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Associations Between Systemic and Local Corticosteroid Use With Metabolic Syndrome and Body Mass Index

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

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

Design: Cross-sectional cohort study.

Setting: General population from the northern Netherlands.

Participants: A total of 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 CS use was associated with higher odds of having MetS. Among local female users, only nasal (odds ratio [OR], 1.20 [95% confidence interval (CI), 1.06 to 1.36]) and inhaled CSs [OR, 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 CS use and presence of MetS. Use of local-only CSs in women, specifically inhaled CSs in both sexes, was associated with higher BMI.

Conclusions: Use of local CSs, particularly inhaled types, as well as systemic CSs, was associated with higher likelihood of having MetS, higher BMI, and other adverse cardiometabolic traits, especially among women. Because the inhaled agents are the main group of prescribed CSs, this might be a substantial risk to public health in case of a yet-to-be-proven causal relationship. (***J Clin Endocrinol Metab*** **102: 3765–3774, 2017)**

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Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CS, corticosteroid; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MetS, metabolic syndrome; OR, odds ratio; SBP, systolic blood pressure; WC, waist circumference.

Synthetic glucocorticoids, also known as corticosteroids (CSs), 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 CSs 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 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 CSs may also be associated with an increased systemic glucocorticoid exposure exemplified by the increased risk of adrenal insufficiency in users of local types (7). Because many of the CS users are often prescribed a local administration form, it could be hypothesized that use of local CSs 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 multidisciplinary, prospective, population-based cohort study examining, in a unique three-generation design, the health and health-related behaviors of 167,729 persons living in the northern Netherlands (8). It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. For this study, we included baseline information on 152,180 adult participants. Subjects with incomplete report on drug use, nonfasting 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 were obtained according to 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 to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. Concurring with the ATC methodology, we classified CSs 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 gynecological forms. The last three forms were combined as "other CSs" 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 in women and the use of other exogenous sex hormones and potentially weight-inducing psychotropics (9, 10) in all subjects to adjust for their potential metabolic alterations (see Supplemental Table 1 for further details).

Measures of MetS 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 10 times with a 1-minute interval with an automatic blood pressure monitor (DinaMap Monitor; GE Health Care, 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, high-density lipoprotein (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 MetS

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 $\geq$88 cm in women and $\geq$102 cm in men; (2) SBP $\geq$130 mm Hg, DBP $\geq$85 mm Hg, and/or use of antihypertensives in patients with known hypertension; (3) triglycerides $\geq$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; and (5) fasting serum glucose $\geq$5.6 mmol/L and/or use of blood glucose–lowering drugs.

Assessment of covariates

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 preuniversity secondary education, higher vocational education, university, and others. Smoking was categorized under the following three statuses: nonsmokers (*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 had smoked for a full year or more in the past), 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 nonusers and users of up to one drink per day, one to two drinks per day, or more than two drinks per 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), semiactives (1 to 4 days per week), and norm-actives ($\geq$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 World Health Organization/International Diabetes Federation (12) and was deemed present in case of fasting serum glucose level $\geq$7.0 mmol/L and/or use of blood glucose–lowering drugs. Corresponding to the report of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (13), hypertension was defined as SBP $\geq$140 mm Hg, DBP $\geq$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 (COPD), and asthma] were all deemed present if the subject had indicated to be known with the diagnosis and, in the case of asthma, the diagnosis was confirmed by a doctor.

Statistical analysis

Crude differences in continuous variables were assessed with analysis of variance and in categorical variables with χ^2 tests. Triglyceride levels were positively skewed and were therefore log10-transformed to achieve normal distribution. Initial inferential analyses showed strong interaction effect ($P_{int} < 0.001$) 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 (1) by combining all types of CSs and (2) by differentiating between 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, because the last has been previously shown to be associated with substantial risk of 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 analysis of covariances 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 two sided, with 0.05 as level of significance, and performed with IBM SPSS Statistics version 21.0.01 (IBM Corp., Armonk, NY).

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 to, or above 50 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, because adiposity is evidently related to MetS and adverse cardiometabolic traits, we also stratified our main analysis by obesity levels (BMI <30.0 and $\geq$30.0 kg/m^2).

