremia. During 7 months of follow up, the rates of hypotension and

agency/introduction-to-the-danish-data-protection-agency/). The authors do not have special access privileges to these data.

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Competing interests: The authors have declared that no competing interests exist.

gastrointestinal symptoms remained elevated compared to the reference period. Risk factors included use of antibiotics, increasing average daily dose of glucocorticoids, cumulative dose, and age.

Conclusion

Oral glucocorticoid withdrawal was associated with adverse outcomes attributable to adrenal insufficiency. Our study underscores the need for future research to establish evidence-based clinical guidance on management of patients who discontinue oral glucocorticoids.

Introduction

Primary adrenal insufficiency and secondary adrenal insufficiency due to a pituitary disorder are rare but serious conditions necessitating appropriate replacement therapy [1–3]. In contrast, adrenal insufficiency induced by pharmacological glucocorticoid treatment, *i.e.*, iatrogenic or tertiary adrenal insufficiency, is highly prevalent but the clinical implications are less certain [4, 5].

Cortisol regulates an array of vital physiologic functions related to maintenance of basal and stress-related homeostasis [6–8]. The cardiovascular response to stress depends on cortisol-mediated activation of adrenergic receptors [7]. Cortisol also acts in concert with glucagon, catecholamines, and growth hormone to stimulate hepatic glucose output and lipolysis [7], and exerts effects that dampen stress-induced inflammatory and immune responses [7].

Glucocorticoid treatment suppresses the hypothalamic-pituitary-adrenal (HPA) axis, which may compromise endogenous cortisol secretion in response to stress and thus induce a state of relative adrenal insufficiency [1, 2]. In addition, discontinuation of glucocorticoid treatment can induce prolonged or even permanent suppression of endogenous cortisol secretion, as assessed by biochemical stimulation tests [4, 9–15]. A recent meta-analysis estimated a 50% pooled risk of biochemical adrenal insufficiency among oral glucocorticoid users [4]. This is noteworthy, considering that the annual prevalence of systemic glucocorticoid use is 3% in the Danish population [16]. Nonetheless, current knowledge regarding the clinical implications of glucocorticoid-induced adrenal insufficiency is restricted to anecdotal reports of fatigue, muscle weakness, gastrointestinal symptoms, hypotension, syncope, cardiovascular collapse, hyponatremia, and hypoglycemia [17–19]. The knowledge gap is reflected in current guidelines by the lack of evidence-based recommendations about management of iatrogenic adrenal insufficiency [20, 21]. We therefore conducted a population-based self-controlled case series analysis of clinical indicators of adrenal insufficiency during and after withdrawal of oral glucocorticoids. We defined putative clinical indicators of adrenal insufficiency and reported incidence rates before and after withdrawal of glucocorticoid treatment. We then used a self-controlled case series design [22, 23], in which each individual served as their own control and adverse event rates during and after glucocorticoid treatment were compared to a reference period.

Material and methods

Setting

Denmark provides its entire population with tax-supported healthcare, guaranteeing access to primary and secondary care free-of-charge. A unique personal civil registration number is

assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous individual-level linkage of relevant registries [24].

Study population

We used the Danish National Prescription Registry [25] (DNPR) to identify all persons who discontinued long-term ($\geq$ 3 months) treatment with oral glucocorticoids between January 1, 1996 and December 31, 2014 [26]. A flow chart of the study population is presented in Fig 1. The DNPR records information on pharmacy customers' civil registration number, the redeemed medication's classification code [Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization], date of dispensing, the number of packages dispensed, the number of tablets in a package, tablet strength, and amount dispensed, expressed in terms of "defined daily doses" (DDDs) developed by WHO. Subjects with a prior diagnosis of adrenal insufficiency, as well as subjects on continuous hydrocortisone treatment indicative of adrenal insufficiency, were excluded (n = 4,272). ATC codes for glucocorticoids and other relevant medications are provided in S1 Table.

Exposure

We defined an observation period ranging from 3 months before initiation of an oral glucocorticoid to 7 months after the date of the last glucocorticoid prescription (cessation) for each person in the study population. The observation period was then divided into five risk periods (Fig 2). The definition of observation period and risk periods were based on findings of biochemical adrenal insufficiency in prior clinical studies [4, 5, 9–15]. Risk period 0 covered the time from the date of glucocorticoid therapy initiation to 1 month before redemption of the last glucocorticoid prescription. Risk period 1 (withdrawal period) covered the time from 1 month before redemption of the last prescription for a glucocorticoid to 1 month after this redemption (Days -30 to day 29). Risk period 2 covered months 2–3 after redemption of the last glucocorticoid prescription (Days 30 to 89); risk period 3 covered months 4–5 after redemption of the last glucocorticoid prescription (Days 90 to 149), and risk period 4 corresponded to months 6–7 after redemption of the last prescription (Days 150 to 210). Finally, the reference period was defined as months 3 and 2 before the date of oral glucocorticoid initiation.

Clinical indicators

The following putative clinical indicators of adrenal insufficiency were identified in the Danish National Patient Registry (DNPR): hypotension, syncope, cardiovascular collapse, hyponatremia, hypoglycemia, and gastrointestinal symptoms [1]. Among persons with gastrointestinal symptoms, we excluded those with inflammatory bowel disease (IBD) from the analyses. Persons receiving insulin or sulfonylurea treatment were excluded from the hypoglycemia analyses.

Only primary inpatient diagnoses were included to obtain the most accurate date of diagnosis. An exception was syncope; for this indicator, emergency department visits were included in addition to inpatient diagnoses, as medical assessment of this condition usually occurs in the emergency setting. The DNPR has tracked all inpatient stays at Danish public hospitals since 1977, and outpatient clinic and emergency room visits at all public hospitals since 1995. Data recorded in the DNPR include the patient's civil registration number, dates of admission and discharge or outpatient visit dates, discharge diagnoses for each contact, classified according to the *Eighth Revision* of the *International Classification of Diseases* (ICD-8) until 1994 and

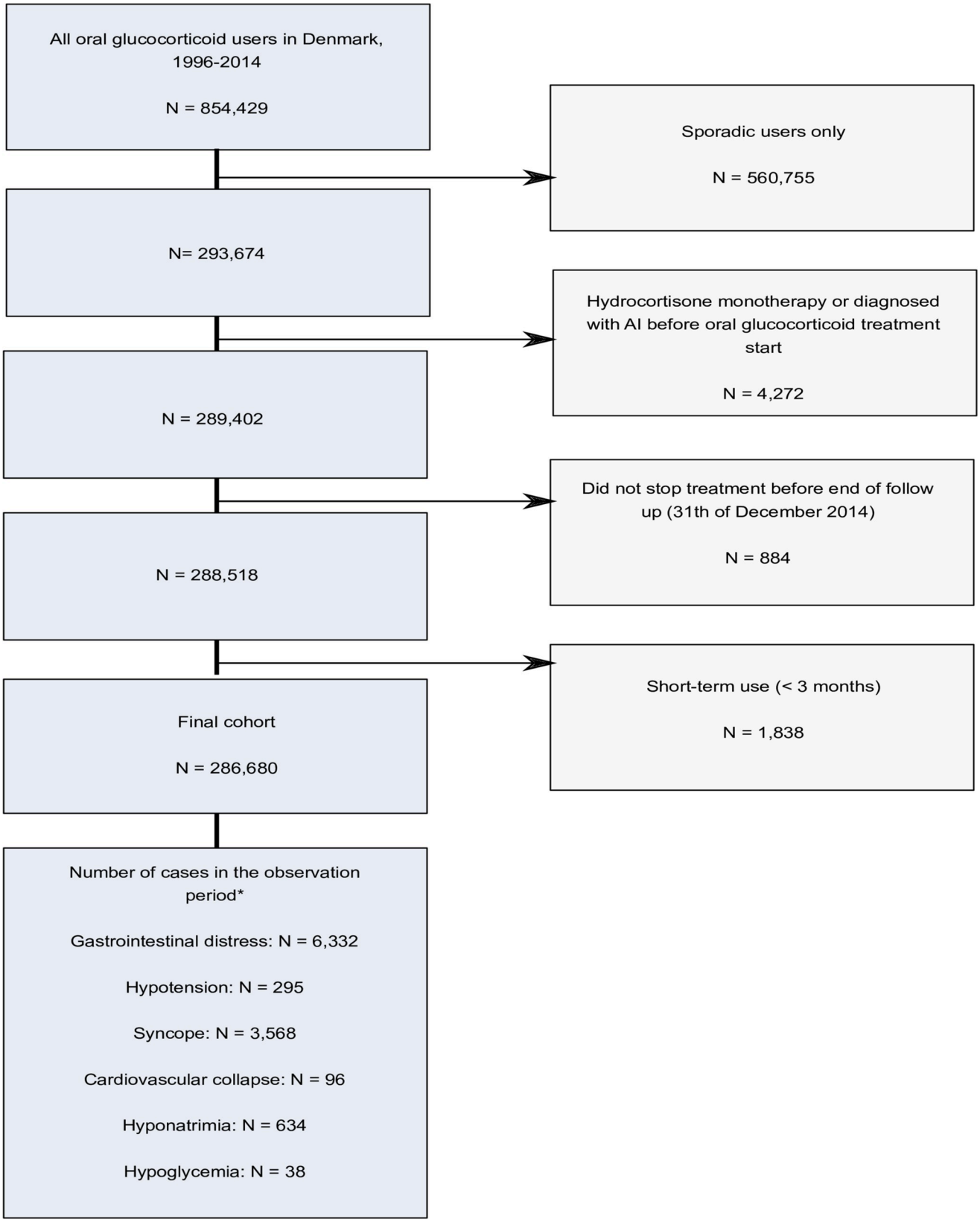

Fig 1. Flow chart of the study population. * The observation period ranges from 3 months before initiation of first long-term (≥ 3 months) oral glucocorticoid treatment to 7 months after the date of last glucocorticoid prescription (cessation).

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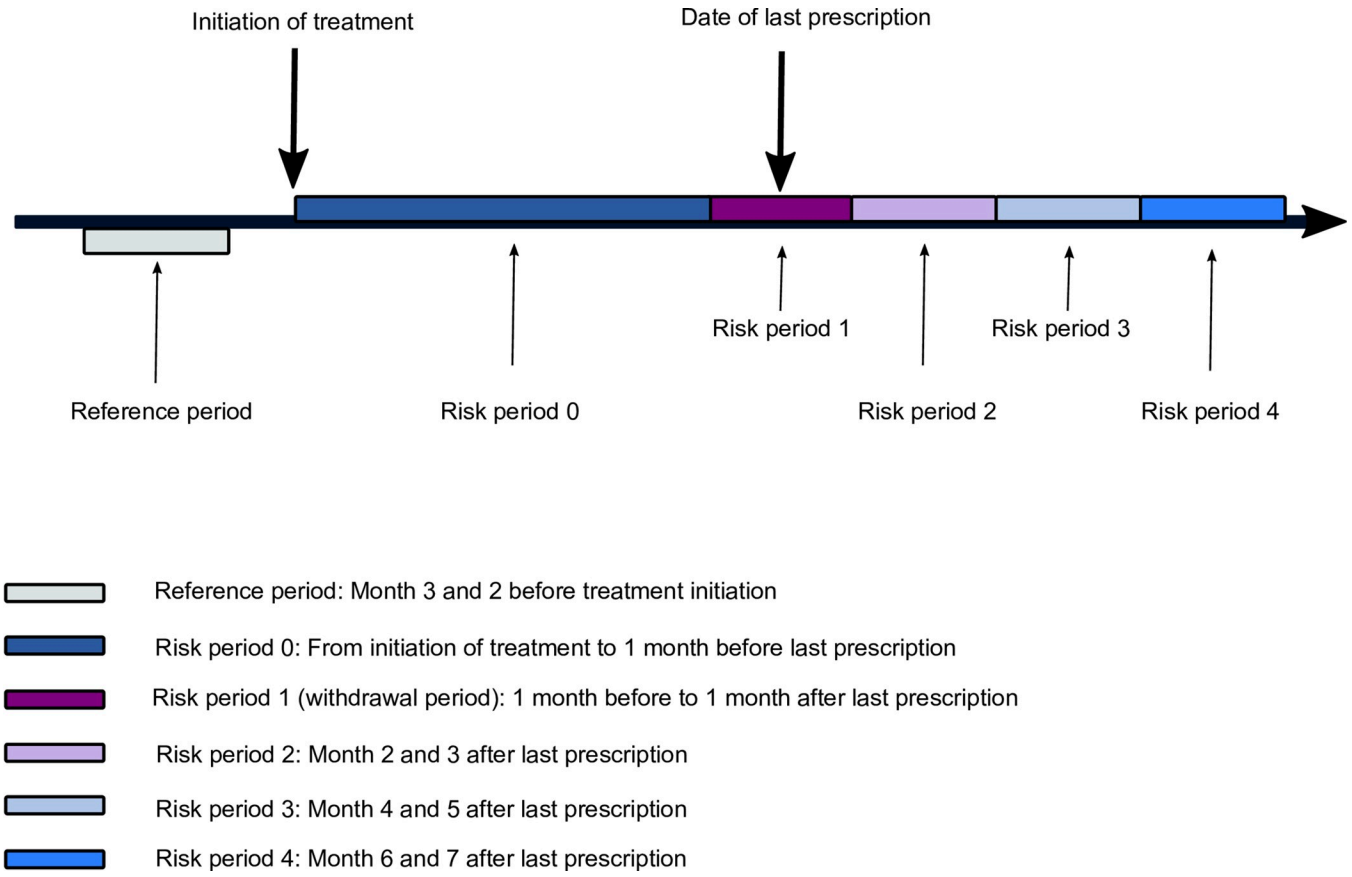

