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Use of systemic glucocorticoids and lifestyle: A Danish population-based cross-sectional study

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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) and former use (prescription redemption > 365 days before completing the questionnaire). 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% confidence intervals (CI), comparing the categories of glucocorticoid users vs. 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, 3,054 (10%) were former users, and 25,743 (85%) were never users. Ever users of glucocorticoids had a higher prevalence of obesity than never users [18% versus 14%, aPR=1.4, 95% CI 1.2 to 1.5 in women and 17% versus 15%, aPR=1.2, 95% CI 1.1 to 1.4 in men]. In women, ever users of glucocorticoids had a lower prevalence of

high-risk alcohol consumption compared to never users [17% versus 20%, aPR=0.8, 95% CI 0.7 to 1.0]. Smoking habits, diet and physical activity did not differ substantially according to use of glucocorticoids.

Conclusion: Glucocorticoid users had a higher prevalence of obesity and female glucocorticoid users had a lower prevalence of high-risk alcohol consumption compared to never users. Our findings should be considered when observational studies on glucocorticoids are conducted. Especially, when data on lifestyle is not available.

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 is 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 minimize 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] However, glucocorticoids also are associated with several adverse events, including truncal obesity, hypertension, dyslipidemia,[2] cardiac disease,[3-6] venous thromboembolism,[5] diabetes mellitus,[7] psychiatric illnesses,[8] and osteoporosis.[9]

Lifestyle factors, including smoking, alcohol consumption, physical inactivity, and obesity, are well-described risk factors for many adverse events associated with glucocorticoids.[10-13] Moreover, prior studies have found that unhealthy lifestyle is abundant in populations with diseases frequently treated with glucocorticoids, e.g. chronic obstructive pulmonary disease (COPD), inflammatory bowel disease, and rheumatoid arthritis, and also associated with severity of disease development.[14-20] Thus, lifestyle factors potentially can confound observed associations between glucocorticoid exposure and adverse events. Pharmacosurveillance of glucocorticoids is often performed using observational studies, in which control of such confounders is important. However, many data sources used for surveillance may lack data on lifestyle. This has been acknowledged as a limitation in prior studies.[5, 21]

To our knowledge, no prior studies have specifically investigated lifestyle in glucocorticoid users. Using data from a population-based health survey in Denmark, we therefore conducted a cross-sectional study to examine lifestyle among the adult Danish population according to use of systemic glucocorticoids.

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.[22] 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).[23] Between February and May 2010, a random sample of 52,400 people (7,026 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).

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 meters, squared. 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).[24] 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 summarize 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 categorized as never, former, or current (daily or occasional). We categorized 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 and inhaled medicine for COPD 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.[25] 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 categorized further according to timing of exposure and total number of redeemed prescriptions. 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 total number of redeemed prescriptions was categorized as a single prescription, two-five and > five redeemed prescriptions. [See Supplementary Table 1 for codes used in the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization.]

Statistical analyses

First, prevalence of lifestyle factors was computed according to glucocorticoid use.
Second, adjusted prevalence ratios (aPRs) and 95% confidence intervals (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 one, two-five, and > five redeemed prescription in total) were compared to the reference of never use. The PRs were adjusted for age (10-year age groups). All analyses were stratified by sex.
Third, an analysis stratified by presence of COPD (yes/ no) were conducted. Based on history of medication use, 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 (ICS) (or combinations thereof). These analyses were adjusted for sex and age (10-year age groups).

In estimating prevalence and PRs, post-survey weights computed at Statistic Denmark were used to account for survey design and non-response.[26]

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, 3,054 (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 Tables 1a and 1b and in the Supplementary Table 2, Supplementary Table 3a, and Supplementary Table 3b. Adjusted PRs are presented in Figure 1, Figure 2, Figure 3, and Figure 4 as well as in the Supplementary Table 4 and Supplementary Table 5.

Table 1a. Prevalence of lifestyle factors according to glucocorticoid use in women. Percentages are weighted

	Ever use	Current use	Recent use	Former use	Never use	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All	2,460 (100)	301 (100)	489 (100)	1,670 (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	1,113 (45)	126 (38)	218 (44)	769 (46)	7,203 (54)	8,316 (52)
25-29	717 (28)	89 (31)	120 (23)	508 (29)	3,718 (27)	4,435 (27)
≥30	444 (18)	50 (17)	105 (22)	289 (17)	1,862 (14)	2,306 (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)	2,744 (21)	3,296 (21)
Former	765 (30)	111 (35)	148 (30)	506 (29)	3,913 (28)	4,678 (28)
Never	1,047 (44)	107 (40)	206 (42)	734 (45)	6,535 (49)	7,582 (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)	1,043 (7.0)
Reasonably healthy	1,425 (58)	181 (62)	280 (57)	964 (57)	8,021 (60)	9,446 (59)
Healthy	730 (29)	72 (22)	143 (27)	515 (31)	4,234 (30)	4,964 (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	1,832 (76)	231 (80)	376 (77)	340 (74)	10,146 (75)	11,978 (75)
High risk consumption	458 (17)	43 (12)	75 (13)	1,225 (18)	2,730 (20)	3,188 (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	1,179 (49)	171 (59)	245 (53)	763 (46)	5,853 (44)	7,032 (45)
Yes	1,209 (48)	121 (39)	228 (44)	860 (50)	7,354 (54)	8,563 (53)
Missing	72 (3.2)	9 (2.3)	16 (3.2)	47 (3.3)	278 (2.3)	350 (2.4)

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.

Table 1b. Prevalence of lifestyle factors according to glucocorticoid use in men. Percentages are weighted

	Ever use N (%)	Current use N (%)	Recent use N (%)	Former use N (%)	Never use N (%)	Total N (%)
All	2,042 (100)	262 (100)	396 (100)	1,384 (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)	4,572 (39)	5,216 (38)
25-29	959 (46)	116 (41)	188 (46)	655 (47)	5,566 (44)	6,525 (44)
≥30	365 (17)	47 (19)	65 (14)	253 (18)	1,864 (15)	2,229 (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)	3,072 (27)	3,590 (27)
Former	843 (38)	126 (43)	157 (36)	560 (38)	4,022 (30)	4,865 (31)
Never	630 (32)	67 (27)	132 (35)	431 (32)	4,968 (42)	5,598 (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)	1,906 (16)	2,216 (16)
Reasonably healthy	1,301 (64)	159 (62)	253 (65)	889 (64)	7,874 (64)	9,175 (64)
Healthy	342 (15)	38 (13)	68 (16)	236 (15)	2,069 (17)	2,411 (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	1,489 (72)	184 (70)	293 (73)	1,012 (72)	9,231 (75)	10,720 (75)
High risk consumption	443 (22)	62 (21)	81 (19)	300 (22)	2,588 (21)	3,031 (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	1,128 (54)	82 (65)	214 (52)	739 (52)	6,265 (50)	7,393 (51)
Yes	874 (44)	175 (32)	171 (45)	621 (46)	5,791 (48)	6,665 (48)
Missing	40 (2.2)	5 (2.6)	11 (2.7)	24 (2.0)	202 (1.6)	242 (1.7)

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.

Body Mass Index

In women, ever users of glucocorticoids were more obese than never users [18% versus 14%; aPR 1.4 (95% CI 1.2 to 1.5)] (Table 1a and Figure 1) with highest prevalence in current continuing users (21%) and recent users (22%) (Table1a and Supplementary Table 2). Also,

male ever users were more obese than never users [17% versus 15%; aPR 1.2 (95% CI 1.1 to 1.4)] (Table 1b and Figure 2).

Smoking and COPD

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)] (Figure 1 and Figure 2). The finding of a similar prevalence of smoking compared to never users were consistent across all categories of glucocorticoid users (Figure 1, Figure, 2, Supplementary Table 4) and when stratifying on COPD (Figure 3, Figure 4 and Supplementary Table 5)

Alcohol Intake

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

Physical activity

Physical activity did not differ 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)] (Figure 1a and Figure 1b).

DISCUSSION

This population-based study found that users of systemic glucocorticoids had a 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.

Although abdominal obesity is a common feature of excess glucocorticoid exposure,[2, 27] no studies to date have examined whether obesity differ according to glucocorticoid use. Several studies, however, have investigated obesity in different inflammatory diseases. One study found that BMI is an important risk factor for self-reported arthritis, with a prevalence of arthritis of 25.9% among normal weight, 32.1% among overweight (25 to 29.9 BMI), and 43.5% among obese (>30 BMI) adults.[18] In contrast, studies of inflammatory bowel disease found that the prevalence of overweight and obesity was lower than in the general population.[19] 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.[20] 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.[20] In our study, we found no difference in physical activity according to glucocorticoid use. In any case, patients with arthritis or inflammatory bowel disease are not comparable to our population-based cohort.

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 minimize such bias, we used a weighting method developed by Statistic Denmark for this particular survey.[26] 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. Misclassification of

glucocorticoid use may lead to an underestimation of the associations. The algorithm used to define people as having COPD is also imperfect. In particular, certain persons identified as having COPD actually may have asthma. To address this issue, redeemed prescriptions for 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. Truncal obesity is a well-known adverse effect of excess glucocorticoid use. We found that current continuing and recent users of glucocorticoids had higher prevalence of obesity than current new users in women, which could indicate that obesity arises after glucocorticoid treatment.

