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Complete List of Authors:	Laugesen, Kristina; Aarhus University Hospital, Department of Clinical Epidemiology Jørgensen, Jens Otto; Aarhus University Hospital, Department of Endocrinology and Internal Medicine Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology Petersen, Irene; University College London Medical School, Department of Primary Care and Population health
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Systemic glucocorticoid use in Denmark: A population-based prevalence study

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

Affiliations:

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

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

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

Correspondence: Kristina Laugesen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Telephone number: +45 871 68063

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ABSTRACT

Objectives: Glucocorticoid (GC) use is widespread and associated with many adverse effects. Thus, it is important to ascertain GC utilization patterns. In this study, we examined the annual prevalence of redeemed prescriptions and amount of sales of systemic GCs.

Design: Population-wide prevalence study.

Setting: The primary health care and hospital sectors in Denmark from 1999 to 2015.

Results: Approximately 3% of the Danish population redeemed at least one prescription for a systemic GC annually between 1999 and 2015, with annual prevalence remaining constant over the period. However, after adjusting for age and sex, we observed a decrease in annual prevalence from 1999 to 2015, with a prevalence ratio of 0.92 (95% confidence interval [CI]: 0.91-0.92). Annual prevalence was highest among the elderly (7.0%-8.2% among persons 65-79 years of age and 8.4%-10% among persons 80+ years of age). Prednisolone was the most frequently redeemed systemic GC, with annual prevalence increasing from 1.4% to 2.1% during the 1999-2015 period. The amount of systemic GCs provided to the hospital sector increased from 2.3 defined daily doses (DDD)/1000 inhabitants/day in 1999 to 3.5 DDD/1000 inhabitants/day in 2015, while the amount provided to the primary health care sector remained constant in the range of 10-11 DDD/1000 inhabitants/day.

Conclusion: The prevalence of systemic GC use in our study is high as compared to previous reports although it seems to decrease slightly over time. At the same time, however, the prevalence increases dramatically with age.

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Strengths and limitations of this study

- Current knowledge of glucocorticoid (GC) utilization patterns is in need of updating and expansion.
- This study is a population-wide study of annual prevalence of systemic GC use in Denmark from 1999 to 2015 according to age, sex and subtype of GC.
- Annual amount of systemic GC sold to both primary health care sector and hospital sectors in Denmark was examined.
- The results of this study apply only to redeemed prescriptions and sales of systemic GCs, and not necessarily to actual adherence and use.

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BACKGROUND

Glucocorticoids (GCs) are potent anti-inflammatory drugs used widely since the 1950s to treat common conditions such as asthma, chronic obstructive pulmonary disease, chronic inflammatory bowel diseases, rheumatic diseases, and malignancies.[1] Besides their beneficial effects in treating inflammatory diseases, GCs are associated with increased risk of a number of adverse outcomes, including iatrogenic adrenocortical insufficiency,[2] venous thromboembolism,[3] and cardiac disease.[4-6] In addition, GCs can cause metabolic diseases such as hyperglycemia, diabetes,[7] and dyslipidemia.[8] They also are associated with increased risk of osteoporosis,[9] and neuropsychiatric disorders.[10]

Current knowledge of GC utilization patterns is in need of updating and expansion. Earlier studies estimated that the prevalence of oral GC use is approximately 1% in the U.K. and the U.S. adult populations, respectively.[11-13] However, these studies did not include use of both oral and injectable formulations of GCs or assessed their use in a nationwide population. In the current population-based study, we examined the prevalence of redeemed prescriptions for all systemic GCs and ascertained the volume of GC sales within the primary health care and hospital sectors in Denmark during 1999-2015.

METHODS

We examined the utilization pattern of systemic GCs, focusing on trends in prescription redemption patterns overall and according to age, sex, and GC subtype.

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Setting

Our study population included the entire Danish population from 1 January 1999 to 31 December 2015. The Danish National Health Service provides universal tax-supported health care, guaranteeing free and equal access to general practitioners and hospitals and partial reimbursement for prescribed medications, including GCs. A unique central personal registration number (civil registration number) is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous linkage of relevant registries at the individual level.[14]

Utilization of systemic glucocorticoids in Denmark

In Denmark, all systemic GCs (ATC code H02AB) are available by prescription only. We used Medstat (http://www.medstat.dk) to retrieve data on systemic GC sales and prevalence of redeemed prescriptions in Denmark.[15] The publicly available Medstat website hosted by the Danish Serum Institute provides aggregate statistics on the sale of pharmaceutical preparations in Denmark since 1995, based on data reported to the Danish National Prescription Registry.[16] Aggregated Medstat statistics are complete from 1999 on, and allow for stratification by age, sex, region, and health care sector (primary or hospital sectors).[15]

Statistical analysis

First, we focused on prescriptions for systemic GCs in the primary health care sector. The annual prevalence of systemic GC prescription redemption was defined as the number of people who redeemed at least one prescription for a systemic GC each year divided by the number of people in the population each year (as of 1 January). We calculated overall annual prevalence and then stratified by sex and age group (0-4 years, 5-9 years, 10-14 years, 15–19 years, 20–39 years, 40–64 years, 65–79 years, and ≥80 years). Age was defined as the age at which the first prescription was redeemed each year. We further stratified by subtype of systemic GC. In our computation of the

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annual prevalence of GC use, the entire Danish population served as the reference group. When we computed the prevalence in subgroups (age and sex), the subgroup of interest served as the reference population. We used a Poisson regression model to examine changes in prescription patterns according to age, sex, and calendar year. Finally, we calculated the amount (defined daily dose [DDD]/1000 inhabitants/24 hours) of systemic GC sold according to health care sector (primary care and hospital sectors). We conducted our statistical analyses using Stata 12 for Windows (Stata Corp, College Station, TX).

RESULTS

In any given year between 1999 and 2015, 3% (range: 3.0% - 3.4%) of the total Danish population redeemed at least one prescription for a systemic GC (Table 1). Overall, the pattern of systemic GC redemption during this period, adjusted for age and sex, was fairly stable with a slight decrease towards the end of the period (Table 3).

The annual prevalence of redemption of prescriptions for systemic GCs was higher among women (range: 3.3%-3.7%) than among men (range: 2.7%-3.1%) (Table 2). The prevalence ratio was 1.11 (95% CI: 1.11-1.11). The prevalence of redemption of prescriptions for GCs increased substantially with age. Thus, persons aged 40-64 were more than 10 times as likely and persons aged 80+ were more than 25 times as likely to receive GC treatment than those aged below 19 (Table 3). While time trends were relatively constant between 1999 and 2015, the prevalence fell from 8.2% to 7.0% among persons aged 65-79 years and increased from 8.4% to 10.0% among those aged 80 or above (Table 2).

The most frequently redeemed systemic GC subtype was prednisolone. Its annual prevalence of redemption in the Danish population increased from 1.4% to 2.1% during 1999 and 2015. In 2015,

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prednisolone accounted for 50% of all GC prescriptions redeemed in the period (taking into account only the first prescription each year). There was a decrease in redemptions of prednisone and betamethasone, from 0.4% to 0.1% and from 1.0% to 0.4% of the Danish population, respectively, from 1999 to 2015 (Table 1).

