Anthropometrics and Metabolic Syndrome in Relation to Glucocorticoid Receptor Polymorphisms in Corticosteroid Users

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\textbf{Keywords}\n
Glucocorticoid receptor · Polymorphisms · Corticosteroids · BMI · Waist circumference · Metabolic syndrome

\textbf{Abstract}

\textbf{Introduction:} Corticosteroids are widely prescribed and their use has been linked to adverse cardiometabolic outcomes. A pivotal role in the action of corticosteroids is reserved for the glucocorticoid receptor (GR). Here, we assessed the relationship of glucocorticoid sensitivity-altering GR polymorphisms with anthropometrics and metabolic syndrome (MetS) in corticosteroid users. \textbf{Methods:} In this population-based cohort study (Lifelines), we genotyped 10,621 adult participants for GR hypersensitive (1/2 copies Bcl and/or N363S) and GR resistant (1/2 copies ER22/23EK and/or 9β) variants. We assessed the relationship between functional GR polymorphisms with BMI, waist circumference (WC), and MetS in users of corticosteroids. \textbf{Results:} Overall corticosteroid use was associated with a significantly higher BMI and WC in GR wild-type (WT) users (BMI, +0.63 kg/m\textsuperscript{2} [0.09–1.16], \textit{p} = 0.022; WC, +2.03 cm [0.61–3.44], \textit{p} = 0.005) and GR hypersensitive (BMI, +0.66 kg/m\textsuperscript{2} [95% CI, 0.31–1.01]; WC, +2.06 cm [1.13–2.98], both \textit{p} < 0.001) but not in GR resistant users. Significantly higher WC in GR resistant carriers was observed only for inhaled corticosteroid users. With respect to MetS, again only GR WT users (odds ratio [OR] 1.44 [1.07–1.94], \textit{p} = 0.017) and GR hypersensitives (OR 1.23 [95% CI, 1.00–1.50], \textit{p} = 0.046) were more likely to have MetS; even more pronounced in only inhaled corticosteroid users (GR WT users, OR 1.64 [1.06–2.55], \textit{p} = 0.027; GR hypersensitive users, OR 1.43 [1.08–1.91], \textit{p} = 0.013). \textbf{Conclusions:} Polymorphisms associated with increased GR sensitivity and WT GR are related to increased BMI, WC, and an increased MetS presence in corticosteroid users, especially of the inhaled types, when compared to nonusers. The adverse effects of corticosteroid use are less pronounced in users harboring GR resistant polymorphisms.

\textbf{Introduction}

Corticosteroids are among the most commonly used drugs. We previously reported that >10% of the Dutch general population was using any type of corticosteroids.
steroid users in the general population. Hence, we investigated whether the GC sensitivity-altering polymorphisms have been shown to be associated with alterations in body composition and several cardiometabolic parameters [9]. It remains unclear whether the GC sensitivity-altering polymorphisms could affect the vulnerability for developing adverse effects in corticosteroid users. This would especially be interesting for local types since the vast majority of the corticosteroid users are prescribed one of these forms, and therefore has a higher prevalence of users [1]. Moreover, our previous findings hint at systemic availability of the local corticosteroids, particularly of the inhaled forms, giving the association between these types with unfavorable cardiometabolic profile and metabolic syndrome (MetS) [1] as well as neuropsychiatric conditions and reduced executive functioning [10]. Hence, we investigated the relationship between 4 functional GR polymorphisms with anthropometric measurements and MetS in corticosteroid users in the general population.

Subjects and Methods

Study Population

Data of adult individuals participating in the Lifelines cohort study were evaluated for the current study. Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique 3-generation design the health and health-related behaviors of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics [11]. GWAS data were available for 13,378 participants of whom we included 10,621 after exclusion for subjects harboring both hypersensitive and resistant variants, nonreliable drug use data, non-fasting lab, and missing data on anthropometrics and/or MetS components. Written informed consent was provided by participants and study approval was obtained from the Medical Ethics Committee of the University Medical Center Groningen, Groningen, The Netherlands.

