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The Effect of Low-Dose Glucocorticoids Over Two Years on Weight and Blood Pressure in Rheumatoid Arthritis: Individual Patient Data From Five Randomized Trials

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Background: Weight gain and hypertension are well known adverse effects of treatment with high-dose glucocorticoids.

Objective: To evaluate the effects of 2 years of low-dose glucocorticoid treatment in rheumatoid arthritis (RA).

Design: Pooled analysis of 5 randomized controlled trials with 2-year interventions allowing concomitant treatment with disease-modifying antirheumatic drugs.

Setting: 12 countries in Europe.

Patients: Early and established RA.

Intervention: Glucocorticoids at 7.5 mg or less prednisone equivalent per day.

Measurements: Coprimary end points were differences in change from baseline in body weight and mean arterial pressure after 2 years in intention-to-treat analyses. Difference in the change of number of antihypertensive drugs after 2 years was a secondary end point. Subgroup and sensitivity analyses were done to assess the robustness of primary findings.

Results: A total of 1112 participants were included (mean age, 61.4 years [SD, 14.5]; 68% women). Both groups gained weight in 2 years, but glucocorticoids led, on average, to 1.1 kg (95% CI, 0.4 to 1.8 kg; $P < 0.001$) more weight gain than the control treatment. Mean arterial pressure increased by about 2 mm Hg in both groups, with a between-group difference of −0.4 mm Hg (CI, −3.0 to 2.2 mm Hg; $P = 0.187$). These results were consistent in sensitivity and subgroup analyses. Most patients did not change the number of antihypertensive drugs, and there was no evidence of differences between groups.

Limitation: Body composition was not assessed, and generalizability to non-European regions may be limited.

Conclusion: This study provides robust evidence that low-dose glucocorticoids, received over 2 years for the treatment of RA, increase weight by about 1 kg but do not increase blood pressure.

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For author, article, and disclosure information, see end of text.
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Glucocorticoids are often used in the management of rheumatoid arthritis (RA). They reduce disease activity and have disease-modifying properties, that is, retard progression of joint damage (1, 2). However, glucocorticoids are associated with various adverse events (AEs), especially if used at higher dosages for prolonged periods of time. In a survey of rheumatologists and patients with inflammatory rheumatic diseases, weight gain and hypertension were ranked among the most worrisome AEs (3). In observational studies, use of glucocorticoids in RA has repeatedly been associated with both hypertension (4, 5) and weight gain (6–9).

However, observational studies investigating glucocorticoids in RA are prone to various sorts of confounding. Because patients with more severe disease, including higher disease activity, are more likely to be treated with glucocorticoids, and dose and duration are also strongly associated with disease severity, it is almost impossible to disentangle the effects of glucocorticoids and disease severity in an observational study. Randomized controlled trials (RCTs) are protected from bias because allocation to treatment with or without glucocorticoids is by chance. Only inference from trials can prove causality. However, trials often have small sample sizes, which reduce statistical power.

We acquired and combined individual participant data from 5 RCTs of glucocorticoid treatment in RA. Analyzing individual participant data has many advantages compared with simple aggregate-level meta-analysis, including the ability to assess and impute missing data, validate results from original studies, include nonpublished data, evaluate prerequisites for statistical modeling, use the same statistical model for all studies, and allow for subgroup analyses (10).

In this pooled analysis of individual participant data, by combining data from RCTs, we quantified the effects of glucocorticoids at a dose of 7.5 mg or less prednisone equivalent per day over 2 years on weight and blood pressure in RA.

Methods

We registered a detailed protocol for this study with protocols.io (dx.doi.org/10.17504/protocols.io.x54v9y4d1g3e/v1)

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before the study was initiated. All included trials were approved by either central or individual site institutional ethics committees.

Included Trials

Eligibility criteria for our study (including only RCTs) were as follows: population: participants with RA (either the 1987 American College of Rheumatology criteria or the 2010 European League Against Rheumatism/American College of Rheumatology criteria)–both early and established RA; intervention: low-dose glucocorticoids (prednisone equivalent, ≤7.5 mg/d) (11) over at least 2 years; control: any; and outcome: blood pressure and/or body weight had to have been measured.

