

# Taking Glucocorticoids by Prescription Is Associated with Subsequent Cardiovascular Disease

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**Background:** Glucocorticoids have adverse systemic effects, including obesity, hypertension, and hyperglycemia, that may predispose to cardiovascular disease. The effect of glucocorticoid use on cardiovascular disease has not been quantified.

**Objective:** To test the hypothesis that users of exogenous glucocorticoids have an increased risk for cardiovascular disease.

**Design:** A cohort study using a record linkage database.

**Setting:** Tayside, Scotland, United Kingdom.

**Patients:** 68 781 glucocorticoid users and 82 202 nonusers without previous hospitalization for cardiovascular disease who were studied between 1993 and 1996.

**Measurements:** The average daily dose of glucocorticoid exposure during follow-up was categorized as low (inhaled, nasal, and topical only), medium (oral, rectal, or parenteral <7.5 mg of prednisolone equivalent), or high ( $\geq 7.5$  mg of prednisolone equivalent). Poisson regression model, sensitivity analysis, and propensity score methods were used to investigate the asso-

ciation between glucocorticoid exposure and cardiovascular outcome.

**Results:** 4383 cardiovascular events occurred in 257 487 person-years of follow-up for a rate of 17.0 (95% CI, 16.5 to 17.5) per 1000 person-years in the comparator group, and 5068 events occurred in 212 287 person-years for a rate of 23.9 (CI, 23.2 to 24.5) per 1000 person-years in the group exposed to glucocorticoids (22.1, 27.2, and 76.5 in low, medium, and high groups, respectively). The absolute risk difference was 6.9 (CI, 6.0 to 7.7) per 1000 person-years (5.1, 10.1, and 59.4, respectively). After adjustment for known covariates, the relative risk for a cardiovascular event in patients receiving high-dose glucocorticoids was 2.56 (CI, 2.18 to 2.99).

**Limitations:** Because the data were observational, residual confounding cannot be excluded.

**Conclusion:** Treatment with high-dose glucocorticoids seemed to be associated with increased risk for cardiovascular disease.

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Glucocorticoids are commonly used as anti-inflammatory and immunosuppressive therapy in diseases such as asthma, inflammatory bowel disease, and inflammatory arthritis. Well-known adverse effects of glucocorticoids include hypertension, diabetes mellitus, and obesity (1–3), all of which are independent risk factors for cardiovascular disease. The principal physiologic glucocorticoid is cortisol. Increased cortisol secretion and action, even within the “physiologic” range, is associated with several risk factors for cardiovascular disease (4, 5). Indeed, studies have proposed that subclinical Cushing syndrome may be an important cardiovascular risk factor (6, 7). However, whether, and to what extent, the adverse effects of exogenous glucocorticoids on these risk factors for cardiovascular disease cause cardiovascular morbidity and death has not been established (8, 9). This is not predictable, especially since glucocorticoids may also have cardioprotective effects mediated by their anti-inflammatory and antiproliferative actions in the vessel wall (10, 11).

We tested the hypothesis that users of exogenous glucocorticoids have an increased risk for cardiovascular disease. In particular, we hypothesized that high doses will be associated with cardiovascular disease, while doses equivalent to or below the physiologic range of endogenous glucocorticoid secretion may be compensated for by decreased cortisol levels and will not incur excessive risk. We have tested this by using the MEDicines MONitoring unit (MEMO) record linkage database to compare peo-

ple who were exposed and not exposed to glucocorticoid therapy.

## METHODS

We performed this study in the Tayside region in Scotland by using the MEMO record linkage database. The MEMO database covers a geographically compact population and serves about 400 000 patients in the National Health Service (NHS) in Scotland, 97% of whom are white. The NHS in Scotland is tax-funded and free at the point of consumption and covers the entire population. In Tayside, almost no health care is delivered without the NHS. The data collection methods for this database have previously been described (12). In brief, this database contains several data sets, including all dispensed community prescriptions, hospital discharge data, mortality data, biochemistry data, and other data, that are linked by a unique patient identifier, the community health index number. These data are made anonymous for the purposes of research, as approved by the Tayside Caldicott Guardians (a group appointed by the government to protect the confidentiality of medical records). The Tayside committee on research medical ethics also approved the project. We cleaned and validated all data before analysis.

We included all patients who resided in Tayside and registered with a general practitioner in January 1993, who were 40 years of age or older, and who remained a resident

in Tayside until December 1997 or who died during the study period.

