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ORIGINAL RESEARCH

Predicting Risk of Morbidities Associated with Oral Corticosteroid Prescription for Asthma

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Background: Oral corticosteroids (OCS) are commonly used to treat asthma but increase the risks for multiple morbidities; reducing OCS exposure may benefit patients. We analysed independent risk factors and longitudinal changes in OCS usage among patients with asthma to predict future risks of OCS-related adverse outcomes.

Methods: Optimum Patient Care Research Database United Kingdom primary care electronic medical records (EMR) from January 1990 to June 2021 were used to select adults (18–93 years) with asthma who had follow-up data from ≥2 years before to ≥3 years after an index visit for active symptoms; this date was defined by the largest pre-visit to post-visit change in mean annual OCS use. OCS usage during every follow-up year was categorised as none, low (mean <2 prescriptions/year), or high (mean ≥2 prescriptions/year). Pre-index to post-index changes between usage categories were calculated. Risk modelling selected cohorts without 17 morbidities (documented pre-index) reported to be associated with OCS exposure, including type 2 diabetes, osteoporosis, hypertension, and pneumonia. Cox regression analyses selected published risk factors associated with each condition and available in EMR for inclusion in proportional hazards models.

Results: The pre-index to post-index OCS usage category remained unchanged in 38.6% of patients, increased in 39.2%, and decreased in 22.2%, with 20.7% having no further OCS prescriptions. In models, the risks of all adverse outcomes increased with projected categoric OCS use; for example, hazard ratios for a one-category increment (none to low, low to high) were 1.55 (1.42–1.69) for type 2 diabetes, 1.56 (1.36–1.78) for post-menopausal osteoporosis, 1.05 (1.00–1.10) for hypertension, and 1.67 (1.52–1.83) for pneumonia (all $p < 0.001$).

Conclusion: OCS exposure in this primary care asthma population usually continued longitudinally. Our models predict increased risk of multiple morbidities with higher projected OCS exposure. These findings support early initiation of strategies to minimise OCS use in asthma.

Keywords: Optimum Patient Care Research Database, OPCRD, asthma, oral corticosteroids, risk assessment, diabetes, osteoporosis, cardiovascular disease

Introduction

Oral corticosteroids (OCS) have been a mainstay of treatment for asthma since the late 1950s and provide an accessible and effective emergency intervention to prevent or rescue unavoidable life-threatening exacerbations.[1–4] However, there is increasingly clear evidence that regular or even occasional OCS use by patients with asthma is associated with substantially increased risk for multiple morbidities, such as type 2 diabetes mellitus (T2DM), osteoporosis, and cardiovascular diseases,[5–12] as well as mortality.[11,13–15] These adverse outcomes impose considerable burdens of healthcare utilization and expenditure.[4,5,8,16–18] Although certain genetic factors are associated with higher sensitivity

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to OCS,[19] multiple studies have shown that the risk of OCS-related morbidity increases significantly with cumulative OCS exposure[1,9,10,12] and accrues from inception, even at doses once considered unharmful; even a single short course[20] or short courses with lifetime exposure of <1.0 g have been associated with an increased risk of adverse outcomes.[9,12] Accordingly, Global Initiative for Asthma guidelines strongly recommend strategies to prevent or minimise exacerbations that may require OCS treatment, and recommend against daily maintenance OCS, except as a last resort.[21–23] Guidelines for rheumatoid arthritis and ulcerative colitis likewise recommend OCS-sparing strategies.[24,25]

Real-world data show a lag between asthma guidelines and real-world practice, with continuing widespread use of long-term OCS or recurrent bursts to treat exacerbations.[1–3,26,27] Although severe asthma affects only 5–10% of asthma patients and increased use of biologic treatments may lessen the need to prescribe OCS,[27] up to 50% of patients in a year use OCS and more than 20% in some countries receive maintenance therapy.[1,2] In a United Kingdom (UK) study of systemic glucocorticoid (SGC) prescribing trends from 1990 to 2019, asthma consistently accounted for the largest proportion of total SGC utilisation.[27] Long-term SCG use in rheumatoid arthritis, ulcerative colitis, and Crohn's disease declined noticeably after biologics were introduced, although recurrent short-term use does persist.[27,28] Clinical trials and registries have also reported substantial reductions in SGC prescription when biologic therapies were used to treat severe asthma;[23,27] however, such trends are not as evident in community-based treatment settings.[1,4,27,28] This lag may be attributable to several reasons, including that OCS is prescribed predominantly to patients with non-severe asthma,[27] a conservative prescribing mindset,[2,3] patient satisfaction with short-term efficacy despite potential long-term risks,[29] and accessibility compared to biologics, which are more expensive and vary in availability internationally.[30] Some countries require substantial OCS exposure before state-funded biologic therapy can be prescribed,[31] and in many low- or middle-income countries, clinicians may only have access to orally administered salbutamol, theophylline, or prednisone, due to unavailability or unaffordability of inhaled corticosteroids (ICS).[32]

Real-world evidence supports ending over-reliance on OCS by clinicians and relegating maintenance therapy to a last resort.[4,22] Greater awareness about the potential risks of OCS use may inform clinical strategies to optimise inhaled therapy and treat modifiable risk factors to reduce the frequency or dosage of OCS prescriptions, as well as considerations in assessing the potential benefits of alternative treatments. Hence, this study analysed data from electronic medical records (EMR) to develop a model for predicting future health risks from OCS use in patients with asthma, based on known risk factors associated with adverse outcomes and projected longitudinal changes in OCS exposure. This report focuses on outcomes that are particularly sensitive to OCS and/or associated with substantial healthcare burdens, including T2DM, post-menopausal osteoporosis, hypertension, and pneumonia.