Before the start of the study, the primary investigator team at Charité contacted the principal investigators of the trials that were identified during a prior systematic literature review (12): the GLORIA (Glucocorticoid Low-dose Outcome in RheumatoId Arthritis) trial (Boers and colleagues [1]), ARC (Arthritis and Rheumatism Council Low-Dose Glucocorticoid Trial) (Kirwan [2]), Intramuscular Methylprednisolone Study (Choy and colleagues [13]), LDPT (Low-Dose Prednisolone Therapy) trial (Wassenberg and colleagues [14]), and BARFOT (Better Anti-rheumatic Farmacotherapy) trial (Svensson and colleagues [15]). Concomitant treatment with disease-modifying antirheumatic drugs (DMARDs) was allowed in all trials. **Supplement Table 1** (available at Annals.org) shows DMARD use in these trials. Concerning glucocorticoids, Choy and colleagues (13) used once-monthly depot intramuscular glucocorticoids. Three trials (1, 13, 14) used a dose of 5 mg prednisone equivalent per day (ARC [2] and BARFOT [15]: 7.5 mg/d). All trials were done in Europe (12 countries).

In 4 trials (all except BARFOT [15]), patients, care providers, and investigators were blinded. The control treatment in 4 trials was a placebo (in addition to DMARD treatment). In the BARFOT trial, the control treatment consisted of Swedish standard of care DMARD treatment and no placebo.

Of note, GLORIA was the only trial with a mean population age of 65 years or older. Furthermore, this trial contributed about 40% of the overall study population. For weight, we had access to data from all 5 trials. For blood pressure analyses, only 4 of 5 trials could be included. Generally, a sixth trial would have fit our study (WOSERACT [West of Scotland Early Rheumatoid Arthritis Corticosteroid Therapy] trial, Capell and colleagues) (16), but the principal investigator and coauthors did not respond to our repeated inquiries.

Outcome Measures

We defined change in body weight in kilograms and mean arterial pressure ([MAP] which has been shown to be a predictor of cardiovascular disease similarly to systolic or diastolic blood pressure) (17) in millimeters of mercury from baseline until 24 months as coprimary outcomes. Mean arterial pressure was estimated as follows (18):

$$\text{MAP} = (\text{systolic blood pressure} + [2 * \text{diastolic blood pressure}])/3$$

As a secondary outcome, we included the change in number of antihypertensive drugs. This outcome measure was chosen because patients may start to take antihypertensives during the course of the study, thereby leading to overall stable MAP values. Of note, all participants received standard of care with regard to blood pressure management.

Data Management and Extraction

The primary investigator team at Charité received the data from the principal investigator of each trial. The requested data were defined beforehand; details are available in the protocol referenced earlier.

Risk of Bias Within Trials

Because it was suggested during peer review, version 2 of the Cochrane Risk of Bias Tool for randomized trials (19) was used to judge, separately for each outcome and each trial, the risk of bias in the following domains: randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Two authors (A.P. and Z.B.) not involved in any of the original trials independently judged the risk of bias and met to agree on final decisions. Of note, judgments about appropriate analyses, missing outcome data, and selection of the reported results pertain to our very own study methods, as weight and blood pressure were not comprehensively analyzed and reported in the original trial reports.

Statistical Analysis

We summarized the baseline characteristics for each trial by number (percentage) and mean (SD) or median (inner quartiles, depending on the variable's distribution). The primary analyses were based on analyses of covariance with a model containing the following terms: treatment (2 levels), baseline value of the outcome (1 for each participant), and trial identifier (5 levels). Trial identifier was treated as a random-effects factor and accounted for clustering of patients within trials. Contrasts between groups were reported as least-squares mean with 95% CI.

All analyses were based on the intention-to-treat approach, meaning that all patients were included in the statistical analyses regardless of any protocol violations or loss to follow-up. Nine patients in the BARFOT trial who did not receive any study medication could not be included in the analyses. Flow charts of all trials and the number of participants contributing to our analyses can be found in **Supplement Figures 1** to **6** (available at Annals.org).