Fig 2. Observation period and defined risk periods for an individual person receiving oral glucocorticoid treatment who stops treatment before end of follow up.

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the *Tenth Revision* thereafter (ICD-10) [27]. The ICD codes used in this study are provided in S2 Table.

Statistical analysis

We characterized our study population according to type of last glucocorticoid prescription, duration of treatment (median, IQR), cumulative dose in prednisolone equivalents (median, IQR), average daily dose in prednisolone equivalents, and according to age, sex, morbidity, and concomitant treatment with inhaled, topical or injectable glucocorticoids and glucocorticoids acting on the intestine. The codes for morbidity are provided in S3 Table. Calculations for prednisolone-equivalent cumulative doses are provided in S4 Table.

Based on the entire study population of persons who discontinued oral glucocorticoid treatment, we calculated incidence rates and 2-week prevalence. We estimated incidence rates in the reference period and the five risk periods. Each type of clinical indicator was analysed separately and persons were followed from start of the period of interest until first event, emigration, death or end of the period of interest, whichever came first. We calculated and presented graphically the 2-week prevalence during the period of 12 months before to 7 months after redemption of the last glucocorticoid prescription.

Self -controlled case series design. We estimated incidence rate ratios (IRRs) using the self-controlled case series design [22, 28]. This design is a case-only design and each case serves

as their own control. Thus, the method inherently accounts for confounding factors that are stable over time (*e.g.*, sex, ethnicity and genetics). First, we identified cases in the observation period (Fig 2). We analysed each type of clinical indicator as a distinct case variable. In addition, we only considered the first event (*e.g.* recurrent events were not included in the analyses). This is the recommended approach by Petersen et al., when recurrent events cannot be assumed independent [22]. Second, we used a conditional fixed-effect Poisson regression to compare incidence rates in the pre-defined risk periods with the incidence rate in the reference period. The follow-up time was not censored at an event. Hence, all time occurring within the observation period (both before and after individuals have experienced the event) was included in the analysis. Nevertheless, individuals were censored at the end of the observation period or death, whichever came first.

In a sub-analysis we stratified on cumulative glucocorticoid dose ($<$ 0.5 g, 0.5–5 g, $>$5g).

Risk factors for adrenal insufficiency. We used Cox proportional hazard regression to identify potential risk factors, such as sex, age ($<$ 30, 30–49, 50–69, and $\geq$ 70 years of age), treatment duration ($<$ 6 months, 6–12 months, 1–2 years, and $>$ 2 years), cumulative treatment dose ($<$ 0.5 gram (g), 0.5–5 g, $>$ 5 g expressed in prednisolone equivalents), average daily dose ($<$ 5 mg/day, 5–9 mg/day, 10–20 mg/day and $>$ 20 mg/day expressed in prednisolone equivalents), and use of antibiotics. As infections are major precipitating causes of adrenal crisis, we assessed use of antibiotics as a proxy for infection. Antibiotic use was modelled as a time-varying exposure and a person was counted as exposed 30 days after a prescription redemption. We followed our study population from date of cessation until a diagnosis of a clinical indicator (only those indicators showing increased risk during or after withdrawal), death, emigration or end of the observation period, whichever came first. The assumption of proportional hazards was verified graphically.

Sensitivity analyses. We conducted several sensitivity analyses to ensure the validity of our results. First, we addressed the concern that if an event increases the probability of death, then the observation periods could be shortened as a direct result of the event. This event-dependent censoring can lead to bias in the self-controlled case series design [22]. Therefore, in a sensitivity analysis we excluded persons who died 60 days after an event. Any major differences in the results of the sensitivity analysis compared to our main results would suggest bias. Second, as the self-controlled case series design can be sensitive to changes in health care utilization, a negative outcome analysis was conducted using erysipelas as outcome. Erysipelas is assumed to be unrelated to both adrenal insufficiency and the condition for which glucocorticoid was prescribed. Third, since alternative routes of glucocorticoid administration (*i.e.*, injection, inhalation, topical, or glucocorticoids acting on the intestine) also may induce adrenal insufficiency, concomitant use of these types of glucocorticoids could potentially affect our results. To control for this factor, we conducted a sensitivity analysis restricted to persons treated only with oral glucocorticoids.

All statistical analyses were conducted using Stata 14 for Windows.

This study was approved by the Danish Data Protection Agency (Record number: 2016-051-000001, serial number 448). According to Danish legislation, informed consent or approval from an ethical committee is not required for registry based studies.

Results

In total, we identified 286,680 persons who discontinued long-term ($\geq$ 3 months) oral glucocorticoid treatment (Fig 1). The most frequent type of last redeemed prescription was prednisolone [n = 280,010 (98%)] (Table 1). Median treatment duration was 297 days [interquartile range (IQR): 179–584 days]; median cumulative dose was 3000 mg prednisolone equivalents

Table 1. Characteristics of 286,680 oral glucocorticoid users according to sex, age, glucocorticoid type, dose, and morbidity as of the date of cessation.

Characteristics	Number (%)
Sex	
Female	163,077 (57)
Male	123,603 (43)
Age, years	
0–19	4,188 (1.5)
20–39	21,806 (7.6)
40–59	55,894 (20)
60–79	140,056 (49)
≥80	64,736 (23)
Type of glucocorticoid use (last prescription)	
Betamethasone	68 (0.02)
Dexamethasone	215 (0.07)
Methylprednisolone	6,126 (2.1)
Prednisolone	280,010 (98)
Prednisone	0 (0)
Hydrocortisone	261 (0.09)
Cumulative dose [a]	
< 0.5 g	21,114 (7.4)
0.5–5 g	171,566 (60)
5+ g	94,000 (33)
Average daily dose [a]	
< 5 mg /day	86,099 (30)
5–9 mg/day	114,194 (40)
10–20 mg/day	57,970 (20)
20 + mg/day	28,417 (9.9)
Morbidity	
Polymyalgia rheumatica/ giant cell arteritis	28,220 (9.8)
Rheumatoid arthritis	21,256 (7.4)
Psoriasis arthritis	1,943 (0.68)
Ankylosing spondylitis	881 (0.31)
Other rheumatological diseases	9,129 (3.2)
Other autoimmune diseases	1,900 (0.66)
Renal diseases	12,568 (4.4)
Cancer	64,503 (23)
Dermatological diseases	1,851 (0.65)
Ulcerative colitis	10,841 (3.8)
Crohn's disease	6,264 (2.2)
Ashma	29,573 (10)
COPD	63,685 (22)
Multiple sclerosis	1,656 (0.58)
Concomitant glucocorticoid treatment[b]	
Locally acting (inhaled, acting on the intestine, or topical)	90,937 (32)
Injections	15,971 (5.6)

[a] In prednisolone equivalents.

[b] Defined as prescription redemption throughout the observation period.

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Table 2. Incidence rates per 1000 person-years with 95% confidence intervals (CI) (n = 286,680).

		Incidence rates per 1000 person years with 95% CIs				
	Reference period	Risk period 0	Risk period 1 (withdrawal period)	Risk period 2	Risk period 3	Risk period 4
Hypotension	0.4 (0.3–0.6)	0.5 (0.5–0.6)	0.9 (0.7–1.2)	0.7 (0.5–1.1)	0.5 (0.3–0.8)	0.4 (0.2–0.7)
Syncope	8.8 (8.0–9.7)	6.1 (5.8–6.3)	8.6 (7.8–9.5)	0.7 (6.6–8.3)	6.7 (5.9–7.6)	5.6 (4.8–6.6)
Cardiovascular collapse	NA	NA	0.5 (0.3–0.7)	0.6 (0.4–0.9)	NA	NA
Hyponatremia	1.7 (1.4–2.1)	0.9 (0.8–1.0)	2.4 (2.0–2.9)	1.4 (1.1–1.9)	1.1 (0.8–1.6)	0.8 (0.5–1.2)
Gastrointestinal symptoms	19 (18–21)	14 (13–14)	30 (28–31)	24 (22–36)	15 (13–16)	14 (12–15)
Hypoglycemia	NA	NA	0.2 (0.1–0.4)	0.3 (0.1–0.7)	NA	NA

NA: Not applicable.

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(IQR: 1,125–6,500 mg), and median average daily dose was 6.8 mg prednisolone equivalents per day (IQR: 4.6–12 mg per day). Median age at cessation was 69 years (IQR: 57–78 years) and 163,077 (57%) were female (Table 1). Inhaled glucocorticoids, topical or glucocorticoids acting on the intestine were used concomitantly by 90,937 persons (32%), and 15,971 persons (5.6%) received glucocorticoid injections (Table 1). Morbidities frequently recorded at any time prior to glucocorticoid cessation included cancer [64,503 (23%)], COPD [63,685 (22%)], asthma [29,573 (10%)], polymyalgia rheumatica/giant cell arteritis [28,220 (9.8%)], and rheumatoid arthritis [21,256 (7.4%)] (Table 1).

In total, 10,963 incident cases of clinical indicators were identified in the observation period (hypotension: 295 cases; syncope: 3,568 cases; cardiovascular collapse: 96 cases; gastrointestinal symptoms: 6,332 cases; hyponatremia: 634 cases; hypoglycemia: 38 cases) (Fig 1). Only 49 persons were coded with treatment-induced adrenal insufficiency during the observation period. Compared to the reference period, the incidence rates of gastrointestinal symptoms, hypotension, cardiovascular collapse, hyponatremia, and hypoglycemia were all elevated in risk period 1 (the withdrawal period) and in risk period 2 (except for hyponatremia). The incidence rate of gastrointestinal symptoms increased to a maximum of 30 per 1000 person-years (P-Y) [95% confidence interval (CI): 28–31 per 1000 P-Y] in risk period 1 (withdrawal period), and remained elevated in risk period 2 with an incidence rate of 24 per 1000 P-Y (95% CI: 22–36 per 1000 P-Y) (Table 2). The incidence rate of hyponatremia was 2.4 per 1000 P-Y (95% CI: 2.0–2.9 per 1000 P-Y) in risk period 1 (Table 2). The incidence rate of hypotension was 0.9 per 1000 P-Y (95% CI: 0.7–1.2 per 1000 P-Y) in risk period 1 and 0.7 per 1000 P-Y (95% CI: 0.5–1.1 per 1000 P-Y) in risk period 2 (Table 2). The incidence rate of hypoglycemia was 0.2 per 1000 P-Y (95% CI: 0.1–0.4 per 1000 P-Y) in risk period 1 and 0.3 per 1000 P-Y (95% CI: 0.1–0.7 per 1000 P-Y) in risk period 2 (Table 2). No diagnoses of cardiovascular collapse occurred in the reference period, but incidence rates in risk periods 1 and 2 were 0.5 per 1000 P-Y (95% CI: 0.3–0.7 per 1000 P-Y) and 0.6 per 1000 P-Y (95% CI: 0.4–0.9 per 1000 P-Y), respectively (Table 2).