Methods

Study Design and Population Selection

This study analysed anonymised longitudinal data from the Optimum Patient Care Research Database (OPCRD), which is a large UK primary care data source used regularly in medical research;[33] EMR from January 1990 through June 2021 were searched to identify patients with a diagnostic code for asthma. Eligibility screening excluded patients: with diagnoses of adrenal insufficiency or hypopituitarism (those with known cause for these conditions, such as post-radiotherapy hypopituitarism, were excluded from incidence year onward, rather than from all time-points); missing data on birth year or gender; classified intersex (due to insufficient sample size).

First, the follow-up period for each patient was determined, starting at the date of joining an OPCRD participating practice, of their first asthma diagnosis, or 1 January the year they reached age 16 years, whichever was latest. End of follow-up was defined as the date of leaving the practice, death, the date patient data were last extracted, the date of an "asthma resolved" EMR code, or December 31 the year a patient reached age 93, whichever occurred earliest. Patients with <5-years follow-up and patients who were <18 years old when follow-up ended or >90 years old when follow-up started (approximate based on birth year) were excluded.

To ensure that an index visit designated for each eligible individual would meet inclusion criteria of having follow-up data for ≥2 years pre-index and ≥3 years afterwards (≥5 years total), all asthma consultations that occurred between 2 years after the start of follow-up and 3 years before the end of follow-up were examined to select patients with active

asthma at a visit, defined as ≥2 asthma prescriptions from ≤1 year before that visit until ≤1 year afterwards. Patients with no consultations for active asthma during the follow-up period and those with no consultation for active asthma that had follow-up of ≥2 years before and ≥3 years afterwards, were excluded. Potential index visit selection excluded consultations where: a patient was >90 years old; cancer was diagnosed ≤5 years before or ≤3 months afterwards; asthma was not active according to the study inclusion criteria; the visit predated 1 January 1990 (due to poor EMR capture before then).

For every eligible asthma-related consultation within each patient's OPCRD follow-up period, the mean number of annual OCS prescriptions was calculated for the entire follow-up time before that visit and afterwards; the visit with the largest absolute pre- to post-consultation change in the mean annual number of OCS prescriptions was defined as the index date. For patients who had no change in average annual OCS prescriptions (eg, zero prescriptions before and after a visit) an index visit was selected at random, so that these visits would be dispersed at different timepoints through follow-up. In instances of ties for the largest change, one tied visit was selected at random.

This process ensured that all patients selected for risk prediction modelling fulfilled the inclusion criteria of having follow-up of at least 2 years before their index visit, with a minimum of 3 years post-index follow-up.

Ethics Approval

This study followed the European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct (EMA/929209/2011, Revision 4, 2018), and is registered with the Heads of Medicines Agencies/European Medicines Agency (HMA-EMA) Catalogues of real-world data sources and studies (EUPAS1000000336). The study protocol was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT-1120), which is the independent scientific advisory committee for the OPCRD.

Study Variables and Outcomes

OCS Exposure

OCS exposure was defined as prescriptions for oral prednisolone or other OCS used to treat asthma during follow-up, and was standardised into prednisolone equivalents for dose analyses based on the UK National Institute for Health and Care Excellence equivalence table for anti-inflammatory doses of OCS (Table S1).[34] Annual OCS prescriptions (short-course and/or maintenance) were grouped into three categories: no OCS; low OCS (mean <2 prescriptions/year); and high OCS (mean ≥2 prescriptions/year). To account for prior OCS exposure, modelling was adjusted for the mean annual number of prescriptions from start of follow-up until the index date (≥2 years pre-index period). To predict the impact of changing OCS usage, modelling included the difference between pre- and post-index exposure categories; pre-index categories 0–2 were subtracted from the post-index categories 0–2, to give a five-level variable for changed OCS use after the index asthma consultation: −2 (high to none); −1 (high to low, low to none); 0 (unchanged); +1 (none to low, low to high); +2 (none to high).

OCS-Related Adverse Outcomes

Previous studies have identified multiple adverse health outcomes associated with OCS use by patients with asthma.[6,9] Based on published evidence, this study analysed data on 17 documented OCS-related adverse outcomes: anxiety/depression; increased body mass index (BMI); cataracts; cerebrovascular accident; cerebro-cardiovascular disease (any among: cerebrovascular accident, heart failure, myocardial infarction); dyslipidaemia; glaucoma; heart failure; hypertension; myocardial infarction; osteoporosis; osteoporotic fractures; peptic ulcer; pneumonia; renal impairment (chronic kidney disease stage ≥3a); T2DM; and sleep apnoea. Table S2 shows the criteria defining each risk cohort. BMI increase was modelled separately in patient subgroups with increases of ≥1 kg/m^2 or ≥5 kg/m^2 from their pre-index BMI. Risk cohorts for osteoporosis and osteoporotic fractures were divided into non-menopausal and post-menopausal groups; for women ≥51 years old with menopause start date unknown based on EMR, menopause status was imputed from 1 January the year they turned 51, which is the average age of menopause onset in the UK.[35] Time from index date to each outcome (or time to end of follow-up if no event occurred) was analysed in a risk cohort comprising patients without a diagnosis or clinical indications (medication use, laboratory measurements) of that condition before their index date (the pneumonia risk cohort excluded patients diagnosed ≤4 weeks pre-index) (Table S2). Patients diagnosed before the index date

or with missing data in identified covariates were excluded (the pneumonia risk cohort included patients diagnosed >4 weeks pre-index).