Missing data were handled via multiple imputation by chained equations under the "missing at random" assumption. No imputations were done for trials with missing data for all patients for a given outcome. All *P* values and 95% CIs are 2-sided, and the threshold for statistical significance α was set at 0.05. R software, version 4.0.3 (R Foundation for Statistical Computing), with packages *lme4* (20), *emmeans* (21), and *mice* (22), was used for all statistical analyses.

Additional Analyses

To underpin the findings of our primary analyses, several additional analyses were planned in our study protocol. An analysis differentiating between effects of low-dose glucocorticoids on systolic and diastolic blood pressure was done, although the main analysis did not indicate a statistically significant difference because it was encouraged during peer review. Further subgroup analyses compared patients with arterial hypertension (that is, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or antihypertensive drug intake) at baseline with those without hypertension at baseline. Another analysis compared patients being overweight (body mass index ≥25 kg/m^2) with those not being overweight at baseline. Subgrouping of individual patients was based on nonimputed baseline data. In addition, we assessed whether the effects differed at glucocorticoid doses of 7.5 mg/d versus 5 mg/d and whether the effects differed with the type of application (oral vs. subcutaneous). Furthermore, we conducted sensitivity analyses using a simplistic nonresponder imputation assuming data is "missing not at random" as well as an analysis based on data "as observed" assuming data is "missing completely at random." Finally, as a sensitivity analysis, standard fixed-effects meta-analyses were done for our coprimary outcomes. These standard meta-analyses also served as a means to estimate the inconsistency measure I^2, which translates into the proportion of variation across studies that is due to heterogeneity between studies and not due to random sampling error (23).

Multiplicity

We did not apply explicit adjustments for multiplicity, rather we kept the number of statistical tests at an absolute minimum and used a gatekeeping (hierarchical) procedure. First, we did tests for statistical significance only for our 2 coprimary outcomes. Following peer reviewers' requests, we conducted a sensitivity analysis differentiating between systolic and diastolic blood pressure. No tests for statistical significance were done for subgroup analyses (that is, no *P* values are provided).

Role of the Funding Source

No specific funding was acquired for this study.

RESULTS

Baseline Characteristics

Data from 1112 randomized patients (low-dose glucocorticoids, 548; control, 564) were included in the pooled

Table 1. Baseline Characteristics Stratified by Trial*

Characteristic	Boers et al., 2022 (1) (*n* = 451; Oral Prednisolone, 5 mg/d)	Choy et al., 2005 (13) (*n* = 91; Subcutaneous Methylprednisolone, 120 mg/mo)	Kirwan, 1995 (2) (*n* = 128; Oral Prednisolone, 7.5 mg/d)	Svensson et al., 2005 (15) (*n* = 250; Oral Prednisolone, 7.5 mg/d)	Wassenberg et al., 2005 (14) (*n* = 192; Oral Prednisolone, 5 mg/d)
Median age (IQR), *y*	72 (68–76)	58 (12)†‡	48 (42–58)	56 (46–66)	56 (41–62)
Women, *n* (%)	317 (70)	71 (78)‡	81 (63)	159 (64)	134 (70)
Seropositivity, *n* (%)					
ACPA positive	253 (64)	NA	NA	149 (64)	NA
RF positive	299 (68)	47 (59)‡§	102 (86)‖	163 (66)	103 (54)
Smoking status, *n* (%)					
Never	221 (49)	NA	NA	92 (37)	NA
Current	62 (14)	NA	NA	76 (31)	NA
Previous	166 (37)	NA	NA	81 (33)	NA
Mean BMI (SD), *kg/m^2*	27.3 (4.5)	NA	NA	25.8 (4.2)	25.7 (4.5)
Mean DAS28 score (SD)	4.52 (1.05)	5.39 (1.29)	NA	5.35 (1.08)	NA
Median disease duration (IQR), *y*	7.0 (3–15)	14 (9)†‡	1.3 (0.29)†‡	0.5 (0.3–0.7)	0.5 (0.3–0.1)
Mean pain score (SD)	5.5 (2.4)	4.6 (2.4)	4.8 (2.5)	4.8 (2.2)	5.7 (2.2)
Median ESR (IQR), *mm/h*	25.0 (14–40)	26.0 (11–40.5)	45.0 (26–60)	32.5 (18–52)	38.0 (24–60)
Median CRP (IQR), *mg/L*	5.0 (2.7–13.7)	11.1 (5–28.2)	19.0 (10–36)	23.0 (10–52)	NA
Median HAQ score (IQR)	1.25 (0.63–1.75)	1.75 (1–2)¶	1.3 (0.7–1.8)	1.0 (0.5–1.4)	NA**
Mean weight (SD), *kg*	74.8 (13.5)	71.0 (21.7)	69.2 (13.7)	74.0 (13.9)	72.2 (14.2)
Mean MAP (SD), *mm Hg*	98.7 (11.6)	93.8 (11.7)	98.4 (12.6)	NA	95.2 (10.8)
Mean systolic blood pressure (SD), *mm Hg*	138.4 (19.6)	129.6 (21.1)	131.1 (19.4)	NA	128.0 (16.3)
Mean diastolic blood pressure (SD), *mm Hg*	78.8 (10.0)	75.9 (9.0)	82.1 (10.8)	NA	78.7 (9.5)
Median number of antihypertensive drugs (IQR)	1 (0–2)	NA	0 (0–0)	NA	NA

