Can genomics enhance care and quality of life in psychosis?

Investigating the cost-effectiveness of pharmacogenomics in mental health

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at

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Declaration

I, Noushin Saadullah Khani, confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

Abstract

Schizophrenia is a complex psychotic disorder which is a leading cause of disability and reduced quality of life worldwide. Individuals with schizophrenia have an increased risk of mortality due to poor physical health, such as metabolic syndrome. In this thesis, I aim to address whether a genomics-guided approach can individualise antipsychotic treatment to improve care and quality of life for individuals with psychosis, and whether this approach is cost-effective.

In Chapter 2, I conducted a systematic review to investigate whether the use of pharmacogenetics to optimise the prescribing of antipsychotics improves health or economic outcomes. Chapter 2 revealed a lack of studies to assess the clinical utility and cost-effectiveness of pharmacogenetic testing in the UK. Chapter 3 involves an investigation of the causal relationship between schizophrenia and cardiovascular abnormalities, such as diabetes. No evidence of a causal relationship was identified, suggesting that the relationship is likely to be explained by other factors, such as antipsychotic-induced adverse drug reactions. In Chapter 4, I explored whether genetic variation in a pharmacogene (*CYP2D6*) was associated with healthcare costs from a sample of individuals with psychosis participating in the ongoing Pharmacogenetics in Mental Health Study, which showed that intermediate metabolisers had significantly higher primary care costs compared to normal metabolisers. Finally, in Chapter 5, I ran a cost-effectiveness analysis investigating the use of pharmacogenetic testing for *CYP2D6* and *CYPC19* to guide prescribing for individuals with schizophrenia, using a decision tree and Markov model, from a healthcare perspective. The genomics-guided approach was found to be cost-effective, although further evidence demonstrating clinical utility is required. This thesis suggests that while a genomics-guided approach could potentially improve health and economic outcomes in schizophrenia, further research is ultimately required to support these findings.

Impact statement

Pharmacogenomics is a growing field which offers promise in reducing adverse effects and improving therapeutic efficacy, and the NHS Genomic Medicine Service is currently developing the rollout of pharmacogenomics and medicines optimisation in the NHS. However, the majority of the evidence supporting the use of pharmacogenetics pertains to physical health conditions, such as cancer and cardiovascular disease. Thus, this thesis aimed to evaluate whether a genomics-guided approach demonstrated improvements in clinical and economic outcomes in schizophrenia to support implementation.

This thesis begins by conducting a systematic review to evaluate whether pharmacogenetic testing for antipsychotic medication may improve clinical and/or economic outcomes. This chapter highlighted the heterogeneity of the current evidence base, which demonstrates a potential challenge for evidence-based implementation. I identified several gaps in the literature, including limited participant diversity and a lack of UK-based studies, and I made several recommendations for future studies, including optimal study design and recommended study outcomes to address issues related to heterogeneity.

Chapter 3 uses Mendelian randomisation to investigate the causal relationship between schizophrenia and cardiometabolic abnormalities to address the increased mortality rate in schizophrenia. This chapter demonstrates that there is no evidence of a causal relationship; rather, cardiometabolic abnormalities in schizophrenia may be attributable to other factors such as lifestyle and adverse effects of antipsychotic medications. Evaluating this relationship enhances our understanding of disease aetiology and may lead to more effective interventions for prevention and treatment strategies.

Chapters 4 and 5 address the gaps identified by my systematic review. In Chapter 4, I investigate the impact of a pharmacogene on healthcare expenditures using baseline

data from a clinical trial, the Pharmacogenetics in Mental Health study. This is the first and largest investigation of the use of pharmacogenetics in individuals with a psychotic disorder, specifically in the UK. More than one-third of the participants in the sample were from a Black, Asian, and minority ethnic background, directly addressing the lack of diversity in pharmacogenetic research. Furthermore, Chapter 5 uses decision analytic modelling to demonstrate that pharmacogenetic testing in schizophrenia is cost-effective from a healthcare provider perspective in the UK's NHS. By demonstrating the cost-effectiveness of pharmacogenetic testing, this work provides a strong economic rationale for wider implementation in psychosis care. Together, the findings suggest that pharmacogenetic testing has the potential to enhance cost-effective care for individuals with schizophrenia, though robust evidence of clinical utility is still needed to support implementation in routine practice.

Publications directly related to the thesis:

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Statement of contributions

Chapter 1

Chapter 1, i.e., the introduction, was written independently by me.

Chapter 2

Chapter 2 contains content from a paper that I wrote and published in Nature Mental Health. For more detail, please see Research Paper Declaration Form 1. For this chapter, I wrote a systematic review protocol, which was published on PROSPERO. I designed the eligibility criteria and search strategy. The search strategy was conducted by Soumita Ramesh, Georgina Mills, Georgie Hudson and I. I extracted the data from the included studies, and Gesche Jürgens, Lorena Carrascal-Laso, Manuel Franco-Martin, and Benjamin Skov Kaas-Hansen assisted in acquiring unpublished data from their studies to include in the systematic review. Quality assessment and synthesis of the data was conducted by me.

Chapter 3

Chapter 3 contains content from a paper that I wrote and published in Frontiers in Genetics. For more detail, please see Research Paper Declaration Form 2. In this chapter, I planned the methodology, sourced the data for analysis, and conducted the analysis. Benjamin I. Perry and Golam M. Khandaker assisted with interpretation of results.

Chapter 4

Chapter 4 was conducted as part of the ongoing Pharmacogenetics in Mental Health study[1]. I was involved in trial management in the early phase of the study, and this was subsequently taken over by Rosemary Abidoph. The data for this study has been collected

by 11 NHS trusts across England. Rosemary Abidoph, Daisy Mills, and Maria Richards-Brown have led data collection for self-referrals at UCL. DNA extraction and processing of blood and saliva samples was conducted by Marius Cotic, and genotyping and phenotype assignment was performed by an NHS laboratory in Birmingham, UK, and industry-based facility in Houston, USA. Lauren Varney performed quality control checks of the clinical data (medication, demographics and other data) and managed the trial database. I conducted the quality control of all health economic data for the study (healthcare resource usage) and conducted the analyses.

Chapter 5

In this chapter, I conceptualised the health economic model structure, with guidance from Huajie Jin and Elvira Bramon. I conducted literature searches for parameterisation of the model. This was supported by Huajie Jin, who assisted with data acquisition for the model. The R scripts for the model were adapted from the scripts provided in the Decision Modelling for Health Economic Evaluation course by the University of York and London School of Hygiene and Tropical Medicine, and they are available at `https://github.com/LSHTM-GHECO/DM4HEE_RCode`. I conducted base-case, scenario and sensitivity analysis, and interpreted the results, with help from Huajie Jin and Barbara Barrett. I wrote the chapter independently.

Chapter 6

Chapter 6, i.e., the discussion, was written independently by me.

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Chapter 1

Introduction

1.1 Psychosis

Psychosis represents a combination of symptoms where reality is perceived and interpreted differently, resulting in distress or alterations in function and behaviour. The World Health Organisation (WHO) ICD-11 classification system group psychotic disorders together as “Schizophrenia or other primary psychotic disorders”, comprising schizophrenia, schizoaffective disorder, schizotypal disorder, delusional disorder, acute and transient psychotic disorder, and other specified schizophrenia or primary psychotic disorders[2].

1.2 Schizophrenia

1.2.1 Diagnosis

Schizophrenia is the most common psychotic disorder. There are currently no diagnostic tests or biomarkers available for the diagnosis of schizophrenia, thus, it is based on an assessment of numerous psychiatric symptoms, as described in ICD-11[2]. Each symptom is important to distinguish schizophrenia from other psychotic disorders such as schizoaf-

fective disorder, depressive disorder with psychotic features, and bipolar disorder with psychotic features through an assessment of the duration of illness, timing of delusions or hallucinations, and the severity of depressive episodes[3]. Schizophrenia is characterised by the presence of positive symptoms, such as delusions or hallucinations (auditory, visual, tactile), and negative symptoms, such as social withdrawal and diminished emotional expression. While the positive symptoms of schizophrenia are easily identifiable, the negative symptoms are more difficult to diagnose, as they can be primary to a diagnosis of schizophrenia or secondary to a concomitant psychiatric diagnosis, medication, or environmental factor[3]. Previous research suggests that positive symptoms tend to relapse (although some patients experience long-term psychotic symptoms), whilst negative and cognitive symptoms tend to be long-lasting[4]. In addition to the two core sets of symptoms mentioned, individuals with schizophrenia may also experience cognitive symptoms, such as disorganised speech, thought, and/or attention. Importantly, for diagnosis, these symptoms must not be the result of another medical condition, such as a brain tumour, or due to substance or medication use[3].

1.2.2 Aetiology

The aetiology of schizophrenia is complex and heterogeneous, and involves a combination of genetic and environmental factors. Schizophrenia is highly heritable, with a heritability estimate of approximately 60-80%[5]. For monozygotic twins, the risk of one twin having schizophrenia is 48% if the other has the disorder, whereas the risk is 12-14% in dizygotic twins[3]. Parents who both have schizophrenia have a 40% risk of producing a child who also has schizophrenia[3]. Schizophrenia is highly polygenic, with a significant portion of the heritability attributed to common single nucleotide polymorphisms (SNPs, >10% population frequency) but individually have weak effects[5] and therefore low penetrance. SNPs are changes in a single nucleotide that occur in $\geq$1% of the population. A recent genome-wide association study (GWAS) by the Psychiatric Genomics Consortium (PGC)

identified 287 distinct genetic loci containing relatively common alleles of small effect from a sample of 76,755 cases and 243,649 control individuals[6]. The SNP with the largest effect size, rs140365013, had an odds ratio (OR), of 1.23. Alternatively, rare copy number variants (CNVs) at multiple loci are associated with a high risk of schizophrenia. CNVs are segments of DNA ($\geq$50 base pairs) that can be deleted or duplicated, and lead to disruptions in gene structure and function[7]. They only occur in a small proportion of patients with schizophrenia but are highly penetrant. For example, deletions at 22q11.2 and 3q29 have been associated with the highest risk of schizophrenia (>50-fold risk)[8][7].

Although there is a well-established genetic component to the aetiology of schizophrenia, GWAS studies only explain a minority of the variance in the liability for schizophrenia. Thus, a significant proportion of the liability may be explained by non-genetic factors[9]. Childhood adversity (such as loss of a parent, maltreatment, abuse, and bullying), high urbanicity, high paternal age, and first- and second-generation immigrant background are also associated with the development of schizophrenia[9]. Emerging evidence indicates that these environmental factors have additive effects on the risk of developing psychosis[9][10]. Stepniak et al[11] demonstrated that exposure to multiple environmental factors increases the risk for early schizophrenia onset when accumulated. In their study, individuals with no risk factors experienced disease onset 8 years later and prodromal onset 9 years later compared to those with four our more risk factors. They also had significantly higher years of education, lower number of psychiatric hospital admissions, and were less likely to be unemployed. An aggregate measure of environmental risk for psychoses in asymptomatic individuals was developed by Vassos et al[12], coined the Maudsley environmental risk score for psychosis. It uses 6 risk factors: migration, urbanicity, paternal age, obstetric complications, cannabis, and childhood adversity, to quantify an individual's risk for psychosis.

Genetic factors and environmental factors also interact to increase the risk for schizophrenia. For example, the neurodevelopmental hypothesis proposes that disruption of brain development during the prenatal and perinatal period underlies the incidence of schizophrenia during adulthood. Walsh et al. [13], identified novel CNVs which are thought to disrupt neurodevelopmental pathways, such as synaptic long-term transmission, neuregulin signaling, axonal guidance, and integrin signaling. Moreover, environmental risk factors during pregnancy, including maternal stress, maternal infections (such as influenza, toxoplasmosis, and herpes simplex virus type 2[9]), nutritional deficiency, and birth complications, may lead to disruptions to normal neutral development throughout foetal life, childhood, and adolescence[14].

1.2.3 Epidemiology

The Global Burden of Disease (GBD) study conducted by the World Health Organization (WHO) has quantified the prevalence, incidence, and the burden of disease attributed by schizophrenia since 1990[15][16]. The main metric used to quantify disease burden in the GBD study has been disability-adjusted life years (DALYs), with one DALY equal to one healthy year of life lost to a disease. The absolute global prevalence estimated by the 2019 GBD study was 0.29%[15], although a previous systematic review including 188 studies reported a slightly higher prevalence of 0.72% (interquartile range: 0.47-1.72%)[17]. The 2021 GBD study found that from 1990 to 2021, schizophrenia raw prevalence, incidence, and DALYs has increased by over 48% (14.2 to 23.2 million), 24% (941,000 to 1.2 million), and 47% (9.1 to 14.8 million), respectively [15][16]. The 2019 GBD study demonstrated that, out of 12 mental disorders, schizophrenia had the lowest prevalence (2 million, 0.08%) in individuals aged 5-24 years. [18]. However, it ranks fifth as a cause of burden in individuals aged 15-24 years, third in individuals aged 25-69-years, and fourth in individuals over 70 years, out of 12 mental disorders. Thus, despite being a low prevalence disorder, the burden of disease is substantial[19].

The average age of onset of schizophrenia for most individuals tends to be in early adult life; the proportion of individuals with onset of schizophrenia-spectrum disorders before the ages of 14, 18 and 25 are 3%, 12.3%, and 47.8%, respectively, and a median age at onset of 25 years[20]. Indeed, a systematic review found that the incidence of schizophrenia peaks in the early twenties in women and men and declines thereafter, being steeper for men[21]. There is also suggestive evidence that women have a secondary peak in their mid- to late-forties[21].

1.2.4 Prognosis

There is considerable variation between patients in regards to different degrees of deterioration[22]. A systematic review and meta-analysis of prospective follow-up studies on schizophrenia, spanning 20 years or more, found that 24.2% of patients with schizohrenia had "recovered", 35.5% had a "good or better" outcome (which included "recovered"), 59.7% had a "moderate or better" outcome (which included "good or better" and "recovery"), leaving 40.3% with a poor long-term outcome[23]. Another study found that approximately 20% of patients significantly improve and experience full recovery, while others experience chronic symptoms, social and occupational difficulties, and may require support in daily living[3]. The disabilities experienced by people with psychosis and schizophrenia are not solely due to recurrent episodes or continuing symptoms, but also due to adverse drug reactions, social adversity and isolation, poverty, and homelessness. These disabilities are exacerbated due to the continuing prejudice, stigma and social exclusion associated with the diagnosis. Thus, patients may be affected in their ability to live independently, perform activities of daily living, maintain personal relationships, and participate in social, work and study activities[24].

1.3 Burden in schizophrenia

1.3.1 Economic burden

As previously mentioned, schizophrenia is a leading cause of disability worldwide, and consequently entails a tremendous health, social, and economic burden, not only for patients themselves but also for families, caregivers, healthcare systems, and wider society. A recent systematic review indicated that the annual societal cost of schizophrenia greatly varies per patient, from USD$819 in Nigeria to USD$94,587 in Norway[25]. This study indicated that 32-83% is attributed to the indirect costs, which refers to the "invisible costs" associated with income losses due to mortality, disability and loss of productivity due to work absence or early retirement[25][26]. It is believed that productivity losses are the primary driver of the societal cost of schizophrenia; even though 97.5% of individuals with schizophrenia have previously reported interest in employment, the employment rate for people with schizophrenia ranges from 4% to 50.4%[27]. After productivity losses, the other costs that contribute largely to the total societal costs are direct healthcare costs, followed by direct non-healthcare costs[25]. Direct costs associated with diagnosis and treatment, which make up approximately 11-87% of the total cost in the UK. Direct medical costs include medical services for diagnosis, treatment, medication, care, rehabilitation, counselling, while direct non-medical costs include costs of other services related to the disease, such as accommodation and transportation to the clinic.

1.3.2 Clinical burden

Patients with mental disorders have significant reductions in average life expectancy of 10-20 years[28]. A recent meta-analysis of 135 studies found that patients with schizophrenia had a 2.5-fold increased risk of all-cause mortality compared to the general population, and was highest in patients with first-episode schizophrenia, who had a seven-fold increased risk[29]. Increased mortality is attributable to poor physical health, as patients

have a higher risk of metabolic syndrome, which can increase the risk for the development of type 2 diabetes mellitus and cardiovascular disease[30]. Metabolic syndrome is a condition which is diagnosed by the presence of at least 3 of the following risk factors: obesity, hypertension, increased triglycerides, low high-density lipoprotein cholesterol, and increased fasting glucose[30]. The risk for patients with schizophrenia is 10-15% for diabetes, 45-55% for obesity, 19-58% for hypertension, 25-69% for dyslipidaemia, and 37-63% for metabolic syndrome[24], which ultimately contributes to the increased mortality rate. As well as poor physical health, mortality can be attributed to suicide, which is ten-fold higher compared to the general population[29]. Indeed, it is estimated that between 4 and 13% of patients with schizophrenia attempt suicide. Risk factors include previous depressive disorders, young age, male gender, among other factors[24]. Depression is a common co-morbidity in schizophrenia and the prevalence of depression is higher in patients with schizophrenia than the general population, with rates of depressive symptoms in schizophrenia ranging between 13% to 81%. The presence of depressive symptoms reduces quality of life, and increases suicidality, psychotic relapse, and psychiatric hospitalisation[24].

1.3.3 Humanistic burden

The WHO define quality of life (QoL) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"[31]. A previous meta-analysis found that schizophrenia subjects scored significantly lower on QoL scales such as the SF-36 and WHOQOL/WHOQOL-BREF scales compared to controls, in domains such as physical health, psychological and mental health, social relationships, and environmental domains[32]. While many people with schizophrenia can live independently, others may have difficulty and may have a reduced capacity to care for their own day-to-day needs, which may partly explain these lower QoL scores. As a result, these individuals may have

formal or informal daily living support[24]. Indeed, the development of community mental health services has led to the return of long-term hospitalised patients to their families, also referred to as deinstitutionalization, in Western countries such as the US, France, and Ireland, since the 1950s[25]. It has become common for family members to become caregivers, with 41% of caregivers being a parent, 12% a sibling, and 7% a spouse or partner[24]. Previous literature indicates that the burden of schizophrenia extends beyond the patient to the caregivers and impacts the physical, psychological, emotional, social and financial lives of the caregivers[24]. Previous studies have also emphasised the productivity losses for caregivers, who are also affected as they may reduce work hours or take a leave of absence to look after a patient. It is estimated that 1.2% and 2.5% of caregivers have given up work for a first-episode and highly dependent patient, respectively. In addition, caregiver burden includes emotional distress, decreased life satisfaction, sleep disturbances, poorer physical health, among others[24].

1.4 Treatment

Antipsychotic medications have been primarily indicated for the treatment of schizophrenia and other psychotic disorders since the 1950s. They are used to improve symptoms, prevent relapse, and improve adaptive functioning so that the patient can be integrated back into the community[3]. There are more than 20 different antipsychotic drugs licensed for the treatment of psychotic disorders in the UK and they are usually prescribed within the recommended British National Formulary dosage range. They can be classified into two major groups: first generation antipsychotics introduced in the early 1950's and second-generation antipsychotics introduced since the 1990s [33][34][35]. Examples of first-generation antipsychotics include chlorpromazine, trifluoperazine, and haloperidol[34]. Examples of second-generation antipsychotics include quetiapine, amisulpride, risperidone, and olanzapine[34]. A previous systematic review including 278 randomised con-

trol trials, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, found that second-generation antipsychotics and first-generation antipsychotics have comparable efficacy, except for clozapine which improved symptoms more than most other drugs [36]. They are available as oral, intramuscular (medium- or long-acting depot preparations), and intravenous preparations. According to the National Institute for Health and Care Excellence (NICE), choice of first-line antipsychotic depends on based on patient's personal choice, medication history, symptoms, adverse effects, and degree of sedation. If the patient does not respond to a first-line conventional antipsychotic, they are switched to a second-line conventional antipsychotic. After not responding adequately two lines of antipsychotic therapy, the patient is switched to clozapine, which would require mandatory white blood cell and absolute neutrophil count monitoring[37] due to the risk of neutropenia and agranulocytosis[3].

1.4.1 Treatment response

The majority of people experience symptom improvements after antipsychotic treatment and it is key in helping people with psychosis to live in the community[33]. Indeed, a meta-analysis with 65 trials, in which patients were randomised to continue antipsychotic medication or switch to placebo, demonstrated that antipsychotic treatment was significantly more effective compared to placebo, effectively reducing the relapse and readmission rates to less than half[38].

However, approximately 34% of patients diagnosed with schizophrenia are treatment resistant, which is defined by NICE as a lack of therapeutic response after the use of at least two different antipsychotics, including an atypical antipsychotic[39]. Clozapine is a second-generation antipsychotic which is currently only licensed for use in the UK for patients with treatment-resistant schizophrenia, and is effective for 60-70% of patients. However, clozapine is an underutilised medication, and nearly 50% of patients with treatment-

resistant schizophrenia do not receive a proper trial of clozapine due to its adverse effects and the need for therapeutic blood monitoring[40]. Combining antipsychotics is relatively common in clinical practise to improve therapeutic response when there has been an unsatisfactory response to a single antipsychotic, but there is limited evidence for this and it is not recommended by NICE or the Maudsley Prescribing Guidelines, except at a last resort when conventional antipsychotics and clozapine have failed[39][34]. A recent study of patient electronic health data found that almost a quarter (24.7%) of patients prescribed antipsychotics had at least one period of antipsychotic polypharmacy which lasted at least 30 days[41]. However, this can lead to a high total dose and increased incidence and severity of adverse effects[34]. There are reports of increased mortality rates in patients that received more than one antipsychotic concurrently, although this evidence is inconsistent[42]. There is currently limited evidence to suggest that the administration of high dose antipsychotics (i.e., doses above the recommended maximum) or combined antipsychotics improves efficacy.