Covariates

A targeted literature review for each outcome identified candidate baseline covariates for inclusion in regression analyses (Table S3); these were divided into risk factors with documented correlation with that outcome, those showing some association with risk of the outcome, and others, such as family history, diet, physical inactivity, education, and socioeconomic status, which were excluded intentionally because they might not be available from EMR or easily quantifiable for input into a risk prediction algorithm.

Data Analysis and Modelling

Data were prepared and analysed using R version 4.0.0, "Arbor Day" (2020–04-24),[36] and SQL Server 2019, version 15.0.2080.9 (Microsoft Corporation). Univariable binary regression analyses comparing patients in each risk cohort who did or did not develop each outcome were done to obtain unadjusted estimates of the significance for study variables (age, gender, smoking status, OCS exposure, comorbid risk factors, etc). For risk modelling, patients in each cohort were assigned at random to either a training dataset (75%) or a validation dataset (25%). Cox regression analyses with backward stepwise selection (R function "selectCox", riskRegression package),[37,38] screened all candidate risk factors to select the significant variables for inclusion in a final fitted Cox proportional hazards model for each outcome. Values for variables in the final model were chosen to characterize a hypothetical patient and input to another Cox proportional hazards model (R function "cph", Regression Modelling Strategies package),[39] which was then used to estimate the probability of survival without the outcome being modelled (R function "survest", Regression Modelling Strategies package)[39] in scenarios where the future OCS prescription category was either unchanged, increased by 1 (none to low, low to high), or decreased by 1 (high to low, low to none), with all other variables held constant. Longitudinal survival probabilities were subtracted from 1 and the resulting values plotted to give curves showing predicted risk through 5, 10, 15, and 20 years post-index.

Model Validation

Validation testing applied methods described by Royston and Altman.[40] Measures of discrimination included regression on the prognostic index, Harrell's *c*-index, and Gönen and Heller's K statistic, and goodness-of-fit was evaluated using check model misspecification. Discrimination and calibration were also assessed subjectively, by comparing the Kaplan–Meier curves of four risk groups stratified by cut-points at approximately the mean of the prognostic index for the training dataset, and one standard deviation either side; wider separation between these risk groups shows better discrimination, while closely matched curves for corresponding risk groups in the training and validation datasets indicates good calibration.[40]

Missing Data

Missing data were imputed by following sequential steps until a value was obtained. Missing OCS strength: 1) strength of the prescription closest in time, if for the same drug, limited to within 1 year; 2) modal strength of the same drug at patient level; 3) modal strength of the same drug at population level. Missing OCS quantity: 1) quantity of the prescription closest in time, if for the same drug and strength, limited to within 1 year; 2) modal quantity of the same drug and strength at patient level; 3) quantity of prescription closest in time, if for the same drug, limited to within 1 year; 4) modal quantity of the same drug at patient level; 5) modal quantity of the same drug and strength at patient level; 6) modal quantity of the same drug at population level.

Results

Patient Selection and Sample Dispositions

Among 1,316,386 OPCRD patients between 1 January 1990 and 30 June 2021 with a diagnostic code for asthma, 249,226 met criteria for inclusion in risk modelling cohorts (Figure 1); Table S4 shows the sample selection flow for all 18 risk cohorts, which ranged from 73,327 to 114,263 patients.