ACPA = antibody citrullinated protein antibodies; BMI = body mass index; CRP = C-reactive protein; DAS28 = Disease Activity Score-28 joints; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; IQR = interquartile range; MAP = mean arterial pressure; NA = not available; RF = rheumatoid factor.

* Values are based on individual participant data that were available to the study team unless otherwise stated.

† Value is mean (SD).

‡ Numbers not available on an individual level (extracted from published aggregate data).

§ Rheumatoid factor status known in 80 persons.

‖ Positive latex agglutination test.

¶ Modified HAQ was used in this study.

** The Hannover Functional Ability Questionnaire was used in this study to evaluate disability.

Table 2. Changes in Weight, Blood Pressure, and Number of Antihypertensive Drugs in the Glucocorticoid and Control Groups*

Outcome	Patients, *n*	Glucocorticoid Group†	Patients, *n*	Control Group†	Contrast‡	*P* Value
Weight, *kg*	548	1.8 (0.8)	564	0.7 (0.8)	1.1 (0.4 to 1.8)	<0.001
MAP, *mm Hg*	429	2.3 (1.3)	433	2.7 (1.4)	−0.4 (−3.0 to 2.2)	0.187
Systolic blood pressure, *mm Hg*	429	2.9 (2.0)	433	3.9 (2.7)	−0.9 (−7.8 to 5.9)	0.062
Diastolic blood pressure, *mm Hg*	429	1.8 (1.3)	433	2.0 (1.3)	−0.1 (−1.6 to 1.3)	0.72
Number of antihypertensive drugs§	276	0 (0 to 0)	282	0 (0 to 0)	0 (0 to 0)	‖

MAP = mean arterial pressure.
* Heterogeneity and inconsistency measures from standard meta-analyses corresponded to I^2 = 0% for weight and I^2 = 0% for MAP; see Supplement Figure 7 (available at Annals.org).
† Values are least-squares mean changes (SE).
‡ Differences in least-squares mean changes (95% CIs).
§ Nonnormal distribution: The group estimates are median changes (inner quartiles), and effect estimate is the median of differences between the 2 groups with corresponding 95% CIs, with no imputation for missing data and ignoring the grouping within studies. Analysis on the studies separately, and separate analyses on each imputed data set showed similar results.
‖ In line with the study protocol, no significance test was done for this secondary outcome.

analyses. The mean age of patients was 61.4 years (SD, 14.5); 68% were women (Table 1). A mean Disease Activity Score-28 joints of 4.87 (SD, 1.16) indicates moderate disease activity at baseline. Mean body weight and MAP before treatment were 73 kg (SD, 14) and 98 mm Hg (SD, 12), respectively. There was heterogeneity across trials, especially regarding disease duration. Weight and blood pressure levels were mostly similar at baseline. Flow charts of all individual trials and of the participants included in our analyses can be found in Supplement Figures 1 to 6.

