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Title: Altered Metabolic Parameters in Association with Antipsychotic Medication Use in Diabetes; a Population Based Case-Control Study.

Short Title: Diabetes and Antipsychotic Medication

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ABSTRACT

Aims

This study assess differences in clinical variables in diabetes patients prescribed antipsychotic medication and determines relative schizophrenia prevalence in the diabetes population.

Methods

This population-based case-control study utilising Scotland's national diabetes registry (SCI-diabetes) and linked psychiatric hospital discharge data (SMR04) established diabetes phenotypes in a patient cohort prescribed long term antipsychotic medication (n=2362)(cases). Cases were matched 1:10 to diabetes patients not prescribed antipsychotic medication (controls) for BMI, gender; diabetes type; birth year; diagnosis date; smoking status. Sub-groups with defined schizophrenia (n=196) or bipolar disorder (n= 190) were further examined. Schizophrenia prevalence in the diabetes versus general population was compared.

Results

During follow up, antipsychotic prescription was associated with lower HbA1c (55.1 (95% CI 54.5-55.8) or 7.2 (95% CI 7.1-7.3)% vs 58.2 (58.0-58.4) mmol or 7.5 (95% CI 7.5-7.5)% p<0.001) lower serum total cholesterol, 4.2 (4.1-4.2) vs 4.3 (4.2-4.3) mmol/ l, p<0.001), lower blood pressure (systolic 130 (130.17-131.29) vs 134 (134.3-134.7) mmHg, p<0.001), higher prescription of oral hypoglycaemic medication (42% (40-45) vs 38% (37-39) *p<0.001*), similar statin prescriptions (85% (81-89) vs 85% (84-86), p=.55), and lower retinopathy rates (28% (25.6-30.5) vs 32% (31.5-33.1), *p<0.001*). HbA1c at diagnosis was similar (p=.27). Schizophrenia prevalence was higher in the diabetes versus general population with differences across age groups (Scottish population versus diabetic population rate of 522.2

(522.1 - 522.3) versus 717.4 (703.4 - 731.9) per 100,000).

Conclusions

We confirm higher diabetes rates in schizophrenia up to age 70, similar attendance rates and clinical measurements that are not worse in a large well-matched population-based Scottish sample prescribed antipsychotic medication versus matched general diabetes patients.

Keywords:

Antipsychotics, Diabetes, Schizophrenia, Mental Health, Case-Control, Metabolic

1.0 Introduction

Diabetes is around 2-4 times more prevalent in patients with Schizophrenia (Fernandez-Egea et al., 2009; Kirkpatrick et al., 2012), which may be due to shared susceptibility genes (Lin and Shuldiner, 2010), stress (and related hormones, i.e., raised cortisol levels) (Dinan, 2004), demographic characteristics (age, gender, ethnicity, geographic location) (Holt et al., 2005; Lin and Shuldiner, 2010; Melkersson and Dahl, 2004), or comorbid illness (Holt et al., 2005).

Weight gain and other lifestyle factors (such as smoking, sedentary lifestyle, diet, etc.) that are common in patients with schizophrenia can influence diabetes development irrespective of medication (De Hert et al., 2009; Haddad, 2004; Holt et al., 2005; Rouillon and Sorbara, 2005). However schizophrenia may be an independent risk factor, as glycaemic abnormalities have been observed in patients irrespective of other factors (Bushe and Leonard, 2004). Diabetes conversely may increase the risk of schizophrenia (Haddad, 2004; Lin and Shuldiner, 2010; Rouillon and Sorbara, 2005).

Much of the literature however focuses on the gluco-toxic effects of anti-psychotic (atypical drugs in particular, e.g. clozapine) suggesting medication induced weight gain drives the association with diabetes (Jafari et al., 2012; Lin and Shuldiner, 2010; Melkersson and Dahl, 2004; Rouillon and Sorbara, 2005). Emerging evidence suggests that antipsychotic medication may alter gut microbiota which may precipitate weight gain and predispose patients to diabetes (Bahr et al., 2015; Morgan et al., 2015).

