Final report

Does co-payment for inhaler devices affect therapy adherence and disease outcomes?

Observational historical cohort study to examine the effect of prescription charges for inhaler devices on maintenance therapy adherence and disease outcomes in patients with asthma and/or COPD.

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List of abbreviations

A&E	Accident and Emergency
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in one second
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled Corticosteroid
IDX	Index date: start of Seretide use
IQR	Interquartile Range
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LCP	Likely co-payment
LTRA	Leukotriene receptor antagonist
MPR	Medication Possession Ratio
MRC	Medical Research Council questionnaire for severity of breathlessness
NCP	Non-co-payment
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds Ratio
QOF	Quality and Outcomes Framework
PEF	Peak expiratory flow
RCC	Relative coefficient change
RR	Rate Ratio
SABA	Short-Acting Beta2 Agonist
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard deviation
SDD	Standardised difference

1.0 Executive summary

1.1 Introduction

In England, one way residents contribute to the National Health Service (NHS) is by paying a co-payment for their prescription. In contrast, since 1 April 2011, Scottish prescriptions (GP10) dispensed in Scottish pharmacies do not require a co-payment from patients. A comparison of patients who inherit a prescription charge in England with patients who do not pay a fee in Scotland provides an unique opportunity to investigate the effects of prescription co-payment on maintenance therapy adherence and disease outcomes in patients with asthma or COPD.

Adherence is when a patient takes a prescribed medication at doses and times recommended by a health care professional. Lack of adherence can diminish or undermine the efficacy of treatment. Research has shown various patient-level drivers of adherence, such as comorbidities or personal beliefs, but less has focused on the health system-level factors of adherence. Therefore, here we compared adherence achieved between two prescription financing systems.

1.2 Study aims and objectives

The aim of the study is to investigate whether a prescription charge for patients affects maintenance therapy adherence and disease outcomes in patients with asthma or COPD.

1.3 Methods

An observational historical, matched cohort study on patients with asthma only (asthma group) or COPD (COPD group) consisting of a one-year baseline period and a one-year outcome period, on either side of an index date, which was the date of first prescription for Seretide. Asthma or COPD patients were identified using diagnostic read codes and refill rate was derived from total medication possession days. All data elements were extracted from both the Optimum Patient Care Research Database (OPCRD) and the Clinical Practice Research Datalink (CPRD), which include primary care data from England and Scotland. Adherence was assessed during the one-year outcome period using the Medication Possession Ration derived from prescription information. A value of 80% or more was considered as adherent.

Patients from Scotland (*non co-payment, NCP cohort*) were matched to patients from England (*likely co-payment, LCP cohort*) on a limited number of identified confounders as well as a propensity score constructed from all baseline variables with a bias potential of at least 0.5%. The difference in the primary outcome (achieving adherence) in all patients, and the secondary outcomes (achieving risk domain control, number of exacerbations, numbers of acute respiratory events (asthma only), reliever medication use) was calculated per disease group. Additionally, sensitivity analyses were conducted

by 1) restricting the analysis to patients with at least nine months of persistent Seretide use, 2) restricting the analyses to patients in the asthma group.

1.4 Results

There were a total of 6,716 (NCP cohort = 716, LCP cohort = 6,000) patients with asthma or COPD that initiated Seretide from 2012 onwards. When asthma only and COPD patients were combined, the odds of adherence for those that paid a fee for prescription was 4% higher (Odds Ratio (OR) 1.04, 95% confidence interval [CI]: 0.85, 1.27) than those that did not pay a fee for prescription. When only patients with at least nine months of persistence were considered, 1% lower odds of adherence was seen for the LCP cohort compared to the NCP cohort (OR 0.99, [CI]: 0.79, 1.24). Both results did not reach statistical significance (p=0.704 and p=0.929, respectively).

Asthma only patients showed similar results: OR 1.06 (CI: 0.85, 1.33) and OR 1.09 (CI: 0.84, 1.34) for those with 9 months minimal persistence). Again, these results were not statically significant (p=0.604 and p=0.523, respectively).

As for the secondary outcomes, in both the asthma only group and COPD group, patients in the LCP cohort were less likely to achieve risk-domain control (OR 0.89, [CI]: 0.71, 1.11 for asthma group and OR 0.89, [CI]: 0.53, 1.48 for COPD group), but these difference were not statistically significant. The other secondary outcome (number of exacerbations, numbers of acute respiratory events (asthma only), and reliever medication use) odds were higher (but not significantly) for patients in the LCP cohort compared to patients in the NCP cohort.

1.5 Conclusion

Our results did not show a difference in adherence levels between patients in the NCP and LCP cohorts. Also, both patient arms achieved a similar level of Risk Domain Control, experienced similar number of exacerbations and had similar reliever medication usage.

2.0 Background

Asthma and chronic obstructive pulmonary disease (COPD) are, with a prevalence of 235 and 200 million patients respectively, two of the leading causes of morbidity and economic burden worldwide[1]. COPD comprises 5-6% of the total mortality rate (28,000 deaths in 2012) in the UK. A developed country is yearly spending 1-2 percent of their total health care expenditures on asthma, which makes it an expensive condition. Scotland spends an excess of £130 million on asthma. The cost of COPD is projected to increase from £1.40 billion and £159 million in 2011 to £2.32 billion and £207 million in 2030 for England and Scotland, respectively. It is possible to lower the costs of emergency care by investing in prevention medication[2]. Asthma and COPD are costly, preventable diseases.
A good adherence to maintenance medication in asthma and COPD is associated with significantly lower risk of hospitalisation and reduced expenditures.[3,4,5,6,7,8]

Research suggests that high prescription costs may have negative impacts on therapy adherence and disease outcomes across a range of chronic illnesses,[9,10,11,12,13,14] though their effect in patients with chronic respiratory ailments is not well known yet.[15,16,17] Patients in the lowest income category showed a decrease in medication adherence for chronic conditions compared to higher income categories, which may worsen disparities and adversely affect health.[18,19] This is even more relevant as COPD is inversely associated with socio-economic status.[20,21]
In England, for residents non-exempt from paying for prescriptions, there is a flat rate patient contribution of £8.40 per prescription. A resident of England can cap the prescription cost by purchasing a monthly (£29) or annual (£104) prescription prepayment certificate (PPC). In contrast, since 1 April 2011, Scottish prescriptions (GP10) dispensed in Scottish pharmacies do not require a co-payment from the patients. A comparison of patients who have to pay a prescription charge in England with patients who receive prescriptions without a co-payment in Scotland provides an unique opportunity to investigate the effects of prescription co-payment on maintenance therapy adherence and disease outcomes in patients with asthma and COPD, accounting for disease severity.

3.0 Study aims and objectives

3.1 Aims

The aim of the study is to investigate whether a prescription charge for patients affects maintenance therapy adherence and disease outcomes in patients with asthma or COPD.

3.2 Objectives

To compare maintenance therapy adherence and disease control between patients with asthma and/or COPD who likely need to pay a prescription charge (England) and patients who receive their medication free of charge (Scotland).

4.0 Study design

This study was a historical, matched cohort study of patients with asthma and/or COPD initiating on Seretide therapy. Patients with asthma only will be referred to as the *asthma group*, and patients with COPD as the *COPD group* (which contains patients with COPD and asthma, or patients with COPD only).

There was a one-year baseline period and a one-year outcome period (Figure 1). These periods were separated by an index date (IDX), which was defined as the date of first prescription for Seretide, after a period of at least 6 months of no prescriptions for Seretide. The baseline period was intended for patient characterisation and confounder identification. The outcome period started at the index date and was used to assess adherence and clinical outcomes.

Patients were divided into an arm with likely co-payment (from general practices in England), hereafter referred to as the *LCP cohort*, and an arm with no-co-payment for prescriptions (from general practices in Scotland), hereafter referred to as the *NCP cohort*.

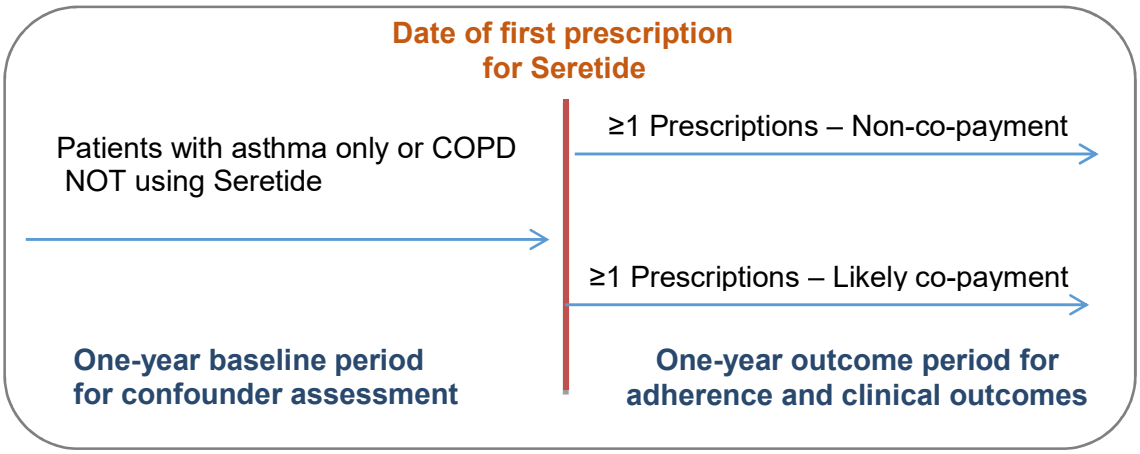

Figure 1: Study design

5.0 Study population

5.1 Inclusion and exclusion criteria

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Diagnosis for asthma or COPD
For asthma: aged ≥ 40 years and ≤ 60 years at the index date; for COPD: aged ≥ 40 years and ≤ 60 years at the index date
At least 2 years of continuous clinical data (1 year of baseline and 1 year of outcome data)
Initiation of Seretide (at least 365 days before without precription for Seretide)
At least one further Seretide prescription in outcome period
Exclusion criteria
Any other chronic respiratory disease other than asthma and COPD at any time
Those with the following co-payment exemption conditions: • Being pregnant during the study period, or within 12 months before the study period • Having a "prescription exemption status" recorded before or during the study period. • Having a hospitalisation during the study period.

5.2 Data sources

The studies used patient data from both the Optimum Patient Care Research Database (OPCRD)[22] and the Clinical Practice Research Datalink (CPRD).[23] The study team worked with fully anonymised data, removed of any patient identifiable information.

The OPCRD is developed, maintained, and owned by Optimum Patient Care (OPC), a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely-recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. The OPCRD is the only database in the UK that complements routinely-recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[24] to govern the standard of research conducted on internationally recognised databases. All research using OPCRD is registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).[25]

The CPRD is a large computerised primary care database, containing de-identified, longitudinal data from 5 million active medical records from more than 600 subscribing practices throughout the UK. A practice-based quality marker, the "up-to-standard date", is generated by the CPRD for each subscribing practice and data subsequent to the practice up-to-standard date are considered to be acceptable, research-quality, prospectively-recorded data. The CPRD is well-validated and used frequently for medical and health research.

The OPCRD and CPRD datasets for this study were constructed separately and checked for overlap (previously quantified at 2-3%), before pooling for analyses, in order to exclude patients with duplicate data. Identification of patients who were present in both OPCRD and CPRD datasets was conducted by matching on a number of variables, such as the year of birth, gender and index date.

6.0 Study variables and study outcomes

6.1 Exposure

The exposure of interest in this study was the need for co-payment (exposed, England) or not (unexposed, Scotland) for medication prescriptions. These cohorts are referred to as the *likely co-payment* (LCP) cohort and the *non-co-payment* (NCP) cohort.

6.2 Primary outcome

The primary outcome of this study was adherence to Seretide therapy, evaluated in terms of percentage of refill rate (Medication Possession Ratio, MPR[26]) over a 1 year period. An MPR of 80% or more was used to indicate good adherence.

$$\text{Calculated prescription duration} = \frac{\text{Number of doses in the prescription}}{\text{Number of doses per day}}$$ (Only counting the period of the prescription that falls within the outcome period)

$$\text{Total medication possession days} = \Sigma\,(\text{Prescription duration})$$

$$\text{Medication Possession Ratio over 1 year} = \frac{\text{Total medication possession days}}{365} * 100$$

Missing dosing information was assumed to be 4 puffs/day for a Metered-Dose Inhaler and 2 puffs/day for Dry Powder inhalers. Exact duplicate prescriptions were removed before calculating the total medication possession days.

6.3 Secondary outcomes

For patients with asthma the following secondary outcomes of this study are:

Number of severe exacerbations	See 13.1.1
Number of acute respiratory events	See 13.1.3
Risk-domain asthma control (RDAC)	Controlled: absence of acute respiratory events
SABA reliever usage	Average daily SABA dosage during outcome year, calculated as average number of puffs per day over the year multiplied by strength (in μg); $\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength \text{ in } \mu g$

For patients with COPD the secondary outcomes of this study are:

Number of moderate/severe exacerbations	See 13.1.2
Risk-domain control (RDAC)	Absence of moderate/severe exacerbations
SABA reliever usage	Average daily SABA dosage during outcome year, calculated as average number of puffs per day over the year multiplied by strength (in μg); $\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$ in μg

6.4 Baseline variables

6.4.1 Demographics

Age and gender	At index date
Body Mass Index	Closest to the index date. Defined as the ratio of weight (kg) to squared height (m^2), and categorised as *underweight* (< 18.5 kg/m^2), *normal weight* (≥ 18.5 kg/m^2 and < 25 kg/m^2), *overweight* (≥ 25 kg/m^2 and < 30 kg/m^2) and *obese* (≥ 30 kg/m^2)
Smoking status	Closest to the index date; categorised as *non-smoker*, *current smoker* and *ex-smoker*.

6.4.2 Comorbidities

The following comorbidities were based on a diagnostic code recorded at any time prior to or at the index date:	
Asthma (in COPD group)	*i.e.* ACOS; unresolved asthma Read code in patients with COPD
Ischaemic heart disease	
Heart failure	
Diabetes	Non-specific
Pneumonia	*Probable*: Read code *Definite*: Read code with hospital admission or chest x-ray within 1 month
Charlson comorbidity index score (CCI)	A weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases
Cancer (malignant neoplasm)	
Oral Candidiasis	
Eczema	

The following comorbidities were based on a diagnostic code recorded OR treatment at any time prior to the index date:	
Gastro-oesophageal reflux disease (GERD)	
Allergic and non-allergic rhinitis	
Hypertension	
The following comorbidities were based on a diagnostic code OR treatment recorded in the one-year baseline period	
Active Gastro-oesophageal reflux disease (GERD)	
Active Allergic and non-allergic rhinitis	
The following co-medications were based on a diagnostic code OR treatment recorded in the one-year baseline period	
Non-steroidal anti-inflammatory drug Prescription	
Beta Blocker Prescription	

6.4.3 Lung function

Lung function was measured by FEV1, recorded closest to the index date and defined as:	
FEV_1	Forced Expiratory Volume in one second (L), and the % of the predicted normal value for age, gender and height

6.4.4 Disease severity and control

The following were recorded in the baseline period:

COPD group	
Risk domain control	See 13.1.8
Moderate/severe exacerbations	See 13.1.2
Asthma group	
Severe exacerbations	See 13.1.1
Acute respiratory events	See 13.1.3
Risk domain control	See 13.1.7
Both groups	
Inpatient admissions	See 13.1.9
Outpatient visits	See 13.1.10

The following were recorded for patients in the COPD group, closest to the index date:

mMRC score	Refers to the *modified British Medical Research Council* questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness. Both routine medical practice recorded and patient questionnaire mMRC scores were used, with the most recent score taking precedence.	
GOLD group	Classification based on the 2014 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines:	
	A = low risk, less symptoms	mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations).
	B = low risk, more symptoms	mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations)..
	C = high risk, less symptoms	mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation).
	D = high risk, more symptoms	mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation).

The following were recorded for patients in the asthma group, closest to the index date:

GINA control	Based on Global Initiative for Asthma (GINA) guidelines 2014.	
	Step 1	Symptoms < once weekly; brief acute respiratory events; nocturnal symptoms ≤ twice monthly; PEF or FEV_1 variability < 20%
	Step 2	Symptoms > once weekly but < once daily; acute respiratory events may affect activity and sleep; nocturnal symptoms > twice monthly; PEF or FEV_1 variability 20-30%
	Step 3	Symptoms daily; acute respiratory events may affect activity and sleep; nocturnal symptoms > once weekly; PEF or FEV_1 variability > 30%
	Step 4	Symptoms daily; frequent acute respiratory events; frequent nocturnal asthma symptoms; limitations of physical activities; PEF or FEV_1 variability > 30%

6.4.5 Medication

Number of prescriptions in the year prior to the index date was recorded for the following medications:	
ICS	Inhaled corticosteroids, single or combination
Oral CS, maintenance	Oral corticosteroids for maintenance use (see 13.1.12)
Oral CS, acute	Oral corticosteroids for acute use (see 13.1.12)
Antibiotics	Antibiotics prescribed with lower respiratory consultation
LAMA	Long-acting muscarinic antagonist, for COPD only
LABA	Long-acting beta2-agonist
SAMA	Short-acting muscarinic antagonist; for COPD
SABA	Short-acting beta2-agonist
LTRA	Leukotriene receptor antagonists
Methyl	Methylxanthines
Average daily dose in the year prior to the index date was recorded for:	
SABA	µg/day salbutamol equivalent, calculated as ([count of inhalers x doses in pack x µg strength] / 365)
ICS	µg/day beclometasone equivalent, calculated as ([count of inhalers x doses in pack x µg strength] / 365)

7.0 Statistical analysis

7.1 Software used

All statistical analyses have been conducted using Stata MP6 version 12 and Stata SE version 14 (StataCorp, College Station, TX, USA).

A statistically significant result is defined as a $p < 0.05$.

7.2 Quality control and assurance

The data were obtained from routine clinical care. Therefore, we investigated for potential data entry errors, checked for completeness, and depleted implausible entries or outliers from the final analytical dataset before analysis.
As much as possible previously used and proven analytical code was used for the data processing, matching and analyses. A second researcher reviewed all remaining code.

7.3 Baseline characterisation

Binary and categorical variables were summarised using the percentage of non-missings, the frequency and percentages (based on the non-missing sample size) of observed levels, and a P-value for the Pearson's chi-square test of independent categories. Continuous variables were summarised using mean (standard deviation) and median (interquartile range), and a P-value for the Kruskal-Wallis equality-of-populations rank test. Also, a statistics of imbalance between strata is presented (standardised difference) and a measure of bias potential of the variable on the association between exposure and outcome.

7.4 Matching

This section describes the approach used to handle confounding. Potential confounders were identified based on a combination of baseline imbalance, bias potential and expert judgement, and the most relevant confounders were used for direct matching.
Direct matching can only use a limited number of variables to match on without restricting the patient population too much, and it is therefore necessary to exclude variables that do not relevantly affect the association of interest.
After matching this approach was repeated in the matched sample to identify any residual confounding, selecting confounders for direct adjustment in the outcome analyses.

7.5 Confounder identification and handling

7.5.1 Baseline balance

A characterisation of all baseline demographics, co-morbidities, indicators of disease severity and other patient characteristics was carried out and presented for each arm. The difference between the arms was quantified using the Standardised Difference (SDD) (Table 2).[2728] This measure is not affected by the number of observations, and thus a better way to judge imbalance than a P-value of a hypothesis test of difference. The SDD was calculated for both continuous and categorical variables as described below: An SDD ≤10% indicates sufficient balance between the groups.

Table 2. Formulae for Standardised Difference

Covariate type	Formula
Continuous	$SDD = \frac{(\bar{x_t} - \bar{x_r})}{\sqrt{\frac{s_t^2 + s_r^2}{2}}}$, where $\bar{x_t}$, $\bar{x_r}$ denote the sample means and s_t, s_r the standard deviations
Binary	$SDD = \frac{(\hat{p_t} - \hat{p_r})}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t)+\hat{p}_r(1-\hat{p}_r)}{2}}}$, where $\hat{p_t}$, $\hat{p_r}$ denote the proportion of patients in each category
Categorical (>2 categories)	$SDD = \sqrt{(T-C)'S^{-1}(T-C)}$ where S is a $(k-1)\times(k-1)$ covariance matrix: $S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}(1-\hat{p}_{1k}) + \hat{p}_{2k}(1-\hat{p}_{2k})}{2}, & k = l \\ \frac{\hat{p}_{1k}\hat{p}_{1l} + \hat{p}_{2k}\hat{p}_{2l}}{2}, & k \neq l \end{cases}$, $T = (\hat{p}_{12}, \ldots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \ldots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P(category\ k | treatment\ arm\ j)$, $j = 1,2$, $k = 2,3, \ldots, k$

7.5.2 Bias potential

Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on the variable. Bias potential was measured using the relative change in co-efficient (RCC)[29] of the exposure when the covariate is added into the model predicting outcome (Table 3).

