Long term systemic glucocorticoid therapy and weight gain: a population-based cohort study

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Competing interests: No authors have any competing interests
Potential conflicts of interest: no reported conflicts
Funding: no funding was received for this work
Short title: glucocorticoids, weight and metabolic disorders
Key words: glucocorticoids; weight; diabetes; dyslipidemia; population-based

ABSTRACT

Background: The effects of systemic glucocorticoids on weight have been relatively neglected. The aims of this study were to describe weight variations in people chronically exposed to systemic glucocorticoids, and to search for risk factors for glucocorticoid-induced weight gain.
Methods and findings: Data recorded in the British database The Health Improvement Network (THIN) were analyzed. The study population included 31,516 adults prescribed systemic glucocorticoids for at least 3 months at a mean dosage ≥ 10 mg/day (women: 56.6%, mean age: 67±15 years), and 26,967 controls. Weight measurements recorded within the three years before glucocorticoid initiation and during exposure were analyzed. Risk factors for glucocorticoid-induced weight gain ≥ 10% of the usual weight were assessed. In the exposed population, weight variations were very different according sex and age. Younger women were those who put more weigh on glucocorticoids. The mean of the maximal weight gain in 18-39 year-old women chronically exposed to systemic glucocorticoids was 3.6±8.6 kg, while during the same period of time it was 2±7.3 kg in the control group (absolute mean difference: 1.6 kg 95%CI [0.9- 2.2], $p<0.001$). Weight gain ≥ 10% of the usual weight was observed in 10.2% (n=3,208) of those chronically exposed to systemic glucocorticoids. Women, young and deprived people, those previously exposed to systemic glucocorticoids, and those exposed to the highest dosage were at higher risk while the risk was lower in people prescribed glucocorticoids for an inflammatory condition (e.g., rheumatoid arthritis) by comparison to asthma or COPD, and inversely associated with the usual weight.

Conclusion: Taking into account usual weight rather than weight just before glucocorticoid initiation and the natural history of weight variations, the amount of weight gain induced by systemic glucocorticoids is lower than usually thought. Only 10% of patients gained more than 10% of their usual weight. These results could be reassuring for patients.

Since 1948-1949 and their first successful use on arthritic patients, cortisone and synthetic glucocorticoids have been the cornerstone in the treatment of many inflammatory, allergic and neoplastic diseases. Nowadays, glucocorticoids are among the most prescribed drugs. In France, it has recently been estimated that up to 17% of the general population is exposed at least once a year to systemic glucocorticoids (1). In Europe and in the USA, it has been evidenced that 1-2% of the general population is chronically exposed to systemic glucocorticoids (1-4). If the efficacy of this treatment is rapid and obvious for many treated conditions, their use is often limited by the frequent occurrence of adverse events, in particular in individuals exposed to the higher dosages and for the longer periods of time. Glucocorticoids are among the drugs most commonly associated with hospitalizations for adverse drug events (5). Weight gain is among the most feared complications of glucocorticoids, both by patients and physicians. It is associated with strong beliefs about the drug being unsafe and with a poor adherence to the drug (6-13). This is likely to explain why information most sought by glucocorticoid-treated patients is related to the effects of glucocorticoids on weight and to the recommended diet (14).

However, to date, the effects of glucocorticoids on weight gain have been relatively neglected, and there are questions on what proportion of the observed weight gain is explain by the treatment or by a better control of the disease activity (15). Further, there are very few studies focusing on the amount of weight gain and the risk factors for glucocorticoid-induced weight gain are surprisingly unknown. For instance, it is unclear whether effects on body weight are uniform across different populations or conditions (16). The aims of this population-based study were to describe weight variations in people chronically exposed to systemic glucocorticoid therapy, and to search for risk factors for glucocorticoid-induced weight gain.

MATERIEL AND METHODS

1- Data source: The Health Improvement Network (THIN)

Approximately 98% of the population in the UK is registered with a general practitioner. THIN is a database of anonymised electronic medical records from UK general practices. Participating general practitioners systematically and prospectively retrieve and enter clinical information on patients, including prescriptions and demographic, clinical and biological data, so that the database provides a longitudinal medical record for each patient. THIN is representative of the UK population. All sections of the population are represented in THIN. Comparisons to external statistics and other independent studies have shown that both the clinical diagnostic and prescribing information is well recorded and accurate (17,18). The data are collected in a non-interventional way during the routine general practice and therefore reflect "real life" clinical care. The information is continually updated. Prescribing is well recorded in terms of general practitioner prescriptions since the computerized entry made by the doctor is also used to issue a prescription to the patient. To minimize any bias on disease occurrence and/or prescriptions issued, we restricted our analyses to high quality data by using quality indicators (e.g., Acceptable Mortality Reporting) defined elsewhere (19,20). We exclude patients with less than one year of follow-up after registration. We also excluded events and prescriptions that happened within six months following registration with the general practice as this may represent retrospective recording of a past history rather than a new episode of a problem (21). To date, THIN includes data from almost 700 general practices and more than 12 million individuals. For this study, we used data up to 31 December 2016 from all general practices that contributed to the database during this period.

