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Metabolic adverse events associated with systemic corticosteroid therapy—a systematic review and meta-analysis

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ABSTRACT

Objectives To assess the risk of new-onset or worsening hyperglycaemia, hypertension, weight gain and hyperlipidaemia with systemic corticosteroid therapy (CST) as reported in published randomised control trial (RCT) studies.

Data sources Literature search using MEDLINE, EMBASE, Cochrane library, Web of Science and Scopus

Study eligibility criteria Published articles on results of RCT with a systemic CST arm with numerical data presented on adverse effect (AE).

Participants and interventions Reports of hyperglycaemia, hypertension, weight gain and hyperlipidaemia associated with systemic CST in patients or healthy volunteer's ≥17 years of age.

Study appraisal methods Risk of bias tool, assessment at the level of AE and key study characteristics.

Results A total of 5446 articles were screened to include 118 studies with 152 systemic CST arms (total participants=17 113 among which 8569 participants treated with CST). Pooled prevalence of hyperglycaemia in the CST arms within the studies was 10% (95% CI 7% to 14%), with the highest prevalence in respiratory illnesses at 22% (95% CI 9% to 35%). Pooled prevalence of severe hyperglycaemia, hypertension, weight gain and hyperlipidaemia within the corticosteroid arms was 5% (95% CI 2% to 9%), 6% (95% CI 4% to 8%), 13% (95% CI 8% to 18%), 8% (95% CI 4% to 17%), respectively. CST was significantly associated hyperglycaemia, hypertension and weight gain as noted in double-blinded placebo-controlled parallel-arms studies: OR of 2.13 (95% CI 1.66 to 2.72), 1.68 (95% CI 0.96 to 2.95) and 5.20 (95% CI 2.10 to 12.90), respectively. Intravenous therapy posed higher risk than oral therapy: OR of 2.39 (95% CI 1.16 to 4.91).

Limitations There was significant heterogeneity in the AE definitions and quality of AE reporting in the primary studies and patient populations in the studies. The impact of cumulative dose effect on incidental AE could not be calculated.

Conclusions and implications of key findings Systemic CST use is associated with increased risk of metabolic AEs, which differs for each disease group and route of administration.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a comprehensive large systematic review and meta-analysis of metabolic adverse effect (AE) associated with systemic corticosteroid therapy (CST) based on data from randomised control trials, thus presenting high quality data.
⇒ The data were studied within several disease group, stratified by dose and duration in an adult population allowing for assessment of several factors that can have an impact on AE.
⇒ Impact of cumulative doses of systemic CST on AE could not be studied. Some AEs which are associated with duration of intervention exposure and factors affecting this are better studied in observational studies.
⇒ The study did not allow for analysis of geographic, ethnic or genetic variations in corticosteroid associated AEs.

INTRODUCTION

Rationale

Systemic corticosteroids are potent anti-inflammatory and immunomodulatory agents. They are an integral tool in the armamentarium of therapies for various medical conditions such as autoimmune disease groups, malignancies, asthma and more recently in COVID-19 related inflammation. Corticosteroids were first proposed for therapy in the 1950s. As research on corticosteroid therapy (CST) progressed, low dose (<15 mg/day) and even lower dose steroids (<5 mg/day) gained recognition as a 'bridge' therapy and emerged as an alternative to non-steroidal anti-inflammatory drugs (NSAIDs) in inflammatory conditions.

With experience of CT use, a myriad of challenging AEs including alterations in glucose and lipid metabolism, cardiovascular disease, impaired immune response and wound healing and psychiatric disturbances posed a dilemma to the treating physician. Immediate AEs include fluid changes, insomnia

and weight gain. Hyperglycaemia, central obesity, hypertension and osteopenia seem to be associated with both short-term and long-term use, while osteoporosis, adrenal suppression and skin changes usually occur with long-term CST use. These well-characterised AEs seem to be related to CST dose and duration; however, the severity and impact of AEs is still variable and unpredictable and cannot be generalised to all agents within the CST class. For instance, the anti-inflammatory potential of dexamethasone is six times higher than prednisolone and it is generally associated with a higher rate of AEs. The underlying pharmacokinetic and pharmacodynamic factors of the specific drug and the underlying disease probably account for this variability. Dexamethasone is longer acting in comparison to prednisolone with duration of biological action ranging from of 36 to 72 hours and 12 to 36 hours, respectively. A Cochrane systematic review concluded that intravenous (IV) CST resulted in more AEs in comparison to oral CST in chronic obstructive pulmonary disease (COPD).[1 2] Diurnal variation is well known with surges in glucose levels associated with CST being greater in the afternoon and evening.[3] The underplays of the culprit disease group contributing to AE cannot be overlooked, for example an acute inflammatory state is likely to be associated with stress hyperglycaemia.

Metabolic adverse effects secondary to corticosteroid therapy

High dose (HD) CST use is thought to drive both insulin resistance and reduced insulin secretion. Whether long-term low dose (LD) CST therapy leads to a more modest effects on fasting plasma glucose (FPG) versus postprandial glucose (PPG) is unknown.[4] Mechanistic studies to delineate factors leading to metabolic AEs in particular hyperglycaemia have been undertaken in small numbers of young healthy individuals,[5 6] patients>40 years with inflammatory arthritis.[7] Another small study delineated impact of acute and chronic CST on fasting and postprandial energy expenditure.[8] However, this exercise has not been undertaken in all populations where steroids have been used, have been studied and risks in every disease-drug pair might be variable. A large population-based UK cohort study estimated the incidence of hypertension secondary to oral CST to be 46.7 (95% CI 46.0 to 47.3) per 1000 person-years with an effect of cumulative steroid dose[9]). In some retrospective studies, incidence of new-onset diabetes mellitus (DM) in patients without a prior history of hyperglycaemia varied from 34.3% to 56% with a relative risk of 1.36 to 2.31 and a number needed to harm ranging from 16 to 41[10–13]). In a cross-sectional study in patients with pemphigus, the OR of CST induced hyperglycaemia was estimated to be 10.7 (95% CI 1.38 to 83.50).[14] In comparison to this, a prospective study of prescriptions of oral CST in a primary care population estimated the incidence of DM to be 2%.[15]

Should the prescriber of CST, then arrange a follow-up appointment to monitor AEs like hyperglycaemia, weight gain and hypertension for all patients? A comprehensive review of all metabolic AE's is lacking in literature and this study aims to generate high-quality evidence on AEs associated with CST as reported in randomised control trials (RCTs). Metabolic AEs reported in this paper include hyperglycaemia, hypertension, weight gain and hyperlipidaemia, with a primary focus on hyperglycaemia. Secondary aims were to study the factors that may have an impact on development of AE.

RESEARCH DESIGN AND METHODS

Search strategy and selection criteria

A systematic literature search with no language restrictions was performed to identify RCTs in which any systemic corticosteroid (defined as oral, IV or intramuscular) had been administered to randomly selected groups of patients in the treatment of defined medical disorder or to healthy participants. We searched Medline, Embase, Cochrane Library, Web of Science and Scopus for studies reporting AEs of CST in trials since database inception to 13 January 2020. For the full-search strategy and terms, see text in online supplemental file 1. No specific protocol was published.

Study selection

Inclusion criteria: randomised controlled trials describing rates of AEs in numeric values including zero events in patients aged ≥17 years. Systemic CST arms and comparative arms (placebo or other treatments arms not treated by systemic corticosteroids) as described by the authors of the articles were included. Articles excluded included studies focused on non-humans, paediatric populations and non-systemic CST (eg, topical). Studies with fewer participants n<5 or studies undertaken in the context of palliative care, cancer and transplant were excluded. Studies describing steroid arms with a concomitant confounding agent (for instance, cyclosporine) and/or studies where the causality of AEs was unclear or conflicting based on the authors' reporting, were excluded. Finally, deduplicated published articles with full texts available were included for further analysis. Studies which showed considerable risk of bias in multiple areas of assessment were excluded.

Data abstraction

All identified articles were entered into the reference manager (EndNoteX V.8.2). Titles, abstracts and full-text articles were evaluated and reviewed for inclusion by at least two authors per disease category. Disagreements were resolved by consensus among the authors.

From each independent study, data were collected on title, authors, methods including study period, design, sample size demographics of study populations, inclusion/exclusion criteria, underlying disease/condition, type, dose and duration of the CST used, safety results namely reported individual AE rate, and acknowledged limitations on a master excel sheet. The steroid arms were subgrouped based on dose namely HD as oral prednisolone equivalent ≥30 mg/day, IV methylprednisolone ≥500 mg or ≥0.5 mg/kg, dexamethasone ≥3–6 mg/day

and other steroids as equivalent. Studies were assigned to LD when oral prednisolone equivalent was ≤10 mg/day and medium dose (MD) ranged between HD and LD. When the duration of exposure was ≤1 week, it was short term (ST), long term (LT) was when the exposure lasted more than 1 month and medium term (MT) ranged between ST and LT. Recurring pulsed dose (PD) steroid dosing regimens were categorised as PD.