### Definitions of Exposure to Glucocorticoids

#### Exposed and Comparator Cohorts

All patients who received 1 or more dispensed prescriptions for glucocorticoids (including inhaled steroids, topical steroids, oral and parenteral steroids, rectal application steroids, and nasal steroids) between July 1993 and December 1996 formed the exposed cohort. They entered the study at their date of first prescription.

The rest of the study sample made up the comparator cohort. We excluded patients who were hospitalized for inflammatory bowel disease and chronic obstructive airways disease during the follow-up period because they may have been given glucocorticoids as hospital inpatients without the prescriptions being identified by MEMO. We generated a random date of entry to the study for each member of the comparator cohort by using a frequency-matched calendar year generated from the dates of entry to the study in the exposed cohort.

We excluded patients from both cohorts if they were hospitalized for cardiovascular disease before study entry.

#### Dose of Glucocorticoids

For about two thirds of dispensed oral or systemic glucocorticoid prescriptions, we recorded the date of prescription, dose of tablets, amount dispensed, and instructions on how medication should be taken. For these prescriptions, we could determine daily exposure during prescribed courses. For the remainder, we knew the total dose dispensed but, because prescriptions were marked “take as directed,” could not accurately determine the daily dose and duration. We therefore calculated the average daily dose by dividing the total amount of glucocorticoid dispensed by the total number of days of observation. For multiple simultaneous formulations (oral and inhaled) of glucocorticoids, we used only the oral glucocorticoids to calculate the daily dose. We categorized glucocorticoid exposure according to average daily doses throughout the follow-up period for each patient as high (oral, parenteral, and rectal steroids with daily dosage  $\geq 7.5$  mg [that is, supraphysiologic doses]); medium (oral, parenteral, and rectal steroids with daily dosage  $< 7.5$  mg [that is, approximately equivalent to the physiologic range of endogenous glucocorticoid secretion]); or low (inhaled, topical, and nasal steroids with daily dosage less than the equivalent physiologic range). As a result of this calculation, we included patients who took large dosages for a short period in the medium-dose group. We calculated “dose equivalents” of prednisolone as follows: 1 mg of prednisolone = 5 mg of cortisone = 4 mg of hydrocortisone = 1 mg of prednisone = 0.8 mg of triamcinolone = 0.8 mg of methylprednisolone = 0.15 mg of dexamethasone = 0.15 mg of betamethasone (13).

The MEMO database does not collect information for

#### Context

Patients who take glucocorticoids appear to have an increased risk for cardiovascular disease. However, data about the magnitude of this increased risk are lacking

#### Contribution

In this large, population-based study, the use of glucocorticoids was associated with an increased risk for cardiovascular events, with a clear dose–response relationship. Patients who received high-dose glucocorticoids were more than 2.5 times as likely as patients who did not use glucocorticoids to experience a cardiovascular event.

#### Implications

These data will help clinicians estimate cardiovascular risk among patients who require glucocorticoids.

—The Editors

prescriptions dispensed in hospitals. We considered participants hospitalized for asthma, inflammatory bowel disease, or chronic obstructive pulmonary disease (disorders usually treated with high-dose glucocorticoids in the hospital) as being exposed to a typical dosage of glucocorticoids (30 mg/d, prednisolone) during that period.

#### Analysis of Events during Glucocorticoid Exposure (On Treatment vs. Off Treatment)

We did a subgroup analysis of those patients for whom we had data on daily dose of glucocorticoid exposure. For each patient, we divided exposure to glucocorticoid into the time that the patient was exposed (on treatment) and the time that the patient was not exposed (off treatment). We then temporally related these periods to the occurrence of cardiovascular events.

#### Incident versus Prevalent Use

For each patient in the cohort exposed to glucocorticoids, we used the 6 months before entry to the study as a screening period. We classified patients who did not receive glucocorticoids during this period as “incident” users of glucocorticoids and patients who received glucocorticoids during this period as “prevalent” users.

#### Continuous versus Intermittent Use

We did an analysis comparing cardiovascular risk in continuous use ( $\leq 180$  days between prescriptions) versus intermittent use ( $> 180$  days between prescriptions).

#### Exposure by Disease Indication

We identified patients with chronic obstructive pulmonary disease if they were hospitalized for asthma or chronic obstructive pulmonary disease or were prescribed an inhaled steroid or bronchodilator drug before study entry.