Genetic Analysis

Participants were genotyped using the Illumina HumanCytoSNP GWAS platform. GWAS data were enriched using imputation with 1,000 genomes as a reference. Using PLINK version 1.08p (Shaun Purcell, Harvard University), we extracted genotypes of functional GR SNPs: BclI, rs41423247; N363S, rs56149945; ER22/23EK, rs 6189 and 6190; and GR9β, rs6198. Users of corticosteroids were based on their genotype classified as either GR resistsants (1/2 copies of ER22/23EK and/or 9β polymorphisms), GR wild types (WT; in case of 2 WT alleles), or GR hypersensitives (1/2 copies of BclI and/or N363S polymorphisms).

Use of Corticosteroids

The currently used drugs were, after on-site container inspection, classified conforming to the WHO Anatomical Therapeutical Chemical code. We listed the Anatomical Therapeutical Chemical codes belonging to the various systemic corticosteroids (i.e., oral and parenteral) and local corticosteroids (i.e., dermal, nasal, inhaled, otological, ocular, intestinal, local oral, hemorrhoidal, and gynecological). Participants using any type of corticosteroids were classified as “corticosteroid users” and further specified as “systemic users” (i.e., systemic with or without local types) or “local users” (i.e., users of only local type[s]). To assess the specific associations with the different local administration forms, we additionally subclassified local users according to single-type use of 3 most prevalent forms: “inhaled types,” “nasal types,” and “dermal types.”

Anthropometrics and MetS

Trained technicians performed all measurements according to standardized operating protocols as described previously [1]. Weight (kg) and height (m) were used to compute BMI (kg/m²). WC was measured at halfway the distance between front edge of lower ribs and the iliac crest. MetS was deemed present in case of at least 3 of the following 5 criteria as defined by the joint interim statement [12]: (1) WC ≥88 cm (women) or ≥102 cm (men); (2) systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, and/or use of antihypertensive agents given a previous diagnosis of hypertension; (3) triglycerides ≥1.7 mmol/L and/
or use of lipid-modifying drugs; (4) HDL-cholesterol <1.3 mmol/L (women) or <1.0 mmol/L (men) and/or use of lipid-modifying drugs; and (5) fasting serum glucose ≥5.6 mmol/L and/or use of blood glucose-lowering drugs.

**Covariates**

We considered data on age, sex, educational attainment, smoking, and physical activity in order to control for confounding in the analyses. All covariates were self-reported and explained in detail elsewhere [1]. Educational attainment is related to the highest completed educational level and was categorized as: low (i.e., no education, primary, lower or preparatory vocational education, and lower general secondary education), middle (i.e., intermediate vocational education or apprenticeship, and higher general secondary education or preuniversity secondary education), high (i.e., higher vocational education and university) and other. With regard to smoking, participants were classified as nonsmoker, former smoker, or current smoker. Physical activity was based on the average number of days per week in which participants did at least half an hour of odd jobs, gardening, bicycling, or exercises combined. The percentage of missing data were 0.7% (educational attainment), 15.6% (smoking), and 9.0% (physical activity).

**Statistical Analysis**

Analyses were carried out with IBM SPSS Statistics version 22.0.0.2 (IBM Corp., Armonk, NY, USA). Student’s t test, Mann-Whitney U test, or χ² test was performed to assess the crude differences in descriptive characteristics between nonusers and users of corticosteroids. Categorical variables were computed for separate analyses regarding specific corticosteroid user groups. For this, all nonusers were taken as reference group with each of the following user groups labelled separately based on GR genotypes (i.e., GR resistant, WT, or GR hypersensitive): “overall users,” “systemic (with or without local)-type users,” “local-types-only users,” “inhaled-types-only users,” “nasal-types-only users,” and “dermal-types-only users.” With respect to BMI and WC, we performed analyses of covariance to analyze the differences between nonusers and corticosteroid user groups. Logistic regression analyses were carried out for the association between MetS and corticosteroid use. For both type of analyses, we report the main models in which adjustments were made for age, sex, educational attainment, smoking, and physical activity. Interaction with sex was additionally assessed in all main models. Multiple imputation was carried out to handle missing data on covariates. p values <0.050 were considered statistically significant.