The amount of systemic GC used in the primary health care sector consistently remained at 10 DDD/1000 inhabitants/24 hours (range: 10.0-10.8 DDD/1000 inhabitants/24 hours) from 1999 to 2015. The amount of systemic GCs used in the hospital sector increased from 2.3 DDD/1000 inhabitants/24 hours in 1999 to 3.5 DDD/1000 inhabitants/24 hours in 2015 (Table 4).

DISCUSSION

This population-based nationwide study found a high prevalence (3%) of systemic GC use from 1999 to 2015 in Denmark, especially among the elderly. This underscores the importance of clinical awareness of the adverse effects of GC treatment. Still, when changes in the age structure of the population were taken into consideration, a decrease in GC prescriptions was observed during the study period.

Previous studies conducted in the U.K. and the U.S. reported a lower prevalence of approximately 1%.[11-13] However, the U.K. and U.S. estimates were limited to the use of oral GCs. Our inclusion of all systemic GCs – both oral and injectable formulations –might explain in part the higher estimates of prevalence of use in the Danish population. Also, the U.K. study covered only long-term (≥1 year) GC use,[11] while our study included all use. Still, the results from our study most likely reflect a higher use of systemic GCs in Denmark compared to the U.K. and U.S.

The U.K. study reported an increase in prescriptions for long-term oral GCs of nearly 34% between 1989 and 2008.(11) Our study found that overall annual prevalence did not vary substantially

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between 1999 and 2015. Taking into account changes in age and sex distribution of the population, we found a decrease in the annual prevalence of systemic GC redemption towards the end of our study period.

Our finding that prednisolone was the most frequent subtype of redeemed GC prescription (50%) is consistent with the U.K. and U.S. studies, which reported that 92.3% and 76.6% of total GC prescriptions were for prednisolone.[11, 13]

The U.K. study found the highest prevalence of use of oral GCs among women aged 80-90 years (3.05% [95% CI: 3.01%, 3.09%]) and the lowest prevalence among men aged 18-29 years (0.08% [95% CI: 0.07%, 0.09%]).[11] In the U.S. population, the highest prevalence of use was found among men aged ≥80 years (3.5% [95% CI: 2.3%–4.7%]) and among women aged 70–79 years (2.7% [95% CI: 1.7%–3.7%]).[13] The high prevalence of GC use observed among the elderly in our study is noteworthy, as it is well established that persons in the highest age groups are particularly prone to adverse outcomes due to higher levels of comorbidity, senescent changes in the body composition, and polypharmacy.[17]

The pattern of disease has changed from 1999 to 2014 [11, 18-20] with increasing prevalence of many inflammatory diseases. Despite this, we have observed a decrease in systemic GC use. An explanation for this can be an increased clinical awareness of the adverse effects of GC treatment as well as increased use of alternative immunomodulatory treatments. The use of methotrexate, azathioprine and anti-TNF alpha therapy has increased and newer biologic agents have been approved for treatment in Denmark during our study period.[15]

The results of this study apply only to redeemed prescriptions and sales of systemic GCs, and not necessarily to actual use or dose. As well, we were not able to estimate adherence to the prescribed

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medication, to obtain incidence of use, or information on co-medication, which is relevant when describing utilization patterns in a population.

In conclusion, the prevalence of GC use remains high especially among the elderly, wherefore continued awareness of its adverse effects is mandated.

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TABLES

Table 1. Annual prevalence of systemic glucocorticoid (GC) use in Denmark, 1999-2015.

	Prevalence of prescription use (% of the national population)							
	All systemic GCs	Prednisolone	Beta-methasone	Methyl-prednisolone	Prednisone	Triam-cinolone	Hydro-cortisone	Dexa-methasone
1999	3.2	1.4	0.9	0.5	0.4	0.2	0.04	0.02
2000	3.3	1.4	0.9	0.5	0.4	0.2	0.04	0.02
2001	3.3	1.5	1.0	0.5	0.4	0.1	0.04	0.02
2002	3.3	1.6	1.0	0.6	0.4	0.03	0.04	0.003
2003	3.2	1.6	0.9	0.5	0.3	0.04	0.04	-
2004	3.2	1.7	0.9	0.5	0.3	0.04	0.04	<0.001
2005	3.3	1.7	0.9	0.5	0.3	0.05	0.04	<0.001
2006	3.4	1.8	0.9	0.5	0.3	0.07	0.04	-
2007	3.4	1.8	0.9	0.5	0.2	0.07	0.04	-
2008	3.4	1.8	0.9	0.5	0.2	0.07	0.03	-
2009	3.3	1.9	0.8	0.6	0.2	0.07	0.03	-
2010	3.3	2.0	0.7	0.5	0.2	0.07	0.03	-
2011	3.2	2.0	0.7	0.5	0.1	0.07	0.03	-
2012	3.1	2.0	0.6	0.4	0.1	0.07	0.03	-
2013	3.1	2.1	0.5	0.4	0.1	0.08	0.03	<0.001
2014	3.1	2.1	0.5	0.5	0.1	0.08	0.03	0.002
2015	3.0	2.1	0.4	0.4	0.1	0.07	0.03	0.002

Reference group: All members of the Danish population as of 1 January in the year of interest.

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Table 2. Annual prevalence of systemic glucocorticoid use in Denmark, 1999-2015, stratified by sex and age.

	Prevalence of prescription use (% of the national population)									
	Sex		Age groups (years)							
	Women	Men	0-4	5-9	10-14	15-19	20-39	40-64	65-79	80+
1999	3.4	2.9	0.06	0.1	0.2	0.9	2.2	3.8	8.1	8.4
2000	3.6	3.0	0.06	0.1	0.2	1.0	2.4	3.9	8.1	8.7
2001	3.6	3.0	0.09	0.1	0.2	1.0	2.4	3.9	8.2	8.8
2002	3.6	3.0	0.06	0.1	0.3	1.1	2.6	3.9	8.1	8.9
2003	3.5	2.9	0.07	0.1	0.2	1.0	2.3	3.8	8.0	8.9
2004	3.5	2.9	0.06	0.1	0.2	0.9	2.3	3.8	8.0	8.9
2005	3.6	3.0	0.06	0.1	0.2	1.0	2.5	3.8	8.0	9.2
2006	3.7	3.0	0.07	0.1	0.3	1.1	2.5	4.0	8.0	9.3
2007	3.7	3.1	0.07	0.1	0.3	1.2	2.6	4.0	8.0	9.4
2008	3.7	3.1	0.07	0.1	0.3	1.2	2.6	3.9	7.7	9.5
2009	3.6	3.0	0.08	0.1	0.3	1.1	2.4	3.9	7.7	9.5
2010	3.6	2.9	0.07	0.1	0.2	1.0	2.2	3.8	7.6	9.7
2011	3.5	2.9	0.08	0.1	0.2	1.0	2.1	3.7	7.4	9.7
2012	3.4	2.8	0.07	0.1	0.2	0.9	2.0	3.6	7.2	9.7
2013	3.4	2.8	0.08	0.1	0.2	0.8	1.9	3.5	7.1	10.0
2014	3.4	2.8	0.07	0.1	0.2	0.8	1.9	3.5	7.0	9.8
2015	3.3	2.7	0.07	0.1	0.2	0.7	1.7	3.3	7.0	9.9

Reference group: All members in the subpopulation of interest as of 1 January of each year.

