Online Data Supplement

Comorbidity in Severe Asthma requiring systemic corticosteroid therapy - Cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry

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Methods

The British Thoracic Society (BTS) Difficult Asthma Registry

In 2007, the BTS Research Committee, in conjunction with physicians with a specialist interest in difficult asthma, established a National Registry for dedicated UK Difficult Asthma services. The aims of the group were to define clinical phenotypes in subjects with well-characterized severe asthma (SA), to facilitate research into the assessment and clinical management of difficult asthma, to develop and increase access to dedicated difficult asthma service and to standardise clinical care in specialist clinical supra-regional clinical centres (1).

There are currently eight dedicated Specialist Difficult Asthma Services submitting data to the UK Registry - Royal Brompton Hospital, London; Glenfield Hospital, Leicester; University Hospital of South Manchester; Birmingham Heartlands Hospital; Gartnavel Hospital, Glasgow; Stobhill Hospital, Glasgow, Southampton General Hospital and Belfast City Hospital. The Registry is hosted online by Dendrite Clinical Systems Ltd and collects password-protected, anonymous data after fully informed written consent has been obtained from patients. The registry records patient demographics including gender, age at diagnosis, occupation and BMI as well as disease characteristics such as asthma medication, exacerbations, and pulmonary function. Patients at all centres undergo a standardised multidisciplinary, systematic assessment of their asthma. All Registry centres follow protocols whereby patients have multiple investigations, including a thorough medical history and examination, pulmonary function tests, allergy assessment (skin-prick testing and/or radioallergosorbent test), blood tests (incorporating serum eosinophil count and

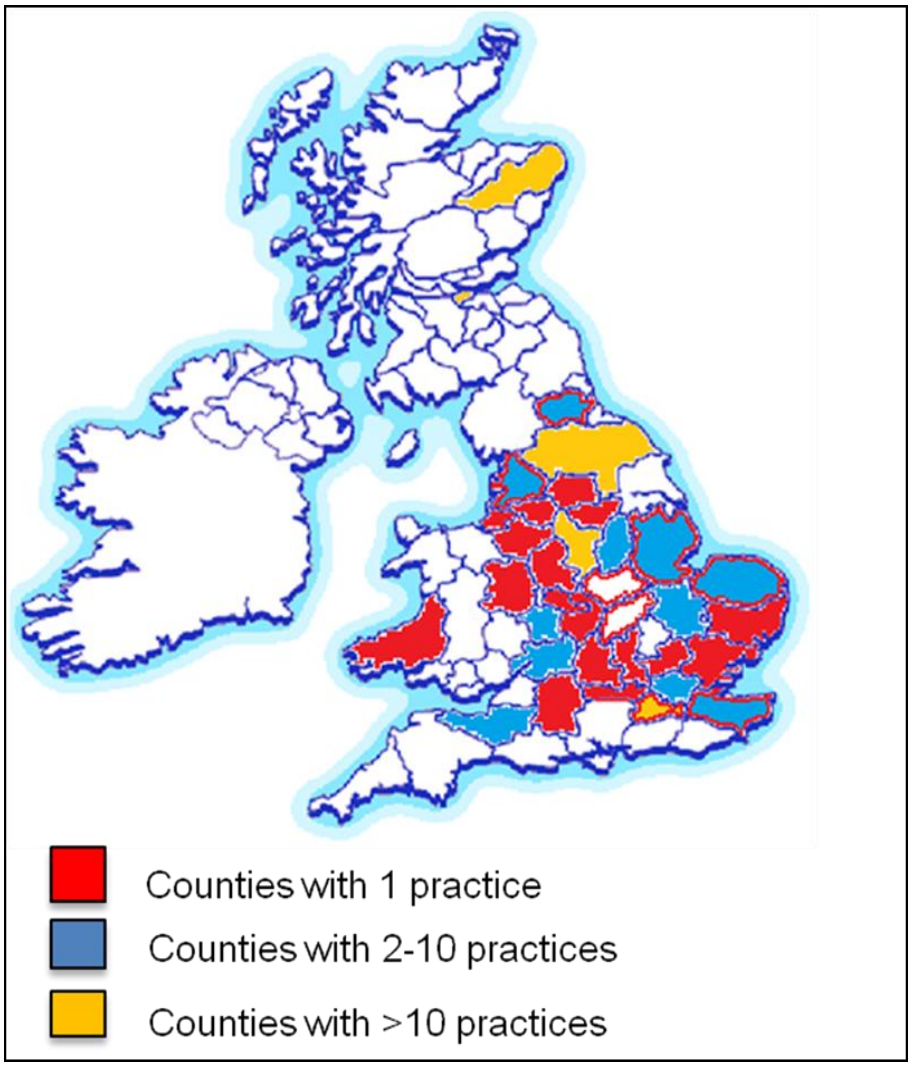
IgE), bone densitometry and complete health related quality of life and asthma control questionnaires (Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), EuroQol EQ-5D-Generic quality of life questionnaire, Hospital, Anxiety and Depression Scale (HAD)). Epworth Sleepiness Scale is also completed by patients and overnight oximetry/polysomnography performed if indicated. All Registry data including objective measures as listed above were examined for analysis.