Table 3. Formulae for Relative Change in Co-efficient

Outcome type	Regression type	Formula
Continuous	Linear	$RCC = abs\left\{\frac{\left(\beta_{crude} - \beta_{adjusted}\right)}{\beta_{crude}}\right\}$
Binary	Logistic	$RCC = abs(1 - e^{(\beta_{crude} - \beta_{adjusted})})$
Time-to-event	Cox-Proportional Hazard	
Count	Poisson	
Where β_{crude} is the co-efficient of exposure in the crude model and $\beta_{adjusted}$ is the co-efficient of exposure after adding the covariate in the model.		

It is called *bias potential* since the bias was estimated without other covariates in the model. To what extent a variable introduces bias into a model will depend on the total model.
The baseline variables with the highest bias potential, that also were sufficiently imbalanced (SDD > 10%) were presented to a panel of clinical experts of the current study for the final selection of variables to use for matching.

7.5.3 Matching process

Exact matching for categorical variables and matching within a maximum calliper (maximum distance allowed between a case and a control) for continuous variables was used to match patients using nearest neighbour variable mixed matching with a match maximum of 3:1 without replacement. Mixed matching is a process that helps utilise more of the data by matching varying numbers of control arm patients to a treatment arm patient. In other words, we used a cohort of unique patients matched 1:1, another cohort of unique patients matched 1:2, and a third cohort of unique patients matched 1:3. The analysis was conducted using all of the matched patients even though some patients have 1 match while other patients may have 3 matches.
In the case of repeated measurements for a patient, only one record contributed to the matching. Matching was repeated several times with a difference patient sequence to select the run that resulted in the highest number of patients and/or the best baseline balance. The actual number of variables used for the matching depended on the degree of restriction caused by the matching process. In the case that too many patients were excluded, because they could not be matched to controls, the number of matching variables was reduced or the calliper of individual variables was increased.
If no satisfactory number of matched patients was achieved with a minimum set of confounders, a different approach towards handling confounding will be chosen, namely direct matching on a limited set of confounders as well as on a propensity score.
Missing data was treated as missing completely at random and was not imputed. If a selected confounder has more than 10% of missing data it will not be used for matching. If missingness was

below 10%, the variable was encoded as a categorical variable, adding a category for the observations with missing values, enabling this variable to be used for matching.

7.5.4 Post-matching evaluation

The quality of the matching was evaluated using the same methods as used to identify the confounders: standardised mean difference in combination with bias potential.
For each outcome cohort baseline characterisation of the matched sample was carried out using the same statistics as used in the unmatched baseline characterisation: descriptive statistics, standardised difference and bias potential.
All variables with less than 10% missing values in each treatment arm, showing a bias potential of at least 2% were identified.
The conditional regression analysis used to analyse the study outcomes took into account the matched pairs.
Adjustment for variables with residual confounding was carried out. Since it can be expected that these variables can have similar associations with exposure and/or outcome their conditional bias, on the variables already in the model, was assessed.
Starting with a model with exposure as the only explanatory variable, the variables were added one by one in order of their individual bias potential, highest first. After a variable was added to the model it was kept in if it caused a change-in-estimate of at least 2%, relative to the prior model.
Assumptions for regression models were assessed as appropriate.

7.6 Analysis of study outcomes

7.6.1 Primary outcome

Conditional logistic regression in the matched sample of the between-patient difference in the primary outcome was performed to provide an Odds Ratio with its 95% CI. The model was adjusted for baseline variables that remained causing bias after matching.

Two sensitivity analyses were conducted on the primary outcome, by 1) restricting the analysis to patients with at least nine months of persistence, 2) restricting the analyses to patients in the asthma group.

7.6.2 Secondary outcomes

The secondary outcomes were assessed separately by disease group.

Conditional logistic regression in the matched sample was used to assess the between-patient difference in

- Risk-domain asthma control

Conditional Poisson regression in the matched sample was used to assess the between-patient difference in

- Number of severe exacerbations (asthma)
- Number of acute respiratory events (asthma)
- Number of moderate and severe exacerbations (COPD)

Conditional ordinal logistic regression in the matched sample was used to assess the between-patient difference in

- SABA, average daily dose (salbutamol equivalent)

8.0 Results

8.1 Patient selection

Patients with asthma only or COPD using Seretide from 2012 onwards in Scotland and England were selected. Table 4 shows the inclusion and exclusion applied to create the final dataset.

Table 4. Patient selection criteria

	OPCRD	CPRD
Seretide prescription after 2011	87,285	104,099
Patients have at least one year of baseline and outcome data available from the index date	57,282	75,635
No Seretide in previous year	18,709	23.933
Asthma diagnosis or COPD diagnosis prior to index	15,848	19,157
Asthma patients age >=20 and <60 and COPD patients age>=40 and <=60	6,651	8,422
No Other chronic respiratory disease	6,523	8,237
Not pregnant during the study period	6,216	8,136
Do not have a “prescription exemption status”	6,101	8,005
At least 1 extra Seretide prescription	4,392	5,465
No hospitalisation during the study period	3,785	3,988
Country England or Scotland	3,715	3,398
Not in OPCRD		3,001
Final cohort	3,715	3,001
Combined	6,716	

A total of 716 patients in the NCP and 6,000 in the LCP cohort were in the final dataset (Table 5), of whom 81% were in the asthma group.

Table 5. Number of patients by cohort and disease group

Group	NCP	LCP	Total
Asthma	582	4,882	5,464
COPD	134	1,118	1,252
Total	716	6,000	6,716

NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

8.2 Unmatched baseline characterisation

The baseline characterisation for the patients in the asthma group is presented in Table 6, and for the COPD group in Table 7. Graphical presentation of distributions are available in Appendix 0.

Demographics were well balanced in patients in the asthma group (i.e. SDD <10%). As for comorbidities, Gastroesophageal reflux disease (NCP 13.1% vs. 9.5% LCP) and oral candidiasis (2.7 % vs. 4.8%) were imbalanced between the arms. In respiratory medication the use of reliever medication (SABA) was imbalanced between the arms, with patients in the LCP cohort having more frequent usage. This also resulted in relevant bias potential (RCC ≥2%). GINA control showed to be imbalanced between the arms, but since about 30% of the observations were missing, this variable did not receive further consideration.

Patients in the COPD group showed imbalance in gender, smoking status, diabetes, active rhinitis, active Gastroesophageal reflux disease, eczema, oral Candidiasis, prescription of LAMA, Methylxanthines and LTRA, acute OCS use, A&E attendance, and the MRC score.

Table 6. Baseline characterisation - Asthma group

Variable		NCP	LCP	P	SDD	RCC
Index year	N (% non-missing)	582 (100.0)	4,882 (100.0)	<0.0001	14.8	1.2
	2012, n (%)	291 (50.0)	2,679 (54.9)			
	2013, n (%)	183 (31.4)	1,461 (29.9)			
	2014, n (%)	75 (12.9)	667 (13.7)			
	2015, n (%)	33 (5.7)	75 (1.5)			
Age (years)	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0592	6.0	1.3
	Mean (SD)	42.5 (11.2)	41.8 (10.6)			
	Median (IQR)	45.0 (18.0)	43.0 (16.0)			
Gender	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.1579	6.2	0.3
	Male, n (%)	264 (45.4)	2,065 (42.3)			
Smoking status	N (% non-missing)	582 (100.0)	4,864 (99.6)	0.2591	6.7	0.7
	Never, n (%)	299 (51.4)	2,673 (55.0)			
	Current, n (%)	143 (24.6)	1,115 (22.9)			
	Ex, n (%)	140 (24.1)	1,076 (22.1)			
BMI	N (% non-missing)	554 (95.2)	4,705 (96.4)	0.3347	4.6	0.6
	<18.5, n (%)	10 (1.8)	85 (1.8)			
	18.5-<25, n (%)	172 (31.0)	1,299 (27.6)			
	25-<30, n (%)	167 (30.1)	1,554 (33.0)			
	>=30, n (%)	205 (37.0)	1,767 (37.6)			
Cardiovascular disease	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.6015	2.3	0.1
	Yes, n (%)	35 (6.0)	268 (5.5)			
Ischaemic heart disease	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.4644	3.1	0.2
	Yes, n (%)	11 (1.9)	73 (1.5)			
Hypertension	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.3134	4.3	0.8
	Yes, n (%)	74 (12.7)	552 (11.3)			
Cancer	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0538	8.1	0.0
	Yes, n (%)	58 (10.0)	375 (7.7)			
Diabetes	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0758	7.3	0.8
	Yes, n (%)	33 (5.7)	200 (4.1)			
Rhinitis	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.2987	4.5	0.2
	Yes, n (%)	198 (34.0)	1,557 (31.9)			
Active Rhinitis	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.7194	1.6	0.2
	Yes, n (%)	88 (15.1)	711 (14.6)			
Gastroesophageal reflux disease	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0070	11.2	1.4
	Yes, n (%)	76 (13.1)	465 (9.5)			
Active Gastroesophageal reflux disease	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.2779	4.6	0.5
	Yes, n (%)	57 (9.8)	413 (8.5)			

Variable		NCP	LCP	P	SDD	RCC
Eczema	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.1218	6.9	0.5
	Yes, n (%)	174 (29.9)	1,615 (33.1)			
Active Eczema	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.3420	4.0	0.0
	Yes, n (%)	15 (2.6)	97 (2.0)			
Pneumonia	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.2096	5.2	0.2
	Yes, n (%)	25 (4.3)	161 (3.3)			
Oral Candidiasis	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0269	10.6	0.3
	Yes, n (%)	16 (2.7)	233 (4.8)			
Beta Blockers	N (% non-missing)	582 (100.0)	4,882 (100.0)	1.0000	0.3	0.0
	Mean (SD)	0.1 (0.8)	0.1 (0.8)			
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
NSAIDs	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.3542	4.1	0.2
	≥1, n (%)	100 (17.2)	916 (18.8)			
Charlson Comorbidity Index	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.6345	0.5	0.1
	Mean (SD)	3.1 (2.4)	3.1 (2.0)			
	Median (IQR)	4.0 (4.0)	4.0 (4.0)			
LABA prescriptions, solo	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.1655	5.9	1.5
	≥1, n (%)	78 (13.4)	559 (11.5)			
SAMA prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.9577	0.2	0.1
	≥1, n (%)	5 (0.9)	43 (0.9)			
LAMA prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.9976	0.0	0.0
	≥1, n (%)	5 (0.9)	42 (0.9)			
Methylxanthines prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0265	13.0	1.0
	≥1, n (%)	0 (0.0)	41 (0.8)			
LTRA prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.9535	0.3	0.1
	≥1, n (%)	36 (6.2)	305 (6.2)			
Phosphodiesterase-4 inhibitor prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)		0.0	0.0
Acute OCS prescriptions, sensitive	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.2893	0.8	0.1
	0, n (%)	441 (75.8)	3,660 (75.0)			
	1, n (%)	86 (14.8)	824 (16.9)			
	≥2, n (%)	55 (9.5)	398 (8.2)			
Acute OCS courses, probable	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.1393	1.1	0.4
	0, n (%)	404 (69.4)	3,335 (68.3)			
	1, n (%)	104 (17.9)	1,017 (20.8)			
	≥2, n (%)	74 (12.7)	530 (10.9)			
Acute OCS courses, sensitive	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.4206	0.3	0.4
	0, n (%)	441 (75.8)	3,660 (75.0)			
	1, n (%)	95 (16.3)	885 (18.1)			
	≥2, n (%)	46 (7.9)	337 (6.9)			

Variable		NCP	LCP	P	SDD	RCC
Maintenance OCS prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.2794	2.8	0.2
	0, n (%)	571 (98.1)	4,812 (98.6)			
	1, n (%)	2 (0.3)	5 (0.1)			
	≥2, n (%)	9 (1.5)	65 (1.3)			
All OCS prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.1832	0.1	0.2
	0, n (%)	403 (69.2)	3,308 (67.8)			
	1, n (%)	89 (15.3)	889 (18.2)			
	≥2, n (%)	90 (15.5)	685 (14.0)			
Antibiotic prescriptions, LR	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.7430	3.1	0.5
	0, n (%)	396 (68.0)	3,244 (66.4)			
	1, n (%)	112 (19.2)	988 (20.2)			
	≥2, n (%)	74 (12.7)	650 (13.3)			
Acute OCS prescriptions, probable	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.3263	1.8	0.1
	0, n (%)	404 (69.4)	3,335 (68.3)			
	1, n (%)	92 (15.8)	907 (18.6)			
	2, n (%)	46 (7.9)	353 (7.2)			
	≥3, n (%)	40 (6.9)	287 (5.9)			
SABA inhaler prescriptions	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.0004	15.5	3.7
	0, n (%)	262 (45.0)	1,776 (36.4)			
	1, n (%)	84 (14.4)	690 (14.1)			
	2-4, n (%)	112 (19.2)	1,229 (25.2)			
	5-10, n (%)	83 (14.3)	843 (17.3)			
	11+, n (%)	41 (7.0)	344 (7.0)			
SABA inhalers	N (% non-missing)	582 (100.0)	4,882 (100.0)	<0.0001	7.6	3.2
	0, n (%)	262 (45.0)	1,776 (36.4)			
	1, n (%)	47 (8.1)	551 (11.3)			
	2-4, n (%)	115 (19.8)	1,192 (24.4)			
	5-10, n (%)	76 (13.1)	859 (17.6)			
	11+, n (%)	82 (14.1)	504 (10.3)			
ICS prescriptions (mono- and combi)	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.1860	7.7	5.1
	0, n (%)	233 (40.0)	2,052 (42.0)			
	1, n (%)	58 (10.0)	616 (12.6)			
	2-4, n (%)	164 (28.2)	1,261 (25.8)			
	5-10, n (%)	101 (17.4)	774 (15.9)			
	11+, n (%)	26 (4.5)	179 (3.7)			

Variable		NCP	LCP	P	SDD	RCC
SABA, avg daily dose (salbutamol equivalent)	N (% non-missing)	582 (100.0)	4,882 (100.0)	<0.0001	4.3	3.0
	0, n (%)	262 (45.0)	1,776 (36.4)			
	>0 - ≤200, n (%)	139 (23.9)	1,389 (28.5)			
	>200 - ≤400, n (%)	68 (11.7)	887 (18.2)			
	>400 - ≤600, n (%)	33 (5.7)	380 (7.8)			
	>600, n (%)	80 (13.7)	450 (9.2)			
A&E attendances	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.4593	3.5	0.0
	≥1, n (%)	3 (0.5)	39 (0.8)			
Inpatient admissions, definite	N (% non-missing)	582 (100.0)	4,882 (100.0)		0.0	0.0
Inpatient admissions, probable	N (% non-missing)	582 (100.0)	4,882 (100.0)		0.0	0.0
Outpatient visits	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.3903	4.0	0.4
	≥1, n (%)	7 (1.2)	82 (1.7)			
Acute respiratory events	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.6090	3.6	0.6
	0, n (%)	333 (57.2)	2,674 (54.8)			
	1, n (%)	136 (23.4)	1,245 (25.5)			
	2, n (%)	69 (11.9)	562 (11.5)			
	≥3, n (%)	44 (7.6)	401 (8.2)			
Severe exacerbations (asthma)	N (% non-missing)	582 (100.0)	4,882 (100.0)	0.2696	1.4	0.5
	0, n (%)	404 (69.4)	3,320 (68.0)			
	1, n (%)	104 (17.9)	1,022 (20.9)			
	2, n (%)	46 (7.9)	347 (7.1)			
	≥3, n (%)	28 (4.8)	193 (4.0)			
FEV_1	N (% non-missing)	136 (23.4)	944 (19.3)	0.6610	8.0	7.6
	Mean (SD)	2.8 (1.2)	2.7 (1.2)			
	Median (IQR)	2.6 (1.4)	2.6 (1.1)			
GINA control	N (% non-missing)	402 (69.1)	3,586 (73.5)	<0.0001	23.9	0.5
	Controlled, n (%)	51 (12.7)	569 (15.9)			
	Partly Controlled, n (%)	222 (55.2)	2,284 (63.7)			
	Uncontrolled, n (%)	129 (32.1)	733 (20.4)			

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential; NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

Table 7. Baseline characterisation - COPD group

Variable		NCP	LCP	P	SDD	RCC
Index year	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0095	20.5	0.9
	2012, n (%)	63 (47.0)	592 (53.0)			
	2013, n (%)	40 (29.9)	352 (31.5)			
	2014, n (%)	24 (17.9)	158 (14.1)			
	2015, n (%)	7 (5.2)	16 (1.4)			
Age (years)	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.9158	7.9	1.3
	Mean (SD)	53.9 (4.9)	53.4 (6.0)			
	Median (IQR)	55.0 (7.0)	55.0 (8.0)			
Gender	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.2425	10.7	0.9
	Male, n (%)	72 (53.7)	541 (48.4)			
Smoking status	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0227	18.7	4.7
	Never, n (%)	3 (2.2)	103 (9.2)			
	Current, n (%)	83 (61.9)	654 (58.5)			
	Ex, n (%)	48 (35.8)	361 (32.3)			
BMI	N (% non-missing)	133 (99.3)	1,105 (98.8)	0.0292	4.3	2.9
	<18.5, n (%)	13 (9.8)	57 (5.2)			
	18.5-<25, n (%)	33 (24.8)	365 (33.0)			
	25-<30, n (%)	48 (36.1)	326 (29.5)			
	>=30, n (%)	39 (29.3)	357 (32.3)			
Cardiovascular disease	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.7083	3.5	0.1
	Yes, n (%)	17 (12.7)	155 (13.9)			
Ischaemic heart disease	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.5910	4.7	0.0
	Yes, n (%)	10 (7.5)	70 (6.3)			
Hypertension	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.2974	9.8	2.0
	Yes, n (%)	22 (16.4)	226 (20.2)			
Cancer	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.5443	5.4	0.2
	Yes, n (%)	19 (14.2)	138 (12.3)			
Diabetes	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.2351	11.7	0.4
	Yes, n (%)	7 (5.2)	91 (8.1)			
Rhinitis	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.8044	2.3	0.0
	Yes, n (%)	18 (13.4)	159 (14.2)			
Active Rhinitis	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.2576	11.2	0.1
	Yes, n (%)	5 (3.7)	69 (6.2)			
Gastroesophageal reflux disease	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.6538	4.2	0.2
	Yes, n (%)	16 (11.9)	149 (13.3)			
Active Gastroesophageal reflux disease	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0583	19.3	0.2
	Yes, n (%)	7 (5.2)	116 (10.4)			

Variable		NCP	LCP	P	SDD	RCC
Eczema	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.1511	13.5	0.4
	Yes, n (%)	28 (20.9)	298 (26.7)			
Active Eczema	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.5831	4.6	0.0
	Yes, n (%)	2 (1.5)	11 (1.0)			
Pneumonia	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.6367	4.5	0.0
	Yes, n (%)	7 (5.2)	70 (6.3)			
Oral Candidiasis	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0493	21.0	0.2
	Yes, n (%)	3 (2.2)	73 (6.5)			
Beta Blockers	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.7064	5.5	0.3
	Mean (SD)	0.4 (1.9)	0.3 (2.3)			
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
NSAIDs	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.5056	6.2	0.1
	≥1, n (%)	29 (21.6)	271 (24.2)			
Charlson Comorbidity Index	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.6479	4.7	0.0
	Mean (SD)	1.7 (2.5)	1.6 (2.4)			
	Median (IQR)	0.0 (4.0)	0.0 (4.0)			
LABA prescriptions, solo	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.6306	4.3	0.5
	≥1, n (%)	23 (17.2)	174 (15.6)			
SAMA prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.7945	2.4	0.4
	≥1, n (%)	9 (6.7)	82 (7.3)			
LAMA prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0003	32.8	9.6
	≥1, n (%)	72 (53.7)	420 (37.6)			
Methylxanthines prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0657	13.8	3.0
	≥1, n (%)	5 (3.7)	17 (1.5)			
LTRA prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0503	14.8	2.2
	≥1, n (%)	6 (4.5)	21 (1.9)			
Phosphodiesterase-4 inhibitor prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)		0.0	0.0
Acute OCS prescriptions, sensitive	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.4452	11.3	0.8
	0, n (%)	88 (65.7)	790 (70.7)			
	1, n (%)	28 (20.9)	210 (18.8)			
	≥2, n (%)	18 (13.4)	118 (10.6)			
Acute OCS courses, probable	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.4068	11.3	0.8
	0, n (%)	72 (53.7)	668 (59.7)			
	1, n (%)	34 (25.4)	249 (22.3)			
	≥2, n (%)	28 (20.9)	201 (18.0)			
Acute OCS courses, sensitive	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.4905	9.7	0.3
	0, n (%)	88 (65.7)	790 (70.7)			
	1, n (%)	31 (23.1)	220 (19.7)			
	≥2, n (%)	15 (11.2)	108 (9.7)			