1.4.2 Adverse drug reactions

Antipsychotics have been associated with developing extrapyramidal symptoms, such as akathisia, tardive dyskinesia, acute dystonic reactions[36]. This can be attributed to the binding and antagonism of dopamine receptors, notably D_2 and D_3 receptors, as demonstrated by the absence of haloperidol-induced catalepsy in D_2 receptor knockout mice [43]. Thus, second-generation antipsychotics were introduced as having possibly lower risk of extrapyramidal symptoms compared to first-generation antipsychotics[36]. These also bind to dopamine receptors to some degree, and the presence of motor effects may be related to the rate of dissociation of second-generation antipsychotics from dopamine receptors. For example, second-generation antipsychotics with rapid dissociation and lower potency, such as quietapine, have a lower propensity to cause extrapyramidal symptoms compared to second-generation antipsychotics with high affinity and tighter binding, such

as aripiprazole [44]. In addition, second-generation antipsychotics are associated with weight gain, hyperlipidaemia, and diabetes mellitus and therefore have an increased risk of cardiovascular disease[36]. second-generation antipsychotics bind to a variety of other neurotransmitter receptors, including serotonergic (5HT1, 5HT2a, and 5HT2c), adrenergic (α_1, α_{2A}, α_{2B}, α_{2C}), histaminergic (H1), and muscarinic M1 and M3 receptors[35]. Thus, antipsychotic-induced metabolic side effects may be attributed to the affinity for binding to receptors in the central nervous system and peripheral organs. Given the comparable efficacy between first- and second-generation antipsychotics[36], the main difference is, therefore, their propensity to cause different types of ADRs due to their binding affinity for a variety of different receptors. In addition to motor and metabolic effects, second-generation antipsychotics can also cause sedation, dry mouth, dental caries, gastrointestinal symptoms and sexual dysfunction, among other events[44]. Unfortunately, individuals who experience adverse drug reactions are more likely to discontinue their medication, increasing the risk of relapse and hospital readmission[24].

1.4.3 Non-adherence to treatment

The definition of non-adherence, according to the WHO, is “a case in which a person’s behavior in taking medication does not correspond with agreed recommendations from health personnel”[45]. According to a recent meta-analysis, over half (56%) of patients with schizophrenia do not adhere to psychotropic medication[46]. Medication adherence lies on a spectrum, with patients who may not take any medication at all on one end, and patients who take all of the medication prescribed to them on the other. In the middle of these extremes are patients who take medication some of the time but not as consistently as they were prescribed. Medication non-adherence is a challenge throughout medicine, but can be especially difficult for individuals diagnosed with schizophrenia due to lack of insight about their illness and treatment, the direct impact of symptoms (such as depression, cognitive impairment, and positive and negative symptoms), co-morbid

substance misuse, and limited access to mental health care[47][48]. The prevalence of non-adherence in psychosis is, therefore, at least as high (if not higher) as many chronic medical disorders[48]. Non-adherence in schizophrenia is associated with worse prognosis, poor quality of life or psycho-social outcomes, increased frequency of relapse, rehospitalisation, and therefore increased utilisation of healthcare resources[49]. Indeed, a previous study found that non-adherence to antipsychotic medication was associated with an excess annual cost per patient of £2481 for inpatient hospital services and £5231 for total healthcare services[50]. Furthermore, a 20-year follow-up study of patients with first-episode psychosis found that non-adherence was associated with decreased survival: the risk of death was 174-214% higher among nonusers and patients who discontinued antipyschotics after discharge compared to patients who received antipsychotic treatment[51]. Thus, ongoing adherence is key to optimal outcomes in patients.

1.4.4 Pharmacokinetics of antipsychotics

Antipsychotics undergo a process of metabolism in the liver after they undergo absorption. The phases of antipsychotic biotransformation include phase I (modification), and phase II (conjugation). Drugs are transformed by oxidation, reduction, or hydrolysis in phase I reactions to more soluble compounds to facilitate their excretion from the body[52]. They subsequently undergo phase II metabolism, which consists of a conjugation of a drug or its metabolite with a highly polar compound, such as glutathione, glycine, sulfate, or glucuronic acid to decrease drug activity and increase polarity. Thus, phase II reactions also facilitate their excretion from the body[52]. Phase I and II can be sequential, or they can occur in reverse order or concurrently[52].

1.4.5 Cytochrome P450 enzymes

When pharmacokinetics are considered, it is important to take into account the cytochrome P450 (CYP450) system. The CYP450 system comprises a superfamily of enzymes are

responsible for metabolism of endobiotics, which are endogenous compounds such as hormones, steroids, and cholesterol, and xenobiotics, which are foreign compounds such as drugs[53][54]. Indeed, they are involved in phase I reactions for the metabolism of antipsychotics and other medications such as antidepressants, analgesics, and beta-blockers[55]. Drug metabolism primarily occurs in the endoplasmic reticulum of hepatic cells, but CYP enzymes can be found in a variety of other tissues, such as the central nervous system[54]. In total, the human genome encodes at least 57 CYPs, and the genes are organised into 18 families and 43 subfamilies[53]. Sequences that are 40% or more identical at the amino acid level belong to the same family, represented by a number[54]. Isoforms belonging to the CYP1, CYP2, and CYP3 families are responsible for metabolising approximately 80% of drugs[53]. Sequences that are 60% or more identical belong to the same subfamily, designated by a capital letter. After this, the individual genes are arbitrarily numbered[54]. Regarding the biotransformation of antipsychotic drugs, 40% of antipsychotics are major substrates of the CYP2D6 enzyme, 23% are major substrates of CYP3A4, and 18% are major substrates of CYP1A2. Although CYP2C19 plays a larger role in the metabolism of antidepressants, clozapine is a substrate of CYP2C19[56]. It is important to note that phase I reactions mediated by CYPs are dependent on many factors, including demographics (age, ethnicity), lifestyle (nutritional status, smoking) and, concurrent medication [52]. These enzymes can also be induced by other xenobiotics, for example, tobacco is a potent inducer of CYP1A2, indicating that its consumption and withdrawal may lead to pharmacokinetic drug interactions. It is also clear that an individual's genetics plays an important role in metabolism of CYP450 enzyme[57].

1.4.6 Genetic variation of cytochrome P450

The genes coding CYP isoforms are highly polymorphic. For example, there are more than 100 genetic variations identified for the *CYP2D6* gene on chromosome 22q13.2 by the Pharmacogene Variation Consortium[58]. These variants reflect structural variants,

such as copy number variants, including duplications or deletions of DNA sequence or short insertions/deletions of nucleotides, or most commonly, SNPs[59]. Variation in CYP genes are described using the star (*) allele nomenclature and used to translate an individual's genotype (the genetic makeup of an individual, comprised of one maternal allele and one paternal allele present at each genetic locus) to phenotype (a physical characteristic of an individual)[60].

The wild-type, or reference allele to which other alleles are compared against, is represented by **1*. Thus, changes in the wild-type alleles (e.g., **2* or **3*) represent one or more variants in the CYP gene, and potentially altered CYP functionality[60]. It is important to note that a single star allele can identify not just one variant, but a group of variants. For example, *CYP2D6*2* includes two variants: rs16947 (c.2851C>T) and rs1135840 (c.4181G>C). The combination of alleles determines an individual's genotype, such as *CYP2D6*1/*2*. To translate this to the individual's phenotype, a value is assigned to each star allele, ranging from 0-1, where 0 represents absent function, 0.5 for reduced function, and 1.0 for normal function (Table 1.1)[60]. As mentioned, genes can also have a variable copy number, due to duplications (e.g., x2, x3), or deletions. In this instance, the activity value is multiplied by the number of gene copies (Table 1.1)[60]. The activity score is calculated as the sum of the activity values assigned to each allele. This results in four different categories of metabolic phenotypes: poor metabolizers (PMs) who have an activity score of 0 (i.e., absent CYP2D6 activity), intermediate metabolisers (IM) who have an activity score between 0.25-1 (i.e., reduced CYP2D6 activity), extensive/normal metabolizers (EMs/NMs) who have an activity score between 1.25-2.25 (i.e., normal CYP2D6 activity) and ultrarapid metabolizers (UMs) who have an activity score greater than 2.25 (i.e., increased CYP2D6 activity) [60].

Increased or reduced enzyme activity affects the rate of clearance of a drug, which

Table 1.1: Functionality of selected *CYP2D6* alleles. Adapted from Koopmans et al. [61], and Kane [62]. A full list of *CYP2D6* alleles can be found on `https://www.pharmvar.org/gene`.

Allele type	CYP2D6 alleles	Value for activity score calculation
Normal function	**1, *2, *35*	1
Decreased function	**9, *17, *29, *41*	0.5
"Severely" decreased function	**10*	0.25
No function	**3, *4, *5, *6, *40*	0
Increased function	**1x2, *2x2*	2
Unknown	**43, *60, *65, *82, *84*	N/A

affects plasma drug concentrations and subsequently an individual's response to antipsychotics and their adverse effect profile[55][63]. For example, individuals with the PM phenotype are likely to have increased plasma drug concentration to antipsychotic drugs compared to NMs, increasing the risk of adverse drug reactions (ADRs). Alternatively, UMs have a reduced plasma drug concentration, which can lead to subtherapeutic levels of drug at doses that would be effective in NMs. These examples assume that metabolism of the drug results in an inactive metabolite; in a scenario where an individual is taking a prodrug, it would result in the reverse[55]. For example, an ultrarapid metaboliser which takes a prodrug would need lower doses to achieve a therapeutic effect, as the standard dose could lead to toxicity. Although phenotype frequencies of pharmacogenes vary among ethnic groups, normal and intermediate metabolisers are the most common phenotypes observed globally[64]. Frequencies of CYP2D6 predicted phenotypes by ethnic group are summarised in Table 1.2. Poor metabolisers of CYP2D6 are more frequently observed in Europeans, such as the British (12.1%), the Danish (10.6%), and Basque (French) people (9.7%). This is thought to be attributed to the high frequency of *CYP2D6*4*[61]. Ultrarapid metabolisers are more commonly observed in individuals of Middle Eastern, Oceanian or Jewish ancestry[64]. For example, non-Austronesian Melanesians have an ultrarapid

Table 1.2: Average phenotype frequencies for *CYP2D6* across ethnic groups (in %). Adapted from Gaedigk et al [64]. PM, poor metaboliser; IM, intermediate metaboliser; NM, normal metaboliser; UM, ultrarapid metaboliser.

Major ethnicities	PM	IM	NM	UM
African American	2.4	39.0	55.7	3.7
African	2.8	38.5	56.5	3.8
From the Americas	1.9	22.9	72.2	4.6
East Asian	0.4	34.5	64.7	1.4
European	5.4	35.3	59.4	3.1
Middle Eastern or Oceanian	0.9	24.9	67.2	11.2
South Central Asian	1.1	28.6	68.7	2.7
Jewish	6.0	37.7	44.9	11.5

metaboliser frequency of 21.5% due to the high frequency of allele duplications[61].

1.5 Pharmacogenetic testing

Like almost every medication, antipsychotics are typically prescribed in a prioritised order based on our knowledge of their tolerability and are subsequently adapted to the patient's needs using clinical observations to identify the optimal medication and dose that will maximise response and minimise toxicity[55]. However, this empirical process can lead to substantial delays finding the drug and dose of choice for each patient. As already discussed, the response to antipsychotics is highly variable among individuals and many patients experience a range of adverse effects or non-response[33]. A qualitative study of young people with a mental health condition viewed this trial-and-error process as a challenging one, as there was the potential that the individual's condition could be worsened during the medication change-over process[65].

Inter-individual variability to food and drugs has origins dating 510 BC, when Pythago-

ras discovered the occurrence of red blood cell haemolysis after the ingestion of fava beans, later discovered in the 1950s to be the result of mutations in the *G6PD* gene, which leads to glucose-6-phosphate dehydrogenase deficiency[66]. Consequently, this was coined "pharmacogenetics", the study of genetic variation of drug-metabolizing enzymes (as well as drug receptors, transporters and drug targets), and how these genetic variations can lead to drug-related phenotype, such as drug response or toxicity. While this term is used interchangeably with pharmacogenomics, it is important to make the distinction that pharmacogenetics refers to the impact of variation in individual genes on treatment response, whereas pharmacogenomics is a broader term which refers to the impact of variation in the entire genome on treatment response[66]. Thus, the inter-individual variability in response to antipsychotic therapy is partly explained by genetics in conjunction with clinical, demographic and environmental factors[59]. The majority of research in this field focuses on pharmacokinetics, such as the CYP450 genes mentioned previously, with less research on pharmacodynamic genes, such as genes encoding serotonin and dopamine receptors. Genetic variants in relevant pharmacogenes, such as the CYP450 superfamily, offer potential for clinical application to optimise and guide treatment. Knowledge of patients' drug metabolizer status through pharmacogenetic testing could optimise the selection of antipsychotic medication and adjustment of therapeutic doses, which may help to prevent adverse drug reactions and improving treatment efficacy and compliance, therefore relieving a major cost-burden on the healthcare system[63].

1.6 Genomic medicine in the NHS

Over the past decade, genomics has become a priority in the healthcare agenda. In 2013, the UK's Department of Health and Social Care established Genomics England to deliver the 100,000 Genomes Project. The aim was to conduct whole-genome sequencing on 100,000 genomes from individuals with cancer and rare disease to improve early detec-

tion and treatment[67][68]. This project was facilitated by 13 NHS Genomic Medicine Centres (GMCs) across England, which each included several NHS trusts and hospitals, to recruit and collect DNA samples and clinical information[68]. While analysis remains ongoing, a pilot study including 4,660 participants found that a genetic diagnoses was made for 25% of participants which had immediate ramifications for clinical decision making, thus demonstrating an improvement in the diagnosis of rare diseases and a reduction in diagnostic journeys for participants[67]. Recruitment for this project was completed in 2018, and it paved the way for the launch of the national Genomic Medicine Service (GMS), which aims to integrate genomics into routine care, covering use of all technologies from targeted genomic testing to whole-genome sequencing for both paediatric and adult populations[69]. The GMS is delivered through seven regional Genomic Medicine Service Alliances which are responsible for overseeing and coordinating the integration of genomics into routine care in England[69]. Although the focus of genomic medicine had been early diagnosis and treatment thus far, in 2022, NHS England announced their plan to develop eight "genomic networks of excellence", with a dedicated network for pharmacogenetics and medicines optimisation to develop the rollout of pharmacogenomics in the NHS, including furthering the rollout in primary care.

The widespread implementation of pharmacogenetics into healthcare systems across the globe has been a slow process. The Netherlands is currently the most advanced country in this field, as pharmacogenetic testing is offered in at least 16 clinical pharmacies for individuals who have started a pharmacological treatment and experience inefficacy or adverse drug reactions, and the cost is reimbursed by Dutch health insurance companies[70]. However, this is not the case for the majority of countries, including the UK, where pharmacogenetic testing is available only in specialised clinical settings or research centres[71]. For example, the Tanenbaum Centre for Pharmacogenetics is a research facility established in 2012, and has genotyped over 10,000 individuals referred

by over 3,000 clinicians across Ontario, Canada, as part of the Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) study[72]. In addition, the Pharmacogenetics in Psychiatry (PSY-PGX) and Ubiquitous Pharmacogenetics (U-PGx) consortia are collaborative efforts with the aim to conduct pharmacogenetic testing at a large scale, across multiple research groups from multiple different countries in the world[70]. Several countries Asia, including Thailand, Vietnam, South Korea, Indonesia, and Malaysia, have also established the South East Asian Pharmacogenomics Research Network (SEAPharm) program to conduct pharmacogenetic studies in Asian populations[73].

Currently, for a pharmacogenetic test to be available nationally in the UK, an application must be firstly submitted to the National Genomic Test Directory, a feature of the GMS, where they are considered by a test evaluation committee which consist of clinical and scientific experts, and patient and public representatives. The application undergoes a thorough assessment of the clinical utility, scientific validity, and overall benefit to patients, as supported by evidence from the literature[69][74]. The pharmacogenetic tests that are available in the test directory are only used in specialised clinical settings. For example, routine screening for four dihydropyrimidine dehydrogenase (DPYD) variants prior to the administration of fluoropyrimidine-based therapies was made available in the NHS in 2020[75]. Fluoropyrimidines are chemotherapy drugs used to treat cancers (such as breast, head and neck, colorectal and gastrointestinal); individuals with variants in the *DPYD* gene have reduced DPYD activity and, therefore, an increased risk of developing of adverse drug reactions, which can be severe or even fatal[75]. This test represented a significant milestone for the implementation of pharmacogenetics in the UK[75]. Since then, the NHS is moving towards implementing pharmacogenetic testing for more commonly prescribed drugs. Indeed, the NICE has published guidance which recommends pharmacogenetic testing to guide clopidogrel use after ischaemic stroke or transient is-

chaemic attack. Clopidogrel is an anti-platelet medicine which prevents further occlusive vascular events such as heart attacks and peripheral vascular disease[76]. It is a pro-drug which requires activation by CYP2C19, thus, NICE has recommended CYP2C19 genotyping to identify individuals with loss-of-function variants which increase the risk of recurrent events[76]. In their report, they state that they are working with NHS England to develop a national pilot to inform future implementation[76]. Furthermore, the Pharmacogenetics Roll Out - Gauging Response to Service (PROGRESS) study, led by NHS Manchester University NHS Foundation Trust and the NHS North West Genomic Medicine Service Alliance, will be conducting pharmacogenetic testing to optimise the prescribing of selective serotonin reuptake inhibitors, tricyclic antidepressants, statins, and proton pump inhibitors, in primary care [77].

Despite advancements in genomic research in therapeutic areas such as cancer and cardiovascular disease, mental health remains an under-researched field. The most recent Royal College of Psychiatrists' report states that there is a "lack of evidence demonstrating a beneficial impact of pharmacokinetic genomic testing on patient outcomes" and as such, there is "no substantive support for the routine use of such pharmacogenomic testing in clinical care"[74]. They indicate that further research is required, particularly research that demonstrates the clinical utility of testing. Although the PROGRESS trial is important in providing evidence of clinical utility for multiple therapeutic areas such as depressive disorders, it does not provide evidence for psychosis, and it only focuses on primary care. Considering the majority of patients with psychosis are treated in secondary care, this evidence is insufficient for this patient population.

Given the high economic, clinical and humanistic burden in schizophrenia, there is a need for further research to improve therapeutic outcomes, such as symptom severity, and adverse drug reactions (including extra-pyramidal symptoms and cardiometabolic

abnormalities). A genomics-guided approach is a promising avenue for schizophrenia management. Pharmacokinetic genes such as *CYP2D6* play a key role in antipsychotic metabolism and may therefore be clinically useful in optimising treatment for schizophrenia. However, there is currently insufficient evidence exploring the clinical and economic benefits of using genetic testing to guide prescribing for antipsychotics.

1.7 Aims of the thesis

To address the aforementioned gaps in the literature, the overall aim of this PhD project is to address whether genomics can improve care and quality of life for individuals with psychosis, and whether this approach could potentially have cost-effective benefits. My hypothesis is that genomics could play an important role in the clinical management of psychosis and may improve economic and clinical outcomes. I addressed this hypothesis through four ways:

1. Conduct a systematic review investigating whether the use of pharmacogenetics to guide and optimise the prescribing of antipsychotics improves patient outcomes (adverse drug reactions, symptom severity, hospitalisation, medication prescribing, quality of life), and is cost-effective.

2. Investigate the causal relationship between schizophrenia and cardiometabolic abnormalities, such as BMI, using a genetic instrumental variable analysis (Mendelian randomisation).

3. Conduct a study (Pharmacogenetics in Mental Health) to investigate the influence of CYP2D6 metaboliser phenotype on healthcare costs from a sample of individuals with psychosis, currently being prescribed or being considered for antipsychotics.

4. Run a cost-effectiveness analysis investigating the use of pharmacogenetic testing

to guide prescribing of antipsychotics for individuals with schizophrenia using a decision analytic model.

Chapter 2

A systematic review of pharmacogenetic testing to guide antipsychotic treatment

2.1 Abstract

Pharmacogenomics could optimise antipsychotic treatment by preventing adverse drug reactions, improving treatment efficacy and ultimately relieving the cost-burden on the healthcare system. I conducted a systematic review to investigate whether pharmacogenetic testing in individuals undergoing antipsychotic treatment influences clinical or economic outcomes. On 8th October 2024, the following electronic databases were searched: MEDLINE, EMBASE, PsycINFO and Cochrane Centrale Register of Controlled Trials. Quality assessment was conducted using a modified Downs and Black checklist for randomised and non-randomised control studies that assessed clinical outcomes; the quality of economic evaluations were assessed separately using the Consolidated Health Economic Evaluation Reporting Standards 2022 checklist. The results were sum-

marised using a narrative approach, and summary tables. In total, 16 studies were eligible for inclusion in the systematic review. The current evidence base is either in favour of pharmacogenetic-guided prescribing or showed no difference between pharmacogenetics and treatment as usual for clinical and economic outcomes. Further research is required, using sufficient sample sizes that provide recommendations for patients who take antipsychotics based on a broad, multigene panel, with consistent and comparable clinical outcomes.