Fig 3 presents the 2-week prevalence of all clinical indicators of adrenal insufficiency (gastrointestinal symptoms, hypotension, cardiovascular collapse, hyponatremia, hypoglycemia, syncope), and the negative outcome (erysipelas). The prevalence of a composite of all clinical indicators increased to a maximum of 2.6 per 1000 in the 2 weeks after the last glucocorticoid prescription and remained higher than before discontinuation during 1.5 months following the last prescription. Gastrointestinal symptoms had the highest prevalence, with a maximum of 1.8 events per 1000 in the 2 weeks after the last prescription redemption.

The distribution of the total number of admissions per person during risk periods 0–4 is presented in S5 Table.

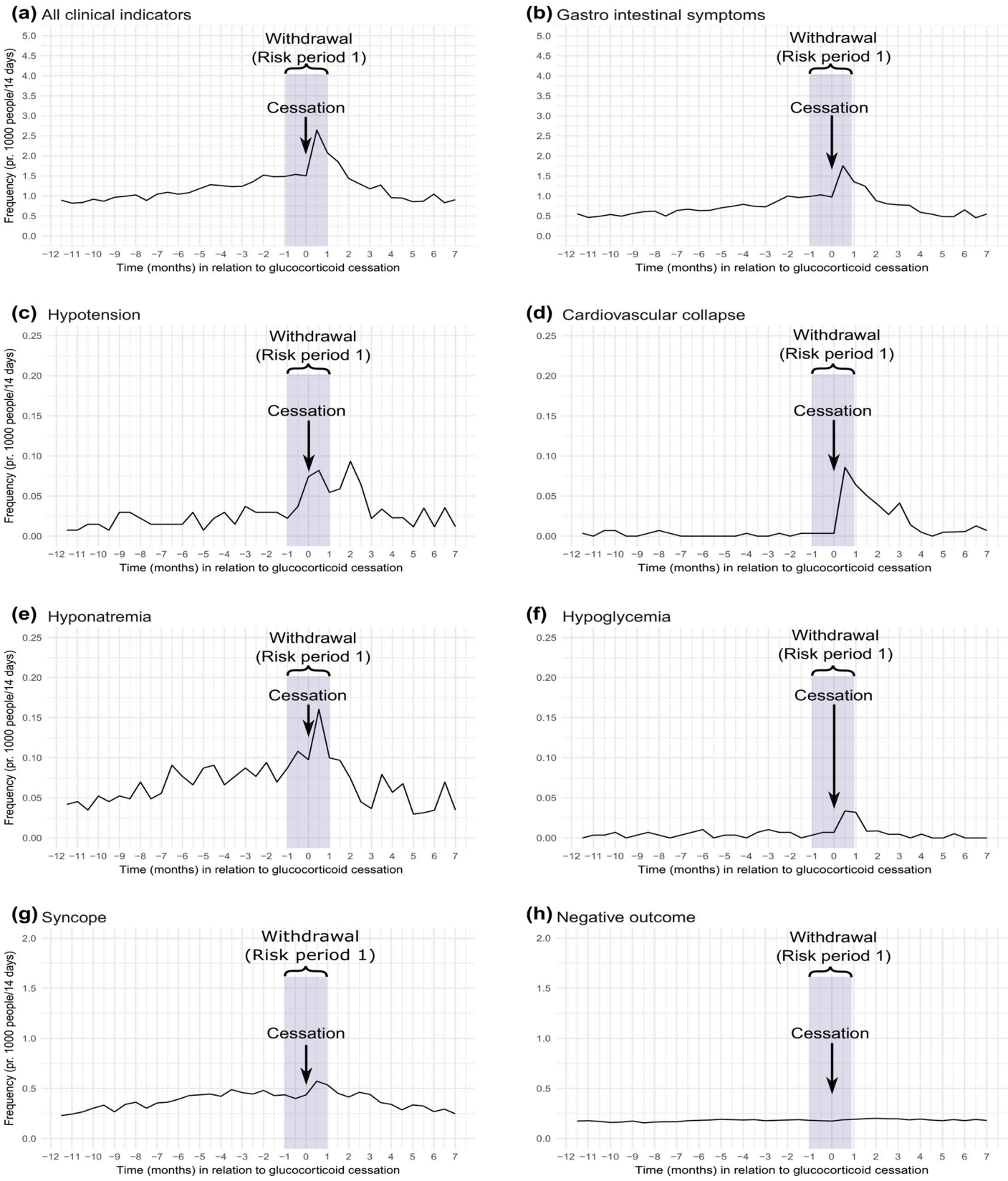
(a) All clinical indicators
(b) Gastro intestinal symptoms
(c) Hypotension
(d) Cardiovascular collapse
(e) Hyponatremia
(f) Hypoglycemia
(g) Syncope
(h) Negative outcome
Withdrawal
(Risk period 1)
Cessation
Frequency (pr. 1000 people/14 days)
Time (months) in relation to glucocorticoid cessation

Fig 3. The 2-week prevalence (per 1000 persons) of clinical indicators of adrenal insufficiency and the negative outcome during the period of 12 month before the last glucocorticoid prescription to 7 months after this prescription. (a) All clinical indicators. (b) Gastrointestinal symptoms. (c) Hypotension. (d) Cardiovascular collapse. (e) Hyponatremia. (f) Hypoglycemia. (g) Syncope. (h) Negative outcome.

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Self-controlled case series design

The incidence rates of hypotension, gastrointestinal symptoms, hypoglycemia and hyponatremia were increased in the withdrawal period compared to before treatment started (reference period). The IRRs were 2.5 (95% CI: 1.4–4.3) for hypotension, 1.7 (95% CI: 1.6–1.9) for gastrointestinal symptoms, 2.2 (95% CI: 0.7–7.3) for hypoglycemia, and 1.5 (95% CI: 1.1–2.0) for hyponatremia (Table 3). The risk of hypotension, gastrointestinal symptoms, and hypoglycemia remained elevated, although at a declining rate, during the 7 months of follow up (Table 3). The results of our sensitivity analyses showed that our estimates were robust (S6 and S7 Tables), although the IRRs for hyponatremia attenuated after exclusion of persons with concomitant use of other glucocorticoids (*i.e.*, those administered by injection, topical, or inhalation, or glucocorticoids acting on the intestine) (S7 Table). No incident cases of cardiovascular collapse were identified in the reference period, so IRRs could not be computed. Our negative outcome (erysipelas) revealed IRRs close to one (Table 3). The results, when stratifying on cumulative glucocorticoid dose, are shown in S8 Table.

Risk factors

Risk factors for clinical indicators of adrenal insufficiency were use of antibiotics, increasing average daily dose, increasing cumulative dose, and increasing age (Table 4).

Discussion

Our main finding were (1) the risks of hypotension, gastrointestinal symptoms, hyponatremia, and hypoglycemia in the glucocorticoid withdrawal period were increased compared to before starting glucocorticoid treatment and remained elevated for hypotension and gastrointestinal symptoms during 7 months of follow up, (2) use of antibiotics, cumulative dose of oral glucocorticoids, average daily dose, and age were associated with increased risk of clinical indicators of adrenal insufficiency during and after withdrawal of glucocorticoid therapy.

To the best of our knowledge, this study is the first to systematically investigate the clinical impact of adrenal insufficiency following oral glucocorticoid withdrawal and it extends anecdotal reports in the literature [17–19]. Prior randomized controlled trials [9, 10] (range: n = 10–42 included persons) and cohort studies [11–15] (range: n = 10–150 persons included)

Table 3. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for events by risk period.

	IRR and (95% CI)					
	Syncope	Hypo-natremia	Hypotension	Gastrointestinal symptoms	Hypoglycemia	Negative outcome (erysipelas)
Number of cases	3,568	634	295	6,332	38	1,850
Reference period	1	1	1	1	1	1
Risk period 0	0.8 (0.7–0.9)	0.7 (0.6–1.0)	1.5 (0.9–2.5)	1.0 (0.9–1.1)	0.6 (0.2–2.1)	1.0 (0.8–1.2)
Risk period 1	1.1 (0.9–1.2)	1.5 (1.1–2.0)	2.5 (1.4–4.3)	1.7 (1.6–1.9)	2.2 (0.7–7.3)	1.1 (0.9–1.4)
Risk period 2	1.0 (0.9–1.2)	1.1 (0.7–1.5)	2.3 (1.3–4.3)	2.0 (1.8–2.2)	2.4 (0.6–9.5)	1.0 (0.8–1.3)
Risk period 3	1.0 (0.8–1.2)	0.9 (0.6–1.4)	2.0 (1.0–3.9)	1.5 (1.3–1.7)	NA	1.1 (0.9–1.5)
Risk period 4	0.9 (0.7–1.0)	0.7 (0.4–1.1)	1.7 (0.8–3.6)	1.5 (1.3–1.7)	0.9 (0.1–8.9)	1.1 (0.8–1.4)

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Table 4. Risk factors for clinical indicators of adrenal insufficiency.

Variable	Hazard ratios and 95% CIs
Sex	
Women	1
Men	0.99 (0.92–1.07)
Age, y	
< 30	1
30–49	1.24 (0.95–1.63)
50–69	1.80 (1.41–2.32)
≥70	3.00 (2.35–3.82)
Average daily dose in prednisolone equivalents	
< 5 mg /day	1
5–9 mg/day	1.13 (1.02–1.25)
10–20 mg/day	1.76 (1.59–1.94)
20 + mg/day	3.28 (2.89–3.73)
Treatment duration	
< 6 months	1
6–12 months	1.12 (1.01–1.24)
1–2 years	1.03 (0.92–1.16)
> 2 years	1.21 (1.07–1.36)
Cumulative dose in prednisolone equivalents	
< 0.5 g	1
0.5-5g	1.25 (1.10–1.41)
5+ g	2.06 (1.81–2.34)
Use of antibiotics[a]	
No	1
Yes	1.83 (1.64–2.05)

[a] Proxy for infection. The antibiotic prescription had to be redeemed up to 30 days prior to an event to count as a precipitating factor (modelled as a time-varying exposure)

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have been unable to establish a time course for adrenal recovery after glucocorticoid cessation. The systematic review by Joseph *et al*. reported a percentage range for biochemical adrenal insufficiency of 27%-69% in patients tested more than 30 days after their last glucocorticoid dose [5]. Our findings suggest that symptomatic adrenal insufficiency peaks up to 3 months after cessation of treatment and remains increased for at least 7 months. Previous studies have debated the association between dose and duration of glucocorticoid treatment and iatrogenic biochemical adrenal insufficiency. In general, high dose and longer treatment duration have been associated with higher adrenal insufficiency risk [4, 5]. Our study confirmed that glucocorticoid dose is a risk factor for clinical adrenal insufficiency. In addition, persons exposed to an infection (potential stressor) were also at increased risk of clinical adrenal insufficiency, which fits well with the underlying pathophysiology of cortisol deficiency [7]. Our study has several strengths. The nationwide population-based design allowed us to assess clinical indicators of adrenal insufficiency in a large heterogeneous population representative of clinical practice. Further, using the self-controlled case series analysis, we were able to take into account patient characteristics that are stable over time, including potential unmeasured or unknown confounders (*i.e*. sex, genetics and lifestyle).