Others suggest it is independent of weight gain (Bushe and Leonard, 2004). The type of anti-psychotic drug or illness itself might increase the risk of developing diabetes (Bushe and Leonard, 2004; Melkersson and Dahl, 2004; Rummel-Kluge et al., 2010) and secondary hormonal changes may influence the metabolic changes (Bushe and Leonard, 2004; Melkersson and Dahl, 2004; Rummel-Kluge et al., 2010). .

Most studies to date have evaluated the risk of diabetes development in this population, but

not on the metabolic changes, attendance behaviour and outcomes of those with established diabetes, which is the focus of this study.

1.1 *Background*

In July-Aug 2012, the authors conducted a small pilot case control study within high risk schizophrenia patients attending a specialised clozapine prescription clinic (n=63) demonstrating a 12.7% prevalence of diabetes with a 7:1 male: female ratio (prevalence of diabetes within the Scottish population for a similar age group is 3.95%). This study suggested that diabetes may be associated with longer duration of schizophrenia (p=0.08), but not with clozapine daily dose (p=0.64). Diabetes patients prescribed clozapine (mean age of 47.9yrs (+/- 7.6 (SD)), were compared with age and diabetes type matched controls, and demonstrated significantly better glycaemic and cholesterol control (HbA1c (50.8 vs 63.9 mmol/mol, p<0.012), total cholesterol (4.1 vs 4.8mmol/L, p=0.038))(Perera et al., 2013)). These findings were contrary to expectation and fuelled this more powerful population study.

1.2. *Aims*

This study aims to a) explore whether schizophrenia patients are overrepresented in the Scottish diabetes population, and b) assesses whether patients prescribed regular antipsychotic medication (with presumed underlying mental health conditions) who have developed diabetes have i) differences in glycaemic control, blood pressure, plasma lipids and complication rates/ complications risk compared to those developing diabetes de-novo, and ii) poorer attendance for clinic or complications screening.

2.0 Methods

2.1 Background

We performed a population based case control study, using nationwide data linked from psychiatric hospital discharges and Scotland's national diabetes registry (SCI- Diabetes). SCI-Diabetes contains detailed linked clinical data on all patients in Scotland registered with diabetes. It collates information from multiple sources including medication, screening (retinopathy screening service, foot screening tool), laboratory data and metabolic variables collected during routine care.

2.2 Population Data Sources

National psychiatric hospital summary discharge data (for Scottish residents 1981-2011 with any diagnosis of schizophrenia who were alive at the end of 2011) were used for prevalence calculations. Data for detailed diabetes phenotype analysis was obtained from SCI-diabetes (see flow chart; figure 1). Linkage across healthcare related datasets was facilitated by the unique patient identifier (CHI number). Hospital discharge information for mental health conditions (Scottish Morbidity Record (SMR) 04) was made available through Information Services Division (ISD) using tenth revision of International Classification of Diseases (ICD-10) codes.

2.3 Prevalence Calculation

Comparison was made of the prevalence of schizophrenia in the general Scottish population who were alive in 2011 (identified from history of a psychiatric hospital admission with the relevant ICD code) and the prevalence of schizophrenia in the national diabetes population (SCI-diabetes) by age.

2.4 Case Selection

From a May 2011 research extract of SCI-diabetes national data, we established cases, namely patients recorded in SCI-diabetes as receiving a prescription for antipsychotic medication. We identified 2386 patients during 2010 prescribed drugs with a BNF code of 4.2.1 (anti-psychotic medication) for at least 12 months in total (including all or part of 2010)

regardless of any diagnosis for mental illnesses, referred to as All Antipsychotics (AA) group. Of these 2362 patients were matched and used in further analysis. From within this cohort we identified 196 diabetes patients with a record of psychiatric hospital discharge recording schizophrenia or a related psychosis prior to 2010 (ICD-10 codes F20- F29) (SA group), and 190 patients with a hospital discharge record for bipolar disorder (ICD10 code F31) (BA group). SA and BA groups were established to assess whether effects identified were associated with specific mental health disorders.