**Table 1. Characteristics of Patients in the Glucocorticoid-Exposed and Comparator Cohorts\***

| Characteristic   | Exposure Cohort<br>(n = 68 781) | Comparator Cohort<br>(n = 82 202) |
|--|---------------------------------|-----------------------------------|
| <b>Sex, n (%)</b>  |                                 |                                   |
| Women  | 40 853 (59.40)                  | 42 070 (51.18)                    |
| Men  | 27 928 (40.60)                  | 40 132 (48.82)                    |
| <b>Mean age ± SD, y</b>                                      |                                 |                                   |
|  | 62.54 (12.73)                   | 59.36 (12.63)                     |
| <b>Glucocorticoid exposure, n (%)</b>                        |                                 |                                   |
| Low  | 51 960 (75.54)                  | –                                 |
| Medium   | 15 295 (22.24)                  | –                                 |
| High   | 1526 (2.22)                     | –                                 |
| <b>Carstairs deprivation category, n (%)</b>                 |                                 |                                   |
| 1 (least deprived)   | 6023 (8.88)                     | 6784 (8.38)                       |
| 2  | 12 441 (18.35)                  | 16 937 (20.98)                    |
| 3  | 17 296 (25.51)                  | 21 894 (27.04)                    |
| 4  | 12 939 (19.08)                  | 14 983 (18.51)                    |
| 5  | 7343 (10.83)                    | 8038 (9.93)                       |
| 6 (most deprived)  | 11 759 (17.34)                  | 12 329 (15.23)                    |
| <b>Use of any cardiovascular drug in past 6 mo, n (%)</b>    |                                 |                                   |
| ACE inhibitors   | 2144 (3.12)                     | 1516 (1.84)                       |
| Anticoagulants   | 754 (1.10)                      | 395 (0.48)                        |
| Antiplatelets  | 3302 (4.80)                     | 2135 (2.60)                       |
| α-Blockers   | 539 (0.78)                      | 300 (0.36)                        |
| β-Blockers   | 6131 (8.91)                     | 5360 (6.52)                       |
| Calcium-channel blockers                                     | 5245 (7.63)                     | 3526 (4.29)                       |
| Cardiac glycosides   | 1421 (2.07)                     | 920 (1.12)                        |
| Diuretics  | 12 925 (18.79)                  | 7586 (9.23)                       |
| Nitrates   | 3184 (4.63)                     | 1620 (1.97)                       |
| Lipid-lowering drugs   | 597 (0.87)                      | 397 (0.48)                        |
| HRT and oral contraceptives                                  | 4940 (7.18)                     | 3574 (4.35)                       |
| NSAIDs   | 14 814 (21.54)                  | 8879 (10.80)                      |
| DMARDs   | 277 (0.40)                      | 63 (0.08)                         |
| Bronchodilators  | 12 130 (17.64)                  | 1018 (1.24)                       |
| <b>Noncardiovascular hospitalization in past 6 mo, n (%)</b> |                                 |                                   |
|  | 8369 (12.17)                    | 10 813 (13.15)                    |
| <b>Disease history, n (%)</b>                                |                                 |                                   |
| Diabetes mellitus  | 1695 (2.46)                     | 1258 (1.53)                       |
| Cancer   | 4642 (6.75)                     | 3137 (3.82)                       |
| Renal disease  | 199 (0.29)                      | 80 (0.10)                         |

\* ACE = angiotensin-converting enzyme; DMARD = disease-modifying antirheumatic drug; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug.

We identified patients with inflammatory bowel disease if they were hospitalized for colitis or were prescribed a rectal steroid preparation before study entry.

We identified patients with inflammatory arthritis if they were hospitalized for inflammatory arthritis or were prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs before study entry.

### Outcome Variables

We collected the outcome data on each patient until 31 December 1997. The outcome of the study was a car-

diovascular event defined as the composite end point of hospitalization with a primary diagnosis of myocardial infarction, angina, angioplasty or coronary revascularization, stroke, transient ischemic attack, congestive cardiac failure, or cardiovascular death during follow-up.

We censored patients at their first event if they had several events. We ascertained diagnoses of myocardial infarction, angina, angioplasty and coronary revascularization, stroke, transient ischemic attack, and congestive cardiac failure from the hospital discharge diagnosis data, which were validated (14) in the Scottish Morbidity Record 1 by primary International Classification of Diseases, Ninth or Tenth Revisions, codes. We also ascertained diagnoses of angioplasty and coronary revascularization by the code of classification of surgical operations and procedures. We also obtained the death certification data for all Tayside residents who died.