The primary outcome was the description and quantification of prevalence of AEs. In this paper, we focused on hyperglycaemia, hypertension, dyslipidaemia and weight gain. Definition of the AEs was utilised as mentioned by the authors of the published studies. Below we present the analysis from data obtained from RCTs.

Methodological quality assessment of eligible RCTs was conducted using Cochrane risk of bias tool 2 (ROB2)[16] at AE outcome level by recording methods used for reporting of the AEs, description of AEs, randomisation,and selection criteria. Study characteristics that could potentially bias an association between exposure (CST use) and outcome (development of relevant AE) were assessed for all included articles.

Statistical analysis

The main outcomes of this meta-analysis were the pooled prevalence of patients with defined AE after CST use. The relative frequencies of the AE in each CST arm in each RCT were evaluated separately. For this analysis, studies with placebo arms with background CST were included as a CST arm only if the dose, duration of the steroid used and AE causality assessment was defined.

For studies comparing CST arms versus placebo, combined effect size in the form of OR and 95% CIs were calculated using meta-analysis. Subgroup analysis for underlying disease area, steroid form, steroid dose and duration were performed. All tests were two-tailed, and $p<0.05$ was statistically significant. All pooled analyses were conducted with Meta-XL V.5.3 (EpiGear International, Sunrise beach, Queensland, Australia), and/or meta-essentials excel add-in[17] using the Mantel-Haenszel or inverse ratio method with fixed-effects model and random-effect model. We assessed heterogeneity between studies using the I^2-statistic. Mean age, sex (no. of females as a percentage) and year of publication were used as moderators. To investigate publication bias, regression analysis using funnel plot was undertaken. Missing data were not imputed. For other statistics, SPSS V.28 and excel were used.

Patient and public involvement

No patients involved.

Ethics approval

No ethical approval was taken, as only accessible published data was utilised for this review.

RESULTS

Literature search and study selection

A total of 5948 records were identified namely Medline (2612), Embase (2899), Web of Science (321) and Scopus (116). Deduplicated records identified through databases and Cochrane library resulted in 5446 records; 928 articles were further reviewed for inclusion by searching for full texts. A total of 118 studies with 152 steroid arms were included (figure 1), encompassing 17 113 participants in total and 8569 participants in CT arms. All the study characteristics are shown in online supplemental table 1.

Methodological quality assessment of the eligible trials was conducted for the RCTs included based on quantification of outcomes of AEs as defined by the authors, and key study level characteristics (figure 2, online supplemental table 2). In many studies, the specific description of randomisation, allocation of concealment, blinding methods or handling of withdrawals was missing. The statements made by authors in this regard were assumed to be valid. Intention to treat analysis was used where data were available. In the studies undertaken in earlier decades, specific description of randomisation, allocation concealment, blinding methods or handling of withdrawals were lacking, reflecting evolution of clinical trial design and standards of reporting over the decades. On the other hand, some early studies had more complete reporting of specific AE at participant level.[18 19] Reporting bias could not be assessed vigorously in several articles with most studies powered for efficacy rather than safety. The reporting was assessed based on the clinical trial study protocol when available. There was significant heterogeneity in definition of specific AEs (online supplemental table 3a-d) as well as exclusion criteria based on previous AEs to CST therapy and uncontrolled DM, depending on the disease group.

As the original search was undertaken before the COVID-19 pandemic, Cochrane library and Prospero were searched on 7 November 2022 for publication of similar reviews and similar efforts to quantify risk of harms secondary to CST. As the COVID-19 therapeutic area was not one of the disease areas included in the original search, we have excluded studies focused in this area.

Study characteristics

Included studies were published from 1975 to 2019. Of the 118 studies, 43 studies were open-label, 63 were double-blinded, 11 were single/assessor blinded and 1 study had both double-blinded and open label arms (this study was excluded from meta-analysis); 8 studies were cross-over studies, 26 studies were double-blinded placebo-controlled parallel group studies arm. Sample size of participants per steroid arm ranged from 9 to 392. Mean age was 50.4±11.7 (24–81), with 59% being female participants.

The disease groups with highest number of eligible studies for AEs reporting (unselected) were rheumatoid arthritis (RA) (36 studies, 2160 participants), Graves' ophthalmopathy (21 studies with 678 participants in steroid arms) and giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) with a combined 13 studies with 377 participants. Studies conducted within community acquired pneumonia, had higher cumulative participants

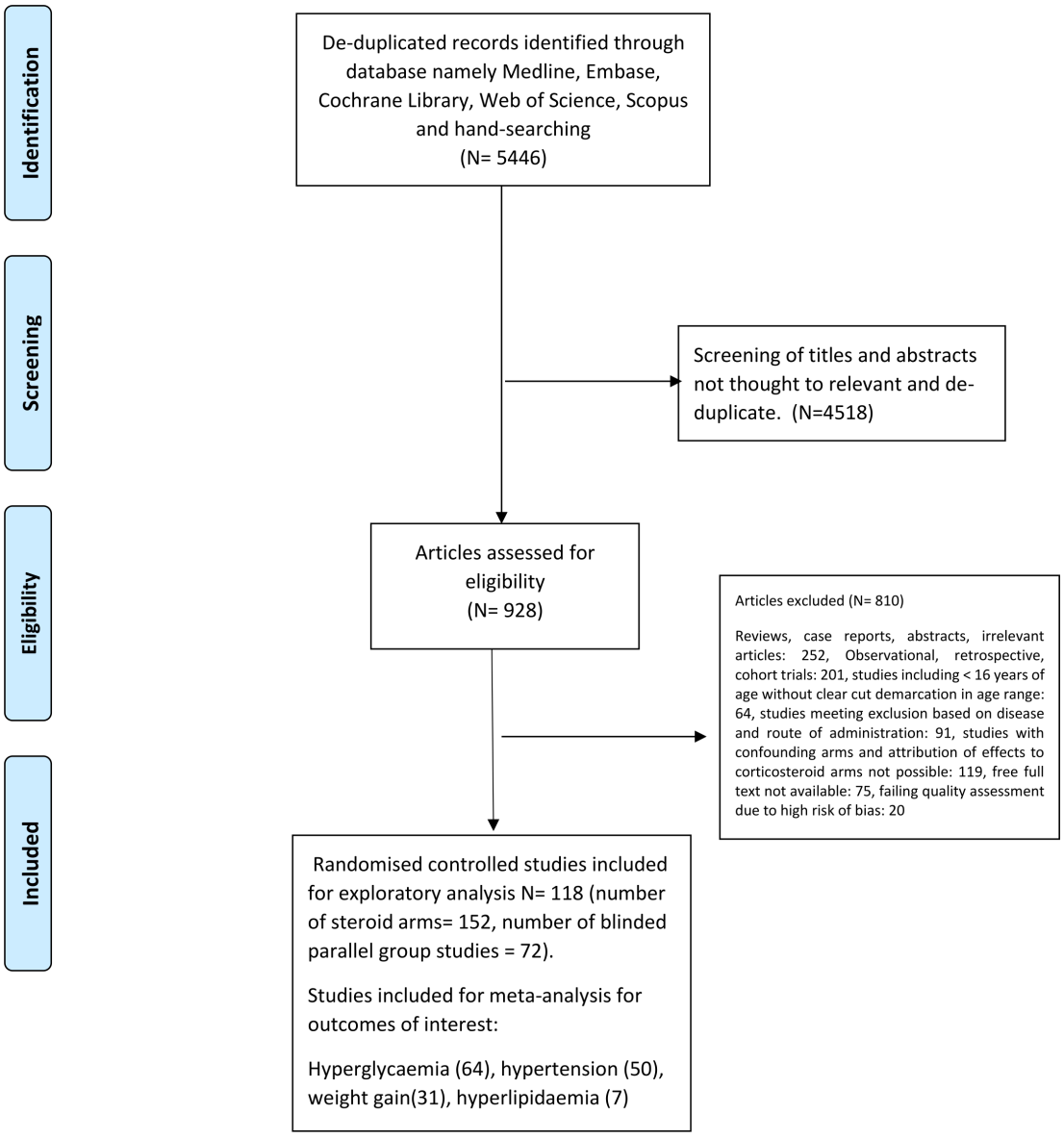

Figure 1 Flow chart of inclusion of studies in the systematic review.

per steroid arm with (n=906); 10 studies conducted in idiopathic thrombocytopenia purpura, multiple sclerosis (MS) and/or optic neuritis and nephropathy which encompassed idiopathic membranous nephropathy, lupus nephritis and IgA nephropathy were major disease categories included (table 1).