**Table 1.** Descriptive characteristics of nonusers and corticosteroid users

|                     | All (N = 10,621) | Nonusers (N = 9,577) | Corticosteroid users (N = 1,044) | p value |
|---------------------|------------------|----------------------|-------------------------------|---------|
| Age, years          | 48.5 (±11.5)     | 48.3 (±11.4)         | 50.2 (±11.7)                  | <0.001  |
| Sex (female)        | 6,187 (58.3)     | 5,549 (57.9)         | 638 (61.1)                    | 0.049   |
| Educational attainment |                 |                      |                               |         |
| Low                 | 3,883 (36.6)     | 3,463 (36.2)         | 420 (40.2)                    |         |
| Middle              | 3,823 (36.0)     | 3,465 (36.2)         | 358 (34.3)                    | 0.076   |
| High                | 2,693 (25.4)     | 2,448 (25.6)         | 245 (23.5)                    |         |
| Other               | 222 (2.1)        | 201 (2.1)            | 21 (2.0)                      |         |
| Smoking             |                  |                      |                               |         |
| Nonsmoker           | 4,081 (38.4)     | 3,638 (38.0)         | 443 (42.4)                    |         |
| Former smoker       | 3,728 (35.1)     | 3,358 (35.1)         | 370 (35.4)                    | 0.001   |
| Current smoker      | 2,812 (26.5)     | 2,581 (26.9)         | 231 (22.1)                    |         |
| Physical activity   |                  |                      |                               |         |
| 0 days/wk           | 421 (4.0)        | 381 (4.0)            | 40 (3.8)                      |         |
| 1–4 days/wk         | 4,477 (42.2)     | 4,041 (42.2)         | 436 (41.8)                    | 0.927   |
| ≥5 days/wk          | 5,723 (53.9)     | 5,155 (53.8)         | 568 (54.4)                    |         |
| BMI, kg/m²           | 26.4 (±4.3)      | 26.3 (±4.2)          | 27.0 (±4.8)                   | <0.001  |
| WC, cm              | 92.1 (±12.1)     | 91.8 (±12.1)         | 94.0 (±12.7)                  | <0.001  |
| MetS                | 2,446 (23.0)     | 2,153 (22.5)         | 293 (28.1)                    | <0.001  |
| Genotype*           |                  |                      |                               |         |
| GR resistant        | 2,162 (20.4)     | 1,937 (20.2)         | 225 (21.6)                    |         |
| GR WT               | 2,286 (21.5)     | 2,046 (21.4)         | 240 (23.0)                    | 0.185   |
| GR hypersensitive   | 6,173 (58.1)     | 5,594 (58.4)         | 579 (55.5)                    |         |

Data are shown as numbers (percentage) and mean (± standard deviation). WC, waist circumference; MetS, metabolic syndrome; GR, glucocorticoid receptor; WT, wild type. *GR resistant group includes participants with 1 or 2 copies of the GR ER22/23EK and/or 9β polymorphisms. GR hypersensitive group includes participants with 1 or 2 copies of the GR BclI and/or N363S polymorphisms.
## Results

