Relative risks of cardiovascular disease in people prescribed olanzapine, risperidone and quetiapine.

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Abstract

Antipsychotics may confer long term benefits and risks, including cardiovascular disease (CVD) risk. Several studies using routine clinical data have reported associations between antipsychotics and CVD but potential confounding and unclear classification of drug exposure limits their interpretation.

Method

We used data from The Health Improvement Network, a large UK primary care database to determine relative risks of (CVD) comparing similar groups of people *only* prescribed olanzapine versus either risperidone or quetiapine. We included participants over 18 between 1995 and 2011. To assess confounding we created propensity scores for being prescribed each antipsychotic. We used propensity score matching and Poisson regression to calculate the CVD incidence rate ratios for olanzapine versus the other two drugs.

Results

We identified 18,319 people who received a single antipsychotic during follow-up (n=5090 risperidone, 7797 olanzapine and 4613 quetiapine). In unmatched analyses, the CVD incidence rate ratio (IRR) for olanzapine versus risperidone was 0.63 (0.51-0.77) but the propensity score matched IRR was 0.78 (0.61-1.02). In the unmatched olanzapine versus quetiapine analysis the IRR adjusted for age and sex for olanzapine was 1.52 (1.16-1.98) but the propensity score matched analysis gave an IRR of 1.08 (0.79-1.46).

Conclusions

After propensity score matching, we found no statistical differences in CVD incidence between olanzapine and either risperidone or quetiapine. Analyses which did not account for confounding produced very different results. Researchers must address confounding

when designing observational studies to assess adverse outcomes of drugs, including antipsychotics.

Key words

Cardiovascular disease
Second generation antipsychotics
Olanzapine
Risperidone
Quetiapine
Primary Care

Introduction

Cardiovascular disease (CVD) mortality and morbidity is markedly elevated in people with severe mental illnesses such as schizophrenia, for reasons including smoking, deprivation and health care (Osborn et al. 2007). The contribution of antipsychotic medication to CVD risk and CVD mortality has generated scientific, clinical and policy-focused debate. The mechanism might include the cumulative adverse effects of different agents, including weight gain, glucose, ECG abnormalities and lipid levels. A systematic review in 2009 concluded that antipsychotics were associated with increased CVD mortality in schizophrenia (Weinman et al. 2009). However contradictory evidence has emerged in the past five years. Large cohort studies have been published using linked national data in Finland (Kiviniemi et al. 2013, Tiihonen et al. 2009), Sweden (Torniainen et al. 2014, Crump et al. 2014) of people with long term or first onset schizophrenia as well as UK studies including all people using antipsychotics in primary care (Murray-Thomas et al. 2013). These studies have shown varying results, reporting that second generation antipsychotic users are either more or less likely to develop from cardiovascular disease. There has been particular concern regarding olanzapine in terms of cardiovascular risks, including weight gain, and it is one of the most commonly prescribed antipsychotics in the UK and internationally (Weinman et al. 2009, Marston et al. 2014).

Comparing the risk for CVD with individual antipsychotics such as olanzapine is methodologically challenging; it requires large studies with sufficient person years of follow-up. Most studies addressing these questions use large routinely collected data sources, since bespoke trials and cohort studies of this size and length of follow-up are probably unfeasible. However using routine data bring major challenges. This includes the highly heterogeneous groups of people in the data source, often deriving from quite different time

periods. More historical cohorts may have poorer quality information on older exposures, but they often have greater statistical power by virtue of larger numbers of CVD events. More contemporary cohorts of younger people may provide higher quality data on exposures (such as smoking or drug dose), but will have fewer CVD events. The theoretical pathway by which antipsychotics may predispose to CVD is probably complex and lengthy. Different agents may affect different parts of this pathway. These effects cannot be differentiated unless we select "purer" cohorts exposed to single antipsychotic agents during follow-up. However in real life clinical setting, from which data are often derived, patients switch between medications, stopping and starting medications for periods of time (Leiberman et al. 2005). This makes it difficult to establish which agent might be associated with any elevated or decreased risk of CVD mortality. It is also important to carefully select outcomes in research using routine databases. Many studies of antipsychotic outcomes simply combine all causes of mortality however this approach is unlikely to yield meaningful evidence when the mechanisms underlying different diseases and causes of death (such as suicide and CVD) are so varied (Weinman et al. 2009, De Hert et al. 2010).

A further challenge with routine data is assessing the role of confounding, when estimating the relationship between different antipsychotics and CVD. To do this we need good quality data on potential confounding factors such as co-morbid physical health, diagnoses, or substance misuse. These variables are not available in many large observational datasets. We designed a study to compare risk of incident CVD in people prescribed the three most commonly used antipsychotic agents in the UK, olanzapine, risperidone and quetiapine. We aimed to address some of the aforementioned challenges when using routinely available clinical data. We aimed to select groups of people with who only used one of the three most

common antipsychotics during their follow-up and to compare their risk of incident CVD. We assessed whether olanzapine confers greater risk of CVD than other second generation antipsychotics. We used propensity score matching to select three groups of antipsychotic users who were similar in terms of their balance of known confounders.

Methods

Study design

A prospective cohort study using routinely collected data in UK primary care

Setting

We extracted data from The Health Improvement Network (THIN) (THIN, 2015), a United Kingdom primary care database which derives data from routine administrative and clinical practice. We used data from an established cohort of THIN patients prescribed first and second generation antipsychotics in UK primary care (Marston et al. 2014). THIN includes longitudinal data from more than 12 million patients with a geographical spread that is generally representative of the UK general population (Blak et al. 2011). Staff at general practices enter data using a hierarchical system of Read codes (Chisholm 1990, Dave and Petersen 2009), for information such as symptoms, signs and diagnoses. THIN has been successfully used for a range of mental health and pharmaco-epidemiological research including work regarding antipsychotics, severe mental illnesses and cardiovascular disease (Marston et al. 2014; Hayes et al. 2016; Osborn et al. 2014).