Variable		NCP	LCP	P	SDD	RCC
Maintenance OCS prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.7893	0.2	0.3
	0, n (%)	129 (96.3)	1,078 (96.4)			
	1, n (%)	1 (0.7)	4 (0.4)			
	≥2, n (%)	4 (3.0)	36 (3.2)			
All OCS prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.5203	9.7	0.9
	0, n (%)	71 (53.0)	650 (58.1)			
	1, n (%)	30 (22.4)	225 (20.1)			
	≥2, n (%)	33 (24.6)	243 (21.7)			
Antibiotic prescriptions, LR	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.4271	7.2	0.0
	0, n (%)	64 (47.8)	548 (49.0)			
	1, n (%)	31 (23.1)	298 (26.7)			
	≥2, n (%)	39 (29.1)	272 (24.3)			
Acute OCS prescriptions, probable	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.4248	13.7	1.6
	0, n (%)	72 (53.7)	668 (59.7)			
	1, n (%)	30 (22.4)	231 (20.7)			
	2, n (%)	13 (9.7)	106 (9.5)			
	≥3, n (%)	19 (14.2)	113 (10.1)			
SABA inhaler prescriptions	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.6139	1.9	0.8
	0, n (%)	41 (30.6)	302 (27.0)			
	1, n (%)	13 (9.7)	156 (14.0)			
	2-4, n (%)	34 (25.4)	292 (26.1)			
	5-10, n (%)	33 (24.6)	247 (22.1)			
	11+, n (%)	13 (9.7)	121 (10.8)			
SABA inhalers	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.4968	0.8	2.6
	0, n (%)	41 (30.6)	302 (27.0)			
	1, n (%)	12 (9.0)	136 (12.2)			
	2-4, n (%)	27 (20.1)	277 (24.8)			
	5-10, n (%)	32 (23.9)	229 (20.5)			
	11+, n (%)	22 (16.4)	174 (15.6)			
ICS prescriptions (mono- and combi)	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.6211	9.1	2.8
	0, n (%)	81 (60.4)	699 (62.5)			
	1, n (%)	7 (5.2)	91 (8.1)			
	2-4, n (%)	18 (13.4)	132 (11.8)			
	5-10, n (%)	19 (14.2)	141 (12.6)			
	11+, n (%)	9 (6.7)	55 (4.9)			

Variable		NCP	LCP	P	SDD	RCC
SABA, avg daily dose (salbutamol equivalent)	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.0807	2.2	2.8
	0, n (%)	41 (30.6)	302 (27.0)			
	>0 - ≤200, n (%)	29 (21.6)	348 (31.1)			
	>200 - ≤400, n (%)	33 (24.6)	198 (17.7)			
	>400 - ≤600, n (%)	11 (8.2)	122 (10.9)			
	>600, n (%)	20 (14.9)	148 (13.2)			
A&E attendances	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.2717	13.4	0.9
	≥1, n (%)	0 (0.0)	10 (0.9)			
Inpatient admissions, definite	N (% non-missing)	134 (100.0)	1,118 (100.0)		0.0	0.0
Inpatient admissions, probable	N (% non-missing)	134 (100.0)	1,118 (100.0)		0.0	0.0
Outpatient visits	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.5829	4.8	0.0
	≥1, n (%)	7 (5.2)	47 (4.2)			
Moderate/severe exacerbations (COPD)	N (% non-missing)	134 (100.0)	1,118 (100.0)	0.7278	6.6	0.6
	0, n (%)	47 (35.1)	442 (39.5)			
	1, n (%)	39 (29.1)	307 (27.5)			
	2, n (%)	26 (19.4)	185 (16.5)			
	≥3, n (%)	22 (16.4)	184 (16.5)			
FEV_1	N (% non-missing)	112 (83.6)	926 (82.8)	0.6814	9.6	5.6
	Mean (SD)	1.8 (0.6)	1.9 (0.8)			
	Median (IQR)	1.7 (0.8)	1.8 (1.0)			
MRC score	N (% non-missing)	130 (97.0)	1,046 (93.6)	0.0769	15.6	4.4
	1, n (%)	21 (16.2)	181 (17.3)			
	2, n (%)	60 (46.2)	424 (40.5)			
	3, n (%)	40 (30.8)	278 (26.6)			
	4, n (%)	9 (6.9)	139 (13.3)			
	5, n (%)	0 (0.0)	24 (2.3)			
Gold severity	N (% non-missing)	121 (90.3)	966 (86.4)	0.8691	3.4	3.8
	Mild, n (%)	22 (18.2)	167 (17.3)			
	Moderate, n (%)	65 (53.7)	527 (54.6)			
	Severe, n (%)	29 (24.0)	216 (22.4)			
	Very Severe, n (%)	5 (4.1)	56 (5.8)			

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential; NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

8.2.1 Matching decision

In Table 8 the variables with relevant bias potential (≥2%) are presented for both cohorts, together with the standardised difference between the NCP and LCP arms. Variables considered important by an expert panel, but not reaching relevance in terms of bias potential, are also included in the table.

Table 8. Standardised mean differences and bias potential for high bias potential baseline variables, by disease group.

	Asthma		COPD	
Variable	SDD	RCC	SDD	RCC
Age*	6.0	1.3	7.9	1.3
Gender*	6.2	0.3	10.7	0.9
Smoking status			18.7	4.7
BMI (kg/m^2), category			4.3	2.9
Hypertension			9.8	2.0
Oral Candidiasis**	10.6	0.3	21.0	0.2
LAMA prescriptions			32.8	9.6
Methylxanthines prescriptions			13.8	3.0
LTRA prescriptions			14.8	2.2
ICS prescriptions (mono- and combi)	7.7	5.1	9.1	2.8
Gold severity***			3.4	3.8
SABA, average daily dose (salbutamol equivalent)	4.3	3.0	2.2	2.8
SABA inhaler prescriptions	15.5	3.7		
SABA inhalers	7.6	3.2	0.8	2.6

* Consensus addition; ** Side effect ***13.6-9.7% missing; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential.

8.2.2 Matching process

Test runs using all identified confounders from Table 8 resulted in low percentages of matched patients (<<50%). Therefore the decision was taken to use a combination of a limited set of the 5 most critical variables and a propensity score for the matching; see Table 9 for their callipers.

The propensity score was created separately for the asthma and COPD groups. Also, matching was done separately for the groups. The distribution of the propensity scores are shown in Appendix 13.5. The scores for the two arms had acceptable overlap.

In the asthma group 88% of the patients in the NCP cohort could be matched, while in the COPD group 79% were matched (Table 9).

Table 9. Matching variables and their callipers

Variable	Asthma Direct + PS	COPD Direct + PS
Age*	5	5
Gender*	0	0
Smoking status	0	0
BMI (kg/m^2), category	0	0
Oral Candidiasis	0	0
PS	0.25*SD	0.25*SD
Number matched	513	106
Percentage matched	88.1%	79.1%

SD= standard deviation; PS=propensity score

For the asthma and COPD groups separately, 20 matching runs were performed with different random patient order to select the one with an optimal combination of numbers matched, balance achieved and residual confounding. The results of these runs are in appendices 0 and 13.4.

Using the chosen patient order, a 3:1 LCP:NCP matching was performed.
Of the 619 matched patients in the NCP arm, 78% were matched to three patients in the LCP arm, 9% to 2 patients and for 13% of the patients in the NCP arm only a single match in the LCP arm could be found (Table 10).

Table 10. Results of 3:1 matching

Number of matches	NCP	LCP	Total
1	80	80	160
2	57	114	171
3	482	1,446	1,928
Total	619	1,640	2,259

NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

8.2.2.1 Power calculation

With 619 patients in the NCP arm and 1,640 patients in the LCP arm our study was able to detect a difference in percentage of adherent patients between the arms of 6.7% with 80% power, and of 7.7% with 90% power, with a 0.050 two-sided significance level.

8.2.3 Matched baseline data

In the combined groups, of all baseline covariates only the use of Methylxanthines was slightly imbalanced between the arms (Table 11), but this only resulted in 1.2% bias potential. The only variable with relevant bias potential was the number of antibiotics prescriptions with lower respiratory indication. The matched baseline characterisation for only the asthma group and the COPD group are in appendices 13.6 and 13.7.

Table 11. Baseline characterisation of the matched arms; Asthma and COPD combined

Variable		NCP	LCP	P	SDD	RCC
Index year	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.1756	5.9	0.3
	2012, n (%)	322 (52.0)	879 (53.6)			
	2013, n (%)	191 (30.9)	509 (31.0)			
	2014, n (%)	90 (14.5)	231 (14.1)			
	2015, n (%)	16 (2.6)	21 (1.3)			
Age (years)	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.3406	3.7	0.8
	Mean (SD)	44.4 (11.2)	44.0 (11.1)			
	Median (IQR)	47.0 (17.0)	46.0 (17.0)			
Gender	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.7068	1.8	0.0
	Male, n (%)	298 (48.1)	775 (47.3)			
Smoking status	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.6868	3.6	0.5
	Never, n (%)	275 (44.4)	762 (46.5)			
	Current, n (%)	184 (29.7)	469 (28.6)			
	Ex, n (%)	160 (25.8)	409 (24.9)			
BMI	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.3564	2.5	1.0
	<18.5, n (%)	11 (1.8)	15 (0.9)			
	18.5-<25, n (%)	206 (33.3)	557 (34.0)			
	25-<30, n (%)	186 (30.0)	478 (29.1)			
	>=30, n (%)	216 (34.9)	590 (36.0)			
Cardiovascular disease	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.7835	1.3	0.3
	Yes, n (%)	41 (6.6)	114 (7.0)			
Ischaemic heart disease	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8222	1.1	0.5
	Yes, n (%)	13 (2.1)	37 (2.3)			
Hypertension	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8174	1.1	1.0
	Yes, n (%)	80 (12.9)	218 (13.3)			
Cancer	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.0541	8.8	0.0
	Yes, n (%)	70 (11.3)	142 (8.7)			
Diabetes	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.2485	5.3	0.4
	Yes, n (%)	36 (5.8)	76 (4.6)			
Rhinitis	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.2924	4.9	0.1
	Yes, n (%)	191 (30.9)	469 (28.6)			
Active Rhinitis	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.3485	4.4	0.2
	Yes, n (%)	81 (13.1)	191 (11.6)			
Gastroesophageal reflux disease	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.2494	5.3	0.0
	Yes, n (%)	73 (11.8)	166 (10.1)			

Variable		NCP	LCP	P	SDD	RCC
Active Gastroesophageal reflux disease	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.6655	2.0	0.1
	Yes, n (%)	49 (7.9)	121 (7.4)			
Eczema	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.3108	4.8	0.2
	Yes, n (%)	170 (27.5)	486 (29.6)			
Active Eczema	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.5730	2.6	0.1
	Yes, n (%)	14 (2.3)	31 (1.9)			
Pneumonia	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.5898	2.6	0.1
	Yes, n (%)	24 (3.9)	72 (4.4)			
Oral Candidiasis	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.6407	2.1	0.3
	Yes, n (%)	7 (1.1)	15 (0.9)			
Beta Blockers	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8844	1.4	0.1
	Mean (SD)	0.1 (1.0)	0.2 (1.8)			
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
NSAIDs	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.7872	1.3	0.3
	≥1, n (%)	114 (18.4)	294 (17.9)			
Charlson Comorbidity Index	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.5538	3.1	0.4
	Mean (SD)	2.9 (2.4)	2.8 (2.3)			
	Median (IQR)	4.0 (4.0)	4.0 (4.0)			
LABA prescriptions, solo	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.9786	0.1	0.6
	≥1, n (%)	79 (12.8)	210 (12.8)			
SAMA prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8036	1.2	0.0
	≥1, n (%)	10 (1.6)	29 (1.8)			
LAMA prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.3227	4.6	1.1
	≥1, n (%)	55 (8.9)	125 (7.6)			
Methylxanthines prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.0458	10.8	1.2
	≥1, n (%)	1 (0.2)	16 (1.0)			
LTRA prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.6422	2.2	1.7
	≥1, n (%)	32 (5.2)	93 (5.7)			
Acute OCS prescriptions, sensitive	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.5907	4.5	1.4
	0, n (%)	466 (75.3)	1,260 (76.8)			
	1, n (%)	96 (15.5)	250 (15.2)			
	≥2, n (%)	57 (9.2)	130 (7.9)			
Acute OCS courses, probable	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.7269	3.6	0.7
	0, n (%)	422 (68.2)	1,141 (69.6)			
	1, n (%)	117 (18.9)	306 (18.7)			
	≥2, n (%)	80 (12.9)	193 (11.8)			

Variable		NCP	LCP	P	SDD	RCC
Acute OCS courses, sensitive	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.5225	4.8	1.0
	0, n (%)	466 (75.3)	1,260 (76.8)			
	1, n (%)	104 (16.8)	272 (16.6)			
	≥2, n (%)	49 (7.9)	108 (6.6)			
Maintenance OCS prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.9725	0.4	0.3
	0, n (%)	608 (98.2)	1,612 (98.3)			
	1, n (%)	1 (0.2)	2 (0.1)			
	≥2, n (%)	10 (1.6)	26 (1.6)			
All OCS prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8642	2.2	0.4
	0, n (%)	420 (67.9)	1,132 (69.0)			
	1, n (%)	102 (16.5)	259 (15.8)			
	≥2, n (%)	97 (15.7)	249 (15.2)			
Antibiotic prescriptions, with LR indication	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.4319	5.5	2.2
	0, n (%)	406 (65.6)	1,108 (67.6)			
	1, n (%)	119 (19.2)	317 (19.3)			
	≥2, n (%)	94 (15.2)	215 (13.1)			
Acute OCS prescriptions, probable	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.9125	3.1	0.7
	0, n (%)	422 (68.2)	1,141 (69.6)			
	1, n (%)	104 (16.8)	265 (16.2)			
	2, n (%)	51 (8.2)	133 (8.1)			
	≥3, n (%)	42 (6.8)	101 (6.2)			
SABA inhaler prescriptions	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8847	4.3	0.7
	0, n (%)	270 (43.6)	745 (45.4)			
	1, n (%)	76 (12.3)	208 (12.7)			
	2-4, n (%)	131 (21.2)	338 (20.6)			
	5-10, n (%)	92 (14.9)	220 (13.4)			
	11+, n (%)	50 (8.1)	129 (7.9)			
SABA inhalers	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.7429	5.8	0.8
	0, n (%)	270 (43.6)	745 (45.4)			
	1, n (%)	54 (8.7)	150 (9.1)			
	2-4, n (%)	118 (19.1)	321 (19.6)			
	5-10, n (%)	92 (14.9)	229 (14.0)			
	11+, n (%)	85 (13.7)	195 (11.9)			

Variable		NCP	LCP	P	SDD	RCC
ICS prescriptions (mono- and combi)	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8336	3.2	0.3
	0, n (%)	286 (46.2)	785 (47.9)			
	1, n (%)	61 (9.9)	156 (9.5)			
	2-4, n (%)	147 (23.7)	392 (23.9)			
	5-10, n (%)	100 (16.2)	235 (14.3)			
	11+, n (%)	25 (4.0)	72 (4.4)			
SABA, average daily dose (salbutamol equivalent)	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.5974	6.9	1.0
	0, n (%)	270 (43.6)	745 (45.4)			
	>0 - ≤200, n (%)	144 (23.3)	397 (24.2)			
	>200 - ≤400, n (%)	82 (13.2)	221 (13.5)			
	>400 - ≤600, n (%)	42 (6.8)	94 (5.7)			
	>600, n (%)	81 (13.1)	183 (11.2)			
A&E attendances	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.7443	1.5	0.0
	≥1, n (%)	2 (0.3)	4 (0.2)			
Inpatient admissions, definite	N (% non-missing)	619 (100.0)	1,640 (100.0)		0.0	0.0
Inpatient admissions, probable	N (% non-missing)	619 (100.0)	1,640 (100.0)		0.0	0.0
Outpatient visits	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8950	0.6	0.3
	≥1, n (%)	13 (2.1)	33 (2.0)			
Moderate/severe exacerbations (COPD)	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.6883	5.6	1.8
	0, n (%)	339 (54.8)	941 (57.4)			
	1, n (%)	147 (23.7)	376 (22.9)			
	2, n (%)	80 (12.9)	199 (12.1)			
	≥3, n (%)	53 (8.6)	124 (7.6)			
Severe exacerbations (asthma)	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8449	4.0	0.7
	0, n (%)	422 (68.2)	1,141 (69.6)			
	1, n (%)	117 (18.9)	306 (18.7)			
	2, n (%)	48 (7.8)	121 (7.4)			
	≥3, n (%)	32 (5.2)	72 (4.4)			
FEV_1	N (% non-missing)	205 (33.1)	530 (32.3)	0.9390	3.4	2.1
	Mean (SD)	2.4 (1.1)	2.4 (1.1)			
	Median (IQR)	2.2 (1.2)	2.3 (1.3)			

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential. LR=lower respiratory; NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

8.2.4 Bias potential in matched sample

After the matching process, variables that sustained a relevant level of residual confounding during a forward model selection are marked with an X (Table 12). These baseline characteristics were adjusted for in the final multivariate models.

Table 12. Post-matching residual confounding in outcomes models

		Outcomes						
		Asthma				COPD		
Variable	Adherence	RDC	SE	ARE	SAD	RDC	MSE	SAD
Eczema						X		
Cancer						X		
Active Gastroesophageal reflux disease						X		
Rhinitis						X		
ICS prescriptions (mono- and combi)							X	
Antibiotic prescriptions, LR	X	X		X				
Acute OCS courses, sensitive			X					
LTRA prescriptions			X	X				
Maintenance OCS prescriptions			X					
Acute OCS prescriptions, probable							X	
SABA, average daily dose (salbutamol equivalent)					X			X
SABA inhalers						X		
SABA inhaler prescriptions							X	
All OCS prescriptions						X		
Acute OCS courses, sensitive						X		
MRC score							X	
Gold severity							X	X

RDC: Risk Domain Control; SE: Severe exacerbations; ARE: Acute respiratory events; MSE: Moderate/severe exacerbations; SAD: SABA average daily dose; X: variable with ≥ 2% bias from forward selection

8.2.5 Outcomes

8.2.5.1 Descriptive results

The matched sample to be analysed contained 2,259 patients in total, and sample sizes by disease group and cohort can be seen in Table 13.

Table 13. Number of patients by cohort and disease group; matched patients

Group	NCP	LCP	Total
Asthma	512	1,378	1,890
COPD	107	262	369
Total	619	1,640	2,259

NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

The distribution of primary and secondary outcomes did not differ significantly by those in the LCP arm and those in the NCP arm; details are presented in Table 14.

Table 14. Descriptive statistics of outcomes by exposure group; matched patients

Variable		NCP	LCP	P
Disease group	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.4524
	COPD, n (%)	107 (17.3)	262 (16.0)	
Adherent	N (% non-missing)	619 (100.0)	1,640 (100.0)	0.8008
	Yes, n (%)	216 (34.9)	563 (34.3)	
Adherence, asthma	N (% non-missing)	512 (82.7)	1,378 (84.0)	0.9924
	Yes, n (%)	161 (31.4)	433 (31.4)	
Adherence, COPD	N (% non-missing)	107 (17.3)	262 (16.0)	0.7559
	Yes, n (%)	55 (51.4)	130 (49.6)	
Adherence, 9m persistence only	N (% non-missing)	481 (77.7)	1,315 (80.2)	0.4139
	Yes, n (%)	213 (44.3)	554 (42.1)	
Risk Domain Control, asthma	N (% non-missing)	512 (82.7)	1,378 (84.0)	0.5490
	Controlled, n (%)	325 (63.5)	854 (62.0)	
Severe exacerbations, asthma	N (% non-missing)	512 (82.7)	1,378 (84.0)	0.9496
	0, n (%)	389 (76.0)	1,053 (76.4)	
	1, n (%)	79 (15.4)	216 (15.7)	
	2, n (%)	27 (5.3)	70 (5.1)	
	≥3, n (%)	17 (3.3)	39 (2.8)	
Acute respiratory events, asthma	N (% non-missing)	512 (82.7)	1,378 (84.0)	0.8654
	0, n (%)	325 (63.5)	854 (62.0)	
	1, n (%)	121 (23.6)	341 (24.7)	
	2, n (%)	40 (7.8)	103 (7.5)	
	≥3, n (%)	26 (5.1)	80 (5.8)	

Variable		NCP	LCP	P
SABA, average daily dose (salbutamol equivalent), asthma	N (% non-missing)	512 (82.7)	1,378 (84.0)	0.7062
	0, n (%)	174 (34.0)	463 (33.6)	
	>0 - ≤200, n (%)	133 (26.0)	389 (28.2)	
	>200 - ≤400, n (%)	98 (19.1)	257 (18.7)	
	>400 - ≤600, n (%)	42 (8.2)	121 (8.8)	
	>600, n (%)	65 (12.7)	148 (10.7)	
Risk Domain Control, COPD	N (% non-missing)	107 (17.3)	262 (16.0)	0.7167
	Controlled, n (%)	50 (46.7)	117 (44.7)	
Moderate/severe exacerbations (COPD)	N (% non-missing)	107 (17.3)	262 (16.0)	0.3934
	0, n (%)	50 (46.7)	117 (44.7)	
	1, n (%)	26 (24.3)	62 (23.7)	
	2, n (%)	17 (15.9)	31 (11.8)	
	≥3, n (%)	14 (13.1)	52 (19.8)	
SABA, average daily dose (salbutamol equivalent), COPD	N (% non-missing)	107 (17.3)	262 (16.0)	0.1552
	0, n (%)	33 (30.8)	74 (28.2)	
	>0 - ≤200, n (%)	14 (13.1)	52 (19.8)	
	>200 - ≤400, n (%)	28 (26.2)	48 (18.3)	
	>400 - ≤600, n (%)	12 (11.2)	46 (17.6)	
	>600, n (%)	20 (18.7)	42 (16.0)	

P = P-value for the Pearson's chi-square test of independent categories; NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

The distribution of the Medication Possession Ratio over the study arms was very similar (Figure 2).