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Table 3. Prevalence ratios of redemption of systemic glucocorticoid prescriptions according to sex, age, and calendar year, modelled using a multivariable Poisson regression.

	*Prevalence ratios (95%)
Sex	
Men	1 (ref)
Women	1.11 (1.11-1.11)
Age groups (years)	
0-19	1 (ref)
20-39	6.84 (6.79-6.89)
40-64	10.7 (10.7-10.8)
65-79	21.3 (21.1-21.4)
80+	25.3 (25.1-25.5)
Calendar year	
1999	1 (ref)
2000	1.03 (1.03-1.04)
2001	1.03 (1.03-1.04)
2002	1.05 (1.05-1.06)
2003	1.01 (1.00-1.02)
2004	1.02 (1.01-1.03)
2005	1.04 (1.03-1.04)
2006	1.06 (1.05-1.07)
2007	1.06 (1.06-1.07)
2008	1.06 (1.05-1.07)
2009	1.05 (1.04-1.06)
2010	1.02 (1.01-1.03)
2011	1.00 (1.00-1.01)
2012	0.97 (0.96-0.98)
2013	0.95 (0.94-0.96)
2014	0.95 (0.94-0.96)
2015	0.92 (0.91-0.92)

*Adjusted for other variables considered

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Table 4. Amount of systemic glucocorticoids sold to the primary health care sector, hospital sector, and in total, Denmark, 1999-2015.

	Defined daily dose/1000 inhabitants/24 hours		
	Primary sector health care sector	Hospital sector	Total
1999	10.4	2.3	12.7
2000	10.5	2.3	12.8
2001	10.8	2.3	13.1
2002	11.0	2.6	13.5
2003	10.8	2.5	13.3
2004	10.8	2.4	13.2
2005	10.8	2.5	13.3
2006	10.8	2.6	13.4
2007	10.7	2.7	13.4
2008	10.7	2.7	13.4
2009	10.6	3.0	13.6
2010	10.5	3.1	13.6
2011	10.3	3.1	13.5
2012	10.2	3.3	13.5
2013	10.1	3.4	13.5
2014	10.1	3.6	13.7
2015	10.0	3.5	13.5

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FOOTNOTES

None of the authors reports conflicts of interest or financial disclosures.

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Authorship: KL, IP, JOLJ, and HTS made primary contributions to the study conception and wrote the manuscript. KL extracted results from Medstat (http://www.medstat.dk/en) and performed statistical analyses. KL, IP, JOLJ, and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript. KL is the guarantor for this study.

Ethical Approval: Ethical approval is not required to retrieve data from Medstat (http://www.medstat.dk/en).

Data sharing statement: No additional data are available.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	None missing
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,7
		(b) Give reasons for non-participation at each stage	Not relevant
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not relevant
		Cross-sectional study—Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8,9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Systemic glucocorticoid use in Denmark: A population-based prevalence study

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Systemic glucocorticoid use in Denmark: A population-based prevalence study

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

Affiliations:

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

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

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

Correspondence: Kristina Laugesen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. Telephone number: +45 871 68063

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ABSTRACT

Objectives: Glucocorticoid (GC) use is widespread and associated with many adverse effects. Thus, it is important to ascertain GC utilisation patterns. In this study, we examined the annual prevalence of prescription users and amount of use of systemic GCs.

Design: Population-wide prevalence study.

Setting: The primary health care and hospital sectors in Denmark from 1999 to 2015.

Results: Approximately 3% of the Danish population redeemed at least one prescription for a systemic GC annually between 1999 and 2015, with annual prevalence remaining constant over the period. However, after adjusting for age and sex, we observed a decrease in annual prevalence from 1999 to 2015, with a prevalence ratio of 0.92 (95% confidence interval [CI]: 0.91-0.92). Annual prevalence was highest among the elderly (7.0%-8.2% among persons 65-79 years of age and 8.4%-10% among persons 80+ years of age). Prednisolone was the most frequently redeemed systemic GC, with annual prevalence increasing from 1.4% to 2.1% during the 1999-2015 period. The amount of systemic GCs provided to the hospital sector increased from 2.3 defined daily doses (DDD)/1000 inhabitants/day in 1999 to 3.5 DDD/1000 inhabitants/day in 2015, while the amount provided to the primary health care sector remained constant in the range of 10-11 DDD/1000 inhabitants/day.

Conclusion: We found a high prevalence of systemic GC use of 3% with a remarkably high prevalence in elderly of up to 10%, wherefore continued awareness of its effects is mandated.

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Strengths and limitations of this study

- Current knowledge of glucocorticoid (GC) utilisation patterns is in need of updating and expansion.
- This study is a population-wide study of annual prevalence of systemic GC users in Denmark from 1999 to 2015 according to age and sex.
- Annual amount of systemic GC used in both primary health care sector and hospital sectors in Denmark was examined.
- The results of this study apply only to redeemed prescriptions and sales of systemic GCs, and not necessarily to actual adherence and use.
- As we used aggregated data, we were not able to address number of prescriptions on individual level, to separate oral and injectable formulations, to obtain incidence use, and to assess use of co-medication.

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BACKGROUND

Glucocorticoids (GCs) are potent anti-inflammatory drugs used widely since the 1950s to treat common conditions such as asthma, chronic obstructive pulmonary disease, chronic inflammatory bowel diseases, rheumatic diseases, and malignancies.[1] Besides their beneficial effects in treating inflammatory diseases, GCs are associated with increased risk of a number of adverse outcomes, including iatrogenic adrenocortical insufficiency,[2] venous thromboembolism,[3] and cardiac disease.[4-6] In addition, GCs can cause metabolic diseases such as hyperglycemia, diabetes,[7] and dyslipidemia.[8] They also are associated with increased risk of osteoporosis,[9] and neuropsychiatric disorders.[10]

Current knowledge of GC utilisation patterns is in need of updating and expansion. Earlier studies estimated that the prevalence of oral GC use is approximately 1% in the U.K. and the U.S. adult populations, respectively.[11-13] In the current population-based study, we examined the annual prevalence of systemic GC prescription users (one or more redeemed prescriptions in a year) in the primary health care sector and ascertained the amount of GC used within the primary health care and hospital sectors in Denmark during 1999-2015.

