Appendix 1 (as supplied by the authors): Supplementary material content

TABLES

FIGURES

METHODS

Appendix to: 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. *CMAJ* 2020. doi:10.1503/cmaj.191012.

Table 1. List of diagnostic codes for chronic inflammatory diseases

Code type	List of codes	Chronic inflammatory disease
Read		
	J40z.00, J400200, J40..12, J401.00, J400500, J401000, J400100, J400.00, J08z900, J401100, ZR3S.11, ZR3S.00, J400z00, J40..11, J400300, J402.00, Jyu4000, J400400, J40z.11, J401z11, J401z00, N031100, J40..00, J4z2.00, J400000, J401200, J57yA00, J57y900, N031000, J41yz00, 41y100, J410400, J41y.00, J410200, J41z.00, J412.00, J410300, J410z00, Jyu4100, J410.00, J410100, J410000, J411.00, N045400, J41..12, J413.00, J41..00, J4...12, 8Cc5.11, 8CA4W00, 8Cc5.00,	Inflammatory bowel disease
	2G27.00 , 66H..13, F371200, F396400, G5y8.00, G5yA.00, H570.00, N005.00, N040.00, N040000, N040100, N040200, N040500, N040600, N040700, N040800, N040900, N040A00, N040B00, N040D00, N040F00, N040G00, N040H00, N040J00, N040K00, N040N00, N040P00, N040Q00, N040R00, N040S00, N040T00, N041.00, N042.00, N042100, N042200, N042z00, N047.00, N04X.00, N04y000, N04y011, N04y012, N04y200, Nyu1100, Nyu1200, Nyu1G00, N040L00, N040C00, N040400, Nyu1000, N040M00, N040E00, N040300,	Rheumatoid arthritis
	N20..00, N20..11	Polymyalgia rheumatica
	N200.00, G755.00, G755z00	Giant cell arteritis
	G757.00, G757.12, G751000, G758.00, G754.11, G754.00, G752112, G752111, C332100, D310100, D310000, D310011, G750.00, F371100, F396300, K01x300, G75..00, G75z.00, F421E00, G76B.00, N040N00, N012700, N012011, N012000, N012.00, K425200, N012x00, AD61.00	Vasculitis
	M154.00, M154z00, N000.00, N000400, N000000, K01x411, M154700, N000300, H57y400, N000200, K0B4000, N000z00, F371000, ZRq9.00, K01x400,	Systemic lupus erythematosus

	ZRq8.00, N000100, Nyu4300, ZRq9.11	
ICD 10		
	K50.0, K50.1, K50.8, K50.9, M07.4, M09.1, K51.0, K51.1, K51.2, K51.3, K51.5, K51.8, K51.9, M07.5, M09.2	Inflammatory bowel disease
	I52.8, J99.0, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06.0, M06.1, M06.2, M06.3, M06.8, M06.9	Rheumatoid arthritis
	M35.3, M31.5	Polymyalgia rheumatica
	M31.5, M31.6	Giant cell arteritis
	M31.4, M30.3, M30.1, M31.3, D69.0, M30, M30.0, M30.8, M31.7, H35.0, M05.29, M05.24, M05.27, M05.21, M05.28, M05.26, M05.2, M05.23, M05.22, M05.25, M05.20, M35.2	Vasculitis
	M32.0, M32.1, M32.8, M32.9	Systemic lupus erythematosus

Note: CPRD = Clinical Research Data link, HES = Hospital Episode Statistics, ICD = International Classification of Diseases

Table 2. List of diagnostic codes for hypertension and covariates

Disease	Code type	List of codes
Hypertension	**Read**	F282.00, F404200, F421300, G2...00, G2...11, G20..00, G20..11, G20..12, G200.00, G201.00, G202.00, G203.00, G20z.00, G20z.11, G21..00, G210.00, G210000, G210100, G210z00, G211.00, G211000, G211100, G211z00, G21z.00, G21z000, G21z011, G21z100, G21zz00, G22..00, G220.00, G221.00, G222.00, G22z.00, G22z.11, G23..00, G230.00, G231.00, G232.00, G233.00, G23z.00, G25..00, G25..11, G26..00, G26..11, G27..00, G28..00, G2y..00, G2z..00, G672.00, G672.11, Gyu2.00, G22z.11, G24..00, G240.00, G240000, G240z00, G241.00, G241000, G241z00, G244.00, G24z.00, G24z000, G24z100, G24zz00, Gyu2000, Gyu2100
	ICD 10	I10.X, I11.0, I11.9, I1.2, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, O11.X, I15, I15.0, I15.1, I15.2, I15.8, I15.9
Scleroderma	**Read**	F396600, H572.00, K0H..00,K0J0.00 ,M210.00, M210000, M210400, M210z00, N001.00, N001.12, N001000, Nyu4500, N001100
	ICD 10	L94.0, L94.1, M34, M34.0, M34.8, M34.9
Stage 3 or 4 chronic kidney disease	**Read**	1Z12.00, 1Z13.00, 1Z14.00, 1Z15.00, 1Z16.00, 1Z1B.00, 1Z1C.00, 1Z1D.00, 1Z1E.00, 1Z1F.00, 1Z1G.00, 1Z1H.00, 1Z1J.00, 1Z1K.00, 1Z1L.00, 4I29.00, 7L1A100, 7L1A200, 7L1A400, 7L1A500, 7L1A600, 7L1A.11, 7L1B000, 7L1B.00, 7L1B100, 7L1B200, 7L1C000, 7L1f000, 8882, G72C.00, K04E.00, K050.00, K05..12, K053.00, K054.00, K055.00, K0D..00, SP01500, SP05613, SP06B00, SP0E.00, SP0F.00, SP0G.00, SP0H.00, Gy1..00, Gy2..00, Gy3..00, Gy4..00, Gy5..00, TA02000, TA22000, TB11.00, TB11.11, Z91A.00, ZVu3G00
	ICD 10	N18