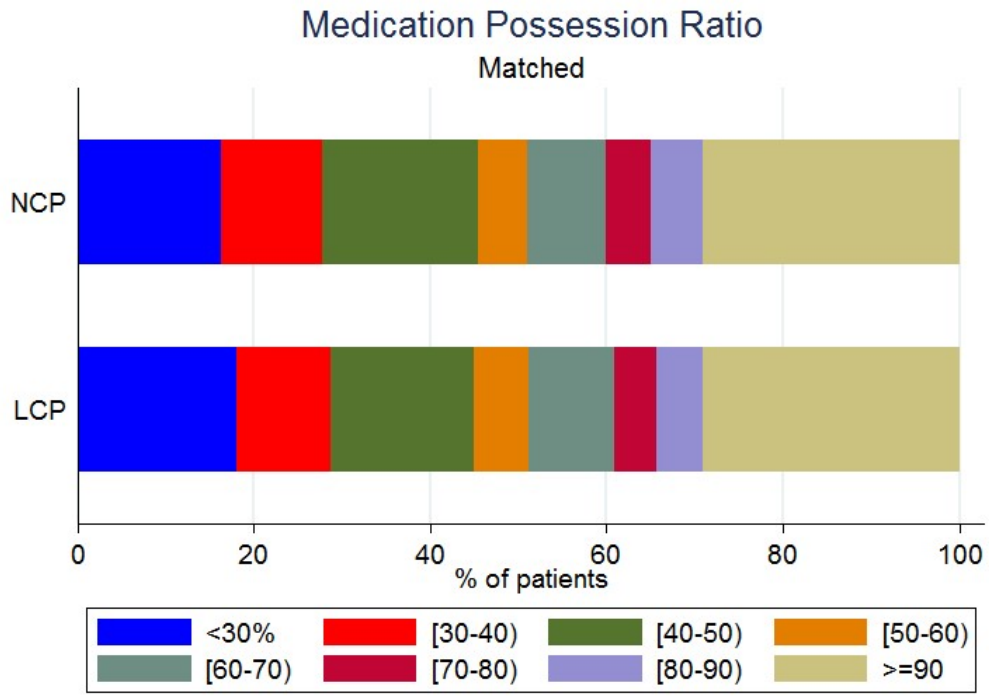

Figure 2. Adherence levels in matched patients from the NCP and LCP cohorts.

8.2.5.2 Matched analyses results

Adherence for the combined groups did not differ significantly between the study arms (OR 1.04, CI 0.85-1.27), Table 15. The wide confidence interval for this adjusted analysis results confirms what the visual comparison of unadjusted distribution of adherence categories (Figure 2) between the patients from the NCP and LCP cohorts indicated: no difference in adherence to Seretide between the cohorts. The results from the sensitivity analyses (Table 16) show that neither restricting the patient population to those without COPD nor restricting the population to patients who had a minimum persistence of 9 months changed the association between cohort membership and being adherent meaningfully.

Table 15. Model results

	Effect				Difference in outcome		
	OR/RR	95% CI		P		95% CI	
Adherence	1.04	0.85	1.27	0.704	1.0	-4.0	5.9
Asthma							
Risk-domain control	0.89	0.71	1.11	0.294	-2.7	-7.7	2.3
Number of severe exacerbations	1.01	0.85	1.21	0.907	0.01	-0.17	0.19
Number of acute respiratory events	1.10	0.96	1.27	0.163	0.10	-0.04	0.24
SABA average daily dose	1.05	0.86	1.27	0.655			
COPD							
Risk-domain control	0.89	0.53	1.48	0.641	-2.3	-11.5	7.0
Number of moderate/severe exacerbations	1.27	0.98	1.65	0.067	0.24	-0.17	0.50
SABA average daily dose	1.03	0.65	1.63	0.907			

Models adjusted for variables shown in Table 12. OR=odds ratio; RR=rate ratio

Table 16. Model results for the sensitivity analyses

	Effect				Difference in outcome		
	OR/RR	95% CI		P		95% CI	
Adherence, 9-month persistence	0.99	0.79	1.24	0.929	-0.3	-5.9	5.4
Adherence, asthma only	1.06	0.85	1.33	0.604	1.5	-4.1	7.0
Adherence, asthma only 9-month persistence	1.09	0.84	1.41	0.523	2.1	-4.3	8.4

Models adjusted for categories of number of antibiotic prescriptions. OR=odds ratio; RR=rate ratio

Of the secondary outcomes in the asthma group, none showed a significant difference between the arms.

In the COPD group there were no secondary outcomes achieving statistical significance at the 5% level. The number of moderate/severe exacerbations showed a Rate Ratio of 1.27 ([CI] 0.98, 1.65), and its absolute adjusted effect was estimated to be 0.24 exacerbations ([CI] -0.17, 0.50).

9.0 Discussion and overall conclusions

This study did not detect a significant difference in adherence of initiated Seretide maintenance therapy nor in clinical outcomes between patients with COPD and/or asthma who either likely pay a prescription charge or receive medication free of charge (Scotland).

The adherence levels we observed, about 35% in the asthma group and 50% in the COPD group, are within the range reported in other studies.[7,30,31,32,33]

Several studies were able to link better adherence to maintenance therapy in asthma and COPD to improved short and long-term outcomes.[34,7] Therefore, it is not surprising that, since in our study we did not detect an effect of co-payment on the level of adherence, we did not find an association between co-payment and disease outcome indicators either.

Two meta-analyses on the relationship between co-payment and adherence showed an inverse relationship.[34,12] The latter meta-analysis[12] estimated an overall 11% increase in odds of non-adherence in co-payment versus non co-payment, but the studies they used for their meta-analysis were mainly with cardiometabolic medication groups. The first meta-analysis[34] reported on asthma and COPD studies separately, showing that in 6 of the 9 included studies there was a significant inverse relationship reported.

A strong point of this study is that we used data from an unselected population of patients with asthma and/or COPD. Thanks to the high granularity of the medical record based data we were able to handle confounding by measured aspects of demography, comorbidity, disease severity and medication use through a powerful approach of direct matching combined with a propensity score.

For the same reason we think the results of this study to be generalisable to similar health systems beyond England and Scotland. However, medication-taking behaviour can be affected by many factors[10,35] that play a role at different levels. Therefore, comparing adherence levels between regions can be of limited value if the cultural, social, economic or healthcare characteristics differ too much.

10.0 Limitations

The data used here were collected for routine GP care purposes not for research, therefore, we relied on what was registered.

Medication adherence was assessed using refill patterns over a fixed one-year period. This approach does not distinguish between patients being non-persistent and patients that do refill their medication but are non-adherent. Since these aspects of medication-taking are the result of different processes,[36] assessing persistence and taking adherence separately could have provided more insights into the effect of co-payment on medication-taking behaviour. However, our sensitivity analysis restricting the population to patients with at least 9 months of persistent use did show similar results to those of the

full population.

The primary outcome was the binary presentation of adherence, taking a cut-off level of the Medication Possession Ration of 80%. Dichotomisation of the outcome could have resulted in loss of information. However, knowing that the distribution of MPR categories over the study arms were very similar, it is unlikely that a categorical adherence outcome measure would have resulted in a different conclusion on the effect of co-payment on maintenance medication adherence.

There are other possible confounders that we were not able to take into account, such as cultural attitude towards medication use[37] and socioeconomic level.

The exposure of interest could have suffered some misclassification, since we could not capture all conditions (such as war pension exemptions) patients in England may have, allowing them to be exempt from the co-payment.

11.0 Advisory group

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12.0 Research team

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Project research lead: Jaco Voorham (jaco@opri.sg)

Senior statistician: Liz Gardener (liz@crs-ltd.org)

Project lead statistician: Jaco Voorham (jaco@opri.sg)

Senior data analyst: Derek Skinner (derek@optimumpatientcare.org)

13.0 Appendices

13.1 Definitions

13.1.1 Asthma severe exacerbation

Definition based on the ATS/ERS Position Statement – sensitive definition

An exacerbation is defined as an occurrence of the following:

- Asthma-related:
  a. Hospital admissions OR
  b. A&E attendance; OR
- An acute course of oral steroids with lower respiratory consultation.

13.1.2 COPD Moderate/Severe Exacerbation

Defined as an occurrence of (sensitive definition):

- COPD-related: Unscheduled hospital admission / A&E attendance; OR
- An acute course of oral steroids with lower respiratory consultation; OR
- Antibiotics prescribed with lower respiratory consultation.

13.1.3 Acute respiratory event

Defined as an occurrence of the following:

- Asthma-related:
  - Hospital admissions OR
  - A&E attendance; OR
- An acute course of oral corticosteroids; OR
- Antibiotics prescribed with lower respiratory consultation

13.1.4 Lower Respiratory Consultation

Consists of the following:

- Lower Respiratory Read codes (including Asthma, COPD and LRTI Read codes);
- Asthma/COPD review codes excl. any monitoring letter codes;
- Lung function and/or asthma monitoring

13.1.5 Antibiotics prescribed with a lower respiratory consultation

Identified by Read codes for any of the following:

- Lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes)
- Asthma/COPD review codes excluding any monitoring letter codes
- Lung function and/or asthma monitoring codes
- Any additional respiratory examinations, referrals, chest x-rays, or events.

13.1.6 Unscheduled hospital admission / emergency department attendance

Identified by Read codes for any of the following:

- Definite asthma or COPD emergency attendance or definite asthma or COPD hospital admission Generic hospitalisation code which has been recorded on the same day as a lower respiratory consultation (13.1.4) (excluding those where the lower respiratory code was for a lung function test only).

13.1.7 Risk-domain asthma control

Asthma treatment success is defined as:

- Controlled: No acute respiratory events (13.1.3)
- Uncontrolled: all others.

13.1.8 Risk-domain COPD control

COPD treatment success is defined as:

- Controlled: No exacerbations of COPD (13.1.2)
- Uncontrolled: all others.

13.1.9 Inpatient admissions

Definite	Inpatient admission for Asthma/COPD or lower respiratory code or generic inpatient code on same day as respiratory consultation
Probable	Inpatient admission for Asthma/COPD or lower respiratory code or generic inpatient code within 7 days of respiratory consultation

13.1.11 Outpatient visits

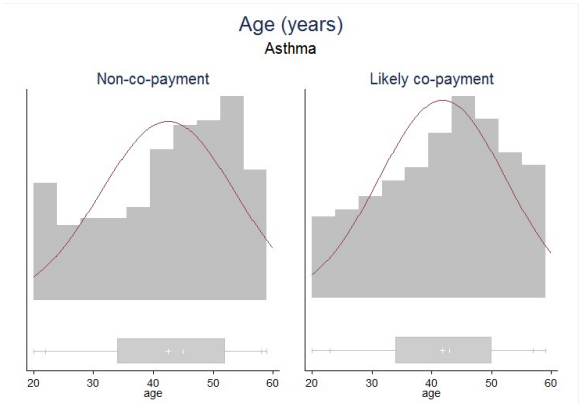
Outpatient visits for Asthma or lower respiratory code or generic outpatient code on same day as respiratory consultation

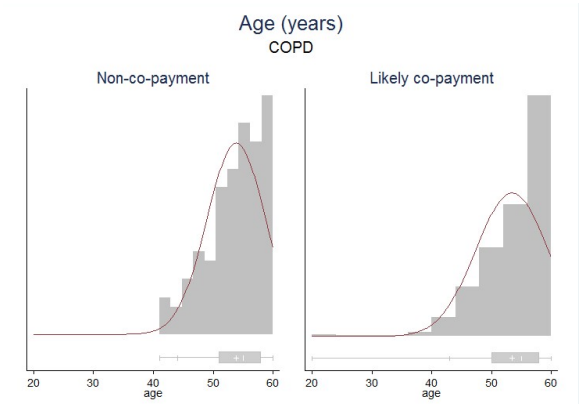
13.1.12 Oral corticosteroids

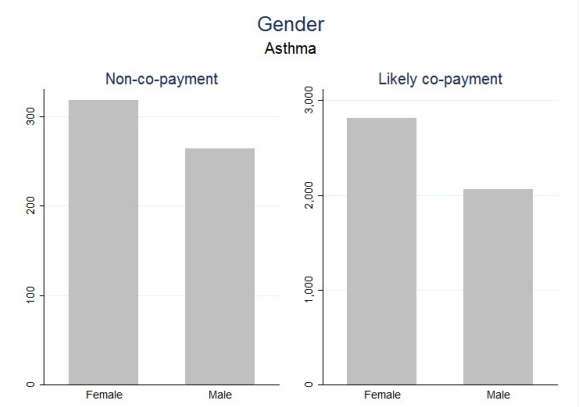
Acute	
Probable	Dosing instructions are for tapered or short course OR
	Daily dosage is greater than 10mg OR
	Strength of drug is greater than 10mg if daily dosage is unavailable OR
	Lower respiratory tract infection on same day
	Not maintainance and 4 or less prescriptions in 12 months
Sensitive	Same as for Probable, but on the same date as lower respiratory events
Maintenance	
Probable	Daily dosage is lesss than or equal to 10mg OR
	Strength of drug is less than or equal to 2.5mg if daily dosage is unavailable OR
	Not acute and 5 or more prescriptions in 12 months
Sensitive	Same as for Probable, except when on the same date as lower respiratory events

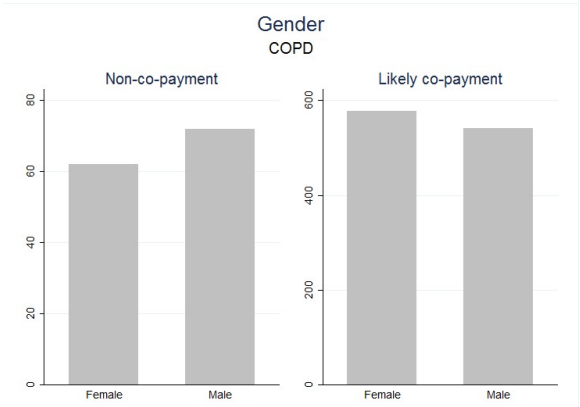
Prescriptions are counted as *courses* in case they are >14 days apart.