Participants

The cohort included all people aged over 18 with an electronic record of being prescribed olanzapine, risperidone or quetiapine during follow-up, between 1995 and December 2011. We excluded people with pre-existing cardiovascular disease, heart failure or dementia.

Main exposure

Since we aimed to identify sole users of the most common three antipsychotics, we excluded people who were prescribed additional first or second antipsychotics during follow-up, in addition to their index drug. This derived three groups of people solely receiving 1) olanzapine 2) risperidone or 3) quetiapine.

Follow-up period

Follow up commenced at first prescription of risperidone, olanzapine or quetiapine and ended at death, incident CVD, the patient leaving the practice or December 2011. We excluded those with less than 6 months follow-up data.

Covariates for propensity score matching

In order to balance the observed characteristics of the groups receiving the different antipsychotics, we generated propensity scores for receiving olanzapine, versus either risperidone or quetiapine. We created plots of propensity score distributions to visually compare 1) olanzapine versus risperidone sole users and 2) olanzapine versus quetiapine sole users. We then used propensity score matching to select groups of patients receiving the pairs of drugs of interest. We included people whose propensity scores overlapped using predefined criteria below and we excluded patients for whom we could not find an eligible comparison. We selected patients using 1:1 matching of propensity score, without replacement, but including individuals with tied scores. Calipers for matching pairs of patients were set at 0.2 of a standard deviation of the propensity score as recommended by Austin (2011) for observational studies.

We calculated the propensity scores for each patient using logistic regression. We included a range of relevant variables in the model. These variables were selected by the research team, including epidemiologists, experts in primary care data, academic GPs and psychiatrists. We were deliberately inclusive and made use of any socio-demographic, biometric, diagnostic or co-prescribing variable which might plausibly influence or be related to the choice of olanzapine risperidone quetiapine or which might influence the CVD outcome.

We included the following variables: Mental health diagnoses (category of Severe Mental Illness diagnosis, namely schizophrenia, bipolar disorder or other psychosis (Hardoon et al. 2013)), ADHD, anxiety, depression, OCD, personality disorder, post-traumatic stress disorder, sleep disorders (Marston et al. 2014); chronic physical illnesses at any time (defined as asthma, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, hypothyroid, learning disability, on the palliative care register); receipt of other main classes of medication at any time (antidepressants, diabetes medication, anti-hypertensive medication at any time, hypnotics, insulin, statin use); socio-demographic factors and health indicators at any time before baseline, using the value closest to baseline where there was more than one measurement. These included age at baseline, sex, Townsend quintile (The Townsend index, a widely used measure of geographical social deprivation; Townsend 1986) , time period when the person entered the cohort, high alcohol intake, illicit drug use, ethnicity, smoking status, number of drug subchapters from the BNF prescribed from taken in the year before baseline, systolic blood pressure, height, weight, blood glucose, HbA1c, HDL cholesterol, total cholesterol); mental health consultations (a record of seeing a psychologist, a psychiatrist, or mental health

crisis). These definitions have previously been published (Marston et al. 2014; Osborn et al. 2014).

Main outcome

New records of fatal or non-fatal cardiovascular disease, defined as a myocardial infarction, coronary heart disease, angina pectoris, major coronary surgery and revascularisation, cerebrovascular accident (CVA) and transient ischaemic attacks (TIA) (Osborn et al. 2014).

Analysis

Summary descriptive statistics were calculated for people who were and were not included in the propensity score matched groups, for each pair of antipsychotics namely olanzapine versus risperidone and olanzapine versus quetiapine. We then determined the number of CVD events occurring during follow-up for each group of matched antipsychotic users. We calculated incidence rate ratios for cardiovascular disease comparing sole users of olanzapine against 1) sole users of risperidone and 2) sole users of quetiapine, using Poisson regression. We performed a supplementary analysis to explore the impact of matching on propensity scores by calculating Incident rate ratios for the total, unmatched sample.

Finally we performed an additional, more restricted propensity score analysis, where we only included medical variables which had recorded *before* baseline and therefore *before* the first prescription of antipsychotic, in case any of the variables within our propensity score might have resulted directly from the prescription of the antipsychotic.

Analyses were carried out using Stata version 13 (StataCorp 2013).

Results

We identified 18,319 people who were sole users of one of the three antipsychotics of interest, including 5909 sole users of risperidone, 7,797 sole users of olanzapine and 4613 sole users of quetiapine. Figure one is a flow chart of people included and excluded from this sample. The median follow-up period across the three groups of sole users was 2.3 years (IQR 1.2-4.4); giving a total of 57,448 person years. The commonest additional prescriptions in the excluded groups were additional first generation antipsychotics during follow-up (n=7078; 22.3%) and also receiving an additional drug out of the three most common namely olanzapine, risperidone or quetiapine (n=2907; 9.2%). The mean time from GP registration to first prescription of each antipsychotic was risperidone 2.11 years (sd 3.10); olanzapine 2.40 years (sd 3.37) and quetiapine 3.19 years (4.01).

Olanzapine vs. risperidone

The distribution of the propensity scores and the characteristics of olanzapine versus risperidone users before and after matching are shown in figure 2, Tables 1 and 2. The propensity score distributions in figure 2 are very different for olanzapine and risperidone users prior to matching. The total unmatched risperidone group was more likely to be male, fewer were recorded as having white ethnicity, fewer lived in deprived areas of the UK and fewer had one of the SMI diagnoses such as schizophrenia (table 1). However there were more people diagnosed with diabetes mellitus in the risperidone group, mean weight in Kg was higher in the risperidone group and the people receiving olanzapine were more likely to have had contact with secondary mental health services (table 2).