Risk of Bias

Risk of bias assessments can be found in Supplement Table 2 (available at Annals.org). Regarding weight, 2 trials had a low risk of bias, there were some concerns for 1 trial, and 2 trials had a high risk of bias. The high risk of bias was connected to unclear concealment of the allocation sequence, although lack of baseline imbalances did not suggest a problem with the randomization process. For blood pressure, the risk of bias judgments were similar.

Body Weight

After 2 years, participants in both groups had gained weight, but more in the glucocorticoid group (glucocorticoids, mean gain 1.8 kg [SE, 0.8]; control, 0.7 kg [SE, 0.8]; difference, 1.1 kg [95% CI 0.4 to 1.8 kg]; $P < 0.001$) (Table 2). These results were consistent in 3 of 4 subgroup analyses stratified by dose and way of administration (Table 3). Only in the subgroup analysis focusing on subcutaneous administration there was no statistically significant difference between the glucocorticoid and placebo group. However, this analysis included only 1 trial with 91 participants (13). Interestingly, the participants of this trial were the only ones to lose instead of gain weight over 2 years (1.2 kg and 0.8 kg in the glucocorticoid and placebo group, respectively).

In addition, we performed a subgroup analysis looking at patients with or without arterial hypertension or overweight body mass index status at baseline, but the results remained consistent (Figure, *top*). Sensitivity analyses based on nonresponder imputation and data as observed did not lead to different interpretations compared with the primary analysis results (Supplement Table 3, available at Annals.org).

Blood Pressure

Data were available to calculate MAP in 4 trials. The MAP increased by more than 2 mm Hg in both groups after 2 years. However, there was no statistically significant difference in change between patients treated with glucocorticoids and control participants (contrast, -0.4 mm Hg [CI, -3.0 to 2.2 mm Hg]; $P = 0.187$) (Table 2). These results were also consistent across different subgroup analyses (Table 3). There were no statistically significant differences in change from baseline in the 5 mg/d or 7.5 mg/d groups compared with control or in oral or subcutaneous glucocorticoids compared with control.

Once again, subgroup analyses assessed whether the results were consistent in patients being hypertensive or overweight at baseline (Figure, *bottom*). In a sensitivity analysis, we also differentiated between systolic and diastolic blood pressure (Table 2). Differences in point estimates between glucocorticoid and control groups were small, and *P* values did not reach the threshold of statistical significance. Again, sensitivity analyses (based on nonresponder imputation and data as observed) did not lead to different interpretations compared with the primary analysis results (Supplement Table 3).

Number of Antihypertensive Drugs

For 2 trials, data were available on the number of antihypertensive drugs taken by each participant (n = 577 at baseline and n = 558 at follow-up). The median change in number of antihypertensives was 0 in both groups (0 [CI, 0 to 0]) (Table 2). Nineteen participants of 143 with available data and no antihypertensive at baseline had started at least 1 antihypertensive treatment at follow-up in the glucocorticoid groups, and 12 out of 152 in the control groups (13% vs. 8%). In the GLORIA trial, which recorded antihypertensive drug use in detail, 95 patients and 92 patients in the glucocorticoid and placebo groups, respectively, took the same antihypertensive substances without any change in dosage or the addition of another substance after 2 years. Of the patients who took the same substances without an additional substance at baseline and 2 years, 3 and 5 had a dose increase in the glucocorticoid and placebo group, respectively, and 1 and 2 patients had a dose decrease.

Discussion

In this pooled analysis of 5 RCTs, all patients gained weight and increased their blood pressure slightly over 2 years. Patients receiving low-dose glucocorticoids gained about 1 additional kilogram of weight compared with control participants, but we found no evidence of glucocorticoid effects on blood pressure or indirectly on the number of antihypertensive drugs. These results proved consistent in many subgroup and sensitivity analyses.