Our study also has limitations. First, we used prescription redemption as a proxy for use. Thus, we were unable to assess adherence or to include inpatient hospital medication use.

Moreover, we were unable to ascertain the exact timing of the last glucocorticoid dose. It is likely that patients tapered their glucocorticoid therapy for weeks after redemption of their last prescription. To accommodate these inaccuracies, we defined the withdrawal period as a 2-month period encompassing the redemption date of the last prescription. Use of wide risk periods may have biased the IRR estimates toward the null. In addition, we were unable to investigate different tapering schedules.

Second, although the self-controlled case series design accounts for time-independent confounders, it remains sensitive to changes over time in such factors as morbidity or health care utilization. Therefore, confounding by indication or disease severity could affect some of our IRR estimates. For example, gastrointestinal symptoms may be related to IBD relapse. To overcome this, we excluded IBD patients in the assessment of gastrointestinal symptoms. Confounding by use of insulin and sulfonylurea, also were eliminated by exclusion. It is well known that use of other glucocorticoid formulations, such as inhaled and injectable forms and glucocorticoids acting on the intestine, also increases the risk of iatrogenic adrenal insufficiency [29, 30]. In our study, 32% of patients used locally acting glucocorticoids (inhaled, topical, or glucocorticoids acting on the intestine) and 5.6% of patients were treated with glucocorticoid injections in addition to oral glucocorticoids. However, our sensitivity analysis excluding persons with concomitant glucocorticoid treatment did not affect our estimates substantially. We found no association between discontinuation and erysipelas (our negative outcome) indicating that changes in health care utilization were not a major issue.

Third, the self-controlled case series analysis can be sensitive to reverse causation. We did not expect that any of the outcome events would change the decision to prescribe glucocorticoids. However, a change in exposure status from continuous user to discontinued user may be correlated to the terminal phase of illness. Therefore, we were not able to assess death as an outcome. In addition, in the terminal phase, morbidity and frequency of hospitalization often increase, which could potentially lead to incorrect associations. Nevertheless, excluding persons who died 60 days after an event did not alter our results, indicating this was not a major issue in our study.

Fourth, our use of hospital registry data to assess outcomes raises the possibility of misclassification. Hyponatremia and cardiovascular collapse diagnoses have been validated and the positive predictive values are $> 90\%$, however, other outcomes used in our study lack validation [27]. Still, misclassification of outcomes is unlikely to vary systematically according to reference and risk periods. Thus, it could not explain any associations found in the self-controlled case series analysis. Another concern is that low data completeness could lead to underestimation of our incidence rates and 2-week prevalence. Furthermore, the defined clinical indicators are not specific for adrenal insufficiency. In addition, we were only able to assess outcomes that led to a hospital contact. Hence, less severe indicators, such as fatigue and muscle weakness, were not captured. We also lacked access to biochemical data, hence cortisol measurements could not be assessed. Finally, only 49 persons in our study had a recorded diagnosis of treatment-induced adrenal insufficiency. This small number most likely reflects lack of awareness and failure to diagnose iatrogenic adrenal insufficiency, considering that discontinuation of glucocorticoids may induce biochemical adrenal insufficiency in 50% of patients [4].

In conclusion, we found that oral glucocorticoid withdrawal was associated with observable clinical outcomes attributable to adrenal insufficiency, although the incidence rates were low. Our study underscores the importance for future research to establish evidence-based clinical guidance on procedures for patients' withdrawal from glucocorticoid use, as well as guidance for identifying patients in need of biochemical testing.

Supporting information

S1 Table. Anatomical Therapeutic Classification (ATC) codes, Nordic article numbers, and procedure codes for medications.
(PDF)

S2 Table. *Tenth Revision of the International Classification of Diseases* (ICD-10) codes for outcome events.
(PDF)

S3 Table. Morbidity. *Eighth Revision of the International Classification of Diseases* (ICD-8) until 1994 and the *Tenth Revision* (IDC-10) codes.
(PDF)

S4 Table. Equivalency table presenting systemic glucocorticoids and corresponding prednisolone conversion factors. Cumulative dose calculation: The cumulative dose was calculated by multiplying the number of pills, dose per pill, and prednisolone conversion factor for each prescription and then adding them up across all prescriptions.
(PDF)

S5 Table. Distribution of total number of hospital admissions per person during risk periods 0–4.
(PDF)

S6 Table. Sensitivity analysis excluding persons who died within 60 days after an event. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for events by risk period.
(PDF)

S7 Table. Sensitivity analysis excluding persons with concomitant use of injectable or locally administrated glucocorticoids. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for events by risk period.
(PDF)

S8 Table. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for events by risk period. Sub-analysis stratified on cumulative glucocorticoid dose.
(PDF)

Author Contributions

Conceptualization: Kristina Laugesen, Irene Petersen, Henrik Toft Sørensen, Jens Otto Lunde Jørgensen.

Data curation: Kristina Laugesen.

Formal analysis: Kristina Laugesen.

Funding acquisition: Kristina Laugesen, Henrik Toft Sørensen, Jens Otto Lunde Jørgensen.

Investigation: Kristina Laugesen.

Methodology: Kristina Laugesen, Irene Petersen, Henrik Toft Sørensen, Jens Otto Lunde Jørgensen.

Project administration: Kristina Laugesen.

Supervision: Irene Petersen, Henrik Toft Sørensen, Jens Otto Lunde Jørgensen.

Writing – original draft: Kristina Laugesen, Irene Petersen, Henrik Toft Sørensen, Jens Otto Lunde Jørgensen.

Writing – review & editing: Irene Petersen, Henrik Toft Sørensen, Jens Otto Lunde Jørgensen.

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S1 Table. Anatomical Therapeutic Classification (ATC) codes, Nordic article numbers, and procedure codes for medications.

Drug	ATC code	Nordic article number	Procedure codes
Oral glucocorticoids			
Betamethasone	H02AB01	499590	
Dexamethasone	H02AB02	039413; 126955; 188988; 113331; 190108; 190132; 374319; 418122; 579043; 591445	
Methylprednisolone	H02AB04	046557; 050487; 072601; 109119; 111245; 112671; 159103; 174284; 450619; 499772; 500074; 509125; 509133; 536422	
Prednisolone	H02AB06	042448; 164118; 164130; 164141; 164153; 164164; 164175; 168548; 184382; 398747; 425905; 502076; 507660; 516005; 516013; 516021; 516039; 521930; 521948; 521955; 530899: 564513; 743542; 743559; 743567;748756	
Prednisone	H02AB07		
Hydrocortisone	H02AB09	049319; 141569; 155579; 393735; 424199; 445320; 487361; 490667; 490667; 503581; 746628; 746636	
Glucocorticoids by injection			
Betamethasone	H02AB01	006595; 006634; 013802; 013815; 013824; 013835; 034731; 038661; 042812; 058396; 123372; 131796; 143773; 145143; 177360; 181595; 192914; 192922; 194713; 385214; 399765; 413438; 473824; 477631; 483156; 488471; 498048, 504332; 523266; 556860	
Dexamethasone	H02AB02	053066; 057984; 421131; 570853; 570861	
Methylprednisolone	H02AB04	042093; 047663; 067283; 130683; 134940; 134965; 141044; 143339; 143347; 153928; 161075; 161637; 165613; 171016;180299; 189506; 189522; 195389; 390762; 397856; 420151; 434274; 453162; 465187; 488496; 489011; 530391; 549923; 560425; 563956; 583158; 590659	
Prednisolone	H02AB06	189811	
Triamcinolone	H02AB08		
Locally-acting glucocorticoids			
Beclomethasone (inhaled)	R03BA01; R03AK08		
Budesonide (inhaled)	R03BA02; R03AK07		
Flunisolide (inhaled)	R03BA03		
Fluticasone (inhaled)	R03BA05; R03AK06; R03AK10; R03AK11		
Mometasone (inhaled)	R03BA07		
Ciclesonide	R03BA08		
Prednisolone (acting on the intestine)	A07EA01		
Hydrocortisone (acting on the intestine)	A07EA02		
Budesonide (acting on the intestine)	A07EA06		
Various glucocorticoids for hemorrhoids	C05AA		
Prednisolone (suppositories)	H02AB06	685546	
Glucocorticoids for skin conditions	D07		
Treatments for IBD besides oral glucocorticoids			
Hydrocortisone (acting on the intestine)	A07EA02		
Budesonide	A07EA06		
Azathioprin	L04AX01		
Methotrexate	L01BA01, L04AX03		BWHA115
Mesalazin	A07EC02		
Sulfazalazine	A07EC01		
Infliximab	L04AB02		BOHJ18A1
Adalinumab	L04AB04		BOHJ18A3
Vedolizumab	L04AA33		BOHJ19H4
Ustekinumnab	L04AC05		BOHJ18B3
Golinumab	L04AB06		BOHJ18A4

Other medications	
Insulin	A10A
Sulfonylureas	A10BB
Antibiotics	J01

S2 Table. Tenth Revision of the International Classification of Diseases (ICD-10) codes for outcome events.

Diagnoses	ICD-10 codes
Syncope	R55
Hyponatraemia	E871
Hypotension	I95
Cardiovascular collapse	
Cardiogenic shock or	R570
Hypovolemic shock	R571
Gastrointestinal symptoms	
Nausea/vomiting	R11
Abdominal pain	R10
Diarrhea	K529B
Obstipation	K590
Hypoglycaemia	E15 E162
Treatment-induced adrenal insufficiency	E273
Erysipelas (negative outcome)	A46

S3 Table. Morbidity. Eighth Revision of the International Classification of Diseases (ICD-8) until 1994 and the Tenth Revision (IDC-10) codes.

Disease	ICD-10	ICD-8
Pulmonary diseases		
Asthma	J45, J46	493
Chronic obstructive pulmonary disease	J41, J42, J43, J44	491, 492
Rheumatic diseases		
Polymyalgia rheumatica/ Giant cell arthritis	M315, M316, M35.3	446.30, 446.31, 446.39
Rheumatoid arthritis	M05, M06	712.19, 712.29, 712.39, 712.59
Psoriasis arthritis	M07.0-M07.3	696.09
Ankylosing spondylitis	M45	712.49
Other rheumatic diseases	L94.0, L94.1 (Sclerodermia) M35.1 (mixed connective disease) M34.0-9 (LE), M32, G73.7C, N08.5A, N16.4B (SLE), M33 (polymyositis/dermatomyositis). M35.0, G73.7A (Sjögren's syndrome) M30.0 (Polyarteritis nodosa) M31.3 (Wegener´s granulomatosis) D69.0B, M31.0B (Schonlein henochs purpura) I77.6, DL95 (Vasculitis/arteritis)	734.00, 734.02, 734.03, 734.04 734.08, 734.09 (Sclerodermia) 695.49 (LE), 734.19 (SLE) 716.09, 716.19 (polymyositis/dermatomyositis), 734.90 (Sjögren's syndrome) 446.29 (Wegener´s granulomatosis) 287.09 (Schonlein henochs purpura) 446.09 (Vasculitis/arteritis)
Gastrointestinal diseases		
Crohn's disease	K500-509	563.01, 563.02, 563.09
Ulcerative colitis	K510-519	563.19
Unclassified IBD	K519, DK529	
Cancer	C00-97	140-209
Dermatological diseases Pemphigus / pemphigoid dermatitis herpetiformis Bullous disorders	L10.0, L10.2, L10.4, L12.0, L13.0, L00, L51.2, L11, L13,14	694 , 693.00, 693.08, 693.09, 684.00
Renal diseases	N00, N01, N03, N04, N05 N06, N07, N08, N11, N14, N15, N16, N18, N19, N26, N27, I12. I13, I15.0, I15.1, E10.2, E11.2, E14.2, Q61.1-Q61.4	249.02, 250.02, 403, 404, 580-584, 590.09, 593.20, 753.10-753.19
Other autoimmune diseases	D59.0 D59.1 (autoimmune hemolytic anemia) D69.3 (Idiopathic thrombocytopenic purpura) K75.4 (autoimmune hepatitis)	283.90 283.91 (autoimmune hemolytic anemia) 287.10 (Idiopathic thrombocytopenic purpura) 571.93 (autoimmune hepatitis)
Neurological diseases		
Multiple sclerosis	G35	340
Adrenal insufficiency	E230, E240, E271, E272, E274, E893	253, 25510, 25511

S4 Table. Equivalency table presenting systemic glucocorticoids and corresponding prednisolone conversion factors.