### Statistical Analysis

We counted events that occurred during the study period and compared rates of events between cohorts. We used the Poisson regression model to investigate the association between glucocorticoid exposure and cardiovascular outcome. We included the following covariates: age at study entry; sex; social deprivation; use of angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelet agents, α-blockers, β-blockers, calcium-channel blockers, cardiac glycosides, diuretics, nitrates, lipid-lowering drugs, hormone replacement therapy, oral contraceptives, NSAIDs, disease-modifying antirheumatic drugs, or bronchodilators; noncardiovascular hospitalization in the 6 months before study entry; diabetes mellitus; cancer; and renal disease. To minimize confounding by indication, wherein higher doses of glucocorticoids would be given to patients with more severe illness, we calculated a multiple propensity score (15) to perform a subgroup analysis. In this analysis, we matched cohorts of patients who were exposed and not exposed to glucocorticoids for propensity score. This propensity score is an extension of the ordinary propensity score and is defined as the conditional probability of a patient receiving a particular dose, given all observed covariates. We also did a sensitivity analysis to assess the potential effects of unmeasured confounding on the relative risk for cardiovascular disease by varying both the prevalence of the unmeasured confounding in the high-dose exposure group and the comparator group (16).

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The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

### RESULTS

Table 1 shows characteristics of the 2 cohorts. In the glucocorticoid-exposed group, 76% had low-dose exposure and 2% had high-dose exposure, equivalent to at least 7.5 mg of prednisolone per day. Patients in the glucocorticoid-

**Table 2. Influence of Dose of Glucocorticoids on All Cardiovascular Events**

| Steroid Exposure | Events, <i>n</i> | Unadjusted Rate Ratio (95% CI) | Adjusted Rate Ratio (95% CI)* | Adjusted Rate Ratio (95% CI)† |
|------------------|------------------|--------------------------------|-------------------------------|-------------------------------|
| Comparator       | 4383             | 1.00                           | 1.00                          | 1.00                          |
| Low dose         | 3521             | 1.30 (1.24–1.36)               | 1.00 (0.95–1.05)              | 1.00 (0.95–1.05)              |
| Medium dose      | 1380             | 1.60 (1.50–1.70)               | 1.03 (0.96–1.10)              | 1.04 (0.95–1.14)              |
| High dose        | 167              | 4.50 (3.86–5.25)               | 2.56 (2.18–2.99)              | 3.09 (2.51–3.80)              |

\* Adjusted for age; sex; social deprivation; use of angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelets,  $\alpha$ -blockers,  $\beta$ -blockers, calcium-channel blockers, cardiac glycosides, diuretics, nitrates, lipid-lowering drugs, hormone replacement therapy and oral contraceptives, nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and bronchodilators during the follow-up; noncardiovascular hospitalization in the past 6 months; diabetes mellitus; cancer; and renal disease.  
 † Results of matched cohorts.

exposed group had higher levels of baseline risk factors for cardiovascular disease than in the comparator group.

In 257 487 person-years of follow-up in the comparator group, 4383 cardiovascular events occurred, for a rate of 17.0 (95% CI, 16.5 to 17.5) per 1000 person-years. In 212 287 person-years in the group exposed to glucocorticoids, 5068 events occurred, for a rate of 23.9 (CI, 23.2 to 24.5) per 1000 person-years (22.1, 27.2, and 76.5 in low-dose, medium-dose, and high-dose groups, respectively). The absolute risk difference was 6.9 (CI, 6.0 to 7.7) per 1000 person-years (5.1, 10.1, and 59.4, respectively). Compared with the comparator group, the high-dose glucocorticoid exposure group had significantly higher risk for cardiovascular disease after adjustment for known covariates (Table 2). Table 2 also shows results of the further propensity score–matched analysis. In this analysis, we included 102 758 patients (51 379 in each cohort) to provide matched cohorts. By design, both glucocorticoid users and comparators had similar baseline risk for cardiovascular disease in this subgroup analysis (data not shown). Despite this, a similar association of glucocorticoid exposure with cardiovascular disease was apparent when compared with

the whole study. We also did an analysis that excluded the “softer” end points of angina and transient ischemic attack from the main analysis. However, the results changed little.

In addition, we did a further analysis of the total dose of glucocorticoid exposure (excluding the low-dose group) in patients with follow-up lasting more than 60 days. We categorized the total glucocorticoid exposure into tertiles. The results showed that patients in the second and third tertiles had an increased risk for cardiovascular risk when compared with nonusers (relative risk in the second tertile, 1.27 [CI, 1.14 to 1.41]; relative risk in the third tertile, 1.30 [CI, 1.17 to 1.45]).