2.5 Control Selections

For each set of index cases, a comparison group was created by identifying 10 controls for each case from SCI-diabetes matched for gender; diabetes type; birth year (+/- 1 year); diagnosis date (+/- 1 year); smoking status (the lowest status recorded in 2009 and 2010 was used (in order – current smoker (lowest); ex-smoker; never smoked); and BMI (mean for 2010) (+/- 3kg/m^2). Patients with a history of any antipsychotic use or any schizophrenia diagnosis (including those excluded from the index cases) were not used as controls. Where there were more than 10 potentially matching records, controls were randomly chosen from those available. Records with fewer than 10 matching records were excluded from analysis.

Of the total available patients using anti-psychotic medication, the percentage matched to 10 controls was 99.0% (AA group), 83.0% (SA group) and 90.5% (BA group). Excluded patients tended to be younger than those matched and with a lower BMI (See Table 1 a) and b)). For all groups smokers and ex-smokers are more likely to be excluded than non-smokers, albeit with small numbers. There was no significant difference in gender.

2.6 Clinical Measures and Outcomes

Various measures for 2010 (i.e. from Jan 1st 2010 to Dec 31st 2010 inclusive) were extracted to compare the control patients with the cases to test for a difference. These were, a) the mean value of all HbA1c, systolic and diastolic blood pressure, total cholesterol readings taken in 2010, b) the HbA1c, systolic and diastolic blood pressure, total cholesterol, foot screening and eye screening record counts (the number of times each was recorded e.g. at a screening visit for each patient in 2010), c) the foot risk score (worst record of 2010), d) retinopathy status (worst record of 2010), e) statin prescription (whether prescribed at any point in 2010), f) hypoglycaemic medication (whether prescribed at any point in 2010).

Patients with missing data were removed for any comparison where that data was missing, however in the case of data used for matching purposes all data had to be present for the patient to be considered.

HbA1c at diagnosis of diabetes (first reading within 90 days of diagnosis) was compared between groups to determine whether differences in glycaemic control could be explained by baseline HbA1c.

T-tests were carried out to compare variables between the control and experimental group. Chi-squared analysis was used for categorical variables.

2.7 Permissions

Data linkage between SCI-diabetes and psychiatric hospital discharge data was performed with permission from a multi-centre research ethics committee, the Privacy Advisory Committee and Caldicott Guardians.

3.0 Results

3.1 Prevalence (see figure 2)

Diabetes patients in the 25-54 age group had a higher prevalence of schizophrenia, but in the over 70 age group diabetes patients had a lower prevalence of schizophrenia than that seen in the general population.

3.2 Diagnosis

There was no significant difference in HbA1c at diagnosis (within 90 days of the diagnosis date) between the antipsychotic medication group (AA) and controls. Mean HbA1c for the control group was 73.0 mmol/mol (8.8%) and 72.1 mmol/mol (8.7%) for the All Antipsychotic (AA) group (t-test result was $t(290.435) = -0.36$, $p = 0.72$).

3.3 Diabetes Phenotype and Metabolic Outcomes (see table 2)

Table 2 summarises differences in metabolic variables between the three groups (AA, SA and BA) and their matched controls. Mean BMI, which was matched with controls, was 31.3 kg/m^2 (95% CI 31.2 – 31.5) in the schizophrenia (SA) group, 31.4 kg/m^2 (95% CI 31.3 – 31.6) in the bipolar (BA) group and 30.3 kg/m^2 (95% CI 30.2 – 30.3) in the all antipsychotic group (AA).

HbA1c was lower in patients prescribed antipsychotic medication than in the matched population with diabetes. This difference was also present in the defined bipolar (BA) and schizophrenia (SA) groups (most marked differences in the later).

Blood Pressure was generally lower in the anti-psychotic prescription groups (AA, SA and BA) versus their comparison groups. This was more marked for systolic blood pressure.

Total serum cholesterol was lower in the experimental group on antipsychotics (AA) and the bipolar-antipsychotic group (BA), but not statistically significantly different between the schizophrenia-antipsychotic group (SA) and their comparison group.