### Baseline Characteristics

Descriptive characteristics are shown in Table 1. Corticosteroids were used by 9.8% of the study population. A large proportion of the study population was harboring at least 1 GR hypersensitive variant (58.1%) with no significant differences in the distribution of the different genotypes between corticosteroid users and nonusers ($p = 0.185$). Distribution of the GR variants in nonusers and user groups are depicted in Table 2. The group of users consisted of more women (61.1 vs. 57.9%, $p = 0.049$) and was on average older (50.2 [±11.7] vs. 48.3 [±11.4] years, $p < 0.001$) in comparison to nonusers. Majority was using only local corticosteroids (94.7%) with highest number of users for inhaled ($n = 575$), nasal ($n = 312$), and dermal ($n = 226$) types whereas 55 subjects were using systemic corticosteroids. After excluding 155 multiple-type users, the number and percentage of single-type local corticosteroid use was as follows: 444 (77%) inhaled corticosteroids, 201 (64%) nasal corticosteroids, and 178 (79%) dermal corticosteroids.

### BMI and WC by GR Genotypes in Corticosteroid Users

Differences in BMI and WC between nonusers and users are shown in Figure 1. In the complete group of users, overall corticosteroid use was associated with increased BMI (+0.69 kg/m$^2$ [95% CI, 0.41–0.96]) and WC (+2.11 cm [95% CI, 1.34–2.88], both $p < 0.001$). All 3 genotypes had on average higher BMI and WC when compared to nonusers; however, differences reached only statistical significance in GR WT users (BMI, +0.63 kg/m$^2$ [95% CI, 0.09–1.16], $p = 0.022$; WC, +2.03 cm [95% CI, 0.61–3.44], $p = 0.005$) and GR hypersensitive users (BMI, +0.66 kg/m$^2$ [95% CI, 0.31–1.01], $p < 0.001$; WC, +2.06 cm [95% CI, 1.13–2.98], $p < 0.001$).

No significant differences were found in systemic type users regarding BMI; however, GR WT users had an increased WC (+6.55 cm [95% CI, 1.16–11.94], $p = 0.017$) in comparison to nonusers. In the combined group of users of locally applied corticosteroids, only participants with GC hypersensitive variants had higher BMI (+0.72 kg/m$^2$ [95% CI, 0.36–1.08], $p < 0.001$), whereas all 3 genotypes had increased WC as compared to nonusers (GR resistant, +1.67 cm [95% CI, 0.16–3.17], $p = 0.030$; WT, +1.71 cm [95% CI, 0.24–3.17], $p = 0.022$; GR hypersensitive, +2.18 cm [95% CI, 1.24–3.13], $p < 0.001$).

Stratification for single-type users showed that differences were mainly due to inhaled corticosteroid use. BMI

### Table 2. Distribution of the GR variants in nonusers and corticosteroid user groups

| Genotype | First allele | Second allele | Overall users (N = 1,044) | Nonusers (N = 9,577) | Local users (N = 989) | Inhaled types only (N = 444) | Nasal types only (N = 201) | Dermal types only (N = 178) |
|----------|--------------|---------------|---------------------------|----------------------|-------------------------|----------------------------|--------------------------|--------------------------|
| GR resistant | WT | ER22/23EK | 1,404 14.7 | 151 14.5 | 11 10.0 | 200 20.0 | 45 4.4 | 20 2.0 |
| GR WT | WT | WT | 2,046 21.4 | 240 23.0 | 16 15.4 | 380 38.4 | 38 3.8 | 20 2.0 |
| GR hypersensitive | WT | WT | 2,046 21.4 | 240 23.0 | 16 15.4 | 380 38.4 | 38 3.8 | 20 2.0 |

GR, glucocorticoid receptor; WT, wild-type glucocorticoid receptor genotype.

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Corticosteroid Use and Glucocorticoid Receptor

was only significantly increased in inhaled-type users with GR WT (+1.17 kg/m² [95% CI, 0.34–1.99], p = 0.005) and GR hypersensitive genotypes (+1.69 kg/m² [95% CI, 1.16–2.11], p < 0.001) and not in GR resistant users (+0.60 kg/m² [95% CI, −0.24–1.45], p = 0.163). WC was however higher in users of each GR genotype group when compared to nonusers (GR resistant, +2.34 cm [95% CI, 0.10–4.59], p = 0.040; WT, +3.80 cm [95% CI, 1.62–5.97], p = 0.001; GR hypersensitive genotype, +4.72 cm [95% CI, 3.34–6.11], p < 0.001). No interaction with sex was observed in any of the analyses.