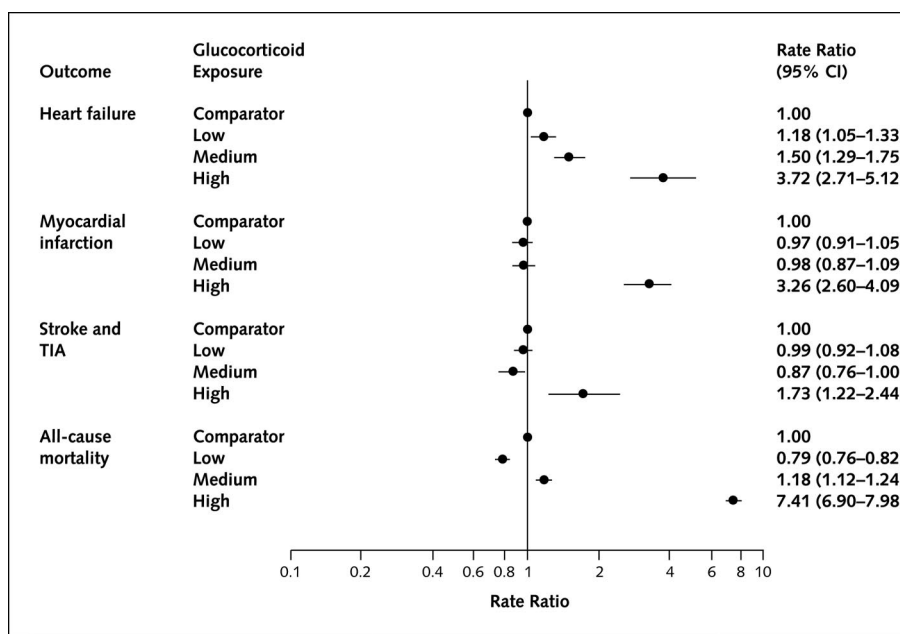
In the glucocorticoid exposure group, prevalent users had higher risk for cardiovascular disease than incident users (adjusted relative risk, 1.08 [CI, 1.02 to 1.15]). Patients receiving glucocorticoid therapy at the time of the event had higher risk than those not receiving glucocorticoid therapy (unadjusted relative risk, 3.82 [CI, 2.85 to 5.13]). We did an exploratory analysis to compare continuous versus intermittent users. This showed that continuous use was associated with a higher risk for cardiovascular disease (relative risk, 2.31 [CI, 1.29 to 4.15]). We also tested for

**Table 3. Cardiovascular Events and Glucocorticoid Use for Different Disease Indications**

| Steroid Exposure  | Rate Ratio (95% CI)                       |  |   |
|-------------------|---|--|---|
|                   | Inflammatory Arthritis ( <i>n</i> = 1165) | Chronic Obstructive Pulmonary Disease ( <i>n</i> = 14 851) | Inflammatory Bowel Disease ( <i>n</i> = 1753) |
| Comparator        | 1.00                                      | 1.00   | 1.00  |
| <b>Unadjusted</b> |   |  |   |
| Low dose          | 1.10 (0.64–1.57)                          | 0.90 (0.77–1.06)   | 1.07 (0.70–1.65)                              |
| Medium dose       | 1.20 (0.81–1.77)                          | 0.90 (0.77–1.05)   | 0.82 (0.54–1.26)                              |
| High dose         | 2.31 (1.14–4.68)                          | 2.52 (1.93–3.28)   | 1.11 (0.55–2.26)                              |
| <b>Adjusted*</b>  |   |  |   |
| Low dose          | 0.98 (0.62–1.57)                          | 1.08 (0.92–1.27)   | 0.92 (0.59–1.44)                              |
| Medium dose       | 1.50 (0.98–2.30)                          | 0.97 (0.82–1.16)   | 0.89 (0.56–1.39)                              |
| High dose         | 3.30 (1.56–6.96)                          | 2.20 (1.67–2.92)   | 1.13 (0.54–2.38)                              |
| <b>Adjusted†</b>  |   |  |   |
| Low dose          | 0.95 (0.46–1.99)                          | 0.92 (0.74–1.14)   | 1.26 (0.47–3.38)                              |
| Medium dose       | 1.26 (0.68–2.32)                          | 0.98 (0.75–1.29)   | 1.62 (0.68–3.86)                              |
| High dose         | 5.17 (1.56–17.18)                         | 4.27 (2.44–7.48)   | 2.61 (0.67–10.09)                             |

\* Adjusted for age; sex; social deprivation; use of angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelets,  $\alpha$ -blockers,  $\beta$ -blockers, calcium-channel blockers, cardiac glycosides, diuretics, nitrates, lipid-lowering drugs, hormone replacement therapy and oral contraceptives, nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and bronchodilators during the follow-up; noncardiovascular hospitalization in the past 6 months; diabetes mellitus; cancer; and renal disease.  
 † Results of matched cohorts.

Figure. Glucocorticoid use with different cardiovascular diseases.