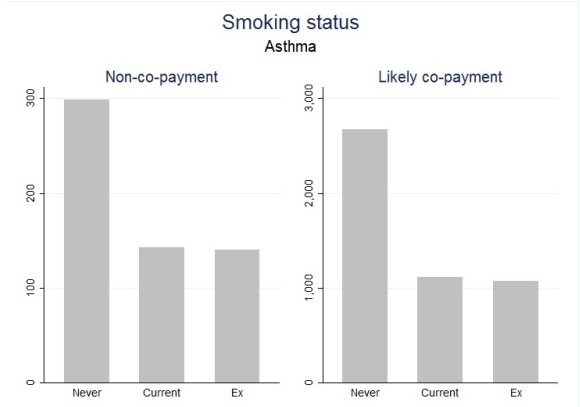
13.2 Distribution of baseline variables

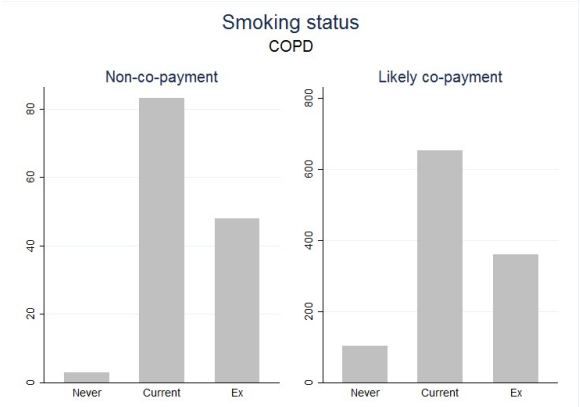


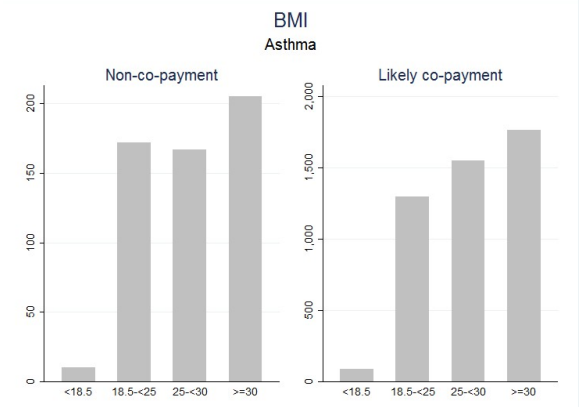


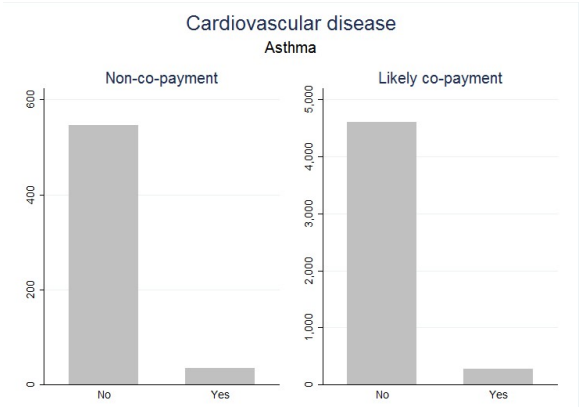








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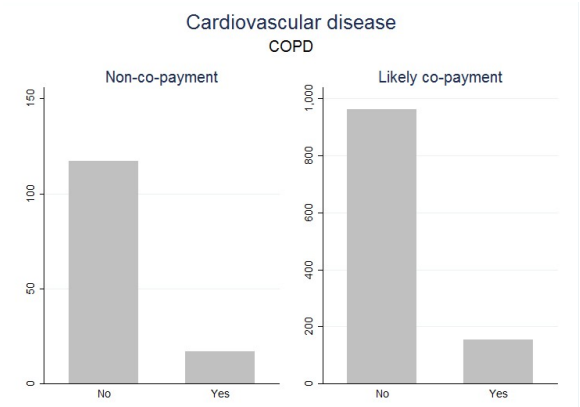
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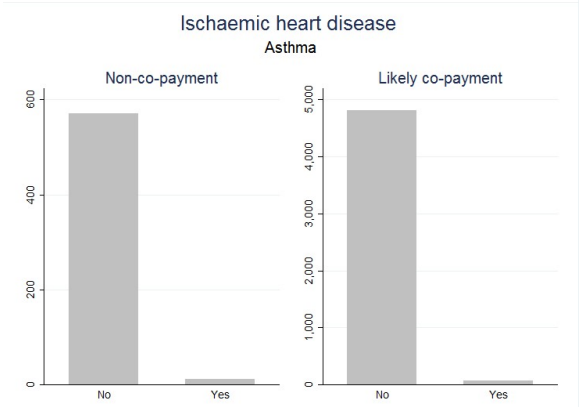
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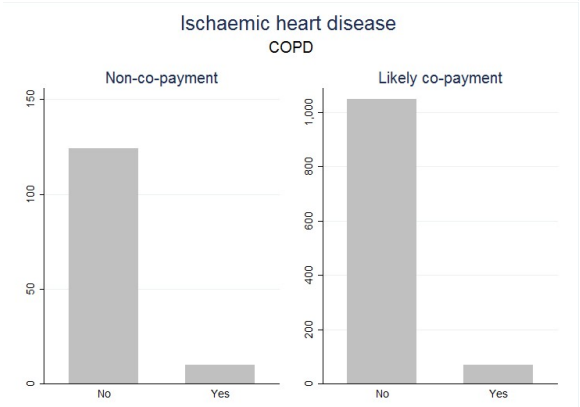
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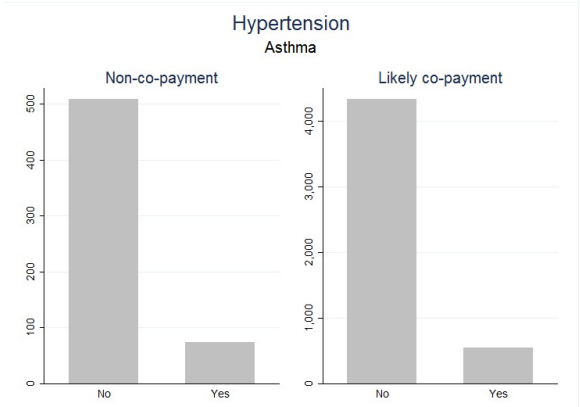
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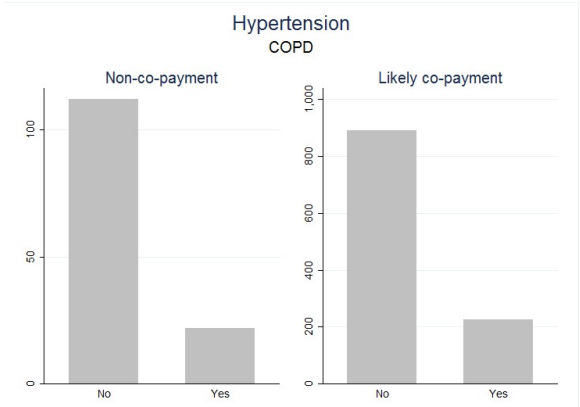
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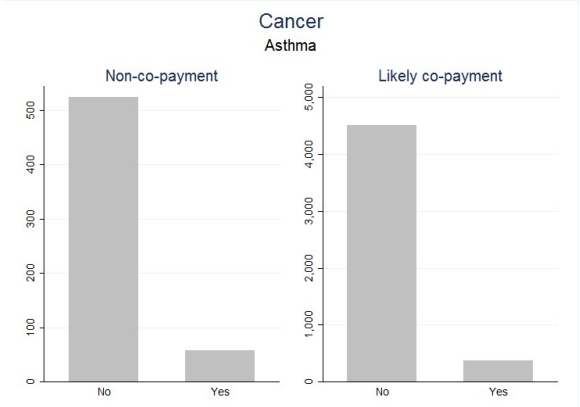
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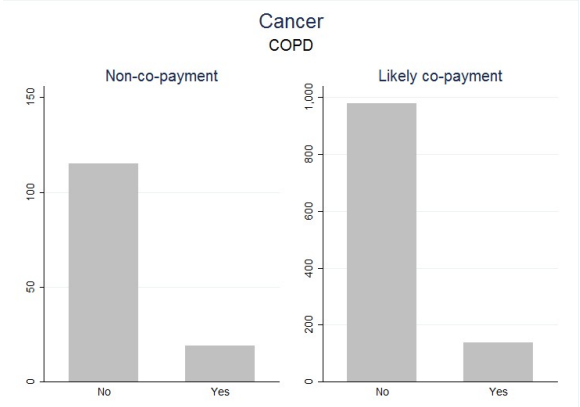
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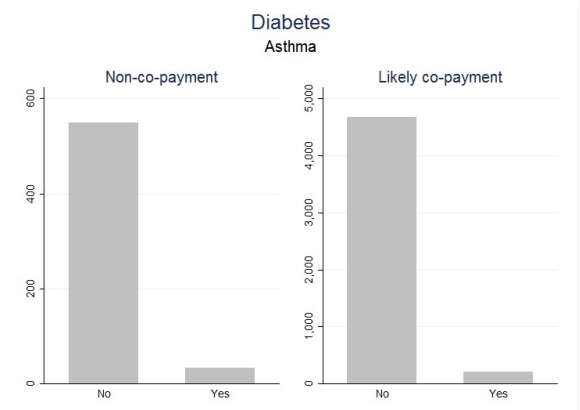
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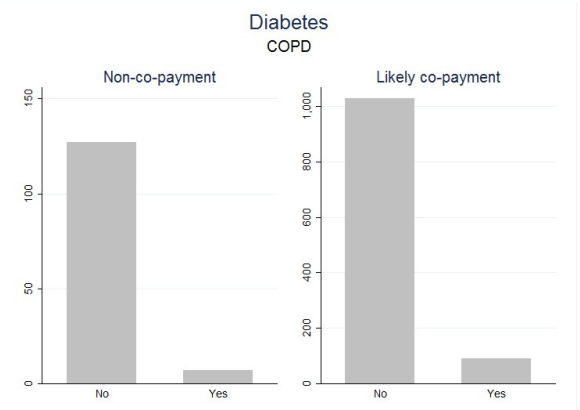
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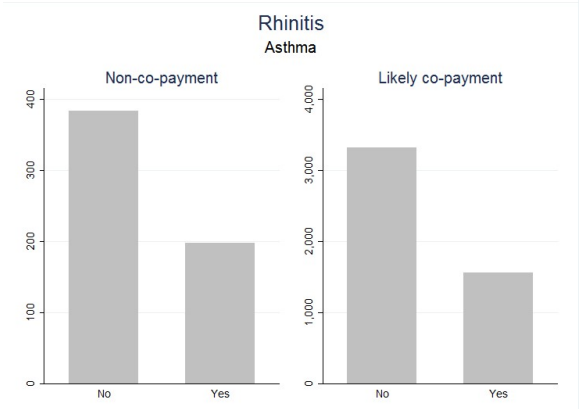
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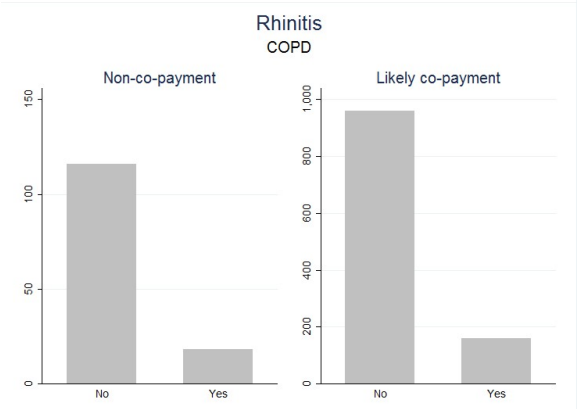
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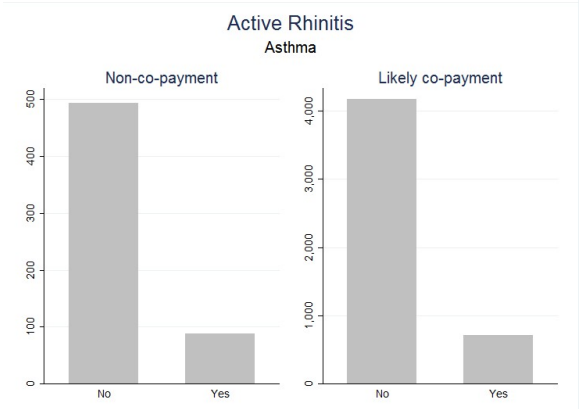
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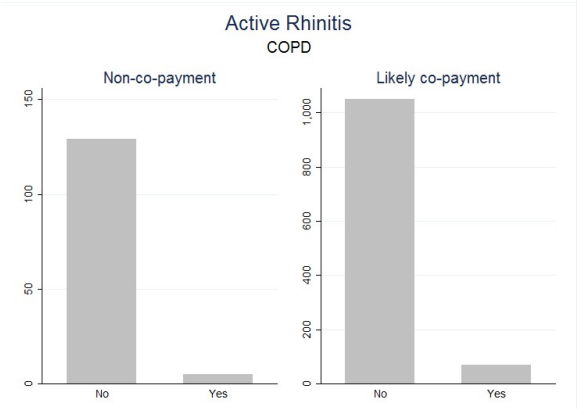
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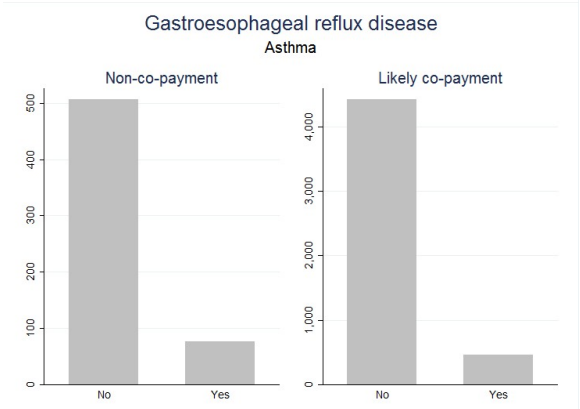
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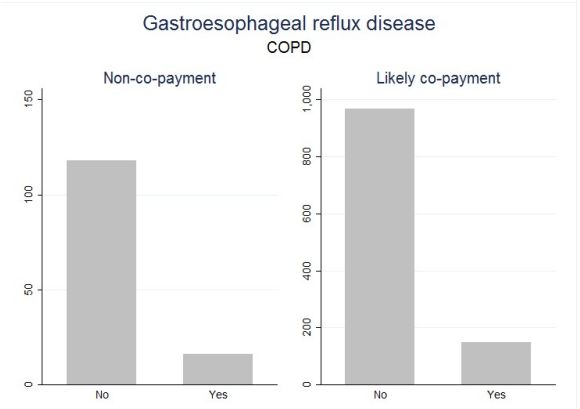
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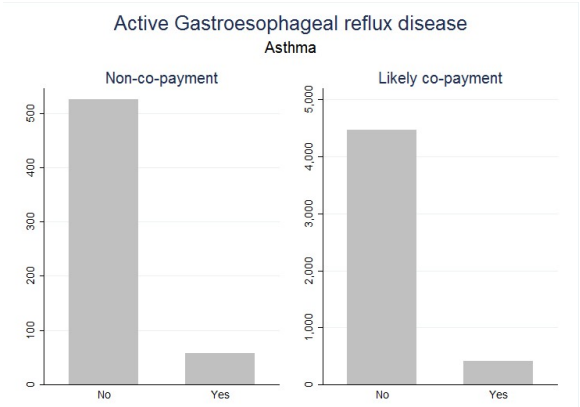
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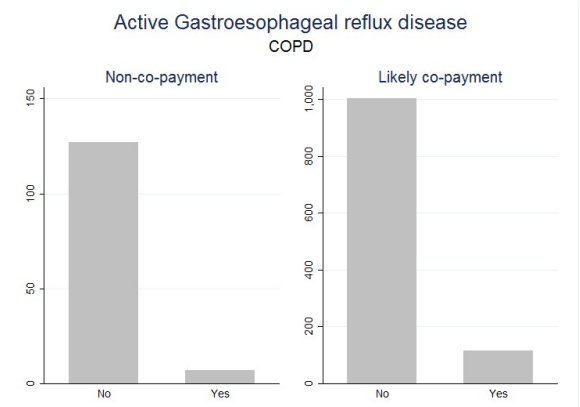
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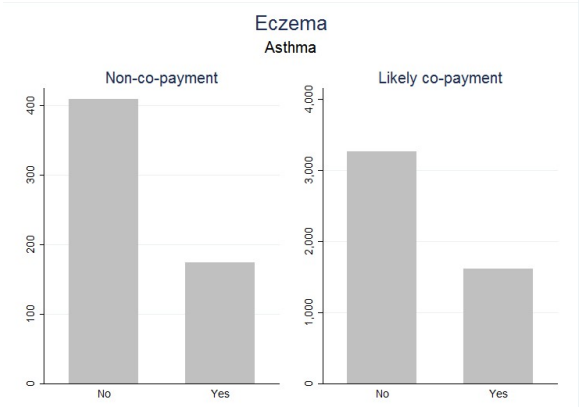
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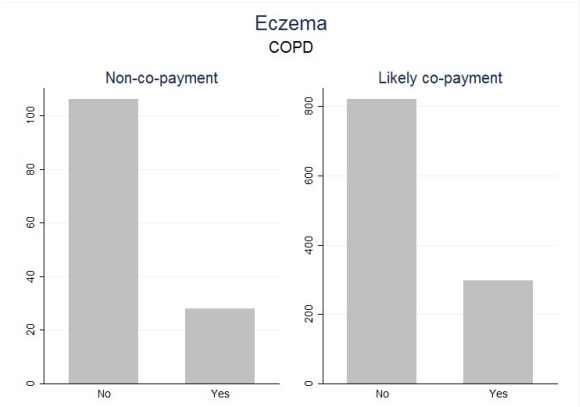
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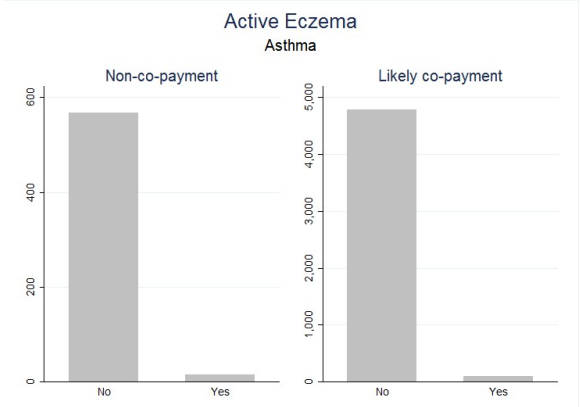
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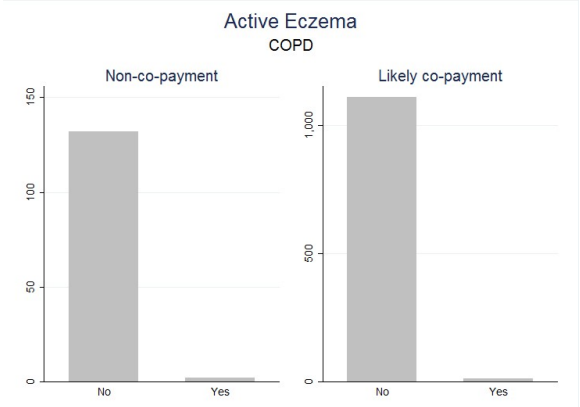
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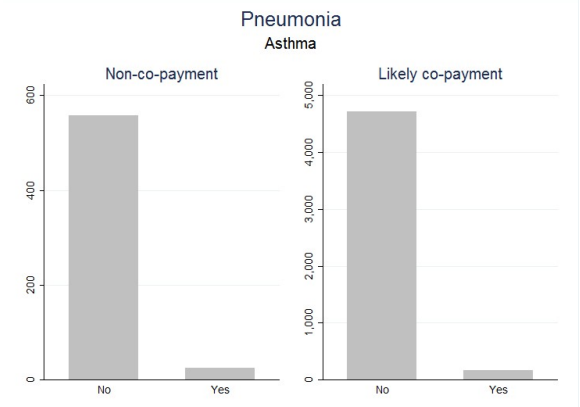
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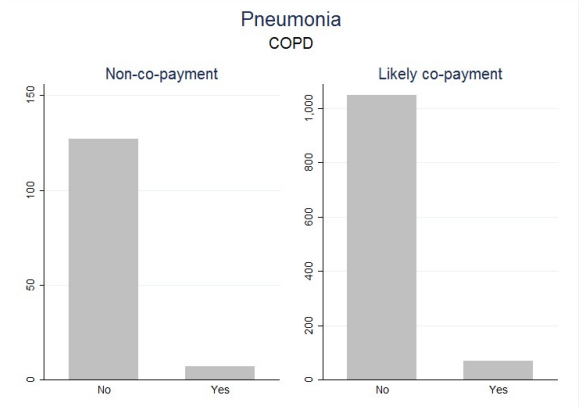
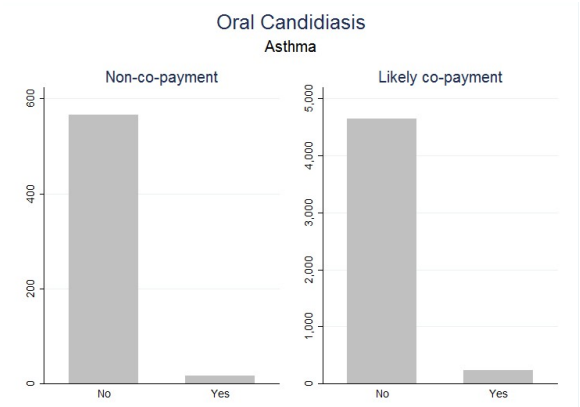
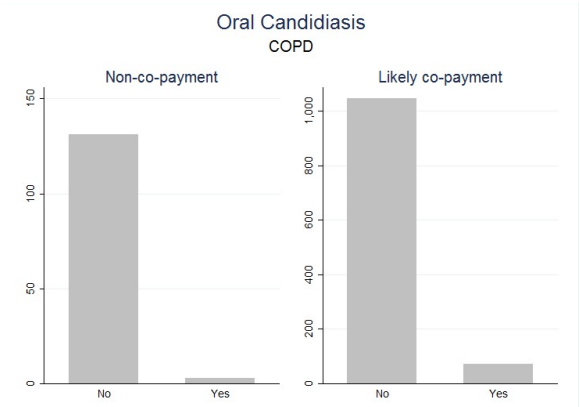
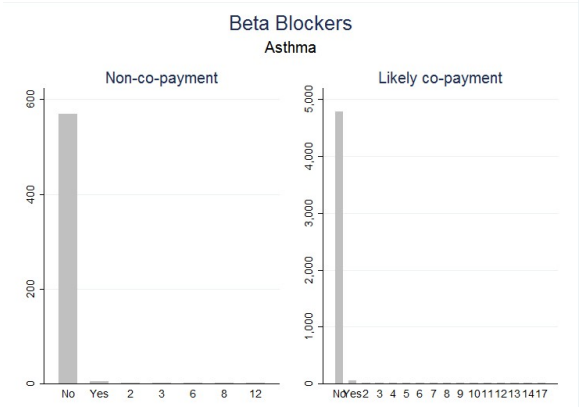
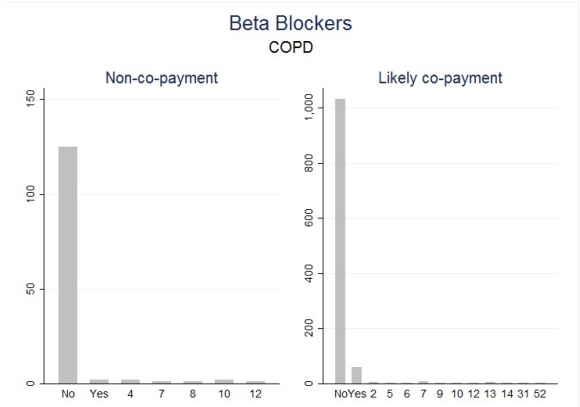
Yes