MetS prevalence in the reference group of nonusers (N = 9,577) was 22.5%. Analyses are adjusted for age, sex, educational attainment, smoking, and physical activity. Results in bold indicate statistically significant differences. GR, glucocorticoid receptor; MetS, metabolic syndrome; WT, wild type glucocorticoid receptor genotype; OR, odds ratio. * Excluding individuals with multiple-type use. * p < 0.050.

**Table 3. Association between MetS and corticosteroid use by GR genotype**

| GR resistant users | GR WT users | GR hypersensitive users |
|--------------------|-------------|-------------------------|
| MetS n/N | MetS % | OR | 95% CI | MetS n/N | MetS % | OR | 95% CI | MetS n/N | MetS % | OR | 95% CI |
| Overall users | 61/225 | 27.1 | 1.15 | 0.84–1.58 | 73/240 | 30.4 | **1.44** | **1.07–1.94** | 159/579 | 27.5 | **1.23** | **1.00–1.50** |
| Systemic users | 5/14 | 35.7 | 1.17 | 0.36–3.81 | 8/16 | 50.0 | 2.45 | 0.84–7.21 | 8/25 | 32.0 | 0.99 | 0.40–2.43 |
| Local users | 56/211 | 26.5 | 1.14 | 0.82–1.59 | 65/224 | 29.0 | **1.38** | **1.01–1.88** | 151/554 | 27.3 | **1.24** | **1.01–1.52** |
| Inhaled types | 28/94 | 29.8 | 1.10 | 0.69–1.77 | 34/100 | 34.0 | **1.64** | **1.06–2.55** | 80/250 | 32.0 | **1.43** | **1.08–1.91** |
| Nasal types | 7/40 | 17.5 | 0.86 | 0.37–2.00 | 9/47 | 19.1 | 0.83 | 0.38–1.77 | 23/114 | 20.2 | 1.02 | 0.63–1.63 |
| Dermal types | 7/34 | 20.6 | 0.95 | 0.39–2.28 | 14/47 | 29.8 | 1.63 | 0.83–3.19 | 20/97 | 20.6 | 0.96 | 0.57–1.62 |

**Fig. 1. Differences in BMI and WC between nonusers and corticosteroid users by GR genotype.** Mean differences with the reference group of nonusers of corticosteroids (N = 9,577) are shown in kg/m² (95% CI) for BMI and cm (95% CI) for WC. Analyses are adjusted for age, sex, educational attainment, smoking, and physical activity. Individuals with multiple-type use are excluded for the analyses regarding inhaled, nasal, and dermal corticosteroid use. WC, waist circumference; GR, glucocorticoid receptor.
MetS and Corticosteroid Use by GR Genotype in Corticosteroid Users

Table 3 depicts the findings regarding differences in MetS presence between nonusers and users. MetS was in general more prevalent in corticosteroid users when compared to nonusers (28.1 vs. 22.5%, \( p < 0.001 \)). Within complete group of users, only those with a GR WT genotype (OR 1.44 [95% CI, 1.07–1.94], \( p = 0.017 \)) or GR hypersensitive genotype (OR 1.23 [95% CI, 1.00–1.95], \( p = 0.046 \)) were more likely to have MetS. Similar outcome was also observed in the combined local corticosteroid group, whereas no significant association was found in systemic-type users. With respect to the former group, only inhaled corticosteroid use was linked to higher prevalence of MetS with GR WT and GR hypersensitive users being, respectively, 1.64 (95% CI, 1.06–2.55, \( p = 0.027 \)) and 1.43 (95% CI, 1.08–1.91; \( p = 0.013 \)) times more likely to have MetS in comparison to nonusers. There was no significant interaction with sex.