2- Identification of the long term glucocorticoid exposed group

In THIN, each prescription of a drug is recorded as encrypted codes referenced to the relevant chapter in the *British National Formulary*. We selected all synthetic glucocorticoids prescribed orally and this included prednisolone, prednisone, dexamethasone, triamcinolone, betamethasone, methylprednisolone and deflazacort. We included people aged 18 years and older and identified all who were prescribed such treatment for at least 3 months (at least 2 glucocorticoid prescriptions during the first 3 months of exposure) at a mean dosage over the first 3 months of exposure ≥ 10 mg/day. In the case of multiple consecutive prescriptions, we considered that the prescriptions were part of a single course of therapy if there was a gap of less than three months between two consecutive prescriptions. The start of glucocorticoid therapy was defined as the day of the first prescription. The end was defined as the last day of the last prescription. This was derived from two variables available in the database, total number of pills prescribed and number of pills that have to be taken per day. We calculated the average daily dosage during a period of time by multiplying the number of pills prescribed by the dose/pill (calculated in prednisone-equivalent) and this was then divided by the number of days during the period of interest. The medical diagnosis recorded on the date of starting glucocorticoids was used as the indication for the glucocorticoid prescription. If there was no medical diagnosis recorded on this date, we searched for seven relevant chronic conditions (i.e., asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, inflammatory bowel disease, polymyalgia rheumatica/giant cell arteritis (PMR/GCA), connective tissue diseases (lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis or undifferentiated connective tissue disease) or cancer) entered on the records one year prior or one year after this prescription.

3- Identification of the control group

The control group was defined to describe natural weight variations in people differing from the exposed population mainly by duration of the glucocorticoid exposure. Therefore, the control group was made of individuals suffering from the same underlying diseases as those chronically exposed to systemic glucocorticoids (i.e. asthma, COPD, rheumatoid arthritis, inflammatory bowel disease, PMR/GCA, connective tissue diseases or cancer), exposed at least once to systemic glucocorticoids (in order to select diseases as similar as possible in term of severity), but never exposed to the drug for more than 30 days. For each control individual, a randomly selected 'index date' was defined after the last exposure to systemic glucocorticoid in order to make sure that the control individuals were not exposed to systemic glucocorticoids during the analysis period. When selecting the control group we stratified the samples in term of general practice, sex and age at 'index date' (within five years age bands) to ensure the distribution was similar to the long-term exposed group. Up to one control individual was selected for every long-term exposed individual.

4- Weight

Weight measurements recorded within the three years before glucocorticoid initiation (or before 'index date' for the control group) and during exposure (up to one year after start of exposure) were extracted for each individual included in the exposed and control groups. Four periods of time were defined *before* glucocorticoid initiation (or the 'index date'): from year 3 to year 2 (period 1), from year 2 to year 1 (period 2), from year 1 to month 3 (period 3), from month 3 to day 0 (period 4). Four periods of time were defined *after* glucocorticoid initiation: from day 1 to month 3 (period 5), from month 4 to month 6 (period 6), from month 7 to month 9 (period 7), and from month 10 to month 12 (period 8). In the cases of several available data during a period of interest, means were calculated and used in the analyses.

5- Statistical analysis

Weight variations were described both in the long-term glucocorticoid-exposed people and in the control population, first in the overall population and second in age and sex subgroups. In a second step, multivariable Cox proportional hazard models were used to assess risk factors for glucocorticoid-induced significant weight gain defined as the weight on glucocorticoids ≥ 10% of the usual weight. Since an exacerbation of the underlying condition may have induced unusual weight variations just before glucocorticoid initiation, the usual weight was defined as the mean of weights measured between 3 years and 3 months *before* glucocorticoid initiation. Sensitivity analyses were performed by defining weight gain as weight gain ≥ 2 kg or weight gain ≥ 5 kg on glucocorticoids by comparison to usual weight. The variables included in the models were: sex, age and smoking status at glucocorticoid initiation, Townsend deprivation index (in quintiles), the underlying condition, usual weight (in quartiles), overall mean daily glucocorticoid dosage at time of outcome (i.e., weight gain ≥ 10% of usual weight, end of exposure or end of follow-up) (in quartiles), type of glucocorticoid, previous short term systemic glucocorticoid exposure, concomitant use of other immunosuppressants (i.e., methotrexate, azathioprine, ciclosporin, cyclophosphamide, or mycophenolate mofetil). Categorical variables are presented as number (proportions). Continuous variables are presented as mean ± standard deviation. The proportional-hazard assumption for Cox models was checked graphically using the Schoenfeld residuals. No interaction term was included in the models. All statistical tests were two-sided. A p-value of <0.05 was considered statistically significant. All analyses were done using Stata, version 15.1. The THIN scheme for obtaining and providing anonymous patient data to researchers was approved by the National Health Service South-East Multicenter Research Ethics Committee (MREC) in 2002. The present study was approved by UCL THIN steering committee and by the THIN scientific review committee (number 18THIN081).

RESULTS

1- Study population

Overall, 96,592 patients received at least one long-term systemic glucocorticoid course at mean dosage over the first 3 months of exposure ≥ 10 mg/day (women: 56.5%, age: 65 ± 16 years). Weight measurement was available both before and after glucocorticoid initiation in 31,516 (32.6%) of them. These patients were considered in the chronically exposed group (**Table 1**).

75,408 individuals (women: 57.3%, age: 63 ± 16 years) were selected in the group of patients with the same underlying condition as the chronically exposed patients but not exposed for systemic glucocorticoids for more than 30 days. Weight measurement was available both before and after 'index date' in 26,967 (35.8%) of them. These patients were included in the control group (**Table 1**).

2- Weight variations

Weight variations in the chronically exposed group and in the control group are reported in **Figure 1**. Among those chronically exposed to systemic glucocorticoids, the maximal weight on glucocorticoids was equal or lower than the maximal weight before exposure in 14,189 (45.0%) patients, higher of less than 2 kg in 4,852 (15.4%) patients, and higher of more than 2 kg in 12,475 (39.6%) patients. Further, there were strong differences according sex and age (**Figure 2**). Younger women were those who put more weigh on glucocorticoids while people over 70 year-old returned to their usual weight without extra weight gain. The mean of the maximal weight gain in 18-39 year-old women chronically exposed to systemic glucocorticoids was 3.6±8.6 kg, while during the same period of time it was 2±7.3 kg in the control group

(absolute mean difference: 1.6 kg 95%CI [0.9- 2.2], p<0.001). The absolute mean differences were 2 [0.6-3.4] kg (p=0.005) in 18-39 year old men, 1.5 [1.2-1.7] (p<0.001) in 40-69 year-old women, 0.5 [0.2-0.7] (p=0.003) in 40-69 year-old men, 0.8 [0.6-1] (p<0.001) in ≥ 70 year-old women, and -0.1 [-0.4 – 0.1] (p=0.28) in ≥ 70 year-old men.