The Optimum Patient Care Research Database

The OPCRD is a large, longitudinal, primary care database offering anonymised research quality data with a focus on respiratory disease. It contains all point of care records for respiratory patients including comorbid disease information and prescriptions issued at time of healthcare contact. OPCRD currently holds anonymised data on approximately 700,000 patients with asthma. The distribution of participating practices across the UK is shown in Figure E1. For the purposes of statistical analysis, geographical areas of practices were aggregated into six regions as follows.

Region	Postcode Areas
London	CR, E, EN, HA, IG, KT, N, NW, RM, SM, TW, UB, W
South	BA, BS, CT, GL, GU, HP, ME, MK, OX, PL, RG, RH, SL, SN, TA
East	CB, CO, IP, LN, LU, NR, PE, SS
Midlands	B, CV, DE, LE, NG, NN, ST, WS, WV
North	BD, CA, CH, CW, DH, FY, HD, HG, HX, L, LA, LS, M, NE, OL, SR, TS, WA, WN, YO
Outside England or missing	AB, BT, DD, EH, G, ML, PH, SY

Figure E1 **OPCRD practice distribution**



OPCRD Cohort Definition

Severe Asthma population

All subjects must have had a Read Code diagnosis of asthma in the GP record and have received prescriptions for Step 5 GINA asthma treatment during a 2-year qualification period defined as continuous or frequent use of OCS and high dose inhaled corticosteroid maintained at 2000mcg BDP equivalent/day (2). It is not possible to identify maintenance or daily OCS use from GP prescription records so in order to capture subjects receiving continuous or with frequent use of OCS, an inclusion criterion of ≥4 prescriptions for

systemic corticosteroids in each of the two study years was specified for this population. A sub-group of SA subjects who received maintenance systemic corticosteroids quantified by ≥6 OCS prescriptions in both years of the study was further evaluated in a sensitivity analysis.

Mild/moderate asthma population

The asthma population within OPCRD are coded according to their asthma therapy and corresponding GINA steps of asthma management. To be included in the mild/moderate asthma population, all subjects must have had a Read Code diagnosis of asthma and have received prescriptions for Step 2-3 GINA (Read Code for GINA Step 2 or Step 3) treatment during the 2-year qualifying period defined as 'regular preventer therapy with add on asthma therapy'. This included inhaled corticosteroid therapy of 200-800mcg BDP equivalent dose/day with or without long-acting beta-agonist therapy or if control was still inadequate other asthma therapies such as leukotriene receptor antagonist or SR theophylline may have been prescribed (2). This mild/moderate population may have received none or rescue courses of OCS only during the 2 year qualifying period.

Control population

To be considered part of the 'non-asthmatic control' population, subjects must not have had a Read Code diagnosis of asthma but must have had a Read Code diagnosis of rhinitis or received therapy to treat rhinitis (i.e. drugs used in nasal allergy). As the OPCRD is a respiratory database, this population was chosen as the 'non-asthmatic controls' as they did

not have any exposure to OCS or have any other condition that warranted OCS use and they did not have a Read Code/ diagnosis for asthma.