Our study has important implications for evaluating prior observational studies and for conducting future studies. While lifestyle factors may be risk factors for study outcomes, they also constitute potential confounders. 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 is not available.[5, 6, 28] Yet, it must be acknowledged that any assessment should not be based solely on associations found in this study. Directed acyclic graphs (DAGs) could be applied to ensure that recorded lifestyle factors are not mediators or colliders.[29]

In conclusion, glucocorticoid users had a higher prevalence of obesity and female glucocorticoid users had a lower prevalence of high-risk alcohol consumption compared to never users. Smoking habits, diet and physical activity did not differ substantially according to use of glucocorticoids. Observational studies on glucocorticoids should take these findings into consideration. Especially, when data on life style is not available.

FOOTNOTES

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Competing interests: The authors report no conflicts of interest and have no financial disclosures.

Author statement: KL, IP, FBL, LP, JOLJ, and HTS made primary contributions to the concept of the study and wrote the manuscript. KL performed statistical analyses. KL, IP, FBL, LP, JOLJ, and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript.

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.

Data sharing statement: Data are available as presented in the paper and in the supplementary files. According to Danish legislation, our own approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Interested researchers may contact Julie Christiansen (juechi@rm.dk) for access to the questionnaire “Hvordan har du det?” (How Are You?). (For updated information please visit: http://www.defactum.dk/om-DEFACTUM/projektsite/hvordan-har-du-det/ansogning-om-adgang-til-data/). For access to prescription data from the Danish National Health Service Prescription Database please contact Helle Schleicher Kjær (hsk@clin.au.dk) (For updated information please visit: http://kea.au.dk/research/registries-and-biobanks/the-danish-national-health-service-prescription-database/).

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FIGURES

Fig. 1. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in women.

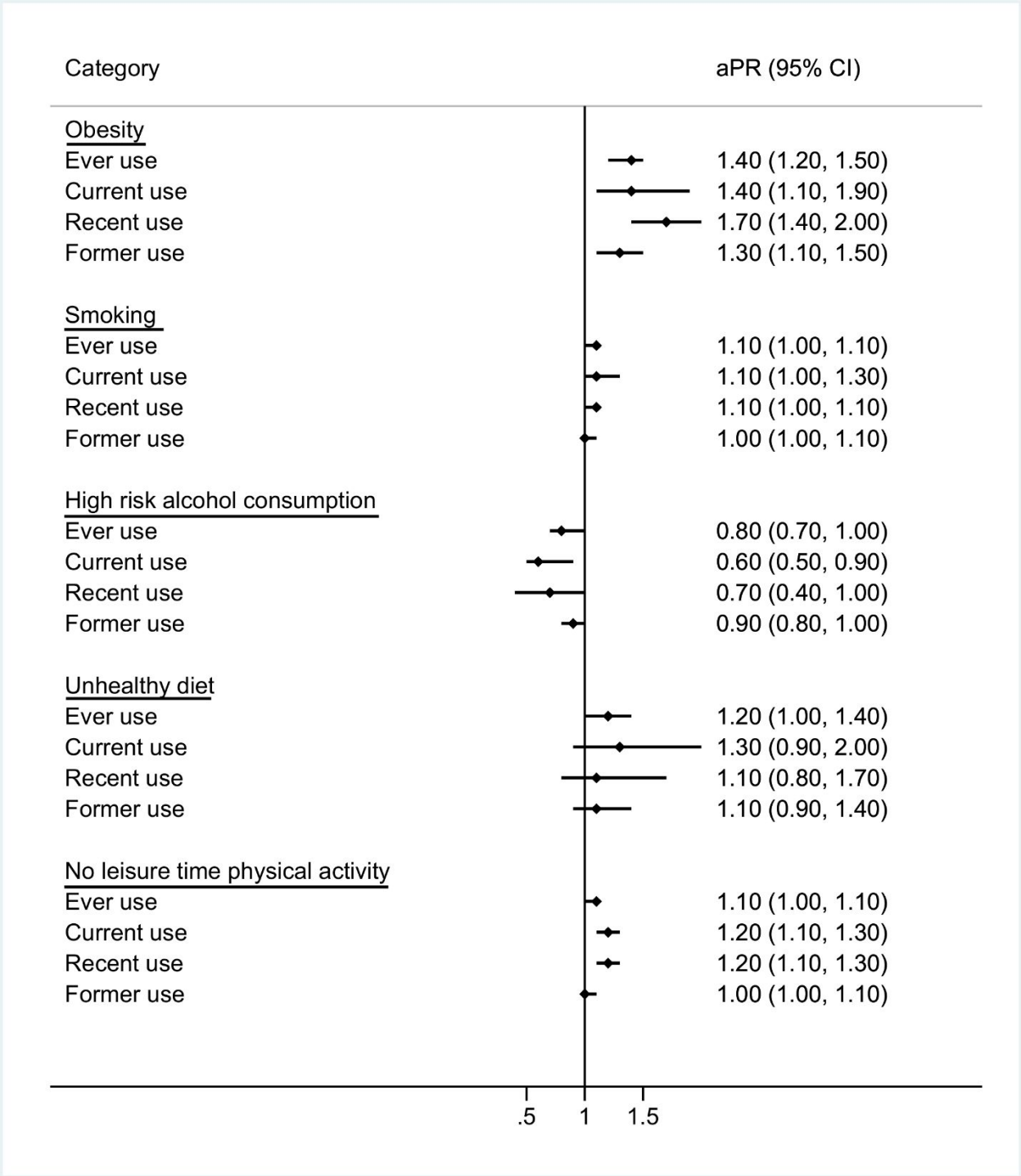


Fig. 2. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in men.