3- Risk factors for weight gain

Among the 31,516 patients chronically exposed to systemic glucocorticoids with available weight measurement before and after glucocorticoid initiation, 3,208 (10.2%) gained 10% or more of their usual weight during glucocorticoid exposure. The risk factors for gaining ≥10% of the usual weight during glucocorticoid exposure are reported in **Table 2**. Women, young and deprived people, those who smoke and those previously exposed to systemic glucocorticoids were at higher risk. The risk of significant weight gain was also positively associated with the overall mean glucocorticoid dosage. On the other hand, the risk was lower in people prescribed systemic glucocorticoids for an inflammatory condition (e.g., PMR/GCA, rheumatoid arthritis, inflammatory bowel disease, connective tissue disease) by comparison to asthma or COPD. It was also inversely associated with the usual weight. Sensitivity analyses taken into account a weight gain ≥ 2 kg or ≥ 5 kg rather than ≥ 10% of the usual weight showed similar results, except for usual weight: those with the higher usual weight was at higher risk of gaining more than 5 kg by comparison to those with lower usual weight (**Supplementary Tables 1 and 2**). Further, the strengths of the associations were overall lower when glucocorticoid-induced weight gain was defined as + 5 kg rather as ≥ 10% of usual weight, and even lower was it was defined as + 2 kg, reinforcing the role of the evidenced risk factors for glucocorticoid-induced weight gain.

DISCUSSION

This population-based cohort study confirms that a chronic exposure to high dose systemic glucocorticoid therapy is associated with a significant weight gain, in particular in young women. However, when taking into account usual weight (rather of weight just before glucocorticoid initiation) and the natural history of weight variations (by taking into account weight variations in unexposed individuals), the amount of weight gain is lower than usually thought: the absolute maximal difference is only 1.6 [0.9- 2.2] kg in young women, and only 10% of those with available weight measurements gained more than 10% of their usual weight. These results could be reassuring for patients.

Most data available regarding weight gain in adults chronically exposed to systemic glucocorticoids is issued from cross-sectional studies and is mainly declarative. In these studies, weight gain is reported by 20 to 80% of subjects (12,13,22,23). Few data are issued from prospective studies. In a prospective cohort study of 157 patients with Wegener's granulomatosis receiving long-term, high dose glucocorticoid therapy, the mean weight gain at one year was 3.9 ± 6.9 kg, representing a 4.4% increase from the mean baseline weight. Thirty-eight (24%) patients gained ≥ 10 kg (i.e., 13.5% increases over the baseline weight) during the first year of treatment (24). In a prospective cohort study of 80 patients initiating long-term systemic glucocorticoid therapy ≥ 20 mg/day, 49% reported weight gain ≥ 3 kg over the first 3 months of exposure (13). Noteworthy, the baseline weight taken into account in these studies was the weight at enrollment, i.e., hypothetically an abnormal low weight because of activity of the underlying condition.

Regarding risk factors, cross-sectional studies have evidenced a positive association between weight gain and glucocorticoid dosage or duration (12,23). Women and younger individuals were also found to be at higher risk in a cross-sectional study of 820 patients (12). In the prospective cohort of Wung et al (157 patients with Wegener's granulomatosis), new diagnosis

of Wegener's granulomatosis was the only significant risk factor for weight gain ≥ 10 kg (24). Sex, age, and baseline weight were not predictive of such weight gain. As a comparison, it has been showed that women were at higher risk of weight gain in 481 patients with endogenous Cushing's syndrome (25). In the present study, we further found that smokers and ex-smokers were at higher risk of weight gain (this was also found in the study by Wung et al (24), where those with no history of smoking tended to be at lower risk, OR: 0.3 [0.1-1.0], p=0.06). Changes of habits at time of glucocorticoid initiation (i.e., underlying condition exacerbation) with smoking cessation for instance may be hypothesized. We also found a quite linear association between deprivation increase and the risk of weight gain. This can probably be explained by different lifestyle habits, the more deprived patients having overall least healthy lifestyle (e.g., poor diet, low physical activity) (26). We also found that people receiving glucocorticoids for a systemic inflammatory condition were a lower risk of significant weight gain than those with conditions usually not associated with systemic inflammation. This is not easily explainable, even though inflammation may modulate glucocorticoids action by promoting their liberation from their binding protein, and therefore their access to target cells, or, hypothetically, may modulate their genomic actions (27).

This study has several important strengths. First, it is one of the first available studies focussing on incidence and risk factors for weight gain in individuals exposed to long-term, high dose, systemic glucocorticoids. It evidenced that the amount of weight gain directly attributed to glucocorticoids may be lower than previously thought, and that clinically significant weight gain concerns only 10% of patients. This would probably be important information for patients. Second, the question has been raised of whether observed weight gain in glucocorticoid-exposed patients was an adverse event of the treatment or was explained by a better control of the disease activity (15,24). Our results evidenced that there is indeed a weight decrease just before glucocorticoid initiation, probably because of the underlying condition activity.

Therefore, we suggest that further studies on this topic should define reference weight as the weight months before glucocorticoid initiation rather than the weight at glucocorticoid initiation. Third, our study identified at-risk patients who should be particularly targeted for weight gain prevention (e.g., dietary habits, increased physical exercise), even though the best prevention of weight gain is unknown to date (28).