Glucocorticoids are "old" drugs; their discovery led to the only Nobel Prize ever awarded to a rheumatologist, Philip Hench, in 1951 as a previously untreatable and debilitating disease received its first effective remedy (24). Hench and colleagues were aware of the potential AEs right from the beginning, but despite their warnings, glucocorticoids were released to the profession without proper documentation or training in the absence of regulatory oversight. As a consequence, glucocorticoids were often used in high dosages over long periods of time. The resulting high incidence of glucocorticoid-related AEs made glucocorticoids fall out of favor (25).

Since then, many other drug classes to treat RA have been approved. Rheumatologists can choose from various effective drugs and drug classes to treat RA. Nevertheless, at present, a substantial number of patients with RA receive glucocorticoids over long periods of time. For example, in the German CAPEA (Course And Prognosis of Early Arthritis) cohort, 47% of patients were still receiving glucocorticoids after 2 years (26). In a French cohort study enrolling patients with early RA, 64% received glucocorticoids for the whole follow-up (median, 7 years) (27). Interestingly, with a mean of 3.1 mg (SD, 2.9) prednisone equivalent per day, the patients received an even lower dose than the ones investigated in our pooled analysis. Data from Australia (28), North America (29–31), and China (32) also show that glucocorticoids are often prescribed for long-term treatment. This is especially surprising given that both European and American RA recommendations and guidelines advise against long-term use of low-dose glucocorticoids (33, 34).

Guidelines advise against long-term low-dose glucocorticoid use not because of lack of efficacy—glucocorticoids have an effect on disease activity and radiographic progression even at a low dose (1, 2) and the risk for flare is lower in patients continuing low-dose glucocorticoids versus those withdrawing them (35)—but because of a fear of AEs. However, although it is beyond doubt that medium-to-high dose glucocorticoids can cause various serious and nonserious AEs, the evidence for toxicity of low-dose glucocorticoids is much less clear.

Most research on long-term low-dose glucocorticoid safety in RA is observational—that is, from nonrandomized studies. However, observational studies in glucocorticoids are confounded by indication. Patients with higher disease activity and more severe disease are at higher risk for AEs regardless of therapy, and many of these AEs resemble glucocorticoid-related AEs—for example, cardiovascular disease, glucose intolerance, infections, and osteoporosis. However, these patients also receive more and higher doses of glucocorticoids with a similar spectrum of AEs, so it is almost impossible to disentangle the effects of these 2 exposures. The best approach would be to meticulously document disease severity and activity over time as well as document the reasons to start, stop, or change the glucocorticoid dose, and likewise other antirheumatic drugs; however, prospective (cohort) studies with such rigorous documentation have not yet been done. Randomized controlled trials are protected from various sorts of bias as patients are selected by chance whether to receive glucocorticoids. Unfortunately, RCTs often have small sample sizes and inadequate statistical power. By conducting a pooled analysis of trials with individual participant data from a total of more than 1000 patients, we were able to overcome this hurdle and provide high-quality evidence.

In the past, several observational studies associated glucocorticoids with arterial hypertension in RA, some at moderate-to-high doses and some at low doses. However, most of these studies did not adjust for disease activity or document reasoning behind glucocorticoid therapy as suggested earlier (4, 5, 36). In our individual participant data analysis of several RCTs, we did not find a link between glucocorticoids and changes in blood pressure with 7.5 mg or less prednisone equivalent per day. Interestingly, even a trial of 10 mg of prednisone per day in RA (37), which we did not include here, did not find a statistically significant effect on blood pressure, although it may have been underpowered, with only 81 patients

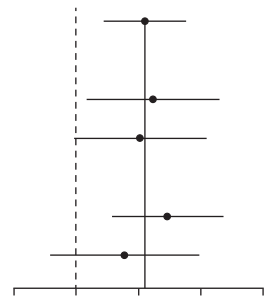
Table 3. Subgroup Analyses Comparing the Effects of Glucocorticoid Dosage (5 vs. 7.5 mg/d)* and Way of Administration (Oral vs. Subcutaneous)