The dose and duration of CST among the included studies are presented in table 2.

HD regimen (61 CST arms, 3563 participants) and LT exposure (108 steroid arms, 5694 participants) were the the most common subcategories in CST arms. Oral prednisolone/prednisone was the the most common steroid used (6493 participants in CST arms). The major corticosteroid types used included prednisolone or prednisone (64%), methylprednisolone (21%), budesonide (5%) and dexamethasone (4%). Combinations of CST forms were employed in minority of studies (table 3).

Adverse effects of interest

Hyperglycaemia

Of note, 62 studies (81 steroid arms, n=4311) reported (n=516) onset of hyperglycaemia in study participants; 35 studies excluded patients with known corticosteroid intolerance or contraindication and 17 studies excluded patients with uncontrolled DM; 18 studies reported baseline prevalence rates of hyperglycaemia/DM at the start of the trial, 14 studies mentioned a clear-cut criteria used to report hyperglycaemia and/or new-onset DM as an AE. Reporting criteria for hyperglycaemia ranged from FPG, PPG, fasting and PPG cut-offs,[18] change from baseline,[20] oral glucose tolerance test,[21] glycosylated haemoglobin (HbA1C)[22] using WHO, American Diabetes Association (ADA) and Common Terminology Criteria for AE (CTCAE) criteria. Further hyperglycaemia could be subdivided into impaired fasting glucose, impaired

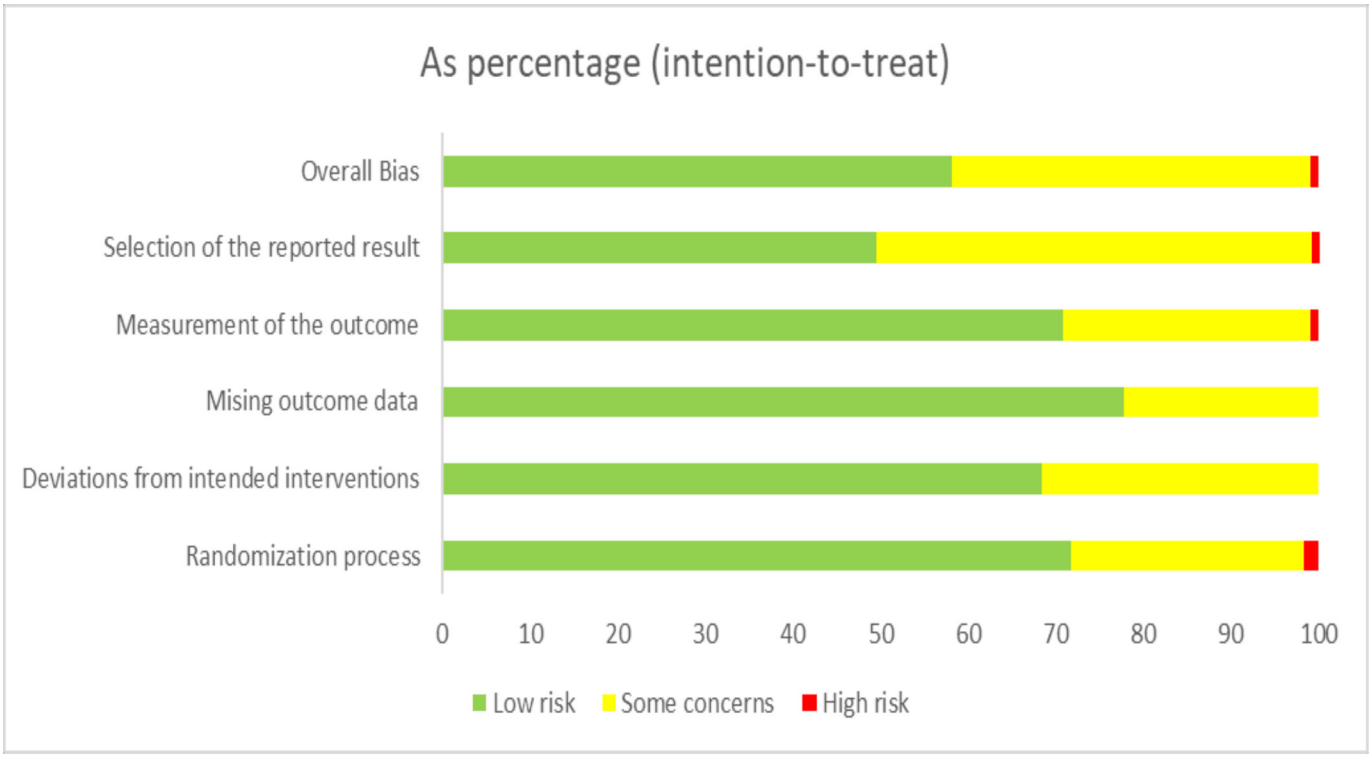

Figure 2 Summary of risk of bias of studies included in the study.

PPG and new-onset DM in certain studies.[23] Hyperglycaemia needing insulin treatment,[24 25] DM needing treatment[26] or reported as a serious AE (SAE) was a criterion for reporting in few studies.[22 27–29] Urine testing was mentioned as a method to monitor glucose control in one study.[30] The time range of onset of AE was mentioned in four studies.[26 31–33] The summary of various definitions used in the individual studies is in online supplemental table 3a. We used the term 'hyperglycaemia' to include all definitions of incidental hyperglycaemia and/or worsening of glucose control. We defined 'severe hyperglycaemia' to include participants with hyperglycaemia needing treatment, hyperglycaemia reported as a SAE, new diagnosis of DM needing treatment and/or hyperglycaemia as the main reason for treatment withdrawal.

Pooled prevalence of hyperglycaemia in CST arms calculated using double arsine method was 10% (95% CI 0% to 87% (I^2=86%, p=0.00)) (online supplemental figure 1). Further analysis by disease categories (summarised in table 4 and online supplemental figures 2-11) showed pooled prevalence of hyperglycaemia highest among the respiratory illness group at 22%, whereas the least prevalence was 2% in autoimmune hepatitis and alcoholic hepatitis.

Risk analysis of hyperglycaemia in studies comparing systemic corticosteroid therapy with placebo

Based on 15 double-blinded placebo-controlled parallel group studies (n=3386) included in the random model of meta-analysis of binary outcomes, OR of hyperglycaemia was 2.13 (95% CI 1.66 to 2.72, p=0.00 (I^2=0%, p=0.60)) (figure 3a)). Subgroup analysis using duration of treatment (three groups LT, MT and ST) showed a non-significant trend of higher OR for LT versus MT or ST. Studies employing HD-CT had higher OR compared with LD, MD or PD, OR of 2.33 versus 1.25. Four out of the 15 studies[20 30 34 35] excluded patients with uncontrolled DM. Meta-regression using age, female sex as percentage and year of publication as moderators for risk of hyperglycaemia was not found to be statistically significant.

The OR of severe hyperglycaemia was 2.06 (95% CI 1.23 to 3.47 (I^2=0, p=0.90)) in (n=2709) double-blinded placebo-controlled parallel studies (n=10 studies) (figure 3b).

Intravenous versus oral corticosteroid therapy

The studies that were designed to compare IV CST versus oral CST for the underlying disease condition were utilised for this analysis. The details of the doses used in each arm are shown in online supplemental table 4.

The OR for incidental or worsening hyperglycaemia for oral prednisone/prednisolone/methylprednisolone versus approximately equivalent doses of IV methylprednisolone therapy within the same trial (five studies, n=526) was 2.39 (95% CI 1.16 to 4.91, p=0.00 (I^2=0.00%, p=0.94)), with a higher risk noted for the IV arm (figure 4). Funnel plot analysis using Egger regression showed no publication bias (figure 5).