Matching criteria

Matching criteria was based on subjects:

- Age
- Gender
- Year of birth

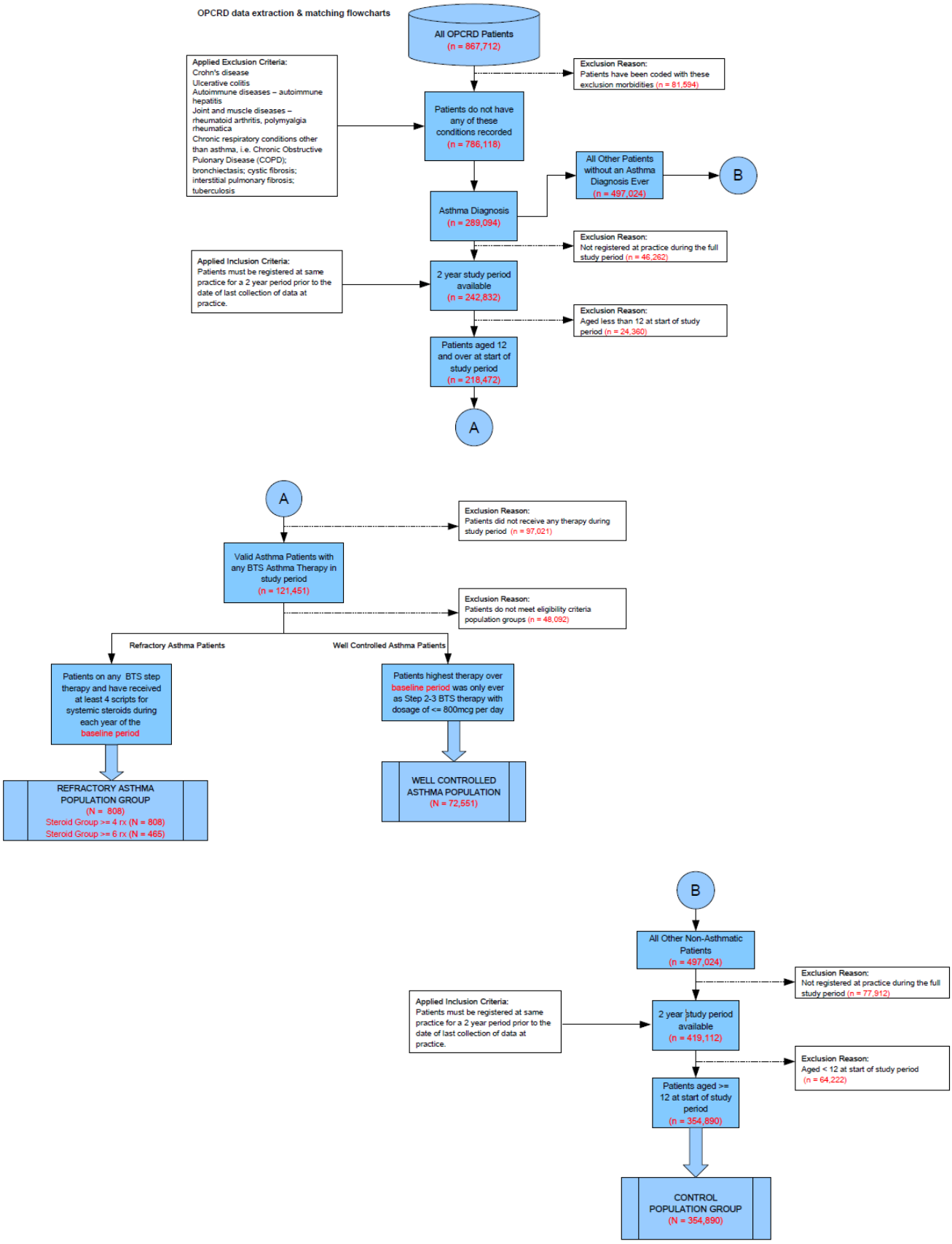
Exclusion criteria

For all study subjects and to minimize the risk of confounding by non-asthmatic systemic steroid exposure, subjects with any of the following conditions (for which systemic corticosteroid treatment could be prescribed) were excluded from the study population:

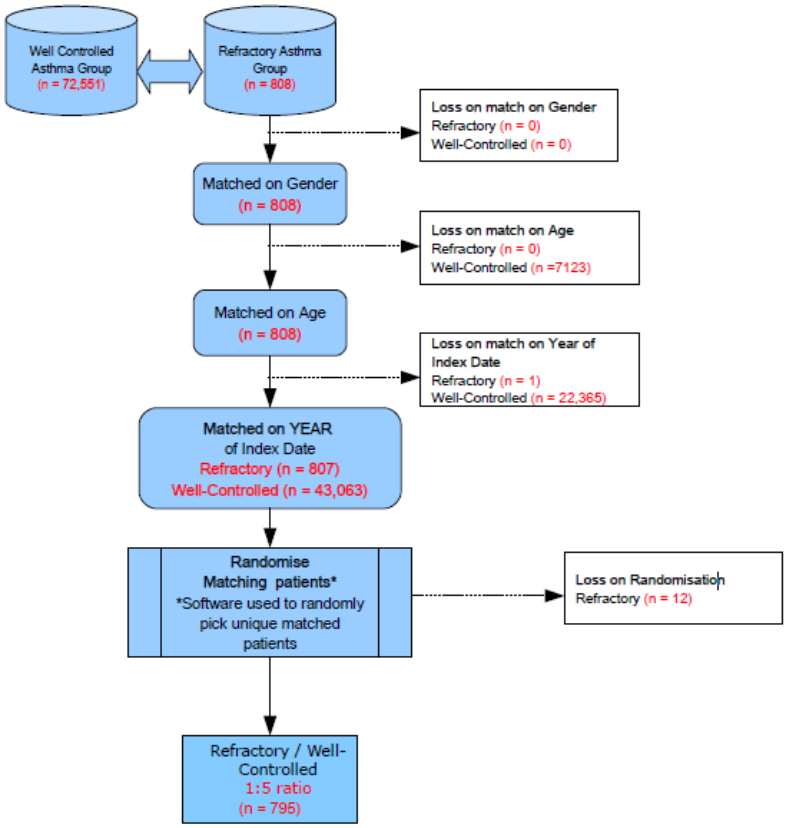
- Crohn's disease
- Ulcerative colitis
- Autoimmune diseases – autoimmune hepatitis
- Joint and muscle diseases – rheumatoid arthritis, polymyalgia rheumatica
- Chronic respiratory conditions other than asthma, i.e. Chronic Obstructive Pulonary Disease (COPD); bronchiectasis; cystic fibrosis; interstitial pulmonary fibrosis; tuberculosis.

Figure E2 presents flowcharts for OPCRD data extraction and cohort matching.

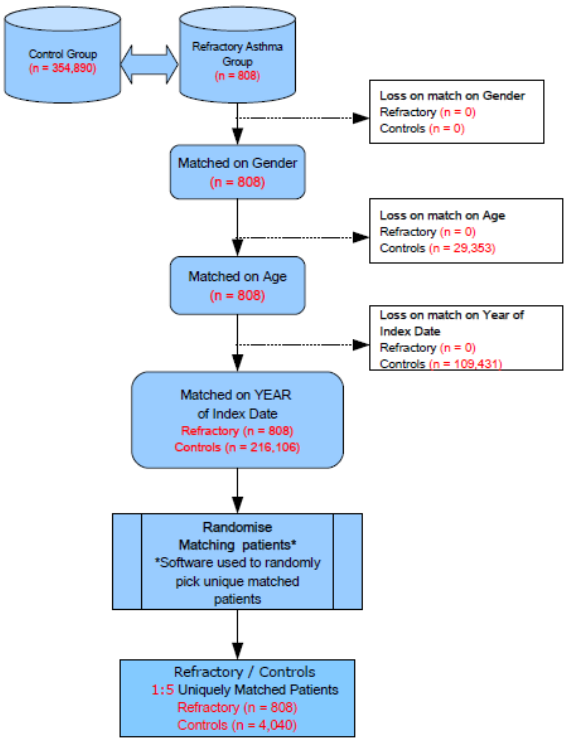
Figure E2 OPCRD data extraction and cohort matching flowcharts for severe (refractory) asthma and controls



Matching of well controlled asthma patients to severe (refractory) asthma patients