Subgroup	Patients, *n*	Glucocorticoid Group†	Patients, *n*	Control Group†	Contrast‡
Weight, *kg*					
Trials with 5 mg of glucocorticoids per day	368	0.9 (0.9)	366	−0.1 (0.9)	1.0 (0.2 to 1.9)
Trials with 7.5 mg of glucocorticoids per day	180	3.3 (0.8)	198	2.1 (0.8)	1.2 (0.3 to 2.2)
Trials with oral glucocorticoids	500	2.5 (0.6)	521	1.3 (0.7)	1.2 (0.6 to 1.9)
Trials with subcutaneous glucocorticoids	48	−1.2 (0.8)	43	−0.8 (0.8)	−0.4 (−2.8 to 2.0)
Mean arterial pressure, *mm Hg*					
Trials with 5 mg of glucocorticoids per day	368	2.1 (1.5)	366	2.0 (1.7)	0.1 (−2.8 to 2.9)
Trials with 7.5 mg of glucocorticoids per day	61	1.8 (1.6)	67	4.9 (1.7)	−3.1 (−7.6 to 1.5)
Trials with oral glucocorticoids	381	2.2 (1.6)	390	2.8 (1.7)	−0.6 (−3.3 to 2.1)
Trials with subcutaneous glucocorticoids	48	4.0 (2.6)	43	2.8 (2.2)	1.2 (−5.6 to 8.0)

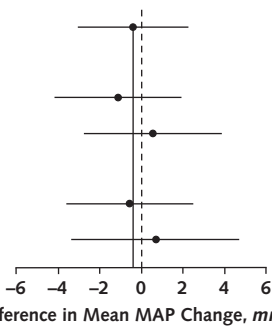
* Glucocorticoid dosage is in prednisone equivalent units.
† Values are least-squares mean changes (SE).
‡ Differences in least-squares mean changes (95% CIs).

Figure. Subgroup analyses stratifying patients by their baseline weight and blood pressure status.

Subgroup	Trials, *n*	Patients, *n* (Glucocorticoid/ Control)	Mean Change (SE)		Mean Difference (95% CI)	
			Glucocorticoid	Control	Contrast	Contrast Between Subgroups
Overall	5	548/564	1.8 (0.8)	0.7 (0.8)	1.1 (0.4 to 1.8)	
Hypertension	4					0.2 (–1.3 to 1.7)
Yes		224/232	1.8 (0.9)	0.6 (1.0)	1.2 (0.2 to 2.3)	
No		176/179	1.7 (0.9)	0.6 (0.9)	1.0 (–0.0 to 2.1)	
Overweight	3					0.7 (–0.9 to 2.2)
Yes		249/270	2.2 (0.6)	0.7 (0.6)	1.5 (0.6 to 2.3)	
No		185/174	1.7 (0.6)	0.9 (0.7)	0.8 (–0.4 to 2.0)	



Overall	4	429/433	2.3 (1.3)	2.7 (1.4)	–0.4 (–3.0 to 2.2)	
Hypertension	4					–1.7 (–5.1 to 1.7)
Yes		224/232	2.6 (1.6)	3.7 (1.7)	–1.1 (–4.2 to 1.9)	
No		176/179	1.3 (1.6)	0.7 (1.7)	0.5 (–2.7 to 3.8)	
Overweight	2					–1.3 (–5.1 to 2.6)
Yes		194/193	2.0 (2.5)	2.6 (2.6)	–0.6 (–3.6 to 2.4)	
No		121/122	2.0 (2.7)	1.3 (2.6)	0.7 (–3.3 to 4.7)	



MAP = mean arterial pressure. **Top.** The difference in mean weight change was assessed. **Bottom.** The difference in MAP change was analyzed.

enrolled. Again, there is some increase in blood pressure overall that could be observed in the individual patient but cannot be attributed to glucocorticoids.

