1   **SUPPLEMENTAL MATERIAL**

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5   **Contents**

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24　**Supplementary Material 1:** Supplemental methods

25　**Exclusion criteria**

26　Patients were excluded from the study population if they were diagnosed with adrenal insufficiency or

27　hypopituitarism at any time point, except those with traumatic disease onset (eg, postradiotherapy

28　hypopituitarism), in which case they were excluded from the onset year forward. Patients diagnosed with cancer

29　were removed from the population starting from the year prior to first diagnosis.

30

31　**Systemic glucocorticoid exposure**

32　Systemic glucocorticoid (SGC) prescriptions that occurred on the same day as a lower or upper respiratory

33　diagnostic code, and without a diagnostic code suggesting another indication, were assumed to be for the

34　treatment of an acute respiratory condition and were excluded from analyses of conditions other than asthma or

35　chronic obstructive pulmonary disease. In the UK primary care setting, glucocorticoids administered via injection

36　are generally local rather than systemic and were excluded from analyses of conditions other than those for which

37　SGC injections are commonly used: multiple sclerosis, psoriatic arthritis, and rheumatoid arthritis.

38

39　**Definition of severe asthma**

40　Patients with severe asthma were identified by a prescription in the analysis year for medium-dose inhaled

41　corticosteroids with a long-acting β-agonist and/or a leukotriene receptor antagonist, high-dose inhaled

42　corticosteroids, biologic therapies, or long-term SGC.

43

44　**Systemic glucocorticoid utilization metrics**

45　Variables assessed included the percentage of patients prescribed SGC, average number of prescriptions per

46　year, percentage of patients by the average total yearly dose category (>0 to ≤500 mg, >500 to ≤1000 mg, or

47　>1000 mg), percentage of patients by average prescribed daily dose category (>0 to ≤7.5 mg/day, >7.5 to ≤15

48　mg/day, or >15 mg/day), and average total dose per course. Dose category thresholds were derived from

49　previous data indicating differences in adverse event risk and/or healthcare resource utilization/costs at these

50　SGC exposure levels.[1]

51

52　**Reference**

53　1.　Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma:

54　　long-term observational study. *J Asthma Allergy.* 2018;11:193–204. doi:10.2147/JAA.S176026

55   **Table S1** Listing of systemic glucocorticoids contributing to exposure data

Drug name	Prednisolone equivalent conversion factor	ATC code systemic use	Defined daily dose[a]
Betamethasone	6.67	H02AB01	1.5
Betamethasone, injected	6.67 (25 for depot)	H02AB01	1.5 (0.4 for depot)
Cortisone	0.27	H02AB10	37.5
Deflazacort	0.67	H02AB13	15.0
Dexamethasone	6.67	H02AB02	1.5
Hydrocortisone	0.33	H02AB09	30.0
Methylprednisolone	1.33	H02AB04	7.5
Methylprednisolone, injected	0.50	H02AB04	20.0
Prednisolone	1.00	H02AB06	10.0
Prednisolone, injected	1.00	H02AB06	10.0
Prednisone	1.00	H02AB07	10.0
Triamcinolone	1.33	H02AB08	7.5

56

57   **Abbreviations:** ATC, Anatomical Therapeutic Chemical classification system.

58   [a]The assumed average maintenance dose per day for a drug used for its main indication in adults.

