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

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Keywords
Glucocorticoid receptor · Polymorphisms · Corticosteroids · BMI · Waist circumference · Metabolic syndrome

Abstract
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. ***Methods:*** In this population-based cohort study (Lifelines), we genotyped 10,621 adult participants for GR hypersensitive (1/2 copies *Bcl*I 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. ***Results:*** Overall corticosteroid use was associated with a significantly higher BMI and WC in GR wild-type (WT) users (BMI, +0.63 kg/m^2 [0.09–1.16], $p = 0.022$; WC, +2.03 cm [0.61–3.44], $p = 0.005$) and GR hypersensitive (BMI, +0.66 kg/m^2 [95% CI, 0.31–1.01]; WC, +2.06 cm [1.13–2.98], both $p < 0.001$) 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], $p = 0.017$) and GR hypersensitives (OR 1.23 [95% CI, 1.00–1.50], $p = 0.046$) were more likely to have MetS; even more pronounced in only inhaled corticosteroid users (GR WT users, OR 1.64 [1.06–2.55], $p = 0.027$; GR hypersensitive users, OR 1.43 [1.08–1.91], $p = 0.013$). ***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.

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

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[1], which could be explained by the high effectiveness and applicability of corticosteroids in extensive number of illnesses. Unfortunately, use of corticosteroids is also accompanied with widespread adverse effects. These adverse effects are especially observed with use of systemic corticosteroids due to their high systemic availability. Corticosteroid users have reported to suffer mainly from weight gain and neuropsychiatric changes [2], which are also frequently observed in patients with Cushing's syndrome. There is however increasing evidence that local corticosteroids can also induce systemic adverse effects. A large meta-analysis including users of corticosteroids showed that use of local forms, particularly of the inhaled formulations, also have increased risk of developing adrenal insufficiency [3].

The mode of action of corticosteroids does, however, not only depends on the amount of exposure but also on conditions at cellular level. An essential role in the pathway of glucocorticoid (GC) action is reserved for the glucocorticoid receptor (GR). Various GR polymorphisms have been reported of which some functional variants have extensively been investigated and shown to be associated with altered GC sensitivity [4]. In vivo as well as clinical studies assessing these have suggested that the intronic *Bcl*I variant and the N363S variant, the latter leading to a missense mutation in exon 2, are associated with increased GC sensitivity [5, 6]. On the other hand, the ER22/23EK and the 9β polymorphisms have been linked to GC resistance with carriers having, for instance, less cortisol suppression after dexamethasone administration [7] and smaller waist circumference (WC) in comparison to noncarriers [8].

These GR 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 multi-morbidity 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, non-reliable 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: *Bcl*I, rs41423247; N363S, rs56149945; ER22/23EK, rs 6189 and 6190; and GR9β, rs6198. Users of corticosteroids were based on their genotype classified as either GR resistants (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 *Bcl*I 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/m^2). 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/

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/m^2	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 *Bcl*I and/or N363S polymorphisms.

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 χ^2 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 2. Distribution of the GR variants in nonusers and corticosteroid user groups

Genotype	First allele	Second allele	Nonusers (N = 9,577)		Overall users (N = 1,044)		Systemic users (N = 55)		Local users (N = 989)		Inhaled types only (N = 444)		Nasal types only (N = 201)		Dermal types only (N = 178)	
			n	%	*N*	%	*n*	%	*n*	%	*N*	%	*n*	%	*n*	%
GR resistant	WT	ER22/23EK	200	2.1	38	3.6	0	0.0	38	3.8	20	4.5	4	2.0	7	3.9
	WT	9β	1,404	14.7	151	14.5	11	20.0	140	14.2	57	12.8	28	13.9	23	12.9
	ER22/23EK	ER22/23EK	9	0.1	5	0.5	1	1.8	4	0.4	1	0.2	0	0.0	1	0.6
	ER22/23EK	9β	92	1.0	13	1.2	1	1.8	12	1.2	6	1.4	4	2.0	1	0.6
	9β	9β	232	2.4	18	1.7	1	1.8	17	1.7	10	2.3	4	2.0	2	1.1
GR WT	WT	WT	2,046	21.4	240	23.0	16	29.1	224	22.6	100	22.5	47	23.4	47	26.4
GR hypersensitive	WT	*BclI*	3,490	36.4	348	33.3	16	29.1	332	33.6	142	32.0	67	33.3	63	35.4
	WT	N363S	341	3.6	32	3.1	1	1.8	31	3.1	16	3.6	7	3.5	4	2.2
	BclI	*BclI*	1,495	15.6	166	15.9	7	12.7	159	16.1	75	16.9	36	17.9	23	12.9
	BclI	N363S	263	2.7	31	3.0	1	1.8	30	3.0	15	3.4	4	2.0	7	3.9
	N363S	N363S	5	0.1	2	0.2	0	0.0	2	0.2	2	0.5	0	0.0	0	0.0

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

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 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[a]	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[a]	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[a]	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

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. [a] Excluding individuals with multiple-type use. * $p < 0.050$.