METHODS

Setting

Our study population included the entire Danish population from 1 January 1999 to 31 December 2015. Denmark provides its entire population (5.6 million) with universal tax-supported health care, guaranteeing free and equal access to general practitioners and hospitals and partial reimbursement for prescribed medications, including GCs. A unique central personal registration number (civil

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registration number) is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous linkage of relevant registries at the individual level.[14]

Utilisation of systemic glucocorticoids in Denmark

In Denmark, all systemic GCs (ATC code H02AB) are available by prescription only. We used Medstat (http://www.medstat.dk) to retrieve data on systemic GC amount and prevalence of prescription users in Denmark.[15] The publicly available Medstat website hosted by the Danish Serum Institute provides aggregate statistics on the sale of pharmaceutical preparations in Denmark since 1995, based on data reported to the Register of Medicinal Product Statistics.[16] Aggregated Medstat statistics are complete from 1999 on, and allow for extraction of both amount (in primary health care and hospital sector) and number of users (in primary health care) each year.[15] Amount is expressed in defined daily doses (DDD)/1000inhabitants/24 hours and can be assessed in primary health care sector, hospital sector, and in total. DDD is developed by WHO and defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.[17] However, it should be emphasised that the DDD is a unit of measurement and does not necessarily reflect the recommended prescribed dose. As an example, the DDD for prednisolone is 10 mg per day. Medicines to the hospital sector are distributed to departments, and the people who are treated with the medicines are not reported, hence only amount and not prevalence of users can be assessed in this sector. Use in primary health care includes individual dispensing of medicines in pharmacies. As the civil registration number is registered at each prescription redemption at pharmacies in Denmark, we were able to retrieve number of prescription users in primary care in addition to amount, and stratify on age and sex.

Statistical analysis

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First, we focused on prescriptions for systemic GCs in the primary health care sector. The annual prevalence of systemic GC prescription users was defined as the number of people who redeemed at least one prescription for a systemic GC each year divided by the number of people in the population each year (as of 1 January). We calculated overall annual prevalence and then stratified by sex and age group (0-4 years, 5-9 years, 10-14 years, 15–19 years, 20–39 years, 40–64 years, 65–79 years, and ≥80 years). Age was defined as the age at which the first prescription was redeemed each year. We further stratified on generic type of systemic GC. In our computation of the annual prevalence of GC use, the entire Danish population served as the reference group. When we computed the prevalence in subgroups (age and sex), the subgroup of interest served as the reference population. To examine changes in prevalence, we used a Poisson regression model to estimate adjusted prevalence ratios according to age, sex, and calendar year. 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. Finally, we calculated the amount (defined daily dose [DDD]/1000 inhabitants/24 hours) of systemic GC used in total and according to health care sector (primary health care sector and hospital sector). We conducted our statistical analyses using Stata 12 for Windows (Stata Corp, College Station, TX).

RESULTS

In any given year between 1999 and 2015, 3% (range: 3.0% - 3.4%) of the total Danish population redeemed at least one prescription for a systemic GC (Table 1). Overall, prevalence of systemic GC prescription users during this period, adjusted for age and sex, was fairly stable with a slight decrease towards the end of the period (Table 2).

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The annual prevalence of systemic GC prescription users was higher among women than among men with a prevalence ratio of 1.11 (95% CI: 1.11-1.11) (Table 2) and prevalence ranging from 3.3%-3.7% in women and 2.7%-3.1% in men (Table 1). The prevalence of prescription users increased substantially with age. Thus, persons aged 40-64 were more than 10 times as likely and persons aged 80+ were more than 25 times as likely to receive GC treatment than those aged below 19 (Table 2). While prevalence was relatively constant between 1999 and 2015, the prevalence fell from 8.2% to 7.0% among persons aged 65-79 years and increased from 8.4% to 10.0% among those aged 80 or above (Table 1).

The most frequently redeemed systemic GC was prednisolone. Its annual prevalence of redemption in the Danish population increased from 1.4% to 2.1% during 1999 and 2015. In 2015, prednisolone accounted for 50% of all GC prescriptions redeemed in the period (taking into account only the first prescription each year). There was a decrease in redemptions of prednisone and betamethasone, from 0.4% to 0.1% and from 1.0% to 0.4% of the Danish population, respectively, from 1999 to 2015 (Figure 1).

The amount of systemic GC used in the primary health care sector consistently remained at 10 DDD/1000 inhabitants/24 hours (range: 10.0-10.8 DDD/1000 inhabitants/24 hours) from 1999 to 2015. The amount of systemic GCs used in the hospital sector increased from 2.3 DDD/1000 inhabitants/24 hours in 1999 to 3.5 DDD/1000 inhabitants/24 hours in 2015 (Table 3).

DISCUSSION

This population-based nationwide study found a high prevalence (3%) of systemic GC users from 1999 to 2015 in Denmark, especially among the elderly (10%). This underscores the importance of clinical awareness of the adverse effects of GC treatment. Still, when changes in the age structure of

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the population were taken into consideration, a minor decrease in prevalence of GC prescriptions users was observed during the study period. When assessing amount of systemic GC use, we observed a slight increase from 1999 to 2015, mainly due to inclined use in the hospital sector.

Previous studies conducted in the U.K. and the U.S. reported a lower prevalence of approximately 1%.[11-13] However, the U.K. and U.S. estimates were limited to the use of oral GCs. Our inclusion of all systemic GCs – both oral and injectable formulations –might explain in part the higher estimates of prevalence of use in the Danish population. Also, the U.K. study covered only long-term (≥1 year) GC use,[11] while our study included all use. Still, the results from our study most likely reflect a higher use of systemic GCs in Denmark compared to the U.K. and U.S.

The U.K. study reported an increase in prescriptions for long-term oral GCs of nearly 34% between 1989 and 2008.[11] Our study found that overall annual prevalence did not vary substantially between 1999 and 2015. Taking into account changes in age and sex distribution of the population, we found a decrease in the annual prevalence of systemic GC prescription users towards the end of our study period. Due to use of aggregated data, we were not able to investigate long-term use.

Our finding that prednisolone was the most frequent subtype of redeemed GC prescription (50%) is consistent with the U.K. and U.S. studies, which reported that 92.3% and 76.6% of total GC prescriptions were for prednisolone.[11, 13]

The U.K. study found the highest prevalence of use of oral GCs among women aged 80-90 years (3.05% [95% CI: 3.01%, 3.09%]) and the lowest prevalence among men aged 18-29 years (0.08% [95% CI: 0.07%, 0.09%]).[11] In the U.S. population, the highest prevalence of use was found among men aged ≥80 years (3.5% [95% CI: 2.3%–4.7%]) and among women aged 70–79 years (2.7% [95% CI: 1.7%–3.7%]).[13] The high prevalence of GC use observed among the elderly in our study is noteworthy, as it is well established that persons in the highest age groups are

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particularly prone to adverse outcomes due to higher levels of comorbidity, senescent changes in the body composition, and polypharmacy.[18]

When assessing amount of systemic GC use, we observed an increase of use in the hospital sector. A possible explanation for this can be a higher frequency of elderly admitted to the Danish hospitals from 1999 to 2015.[19] When patients are hospitalised treatment with medicine is not registered on individual level in our national registries, hence we were not able to examine use according to age; neither could we include GC use in the hospital sector in our prevalence analyses.