	Equivalent glucocorticoid dose	Prednisolone conversion factor
Cortisone	25	0.2
Cortisol	20	0.25
Methylprednisolone	4	1.25
Prednisolone	5	1
Prednisone	5	1
Triamcinolone	4	1.25
Dexamethasone	0.75	6.67
Betamethasone	0.6	8.33

Cumulative dose calculation:

The cumulative dose was calculated by multiplying the number of pills, dose per pill, and prednisolone conversion factor for each prescription and then adding them up across all prescriptions.

S5 Table. Distribution of total number of hospital admissions per person during risk periods 0–4.

Number of admissions in risk period 0-4 per person	Number (%)
Persons with any admission	9,058 (100)
Persons with only 1 admission in total	7,517 (83)
Persons with 2 admissions in total	1,158 (13)
Persons with 3 admissions in total	260 (2.9)
Persons with 4 admissions in total	68 (0.75)
Persons with 5 admissions in total	30 (0.33)
Persons with 6 admissions in total	14 (0.15)
Persons with ≥ 7 admissions in total	11 (0.12)

S6 Table. Sensitivity analysis excluding persons who died within 60 days after an event.

	IRR and (95% CI)				
	Syncope	**Hypo-natremia**	**Hypotension**	**Gastrointestinal symptoms**	**Hypoglycemia**
Number of cases	3,527	629	292	6,220	37
Reference period	1	1	1	1	1
Risk period 0	0.8 (0.7 - 0.9)	0.7 (0.6 - 1.0)	1.5 (0.9 - 2.5)	1.0 (0.9 - 1.1)	0.7 (0.2 - 2.2)
Risk period 1	1.0 (0.9 - 1.2)	1.4 (1.1 - 2.0)	2.3 (1.3 - 4.1)	1.6 (1.5 - 1.8)	2.2 (0.7 - 7.3)
Risk period 2	1.0 (0.8 - 1.1)	1.1 (0.7 - 1.5)	2.2 (1.2 - 4.1)	1.8 (1.6 - 2.0)	1.9 (0.5 - 7.9)
Risk period 3	1.0 (0.8 - 1.1)	0.9 (0.6 - 1.4)	1.9 (1.0 - 3.8)	1.4 (1.3 - 1.6)	NA
Risk period 4	0.8 (0.7 - 1.0)	0.7 (0.4 - 1.1)	1.7 (0.8 - 3.5)	1.4 (1.3 - 1.7)	0.9 (0.1 - 8.5)

S7 Table. Sensitivity analysis excluding persons with concomitant use of injectable or locally administrated glucocorticoids.

	IRR and (95% CI)				
	Syncope	**Hypo-natremia**	**Hypotension**	**Gastro intestinal symptoms**	**Hypoglycemia**
Number of cases	2,367	376	192	3,904	28
Reference period	1	1	1	1	1
Risk period 0	0.8 (0.7 - 0.9)	0.7 (0.5 - 1.0)	1.2 (0.7 - 2.1)	1.0 (0.9 - 1.1)	0.8 (0.2 - 3.1)
Risk period 1	1.0 (0.8 - 1.2)	1.1 (0.7 - 1.6)	2.2 (1.2 - 4.1)	1.6 (1.4 - 1.8)	1.9 (0.5 - 8.0)
Risk period 2	0.9 (0.8 - 1.1)	0.7 (0.4 - 1.2)	1.2 (0.6 - 2.5)	1.7 (1.5 - 2.0)	3.0 (0.6 - 15)
Risk period 3	1.0 (0.8 - 1.2)	0.7 (0.4 - 1.2)	1.3 (0.6 - 2.9)	1.2 (1.0 - 1.5)	NA
Risk period 4	0.8 (0.6 - 1.0)	0.6 (0.3 - 1.1)	1.6 (0.7 - 3.7)	1.3 (1.1 - 1.6)	1.3 (0.1 - 14)

S8 Table. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for events by risk period.

	IRR and 95% CI				
	Syncope	Hypo-natremia	Hypotension	Gastrointestinal symptoms	Hypoglycemia
Reference period	1	1	1	1	1
Cumulative dose < 0.5 g					
Cases	87	16	6	179	0
Risk period 0	1.1 (0.5 – 3.5)	2.0 (0.4 – 9.8)	NA	0.7 (0.4 – 1.4)	NA
Risk period 1	1.3 (0.5 – 3.1)	1.1 (0.1 - 11)	NA	0.8 (0.4 – 1.6)	NA
Risk period 2	0.9 (0.4 – 1.8)	0.3 (0.03 – 3.2)	NA	1.2 (0.8 – 1.9)	NA
Risk period 3	1.1 (0.6 – 3.5)	2.5 (0.6 – 9.6)	NA	1.2 (0.7 – 1.9)	NA
Risk period 4	1.7 (0.8 – 3.5)	0.5 (0.04 – 4.8)	NA	1.8 (1.1 – 2.9)	NA
Cumulative dose 0.5-5 g					
Cases	1,432	263	117	2,501	15
Risk period 0	0.8 (0.7 – 0.9)	0.8 (0.6 – 1.2)	1.2 (0.6 – 2.4)	1.1 (1.0 – 1.3)	0.4 (0.1 – 1.8)
Risk period 1	1.0 (0.9 – 1.3)	1.3 (0.9 – 2.0)	2.2 (1.1 – 4.4)	1.7 (1.5 – 2.0)	0.7 (0.1 – 4.3)
Risk period 2	1.0 (0.8 – 1.2)	0.9 (0.6 – 1.5)	2.6 (1.3 – 5.4)	1.9 (1.7 – 2.3)	1.1 (0.2 – 6.7)
Risk period 3	1.0 (0.8 – 1.2)	0.7 (0.4 – 1.2)	2.0 (0.9 – 4.4)	1.5 (1.3 – 1.8)	NA
Risk period 4	0.8 (0.6 – 1.0)	0.6 (0.3 – 1.1)	0.9 (0.3 – 2.7)	1.5 (1.2 – 1.8)	NA
Cumulative dose > 5 g					
Cases	2,049	355	172	3,652	23
Risk period 0	0.8 (0.7 – 1.0)	0.7 (0.5 – 1.0)	1.8 (0.8 – 4.2)	1.0 (0.9 – 1.1)	1.4 (0.2 - 12)
Risk period 1	1.1 (0.9 – 1.3)	1.8 (1.1 – 2.8)	3.2 (1.3 – 8.2)	1.8 (1.6 – 2.1)	6.7 (0.8 - 56)
Risk period 2	1.1 (0.8 – 1.4)	1.4 (0.8 – 2.5)	1.4 (0.4 – 5.1)	2.1 (1.8 – 2.5)	7.0 (0.7 - 71)
Risk period 3	1.0 (0.7 – 1.4)	1.2 (0.6 – 2.5)	2.6 (0.8 – 8.7)	1.5 (1.1 – 1.9)	NA
Risk period 4	0.8 (0.6 – 1.2)	0.7 (0.3 – 1.9)	4.2 (1.3 - 14)	1.4 (1.1 – 1.9)	7.0 (0.4 - 129)

Appendix V

Paper V

Title: Glucocorticoid use and risk of suicide: A Danish population-based case-control study

Running title: Suicide and glucocorticoid treatment

Authors: Kristina Laugesen[1], Dora Farkas[1], Mogens Vestergaard[2], Jens Otto L. Jørgensen[3], Irene Petersen[1,4], Henrik Toft Sørensen[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Public Health - Institute of General Medical Practice, Aarhus University, Aarhus, Denmark

[3]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus Denmark

[4]Department of Primary Care and Population Health, University College London, London, UK

Background: Glucocorticoid use is prevalent and associated with severe adverse effects, including neuropsychiatric symptoms. The association with suicide has been only sparsely investigated.

Objective: To examine the association between glucocorticoid use and suicide.

Design: Population-based case-control study using Danish medical registries.

Setting: The cumulated Danish population during 1995-2015 (7,559,392 persons).

Participants: We identified 14,028 suicides and 140,278 population controls using risk-set sampling and matching by birth year and sex. The suicide date served as the index date for cases and controls.

Exposure: We defined new users of glucocorticoids as individuals who redeemed their first-ever glucocorticoid prescription 90 days or less before the index date. We further classified individuals who redeemed a prescription 90 days or less, 91 to 365 days, and more than 365 days before the index date as present, recent, and former users, respectively.

Measurements: We used logistic regression to estimate adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) of suicide, comparing users with never users.

Results: New use of oral glucocorticoids was associated with a 7-fold increased risk of suicide in individuals diagnosed with cancer at any time before the index date [adjusted IRR: 7.2 (95% CI: 5.0-11), E-value: 14] and with a 2-fold increased risk in individuals without cancer [adjusted IRR: 2.0 (95% CI: 1.5-2.8), E-value: 3.4], compared to never use. We observed a dose-response effect. Recent and former use as well as other glucocorticoid administration forms were not associated with suicide.

Limitations: This study is limited by potential confounding by indication and severity.

Conclusion: Glucocorticoid use increases suicide risk especially among cancer patients. Given its widespread use, our findings merit clinical attention.

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INTRODUCTION

Suicide is an important global health problem, with nearly 800,000 people dying from suicide worldwide every year.(1, 2) In 2016, age-standardized suicide rates reached 13.2 per 100,000 persons in Denmark.(1) The World Health Organization (WHO) emphasizes that prevention is an international priority.(1, 2)

Glucocorticoids are associated with many adverse effects, including neuropsychiatric symptoms.(3-8) Still, this medication is used by 3% of the Danish population each year.(9, 10) The association with suicide has been investigated only sparsely, with evidence limited to two prior studies.(6, 11) A population-based cohort study (n = 922,048) conducted in the United Kingdom (UK) found that persons initiating oral glucocorticoids were 7-fold more likely to commit or attempt suicide compared to persons with the same underlying conditions who did not receive these medications.(6) It further identified a prior suicide attempt and young age as predictors of suicide.(6) A Canadian case-control study (n = 602 suicide cases and n = 2999 controls) found a more moderate association [unadjusted odds ratio = 1.33; 95% confidence interval (CI): 0.88 - 2.00).(11)

The etiology behind the association between glucocorticoid use and suicide remains poorly understood.(3-8) , but neuropsychiatric symptoms often present early after treatment start with higher daily dose as a risk factor.(4) Endogenous cortisol plays an important role in human behavior, cognition, and mood, mediated through glucocorticoid and mineralocorticoid receptor activation in the central nervous system (CNS) and through effects on the serotonin neurotransmitter system.(7, 8) Confounding by severity of underlying medical conditions cannot be ruled out in the earlier observational studies of the association between glucocorticoid use and suicide.(6, 11)

More evidence is needed on the potential association between glucocorticoid use and suicide. Given widespread use of glucocorticoids, such an association would have important clinical implications. We therefore conducted a nationwide population-based case-control study to examine the association between glucocorticoid use and suicide risk. To help identify subgroups most at risk, we further evaluated whether the association varied by age, sex, and underlying medical conditions.

METHODS

Setting

We conducted this study in Denmark using data from the period 1 January 1995 to 31 December 2015 (cumulative source population = 7,559,392). Denmark provides its entire population with tax-supported healthcare, guaranteeing access to primary and secondary care free-of-charge. A unique personal civil registration number is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous individual-level linkage of relevant registries.(12, 13)

Suicides

We used the Danish Register of Causes of Death to identify all suicides during the study period.(14-16) This register contains information on all deaths among Danish residents, including causes of death (*e.g.*, suicide), as well as information on date of death.(14) The suicide date was considered the index date for cases. The Danish legal regulation of death certification states that cases of unexpected or sudden death must be reported to the police, and only after medicolegal examination the death certificate may be issued.