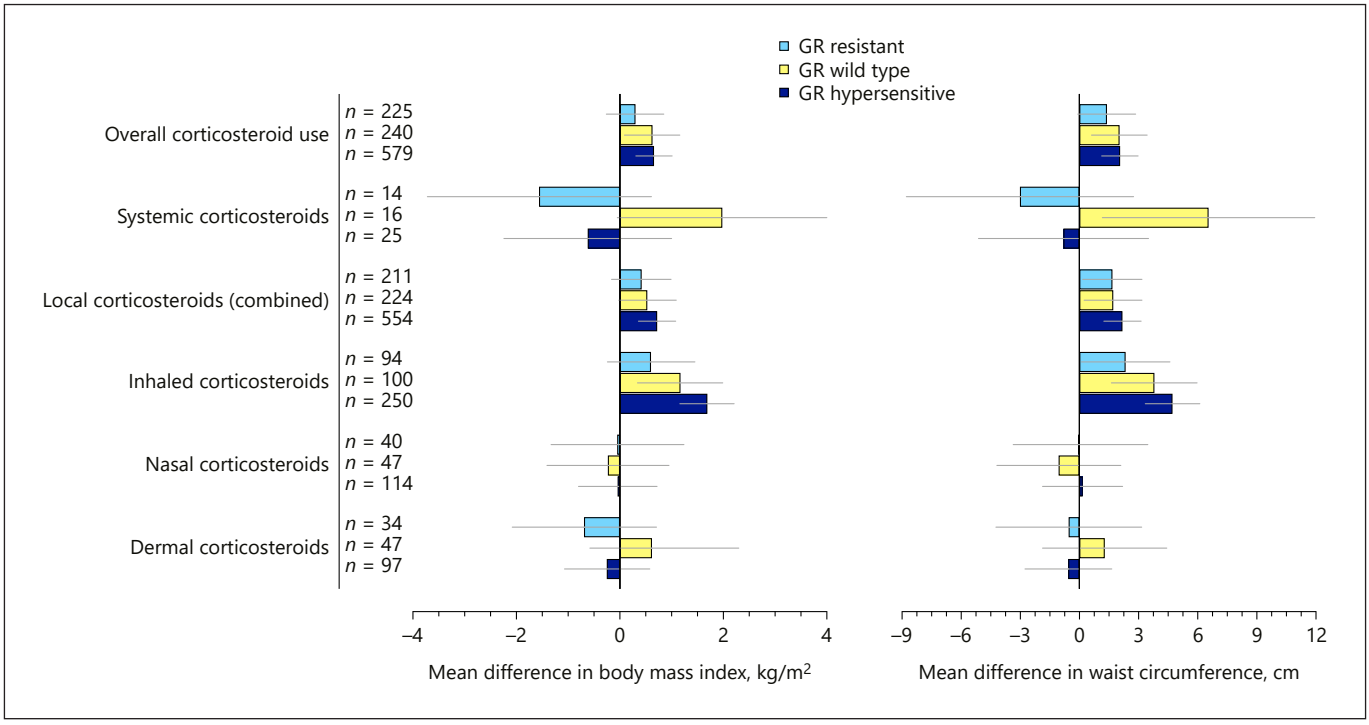

Fig. 1. Differences in BMI and WC between nonusers and corticosteroid users by GR genotype. Mean differences with the reference group of nonusers of corticosteroids (N = 9,577) are shown in kg/m^2 (95% CI) for BMI and cm (95% CI) for WC. Analyses are adjusted for age, sex, educational attainment, smoking, 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.

was only significantly increased in inhaled-type users with GR WT (+1.17 kg/m^2 [95% CI, 0.34–1.99], p = 0.005) and GR hypersensitive genotypes (+1.69 kg/m^2 [95% CI, 1.16–1.21], $p < 0.001$) and not in GR resistant users (+0.60 kg/m^2 [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 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 (*Bcl*I 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. Transactivational activity was increased with the N363S variant and decreased in case of ER22/23EK polymorphism [14], while the in vitro transrepressional 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 *Bcl*I 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 *Bcl*I 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 *Bcl*I 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.