Note: ICD = International Classification of Diseases. Codes in blue were used to define secondary hypertension.

Table 3. Prednisolone equivalent dose conversion factors for oral glucocorticoids

Type of glucocorticoid	10mg prednisolone equivalent, mg
Betamethasone	1.5
Beclomethasone	0.96
Budesonide	1.09
Cortisone	50
Deflazacort	12
Dexamethasone	1.5
Hydrocortisone	40
Methylprednisolone	8
Prednisone	10
Triamcinolone	8

Table 4. Description of prescribed hypertension inducing drugs during the study period

Medication use*, n (%)	Overall (N=71,642)	No. of patients with incident hypertension (N=24,896)	No. of patients without incident hypertension (N=46,746)
Selective serotonin reuptake inhibitors	14,200 (19.8)	3385 (13.6)	10,815 (23.1)
Tricyclic antidepressants	15,253 (21.3)	4762 (19.1)	10,491 (22.4)
Oral oestrogen	6518 (9.1)	930 (3.7)	5588 (12.0)
Hormone replacement therapy	6960 (9.7)	2736 (11.0)	4224 (9.0)
Cyclosporine	419 (0.6)	133 (0.5)	286 (0.6)
Leflunomide	1488 (2.1)	479 (1.9)	1009 (2.2)
Mycophenolate mofetil	285 (0.4)	57 (0.2)	228 (0.5)
Non-steroidal anti-inflammatory drugs	45,144 (63.0)	16,394 (65.9)	28,750 (61.5)
Any hypertensive medication	52,711 (73.6)	18,370 (73.8)	34,341 (73.5)

*Defined as 1 or more prescriptions at any time during the study follow-up

Table 5. Timing of diagnosis of the underlying chronic inflammatory diseases and description of oral glucocorticoid exposure during the study period

Chronic inflammatory disease	**Diagnosed before the start of follow-up** (%) *	**Diagnosed at follow-up start** (%)	**Mean (SD) cumulative PED in mg**	**Median (P25-P75) cumulative PED in mg**	**Median (P25-P75) duration of glucocorticoid exposure in years**
Inflammatory bowel disease	14,560 (57.9)	10,602 (42.1)	2591 (7447)	0 (0-1691)	6.6 (2.6-11.9)
Rheumatoid arthritis	9437 (46.7)	10,777 (53.3)	3044 (8107)	0 (0-1614)	5.8 (2.5-11.0)
Polymyalgia rheumatica	3117 (20.5)	12,128 (79.6)	4364 (7957)	1209 (0-5665)	6.1 (2.6-11.4)
Giant cell arteritis	724 (22.5)	2495 (77.5)	4410 (7851)	635 (0-6226)	6.6 (2.8-11.8)
Vasculitis	1453 (32.5)	3020 (67.5)	3137 (8621)	0 (0-584)	6.6 (2.6-11.8)
Systemic lupus erythematosus	1703 (51.2)	1626 (48.8)	2608 (8147)	0 (0-886)	6.4 (2.7-11.5)
All diseases	30,994 (43.3)	40,648 (56.7)	3204 (7898)	0 (0-2865)	6.6 (2.6-11.9)

Note: PED = prednisolone-equivalent dose, P25 = 25th centile, P75 = 75th centile.