Results

Overall, 58.5% of the subjects were women and a total of 10.9% was currently using any form of CSs. 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 local-only administration forms (95.4% and 95.3%) and single-type users (81.9% and 84.8%). The most prescribed CSs in both single- and multiple-type users were inhaled, nasal, and topical agents, consecutively (Table 2). MetS was more common in men when compared with women. Both male and female CS users were more likely to have MetS when compared with nonusers, but the relative difference in women was much higher than in men (+5.3% vs +2.7%, $P < 0.001$).

CS use and MetS diagnosis

Female CS users had higher likelihood of having MetS in comparison with nonusers, which remained statistically significant after full adjustments for covariates (odds ratio [OR], 1.24 [95% confidence interval (CI), 1.17 to 1.32], $P < 0.001$; Table 3). Stratified analyses for

Table 1. Descriptive Characteristics of the Study Population

	Women (n = 82,443)			Men (n = 58,436)		
	Non-CS Users	CS Users	P	Non-CS Users	CS Users	P*diff*
Numbers	72,832 (88.3%)	9611 (11.7%)		52,719 (90.2%)	5717 (9.8%)	
Age (y)	44.2 (13.0)	45.6 (13.4)	<0.001	45.3 (13.1)	47.4 (13.6)	<0.001
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%)	<0.001	286 (0.5%)	40 (0.7%)	<0.001
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 preuniversity 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						
Nonsmoker	35,502 (48.7%)	4779 (49.7%)	<0.001	22,793 (43.2%)	2540 (44.4%)	<0.001
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%)	<0.001	5652 (10.7%)	683 (11.9%)	0.003
≤1 drink/d	39,501 (54.2%)	5016 (52.2%)		23,279 (44.2%)	2582 (45.2%)	
1 to 2 drinks/d	10,814 (14.8%)	1350 (14.0%)		15,348 (29.1%)	1579 (27.6%)	
>2 drinks/d	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
Semiactive	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%)	<0.001	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%)	<0.001	1927 (3.7%)	254 (4.4%)	0.003
Hypertension	15,451 (21.2%)	2602 (27.1%)	<0.001	16,916 (32.1%)	2144 (37.5%)	<0.001
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%)	<0.001	1686 (3.2%)	237 (4.1%)	<0.001
Cancer	3757 (5.2%)	544 (5.7%)	0.038	1919 (3.6%)	280 (4.9%)	<0.001
Osteoarthritis	5970 (8.2%)	1113 (11.6%)	<0.001	2916 (5.5%)	405 (7.1%)	<0.001
COPD	2071 (2.8%)	2371 (24.7%)	<0.001	1623 (3.1%)	1469 (25.7%)	<0.001
Asthma	3459 (4.7%)	3584 (37.3%)	<0.001	2721 (5.2%)	1917 (33.5%)	<0.001
Drug use[a]						
Antihypertensives	8643 (11.9%)	1649 (17.2%)	<0.001	6809 (12.9%)	1011 (17.7%)	<0.001
Blood glucose–lowering drugs	1126 (1.5%)	244 (2.5%)	<0.001	1254 (2.4%)	181 (3.2%)	<0.001
Lipid-modifying drugs	3555 (4.9%)	687 (7.1%)	<0.001	4618 (8.8%)	642 (11.2%)	<0.001
HRT, only female sex hormones	13,054 (17.9%)	1957 (20.4%)	<0.001	N/A	N/A	
HRT, other sex hormones	824 (1.1%)	144 (1.5%)	0.002	85 (0.2%)	30 (0.5%)	<0.001
Psychotropics	4829 (6.6%)	868 (9.0%)	<0.001	1870 (3.5%)	261 (4.6%)	<0.001
Cardiometabolic traits						
BMI (kg/m^2)	25.7 (4.6)	26.7 (5.3)	<0.001	26.4 (3.7)	26.7 (3.9)	<0.001
WC (cm)	86.4 (12.1)	89.1 (13.4)	<0.001	95.0 (10.8)	96.7 (11.5)	<0.001
SBP (mm Hg)	121.9 (15.3)	123.5 (15.4)	<0.001	130.3 (14.1)	131.1 (14.2)	<0.001
DBP (mm Hg)	71.7 (8.8)	72.0 (8.7)	<0.001	76.4 (9.4)	77.2 (9.3)	<0.001
Triglycerides (mmol/L)[b,c]	1.02 (0.58)	1.08 (0.61)	<0.001	1.40 (1.02)	1.40 (0.93)	0.298
HDL-cholesterol (mmol/L)[c]	1.62 (0.40)	1.61 (0.40)	0.026	1.31 (0.32)	1.32 (0.33)	0.011
Glucose (mmol/L)[c]	4.89 (0.76)	4.96 (0.86)	<0.001	5.18 (0.90)	5.20 (0.92)	0.100
MetS	10,323 (14.2%)	1874 (19.5%)	<0.001	11,020 (20.9%)	1348 (23.6%)	<0.001

Data are provided as mean (standard deviation) or numbers (%).