After the propensity score matching, the groups who were users of olanzapine and risperidone were more similar regarding variables such as gender, diagnosis, ethnicity, co-prescribing, weight and diabetes. (tables 1 and 2).

Olanzapine vs. quetiapine

The unmatched groups of sole users of olanzapine and quetiapine were also different in terms of their propensity score distributions (figure 2), as well as the individual variables contributing to the propensity score (tables 1 and 2). People receiving only quetiapine during their follow-up were more likely to be male, white, and less likely to have a SMI diagnosis including schizophrenia, compared to those receiving olanzapine (table 1). However they were more likely to have a diagnosis of diabetes and to be in receipt of anti-diabetic or anti-hypertensive medication (table 2). After the propensity score matching, the two groups were far more similar in terms of their baseline characteristics.

Relative incidence rates of cardiovascular events

Head to head comparisons of individual antipsychotic agents

The propensity score matching exercise resulted in 4557 olanzapine sole users and 4753 risperidone sole users with 15,805 and 16,171 years of follow-up respectively. The numbers developing a CVD event were 100 (2.2%) for olanzapine and 132 (2.8%) for risperidone. The incidence rate ratio (IRR) for CVD in olanzapine compared to risperidone was 0.78 (0.60-1.01) (table 3). In the supplementary analysis using the unmatched sample, the unadjusted IRR suggested that CVD rates were significantly lower in the olanzapine users compared to risperidone users (model 2; table 3), however this association within the unmatched sample disappeared after adjusting for age, sex and deprivation (model 3 , table 3).

The additional propensity score matching exercise, only including variables recorded before baseline, resulted in fewer people being included in each antipsychotic group (supplementary tables 1- 2 and supplementary figure). However there was still no difference

in CVD incidence between the two olanzapine and risperidone (IRR 1.07; 0.78-1.45) supplementary table 3).

In the olanzapine versus quetiapine analysis, there were 3789 olanzapine sole users, with 10,323 years of follow-up eligible for comparison with the 4133 quetiapine sole users with 10,601 years follow-up. The numbers developing a CVD event were 81 (2.1%) and 82 (2.0%) respectively. After accounting for person years of follow-up, the incidence rate ratio for CVD in olanzapine users (compared to quetiapine users) was 0.96 (0.71-1.31). In the supplementary analysis using the unmatched sample, the unadjusted IRR also showed no significant differences in CVD rates between the olanzapine users and quetiapine users (model 2; table 3). However when this unmatched IRR was adjusted for age, sex and deprivation, the olanzapine users were significantly more likely to develop CVD (IRR 1.52 1.16 to 1.98 ; model 3, table 3).

The additional propensity score matching exercise, again resulted in fewer people being included in each antipsychotic group (supplementary tables 1- 2). However there was still no difference in CVD incidence between the olanzapine and quetiapine (IRR 0.90; 0.62-1.30) supplementary table 3).

Discussion

This large study aimed to address methodological criticisms of previous studies reporting the risks of CVD with antipsychotics (De Hert et al. 2010). When we included a large number of variables to create propensity scores, and matched by these scores, we found no

significant differences in rates of cardiovascular disease when comparing sole users of olanzapine with sole users of either risperidone or quetiapine.

We used routinely collected primary care data and endeavoured to address some of the problems inherent to these types of data. We found evidence that people receiving these three individual drugs differed considerably at baseline, in terms of very important variables such as gender, ethnicity, and key cardiovascular risk factors such as weight and diabetes. Perhaps surprisingly, those prescribed olanzapine had lower weight and lower rates of diabetes and obesity, which could lead to erroneous results if not accounted for. Through propensity score matching, we identified groups who were similar in terms of these characteristics. We derived sample sizes of three to four thousand people solely prescribed each drug, with between 10 and 15 thousand person years of follow-up for each drug, and did not find different rates of cardiovascular disease. In our study we sought to make our groups as similar as possible in terms of the variables we assessed, however some residual confounding is likely to still be present (Freemantle et al, 2013). For instance the severity of the diseases for which the drugs are prescribed may be different, as well as the associated level of impairment, which might influence CVD risk.

Our study identified more CVD events for each individual antipsychotic agent than many of the recent antipsychotic mortality cohort studies which have reported that antipsychotics are harmful or beneficial in relation to all-cause mortality, or in terms of suicide and in terms of CVD mortality (Murray Thomas et al. 2013; Kiviniemi et al. 2013). THIN also offers more information regarding possible confounding variables, compared to studies based on national linked samples such as the large Scandinavian databases. Our work demonstrates

the challenges of designing studies to assess long term associations between medications used for long term mental health conditions and events such as CVD.

The methodological strengths of our study include restricting the exposed samples to people who only received one individual antipsychotic of interest during their follow-up, and the propensity score matching to account for known confounders. This allowed head to head comparisons of sole users, which has rarely been done in previous studies; many researchers group antipsychotic drugs by class or simply look at people exposed and unexposed to any antipsychotic. An exception is Crump et al. (2014), who divided antipsychotic users into subgroups of 'any use' and 'sole use'. However their analysis was also limited by small numbers of CVD deaths in their large Swedish cohort, and they only report all-cause (not CVD) mortality for each individual antipsychotic agent.

Limitations

All routine databases have limitations in terms of missing data on covariates, lack of information regarding prescriptions outside follow-up time, and in our case, lack of data regarding prescriptions in secondary care. However in the UK most people are registered with a general practitioner (Lis and Mann, 1995) and most prescribing for long term conditions is performed by general practitioners (Prah et al. 2007) . An exception is clozapine which is mainly prescribed by psychiatric outpatient clinics- so we did not aim to assess CVD risk in people receiving this medication. The selection of sole users is methodologically pure, but in reality many people switch between agents over time (Lieberman et al. 2005). The effects of switching between different agents and CVD outcomes would be hard to study and are not be addressed by our study design.