Population controls

We accessed the Danish Civil Registration System (12) to match 10 population controls to each case by birth year and sex, using risk-set sampling.(17) Eligible controls had to be alive on the index date of the matched case. Controls were assigned an index date identical to that of corresponding cases.

Glucocorticoid use

In Denmark glucocorticoids are available by prescription only. We used the Danish National Prescription Registry to identify all prescriptions for glucocorticoids redeemed by cases and controls before their index date.(18) Since 1995, the prescription registry has recorded information on customers' civil registration number, the medication classification code [Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization], the Nordic article number, date of dispensing, number of packages dispensed, number of tablets in a package, tablet strength, and volume dispensed expressed in defined daily doses (DDD).(18) ATC codes and Nordic article numbers are provided in Appendix Table 1. Although the prescription registry is considered complete for medications dispensed in community pharmacies, it does not capture in-hospital treatments.

We first defined oral glucocorticoids users as individuals who redeemed at least one prescription for an oral glucocorticoid during the study period. We then defined five exposure groups based on timing of exposure:

- Present users: individuals who redeemed their most recent prescription ≤ 90 days before their index date. We further divided present users in new users and prevalent users as defined below.

- New users: individuals who redeemed their first-ever prescription ≤ 90 days before their index date (*i.e*. treatment-naïve individuals).
- Prevalent users: individuals who redeemed their most recent prescription ≤ 90 days before their index date and had a prior prescription redemption.
- Recent users: individuals who redeemed their most recent prescription 91-365 days before their index date.
- Former users: individuals who redeemed their most recent prescription >365 days before their index date.
- Never users: individuals who redeemed no prescriptions for a glucocorticoid during the study period.

We then separately examined injectable glucocorticoids, inhaled glucocorticoids, and glucocorticoids acting on the intestine, considering only exclusive use of each type of glucocorticoid. For example, for inhaled glucocorticoids, we considered only individuals without concomitant use of systemic glucocorticoids or glucocorticoids acting on the intestines.

Covariables

We identified relevant medical conditions and co-medication use using the National Prescription Registry (18), the Danish National Patient Registry (19), the Danish Psychiatric Central Research Registry (20), and the Danish Cancer Registry.(21) We also identified a wide range of potential disease indications for glucocorticoid treatment such as obstructive pulmonary disease [chronic obstructive lung disease (COPD) and asthma], rheumatic diseases, renal diseases, inflammatory bowel disease (IBD), skin diseases, other autoimmune diseases, and cancer. In addition, we identified comorbidities and co-medication use,

including psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications (Appendix Table 2).

Statistical analyses

We described cases and controls according to sex, age, potential treatment indications, non-psychiatric comorbidity, psychiatric comorbidity, and co-medication use.

We then used logistic regression to estimate IRRs for suicide among new, present, recent, and former users of glucocorticoids compared to never users. We first adjusted for matching factors only (calendar year of index date, age, and sex) and then adjusted for matching factors and selected covariates as described above. We found (post-hoc) that cancer modified the association and therefore stratified our analyses by presence/absence of a cancer diagnosis at any time before the index date. As we used risk-set sampling, the estimated odds ratios provided unbiased estimates of the incidence rate ratios (IRRs).(17)

We next performed a dose-response analysis. Neuropsychiatric symptoms often present early in treatment with the amount of the daily dose constituting a risk factor.(4) As the Danish prescription registry does not capture daily dose, we assessed the dose of glucocorticoid use near the index date based on the cumulative dose of the latest prescription among new users of oral glucocorticoids, expressed as prednisolone equivalents (<250, 250-499, 500-999, 1000-1999, ≥ 2000 mg). Calculations of prednisolone-equivalent cumulative doses were based on methods described elsewhere (Appendix Table 3).(22, 23)

We also estimated incidence rate differences using a back-calculation method.(24) We extrapolated the exposure distribution among the controls to the person-years of the general population (obtained from the Danish Civil Registration System and stratified by age, sex, and calendar year), in order to calculate the suicide incidence rate among users and never

users, and then standardized the difference to the sex and age distribution among suicide cases.

Subgroup analyses

To investigate whether a potential association was uniform across all patient groups or if any subgroups were at higher risk of suicide, we conducted analyses stratified by sex, age, potential treatment indications, and non-psychiatric or psychiatric comorbidity. We adjusted these analyses for all covariates except for the stratifying factor itself.

Sensitivity analyses

We performed the following sensitivity analyses to examine the robustness of our findings:

1) Potential confounding by cancer severity was investigated by examining the association between new use of oral glucocorticoids and suicide, stratified by cancer stage. For solid cancers, cancer stage was divided into localized, lymph node spread, and distant metastatic spread (Appendix Table 4). Because of the limited number of hematological cancers and cancers in the central nervous system, we were unable to obtain meaningful estimates for these cancer types by stage.
2) Potential confounding by timing of cancer diagnosis was investigated by examining the association between new use of oral glucocorticoids and suicide, restricted to a subpopulation of patients with a newly diagnosed cancer (≤ 90 days before the index date).
3) The potential effect of unmeasured (both known and unknown) confounding was examined by estimating E-values. The E-value provides the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both glucocorticoid use and suicide to fully account for our findings. (25)

4) To explore our definition of new users (individuals who redeemed their first-ever prescription ≤ 90 days before their index date), we subdivided new users into those who redeemed their first prescription <14 days, 14-60 days, or 61-90 days before their index date.
5) Finally, we addressed the challenge that psychiatric disease, cardiovascular disease, diabetes, and osteoporosis may fulfill criteria for both confounding and mediation. To rule out potential bias from including mediators in our models, we performed a sensitivity analysis that did not adjust for those variables.

All statistical analyses were conducted using SAS version 9.4. This study was approved by the Danish Data Protection Agency (Record number: 2016-051-000001, serial number 572). According to Danish legislation, informed consent or approval from an ethics committee is not required for registry-based studies.

Role of the Funding source

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RESULTS

Table 1 presents the characteristics of the 14,028 suicide cases and 140,278 general population controls included in the study. Median age was 53 years (interquartile range, 40-68 years), 72% were men, n = 11,617 had a prior cancer diagnosis and n = 37,277 had a prior psychiatric disease.

Glucocorticoid use and suicide risk

New use of oral glucocorticoids was associated with a 7-fold increased risk of suicide in individuals with a cancer diagnosis [adjusted IRR: 7.2 (95% CI: 5.0-11), E-value: 14] and a 2-fold increased risk in individuals without cancer [adjusted IRR: 2.0 (95% CI: 1.5-2.8), E-value: 3.4] compared to never use (Table 2). The corresponding rate differences were 7.6 per 10,000 person years (95% CI: 0-17) and 1.4 per 10,000 person years (95% CI: 0-12), respectively (Table 3). Stratification by cumulative dose of the most recent oral glucocorticoid prescription in new users revealed a dose-response effect (Table 4). Recent and former use of oral glucocorticoids, as well as glucocorticoids administered in other forms, were not associated with suicide. (Appendix Table 5).

Subgroups

We found an elevated risk of suicide across all relevant treatment indications and comorbidities, except for skin diseases and inflammatory bowel diseases. However, these estimates were limited by sparse data and imprecise estimates). Age below 30 years and age 70 years or over were risk factors for suicide (Figure 1). The association was similar among men and women (adjusted IRR: 1.9 vs. 1.7) (Figure 1)

Sensitivity analyses

We found an association between new use of oral glucocorticoids and suicide in persons with every stage of cancer [adjusted IRR: 4.6 (95% CI: 2.3-9.4) for localized cancer; adjusted IRR: 8.1 (95% CI: 3.0-22) for cancer with lymph node spread, and adjusted IRR: 7.7 (95% CI: 3.2-18) for cancer with distant metastatic spread] (Appendix Table 6). Further, when the study population was restricted to individuals with newly diagnosed cancer, new use of oral glucocorticoids remained associated with a nearly 6-fold increased risk of suicide compared to never use (Appendix Table 7). Regarding the potential impact of unmeasured confounding, we estimated E-values of 14 and 3.4 for the association between new use of oral

glucocorticoids and suicide (Table 2) among patients with and without cancer. Finally, excluding potential mediation variables from the adjusted models did not change our estimates.

DISCUSSION

We found that treatment with oral glucocorticoids was associated with an increased risk of suicide. New use of oral glucocorticoids was associated with a 7-fold increased risk of suicide in individuals with a cancer diagnosis (prior or present) compared to never use and a 2-fold increased risk among individuals without cancer. The risk increased with increasing dose. Recent and former use of oral glucocorticoids as well as glucocorticoids administered via other routes were not associated with suicide.

Our study supports the earlier UK cohort study that reported a 7-fold increased risk of suicide/attempted suicide among glucocorticoid users compared to nonusers after adjusting for potential treatment indications.(6) Further, our findings correlate well with the evidence that neuropsychiatric symptoms often occur early in treatment and that risk increases with higher daily dose.(3, 4, 7) The Canadian case-control study found a more moderate association [unadjusted odds ratio = 1.33 and 95% confidence interval (CI): 0.88 - 2.00).(11) However, glucocorticoid administration forms were not specified. In our setting, we found no effect of inhaled glucocorticoids, injectable glucocorticoids, or glucocorticoids acting on the intestines. These findings might be explained by lower bioavailability of inhaled glucocorticoids and glucocorticoids acting on the intestine compared to oral glucocorticoids.(26, 27) Regarding injectable glucocorticoids, we were unable to capture treatment provided by the hospital sector (*i.e.* intra-articular and intravenous treatment). Our finding of no association between injectable glucocorticoids and suicide therefore reflects only a minor portion of injectable use (*e.g.* treatment for allergies in the primary sector).

Endogenous cortisol plays an important role in human behavior, cognition, and mood, mediated through glucocorticoid and mineralocorticoid receptor activation in the CNS.(7, 8) Compared to synthetic glucocorticoids, cortisol has a high affinity for the mineralocorticoid receptor. The combination of excess synthetic glucocorticoid and diminished endogenous cortisol (suppression of the hypothalamic-pituitary-adrenal axis) may therefore result in imbalanced receptor activation.(7, 8) Further, excess glucocorticoid may cause dysregulation of the serotonin neurotransmitter system.(8) Finally, onset or flare up of the underlying medical conditions, for which glucocorticoids are prescribed, may also have an impact.

Our large population-based study was conducted in a universal tax-supported healthcare system, which largely eliminated selection biases.(13) We had complete information on prescribed glucocorticoids and complete and valid information on suicides.(15, 16) However, the study also had limitations. First, we used prescription redemption as a proxy for glucocorticoid use. Some glucocorticoid users may have been misclassified as never users due to lack of information on in-hospital treatments. Approximately 20% of total systemic glucocorticoid volume (DDD) is used in-hospital.(9) As well, never users may have been misclassified as users if they redeemed a glucocorticoid prescription but did not adhere to the treatment. However, we relied on dispensed glucocorticoids rather than written prescriptions, and copayments increase the likelihood of adherence in Denmark. Misclassification of glucocorticoid use would be independent of suicide and vice versa and lead to bias towards the null due to non-differential misclassification.(28) Hence, misclassification cannot explain our findings. Second, confounding by treatment indication or by severity of underlying medical conditions cannot entirely be ruled out. Our results remained robust to confounding by cancer stage and timing, although the association was stronger in patients with lymph node spread/metastatic spread compared to those with localized cancer. We adjusted our models for potential confounders, including sex, age, treatment indications, comorbidity, and

co-medication use, and calculated E-values to examine the impact of potential unmeasured confounding. The E-values indicated that an unmeasured confounder associated with both glucocorticoid use and suicide would need to have a relative risk of 14 and 3.4, respectively, to fully explain our findings (*i.e.*, only a strong confounder could explain our findings). As an example, we lacked information on lifestyle factors and socioeconomic status. However, a prior Danish study found no or only modest associations between glucocorticoid use and less healthy lifestyles.(29) Thus potential confounding from lifestyle would not be significant in our study and, combined with the E-values, cannot explain our results. As well, an association between low socioeconomic status and suicide has been found in Danish settings.(30) Based on the same arguments as for lifestyle, confounding from socioeconomic status cannot explain our findings. Finally, we found no association for former or recent use of glucocorticoids, indicating that unmeasured confounding that is stable over time was not an issue in our study.