3.4 Clinic/ Screening Visits (see table 2)

There were no significant differences in number of HbA1c or blood pressure checks compared with controls except a small increase in HbA1c checks in the bipolar group. There was a slightly lower rate of foot screening in the all-antipsychotic (AA) group, which was only significant for bipolar group (BA), and a slightly lower attendance at eye screening in AA group and BA groups.

3.5 Complications (see table2)

3.5.1 Foot Risk

We assessed foot disease risk by comparing numbers of patients with a medium and high risk foot score versus those with a no or low risk foot score (using the Scottish foot screening classification (Leese et al., 2007, 2006)). Moderate or high risk feet were more common in the AA group (11% vs 7%), p=0.05, and the BA group (14% vs 6%), p=0.047 versus controls.

3.5.2 *Retinopathy Risk*

There was a lower rate of retinopathy (32% vs 28%) and maculopathy (5% vs 4%) in the AA group (also significant in the bipolar (BA) group (22% vs 30%)). Differences were not seen in the schizophrenia (SA) group (p>0.9).

3.6 Medications

Patients on antipsychotic medication (AA) may be less likely to be treated by diet alone, and more likely to be prescribed hypoglycaemic medication. Statin use was slightly lower in the patients on antipsychotic medication than their comparison group. Overall difference between all 6 groups is significant with a small effect size χ^2 = 28.97, p<0.01, however the difference between experimental and control groups is not significant χ^2= 0.36, p=0.55.

4 Discussion

4.1 Increased Prevalence

This study substantiates evidence that there is a strong association between diabetes and schizophrenia (figure 2), with higher schizophrenia prevalence in diabetes patients aged 25-54, but demonstrate lower incidence of schizophrenia in older diabetes patients (over 70) perhaps due to a survivor effect i.e. those with diabetes dying younger. NICE suggests screening for diabetes by fasting glucose and HbA1c before initiating antipsychotic treatment and at 6 weeks, 12 weeks, 1 year and then annually (NICE, 2014).

4.2 Impact of Antipsychotic Medication on Glycaemic Control

Perhaps the most novel finding is around glycaemic control, which is not worse in patients prescribed antipsychotic medication compared with controls matched for age, gender, diabetes type, BMI, diabetes duration, smoking status. HbA1c was marginally better in the antipsychotic cohort (average HbA1C -3 mmol/mol). The clinical significance of this marginal HbA1C reduction is debatable, but the finding is consistent in all study cohorts and concurs with a previous conducted Clozapine clinic audit (Perera et al., 2013).

Patients prescribed anti-psychotic medication are more likely to develop diabetes (Bushe et al., 2009; Haddad, 2004), but this study aims to determine how their diabetes progresses after diagnosis. Diabetes induced by anti-psychotic medication may have different features to diabetes developing de novo. Differences may be due to underlying pathophysiology, psychiatric medication effects, or other confounding factors associated with antipsychotic use and mental health diagnosis such as institutionalized care, physical activity levels or other lifestyle factors. Genetic factors may be more likely to underpin diabetes development in the control population leading to a different disease profile. Further research is needed to determine whether these groups have differences in fat deposition, glucose excursion or insulin resistance. A controversial hypothesis is that some antipsychotics, despite weight

gain, may actually have modest glucose lowering effect perhaps in combination with other medications.

In this study, antipsychotic prescription associated with higher prescription rates for hypoglycaemic medication, but insulin prescription was lower. The effect size for medication differences is small. Metformin may limit antipsychotic induced weight gain (Bushe et al., 2009; Ellinger et al., 2010), and Scottish Intercollegiate Guideline Network (SIGN) guidelines recommend consideration of metformin in those experiencing such drug induced weight gain (regardless of diabetes diagnosis) (Scottish Intercollegiate Guidelines Network (SIGN), 2013). These 2013 guidelines may influence future prescribing habits but should not have impacted on this 2010 data extract. Although Mitchell et al (2012) suggested lower medication prescription for physical disorders in those with mental illness (Mitchell et al., 2012), our data suggest this may not be the case for oral hypoglycaemic agents in patients with known diabetes.