*Median duration from date of diagnosis until date of entry was 5 years (P25=1.7, P75=10.6) and mean duration was 7.6 years (SD=8)

Table 6. Time-variant prescribed prednisolone-equivalent dose of oral glucocorticoids and the risk of hypertension further adjusted for flare status in the overall study population

Dose exposure	HRs (95% CI)*†	HRs (95% CI) *‡
Daily dose category, mg		
Non-use (Ref.)	1	1
>0–4.9	0.97 (0.90-1.05)	0.98 (0.91-1.06)
5.0–7.4	0.95 (0.86-1.06)	1.02 (0.94-1.12)
≥7.5	0.95 (0.84-1.08)	1.09 (1.00-1.20)
Overall cumulative dose category, mg		
Non-use (Ref.)	1	1
>0–959.9	1.14 (1.09-1.14)	1.14 (1.09-1.19)
960–3054.9	1.22 (1.15-1.28)	1.21 (1.15-1.21)
≥3055	1.33 (1.27-1.38)	1.32 (1.27-1.37)

*Models were adjusted for age, index of multiple deprivation, non-oral glucocorticoids (inhaled, nasal, intra-muscular, intra-articular, topical or rectal), comorbidities (cardiovascular disease, chronic kidney disease and scleroderma), type of chronic inflammatory diseases and time-variant flare status

†Flare status defined as an increase in daily dose by >5mg, or a c-reactive protein (CRP) measurement ≥10mg/mL, or an erythrocyte sedimentation rate (ESR) ≥30mm/h

‡Flare status defined on an increase in daily dose by >10mg, or a CRP measurement ≥10mg/mL, or ESR≥30mm/h

Table 7. Time-variant prescribed prednisolone-equivalent dose of oral glucocorticoids and the risk of hypertension further adjusted for flare status by type of chronic inflammatory disease

Dose exposure	Inflammatory bowel disease	Rheumatoid arthritis	Polymyalgia rheumatica	Giant cell arteritis	Vasculitis	Systemic lupus erythematosus
	HRs (95% CI)*†	HRs (95% CI)*†	HRs (95% CI)*†	HRs (95% CI)*†	HRs (95% CI)*†	HRs (95% CI)*†
Daily dose category, mg						
Non-use (Ref.)	1	1	1	1	1	1
>0–4.9	0.79 (0.55-1.15)	1.01 (0.85-1.18)	0.76 (0.69-0.85)	0.89 (0.71-1.22)	0.74 (0.42-1.29)	0.68 (0.39-1.19)
5.0–7.4	0.94 (0.66-1.35)	0.94 (0.79-1.11)	0.70 (0.59-0.83)	0.89 (0.61-1.29)	1.63 (1.08-2.48)	1.43 (0.94-2.16)
≥7.5	0.79 (0.53-1.18)	0.86 (0.69-1.06)	1.00 (0.83-1.21)	1.19 (0.77-1.84)	2.17 (1.24-3.79)	1.57 (0.76-3.25)
Overall cumulative dose category, mg						
Non-use (Ref.)	1	1	1	1	1	1
>0–959.9	1.08 (0.98-1.18)	1.12 (1.04-1.21)	1.21 (1.11-1.31)	1.13 (0.96-1.33)	1.15 (0.97-1.38)	1.06 (0.84-1.34)
960–3054.9	0.93 (0.83-1.05)	1.19 (1.07-1.32)	1.22 (1.13-1.33)	1.29 (1.08-1.55)	1.31 (1.02-1.70)	1.23 (0.87-1.73)
≥3055	1.12 (1.02-1.23)	1.47 (1.37-1.59)	1.14 (1.07-1.21)	1.22 (1.07-1.39)	1.43 (1.18-1.72)	1.44 (1.16-1.80)

*Models were adjusted for age, index of multiple deprivation, non-oral glucocorticoids (inhaled, nasal, intra-muscular, intra-articular, topical or rectal), comorbidities (cardiovascular disease, chronic kidney disease and scleroderma), type of chronic inflammatory diseases and time-variant flare status;

†Flare status defined as an increase in daily dose by >5mg, or a c-reactive protein measurement ≥10mg/mL, or an erythrocyte sedimentation rate ≥30mm/h

Table 8. Time-variant prescribed prednisolone-equivalent dose of oral glucocorticoids and the risk of hypertension from mixed-effect models

Dose variables	HRs (95% CI)*
Daily dose category, mg	
Non-use (Ref.)	1
>0–4.9	0.97 (0.90 to 1.05)
5.0–7.4	1.02 (0.94 to 1.11)
≥7.5	1.07 (1.01 to 1.14)
Overall cumulative dose category, mg	
Non-use (Ref.)	1
>0–959.9	1.13 (1.08 to 1.18)
960–3054.9	1.19 (1.13 to 1.26)
≥3055	1.29 (1.24 to 1.33)

*Models were adjusted for age, index of multiple deprivation, non-oral glucocorticoid use (inhaled, nasal, intra-muscular, intra-articular, topical or rectal), comorbidities (cardiovascular disease, chronic kidney disease and scleroderma) and type of chronic inflammatory disease,

Table 9. Time-variant prescribed prednisolone-equivalent dose of oral glucocorticoids and the risk of hypertension when the 29,968 patients for whom the duration of their underlying chronic disease was ≥3 months

Dose	HRs (95% CI)*
Daily dose category, mg	
Non-use (Ref.)	1
>0–4.9	0.99 (0.88-1.12)
5.0–7.4	0.97 (0.87-1.10)
≥7.5	0.91 (0.83-1.01)
Overall cumulative dose category, mg	
Non-use (Ref.)	1
>0–959.9	1.12 (1.03-1.22)
960–3054.9	1.07 (0.98-1.18)
≥3055	1.31 (1.23-1.38)

Note: Visits to specialists are more likely to happen around the time of diagnosis and medication prescribed during these outpatient visits was not available for the analysis. We therefore performed a sensitivity analysis including only patients who were diagnosed 3 months or more before the start of the study follow-up.