Abbreviations: HRT, hormonal replacement therapy; N/A, not applicable.

[a]The ATC codes for the included drugs are depicted in Supplemental Table 1.

[b]Descriptive data shown for original untransformed data.

[c]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.

Table 2. CS Use Categorized by Route of Administration and Number of Types

	Female CS Users (n = 9611)			Male CS Users (n = 5717)		
Administration route	Local-only use 9170 (95.4%)	Systemic use[a] 441 (4.6%)		Local-only use 5451 (95.3%)	Systemic use[a] 266 (4.7%)	
Number of types	All users[b]	Single-type use[c]	Multiple-type use[d]	All users[b]	Single-type use[c]	Multiple-type use[d]
Systemic CSs	441 (4.6%)	311(3.9%)	130 (7.5%)	266 (4.7%)	192 (4.0%)	74 (8.5%)
Topical CSs	2122 (22.1%)	1566 (19.9%)	556 (32.0%)	1428 (25.0%)	1124 (23.2%)	304 (35.1%)
Nasal CSs	3566 (37.1%)	2201 (27.9%)	1365 (78.7%)	1965 (34.4%)	1321 (27.2%)	644 (74.3%)
Inhaled CSs	4969 (51.7%)	3529 (44.8%)	1440 (83.0%)	2750 (48.1%)	2032 (41.9%)	718 (82.8%)
Otological CSs	109 (1.1%)	61 (0.8%)	48 (2.8%)	59 (1.0%)	37 (0.8%)	22 (2.5%)
Ocular CSs	134 (1.4%)	102 (1.3%)	32 (1.8%)	102 (1.8%)	89 (1.8%)	13 (1.5%)
Intestinal CSs	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 CSs	40 (0.4%)	23 (0.3%)	17 (1.0%)	32 (0.6%)	14 (0.3%)	18 (2.1%)
Local oral CSs	35 (0.4%)	17 (0.2%)	18 (1.0%)	17 (0.3%)	9 (0.2%)	8 (0.9%)
Gynecological CSs	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 (%).

[a]Also includes subjects using systemic CSs in combination with local forms.

[b]Percentages indicate the proportion of users within the group of total CS users.

[c]Percentages indicate the proportion of users within the group of single-type users.

[d]Percentages indicate the proportion of users within the group of multiple-type users.

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) and 1.22 (95% CI, 1.14 to 1.30), both $P < 0.001$, respectively]. The associations in female users of local-only CSs were mainly driven by subjects using nasal [OR, 1.20 (95% CI, 1.06 to 1.36), $P = 0.005$] and inhaled CSs [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.

CS use and MetS 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 (Fig. 1). These findings were consistent for both users of systemic and local-only CSs, 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 local-only 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 components.

CS use and cardiometabolic traits

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

Female CS users had higher BMI [+0.47 kg/m^2 (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 with nonusers. Similar findings together with nominally significant higher fasting serum glucose levels [+0.01 mmol/L (95% CI, 0.001 to 0.03)] were also present in users of local-only CSs. 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 also had higher BMI [+0.86 kg/m^2 (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)].

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 CSs in men was also associated with higher BMI [+0.25 kg/m^2 (95% CI, 0.09 to 0.41)], WC