References

1 Savas M, Muka T, Wester VL, van den Akker ELT, Visser JA, Braunstahl GJ, et al. Associations between systemic and local corticosteroid use with metabolic syndrome and body mass index. J Clin Endocrinol Metab. 2017 Oct 01;102(10):3765–74.
2 Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006 Jun 15;55(3):420–6.
3 Broersen LH, Pereira AM, Jørgensen JO, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metab. 2015 Jun; 100(6):2171–80.
4 Savas M, van Rossum EFC. Impact of glucocorticoid receptor polymorphisms on glucocorticoid action. Reference module in biomedical sciences. Elsevier: 2018.
5 Huizenga NA, Koper JW, De Lange P, Pols HA, Stolk RP, Burger H, et al. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. J Clin Endocrinol Metab. 1998 Jan;83(1):144–51.
6 van Rossum EF, Koper JW, van den Beld AW, Uitterlinden AG, Arp P, Ester W, et al. Identification of the BclI polymorphism in the glucocorticoid receptor gene: association with sensitivity to glucocorticoids in vivo and body mass index. Clin Endocrinol. 2003 Nov;59(5): 585–92.
7 van Rossum EF, Koper JW, Huizenga NA, Uitterlinden AG, Janssen JA, Brinkmann AO, et al. A polymorphism in the glucocorticoid receptor gene, which decreases sensitivity to glucocorticoids in vivo, is associated with low insulin and cholesterol levels. Diabetes. 2002 Oct;51(10):3128–34.
8 Syed AA, Irving JA, Redfern CP, Hall AG, Unwin NC, White M, et al. Association of glucocorticoid receptor polymorphism A3669G in exon 9beta with reduced central adiposity in women. Obesity. 2006 May;14(5):759–64.
9 van Rossum EF, Lamberts SW. Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. Recent Prog Horm Res. 2004;59:333–57.
10 Savas M, Vinkers C, Rosmalen J, Hartman C, Wester VL, van den Akker ELT, et al. Systemic and local corticosteroid use is associated with reduced executive cognition, and mood and anxiety disorders. Neuroendocrinology. 2019 Jun 21;110(3–4):282–91.
11 Stolk RP, Rosmalen JG, Postma DS, de Boer RA, Navis G, Slaets JP, et al. Universal risk factors for multifactorial diseases: lifelines: a three-generation population-based study. Eur J Epidemiol. 2008;23(1):67–74.
12 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; World heart federation; international atherosclerosis society; and International association for the study of obesity. Circulation. 2009 Oct 20; 120(16):1640–5.
13 Stahn C, Löwenberg M, Hommes DW, Buttgereit F. Molecular mechanisms of glucocorticoid action and selective glucocorticoid receptor agonists. Mol Cell Endocrinol. 2007 Sep 15;275(1–2):71–8.
14 Russcher H, Smit P, van den Akker EL, van Rossum EF, Brinkmann AO, de Jong FH, et al. Two polymorphisms in the glucocorticoid receptor gene directly affect glucocorticoid-regulated gene expression. J Clin Endocrinol Metab. 2005 Oct;90(10):5804–10.
15 van den Akker EL, Russcher H, van Rossum EF, Brinkmann AO, de Jong FH, Hokken A, et al. Glucocorticoid receptor polymorphism affects transrepression but not transactivation. J Clin Endocrinol Metab. 2006 Jul;91(7): 2800–3.
16 Eipel OT, Németh K, Török D, Csordás K, Hegyi M, Ponyi A, et al. The glucocorticoid receptor gene polymorphism N363S predisposes to more severe toxic side effects during pediatric acute lymphoblastic leukemia (ALL) therapy. Int J Hematol. 2013 Feb;97(2):216–22.
17 Kaymak Cihan M, Karabulut HG, Yürür Kutlay N, Ilgın Ruhi H, Tükün A, Olcay L. Association between N363S and BclI polymorphisms of the glucocorticoid receptor gene (NR3C1) and glucocorticoid side effects during childhood acute lymphoblastic leukemia treatment. Turk J Haematol. 2017 Jun 5;34(2): 151–8.
18 de Ruiter RD, Gordijn MS, Gemke RJ, van den Bos C, Bierings MB, Rotteveel J, et al. Adrenal insufficiency during treatment for childhood acute lymphoblastic leukemia is associated with glucocorticoid receptor polymorphisms ER22/23EK and BclI. Haematologica. 2014 Aug;99(8):e136–7.
19 Marin P, Bjorntorp P. Endocrine-metabolic pattern and adipose tissue distribution. Horm Res. 1993;39(Suppl 3):81–5.
20 Epel E, Lapidus R, McEwen B, Brownell K. Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. Psychoneuroendocrinology. 2001 Jan;26(1):37–49.
21 Udden J, Bjorntorp P, Arner P, Barkeling B, Meurling L, Rossner S. Effects of glucocorticoids on leptin levels and eating behaviour in women. J Intern Med. 2003 Feb;253(2):225–31.
22 Rebuffe-Scrive M, Krotkiewski M, Elfverson J, Bjorntorp P. Muscle and adipose tissue morphology and metabolism in cushing's syndrome. J Clin Endocrinol Metab. 1988 Dec;67(6):1122–8.
23 van Rossum EF, Voorhoeve PG, te Velde SJ, Koper JW, Delemarre-van de Waal HA, Kemper HC, et al. The ER22/23EK polymorphism in the glucocorticoid receptor gene is associated with a beneficial body composition and muscle strength in young adults. J Clin Endocrinol Metab. 2004 Aug;89(8):4004–9.
24 Flint AJ, Rexrode KM, Hu FB, Glynn RJ, Caspard H, Manson JE, et al. Body mass index, waist circumference, and risk of coronary heart disease: a prospective study among men and women. Obes Res Clin Pract. 2010 Jul; 4(3):e163–246.
25 Fardet L, Fève B. Systemic glucocorticoid therapy: a review of its metabolic and cardiovascular adverse events. Drugs. 2014 Oct; 74(15):1731–45.