Hypertension

Pooled prevalence of new-onset hypertension/worsening hypertension in 50 studies (64 CST arms) (n=215/3340) was 6% (95% CI 4% to 8% (I^2=72%, p=0.00)) (online supplemental figure 13). OR of new-onset hypertension/

Table 1 Number of studies included in the systematic analysis, subdivided by disease groups

Disease groups	Number of corticosteroid arms in the included studies	Total number of participants in corticosteroid arms	Total number of participants in the studies
Autoimmune inner ear disease	1	116	116
Autoimmune hepatitis	1	203	208
Autoimmune haemolytic anaemia	1	32	64
Alcoholic hepatitis	1	274	546
Behcet's disease	1	34	86
Community acquired pneumonia	5	906	3946
Inflammatory blowel disease (Crohn's disease and ulcerative colitis)	5	407	573
Chronic inflammatory demyelinating polyneuropathy	1	15	32
Chronic obstructive pulmonary disease	6	450	846
Erythema nodosum leprosum	1	30	60
Guillain Barre syndrome	4	185	327
Giant cell arteritis and polymyalgia rheumatica	13	377	631
Grave's ophthalmopathy	21	678	769
Gout	3	309	649
Healthy volunteer	1	18	18
Idiopathic thrombocytopenic purpura	10	410	443
Myasthenia gravis	1	39	80
Multiple sclerosis and optic neuritis	10	705	1093
Nephropathy (IgA nephropathy)	10	406	900
Osteoarthritis	1	52	106
Polyarteritis nodosa and Churg Strauss Syndrome	1	42	78
Pyoderma Gangrenosum	1	53	112
Pemphigus (Pemphigus vulgaris, bullous pemphigoid, pemphigus foliaceus)	7	320	671
Rheumatoid arthritis	36	2160	3849
Systemic lupus erythomatosis	8	330	910
Grand total	152	8569	17 113

worsening hypertension in CST arms versus placebo in double-blinded placebo-controlled parallel group arms (n=1975 in nine studies) was 1.68 (95% CI 0.96 to 2.95 (I^2=0%, p=0.78)) (figure 6) calculated with a random effects model with no reporting bias (online supplemental figure 14).

Weight gain

Pooled prevalence of unintentional weight gain was calculated in CST arms (n=261/1740, 42 CST arms, 31 studies) at 13% (95% CI 8% to 18% (I^2=88%, p=0.00)) (online supplemental figure 15).

The risk of weight gain with CST was calculated with a random-effects model using eight studies (n=721), OR of 5.20 (95% CI 2.10 to 12.90 (I^2=0%, p=0.44)) (figure 7).

Hyperlipidaemia

Pooled prevalence of new-onset/worsening hyperlipidaemia was calculated in seven studies, 11 CST arms (36/390) at 10% (95% CI 4% to 17% (I^2=76%, p=0.00)) (figure 8).

Like definitions of hyperglycaemia as AE, definitions of hypertension, weight gain and hyperlipidaemia were equally heterogeneous (online supplemental table 3a-d).

DISCUSSION

This is a large comprehensive systematic review and meta-analysis based on data from RCTs, thus presenting high-quality data of metabolic risks associated with CST in several diseases, stratified by dose and duration in an adult population. Previous systematic reviews undertaken

Table 2 Included studies based on dose and duration codes

Dose duration of exposure as subgroups	Number of participants in steroid arms
High dose	3563
Long term	1854
Medium term	402
Short term	1307
Low dose	1841
Long term	1681
Medium term	147
Short term	13
Medium dose	1965
Long term	1176
Medium term	399
Short term	390
Medium dose and low dose	41
Short term	41
Pulsed dose	997
Long term	787
Medium term	84
Short term	124
Pulsed dose followed by high dose	14
Long term	14
Pulsed dose followed by low dose	108
Long term	108
Pulsed dose followed by medium dose	40
Long term	40
Grand total	8569
Duration of exposure code key	
Long term	>1 month
Medium term	1 week–1 month
Short term (ST)	<1 week
Dose codes key	
Low dose	Oral prednisolone equivalent <10 mg/day
Medium dose	Oral prednisolone equivalent of 10 mg–30 mg/day
High dose	Oral prednisolone equivalent>30 mg/day, intravenous methylprednisolone>500 mg or >0.5 mg/kg, dexamethasone >3–6 mg/day
Pulsed dose	Pulsed dose includes intermittent short-duration dose

Table 3 Corticosteroid type in the included studies

Row labels	Number of participants in steroid arms
Prednisolone or prednisone	5495
Methylprednisolone	1796
Budesonide	499
Dexamethasone	369
Methylprednisolone f/b prednisone	217
Depomedrone	48
Dexamethasone f/b prednisone	45
Prednisone f/b beclomethasone dipropionate	37
Betamethasone	20
Methylprednisolone f/b prednisolone	16
Budesonide, controlled ileal release	14
Methylprednisolone f/b prednisone	13
Grand total	8569

have described both the burden of AEs and pharmacoeconomic of CST use, however all reviews have focused on a specific disease area, specific duration of treatment and/or a single AE.[36–41] Even though there was heterogeneity in the type of CST used, underlying condition, dose and duration of treatment, there was truly little heterogeneity in the risk analysis of AEs of interest in placebo-controlled double-blind parallel group studies.

One systematic review (32 studies) described AEs secondary to LT systemic CST, namely hypertension>30%, bone fracture (21%–30%) and metabolic issues being fourfold the risk of controls. They also described the economic impact including dose-related increase in healthcare resource utilisation and per-annum incremental costs.[37] The drawbacks of this study were inclusion of retrospective databases, lack of pooled analysis of the risk and lack of consideration of dose of CST. Another meta-analysis calculated the rate of CST-induced hyperglycaemia and diabetes (in non-diabetic individuals) at 32.3% and 18.6%, respectively.[13] This is significantly higher than the 11% noted in the study in question, however the results mirror observational data. The majority of studies (12/13) included in this particular meta-analysis were observational studies. Breakey *et al*[41] studied the risk of hyperglycaemia in respiratory illness in a meta-analysis (8 RCTs, n=2121). The strength of this review was inclusion of RCTs only within a single disease group. The relative risk of hyperglycaemia secondary to CST in comparison to placebo was 1.72 (95% CI 1.50 to 2.04; p<0.001), and the risk was not different for patients with or without DM diagnosis at baseline. This is much lower than the finding in the present study. The findings in the present study are comparable to Cochrane study (n=6 studies) assessing the risk of hyperglycaemia in patients with acute exacerbations of COPD (OR of 2.79 (95% CI 1.86 to 4.19)).[1 2]

The focus of most published RCTs and subsequent meta-analysis of published RCTs is on effectiveness of treatment arms. Analyses of harm are often of inferior quality due to poor documentation of CST exposure, non-homogeneous

Table 4 Single-arm pooled prevalence of incidental hyperglycaemia and or worsening DM in corticosteroid arms within disease subgroups

AE disease subgroup		Number of studies (CST arms)	Total number of participants in steroid arms	Number of participants noted to have hyperglycaemia	Pooled prevalence and 95% CIs	I^2 in percentage
Hyperglycaemia		62 (81)	4311	516	0.10 (0.07 to 0.14)	86
1.	Rheumatoid arthritis	9 (10)	628	39	0.05 (0.00 to 0.10)	81
2.	Graves ophthalmopathy	10 (16)	557	41	0.07 (0.05 to 0.11)	42
3.	Respiratory illness (COPD and community acquired pneumonia)	9 (10)	1158	267	0.22 (0.09 to 0.35)	94
4.	Renal disorders	5 (5)	218	21	0.09 (0.03 to 0.17)	58
5.	GCA/PMR	6 (9)	179	25	0.14 (0.07 to 0.22)	46
6.	Neurological disorders (Guillaine-Barre syndrome, multiple sclerosis)	5 (7)	237	25	0.07 (0.00 to 0.17)	73
7.	ITP	5 (9)	410	33	0.08 (0.03 to 0.13)	62
8.	Dermatological conditions	7 (7)	331	51	0.145 (0.02 to 0.31)	83
9.	Systemic lupus erythomatosis	4 (4)	84	10	0.10 (0.00 0.35)	83
10.	Hepatic disorders (autoimmune hepatitis, alcoholic hepatitis)	2 (3)	477	9	0.02 (0.0 to 0.04)	64

Severe hyperglycaemia occurred in 185/2560 participants (31 studies, 34 CST arms), with pooled prevalence at 5% (95% CI 2% to 9% (I^2=90, p=0.00)) (online supplemental figure 12).
AE, adverse effect; COPD, chronic obstructive pulmonary disease; CST, corticosteroid therapy; DM, diabetes mellitus; GCA, giant cell arteritis; ITP, idiopathic thrombocytopenia purpura; PMR, polymyalgia rheumatica.

models of risk attribution, lack of power in trial designs on reporting of AEs, heterogeneity in indications of CST and observational designs with intrinsic biases. Although risk of bias can be examined using statistical tools and can be assessed across all outcomes of interest, the challenges of a systematic review of AE remain.[42] In this study, the rates of AEs were based on authors' presentation of data which is the major reason for heterogeneity, and this was the reason for excluding some studies. For instance, some studies expressed weight gain in terms of mean change in body mass index between study arms, without explicit reporting on number of patients reaching a particular cut-off.[30 43 44]

The most common CST was oral prednisolone, which mirrors real-world prescription data.[45] The prescription rates for LT and LD, CST increases with increasing age and multimorbidity, as ageing population is affected by conditions such as COPD, asthma, GCA and PMR that drive CST prescriptions.