TIA = transient ischemic attack.

exposure carryover effects by allocating increasing time windows to the end of each prescription (17). We found relative risks of 3.82, 3.40, 3.10, 3.07, and 2.82 for the windows of 0, 7, 30, 90, and 180 days, respectively. We examined the effect of dosage of glucocorticoid exposure during treatment periods only. Using only prescriptions that could be accurately decoded for daily dose and examining events that occurred only during exposure, we found that high-dose exposure was associated with a higher risk for cardiovascular disease than medium-dose exposure (adjusted relative risk, 1.78 [CI, 1.36 to 2.33]).

Table 3 shows the rate ratios of cardiovascular events in different disease indication groups. Associations between high-dose glucocorticoid exposure and cardiovascular disease persisted within each disease indication group, although this was not statistically significant in the inflammatory bowel disease group.

The risks of glucocorticoid therapy occurred with all

major manifestations of cardiovascular disease (Figure). Glucocorticoid exposure was associated with a dose-dependent increased risk for heart failure (linear trend test for relative risk,  $P < 0.001$ ). Patients with high-dose glucocorticoid exposure had significantly increased risk for myocardial infarction, cerebrovascular events, and all-cause mortality. Patients with medium-dose exposure to glucocorticoids also had significantly increased risk for all-cause mortality.

Table 4 shows the sensitivity analysis of the relationship between high-dose glucocorticoid exposure and cardiovascular disease by unmeasured confounding. Unmeasured confounding could account for the observed association only if its distributions between the high-dose glucocorticoid exposure group and the comparator group were extremely unbalanced. For example, if the prevalence of the unmeasured confounding variable was 90% in the high-dose glucocorticoid exposure group and 10% in the comparator group and the relative risk for cardiovascular

Table 4. Sensitivity of the Rate Ratio for Cardiovascular Outcome to an Unmeasured Confounder

| Prevalence of Unmeasured Binary Confounder in the Exposed Group, % | Prevalence of Unmeasured Binary Confounder in the Comparator Group, % | Unmeasured Binary Confounder Rate Ratio | High Exposure Rate Ratio (95% CI)* |
|--|---|---|------------------------------------|
| 90   | 10  | 1.5                                     | 1.20 (1.01–1.42)                   |
| 90   | 50  | 1.5                                     | 1.43 (1.22–1.67)                   |
| 50   | 10  | 1.5                                     | 1.39 (1.18–1.63)                   |
| 90   | 10  | 2                                       | 0.96 (0.81–1.13)                   |
| 90   | 50  | 2                                       | 1.27 (1.11–1.45)                   |
| 50   | 10  | 2                                       | 1.21 (1.03–1.42)                   |
| 90   | 50  | 3                                       | 1.18 (1.01–1.38)                   |
| 50   | 10  | 3                                       | 0.99 (0.85–1.16)                   |
| 90   | 50  | 5                                       | 1.08 (0.85–1.26)                   |

\* Adjusted for age, sex, cardiovascular drug use, and unmeasured binary confounder.

disease associated with this unmeasured confounder was 2.0, only then would the adjusted relative risk for cardiovascular disease for the high-dose glucocorticoid exposure group become insignificant.

## DISCUSSION

Our population-based study shows that patients who were exposed to dosages of glucocorticoids greater than the equivalent of 7.5 mg of prednisolone per day during 1 to 5 years of follow-up had substantially higher rates of all cardiovascular diseases, including myocardial infarction, heart failure, and cerebrovascular disease. Cardiovascular risk in patients exposed to low doses of systemic glucocorticoids was similar to that of patients who were not exposed, except for a higher rate of congestive cardiac failure. Most patients exposed to glucocorticoids received only nonsystemic glucocorticoids, and these prescriptions were not associated with a measurable increase in rates of cardiovascular disease. Our findings are broadly consistent with those of a recently published case-control study, which demonstrated that higher doses of glucocorticoids are more prevalent in patients with cardiovascular disease (18).

Our study did not provide evidence that current use of glucocorticoids protected against occlusive vascular disease. Patients receiving glucocorticoids at the time were more likely to sustain a cardiovascular event than patients who were not receiving glucocorticoids. However, this may reflect an influence of cumulative glucocorticoid dose on cardiovascular outcome. In support of this, we observed an association between cumulative dose of exposure and outcome. In addition, prevalent users had higher risk than incident users. Along with the on-treatment versus off-treatment analyses, this suggests that dose, duration, and cumulative dose of exposure may be important.