However, it has also limitations. First, only one third of potentially includable patients had weight measurements available both before and after glucocorticoid initiation (weight may have been measured but not recorded in the patient's medical file). Therefore, the generalisability of the results is unknown. Second, there was no data available in the patients' medical file regarding important covariables such as diet or physical activity. Therefore, the impact of these parameters could not be assessed, even though they were probably indirectly taken into account in the Townsend deprivation index. Third, in many circumstances, weight variations are mainly explained by adipose tissue modifications. However, glucocorticoid-treated patients, in particular the older ones, are at increased risk of muscle loss and osteoporosis. Since we did not have data about associated myopathy or osteoporosis, the older individuals may have had an increase of adiposity compensated by muscle or bone loss. Lastly, this study is about weight gain and did not study lipodystrophy (e.g., moon face, buffalo neck) which occurs in up to two thirds of patients chronically exposed to glucocorticoids and is not always associated with weight gain (29,30). Weight gain and lipodystrophy are often confused by patients, and even by physicians. Patients should be informed that a visible and anaesthetic lipodystrophy may develop outside any significant weight gain.

In conclusion, this study tends to put into perspective the amount of weight gain induce by long term gluococorticoid exposure. This could be reassuring for patients who consider weight gain as the most worrisome glucocorticoid-induced adverse event. Young and deprived women should be particularly targeted for weight gain prevention. Further studies should be conduct to

confirm these results. Data on mechanisms or prevention of gluococorticoid-induced weight gain would also be of interest.

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Figure 1: Weight variations over time in the study populations

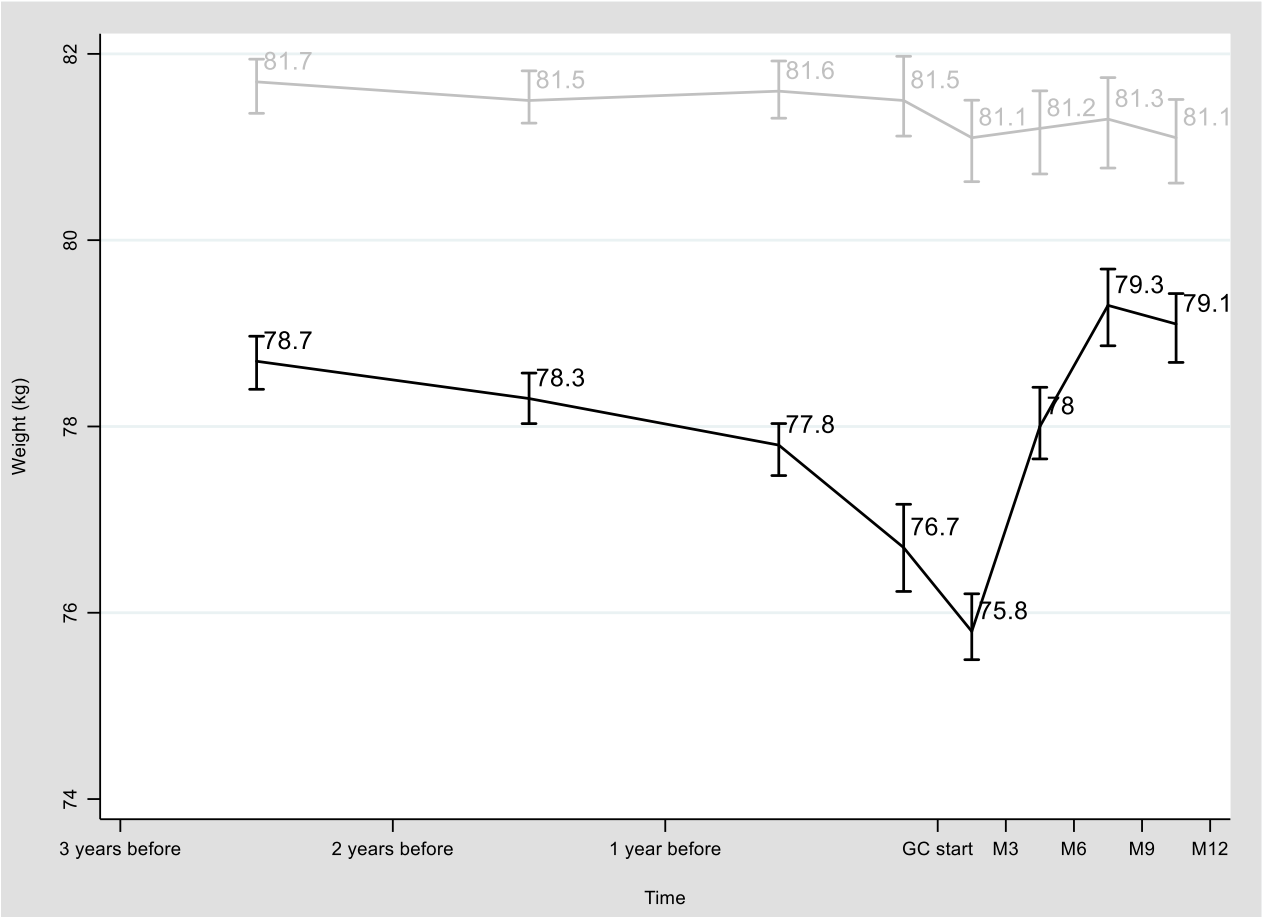


Figure 2: Weight variations over time in the study populations according to age and sex