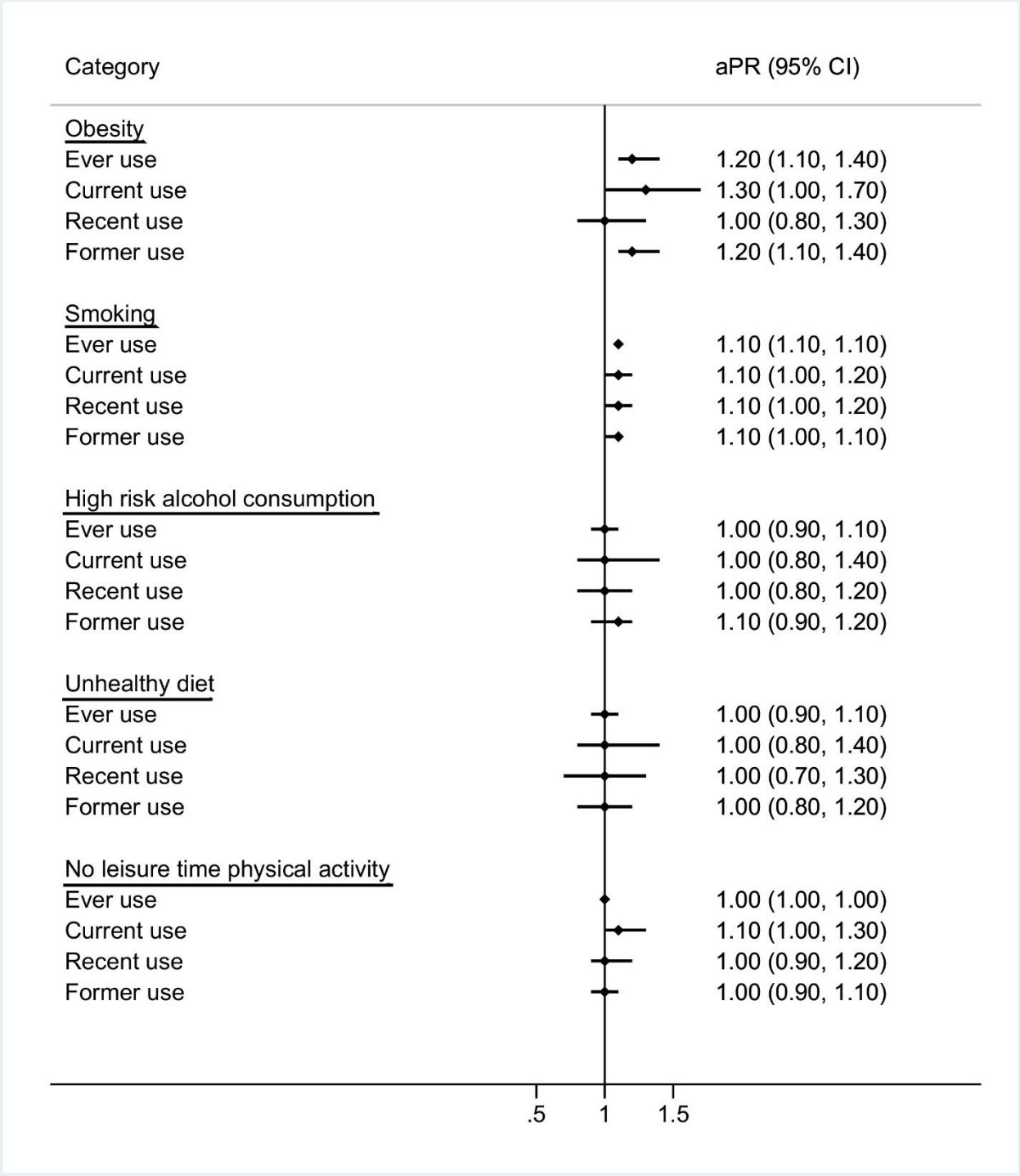
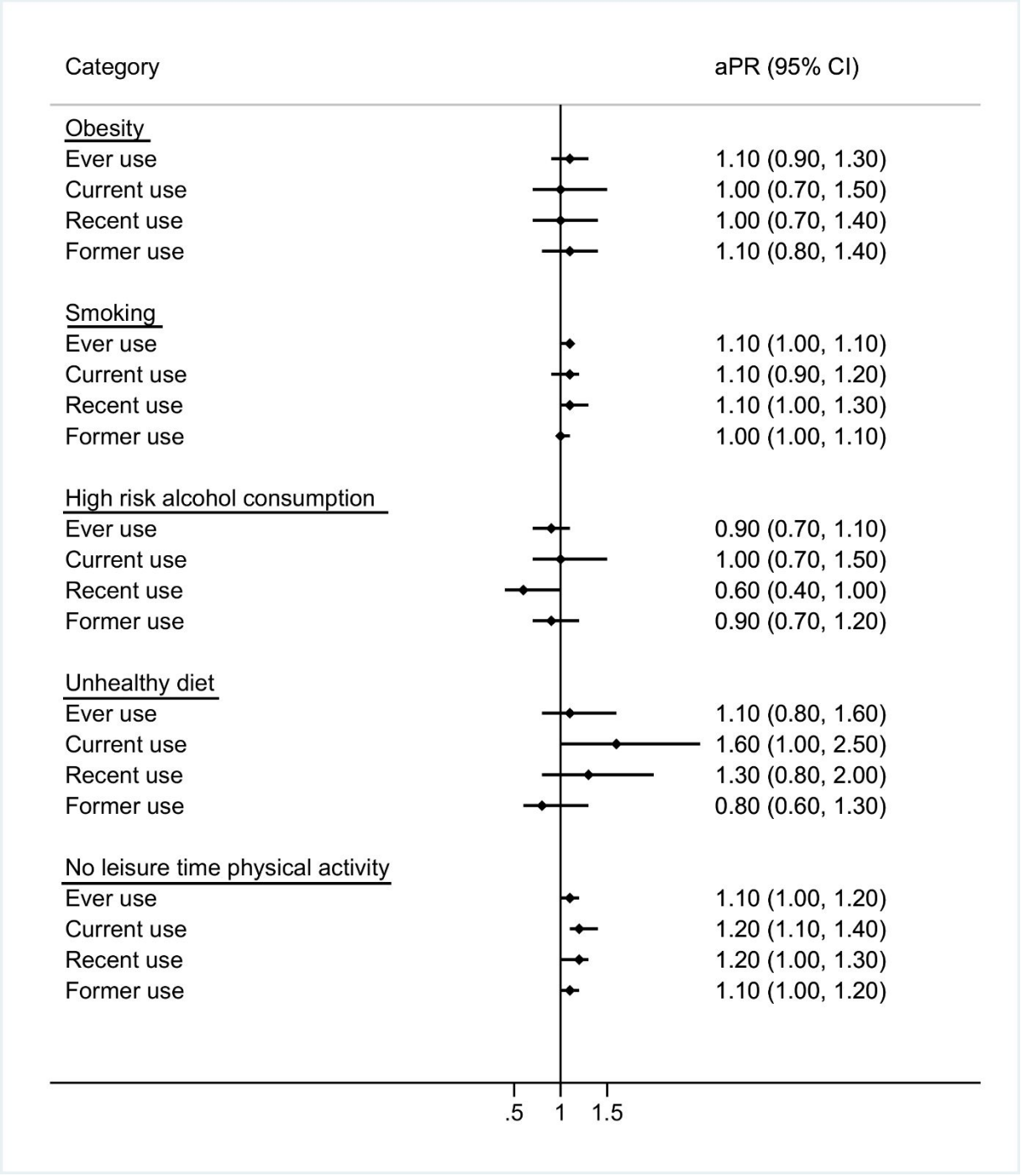
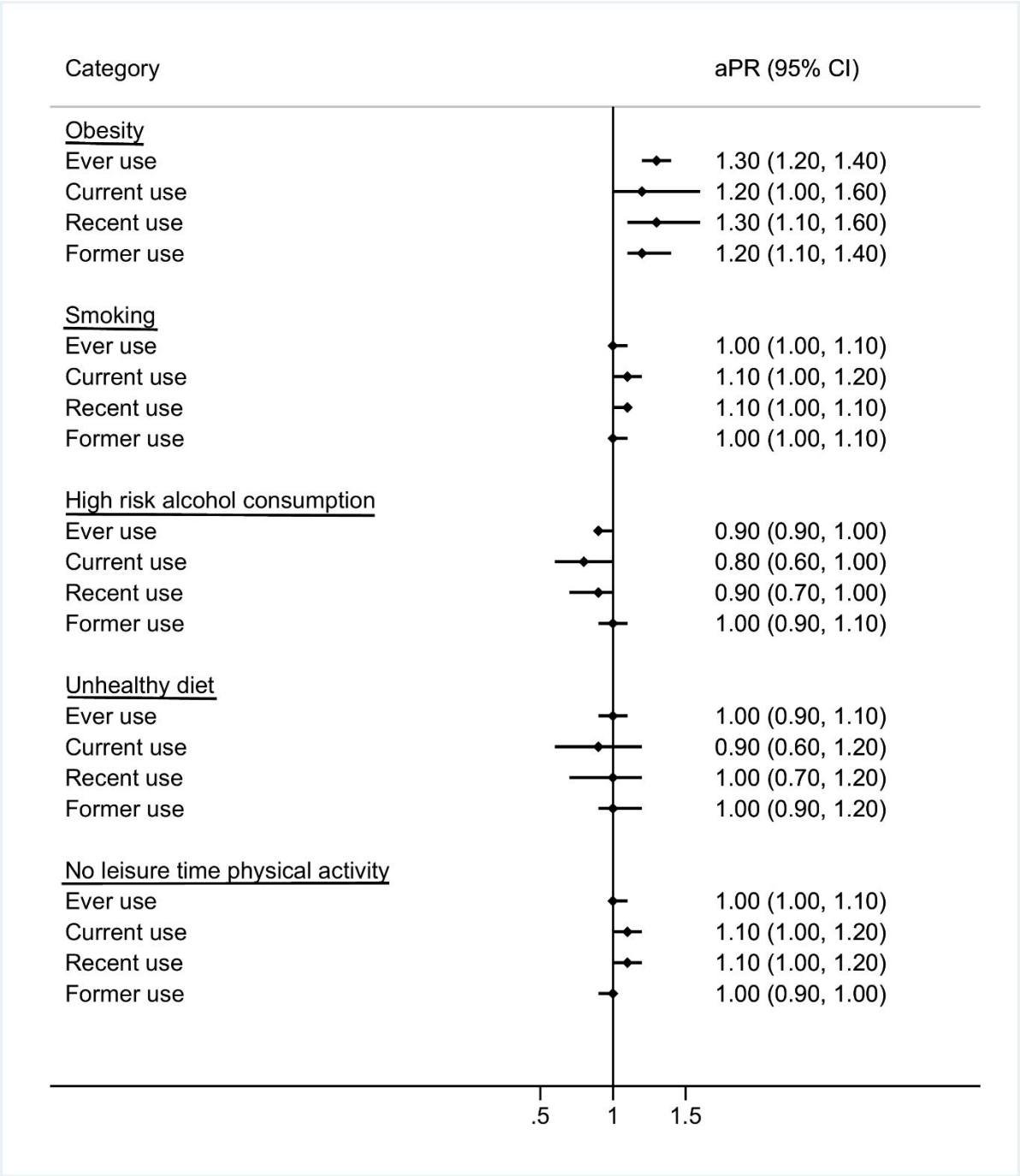


Fig. 3. **Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in people with chronic obstructive pulmonary disease (COPD)**.



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.

Fig. 4. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in people with no chronic obstructive pulmonary disease (COPD).