59

Table S2 Conditions of interest

Disease group	Condition	Active disease definition	
		Always active	Active when criteria met
Respiratory system	Asthma		X[a]
	COPD/bronchitis	X	
	Nasal polyps	X	
Circulatory system	Carditis		X[a]
	Temporal arteritis		X[b]
	Vasculitis		X[a]
Digestive system	Autoimmune hepatitis	X	
	Crohn's disease		X[a]
	Ulcerative colitis		X[a]
Skin and subcutaneous tissue	Autoimmune bullous diseases	X	
	Eczema/dermatitis		X[b]
	Psoriasis	X	
Musculoskeletal system and connective tissue	Ankylosing spondylitis	X	
	Gout	X	
	Polymyalgia rheumatica	X	
	Rheumatoid arthritis	X	
	Psoriatic arthritis		X[b]
	Sjögren's syndrome	X	
	Systemic lupus erythematosus	X	
Nervous system	Bell's palsy		X[b]
	Multiple sclerosis	X	
	Myasthenia gravis		X[b,c]
Eye and adnexa	Iritis		X[b]
	Scleritis		X[b]
	Uveitis		X[b]
Genitourinary system	Nephrotic syndrome		X[b]
Miscellaneous, involving the immune system	Sarcoidosis		X[a]

61

62 **Abbreviation:** COPD, chronic obstructive pulmonary disease.

63 [a]The condition was considered active if the patient had a relevant diagnostic code at any time and medication in

64   the analysis year and/or the patient had a relevant diagnostic code in the analysis year.

65   [b]In order to be considered active, the diagnostic code must have occurred in the analysis year.

66   [c]The condition is not considered always active because thymectomy can reduce the need for medication.

Table S3 Handling of missing prescription attribute data

Missing route	Two types of glucocorticoids are typically topical: hydrocortisone and betamethasone. Because topical steroids are not included in this analysis, when the route was not explicitly provided for hydrocortisone or betamethasone, the prescription was excluded. For the other glucocorticoids in this study (cortisone, deflazacort, dexamethasone, methylprednisolone, prednisolone, prednisone, and triamcinolone), the following sequence was followed until a value was found: • Use modal route of the same drug at the patient level • Use modal route of the same drug at the population level
Missing strength	The following sequence was followed until a value was found: • Use strength of closest prescription in time, if that prescription is for the same drug and route, limited to within 1 year • Use modal strength of the same drug and route at the patient level • Use modal strength of the same drug and route at the population level
Missing quantity	The following sequence was followed until a value was found: • Use quantity of closest prescription in time, if that prescription is for the same drug, strength, and route, limited to within 1 year • Use modal quantity of the same drug, strength, and route at the patient level • Use quantity of closest prescription in time, if that prescription is for the same drug and route, limited to within 1 year • Use modal quantity of the same drug and route at the patient level • Use modal quantity of the same drug, strength, and route at the population level • Use modal quantity of the same drug and route at the population level
Missing dosing instructions (daily dose)	This sequence was followed until a value was found: • Use daily dose of closest prescription in time, if that prescription is for the same drug, strength, and route, limited to within 1 year • Use modal daily dose of the same drug, strength, and route at the patient level • Use daily dose of closest prescription in time, if that prescription is for the same drug and route, limited to within 1 year • Use modal daily dose of the same drug and route at the patient level

- Use modal daily dose of the same drug, strength, and route at the
  population level

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Table S4 European Medicines Agency approval dates for biologic therapies

Drug(s)	Indications[a]	EMA approval date
Abatacept	Rheumatoid arthritis	May 2007
Adalimumab	Crohn's disease	June 2007
	Rheumatoid arthritis	September 2003
	Ulcerative colitis	April 2012
Anakinra	Rheumatoid arthritis	March 2002
Baricitinib	Rheumatoid arthritis	February 2017
Belimumab	Systemic lupus erythematosus	July 2011
Benralizumab	Asthma	January 2018
Certolizumab pegol	Rheumatoid arthritis	October 2009
Etanercept	Rheumatoid arthritis	February 2000
Golimumab	Rheumatoid arthritis	October 2009
	Ulcerative colitis	September 2013
Infliximab	Crohn's disease	August 1999
	Rheumatoid arthritis	June 2000
	Ulcerative colitis	March 2006
Mepolizumab	Asthma	December 2015
Omalizumab	Asthma	October 2005
Reslizumab	Asthma	August 2016
Rituximab	Rheumatoid arthritis	July 2006
Sarilumab	Rheumatoid arthritis	June 2017
Tocilizumab	Rheumatoid arthritis	January 2009
Tofacitinib	Rheumatoid arthritis	March 2017
	Ulcerative colitis	August 2018
Ustekinumab	Crohn's disease	November 2016
	Ulcerative colitis	September 2019
Vedolizumab	Crohn's disease	May 2014
	Ulcerative colitis	May 2014

69   **Abbreviation:** EMA, European Medicines Agency.