2.2 Introduction

Knowledge of patients' drug metabolic status through pharmacogenetic testing might optimise the selection of medication and adjustment of doses. Currently, there are numerous studies reporting associations between pharmacogenetic biomarkers based on genes coding drug metabolizing enzymes and antipsychotic response and adverse effects[78]. These studies are thoroughly reviewed by expert groups, such as the Dutch Pharmacogenetics Working Group (DPWG, accessed at `https://www.pharmgkb.org/page/dpwg`) and the Clinical Pharmacogenetics Implementation Consortium (CPIC, accessed at `https://cpicpgx.org/`) which provide clinical recommendations for gene-drug associations with the highest level of evidence through a standardised and peer-reviewed process. A recent systematic review by the DPWG reported gene-drug associations for CYP2D6 with aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and CYP3A4 with quetiapine[79]. The development of CPIC guidelines for antipyschotics have not been developed yet but are currently in progress[80]. Information on pharmacogenetic biomarkers, CYP2D6 in particular, is also present on drug labels. Indeed, the US Food and Drug Administration (FDA) provide dose adjustment recommendations for seven antipsychotics based on CYP2D6 poor metabolizer status on their labels. These include: aripiprazole, aripiprazole lauroxil, brexpiprazole, clozapine, iloperidone, pimozide,

and thioridazine[81]. In the UK, exposure to drugs with pharmacogenomic recommendations (pharmacogenomic drugs) in primary care is very common: 58% of patients were prescribed at least one pharmacogenomic drug over a 1-year period[82]. As individuals get older, this percentage increases as they are more vulnerable to diseases that will require pharmacotherapy, with over 90% of individuals aged over 70-years old estimated to require a pharmacogenomic drug[82].

It is important to note that these recommendations by the DPWG, CPIC, and FDA only help clinicians understand how genetic test results should be interpreted to optimize drug therapy, rather than addressing whether or not genetic tests should be be ordered to optimise drug therapy. Thus, translating these recommendations into clinical utility and cost-effectiveness in clinical practice is required for its implementation into routine practise[79]. Cost-effectiveness analysis is a type of economic evaluation which evaluates the costs and consequences of two or more interventions (i.e., a new intervention and the standard intervention, placebo, or nothing at all). To summarise the relative cost-effectiveness of one intervention to another, a cost-effectiveness analysis may use an incremental cost-effectiveness ratio (ICER), which is the ratio between the incremental cost and the incremental QALY to determine the cost per additional QALY gained[83]. NICE guidelines indicate that recommendation of an intervention requires an ICER below £20,000 to £30,000 per quality-adjusted life year (QALY)[83]. An ICER above this threshold would require an increasingly stronger case for supporting the intervention[84]. Thus, implementation of a genomics-guided approach to optimising antipsychotic treatment into clinical practise requires robust evidence of improvements in both clinical and economic outcomes.

Over a decade ago, Fleeman et al. [85], conducted a systematic review for pharmacogenetic testing in adults taking antipsychotics. They confirmed the compelling biological

evidence supporting cytochrome P450 genetic testing as well as analytical validity and accuracy of assays but did not identify any observational or randomised studies which investigated its clinical utility or cost-effectiveness. Since then, the Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study was published, conducted by the U-PGx consortium[86][87]. The PREPARE study is the largest randomised clinical trial to evaluate the clinical utility of pharmacogenetic testing using a 12-gene panel[86]. In their trial, they included almost 7000 individuals from 7 European countries (UK, Netherlands, Spain, Austria, Greece, Slovenia, and Italy) who were prescribed any index drug (that is, any drug with recommendations in the guidelines of the Dutch Pharmacogenetics Working Group, including antipsychotics as well as other drugs, such as antidepressants, anticoagulants and analgesics, among others). They found that this approach significantly reduced the incidence of developing an ADR by 30%[86]. Other pharmacogenetic studies focusing on a variety of psychotropic drugs have also been conducted, and have similarly reported improved tolerability (i.e., reduction in the incidence of adverse drug reactions)[88], reduced symptom severity[89][90], and improved adherence[91]. These improvements in clinical outcomes may translate to a reduction in healthcare costs, as a previous study investigating health claims of individuals with a psychiatric diagnosis found that those who had had pharmacogenetic tests ordered had lower outpatient costs over a 4-month follow-up period than individuals who had not undergone this testing by USD$562[92]. Another investigation of pharmacy claims data found that individuals who underwent testing saved USD$1035.60 in pharmacy costs up to 1 year after pharmacogenetic testing, compared to TAU[91]. These cost reductions improved significantly to USD$2774.53 when patients' treatment was congruent with the pharmacogenetic report, i.e., the patient's treatment regimen only included medication that were from the green ("use as directed") category of the report[91].

Several systematic reviews have been published since the review by Fleeman et al.

[85]. An umbrella review and meta-analysis including six meta-analyses and four systematic reviews found that pharmacogenomics-guided antidepressant prescribing in patients with depression improved remission rates by 41% to 78%, compared to treatment as usual[93]. Furthermore, two systematic reviews have been published, focusing on economic evaluations of pharmacogenetic testing to guide prescribing for any drug[94] or for any psychotropic drugs[95]. Morris et al. [94], evaluated the cost-effectiveness of pharmacogenetic testing for any drug with CPIC guidelines and found that the majority (71%) of studies found it to be cost-effective (N=48) or cost-saving (N=29). The remaining studies did not find evidence of cost-effectiveness (20%, N=21), or were uncertain (9%, N=10). However, this study did not identify any studies investigating the cost-effectiveness of pharmacogenetic testing for antipsychotics. In a similar study, Karamperis et al. [95], explored evidence of cost-effectiveness on pharmacogenetics, specifically for any psychotropic medication. They found that 89% of studies (N=16) were cost-effective or cost-saving[95]. Even though these reviews confirmed evidence supporting the use of pharmacogenetics by demonstrating improved efficacy and cost-effective benefits, antidepressants are the most commonly prescribed in these studies. Thus, a review focusing specifically on pharmacogenetics to optimise antipsychotic prescription is lacking in the literature, incorporating both clinical and economic data.

Thus, in this chapter, I conducted a systematic review to investigate whether pharmacogenetic testing for individuals undergoing antipsychotic treatment influences clinical or health economic outcomes.

2.3 Methods

The systematic review was registered with PROSPERO (registration ID: CRD42023380454) and was reported according to the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) 2020 recommendations[96].

2.3.1 Eligibility criteria

On 8th October 2024, I searched for studies of any design, including randomised or non-randomised, controlled or non-controlled, that evaluated clinical and/or economic outcomes after pharmacogenetics-guided treatment in a sample of individuals taking antipsychotics. The inclusion criteria was broad to maximise the number of studies included in the review. No limits were applied on patients' age or diagnosis; no restrictions by country, health care setting, or monetary currency were applied; and no restrictions were imposed on date range or language, although the search was conducted in English. To ensure that all conclusions drawn from the included studies were specific to antipsychotics, I excluded studies where antipsychotics did not comprise the primary prescribed medication, or if the authors did not present data for antipsychotics only. I also excluded studies if they were a protocol, review, commentary, letter, or editorial.

2.3.2 Search strategy

Several electronic databases were searched to identify relevant articles: MEDLINE (via Ovid), EMBASE (via Ovid), PsycINFO (via Ovid) and Cochrane Centrale Register of Controlled Trials. The search strategy is outlined in Table 2.1. Furthermore, a manual search of the reference lists of the included articles and relevant existing reviews and a manual search of papers that have referenced the included articles using Google Scholar Citations was conducted.

2.3.3 Study selection

The first stage of the study selection involved collating articles that appeared eligible from the title and abstract or were of unclear eligibility. The titles and abstracts were ini-

Table 2.1: Search strategy for electronic databases.

#	Search terms
1	antipsychotic*
2	(pharmacogenetic* OR pharmacogenomic* OR pharmacogenetics OR genetic test*)
3	((prospective OR randomi* OR trial OR intervention) OR (cost AND (effect* OR benefit* OR utility OR utilities OR outcome* OR analysis OR analyses OR consequence* OR minimi*)))
4	#1 AND #2 AND #3

tially assessed by independent reviewers, including three colleagues (Soumita Ramesh, Georgina Mills, and Georgie Hudson) and myself using Rayyan[97]. The second stage involved screening full-text articles to determine if the studies met the eligibility criteria. Any discrepancies were resolved by consulting an additional independent reviewer, Elvira Bramon.

2.3.4 Data extraction and presentation of results

The data was extracted from the selected studies using a custom data extraction template in Excel. The extracted data included the following: study authors, year of publication, study title, study design, country, sample size, sample characteristics, test gene composition and outcomes measured. The results were summarised using a narrative approach, and summary tables. The reason for this approach was two-fold. For the clinical outcomes, the studies were not directly comparable due to the range of clinical scales reported. For the economic outcomes, meta-analysis of trial-based cost-effectiveness analyses was deemed to be inappropriate given that the results for these studies are heavily dependent on the study's healthcare system, population, perspective, and country income-level[98]. In addition, model-based analyses are themselves syntheses, so conducting further synthesis is also inappropriate in this circumstance[98].

I rated the certainty of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines[99], which assessed the following domains for each outcome: risk of bias, inconsistency, indirectness, imprecision, and publication bias. A total score was determined to measure certainty: high ($\geq$4 points, high certainty that the true effect is close to the estimated effect), moderate (3 points), low (2 points), or very low ($\leq$1, the true effect is likely different than the estimated effect).

2.3.5 Quality assessment

I conducted quality assessment using a modified Downs and Black checklist for studies that assessed clinical outcomes[100]. This tool was chosen because it has been previously reported as one of the most suitable tools for assessing quality of studies by the Cochrane Handbook[101], and because it accounts for various study designs, i.e., it can be used to assess the quality of both randomised and non-randomised control studies[100]. The modified checklist includes 26 items which assess various methodological components, such as reporting, external validity, internal validity, and power. Each item was either awarded one point if the criteria was met or no points if the criteria was not met, except item 5. This item assessed whether the principal confounders in each group of subjects were clearly described and was awarded one point if the criteria was partially met or two if the criteria was fully met. If the item could not be inferred from the study, it was marked as "unable to determine". In total, studies are awarded a total score ranging from 0 to 27, with higher scores indicative of higher quality.

Moreover, I used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 checklist[102] to assess the quality of reporting in health economic evaluations, including both trial-based and model-based economic evaluations. This tool was used to provide additional information about the reproducibility of the studies. Transparent

reporting informs decision making by providing information to allow decision makers to assess a study's relevance, methodology, validity of findings, and its generalisability, as well as allowing for the comparison of studies[103]. The checklist consists of 28 items, and each item is awarded a point if the criteria was met, or no points if the criteria was met or only partially met. If the item was not applicable to the study (for example, a cost-minimization analysis could not be assessed by items 11-13, which assess the selection, measurement, and valuation of health outcomes), the item was marked "N/A". Studies are awarded a total score ranging from 0 to 28, which was used to calculate a total percentage score. Where an item was marked as "N/A", this item was deducted from the total score to subsequently calculate the total percentage score.

2.4 Results

2.4.1 Inclusion and exclusion of studies

The database search yielded 1001 publications: EMBASE (n=540), MEDLINE (n=252), PsycInfo (n=101) Cochrane Library (n=108) (Figure 2.1). After removing duplicates and screening based on titles and abstracts, this left 28 potentially eligible studies. After applying the pre-specified inclusion criteria to the full text articles, 8 studies remained. An additional 16 potentially eligible studies were identified from manual screening of citations and Google Scholar. After assessing for eligibility, 8 studies remained. In total, 16 eligible studies were included. Information about the excluded studies is detailed in Appendix 1, Table A.1. Table 2.2 summarises the key characteristics of each of the included studies.

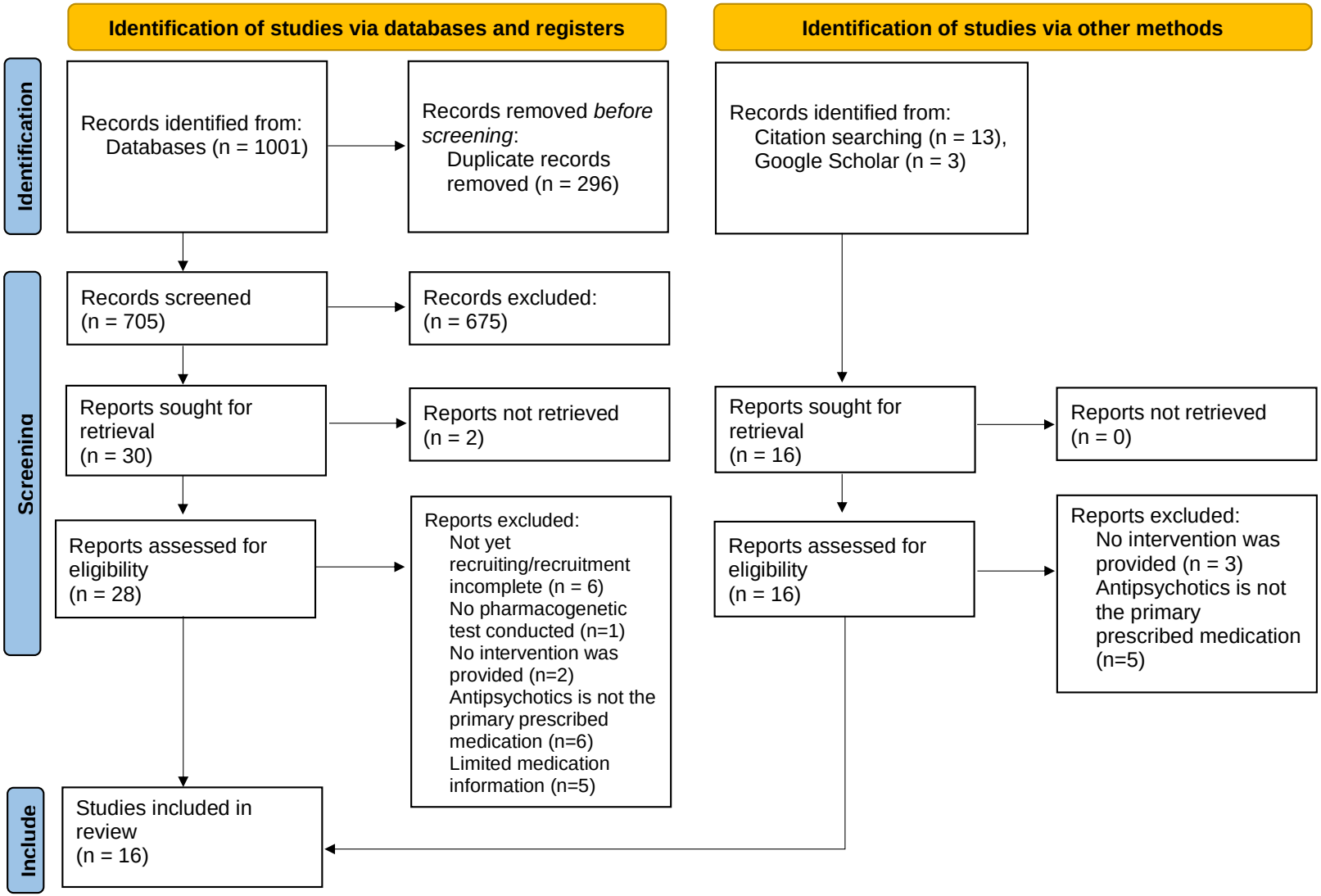


Figure 2.1: PRISMA flow diagram.

Table 2.2: Summary of study characteristics. N/A indicates that information was not reported in the original article. ANCM, absolute neutrophil count monitoring; BARS, Barnes Rating Scale for Drug-Induced Akathisia; BPRS, Brief Psychiatric Rating Scale; CGA, Children's Global Assessment; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Symptoms Scale; PGx, pharmacogenetics; PIP-FQ, Clinicians' opinions and Pharmacogenetics in Psychiatry Follow-up Questionnaire; PSP, Personal and Social Performance Scale (PSP); SAPS, Scale for the Assessment of Positive Symptoms; SHRS, St. Hans Rating Scale; SWN-20, Subjective Well-Being Under Neuroleptics Scale; TAU, treatment as usual; UKU, Udvalg af Kliniske Undersøgelser Side Effect Rating Scale; WHODAS 2.0, WHO Disability Assessment Schedule 2.0

Authors	Country	Study design	Sample characteristics	Outcomes measured	Medication	Genes
Trial-based study with 3 comparators						
Jürgens et al. [104] (2020)	Denmark	Single-blind randomised control trial Three arms: pharmacogenetics vs SCM vs TAU Assessment points: baseline and 1 year	Total n= 161 Pharmacogenetics (n=84) vs TAU (n=77) Age, median (years): 42 vs 42 Sex (% female): 43 vs 46 Ethnicity: N/A Medication: N/A Diagnosis (%): paranoid schizophrenia, 72 vs 65; schizotypal disorder, 20 vs 20; persistent delusional disorders, 3 vs 2; acute and transient psychotic disorders, 1 vs 2; schizoaffective disorders, 2 vs 8	Antipsychotic drug persistence (days to first modification of the initial treatment) Adverse drug response (UKU) Symptom severity (SAPS) Compliance (ROMI)	Antipsychotics	*CYP2D6, CYPC19*
Herbild et al. [105] (2013)	Denmark	Double-blind randomised control trial Three arms: pharmacogenetics vs extensive clinical monitoring vs TAU Assessment points: 1 year	Total n= 207 Pharmacogenetics (n = 103) vs TAU (n = 104) Age, mean (years): 41 vs 42 Sex (% female): 45 vs 44 Ethnicity: N/A Medication: N/A Diagnosis (%): schizophrenia, 74 vs 71; schizotypal disorders, 24 vs 21; other disorders, 5 vs 12	Pharmaceutical costs Hospitalisation costs	Antipsychotics	*CYP2D6, CYP2C19*
Trial-based study with 2 comparators						
Kang et al. [106] (2023)	China	Double-blind randomised control trial Two arms: pharmacogenetics vs TAU Assessment points: baseline, 6 and 12 weeks	Total n= 210 Pharmacogenetics (n=113) vs TAU (n=97) Age, median (years): 29.9 vs 28.3 Sex: male, 100 Ethnicity (%): Han Chinese, 100 Medication (%): quetiapine, 26.5 vs 19.6; risperidone, 31.0 vs 45.4; olanzapine, 13.3 vs 11.3; aripiprazole, 15.0 vs 8.2; ziprasidone, 0.9 vs 3.1; paliperidone, 6.2 vs 7.2; clozapine, 1.8 vs 2.1; amisulpride, 5.3 vs 3.1. Diagnosis (%): schizophrenia, 100	Symptom severity (PANSS) ADRs	Antipsychotics	*CYP1A2*, *CYP2D6*, *CYP3A4*, *DRD2*, *EPM2A*, *HTR1A*, *HTR2A*, *HTR2C*, *MC4R*, *RGS4*, *SH2B1*

Authors	Country	Study design	Sample characteristics	Outcomes measured	Medication	Genes
Qin et al. [107] (2024)	China	Single-blind randomised control trial Two arms: pharmacogenetics vs TAU Assessment points: baseline, 3, 6 and 12 weeks	Total n=186 Pharmacogenetics (n=109) vs TAU (n=77) Age, mean (years): 28.3 vs 28.4 Sex: male, 100 Ethnicity (%): Han Chinese, 100 Medication (%): N/A Diagnosis (%): schizophrenia, 100	Symptom severity (PANSS and CGI) Functioning (GAF and PSP)	Antipsychotics	23 genes including *CYP1A2*, *CYP2B6*, *CYP2C19*, *CYP2D6*
Koopmans et al. [108] (2018)	Curaçao	Prospective observational study Two arms: pharmacogenetics vs TAU Assessment points: baseline, 4 months	Total n=86 Pharmacogenetics (n=45) vs TAU (n=41) Age, mean (years): 52.4 vs 50.3 Sex (% female): 33.3 vs 39.0 Ethnicity (%): Antillean ethnicity, 100 Medication (n, pharmacogenetics group only): haloperidol, 15; risperidone, 21; zuclopenthixol, 9. Diagnosis (%): psychotic disorder, 94; other diagnoses (major depressive disorder, bipolar disorder, substance abuse and intellectual disability), 6%	Symptom severity (BPRS) ADRs (SHRS and BARS) Quality of life (EQ-5D Global functioning (WHODAS 2.0) Well-being (SWN-20)	Antipsychotics and antidepressants	*CYP2D6*
Skokou et al. [109] (2024)	Greece	Open-label randomised control trial Two arms: pharmacogenetics vs TAU Assessment points: baseline, 2, 4, 8 12 weeks, and 19 months	Total n=1076 Pharmacogenetics (n=547) vs TAU (n=529) Age, mean (years): 49.0 vs 49.0 Sex (% female): 47.9 vs 50.5 Ethnicity (%): Greek, 100 Medication (n): antipsychotics, 400; antidepressants, 670. Diagnosis (n): schizophrenia, 330; MDD, 494; bipolar disorder, 252	ADRs Hospitalisations Polypharmacy Cost-effectiveness	Antipsychotics and antidepressants	*CYP2B6*, *CYP3A5*, *SLCO1B1*, *VKORC1*, *CYP2D6*, *DPYD*, *CYP2C9*, *UGT1A1*, *CYP2C19*, *F5*, *TPMT*, *HLA-B*
Arranz et al. [110] (2019)	Spain	Double-blind randomised control trial Two arms: pharmacogenetics vs TAU Assessment points: baseline and 12 weeks	Total n= 290 Pharmacogenetics (n=123) vs TAU (n=167) Age, median (years): 46.1 vs 48.7 Sex (% female): 48.8 vs 43.7 Ethnicity: N/A Medication (%): clozapine, 35 vs 52.7; risperidone, 13 vs 12; olanzapine, 20.3 vs 8.4; paliperidone, 13 vs 13; aripiprazole, 5.7 vs 7.8; quetiapine 8.9 vs 3; ziprasidone, 0.8 vs 1.2; trifluoperazine, 0.8 vs 0.6; haloperidol, 0.8 vs 0.6; asenapine, 0.8 vs 0.6; pimozide, 0.8 vs 0. Diagnosis (%): schizophrenia, 86 vs 69; schizoaffective, 5 vs 4; delusional disorder, 9 vs 27	Symptom severity (PANSS) ADRs (UKU)	Antipsychotics	*CYP2D6, CYPC19, CYP1A2, CYP3A5*