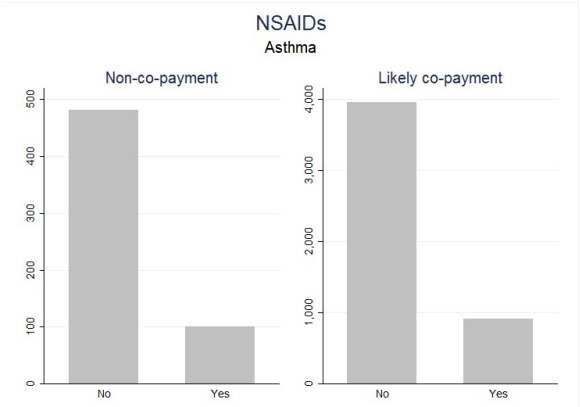

Pneumonia
COPD
Non-co-payment
Likely co-payment
No
Yes

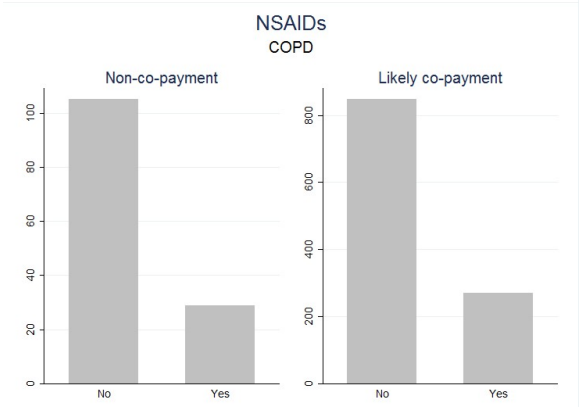

Oral Candidiasis
Asthma
Non-co-payment
Likely co-payment
No
Yes

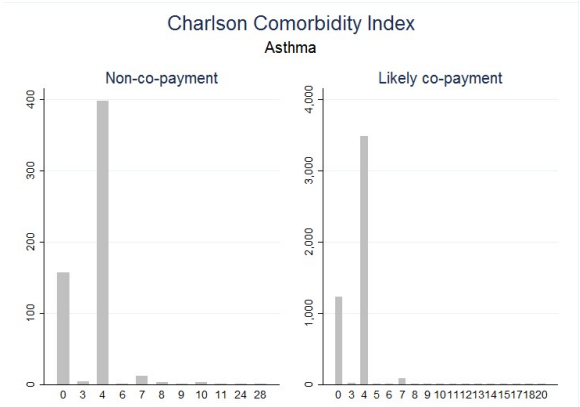

Oral Candidiasis
COPD
Non-co-payment
Likely co-payment
No
Yes

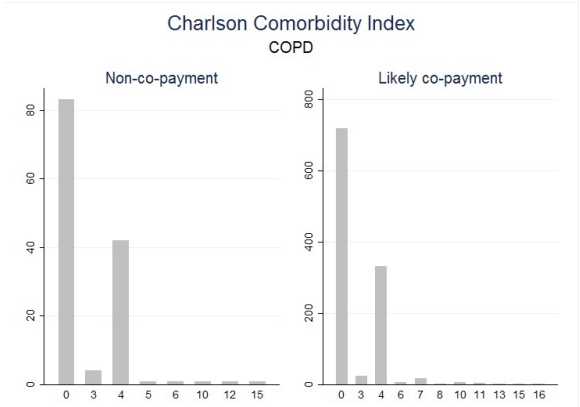

Beta Blockers
Asthma
Non-co-payment
Likely co-payment

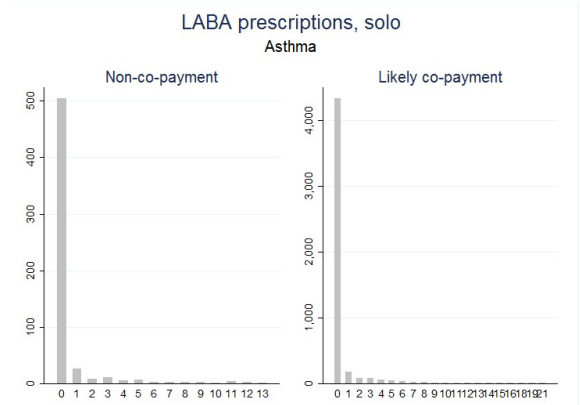

Beta Blockers
COPD
Non-co-payment
Likely co-payment

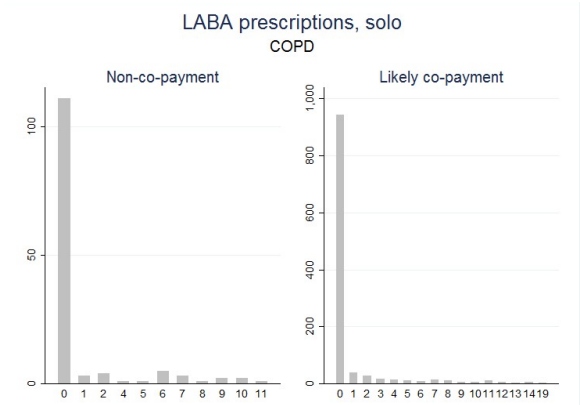

NSAIDs
Asthma
Non-co-payment
Likely co-payment
No
Yes

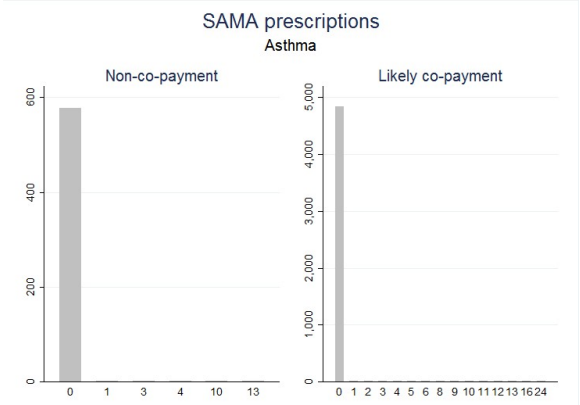

NSAIDs
COPD
Non-co-payment
Likely co-payment
No
Yes

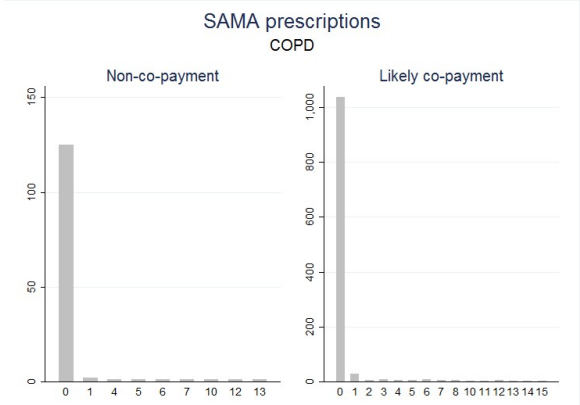

Charlson Comorbidity Index
Asthma
Non-co-payment
Likely co-payment

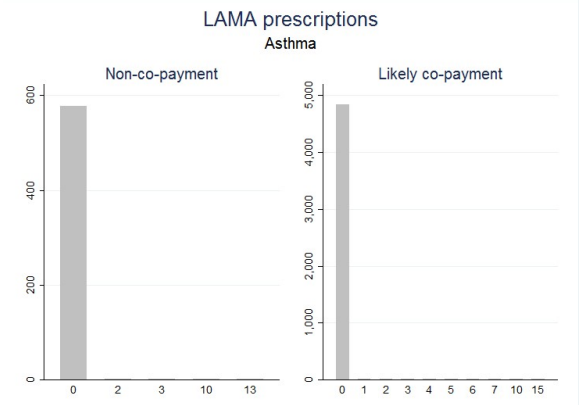

Charlson Comorbidity Index
COPD
Non-co-payment
Likely co-payment

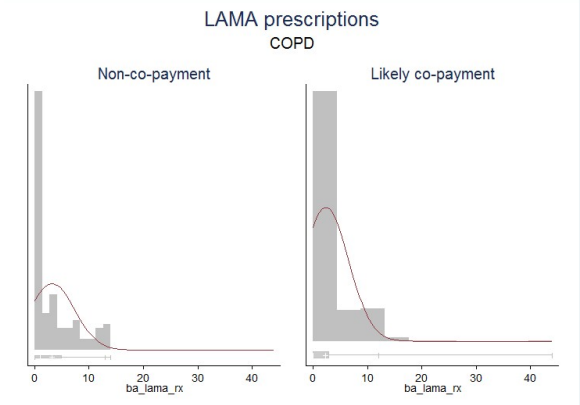

LABA prescriptions, solo
Asthma
Non-co-payment
Likely co-payment

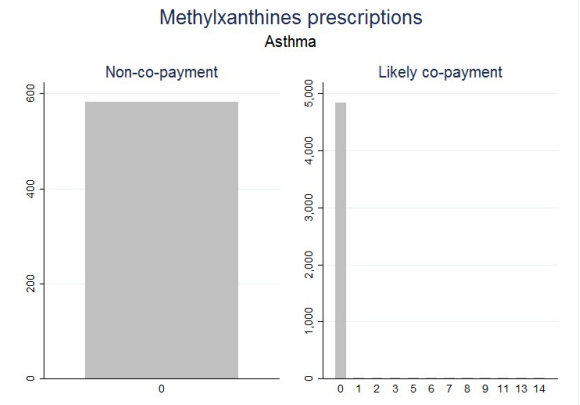

LABA prescriptions, solo
COPD
Non-co-payment
Likely co-payment

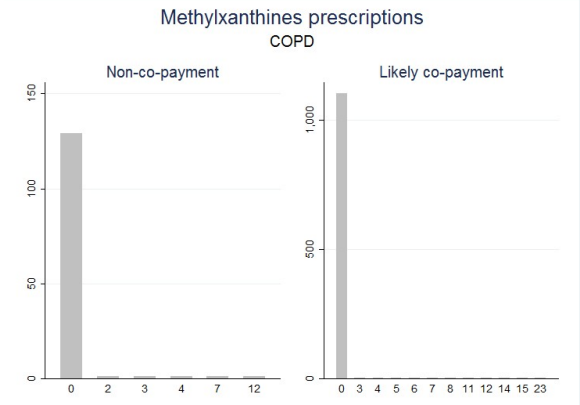

SAMA prescriptions
Asthma
Non-co-payment
Likely co-payment

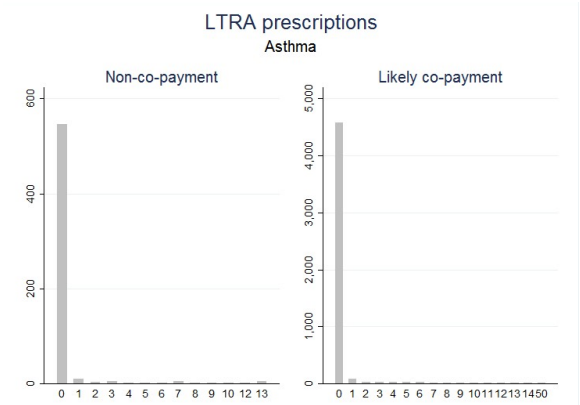

SAMA prescriptions
COPD
Non-co-payment
Likely co-payment

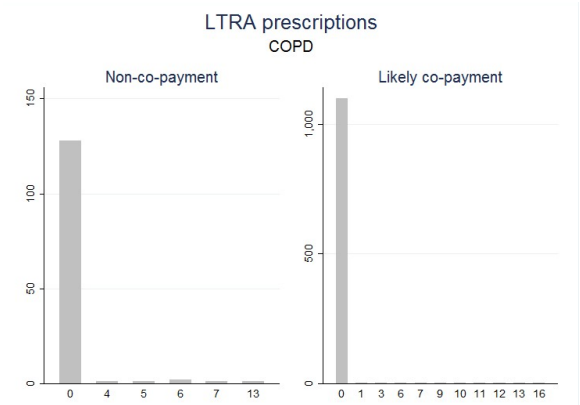

LAMA prescriptions
Asthma
Non-co-payment
Likely co-payment

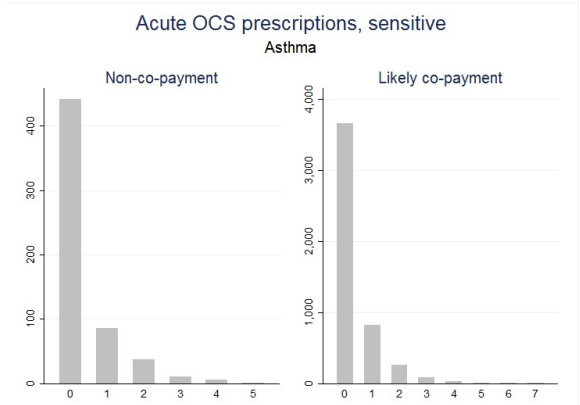

LAMA prescriptions
COPD
Non-co-payment
Likely co-payment
ba_lama_rx
ba_lama_rx

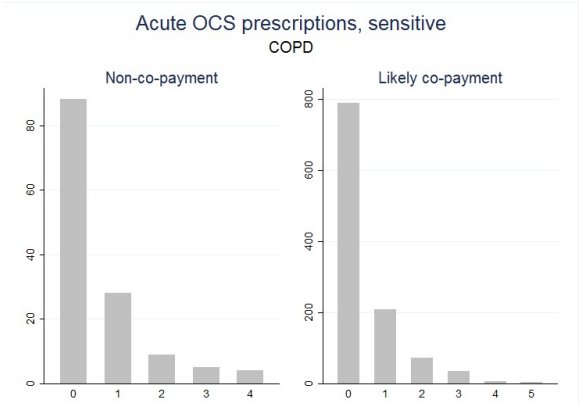

Methylxanthines prescriptions
Asthma
Non-co-payment
Likely co-payment

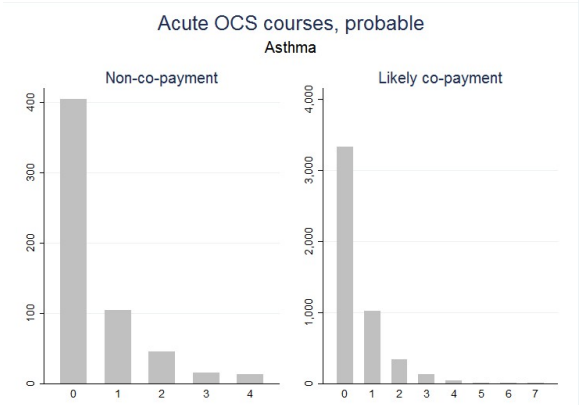

Methylxanthines prescriptions
COPD
Non-co-payment
Likely co-payment

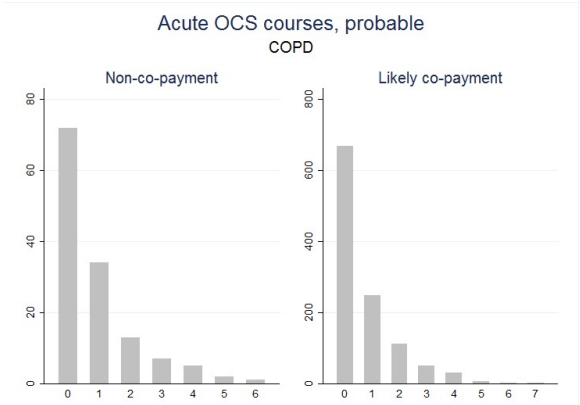

LTRA prescriptions
Asthma
Non-co-payment
Likely co-payment

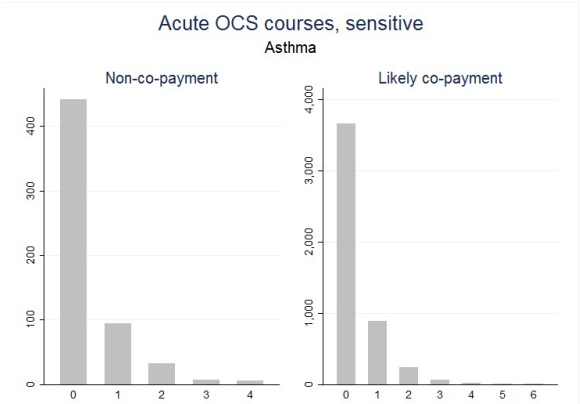

LTRA prescriptions
COPD
Non-co-payment
Likely co-payment

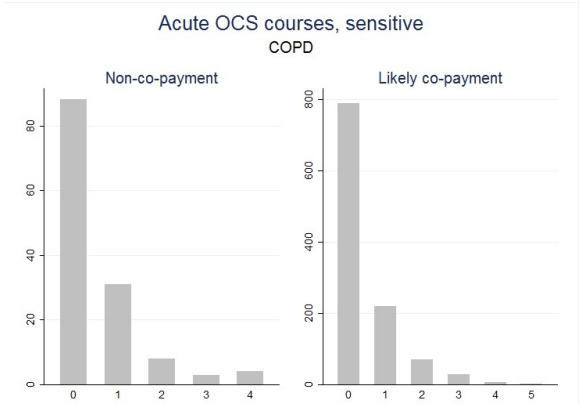

Acute OCS prescriptions, sensitive
Asthma
Non-co-payment
Likely co-payment

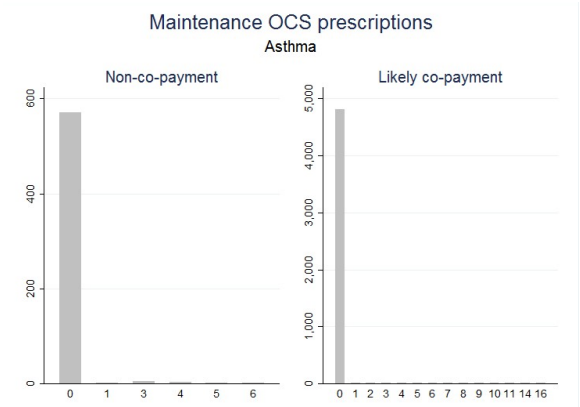

Acute OCS prescriptions, sensitive
COPD
Non-co-payment
Likely co-payment

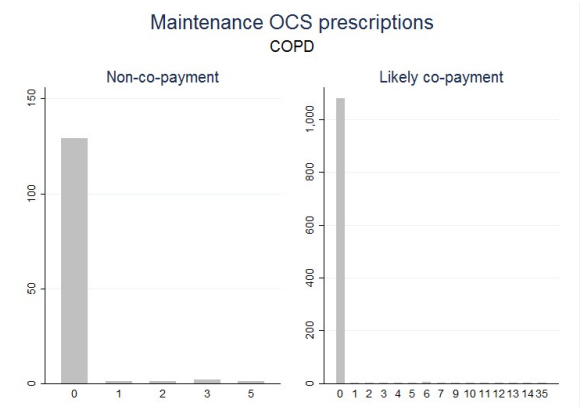

Acute OCS courses, probable
Asthma
Non-co-payment
Likely co-payment

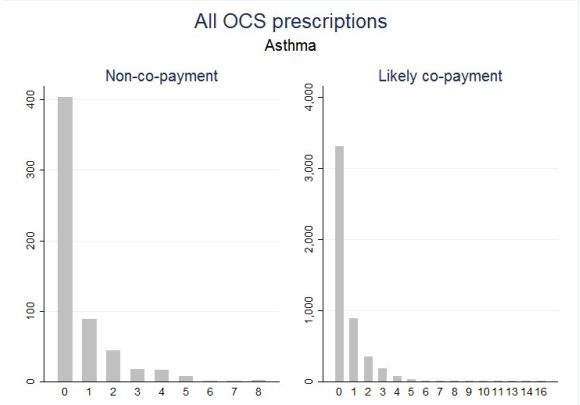

Acute OCS courses, probable
COPD
Non-co-payment
Likely co-payment

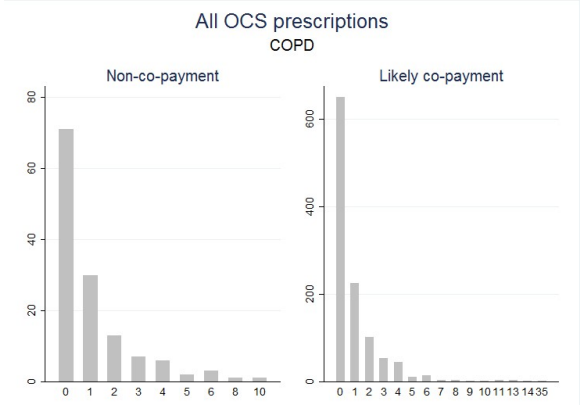

Acute OCS courses, sensitive
Asthma
Non-co-payment
Likely co-payment

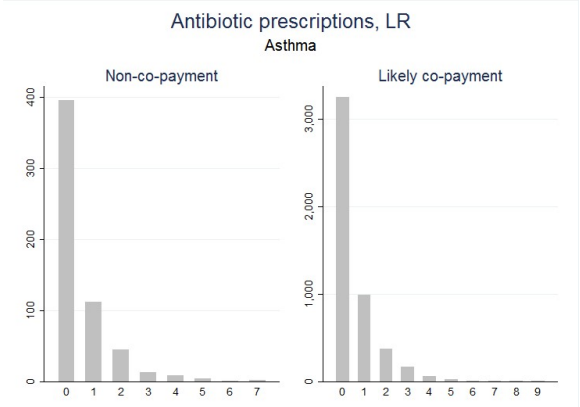

Acute OCS courses, sensitive
COPD
Non-co-payment
Likely co-payment

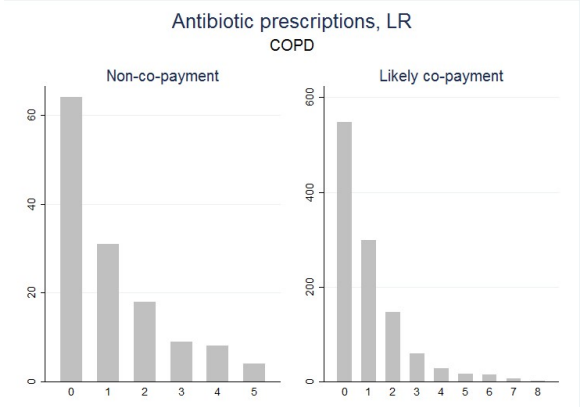

Maintenance OCS prescriptions
Asthma
Non-co-payment
Likely co-payment

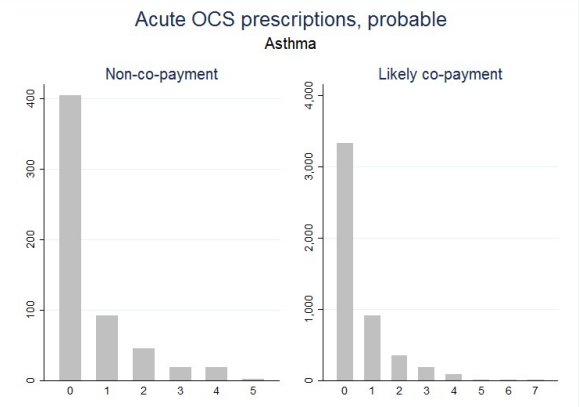

Maintenance OCS prescriptions
COPD
Non-co-payment
Likely co-payment

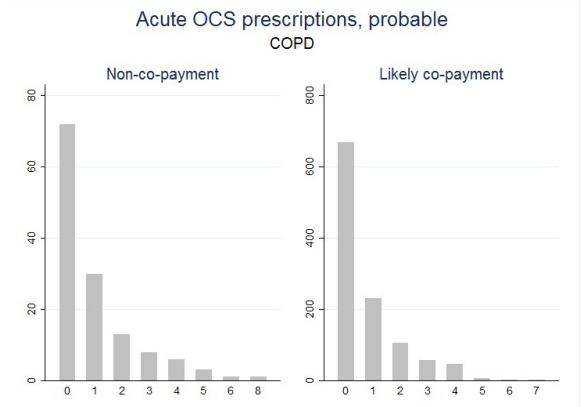

All OCS prescriptions
Asthma
Non-co-payment
Likely co-payment

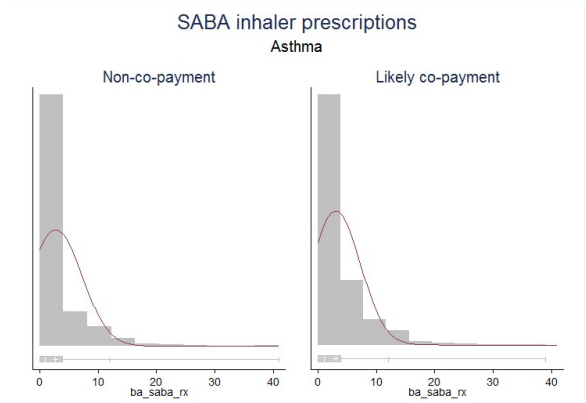

All OCS prescriptions
COPD
Non-co-payment
Likely co-payment

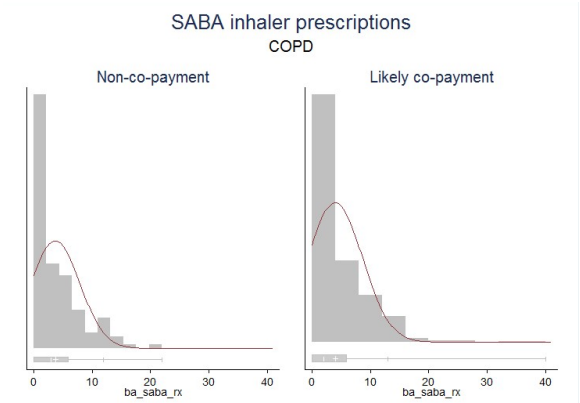

Antibiotic prescriptions, LR
Asthma
Non-co-payment
Likely co-payment

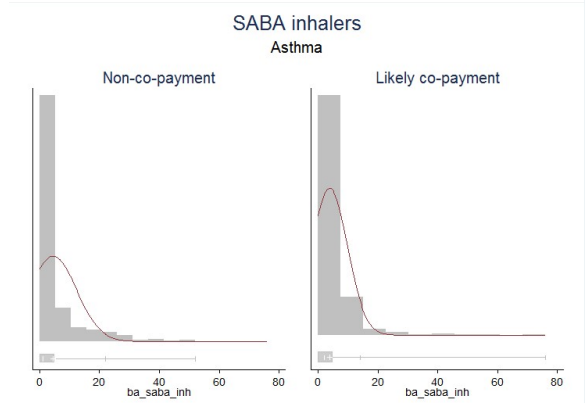

Antibiotic prescriptions, LR
COPD
Non-co-payment
Likely co-payment

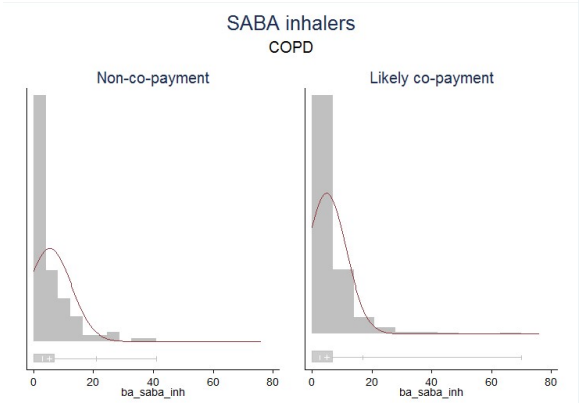

Acute OCS prescriptions, probable
Asthma
Non-co-payment
Likely co-payment

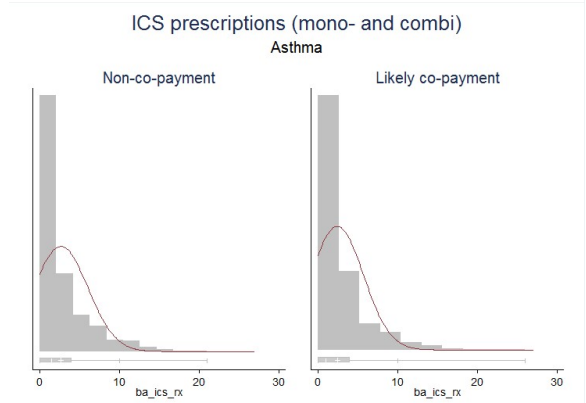

Acute OCS prescriptions, probable
COPD
Non-co-payment
Likely co-payment

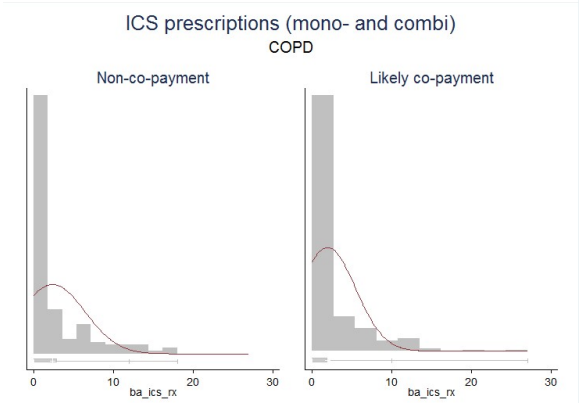

SABA inhaler prescriptions
Asthma
Non-co-payment
Likely co-payment
0 10 20 30 40
ba_saba_rx

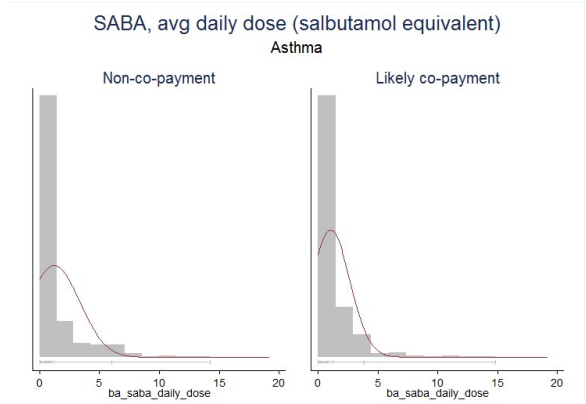

SABA inhaler prescriptions
COPD
Non-co-payment