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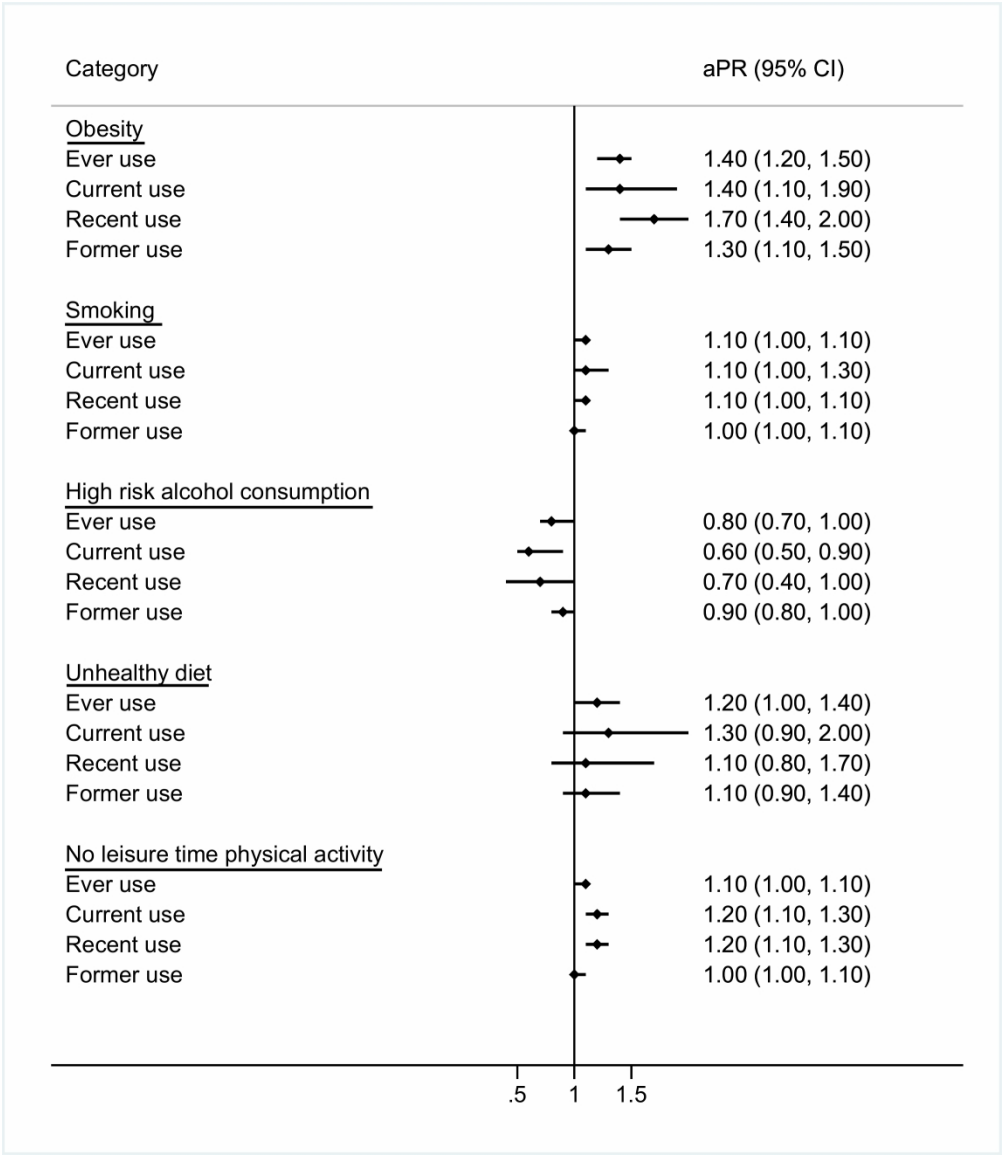
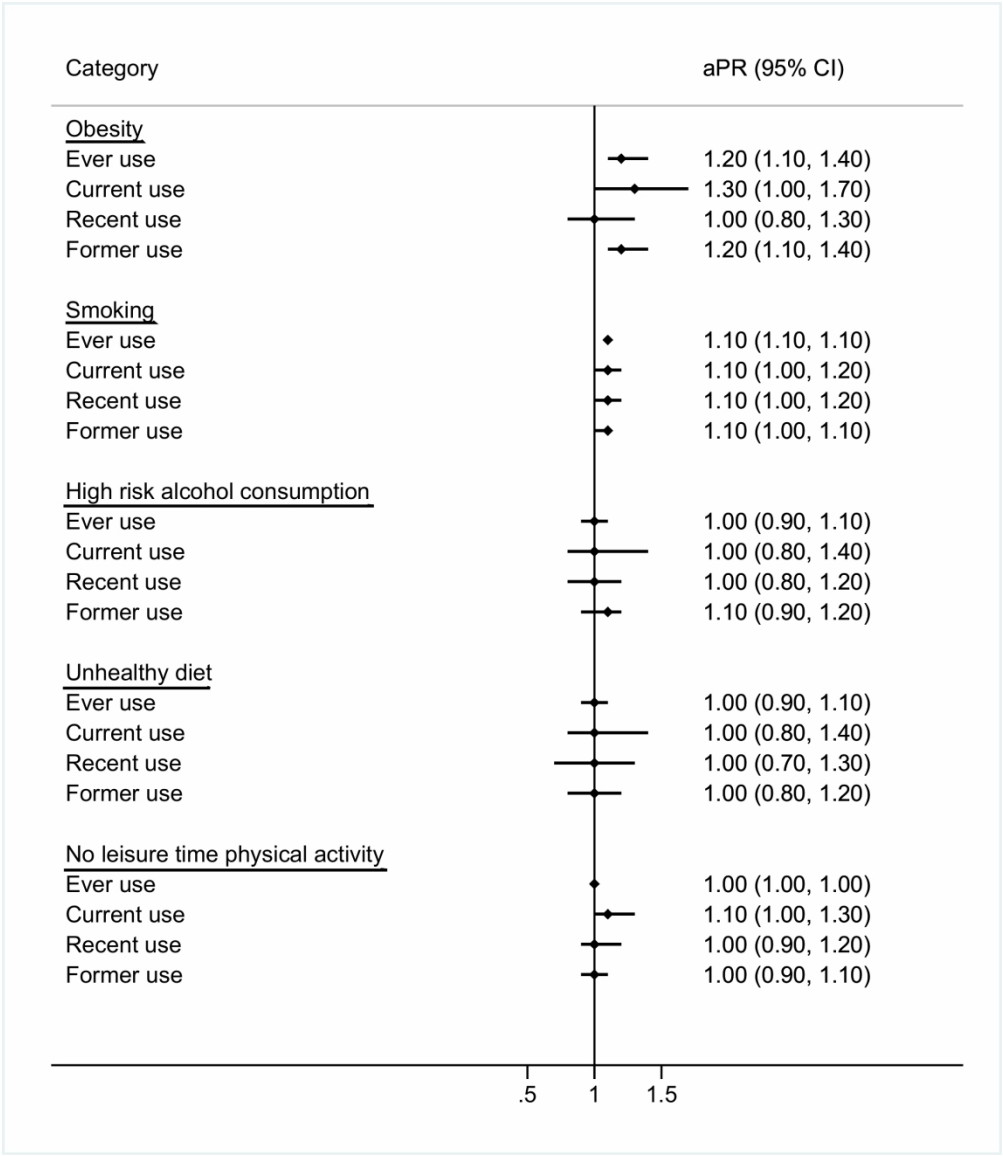


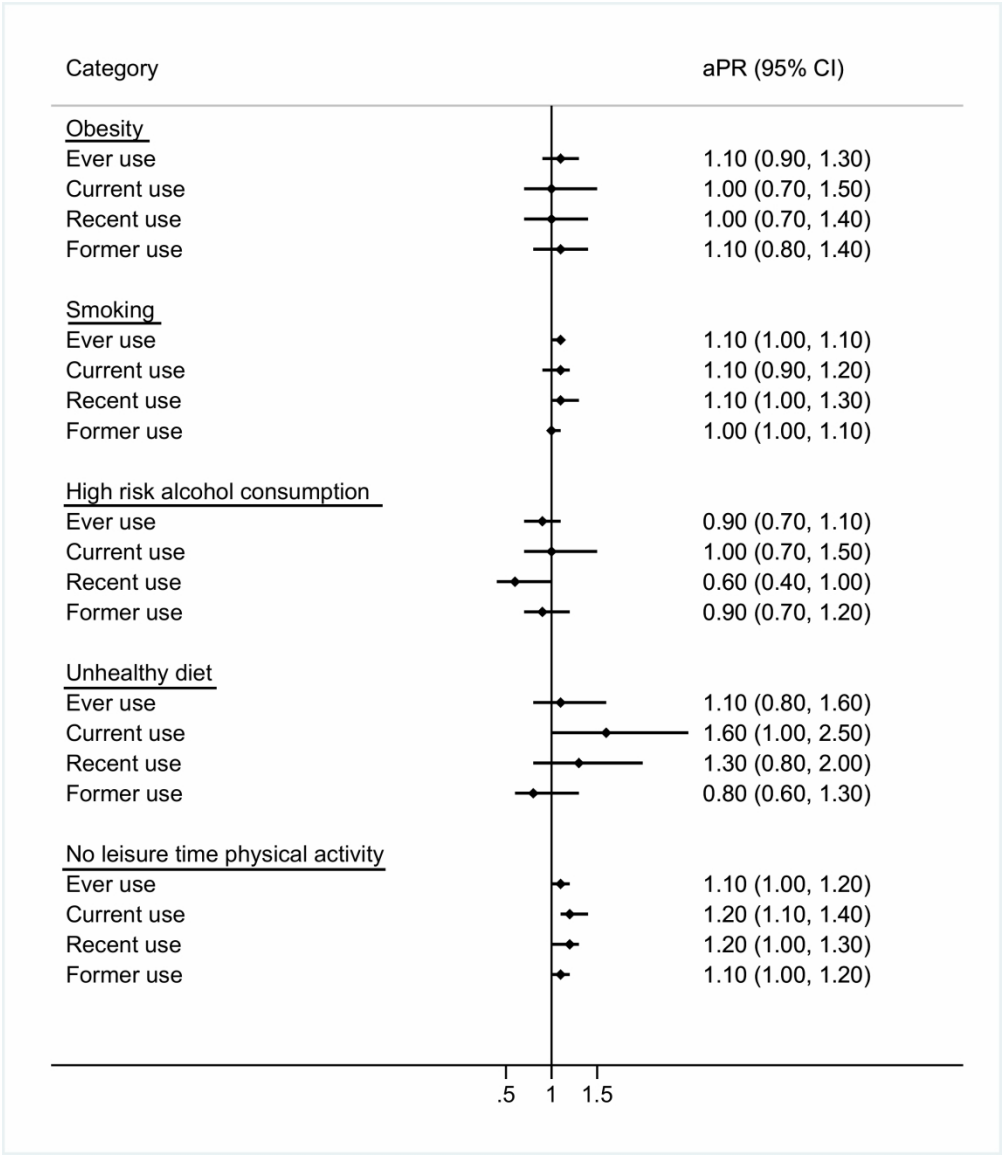
Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in women.