Discussion

In this study, we investigated the relevance of functional polymorphisms of the GR in the association between systemic and local corticosteroid use with cardiometabolic outcomes in the general population. Corticosteroid users, in particular of the inhaled forms, have an increased BMI and WC and are more often burdened with MetS in comparison to nonusers. These differences are significantly evident in users harboring GR polymorphisms associated with GR hypersensitivity (BclI and/or N363S) and WT users, but less in users with GR resistant polymorphisms (i.e., ER22/23EK and/or 9β).

Genomic actions of activated GR are traditionally classified as transactivating or transrepressing. Adverse effects of supraphysiological GC exposure are considered to be mainly due to transactivation whereas the preferred anti-inflammatory response is induced by transrepression [13]. Earlier studies have performed functional assays to assess these GR-dependent effects in leukocytes of individuals with functional GR variants. Transactivation activity was increased with the N363S variant and decreased in case of ER22/23EK polymorphism [14], while the in vitro transrepressational effects were decreased in 9β carriers [15]. These in vitro observations are in line with the differences as observed in the current study with more adverse cardiometabolic effects in GR hypersensitive users of corticosteroids and vice versa in GR resistant users. Interestingly, Eipel and colleagues previously observed that pediatric patients harboring the N363S polymorphism more often developed GC-related hepatotoxicity and glucose abnormalities in the course of acute lymphoblastic leukemia (ALL) treatment [16]. Moreover, previous studies also with pediatric ALL patients showed that BcI carriers were also more likely to develop Cushingoid-like symptoms (e.g., adiposity, hypertension, and diabetes) and depression during treatment with systemic corticosteroids [17], as well as a longer period of adrenal insufficiency after high-dose corticosteroid therapy in homozygous BcI carriers [18].

Supraphysiological exposure to GCs is known to induce lipogenesis and accumulation of central adipocytes conceivably due to the higher presence of GR in visceral area [19]. GCs can additionally increase (high-caloric) food intake [20, 21] and promote redistribution of fat tissue to central regions [22] which could further fuel these changes on adipocyte level. In the current study, we found that overall use of corticosteroids was indeed associated with higher WC but mainly in users with GR WT and GR hypersensitive genotype. This could hint on protective effects of the GR resistant variants on changes in abdominal obesity with corticosteroid use, especially given the previous findings of (tendency to) lower WC in unselected carriers [8, 23]. Our findings in the current study were mainly evident for inhaled corticosteroids and showed nevertheless that also users with GR resistant genotype had significantly higher WC albeit the difference was less pronounced in comparison to other users. It is conceivable that frequent and chronic use of these powerful agents, as would be anticipated in many inhaled type users, and often in combination with systemic corticosteroids would somehow outweigh the potential beneficial effects of GR resistant variants.

Similar differences were also evident with regard to BMI with greatest contrast between nonusers and inhaled corticosteroid users harboring GR hypersensitive variants. In contrast to WC, no significant differences were found for individuals with GR resistant variants. Despite the fact that both anthropometric measures are strongly linked to cardiovascular events [24], WC is, as an estimate for abdominal fat mass, the most important predictor and is in particular of interest in the context of GC effects. Excess of GCs stimulate redistribution of peripheral fat and accumulation of visceral fat by increasing synthesis and storage of lipids and adipose tissue hyperplasia by increasing differentiation of preadipocytes to mature adipocytes [25]. GCs also promote proteolysis in skeletal muscles while inhibiting protein synthesis which together could eventually lead to muscle atrophy [26]. Moreover, GCs also affect bone mineral density through vari-
ous pathways leading to increased osteoclast activity and diminished osteoblast function which ultimately lead to bone loss [27]. This highlights the differential effects of GCs on body composition which can ultimately lead to varying effects regarding BMI. Furthermore, we previously showed that male carriers of the ER22/23EK variant had on average more lean mass and muscle strength [23] which could also contribute to the current observation.