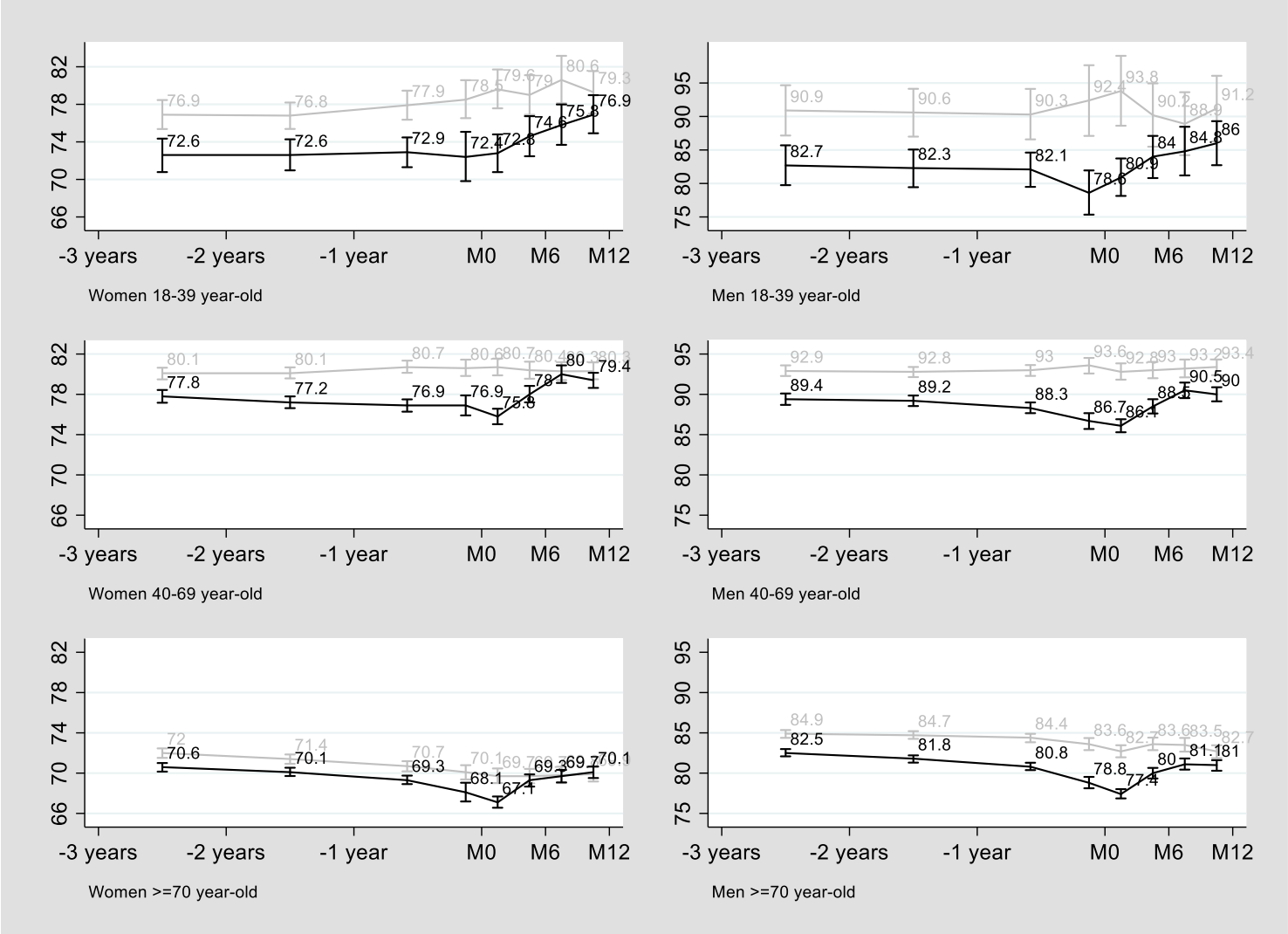


Table 1: Characteristics of patients according to available weight measurements before and after glucocorticoid initiation or index date

	Patients chronically exposed to glucocorticoids (n=96,592)			**Control population with weight measurement before and after**
	No weight measurement	**Weight measurement before or after**	**Weight measurement before and after**	
	N=26,844	N=38,232	N=31,516	N=26,967
Female, n (%)	15,217 (56.7)	21,516 (56.3)	17,851 (56.6)	15,338 (56.9)
Age, years	66 ± 16	64 ± 16	67 ± 15	66 ±14
Townsend deprivation index, n (%)				
1 (less deprived)	7,616 (28.4)	9,633 (25.2)	7,200 (22.9)	6,050 (22.4)
2	6,556 (24.4)	8,872 (23.2)	7,010 (22.2)	5,831 (21.6)
3	5,314 (19.8)	7,708 (20.2)	6,497 (20.6)	5,523 (20.5)
4	3,954 (14.7)	6,341 (16.6)	5,658 (17.9)	4,928 (18.3)
5 (more deprived)	2,240 (8.3)	3,776 (9.9)	3,665 (11.6)	3,432 (12.7)
Missing	1,164 (4.4)	1,902 (4.9)	1,486 (4.8)	1,203 (4.5)
Smoking status, n (%)				
Non-smokers	13,236 (49.3)	17,523 (45.8)	13,003 (41.3)	10,292 (38.2)
Ex-smokers	4,799 (17.9)	7,206 (18.8)	5,299 (16.8)	5,127 (19.0)
Smokers	7,403 (27.6)	13,314 (34.8)	13,199 (41.9)	11,529 (42.8)
Missing	1,406 (5.2)	189 (0.5)	15 (0.05)	19 (0.07)
Underlying disease, n (%)				
PMR/GCA	7,017 (26.1)	9,072 (23.7)	8,585 (27.2)	347 (1.3)
COPD	1,719 (6.4)	3,115 (8.1)	3,937 (12.5)	5,479 (20.3)
Asthma	2,179 (8.1)	3,936 (10.3)	3,714 (11.8)	6,482 (24.0)
Cancer	4,509 (16.8)	6,350 (16.6)	3,353 (10.6)	2,559 (9.5)
Rheumatoid arthritis	2,326 (8.7)	3,366 (16.6)	2,960 (9.4)	2,158 (8.0)
Inflammatory bowel diseases	1,637 (6.1)	2,702 (7.1)	1,780 (5.6)	219 (0.8)
Connective tissue diseases	810 (3.0)	1,322 (3.5)	980 (3.1)	118 (0.4)
Other or missing	6,647 (24.8)	8,369 (21.9)	6,207 (19.7)	9,605 (35.6)
Baseline weight, kg	-	73 [62.7-84.4]	76 [65-88.9]	79.7 [67-93]
Duration of GC exposure, days	367 ± 457	366 ± 453	380 ± 422	-
Mean GC dosage*, mg/day				
Month 0 – month 3	22 ± 27	22 ± 25	21 ± 27	-
Month 4 – month 6	8 ± 14	8 ± 11	7 ± 12	-
Month 7 – month 9	6 ± 8	6 ± 9	5 ± 7	-
Month 10 – month 12	5 ± 7	5 ± 7	4 ± 5	-
Maximum GC dosage*, mg/day	44 ± 93	46 ± 79	44 ± 72	-
Drug, n (%)				
Prednisolone	22,953 (85.5)	32,810 (85.8)	29,089 (92.3)	-
Dexamethasone	3,686 (13.7)	5,154 (13.5)	2,185 (6.9)	-
Betamethasone	124 (0.5)	172 (0.5)	180 (0.6)	-
Prednisone	33 (0.1)	23 (<0.1)	29 (0.1)	-
Methylprednisolone	32 (0.1)	50 (0.1)	20 (0.1)	-
Deflazacort	14 (<0.1)	22 (<0.1)	13 (<0.1)	-
Triamcinolone	2 (<0.1)	1 (<0.1)	0	-
Previous short term systemic GC exposure**, yes vs. no	6,401 (23.9)	9,734 (25.5)	9,387 (29.8)	19,935 (73.9)
Other immunosuppressant*,** n (%)	2,015 (7.5)	3,615 (9.5)	2,892 (9.2)	407 (1.5)