193x223mm (300 x 300 DPI)



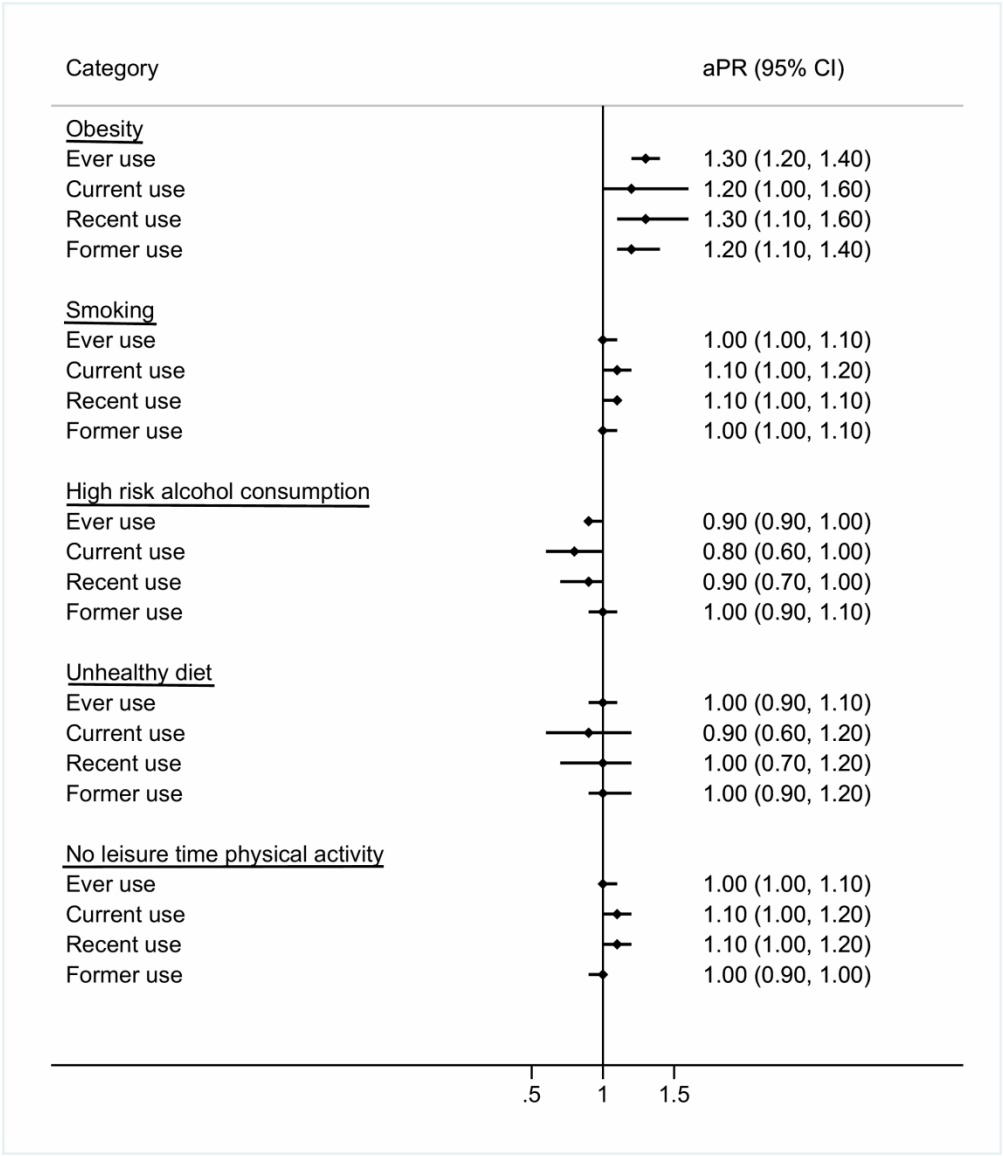
Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in men.

190x219mm (300 x 300 DPI)



Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in people with chronic obstructive pulmonary disease (COPD).
Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in people with chronic obstructive pulmonary disease (COPD)

201x232mm (300 x 300 DPI)



Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in people with no chronic obstructive pulmonary disease (COPD).

203x234mm (300 x 300 DPI)

SUPPLEMENTARY

Supplementary Table 1. Anatomical Therapeutic Classification (ATC) codes

Medication	ATC codes
Systemic glucocorticoids	H02AB
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. 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 3a. Prevalence of lifestyle factors according to total number of redeemed prescriptions of systemic glucocorticoids before filling in the questionnaire in women. Percentages are weighted

	One N (%)	Two-five N (%)	> Five N (%)
All	1,164 (100)	944 (100)	352 (100)
Median age (range)	58 (25-97)	58 (25-98)	67 (25-98)
Body Mass Index			
< 18.5	28 (2.9)	18 (2.3)	12 (2.7)
18.5-24	558 (47)	416 (44)	139 (38)
25.0-29	343 (28)	271 (28)	103 (29)
≥30	190 (16)	185 (20)	69 (21)
Missing	45 (5.5)	54 (6.1)	29 (9.0)
Smoking			
Current	257 (21)	220 (23)	75 (19)
Former	341 (28)	297 (31)	127 (35)
Never	530 (47)	391 (42)	126 (39)
Missing	36 (3.5)	36 (4.2)	24 (6.6)
Diet			
Unhealthy	79 (6.4)	87 (9.7)	25 (8.0)
Reasonably healthy	669 (58)	546 (57)	210 (61)
Healthy	371 (31)	271 (29)	88 (23)
Missing	45 (4.7)	40 (4.9)	29 (7.6)
Alcohol intake			
Low risk consumption	857 (75)	714 (77)	261 (74)
High risk consumption	238 (18)	171 (16)	49 (13)
Missing	69 (7.2)	59 (7.0)	42 (13)
Participation in regular leisure time physical activity			
No	517 (45)	464 (51)	198 (59)
Yes	609 (51)	460 (47)	140 (38)
Missing	38 (3.9)	20 (2.4)	14 (3.0)

Supplementary Table 3b. Prevalence of lifestyle factors according to total number of redeemed prescriptions of systemic glucocorticoids before filling in the questionnaire in men. Percentages are weighted

	One N (%)	Two-five N (%)	> Five N (%)
All	993 (100)	759 (100)	290 (100)
Median age (range)	58 (25-100)	60 (25-91)	64 (25-94)
Body Mass Index			
< 18.5	5 (0.5)	10 (1.9)	6 (2.0)
18.5-24	314 (33)	226 (30)	104 (29)
25.0-29	458 (46)	377 (49)	124 (40)
≥30	190 (18)	127 (16)	48 (16)
Missing	26 (2.7)	19 (2.6)	8 (3.1)
Smoking			
Current	272 (29)	191 (27)	55 (20)
Former	400 (38)	302 (36)	141 (44)
Never	297 (31)	246 (34)	87 (33)
Missing	24 (2.5)	20 (3.2)	7 (2.7)
Diet			
Unhealthy	148 (16)	116 (16)	46 (13)
Reasonably healthy	645 (66)	484 (64)	172 (61)
Healthy	168 (15)	119 (14)	55 (18)
Missing	32 (3.8)	40 (5.9)	17 (7.6)
Alcohol intake			
Low risk consumption	722 (72)	562 (72)	205 (68)
High risk consumption	226 (23)	157 (21)	60 (20)
Missing	45 (5.2)	40 (6.7)	25 (11)
Participation in regular leisure time physical activity			
Yes	526 (51)	426 (56)	176 (59)
No	446 (47)	322 (42)	106 (38)
Missing	21 (2.4)	11 (2.0)	8 (2.1)