In conclusion, our findings indicate that oral glucocorticoid use increases suicide risk. Given the widespread use of glucocorticoids, our study merits clinical attention despite the low rate differences and the potential limitation of confounding.

FOOTNOTES

Conflict of interest: None of the authors reports conflicts of interest or has financial disclosures to make.

Authorship: All authors contributed to the study's conception. KL wrote the initial manuscript. DF performed statistical analyses. IP, MV, DF and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript. HTS is the guarantor for this study.

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TABLES

Table 1. Characteristics of suicide cases and general population controls in Denmark, 1995-2015.

	Number (%)	
Characteristics	**Cases (n= 14,028)**	**Controls (n= 140,278)**
Age, years		
≤30	1,444 (10)	14,440 (10)
30-49	4,558 (33)	45,580 (33)
50-69	4,904 (35)	49,040 (35)
≥70	3,122 (22)	31,218 (22)
Age, median (interquartile range), years	53 (40-68)	53 (40-68)
Male sex	10,037 (72)	100,368 (72)
Obstructive pulmonary disease (chronic obstructive pulmonary disease and asthma)	3,279 (23)	27,615 (20)
Rheumatic diseases	282 (2.0)	2,268 (1.6)
Renal diseases	253 (1.8)	1,524 (1.1)
Skin diseases	144 (1.0)	962 (0.7)
Inflammatory bowel disease	131 (0.9)	1,034 (0.7)
Other autoimmune diseases	23 (0.2)	149 (0.1)
All cancers	1,407 (10)	10,210 (7,3)
Head and neck cancer	59 (0.4)	241 (0.2)
Colorectal cancer	167 (1.2)	1,066 (0.8)
Lung cancer	95 (0.7)	275 (0.2)
Malignant melanoma	55 (0.4)	515 (0.4)
Breast cancer	161 (1.1)	1,061 (0.8)
Female genital cancer	66 (0.5)	475 (0.3)
Prostate cancer	149 (1.1)	1,105 (0.8)
Cancer in the urinary tract system	131 (0.9)	1059 (0.8)
Cancer in the central nervous system	17 (0.1)	89 (0.1)
Cancer in the endocrine system	8 (0.1)	65 (0.1)
Hematological cancers	106 (0.8)	669 (0.5)
Other cancers	550 (3.9)	4,485 (3.2)
Psychiatric disease	9,338 (67)	27,939 (20)
Cardiovascular disease	5,688 (41)	47,221 (34)
Diabetes	825 (5.9)	7,109 (5.1)
Osteoporosis	401 (2.9)	2,538 (1.8)
Alcohol-related disorders	1,842 (13)	3,414 (2.4)
Use of opioids	5,262 (38)	31,840 (23)
Use of antiepileptic medication	2,427 (17)	5,906 (4.2)

Table 2. The association between oral glucocorticoid use and suicide, stratified by cancer (any time before the index date).

Exposure	Cases/controls	Adjusted* IRR (95% CIs)	Fully adjusted** IRR (95% CIs)	E-value for the point estimate (lower bound of the 95% CI)
Cancer				
Never use (Reference)	707/5865	1	1	
New use	71/68	8.7 (6.2-12)	7.2 (5.0 - 11)	14 (9.5)
Present	152/362	3.6 (2.9-4.4)	2.8 (2.2 - 3.6)	
Recent	51/246	1.8 (1.3-2.5)	1.0 (0.7 - 1.5)	
Former	136/1002	1.2 (1.0-1.5)	0.9 (0.7 - 1.1)	
No Cancer				
Never use (Reference)	8548/91,453	1	1	
New use	60/264	2.5 (1.9-3.3)	2.0 (1.5-2.8)	3.4 (2.4)
Present	280/1521	2.0 (1.8-3.2)	1.5 (1.3-1.8)	
Recent	202/1406	1.6 (1.4-1.9)	1.1 (0.9-1.3)	
Former	735/6586	1.2 (1.1-1.3)	0.9 (0.8-1.0)	

* Conventional logistic regression adjusted for calendar year of index date, age, and sex (matching factors).

**Conventional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval

Table 3. Incidence rates and rate differences (per 10,000 person-years) and 95% confidence intervals (95% CIs) for suicide associated with use of oral glucocorticoids, by recency of use.

Exposure	Incidence rates (95% CI)		Rate difference (95% CI)
	Users	Never users	
Cancer			
New use	8.7 (6.1 - 11)	1.1 (0 - 10)	7.6 (0 - 17)
Present	3.5 (2.9 - 4.1)	1.1 (0 – 2.5)	2.4 (1.0 – 3.9)
Recent	1.9 (1.2 – 2.6)	1.1 (0 – 3.6)	0.8 (0 – 3.4)
Former	1.4 (1.1 – 1.7)	1.2 (0.5 – 1.9)	0.1 (0 – 0.8)
No Cancer			
New use	2.5 (1.8 – 3.2)	1.1 (0 - 11)	1.4 (0 - 12)
Present	2.1 (1.8 – 2.4)	1.1 (0 – 3.7)	1.0 (0 – 3.7)
Recent	1.7 (1.4 – 2.0)	1.1 (0 – 3.1)	0.6 (0 – 2.6)
Former	1.4 (1.3 – 1.5)	1.2 (0.8 – 1.6)	0.2 (0 - 0.6)

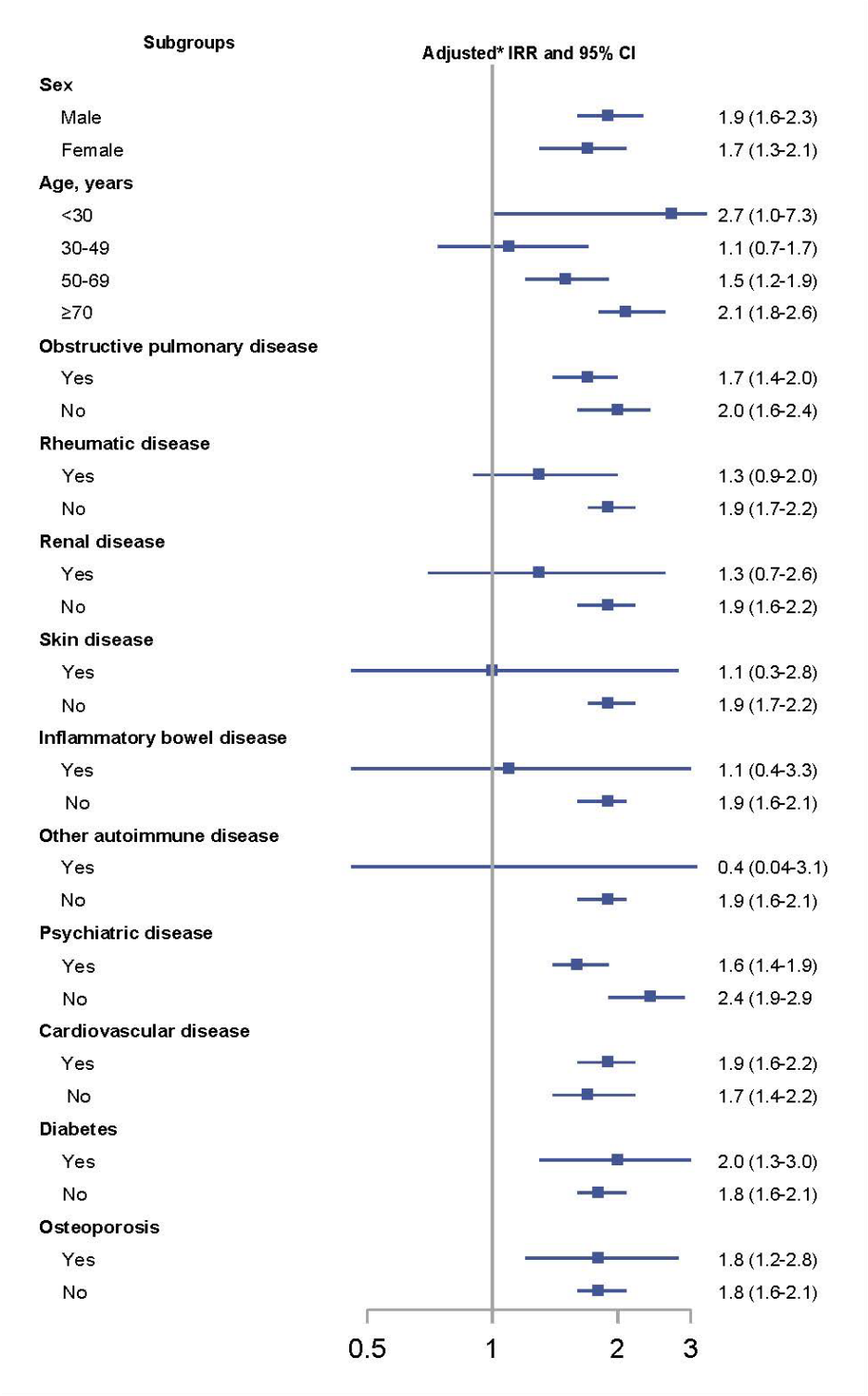
Table 4. Dose-response analysis among new users of oral glucocorticoids. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for suicide according to the prednisolone-equivalent cumulative dose of the most recent oral glucocorticoid prescription.

Dose, mg	Fully adjusted* IRR (95% CI)
Never use (reference)	1
< 250	1.2 (0.36 - 4.0)
250-499	3.0 (1.2 - 7.8)
500-999	3.4 (1.9 - 6.2)
1000-1999	40 (8.1 - 200)
≥ 2000	17 (7.5 - 37)

* Conditional logistic regression with adjustment for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, cancer, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

FIGURE

Figure 1. Subgroup analyses of the association between present use of oral glucocorticoids and suicide.



*Conventional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, cancer, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications (except for the stratifying factor).

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval

APPENDICES

Appendix Table 1. ATC codes and Nordic article number for glucocorticoids (oral, injectable, inhaled, and acting on the intestine).

Medication type	ATC codes	Systemic (injection) Nordic article number	Systemic (oral) Nordic article number
Systemic glucocorticoids	H02AB		
Betamethasone	H02AB01	006595, 006634, 013802, 013815, 013824, 013835, 034731, 038661, 042812, 058396, 123372, 131796, 143773, 145143, 177360, 181595, 192922, 194713, 385214, 399765, 413438, 473824,, 477631, 483156, 488471, 498048, 504332, 523266, 523266, 556860	499590
Dexamethasone	H02AB02	053066, 057984, 421131, 570853, 570861	039413, 126955, 188988, 113331, 190108, 190132, 374319, 418122, 579043, 591445
Methylprednisolone	H02AB04	067283, 189522, 195389, 530391, 141044, 189514, 189506, 489011, 420151, 042093, 047663, 171016, 434274, 453162, 488496, 465187, 180299, 549923, 560425, 563956, 583158, 134940, 134965, 130683, 161075, 165613, 143339, 161637, 143347, 153928, 590659, 390762, 397856, 563956	046557, 050487, 072601, 109119, 111245, 112671, 159103, 174284, 450619, 499772, 500074, 509125, 509133, 536422
Prednisolone	H02AB06	189811	042448, 164118,164130, 164141, 164153, 164164, 164175, 168548, 184382, 398747, 425905, 502076, 507660, 516005, 516013,

			516021, 516039, 521930, 521948, 521955, 530899, 564513, 743542, 743559, 743567,748756
Prednisone	H02AB07		All are oral
Triamcinolone	H02AB08	All are injections	
Hydrocortisone	H02AB09	043186, 096131, 141747, 161091, 161109, 161125, 161117, 161091, 164848, 391522, 400051	049319, 141569, 155579, 393735, 424199, 445320, 487361, 490667, 490667, 503581, 746628, 746636
Inhaled glucocorticoids			
Beclomethasone	R03BA01		
Budesonide	R03BA02		
Flunisolide	R03BA03		
Fluticasone	R03BA05		
Mometasone	R03BA07		
Ciclosonide	R03BA08		
Glucocorticoids acting on the intestines			
Prednisolone	A07EA01		
Hydrocortisone	A07EA02		
Budesonide	A07EA06		
Various local glucocorticoids for haemorrhoids	C05AA		

Abbreviation: ATC code, Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization

Appendix Table 2. ICD and ATC codes used to define covariables.