Since we did not find associations between the individual antipsychotics of interest and CVD, there was no reason to assess subdivisions of exposure such as high and low doses, length of exposure or any interaction between medications and diagnosis. However these subdivisions would not have been possible given the number of CVD events, and this is a lesson for future research studies- they need to be extremely large to look at dose effects of individual agents or to explore specific subtypes of CVD such as coronary heart disease or stroke. Because our sample are matched on propensity scores, we cannot provide estimates of CVD incidence according to the variables within those propensity scores, such as age or diagnosis.

We recommend that future cohort studies of antipsychotics should carefully assess issues of confounding, using propensity score matching or other applicable methods, but must still recognise that it may be impossible to adjust for unmeasured confounders, such as the clinical reasons why a certain drug may be chosen for certain individuals. For the last two decades, clinicians and patients have been warned of the potential for weight gain, particularly with olanzapine (de Hert et al, 2010). Our results suggest that people receiving this drug in real life are less likely to be overweight or have diabetes, which perhaps indicates a deliberate avoidance of the drug in people at risk of these conditions. However, this means that any studies of longer term outcomes must control for the baseline differences in people receiving these agents, or results regarding risks and benefits of antipsychotics may be biased and inaccurate.

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Table 1: Characteristics of people prescribed three antipsychotics as monotherapy, before and after propensity score matching

	Total before matching						Olanzapine versus Risperidone after propensity score matching				Olanzapine versus Quetiapine after propensity score matching			
	Olanzapine (N=7797)		Risperidone (N=5909)		Quetiapine (N=4613)		Olanzapine (N=4557)		Risperidone (N=4753)		Olanzapine (N=3789)		Quetiapine (N=4133)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sociodemographic														
Male	4436	57	3112	53	1869	41	2422	53	2574	54	1586	42	1774	43
Age mean (SD)	42	(16)	47	(22)	45	(19)	45	(18)	45	(20)	45	(17)	45	(19)
White	3206	41	2096	35	2459	53	1653	36	1761	37	1954	52	2164	52
Black	231	3	151	3	61	1	100	2	141	3	91	2	58	1
South Asian	110	1	75	1	54	1	62	1	67	1	58	2	50	1
Other	203	3	127	2	77	2	98	2	114	2	107	3	66	2
Missing	4047	52	3460	59	1962	43	2644	58	2670	56	1579	42	1795	43
Least deprived	1013	13	922	16	709	15	697	15	686	14	580	15	629	15
2	1024	13	915	15	701	15	634	14	665	14	581	15	624	15
3	1448	19	1185	20	902	20	884	19	920	19	731	19	805	19
4	1954	25	1350	23	1106	24	1094	24	1121	24	894	24	1004	24
Most deprived	1993	26	1319	22	988	21	1034	23	1177	25	848	22	888	21
Missing	365	5	218	4	207	4	214	5	184	4	155	4	183	4
Diagnosis*														
Schizophrenia	1799	23	1120	19	432	9	788	17	1081	23	428	11	425	10
Bipolar	987	13	331	6	693	15	492	11	313	7	415	11	660	16
Other psychoses	1278	16	749	13	379	8	736	16	691	15	547	14	361	9
SMI register only	399	5	305	5	165	4	266	6	248	5	148	4	154	4
No SMI diagnosis*	3334	43	3404	58	2944	64	2275	50	2420	51	2251	59	2533	61
ADHD	42	0.5	135	2	41	1	41	1	39	1	31	1	35	1
Anxiety	1245	16	863	15	1246	27	750	16	769	16	947	25	1030	25
Depression	2158	28	1463	25	2041	44	1256	28	1323	28	1578	42	1720	42
OCD	130	2	128	2	121	3	104	2	105	2	93	2	97	2
Personality disorder	341	4	215	4	341	7	173	4	193	4	250	7	288	7
PTSD	158	2	58	1	134	3	39	1	57	1	110	3	120	3
Sleep disorder	697	9	531	9	678	15	423	9	427	9	525	14	560	14
No diagnosis	752	10	1414	24	561	12	695	15	765	16	395	10	517	13

*This includes those with no diagnosis

Table 2. Clinical characteristics of people prescribed three antipsychotics as monotherapy, before and after propensity score matching