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)
One prescription in total	1.2 (1.0 to 1.4)	1.3 (1.1 to 1.5)
Two-five prescriptions in total	1.5 (1.3 to 1.8)	1.1 (0.9 to 1.4)
Over five prescriptions in total	1.7 (1.4 to 2.2)	1.2 (0.9 to 1.6)
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)
One prescription in total	1.0 (0.9 to 1.1)	1.1 (1.1 to 1.2)
Two-five prescriptions in total	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.2)
Over five prescriptions in total	1.1 (1.0 to 1.3)	1.0 (0.9 to 1.2)
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)
One prescription in total	0.9 (0.8 to 1.0)	1.0 (0.9 to 1.2)
Two-five prescriptions in total	0.8 (0.7 to 0.9)	1.0 (0.8 to 1.2)
Over five prescriptions in total	0.7 (0.5 to 1.0)	1.1 (0.8 to 1.4)
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)
One prescription in total	0.9 (0.7 to 1.2)	1.0 (0.8 to 1.2)
Two-five prescriptions in total	1.4 (1.1 to 1.8)	1.0 (0.9 to 1.3)
Over five prescriptions in total	1.1 (0.7 to 1.7)	0.9 (0.6 to 1.2)
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)
One prescription in total	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.0)
Two-five prescriptions in total	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.1)
Over five prescriptions in total	1.2 (1.1 to 1.3)	1.1 (1.0 to 1.2)

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

	aPR	
Category	**COPD**	**No COPD**
Obesity		
Current new use	0.7 (0.2 to 2.1)	1.1 (0.7 to 1.7)
Current continuing use	1.2 (0.8 to 1.3)	1.5 (1.1 to 2.0)
One prescription in total	1.1 (0.8 to 1.6)	1.2 (1.1 to 1.3)
Two-five prescriptions in total	1.0 (0.8 to 1.6)	1.3 (1.2 to 1.5)
Over five prescriptions in total	1.1 (0.8 to 1.6)	1.4 (1.2 to 1.8)
Ever smoking		
Current new use	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.4)
Current continuing use	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.1)
One prescription in total	1.0 (0.9 to 1.2)	1.1 (1.0 to 1.1)
Two-five prescriptions in total	1.1 (1.0 to 1.2)	1.0 (1.0 to 1.1)
Over five prescriptions in total	1.0 (0.9 to 1.2)	1.1 (1.0 to 1.2)
High risk alcohol consumption		
Current new use	0.9 (0.4 to 2.2)	0.7 (0.5 to 1.2)
Current continuing use	1.0 (0.7 to 1.5)	0.8 (0.6 to 1.1)
One prescription in total	0.7 (0.5 to 1.0)	1.0 (0.9 to 1.1)
Two-five prescriptions in total	1.1 (0.8 to 1.4)	0.8 (0.7 to 1.0)
Over five prescriptions in total	0.8 (0.5 to 1.2)	1.0 (0.8 to 1.2)
Unhealthy diet		
Current new use	1.7 (0.7 to 4.4)	0.9 (0.5 to 1.5)

Current continuing use	1.6 (1.0 to 1.3)	0.9 (0.6 to 1.3)
One prescription in total	0.7 (0.4 to 1.1)	1.0 (0.8 to 1.2)
Two-five prescriptions in total	1.4 (1.0 to 2.1)	1.0 (0.9 to 1.3)
Over five prescriptions in total	1.0 (0.6 to 1.6)	0.9 (0.6 to 1.2)
No participation in regular leisure time physical activity		
Current new use	1.1 (0.8 to 1.5)	1.1 (0.9 to 1.3)
Current continuing use	1.2 (1.1 to 1.4)	1.2 (1.0 to 1.3)
One prescription in total	1.1 (1.0 to 1.3)	1.0 (0.9 to 1.0)
Two-five prescriptions in total	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.1)
Over five prescriptions in total	1.2 (1.0 to 1.4)	1.1 (1.0 to 1.2)

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. 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.

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	2,3
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
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,7
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	5,6,7
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	5,6,7
Bias	9	Describe any efforts to address potential sources of bias	7
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	5,6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	8,9,10
		(*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

		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	5
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,9,10,11
		(b) Indicate number of participants with missing data for each variable of interest	8,9,10,11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	8,9,10
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	10,11
		(*b*) Report category boundaries when continuous variables were categorized	8,9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
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.

BMJ Open

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

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Keywords:	glucocorticoids, smoking, alcohol drinking, exercise, body mass index, EPIDEMIOLOGY

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

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Word count: 2,218

Keywords: glucocorticoids; Body Mass Index; Alcohol Drinking; Exercise; Smoking; Diet

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, 1,000 – 1,999, 2,000 – 4,999, ≥ 5,000 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% confidence intervals (CI), comparing the categories of glucocorticoid users vs. 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, 3,054 (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% versus 14%, aPR=1.4, 95% CI 1.2 to 1.5 in women and 17% versus 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 to never users [17% versus 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 is 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 minimize 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, dyslipidemia,[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, e.g. 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 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 (7,026 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 1,000 people answering the questionnaire were promised two tickets for the cinema. In addition, participants were able to win lottery gifts.

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 meters, squared. 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).[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 summarize 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 categorized as never, former, or current (daily or occasional). We categorized 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 categorized 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, 1,000-1,999 mg, 2000 – 4,999 mg and ≥ 5,000 mg. [See Supplementary Table 1 for codes used in the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization and 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% confidence intervals (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 to the reference of never use. The PRs were adjusted for age (10-year age groups). All analyses were stratified by sex.

In supplementary analyses, prevalence ratios 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 (ICS) (or combinations thereof).

In estimating prevalence and PRs, post-survey 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, 3,054 (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 Tables 1a and 1b and in the Supplementary Table 3.

Table 1a. Prevalence of lifestyle factors according to glucocorticoid use in women. Percentages are weighted

	Ever use	Current use	Recent use	Former use	Never use	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All	2,460 (100)	301 (100)	489 (100)	1,670 (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	1,113 (45)	126 (38)	218 (44)	769 (46)	7,203 (54)	8,316 (52)
25-29	717 (28)	89 (31)	120 (23)	508 (29)	3,718 (27)	4,435 (27)
≥30	444 (18)	50 (17)	105 (22)	289 (17)	1,862 (14)	2,306 (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)	2,744 (21)	3,296 (21)
Former	765 (30)	111 (35)	148 (30)	506 (29)	3,913 (28)	4,678 (28)
Never	1,047 (44)	107 (40)	206 (42)	734 (45)	6,535 (49)	7,582 (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)	1,043 (7.0)
Reasonably healthy	1,425 (58)	181 (62)	280 (57)	964 (57)	8,021 (60)	9,446 (59)
Healthy	730 (29)	72 (22)	143 (27)	515 (31)	4,234 (30)	4,964 (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	1,832 (76)	231 (80)	376 (77)	340 (74)	10,146 (75)	11,978 (75)
High risk consumption	458 (17)	43 (12)	75 (13)	1,225 (18)	2,730 (20)	3,188 (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	1,179 (49)	171 (59)	245 (53)	763 (46)	5,853 (44)	7,032 (45)
Yes	1,209 (48)	121 (39)	228 (44)	860 (50)	7,354 (54)	8,563 (53)
Missing	72 (3.2)	9 (2.3)	16 (3.2)	47 (3.3)	278 (2.3)	350 (2.4)

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.

Table 1b. Prevalence of lifestyle factors according to glucocorticoid use in men. Percentages are weighted

	Ever use	Current use	Recent use	Former use	Never use	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All	2,042 (100)	262 (100)	396 (100)	1,384 (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)	4,572 (39)	5,216 (38)
25-29	959 (46)	116 (41)	188 (46)	655 (47)	5,566 (44)	6,525 (44)
≥30	365 (17)	47 (19)	65 (14)	253 (18)	1,864 (15)	2,229 (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)	3,072 (27)	3,590 (27)
Former	843 (38)	126 (43)	157 (36)	560 (38)	4,022 (30)	4,865 (31)
Never	630 (32)	67 (27)	132 (35)	431 (32)	4,968 (42)	5,598 (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)	1,906 (16)	2,216 (16)
Reasonably healthy	1,301 (64)	159 (62)	253 (65)	889 (64)	7,874 (64)	9,175 (64)
Healthy	342 (15)	38 (13)	68 (16)	236 (15)	2,069 (17)	2,411 (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	1,489 (72)	184 (70)	293 (73)	1,012 (72)	9,231 (75)	10,720 (75)
High risk consumption	443 (22)	62 (21)	81 (19)	300 (22)	2,588 (21)	3,031 (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	1,128 (54)	82 (65)	214 (52)	739 (52)	6,265 (50)	7,393 (51)
Yes	874 (44)	175 (32)	171 (45)	621 (46)	5,791 (48)	6,665 (48)
Missing	40 (2.2)	5 (2.6)	11 (2.7)	24 (2.0)	202 (1.6)	242 (1.7)

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.