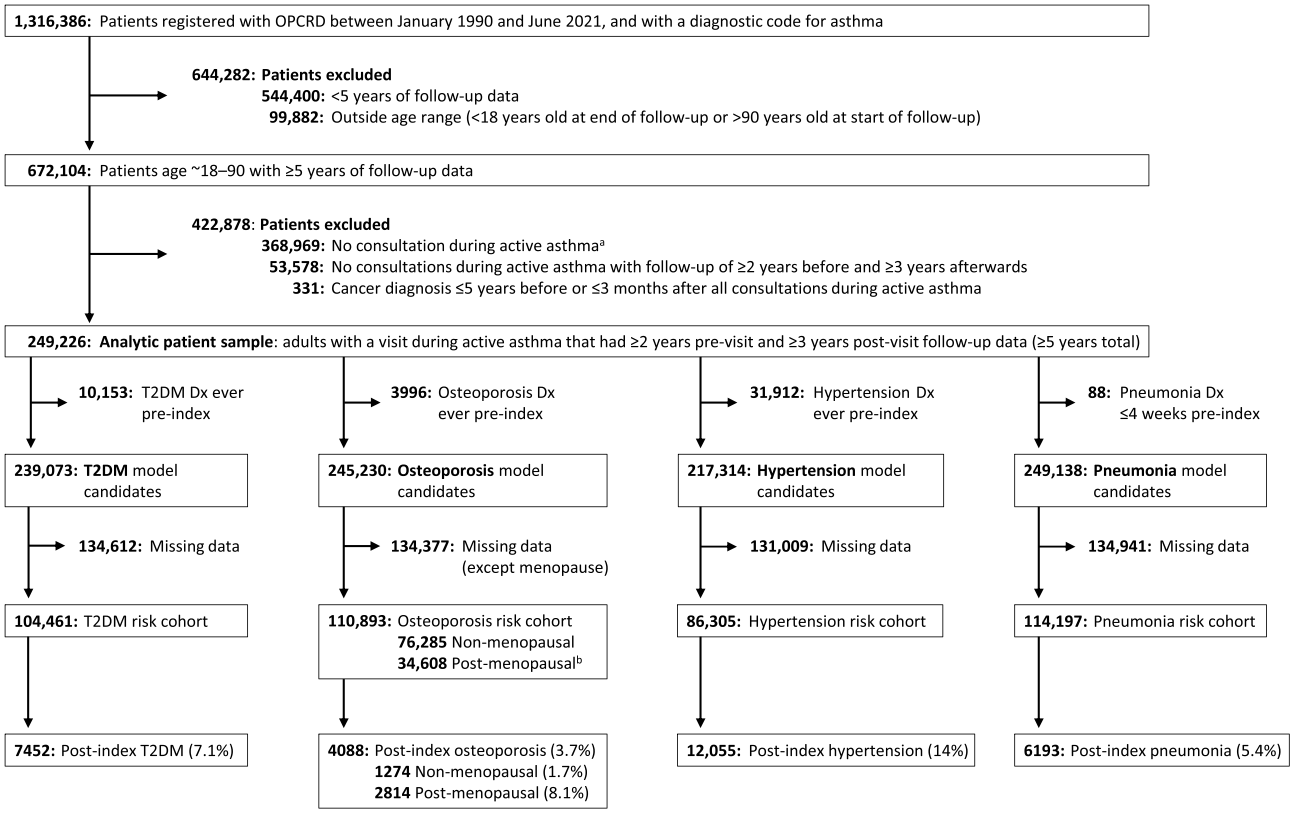

Figure 1 Patient flow diagram, including selection of all eligible asthma patients and those for models of T2DM, osteoporosis, pneumonia, and hypertension. [a]Defined as ≥2 asthma prescriptions from ≤1 year before that visit until ≤1 year afterwards. [b]Menopause status imputed in 15,918 women age ≥51 years without documented menopause start date in electronic medical records.
Abbreviations: OPCRD, Optimum Patient Care Research Database; T2DM, type 2 diabetes mellitus; Dx, diagnostic code.

OCS Prescription Patterns

Table S5 summarizes OCS prescriptions data. Only 4.8% of patients had a pre-index annual average of ≥2 OCS prescriptions, which, because of the selection of the index visit, almost doubled to 9.4% post-index, a difference of 11,345 patients. More than 50% had <2 prescriptions per year on average, and the proportion with any OCS prescriptions increased from 41.5% pre-index to 73.0% post-index, including 87,654 new users (Table S6) – 48.2% of patients prescribed OCS post-index. As shown in Table S6, OCS use changed by two mean annual prescription categories (up or down) in a small fraction of patients; most either remained in the same category (38.6%) or moved to the next higher category (37.0%). Mean annual OCS prescriptions fell by one category (high to low, or low to none) in 21.8% of patients, and 20.7% who had been prescribed OCS pre-index changed to the zero annual average OCS prescription category after their index visit.

Modelling Analyses for T2DM, Osteoporosis, Hypertension, Pneumonia, and Other Adverse Outcomes

Table S3 shows the candidate risk factors for each of the outcomes modelled. Risk factors common to multiple OCS-related adverse outcomes included age, gender, BMI, race/ethnicity, tobacco smoking, and anxiety/depression. Cerebro-cardiovascular disease has been associated with both T2DM and osteoporosis, and antiepileptic drug use with osteoporosis and pneumonia.

Tables S7–S26 show the results of univariable binary regression analyses for T2DM, osteoporosis, hypertension, pneumonia, and the other outcomes modelled. The mean post-index follow-up among patients with onset of adverse outcomes ranged from 4.9 to 7.7 years. Patients without each condition at their index date had onset rates of 7.1% for T2DM, 8.1% for osteoporosis in post-menopausal women, 14.0% for hypertension, and 5.4% for pneumonia. Conditions besides hypertension with post-index incidence >10% were anxiety/depression (19.1%), BMI increase (13.7%), and dyslipidaemia (22.1%) (Tables S4 and S7-S26).

Compared with controls, patients with asthma who subsequently developed these conditions were generally older, with higher pre-index and post-index OCS exposure, and had more prevalent comorbidities.

Tables 1–4 show the final Cox proportional hazard models for T2DM, post-menopausal osteoporosis, hypertension, and pneumonia. Pre-index OCS usage (high or low versus none) was associated with increased risk of future incidence, except in the hypertension model. For all conditions modelled, the future risk increased with higher projected post-index OCS use; hazard ratios for a 1-category increment (none to low, low to high) in mean annual OCS prescriptions were 1.55 (1.42–1.69) for T2DM, 1.56 (1.36–1.78) for osteoporosis in post-menopausal women, 1.05 (1.00–1.10) for hypertension, and 1.67 (1.52–1.83) for pneumonia. Cox proportional hazards models for the other adverse outcomes are shown in Tables S27–S42.

Table 1 Multivariable Cox Proportional Hazard Model for Type 2 Diabetes Mellitus in OPCRD Patients with Asthma

Variable	Hazard Ratio (95% CI)	P-value
Age (1 year increment)	1.024 (1.022, 1.026)	<0.001
Gender		<0.001
Male	1 (Ref)	
Female	0.681 (0.644, 0.720)	
BMI increase (by ≥1 kg/m^2 vs pre-index[a])	1.093 (1.090, 1.097)	<0.001
Ethnicity		<0.001
White	1 (Ref)	
Asian	3.120 (2.811, 3.463)	
Black	2.117 (1.555, 2.884)	
Middle Eastern	3.350 (1.673, 6.708)	
Other/Mixed	1.231 (1.019, 1.485)	
Declined/Unknown	0.984 (0.925, 1.047)	
Smoking status		<0.001
Non-smoker	1 (Ref)	
Former smoker	1.157 (1.087, 1.233)	
Smoker	1.575 (1.465, 1.692)	
Pre-index OCS prescriptions category (mean/year)		<0.001
No OCS (none)	1 (Ref)	
Low OCS (<2)	1.609 (1.475, 1.756)	
High OCS (≥2)	2.392 (2.084, 2.744)	
Change in OCS prescriptions category (score)		<0.001
No change (0)	1 (Ref)	
2 category decrease (−2)	0.589 (0.323, 1.073)	
1 category decrease (−1)	0.812 (0.742, 0.888)	
1 category increase (+1)	1.551 (1.422, 1.691)	
2 category increase (+2)	2.329 (1.991, 2.724)	
Anxiety/Depression		<0.001
No	1 (Ref)	
Yes	1.221 (1.155, 1.292)	
Cerebro-cardiovascular disease		<0.001
No	1 (Ref)	
Yes	1.287 (1.173, 1.411)	
Hypertension		<0.001
No	1 (Ref)	
Yes	1.456 (1.370, 1.547)	