Table 3. ORs (95% CI) for the Association Between CS Use and MetS

	Women (n = 82,443)				Men (n = 58,436)			
			MetS				MetS	
	n	MetS[a]	Model 1	Model 2	n	MetS[a]	Model 1	Model 2
Total CS use	9611	1874 (19.5%)	1.38 (1.30 to 1.46)[b]	1.24 (1.17 to 1.32)[b]	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)[b]	1.22 (1.14 to 1.30)[b]	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)[b]	1.68 (1.34 to 2.10)[b]	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)[b]	1.26 (1.10 to 1.44)[b]	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)[b]	1.24 (1.16 to 1.32)[b]	4850	1139 (23.5%)	1.05 (0.98 to 1.13)	1.01 (0.94 to 1.10)
Systemic CSs	311	101 (32.5%)	1.96 (1.51 to 2.53)[b]	1.74 (1.33 to 2.27)[b]	192	52 (27.1%)	0.97 (0.69 to 1.35)	0.88 (0.62 to 1.26)
Topical CSs	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 CSs	2201	331 (15.0%)	1.18 (1.04 to 1.33)[c]	1.20 (1.06 to 1.36)[c]	1321	262 (19.8%)	0.97 (0.84 to 1.11)	1.00 (0.86 to 1.16)
Inhaled CSs	3529	840 (23.8%)	1.66 (1.52 to 1.80)[b]	1.35 (1.24 to 1.49)[b]	2032	559 (27.5%)	1.21 (1.09 to 1.34)[b]	1.08 (0.96 to 1.21)
Otological CSs	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 CSs	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 CSs	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 CSs	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, HRT [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: HRT, hormonal replacement therapy.

[a] Numbers and percentages of subjects with MetS diagnosis are given for the corresponding group of CS users. Prevalence of MetS in the group of female and male non-CS users were 14.2% and 20.9%, respectively.

[b] $P < 0.001$.

[c] $P < 0.010$.

[+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 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 nonobese females, which was largely explained by the inhaled CS users (Supplemental Table 5).

Discussion

Overall, we found that use of local CSs is associated with MetS, especially in women in the general population. Moreover, users of local CSs in both men and women had more adverse cardiometabolic traits when compared with nonusers. Among the various local CSs, 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 CSs are associated with a decrease in bone mineral density (14, 15) and increased rate of skin bruising in women but not in men (16). CS-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 CSs more often than men and have a higher reported adherence and positive attitude in regard to their medication (21). Moreover, administration of CSs 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 dimorphism in fat distribution, with women having a more gynoid fat deposition, changes in fat differences due to exogenously administered CSs may be more obvious in women.

The strongest relation between local CS use and both increased presence of MetS and adverse cardiometabolic traits was found in inhaled CS users. Previous studies have assessed the safety of inhaled CSs 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),