Body Mass Index

In women, ever users of glucocorticoids were slightly more obese than never users [18% versus 14%; aPR 1.4 (95% CI 1.2 to 1.5)] (Table 1a and Figure 1) with highest prevalence in current continuing users (21%) and recent users (22%) (Table1a, Supplementary Table 3 and Supplementary Table 4). Also, male ever users were slightly more obese than never users [17% versus 15%; aPR 1.2 (95% CI 1.1 to 1.4)] (Table 1b and Figure 2). In addition, prevalence of obesity increased with greater cumulative glucocorticoid dose in both sexes (Figure 3 and Figure 4)

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)] (Figure 1 and Figure 2). These findings were consistent across all categories of glucocorticoid users (Figure 1, Figure, 2, Figure 3 and Figure 4) and when stratifying on potential COPD (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)] (Table 1a and Figure 1). For men there was no difference [aPR 1.0 (95% CI 0.9 to 1.1)] (Table 1b 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)] (Figure 1 and Figure 2). Although, greater cumulative dose of glucocorticoid use was slightly associated with less physical activity (Figure 3 and Figure 4)

The PRs did not differ substantially by age group (Supplementary Table 6 and Supplementary Table 7)

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 is 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 vs. 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 to current new users and increasing prevalence of 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 minimize 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 socio economic 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 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 is 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 (DAGs) 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 to 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.

FOOTNOTES

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Author statement: KL, IP, FBL, LP, JOLJ, and HTS made primary contributions to the concept of the study and wrote the manuscript. KL performed statistical analyses. KL, IP, FBL, LP, JOLJ, and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript.

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.

Data sharing statement: Data are available as presented in the paper and in the supplementary files. According to Danish legislation, our own approvals to use the Danish data sources for the current study do not allow us to distribute or make patient data directly available to other parties. Interested researchers may contact Julie Christiansen (juechi@rm.dk) for access to the questionnaire “Hvordan har du det?” (How Are You?). (For updated information please visit: http://www.defactum.dk/om-DEFACTUM/projektsite/hvordan-har-du-det/ansogning-om-adgang-til-data/). For access to prescription data from the Danish National Health Service Prescription Database please contact Helle Schleicher Kjær (hsk@clin.au.dk) (For updated information please visit: http://kea.au.dk/research/registries-and-biobanks/the-danish-national-health-service-prescription-database/).

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FIGURE LEGENDS

Figure 1. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in women.

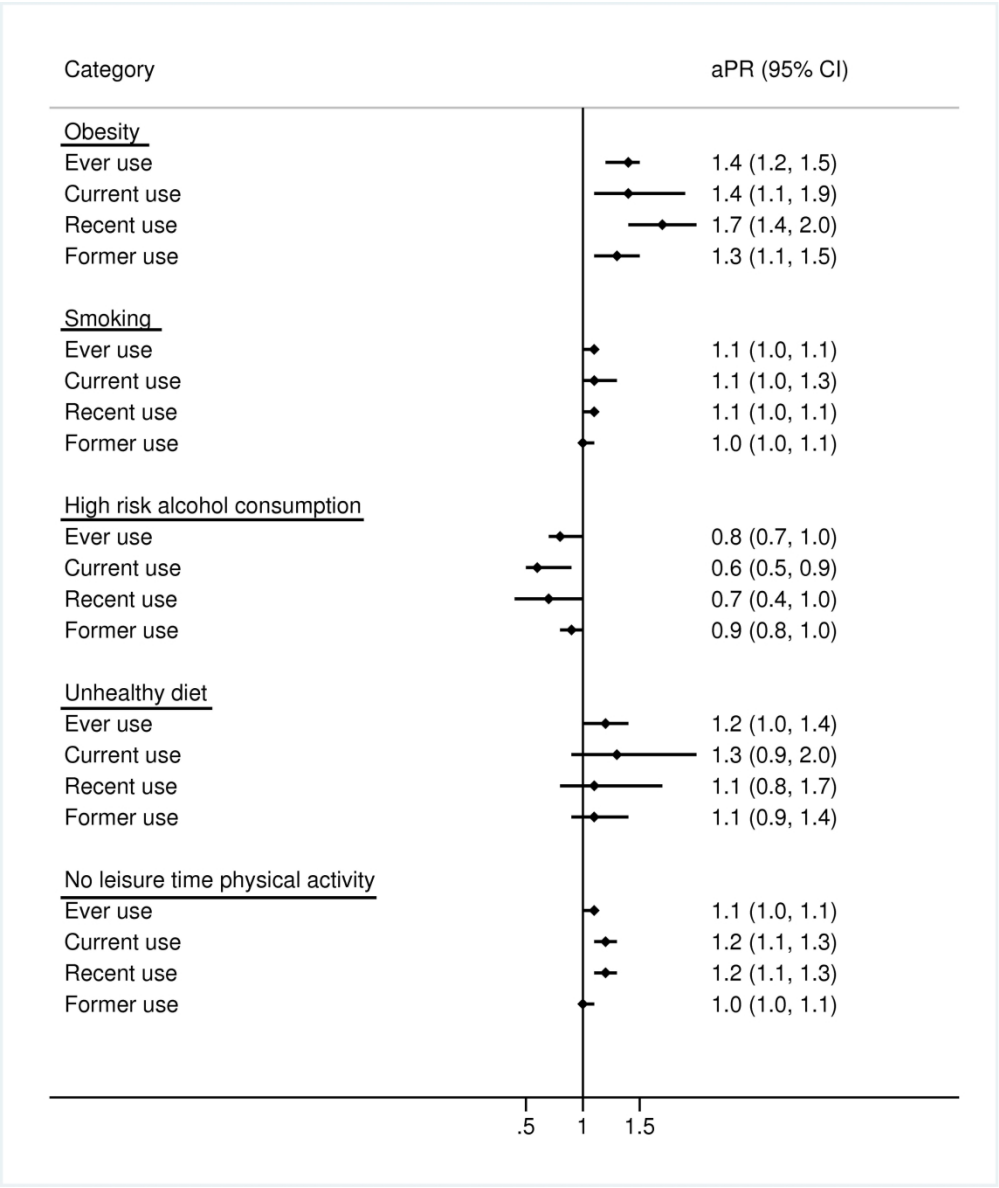
Footnote: Never use: Persons who never redeemed a prescription for a systemic glucocorticoid before completing the questionnaire. Ever use At least one redemption of a prescription for a systemic glucocorticoid before completing the questionnaire. Current use: Redemption of a prescription for a systemic 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.

Figure 2. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in men.

Footnote: 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.

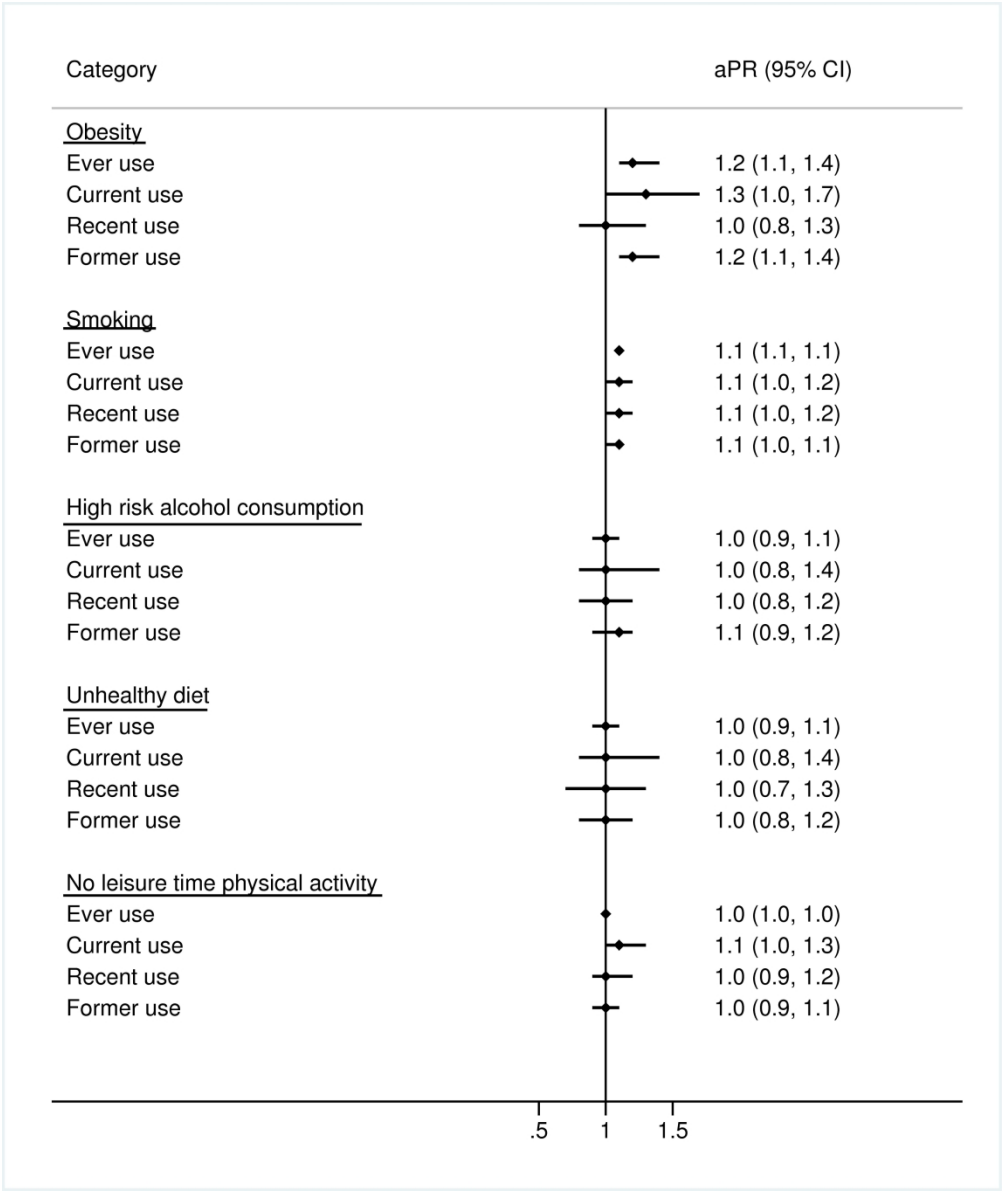
Figure 3. Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing cumulative glucocorticoid dose (in grams of prednisolone equivalents) to never users in women.