Note: [a]BMI increase by ≥1 kg/m^2 compared to the last BMI in the 5 years preceding the index date.
Abbreviations: OPCRD, Optimum Patient Care Research Database; BMI, body mass index; OCS, oral corticosteroids.

Table 2 Multivariable Cox Proportional Hazard Model for Post-Menopausal Osteoporosis in OPCRD Patients with Asthma

Variable	Hazard Ratio (95% CI)	P-value
Years since menopause (1 year increment)	1.031 (1.026, 1.036)	<0.001
BMI increase (by ≥1 kg/m^2 vs pre-index[a])	0.935 (0.928, 0.943)	<0.001
Pre-index OCS prescriptions category (mean/year)		<0.001
No OCS (none)	1 (Ref)	
Low OCS (<2)	1.711 (1.493, 1.961)	
High OCS (≥2)	3.060 (2.492, 3.756)	
Change in OCS prescriptions category (score)		<0.001
No change (0)	1 (Ref)	
2 category decrease (−2)	0.515 (0.228, 1.163))	
1 category decrease (−1)	0.660 (0.566, 0.770)	
1 category increase (+1)	1.557 (1.360, 1.783)	
2 category increase (+2)	2.585 (2.056, 3.250)	
Rheumatoid arthritis		<0.001
No	1 (Ref)	
Yes	1.855 (1.502, 2.290)	
Liver disease		0.002
No	1 (Ref)	
Yes	1.476 (1.153, 1.891)	

Note: [a]BMI increase by ≥1 kg/m^2 compared to the last BMI in the 5 years preceding the index date.
Abbreviations: OPCRD, Optimum Patient Care Research Database; BMI, body mass index; OCS, oral corticosteroids.

Table 3 Multivariable Cox Proportional Hazard Model for Hypertension in OPCRD Patients with Asthma

Variable	Hazard Ratio (95% CI)	P-value
Age (1 year increment)	1.040 (1.038, 1.041)	<0.001
Gender		
Male		
Female		
BMI increase (by ≥1 kg/m^2 vs pre-index[a])	1.051 (1.048, 1.054)	<0.001
Ethnicity		<0.001
White	1 (Ref)	
Asian	1.377 (1.243, 1.524)	
Black	1.698 (1.310, 2.200)	
Middle Eastern	1.900 (1.051, 3.433)	
Other/Mixed	1.065 (0.913, 1.242)	
Declined/Unknown	0.919 (0.876, 0.965)	
Smoking status		0.002
Non-smoker	1 (Ref)	
Former smoker	0.982 (0.936, 1.030)	
Smoker	1.081 (1.022, 1.143)	
Change in OCS prescriptions category (score)		<0.001
No change (0)	1 (Ref)	
2 category decrease (−2)	0.663 (0.392, 1.120)	
1 category decrease (−1)	0.816 (0.762, 0.875)	
1 category increase (+1)	1.048 (1.002, 1.097)	
2 category increase (+2)	1.326 (1.186, 1.482)	

Note: [a]BMI increase by ≥1 kg/m^2 compared to the last BMI in the 5 years preceding the index date.
Abbreviations: OPCRD, Optimum Patient Care Research Database; BMI, body mass index; OCS, oral corticosteroids.

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Table 4 Multivariable Cox Proportional Hazard Model for Pneumonia in OPCRD Patients with Asthma

Variable	Hazard Ratio (95% CI)	P-value
Age (1 year increment)	1.042 (1.040, 1.044)	<0.001
Smoking status		<0.001
Non-smoker	1 (Ref)	
Former smoker	1.225 (1.140, 1.315)	
Smoker	1.570 (1.444, 1.707)	
Pre-index OCS prescriptions category (mean/year)		<0.001
No OCS (none)	1 (Ref)	
Low OCS (<2)	2.038 (1.854, 2.239)	
High OCS (≥2)	4.270 (3.723, 4.898)	
Change in OCS prescriptions category (score)		<0.001
No change (0)	1 (Ref)	
2 category decrease (−2)	0.511 (0.305, 0.855)	
1 category decrease (−1)	0.757 (0.684, 0.838)	
1 category increase (+1)	1.670 (1.523, 1.832)	
2 category increase (+2)	3.533 (3.029, 4.121)	
Pre-index pneumonia[a]		<0.001
No	1 (Ref)	
Yes	1.964 (1.778, 2.169)	
Epilepsy		<0.001
No	1 (Ref)	
Yes	1.266 (1.185, 1.352)	
Chronic obstructive pulmonary disease		<0.001
No	1 (Ref)	
Yes	1.629 (1.515, 1.751)	
Chronic kidney disease (any stage)		<0.001
No	1 (Ref)	
Yes	1.363 (1.228, 1.513)	
Stroke		<0.001
No	1 (Ref)	
Yes	1.380 (1.222, 1.557)	
Liver disease		0.050
No	1 (Ref)	
Yes	1.187 (1.000, 1.410)	
Diabetes mellitus (any)		<0.001
No	1 (Ref)	
Yes	1.381 (1.268, 1.504)	

Note: [a]Diagnostic code for pneumonia >4 weeks before the index date (patients diagnosed with pneumonia ≤4 weeks before the index date were excluded).
Abbreviations: OPCRD, Optimum Patient Care Research Database; OCS, oral corticosteroids.