Authors	Country	Study design	Sample characteristics	Outcomes measured	Medication	Genes
Arranz et al. [111] (2022)	Spain	Prospective observational study Two arms: pharmacogenetics vs TAU Assessment points: baseline and 4 months	Total n= 104 Pharmacogenetics (treatment resistant) (n=42) vs TAU (n=62) Age, mean (years): 18.79 vs 13.83 Sex (% female): 26% vs 8% Ethnicity: N/A Medication (%): antipsychotics, 67 vs 32; antidepressants, 48 vs 11; anxiolytics, anticonvulsants and others, 26 vs 56; no current medication, 7 vs 0 Diagnosis: 100% Autism spectrum disorder	Symptom severity (CGI and CGA)	Antipsychotics, antidepressants, anxiolytics, anticonvulsants	*CYP1A2, CYP2C19, CYP2D6* and *SLC6A4*
Trial-based study with 1 comparator						
Carrascal-Laso et al., [112] (2020)	Spain	Retrospective observational study One arm: pharmacogenetics only Assessment points: 3 years	Total sample (n=188) Age, median (years): 47 Sex (% female): 37.8% Ethnicity: N/A Medication: N/A Diagnosis (%): dementia, 0.53; substance-related disorder 6.38; schizophrenia, 67.02; persistent delusional disorder, 1.06; brief and acute psychotic disorder, 0.53; schizoaffective disorder, 6.92; bipolar disorder, 13.30; major depressive disorder, 0.53; specific personality disorder, 1.06; mixed personality disorder, 0.53; intellectual disability, 1.06	Mean daily dose Polytherapy cases	Antipsychotics	*CYP1A2*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *ABCB1*
Carrascal-Laso et al., [113] (2021)	Spain	Retrospective observational study One arm: pharmacogenetics only Assessment points: 3 years	Total sample (n=188) Age, median (years): 47 Sex (% female): 37.8% Ethnicity: N/A Medication: N/A Diagnosis (%): dementia, 0.53; substance-related disorder 6.38; schizophrenia, 67.02; persistent delusional disorder, 1.06; brief and acute psychotic disorder, 0.53; schizoaffective disorder, 6.92; bipolar disorder, 13.30; major depressive disorder, 0.53; specific personality disorder, 1.06; mixed personality disorder, 0.53; intellectual disability, 1.06	Pharmaceutical costs Hospitalisation costs	Antipsychotics	*CYP1A2*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *ABCB1*

Authors	Country	Study design	Sample characteristics	Outcomes measured	Medication	Genes
Walden et al., [114] (2019)	Canada	Prospective observational study One arm: pharmacogenetics only Assessment points: baseline, 6 weeks, and 12 weeks	Total sample (n=80) Age, mean (years), 43 Sex (% female): 43.8% Ethnicity/race (% of participants): European Caucasian 68.8%, African 3.8%, Asian, 3.8%, Others 12.5%, Mixed 11.3% Medication (%): antipsychotics, 47.5; antidepressants, 23.8; anxiolytics, 7.5; antipsychotics and antidepressants, 11.3; antipsychotics, antidepressants, and anxiolytics, 6.3; no medication, 3.8 Diagnosis: schizophrenia/schizoaffective, 53.8%; anxiety/depression, 40%, others, 6.3%.	Physician's opinions (PIP-FQ) ADRs (UKU)	Antidepressants, anxiolytics and antipsychotics	*CYP2D6, CYP2C19*
Markov/decision models						
Ninomiya et al., [115] (2022)	UK	Decision tree with Markov model Third-party payer perspective Two arms: pharmacogenetics vs TAU Assessment points: 10 years	The target population was adult men and women with treatment resistance schizophrenia.	Incremental cost-effectiveness ratio per QALY	Clozapine	*SLCO1B3-SCLO1B7*, *HLA-DQB1*, *HLA-B*
Girardin et al., [116] (2019)	USA	Decision tree with semi-Markovian model Third-party payer perspective Three arms: (1) PGx-guided clozapine treatment with ANCM for patients who test positive for one or both alleles, (2) PGx-guided clozapine treatment for patients who test negative or alternative antipsychotics for patients who test positive, (3) TAU. Assessment points: 3 years	The target population was adult men and women with treatment resistance schizophrenia.	Incremental cost-effectiveness ratio per QALY	Clozapine	*HLA-DQB1, HLA-B*

Authors	Country	Study design	Sample characteristics	Outcomes measured	Medication	Genes
Kurylev et al., [117] (2018)	Russia	Decision tree Three arms (1) PGx in 100% of patients (2) PGx in 30% of patients (3) TAU. Three arms: (1) PGx-guided clozapine treatment with ANCM for patients who test positive for one or both alleles, (2) PGx-guided clozapine treatment for patients who test negative or alternative antipsychotics for patients who test positive, (3) TAU. Assessment points: N/A	The target population were patients diagnosed with paranoid schizophrenia.	Hospitalisation costs Medication costs	Antipsychotics	*CYP2D6*
Rejon-Parrilla et al., [118] (2014)	UK	Decision tree with Markov model Healthcare provider perspective (NHS) Two arms: (1) traditional dosing, (2) pharmacogenetic testing Assessment points: 2 years	The target population was previously untreated patients newly diagnosed with schizophrenia, aged 25.	Incremental cost-effectiveness ratio per QALY	Risperidone	*CYP2D6*
Perlis et al., [119] (2005)	USA	Decision tree with Markov model Societal perspective Three arms: (1) no PGx test, clozapine as 1st line treatment, (2) PGx testing, clozapine as 1st line if they test positive for or 3rd line if the test negative (3) no PGx testing, clozapine as 3rd line. Assessment points: lifetime	The target population was a 30-year-old patient with schizophrenia.	Incremental cost-effectiveness ratio per QALY	Clozapine	N/A

Study characteristics

The sample size of the studies ranged from 80 to 1076 participants, and the average age ranged from 14 to 52 years. Regarding gender, most studies were well-balanced, except four studies which included less than 40% female participants, and two studies which only included male participants. There were 10 studies conducted in Europe, including Denmark, Spain, Greece, Russia, and the UK; three studies in North America, including the USA and Canada; two studies in China, and one study in the Caribbean. There were only five studies which reported the ethnicity or ancestry of their participants. The primary diagnosis among the studies was a psychotic disorder (schizophrenia, schizotypal disorder, schizoaffective disorder, persistent delusional disorder, brief and acute psychotic disorder, and bipolar disorder). However, one study focused on patients with a diagnosis of autism spectrum disorder; one study included individuals with schizophrenia, anxiety, and depression (although schizophrenia comprised over 50% of the diagnoses in this sample); and one study included individuals with a diagnosis of schizophrenia, major depressive disorder (MDD), and bipolar disorder, with schizophrenia being the second most prevalent diagnosis in the sample. Several studies focused exclusively on antipsychotics (n=12), while others focused on antipsychotics as well as other psychotropic medications, as part of a broader combinatorial treatment (n=4). These four studies reported antipsychotics as the primary prescribed medication, except the study conducted by Skokou et al. [109] which reported antidepressants as the primary prescribed medication due to a large number of individuals in their sample diagnosed with MDD. For this study, I only report the results that are specific to individuals diagnosed with schizophrenia. The genes included in the pharmacogenetic tests varied widely, but *CYP2D6* was found to be a common gene included in many studies. Including the decision/Markov models, five studies had three comparators (e.g., pharmacogenetics vs extensive clinical monitoring vs treatment as usual [TAU]); eight studies had two comparators (e.g., pharmacogenetics vs TAU); and three studies had one group (pharmacogenetics only). There were no industry-funded

studies identified in the review, although some papers were missing details on the source of the funding.

2.4.2 Clinical outcomes

Overall, there were four RCTs, one retrospective and three prospective studies which reported clinical outcomes. Studies reported ADRs, symptom severity, medication, hospitalisations, polypharmacy, quality of life, and physicians' opinions (Table 2.3). The results for the different clinical outcomes can be visualised using Figure 2.2. Most studies had a short follow-up period of 4 months or less (n=6), and 2 studies had a follow-up of 1 year or longer.

Table 2.3: Clinical outcomes included in the systematic review and their corresponding definition/measure of the outcome.

Outcome	Definition/measure of outcome
Adverse drug reactions	Udvalg af Kliniske Undersøgelser Side Effect Rating Scale[105][110] St. Hans Rating Scale [108] Barnes Rating Scale for Drug-Induced Akathisia [108]
Symptom severity	Scale for the Assessment of Positive Symptoms [104] Positive and Negative Symptoms Scale [110] Clinical Global Impression-Severity [111] Children's Global Assessment Scale [111] The Brief Psychiatric Rating Scale [108]
Hospitalisation	Overall hospitalisation stays per patient[113]
Medication prescribing	Antipsychotic drug persistence, measured as time in days to the first modification of the initial antipsychotic treatment (drug or dose change), to indicate tolerability of medication[104] Drug changes[104] Dose changes by visual inspection of temporal dose-adjustment graphs[104] Mean daily dose[112] Polytherapy through the number of antipsychotics prescribed[112].
Quality of life	EuroQoL-5D[108] Subjective Well-Being Under Neuroleptics Scale [108] WHO Disability Assessment Schedule 2.0 [108] Global Assessment of Functioning Scale [107] Personal and Social Performance Scale [107]
Clinicians' opinions	Pharmacogenetics in Psychiatry Follow-up Questionnaire [114]

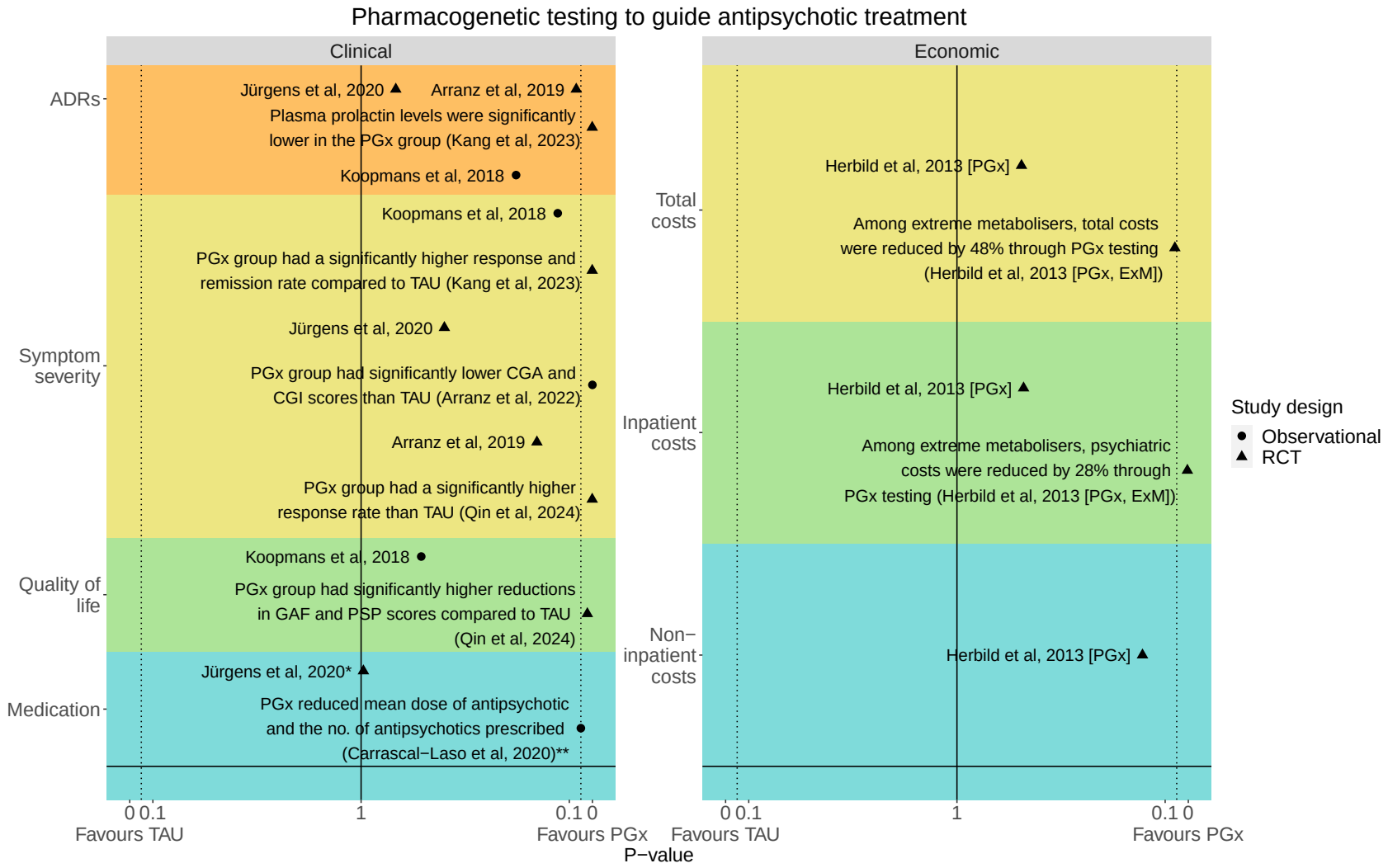


Figure 2.2: Visualisation of the literature with key results for the clinical and economic outcomes. Primary studies which reported a p-value are plotted to depict the direction of effect for each outcome (whether they favour pharmacogenetics, or treatment as usual or whether there is no significant difference between the two treatment arms). The x-axis plots the p value reported in the primary study as a measure of the strength of the evidence. The solid line marks p value of 1 and the dotted line marks the significance threshold of P <0.05. The study design and sample size are displayed. Herbild, et al. [105] conducted a main analysis comparing PGx vs TAU (denoted [PGx]) and a sub-analysis comparing extreme metabolisers in the PGx group (denoted [PGx, ExM]) to TAU. For non-inpatient costs (primary care costs) there was no subgroup analysis for the extreme metabolisers. Studies that did not report p-values were excluded from the visualisation. * Exact p-value not indicated but specified that it is > 0.05; ** Exact p-value not indicated but specified that it is <0.05. ADRs, adverse drug reactions; CGA, Children's Global Assessment; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; PGx, pharmacogenetics; PSP, Personal and Social Performance Scale (PSP); RCT, randomized control trial; TAU, treatment as usual.

Adverse drug reactions Two studies assessed adverse drug reactions (ADRs) using the Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale, neither of which found a statistically significant difference in UKU score between the two treatment arms (pharmacogenetics and TAU)[110, 104]. Koopmans et al. [108] did not find any significant improvements in parkinsonism, dyskinesia, dystonia, or akathisia, measured by the St.Hans Rating Scale (SHRS) for extrapyramidal symptoms and Barnes Rating Scale for drug-induced akathisia (BARS) specifically for akathisia. No significant differences were found in metabolic parameters (body mass index, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, prolactin, fasting plasma glucose, HbA1c) either. Kang, et al. [106] did not identify a significant difference in metabolic profiles (triglycerides, LDL- and HDL-cholesterol, fasting plasma glucose) between the pharmacogenetics and TAU group, except plasma prolactin levels which were significantly lower in the intervention group compared to control at the end of week 12 (29.4ng/mL in the pharmacogenetics group vs 40.4ng/mL in TAU, P = 0.03)

Symptom severity Symptom severity was assessed using a variety of clinical scales, including the Scale for the Assessment of Positive Symptoms (SAPS), Positive and Negative Symptoms Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression-Severity (CGI-S) and Children's Global Assessment (CGA) scale. Koopmans et al.[108], Jürgens, et al. [104], and Arranz, et al. [110] did not identify a significant difference in the change in symptom severity in the pharmacogenetics group compared to TAU using the BPRS, SAPS, and PANSS, respectively. In contrast, Kang, et al. [106] found that the response rate, defined as a PANSS score reduction of 50% or more, at the end of week 6 was significantly higher in the pharmacogenetic group (82.3%) compared to TAU (64.9%) (adjusted OR, 2.48; 95% CI, 1.28-4.80, P=0.01). Similarly, the rates of symptomatic remission at the end of week 12 were also significantly higher in the pharmacogenetics group (62.8%) compared to TAU (45.4%) (adjusted OR, 2.03; 95% CI,

1.11-3.60, P=0.02). Symptomatic remission was defined as a score of 3 or less on eight items in the PANSS (P1, P2, P3, N1, N4, N6, G5, and G9). In their study, they found a similar reduction in PANSS scores between individuals with first-episode psychosis and relapsed schizophrenia. Arranz, et al. [111] also identified an improvement in symptom severity: 39 treatment-resistant patients (93%) demonstrated improvement in their CGI scores and 37 (88%) showed improvements in their CGA scores. Indeed, after pharmacogenetic testing, a 2 and 20 point average improvement in CGI and CGA scores was identified for the pharmacogenetics group, respectively (P = $1x10^{-5}$ for CGI scores, P = $5x10^{-8}$ for CGA scores). Similarly, Qin et al. [107] found that after 12 weeks of antipsychotic treatment, the pharmacogenetics group achieved a treatment response (defined as a PANSS score reduction greater than 50%) rate of 81.7%, compared to 48.8% in the TAU group (OR, 4.67; 95% CI 1.96-11.41; P=0.001). This improvement in efficacy remained significant regardless of whether the patient had a first episode or relapse (P <0.005). They also assessed symptom severity using the CGI scale and found similar significant improvements in the pharmacogenetics group compared to TAU by week 12 (P = 0.017).

Hospitalisation Carrascal-Laso, et al. [113] demonstrated that, prior to applying the pharmacogenetics test, participants in the study accounted for 504 hospitalisation stays. This was reduced to 218 hospitalisations, after adjusting treatment based on the pharmacogenetics test. Arranz et al. [111] also found that pharmacogenetic testing led to a reduction in the visits to their clinicians (10 less visits per patient per year) and a reduction in hospital stays (total reduction of 3 months in hospital stays).

Medication prescribing Jürgens, et al. [104] found no difference in antipsychotic drug persistence (number of days until a medication or dose change) in the pharmacogenetics group compared to TAU, even in a subgroup analysis including only extreme metabolisers (poor and ultrarapid metabolisers for *CYP2D6*). However, Jürgens, et al. [104] showed that extreme metabolisers in the intervention group experienced fewer drug and dose

changes than the TAU group (pharmacogenetic group, β=-1.2; 95% CI, 4.1-1.2; TAU, β=-2.3; 95% CI, -5.0-0.4). Carrascal-Laso, et al. [112] demonstrated that the average number of antipsychotics prescribed per patient reduced from 1.82 at baseline to 1.27 after pharmacogenetics testing and this change was statistically significant (P <0.05). Similarly, at baseline, almost 21% of patients were prescribed more than 5 drugs (any mental/physical health drugs), which was reduced to less than 11% post-pharmacogenetics testing, again a significant reduction in polypharmacy (P <0.05).

Quality of life There were many clinical scales used to evaluate quality of life, including the EuroQoL-5D (EQ-5D), the 20-item Subjective Well-Being under Neuroleptic Treatment Scale (SWN-20), WHO Disability Assessment Schedule 2.0 (WHODAS 2.0), Global Assessment of Functioning (GAF), and Personal and Social Performance Scale (PSP). Koopmans et al. [108] did not find any significant differences in subjective well-being using the SWN-20, global functioning using the WHODAS 2.0 or quality of life using the EQ-5D. In contrast, Qin et al. [107] found a significant improvement in global and social functioning, measured using the GAF and PSP, respectively, compared to TAU. By week 12, the mean GAF scores were 20.52 and 11.70 for the pharmacogenetics and TAU groups, respectively (mean difference, 8.82; 95% CI, 6.96–16.49; P = 0.022), and the mean PSP scores were 21.43 and 11.83 (mean difference, 9.60; 95% CI, 7.44–15.71; P = 0.017) for the pharmacogenetic and TAU groups, respectively.

Clinicians' opinions Physicians' opinions were evaluated using the Pharmacogenetics in Psychiatry Follow-up Questionnaire (PIP-FQ) by Walden et al. [114]. The PIP-FQ revealed that 23% (n=14) of physicians concluded that their patients improved after pharmacogenetics testing for CYP2D6 and CYP2C19. The remaining physicians concluded that the patients did not change (n=25), their patients were not assessed (i.e. due to a lack of follow-up appointment with the patient) (n=21), or no answer was provided (n=20).

2.4.3 Economic outcomes

Overall, there were three trial-based economic evaluations (using patient-level data) and five model-based economic evaluations (using data from existing literature). Most of these were cost-utility analyses (n=5), as well as a few cost-analyses (n=2). There was also one study which conducted a cost-benefit analysis. Among these studies, two studies were conducted from a third-party perspective, two from a healthcare payer system perspective, and one from a societal perspective. The remaining studies did not specify the perspective (n=3). Moreover, the time horizon employed varied widely, including 19 months (n=1), one year (n=1), two years (n=1) three years (n=2), ten years (n=1) and lifetime (n=1). There was one study which did not specify a time horizon. Economic outcomes included overall cost of healthcare resource utilisation, inpatient costs (hospitalisations), non-inpatient costs (primary care and pharmaceutical costs), and incremental cost-effectiveness ratios. The results for the economic outcomes can be visualised using Figure 2.2.

Overall healthcare costs Herbild, et al. [105] demonstrated that there was no statistically significant difference in total costs between the pharmacogenetics and TAU group over 1 year. However, total costs were 177% higher in the extreme metabolisers (poor and ultrarapid metabolisers for *CYP2D6*) than among the normal metabolisers; this difference was reduced by 48% among extreme metabolisers in the intervention group (P = 0.058). Moreover, Carrascal-Laso, et al. [113] found that pharmacogenetics testing was associated with a reduction in total costs for 67% of the patients over a 3-year follow-up period.