Matching of non-asthma patients to severe (refractory) asthma patients

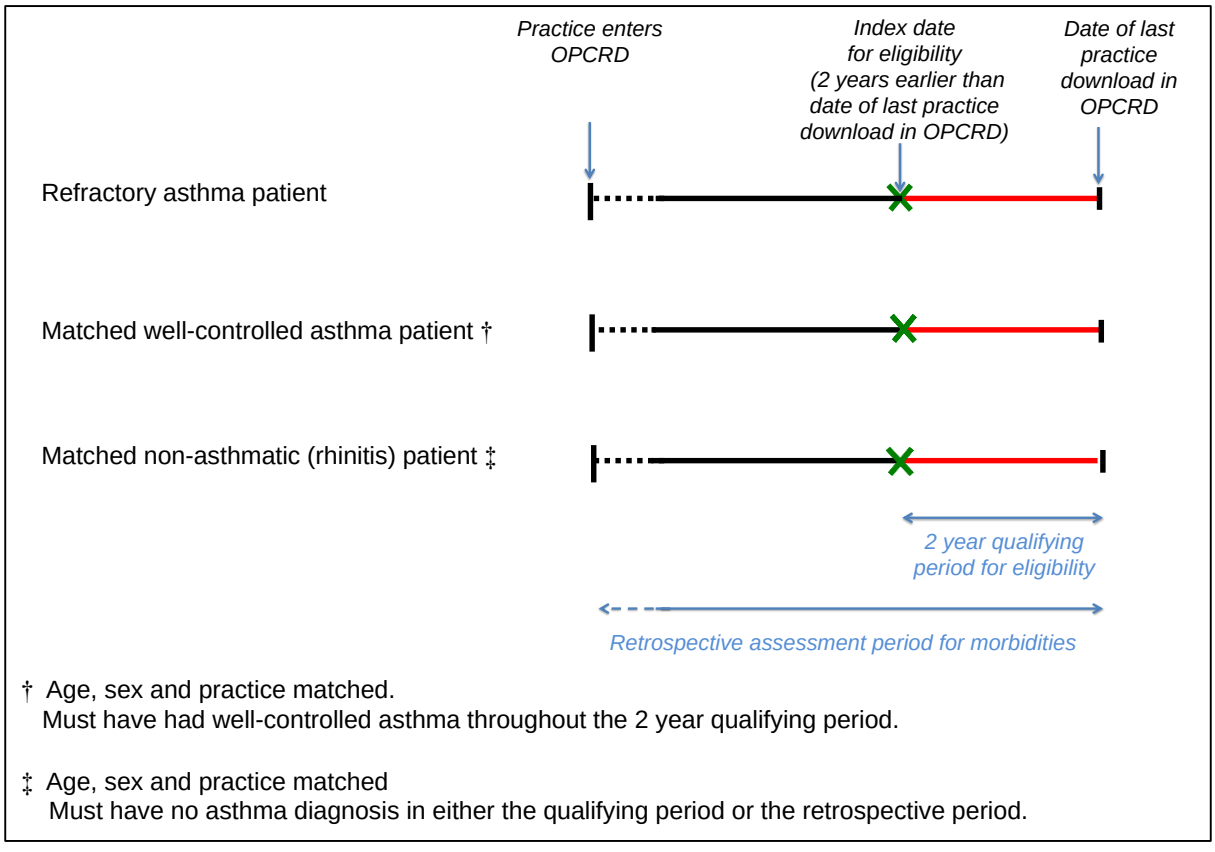


Study period

Eligibility for the cross-sectional analysis was evaluated over a 2-year qualifying period using the previously-defined inclusion/exclusion criteria. This was the latest 2-year period within the OPCRD which at time of protocol design was 1 April 2011– 30 March 2013. In OPCRD the latest date of download from some practices was prior to 1 April 2011 or similarly, the latest download may have taken place after 30 March 2013. In those circumstances, the date of the 2-year qualifying period differed from that stipulated in the protocol.

Figure E3 represents the study period for the OPCRD analysis.

Figure E3 **Schematic for definition of study period.**



Morbidity evaluations OPCRD

The most commonly reported adverse effects of OCS were evaluated (Table E1) (3-16). Read Codes are a coded thesaurus of clinical terms and have been in use in the NHS since 1985.

They are a basic means by which clinicians record patient findings and procedures across health and social care IT systems and are the clinical classification system currently used in primary care in the UK. OPCRD currently uses Version 2 Read Codes and all relevant coding was extracted from the NHS Read Code Browser and codes relating to the adverse effects listed below were then extracted from the OPCRD 'clinical' file for analysis. Rates are reported for each cohort and the rates in SA subjects are compared with the rates in mild/moderate asthma and non-asthmatic controls.