Concerning weight, both observational and trial data consistently point to glucocorticoid-related weight gain (6, 8, 9), although a threshold dose of 5 to 7.5 mg/d has been suggested below which no weight gain is to be expected (9). Our subgroup analyses indicate that a 2-year treatment with glucocorticoids, even at a low dose of 5 mg/d, leads to some weight gain in patients with RA. However, only about 1 additional kilogram is gained on average with 5 mg/d, and only slightly more with 7.5 mg/d. In the clinic setting with individual patients it is important to stress that about only half of the reported weight gain in the trial population is due to glucocorticoids; in other words, patients receiving the control treatment gain weight, too.

Our study has many limitations. First, all trials originated in Europe, which may affect the generalizability of our results, as patients and treatments may differ between different regions. Secondly, populations enrolled in RCTs are often highly selected (for example, regarding comorbidities or age). The generalizability of our results may also be affected by differences in patient characteristics compared with the general RA population, such as smoking or disease activity. In the 2 studies with respective data, smoking was more common (Svensson and colleagues: 31%; Boers and colleagues: 14%) than, for example, in the 2020 U.S. adult population (12.5%) (38). Also, the mean Disease Activity Score-28 joints in our study was lower than what has been reported from trials investigating biologic agents in RA (39). In general, however, trials of glucocorticoids in RA seem to be of better generalizability than, for example, trials of biologics (40). In addition, our data set included 1 trial (GLORIA) (1) that explicitly included elderly patients and patients with multimorbidity who are often excluded from RA trials (40). Another limitation is heterogeneity between trials. In our study, different dosages and ways of glucocorticoid application were studied, eligibility criteria varied, and patients were enrolled in various countries. However, because our overall results were consistent in all subgroups of trials, this actually makes our findings more robust. Also, there are other safety concerns regarding low-dose glucocorticoids, for example, an increased risk for infections (12, 41) or adrenal insufficiency (42), but these were beyond the scope of this study. Moreover, we did not assess body composition, and glucocorticoids have been suggested to cause sarcopenia (43) and lead to fat redistribution from the extremities to the abdomen (44). Furthermore, a systematic search for literature was not part of this study. Yet, we were able to make use of a recent systematic literature review that identified relevant studies

(12). Besides, some trials were done and published years ago. However, methotrexate–which is still considered the "anchor drug" for RA (34)–was already available for all trials included here, as was, for example, sulfasalazine. Also, the GLORIA trial, which provided a large amount of data for the study at hand, is very recent and was published in 2022. On top of that, a potential pitfall of RCTs is differential attrition, that is, if dropout rates differ between treatment groups (45). In 3 trials of our study that had respective data (1, 13, 14), however, no more patients dropped out due to AEs in the glucocorticoid groups compared with the control groups, and in a prior systematic literature review and meta-analysis, we found no increased risk for withdrawals due to AEs with low-dose glucocorticoids compared with placebo (risk ratio, 0.97 [CI, 0.69 to 1.37]) (12). Penultimately, blood pressure measurements in the studies pooled here may not have been done in a strictly protocolized way. This may have led to less precision. Finally, we provide 2-year data, which is arguably a relatively long time frame with regard to randomized trials, but still a limited time frame taking into account the long-term course of RA.

Strengths of our study include the randomized design, high number of patients, protocolized study execution, expertise from several study groups, access to previously unpublished data, and in particular our ability to use individual participant data in contrast to aggregated data.

In conclusion, this pooled analysis of 5 RCTs in RA found that 2 years of low-dose glucocorticoid treatment leads to a modest weight gain of about 1 kg but has no effect on blood pressure.

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Reproducible Research Statement: *Study protocol:* The protocol for this study is available at protocols.io (dx.doi.org/10.17504/protocols.io.x54v9y4d1g3e/v1). *Statistical code:* The computer code is available from the study statistician (S.M.N.) on reasonable request. *Data set:* Our data set was generated by pooling individual data from several RCTs. The respective data sharing agreements for each trial included use of the data for conducting the analyses for this study only, and we do not have the rights to share the data. Requests for the respective data need to be made to the principal investigators of each study (M.B., E.C., J.K., B.S., and S.W.).

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