Most certainly factors such as age,[46] underlying cardiovascular risk factors including pre-existing hypertension, diabetes, peripheral vascular diseases and lifestyle factors such as smoking can increase propensity to develop AEs. It is plausible that pre-existing metabolic dysfunction due to other factors increases susceptibility to the diabetogenic effects of CST.[7 47] A large observational research group showed young men were more likely to be impacted by AEs of CST in asthma management.[48] In the present study, age and sex was not found to significantly affect odds of hyperglycaemia.

More recently published studies included in this study did not report on all AEs of CST and did not have monitoring for hyperglycaemia, hypertension or dyslipidaemia incorporated in their protocols. The most comprehensive study with regard to hyperglycaemic effects of CST compared the impact of prednisolone 30 mg/day versus 60 mg/day in RA with a particular focus on glucose metabolism. A weekly oral glucose tolerance test was performed in this study, increasing the likelihood of identifying metabolic derangements. Incidence of type 2 DM increased from 7% at baseline to 24% at the end of 1 week of treatment (p<0.001). The study concluded that patients who were likely to have metabolic derangements had a longer duration of RA with OR of 1.068 (95% CI 1.01 to 1.12), without a dose effect with large intraindividual variations.[21] Robust quantification may be better derived from cohort studies specifically designed for this purpose.[49–51]

More recent trials included in this study also do not have CST as a separate arm, instead incorporating CST as a background or concomitant medication.[52 53] To ensure this effect was captured, year of publication was used

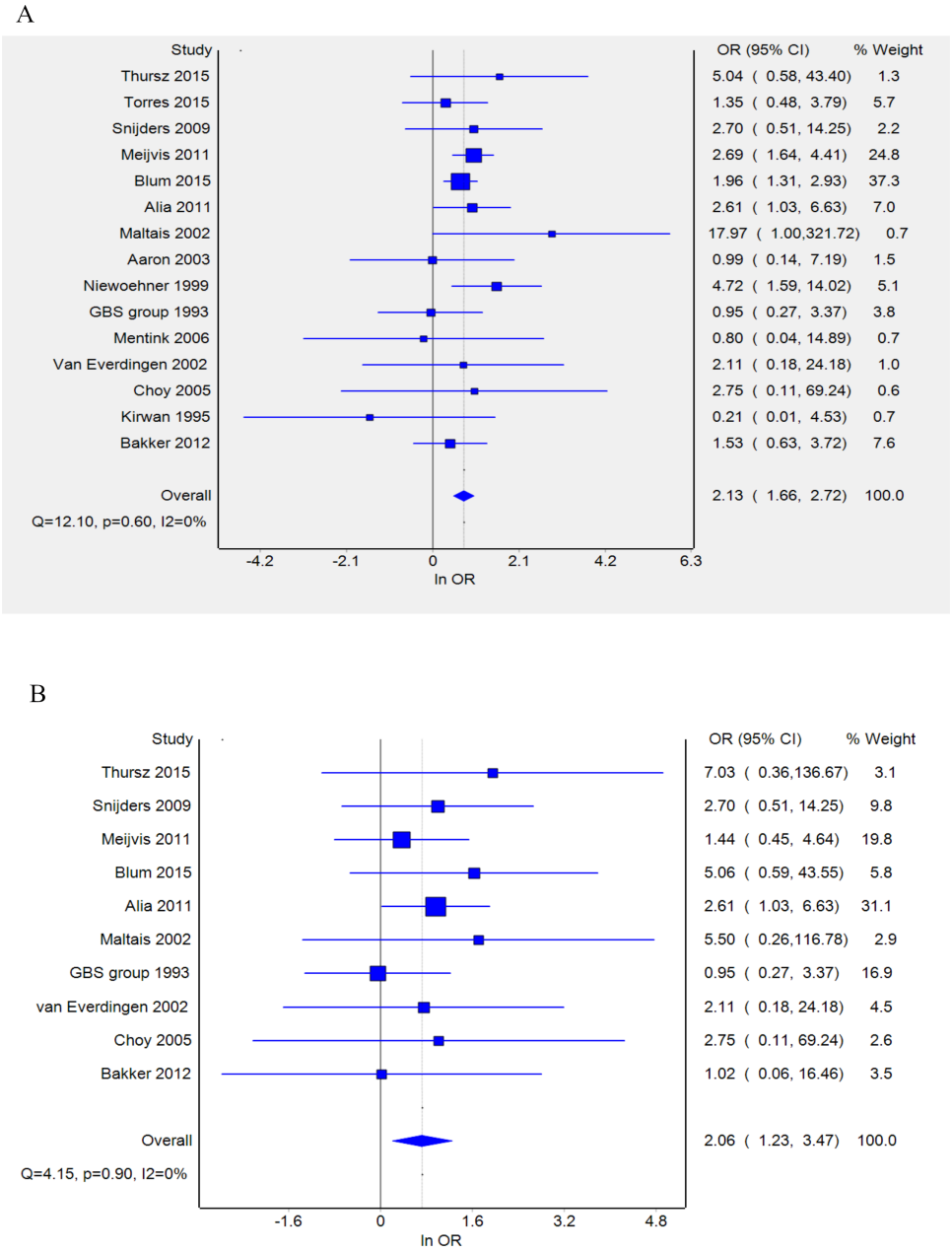

Figure 3 (A) Forest plot of risk (expressed as OR) of hyperglycaemia with corticosteroid therapy in placebo-controlled double-blinded parallel arm studies (15 studies, n=3386). (B) Forest plot of risk (expressed as OR) of severe hyperglycaemia with corticosteroid therapy in placebo-controlled double-blinded parallel arm studies (10 studies, n=2709).

as moderator, which did not however have an effect on the main results. However, it is also possible that studies published after our search period may have improved reporting, attributable to improvement in pharmacovigilance techniques postpandemic. As such a living systematic review of harms would be a better way of dynamically capturing and quantifying these risks.

Pooling of AEs in some RCTs was not feasible in some studies due to significant design heterogeneity. For example, in a study with a primary outcome of efficacy of methotrexate versus placebo in patients with autoimmune inner ear disease, all patients received oral CST as background in phase 1 (open label phase) of the study and dose was tapered in phase 2 (double-blinded) with a methotrexate arm and a placebo arm; 7/116 patients withdrew from the trial within phase 1 due to AEs. Hyperglycaemia attributable to CST occurred in 17.6% of patients and a mean increase in body mass index of 1.6 kg/m^2 (95% CI 0.77 to 2.3) was noted during the 22 weeks CST course. AE quantification was robust in this RCT, however it is impossible to pool the data with other studies due to the unique trial design. This trend was also observed in studies reporting hypertension, weight gain and hyperlipidaemia.

Another major limitation is the definition of AEs as binary outcomes based on reporting by study authors and use of various definitions and cut-offs on continuous values to define AEs. Glucocorticoids predominantly

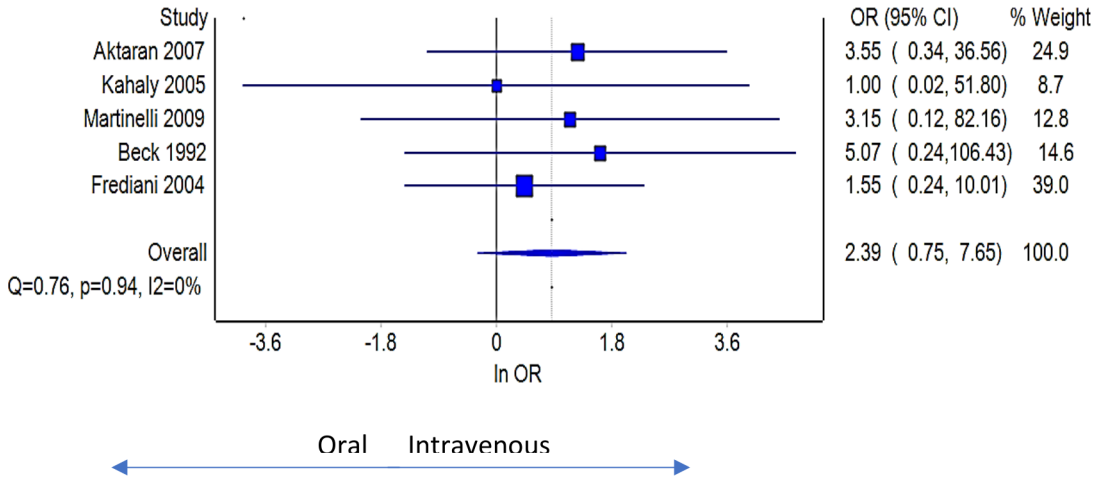

Figure 4 Forest plot of OR of hyperglycaemia in studies (5 studies, n=526) comparing intravenous corticosteroid therapy and oral corticosteroid therapy.

increase PPG, so studies that have only measured fasting glucose will markedly underestimate the prevalence of hyperglycaemia with glucocorticoids. A more rigorous analysis incorporating outcomes as continuous values for example rise in HBA1c measurements themselves or reporting of actual fasting glucose levels would have contributed to a more robust estimates of change in those parameters.