The pattern of disease has changed from 1999 to 2014 [11, 20-22] with increasing prevalence of many inflammatory diseases. Despite this, we have observed a minor decrease in prevalence of systemic GC users when taking changes in age structure into account. An explanation for this can be an increased clinical awareness of the adverse effects of GC treatment as well as increased use of alternative immunomodulatory treatments. The use of methotrexate, azathioprine and anti-TNF alpha therapy has increased and newer biologic agents have been approved for treatment in Denmark during our study period.[15]

The results of this study apply only to redeemed prescriptions and sales of systemic GCs, and not necessarily to actual use or dose, as we were not able to estimate adherence to the medication. Also, as we used aggregated data we were not able to address number of redeemed prescriptions on individual level, to separate oral and injectable formulations, to obtain incidence use, and to assess use of co-medication, which is all relevant when describing utilization patterns. In addition, our study did not aim to describe utilization of inhaled and topical GCs, however, these formulations should also be considered important when addressing adverse effects.

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In conclusion, this population-based nationwide study found a high prevalence of systemic GC use of 3% with remarkably high prevalence in the elderly of up to 10%, wherefore continued awareness of its adverse effects is mandated.

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TABLES

Table 1. Annual prevalence of systemic glucocorticoid (GC) prescription users in Denmark, 1999-2015, overall and stratified by sex and age group.

	Prevalence of prescription users (% of the national population)										
	All	Sex		Age groups (years)							
		Women	Men	0-4	5-9	10-14	15-19	20-39	40-64	65-79	80+
1999	3.2	3.4	2.9	0.06	0.1	0.2	0.9	2.2	3.8	8.1	8.4
2000	3.3	3.6	3.0	0.06	0.1	0.2	1.0	2.4	3.9	8.1	8.7
2001	3.3	3.6	3.0	0.09	0.1	0.2	1.0	2.4	3.9	8.2	8.8
2002	3.3	3.6	3.0	0.06	0.1	0.3	1.1	2.6	3.9	8.1	8.9
2003	3.2	3.5	2.9	0.07	0.1	0.2	1.0	2.3	3.8	8.0	8.9
2004	3.2	3.5	2.9	0.06	0.1	0.2	0.9	2.3	3.8	8.0	8.9
2005	3.3	3.6	3.0	0.06	0.1	0.2	1.0	2.5	3.8	8.0	9.2
2006	3.4	3.7	3.0	0.07	0.1	0.3	1.1	2.5	4.0	8.0	9.3
2007	3.4	3.7	3.1	0.07	0.1	0.3	1.2	2.6	4.0	8.0	9.4
2008	3.4	3.7	3.1	0.07	0.1	0.3	1.2	2.6	3.9	7.7	9.5
2009	3.3	3.6	3.0	0.08	0.1	0.3	1.1	2.4	3.9	7.7	9.5
2010	3.3	3.6	2.9	0.07	0.1	0.2	1.0	2.2	3.8	7.6	9.7
2011	3.2	3.5	2.9	0.08	0.1	0.2	1.0	2.1	3.7	7.4	9.7
2012	3.1	3.4	2.8	0.07	0.1	0.2	0.9	2.0	3.6	7.2	9.7
2013	3.1	3.4	2.8	0.08	0.1	0.2	0.8	1.9	3.5	7.1	10.0
2014	3.1	3.4	2.8	0.07	0.1	0.2	0.8	1.9	3.5	7.0	9.8
2015	3.0	3.3	2.7	0.07	0.1	0.2	0.7	1.7	3.3	7.0	9.9

Reference group for all systemic GCs is all members of the Danish population as of 1 January in the year of interest.
Reference groups for the stratified results are all members in the subpopulation of interest as of 1 January of each year.

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Table 2. Prevalence ratios of redemption of systemic glucocorticoid prescriptions according to sex, age, and calendar year, modelled using a multivariable Poisson regression.

	Prevalence ratios (95% confidence interval)
Sex[a]	
Men	1 (ref)
Women	1.11 (1.11-1.11)
Age groups (years)[b]	
0-19	1 (ref)
20-39	6.84 (6.79-6.89)
40-64	10.7 (10.7-10.8)
65-79	21.3 (21.1-21.4)
80+	25.3 (25.1-25.5)
Calendar year[c]	
1999	1 (ref)
2000	1.03 (1.03-1.04)
2001	1.03 (1.03-1.04)
2002	1.05 (1.05-1.06)
2003	1.01 (1.00-1.02)
2004	1.02 (1.01-1.03)
2005	1.04 (1.03-1.04)
2006	1.06 (1.05-1.07)
2007	1.06 (1.06-1.07)
2008	1.06 (1.05-1.07)
2009	1.05 (1.04-1.06)
2010	1.02 (1.01-1.03)
2011	1.00 (1.00-1.01)
2012	0.97 (0.96-0.98)
2013	0.95 (0.94-0.96)
2014	0.95 (0.94-0.96)
2015	0.92 (0.91-0.92)

[a]: Prevalence ratios adjusted for age group and calendar year, [b]: Prevalence ratios adjusted for sex and calendar year, [c]: Prevalence ratios adjusted for sex and age group.

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Table 3. Amount of systemic glucocorticoids sold to the primary health care sector, hospital sector, and in total, Denmark, 1999-2015.

	Defined daily dose/1000 inhabitants/24 hours		
	Primary sector health care sector	Hospital sector	Total
1999	10.4	2.3	12.7
2000	10.5	2.3	12.8
2001	10.8	2.3	13.1
2002	11.0	2.6	13.5
2003	10.8	2.5	13.3
2004	10.8	2.4	13.2
2005	10.8	2.5	13.3
2006	10.8	2.6	13.4
2007	10.7	2.7	13.4
2008	10.7	2.7	13.4
2009	10.6	3.0	13.6
2010	10.5	3.1	13.6
2011	10.3	3.1	13.5
2012	10.2	3.3	13.5
2013	10.1	3.4	13.5
2014	10.1	3.6	13.7
2015	10.0	3.5	13.5

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FOOTNOTES

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Authorship: KL, IP, JOLJ, and HTS made primary contributions to the study conception and wrote the manuscript. KL extracted results from Medstat (http://www.medstat.dk/en) and performed statistical analyses. KL, IP, JOLJ, and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript. KL is the guarantor for this study.

Ethical Approval: Ethical approval is not required to retrieve data from Medstat (http://www.medstat.dk/en).

Data sharing statement: No additional data are available.