	Total						Olanzapine versus Risperidone after propensity score matching				Olanzapine versus Quetiapine after propensity score matching			
	Olanzapine (N=7797)		Risperidone (N=5909)		Quetiapine (N=4613)		Olanzapine (N=4557)		Risperidone (N=4753)		Olanzapine (N=3789)		Quetiapine (N=4133)	
	n	%	n	%	Quet n	%	n	%	n	%	n	%	n	%
Conditions														
Asthma	1179	15	813	14	913	20	678	15	703	15	715	19	797	19
Atrial Fibrillation	59	1	107	2	76	2	58	1	52	1	47	1	65	2
CKD	274	4	238	4	222	5	188	4	183	4	174	5	192	5
COPD	178	2	140	2	103	2	124	3	122	3	92	2	90	2
Diabetes	459	6	550	9	429	9	369	8	377	8	316	8	350	8
Hypertension	795	10	700	12	621	13	524	12	550	12	479	13	530	13
Hypothyroidism	372	5	321	5	312	7	253	6	253	5	249	7	274	7
Learning disability	276	4	823	14	108	2	276	6	304	6	99	3	106	3
Palliative care register	65	1	58	1	40	1	46	1	46	1	28	1	39	1
Prescribed drugs														
Antidepressants	5599	72	3722	63	3756	81	3046	67	3236	68	3093	82	3322	80
Antidiabetics	291	4	364	6	290	6	239	5	246	5	214	6	227	5
Antihypertensives	1744	22	1392	24	1413	31	1067	23	1124	24	1082	29	1201	29
Hypnotics	3197	41	2109	36	2361	51	1692	37	1788	38	1892	50	2041	49
Insulin	61	1	145	2	96	2	61	1	68	1	51	1	69	2
Statins	909	12	634	11	620	13	473	10	541	11	474	13	534	13
Health indicators (any time before start)														
High alcohol consumption	564	7	296	5	361	8	244	5	286	6	297	8	318	8
Illicit drug taking	1184	15	542	9	577	13	461	10	533	11	481	13	539	13
Non-smoker	259	3	241	4	142	3	203	4	170	4	131	3	122	3
Ex-smoker	3073	39	2469	42	2286	50	1874	41	1986	42	1829	48	1980	48
Current smoker	2837	36	1530	26	1538	33	1363	30	1439	30	1259	33	1414	34
missing	1628	21	1669	28	647	14	1117	25	1158	24	570	15	617	15
Systolic BP mean (SD)	124	(17)	126	(18)	125	(17)	126	(18)	125	(18)	125	(17)	125	(17)
Fasting glucose mmol/L mean (SD)	5.3	(1.7)	5.8	(2.4)	5.4	(2.1)	5.6	(1.9)	5.7	(2.0)	5.3	(1.7)	5.3	(1.7)
HbA_{1c} mmol/mol mean (SD)	48	(21)	54	(21)	51	(20)	50	(20)	52	(21)	49	(20)	49	(19)
Total cholesterol mmol/L mean	5.32	(1.17)	5.14	(1.18)	5.27	(1.18)	5.25	(1.15)	5.17	(1.18)	5.27	(1.13)	5.29	(1.18)

(SD)														
HDL cholesterol mmol/L mean (SD)	1.41	(0.49)	1.39	(0.76)	1.38	(0.43)	1.43	(0.53)	1.39	(0.80)	1.43	(0.51)	1.38	(0.43)
Weight kg mean (SD)	73	(18)	75	(19)	76	(20)	74	(18)	75	(19)	74	(19)	76	(20)
Height m mean (SD)	1.70	(0.10)	1.68	(0.11)	1.68	(0.10)	1.69	(0.10)	1.69	(0.11)	1.68	(0.10)	1.68	(0.10)
Seen a psychologist at least once	1141	15	705	12	864	19	570	13	616	13	671	18	752	18
Seen a psychiatrist at least once	6246	80	3883	66	3608	78	3187	70	3416	72	3005	79	3247	79
Had at least one crisis not MHA	117	2	56	1	73	2	54	1	56	1	63	2	62	2
Had at least one crisis MHA	616	8	287	5	323	7	208	5	271	6	270	7	296	7

BP Blood Pressure. CKD: Chronic Kidney Disease. COPD: Chronic Obstructive Pulmonary Disease. HDL High Density Lipoprotein MHA. Mental Health Act Assessment. SD Standard Deviation.

Table 3 Results from matched and unmatched analysis comparing CVD in three antipsychotics

Olanzapine versus Risperidone

	Main Matched analysis		Supplementary unmatched analyses			
	Model 1		Model 2		Model 3	
	IRR	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**
CVD incidence						
Olanzapine n/N %	100/4557	2.19	166/7797	2.13	166/7797	2.13
Risperidone n/N %	132/4753	2.78	202/5909	3.42	202/5909	3.42
Olanzapine	**0.79**	**(0.61, 1.02)**	**0.63**	**(0.51, 0.77)**	**0.99**	**(0.80, 1.23)**
Risperidone (reference)	1.0		1.0		1.0	
Female					0.82	(0.66, 1.02)
Age					1.05	(1.05, 1.06)
Townsend Quintiles						
1 least deprived (Reference)					1.0	
2					1.00	(0.70, 1.44)
3					1.21	(0.86, 1.71)
4					1.25	(0.89, 1.75)
5 most deprived					1.45	(1.02, 2.07)
Missing					1.64	(0.97, 2.76)

Olanzapine versus Quetiapine

	Main matched analysis		Supplementary unmatched analyses			
	Model 1		Model 2		Model 3	
	IRR	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**
CVD incidence						
Olanzapine n/N %	81/3789	2.14	166/7797	2.13	166/7797	2.13
Quetiapine n/N %	82/4133	1.98	90/4613	1.95	90/4613	1.95
Olanzapine	**1.08**	**(0.79,1.46)**	**1.10**	**(0.85, 1.42)**	**1.52**	**(1.16, 1.98)**
Quetiapine (Reference)	1.0		1.0		1.0	
Female					0.73	(0.56, 0.94)
Age					1.06	(1.05, 1.06)
Townsend Quintiles						
1 least deprived (Reference)					1.0	
2					0.96	(0.62, 1.49)
3					1.09	(0.72, 1.65)
4					1.18	(0.79, 1.76)
5 most deprived					1.25	(0.82, 1.91)
Missing					1.38	(0.75, 2.54)

Model 1 Propensity score matched
Model 2 Unadjusted unmatched analysis
Model 3 Unmatched analysis, adjusted for age sex and deprivation