This study also considered whether the marginally lower HbA1C was due to earlier detection of diabetes in the schizophrenia population, perhaps due to more vigilant screening, but no difference was observed in HbA1c at diagnosis between cases and controls who were otherwise matched for duration of diabetes. Higher plasma HbA1c concentrations at diagnosis may be a surrogate marker for delayed diagnosis.

4.3 *Cardiovascular Risk; Blood Pressure and Cholesterol*

This study suggests that blood pressure was slightly lower in associated with antipsychotic medication prescription (average -3.8mmHg). Hypotension (and postural hypotension) is a recognised side effect of this drug class (Joint Formulary Committee, 2014). In addition total cholesterol was marginally lower in the antipsychotic groups despite no difference in statin prescriptions (average -0.1mmol/l less). Significantly lower cholesterol level in schizophrenia patients have been described in other studies, although this finding has not been explained

(Bly et al., 2014), and the wider literature suggests that second generation antipsychotics generally induce hypertension and dyslipidaemia most likely through weight gain (which this study matches for) over time (O'Donoghue et al., 2014; Roohafza et al., 2013; Rummel-Kluge et al., 2010). A role for statins and anti-hypertensive medications is suggested in patients prescribed antipsychotics long term (Tse et al., 2014; Vincenzi et al., 2013). These small improvements in BP and cholesterol may have limited clinical significance but give some reassurance that patients on antipsychotic medication may not have the raised cardiovascular risk previously assumed. In addition they do not appear to be disadvantaged in term of statin prescription rates, which were equivalent.

4.4 *Clinic/ Screening Attendance*

There was no difference in the number of blood pressure or HbA1c checks suggesting that all patients were receiving similar medical attention in diabetes clinics (secondary or primary care). HbA1c was in fact checked more frequently in the bipolar cohort- probably reflecting opportunistic testing whilst screening drug levels/ testing for biochemical drug side effects. There was however a suggestion of slightly lower interaction with specialist screening services (particularly eye screening which is usually performed out with primary care) in the antipsychotic cohort (AA). More research is needed to understand this, but mechanisms for appointing patients and geographical location of these services may create barriers to access. Patients prescribed antipsychotic medication may for example be more likely to be in long term care with accessibility issues.

4.5 *Complications*

This study demonstrated slightly higher risk of foot disease in group AA. We would hypothesise that the increased risk status may be due to poor ability to self care, which if recorded in SCI-diabetes automatically raises the foot risk to at least moderate. With the

data available, we were not able to assess the presence of actual foot complications such as ulcer or amputation or the presence of neuropathy alone (which could have also explained these findings).

Patients prescribed anti-psychotic medication in this study appeared to have slightly less retinopathy. The slight reduction in attendance at retinal screening would only influence retinopathy results if patients with retinopathy were more likely to avoid screening than those without. The effect size for screening non-attendance is small, so unlikely to explain this finding. Retinopathy is a marker of microvascular damage, We could hypothesise that small improvements in glycaemic, lipid and blood pressure control as described, which individually have limited clinical significance, in combination may influence complications risk. The 4% reduction in retinopathy is however small and a more appropriate conclusion may be that our study does not find any evidence for increased end point microvascular complications in this cohort. Retinopathy is a harder end point for microvascular disease than foot risk, which is a surrogate and more influenced by self management ability.

4.6 *Diabetes Care*

Widespread literature and policy suggests that diabetes care for severe mental health disorders needs to be improved and tailored (NHS Diabetes, 2011; NICE, 2014; Scottish Intercollegiate Guidelines Network (SIGN), 2013), and published evidence suggest that patients with mental health problems have poorer outcomes (Mitchell et al., 2012). Previous studies have not all been matched for confounders such as BMI and smoking status. Contrary evidence comes from one of the few large studies in a London cohort (around 11,000 diabetes patients) with no reduction the 17 quality indicators for diabetes care in people with mental health problems compared to those without (general practice services contract) (Whyte et al., 2007).