70   [a]Indication listing only includes the 7 key conditions of interest. Additional approval and product information are

71   available at www.ema.europa.eu/en/medicines

72

73 **Table S5** Forum for reducing Oral Corticosteroid Use in Severe asthma (FOCUS) International Working Group

74 members

75

Country	Member(s)
Argentina	Jorge F. Máspero, MD
Australia	John W. Upham, MBBS, PhD
Austria	Josef Smolen, MD
Canada	Kenneth R. Chapman, MSc, MD J. Mark FitzGerald, MD
France	Arnaud Bourdin, MD, PhD
Italy	Giorgio Walter Canonica, MD
Singapore	David Price, FRCGP (Chair)
South Korea	Tae-bum Kim, MD, PhD
United Kingdom	Mark Gurnell, MBBS, MA, PhD John Haughney, MBChB David Jackson, MD, PhD Andrew Menzies-Gow, MBBS, PhD Samantha Walker, PhD
United States	Eugene Bleecker, MD Monica Kraft, MD Tonya A. Winders

76

77   **Figure S1** Average total SGC dose per course.[a]

78   Data are for asthma, severe asthma, COPD nasal polyps, Crohn's disease, ulcerative colitis, rheumatoid arthritis,

79   and systemic lupus erythematosus. European Medicines Agency approval dates for biologic therapies are marked

80   by vertical lines.

81   **Abbreviations:** COPD, chronic obstructive pulmonary disease; Rx, prescription; SGC, systemic glucocorticoid.

82   [a]To minimise misattribution of an SGC indication, only one condition (mono-condition) per patient per year for

83   which an SGC could have been prescribed was used for these analyses.

84
85

86 **Figure S2** Percentage of patients prescribed SGC by average prescribed daily dose category.[a]

87 Data are for asthma, severe asthma, COPD, nasal polyps, Crohn's disease, ulcerative colitis, rheumatoid arthritis,

88 and systemic lupus erythematosus. European Medicines Agency approval dates for biologic therapies are marked

89 by vertical lines. A different scale for the 15 mg/day category is shown on the right axis for asthma, severe

90 asthma, COPD, nasal polyps, and ulcerative colitis.

91 **Abbreviations:** COPD, chronic obstructive pulmonary disease; SGC, systemic glucocorticoid.

92 [a]In order to minimize the misattribution of an SGC indication, only 1 condition per patient per year for which an

93 SGC could have been prescribed was used for these analyses.

94

95 **Figure S3** Average total SGC dose prescribed per year.[a]

96 Total SGC dose per year for asthma, severe asthma, Crohn's disease, ulcerative colitis, rheumatoid arthritis, and

97 systemic lupus erythematosus. European Medicines Agency's approval of the first biologic therapy during the

98 observation period is marked by a vertical line.