Model Validation

The models showed generally satisfactory discrimination and accuracy. Table 5 shows validation results for models of T2DM, osteoporosis (pre- and post-menopausal), hypertension, and pneumonia. Slopes for regression on the prognostic index in the validation datasets did not differ significantly from 1.0, indicating that discrimination was preserved. Check model misspecification showed evidence for a lack of fit in the non-menopausal osteoporosis and hypertension models. Harrell's *c*-index values of ≥0.7 indicated reasonable discrimination[41] and were similar in the training and validation datasets, showing good model performance.[40] Figure S1 shows Kaplan–Meier survival curves stratified by risk group for

Table 5 Model Validation Tests for Type 2 Diabetes Mellitus, Osteoporosis, Hypertension, and Pneumonia

Outcome	Dataset	Regression on Prognostic Index		Check Model Misspecification		Harrell's c-Index	Gönen & Heller's K Statistic
		Slope (SE)	P-value	χ^2 (DF)	P-value		
Type 2 diabetes mellitus	Training (n=78,348) Validation (n=26,113)	1.01 (0.02)	0.69	28.7 (19)	0.07	0.783 0.783	0.711 0.711
Non-menopausal osteoporosis	Training (n=57,216) Validation (n=19,069)	0.96 (0.05)	0.34	41.3 (13)	<0.01	0.836 0.829	0.770 0.771
Post-menopausal osteoporosis	Training (n=25,956) Validation (n=8652)	1.05 (0.06)	0.47	11.7 (10)	0.30	0.676 0.677	0.655 0.654
Hypertension	Training (n=64,731) Validation (n=21,574)	0.98 (0.03)	0.38	31.6 (13)	<0.01	0.722 0.715	0.688 0.688
Pneumonia	Training (n=85,650) Validation (n=28,547)	0.99 (0.03)	0.70	16.4 (16)	0.43	0.759 0.750	0.733 0.732

Abbreviations: SE, standard error; DF, degrees of freedom.

the training and validation datasets, which also support good discrimination and calibration for up to 10 years. Table S43 summarises the validation results for the other outcomes; there was evidence for lack of discrimination in the renal impairment and sleep apnoea models, and for lack of fit in the models for cerebro-cardiovascular disease, non-menopausal osteoporosis, and sleep apnoea.

Future Risk of OCS-Related Adverse Outcomes

Figure 2 shows the results of applying the risk prediction formulas derived from the post-menopausal osteoporosis and myocardial infarction models to hypothetical patient profiles in scenarios where future OCS prescriptions remained unchanged, increased by one category, or decreased by one category. The highest future risk of each outcome was predicted among patients whose OCS use was projected to increase by one category. The algorithm predicted that reducing post-index OCS use would lessen the risk of post-menopausal osteoporosis compared to unchanged use, whereas decreasing OCS use would have an insignificant effect on the predicted risk of myocardial infarction (data not plotted). Tables S44−S61 show the predicted 5-, 10-, 15- and 20-year risks of other adverse outcomes in hypothetical patients.

Discussion

We used published evidence of independent risk factors and longitudinal EMR data on OCS exposure to innovate models that predict the risks of multiple adverse outcomes known to affect patients with asthma who are prescribed OCS. The models predicted substantially increased longer-term risks of developing OCS-related morbidities with higher projected OCS exposure. Cumulative OCS exposure continued longitudinally in the majority of OPCRD patients with asthma. The practical implication is to minimize OCS use in asthma wherever possible. This study has shown the feasibility of using EMR data for predictive analysis, although more work is needed to validate the models externally and in different age groups and patient scenarios.

The success of OCS in managing potentially life-threatening asthma exacerbations has contributed to a tendency for clinicians to over-rely on prescribing OCS, potentially exposing patients to further lung damage from exacerbations as well as morbidities arising from cumulative OCS exposure.[3,4,9,12,28,31,42] Pertinently, a minority of our large real-world sample of primary care patients with asthma who were prescribed OCS had declining use over time or ceased OCS use during follow-up, illustrating the limitation of everyday clinical practice in implementing recommendations to minimize OCS dosing to treat asthma. Notably, there was a high post-index incidence of anxiety/depression, which was a risk factor for other adverse outcomes and tended to affect younger patients, highlighting the importance of mental health as an outcome in patients with asthma.