	ICD-8 codes	ICD-10 codes	ATC codes
Obstructive pulmonary disease (any time before index date)			
Asthma or COPD	491, 492, 493	J41-J46	
Agents used to treat asthma or COPD			R03
Rheumatic diseases (any time before index date)			
Rheumatoid arthritis	712.19, 712.29, 712.39, 712.59	M05, M06, G73.7D, I32.8A, I39.8E, I41.8A, I52.8A	
Polymyalgia rheumatica/giant cell arthritis		M315, M316, M35.3	
Juvenile rheumatoid arthritis	712.09	M08	
Ankylosing spondylitis	712.49	M45, H221B	
Polymyositis/dermatomyositis	716.09, 716.19	M33	
Lupus	734.19	M32, G05.8A, G73.7C, I32.8B, I39.8C, L93.1, L93.2, N08.5A, N16.4B	
Systemic scleroderma	734.00-734.09	M34.0-34.9	
Mixed connective tissue disease	734.91	M35.1	
Psoriasis arthritis	696.09	M07.0-M07.3	
Other vasculitis	287.09, 446.09-446.99	D69.0B, I77.6, L95, M30-M31, M35.3, M35.6, M79.3, N08.5B-N08.5E	
Renal disease (any time before the index date)	249.02, 250.02, 403, 404, 580-584, 590.09, 593.20, 753.10-753.19	N00, N01, N03, N04, N05 N06, N07, N08, N11, N14, N15, N16, N18, N19, N26, N27, I12. I13, I15.0, I15.1, E10.2, E11.2, E14.2, Q61.1-Q61.4	
Skin diseases (any time before the index date)			
Atopic dermatitis	691.00	L20	
Pemphigus/pemphigoid	694.00-694.03, 694.05	L10.0, L10.1, L10.2, L10.4, L12.0	
Dermatitis herpetiformis	693.08, 693.09	L13.0	

Psoriasis	696.10, 696.19	L40
Vitiligo	709.01	L80
Inflammatory bowel disease (any time before the index date)	563.19, 563.01	K51, M07.5, K50, M07.4
Other autoimmune diseases	283.90 283.91 287.10 571.93	D59.0, D59.1 D69.3, K75.4
Cancer (any time before the index date)		
Head and neck cancers		C00-C14
Colorectal cancer		C18-20
Lung cancer		C33, C34
Malignant melanoma		C43, C21 (with morphology 872-879)
Breast cancer		C50
Female genital cancers		C51-C58 (excluding morphology 809)
Prostate cancer		C61
Urinary cancers		C64-68, D090-D091, D095-096, D301-309, D411-419 (D-codes restricted to morphology 812-813)
Cancers of the central nervous system, including the eye		C69-72, C751-753, D32-33, D352-354, D42-43, D443-445
Cancers of the endocrine system		C73-74, C750, C754-759
Hematological cancers		C81-96, D459, D471, D473, D475, D46, D474.
Other cancer types		C15-17, C22-26, C30-32, C37-39, C40-41, C44-49, C60-63, C76-80
Psychiatric disease (any time before index date)		
Schizophrenia and related disorders	295, 297, 298, 299	F20-F29
Affective disorders	296	F30- F39
Other psychiatric diagnosis	290, 300-301, 305-308, 310-315	F00-F09, F49, F40-F99

Medications			
Antidepressant use			N06A, N06CA
Antipsychotic use			N05A
Cardiovascular disease (any time before the index date)			
	393-398, 400-404, 410-414, 427.09, 427.10, 427.19	I05-I09, I10-I15, I20-I25, I50	
Cardiovascular medications			C09
ACE inhibitors			
Beta-blockers			C07
Acetylsalicylic acid			B01AC06, N02BA01
Clopidogrel			B01AC04
Calcium channel antagonists			C08
Antihypertensive drugs			C02
Diuretics			C03
Nitrates			C01DA
Diabetes (any time before the index date)			
Type 1 or 2 diabetes	249, 250	E10-E14. O24 (except O24.4), G63.2, H36.0, N08.3	
Antidiabetic treatment			A10A, A10B
Osteoporosis			
	723.09	M80-M82	
Medications used to treat osteoporosis			M05
Alcohol-related disorders (any time before the index date)	980, 291.09–291.99, 303.09–303.99, 571.09–571.11, 577.10	F10 (except F10.0), G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1	
Use of opioids (one year prior to the index date)			N02A
Use of antiepileptic medicine (one year prior to the index date)			N03A

Abbreviations: ATC code, Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization; COPD, Chronic Obstructive Pulmonary disease; ICD, *International Classification of Diseases*

Appendix Table 3. Equivalency table presenting oral glucocorticoids and corresponding prednisolone conversion factors.

	Equivalent glucocorticoid dose	Prednisolone conversion factor
Hydrocortisone	20	0.25
Methylprednisolone	4	1.25
Prednisolone	5	1
Prednisone	5	1
Dexamethasone	0.75	6.67
Betamethasone	0.6	8.33

Cumulative dose calculation:

The cumulative dose was calculated by multiplying the number of pills, dose per pill, and prednisolone conversion factor for the prescription of interest.

Appendix Table 4. Cancer staging (solid cancers).

	Staging (before 2004)	TNM (2004 and onwards)	TNM_T	TNM_N	TNM_M
Localized	0, 1, 2, 5	T1-4 N0 M0	AZCD13-19	AZCD30	AZCD40
		T1-2 N0 Mx	AZCD13-14	AZCD30	AZCD49
		T1 Nx M0	AZCD13	AZCD39	AZCD40,49
Lymph node spread	3,6	T1-4, x	AZCD13-19	AZCD31-33	AZCD40,49
Distant metastatic spread	4,7	T1-4 N1-3 M0-1	AZCD13-19	AZCD31-33	AZCD41
		T1-4 N0 M1	AZCD13-19	AZCD30	AZCD41
		T1-4 Nx M1	AZCD13-19	AZCD39	AZCD41
Unknown	A, B, 9	T2-4 Nx M0	AZCD14-19	AZCD39	AZCD40,49
		T3-4 N0 Mx	AZCD15-19	AZCD30	AZCD49
		T0 N0-3 M0-1	AZCD10-12	AZCD30-33,39	AZCD40-41,49

Abbreviation: TNM, Tumor, Node, Metastasis

Appendix Table 5. Suicide associated with use of glucocorticoids stratified by inhaled glucocorticoid use only, use of glucocorticoids acting on the intestine only, injectable glucocorticoid use only and oral glucocorticoid use only.

Exposure	Cases/controls	Adjusted* IRR (95% CIs)	Adjusted** IRR (95% CIs)
Never use (reference)	9255/97,318	1	1
Inhaled glucocorticoid use only			
New use	12/128	0.96 (0.53 - 1.8)	1.1 (0.54 – 2.1)
Present use	102/1078	1.0 (0.81 - 1.2)	0.9 (0.70 - 1.2)
Recent use	98/871	1.3 (1.0 - 1.6)	1.1 (0.85 - 1.4)
Former use	388/3759	1.1 (0.96 - 1.2)	0.98 (0.85 - 1.1)
Use of glucocorticoids acting on the intestine only			
New use	38/338	1.2 (0.86 - 1.7)	1.1 (0.77 - 1.7)
Present use	94/861	1.2 (0.94 - 1.5)	0.98 (0.76 - 1.3)
Recent use	194/1870	1.1 (0.93 - 1.3)	0.85 (0.77 – 1.0)
Former use	1069/10,647	1.1 (0.98 - 1.1)	0.86 (0.79 - 0.93)
Injectable glucocorticoid use only			
New use	17/203	0.9 (0.5 - 1.5)	0.93 (0.53 – 1.6)
Present use	33/440	0.8 (0.6 - 1.2)	0.72 (0.48 - 1.1)
Recent use	85/1099	0.8 (0.65 - 1.0)	0.67 (0.52 – 0.86)
Former use	654/6571	1.1 (0.97 - 1.2)	0.89 (0.81 – 0.98)
Oral glucocorticoid use only			
New use	73/170	5.0 (3.7 – 6.8)	5.0 (3.5 - 7.2)
Present use	169/799	2.3 (2.0 - 2.8)	2.1 (1.7 - 2.6)
Recent use	97/697	1.5 (1.2 - 1.9)	1.3 (0.98 - 1.7)
Former use	342/3293	1.1 (0.98 - 1.3)	0.91 (0.79 – 1.0)

*Conditional logistic regression adjusted for age, sex, and calendar year of index date (matching factors).

**Conditional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, cancer, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

Abbreviations: IRR, Incidence rate ratio; 95% CI, 95% confidence interval

Appendix Table 6. Sensitivity analysis of the association between oral glucocorticoid use and suicide among individuals with solid cancer (any time before the index date), stratified by cancer stage (localized/lymph node spread/distant metastatic spread).

Exposure	Adjusted* IRR (95% CI)
Localized	
Never use (reference)	1
New use	4.6 (2.3 - 9.4)
Recent use	0.97 (0.6 - 1.5)
Former use	0.96 (0.7 - 1.3)
Lymph node spread	
Never use (reference)	1
New use	8.1 (3.0 - 22)
Recent use	1.7 (0.54 - 5.2)
Former use	0.6 (0.29 - 1.2)
Distant metastatic spread	
Never use (reference)	1
New use	7.7 (3.2 - 18)
Recent use	0.49 (0.14 - 1.7)
Former use	0.52 (0.20 - 1.4)

* Conventional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval

Appendix Table 7. Sensitivity analysis of the association between new use of oral glucocorticoids and suicide among individuals with a newly diagnosed cancer (≤ 90 days before the index date).

	Cases/controls	Adjusted* IRR (95% CIs)	Adjusted** IRR (95% CIs)
Never use (reference)	71/243	1	1
New use	19/12	5.2 (2.4-11)	5.6 (2.4-13)

* Conventional logistic regression adjusted for calendar year of index date, age, and sex (matching factors).

**Conventional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval

Appendix Table 8. Sensitivity analysis of the association between new use of oral glucocorticoids and suicide by timing of the most recent prescription redemption (<14, 14-60 and 61-90 days before the index date).

Exposure	Cases/controls	Adjusted* IRR (95% CIs)
Cancer		
Never use (Reference)	707/5865	1
New use	71/68	7.2 (5.0-11)
<14 days	16/11	11 (4.9-26)
14-60 days	32/42	5.5 (3.1-8.2)
61-90 days	23/15	9.5 (4.8-19)
No Cancer		
Never use (Reference)	8548/91,453	1
New use	60/264	2.0 (1.5-2.8)
< 14 days	13/42	2.7 (1.3-5.5)
14-60 days	34/134	2.7 (1.78-4.1)
61-90 days	13/88	1.0 (0.56-2.0)

*Conventional logistic regression adjusted for calendar year of index date, age, sex, obstructive pulmonary disease, rheumatic diseases, renal diseases, skin diseases, inflammatory bowel disease, other autoimmune diseases, psychiatric disease, cardiovascular disease, diabetes, osteoporosis, alcohol-related disorders, use of opioids, and use of antiepileptic medications.

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval