Associations between systemic and local corticosteroid use with metabolic syndrome and body mass index

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*Associations between systemic and local corticosteroid use with metabolic syndrome and body mass index. J Clin Endocrinol Metab, 2017, 102:3765-3774. *Equal contribution.*

ABSTRACT

Context: Use of systemic corticosteroids may induce adverse cardiometabolic alterations potentially leading to obesity and metabolic syndrome (MetS). Although evidence is accumulating that local corticosteroids have considerable systemic effects, their effects on cardiometabolic factors in the general population remains unclear.

Objective: To investigate the association between overall corticosteroid use and specific corticosteroid types with MetS, body mass index (BMI), and other cardiometabolic traits.

Design: Cross-sectional cohort study.

Setting: General population from the northern Netherlands.

Participants: 140 879 adult participants in the population-based Lifelines Cohort Study.

Main Outcome Measures: BMI, waist circumference, systolic and diastolic blood pressure, fasting metabolic serum parameters, and a comprehensive set of potential confounding factors.

Results: In women, overall, systemic, and local corticosteroid use was associated with higher odds of having MetS. Among local female users, only nasal (OR 1.20 [95% CI, 1.06 to 1.36]) and inhaled corticosteroids (1.35 [95% CI, 1.24 to 1.49]) users were more likely to have MetS. In men, no association was found between overall and specific corticosteroid use and presence of MetS. Use of only local corticosteroids in women, specifically inhaled corticosteroids in both sexes, was associated with higher BMI.

Conclusions: Use of local corticosteroids, particularly inhaled types, as well as systemic corticosteroids, was associated with higher likelihood of having MetS, higher BMI, and other adverse cardiometabolic traits, especially among women. Since the inhaled agents are the main group of prescribed corticosteroids this might be a substantial risk to public health in case of a, yet to be proven, causal relationship.

INTRODUCTION

Synthetic glucocorticoids, also known as corticosteroids (CS), are widely used potent anti-inflammatory drugs with multiple indications and many administration forms used for both systemic and local disorders [1]. Due to the increased prevalence of diseases frequently requiring CS therapy, prescriptions of CS have increased markedly in the last decades [2, 3]. There are increasing concerns that use of systemic administration forms can lead to supraphysiological glucocorticoid exposure and induce adverse cardiometabolic changes such as obesity, diabetes, dyslipidemia and hypertension, all of which are components of the metabolic syndrome (MetS) [4, 5]. The relationship between high glucocorticoid exposure and induction of various cardiometabolic alterations has been consistently reported in patients with Cushing's syndrome who frequently develop these adverse metabolic changes during the course of the disease [6]. Because of these known adverse events, systemic CS users are generally well-monitored after starting treatment [5], in contrast to users of the various local administration forms in whom systemic absorption is usually less expected. However, a recent meta-analysis suggests that local CS may also be associated with an increased systemic glucocorticoid exposure exemplified by the increased risk of adrenal insufficiency in users of local types [7]. Since many of the CS users are often prescribed a local administration form, it could be hypothesized that use of local CS is a contributing factor to MetS and obesity in the general population. Nevertheless, most studies on this topic have been focused on systemic CS therapies [4] and evidence regarding the effect of local CS use on MetS and its components in the general population is scarce. Hence, we assessed the associations between overall CS use and specific CS types with MetS, body mass index (BMI), and other cardiometabolic risk factors in a large population-based cohort study.

METHODS

Study design and population

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167 729 persons living in the North of The Netherlands [8]. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. For this study, we included baseline information on 152 180 adult participants. Subjects with incomplete report on drug use, non-fasting laboratory blood values, or missing information on any of the MetS components or BMI were excluded from the analyses

which resulted in a total study sample size of 140 879 participants. Informed consent and ethical approval of the study protocol was obtained as according the principles of the Declaration of Helsinki and in accordance with the research code of the University Medical Center Groningen.

Assessment of drug use

Drug use was evaluated with a self-reported questionnaire and a visual drug container inspection. All prescribed drugs were coded according the WHO ATC classification system. Concurring with the ATC methodology, we classified CS into the following categories of administration forms: systemic (i.e. oral and parenteral, including intra-articular injections), topical (i.e. dermatological), nasal, inhaled, otological, ocular, intestinal, local oral, hemorrhoidal, and gynaecological forms. The last three forms were combined as "other CS" due to their low prescription numbers. For assessment of the presence of MetS and its components, we assessed the use of antihypertensives, blood glucose-lowering drugs, and lipid-modifying drugs. We also determined the use of hormonal replacement therapy (HRT) in women, and the use of other exogenous sex hormones and potentially weight-inducing psychotropics [9, 10] in all subjects in order to adjust for their potential metabolic alterations (see Supplemental Table 1 for further details).

Measures of metabolic syndrome risk factors

All measurements were done consistently following standardized operating protocols by trained technicians. Body weight (in kg) and height (in cm) were measured without shoes and accurately to the nearest half unit. BMI was calculated by dividing body weight by height in meters squared. Waist circumference (WC) was measured in an upright position and in the middle between the front edge of the lower ribs and the iliac crest. Blood pressure was measured ten times with a one-minute interval with an automatic blood pressure monitor (DinaMap Monitor, GE Healthcare, Freiburg, Germany) and proper sized cuff. The last two successive measurements most representative of resting blood pressure were used to calculate mean systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood samples were taken in the morning after an overnight fast and were processed for measurements on the same day. Measurements for triglycerides, HDL-cholesterol, and glucose were performed on a Roche Modular P chemistry analyzer (Roche, Basel, Switzerland) by using enzymatic colorimetric and hexokinase methods. Data on BMI, WC, SBP, DBP, and fasting serum levels of triglycerides, HDL-cholesterol, and glucose were complete for all subjects.

Assessment of metabolic syndrome

MetS was defined according to the joint interim statement criteria [11]. The diagnosis could be established if at least three of the following components were present: 1. WC

≥88 cm in women and ≥102 cm in men; 2. SBP ≥130 mm Hg, DBP ≥85 mm Hg, and/or use of antihypertensives in patients with known hypertension; 3. triglycerides ≥1.7 mmol/L and/or use of lipid-modifying drugs; 4. HDL-cholesterol <1.3 mmol/L in women and <1.0 mmol/L in men and/or use of lipid-modifying drugs; 5. fasting serum glucose ≥5.6 mmol/L and/or use of blood glucose-lowering drugs.

Assessment of covariates

In order to adjust for factors that might influence the outcome of the analyses, we assessed data for various potential covariates. Ethnicity was grouped into two categories (i.e. Dutch natives and others) and was based on the reported country of birth of both parents. Education was based on the highest completed level and was classified as no education, primary education, lower or preparatory vocational education, lower general secondary education, intermediate vocational education or apprenticeship, higher general secondary education or pre-university secondary education, higher vocational education, university, and others. Smoking was categorized under the following three statuses: non-smokers (i.e. not smoked in the past month and never smoked for a full year), former smokers (i.e. stopped smoking, had not smoked in the past month but did ever smoke for a full year or more), and current smokers (i.e. currently smoking or smoked in the past month). Alcohol use was based on self-reported drinking frequency of alcoholic beverages in the past month and the average amount per drinking day and was computed into categories of non-users and users of ≤1 drink/day, 1-2 drinks/day, or >2 drinks/day. Physical activity was assessed by the reported average days per week of at least half an hour of doing odd jobs, gardening, bicycling, or exercises combined and classified into three categories: inactives (0 days per week), semi-actives (1 to 4 days per week), and norm-actives (≥5 days per week). In women, we additionally assessed their menstrual status (yes/no currently menstruating) at the moment of inclusion.

Diabetes mellitus was defined according the definition of WHO/IDF [12] and was deemed present in case of fasting serum glucose level ≥7.0 mmol/L and/or use of blood glucose-lowering drugs. Corresponding to the report of the 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [13], hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or use of antihypertensives. Cardiovascular diseases were assessed by self-reported health-questionnaire items and were defined as a history of stroke and/or coronary heart disease(s) (i.e., myocardial infarction, balloon angioplasty and/or bypass surgery in the past). The other weight-related comorbidities (i.e. cancer, osteoarthritis, chronic obstructive pulmonary disease, and asthma) were all deemed present if the subject had indicated to be known with the diagnosis and which was confirmed by a doctor in the case of asthma.

Statistical analysis

Crude differences in continuous variables were assessed with ANOVAs and in categorical variables with X2-tests. Triglyceride levels were positively skewed and were therefore log10-transformed to achieve normal distribution. Initial inferential analyses showed strong interaction effect (Pint <0.001) for sex, hence we decided to stratify all analyses for women and men. We used multivariable logistic regression models to assess the relation of overall and specific CS use with the presence of MetS. Considering the multiple potential combinations of the five components required for the diagnosis, we also analyzed the association of CS use with each component separately and with all possible combinations. CS users were analyzed combining all types of CS, and into systemic users (i.e. systemic only or combined with local forms) and local only users (i.e. any of the forms except the systemic). Further, we additionally performed analyses for single type users, and multiple administration forms, since the last has been previously shown to be associated with substantial risk on adrenal insufficiency [7]. In the first model, the association between CS use (total and specified groups) and MetS was adjusted for age. In the second model, we concurrently adjusted for all covariates. We used ANCOVAs to assess the association of CS use with BMI and other cardiometabolic traits. Adjustments were done similarly as in the second logistic regression model, with additional corrections for diabetes mellitus, use of lipid-modifying drugs, and antihypertensive use. Data on the covariates were missing in <4% of the subjects, except for physical activity (5.9%), alcohol use (7.1%), and menstrual status (8.2%). Missing data were iteratively imputed in five imputation data sets by using the Markov Chain Monte Carlo method. All analyses were conducted 2-sided with 0.05 as level of significance and performed with IBM SPSS Statistics (IBM Corp., Armonk, NY) version 21.0.01.

Sensitivity analyses

Adjustment of the main analysis for menstrual status did likely not fully differentiate the effect of menopause on MetS diagnosis. Due to the expected higher prevalence of MetS in postmenopausal women and with increasing age, we repeated these analyses stratified for age below, and equal or above fifty years. To explore the presence of confounding by indication, we additionally repeated the analysis in both sexes in subjects with and without osteoarthritis, asthma, and/or COPD. Moreover, since adiposity is evidently related to MetS and adverse cardiometabolic traits we also stratified our main analysis by obesity levels (BMI <30.0 and ≥30.0 kg/m2).

RESULTS

Overall, 58.5% of the subjects were women and a total of 10.9% was currently using any form of CS. All descriptive characteristics for both sexes and stratified for CS use are shown in Table 1. CS use was present in 11.7% and 9.8% of female and male subjects, respectively, and comprised predominantly the use of only local administration forms (95.4% and 95.3%) and single type users (81.9% and 84.8%). The most prescribed CS in both single and multiple type users were inhaled, nasal, and topical agents consecutively (Table 2). MetS was in users as in non-users higher prevalent in men when compared to women. Both male and female CS users were more likely to have MetS when compared to non-users, but the relative difference in women was much higher than in men (+5.3% vs. +2.7%, P<0.001).

Corticosteroid use and metabolic syndrome diagnosis

Female CS users had higher likelihood of having MetS in comparison to non-users, which remained statistically significant after full adjustments for covariates (odds ratio [OR] 1.24 [95% CI 1.17 to 1.32], P<0.001; Table 3). Stratified analyses for systemic and local only female CS users revealed increased odds for both group of users, with the strongest association in users of systemic agents (ORs 1.68 [95% CI 1.34 to 2.10]; 1.22 [95% CI 1.14 to 1.30], both P<0.001, respectively). The associations in female users of local only CS were mainly driven by subjects using nasal (OR 1.20 [95% CI 1.06 to 1.36], P=0.005) and inhaled CS (OR 1.35 [95% CI 1.24 to 1.49], P<0.001). In contrast, for men there was no association between CS use, neither for systemic nor local only use, and MetS.

Corticosteroid use and metabolic syndrome components

CS use in women was associated with significantly higher odds for each of the five MetS components and all of the possible combinations required for MetS diagnosis in women (Figure 1). These findings were consistent for both users of systemic and local only CS, except for the reduced HDL-cholesterol component in the former group (OR 1.20 [95% CI 0.96 to 1.49], P=0.102). In men, CS use was only associated with the elevated WC component (OR 1.14 [95% CI 1.06 to 1.21], P<0.001]). Considering administration route, the relation with WC component in men remained in only local users (OR 1.15 [95% CI 1.07 to 1.23], P<0.001]) whereas systemic CS use was associated with decreased odds of having the elevated fasting glucose component (OR 0.57 [95% CI 0.41 to 0.80], P=0.001]). Moreover, in men, an inverse relation was found between systemic CS use and nearly all MetS combinations consisting of at least the HDL-cholesterol and fasting glucose component.

Table 1. Descriptive characteristics of the study population

	Women			Men		
	(N=82 443)			(N=58 436)		
	Non-CS users	CS users	Pdiff	Non-CS users	CS users	Pdiff
Numbers	72 832 (88.3%)	9611 (11.7%)		52 719 (90.2%)	5717 (9.8%)	
Age (years)	44.2 (13.0)	45.6 (13.4)	<.001	45.3 (13.1)	47.4 (13.6)	<.001
Ethnicity						
Dutch native	68 707 (94.3%)	9028 (93.9%)	0.110	50 239 (95.3%)	5397 (94.4%)	0.003
Others	4125 (5.7%)	583 (6.1%)		2480 (4.7%)	320 (5.6%)	
Education level						
No education	343 (0.5%)	70 (0.7%)	<.001	286 (0.5%)	40 (0.7%)	<.001
Primary education	1562 (2.1%)	279 (2.9%)		1077 (2.0%)	169 (3.0%)	
Lower or preparatory vocational education	8471 (11.6%)	1258 (13.1%)		8282 (15.7%)	892 (15.6%)	
Lower general secondary education	11 141 (15.3%)	1513 (15.7%)		6000 (11.4%)	668 (11.7%)	
Intermediate vocational education for apprenticeship	21 879 (30.0%)	2839 (29.5%)		16 286 (30.9%)	1603 (28.0%)	
Higher general secondary education or pre-university secondary education	7227 (9.9%)	890 (9.3%)		3730 (7.1%)	393 (6.9%)	
Higher vocational education	16 815 (23.1%)	2057 (21.4%)		12 600 (23.9%)	1443 (25.2%)	
University	3821 (5.2%)	467 (4.9%)		3699 (7.0%)	412 (7.2%)	
Other education	1573 (2.2%)	238 (2.5%)		759 (1.4%)	97 (1.7%)	
Smoking						
Non-smoker	35 502 (48.7%)	4779 (49.7%)	<.001	22 793 (43.2%)	2540 (44.4%)	<.001
Former smoker	22 356 (30.7%)	3151 (32.8%)		17 037 (32.3%)	2126 (37.2%)	
Current smoker	14 974 (20.6%)	1681 (17.5%)		12 889 (24.4%)	1051 (18.4%)	
Alcohol use						
None	20 308 (27.9%)	2935 (30.5%)	<.001	5652 (10.7%)	683 (11.9%)	0.003
≤ 1 drink/day	39 501 (54.2%)	5016 (52.2%)		23 279 (44.2%)	2582 (45.2%)	

Table 1. Descriptive characteristics of the study population (continued)

	Women			Men		
	(N=82 443)			(N=58 436)		
	Non-CS users	CS users	Pdiff	Non-CS users	CS users	Pdiff
1-2 drinks/day	10 814 (14.8%)	1350 (14.0%)		15 348 (29.1%)	1579 (27.6%)	
>2 drinks/day	2209 (3.0%)	310 (3.2%)		8440 (16.0%)	873 (15.3%)	
Physical activity						
Inactive	4390 (6.0%)	639 (6.6%)	0.042	2218 (4.2%)	227 (4.0%)	0.078
Semi-active	32 837 (45.1%)	4265 (44.4%)		25 137 (47.7%)	2651 (46.4%)	
Norm-active	35 605 (48.9%)	4707 (49.0%)		25 364 (48.1%)	2839 (49.7%)	
Menstrual status						
Menstruating	45 678 (62.7%)	5556 (57.8%)	<.001	N/A	N/A	
Not menstruating	27 154 (37.3%)	4055 (42.2%)		N/A	N/A	
Comorbidities						
Diabetes mellitus	1588 (2.2%)	347 (3.6%)	<.001	1927 (3.7%)	254 (4.4%)	0.003
Hypertension	15 451 (21.2%)	2602 (27.1%)	<.001	16 916 (32.1%)	2144 (37.5%)	<.001
Stroke	495 (0.7%)	72 (0.7%)	0.438	476 (0.9%)	70 (1.2%)	0.016
Coronary heart disease	564 (0.8%)	125 (1.3%)	<.001	1686 (3.2%)	237 (4.1%)	<.001
Cancer	3757 (5.2%)	544 (5.7%)	0.038	1919 (3.6%)	280 (4.9%)	<.001
Osteoarthritis	5970 (8.2%)	1113 (11.6%)	<.001	2916 (5.5%)	405 (7.1%)	<.001
Chronic obstructive pulmonary disease	2071 (2.8%)	2371 (24.7%)	<.001	1623 (3.1%)	1469 (25.7%)	<.001
Asthma	3459 (4.7%)	3584 (37.3%)	<.001	2721 (5.2%)	1917 (33.5%)	<.001
Drug use*						
Antihypertensives	8643 (11.9%)	1649 (17.2%)	<.001	6809 (12.9%)	1011 (17.7%)	<.001
Blood glucose-lowering drugs	1126 (1.5%)	244 (2.5%)	<.001	1254 (2.4%)	181 (3.2%)	<.001
Lipid-modifying drugs	3555 (4.9%)	687 (7.1%)	<.001	4618 (8.8%)	642 (11.2%)	<.001

Table 1. Descriptive characteristics of the study population (continued)

	Women			Men		
	(N=82 443)			(N=58 436)		
	Non-CS users	CS users	Pdiff	Non-CS users	CS users	Pdiff
HRT, only female sex hormones	13 054 (17.9%)	1957 (20.4%)	<.001	N/A	N/A	
HRT, other sex hormones	824 (1.1%)	144 (1.5%)	0.002	85 (0.2%)	30 (0.5%)	<.001
Psychotropics	4829 (6.6%)	868 (9.0%)	<.001	1870 (3.5%)	261 (4.6%)	<.001
Cardiometabolic traits						
Body mass index (kg/m2)	25.7 (4.6)	26.7 (5.3)	<.001	26.4 (3.7)	26.7 (3.9)	<.001
Waist circumference (cm)	86.4 (12.1)	89.1 (13.4)	<.001	95.0 (10.8)	96.7 (11.5)	<.001
Systolic blood pressure (mm Hg)	121.9 (15.3)	123.5 (15.4)	<.001	130.3 (14.1)	131.1 (14.2)	<.001
Diastolic blood pressure (mm Hg)	71.7 (8.8)	72.0 (8.7)	<.001	76.4 (9.4)	77.2 (9.3)	<.001
Triglycerides (mmol/L)†,‡	1.02 (0.58)	1.08 (0.61)	<.001	1.40 (1.02)	1.40 (0.93)	0.298
HDL-cholesterol (mmol/L)‡	1.62 (0.40)	1.61 (0.40)	0.026	1.31 (0.32)	1.32 (0.33)	0.011
Glucose (mmol/L)‡	4.89 (0.76)	4.96 (0.86)	<.001	5.18 (0.90)	5.20 (0.92)	0.100
Metabolic syndrome	10 323 (14.2%)	1874 (19.5%)	<.001	11 020 (20.9%)	1348 (23.6%)	<.001

Data are provided as mean (SD) or numbers (%). *The ATC-codes for the included drugs are depicted in Supplemental Table 1; †Descriptive data shown for original untransformed data; ‡Values can be converted to conventional units (i.e. mg/dL) by dividing by the following conversion factors: 0.0113 for triglycerides, 0.0259 for HDL-cholesterol, and 0.0555 for glucose. Abbreviations: CS, corticosteroids; HDL, high density lipoprotein; HRT, hormone replacement therapy; N/A, not applicable.

Table 2. Corticosteroid use categorized by route of administration and number of types.

	Female corticosteroid users (N=9611)			Male corticosteroid users (N=5717)		
Administration route	**Local only use**	**Systemic use***		**Local only use**	**Systemic use***	
	9170 (95.4%)	441 (4.6%)		5451 (95.3%)	266 (4.7%)	
Number of types	**All users†**	**Single type use‡**	**Multiple type use§**	**All users†**	**Single type use‡**	**Multiple type use§**
Systemic corticosteroids	441 (4.6%)	311(3.9%)	130 (7.5%)	266 (4.7%)	192 (4.0%)	74 (8.5%)
Topical corticosteroids	2122 (22.1%)	1566 (19.9%)	556 (32.0%)	1428 (25.0%)	1124 (23.2%)	304 (35.1%)
Nasal corticosteroids	3566 (37.1%)	2201 (27.9%)	1365 (78.7%)	1965 (34.4%)	1321 (27.2%)	644 (74.3%)
Inhaled corticosteroids	4969 (51.7%)	3529 (44.8%)	1440 (83.0%)	2750 (48.1%)	2032 (41.9%)	718 (82.8%)
Otological corticosteroids	109 (1.1%)	61 (0.8%)	48 (2.8%)	59 (1.0%)	37 (0.8%)	22 (2.5%)
Ocular corticosteroids	134 (1.4%)	102 (1.3%)	32 (1.8%)	102 (1.8%)	89 (1.8%)	13 (1.5%)
Intestinal corticosteroids	88 (0.9%)	66 (0.8%)	22 (1.3%)	38 (0.7%)	32 (0.7%)	6 (0.7%)
Others	75 (0.8%)	40 (0.5%)	35 (2.0%)	49 (0.9%)	23 (0.5%)	26 (3.0%)
Hemorrhoidal corticosteroids	40 (0.4%)	23 (0.3%)	17 (1.0%)	32 (0.6%)	14 (0.3%)	18 (2.1%)
Local oral corticosteroids	35 (0.4%)	17 (0.2%)	18 (1.0%)	17 (0.3%)	9 (0.2%)	8 (0.9%)
Gynaecological corticosteroids	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total users	9611 (100.0%)	7876 (81.9%)	1735 (18.1%)	5717 (100.0%)	4850 (84.8%)	867 (15.2%)

Values are provided as numbers (%). *Includes also subjects using systemic corticosteroids in combination with local forms. †, ‡,§Percentages between brackets indicate the proportion of users within the group of total corticosteroid users, single type users, and multiple type users respectively.

Table 3. Odds ratios (95% confidence interval) for the association between corticosteroid use and metabolic syndrome.

	Women (N=82 443)				Men (N=58 436)			
			Metabolic syndrome				Metabolic syndrome	
	N	MetS*	Model 1	Model 2	N	MetS*	Model 1	Model 2
Total corticosteroid use	9611	1874 (19.5%)	1.38 (1.30 to 1.46)***	1.24 (1.17 to 1.32)***	5717	1348 (23.6%)	1.05 (0.98 to 1.12)	1.00 (0.93 to 1.08)
Local only use	9170	1731 (18.9%)	1.35 (1.27 to 1.44)***	1.22 (1.14 to 1.30)***	5451	1265 (23.2%)	1.04 (0.97 to 1.12)	1.00 (0.93 to 1.08)
Systemic use	441	143 (32.4%)	1.97 (1.59 to 2.45)***	1.68 (1.34 to 2.10)***	266	83 (31.2%)	1.15 (0.88 to 1.52)	0.97 (0.72 to 1.30)
Multiple type use	1735	341 (19.7%)	1.40 (1.24 to 1.59)***	1.26 (1.10 to 1.44)***	867	209 (24.1%)	1.03 (0.88 to 1.22)	0.93 (0.78 to 1.10)
Single type use	7876	1533 (19.5%)	1.38 (1.29 to 1.47)***	1.24 (1.16 to 1.32)***	4850	1139 (23.5%)	1.05 (0.98 to 1.13)	1.01 (0.94 to 1.10)
Systemic corticosteroid(s)	311	101 (32.5%)	1.96 (1.51 to 2.53)***	1.74 (1.33 to 2.27)***	192	52 (27.1%)	0.97 (0.69 to 1.35)	0.88 (0.62 to 1.26)
Topical corticosteroid(s)	1566	218 (13.9%)	0.98 (0.84 to 1.15)	0.98 (0.84 to 1.15)	1124	214 (19.0%)	0.86 (0.73 to 1.00)	0.90 (0.77 to 1.06)
Nasal corticosteroid(s)	2201	331 (15.0%)	1.18 (1.04 to 1.33)**	1.20 (1.06 to 1.36)**	1321	262 (19.8%)	0.97 (0.84 to 1.11)	1.00 (0.86 to 1.16)
Inhaled corticosteroid(s)	3529	840 (23.8%)	1.66 (1.52 to 1.80)***	1.35 (1.24 to 1.49)***	2032	559 (27.5%)	1.21 (1.09 to 1.34)***	1.08 (0.96 to 1.21)
Otological corticosteroid(s)	61	11 (18.0%)	1.22 (0.61 to 2.41)	1.14 (0.57 to 2.31)	37	13 (35.1%)	1.76 (0.86 to 3.62)	1.55 (0.71 to 3.38)
Ocular corticosteroid(s)	102	18 (17.6%)	0.96 (0.57 to 1.64)	0.93 (0.54 to 1.60)	89	25 (28.1%)	1.13 (0.70 to 1.84)	1.26 (0.77 to 2.07)
Intestinal corticosteroid(s)	66	11 (16.7%)	1.14 (0.58 to 2.24)	0.91 (0.44 to 1.86)	32	9 (28.1%)	1.22 (0.54 to 2.76)	1.09 (0.45 to 2.63)
Other corticosteroid(s)	40	3 (7.5%)	0.37 (0.11 to 1.24)	0.32 (0.09 to 1.11)	23	5 (21.7%)	1.04 (0.38 to 2.86)	1.12 (0.40 to 3.12)

In model 1, associations were adjusted for age. In model 2, additional adjustments were performed for ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), use of potentially weight-inducing psychotropics, hormonal replacement therapy (only female sex hormones (only in women), and other sex hormones (in both sexes)), and menstrual status (only in women). Non-CS users were taken as reference group for all analyses. Abbreviation: MetS, metabolic syndrome. **P<0.010, ***P<0.001. *Numbers and percentages of subjects with metabolic syndrome diagnosis are given for the corresponding group of corticosteroid users. Prevalences of MetS in the group of female and male non-corticosteroid users were 14.2% and 20.9%, respectively.

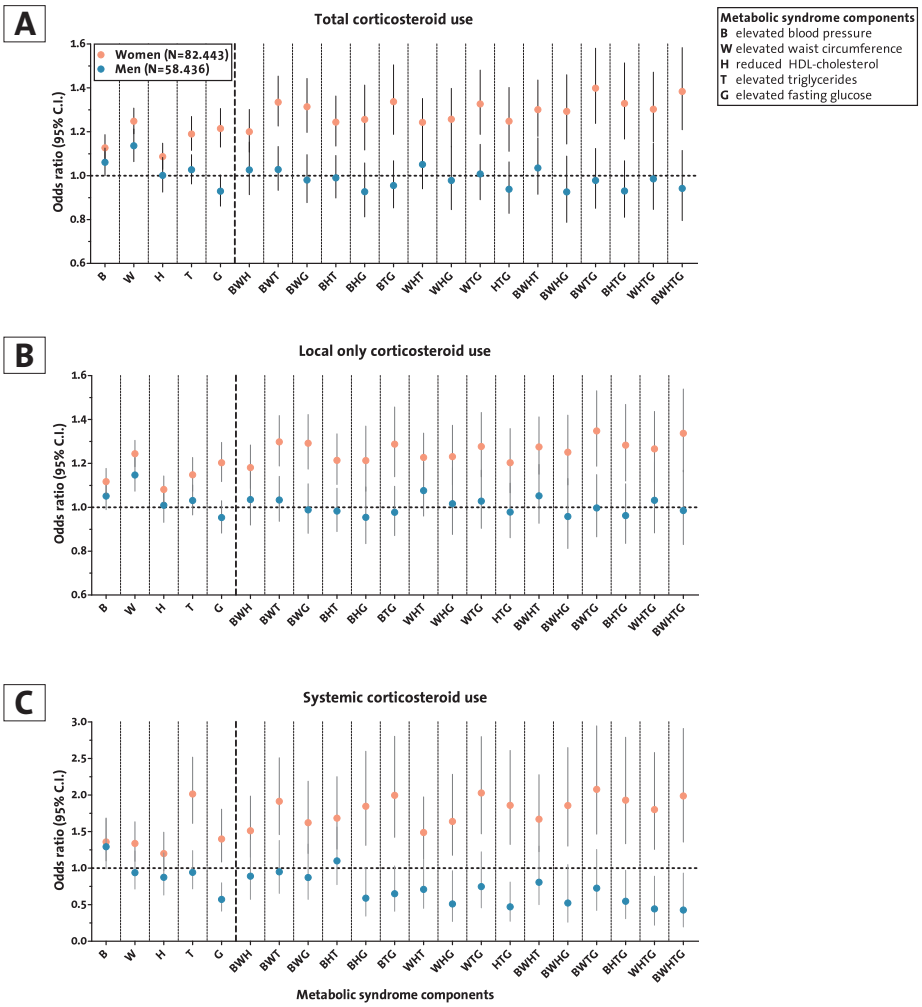

Figure 1. Associations between corticosteroid use and metabolic syndrome components.
The associations (odds ratio with 95% C.I.) between corticosteroid use and the five metabolic syndrome components separately and combined in all corticosteroid users (A), and stratified for only local corticosteroid users (B), and systemic corticosteroid users (C). All analyses are adjusted for age, ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), use of potentially weight-inducing psychotropics, hormonal replacement therapy (only female sex hormones (in women), and other sex hormones (in both sexes)), and menstrual status (in women). Non-corticosteroid users were taken as reference group for all analyses.

Corticosteroid use and cardiometabolic traits

The associations between overall CS use and specific CS administration forms and types with cardiometabolic traits are presented in Figure 2 (see also Supplemental Table 2 for adjusted mean differences).

Female CS users had higher BMI (+0.47 kg/m2 [95% CI, 0.38 to 0.57]), WC (+1.38 cm [95% CI, 1.13 to 1.63]), SBP (+0.37 mm Hg [95% CI, 0.06 to 0.68]), and triglycerides (+0.007 log mmol/L [95% CI, 0.003 to 0.011]) when compared to non-users. Similar findings together with a nominally significant higher fasting serum glucose levels (+0.01 mmol/L [95% CI, 0.001 to 0.03]) were also present in users of only local CS. Systemic CS users, by contrast, had increased HDL-cholesterol (+0.09 mmol/L [95% CI, 0.06 to 0.13]) and decreased fasting serum glucose levels (-0.26 mmol/L [95% CI, -0.32 to -0.21]) in addition to an increased WC (+1.72 cm [95% CI, 0.66 to 2.79]) and triglycerides (+0.050 log mmol/L [95% CI, 0.033 to 0.068]). Inhaled CS users had also higher BMI (+0.86 kg/m2 [95% CI, 0.70 to 1.02]), WC (+2.43 cm [95% CI, 2.02 to 2.83]), SBP (+0.69 mm Hg [95% CI, 0.20 to 1.19]), and fasting serum glucose levels (+0.03 mmol/L [95% CI, 0.01 to 0.05]).

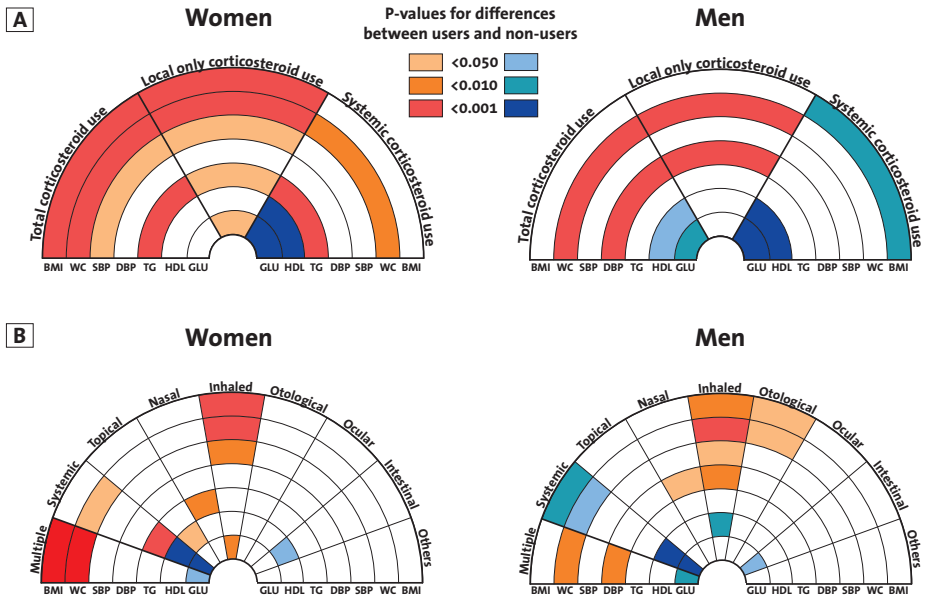

Figure 2. Corticosteroid use and differences in cardiometabolic traits.
Red-tints indicate unfavorable differences whereas the blue-tints signify favorable differences in cardiometabolic traits between users and non-users of corticosteroids (see Supplemental Table 2 for adjusted mean differences). The associations are shown for the main corticosteroid users groups (A) and specified for the multiple type and the various single type users (B) in both sexes. All analyses are adjusted for age, ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), diabetes mellitus, use of potentially weight-inducing psychotropics, use of lipid-modifying drugs, use of antihypertensives, hormonal replacement therapy (only female sex hormones (in women), and other sex hormones (in both sexes)), and menstrual status (in women). Non-corticosteroid users were taken as reference group for all analyses. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GLU, fasting plasma glucose; HDL, HDL-cholesterol; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

In men, local only CS use was associated with a higher WC (+0.79 cm [95% CI, 0.51 to 1.08] and DBP (+0.52 mm Hg [95% CI, 0.26 to 0.78]). Systemic CS use was associated with higher HDL-cholesterol (+0.18 mmol/L [95% CI, 0.14 to 0.21]) and lower fasting serum glucose (-0.34 mmol/L [95% CI, -0.42 to -0.26]). Of the different administration types, use of inhaled CS were also in men associated with higher BMI (+0.25 kg/m2 [95% CI, 0.09 to 0.41]), WC (+1.44 cm [95% CI, 0.97 to 1.90]), and SBP (+0.74 mm Hg [95% CI, 0.11 to 1.37]), in addition to higher DBP (+0.60 mm Hg [95% CI, 0.18 to 1.01]) and HDL-cholesterol (+0.02 mmol/L [95% CI, 0.01 to 0.04]).

Sensitivity analyses

Analyses stratified by menopause status in women, age, and by presence of inflammatory diseases yielded nearly similar results with the main analyses (Supplemental Tables 3 and 4). Stratification by BMI did not change the results in men but revealed higher likelihood of having MetS in local only users only in non-obese females which was largely explained by the inhaled CS users (Supplemental Table 5).

DISCUSSION

Overall, we found that use of local CS is associated with MetS especially in women in the general population. Moreover, users of local CS in both men and women had more adverse cardiometabolic traits when compared to non-users. Among the various local CS, the strongest associations were found in users of inhaled administration forms.

It is unclear why CS use is associated with the presence of MetS in women but not in men. Sex-differences in side effects of CS use have been reported previously with women being more susceptible [14-16]. Emerging evidence shows that CS are associated with a decrease in bone mineral density [14, 15] and increased rate of skin bruising in women but not in men [16]. Corticosteroid-induced lipodystrophy is also more common in women than in men and is associated with hypercholesterolemia, hypertriglyceridemia, and insulin resistance [17-19]. Sex differences exist in drug absorption, distribution, metabolism and elimination, and therefore, men and women might differ in their response to drug treatment [20]. Furthermore, women use inhaled CS more often than men and have a higher reported adherence and positive attitude in regard to their medication [21]. Moreover, administration of CS reduces the levels of sex hormones, including estrogen and testosterone, which have sex-specific cardiometabolic effects [22-25]. Also, high glucocorticoid exposure is well-known to induce visceral fat accumulation [6, 26] which is recognized as a key driver of metabolic alterations [26]. Given the sexual dimor-

phism in fat distribution, with women having a more gynoid fat deposition, changes in fat differences due to exogenously administered CS may be more obvious in women.

The strongest relation between local CS use and both increased presence of MetS and adverse cardiometabolic traits were found in inhaled CS users. Previous studies have assessed the safety of inhaled CS by investigating the risk on various systemic adverse events other than MetS and found, for example, a higher risk for cataract formation [27], loss of bone mineral density [14, 15, 28], and cutaneous atrophy [29]. These and our findings correspond to the general hypothesis that inhaled CS can induce serious systemic effects. Despite several small prospective trials demonstrating systemic absorption of inhaled corticosteroids [30-32], large and long-term randomized placebo-controlled trials in CS-naïve subjects focusing on cortisol-related metabolic effects are currently lacking. Nevertheless, the pharmacological characteristics of inhaled CS have been extensively studied and support the hypothesis that these agents possess a high potential to induce systemic alterations [33-35]. It is known, for example, that the largest proportion of the inhaled dose (i.e. around 50-90%) is deposited in the oropharyngeal area, swallowed, and eventually absorbed in the gut as it is for the systemic variants. Besides, a fraction of the inhaled corticosteroids will be deposited in the lungs and directly absorbed into the circulation without being subjected to the presystemic metabolism of the liver [33, 34].

The distribution of the different types of inhaled CS in this study were similar in both sexes and consisted predominantly of agents containing budesonide or fluticasone (Supplemental Figure 1), which bind to the glucocorticoid receptor with an affinity of 9.4 and 18.0 times greater, respectively, than dexamethasone [33, 35]. Moreover, a relatively high fraction of these two agents is unbound when present in the circulation in contrast to the more recently developed CS (e.g. ciclesonide and mometasone furoate) [33, 35]. These and other factors such as particle size, lipophilicity, clearance rate, but also the type of inhaler device determine the net amount of systemic availability and the potential for systemic adverse events in inhaled CS users [33-35]. Additionally, most of the inhaled users were using combination agents of CS with beta-agonists with the latter also being related to metabolic alterations [36]. It would therefore be conceivable that part of the increased MetS difference is due to the systemic availability of these agents. However, after full adjustment for covariates relevant to MetS as outcome we found rather similar likelihoods for users of only inhaled corticosteroids with and without beta-agonists in both sexes (Supplemental Table 6).

In the current study, we additionally demonstrated increased likelihood for MetS in women using only nasal CS. The prescription pattern of the nasal CS differed slightly from the inhaled forms in our sample with fluticasone and mometasone furoate com-

prising the majority of the agents being used (Supplemental Figure 2). These agents can, just as the inhaled forms, be absorbed directly into the circulation by local uptake in the nasopharynx or via the gastrointestinal tract after transportation by the nasociliary mucosa and hence theoretically exert systemic effects [34, 37]. However, both agents are considered to have very low systemic bioavailability of <1% with nasal administration [37] and have previously been shown not to evidently alter the hypothalamic-pituitary-adrenal axis function even when regularly administered or in high doses [38-40]. As the main indications for nasal and inhaled forms, i.e. allergic rhinitis and asthma, are often present alongside [41], the effects of nasal CS could perhaps be overestimated by prior use of inhaled CS.

The relevance of this work could be put in context with the results of a previous large observational study by Souverein et al [42] showing that users of systemic CS, including also systemic with inhaled CS users, have increased risk for ischaemic heart disease and heart failure events. Similar results were also shown in other large studies in which use of CS was found to be associated with higher risk of cardiovascular events [43, 44]. This was especially evident in the proportion of the CS users who eventually developed an iatrogenic Cushing syndrome, who were found to have higher risk in comparison to both non-users as CS users not developing a Cushing-like phenotype [45]. Given the fact that from the different administration forms our findings were especially evident in users of systemic and inhaled CS, both agents with high potential to enter the bloodstream, and since Cushing syndrome patients are known to have increased cardiovascular disease risk [6], our results strengthens the hypothesis that these users could also be at risk for metabolic syndrome complications.

There are several strengths of our present study. This is the first population-based study to examine the association between overall and specific use of CS and presence of MetS and its components. High-quality information about exposure and well-characterized participants are other strengths of the current investigation. Furthermore, the large sample size allowed us to perform several subgroup analyses. However, there are several limitations that need to be taken into account. First, the cross-sectional design does not allow us to address the temporality of the observed associations. Therefore, we cannot draw any conclusions with regard to the causality of the observations. Second, we cannot rule out that confounding by indication may be present. However, analysis restricted to non-obese participants and inflammatory diseases confirmed the findings in the general population. Although we corrected for a broad range of confounding factors in our analysis, we cannot exclude the possibility of residual confounding, because of the observational study design.

CONCLUSIONS

Use of local CS, particularly inhaled types, as well as systemic CS was associated with higher likelihood of having MetS, higher BMI, and other adverse cardiometabolic traits, especially among women. Since the inhaled CS are the main group of prescribed CS this might be a substantial risk to public health. Further studies are needed to confirm these findings and evaluate the direction of causality and mechanisms behind these associations.

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SUPPLEMENTAL DATA

Supplemental Table 1. ATC codes for evaluated drugs.

Drug group	ATC-code			
Metabolic syndrome definition				
Antihypertensives	C02	C03	C04	C07
	C08	C09		
Blood glucose-lowering drugs	A10A	A10B		
Lipid-modifying drugs	C10A	C10B		
Other drugs				
Hormonal replacement therapy				
• **Only female sex hormones**	G03A	G03C	G03D	G03F
• **Other sex hormones**	G03B	G03E	G03H	G03X
Psychotropics*				
• **Anticonvulsants**	N03AF01	N03AG01	N03AX12	N03AX16
• **Antidepressants**	N06AA09	N06CA01	N06AB04	N06AA04
	N06AB08	N06AA01	N06AA12	N06AX21
	N06AB10	N06AB03	N06CA03	N06AA02
	N06AA21	N06AX11	N06AA10	N06AB05
	N06AF03	N06AB06	N06AF04	N06AA06
• **Antipsychotics**	N05AX12	N05AA01	N05AH02	N05AB02
	N05AD01	N05AN	N05AN01	N05AH03
	N05AX13	N05AB03	N05AH04	N05AX08
	N05AC02	N05AF04	N05AB06	N05AE04

*For each drug group of the psychotropics, we only assessed the substances which were likely to induce weight gain as an adverse event (1,2).

Supplemental Table 2. Adjusted mean differences in cardiometabolic traits between users and non-users of corticosteroids.

	Women (N=82 443)						
	BMI (kg/m^2)	**WC (cm)**	**SBP (mm Hg)**	**DBP (mm Hg)**	**TG (log mmol/L)[a]**	**HDL (mmol/L)**	**GLU (mmol/L)**
Total corticosteroid use	**+0.47 (0.38 to 0.57)*****	**+1.38 (1.13 to 1.63)*****	**+0.37 (0.06 to 0.68)***	+0.09 (-0.10 to 0.28)	**+0.007 (+0.003 to 0.011)*****	+0.001 (-0.01 to 0.01)	+0.001 (-0.01 to 0.01)
Local only use	**+0.48 (0.38 to 0.58)*****	**+1.36 (1.10 to 1.62)*****	**+0.33 (0.02 to 0.65)***	+0.09 (-0.10 to 0.28)	**+0.005 (0.001 to 0.009)***	-0.004 (-0.01 to 0.01)	**+0.01 (0.001 to 0.03)***
Systemic use	+0.34 (-0.08 to 0.75)	**+1.72 (0.66 to 2.79)****	+1.08 (-0.23 to 2.38)	+0.09 (-0.71 to 0.89)	**+0.050 (0.033 to 0.068)*****	**+0.09 (0.06 to 0.13)*****	**-0.26 (-0.32 to -0.21)*****
Multiple type use	**+0.68 (0.46 to 0.89)*****	**+1.67 (1.12 to 2.22)*****	+0.64 (-0.03 to 1.32)	+0.37 (-0.05 to 0.78)	+0.005 (-0.004 to 0.014)	+0.01 (-0.01 to 0.03)	**-0.03 (-0.06 to -0.01)***
Single type use	**+0.43 (0.33 to 0.54)*****	**+1.32 (1.05 to 1.59)*****	+0.31 (-0.02 to 0.65)	+0.03 (-0.17 to 0.24)	**+0.008 (0.003 to 0.012)*****	-0.001 (-0.01 to 0.01)	+0.01 (-0.01 to 0.02)
Systemic corticosteroid(s)	+0.10 (-0.39 to 0.60)	**+1.34 (0.08 to 2.60)***	+0.95 (-0.60 to 2.50)	-0.08 (-1.03 to 0.87)	**+0.049 (0.028 to 0.069)*****	**+0.08 (0.04 to 0.12)*****	**-0.26 (-0.32 to -0.19)*****
Topical corticosteroid(s)	+0.13 (-0.09 to 0.35)	+0.45 (-0.12 to 1.01)	+0.20 (-0.50 to 0.89)	-0.23 (-0.66 to 0.20)	+0.007 (-0.002 to 0.017)	**-0.02 (-0.04 to -0.004)***	+0.01 (-0.02 to 0.04)
Nasal corticosteroid(s)	+0.13 (-0.06 to 0.32)	+0.44 (-0.04 to 0.92)	-0.08 (-0.67 to 0.51)	-0.06 (-0.42 to 0.31)	**+0.010 (0.003 to 0.018)****	-0.01 (-0.02 to 0.01)	+0.01 (-0.01 to 0.04)
Inhaled corticosteroid(s)	**+0.86 (0.70 to 1.02)*****	**+2.43 (2.02 to 2.83)*****	**+0.69 (0.20 to 1.19)****	+0.30 (-0.01 to 0.61)	+0.002 (-0.004 to 0.009)	+0.01 (-0.01 to 0.02)	**+0.03 (0.01 to 0.05)****
Otological corticosteroid(s)	+0.68 (-0.43 to 1.79)	+1.82 (-1.02 to 4.66)	-2.92 (-6.40 to 0.56)	-1.92 (-4.06 to 0.22)	-0.009 (-0.055 to 0.038)	-0.09 (-0.18 to 0.003)	+0.01 (-0.13 to 0.16)
Ocular corticosteroid(s)	-0.05 (-0.91 to 0.81)	-0.25 (-2.45 to 1.95)	-0.65 (-3.34 to 2.04)	-0.47 (-2.13 to 1.19)	+0.014 (-0.022 to 0.050)	+0.06 (-0.01 to 0.13)	-0.07 (-0.18 to 0.05)
Intestinal corticosteroid(s)	-0.33 (-1.40 to 0.74)	+0.44 (-2.29 to 3.17)	+1.08 (-2.26 to 4.43)	+0.21 (-1.85 to 2.27)	+0.003 (-0.041 to 0.048)	**+0.09 (0.002 to 0.18)***	+0.08 (-0.06 to 0.22)
Other corticosteroid(s)	+0.35 (-1.02 to 1.72)	+2.05 (-1.46 to 5.55)	-1.73 (-6.02 to 2.56)	-0.57 (-3.22 to 2.07)	+0.023 (-0.035 to 0.080)	-0.00 (-0.12 to 0.12)	-0.08 (-0.26 to 0.09)

Supplemental Table 2. Adjusted mean differences in cardiometabolic traits between users and non-users of corticosteroids (continued).

	Men (N=58 436)						
	BMI (kg/m^2)	**WC (cm)**	**SBP (mm Hg)**	**DBP (mm Hg)**	**TG (log mmol/L)[a]**	**HDL (mmol/L)**	**GLU (mmol/L)**
Total corticosteroid use	+0.07 (-0.03 to 0.17)	**+0.72 (0.44 to 1.01)*** **	+0.25 (-0.14 to 0.63)	**+0.48 (0.22 to 0.73)*** **	0.000 (-0.007 to 0.006)	**+0.01 (0.002 to 0.02)***	**-0.03 (-0.05 to -0.01)** **
Local only use	+0.10 (-0.002 to 0.20)	**+0.79 (0.51 to 1.08)*** **	+0.26 (-0.13 to 0.65)	**+0.52 (0.26 to 0.78)*** **	0.000 (-0.006 to 0.007)	+0.002 (-0.01 to 0.01)	-0.01 (-0.03 to 0.01)
Systemic use	**-0.58 (-1.00 to -0.16)** **	-0.69 (-1.88 to 0.51)	-0.06 (-1.69 to 1.57)	-0.43 (-1.50 to 0.65)	-0.013 (-0.040 to 0.014)	**+0.18 (0.14 to 0.21)*** **	**-0.34 (-0.42 to -0.26)*** **
Multiple type use	+0.13 (-0.11 to 0.37)	**+1.05 (0.38 to 1.73)** **	+0.40 (-0.53 to 1.32)	**+0.87 (0.26 to 1.48)** **	-0.003 (-0.018 to 0.013)	+0.02 (-0.004 to 0.04)	**-0.06 (-0.11 to -0.02)** **
Single type use	+0.06 (-0.05 to 0.16)	**+0.67 (0.37 to 0.97)*** **	+0.22 (-0.19 to 0.63)	**+0.41 (0.14 to 0.68)** **	0.000 (-0.007 to 0.007)	**+0.01 (0.00 to 0.02)***	**-0.02 (-0.04 to -0.001)***
Systemic corticosteroid(s)	**-0.76 (-1.26 to -0.27)** **	**-1.64 (-3.04 to -0.23)***	-0.27 (-2.18 to 1.65)	-0.40 (-1.67 to 0.86)	-0.023 (-0.055 to 0.009)	**+0.18 (0.13 to 0.22)*** **	**-0.36 (-0.45 to -0.27)*** **
Topical corticosteroid(s)	-0.13 (-0.33 to 0.08)	+0.11 (-0.47 to 0.70)	-0.06 (-0.85 to 0.74)	+0.02 (-0.51 to 0.54)	+0.001 (-0.012 to 0.014)	-0.02 (-0.03 to 0.003)	+0.01 (-0.03 to 0.04)
Nasal corticosteroid(s)	+0.02 (-0.18 to 0.21)	+0.33 (-0.22 to 0.87)	-0.20 (-0.94 to 0.54)	**+0.63 (0.14 to 1.11)***	+0.001 (-0.011 to 0.013)	-0.01 (-0.02 to 0.01)	+0.02 (-0.02 to 0.06)
Inhaled corticosteroid(s)	**+0.25 (0.09 to 0.41)** **	**+1.44 (0.97 to 1.90)*** **	**+0.74 (0.11 to 1.37)***	**+0.60 (0.18 to 1.01)** **	-0.001 (-0.012 to 0.009)	**+0.02 (0.01 to 0.04)** **	-0.03 (-0.06 to 0.004)
Otological corticosteroid(s)	**+1.32 (0.19 to 2.44)***	**+3.49 (0.30 to 6.67)***	+0.84 (-3.51 to 5.18)	-1.84 (-4.71 to 1.02)	+0.063 (-0.009 to 0.136)	-0.06 (-0.16 to 0.04)	+0.13 (-0.08 to 0.34)
Ocular corticosteroid(s)	+0.26 (-0.46 to 0.99)	+1.14 (-0.92 to 3.20)	+0.08 (-2.73 to 2.88)	+1.19 (-0.66 to 3.03)	+0.013 (-0.034 to 0.059)	-0.02 (-0.08 to 0.05)	-0.07 (-0.21 to 0.07)
Intestinal corticosteroid(s)	-0.36 (-1.57 to 0.84)	+0.31 (-3.12 to 3.74)	-0.92 (-5.59 to 3.76)	+0.07 (-3.01 to 3.15)	-0.025 (-0.103 to 0.053)	-0.02 (-0.13 to 0.08)	**-0.29 (-0.52 to -0.06)***
Other corticosteroid(s)	+0.71 (-0.71 to 2.13)	+0.32 (-3.73 to 4.36)	+2.47 (-3.04 to 7.98)	+0.77 (-2.86 to 4.40)	+0.036 (-0.056 to 0.127)	-0.10 (-0.23 to 0.02)	+0.02 (-0.25 to 0.29)

All analyses are adjusted for age, ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), diabetes mellitus, use of potentially weight-inducing psychotropics, use of lipid-modifying drugs, use of antihypertensives, hormonal replacement therapy (only female sex hormones (in women), and other sex hormones (in both sexes)), and menstrual status (in women). Non-corticosteroid users were taken as reference group for all analyses. Values can be converted to conventional units (i.e. mg/dL) by dividing by the following conversion factors: 0.0113 for triglycerides, 0.0259 for HDL-cholesterol, and 0.0555 for glucose. Abbreviations: *BMI*, body mass index; *DBP*, diastolic blood pressure; *GLU*, fasting plasma glucose; *HDL*, HDL-cholesterol; *SBP*, systolic blood pressure; *TG*, triglycerides; *WC*, waist circumference. *P<0.050, **P<0.010, ***P<0.001. [a]Adjusted mean differences (95% C.I.) are shown for log10-transformed triglycerides values.

Supplemental Table 3. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome (in pre- and postmenopausal women) based on age.

Women (N=82 443)	**<50 years (N=56 658)**				**≥50 years (N=25 785)**			
			Metabolic syndrome				***Metabolic syndrome***	
	N	**MetS, No. (%)[a]**	**Model 1**	**Model 2**	**N**	**MetS, No. (%)[a]**	**Model 1**	**Model 2**
Total corticosteroid use	6241	759 (12.2)	**1.46 (1.34 to 1.58)*****	**1.28 (1.17 to 1.41)*****	3370	1115 (33.1)	**1.32 (1.22 to 1.43)*****	**1.19 (1.09 to 1.30)*****
Local only use	6025	718 (14.1)	**1.43 (1.31 to 1.56)*****	**1.26 (1.15 to 1.39)*****	3145	1013 (32.2)	**1.28 (1.18 to 1.39)*****	**1.16 (1.06 to 1.27)*****
Systemic use	216	41 (19.0)	**2.25 (1.59 to 3.19)*****	**1.79 (1.25 to 2.57)****	225	102 (45.3)	**1.84 (1.40 to 2.41)*****	**1.62 (1.22 to 2.16)*****
Multiple type use	1150	144 (12.5)	**1.49 (1.24 to 1.78)*****	**1.32 (1.09 to 1.60)****	585	197 (33.7)	**1.33 (1.11 to 1.59)****	**1.19 (0.98 to 1.43)**
Single type use	5091	615 (12.1)	**1.45 (1.33 to 1.59)*****	**1.28 (1.16 to 1.41)*****	2785	918 (33.0)	**1.32 (1.21 to 1.43)*****	**1.19 (1.09 to 1.31)*****
Systemic corticosteroid(s)	148	26 (17.6)	**2.03 (1.32 to 3.12)****	**1.66 (1.07 to 2.59)***	163	75 (46.0)	**1.93 (1.40 to 2.65)*****	**1.79 (1.28 to 2.49)*****
Topical corticosteroid(s)	1081	97 (9.0)	1.13 (0.91 to 1.39)	1.16 (0.93 to 1.44)	485	121 (24.9)	0.87 (0.71 to 1.08)	0.85 (0.68 to 1.06)
Nasal corticosteroid(s)	1590	164 (10.3)	**1.22 (1.03 to 1.44)***	**1.24 (1.04 to 1.47)***	611	167 (27.3)	1.13 (0.94 to 1.35)	1.14 (0.95 to 1.38)
Inhaled corticosteroid(s)	2112	314 (14.9)	**1.79 (1.58 to 2.03)*****	**1.37 (1.19 to 1.58)*****	1417	526 (37.1)	**1.55 (1.38 to 1.74)*****	**1.32 (1.17 to 1.49)*****
Otological corticosteroid(s)	41	5 (12.2)	1.28 (0.50 to 3.29)	1.18 (0.45 to 3.13)	20	6 (30.0)	1.14 (0.43 to 3.05)	1.14 (0.42 to 3.12)
Ocular corticosteroid(s)	52	4 (7.7)	0.82 (0.29 to 2.30)	0.76 (0.27 to 2.14)	50	14 (28.0)	1.02 (0.54 to 1.92)	1.01 (0.53 to 1.94)
Intestinal corticosteroid(s)	42	4 (9.5)	1.14 (0.40 to 3.21)	0.84 (0.28 to 2.48)	24	7 (29.2)	1.14 (0.47 to 2.79)	0.92 (0.35 to 2.41)
Other corticosteroid(s)	25	1 (4.0)	0.40 (0.05 to 3.00)	0.43 (0.06 to 3.24)	15	2 (13.3)	0.36 (0.08 to 1.61)	0.28 (0.06 to 1.37)

Supplemental Table 3. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome (in pre- and postmenopausal women) based on age.

Men (N=58 436)	<50 years (N=38 585)				≥50 years (N=19 851)			
			Metabolic syndrome				*Metabolic syndrome*	
	N	MetS, No. (%)[a]	Model 1	Model 2	N	MetS, No. (%)[a]	Model 1	Model 2
Total corticosteroid use	3495	582 (16.7)	**1.12 (1.02 to 1.23)***	1.08 (0.97 to 1.20)	2222	766 (34.5)	1.00 (0.91 to 1.09)	0.92 (0.83 to 1.02)
Local only use	3378	557 (16.5)	**1.10 (1.00 to 1.22)***	1.07 (0.97 to 1.19)	2073	708 (34.2)	0.99 (0.90 to 1.09)	0.92 (0.83 to 1.03)
Systemic use	117	25 (21.4)	1.47 (0.94 to 2.32)	1.22 (0.76 to 1.96)	149	58 (38.9)	1.06 (0.76 to 1.49)	0.90 (0.63 to 1.30)
Multiple type use	496	85 (17.1)	1.13 (0.89 to 1.44)	1.04 (0.81 to 1.34)	371	124 (33.4)	0.96 (0.77 to 1.20)	0.81 (0.64 to 1.03)
Single type use	2999	497 (16.6)	**1.11 (1.01 to 1.23)***	1.09 (0.97 to 1.21)	1851	642 (34.7)	1.00 (0.91 to 1.11)	0.94 (0.84 to 1.05)
Systemic corticosteroid(s)	93	16 (17.2)	1.14 (0.66 to 1.97)	0.95 (0.53 to 1.68)	99	36 (36.4)	0.92 (0.61 to 1.40)	0.91 (0.58 to 1.42)
Topical corticosteroid(s)	738	99 (13.4)	0.91 (0.73 to 1.13)	0.98 (0.78 to 1.22)	386	115 (29.8)	0.82 (0.65 to 1.02)	0.85 (0.67 to 1.07)
Nasal corticosteroid(s)	917	133 (14.5)	0.95 (0.78 to 1.14)	1.00 (0.82 to 1.21)	404	129 (31.9)	0.97 (0.79 to 1.21)	0.97 (0.77 to 1.21)
Inhaled corticosteroid(s)	1159	227 (19.6)	**1.33 (1.14 to 1.55)*****	1.17 (0.995 to 1.39)	873	332 (38.0)	1.12 (0.97 to 1.29)	0.99 (0.84 to 1.16)
Otological corticosteroid(s)	18	5 (27.8)	**3.04 (1.05 to 8.84)***	**3.66 (1.25 to 10.76)***	19	8 (42.1)	1.33 (0.53 to 3.33)	0.95 (0.35 to 2.58)
Ocular corticosteroid(s)	42	11 (26.2)	1.99 (0.98 to 4.02)	**2.05 (1.00 to 4.19)***	47	14 (29.8)	0.79 (0.42 to 1.50)	0.92 (0.47 to 1.78)
Intestinal corticosteroid(s)	17	3 (17.6)	1.30 (0.37 to 4.64)	1.52 (0.43 to 5.44)	15	6 (40.0)	1.21 (0.42 to 3.48)	0.98 (0.32 to 3.06)
Other corticosteroid(s)	15	3 (20.0)	1.14 (0.31 to 4.15)	1.21 (0.32 to 4.55)	8	2 (25.0)	0.78 (0.16 to 3.94)	0.86 (0.17 to 4.38)

In model 1, associations were adjusted for age. In model 2, additional adjustments were performed for ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), use of weight-inducing psychotropics, hormonal replacement therapy (only female sex hormones (only in women), and other sex hormones (in both sexes)), and menstrual status (only in women). Non-corticosteroid users were taken as reference group for all analyses. Values are shown as odds ratios with 95% C.I. *P<0.050, **P<0.010, ***P<0.001. [a]Numbers and percentages of subjects with metabolic syndrome diagnosis are given for the corresponding group of corticosteroid users.