In our observational study, a key question was whether the association of glucocorticoid use with cardiovascular disease reflects an effect of glucocorticoids or an association with the underlying disease for which glucocorticoids were prescribed. Increased mortality from ischemic heart disease has been reported in patients with asthma (19), chronic obstructive pulmonary disease (20, 21), inflammatory arthritis (22–26), and giant-cell arteritis (27). Disease activity may be directly associated with the risk for cardiovascular disease given the association of serum markers of inflammation with cardiovascular event rates in other studies (28). However, many of these patients were also receiving high doses of systemic glucocorticoids, and previous studies were not powered or designed to separate the influence of underlying disease from the influence of steroid therapy. Patients with inflammatory arthritis also take NSAIDs, which may increase the risk for congestive heart failure (29) and elevate blood pressure (30, 31). Furthermore, the presence of comorbid conditions may have introduced bias, such that clinicians were more likely to identify cardiovascular disease in patients with diseases being treated

with glucocorticoids. In our study, we found that relationships between glucocorticoid use and increased cardiovascular event rates persisted after correction for co-prescription of NSAIDs, bronchodilators, and disease-modifying antirheumatic drugs. Furthermore, we examined the consistency of the association between glucocorticoid use and cardiovascular disease in subgroups with identified underlying diseases. Our results argue strongly against the association's being confounded by indication and suggest that the association between cardiovascular disease and use of glucocorticoids was greater than any measured effect of underlying disease activity. The association was less marked in patients with inflammatory bowel disease, perhaps because a substantial proportion (about 37%) of steroid use in these patients was rectally administered topical steroids and the systemic absorption of steroid by this route may be less than that of orally administered drug.

We have not dissected the mechanisms of the association of glucocorticoid use and cardiovascular disease. If the association were entirely explained by adverse effects of glucocorticoids on "conventional" cardiovascular risk factors (blood pressure, blood glucose, and lipid profile), then adjustment for antihypertensive, lipid-lowering therapy and presence of diabetes would substantially attenuate the relationship. However, strong associations between glucocorticoid use and cardiovascular event rates remained after adjustment for these factors. This finding should, however, be interpreted with caution, since small adverse changes in blood pressure or metabolic profile might not have resulted in prescriptions of drug treatment to manage these risk factors. In addition, the effect on heart failure may be explained by sodium-retaining effects of glucocorticoids independent of any atherogenic effect.

Some other potential confounders could not be adjusted for from our data. We did not have information on disease severity, smoking, obesity, exercise, and diet, all of which might be adverse factors in patients who are prescribed glucocorticoids. However, we used propensity score methods and the Carstairs socioeconomic deprivation score as a surrogate to adjust for at least some of these factors (32, 33). We also performed a sensitivity analysis. Our results suggested that the association between high-dose glucocorticoid exposure and cardiovascular disease was robust to changes in any unmeasured confounders. Nevertheless, our study is observational, and we cannot exclude the possibility of unmeasured confounding.

The strengths of our study are the population-based cohort design and complete follow-up over the study period. This approach allows study of a "real world" population that represents all socioeconomic groups in a universal health care coverage scheme (34). Against this background, these data indicate that glucocorticoid therapy may be associated with an increased risk for cardiovascular disease and show that the adverse effect is substantial.

In summary, our study suggests that treatment with

high-dose glucocorticoids seemed to be associated with an increased risk for cardiovascular disease.

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## References

- Andrews RC, Walker BR. Glucocorticoids and insulin resistance: old hormones, new targets. *Clin Sci (Lond)*. 1999;96:513-23. [PMID: 10209084]
- Björntorp P, Holm G, Rosmond R. Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. *Diabet Med*. 1999;16:373-83. [PMID: 10342336]
- Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol, and cardiovascular disease. *Hypertension*. 2000;36:912-6. [PMID: 11082166]
- Walker BR, Phillips DI, Noon JP, Panarelli M, Andrew R, Edwards HV, et al. Increased glucocorticoid activity in men with cardiovascular risk factors. *Hypertension*. 1998;31:891-5. [PMID: 9535410]
- Fraser R, Ingram MC, Anderson NH, Morrison C, Davies E, Connell JM. Cortisol effects on body mass, blood pressure, and cholesterol in the general population. *Hypertension*. 1999;33:1364-8. [PMID: 10373217]
- Etzabe J, Vazquez JA. Morbidity and mortality in Cushing disease: an epidemiologic approach. *Clin Endocrinol (Oxf)*. 1994;40:479-84. [PMID: 8187313]
- Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M, et al. Persistence of increased cardiovascular risk in patients with Cushing disease after five years of successful cure. *J Clin Endocrinol Metab*. 1999;84:2664-72. [PMID: 10443657]
- Nashel DJ. Is atherosclerosis a complication of long-term corticosteroid treatment? *Am J Med*. 1986;80:925-9. [PMID: 3518440]
- Maxwell SR, Moots RJ, Kendall MJ. Corticosteroids: do they damage the cardiovascular system? *Postgrad Med J*. 1994;70:863-70. [PMID: 7870631]
- Rab ST, King SB 3rd, Roubin GS, Carlin S, Hearn JA, Douglas JS Jr. Coronary aneurysms after stent placement: a suggestion of altered vessel wall healing in the presence of anti-inflammatory agents. *J Am Coll Cardiol*. 1991;18:1524-8. [PMID: 1939956]
- Versaci F, Gaspardone A, Tomai F, Ribichini F, Russo P, Proietti I, et al. Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). *J Am Coll Cardiol*. 2002;40:1935-42. [PMID: 12475452]
- Evans JMM, MacDonald TM. The Tayside Medicines Monitoring Unit (MEMO). In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. Chichester, United Kingdom: J Wiley; 2000:361-74.
- British National Formulary. Number 35. London, United Kingdom: British Medical Association and Royal Pharmaceutical Society of Great Britain; 1998.