26 Salehian B, Kejriwal K. Glucocorticoid-induced muscle atrophy: mechanisms and therapeutic strategies. Endocr Pract. 1999 Sep–Oct;5(5):277–81.
27 Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002 Oct;96(1):23–43.
28 Wester VL, Koper JW, van den Akker EL, Franco OH, Stolk RP, van Rossum EF. Glucocorticoid receptor haplotype and metabolic syndrome: the lifelines cohort study. Eur J Endocrinol. 2016 Dec;175(6):645–51.
29 Weaver JU, Hitman GA, Kopelman PG. An association between a Bc1I restriction fragment length polymorphism of the glucocorticoid receptor locus and hyperinsulinaemia in obese women. J Mol Endocrinol. 1992 Dec;9(3):295–300.
30 Lin RC, Wang XL, Morris BJ. Association of coronary artery disease with glucocorticoid receptor N363S variant. Hypertension. 2003 Mar;41(3):404–7.
31 Srivastava N, Prakash J, Lakhan R, Agarwal CG, Pant DC, Mittal B. Influence of Bcl-1 gene polymorphism of glucocorticoid receptor gene (NR3C1, rs41423247) on blood pressure, glucose in Northern Indians. Indian J Clin Biochem. 2011 Apr;26(2):125–30.
32 Di Blasio AM, van Rossum EF, Maestrini S, Berselli ME, Tagliaferri M, Podestà F, et al. The relation between two polymorphisms in the glucocorticoid receptor gene and body mass index, blood pressure and cholesterol in obese patients. Clin Endocrinol. 2003 Jul;59(1):68–74.
33 Mora M, Sánchez L, Serra-Prat M, Palomera E, Blanco J, Aranda G, et al. Hormonal determinants and effect of ER22/23EK glucocorticoid receptor gene polymorphism on health status deterioration in the participants of the Mataró Ageing Study. Age. 2012 Jun;34(3):553–61.
34 Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. Eur Respir J. 2006 Nov;28(5):1042–50.
35 Keskin O, Uluca Ü, Birben E, Coşkun Y, Ozkars MY, Keskin M, et al. Genetic associations of the response to inhaled corticosteroids in children during an asthma exacerbation. Pediatr Allergy Immunol. 2016 Aug;27(5):507–13.
36 Xue L, Li C, Wang Y, Sun W, Ma C, He Y, et al. Single nucleotide polymorphisms in noncoding region of the glucocorticoid receptor gene and prednisone response in childhood acute lymphoblastic leukemia. Leuk Lymphoma. 2015 Jun;56(6):1704–9.
37 De Iudicibus S, Stocco G, Martelossi S, Drigo I, Norbedo S, Lionetti P, et al. Association of BclI polymorphism of the glucocorticoid receptor gene locus with response to glucocorticoids in inflammatory bowel disease. Gut. 2007 Sep;56(9):1319–20.
38 Teeninga N, Kist-van Holthe JE, van den Akker EL, Kersten MC, Boersma E, Krabbe HG, et al. Genetic and in vivo determinants of glucocorticoid sensitivity in relation to clinical outcome of childhood nephrotic syndrome. Kidney Int. 2014 Jun;85(6):1444–53.
39 Krupoves A, Mack D, Deslandres C, Seidman E, Amre DK. Variation in the glucocorticoid receptor gene (NR3C1) may be associated with corticosteroid dependency and resistance in children with Crohn's disease. Pharmacogenet Genomics. 2011 Aug;21(8):454–60.