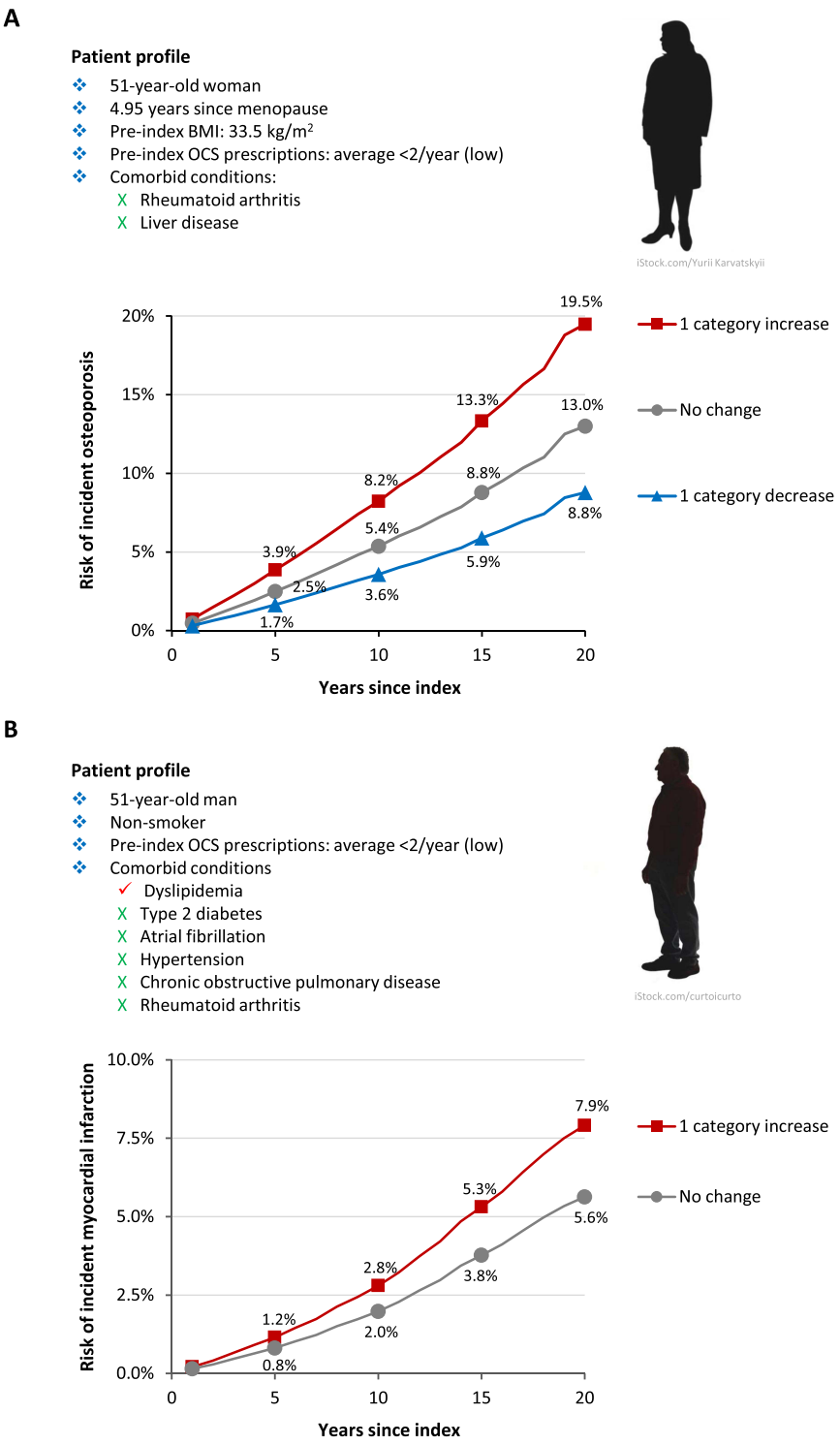

Figure 2 Risk prediction curves by change in mean annual OCS prescription category (with all other risk factors held constant), based on hypothetical patient risk factors. (**A**) Post-menopausal osteoporosis. (**B**) Myocardial infarction (as decreasing OCS use had an insignificant effect on the predicted risk, these data were not plotted). Mean annual OCS prescriptions were categorized as: none, low (<2/year), high (≥2/year). Cox proportional hazards models of post-menopausal osteoporosis (Table 2) and myocardial infarction Table S36) were run for variable values characterizing a hypothetical patient risk profile, then input to survival analyses in which only the change in OCS prescriptions category was varied – unchanged (none to none, low to low, high to high), increased by 1 category (none to low, low to high), or decreased by 1 category (high to low, low to none) – with all other variables held constant. Estimated longitudinal survival probabilities were subtracted from 1 and plotted to obtain predicted incidence curves for each outcome.

Abbreviations: OCS, oral corticosteroids; BMI, body mass index.

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Our research compliments evidence supporting calls to end over-reliance on OCS to treat asthma exacerbations.[3,4,22,23,28,43] Given that even short OCS courses have been shown to increase the risk of adverse outcomes,[9,12,20] we endorse the Global Initiative for Asthma guidance to use steroid-sparing approaches wherever possible, with maintenance OCS as last resort if there is no alternative, and with a strong emphasis on optimising inhaled therapy to reduce the risk of exacerbations and need for further OCS courses.[21,22] In our models, the risks of developing OCS-related morbidities increased with higher projected OCS use, indicating that it is especially important not to increase OCS exposure unless this is unavoidable. Strategies shown to substantially lessen the need to prescribe OCS include using ICS/formoterol as needed in patients with mild asthma[21,44] and as a combined maintenance and reliever therapy for moderate-severe asthma;[21,45] biologic therapy may be added in patients with severe asthma.[21] Nevertheless, lower projected OCS use in our models appeared to reduce future risks relatively modestly compared to unchanged use (eg, myocardial infarction model), possibly due to prior cumulative exposure. Therefore, we contend that inception (or potential inception) of OCS should be regarded as a checkpoint to review the appropriateness of, or adherence to, current treatments and to consider whether OCS is clinically necessary, or if further use could be avoided by using alternative options;[4] while it would be ideal to avoid OCS entirely, we recognize that this is not yet feasible in many settings nor when a patient presents with acute severe asthma.