14. Scottish Health Statistics 1998. Edinburgh, Scotland, United Kingdom: ISD Scotland; 1998. Accessed at [www.show.scot.nhs.uk/isdonline/Scottish\\_Health\\_Statistics/SHS98/Appendix.pdf](http://www.show.scot.nhs.uk/isdonline/Scottish_Health_Statistics/SHS98/Appendix.pdf) in May 2004.

15. Wang J, Donnan PT, Steinke D, MacDonald TM. The multiple propensity score for analysis of dose-response relationships in drug safety studies. *Pharmacoepidemiol Drug Saf*. 2001;10:105-11. [PMID: 11499848]

16. Greenland S. Basic methods for sensitivity analysis and external adjustment. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven; 1998:34-57.

17. McMahon AD, Evans JM, McGilchrist MM, McDevitt DG, MacDonald TM. Drug exposure risk windows and unexposed comparator groups for cohort studies in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 1998;7:275-80. [PMID: 15073990]

18. Souverain PC, Berard A, van Staa TP, Cooper C, Leufkens HGM, Walker BR. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population-based case-control study. *Heart*. 2004;90:859-65.

19. Torén K, Lindholm NB. Do patients with severe asthma run an increased risk from ischaemic heart disease? *Int J Epidemiol*. 1996;25:617-20. [PMID: 8671564]

20. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ*. 1996;313:711-5; discussion 715-6. [PMID: 8819439]

21. Au DH, Lemaitre RN, Curtis JR, Smith NL, Psaty BM. The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists. *Am J Respir Crit Care Med*. 2000;161:827-30. [PMID: 10712329]

22. Mutru O, Laakso M, Isomäki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. *Br Med J (Clin Res Ed)*. 1985;290:1797-9. [PMID: 3924262]

23. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum*. 1994;37:481-94. [PMID: 8147925]

24. McEntegart A, Capell HA, Czeran D, Rumley A, Woodward M, Lowe GD. Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. *Rheumatology (Oxford)*. 2001;40:640-4. [PMID: 11426020]

25. Wällberg-Jonsson S, Johansson H, Ohman ML, Rantapää-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol*. 1999;26:2562-71. [PMID: 10606363]

26. DeMaria AN. Relative risk of cardiovascular events in patients with rheumatoid arthritis. *Am J Cardiol*. 2002;89:33D-38D. [PMID: 11909559]

27. Uddhammar A, Eriksson AL, Nyström L, Stenling R, Rantapää-Dahlqvist S. Increased mortality due to cardiovascular disease in patients with giant cell arteritis in northern Sweden. *J Rheumatol*. 2002;29:737-42. [PMID: 11950015]

28. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115-26. [PMID: 9887164]

29. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med*. 2000;160:777-84. [PMID: 10737277]

30. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med*. 1993;153:477-84. [PMID: 8435027]

31. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med*. 1994;121:289-300. [PMID: 8037411]

32. Turner R. Smoking. In: Dong W, Erins B, eds. *Scotland's Health: Scottish Health Survey 1995*. Vol 1. Edinburgh, Scotland, United Kingdom: Stationary Office; 1997:140-1.

33. Evans JM, Newton RW, Ruta DA, MacDonald TM, Morris AD. Socio-economic status, obesity and prevalence of Type 1 and Type 2 diabetes mellitus. *Diabet Med*. 2000;17:478-80. [PMID: 10975218]

34. MacDonald TM, Morant SV, Robinson GC, Shield MJ, McGilchrist MM, Murray FE, et al. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ*. 1997;315:1333-7. [PMID: 9402773]

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