IRR: Incidence rate ratio

Figure 1. Flow of Participants

R Risperidone O Olanzapine Q Quetiapine CVD Cardiovascular Disease

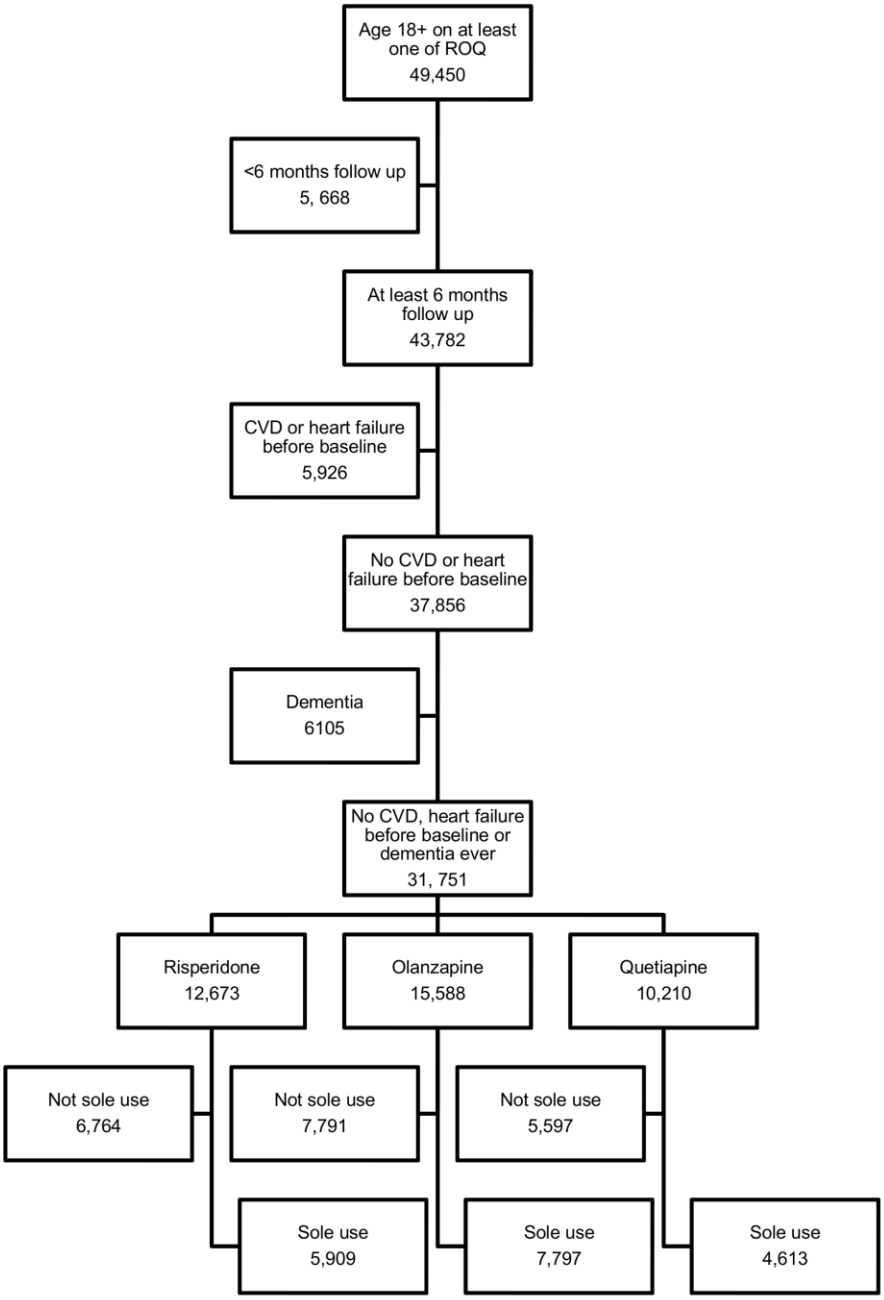
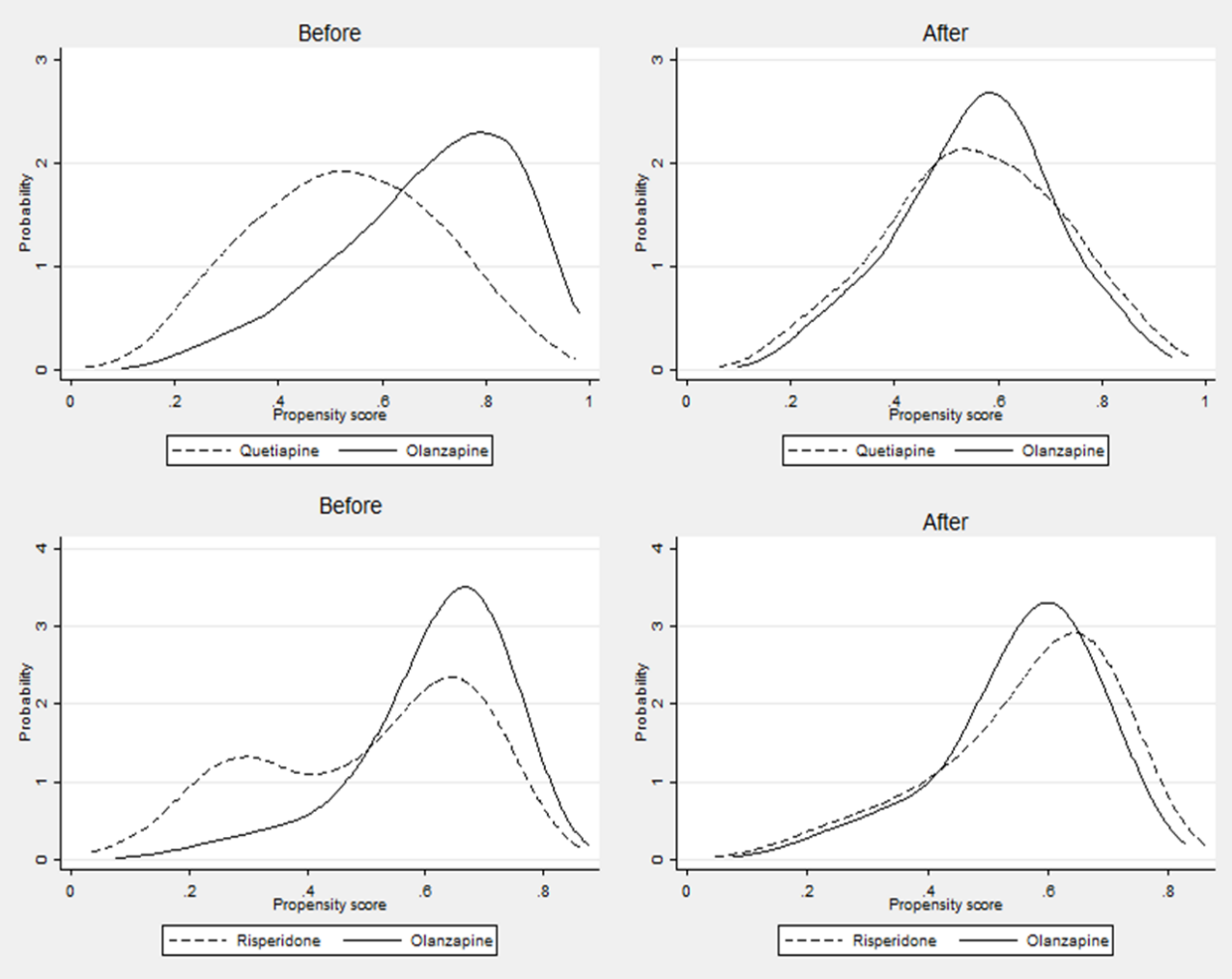