Likely co-payment
0 10 20 30 40
ba_saba_rx

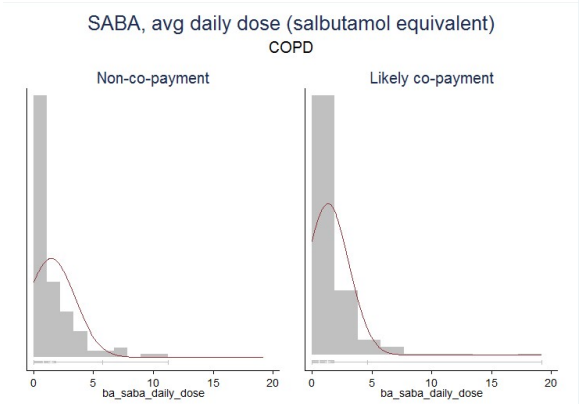

SABA inhalers
Asthma
Non-co-payment
Likely co-payment
0 20 40 60 80
ba_saba_inh

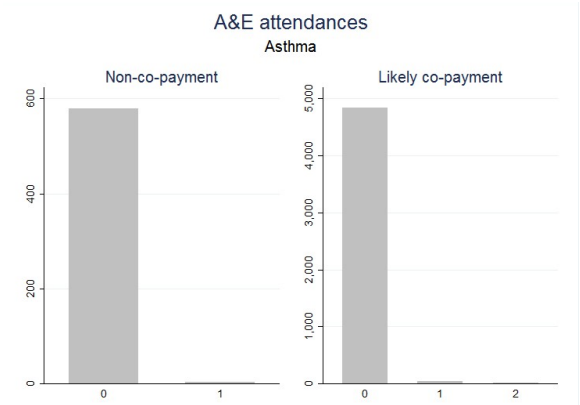

SABA inhalers
COPD
Non-co-payment
Likely co-payment
0 20 40 60 80
ba_saba_inh

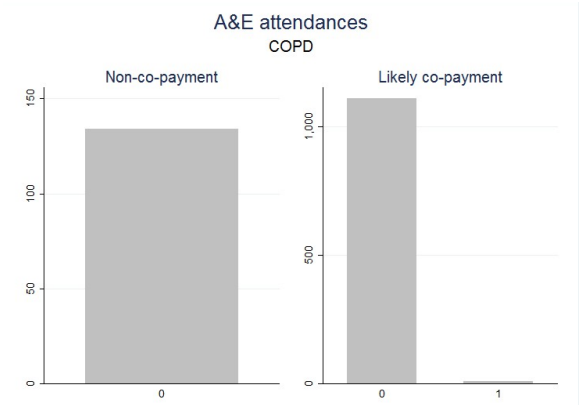

ICS prescriptions (mono- and combi)
Asthma
Non-co-payment
Likely co-payment
0 10 20 30
ba_ics_rx


ICS prescriptions (mono- and combi)
COPD
Non-co-payment
Likely co-payment
0 10 20 30
ba_ics_rx


SABA, avg daily dose (salbutamol equivalent)
Asthma
Non-co-payment
Likely co-payment
0 5 10 15 20
ba_saba_daily_dose

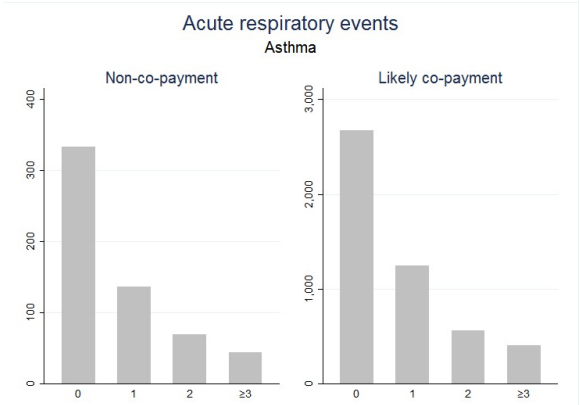

SABA, avg daily dose (salbutamol equivalent)
COPD
Non-co-payment
Likely co-payment
0 5 10 15 20
ba_saba_daily_dose

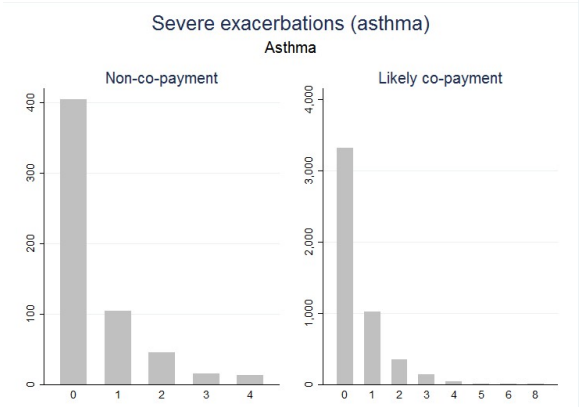

A&E attendances
Asthma
Non-co-payment
Likely co-payment

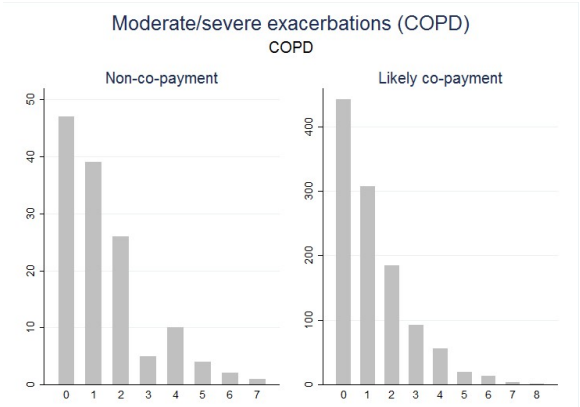

A&E attendances
COPD
Non-co-payment
Likely co-payment

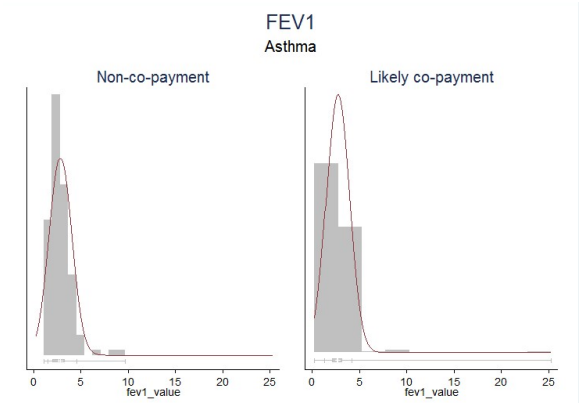

Outpatient visits
Asthma
Non-co-payment
Likely co-payment

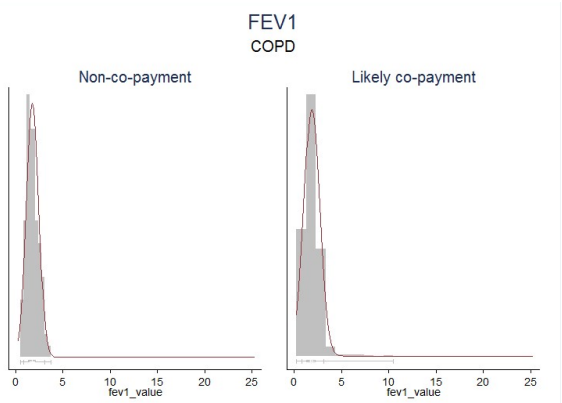

Outpatient visits
COPD
Non-co-payment
Likely co-payment

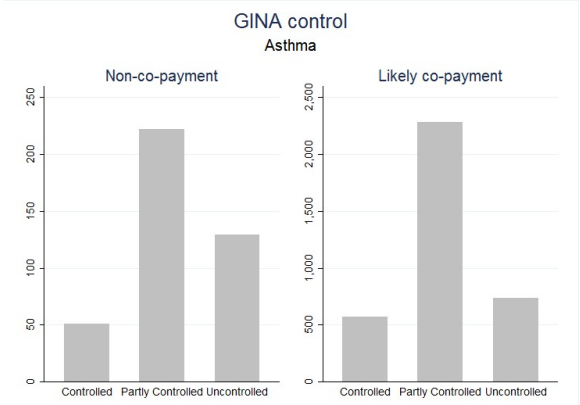

Acute respiratory events
Asthma
Non-co-payment
Likely co-payment


Severe exacerbations (asthma)
Asthma
Non-co-payment
Likely co-payment

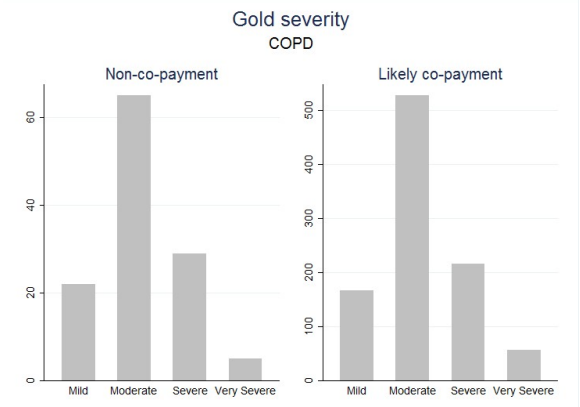

Moderate/severe exacerbations (COPD)
COPD
Non-co-payment
Likely co-payment


FEV1
Asthma
Non-co-payment
Likely co-payment
0 5 10 15 20 25
fev1_value


FEV1
COPD
Non-co-payment
Likely co-payment
0 5 10 15 20 25
fev1_value


GINA control
Asthma
Non-co-payment
Likely co-payment
0 50 100 150 200 250
0 500 1,000 1,500 2,000 2,500
Controlled
Partly Controlled
Uncontrolled


MRC score
COPD
Non-co-payment
Likely co-payment
0 20 40 60
0 100 200 300 400
1 2 3 4
1 2 3 4 5


Gold severity
COPD
Non-co-payment
Likely co-payment
0 20 40 60
0 100 200 300 400 500
Mild
Moderate
Severe
Very Severe

13.3 Matching Test Runs - Asthma

	Matched		SDD		RCC	
Seq	N	%	<10%	<5%	<1%	<0.5%
1	512	88.0	100.0	81.8	84.8	75.8
2	510	87.6	100.0	81.8	90.9	75.8
3	510	87.6	97.0	81.8	81.8	69.7
4	511	87.8	97.0	72.7	90.9	66.7
5	511	87.8	100.0	78.8	84.8	72.7
6	510	87.6	100.0	75.8	78.8	72.7
7	510	87.6	100.0	75.8	87.9	81.8
8	510	87.6	97.0	78.8	87.9	72.7
9	510	87.6	97.0	69.7	78.8	60.6
10	511	87.8	97.0	57.6	78.8	60.6
11	512	88.0	100.0	78.8	90.9	63.6
12	510	87.6	97.0	63.6	72.7	66.7
13	511	87.8	100.0	75.8	81.8	63.6
14	511	87.8	97.0	75.8	84.8	66.7
15	510	87.6	97.0	72.7	87.9	72.7
16	510	87.6	100.0	78.8	78.8	69.7
17	512	88.0	100.0	75.8	87.9	75.8
18	510	87.6	97.0	63.6	75.8	54.5
19	511	87.8	97.0	69.7	78.8	51.5
20	510	87.6	97.0	78.8	81.8	75.8

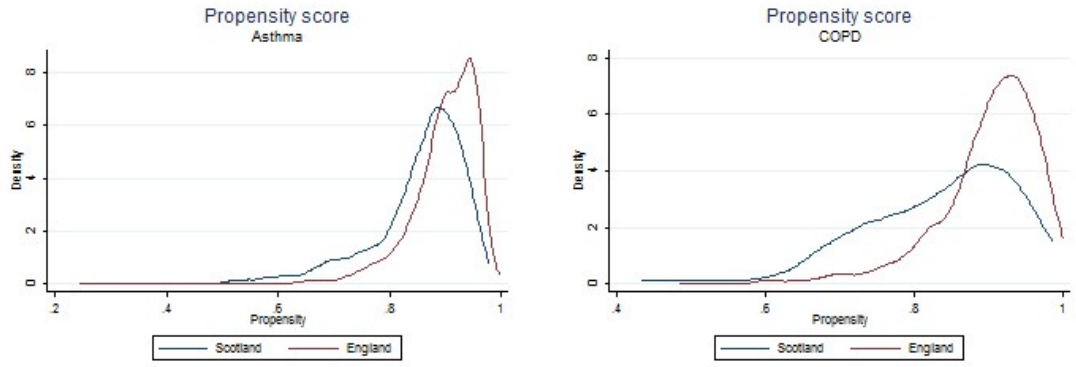
Calliper = 0.0077; LCP: 10,265, NCP: 1,462. Seq = Run number; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential. Red row is the selected run.

13.4 Matching Test Runs - COPD

	Matched		SDD		RCC	
Seq	N	%	<10%	<5%	<1%	<0.5%
1	106	79.1	87.9	63.6	66.7	57.6
2	106	79.1	81.8	54.5	75.8	48.5
3	106	79.1	75.8	63.6	66.7	39.4
4	104	77.6	78.8	63.6	75.8	51.5
5	107	79.9	84.8	54.5	75.8	51.5
6	107	79.9	75.8	60.6	72.7	51.5
7	106	79.1	69.7	48.5	60.6	45.5
8	105	78.4	78.8	51.5	63.6	42.4
9	105	78.4	84.8	63.6	66.7	57.6
10	106	79.1	72.7	54.5	66.7	42.4
11	107	79.9	75.8	39.4	75.8	48.5
12	106	79.1	66.7	51.5	57.6	42.4
13	105	78.4	78.8	54.5	66.7	48.5
14	106	79.1	81.8	57.6	63.6	45.5
15	106	79.1	72.7	48.5	60.6	48.5
16	106	79.1	69.7	51.5	60.6	45.5
17	107	79.9	81.8	57.6	63.6	51.5
18	107	79.9	84.8	72.7	63.6	51.5
19	106	79.1	78.8	54.5	60.6	51.5
20	104	77.6	75.8	48.5	66.7	42.4

Calliper = 0.0126; LCP: 1,506, NCP: 200. Seq = Run number; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential. Red row is the selected run.