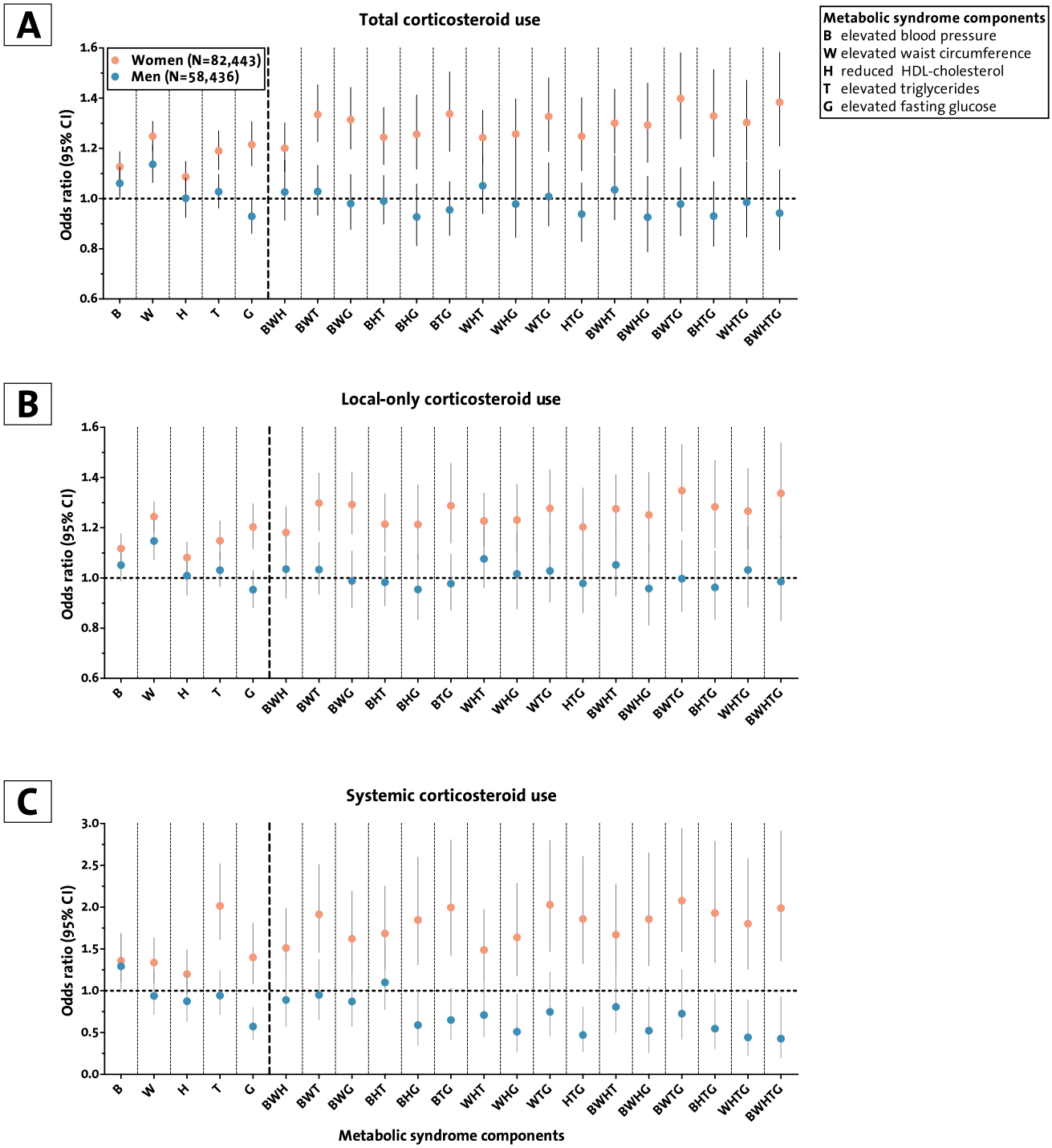

Figure 1. Associations between CS use and MetS components. The associations (OR with 95% CI) between CS use and the five MetS components separately and combined in (A) all CS users and stratified for (B) local-only CS users and (C) systemic CS users. All analyses are adjusted for age, ethnicity, smoking, 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, HRT [only female sex hormones (in women) and other sex hormones (in both sexes)], and menstrual status (in women). Non-CS users were taken as reference group for all analyses. HRT, hormonal replacement therapy.

and cutaneous atrophy (29). These and our findings correspond to the general hypothesis that inhaled CSs can induce serious systemic effects. Despite several small, prospective trials demonstrating systemic absorption of inhaled CSs (30–32), large and long-term randomized, placebo-controlled trials in CS-naive subjects focusing on cortisol-related metabolic effects are currently lacking. Nevertheless, the pharmacological characteristics of inhaled CSs have been extensively studied and support the hypothesis that these agents possess a high potential to