Inpatient costs Regarding inpatient costs, such as the costs attributed to services in the psychiatric hospital sector, Herbild, et al. [105] showed that there was no difference between the pharmacogenetics and TAU group over 1 year. However, extreme metabolisers were incurring significantly higher costs than normal metabolisers; these

excess costs in the extreme metabolisers were significantly reduced by 28% through pharmacogenetic testing (P<0.05). This is equivalent to an average psychiatric cost of DKK 373,682 (£42,045) among the extreme metabolisers, which was reduced to DKK 114,403 (£12,872) by the pharmacogenetic test. Furthermore, no difference was identified for the nonpsychiatric hospital costs between the intervention and TAU group. Carrascal-Laso, et al. [113] found that total hospital costs decreased from US$2335 before pharmacogenetics testing (2013-2015), to US$948 after pharmacogenetics testing (2016-2019), which represents a 59% reduction. This was supported by a pharmacoeconomic model by Kurylev, et al. [117], which found that pharmacogenetic testing reduced the length of stay of patients in hospital, which translated to a total reduction in hospital costs by 382,433 Russian Rubles (US$3,802, follow-up period not known).

Non-inpatient costs Carrascal-Laso, et al. [113] found that the pharmacogenetics intervention led to a reduction of 10% (before vs after pharmacogenetics, US$3,142 vs US$2827 per patient per year) in pharmaceutical costs over 3 years. No statistically significant cost difference was identified by Herbild, et al. [105] between the intervention and TAU group for primary care services over 1 year; there was no subgroup analysis for the extreme metabolisers.

Cost-effectiveness Skokou et al. [109], conducted a trial-based cost-effectiveness analysis for individuals with schizophrenia and found very minor differences in costs and quality of life after pharmacogenetic testing. Although they did not report an ICER, they reported that the mean estimate for QALYs in the intervention group was 0.97, compared to 0.98 of the control group, and the intervention group had slightly higher average costs (€1243) compared to the control group (€1115). Ninomiya et al. [115], compared pharmacogenetics-guided clozapine treatment to TAU and calculated an ICER of £16,215 per QALY, i.e., it would cost an extra £16,215 to gain an additional QALY if the patient was prescribed antipsychotics using the pharmacogenetic-guided strategy, as opposed to the

traditional strategy. Similarly, Rejon-Parrilla, et al. [118] found that pharmacogenetic testing entailed an additional cost of £19,252 per QALY. Both of these values remain below the conventional decision threshold of £20,000-£30,000 per additional QALY gained outlined by the National Institute for Health and Clinical Excellence (NICE)[83]. Perlis, et al. [119] compared pharmacogenetic-guided clozapine treatment as first-line treatment for individuals who test negative for genetic variants in selected pharmacogenes to TAU, involving no testing and clozapine as a third-line treatment. They identified a reduced likelihood of treatment failure and relapse for the pharmacogenetics-guided group taking clozapine as a first-line treatment. Overall, they found that pharmacogenetic testing yields a cost of US$47,705 per QALY gained, compared to TAU, which is below the conventional decision threshold of US$50,000 per additional QALY gained. Finally, Girardin, et al. [116], compared TAU to pharmacogenetic-guided clozapine treatment which would involve absolute neutrophil count monitoring for only patients who test positive for one or both susceptibility alleles. They reported an ICER of $3.9 million per quality-adjusted life year (QALY), meaning TAU cost an extra US$3.93 million (95% CI 2.01-8.17) per additional QALY gained compared to the pharmacogenetic strategy. The results of these studies were primarily sensitive to the pharmacogenetic test parameters, such as sensitivity and cost, as well as clozapine-induced agranulocytosis prevalence, and infection-related death rates.

2.4.4 Quality assessment

Quality assessment was conducted using the Downs and Black checklist for RCTs and non-RCTs that reported a clinical outcome, and results varied from 15 to 25 (out of 27), with a mean score of 19.8 (Table 2.4). The studies demonstrated a good ability to report the study objectives, methods, sample characteristics, and main findings. However, some studies failed to report details of patients lost to follow-up (n=3), and even more failed to report whether they took this into account when conducting analyses (n=5). In addition, more than half of the participants in the studies were not blinded to the intervention (n=5)

and there was no attempt to blind those measuring the main outcomes in 50% of studies (n=4). Moreover, in half of the studies, participants were not randomized to intervention groups (n=4), randomization was not concealed from both patients and staff until recruitment was complete (n=5), and there was inadequate adjustment for confounding 75% of studies (n=6).

Quality assessment was also conducted for economic evaluations using the CHEERS checklist, and results varied widely. Total scores ranged from 43% to 75%, with a mean score of 62% (Table 2.5). For most of the studies, a clear title, abstract, background was provided, findings were summarized effectively in the results, and a comprehensive discussion was provided. However, reporting of methodology was weaker: no study provided a health economics analysis plan, and most studies failed to report or justify their chosen time horizon (n=5), perspective (n=6), or discount rate (n=5). Regarding methodology, only one study attempted to characterise heterogeneity, i.e., how the results may vary for subgroups, and none of the studies incorporated patient and public involvement in the design of the study. Furthermore, sources of funding could have been more transparent as several studies did not specify funding (n=3). I assessed certainty of the evidence using the GRADE guidelines, which demonstrated low certainty for most outcomes (Appendix A, Table A.2).

Table 2.4: Results from the Downs and Black checklist. UTD, unable to determine.

	Jürgens et al. [104]	Arranz et al. [110]	Carrascal-Laso et al. [112]	Walden et al. [114]	Arranz et al. [111]	Kang et al. [106]	Koopmans et al. [108]	Qin et al. [107]
Reporting								
1. Is the objective of the study clear? (Yes/No)	1	1	1	1	1	1	1	1
2. Are the main outcomes clearly described in the Introduction or Methods? (Yes/No)	1	1	1	1	1	1	1	1
3. Are the characteristics of the patients included in the study clearly described? (Yes/No)	1	1	1	0	1	1	1	1
4. Are the interventions clearly described? (Yes/No)	1	1	1	1	1	1	1	1
5. Are the distributions of principal confounders in each group of subjects clearly described? (Yes/Partially/No)	2	2	2	2	2	2	2	2
6. Are the main findings of the study clearly described? (Yes/No)	1	1	1	1	1	1	1	1
7. Does the study estimate random variability in data for main outcomes? (Yes/No)	1	1	1	1	1	1	1	1
8. Have characteristics of patients lost to follow-up been described? (Yes/No)	1	0	0	1	0	1	1	1
9. Have actual probability values been reported for the main outcomes except probability < 0.001? (Yes/No)	1	1	0	1	1	1	1	1
10. Is the source of funding stated? (Yes/No)	1	1	1	1	1	1	1	1
External validity								
11. Were subjects who were asked to participate in the study representative of the entire population recruited? (Yes/UTD/No)	1	UTD	UTD	UTD	UTD	UTD	UTD	UTD

	Jürgens et al. [104]	Arranz et al. [110]	Carrascal-Laso et al. [112]	Walden et al. [114]	Arranz et al. [111]	Kang et al. [106]	Koopmans et al. [108]	Qin et al. [107]
12. Were those subjects who were prepared to participate representative of the recruited population? (Yes/UTD/No)	UTD	UTD	UTD	UTD	UTD	UTD	UTD	UTD
13. Were staff, places, and facilities where patients were treated representative of treatment most received? (Yes/UTD/No)	1	1	1	0	0	1	1	UTD
Internal validity - bias								
14. Was an attempt made to blind study subjects to the intervention? (Yes/UTD/No)	0	1	0	0	0	1	0	1
15. Was an attempt made to blind those measuring the main outcomes? (Yes/UTD/No)	1	1	0	0	0	1	1	0
16. If any of the results of the study were based on data dredging was this made clear? (Yes/UTD/No)	1	1	1	1	1	1	1	1
17. Was the time period between intervention and outcome the same for intervention and control groups or adjusted for? (Yes/UTD/No)	1	1	1	1	1	1	1	1
18. Were the statistical tests used to assess main outcomes appropriate? (Yes/Unclear/No)	1	1	1	1	1	1	1	1
19. Were main outcome measures used accurate? (valid and reliable) (Yes/UTD/No)	1	1	1	1	1	1	1	1
Internal validity - confounding								
20. Were patients in different intervention groups recruited from the same population? (Yes/UTD/No)	1	1	1	1	1	1	1	UTD
21. Were study subjects in different intervention groups recruited over the same period of time? (Yes/UTD/No)	1	UTD	1	UTD	UTD	1	1	1

	Jürgens et al. [104]	Arranz et al. [110]	Carrascal-Laso et al. [112]	Walden et al. [114]	Arranz et al. [111]	Kang et al. [106]	Koopmans et al. [108]	Qin et al. [107]
22. Were study subjects randomized to intervention groups? (Yes/UTD/No)	1	1	0	0	0	1	0	1
23. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete? (Yes/UTD/No)	0	1	0	0	0	1	0	1
24. Was there adequate adjustment for confounding in the analyses from which main findings were drawn? (Yes/UTD/No)	1	1	0	0	0	0	0	0
25. Were losses of patients to follow-up taken into account? (Yes/UTD/No)	1	UTD	UTD	1	UTD	1	UTD	UTD
Power								
26. Did the study conduct a power calculation? (Yes/No)	1	1	1	0	0	1	1	1
Total (/27)	25	22	17	15	15	24	20	20

Table 2.5: Results from the Consolidated Health Economic Evaluation Reporting Standards 2022 checklist. N/A, not applicable.

	Herbild et al. [105]	Carrascal-Laso et al. [113]	Perlis et al. [119]	Ninomiya et al. [115]	Girardin et al. [116]	Kurylev et al. [117]	Rejon-Parrilla et al. [118]	Skokou et al. [87]
Title								
1. Title	1	1	1	1	1	1	1	0
Abstract								
2. Abstract	1	1	1	1	1	1	1	1
Introduction								
3. Background and objectives	1	1	1	1	1	1	1	1
Methods								
4. Health economic analysis plan	0	0	0	0	0	0	0	0
5. Study population	1	1	1	1	1	1	1	1
6. Setting and location	1	1	0	1	1	1	0	1
7. Comparators	1	0	1	1	1	0	1	1
8. Perspective	0	0	0	1	1	0	0	1
9. Time horizon	0	0	0	1	1	0	1	1
10. Discount rate	0	0	0	1	0	0	1	1
11. Selection of outcomes	N/A	N/A	1	1	1	N/A	1	1
12. Measurement of outcomes	N/A	N/A	1	1	1	N/A	1	1
13. Valuation of outcomes	N/A	N/A	1	0	0	N/A	1	1
14. Measurement and valuation of resources and costs	1	1	1	1	1	1	1	1
15. Currency, price date, and conversion	1	1	1	0	0	0	0	0
16. Rationale and description of model	N/A	N/A	1	1	1	1	1	N/A
17. Analytics and assumptions	1	0	0	1	1	0	1	1
18. Characterizing heterogeneity	1	0	0	0	0	0	0	0
19. Characterising distributional effects	0	0	0	0	0	0	0	0
20. Characterizing uncertainty	1	0	1	1	1	1	1	1
21. Approach to engagement with patients and others affected by the study	0	0	0	0	0	0	0	0

	Herbild et al. [105]	Carrascal-Laso et al. [113]	Perlis et al. [119]	Ninomiya et al. [115]	Girardin et al. [116]	Kurylev et al. [117]	Rejon-Parrilla et al. [118]	Skokou et al. [87]
Results								
22. Study parameters	N/A	N/A	1	1	1	1	1	N/A
23. Summary of main results	1	1	1	1	1	1	1	1
24. Effect of uncertainty	1	0	1	1	1	1	1	1
25. Effect of engagement with patients and others affected by the study	0	0	0	0	0	0	0	0
Discussion								
26. Study findings, limitations, generalizability, and current knowledge	1	1	1	1	1	0	1	1
Other relevant information								
27. Source of funding	1	0	0	1	1	0	1	1
28. Conflicts of interest	1	1	0	1	1	1	1	1
Total	70%	43%	57%	75%	71%	48%	71%	72%

2.5 Discussion

In this systematic review, I identified 16 studies investigating the use of pharmacogenetic testing for antipsychotic medication, and there are a few important observations to highlight. Firstly, studies were predominantly focused on adults, with few very studies focused on paediatric psychiatric populations. This may have been due to the fact that psychosis, the primary diagnosis among many studies, is not typically diagnosed until early adult life[20]. There was only 1 study conducted in a paediatric population, and the primary diagnosis in this study was autism spectrum disorder[111]. There were no studies conducted in individuals of older age; caution should be applied when extrapolating evidence from general adult populations to older adults due to unique pharmacokinetic and pharmacodynamic profiles associated with late-life physiology[120]. For example, ageing is associated with reduced first-pass metabolism due to a reduction in liver mass, blood flow, and decreased CYP biotransformation[120]. This could affect the relationship between genetic variants in CYP pharmacogenes with treatment outcomes, highlighting an important gap in the evidence base. Secondly, the majority of the studies were based in the Europe (mainly Denmark and Spain), and therefore limited diversity in the study participants. There was also a lack of transparency regarding the ethnic composition of study samples, with five studies disclosing the ethnicity of their participants. Thirdly, the limited long-term follow-up data was another concern, as there were 5 studies that had a follow-up period of 1 year or longer and only 1 Markov/decision model that adopted a lifetime horizon. This makes it difficult to evaluate whether the beneficial effects of pharmacogenetic testing will be sustained long-term. Finally, there was no standardised method of conducting pharmacogenetic testing between studies. For example, while most studies tested *CYP2D6* and *CYP2C19*, some studies also tested other genes such as *CYP1A2* and *CYP3A4*, as well as non-CYP genes, such as *ABCB1*, *SLC6A4*, *DRD2*, and *HTR1A*.

In total, there were 8 studies that reported clinical outcomes, including ADRs, symp-

tom severity, medication, hospitalisations, polypharmacy, and physicians' opinions. Overall, clinical outcomes showed either no difference with treatment as usual or a benefit in favour of pharmacogenetics, although there was stronger evidence of clinical utility when pharmacogenetic testing was conducted using a multigene panel. It is possible that pharmacogenetic testing for antipsychotics using a multigene panel, such as the 11-gene panels used by Kang, et al. [106], increases the frequency of actionable variants in the sample, which increases statistical power to detect differences between the intervention and TAU groups. It is important to mention that there were no clinical studies conducted in the UK, highlighting an important gap in the evidence base. I identified 8 studies which reported economic outcomes, including cost-effectiveness analysis, cost-benefit analysis and cost-analysis. Studies that conducted cost-effectiveness analyses reported ICERs that differed widely from one another. For example, Ninomiya et al.[115], and Girardin et al. [116], both investigated the cost-effectiveness of pharmacogenetics-guided clozapine treatment but reported two very different ICERs: Ninomiya calculated an ICER of £16,215 per QALY, whereas Girardin et al. [116], calculated an ICER of US$3.93 million per QALY. In general, pharmacogenetics testing either demonstrated no difference in costs or a reduction in overall, inpatient and non-inpatient costs, compared to TAU, particularly for extreme metabolisers which were suggested to incur higher costs. Furthermore, two studies investigating cost-effectiveness were conducted from a UK perspective.

Quality assessment of RCTs and non-RCTs using the Downs and Black checklist revealed several methodological limitations. Firstly, several studies were not blinded and/or randomized. In pharmacogenetic studies, it is extremely difficult to blind clinicians in the intervention arm as they must consult the pharmacogenetic report to make treatment changes, although clinicians in the treatment as usual arm can be blinded to the pharmacogenetic report until after the intervention is complete. Thus, previous studies have chosen to blind patients and raters instead. There was also an underestimation

of the confounding factors, as studies did not consider that participants who opt to undergo pharmacogenetic testing may be more engaged (selection bias) and therefore have greater adherence, or that the effect of closer monitoring by the clinicians may increase patients' adherence; this confounder was only addressed by Jürgens, et al. [104], who included three arms in their study: pharmacogenetics-guided group, treatment as usual, and structured clinical monitoring, in which the patients' primary contact person systematically recorded adverse effects and factors affecting the patient's adherence at least once quarterly. Finally, the studies were limited by statistical power due to small sample sizes, as most studies had less than 300 participants. Given that poor and ultrarapid metabolisers generally make up less than 10% of population[55], these sample sizes would not be large enough to find an adequate number of these individuals to effectively detect differences between the pharmacogenetics-guided group and treatment as usual group. However, this issue was overcome by Herbild et al. [105], by randomly excluding normal and intermediate metabolisers during recruitment to artificially increase the number of poor and ultrarapid metabolisers in their sample by 20%. The CHEERS checklist for economic evaluations revealed that several studies failed to report or justify their chosen perspective, time horizon, and discount rates. There was also uncertainty in the model parameters, particularly clinical utility of pharmacogenetic testing (i.e., the improvement of symptoms or tolerability after pharmacogenetic testing), given the limited data at the time of publication. There was also no consideration of how findings may vary for subgroups, except by Herbild, et al. [105], who explored healthcare costs for extreme metabolizers (poor and ultrarapid metabolisers of *CYP2D6*). However, there was no consideration of how cost-effectiveness may differ among ethnic groups. Based on the quality assessment of the included studies, the results should be interpreted with caution.

A key challenge highlighted by this review is the current lack of standardisation for pharmacogenetic tests. Each study conducted pharmacogenetic testing differently i.e.,

some studies, such as Walden et al. [114], conducted individual gene testing focusing exclusively on *CYP2D6* and *CYP2C19*, whereas others used a multigene panel to test for a variety of pharmacogenes, as done by Carrascal-Laso et al. [112], where 7 genes were tested: *CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5*, and *ABCB1*. Studies that used multigene panels varied in gene content, with some including genes with questionable/minor effects. This ultimately stems from a lack of consensus on which genes should be included on a pharmacogenetics panel[121]. Bousman et al. [122], proposed that, at a minimum, pharmacogenetic tests in psychiatry should include the following 5 genes: *CYP2D6, CYP2C19, CYP2C9, HLA-A,* and *HLA-B*, to guide prescribing for antipsychotics, antidepressants, mood stabilisers, and anticonvulsants. It is also important to consider that the recommendations provided by the DPWG, CPIC and FDA are occasionally discordant. For example, the FDA currently recommends reducing the dose of clozapine in CYP2D6 poor metabolisers. In contrast, the CPIC and DPWG currently do not provide such recommendations[121]. A comparison of CPIC and DPWG recommendations found that there was a high rate of concordance between the two guidelines, but there were some discrepancies due to different methods used to develop guidelines[123]. There is a possibility that this may have lead to differences in prescribing decisions between each study and affected the results[121], although there are ongoing efforts to address these differences between guidelines[73].

There is a considerable need to invest in mental health research, specifically in research that improve service-users' care and quality of life[124, 125]. This systematic review has revealed a limited number of studies with sufficient sample sizes that contains clinical and/or economic data; thus, further research is warranted to address the specific benefits of pharmacogenetic testing for patients. Despite the need for further research in this field, mental health research globally receives significantly less funding than research into physical conditions. Indeed, the median government spending on mental health in

2017 was US$2.50 per person[124]. Furthermore, mental health research funding is predominantly allocated to biological and aetiological research, which makes up over 50% of funding, and only 7% to health services, clinical, and prevention research, each[126]. Thus, this field requires further, high-quality research. For future studies, I recommend studies of an adequate sample size, including a diverse group of participants. Studies should evaluate the impact of pharmacogenetic testing on adverse effects, efficacy, adherence, and cost-effectiveness. Clinical outcomes should ideally be measured using a standardised clinical scale such as the PANSS and UKU, which have also been used by other studies in this field. Ideally, these studies would be conducted using an sufficiently long follow-up period (1 year or longer), to capture the long-term benefits of pharmacogenetic testing.

2.5.1 Strengths and limitations

To my knowledge, this systematic review is the first to evaluate whether pharmacogenetic testing for antipsychotic medication may improve clinical and/or economic outcomes. To comprehensively assess the quality of the evidence, I used the Downs and Black checklist for clinical outcomes; CHEERS checklist for economic outcomes; and I have evaluated certainty of the findings using the GRADE checklist. I have highlighted several gaps in the evidence base and have made recommendations for future research.

However, this study had several limitations. First, the inclusion criteria of this review was broad due to the scarcity of the data. Thus, I included studies that incorporated other psychotropic drugs, conditional on the fact that antipsychotics was the primary prescribed medication in the sample or results for individuals taking antipsychotics was presented separately. I also included studies with different study designs, different types of pharmacogenetic tests, and different types of outcomes measured. This approach meant that there was substantial heterogeneity among the studies and conducting a meta-analysis for

the clinical outcomes was not possible as most studies were assessed using many different clinical scales. Although some studies used comparable clinical scales, (for example, Jurgens et al., [104] and Arranz et al., [110] reported adverse effects using the UKU), the number of studies were too limited to conduct a meta-analysis. It was also difficult to draw conclusions from the studies due to these differences, and I had to be particularly careful about interpreting studies that included a range of drugs in their study. Second, the search picked up very few studies from outside of Europe and North America, indicating limited clinical generalizability of the findings, therefore highlighting an important gap in the literature that should be addressed in future research. This is significant because the prevalence of schizophrenia is high in East and South Asia, with a patient population of approximately 7.2 and 4.0 million[127]. In addition, compared to Caucasian cohorts, these populations have different frequencies of variants for CYP450 enzymes. For example, CYP2D6*10 is a decreased function allele which is highly abundant in East Asian populations (minor allele frequency [MAF] = 58.7%), and much less common in Europeans (MAF = 0.2%)[128]. This allele is typically included in pharmacogenetic testing panels[129]. Thirdly, not all antipsychotics have pharmacogenetic recommendations, which would further reduce the ability to detect differences. In addition, this review identified 50% of the included studies (n=8) outside of electronic databases. This is perhaps due to variation in terminology used to refer to pharmacogenetics within the literature, such as "personalised medicine", "precision medicine", "cytochrome P450 screening", "CYP2D6 testing", as well as many others which were not covered by my search terms. This indicates that the search terms in this chapter were not sufficiently comprehensive to capture the evidence base. Pharmacogenetics in mental health remains a relatively new field, and as a result, there is variation in the way that each study refers to pharmacogenetic testing. This variation reflects the evolving, yet rapidly growing nature of the field, and future studies must consider this and identify a broader range of search terms to describe pharmacogenetics and capture a wider range of studies. Finally, the CHEERS checklist assesses

the quality of reporting, rather than the quality of the methodology. Thus, a high score on the CHEERS checklist may not necessarily indicate high methodological quality. This is because an item might be correctly done but not reported, or reported but incorrectly done.