Table E1 Adverse effects of OCS use

Morbidity/Adverse Effect
Osteoporosis
Fracture
Diabetes
Hypertension
Ophthalmic effects – cataracts, glaucoma
Dyspeptic disorders – peptic ulcer disease
Psychiatric events – anxiety, depression, agitation
Infections
Sleep disturbances – insomnia
Dyslipidaemia
Weight gain
Skin conditions – bruising, thinning, striae, skin atrophy, acne
Muscle weakness/myopathy
Cardiovascular conditions – MI, heart failure
Oral candidiasis
Hyperglycaemia
Adrenal suppression/insufficiency
Osteonecrosis
Cushingoid changes – moon facies, abdominal obesity

Study size

The power of this study to detect excesses of steroid induced morbidity depends on the size of the groups, the frequency of the morbidity in the comparison group (mild/moderate asthmatic population or non-asthmatic population) and the magnitude of the excess rate expressed in terms of the relative risk, the ratio of the morbidity rates in the severe asthma and control groups. Table E2 shows the power of the main study of 800 asthma subjects on maintenance OCS and of the sub-group analysis of 450 receiving ≥6 OCS in each qualifying year to detect various relative risks depending on the prevalence of the morbidity.

Table E.2 Retrospective power assessment of a study of 800/450 asthma subjects on maintenance OCS to detect a given increase in risk as statistically significant (P<0.05) assuming a comparison group 5-times the size.

Prevalence of morbidity in comparison group	Power of study of 800 patients (main analysis)				
	Relative risk				
	x1.25	x1.5	x2.0	x2.5	x3.0
1%	8%†	22%	58%	84%	100%
2%	13%	39%	86%	99%	100%
3%	19%	54%	96%	100%	100%
4%	24%	66%	99%	100%	100%
5%	29%	76%	100%	100%	100%
10%	53%	97%	100%	100%	100%
15%	73%	100%	100%	100%	100%
20%	68%	100%	100%	100%	100%
25%	87%	100%	100%	100%	100%
30%	100%	100%	100%	100%	100%

† Stata sample size and power calculation command: **sampsi 0.0125 0.01, n1(800) r(5)**

Prevalence of morbidity in comparison group	Power of study of 450 patients (sub-group analysis)				
	Relative risk				
	x1.25	x1.5	x2.0	x2.5	x3.0
1%	5%†	13%	38%	62%	84%
2%	9%	24%	64%	89%	97%
3%	12%	34%	80%	97%	100%
4%	15%	44%	90%	99%	100%
5%	18%	52%	95%	100%	100%
10%	33%	83%	100%	100%	100%
15%	49%	96%	100%	100%	100%
20%	63%	99%	100%	100%	100%
25%	76%	100%	100%	100%	100%
30%	86%	100%	100%	100%	100%

† Stata sample size and power calculation command: **sampsi 0.0125 0.01, n1(450) r(5)**

Statistical analysis

The conditional logistic regression model (17) was employed for statistical analysis to take account of the matching of severe asthma cases with well-controlled asthma controls and rhinitis (non-asthma) controls.

Suppose that the i^{th} of I matched groups contains one case and M_i matched controls. Denote by $\mathbf{x_{i0} = (x_{i01},\ldots,x_{i0K})}$ the $\mathbf{K}$-vector of covariates ($\mathbf{k}$=1,…,$\mathbf{K}$) for case i (i=1,…,I), and denote by $\mathbf{x_{ij} = (x_{ij1},\ldots,x_{ijK})}$ the corresponding vector for the jth control (j=1,…,M_i). The conditional likelihood may be obtained as

$$\prod_{i=1}^{I} \frac{\exp(\sum_{k=1}^{K} \beta_k x_{i0k})}{\sum_{j=0}^{M_i} \exp(\sum_{k=1}^{K} \beta_k x_{ijk})} = \prod_{i=1}^{I} \frac{1}{1+\sum_{j=1}^{M_i} \exp\{\sum_{k=1}^{K} \beta_k (x_{ijk}-x_{i0k})\}}$$

where β_k represents the regression parameter for covariate $\mathbf{x_k}$ ($\mathbf{k}$=1,…,$\mathbf{K}$).