Figure 2. Propensity scores for being prescribed individual antipsychotics, before and after propensity score matching



Supplementary propensity score analysis. Restricting propensity scores to only include variables recorded pre-baseline.
Supplementary Table 1: Characteristics of people prescribed three antipsychotics as monotherapy before & after propensity score matching

	Total before matching						Olanzapine versus Risperidone after propensity score matching				Olanzapine versus Quetiapine after propensity score matching			
	Olanzapine (N=7797)		Risperidone (N=5909)		Quetiapine (N=4613)		Olanzapine (N=3049)		Risperidone (N=3212)		Olanzapine (N=2823)		Quetiapine (N=3127)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sociodemographic														
Male	4436	57	3112	53	1869	41	1535	50	1634	51	1135	40	1288	41
Age mean (SD)	42	(16)	47	(22)	45	(19)	45	(18)	45	(20)	45	(17)	45	(19)
White	3206	41	2096	35	2459	53	1028	34	1095	34	1363	48	1528	49
Black	231	3	151	3	61	1	66	2	779	2	63	2	39	1
South Asian	110	1	75	1	54	1	41	1	44	1	36	1	30	1
Other	203	3	127	2	77	2	51	2	80	2	82	3	47	2
Missing	4047	52	3460	59	1962	43	1863	61	1914	60	1279	45	1483	47
Least deprived	1013	13	922	16	709	15	464	15	484	15	434	15	520	17
2	1024	13	915	15	701	15	456	15	487	15	453	16	459	15
3	1448	19	1185	20	902	20	578	19	625	19	544	19	599	19
4	1954	25	1350	23	1106	24	710	23	704	22	642	23	738	24
Most deprived	1993	26	1319	22	988	21	708	23	780	24	640	23	676	22
Missing	365	5	218	4	207	4	133	4	132	4	110	4	135	4
Diagnosis*														
Schizophrenia	1799	23	1120	19	432	9	424	14	550	17	235	8	219	7
Bipolar	987	13	331	6	693	15	340	11	197	6	278	10	488	16
Other psychoses	1278	16	749	13	379	8	420	14	463	14	381	14	250	8
SMI register only	399	5	305	5	165	4	188	6	195	6	126	4	124	4
No SMI diagnosis*	3334	43	3404	58	2944	64	1677	55	1807	56	1803	64	2046	65
ADHD	42	0.5	135	2	41	1	29	1	34	1	23	1	29	1
Anxiety	1245	16	863	15	1246	27	594	19	631	20	793	28	889	28
Depression	2158	28	1463	25	2041	44	987	32	1072	33	1303	46	1457	47
OCD	130	2	128	2	121	3	82	3	86	3	67	2	86	3
Personality disorder	341	4	215	4	341	7	130	4	143	4	183	6	207	7
PTSD	158	2	58	1	134	3	39	1	44	1	86	3	94	3
Sleep disorder	697	9	531	9	678	15	373	12	395	12	443	16	498	16
No diagnosis	752	10	1414	24	561	12	443	15	463	14	288	10	367	12

*This includes those with no recorded diagnosis

Supplementary Table 2. Clinical characteristics of people prescribed three antipsychotics as monotherapy, before and after propensity score matching