Developing and validating risk assessment tools is important for delivering efficient patient-centred healthcare.[46,47] There are needs to raise awareness among healthcare professionals and users about the risks of OCS exposure and the evidence-base supporting OCS use.[20,27,43] One informative tool, the Glucocorticoid Toxicity Index (GTI), quantifies cumulative toxicity arising from glucocorticoid exposure in individual patients.[48] Although patients with asthma who received biologic treatment had a substantially reduced glucocorticoid burden, the GTI showed that this had not diminished established toxicity in all patients.[49] These results highlight the importance of assessing the future risk of adverse outcomes associated with planned treatment.[28] The QRISK calculator is used to assess the 10-year risk of cardiovascular disease in UK patients; QRISK®3 risk factors now include regular OCS use, although not intermittent use.[50]

Our study demonstrates the feasibility of analysing longitudinal EMR data to predict the risks of morbidities known to affect patients with asthma, based on projected OCS exposure. These OCS risk prediction algorithms could potentially be applied to develop assessment charts or a web-based calculator, compatible with EMRs and quality improvement tools internationally. For many older patients who already have, or are at high risk for, OCS-related morbidities, such a tool may enable those at highest risk of adverse outcomes to be identified for close monitoring, so that timely interventions can be initiated as necessary. This concept is analogous to rheumatology guideline recommendations to initiate bisphosphonate therapy if maintenance OCS is considered.[51]

In patients with asthma that is relatively refractory to corticosteroids, monoclonal antibody therapies can effectively target underlying inflammation to reduce exacerbations and significantly lessen the need for short-course or maintenance OCS.[52,53] Using biologics in other inflammatory diseases, such as rheumatoid arthritis, Crohn's disease, and ulcerative colitis, has already made it possible to substantially reduce patients' OCS exposure.[27,28] In this context, it is timely and realistic to consider how best to limit OCS use to treating life-threatening asthma exacerbations or asthma that is refractory to biologics.[4,22,23] There is a strong rationale for initiating biologics earlier in the patient journey, to avoid the typical scenario of patients with asthma in their 50s or 60s presenting with multimorbidities due to chronic OCS exposure.[28] However, there are multifaceted challenges to achieving such a step change in asthma management; most notably, the focus on symptom control in asthma assessment, delayed referral for specialist assessment if patients have frequent exacerbations, and a lack of evidence for benefit from biologics in patients with non-severe asthma. Another barrier is the common assumption that OCS are cost-effective.[1,4] Although OCS are relatively inexpensive, widely available, and effective for acute management, these advantages must be weighed against substantial long-term burdens of resource utilization and costs imposed by treating OCS-related conditions such as T2DM, osteoporosis, and cardiovascular diseases, which may outweigh up-front savings compared with more costly but less harmful treatments.[4,17,18] The long-term cost/benefit of both OCS and biologic agents are complicated to analyse and incompletely understood;[4,30] rigorous health economics research is needed to better inform healthcare providers. On the other hand, despite the commercial availability of effective biologic therapies, there are worldwide variations in accessibility and uptake, reflecting international differences in licensing, and in prescription and reimbursement criteria.[30] Payers may impose barriers to wider access due to budget constraints and some countries require a high level of OCS use to qualify for biologic therapy; for example, asthma patients in the UK are not

eligible for biologics under national health insurance unless they have experienced at least four exacerbations requiring OCS in the past year.[31] Changing the status quo and implementing existing guidelines will require concerted engagement with healthcare providers and policymakers.[4]

Using the OPCRD enabled large-scale data analysis but imposed some practical limitations. Categorizing OCS usage with a coarse cut-off of two prescriptions per year on average did not allow us to distinguish between short-course and maintenance OCS; given an evident dose response for most of the adverse outcomes, this is a major limitation and risk prediction models based on continuous data would be more powerful. Although our models integrated documented risk factors for OCS-related morbidities that were identified by a thorough literature review, for pragmatic reasons they excluded some well-known risk factors that are not well recorded in EMR, for example, family history, genetic polymorphisms, and socioeconomic/lifestyle factors; consequently, some people, such as those with a genetic predisposition[19] may have higher individual risk than the average risk predicted by these models. As this research focused on developing methodology to predict the overall risk of morbidities associated with OCS exposure, it was not designed to elucidate the pathogenesis of these conditions or how they may present clinically. The modelled risks for some conditions may be underestimates resulting from underdiagnosis; for example, osteoporosis is often diagnosed only after a clinically important fracture has occurred. On the other hand, the necessity of analysing atypically large longitudinal changes to show demonstrable impacts of projected changes in OCS exposure may have biased results towards showing larger effects than may be typical in real-life patients. The models were validated internally, but not using another external dataset, and have not been applied over a range of ages, which research suggests might show less additional risk in older patients.[54] The models did not integrate specific interventions as variables (eg, prophylactic bisphosphonates for osteoporosis), which, if effective, would reduce patients' future risk of the corresponding adverse outcome.

Conclusions

Cumulative OCS exposure in this United Kingdom primary care asthma population continued longitudinally in most patients. In EMR-based OCS risk prediction models that integrated known risk-factors and longitudinal changes in OCS use among patients with asthma, the risk of developing multiple OCS-related morbidities increased with higher projected OCS usage. Our findings support early initiation of targeted and steroid-sparing strategies to minimize the use of OCS for treating patients with asthma.

Data Sharing Statement

The dataset supporting the findings of this article was derived from the Optimum Patient Care Research Database (www.opcrd.co.uk). The OPCRD has ethical approval from the United Kingdom National Health Service Research Authority to hold and process anonymised research data (Research Ethics Committee reference: 15/EM/0150). The authors do not have permission to give public access to the study dataset; researchers may request access to OPCRD data for their own purposes. Access to OCPRD can be made via the OCPRD website (https://opcrd.co.uk/our-database/data-requests/) or via the enquiries email: info@opcrd.co.uk.

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Disclosure

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