In this study, we could not study effects of cumulative dose of steroids. For example, one study reporting on the long-term effects of methotrexate on PMR showed that higher cumulative steroid dose was associated with AEs.[54] The dose response curve for AEs may change with chronic treatment in inflammatory disease groups as shown in this study, and anti-inflammatory effects driven by CST therapy may reduce AEs such as hypertension in specific disease groups such as glomerulonephritis. The higher AE risk noted with IV CST in comparison to oral CST should be interpreted in the context of indications of high dose IV therapy designed to tackle high inflammatory states such as Graves' disease, MS and vasculitis. The IV doses though were overall higher in the IV therapy arms in comparison to oral, the mean cumulative doses in both arms were as equivalent as it can get in practice for

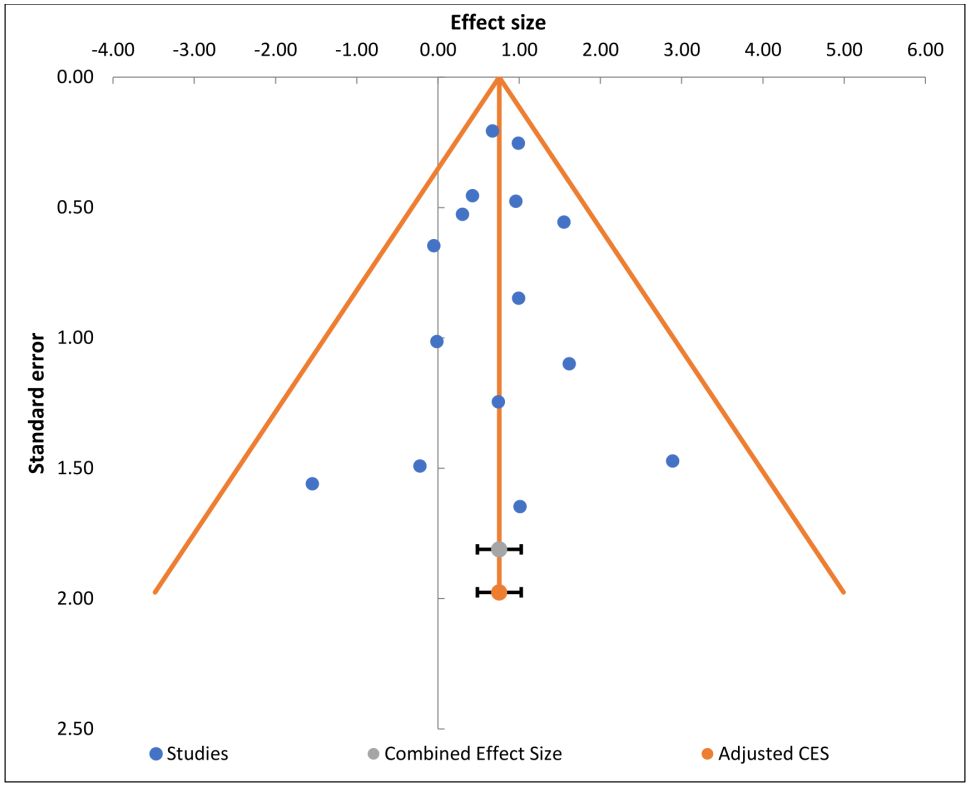

Figure 5 Publication bias analysis using Egger regression analysis for risk of hyperglycaemia associated with corticosteroid therapy arms vs placebo.

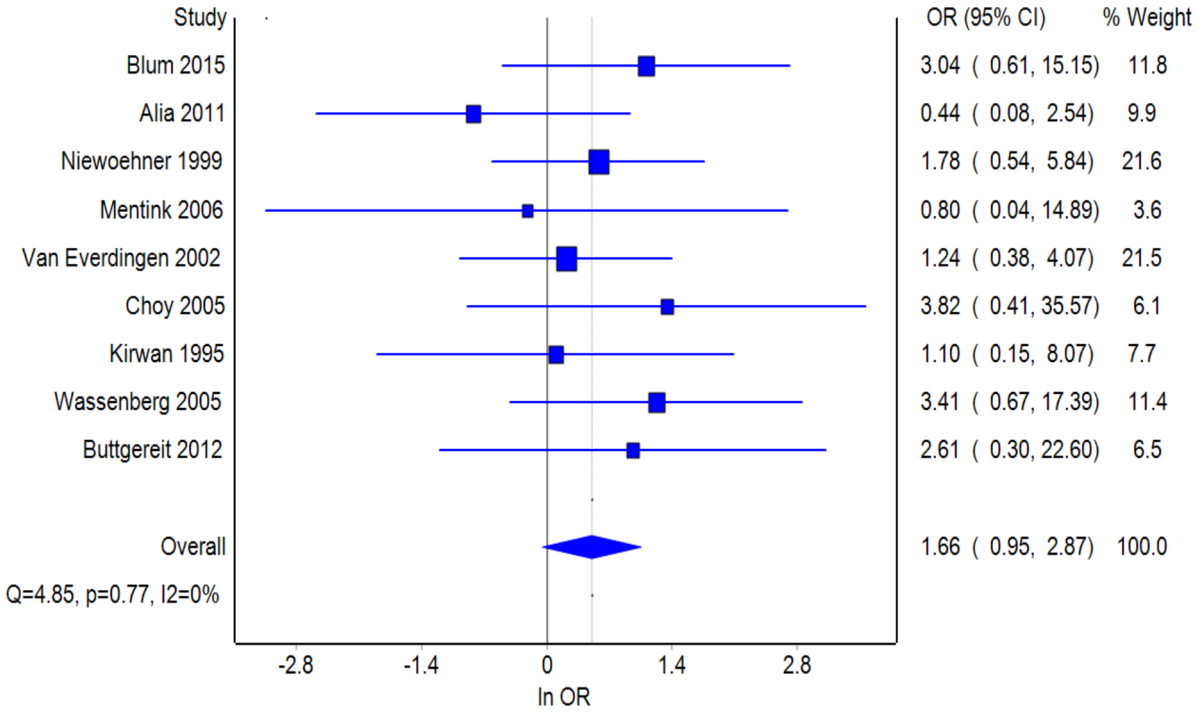

Figure 6 Forest plot of hypertension (incidental and/or worsening) in studies comparing corticosteroid therapy vs placebo (9 studies, n=1975).

such a comparison to be possible. The higher risk is in keeping with the nature of pulse therapies. The effects of duration and doses of CST therapy are as such better studied in prospective observational or cohort studies as most RCTs for obvious pragmatic reasons are much shorter than real-world use cases, thus leading to underestimation of the quantification of AEs.