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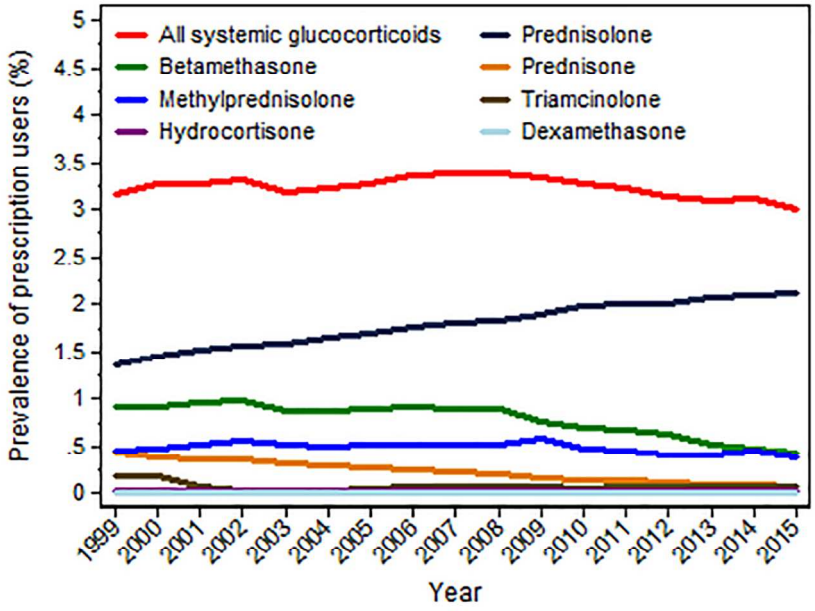

Annual prevalence of systemic glucocorticoid prescription users in Denmark, 1999-2015, overall and stratified on generic type.
Figure 1
125x83mm (300 x 300 DPI)

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	None missing
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,7
		(b) Give reasons for non-participation at each stage	Not relevant
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not relevant
		Cross-sectional study—Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8,9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Systemic glucocorticoid use in Denmark: A population-based prevalence study

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Systemic glucocorticoid use in Denmark: A population-based prevalence study

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

Affiliations:

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

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

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

Correspondence: Kristina Laugesen, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. E-mail: Kristina.laugesen@clin.au.dk. Telephone number: +45 871 68063

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ABSTRACT

Objectives: Glucocorticoid (GC) use is widespread and associated with many adverse effects. Thus, it is important to ascertain GC utilisation patterns. In this study, we examined the annual prevalence of prescription users and amount of use of systemic GCs.

Design: Population-wide prevalence study.

Setting: The primary health care and hospital sectors in Denmark from 1999 to 2015.

Results: Approximately 3% of the Danish population redeemed at least one prescription for a systemic GC annually between 1999 and 2015, with annual prevalence remaining constant over the period. However, after adjusting for age and sex, we observed a decrease in annual prevalence from 1999 to 2015, with a prevalence ratio of 0.92 (95% confidence interval [CI]: 0.91-0.92). Annual prevalence was highest among the elderly (7.0%-8.2% among persons 65-79 years of age and 8.4%-10% among persons 80+ years of age). Prednisolone was the most frequently redeemed systemic GC, with annual prevalence increasing from 1.4% to 2.1% during the 1999-2015 period. The amount of systemic GCs provided to the hospital sector increased from 2.3 defined daily doses (DDD)/1000 inhabitants/day in 1999 to 3.5 DDD/1000 inhabitants/day in 2015, while the amount provided to the primary health care sector remained constant in the range of 10-11 DDD/1000 inhabitants/day.

Conclusion: We found a high prevalence of systemic GC use of 3% with a remarkably high prevalence in elderly of up to 10%, wherefore continued awareness of its effects is mandated.

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Strengths and limitations of this study

- Current knowledge of glucocorticoid (GC) utilisation patterns is in need of updating and expansion.
- A strength of our study is the population-based design that enables us to assess utilisation of systemic GCs in the entire Danish nation from 1999 to 2015.
- An additional advantage was the ability to assess GC use in the hospital sector as well as the primary health care sector, which is normally not captured when using Danish prescription registries for research.
- The results of this study apply only to redeemed prescriptions and sales of systemic GCs, and not necessarily to actual adherence and use.
- As we used aggregated data, we were not able to address number of prescriptions at an individual level, to separate oral and injectable formulations, to obtain incidence use, and to assess use of co-medication.

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BACKGROUND

Glucocorticoids (GCs) are potent anti-inflammatory drugs used widely since the 1950s to treat common conditions such as asthma, chronic obstructive pulmonary disease, chronic inflammatory bowel diseases, rheumatic diseases, and malignancies.[1] Besides their beneficial effects in treating inflammatory diseases, GCs are associated with increased risk of a number of adverse outcomes, including iatrogenic adrenocortical insufficiency,[2] venous thromboembolism,[3] and cardiac disease.[4-6] In addition, GCs can cause metabolic diseases such as hyperglycemia, diabetes,[7] and dyslipidemia.[8] They also are associated with increased risk of osteoporosis,[9] and neuropsychiatric disorders.[10]

Current knowledge of GC utilisation patterns is in need of updating and expansion. Earlier studies estimated that the prevalence of oral GC use is approximately 1% in the U.K. and the U.S. adult populations, respectively.[11-13] In the current population-based study, we examined the annual prevalence of systemic GC prescription users (one or more redeemed prescriptions in a year) in the primary health care sector and ascertained the amount of GC used within the primary health care and hospital sectors in Denmark during 1999-2015.

METHODS

Setting

Our study population included the entire Danish population from 1 January 1999 to 31 December 2015. Denmark provides its entire population (5.6 million) with universal tax-supported health care, guaranteeing free and equal access to general practitioners and hospitals and partial reimbursement

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for prescribed medications, including GCs. A unique central personal registration number (civil registration number) is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous linkage of relevant registries at the individual level.[14]

Utilisation of systemic glucocorticoids in Denmark

In Denmark, all systemic GCs (ATC code H02AB) are available by prescription only. We used Medstat (http://www.medstat.dk) to retrieve data on systemic GC amount and prevalence of prescription users in Denmark.[15] The publicly available Medstat website hosted by the Danish Serum Institute provides aggregate statistics on the sale of pharmaceutical preparations in Denmark since 1995, based on data reported to the Register of Medicinal Product Statistics.[16] Aggregated Medstat statistics are complete from 1999 on, and allow for extraction of both amount (in primary health care and hospital sector) and number of users (in primary health care) each year.[15] Amount is expressed in defined daily doses (DDD)/1000inhabitants/24 hours and can be assessed in primary health care sector, hospital sector, and in total. DDD is developed by WHO and defined as the assumed average maintenance dose per day for a drug used for its main indication in adults.[17] However, it should be emphasised that the DDD is a unit of measurement and does not necessarily reflect the recommended prescribed dose. As an example, the DDD for prednisolone is 10 mg per day. Medicines to the hospital sector are distributed to departments, and the people who are treated with the medicines are not reported, hence only amount and not prevalence of users can be assessed in this sector. Use in primary health care includes individual dispensing of medicines in pharmacies. As the civil registration number is registered at each prescription redemption at pharmacies in Denmark, we were able to retrieve number of prescription users in primary care in addition to amount, and stratify on age and sex.

Statistical analysis

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First, we focused on prescriptions for systemic GCs in the primary health care sector. The annual prevalence of systemic GC prescription users was defined as the number of people who redeemed at least one prescription for a systemic GC each year divided by the number of people in the population each year (as of 1 January). We calculated overall annual prevalence and then stratified by sex and age group (0-4 years, 5-9 years, 10-14 years, 15–19 years, 20–39 years, 40–64 years, 65–79 years, and ≥80 years). Age was defined as the age at which the first prescription was redeemed each year. We further stratified on generic type of systemic GC. In our computation of the annual prevalence of GC use, the entire Danish population served as the reference group. When we computed the prevalence in subgroups (age and sex), the subgroup of interest served as the reference population. To examine changes in prevalence, we used a Poisson regression model to estimate adjusted prevalence ratios according to age, sex, and calendar year. 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. Finally, we calculated the amount (defined daily dose [DDD]/1000 inhabitants/24 hours) of systemic GC used in total and according to health care sector (primary health care sector and hospital sector). We conducted our statistical analyses using Stata 12 for Windows (Stata Corp, College Station, TX).