2.5.2 Conclusion

Overall, the current evidence base shows either no difference or is in favour of pharmacogenetic-guided prescribing for clinical and economic outcomes. To support the clinical implementation of pharmacogenetics testing into routine mental health care, studies with sufficient sample sizes that provide recommendations for patients who take antipsychotics based on a broad, multigene panel are required, with consistent and comparable clinical outcomes. Sufficiently long follow-up periods (1 year or longer) are required to detect differences in costs and health outcomes. Economic evaluations should also consider how cost-effectiveness may vary for subgroups, for example, by ethnicity.

Chapter 3

Investigating the causal association between schizophrenia and cardiometabolic abnormalities

3.1 Abstract

Individuals with a diagnosis of schizophrenia are known to be at high risk of premature mortality due to poor physical health, especially cardiovascular disease, diabetes, and obesity. Despite well-documented cardiometabolic adverse effects of certain antipsychotic drugs and lifestyle factors, schizophrenia may have an independent effect. To investigate if there is evidence that schizophrenia is causally related to cardiometabolic traits, and vice versa, using bi-directional two-sample Mendelian randomisation (MR) analysis. I used 185 genetic variants associated with schizophrenia from the latest Psychiatric Genomics Consortium GWAS (n = 130,644) in the forward analysis (schizophrenia to cardiometabolic traits) and genetic variants associated with the cardiometabolic traits from various consortia in the reverse analysis (cardiometabolic traits to schizophrenia). There was no

evidence of a causal effect of schizophrenia on cardiometabolic traits in the forward analysis, or cardiometabolic traits on schizophrenia in the reverse analysis. Dyslipidemia and obesity in schizophrenia patients are unlikely to be driven primarily by schizophrenia itself. Therefore, lifestyle, diet, adverse drug reactions, could be possible reasons for the increased risk of metabolic disease in people with schizophrenia.

3.2 Introduction

Compared to the general population, individuals with schizophrenia have significant reductions in average life expectancy by 10-20 years[28]. Indeed, a disproportionate rate of morbidity and mortality has been observed in this patient population. A meta-analysis of 135 cohort studies comparing 4.5 million individuals with schizophrenia to 1.11 billion individuals from the general population demonstrated that schizophrenia is associated with a 2.9-fold increased all-cause mortality compared to any non-schizophrenia control group[29]. The premature mortality rate can largely be attributed to an increased risk of suicide, and physical illness, including type 2 diabetes mellitus and cardiovascular disease [130][131][30]. A meta-analysis by Afzal et al. [132], of 120 studies from 43 countries demonstrated that people with severe mental illness (SMI) have a drastically higher prevalence and odds of obesity than the general population. They found that the pooled prevalence of obesity in individuals with an SMI was 25.9%, and individuals had a 3-fold greater likelihood of being obese compared to the general population. Furthermore, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial found that 40.9-42.7% of their participants with schizophrenia (n=1460) met the criteria for metabolic syndrome, although the exact figure varied slightly depending on whether they applied the American Heart Association criteria or National Cholesterol Education Program criteria[133]. Thus, metabolic syndrome is highly prevalent in this population. The reasons for adverse cardiovascular and metabolic health conditions within this patient population are complex, and

enhancing our understanding of these mechanisms may lead to more effective interventions for prevention and treatment strategies based on a personalised medicine approach by identifying individuals diagnosed with schizophrenia at a high risk for metabolic syndrome [134].

Despite well-documented cardiometabolic side effects of certain antipsychotic drugs, previous epidemiological studies have suggested that schizophrenia may have an independent effect through the the high prevalence of metabolic syndrome in drug-naïve patients with schizophrenia [130][30][135]. Indeed, antipsychotic-naïve patients with first-episode psychosis have a 2.5-fold risk for metabolic syndrome compared to age– and gender-matched controls [30]. Multiple studies have demonstrated that drug-naïve individuals with schizophrenia, as well as their unaffected first-degree relatives, demonstrate cardiometabolic risk factors such as increased visceral fat, dyslipidaemia, impaired glucose tolerance, and insulin resistance[130][30][136]. It is possible that insulin sensitivity is perturbed during the early stages of schizophrenia, with one study reporting that 53-67% of antipsychotic-naive individuals with schizophrenia had increased levels of insulin and proteins and peptides which are co-released alongside insulin from pancreatic β cells, such as proinsulin, mature insulin, and C-peptide and chromogranin A, compared to 16-21% of the controls[134].

However, the direction of this relationship is yet to be established, as some studies have suggested that cardiometabolic abnormalities precede the onset of schizophrenia. For example, a previous study demonstrated that persistently high fasting insulin levels in children 9 years of age from the Avon Longitudinal Study of Parents and Children birth cohort was associated with a 3.22 times greater odds of developing psychosis at 24 years, indicating possible early-life origins of this association[137]. Individuals at clinical high risk for psychosis, defined using the Comprehensive Assessment of At Risk Mental

States assessment, who do not have a diagnosis of psychosis and are untreated, have shown metabolic abnormalities, such as dyslipidaemia, hypertension, obesity/overweight, and insulin resistance, which are not explained by medication adverse effects [138][139]. A previous hypothesis proposed that impaired energy metabolism pathways could lead to neuronal dysfunction, which leads to decreased synaptic plasticity, reduced neuronal size, abnormal glutamate transmission and dopamine release[134]. Thus, metabolic syndrome could play a role in the pathophysiology and onset of schizophrenia.

However, observational studies can generate associations in the absence of a true causal relationship due to unmeasured confounding factors[140]. For example, individuals with schizophrenia have higher reported rates of smoking[141], which can confound the schizophrenia-metabolic syndrome relationship if not corrected for in the study, leading to biased causal estimates. Even after measuring known confounders, measurement error can lead to residual confounding[140]. The bias present in observational research, therefore, makes it uncertain whether these associations are causal or spurious findings[140]. Reverse causality is another form of bias in observational studies, whereby the outcome precedes the exposure, making it unclear whether schizophrenia is causally associated with metabolic syndrome or metabolic syndrome is causally related to schizophrenia[140]. In this chapter, I used a genetic instrumental variable analysis (Mendelian randomisation, MR) to establish whether schizophrenia is potentially causally related to cardiometabolic traits or vice versa. MR uses genetic variants as instrumental variables (IVs) to examine whether an exposure is likely to be causally related to an outcome [140]. Genetic variants are randomly allocated during conception and are, therefore, independent of unmeasured confounders. Genetic IVs in MR are subject to three assumptions in order to be valid IVs and these assumptions must be evaluated when interpreting the results (Figure 3.1). Firstly, the relevance assumption states that the IVs must be robustly associated with the exposure; the independence assumptions states that there are no confounders between

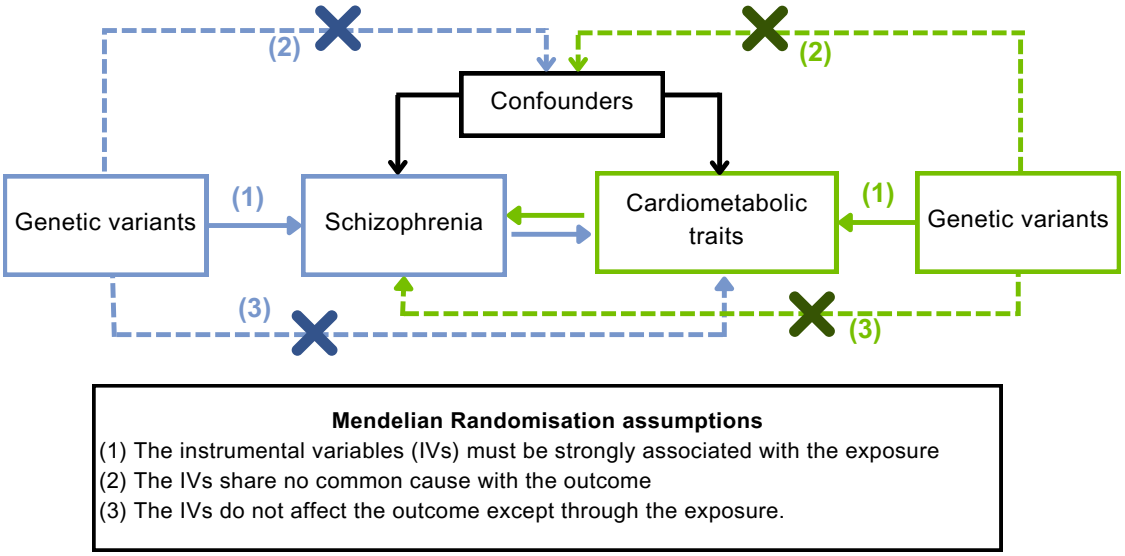


Figure 3.1: The core assumptions of Mendelian randomisation analysis.

the genetic variants and outcome, such as ancestry; and lastly, the exclusion-restriction assumption states that the IVs must not be associated with other exposures which influence the outcome (horizontal pleiotropy)[140][142].

Previous MR studies have focused mainly on the relationship between glucose and insulin-related traits with schizophrenia (or vice versa) with discordant findings, and fewer studies have investigated obesity, blood lipids and blood pressure as a potential exposure or outcome[143][144][145][146][147]. Where obesity is included, it has only been measured using body mass index (BMI). Although BMI is used widely, it has been criticized by previous literature for not being a direct measure of body fat, so the use of other measures are warranted to investigate this relationship[148]. Thus, in this chapter, a bidirectional, two-sample MR analysis was conducted using the largest summary-level dataset on schizophrenia from the Psychiatric Genomic Consortium (PGC), investigating the effect of schizophrenia on the risk of cardiometabolic traits, as well the effect of cardiometabolic

traits on the risk of schizophrenia. I hypothesise that schizophrenia precedes the onset of cardiometabolic traits, given the differences in the average age of onset between diabetes and schizophrenia, with diabetes typically diagnosed during middle age[149] and schizophrenia during early adulthood[20].

3.3 Methods

3.3.1 Study design overview

I conducted a bidirectional MR study to investigate the causal association of schizophrenia on cardiometabolic traits, including anthropometric traits (body mass index [BMI], waist-hip ratio [WHR]), glycaemic traits (HbA1c, fasting glucose, fasting insulin), blood lipids (triglycerides, high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol) and blood pressure (systolic and diastolic blood pressure). These traits were selected to capture the components of metabolic syndrome. I also performed the analysis in the reverse direction, i.e., I investigated the causal association of cardiometabolic traits on schizophrenia. A flowchart presenting the study design is shown in Figure 3.2.

3.3.2 Data

To derive a reliable conclusion on the causal association between schizophrenia and cardiometabolic factors, a two-sample framework was used, i.e., the exposure and the outcome were measured using two non-overlapping samples. Summary-level datasets were obtained from large consortia of genome-wide association studies as summarized data are available for larger sample sizes, improving the power to detect a causal effect[150]. The independence assumption of MR is related to confounding by ancestry or population stratification, thus, only studies with data on individuals of a European ancestry were included to avoid violation of this assumption, and due to the paucity of diverse datasets for some of the key traits[151]. Individual-level studies and multi-ancestry studies were

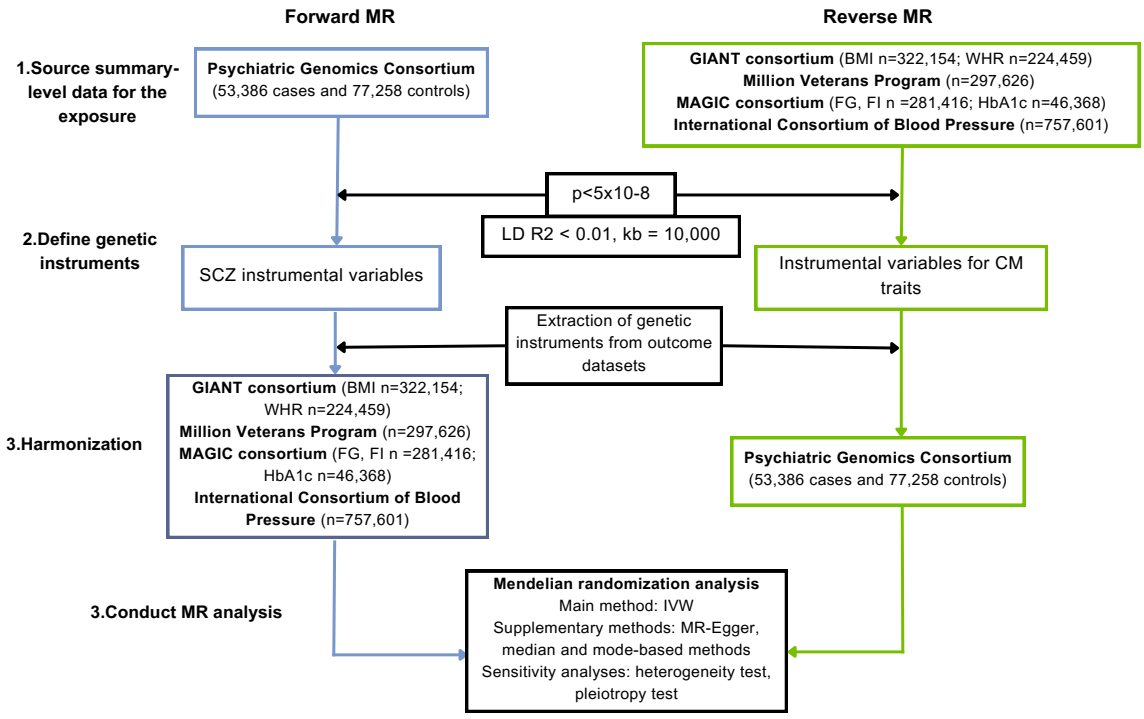


Figure 3.2: Study workflow of the two-sample, bidirectional MR analysis investigating the association between schizophrenia and cardiometabolic traits. BMI, body mass index; CM, cardiometabolic; GIANT, Genetic Investigation of ANthropometric Traits; IVW, inverse-variance weighted; FG, fasting glucose; FI, fasting insulin; LD, linkage disequilibrium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; MR, Mendelian randomisation; SCZ, schizophrenia; SNPs, single-nucleotide polymorphisms; WHR, waist-hip ratio

excluded (unless they provided separate data for Europeans). The datasets used are summarized in Table 3.1.

The largest and most up-to-date GWAS was selected for schizophrenia from the PGC, including a total of 53,386 cases and 77,258 controls of European ancestry [151]. The GWAS summary statistics were downloaded from the PGC website (available at `https://pgc.unc.edu/for-researchers/download-results/`). Cases were defined as

Table 3.1: Sample characteristics for exposures and outcomes in the Mendelian randomisation analysis. BMI, body mass index; GIANT, Genetic Investigation of Anthropometric Traits; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; MVP, Million Veteran Program; PGC, Psychiatric Genomics Consortium; SD, standard deviation; WHR, waist-hip ratio

Trait	Sample size	Reference	Consortium	Population	Units
Schizophrenia	53,386 cases and 77,258 controls	[151]	PGC	European	Log odds
BMI	322,154	[152]	GIANT	European	SD (kg/m2)
WHR	21,244	[153]	GIANT	European	SD
Blood lipids	215,551	[154]	MVP	European	SD (mg/dl)
Fasting glucose	200,622	[155]	MAGIC	European	mmol/l
Fasting insulin	151,013	[155]	MAGIC	European	pmol/l
Hba1c	46,368	[7]	MAGIC	European	%
Systolic blood pressure	757,601	[156]	International Consortium of Blood Pressure	European	mmHg
Diastolic blood pressure	757,601	[156]	International Consortium of Blood Pressure	European	mmHg

individuals diagnosed with schizophrenia spectrum disorder based on DSM-IV criteria. Summary-level data for BMI and WHR was selected from the Genetic Investigation of ANthropometric Traits (GIANT) consortium, including up to 322,154 and 21,244 individuals, respectively [152][153] (available at https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium).

Summary data for blood lipids were obtained from the Million Veteran Program GWAS, including 215,551 individuals of European ancestry [154]. This data is available through dbGaP at https://www.ncbi.nlm.nih.gov/gap/usingtheaccessionnumberphs001672.v1.p1. For glycaemic traits, the MAGIC consortium was used (https://magicinvestigators.org/). Data for fasting glucose and fasting insulin were derived from a sample of 281,416 individuals, and HbA1c was derived from a sample of 46,368 individuals. Both samples included adults of European descent [7][155]. Summary-level data for blood pressure traits were selected from the UK Biobank and the International Consortium of Blood Pressure, including up to 757,601 individuals [156]. Summary statistics for blood pressure are available from the GWAS Catalog (https://www.ebi.ac.uk/gwas/publications/30224653).

3.3.3 Genetic Instruments

To ensure that the genetic variants used in the analysis were valid IVs, several quality control steps were conducted using the TwoSampleMR package in R[157]. Firstly, the MR assumptions indicate that the IVs must be strongly associated with the exposure, thus, the SNPs were filtered and only SNPs strongly associated with the exposure at genome-wide significance ($P<5x10^{-8}$) were selected. Including variants that are not strongly associated with an exposure could introduce horizontal pleiotropy and weak instrument bias[158]. Secondly, SNPs in linkage disequilibrium 10,000 kb pairs apart at an R^2 threshold of 0.01 were pruned against the European 1000 Genomes reference panel[157]. Among pairs

of SNPs with R^2 above this threshold, the SNP with the strongest evidence of association with the key trait (smallest P value) was retained and the other SNP in the pair was excluded. Genetic variants not found in the reference panel were excluded. Finally, harmonization was conducted as the MR analysis involved the use of two independent datasets with genetic variants which may not share the same allele pair. Thus, harmonization ensured that the effect of a SNP on the exposure, and the effect of the same SNP on the outcome, corresponded to the same allele[150]. Genetic variants that did not share the same allele pair between datasets were identified and corrected. Alternatively, palindromic SNPs, i.e., SNPs with alleles on the forward strand that are the same as on the reverse strand, were excluded from the analysis[150]. The SNPs that remained after this selection process were used as IVs in the MR analysis. Summary data of the genetic instruments were subsequently extracted from the outcome dataset, including effect of the SNP on the outcome (beta or odds ratio), standard error, p-value, effect allele, other allele, effect allele frequency, and sample size.

3.3.4 Statistical analyses

All statistical analyses were conducted using the TwoSampleMR package (version 0.5.6) using Rstudio (version 2021.09.0). Individual SNP estimates (β_{IV}) were obtained using the ratio method, where the effect of the SNP on the outcome (β_{ZY}) was divided by the corresponding effect of the SNP from the exposure (β_{ZX})[142].

$$\beta_{IV} = \beta_{ZY}/\beta_{ZX}$$

With multiple genetic variants as IVs, the ratio estimates were subsequently pooled using a meta-analysis process, known as the inverse-variance weighted (IVW) method. This process involves a weighted mean of the ratio estimates to derive an IVW effect estimate, where the weight of each ratio is the inverse of the variance of the association between

the genetic variant and the outcome[142]. While IVW is the most powerful method of MR, it has stringent assumptions: the IVW method requires that all SNPs are valid instruments (i.e., there is no horizontal pleiotropy) or are invalid in a way that the overall bias is zero (i.e., the horizontal pleiotropy is balanced). If all of the genetic variants are valid IVs, then the IVW method will produce a consistent estimate of the causal effect[159].

Altogether, I investigated 11 traits using univariable MR analysis. I reported unadjusted significance values throughout the chapter, but to interpret the results, I used a Bonferroni-corrected P value of 0.005 as being statistically significant (0.05/11). As the traits may not be independent, a P value between 0.005 and 0.05 was interpreted as suggestive evidence of a causal association.

3.3.5 Sensitivity Analyses

Sensitivity analyses was conducted using the TwoSampleMR package in R. Given the polygenic nature of schizophrenia, it is possible that genetic IVs are pleiotropic and affect cardiometabolic outcomes through multiple pathways, potentially violating the exclusion-restriction assumption[158]. The MR analysis in this chapter also uses a large number of genetic variants as IVs, meaning there is an increased likelihood that at least one variant is an invalid IV. Generally, pleiotropy can be ruled out if the biological function of IVs are known, but this is not the case for the majority of SNPs associated with schizophrenia which have unknown biological functions[158]. An alternative approach to evaluating this assumption is conducting sensitivity analyses. In this chapter, I use robust analysis methods, which allows different assumptions than the standard IVW assumptions.

Firstly, the MR-Egger method combines the ratio estimates into a meta-regression with an intercept and slope parameter. Pleiotropic effects of IVs are allowed if they satisfy the Instrument Strength Independent of Direct Effect (InSIDE) assumption, which states that

the size of the pleiotropic effects of genetic variants are independent of the size of the pleiotropic effects on the exposure[160]. The slope represents an estimate of the causal effect and the intercept is used to quantify the extent to which the IVs affect the outcome through pleiotropic pathways other than the exposure[158]. Generally, if the horizontal pleiotropic effects are in a particular direction, constraining the slope to go through zero will lead to bias. Thus, MR-Egger allows the intercept to pass through a value other than zero, and the intercept term represents the average pleiotropic effect. Secondly, the weighted median method takes the weighted median of the ratio estimates, as opposed to the weighted mean as in the IVW method[160]. This method requires the "majority valid" assumption, meaning that it allows up to 50% of the SNPs to be invalid instruments, i.e., violate the MR assumptions, and provides unbiased effect estimates even in the presence of unbalanced horizontal pleiotropy[160]. Lastly, the weighted mode method requires the "plurality valid" assumption, whereby it clusters the IVs based on the similarity of their estimates, and the cluster with the greatest number of SNPs is chosen and is given the most weight for as the final causal estimate[160]. If the IVs contributing to the largest cluster are unbiased, then the causal estimate from this method is unbiased[157]. For example, the plurality assumption would be satisfied if 40% of the IVs are valid, provided that the remaining 60% are not in a cluster with a similar ratio estimate[160].