Supplemental Table 4. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome based on inflammatory status.

Women (N=82 443)	**No inflammatory diseases (N=66 624)**				**Inflammatory disease(s) present (N=15 819)**			
			Metabolic syndrome				***Metabolic syndrome***	
	N	**MetS, No. (%)[a]**	**Model 1**	**Model 2**	**N**	**MetS, No. (%)[a]**	**Model 1**	**Model 2**
Total corticosteroid use	4314	677 (15.7)	**1.22 (1.11 to 1.33)*** **	**1.19 (1.09 to 1.31)*** **	5297	1197 (22.6)	**1.24 (1.14 to 1.35)*** **	**1.21 (1.11 to 1.32)*** **
Local only use	4058	611 (15.1)	**1.18 (1.08 to 1.30)*** **	**1.17 (1.06 to 1.29)** **	5112	1120 (21.9)	**1.21 (1.11 to 1.32)*** **	**1.18 (1.08 to 1.29)*** **
Systemic use	256	66 (25.8)	**1.70 (1.26 to 2.30)*** **	**1.57 (1.15 to 2.14)** **	185	77 (41.6)	**2.07 (1.51 to 2.84)*** **	**1.81 (1.30 to 2.52)*** **
Multiple type use	389	79 (20.3)	**1.64 (1.25 to 2.14)*** **	**1.65 (1.25 to 2.18)*** **	1346	262 (19.5)	1.08 (0.93 to 1.25)	1.10 (0.94 to 1.29)
Single type use	3925	598 (15.2)	**1.18 (1.07 to 1.29)*** **	**1.15 (1.04 to 1.27)** **	3951	935 (23.7)	**1.30 (1.19 to 1.42)*** **	**1.24 (1.13 to 1.37)*** **
Systemic corticosteroid(s)	222	59 (26.6)	**1.71 (1.24 to 2.36)** **	**1.58 (1.13 to 2.20)** **	89	42 (47.2)	**2.35 (1.51 to 3.67)*** **	**2.11 (1.33 to 3.34)** **
Topical corticosteroid(s)	1253	153 (12.2)	0.96 (0.80 to 1.15)	0.96 (0.80 to 1.16)	313	65 (20.8)	1.00 (0.75 to 1.34)	1.02 (0.75 to 1.38)
Nasal corticosteroid(s)	1710	232 (13.6)	**1.17 (1.01 to 1.35)***	**1.19 (1.03 to 1.38)***	491	99 (20.2)	1.10 (0.87 to 1.39)	1.17 (0.92 to 1.49)
Inhaled corticosteroid(s)	526	125 (23.8)	**1.59 (1.28 to 1.98)*** **	**1.42 (1.13 to 1.78)** **	3003	715 (23.8)	**1.34 (1.21 to 1.48)*** **	**1.25 (1.13 to 1.39)*** **
Otological corticosteroid(s)	52	8 (15.4)	1.17 (0.79 to 1.75)	1.04 (0.46 to 2.34)	9	3 (33.3)	1.41 (0.67 to 2.97)	1.60 (0.76 to 3.36)
Ocular corticosteroid(s)	84	14 (16.7)	0.94 (0.69 to 1.28)	0.91 (0.49 to 1.70)	18	4 (22.2)	1.01 (0.56 to 1.80)	0.90 (0.28 to 2.92)
Intestinal corticosteroid(s)	46	5 (10.9)	0.70 (0.27 to 1.83)	0.61 (0.22 to 1.69)	20	6 (30.0)	2.11 (0.76 to 5.81)	1.54 (0.50 to 4.71)
Other corticosteroid(s)	32	2 (6.3)	0.35 (0.17 to 0.74)	0.28 (0.06 to 1.30)	8	1 (12.5)	0.41 (0.14 to 1.22)	0.41 (0.05 to 3.44)

Supplemental Table 4. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome based on inflammatory status.

Men (N=58 436)	No inflammatory diseases (N=48 974)				Inflammatory disease(s) present (N=9462)			
			Metabolic syndrome				*Metabolic syndrome*	
	N	MetS, No. (%)[a]	Model 1	Model 2	N	MetS, No. (%)[a]	Model 1	Model 2
Total corticosteroid use	2868	590 (20.6)	0.94 (0.86 to 1.04)	0.96 (0.87 to 1.06)	2849	758 (26.6)	0.97 (0.88 to 1.08)	0.98 (0.88 to 1.10)
Local only use	2697	542 (20.1)	0.93 (0.84 to 1.03)	0.95 (0.86 to 1.06)	2754	723 (26.3)	0.97 (0.87 to 1.08)	0.99 (0.89 to 1.11)
Systemic use	171	48 (28.1)	1.11 (0.78 to 1.58)	1.05 (0.73 to 1.52)	95	35 (36.8)	1.08 (0.69 to 1.70)	0.87 (0.53 to 1.41)
Multiple type use	218	50 (22.9)	0.91 (0.65 to 1.27)	0.88 (0.61 to 1.27)	649	159 (24.5)	0.89 (0.73 to 1.08)	0.89 (0.72 to 1.09)
Single type use	2650	540 (20.4)	0.95 (0.86 to 1.05)	0.97 (0.87 to 1.08)	2200	599 (27.2)	1.00 (0.89 to 1.12)	1.01 (0.90 to 1.14)
Systemic corticosteroid(s)	152	38 (25.0)	0.93 (0.64 to 1.37)	0.89 (0.60 to 1.34)	40	14 (35.0)	1.01 (0.50 to 2.04)	0.86 (0.40 to 1.84)
Topical corticosteroid(s)	957	170 (17.8)	0.84 (0.71 to 1.00)	0.89 (0.75 to 1.07)	167	44 (26.3)	0.91 (0.63 to 1.31)	0.95 (0.65 to 1.39)
Nasal corticosteroid(s)	1055	189 (17.9)	0.91 (0.77 to 1.07)	0.95 (0.80 to 1.13)	266	73 (27.4)	1.08 (0.81 to 1.44)	1.10 (0.82 to 1.48)
Inhaled corticosteroid(s)	349	106 (30.4)	1.23 (0.96 to 1.57)	1.13 (0.87 to 1.47)	1683	453 (26.9)	0.99 (0.87 to 1.12)	1.00 (0.88 to 1.14)
Otological corticosteroid(s)	30	8 (26.7)	1.27 (0.82 to 1.96)	1.16 (0.46 to 2.90)	7	5 (71.4)	**5.82 (2.39 to 14.16)***	4.87 (0.74 to 32.16)
Ocular corticosteroid(s)	71	21 (29.6)	1.29 (0.98 to 1.69)	1.42 (0.82 to 2.45)	18	4 (22.2)	0.63 (0.35 to 1.14)	0.78 (0.25 to 2.41)
Intestinal corticosteroid(s)	18	4 (22.2)	0.98 (0.54 to 1.79)	0.76 (0.20 to 2.85)	14	5 (35.7)	1.31 (0.73 to 2.35)	1.60 (0.49 to 5.28)
Other corticosteroid(s)	18	4 (22.2)	1.15 (0.64 to 2.07)	1.15 (0.37 to 3.62)	5	1 (20.0)	0.64 (0.20 to 2.06)	0.79 (0.08 to 7.81)

Presence of inflammatory disease was defined as having osteoarthritis, asthma, and/or COPD. Subjects who had none of these three were classified as having no inflammatory diseases. In model 1, associations were adjusted for age. In model 2, additional adjustments were performed for ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), use of weight-inducing psychotropics, hormonal replacement therapy (only female sex hormones (only in women), and other sex hormones (in both sexes)), and menstrual status (only in women). Non-corticosteroid users were taken as reference group for all analyses. Values are shown as odds ratios with 95% C.I. *P<0.050, **P<0.010, ***P<0.001.
[a]Numbers and percentages of subjects with metabolic syndrome diagnosis are given for the corresponding group of corticosteroid users.

Supplemental Table 5. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome stratified for obesity.

Women (N=82 443)	**Non-obese (N=68 760)**				**Obese (N=13 683)**			
			Metabolic syndrome				***Metabolic syndrome***	
	N	**MetS, No. (%)[a]**	**Model 1**	**Model 2**	**N**	**MetS, No. (%)[a]**	**Model 1**	**Model 2**
Total corticosteroid use	7445	896 (12.0)	**1.25 (1.15 to 1.35)*****	**1.16 (1.07 to 1.27)*****	2166	978 (45.2)	**1.15 (1.05 to 1.27)****	1.09 (0.99 to 1.21)
Local only use	7114	826 (11.6)	**1.23 (1.13 to 1.33)*****	**1.15 (1.05 to 1.26)****	2056	905 (44.0)	**1.11 (1.01 to 1.23)***	1.05 (0.95 to 1.17)
Systemic use	331	70 (21.1)	**1.60 (1.19 to 2.13)****	**1.38 (1.02 to 1.86)***	110	73 (66.4)	**2.31 (1.52 to 3.49)*****	**2.16 (1.42 to 3.29)*****
Multiple type use	1300	160 (12.3)	**1.32 (1.10 to 1.57)****	**1.25 (1.03 to 1.50)***	435	181 (41.6)	0.97 (0.79 to 1.19)	0.94 (0.76 to 1.17)
Single type use	6145	736 (12.0)	**1.23 (1.13 to 1.34)*****	**1.15 (1.05 to 1.26)****	1731	797 (46.0)	**1.20 (1.08 to 1.34)*****	**1.13 (1.01 to 1.27)***
Systemic corticosteroid(s)	239	50 (20.9)	**1.54 (1.10 to 2.17)***	1.37 (0.97 to 1.96)	72	51 (70.8)	**2.91 (1.71 to 4.94)*****	**2.76 (1.62 to 4.72)*****
Topical corticosteroid(s)	1306	113 (8.7)	0.91 (0.74 to 1.12)	0.90 (0.73 to 1.12)	260	105 (40.4)	1.03 (0.80 to 1.34)	1.00 (0.77 to 1.31)
Nasal corticosteroid(s)	1835	175 (9.5)	1.15 (0.98 to 1.36)	1.18 (0.99 to 1.39)	366	156 (42.6)	1.22 (0.99 to 1.52)	**1.27 (1.02 to 1.58)***
Inhaled corticosteroid(s)	2546	373 (14.7)	**1.43 (1.26 to 1.61)*****	**1.24 (1.09 to 1.41)****	983	467 (47.5)	**1.20 (1.05 to 1.37)****	1.07 (0.92 to 1.24)
Otological corticosteroid(s)	49	5 (10.2)	0.98 (0.37 to 2.61)	0.97 (0.36 to 2.59)	12	6 (50.0)	1.38 (0.43 to 4.42)	1.26 (0.39 to 4.12)
Ocular corticosteroid(s)	85	13 (15.3)	1.18 (0.63 to 2.22)	1.15 (0.60 to 2.19)	17	5 (29.4)	0.59 (0.20 to 1.71)	0.56 (0.19 to 1.61)
Intestinal corticosteroid(s)	54	6 (11.1)	1.20 (0.50 to 2.92)	0.97 (0.39 to 2.43)	12	5 (41.7)	0.93 (0.28 to 3.06)	0.85 (0.24 to 2.99)
Other corticosteroid(s)	31	1 (3.2)	0.23 (0.03 to 1.72)	0.18 (0.02 to 1.48)	9	2 (22.2)	0.38 (0.08 to 1.94)	0.35 (0.07 to 1.89)

Supplemental Table 5. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome stratified for obesity.