In comparison, present day RCTs conducted in inflammatory conditions have limited reporting on assessment of AEs such as hyperglycaemia and hyperlipidaemia

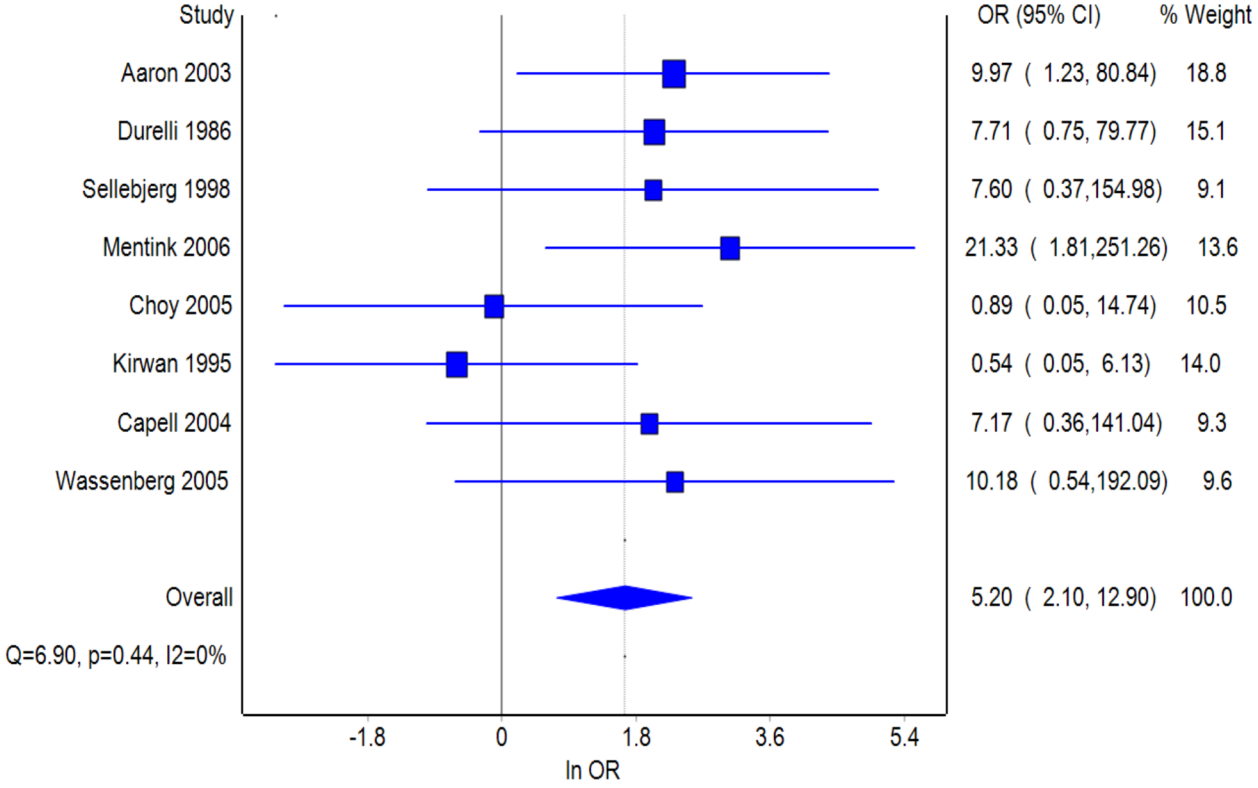

Figure 7 Forest plot of risk (expressed as OR) of new weight gain with corticosteroid therapy in placebo-controlled double-blinded studies (n=721, 8 studies).

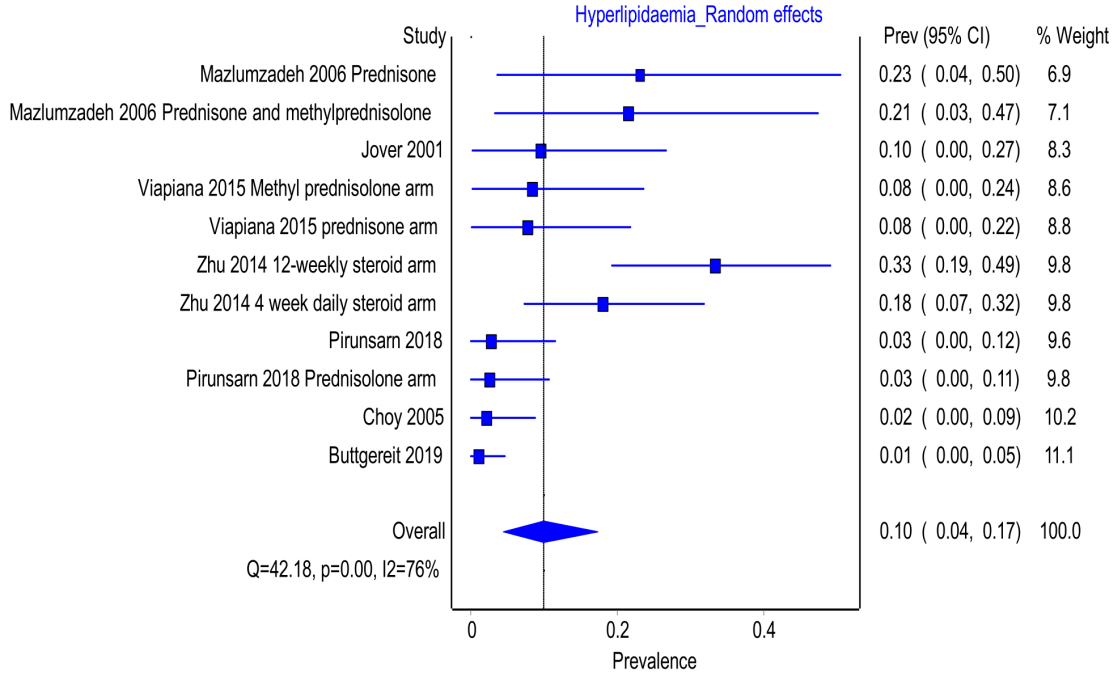

Figure 8 Forest plot of pooled prevalence of hyperlipidaemia in included studies ((n=36/390), 7 studies, 11 corticosteroid arms).

secondary to CST and report SAEs only such as diabetic ketoacidosis. SAEs secondary to CST are probably rare because most patients enrolled in clinical trials tend to be healthier. This makes risk reporting within the context of clinical trials more pragmatic for both investigators and participants. However, the onus is then on the prescriber to predict the risk and ensure a risk mitigation plan is in place.

We used Excel Macro applications for analysis of our results, and this is a less commonly used method to undertake complex meta-analysis, however, the comparison of the two excel applications resulted in homogeneous results with the added advantage of the applications being user friendly. For future complex analysis such as network meta-analysis, sophisticated mathematical tools and other validated software may be necessary.

Though we did not exclude non-English articles, the study did not allow for analysis of geographic, ethnic or genetic variations in corticosteroid effect, receptors, disease groups, with relation to AEs. The reported prevalence of AEs is driven by local variation in drug regulation, availability of healthcare resources and prescriptions.

CONCLUSIONS AND FUTURE

CST therapy continues to be used as rescue treatment in many inflammatory conditions due to their efficacy and overall cost-effectiveness. The findings of this study can help physicians inform patients on likelihood of metabolic AEs with CST therapy and better define and use the benefits risk profile to plan adequate monitoring and/or treatment strategies. Other strategies to help assess benefit versus risk of starting a patient on CST should be further developed, especially where alternative therapies are not available, such as by pooling real-world evidence and building a living systematic review of harms to delineate factors associated with AE risks may help develop predictive risk models. Guidance on management of CST-induced diabetes and hyperglycaemia, currently available is based on observational studies.[55–57] The European Alliance of Associations for Rheumatology (EULAR) task force suggests factors that could help predict lower risk of harm from CST in the RA cohort[58] which could be extended for other conditions. Until further evidence is available, most of the risk mitigation plans by definition will be applicable universally to all rather than personalised. To conclude, CST is associated with metabolic and cardiovascular risk factors that varies according to the underlying disease and route of administration. Development of effective alternative steroid sparing therapies for inflammatory conditions is the need of the hour.

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Contributors All authors approved the final draft for publication. PA is the guarantor. PA, PB and LC conceptualised the study. SK planned the study design, supervised by PB and PA. VP provided search strategies and performed the search. HD, LG, OA and PB screened, collected and assessed the quality of data in various disease groups independently and in parallel with SK. SK undertook the review, and statistical analysis and wrote the manuscript. SN provided statistical expertise and oversaw the analysis. PA and PB provided oversight on all aspects of the study.