RESULTS

In any given year between 1999 and 2015, 3% (range: 3.0% - 3.4%) of the total Danish population redeemed at least one prescription for a systemic GC (Table 1). Overall, prevalence of systemic GC prescription users during this period, adjusted for age and sex, was fairly stable with a slight decrease towards the end of the period (Table 2).

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The annual prevalence of systemic GC prescription users was higher among women than among men with a prevalence ratio of 1.11 (95% CI: 1.11-1.11) (Table 2) and prevalence ranging from 3.3%-3.7% in women and 2.7%-3.1% in men (Table 1). The prevalence of prescription users increased substantially with age. Thus, persons aged 40-64 were more than 10 times as likely and persons aged 80+ were more than 25 times as likely to receive GC treatment than those aged below 19 (Table 2). While prevalence was relatively constant between 1999 and 2015, the prevalence fell from 8.2% to 7.0% among persons aged 65-79 years and increased from 8.4% to 10% among those aged 80 or above (Table 1).

The most frequently redeemed systemic GC was prednisolone. Its annual prevalence of redemption in the Danish population increased from 1.4% to 2.1% during 1999 and 2015. In 2015, prednisolone accounted for 50% of all GC prescriptions redeemed in the period (taking into account only the first prescription each year). There was a decrease in redemptions of prednisone and betamethasone, from 0.4% to 0.1% and from 1.0% to 0.4% of the Danish population, respectively, from 1999 to 2015 (Figure 1).

The amount of systemic GC used in the primary health care sector consistently remained at 10 DDD/1000 inhabitants/24 hours (range: 10.0-10.8 DDD/1000 inhabitants/24 hours) from 1999 to 2015. The amount of systemic GCs used in the hospital sector increased from 2.3 DDD/1000 inhabitants/24 hours in 1999 to 3.5 DDD/1000 inhabitants/24 hours in 2015 (Table 3).

DISCUSSION

This population-based nationwide study found a high prevalence (3%) of systemic GC users from 1999 to 2015 in Denmark, especially among the elderly (10%). This underscores the importance of clinical awareness of the adverse effects of GC treatment. Still, when changes in the age structure of

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the population were taken into consideration, a minor decrease in prevalence of GC prescriptions users was observed during the study period. When assessing amount of systemic GC use, we observed a slight increase from 1999 to 2015, mainly due to inclined use in the hospital sector.

Previous studies conducted in the U.K. and the U.S. reported a lower prevalence of approximately 1%.[11-13] However, the U.K. and U.S. estimates were limited to the use of oral GCs. Our inclusion of all systemic GCs – both oral and injectable formulations –might explain in part the higher estimates of prevalence of use in the Danish population. Also, the U.K. study covered only long-term (≥1 year) GC use,[11] while our study included all use. Still, the results from our study most likely reflect a higher use of systemic GCs in Denmark compared to the U.K. and U.S.

The U.K. study reported an increase in prescriptions for long-term oral GCs of nearly 34% between 1989 and 2008.[11] Our study found that overall annual prevalence did not vary substantially between 1999 and 2015. Taking into account changes in age and sex distribution of the population, we found a decrease in the annual prevalence of systemic GC prescription users towards the end of our study period. Due to use of aggregated data, we were not able to investigate long-term use.

Our finding that prednisolone was the most frequent subtype of redeemed GC prescription (50%) is consistent with the U.K. and U.S. studies, which reported that 92.3% and 76.6% of total GC prescriptions were for prednisolone.[11, 13]

The U.K. study found the highest prevalence of use of oral GCs among women aged 80-90 years (3.05% [95% CI: 3.01%, 3.09%]) and the lowest prevalence among men aged 18-29 years (0.08% [95% CI: 0.07%, 0.09%]).[11] In the U.S. population, the highest prevalence of use was found among men aged ≥80 years (3.5% [95% CI: 2.3%–4.7%]) and among women aged 70–79 years (2.7% [95% CI: 1.7%–3.7%]).[13] The high prevalence of GC use observed among the elderly in our study is noteworthy, as it is well established that persons in the highest age groups are

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particularly prone to adverse outcomes due to higher levels of comorbidity, senescent changes in the body composition, and polypharmacy.[18]

When assessing amount of systemic GC use, we observed an increase of use in the hospital sector. A possible explanation for this can be a higher frequency of elderly admitted to the Danish hospitals from 1999 to 2015.[19] When patients are hospitalised treatment with medicine is not registered at an individual level in our national registries, hence we were not able to examine use according to age; neither could we include GC use in the hospital sector in our prevalence analyses.

The pattern of disease has changed from 1999 to 2014 [11, 20-22] with increasing prevalence of many inflammatory diseases. Despite this, we have observed a minor decrease in prevalence of systemic GC users when taking changes in age structure into account. An explanation for this can be an increased clinical awareness of the adverse effects of GC treatment as well as increased use of alternative immunomodulatory treatments. The use of methotrexate, azathioprine and anti-TNF alpha therapy has increased and newer biologic agents have been approved for treatment in Denmark during our study period.[15]

The strength of our study includes its large nationwide study population making use capable of assessing utilisation of GCs in the entire Danish nation. In addition, we had the ability to assess GC use in the hospital sector. Many drug utilisation studies do not have available information on prescribing in the hospital section. Hence, our study helps to inform which proportion of prescribing may be missing from such studies. However, this study also has limitations. First, the results of this study apply only to redeemed prescriptions and sales of systemic GCs, and not necessarily to actual use or dose, as we were not able to estimate adherence to the medication. Second, as we used aggregated data we were not able to address number of redeemed prescriptions at an individual level, to separate oral and injectable formulations, to obtain incidence use, and to assess use of co-

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medication, which is all relevant when describing utilisation patterns. Third, our study did not aim to describe utilisation of inhaled and topical GCs, however, these formulations should also be considered important when addressing adverse effects.

In conclusion, this population-based nationwide study found a high prevalence of systemic GC use of 3% with remarkably high prevalence in the elderly of up to 10%, wherefore continued awareness of its adverse effects is mandated.

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TABLES AND FIGURES

Table 1. Annual prevalence of systemic glucocorticoid (GC) prescription users in Denmark, 1999-2015, overall and stratified by sex and age group.