Heterogeneity between the estimates was quantified using Cochran's Q statistic using the IVW method and MR-Egger regression. Finally, a "leave-one-out" analysis was performed whereby the MR was repeated while sequentially excluding each SNP to identify any SNPs with a potentially large effect.

3.4 Results

3.4.1 Schizophrenia on Cardiometabolic Traits

In the forward analysis, up to 185 LD-independent SNPs significantly associated with schizophrenia were identified (Appendix B, Table B1). However, not all these SNPs were found in the summary-level dataset for the cardiometabolic traits. In addition, palindromic SNPs were excluded in the harmonization process. This left 164, 164, 163, 153, 117, 80, 150, 150, 178, 178 and 93 SNPs as IVs for MR analyses of schizophrenia on HDL, LDL, triglycerides, total cholesterol, BMI, WHR, systolic blood pressure, diastolic blood pressure, fasting glucose, fasting insulin and HbA1c, respectively.

I found weak evidence for associations between schizophrenia and LDL (0.013 SD change in LDL per log odds increase in schizophrenia, 95% CI, 0.001–0.024 SD; p = 0.027) and total cholesterol level (0.013 SD change in total cholesterol per log odds increase in schizophrenia, 95% CI, 0.002–0.025 SD; p = 0.023) using the primary IVW analysis method (Figure 3.3). The effect sizes for the causal association between schizophrenia and LDL and total cholesterol were relatively consistent across the different methods (Table 3.2). This is further demonstrated in their respective scatter plots (Figure 3.4). The effect sizes for these associations were very small and did not survive correction for multiple testing. Using the MR-Egger regression test, I did not find evidence for horizontal pleiotropy for LDL or total cholesterol. The MR-Egger intercept provided no evidence against the null hypothesis of no unmeasured pleiotropy (LDL, intercept p = 0.937; total cholesterol, intercept p = 0.563). Iterative removal of each individual SNP using leave-one-out analysis did not affect the IVW estimates for LDL or TC, suggesting that they were not driven by one singular SNP (Appendix B, Figure B1-2). However, Cochran's Q statistic demonstrated evidence of heterogeneity between the effect estimates between the 164 LDL and 153 total cholesterol associated genetic variants (LDL, heterogeneity P

= 8.80x10^{-10}; total cholesterol, heterogeneity P = 1.11x10^{-9}).

Furthermore, schizophrenia was not associated with BMI (β, -0.010 SD; 95% CI, -0.032–0.013 SD; p = 0.392), WHR (β, 0.013 SD; 95%, CI -0.009–0.034 SD; p = 0.241), HDL (β, -0.006 SD; 95% CI, -0.023–0.011 SD; p = 0.480), triglycerides (β, 0.005 SD; 95% CI, -0.010–0.019 SD; p = 0.512), fasting glucose (β, 0.001 mmol/l; 95% CI, -0.005–0.006 mmol/l; p = 0.837), fasting insulin (β, 0.001 pmol/l; 95% CI, -0.006–0.008 pmol/l; p = 0.708), HbA1c (β, -0.008%; 95% CI, -0.020–0.004%; p = 0.180), systolic blood pressure (β, -0.042 mmHg; 95% CI, -0.364–0.279 mmHg; p = 0.796) or diastolic blood pressure (β, 0.032 mmHg; 95% CI, -0.144–0.208 mmHg; p = 0.721) using the primary IVW analysis method (Figure 3.3) or other methods (Table 3.2). The MR-Egger intercept revealed generally minimal pleiotropy (Table 3.2) and leave-one-out analysis demonstrated robustness of the effect estimates (Appendix B, Figure B3-11). However, Cochran's Q test demonstrated heterogeneity for all traits except HbA1c (Table 3.2).

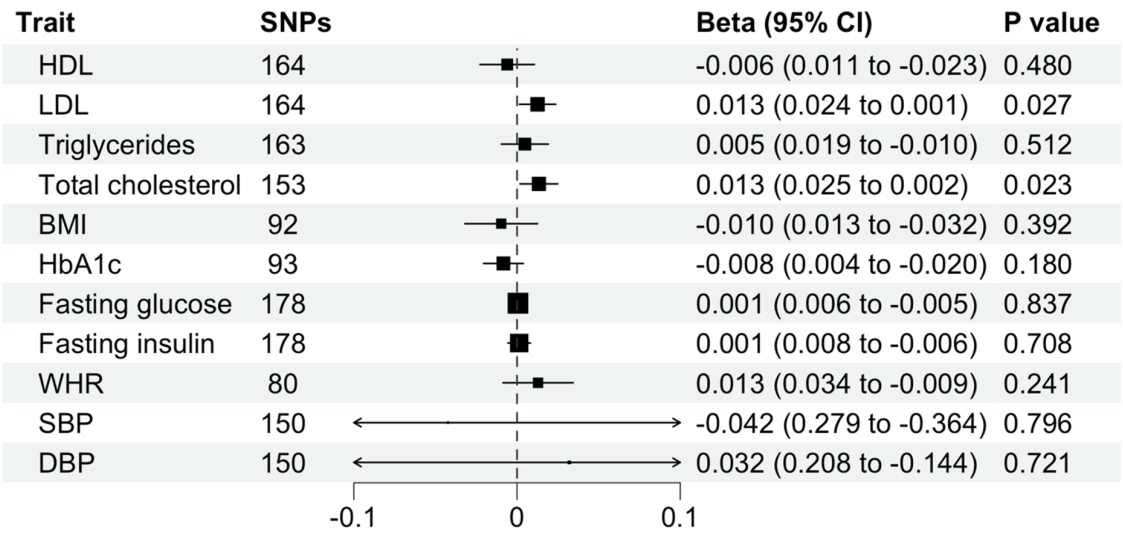
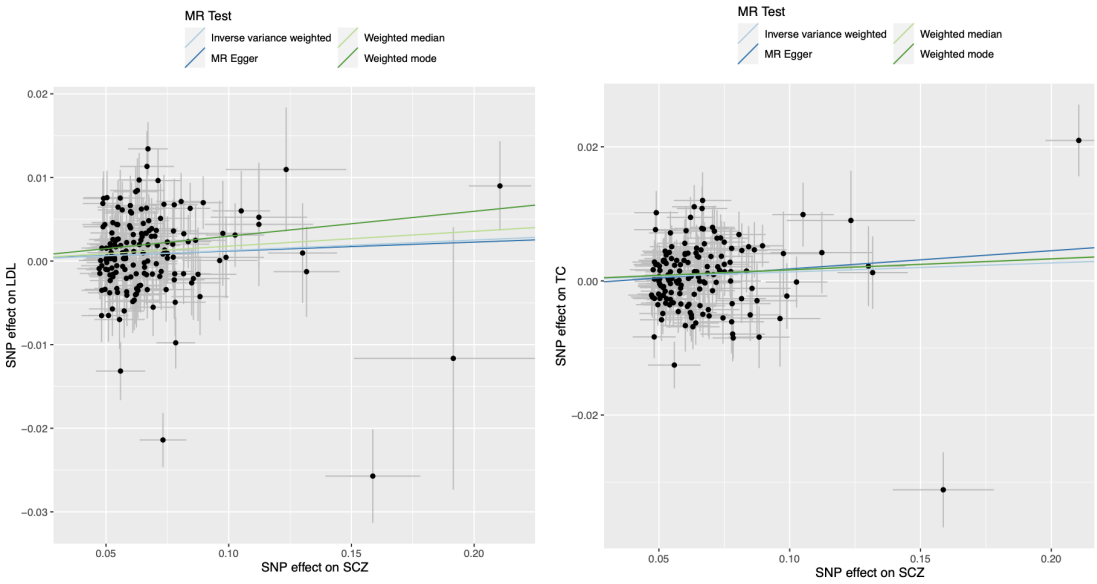


Figure 3.3: Mendelian randomisation estimates (beta and 95% confidence intervals) for the association between schizophrenia (exposure) and cardiometabolic traits (outcome) using the inverse variance weighted method. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; TC, total cholesterol; WHR, waist-hip ratio.



(**a**) (**b**)

Figure 3.4: Mendelian randomisation scatter plot for the association between schizophrenia (exposure) and (a) LDL and (b) total cholesterol (outcomes). Each black dot represents the estimate of an individual genetic variant and its corresponding 95% confidence interval. LDL, low-density lipoprotein; MR, Mendelian randomisation; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

Table 3.2: Mendelian randomisation estimates (beta and standard error) for the association between cardiometabolic traits (exposure) and schizophrenia (outcome) using the inverse variance weighted method, MR-egger and weighted median- and mode-based methods. BMI, body mass index; HDL, high-density lipoprotein; IVW, inverse variance-weighted; LDL, low-density lipoprotein; MR, Mendelian randomisation; SE, standard error; nSNP, number of single nucleotide polymorphisms used in the analysis; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Trait	Cochran's Q P value	MR-Egger intercept P value	nSNP	Method	β (SE)	P
HDL	4.68x10^{-59}	0.085	164	IVW	-0.006 (0.008)	0.48
			164	MR-Egger	-0.065 (0.035)	0.066
			164	Weighted median	-0.009 (0.007)	0.237
			164	Weighted mode	-0.022 (0.022)	0.315
LDL	1.19x10^{-9}	0.937	164	IVW	0.013 (0.006)	0.027
			164	MR-Egger	0.011 (0.024)	0.649
			164	Weighted median	0.018 (0.007)	0.006
			164	Weighted mode	0.030 (0.016)	0.065
Triglycerides	3.70x10^{-33}	0.037	163	IVW	0.005 (0.006)	0.512
			163	MR-Egger	0.067 (0.024)	0.029
			163	Weighted median	0.001 (0.007)	0.882
			163	Weighted mode	-0.007 (0.022)	0.727
Total cholesterol	1.109x10^{-9}	0.563	153	IVW	0.013 (0.006)	0.023
			153	MR-Egger	0.027 (0.024)	0.267
			153	Weighted median	0.017 (0.007)	0.013
			153	Weighted mode	0.016 (0.022)	0.454
BMI	5.00x10^{-20}	0.921	117	IVW	-0.010 (0.011)	0.392
			117	MR-Egger	-0.014 (0.043)	0.749
			117	Weighted median	0.005 (0.012)	0.688
			117	Weighted mode	0.012 (0.023)	0.612
WHR	4.86x10^{-7}	0.646	80	IVW	0.013 (0.011)	0.241
			80	MR-Egger	-0.006 (0.041)	0.894
			80	Weighted median	0.013 (0.013)	0.325
			80	Weighted mode	0.015 (0.026)	0.558
SBP	0	0.484	150	IVW	-0.042 (0.164)	0.796
			150	MR-Egger	0.404 (0.658)	0.54
			150	Weighted median	0.052 (0.093)	0.572
			150	Weighted mode	0.240 (0.247)	0.333
DBP	8.86x10^{-317}	0.208	150	IVW	0.032 (0.090)	0.721
			150	MR-Egger	0.469 (0.357)	0.191
			150	Weighted median	-0.039 (0.050)	0.438
			150	Weighted mode	-0.210 (0.180)	0.247
Fasting glucose	1.36x10^{-3}	0.131	178	IVW	-0.148 (0.081)	0.069
			178	MR-Egger	-0.184 (0.155)	0.239
			178	Weighted median	-0.126 (0.092)	0.171
			178	Weighted mode	-0.157 (0.080)	0.053
Fasting insulin	4.89x10^{-8}	0.149	178	IVW	-0.135 (0.177)	0.445
			178	MR-Egger	-0.046 (0.536)	0.932

Trait	Cochran's Q P value	MR-Egger intercept P value	nSNP	Method	β (SE)	P
			178	Weighted median	-0.029 (0.156)	0.852
			178	Weighted mode	-0.017 (0.216)	0.936
HbA1c	0.691	0.629	93	IVW	-0.008 (0.006)	0.18
			93	MR-Egger	-0.019 (0.023)	0.407
			93	Weighted median	-0.009 (0.009)	0.311
			93	Weighted mode	-0.012 (0.017)	0.479

3.4.2 Cardiometabolic Traits on Schizophrenia

In the reverse analysis, 105, 71, 93, 72, 68, 29, 455, 454, 87, 43 and 11 LD-independent, genome-wide significant SNPs were identified for HDL, LDL, triglycerides, total cholesterol, BMI, WHR, systolic blood pressure, diastolic blood pressure, fasting glucose, fasting insulin and HbA1c, respectively. After excluding SNPs missing in the summary-level dataset for schizophrenia and palindromic SNPs, 101, 65, 84, 66, 67, 28, 392, 393, 75, 38, and 11 SNPs remained as instrumental variables.

Cardiometabolic traits were not associated with schizophrenia, including BMI (OR, 1.069; 95% CI, 0.887-1.288; p = 0.482), WHR (OR, 1.005; 95% CI 0.843-1.198 SD; p = 0.954), HDL (OR, 0.982; 95% CI, 0.900-1.072; p = 0.690), LDL (OR, 1.016; 95% CI, 0.923-1.118; p = 0.512), total cholesterol (OR, 1.000; 95% CI, 0.892-1.121; p = 0.996), triglycerides (OR, 1.068; 95% CI, 0.985-1.158; p = 0.113), fasting glucose (OR, 0.863; 95% CI, 0.735-1.012; p = 0.069), fasting insulin (OR, 0.874; 95% CI, 0.618-1.236; p = 0.445), HbA1c (OR, 1.104; 95% CI, 0.899-1.355; p = 0.345), systolic blood pressure (OR, 1.000; 95% CI, 0.994-1.006; p = 0.926) or diastolic blood pressure (OR, 1.002; 95% CI, 0.992-1.012; p = 0.710) and schizophrenia using the primary IVW analysis method (Figure 3.5) or other methods (Table 3.3). Leave-one-out analysis demonstrated robustness of the effect estimates (Appendix B, Figures B12-22). However, the MR-Egger intercept indicated potential pleiotropy for LDL and HbA1c. In addition, Cochran's Q test demonstrated heterogeneity for all traits except HbA1c (Table 3.3).

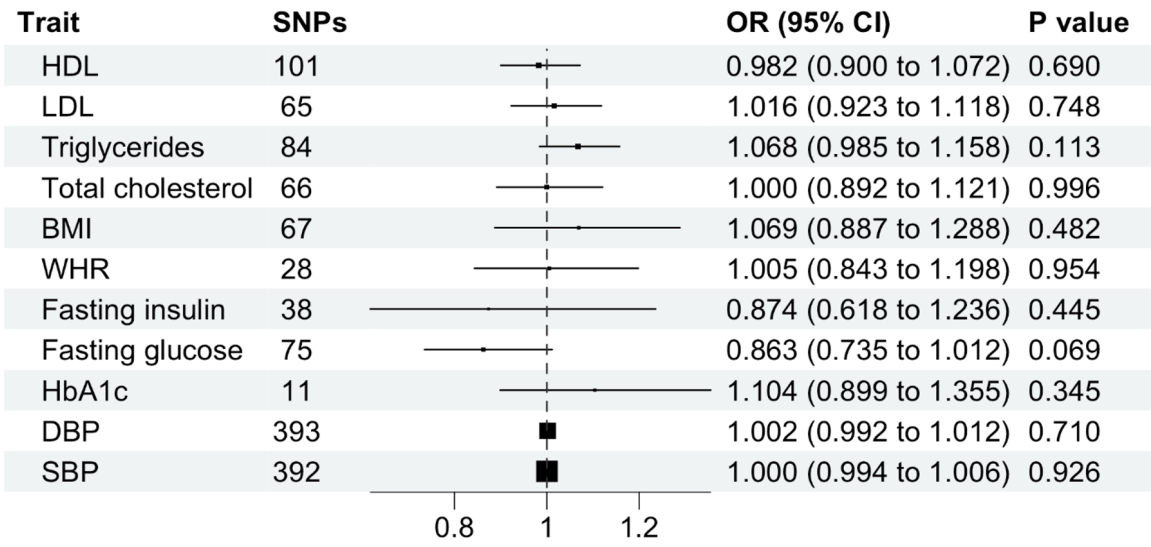


Figure 3.5: Mendelian randomisation estimates (odds ratio and 95% confidence intervals) for the association between cardiometabolic traits (exposure) and schizophrenia (outcome) using the inverse variance weighted method. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; WHR, waist-hip ratio.

Table 3.3: Mendelian randomisation estimates (beta and standard error) for the association between cardiometabolic traits (exposure) and schizophrenia (outcome) using the inverse variance weighted method, MR-egger and weighted median- and mode-based methods. BMI, body mass index; HDL, high-density lipoprotein; IVW, inverse variance-weighted; LDL, low-density lipoprotein; MR, Mendelian randomisation; SE, standard error; nSNP, number of single nucleotide polymorphisms used in the analysis; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Trait	Cochran's Q P value	MR-Egger intercept P value	nSNP	Method	β (SE)	P
HDL	1.11x10^{-31}	0.306	101	IVW	-0.018 (0.045)	0.69
			101	MR-Egger	-0.078 (0.073)	0.292
			101	Weighted median	-0.041 (0.041)	0.308
			101	Weighted mode	-0.052 (0.038)	0.168
LDL	9.39x10^{-11}	0.015	65	IVW	0.016 (0.049)	0.748
			65	MR-Egger	-0.149 (0.081)	0.07
			65	Weighted median	-0.050 (0.049)	0.306
			65	Weighted mode	-0.052 (0.047)	0.276
Triglycerides	1.21x10^{-16}	0.164	84	IVW	0.065 (0.041)	0.113
			84	MR-Egger	0.003 (0.061)	0.964
			84	Weighted median	0.048 (0.038)	0.209
			84	Weighted mode	0.058 (0.033)	0.084
Total cholesterol	1.16x10^{-19}	0.537	66	IVW	0.000 (0.058)	0.023
			66	MR-Egger	-0.058 (0.110)	0.267
			66	Weighted median	0.050 (0.052)	0.013
			66	Weighted mode	0.024 (0.051)	0.454
BMI	6.01x10^{-33}	0.022	67	IVW	0.067 (0.095)	0.482
			67	MR-Egger	0.665 (0.272)	0.017
			67	Weighted median	0.074 (0.085)	0.385
			67	Weighted mode	0.168 (0.185)	0.368
WHR	0.026	0.606	28	IVW	0.005 (0.090)	0.954
			28	MR-Egger	-0.207 (0.416)	0.623
			28	Weighted median	-0.036 (0.116)	0.758
			28	Weighted mode	-0.094 (0.158)	0.554
SBP	4.36x10^{-101}	0.09	392	IVW	0.000 (0.003)	0.926
			392	MR-Egger	0.013 (0.008)	0.109
			392	Weighted median	0.003 (0.003)	0.354
			392	Weighted mode	0.004 (0.006)	0.539
DBP	3.74x10^{-99}	0.294	393	IVW	0.002 (0.005)	0.71
			393	MR-Egger	0.014 (0.013)	0.267
			393	Weighted median	0.004 (0.005)	0.51
			393	Weighted mode	0.006 (0.011)	0.551
Fasting glucose	3.93x10^{-9}	0.783	75	IVW	0.001 (0.003)	0.837
			75	MR-Egger	-0.016 (0.012)	0.156
			75	Weighted median	0.003 (0.004)	0.48
			75	Weighted mode	0.012 (0.012)	0.353
Fasting insulin	2.68x10^{-9}	0.861	38	IVW	0.001 (0.004)	0.708
			38	MR-Egger	0.022 (0.015)	0.136

Trait	Cochran's Q P value	MR-Egger intercept P value	nSNP	Method	β (SE)	P
			38	Weighted median	-0.002 (0.004)	0.723
			38	Weighted mode	-0.001 (0.011)	0.918
HbA1c	0.127	0.009	11	IVW	0.099 (0.105)	0.345
			11	MR-Egger	0.434 (0.225)	0.085
			11	Weighted median	0.110 (0.124)	0.378
			11	Weighted mode	0.386 (0.144)	0.023

3.5 Discussion

In this study, I conducted bidirectional two-sample MR analyses using publicly available large-scale genomic summary data to examine potential causal effects of schizophrenia on cardiometabolic traits and vice versa. The results do not support a causal effect of schizophrenia on cardiometabolic traits, or of cardiometabolic traits on schizophrenia. Taken together, these findings suggest that cardiometabolic alteration in schizophrenia patients is unlikely to be fully attributable to an independent effect of schizophrenia on these outcomes. Rather, dyslipidaemia and obesity in schizophrenia patients may be attributable to other factors such as lifestyle and adverse effects of antipsychotic medications.

Previous literature have reported similar findings. Adams et al. [145], Polimanti et al. [146], and Aoki et al. [147], conducted MR analysis to investigate the SCZ-cardiometabolic abnormalities association. None of the 3 studies reported a causal association between schizophrenia and fasting glucose. Adams et al. [145] and Polimanti et al. [146] explored causal associations between schizophrenia and other glycaemic traits. Although Polimanti et al. [146] did not report any causal associations between schizophrenia and their glycaemic traits of interest (fasting insulin, fasting proinsulin, homeostatic model assessment–insulin resistance, HbA1c), Adams et al. [145] found weak evidence of an association between schizophrenia and fasting insulin (P=0.016). However, this association did not survive multiple testing corrections. Aoki et al. [147] also explored additional cardiometabolic traits, such as BMI, blood lipids, and blood pressure, which were also not causally related to schizophrenia. Thus, findings for the schizophrenia-cardiometabolic traits relationship in previous studies are consistent with the results presented in this study.