In our selected population with diabetes patients prescribed anti-psychotic medication,

diabetes clinic attendance and measured metabolic variables and outcomes (with the exception of foot risk) were not worse despite the potential influence of factors such as social isolation, reduced peer support and more chaotic lifestyle. The patients studied here with presumed mental illness prescribed anti-psychotic medication appear to attend for routine measures of diabetes care (likely in primary care) but may not engage so well with specialist screening services. This may be an area where service delivery could be better tailored better to meet needs.

4.7 *Study Limitations*

This population level study has the advantage of a large dataset with power to detect subtle differences in clinical variables, but is limited to big routinely collected clinical data which lack detail that may give deeper insight (such as living environment, assistance with medication, and circumstances of diabetes diagnosis). This study cannot ascertain whether effects in this population are due to medication or other factors associated with a mental health diagnosis. The case control population is a small subset of the national population who are prescribed antipsychotic medication, and mental health diagnosis in the subgroups is dependent on a hospital admission. The selection process has achieved an extremely well characterized cohort with certainty around diagnosis and long term prescription use (at least 1 year prescription required), but limits the applicability of findings to a more heterogeneous population with intermittent antipsychotic use. Antipsychotic medications have differing and potentially opposite effects on insulin sensitivity (Smith et al., 2008). The study would not have been sufficiently powered to analyse different types of antipsychotic drugs individually, but as a result subtleties around specific drug effects may be lost.

5 Conclusions

The evidence for an association between diabetes and mental ill-health is overwhelming but the role of various factors, such as lifestyle, medication and genetics remains unclear. This

study confirms an association between diabetes and schizophrenia, but suggests, when matched with similar diabetes patients, patients prescribed antipsychotic medication prescription do not have worse clinical measurements of metabolic control (glycaemic, blood pressure and lipids) or more microvascular complications (as assessed by retinopathy rates), which gives some reassurance around their management. Maintenance of cholesterol, BP and glucose management in this cohort may be due to proactive healthcare management. This study raises intriguing questions about the pathophysiology behind diabetes outcomes in patients on antipsychotic medications. Further studies with more detailed population characterization, and stratification of outcome for specific anti-psychotic drugs could potentially identify new targets for managing metabolic disease.

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Figure Legends:

Figure 1 Title:

Population Cohort Selection using SCI-Diabetes and SMR04 databases

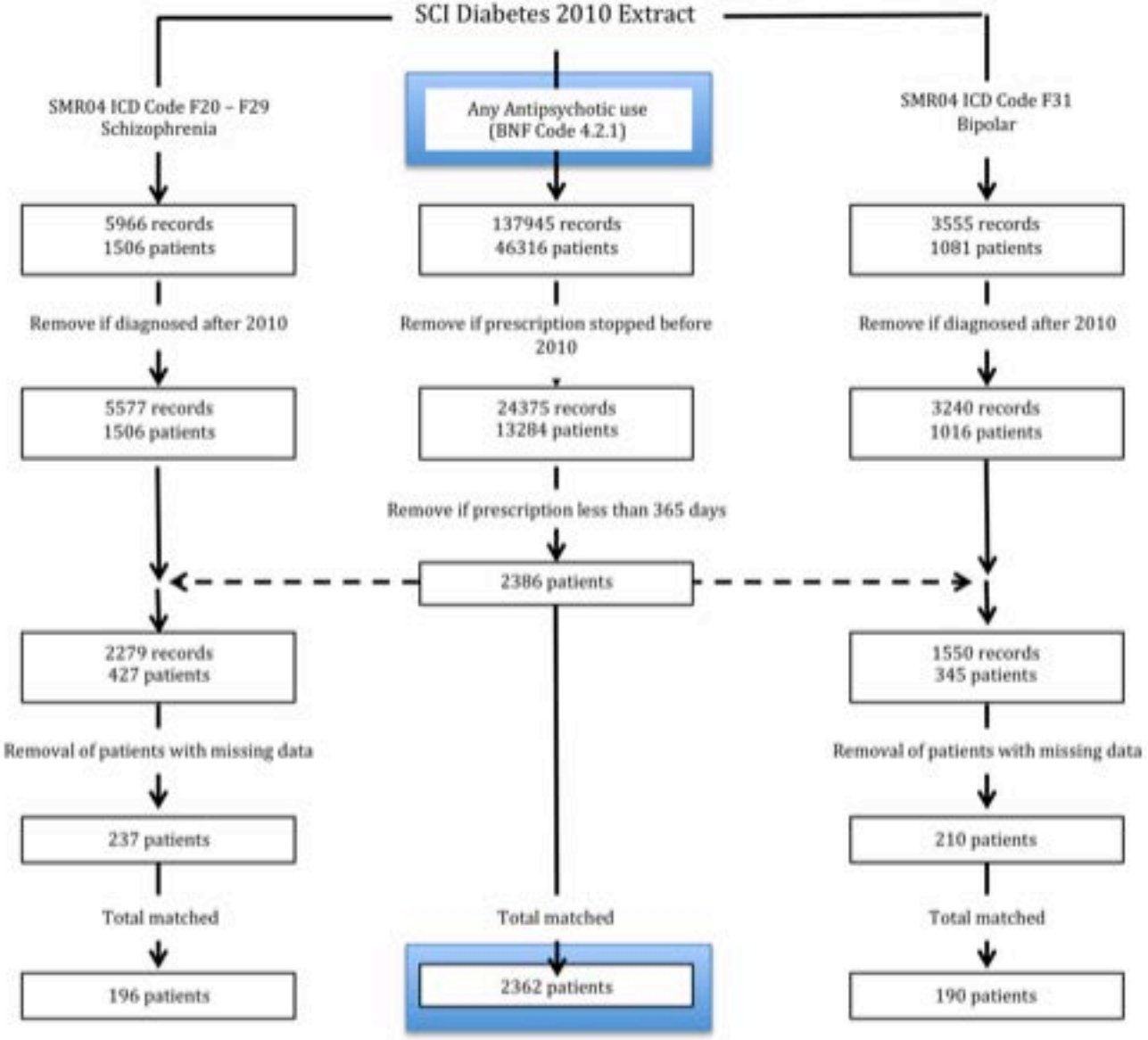
Figure 1 Legend: Schemata showing steps in cohort selection, with the main cohort (patients prescribed antipsychotic medications) shown in the middle, and subgroups schizophrenia (on left) and bipolar patients (on right**).**