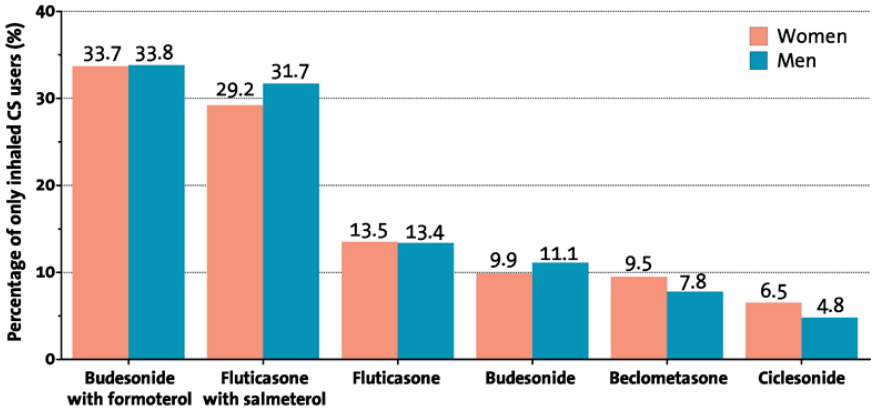
Men (N=58 436)	Non-obese (N=49 938)				Obese (N=8498)			
			Metabolic syndrome				*Metabolic syndrome*	
	N	MetS, No. (%)[a]	Model 1	Model 2	N	MetS, No. (%)[a]	Model 1	Model 2
Total corticosteroid use	4739	785 (16.6)	1.01 (0.93 to 1.10)	1.00 (0.91 to 1.10)	978	563 (57.6)	0.92 (0.80 to 1.06)	0.91 (0.78 to 1.05)
Local only use	4521	734 (16.2)	1.01 (0.92 to 1.10)	1.01 (0.92 to 1.11)	930	531 (57.1)	0.91 (0.79 to 1.05)	0.90 (0.78 to 1.05)
Systemic use	218	51 (23.4)	1.06 (0.76 to 1.49)	0.96 (0.67 to 1.36)	48	32 (66.7)	1.21 (0.66 to 2.24)	1.11 (0.58 to 2.11)
Multiple type use	710	124 (17.5)	1.03 (0.84 to 1.27)	0.99 (0.79 to 1.23)	157	85 (54.1)	0.78 (0.56 to 1.08)	0.74 (0.52 to 1.04)
Single type use	4029	661 (16.4)	1.01 (0.92 to 1.10)	1.01 (0.91 to 1.11)	821	478 (58.2)	0.95 (0.82 to 1.10)	0.94 (0.81 to 1.11)
Systemic corticosteroid(s)	162	34 (21.0)	0.95 (0.63 to 1.42)	0.89 (0.58 to 1.36)	30	18 (60.0)	0.95 (0.45 to 2.00)	0.97 (0.44 to 2.10)
Topical corticosteroid(s)	978	137 (14.0)	0.90 (0.74 to 1.09)	0.97 (0.80 to 1.18)	146	77 (52.7)	0.78 (0.56 to 1.09)	0.76 (0.54 to 1.08)
Nasal corticosteroid(s)	1129	154 (13.6)	0.94 (0.79 to 1.13)	0.99 (0.83 to 1.19)	192	108 (56.3)	0.99 (0.74 to 1.33)	0.96 (0.71 to 1.30)
Inhaled corticosteroid(s)	1616	308 (19.1)	1.10 (0.97 to 1.26)	1.04 (0.89 to 1.20)	416	251 (60.3)	0.99 (0.80 to 1.22)	1.00 (0.80 to 1.25)
Otological corticosteroid(s)	25	5 (20.0)	1.24 (0.44 to 3.53)	1.17 (0.40 to 3.49)	12	8 (66.7)	1.23 (0.36 to 4.23)	1.05 (0.28 to 3.89)
Ocular corticosteroid(s)	70	12 (17.1)	0.91 (0.47 to 1.74)	0.95 (0.48 to 1.88)	19	13 (68.4)	1.23 (0.46 to 3.30)	1.40 (0.52 to 3.77)
Intestinal corticosteroid(s)	28	7 (25.0)	1.45 (0.58 to 3.63)	1.47 (0.56 to 3.84)	4	2 (50.0)	0.85 (0.12 to 6.20)	0.53 (0.07 to 4.15)
Other corticosteroid(s)	21	4 (19.0)	1.37 (0.44 to 4.21)	1.50 (0.49 to 4.66)	2	1 (50.0)	0.69 (0.04 to 10.95)	0.87 (0.05 to 14.93)

Non-obese is defined as having a BMI <30.0 kg/m^2 and obese as BMI ≥30.0 kg/m^2. In model 1, associations were adjusted for age. In model 2, additional adjustments were performed for ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), use of weight-inducing psychotropics, hormonal replacement therapy (only female sex hormones (only in women), and other sex hormones (in both sexes)), and menstrual status (only in women). Non-corticosteroid users were taken as reference group for all analyses. Values are shown as odds ratios with 95% C.I. *P<0.050, **P<0.010, ***P<0.001. [a]Numbers and percentages of subjects with metabolic syndrome diagnosis are given for the corresponding group of corticosteroid users.

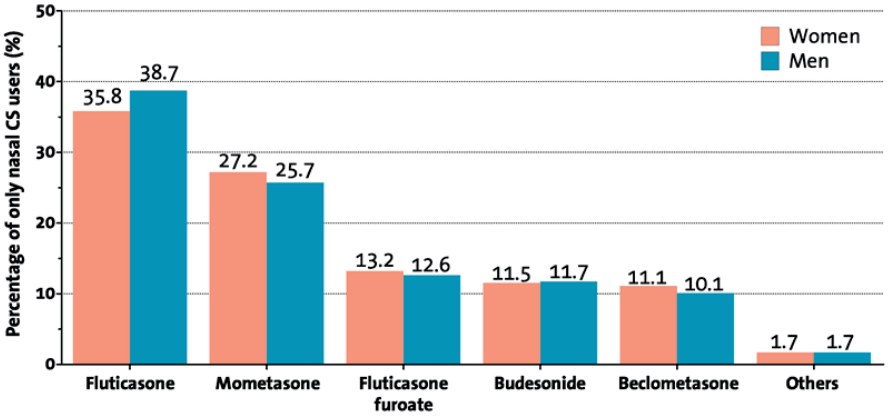
Supplemental Table 6. Sensitivity analysis for the association between corticosteroid use and metabolic syndrome in single type inhaled corticosteroid(s) users.

	Women				Men			
			Metabolic syndrome				*Metabolic syndrome*	
	N	**MetS, No. (%)[a]**	**Model 1**	**Model 2**	**N**	**MetS, No. (%)[a]**	**Model 1**	**Model 2**
Single type inhaled corticosteroid(s) use	3529	840 (23.8)			2032	559 (27.5)		
Without beta-agonists	1318	290 (22.0)	**1.59 (1.38 to 1.82)*** **	**1.35 (1.17 to 1.57)*** **	705	166 (23.5)	1.04 (0.86 to 1.25)	1.01 (0.83 to 1.23)
With beta-agonists	2211	550 (24.9)	**1.70 (1.53 to 1.88)*** **	**1.35 (1.20 to 1.51)*** **	1327	393 (29.6)	**1.30 (1.15 to 1.48)*** **	1.12 (0.98 to 1.29)

In model 1, associations were adjusted for age. In model 2, additional adjustments were performed for ethnicity, smoking, education level, alcohol use, physical activity, cardiovascular diseases (i.e. stroke and/or coronary heart disease), other comorbidities (i.e. cancer, osteoarthritis, COPD, and/or asthma), use of weight-inducing psychotropics, hormonal replacement therapy (only female sex hormones (only in women), and other sex hormones (in both sexes)), and menstrual status (only in women). Non-corticosteroid users were taken as reference group for all analyses. Values are shown as odds ratios with 95% C.I. ***P<0.001. [a]Numbers and percentages of subjects with metabolic syndrome diagnosis are given for the corresponding group of corticosteroid users.



Supplemental Figure 1. Distribution of use of inhaled corticosteroid agents in single type corticosteroid users.
Abbreviation: CS, corticosteroids.



Supplemental Figure 2. Distribution of use of nasal corticosteroid agents in single type corticosteroid users.
Abbreviation: CS, corticosteroids.

SUPPLEMENTAL REFERENCES

1. Sheehan AH. *Weight gain*. In: Tisdale JE, Miller DA, eds. Drug-induced Diseases: Prevention, Detection, and Management. Bethesda, MD: American Society of Health-System Pharmacists; 2010. p. 629-642.
2. Apovian, C.M., et l., *Pharmacological management of obesity: an endocrine Society clinical practice guideline.* J Clin Endocrinol Metab, 2015. **100**: p. 342-362.