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REFERENCES

1 Wood-Baker RR, Gibson PG, Hannay M, *et al*. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;1:CD001288.
2 Walters JAE, Tan DJ, White CJ, *et al*. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2014;348.
3 Burt MG, Roberts GW, Aguilar-Loza NR, *et al*. Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. *J Clin Endocrinol Metab* 2011;96:1789–96.
4 Burt MG, Willenberg VM, Petersons CJ, *et al*. Screening for diabetes in patients with inflammatory rheumatological disease administered long-term prednisolone: a cross-sectional study. *Rheumatology* 2012;51:1112–9.
5 van Raalte DH, Brands M, van der Zijl NJ, *et al*. Low-dose glucocorticoid treatment affects multiple aspects of intermediary metabolism in healthy humans: a randomised controlled trial. *Diabetologia* 2011;54:2103–12.
6 Lal R, Bell S, Challenger R, *et al*. Pharmacodynamics and tolerability of repository corticotropin injection in healthy human subjects: a comparison with intravenous methylprednisolone. *J Clin Pharmacol* 2016;56:195–202.
7 Petersons CJ, Mangelsdorf BL, Jenkins AB, *et al*. Effects of low-dose prednisolone on hepatic and peripheral insulin sensitivity, insulin secretion, and abdominal adiposity in patients with inflammatory rheumatologic disease. *Diabetes Care* 2013;36:2822–9.
8 Radhakutty A, Mangelsdorf BL, Drake SM, *et al*. Effects of prednisolone on energy and fat metabolism in patients with rheumatoid arthritis: tissue-specific insulin resistance with commonly used prednisolone doses. Clin Endocrinol, 2016;85: 741-747..
9 Mebrahtu TF, Morgan AW, West RM, *et al*. Oral glucocorticoids and incidence of hypertension in people with chronic inflammatory diseases: a population-based cohort study. *Can Med Assoc J* 2020;192:E295–301.
10 Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, *et al*. Hyperglycemia related to high-dose glucocorticoid use in noncritically ill patients. *Diabetol Metab Syndr* 2013;5:18.
11 Perez A, Jansen-Chaparro S, Saigi I, *et al*. Glucocorticoid-Induced hyperglycemia. *J Diabetes* 2014;6:9–20.
12 Strohmayer EA, Krakoff LR. Glucocorticoids and cardiovascular risk factors. *Endocrinol Metab Clin North Am* 2011;40:409–17.
13 Liu X-xia, Zhu X-ming, Miao Q, *et al*. Hyperglycemia induced by glucocorticoids in nondiabetic patients: a meta-analysis. *Ann Nutr Metab* 2014;65:324–32.
14 Alavi A, Lowe J, Walsh S, *et al*. Corticosteroid-induced hyperglycemia is increased 10-fold in patients with pemphigus. *Int J Dermatol* 2012;51:1248–52.
15 Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. *Diabetes Care* 2006;29:2728–9.
16 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
17 Suurmond R, van Rhee H, Hak T. Introduction, comparison, and validation of Meta-Essentials: a free and simple tool for meta-analysis. *Res Synth Methods* 2017;8:537–53.
18 Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Report of a prospective controlled trial in 24 patients. *Ann Intern Med* 1975;83:597–605.
19 Mackworth-Young CG, David J, Morgan SH, *et al*. A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. *Ann Rheum Dis* 1988;47:496–502.
20 Bakker MF, Jacobs JWG, Welsing PMJ, *et al*. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329–39.
21 den Uyl D, van Raalte DH, Nurmohamed MT, *et al*. Metabolic effects of high-dose prednisolone treatment in early rheumatoid arthritis: balance between diabetogenic effects and inflammation reduction. *Arthritis Rheum* 2012;64:639–46.
22 Salvi M, Vannucchi G, Currò N, *et al*. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. *J Clin Endocrinol Metab* 2015;100:422–31.
23 Choy EH, Kingsley GH, Khoshaba B, *et al*. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. *Ann Rheum Dis* 2005;64:1288–93.
24 Meijvis SCA, Hardeman H, Remmelts HHF, *et al*. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:2023–30.
25 Blum CA, Nigro N, Briel M, *et al*. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015;385:1511–8.
26 Bartalena L, Krassas GE, Wiersinga W, *et al*. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab* 2012;97:4454–63.
27 Austin HA, Illei GG, Braun MJ, *et al*. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *J Am Soc Nephrol* 2009;20:901–11.
28 Joly P, Roujeau J-C, Benichou J, *et al*. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002;346:321–7.
29 Abroug F, Ouanes-Besbes L, Fkih-Hassen M, *et al*. Prednisone in COPD exacerbation requiring ventilatory support: an open-label randomised evaluation. *Eur Respir J* 2014;43:717–24.
30 van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, *et al*. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002;136:1–12.
31 Alía I, de la Cal MA, Esteban A, *et al*. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med* 2011;171:1939–46.
32 Mentink LF, Mackenzie MW, Tóth GG, *et al*. Randomized controlled trial of adjuvant oral dexamethasone pulse therapy in pemphigus vulgaris: PEMPULS trial. *Arch Dermatol* 2006;142:570–6.

33 Anonymous. Double-Blind trial of intravenous methylprednisolone in Guillain-Barré syndrome. Guillain-Barré syndrome steroid trial group. *Lancet* 1993;341:586–90.
34 Torres A, Sibila O, Ferrer M, *et al*. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015;313:677–86.
35 Aaron SD, Vandemheen KL, Hebert P, *et al*. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003;348:2618–25.
36 Manson SC, Brown RE, Cerulli A, *et al*. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009;103:975–94.
37 Rice JB, White AG, Scarpati LM, *et al*. Long-term systemic corticosteroid exposure: a systematic literature review. *Clin Ther* 2017;39:2216–29.
38 Bleecker ER, Menzies-Gow AN, Price DB, *et al*. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med* 2020;201:276–93.
39 Fernandes RM, Wingert A, Vandermeer B, *et al*. Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis. *BMJ Open* 2019;9:e028511.
40 Broersen LHA, Pereira AM, Jørgensen JOL, *et al*. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015;100:2171–80.
41 Breakey S, Sharp SJ, Adler AI, *et al*. Glucocorticoid-induced hyperglycaemia in respiratory disease: a systematic review and meta-analysis. *Diabetes Obes Metab* 2016;18:1274–8.
42 Loke YK, Price D, Herxheimer A, *et al*. Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol* 2007;7:32.
43 Frediani B, Falsetti P, Bisogno S, *et al*. Effects of high dose methylprednisolone pulse therapy on bone mass and biochemical markers of bone metabolism in patients with active rheumatoid arthritis: a 12-month randomized prospective controlled study. *J Rheumatol* 2004;31:1083–7.
44 Pozzi C, Bolasco PG, Fogazzi GB, *et al*. Corticosteroids in IgA nephropathy: a randomised controlled trial. *Lancet* 1999;353:883–7.
45 Chalitsios CV, Shaw DE, McKeever TM. A retrospective database study of oral corticosteroid and bisphosphonate prescribing patterns in England. *NPJ Prim Care Respir Med* 2020;30:5.
46 Mills E, Devendra S. Steroid-induced hyperglycaemia in primary care. *London J Prim Care* 2015;7:103–6.
47 Ha Y, Lee K-H, Jung S, *et al*. Glucocorticoid-induced diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. *Lupus* 2011;20:1027–34.
48 Barry LE, O'Neill C, Patterson C. Age and sex associations with systemic corticosteroid-induced morbidity in asthma. The Journal of allergy and clinical immunology. *Practice* 2018;6:2014–23.
49 Hoes JN, van der Goes MC, van Raalte DH, *et al*. Glucose tolerance, insulin sensitivity and β-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. *Ann Rheum Dis* 2011;70:1887–94.
50 Movahedi M, Beauchamp M-E, Abrahamowicz M, *et al*. Risk of incident diabetes mellitus associated with the dosage and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1089–98.
51 Ganapati A, Ravindran R, David T, *et al*. Head to head comparison of adverse effects and efficacy between high dose deflazacort and high dose prednisolone in systemic lupus erythematosus: a prospective cohort study. *Lupus* 2018;27:890–8.
52 Tanaka Y, Bass D, Chu M, *et al*. Efficacy and safety of intravenous belimumab in Japanese patients with systemic lupus erythematosus: a subgroup analysis of a phase 3 randomized placebo-controlled trial. *Mod Rheumatol* 2019;29:452–60.
53 Zhang F, Bae S-C, Bass D, *et al*. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. *Ann Rheum Dis* 2018;77:355–63.
54 Cimmino MA, Salvarani C, Macchioni P, *et al*. Long-term follow-up of polymyalgia rheumatica patients treated with methotrexate and steroids. *Clin Exp Rheumatol* 2008;26:395–400.
55 Radhakutty A, Burt MG. Management of endocrine disease: critical review of the evidence underlying management of glucocorticoid-induced hyperglycaemia. *Eur J Endocrinol* 2018;179:R207–18.
56 Burt MG, Drake SM, Aguilar-Loza NR, *et al*. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. *Intern Med J* 2015;45:261–6.
57 Tatalovic M, Lehmann R, Cheetham M, *et al*. Management of hyperglycaemia in persons with non-insulin-dependent type 2 diabetes mellitus who are started on systemic glucocorticoid therapy: a systematic review. *BMJ Open* 2019;9:e028914.
58 Strehl C, Bijlsma JWJ, de Wit M, *et al*. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR Task force. *Ann Rheum Dis* 2016;75:952–7.