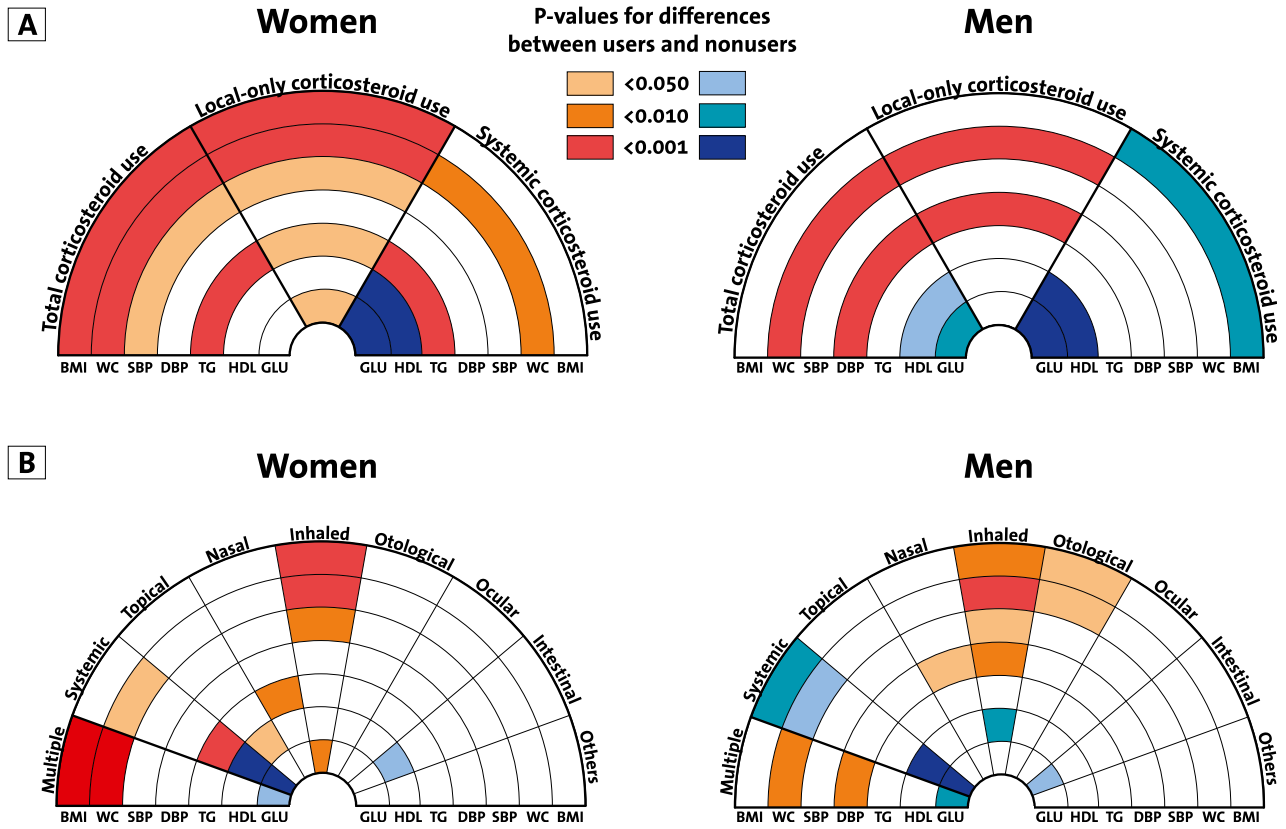

Figure 2. CS use and differences in cardiometabolic traits. Red tints indicate unfavorable differences, whereas the blue tints signify favorable differences in cardiometabolic traits between users and nonusers of CSs (see Supplemental Table 2 for adjusted mean differences). The associations are shown for (A) the main CS users groups and specified for (B) the multiple-type and the various single-type users 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, HRT [only female sex hormones (in women) and other sex hormones (in both sexes)], and menstrual status (in women). Non-CS users were taken as reference group for all analyses. GLU, fasting plasma glucose; HRT, hormonal replacement therapy; TG, triglycerides.

induce systemic alterations (33–35). It is known, for example, that the largest proportion of the inhaled dose (*i.e.*, around 50% to 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 CSs 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 CSs in this study were similar in both sexes and consisted predominantly of agents containing budesonide or fluticasone (Supplemental Fig. 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 CSs (*e.g.*, ciclesonide and mometasone furoate) (33, 35). These and other factors such as particle size, lipophilicity, and clearance rate, as well as 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 CSs 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 an outcome, we found rather similar likelihoods for users of only inhaled CSs with and without beta-agonists in both sexes (Supplemental Table 6).

In the current study, we additionally demonstrated an increased likelihood for MetS in women using only nasal CSs. The prescription pattern of the nasal CSs differed slightly from the inhaled forms in our sample, with fluticasone and mometasone furoate comprising the majority of the agents being used (Supplemental Fig. 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). Because the main indications for nasal and inhaled forms (*i.e.*, allergic rhinitis and asthma) are often present alongside (41), the effects of nasal CSs could perhaps be overestimated by prior use of inhaled CSs.

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 CSs, including also systemic with inhaled CS users, have increased risk for ischemic heart disease and heart failure events. Similar results were also shown in other large studies in which use of CSs 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 with both nonusers and 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 CSs (both agents with high potential to enter the bloodstream) and because patients with Cushing syndrome are known to have increased cardiovascular disease risk (6), our results strengthen the hypothesis that these users could also be at risk for MetS complications.

There are several strengths of our present study. This is, to our knowledge, the first population-based study to examine the association between overall and specific use of CSs and the 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 nonobese 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 CSs, particularly inhaled types, as well as systemic CSs was associated with higher likelihood of having MetS, higher BMI, and other adverse cardiometabolic traits, especially among women. Because the inhaled CSs are the main group of prescribed CSs, 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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