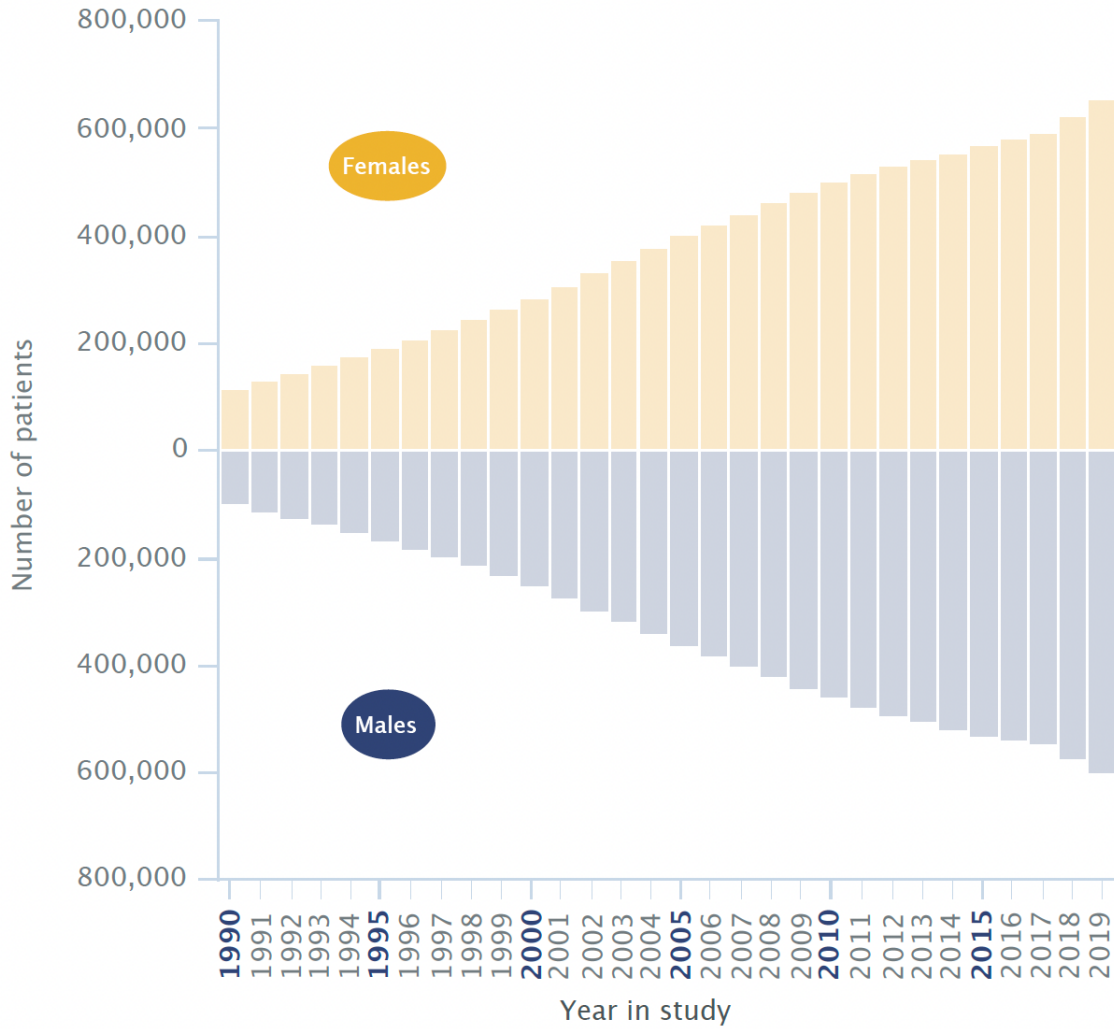99 **Abbreviation:** SGC, systemic glucocorticoid.

100 [a]In order to minimize misattribution of an SGC indication, only 1 condition per patient per year for which an SGC