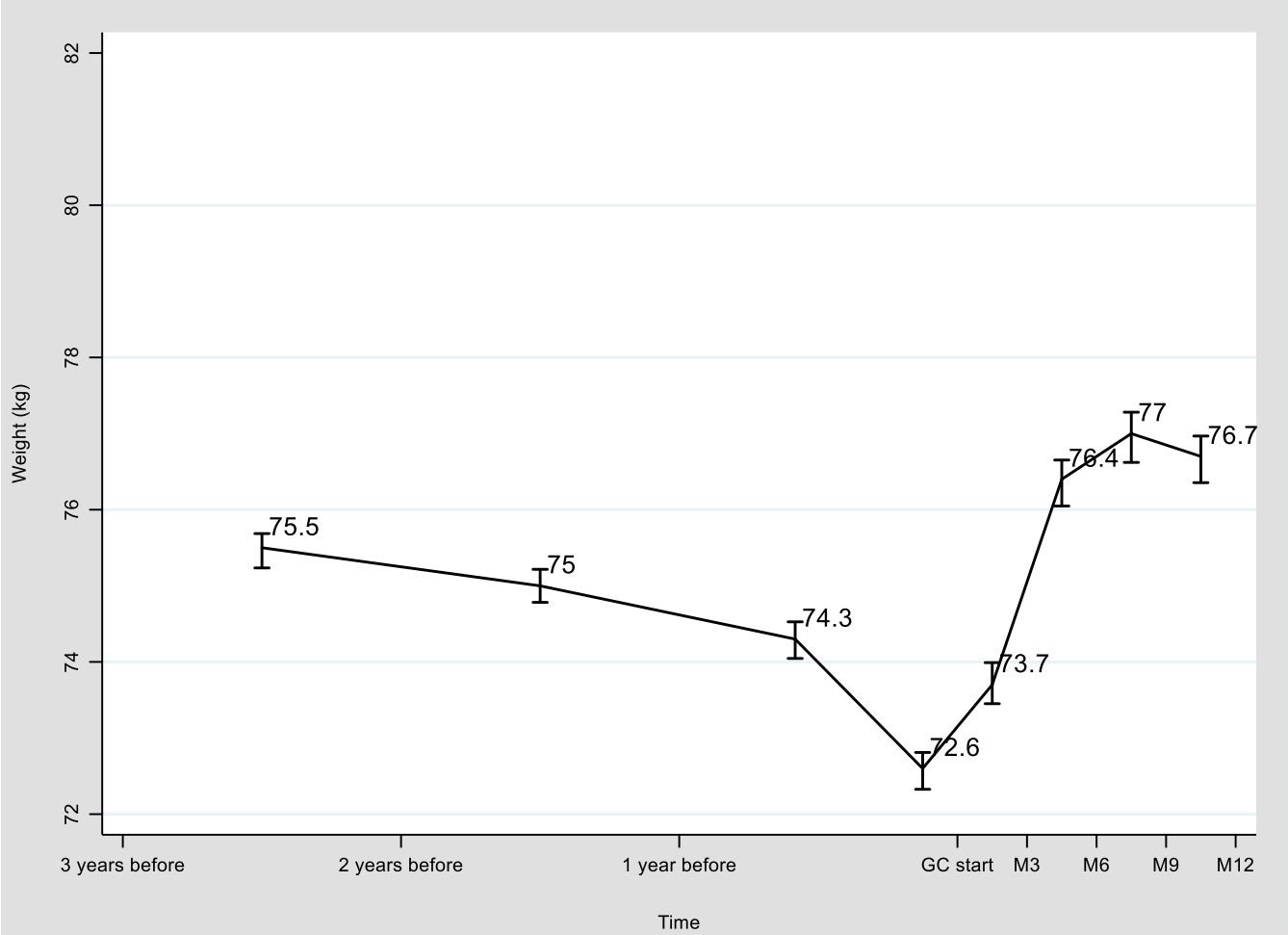
PMR/GCA: polymyalgia rheumatic/giant cell arteritis; COPD: chronic pulmonary pulmonary disease; GC: glucocorticoids
* in prednisone equivalent
** within the 3 years before first long term GC exposure or the index date (for the control group)
*** i.e., methotrexate, azathioprine, ciclosporin, cyclophosphamide, mycophenolate mofetil