This likelihood can be maximised to obtain estimates $\mathbf{b_k}$ of β_k together with their standard errors SE($\mathbf{b_k}$) ($\mathbf{k}$=1,…,$\mathbf{K}$). These estimates may be antilogged to provide odds ratios (OR), exp($\mathbf{b_k}$), and 95% confidence limits (CI), exp($\mathbf{b_k}\pm$1.96 SE($\mathbf{b_k}$)) ($\mathbf{k}$=1,…,$\mathbf{K}$).

The covariates status (coded as case=1, control=0) and geographical region (coded as a series of dummy variables) were included in all analyses. Sample STATA commands for each analysis, with the adverse event non-insulin dependent diabetes (NIDDM), are given below,

xi:clogit NIDDM status i.region, group(MATCH_WELLCNTRL) or
xi:clogit NIDDM status i.region, group(MATCH_RHINITIS) or

where MATCH_WELLCNTRL identifies the matched groups of severe asthma and well-controlled asthma controls

and MATCH_RHINITIS identifies the matched groups of severe asthma and rhinitis (non-asthmatic) controls.

Results

Sub-group analysis of severe asthma subjects receiving ≥6 OCS

Minor change was noted in prevalence rates in this analysis (Table E3). The odds of osteopenia in SA compared to non-asthma controls increased 2-fold from the original analysis to OR of 8.72 (95% CI 5.15-14.75) from OR of 6.68 (4.28-10.43). Prevalence rates and OR for fractures in refractory asthma compared to controls was no longer statistically significant. Similarly, the rates and OR of cardiovascular disease in SA compared to mild/moderate asthma failed to reach statistical significance.

Table E3 Sub-group analysis of severe asthma subjects receiving ≥6 OCS in each qualifying year OPCRD

Morbidity	Severe asthma (%) n=465	Mild/moderate asthma (%) n=2280	OR (95% CI)	p-value	Non-asthma controls (%) n=1375	OR (95%CI)	p-value
Type II diabetes	53(11%)	161(7%)	1.69(1.22-2.35)	0.001	89(7%)	1.86(1.30-2.66)	0.001
Obesity (BMI >30)	194(42%)	808(35%)	1.30(1.06-1.60)	0.010	328(24%)	2.29(1.83-2.85)`	p<0.001
Osteopenia	53(11%)	55(2%)	5.21(3.52-7.69)	p<0.001	20(2%)	8.72(5.15-14.75)	p<0.001
Osteoporosis	86(19%)	99(4%)	5(3.68-7.69)	p<0.001	43(3%)	7.03(4.79-10.31)	p<0.001
Fracture	22(5%)	79(4%)	1.38(0.85-2.24)	0.19	50(4%)	1.32(0.79-2.20)	0.29
Dyspeptic disorders	318(68%)	790(35%)	4.08(3.30-5.05)	p<0.001	337(25%)	6.66(5.29-8.39)	p<0.001
Glaucoma	23(5%)	88(4%)	1.30(0.81-2.07)	0.28	45(3%)	1.54(0.92-2.57)	0.10
Cataract	51(11%)	127(6%)	2.09(1.48-2.94)	p<0.001	59(4%)	2.75(1.86-4.06)	p<0.001
Cardiovascular disease	48(10%)	176(8%)	1.38(0.98-1.93)	0.06	97(7%)	1.52(1.06-2.18)	0.024
Hypertension	163(35%)	680(30%)	1.27(1.03-1.57)	0.026	350(26%)	1.58(1.26-1.98)	p<0.001
Psychiatric conditions/ Anxiety/depression	173(37%)	707(31%)	1.32(1.07-1.62)	0.009	352(26%)	1.72(1.38-2.15)	p<0.001
Hypercholesterolemia	75(16%)	338(15%)	1.10(0.84-1.45)	0.47	148(11%)	1.59(1.18-2.15)	0.002
Sleep disorder	19(4%)	56(3%)	1.69(1.00-2.87)	0.049	22(2%)	2.62(1.41-4.89)	0.002
Chronic kidney disease	74(16%)	202(9%)	1.95(1.46-2.60)	p<0.001	93(7%)	2.61(1.88-3.61)	p<0.001

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