The increased prevalence of MetS in corticosteroid users is in line with our previous observations in the complete cohort population [1]. As shown here, it seems however that this association is only significantly present in users carrying variants linked to GR hypersensitivity or those with a GR WT genotype. We have previously conducted the only study, as far as we know, on the link between GR polymorphisms and MetS in the general population and found increased risk in specific subgroups with the N363S (GR hypersensitive) variant [28]. Other smaller studies have investigated the association between GR variants and cardiometabolic features and demonstrated differences corresponding to altered GR sensitivity [29–31], however findings have not been consistent [5, 32, 33]. Since these studies did not take corticosteroid use into account, and given the relatively high percentage of users, it remains unclear to what extent the differences can be attributed to GR variations.

Contrary to our expectations, the differences in all outcomes between nonusers and users of systemic corticosteroids were highly variable and less consistent. This could largely be due to the small number of systemic corticosteroid users in the current study population (0.5%) and within the total group of users (5.3 vs. 94.7% users of local types). In the group of locally applied corticosteroids, adverse outcomes were only consistently present in users of inhaled types. The majority of the inhaled type only group was using inhalers containing fluticasone (propionate) or budesonide, which are pharmacologically active upon use and are known to have relatively high GR binding affinity and lower protein-binding capacity [34] and thus to be more likely to induce systemic GC-related adverse events when entering circulation. Unfortunately, we have no data regarding the therapeutic effect of corticosteroids in user groups according to GR variants. In studies with selected study populations, however, it was shown that having 2 BclI variants is associated with a better treatment response to inhaled corticosteroids in asthmatic children [35]. Carriers of GR hypersensitive variants were also found to have a better therapeutic response to systemic corticosteroids in ALL [16, 36], inflammatory bowel disease [37], and nephrotic syndrome [38]. The opposite was observed in patients harboring GR resistant ER22/23EK or 9β variants and being treated with systemic corticosteroids [38, 39].

This is the first population-based study to assess cardiometabolic profile in users of systemic as well as local corticosteroid types in relation to GR variations. Among the strengths are the reliable and large-scale data collection on drug use and integrity of data regarding genotyping, BMI, and the MetS components. Since it concerns an observational study design, we cannot exclude residual confounding, despite adjustments for relevant confounders, and are not able to prove causality. Moreover, it remains unknown whether the findings can be extrapolated to other ethnicities given the fact that the study population involves mainly individuals from Caucasian race. Finally, larger longitudinal studies are needed to perform analyses for the separate polymorphisms and to confirm whether in systemic and local corticosteroid use the development of cardiometabolic features but also other clinically relevant GC-related adverse events (e.g., neuropsychiatric conditions) depend on GR variations and/or other factors in the GC pathway.

**Conclusion**

Corticosteroid users, in particular of inhaled corticosteroids, have an increased BMI, WC, and more often MetS in comparison to nonusers. These relationships are significantly evident in carriers of common GR genotypes associated with GR hypersensitivity or the WT genotype, but little to none present in users harboring GR resistant polymorphisms.

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**Statement of Ethics**

The study (reference METc 2007/152) was approved by the Medical Ethics Committee of the University Medical Center Groningen, Groningen, The Netherlands, and informed consent was obtained from participants.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.
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Author Contributions

M.S., V.L.W., J.W.K., E.L.T.v.d.A., and E.F.C.v.R. contributed to the study design and acquisition of data. M.S., V.L.W., J.W.K., and E.F.C.v.R. performed statistical analyses. M.S. and E.F.C.v.R. drafted the manuscript. M.S., V.L.W., B.v.d.V., A.M.I., J.W.K., E.L.T.v.d.A., and E.F.C.v.R. contributed to data interpretation, provided critical revisions, and approved the final version of the manuscript.

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