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



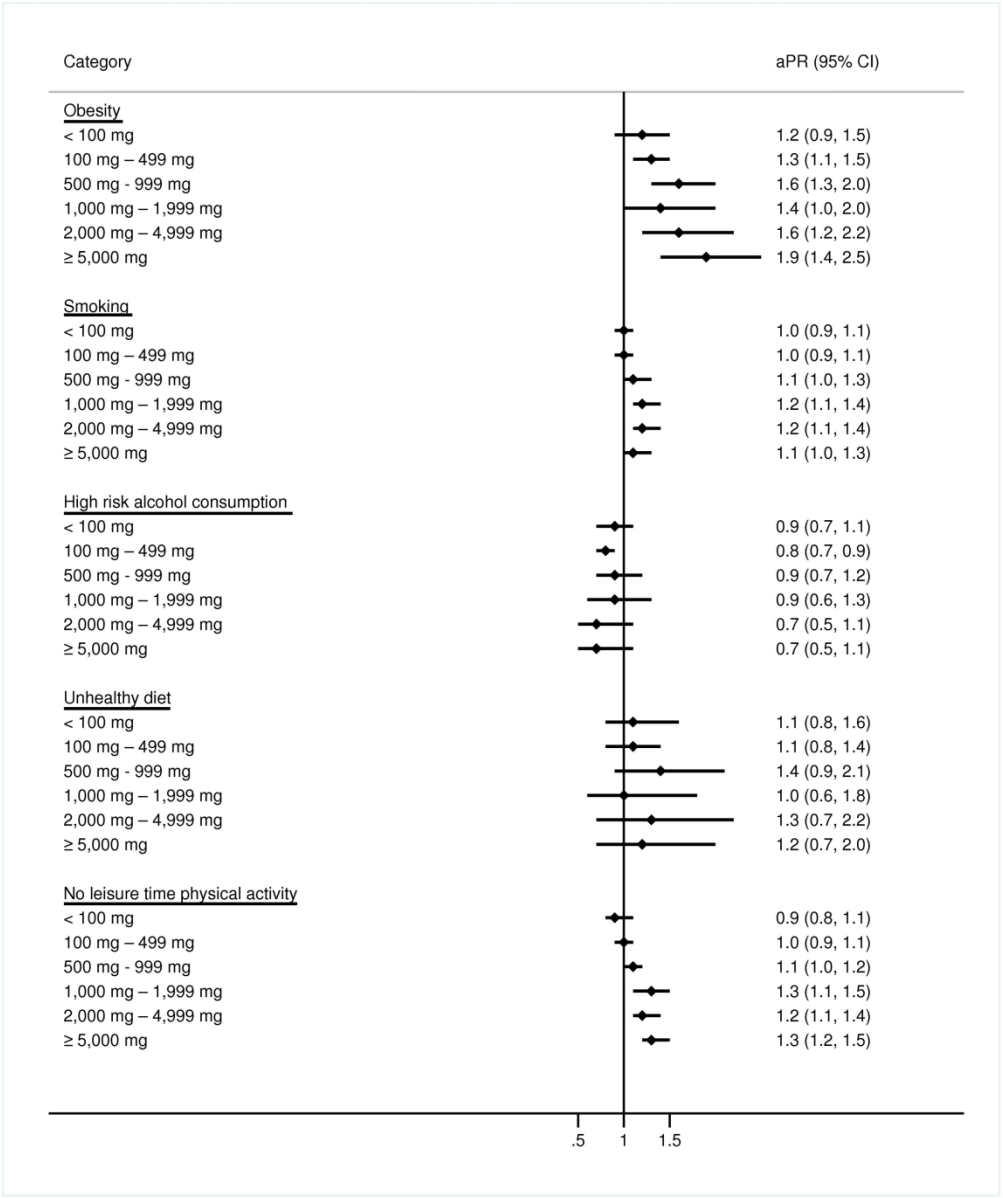
Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in women.

209x248mm (300 x 300 DPI)



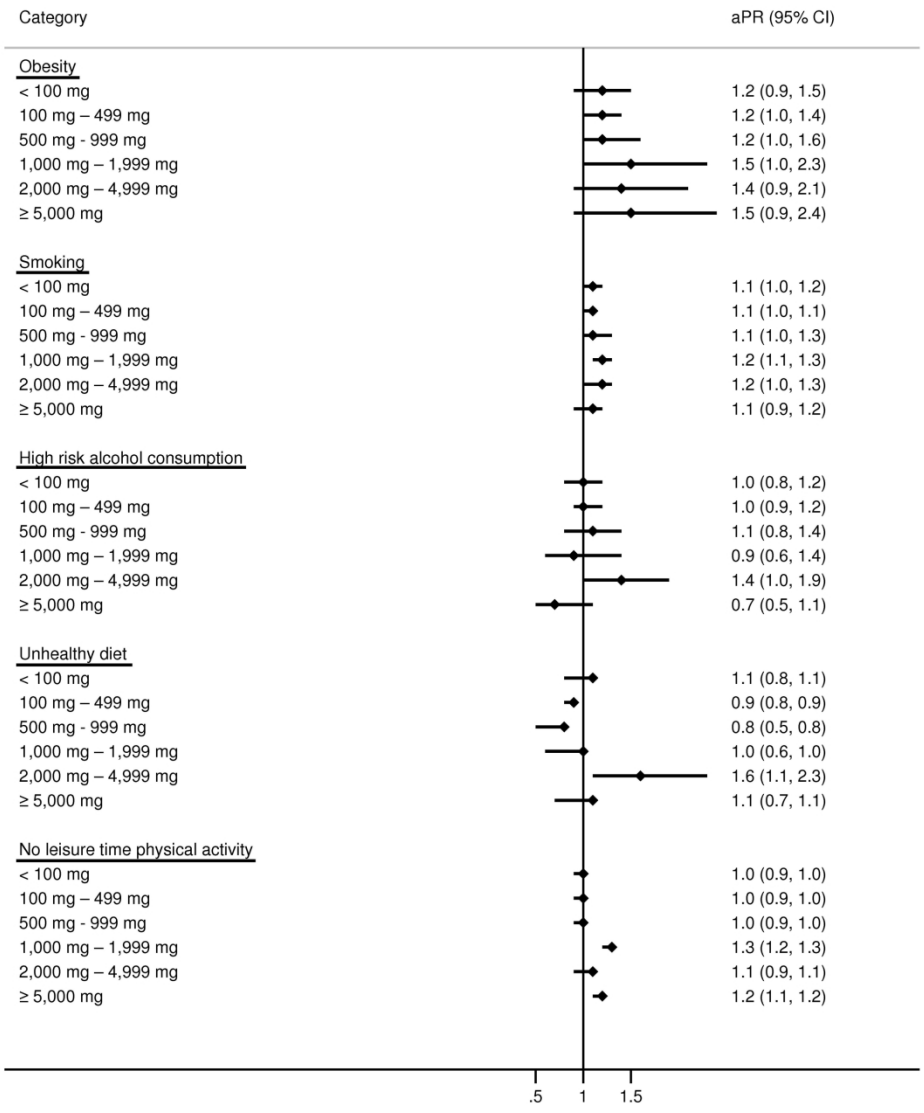
Age-adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for lifestyle factors comparing glucocorticoid users to never users in men.

257x305mm (300 x 300 DPI)



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

208x249mm (300 x 300 DPI)



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

208x249mm (300 x 300 DPI)

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.

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	2,3
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	5,6,7
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	5,6,7
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	5,6,7
Bias	9	Describe any efforts to address potential sources of bias	7,8
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	5,6,7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	8,9,10
		(*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

		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	5
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,9,10,11
		(b) Indicate number of participants with missing data for each variable of interest	8,9,10,11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	8,9,10
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	10,11
		(*b*) Report category boundaries when continuous variables were categorized	8,9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	13,14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	15

*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.