13.5 Propensity score distributions



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13.6 Baseline characterisation of the matched - Asthma

Table 3. Baseline characterisation of the matched – Asthma only

Variable		NCP	LCP	P	SDD	Bias
Index year	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.3517	4.4	0.4
	2012, n (%)	269 (52.5)	745 (54.1)			
	2013, n (%)	162 (31.6)	427 (31.0)			
	2014, n (%)	70 (13.7)	191 (13.9)			
	2015, n (%)	11 (2.1)	15 (1.1)			
Age (years)	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.6152	2.2	0.4
	Mean (SD)	42.4 (11.2)	42.1 (11.0)			
	Median (IQR)	44.0 (18.5)	44.0 (18.0)			
Gender	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8263	1.1	0.0
	Male, n (%)	234 (45.7)	622 (45.1)			
Smoking status	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8358	2.8	0.0
	Never, n (%)	273 (53.3)	756 (54.9)			
	Current, n (%)	119 (23.2)	309 (22.4)			
	Ex, n (%)	120 (23.4)	313 (22.7)			
BMI	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8221	1.2	0.0
	<18.5, n (%)	5 (1.0)	8 (0.6)			
	18.5-<25, n (%)	179 (35.0)	486 (35.3)			
	25-<30, n (%)	146 (28.5)	387 (28.1)			
	>=30, n (%)	182 (35.5)	497 (36.1)			
Cardiovascular disease	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9645	0.2	0.2
	Yes, n (%)	30 (5.9)	80 (5.8)			
Ischaemic heart disease	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8712	0.8	0.5
	Yes, n (%)	8 (1.6)	23 (1.7)			
Hypertension	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9716	0.2	0.6
	Yes, n (%)	61 (11.9)	165 (12.0)			
Cancer	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.0476	9.9	0.1
	Yes, n (%)	54 (10.5)	106 (7.7)			
Diabetes	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.0688	9.0	0.3
	Yes, n (%)	30 (5.9)	54 (3.9)			
Rhinitis	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.2718	5.7	0.1
	Yes, n (%)	176 (34.4)	437 (31.7)			
Active Rhinitis	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.2652	5.7	0.2
	Yes, n (%)	77 (15.0)	180 (13.1)			

Variable		NCP	LCP	P	SDD	Bias
Gastroesophageal reflux disease	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.2512	5.8	0.0
	Yes, n (%)	61 (11.9)	139 (10.1)			
Active Gastroesophageal reflux disease	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.3587	4.7	0.1
	Yes, n (%)	44 (8.6)	101 (7.3)			
Eczema	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.2437	6.1	0.2
	Yes, n (%)	147 (28.7)	434 (31.5)			
Active Eczema	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.3753	4.4	0.1
	Yes, n (%)	13 (2.5)	26 (1.9)			
Pneumonia	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9901	0.1	0.2
	Yes, n (%)	20 (3.9)	54 (3.9)			
Oral Candidiasis	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.5493	3.0	0.0
	Yes, n (%)	6 (1.2)	12 (0.9)			
Beta Blockers	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.6333	1.9	0.2
	Mean (SD)	0.1 (0.8)	0.1 (1.0)			
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
NSAIDs	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.7410	1.7	0.1
	≥1, n (%)	91 (17.8)	236 (17.1)			
Charlson Comorbidity Index	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.4663	3.7	1.1
	Mean (SD)	3.1 (2.3)	3.0 (2.2)			
	Median (IQR)	4.0 (4.0)	4.0 (4.0)			
LABA prescriptions, solo	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9126	0.6	1.1
	≥1, n (%)	63 (12.3)	167 (12.1)			
SAMA prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.7400	1.8	0.1
	≥1, n (%)	4 (0.8)	13 (0.9)			
LAMA prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9891	0.1	0.1
	≥1, n (%)	3 (0.6)	8 (0.6)			
Methylxanthines prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.0274	13.8	0.8
	≥1, n (%)	0 (0.0)	13 (0.9)			
LTRA prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.5945	2.8	2.4
	≥1, n (%)	30 (5.9)	90 (6.5)			
Phosphodiesterase-4 inhibitor prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)		0.0	0.0
Acute OCS prescriptions, sensitive	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8514	2.9	1.1
	0, n (%)	393 (76.8)	1,073 (77.9)			
	1, n (%)	75 (14.6)	196 (14.2)			
	≥2, n (%)	44 (8.6)	109 (7.9)			
Acute OCS courses, probable	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9326	1.8	0.6
	0, n (%)	363 (70.9)	989 (71.8)			
	1, n (%)	92 (18.0)	240 (17.4)			
	≥2, n (%)	57 (11.1)	149 (10.8)			

Variable		NCP	LCP	P	SDD	Bias
Acute OCS courses, sensitive	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8318	3.1	0.7
	0, n (%)	393 (76.8)	1,073 (77.9)			
	1, n (%)	82 (16.0)	215 (15.6)			
	≥2, n (%)	37 (7.2)	90 (6.5)			
Maintenance OCS prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9655	0.7	0.1
	0, n (%)	504 (98.4)	1,358 (98.5)			
	1, n (%)	1 (0.2)	2 (0.1)			
	≥2, n (%)	7 (1.4)	18 (1.3)			
All OCS prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8994	1.0	0.5
	0, n (%)	362 (70.7)	985 (71.5)			
	1, n (%)	79 (15.4)	201 (14.6)			
	≥2, n (%)	71 (13.9)	192 (13.9)			
Antibiotic prescriptions, LR	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.6265	4.8	2.2
	0, n (%)	353 (68.9)	975 (70.8)			
	1, n (%)	94 (18.4)	249 (18.1)			
	≥2, n (%)	65 (12.7)	154 (11.2)			
Acute OCS prescriptions, probable	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9610	1.5	0.9
	0, n (%)	363 (70.9)	989 (71.8)			
	1, n (%)	81 (15.8)	207 (15.0)			
	2, n (%)	40 (7.8)	111 (8.1)			
	≥3, n (%)	28 (5.5)	71 (5.2)			
SABA inhaler prescriptions	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.7070	5.4	1.4
	0, n (%)	235 (45.9)	665 (48.3)			
	1, n (%)	65 (12.7)	178 (12.9)			
	2-4, n (%)	106 (20.7)	281 (20.4)			
	5-10, n (%)	67 (13.1)	149 (10.8)			
	11+, n (%)	39 (7.6)	105 (7.6)			
SABA inhalers	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.5667	7.4	1.9
	0, n (%)	235 (45.9)	665 (48.3)			
	1, n (%)	44 (8.6)	125 (9.1)			
	2-4, n (%)	95 (18.6)	269 (19.5)			
	5-10, n (%)	72 (14.1)	166 (12.0)			
	11+, n (%)	66 (12.9)	153 (11.1)			
ICS prescriptions (mono- and combi)	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.5847	4.6	1.8
	0, n (%)	215 (42.0)	623 (45.2)			
	1, n (%)	55 (10.7)	133 (9.7)			
	2-4, n (%)	139 (27.1)	362 (26.3)			
	5-10, n (%)	84 (16.4)	199 (14.4)			
	11+, n (%)	19 (3.7)	61 (4.4)			

Variable		NCP	LCP	P	SDD	Bias
SABA, average daily dose (salbutamol equivalent)	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.5820	7.7	2.1
	0, n (%)	235 (45.9)	665 (48.3)			
	>0 - ≤200, n (%)	118 (23.0)	331 (24.0)			
	>200 - ≤400, n (%)	63 (12.3)	166 (12.0)			
	>400 - ≤600, n (%)	32 (6.3)	68 (4.9)			
	>600, n (%)	64 (12.5)	148 (10.7)			
A&E attendances	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.5154	3.1	0.1
	≥1, n (%)	2 (0.4)	3 (0.2)			
Inpatient admissions, definite	N (% non-missing)	512 (100.0)	1,378 (100.0)		0.0	0.0
Inpatient admissions, probable	N (% non-missing)	512 (100.0)	1,378 (100.0)		0.0	0.0
Outpatient visits	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8020	1.3	0.6
	≥1, n (%)	7 (1.4)	21 (1.5)			
Acute respiratory events	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.8544	4.2	1.3
	0, n (%)	299 (58.4)	835 (60.6)			
	1, n (%)	119 (23.2)	305 (22.1)			
	2, n (%)	60 (11.7)	154 (11.2)			
	≥3, n (%)	34 (6.6)	84 (6.1)			
Severe exacerbations (asthma)	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.9866	1.6	0.7
	0, n (%)	363 (70.9)	989 (71.8)			
	1, n (%)	92 (18.0)	240 (17.4)			
	2, n (%)	38 (7.4)	99 (7.2)			
	≥3, n (%)	19 (3.7)	50 (3.6)			
FEV_1	N (% non-missing)	117 (22.9)	296 (21.5)	0.6729	12.4	1.3
	Mean (SD)	2.8 (1.2)	2.7 (1.0)			
	Median (IQR)	2.6 (1.2)	2.6 (1.1)			
GINA control	N (% non-missing)	512 (100.0)	1,378 (100.0)	0.1189	8.0	0.3
	Controlled, n (%)	210 (41.0)	591 (42.9)			
	Partly Controlled, n (%)	205 (40.0)	580 (42.1)			
	Uncontrolled, n (%)	97 (18.9)	207 (15.0)			

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential; NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

13.7 Baseline characterisation of the matched - COPD

Variable		Scotland	England	P	SDD	Bias
Index year	N (% non-missing)	107 (100.0)	262 (100.0)	0.4792	11.4	1.1
	2012, n (%)	53 (49.5)	134 (51.1)			
	2013, n (%)	29 (27.1)	82 (31.3)			
	2014, n (%)	20 (18.7)	40 (15.3)			
	2015, n (%)	5 (4.7)	6 (2.3)			
Age (years)	N (% non-missing)	107 (100.0)	262 (100.0)	0.5953	6.2	0.4
	Mean (SD)	54.1 (4.7)	53.8 (4.8)			
	Median (IQR)	55.0 (7.0)	55.0 (7.0)			
Gender	N (% non-missing)	107 (100.0)	262 (100.0)	0.8020	2.9	0.0
	Male, n (%)	64 (59.8)	153 (58.4)			
Smoking status	N (% non-missing)	107 (100.0)	262 (100.0)	0.9633	2.2	0.0
	Never, n (%)	2 (1.9)	6 (2.3)			
	Current, n (%)	65 (60.7)	160 (61.1)			
	Ex, n (%)	40 (37.4)	96 (36.6)			
BMI	N (% non-missing)	107 (100.0)	262 (100.0)	0.4910	8.8	0.0
	<18.5, n (%)	6 (5.6)	7 (2.7)			
	18.5-<25, n (%)	27 (25.2)	71 (27.1)			
	25-<30, n (%)	40 (37.4)	91 (34.7)			
	>=30, n (%)	34 (31.8)	93 (35.5)			
Cardiovascular disease	N (% non-missing)	107 (100.0)	262 (100.0)	0.4726	8.4	0.2
	Yes, n (%)	11 (10.3)	34 (13.0)			
Ischaemic heart disease	N (% non-missing)	107 (100.0)	262 (100.0)	0.7914	3.1	0.0
	Yes, n (%)	5 (4.7)	14 (5.3)			
Hypertension	N (% non-missing)	107 (100.0)	262 (100.0)	0.5866	6.3	1.2
	Yes, n (%)	19 (17.8)	53 (20.2)			
Cancer	N (% non-missing)	107 (100.0)	262 (100.0)	0.7613	3.4	0.0
	Yes, n (%)	16 (15.0)	36 (13.7)			
Diabetes	N (% non-missing)	107 (100.0)	262 (100.0)	0.3585	10.9	0.0
	Yes, n (%)	6 (5.6)	22 (8.4)			
Rhinitis	N (% non-missing)	107 (100.0)	262 (100.0)	0.6370	5.3	0.8
	Yes, n (%)	15 (14.0)	32 (12.2)			
Active Rhinitis	N (% non-missing)	107 (100.0)	262 (100.0)	0.8391	2.3	0.2
	Yes, n (%)	4 (3.7)	11 (4.2)			
Gastroesophageal reflux disease	N (% non-missing)	107 (100.0)	262 (100.0)	0.7965	2.9	0.2
	Yes, n (%)	12 (11.2)	27 (10.3)			

Variable		Scotland	England	P	SDD	Bias
Active Gastroesophageal reflux disease	N (% non-missing)	107 (100.0)	262 (100.0)	0.3045	12.3	1.0
	Yes, n (%)	5 (4.7)	20 (7.6)			
Eczema	N (% non-missing)	107 (100.0)	262 (100.0)	0.7211	4.1	0.3
	Yes, n (%)	23 (21.5)	52 (19.8)			
Active Eczema	N (% non-missing)	107 (100.0)	262 (100.0)	0.5021	8.2	0.1
	Yes, n (%)	1 (0.9)	5 (1.9)			
Pneumonia	N (% non-missing)	107 (100.0)	262 (100.0)	0.2490	14.0	1.2
	Yes, n (%)	4 (3.7)	18 (6.9)			
Oral Candidiasis	N (% non-missing)	107 (100.0)	262 (100.0)	0.8594	2.1	0.0
	Yes, n (%)	1 (0.9)	3 (1.1)			
Beta Blockers	N (% non-missing)	107 (100.0)	262 (100.0)	0.7951	2.3	0.2
	Mean (SD)	0.4 (1.8)	0.5 (3.9)			
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
NSAIDs	N (% non-missing)	107 (100.0)	262 (100.0)	0.8924	1.5	0.2
	≥1, n (%)	23 (21.5)	58 (22.1)			
Charlson Comorbidity Index	N (% non-missing)	107 (100.0)	262 (100.0)	0.6750	5.6	0.2
	Mean (SD)	1.7 (2.7)	1.6 (2.5)			
	Median (IQR)	0.0 (4.0)	0.0 (4.0)			
LABA prescriptions, solo	N (% non-missing)	107 (100.0)	262 (100.0)	0.7286	4.0	0.7
	≥1, n (%)	16 (15.0)	43 (16.4)			
SAMA prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.8541	2.1	0.4
	≥1, n (%)	6 (5.6)	16 (6.1)			
LAMA prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.4905	7.9	1.1
	≥1, n (%)	52 (48.6)	117 (44.7)			
Methylxanthines prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.8594	2.1	4.0
	≥1, n (%)	1 (0.9)	3 (1.1)			
LTRA prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.5851	5.9	0.3
	≥1, n (%)	2 (1.9)	3 (1.1)			
Phosphodiesterase-4 inhibitor prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)		0.0	0.0
Acute OCS prescriptions, sensitive	N (% non-missing)	107 (100.0)	262 (100.0)	0.4601	10.9	0.5
	0, n (%)	73 (68.2)	187 (71.4)			
	1, n (%)	21 (19.6)	54 (20.6)			
	≥2, n (%)	13 (12.1)	21 (8.0)			
Acute OCS courses, probable	N (% non-missing)	107 (100.0)	262 (100.0)	0.5663	9.6	0.5
	0, n (%)	59 (55.1)	152 (58.0)			
	1, n (%)	25 (23.4)	66 (25.2)			
	≥2, n (%)	23 (21.5)	44 (16.8)			

Variable		Scotland	England	P	SDD	Bias
Acute OCS courses, sensitive	N (% non-missing)	107 (100.0)	262 (100.0)	0.3826	11.6	0.8
	0, n (%)	73 (68.2)	187 (71.4)			
	1, n (%)	22 (20.6)	57 (21.8)			
	≥2, n (%)	12 (11.2)	18 (6.9)			
Maintenance OCS prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.8982	1.5	1.7
	0, n (%)	104 (97.2)	254 (96.9)			
	1, n (%)	0 (0.0)	0 (0.0)			
	≥2, n (%)	3 (2.8)	8 (3.1)			
All OCS prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.8684	5.4	1.6
	0, n (%)	58 (54.2)	147 (56.1)			
	1, n (%)	23 (21.5)	58 (22.1)			
	≥2, n (%)	26 (24.3)	57 (21.8)			
Antibiotic prescriptions, LR	N (% non-missing)	107 (100.0)	262 (100.0)	0.7119	6.1	2.9
	0, n (%)	53 (49.5)	133 (50.8)			
	1, n (%)	25 (23.4)	68 (26.0)			
	≥2, n (%)	29 (27.1)	61 (23.3)			
Acute OCS prescriptions, probable	N (% non-missing)	107 (100.0)	262 (100.0)	0.8975	7.6	1.5
	0, n (%)	59 (55.1)	152 (58.0)			
	1, n (%)	23 (21.5)	58 (22.1)			
	2, n (%)	11 (10.3)	22 (8.4)			
	≥3, n (%)	14 (13.1)	30 (11.5)			
SABA inhaler prescriptions	N (% non-missing)	107 (100.0)	262 (100.0)	0.9377	3.4	4.6
	0, n (%)	35 (32.7)	80 (30.5)			
	1, n (%)	11 (10.3)	30 (11.5)			
	2-4, n (%)	25 (23.4)	57 (21.8)			
	5-10, n (%)	25 (23.4)	71 (27.1)			
	11+, n (%)	11 (10.3)	24 (9.2)			
SABA inhalers	N (% non-missing)	107 (100.0)	262 (100.0)	0.8571	4.1	6.8
	0, n (%)	35 (32.7)	80 (30.5)			
	1, n (%)	10 (9.3)	25 (9.5)			
	2-4, n (%)	23 (21.5)	52 (19.8)			
	5-10, n (%)	20 (18.7)	63 (24.0)			
	11+, n (%)	19 (17.8)	42 (16.0)			
ICS prescriptions (mono- and combi)	N (% non-missing)	107 (100.0)	262 (100.0)	0.5936	1.4	5.2
	0, n (%)	71 (66.4)	162 (61.8)			
	1, n (%)	6 (5.6)	23 (8.8)			
	2-4, n (%)	8 (7.5)	30 (11.5)			
	5-10, n (%)	16 (15.0)	36 (13.7)			
	11+, n (%)	6 (5.6)	11 (4.2)			

Variable		Scotland	England	P	SDD	Bias
SABA, average daily dose (salbutamol equivalent)	N (% non-missing)	107 (100.0)	262 (100.0)	0.9235	0.7	9.8
	0, n (%)	35 (32.7)	80 (30.5)			
	>0 - ≤200, n (%)	26 (24.3)	66 (25.2)			
	>200 - ≤400, n (%)	19 (17.8)	55 (21.0)			
	>400 - ≤600, n (%)	10 (9.3)	26 (9.9)			
	>600, n (%)	17 (15.9)	35 (13.4)			
A&E attendances	N (% non-missing)	107 (100.0)	262 (100.0)	0.5222	8.7	0.5
	≥1, n (%)	0 (0.0)	1 (0.4)			
Inpatient admissions, definite	N (% non-missing)	107 (100.0)	262 (100.0)		0.0	0.0
Inpatient admissions, probable	N (% non-missing)	107 (100.0)	262 (100.0)		0.0	0.0
Outpatient visits	N (% non-missing)	107 (100.0)	262 (100.0)	0.6776	4.7	0.6
	≥1, n (%)	6 (5.6)	12 (4.6)			
Moderate/severe exacerbations (COPD)	N (% non-missing)	107 (100.0)	262 (100.0)	0.8965	8.7	1.2
	0, n (%)	40 (37.4)	106 (40.5)			
	1, n (%)	28 (26.2)	71 (27.1)			
	2, n (%)	20 (18.7)	45 (17.2)			
	≥3, n (%)	19 (17.8)	40 (15.3)			
FEV_1	N (% non-missing)	88 (82.2)	234 (89.3)	0.6392	13.8	9.8
	Mean (SD)	1.9 (0.6)	2.0 (1.0)			
	Median (IQR)	1.9 (0.9)	1.9 (1.2)			
MRC score	N (% non-missing)	107 (100.0)	262 (100.0)	0.4503	12.5	1.3
	1, n (%)	22 (20.6)	55 (21.0)			
	2, n (%)	49 (45.8)	107 (40.8)			
	3, n (%)	29 (27.1)	66 (25.2)			
	4, n (%)	7 (6.5)	32 (12.2)			
	5, n (%)	0 (0.0)	2 (0.8)			
Gold severity	N (% non-missing)	97 (90.7)	241 (92.0)	0.6948	6.6	5.3
	Mild, n (%)	19 (19.6)	45 (18.7)			
	Moderate, n (%)	52 (53.6)	129 (53.5)			
	Severe, n (%)	23 (23.7)	52 (21.6)			
	Very Severe, n (%)	3 (3.1)	15 (6.2)			

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised mean difference; RCC = Relative coefficient change, or bias potential; NCP = Non-co-payment cohort; LCP = Likely co-payment cohort

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