	Total						Olanzapine versus Risperidone after propensity score matching				Olanzapine versus Quetiapine after propensity score matching			
	Olanzapine (N=7797)		Risperidone (N=5909)		Quetiapine (N=4613)		Olanzapine (N=3049)		Risperidone (N=3212)		Olanzapine (N=2823)		Quetiapine (N=3127)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Conditions														
Asthma	991	13	670	11	826	18	412	14	446	14	525	19	579	19
Atrial Fibrillation	29	0.4	68	1	55	1	22	1	24	1	19	1	24	1
CKD	78	1	70	1	118	3	40	1	44	1	57	2	72	2
COPD	94	1	72	1	64	1	44	1	52	2	45	2	45	1
Diabetes	192	2	327	6	298	6	130	4	138	4	118	4	170	5
Hypertension	508	7	508	9	505	11	290	10	304	9	291	10	342	11
Hypothyroidism	240	3	231	4	240	5	130	4	136	4	134	5	149	5
Learning disability	177	2	554	9	80	2	108	4	123	4	43	2	42	1
Palliative care register	11	0.1	7	0.1	8	0.2	4	0.1	6	0.2	6	0.2	6	0.2
Prescribed drugs														
Antidepressants	4933	63	3149	53	3494	76	2047	67	2188	68	2325	82	2553	82
Antidiabetics	122	2	223	4	190	4	83	3	90	3	74	3	108	3
Antihypertensives	1117	14	976	17	1107	24	588	19	625	19	696	25	783	25
Hypnotics	2358	30	1509	26	1923	42	1039	34	1091	34	1302	46	1445	46
Insulin	35	0.5	105	2	69	2	30	1	35	1	24	1	42	1
Statins	350	4	306	5	392	9	164	5	181	6	198	7	244	8
Health indicators (any time before start)														
High alcohol consumption	564	7	296	5	361	8	188	6	204	6	222	8	245	8
Illicit drug taking	1184	15	542	9	577	13	285	9	333	10	382	14	408	13
Non-smoker	259	3	241	4	142	3	167	5	156	5	119	4	116	4
Ex-smoker	3073	39	2469	42	2286	50	1383	45	1515	47	1480	52	1656	53
Current smoker	2837	36	1530	26	1538	33	996	33	1027	32	994	35	1103	35
missing	1628	21	1669	28	647	14	503	17	514	16	230	8	252	8
Systolic BP mean (SD)	124	(17)	126	(18)	125	(17)	126	(18)	125	(18)	125	(17)	125	(17)
Fasting glucose mmol/L mean (SD)	5.3	(1.7)	5.8	(2.4)	5.4	(2.1)	5.7	(2.3)	5.6	(1.9)	5.4	(1.7)	5.4	(2.2)
HbA_{1c} mmol/mol mean (SD)	48	(21)	54	(21)	51	(20)	51	(22)	51	(20)	50	(21)	50	(20)
Total cholesterol mmol/L mean	5.32	(1.17)	5.14	(1.18)	5.27	(1.18)	5.30	(1.16)	5.20	(1.19)	5.31	(1.14)	5.29	(1.16)

(SD)														
HDL cholesterol mmol/L mean (SD)	1.41	(0.49)	1.39	(0.76)	1.38	(0.43)	1.43	(0.53)	1.39	(0.81)	1.43	(0.50)	1.39	(0.42)
Weight kg mean (SD)	73	(18)	75	(19)	76	(20)	74	(18)	75	(19)	73	(19)	76	(19)
Height m mean (SD)	1.70	(0.10)	1.68	(0.11)	1.68	(0.10)	1.69	(0.10)	1.68	(0.11)	1.68	(0.10)	1.68	(0.10)
Seen a psychologist at least once	1141	15	705	12	864	19	439	14	465	14	551	20	616	20
Seen a psychiatrist at least once	6246	80	3883	66	3608	78	2151	71	2330	73	2255	80	2479	79
Had at least one crisis not MHA	117	2	56	1	73	2	47	2	46	1	45	2	51	2
Had at least one crisis MHA	616	8	287	5	323	7	155	5	179	6	215	8	237	8

BP Blood Pressure. CKD: Chronic Kidney Disease. COPD: Chronic Obstructive Pulmonary Disease. HDL High Density Lipoprotein MHA. Mental Health Act Assessment. SD Standard Deviation.

Supplementary Table 3. Results from matched and unmatched analysis comparing CVD in three antipsychotics

Olanzapine versus Risperidone

	Main Matched analysis Model 1		Supplementary unmatched analyses Model 2		Model 3	
	IRR	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**
CVD incidence						
Olanzapine n/N %	82/3049	2.69	166/7797	2.13	166/7797	2.13
Risperidone n/N %	81/3212	2.52	202/5909	3.42	202/5909	3.42
Olanzapine	**1.07**	**(0.78, 1.45)**	**0.63**	**(0.51, 0.77)**	**0.99**	**(0.80, 1.23)**
Risperidone (reference)	1.00		1.00		1.00	
Female					0.82	(0.66, 1.02)
Age					1.05	(1.05, 1.06)
Townsend Quintiles						
1 least deprived (Reference)					1.00	
2					1.00	(0.70, 1.44)
3					1.21	(0.86, 1.71)
4					1.25	(0.89, 1.75)
5 most deprived					1.45	(1.02, 2.07)
Missing					1.64	(0.97, 2.76)

Olanzapine versus Quetiapine

	Main matched analysis Model 1		Supplementary unmatched analyses Model 2		Model 3	
	IRR	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**
CVD incidence						
Olanzapine n/N %	53/2823	1.88	166/7797	2.13	166/7797	2.13
Quetiapine n/N %	65/3127	2.08	90/4613	1.95	90/4613	1.95
Olanzapine	**0.90**	**(0.62, 1.30)**	**1.10**	**(0.85, 1.42)**	**1.52**	**(1.16, 1.98)**
Quetiapine (Reference)	1.00		1.00		1.00	
Female					0.73	(0.56, 0.94)
Age					1.06	(1.05, 1.06)
Townsend Quintiles						
1 least deprived (Reference)					1.00	
2					0.96	(0.62, 1.49)
3					1.09	(0.72, 1.65)
4					1.18	(0.79, 1.76)
5 most deprived					1.25	(0.82, 1.91)
Missing					1.38	(0.75, 2.54)

Model 1 Propensity score matched
Model 2 Unadjusted unmatched analysis
Model 3 Unmatched analysis, adjusted for age sex and deprivation

IRR: Incidence rate ratio

Supplementary figure 1: Propensity score analysis