Table 2: Risk factors for weight gain ≥ 10% of the baseline weight (n=3,208)

	HR [95% CI] Univariate analyses	**p-value**	**HR [95% CI] Multivariable analyses**	**p-value**
Sex, women vs men	1.56 [1.45-1.68]	<0.001	1.33 [1.22-1.44]	<0.001
Age, years				
18-39	1	-	1	
40-69	0.46 [0.42-0.51]	<0.001	0.65 [0.58-0.74]	<0.001
≥ 70	0.17 [0.15-0.19]	<0.001	0.29 [0.25-0.33]	<0.001
Townsend deprivation index				
1 (less deprived)	1		1	
2	1.15 [1.03-1.29]	0.02	1.10 [0.98-1.23]	0.11
3	1.32 [1.18-1.48]	<0.001	1.17 [1.05-1.31]	0.005
4	1.57 [1.41-1.76]	<0.001	1.29 [1.15-1.44]	<0.001
5 (more deprived)	1.80 [1.60-2.03]	<0.001	1.33 [1.17-1.50]	<0.001
Smoking status				
Non-smokers	1		1	
Ex-smokers	1.01 [0.94-1.10]	0.76	1.10 [1.01-1.20]	0.02
Smokers	1.77 [1.62-1.94]	<0.001	1.16 [1.05-1.28]	0.004
Underlying disease				
PMR/GCA	0.46 [0.41-0.51]	<0.001	0.64 [0.57-0.72]	<0.001
COPD	1.03 [0.91-1.16]	0.65	0.98 [0.86-1.13]	0.81
Asthma	1.26 [1.12-1.41]	<0.001	1.06 [0.93-1.19]	0.40
Cancer	0.70 [0.60-0.82]	<0.001	0.80 [0.66-0.97]	0.02
Rheumatoid arthritis	0.74 [0.65-0.84]	<0.001	0.79 [0.69-0.91]	0.001
Inflammatory bowel diseases	1.55 [1.33-1.81]	<0.001	0.81 [0.68-0.95]	0.01
Connective tissue diseases	0.94 [0.79-1.13]	0.52	0.77 [0.64-0.93]	0.006
Other or missing	1			
Baseline weight, kg				
<65	1		1	
65-74	0.66 [0.60-0.73]	<0.001	0.78 [0.71-0.86]	<0.001
75-85	0.62 [0.56-0.69]	<0.001	0.72 [0.65-0.80]	<0.001
≥85	0.58 [0.53-0.63]	<0.001	0.61 [0.55-0.68]	<0.001
Overall mean GC dosage*, mg/day				
< 8	1		1	
8-10	1.64 [1.44-1.87]	<0.001	1.58 [1.38-1.81]	<0.001
11-15	5.88 [5.31-6.51]	<0.001	4.67 [4.20-5.19]	<0.001
≥ 16	3.06 [2.69-3.47]	<0.001	2.70 [2.36-3.08]	<0.001
Drug				
Prednisolone/prednisone	1		1	
Dexamethasone	1.16 [0.96-1.40]	0.12	0.98 [0.78-1.23]	0.85
Others	0.61 [0.36-1.06]	0.08	0.49 [0.28-0.84]	0.01
Previous short term systemic GC exposure**, yes vs. no	1.54 [1.43-1.66]	<0.001	1.17 [1.07-1.27]	<0.001
Other immunosuppressant, yes vs. no	1.39 [1.25-1.54]	<0.001	0.93 [0.83-1.04]	0.20

PMR/GCA: polymyalgia rheumatica/giant cell arteritis, COPD: chronic obstructive pulmonary disease, GC: glucocorticoids
* in prednisone equivalent
**within the 3 years before first long term GC exposure

Supplementary figure 1: weight variations over time in the GC exposed individuals with weight measurement before or after GC exposure



Supplementary Table 1: Risk factors for weight gain ≥ 5 kg (n=5,506)