101 could have been prescribed was used for these analyses.
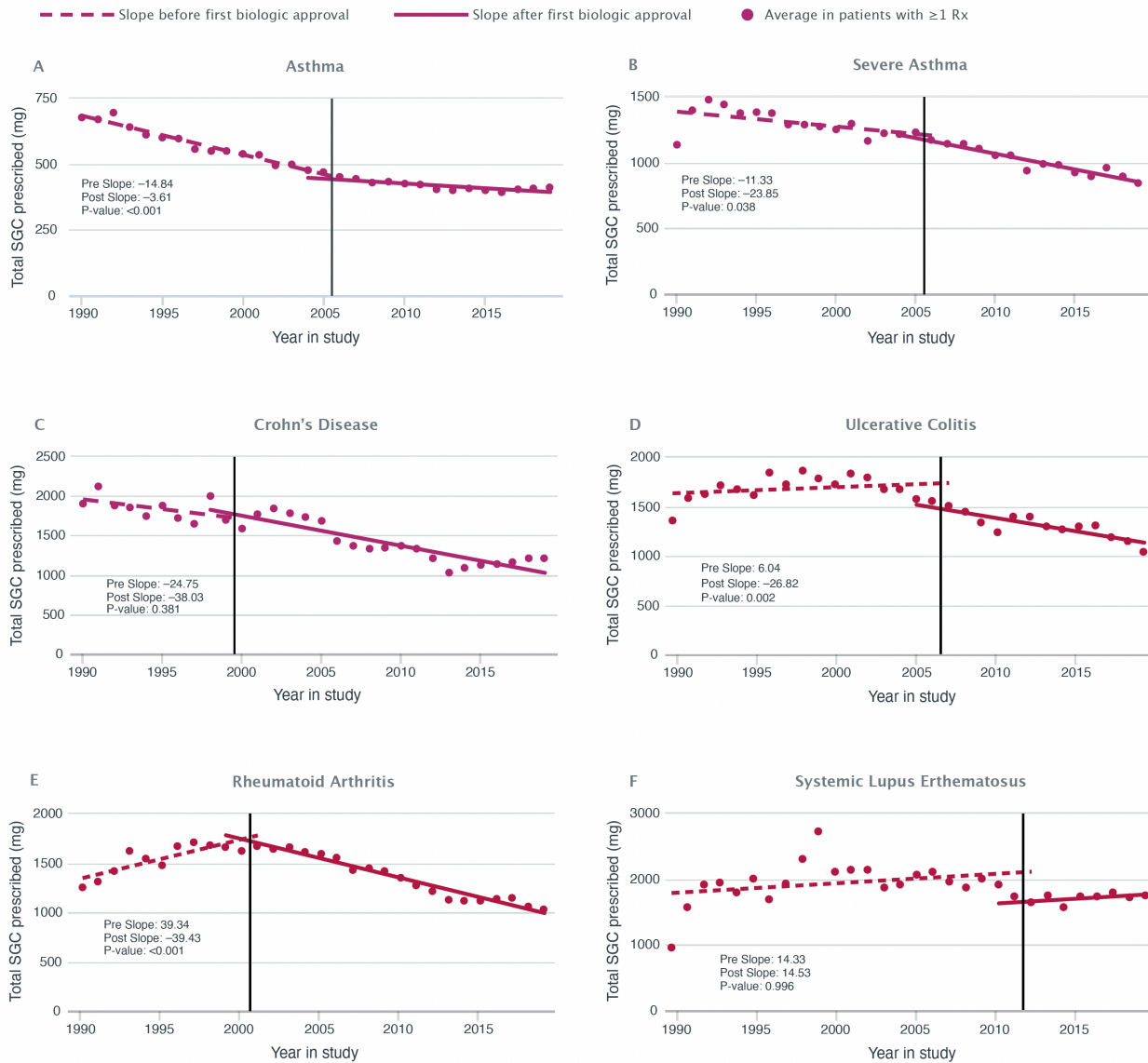
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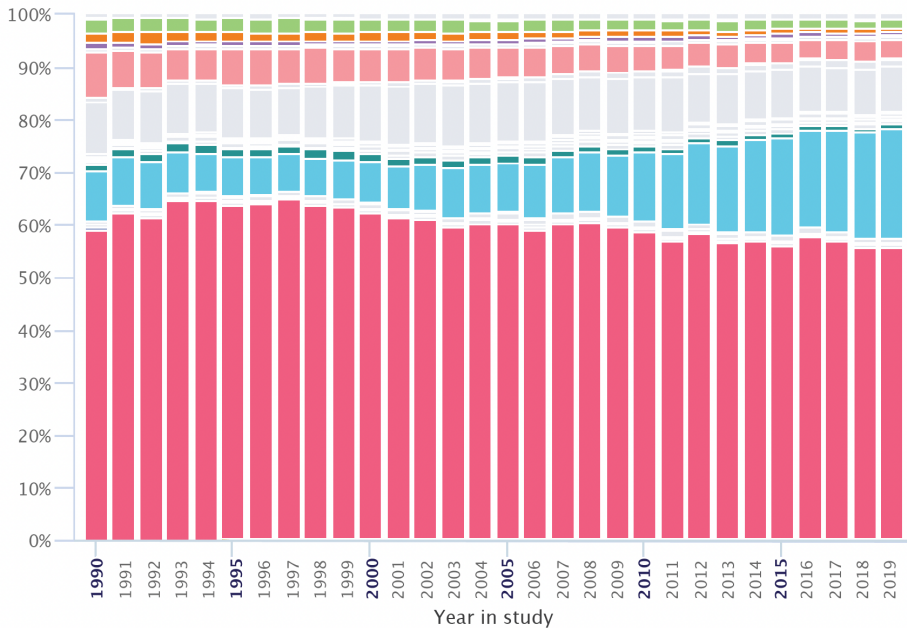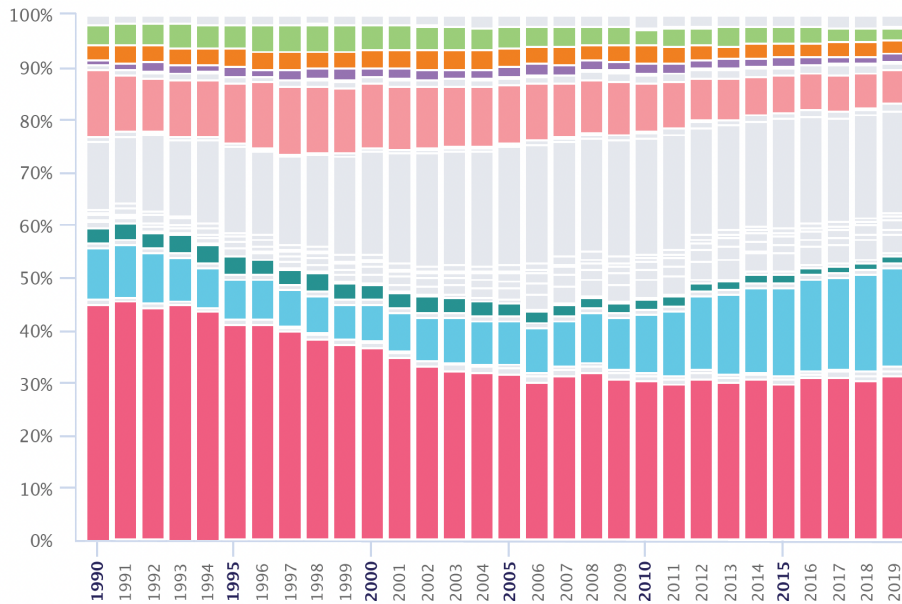106   **Figure S4** Number of patients who met study inclusion criteria per year by sex.

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111 **Figure S5** Relative contribution of 27 conditions of interest to total SGC prescriptions (top) and total SGC dose

112 (bottom) per analysis year.[a]

113 **Abbreviations:** COPD, chronic obstructive pulmonary disease; SGC, systemic glucocorticoid; SLE, systemic

114 lupus erythematosus.

115 [a]The Other category contains SGC data from ankylosing spondylitis, myasthenia gravis, sarcoidosis, uveitis,

116 autoimmune bullous, eczema, nephrotic syndrome, scleritis, vasculitis, autoimmune hepatitis, gout, polymyalgia,

117 Sjögren's syndrome, Bell's palsy, iritis, psoriasis, carditis, multiple sclerosis, psoriatic arthropy, and temporal

118 arteritis.

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