*Models were adjusted for age, index of multiple deprivation, non-oral glucocorticoid use (inhaled, nasal, intra-muscular, intra-articular, topical or rectal), comorbidities (cardiovascular disease, chronic kidney disease and scleroderma) and type of chronic inflammatory disease

Figure 1. Study population flow chart

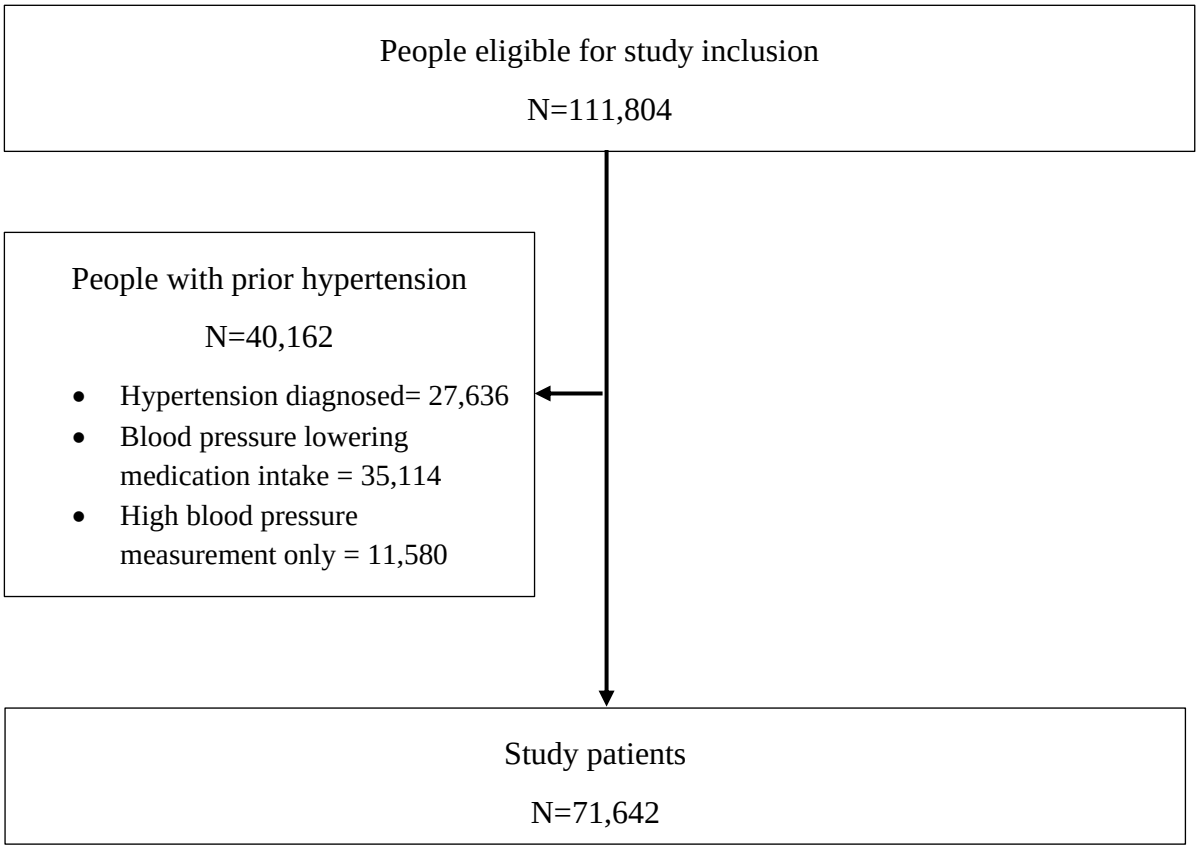
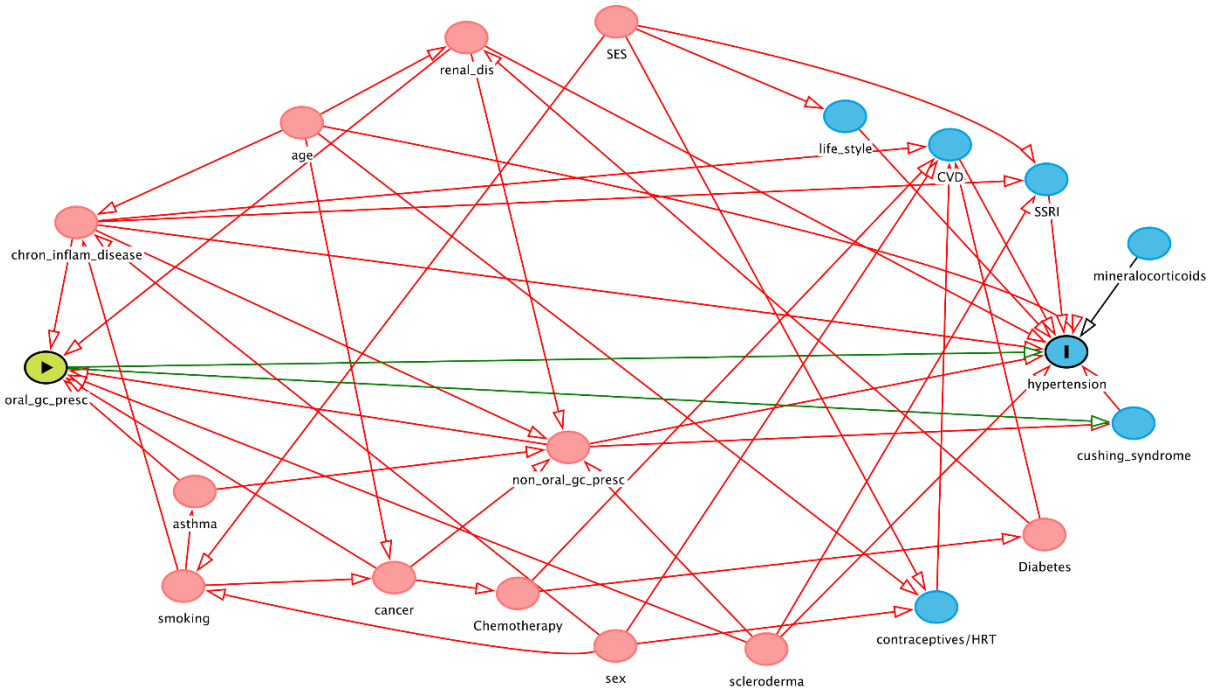


Figure 2. Schematic view of confounding adjustment for investigating the effects of oral glucocorticoids on hypertension



Key: , exposure; ,outcome; , ancestor of outcome; , ancestor of exposure *and* outcome ; ,causal path; , biasing path; chron_inflam_disease, Chronic inflammatory diseases (inflammatory bowel disease, systemic lupus erythematosus, polymyalgia rheumatica, giant cell arteritis, rheumatoid arthritis and vasculitis);CVD, cardio-vascular dieases, non_oral_gc_presc, non-oral glucocorticoids prescribed; HRT, hormone replacement therapy; oral_gc_presc, oral glucocorticoids prescribed; renal_dis, advanced chronic renal disease; SES, socioeconomic status; SSRI, Selective serotonin reuptake inhibitors.

This is the diagram and output obtained with the DAGitty software. Causal diagrams or directed acyclic graphs provide a graphical, yet mathematically rigorous methodology for minimising bias in epidemiology[1]. DAGitty is an open-source license software used to create, edit and analyse causal diagrams[2]. This software produces a list of minimally sufficient sets of variables to be used for confounding analysis. Adjustment for any of the sets listed would produce the same 'unbiased' results given the assumed causal relationships. The minimal sufficient adjustment sets identified for estimating the 'unbiased' causal effect of oral glucocorticoids on hypertension are listed below:

a) CVD, SES, age, chron_inflam_disease, non_oral_gc_presc, renal_dis, scleroderma
b) CVD, SSRI, age, chron_inflam_disease, life_style, non_oral_gc_presc, renal_dis, scleroderma
c) CVD, age, chron_inflam_disease, contraceptives/HRT, non_oral_gc_presc, renal_dis, scleroderma, sex, smoking
d) Chemotherapy, SES, age, chron_inflam_disease, non_oral_gc_presc, renal_dis, scleroderma, sex
e) Chemotherapy, SSRI, age, chron_inflam_disease, contraceptives/HRT, life_style, non_oral_gc_presc, renal_dis, scleroderma, sex
f) Chemotherapy, age, chron_inflam_disease, non_oral_gc_presc, renal_dis, scleroderma, smoking

g) SES, age, cancer, chron_inflam_disease, non_oral_gc_presc, renal_dis, scleroderma, sex

h) SSRI, age, cancer, chron_inflam_disease, contraceptives/HRT, life_style, non_oral_gc_presc, renal_dis, scleroderma, sex

i) asthma, cancer, chron_inflam_disease, non_oral_gc_presc, renal_dis, scleroderma

j) cancer, chron_inflam_disease, non_oral_gc_presc, renal_dis, scleroderma, smoking

The adjustment set highlighted in blue was used in the analysis and was selected so as to ensure that it included variables that were available in the dataset (e.g. chemotherapy use was not) and that clinicians not familiar with the DAG approach would consider important for model adjustment, given current understanding of the pathophysiology of glucocorticoid-induced hypertension (e.g. age, chronic renal disease or scleroderma).

SUPPLEMENTARY METHODS

1. Missing data estimation and dose correction

The end date of every prescription of oral glucocorticoids and the dose prescribed to patients during tapering periods were not documented in electronic health records from primary care. The missing daily doses were therefore imputed.

1.1 Prescription end date and missing data estimation

For each prescription of oral glucocorticoids, the end date was calculated by adding the number of days covered by the prescription to the prescription issue date. The duration of each prescription was calculated as the total number of tablets prescribed divided by the daily dose. The maximum duration for any prescription was capped at 90 days as general practitioners are asked to prescribe medication for a period of less than 3 months.

A total number of 940,671 prescriptions were issued to study patients between 2 Jan 1997-23 March 2017 with a median of 20 prescriptions per patient (P25=8 and P75=46). The median time between prescriptions was 32 days (P25=23 and P75=56). The number of prescriptions with missing number of daily tablets and daily dose were 452,805 (48%) and 1,042 (0.11%), respectively. The median number of missing data per patient were 18 (P25=10 & and P75=42) and 30 (P25=14, P75=59) for number of tablets and daily doses, respectively. Missing data on prescribing was unrelated to GP practice (correlation coefficient obtained using an indicator variable for the missing prescription was 0.0029).

Missing data were imputed using truncated regression [3], with specified lower and upper bound limits of 1 and 45, respectively, for daily dose; and 1 and 500, respectively, for the quantity prescribed. The number of datasets to be imputed was assumed to be at least 100 times the fraction of incomplete cases [4]. Hence, a total of 50 datasets were imputed. Each of the 50 datasets were analysed separately. Parameter estimates and their 95% CIs were then combined using Rubin rules [5]

The imputation was conducted under missing data at random assumption, that is, the data missingness was considered to be at random conditional on the variables included in imputation models [4,6].

Variables included for imputation of missing daily doses and number of tables were as follows:

Variable name	Variable type	Missing (%)	Imputation method
sex	Binary	0	Auxiliary variable

Cardio-vascular disease	Binary	0	Auxiliary variable
Diabetes	Binary	0	Auxiliary variable
Inhaled glucocorticoid	Binary	0	Auxiliary variable
Intramuscular glucocorticoid	Binary	0	Auxiliary variable
Nasal glucocorticoid	Binary	0	Auxiliary variable
Topical glucocorticoid	Binary	0	Auxiliary variable
Rectal glucocorticoid	Binary	0	Auxiliary variable
Chronic inflammatory disease type	categorical	0	Auxiliary variable
Duration of disease	continuous	0	Auxiliary variable
Daily oral prednisolone equivalent dose	continuous	48	Truncated linear regression
Number of tablets	continuous	0.11	Truncated linear regression

1.2 Correction of oral glucocorticoid dose for tapering periods

To take into account oral glucocorticoid dose tapering, a number of rules were implemented:

A. Where only 1 prescription of ≥10 mg prednisolone equivalent dose (PED) for a maximum of 2 weeks was issued and there was no other prescription during the 2 months prior and after the date of prescription, it was assumed to be a glucocorticoid pulse dose. Hence, any zero doses before and after the glucocorticoid pulse prescription period were left unchanged (see snapshot below)

Id	start	end	old_dose	new_dose	gap_days
1	1	80	0	0	80
1	80	87	40	40	7
1	87	287	0	0	200

B. Where a 0 dose gap (duration without prescribed glucocorticoids) was <3 days and the prescribed daily doses during the 2 months before and after the 0 dose gap were the same, the zero doses were left unchanged

Id	start	end	Old_dose	new_dose	gap_days
2	1	14	5	5	14
2	14	21	0	2.5	7
2	21	24	0	0	3
2	24	36	5	5	14
2	36	42	5	5	7
2	42	49	0	2.5	7

C. Replacement of zero dose gaps

i. Where a 0 dose gap was ≤3 months and there were ≥4 prescriptions issued every 2-4 months before the 0 dose gap, the total dose prescribed during the last prescription just before the 0 dose gap was divided by the duration of the last prescription and the 0 dose gap. For example, if the last prescription period was 14 days and the 0 dose gap (duration without a prescription) was 14 days, the total dose of the last prescription was divided into 28 days to obtain the average daily dose. The values of the last prescription and gap were then replaced by this average dose.

Id	start	end	Old_dose	new_dose	gap_days
2	1	28	10	10	28
2	28	49	10	10	21
2	49	63	10	5	14
2	63	77	0	5	14
2	77	91	5	5	14
2	91	98	2.5	2.5	7

ii. Where there were ≥6 prescriptions within 1 year and no 0 dose gaps of >3 months between prescriptions, and any 0 dose gaps of ≤3 months between prescriptions was followed by a minimum of 3 prescriptions in the next 7 months, the total dose prescribed during the last prescription just before the 0 dose gap was divided by the duration of the last prescription and the gap. The values of the last prescription and 0 dose gap were then replaced by this average dose.

Id	start	end	Old_dose	new_dose	gap_days
3	1	28	10	10	28
3	28	49	10	10	21
3	49	63	10	10	14
3	63	77	7.5	7.5	14
3	77	91	7.5	7.5	14
3	91	98	7.5	7.5	14
3	98	119	0	5	21
3	119	140	5	5	21
3	140	161	5	5	21
3	161	175	2.5	2.5	14

iii. Where a 0 dose gap was of >3 days and there was a minimum of 1 prescription of oral glucocorticoids in the previous ≥2 weeks and within the next 3 months of the 0 dose gap period, the 0 dose values were replaced with the daily dose of last prescription before 0 dose gap period.

Id	start	end	Old_dose	new_dose	gap_days
4	1	28	10	10	28
4	28	49	10	10	21
4	49	63	0	10	14
4	63	77	7.5	7.5	14
4	77	91	7.5	7.5	14
4	91	98	7.5	7.5	14

D. Dose tapering for patients who received GCs for ≥6 months

i. Where a daily dose decreased suddenly from between ≥31mg and ≤40mg to <10mg, the duration of the last prescription was divided into 5 periods and the patient was assumed to have taken a prescribed dose of between ≥31mg and ≤40mg (same as recorded-), 30mg, 20mg, 10mg and 5mg during the first, second , third, fourth and fifth period, respectively.

Id	start	end	old_dose	new_dose	gap_days
4	147	161	40	40	14
4	161	168	0	40	7
4	168	182	40	40	14
4	182	189	40	40	7
4	189	196	40	30	7
4	196	203	40	20	7
4	203	210	40	10	7
4	210	217	40	5	7
4	217	224	5	5	7

ii. Where a daily dose decreased suddenly from between ≥21mg and <31mg to <10mg, the duration of the last prescription was divided into 4 periods and the patient was assumed to have taken a prescribed dose between ≥21mg and <31mg (same as recorded), 20mg, 10mg and 5mg during the first, second, third and fourth period, respectively.

Id	start	end	old_dose	new_dose	gap_days
5	147	161	25	25	14
5	161	168	0	25	7
5	168	182	25	25	14
5	182	189	25	25	7
5	189	196	25	20	7
5	196	203	25	10	7
5	203	210	5	5	7
5	210	217	5	5	7

iii. Where a daily dose decreased suddenly from between ≥15mg and <21mg to <10mg, the duration of the last prescription was divided into 3 periods and the patient was assumed to have taken a prescribed dose between ≥15mg and <21mg (same as recorded), 10mg and 5mg during the first, second and third period, respectively.

Id	start	end	old_dose	new_dose	gap_days
6	168	182	15	15	14
6	182	189	15	15	7
6	189	196	15	10	7
6	196	203	15	5	7
6	203	210	5	5	7

iv. Where a daily dose decreased suddenly from between ≥10mg and <15mg to <5mg and the patient received 5mg and 2.5mg tablets, the duration of the last prescription was divided into 4 periods and the patient was assumed to have taken a prescribed dose between ≥10mg and <15mg (same as recorded), 10mg, 7.5mg and 5mg during the first, second, third and fourth period, respectively.

Id	start	end	old_dose	new_dose	gap_days
7	189	196	12.5	12.5	7
7	196	203	12.5	12.5	7
7	203	210	12.5	10	7
7	210	217	12.5	7.5	7
7	217	224	12.5	5	7
7	224	231	2.5	2.5	7

v. Where a daily dose decreased suddenly from between ≥10mg and <15mg to <5mg and the patient received only 5mg tablets, the duration of the last prescription was divided into 3 periods and the patient was assumed to have taken a prescribed dose between ≥10mg and <15mg (same as recorded), 10mg and 5mg during the first, second and third period, respectively.

Id	start	end	old_dose	new_dose	gap_days
8	189	196	10	10	7
8	196	203	10	10	7
8	203	210	10	10	7
8	210	217	10	5	7
8	217	224	2.5	2.5	7

vi. Where a daily dose decreased suddenly from between ≥5mg and <10mg to ≤2 mg, the duration of the last prescription was divided into 3 periods and the patient was assumed to have taken a prescribed dose between ≥5mg and <10mg (same as recorded), 5mg and 2.5mg during the first, second and third period, respectively.

Id	start	end	old_dose	new_dose	gap_days
9	189	196	7.5	7.5	7
9	196	203	7.5	7.5	7
9	203	210	7.5	5	7
9	210	217	7.5	2.5	7
9	217	224	1	1	7

2. Immortal time bias, time-variant covariates and cumulative doses

2.1. Immortal time bias

The snapshot below shows that patient 1 entered the study on 15th September 2001 but received first oral glucocorticoid on the 6th March, 2013. Quite often, the start of the follow-up for each patient is inadvertently assumed to be the date when the first medication is issued[7,8]. Not including the duration before the start of medication, however, leads to the so called immortal time bias [9] due to underestimation of the person-time contributed by the patient. In order to minimise this type of bias, both the exposure and non-exposure periods between the study start and end dates were therefore accounted for. Patient 1 was observed but not exposed during the periods between 15th September 2001 and 6th March 2013, and between 11th March 2013 and 24th November 2014) so the value of daily glucocorticoid dose was 0. The total person-time contributed by the patients to the study was approximately 14 years (i.e. time between 15th September 2001 and 8th June 2015).

2.2 Time-variant covariates

Time-variant covariates (e.g. daily glucocorticoid dose and chronic inflammatory disease) were constructed to reflect the status of a person in relation to a particular variable (e.g. chronic inflammatory disease status) at every follow-up point and would have a value of 0 (No) or 1 (Yes). For example, on the snapshot below, patient 1 was diagnosed for inflammatory disease on 24/11/2014. Therefore, the follow-up periods before and after the diagnosis date were assigned the value of 0 (No) and 1(Yes), respectively.

2.3 Cumulative doses construction

In constructing the cumulative dose variable, daily PEDs were cumulated throughout the entire follow-up period starting from one year before the study start date. For example, patient 1 only started to receive oral glucocorticoids on the 6th March 2013 and the daily PEDs were therefore cumulated from this point until the end of follow-up (i.e. 8th June 2015).

Id	start_dt	end_dt	disease_dt	infla_dise~e	daily_PED	overall_cum
1	15 Sep 2001	6 Mar 2013	24 Nov 2014	No	0	0
1	6 Mar 2013	11 Mar 2013	24 Nov 2014	No	30	150
1	11 Mar 2013	24 Nov 2014	24 Nov 2014	No	0	150
1	24 Nov 2014	17 Dec 2014	24 Nov 2014	Yes	16	517
1	17 Dec 2014	25 Dec 2014	24 Nov 2014	Yes	16	655
1	25 Dec 2014	3 Jan 2015	24 Nov 2014	Yes	10	742
1	3 Jan 2015	12 Jan 2015	24 Nov 2014	Yes	5	785
1	12 Jan 2015	13 Jan 2015	24 Nov 2014	Yes	5	790
1	13 Jan 2015	10 Feb 2015	24 Nov 2014	Yes	18	1287
1	10 Feb 2015	23 Feb 2015	24 Nov 2014	Yes	18	1517
1	23 Feb 2015	4 Mar 2015	24 Nov 2014	Yes	16	1666
1	4 Mar 2015	13 Mar 2015	24 Nov 2014	Yes	10	1759
1	13 Mar 2015	23 Mar 2015	24 Nov 2014	Yes	5	1806
1	23 Mar 2015	30 Mar 2015	24 Nov 2014	Yes	3	1827
1	30 Mar 2015	3 Apr 2015	24 Nov 2014	Yes	17	1904
1	3 Apr 2015	8 Apr 2015	24 Nov 2014	Yes	10	1951
1	8 Apr 2015	13 Apr 2015	24 Nov 2014	Yes	5	1974
1	13 Apr 2015	29 Apr 2015	24 Nov 2014	Yes	3	2022
1	29 Apr 2015	4 Jun 2015	24 Nov 2014	Yes	2.5	2113
1	4 Jun 2015	8 Jun 2015	24 Nov 2014	Yes	12	2160
2	1 Jan 1998	27 Jul 1998	6 Aug 1998	No	0	0
2	27 Jul 1998	6 Aug 1998	6 Aug 1998	No	30	300
2	6 Aug 1998	20 Aug 1998	6 Aug 1998	Yes	25	650

Note: Id, patient identification number; start_dt, start date; end_dt, end date; disease_dt, date of inflammatory disease; infla_disease, inflammatory disease; daily_PED, daily prednisolone equivalent dose; overall_cum, cumulative PED.

2.4 Definition of disease flares

To account for possible variation in the incidence rate of hypertension during instances of disease flares, a time-variant variable was constructed based on blood levels of c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and changes in daily doses of oral glucocorticoids[10]. Briefly, CRP and ESR measurements were not used in defining disease activity for patients with systemic lupus erythematosus and vasculitis, as flares can occur without increase in these biomarkers. An increase of daily dose by >5mg (or >10mg) lasting 3 weeks or a CRP value of ≥10mg/mL or an ESR value of ≥30mm/h indicated active disease (flare). If the daily dose was reduced to <5mg (or <10mg) and/or measurement of CRP and ESR were <10mg/mL and <30mm/h, respectively, the disease was assumed to be inactive (no flare).

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