	HR [95% CI] Univariate analyses	**p-value**	**HR [95% CI] Multivariable analyses**	**p-value**
Sex, women vs. men	1.17 [1.11-1.23]	<0.001	1.21 [1.14-1.29]	<0.001
Age, years				
18-39	1	-	1	
40-69	0.62 [0.57-0.68]	<0.001	0.73 [0.67-0.80]	<0.001
≥ 70	0.25 [0.23-0.28]	<0.001	0.37 [0.34-0.41]	<0.001
Townsend deprivation index				
1 (less deprived)	1		1	
2	1.08 [0.99-1.17]	0.08	1.05 [0.97-1.14]	0.21
3	1.20 [1.10-1.30]	<0.001	1.10 [1.01-1.19]	0.02
4	1.37 [1.26-1.48]	<0.001	1.16 [1.07-1.26]	0.001
5 (more deprived)	1.52 [1.39-1.66]	<0.001	1.23 [1.13-1.35]	<0.001
Smoking status				
Non-smokers	1		1	
Ex-smokers	1.05 [0.99-1.11]	0.08	1.06 [1.00-1.13]	0.06
Smokers	1.44 [1.34-1.54]	<0.001	1.04 [0.96-1.12]	0.38
Underlying disease				
PMR/GCA	0.57 [0.53-0.61]	<0.001	0.79 [0.73-0.86]	<0.001
COPD	1.03 [0.94-1.13]	0.51	1.08 [0.98-1.20]	0.14
Asthma	1.28 [1.17-1.39]	<0.001	1.06 [0.97-1.16]	0.21
Cancer	0.73 [0.65-0.82]	<0.001	0.84 [0.73-0.96]	0.01
Rheumatoid arthritis	0.79 [0.72-0.87]	<0.001	0.87 [0.79-0.97]	0.008
Inflammatory bowel diseases	1.36 [1.21-1.54]	<0.001	0.85 [0.75-0.97]	0.01
Connective tissue diseases	0.91 [0.79-1.04]	0.18	0.77 [0.66-0.88]	<0.001
Other or missing	1		1	
Baseline weight, kg				
<65	1		1	
65-74	0.95 [0.88-1.03]	0.20	1.04 [0.95-1.12]	0.40
75-85	1.01 [0.93-1.09]	0.86	1.08 [1.00-1.18]	0.05
≥85	1.30 [1.22-1.39]	<0.001	1.25 [1.16-1.35]	<0.001
Overall mean GC dosage, mg/day				
< 8	1		1	
8-10	1.69 [1.53-1.86]	<0.001	1.63 [1.47-1.80]	<0.001
11-15	4.73 [4.38-5.11]	<0.001	3.90 [3.61-4.23]	<0.001
≥ 16	3.01 [2.73-3.31]	<0.001	2.70 [2.45-2.99]	<0.001
Drug				
Prednisolone/prednisone	1		1	
Dexamethasone	1.06 [0.92-1.22]	0.44	0.92 [0.78-1.10]	0.37
Others	0.57 [0.37-0.86]	0.008	0.47 [0.31-0.72]	0.001
Previous short term systemic GC exposure*, yes vs. no	1.44 [1.37-1.53]	<0.001	1.15 [1.08-1.22]	<0.001
Other immunosuppressant, yes vs. no	1.25 [1.15-1.35]	<0.001	0.92 [0.85-1.01]	0.08

PMR/GCA: polymyalgia rheumatica/giant cell arteritis, COPD: chronic obstructive pulmonary disease, GC: glucocorticoids
*within the 3 years before first long term GC exposure

Supplementary Table 2: Risk factors for weight gain ≥ 2 kg (n=10,690)

	HR [95% CI] Univariate analyses	**p-value**	**HR [95% CI] Multivariable analyses**	**p-value**
Sex, women vs. men	1.10 [1.05-1.14]	<0.001	1.11 [1.06-1.16]	<0.001
Age, years				
18-39	1		1	
40-69	0.74 [0.69-0.79]	<0.001	0.83 [0.77-0.90]	<0.001
≥ 70	0.43 [0.40-0.46]	<0.001	0.57 [0.52-0.61]	<0.001
Townsend deprivation index				
1 (less deprived)	1		1	
2	1.04 [0.98-1.10]	0.22	1.02 [0.96-1.08]	0.50
3	1.11 [1.05-1.18]	0.001	1.04 [0.98-1.11]	0.16
4	1.19 [1.12-1.27]	<0.001	1.07 [1.01-1.14]	0.02
5 (more deprived)	1.22 [1.14-1.31]	<0.001	1.07 [1.00-1.15]	0.04
Smoking status				
Non-smokers	1		1	
Ex-smokers	1.05 [1.01-1.10]	0.02	1.06 [1.01-1.11]	0.01
Smokers	1.27 [1.20-1.34]	<0.001	1.04 [0.98-1.10]	0.20
Underlying disease				
PMR/GCA	0.73 [0.69-0.78]	<0.001	0.92 [0.86-0.97]	0.005
COPD	1.08 [1.01-1.16]	0.03	1.10 [1.02-1.18]	0.02
Asthma	1.27 [1.19-1.36]	<0.001	1.12 [1.05-1.20]	0.001
Cancer	0.81 [0.74-0.89]	<0.001	0.91 [0.83-1.01]	0.08
Rheumatoid arthritis	0.87 [0.81-0.94]	<0.001	0.94 [0.88-1.02]	0.13
Inflammatory bowel diseases	1.29 [1.18-1.41]	<0.001	0.91 [0.83-1.00]	0.06
Connective tissue diseases	0.91 [0.82-1.01]	0.09	0.82 [0.74-0.92]	0.001
Other or missing	1		1	
Baseline weight, kg				
<65	1		1	
65-74	0.99 [0.94-1.05]	0.72	1.04 [0.98-1.10]	0.22
75-85	1.01 [0.96-1.07]	0.66	1.04 [0.98-1.10]	0.21
≥85	1.12 [1.06-1.18]	<0.001	1.08 [1.02-1.14]	0.01
Overall mean GC dosage, mg/day				
< 8	1		1	
8-10	1.64 [1.52-1.76]	<0.001	1.61 [1.49-1.73]	<0.001
11-15	3.27 [3.10-3.46]	<0.001	2.93 [1.76-3.11]	<0.001
≥ 16	2.84 [2.65-3.05]	<0.001	2.73 [2.53-2.93]	<0.001
Drug				
Prednisolone/prednisone	1		1	
Dexamethasone	0.92 [0.82-1.03]	0.14	0.80 [0.70-0.92]	0.002
Others	0.73 [0.56-0.95]	0.02	0.66 [0.50-0.87]	0.003
Previous short term systemic GC exposure*, yes vs. no	1.31 [1.26-1.37]	<0.001	1.11 [1.06-1.16]	<0.001
Other immunosuppressant, yes vs. no	1.09 [1.03-0.16]	0.005	0.93 [0.87-0.99]	0.03

PMR/GCA: polymyalgia rheumatica/giant cell arteritis, COPD: chronic obstructive pulmonary disease, GC: glucocorticoids
*within the 3 years before first long term GC exposure