	Prevalence of prescription users (% of the national population)										
	All	Sex		Age groups (years)							
		Women	Men	0-4	5-9	10-14	15-19	20-39	40-64	65-79	80+
1999	3.2	3.4	2.9	0.06	0.1	0.2	0.9	2.2	3.8	8.1	8.4
2000	3.3	3.6	3.0	0.06	0.1	0.2	1.0	2.4	3.9	8.1	8.7
2001	3.3	3.6	3.0	0.09	0.1	0.2	1.0	2.4	3.9	8.2	8.8
2002	3.3	3.6	3.0	0.06	0.1	0.3	1.1	2.6	3.9	8.1	8.9
2003	3.2	3.5	2.9	0.07	0.1	0.2	1.0	2.3	3.8	8.0	8.9
2004	3.2	3.5	2.9	0.06	0.1	0.2	0.9	2.3	3.8	8.0	8.9
2005	3.3	3.6	3.0	0.06	0.1	0.2	1.0	2.5	3.8	8.0	9.2
2006	3.4	3.7	3.0	0.07	0.1	0.3	1.1	2.5	4.0	8.0	9.3
2007	3.4	3.7	3.1	0.07	0.1	0.3	1.2	2.6	4.0	8.0	9.4
2008	3.4	3.7	3.1	0.07	0.1	0.3	1.2	2.6	3.9	7.7	9.5
2009	3.3	3.6	3.0	0.08	0.1	0.3	1.1	2.4	3.9	7.7	9.5
2010	3.3	3.6	2.9	0.07	0.1	0.2	1.0	2.2	3.8	7.6	9.7
2011	3.2	3.5	2.9	0.08	0.1	0.2	1.0	2.1	3.7	7.4	9.7
2012	3.1	3.4	2.8	0.07	0.1	0.2	0.9	2.0	3.6	7.2	9.7
2013	3.1	3.4	2.8	0.08	0.1	0.2	0.8	1.9	3.5	7.1	10
2014	3.1	3.4	2.8	0.07	0.1	0.2	0.8	1.9	3.5	7.0	9.8
2015	3.0	3.3	2.7	0.07	0.1	0.2	0.7	1.7	3.3	7.0	9.9

Reference group for all systemic GCs is all members of the Danish population as of 1 January in the year of interest.
Reference groups for the stratified results are all members in the subpopulation of interest as of 1 January of each year.

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Table 2. Prevalence ratios of redemption of systemic glucocorticoid prescriptions according to sex, age, and calendar year, modelled using a multivariable Poisson regression.

	Prevalence ratios (95% confidence interval)
Sex[a]	
Men	1 (ref)
Women	1.11 (1.11-1.11)
Age groups (years)[b]	
0-19	1 (ref)
20-39	6.84 (6.79-6.89)
40-64	10.7 (10.7-10.8)
65-79	21.3 (21.1-21.4)
80+	25.3 (25.1-25.5)
Calendar year[c]	
1999	1 (ref)
2000	1.03 (1.03-1.04)
2001	1.03 (1.03-1.04)
2002	1.05 (1.05-1.06)
2003	1.01 (1.00-1.02)
2004	1.02 (1.01-1.03)
2005	1.04 (1.03-1.04)
2006	1.06 (1.05-1.07)
2007	1.06 (1.06-1.07)
2008	1.06 (1.05-1.07)
2009	1.05 (1.04-1.06)
2010	1.02 (1.01-1.03)
2011	1.00 (1.00-1.01)
2012	0.97 (0.96-0.98)
2013	0.95 (0.94-0.96)
2014	0.95 (0.94-0.96)
2015	0.92 (0.91-0.92)

[a]: Prevalence ratios adjusted for age group and calendar year, [b]: Prevalence ratios adjusted for sex and calendar year, [c]: Prevalence ratios adjusted for sex and age group.

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Table 3. Amount of systemic glucocorticoids sold to the primary health care sector, hospital sector, and in total, Denmark, 1999-2015.

	Defined daily dose/1000 inhabitants/24 hours		
	Primary sector health care sector	Hospital sector	Total
1999	10.4	2.3	12.7
2000	10.5	2.3	12.8
2001	10.8	2.3	13.1
2002	11.0	2.6	13.5
2003	10.8	2.5	13.3
2004	10.8	2.4	13.2
2005	10.8	2.5	13.3
2006	10.8	2.6	13.4
2007	10.7	2.7	13.4
2008	10.7	2.7	13.4
2009	10.6	3.0	13.6
2010	10.5	3.1	13.6
2011	10.3	3.1	13.5
2012	10.2	3.3	13.5
2013	10.1	3.4	13.5
2014	10.1	3.6	13.7
2015	10.0	3.5	13.5

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Figure 1. Annual prevalence of systemic glucocorticoid prescription users in Denmark, 1999-2015, overall and stratified by generic type. All systemic glucocorticoids (red line), prednisolone (dark blue line), betamethasone (green line), prednisone (orange line), methylprednisolone (blue line), triamcinolone (dark green line), hydrocortisone (purple line), dexamethasone (light blue line).

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FOOTNOTES

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Authorship: KL, IP, JOLJ, and HTS made primary contributions to the study conception and wrote the manuscript. KL extracted results from Medstat (http://www.medstat.dk/en) and performed statistical analyses. KL, IP, JOLJ, and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript. KL is the guarantor for this study.

Ethical Approval: Ethical approval is not required to retrieve data from Medstat (http://www.medstat.dk/en).

Data sharing statement: No additional data are available.

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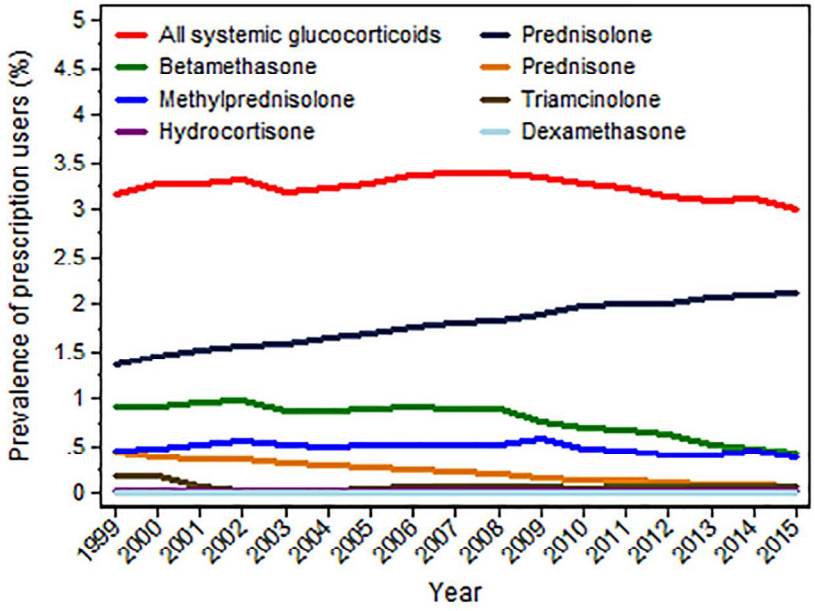

Annual prevalence of systemic glucocorticoid prescription users in Denmark, 1999-2015, overall and stratified on generic type. All systemic glucocorticoids (red line), prednisolone (dark blue line), betamethasone ┼ (green line), prednisone (orange line), methylprednisolone (blue line), triamcinolone (dark green line),┼ hydrocortisone (purple line), dexamethasone (light blue line).┼

Figure 1

125x83mm (300 x 300 DPI)

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	None missing
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not applicable

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		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,7
		(b) Give reasons for non-participation at each stage	Not relevant
		(c) Consider use of a flow diagram	Not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not relevant
		Cross-sectional study—Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8,9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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