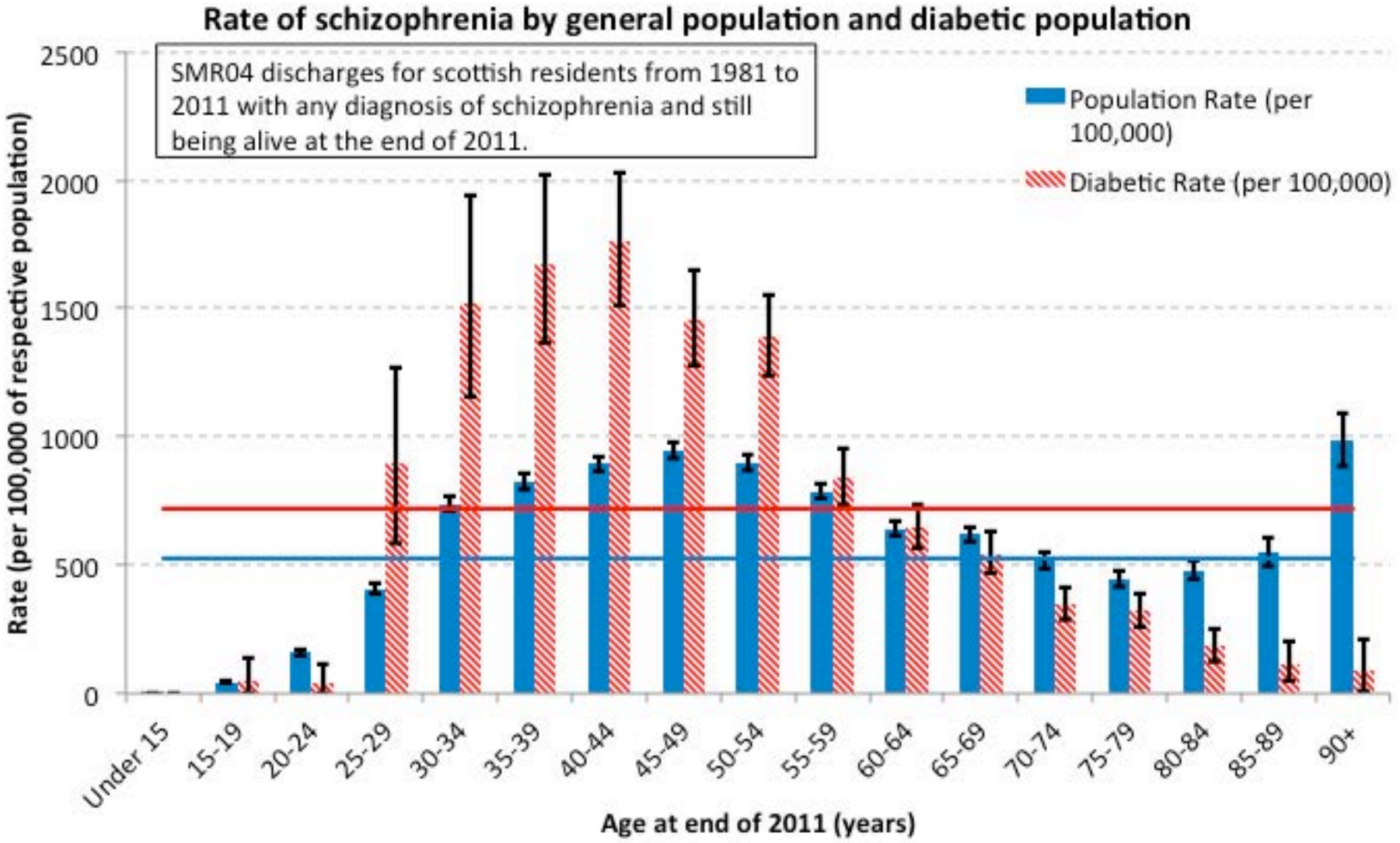
Figure 2 Title:

Prevalence of history of hospital discharge with diagnosis of schizophrenia for the general population and the diabetes population in Scotland for 2010 by age

Figure 2 Legend: Graphical representation of the prevalence of schizophrenia in the general population (in blue) compared with prevalence of schizophrenia in the diabetes population (in red). Blue and red lines represent the average for the populations. Data utilizes SCI-diabetes data and the SMR04 discharge data for Scottish residents from 1981 to 2011 with any diagnosis of schizophrenia and still being alive at the end of 2011.

Figure 1


SCI Diabetes 2010 Extract
SMR04 ICD Code F20 – F29
Schizophrenia
Any Antipsychotic use
(BNF Code 4.2.1)
SMR04 ICD Code F31
Bipolar
5966 records
1506 patients
137945 records
46316 patients
3555 records
1081 patients
Remove if diagnosed after 2010
Remove if prescription stopped before 2010
Remove if diagnosed after 2010
5577 records
1506 patients
24375 records
13284 patients
3240 records
1016 patients
Remove if prescription less than 365 days
2386 patients
2279 records
427 patients
1550 records
345 patients
Removal of patients with missing data
Removal of patients with missing data
237 patients
210 patients
Total matched
Total matched
Total matched
196 patients
2362 patients
190 patients


Rate of schizophrenia by general population and diabetic population
SMR04 discharges for scottish residents from 1981 to 2011 with any diagnosis of schizophrenia and still being alive at the end of 2011.
Population Rate (per 100,000)
Diabetic Rate (per 100,000)
Rate (per 100,000 of respective population)
2500
2000
1500
1000
500
0
Under 15
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90+
Age at end of 2011 (years)