The reverse association, i.e., the cardiometabolic traits-schizophrenia association, was explored by Aoki et al. [147], Li et al. [143], and Hartwig et al[144]. Hartwig et al[144],

focused exclusively on the relationship between BMI and schizophrenia, and found no evidence of a causal relationship. Aoki et al. [147] and Li et al. [143] focused on several glycaemic traits, and both studies did not identify causal associations between HbA1c or fasting glucose on schizophrenia. However, Li et al. [143] found that a 1-SD increase in fasting insulin levels increased the risk of schizophrenia by an odds ratio of 2.33 (p=0.001), suggesting that impaired insulin sensitivity may play a causal role in the pathogenesis of schizophrenia. They proposed that the development of schizophrenia could be mediated by other pathways other than the diabetes-related insulin signaling pathway, given that other glycaemic traits were not causally related to schizophrenia in their analysis. These results contradict the ones reported in this chapter, where I reported no evidence of an effect on the risk of schizophrenia with increased fasting insulin levels. However, it is worth mentioning that their results were no longer significant when adjusting for BMI ($P > 0.05$), indicating a source of pleiotropy. None of the three studies investigated the causal relationships between blood lipids or blood pressure on schizophrenia.

Given the results of this chapter, the schizophrenia-cardiometabolic trait associations reported in observational studies may not correspond to a causal one. Rather, these associations are likely to be driven by other factors. There is compelling evidence that social determinants of health, such as economic stability, structural discrimination, healthcare access, neighbourhood and built environment, as well as others, are all potential causes of cardiovascular disease[161]. In particular, psychosis and cardiometabolic abnormalities disproportionately affect marginalised communities, and a previous umbrella review found evidence of associations between racial/ethnic discrimination and psychosis in both clinical (i.e., help-seeking) and non-clinical populations (i.e., population-based)[162]. These social determinants of health can contribute to and compound the effect of lifestyle factors. Regarding lifestyle factors, individuals with schizophrenia show deficits in cognition, perception, and volition, which can impact their activities of daily living, self-care, and

finances[163]. For example, they are more likely to have low physical activity, a diet with high-calorie fast foods (also related to income) and higher rates of alcohol and tobacco consumption [30][163]. Indeed, the self-medication hypothesis proposes that patients with schizophrenia may use substances to cope with their symptoms [141]. Individuals who smoke are also significantly more likely to be affected by a cardiovascular event than the non-smokers[163]. An MR study by Wootton et al[164] supported this hypothesis by demonstrating that genetic liability for schizophrenia was significantly associated with lifetime smoking. However, the evidence was stronger for smoking as a risk factor for schizophrenia, indicating a potential bidirectional mechanism. Given that social determinants of health and lifestyle factors potentially play a role in the development of cardiometabolic abnormalities, multiple levels of interventions at the policy, community, and individual levels are required to reduce health disparities, improve health behaviours and healthcare access[161]. For example, promoting policies that promote the building of social housing (policy level), funding community-based organisations (community level) and patient education (individual level).

Aside from the aforementioned lifestyle factors, the use of second-generation antipsychotics by patients with schizophrenia have been shown to lead to key features of metabolic syndrome, including weight gain, obesity, impaired glucose tolerance, and dyslipidaemia [30][163][165]. Despite their benefits to treat symptoms of psychosis, clozapine and olanzapine are most commonly linked to these cardiometabolic traits [166]. A meta-analysis found that the rate of metabolic syndrome was the highest for individuals taking clozapine (51.9%), and the lowest for individuals who were unmedicated (20.2%)[167]. The relationship between antipsychotics and cardiometabolic traits are complex, and are thought to involve both genetic and hormonal factors. Regarding genetic factors, a systematic review by Wannasuphroprasit et al. [168], identified 12 cohort studies suggesting that reduced function or non-functional alleles for *CYP2D6* was significantly associ-

ated with increased antipsychotic-induced weight gain. The role of the *HTR2C* gene in antipsychotic-induced weight gain has also been demonstrated in multiple genetic association studies[169]. These traits may also be attributed to the effect of antipsychotics on metabolic hormones. For example, adiponectin is a cytokine secreted by the adipose tissue with insulin-sensitising and anti-inflammatory effects [170]. Patients with schizophrenia treated with antipsychotics demonstrate lower adiponectin levels, particularly those with metabolic syndrome, compared with healthy controls. These patients had increased insulin resistance, hypertension, hypertriglyceridemia, and lower HDL levels. Leptin is also an adipokine involved in regulating energy balance by inhibiting hunger. Previous studies have shown that patients with schizophrenia taking antipsychotics have higher leptin levels, particularly in those taking second-generation antipsychotics [30][171]. The use of antipsychotic medication may initiate a vicious cycle whereby increased adipose tissue mass induces a state of hyperleptinaemia, increasing appetite suppression to regulate energy balance. Hyperleptinaemia leads to a lack of sensitivity to leptin, also known as leptin resistance, ultimately contributing to an increased appetite, further weight gain and further leptin production [30][155][172]. Pharmacogenetic testing is, therefore, a promising approach to optimise antipsychotic medication to each individual and reduce the burden of adverse effects, including cardiometabolic abnormalities. Kang et al. [106] demonstrated that pharmacogenetic testing for individuals diagnosed with schizophrenia reduced fasting plasma glucose by 6.1mg/dL (95% CI, -12.6 to 0.4) compared to the treatment as usual group after 12 weeks, although this difference was not statistically significant (P=0.06). Further research is required to demonstrate the benefits of optimising antipsychotic medication using pharmacogenetic testing on cardiometabolic outcomes, such as BMI, lipids, glycaemic traits, and blood pressure.

3.5.1 Strengths and Limitations

In this study, I employed a bidirectional MR framework, which avoided reverse causality and minimised residual confounding. This study is the first to use updated data from the PGC (n=130,644), improving the power to detect a causal association and accurately estimate the magnitude of the effect compared to previous studies. Furthermore, I included a complete set of traits (blood lipids, anthropometric traits, blood pressure, glycaemic traits) to be comprehensive and fully representative of metabolic syndrome, a phenotype which has not been captured in previous studies. Moreover, the three assumptions of MR analysis was thoroughly evaluated in this study. The first assumption, which indicates that the genetic variants are associated with the exposure of interest, was satisfied by excluding SNPs that did not reach genome-wide significance (P>5x10^{-8}). The second assumption which states that the genetic variants must not be associated with confounders was minimised due to the homogenous sample used in this study, reducing confounding by ancestry or population stratification. The third assumption, which requires the genetic variants do not affect the outcome unless it is through the exposure, is difficult to explicitly test but I conducted sensitivity analysis (MR-Egger, Cochran's Q and leave-one-out analysis) to quantify the extent to which pleiotropy affected the results. However, this study was restricted to individuals of European ancestry as these were the datasets with appropriate sizes to enable the MR analysis. Nevertheless, despite using the largest dataset available for schizophrenia, the study could still have lacked statistical power. Whether these results also apply to other populations will require investigating in diverse, large-scale samples which are currently being collected. This is important because causal variants or linkage disequilibrium patterns differs between ancestral groups, meaning that each ancestral group may have a different set of IVs, which could influence the results.

3.5.2 Conclusion

In conclusion, using a bidirectional MR framework I found that the relationship between schizophrenia and various cardiometabolic traits is unlikely to be a causal one, i.e., cardiometabolic abnormalities are not induced by schizophrenia *per se*. Multiple hypotheses to account for this relationship has been raised in the literature, including social determinants of health, lifestyle factors (e.g., smoking, diet, physical activity), antipsychotic medication, among others. However, further research with larger populations from different ancestries is required to elucidate the links between schizophrenia and metabolic syndrome. Moreover, pharmacogenetic testing is a promising approach to reduce the burden of cardiometabolic abnormalities in individuals with schizophrenia by optimising the prescribing of antipsychotic medication.

Chapter 4

Impact of *CYP2D6* genetic variation on healthcare costs in psychosis

4.1 Abstract

Variation in the *CYP2D6* gene is an important contributor to the interindividual variability in antipsychotic metabolism. Previous literature have identified a significantly higher prevalence of adverse effects, inefficacy, and non-adherence to antipsychotics among individuals with genetic variation in *CYP2D6* (i.e., poor and ultrarapid metabolisers). However, there is limited information on whether these individuals may have higher resource utilisation and therefore higher overall healthcare costs. In this chapter, I conducted a two-part model to identify differences in total costs, psychiatric care costs, nonpsychiatric care costs, and primary care costs, between *CYP2D6* extreme metabolisers (poor and ultrarapid metabolisers, n=27), intermediate metabolisers (n=121), and normal metabolisers (n=180) with a psychotic disorder, over 3 months. This chapter used baseline data from the Pharmacogenetics in Mental Health study, i.e., before the pharmacogenetic intervention was delivered. There was substantial variation in costs across all the participants, thus, the two-part model did not find a significant difference in neither the likelihood of

having healthcare expenditures, nor the cost of treating extreme metabolisers compared to normal metabolisers. However, intermediate metabolisers had 75% higher primary care costs compared to normal metabolisers. Future studies should strategically enrich their sample with *CYP2D6* poor and ultrarapid metaboliser participants to improve sample sizes and have sufficient statistical power to detect differences between groups.

4.2 Introduction

The cytochrome P450 (CYP) family represents a superfamily of enzymes responsible for oxidative metabolism of xenobiotics, such as drugs[57]. CYP2D6 (cytochrome P450 family 2 subfamily D member 6) is a well-studied member of the CYP450 superfamily, and is involved in the metabolism of approximately 20% of commonly prescribed drugs, including antipsychotics, which are the primary treatment for psychotic disorders, such as schizophrenia, and are used to improve symptoms and prevent relapse[3]. The *CYP2D6* gene is highly polymorphic, and is an important contributor to the interindividual variability in antipsychotic drug response as variation can result in altered CYP2D6 enzyme activity (i.e., *CYP2D6* phenotype)[173]. The *CYP2D6* phenotype classification system includes: poor and intermediate metabolisers, who have functionally deficient or reduced CYP2D6 enzyme activity, respectively; ultrarapid metabolisers who have increased enzyme activity; and normal metabolisers have normal CYP2D6 enzyme activity[173]. Pharmacokinetic studies have demonstrated that altered CYP2D6 enzyme activity subsequently affects drug plasma concentration, as poor and intermediate have been shown to have higher drug plasma concentrations[174][175] and ultrarapid metabolisers have been shown to have lower drug plasma concentrations[175].

Multiple systematic reviews have investigated the role of genetic variation in *CYP2D6* on adverse effects in psychiatric populations and have identified a significantly higher

prevalence of adverse effects in individuals with reduced CYP2D6 enzyme activity (i.e., poor and intermediate metabolisers) compared to individuals with normal CYP2D6 enzyme activity (i.e., normal metabolisers), such as metabolic effects, extrapyramidal symptoms, and hyperprolactinaemia[175][175][168]. Wannasuphoprasit et al., [168] reported significantly increased weight gain in individuals with reduced function or non-functional alleles for *CYP2D6* in 12 cohort studies. Fleeman et al., [85] found that genetic variation in *CYP2D6* was significantly associated with tardive dyskinesia and parkinsonism. There is also some evidence indicating that *CYP2D6* phenotype influences prolactin levels[175], but this evidence is mixed, as a previous meta-analysis found no significant differences in prolactin levels between *CYP2D6* metabolic groups[176]. In addition, a systematic review by Maruf et al. [175], found that the ultrarapid metaboliser phenotype was associated with a lack of response in two studies. Given the reduced tolerability and inefficacy observed in poor and ultrarapid metabolisers, respectively, this could increase medication switches and reduce adherence. Indeed, a retrospective cohort study found that the incidence of switching from risperidone to another antipsychotic within 1 year was significantly increased in poor and ultrarapid metabolisers[174]. A retrospective chart review found that *CYP2D6* phenotype was associated with discontinuation of risperidone due to significantly higher lack of efficacy in ultrarapid metabolisers, as well as discontinuation of paliperidone due to significantly higher adverse effects in poor and intermediate metabolisers, compared to normal metabolisers[177].

Given the previously reported increased risk of adverse effects, inefficacy, and non-adherence among poor and ultrarapid metabolisers, it is possible that individuals with genetic variation in *CYP2D6* may have higher resource utilisation and therefore higher overall healthcare costs. A previous study has shown that the burden of adverse events on the NHS for any drug is high, with that 6.5% of admissions are related to an adverse events and accounted for 4% of the hospital bed capacity[178]. The projected annual cost

of these admissions to the NHS were found to be £466 million[178]. Adverse drug reactions or lack of efficacy can lead to nonadherence, which is a significant cost burden. The annual cost of non-adherence for any drug is approximately $100 to $290 billion in the USA, €1.25 billion in Europe, and approximately $7 billion in Australia[179]. Furthermore, a systematic review found that the annual all-cause economic cost of non-adherence per person can be as high as $52,341 (in 2015 USD)[179]. Non-adherence to medication is a major predisposing factor for readmission of individuals with schizophrenia, with readmission rates as high as 33-55% for patients who followed up after 1-10 years[180][181].

To my knowledge, only two studies have previously explored the subsequent impact of *CYP2D6* metaboliser status on healthcare costs. Chou et al. [182], collected cost data from a sample of individuals with a severe mental illness over a 1-year time horizon and found that, on average, poor and ultrarapid metabolisers incurred additional healthcare costs of up to $4,000 to $6,000 (in 2005 USD) compared to normal and intermediate metabolisers. However, these cost differences were not found to be statistically significant due to their small sample size (n=100). This study was based in the US, where there is a range of services to care for individuals with mental disorders, including mental health professionals (psychiatrists, psychologists, psychiatric nurses, etc), general medical practitioners, and social services providers. Service use is paid for by a combination of public and private sources, including public funding, such as Medicaid and Medicare, private insurance, and out-of-pocket individual/self-pay[183]. Herbild et al. [105], conducted a similar study in a larger sample of individuals with schizophrenia (n=207) and found that extreme metabolisers (poor and ultrarapid metabolisers) had 239% higher psychiatric care costs, and 22% higher primary care costs compared to normal metabolisers, over a 1-year time horizon. These differences were highly statistically significant. Interestingly, extreme metabolisers did not incur significantly higher costs related to nonpsychiatric (i.e., physical health) hospital services, indicating that the excess costs are likely attributed to readmis-

sions, rather than adverse drug reactions. Herbild et al. [105], is based in Denmark, where psychiatric health care is provided for by general practitioners, specialists in psychiatry in inpatient wards, outpatient clinics, and district centres. Service use is reimbursed by national health insurance, except for pharmacological treatment, dental services, and other services such as physiotherapy[105].

Both of the studies mentioned were published over a decade ago, and cost estimates may therefore be outdated. In addition, neither of these studies were conducted in a UK NHS setting. Thus, in this chapter, I provide an up-to-date investigation on the influence of *CYP2D6* metaboliser status on healthcare costs in individuals with psychosis using a two-part model.

4.3 Methods

4.3.1 Recruitment

The Health Research Authority provided ethical approval for the Pharmacogenetics in Mental Health study on 28/10/2019 (19/LO/1403). The protocol is published and available online (`https://osf.io/qw4gj`)[1]. Recruitment for the study was conducted in England across 11 NHS trusts, as shown in Figure 4.1. In addition to recruiting from NHS trusts, the study was advertised through the study website (available at `https://www.ucl.ac.uk/psychiatry/research/mental-health-neuroscience-department/projects/pharmacogenetics-genetics-and-environment`), Be Part of Research, service user groups, posters in hospitals, outpatient clinics, and GP surgeries. Those who volunteered to participate in the study and were cared for at any NHS service located in England and Wales were also included in the study as self-referrals if they were deemed eligible.

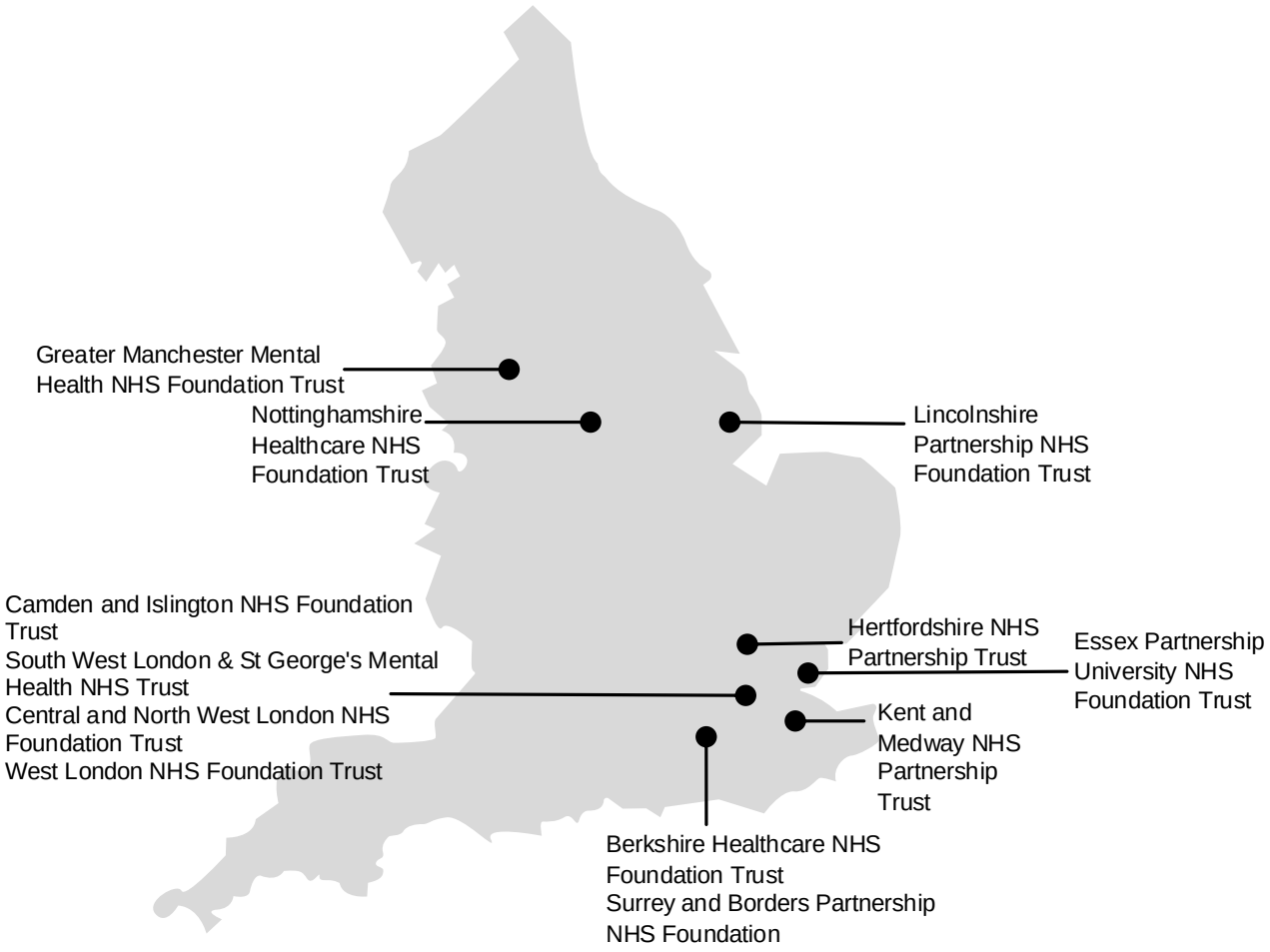


Figure 4.1: The recruiting NHS trusts for the Pharmacogenetics in Mental Health study.

As per the inclusion criteria, the study recruited adults aged 18 or older of any sex and any ethnicity, with a diagnosis of psychosis according to DSM-IV or ICD-10, currently prescribed or being considered prescription for antipsychotic medication. The inclusion criteria was broad to ensure that the results could be generalised to a large patient population. Individuals must have had the capacity to provide informed and voluntary consent for participation in the study. Any potential participants meeting the inclusion criteria were identified by the research team at the individual sites and their clinician was contacted to seek approval for the study. Alternatively, potential participants were referred by the clinicians themselves to the research team. All potential participants were provided a participant information sheet by a suitably trained member of the research team at each site and were given adequate time (i.e., at least 24 hours) to consent to enrolling in the study, and individuals were encouraged to ask any questions or raise concerns they had regarding the study during this time.

This chapter uses data from baseline assessments (i.e., before the pharmacogenetic intervention), which involved collecting participants' DNA in the form of a blood or saliva sample, and a questionnaire outlining their demographics, service use over the last 3 months, health and wellbeing. Service use was collected used a modified version of the Client Socio-Demographic and Service Receipt Inventory–European Version (CSSRI-EU) instrument[184] (Appendix C, Figure C1). This is a standardised instrument used to collect mental health service use. The instrument was adapted by capturing additional information relevant for this study, such as contacts with crisis resolution and accident and emergency teams. Information that was not directly relevant were removed, such as contacts with criminal justice services, and hospital or community accommodation information (such as the number of hospital beds and staff in the hospital ward). The baseline assessment could be conducted face-to-face (in NHS hospital wards, community services, or at the participant's home), by telephone, or via online methods. Participants were informed

that they were able to withdraw from the study at any time without giving reason and without affecting future care and management in any way. DNA samples from withdrawn participants were safely disposed.

Deoxyribonucleic acid (DNA) from saliva and blood samples were extracted using the Omega Bio-tek Mag-Bind® Blood and Tissue HDQ Kit (M6399) at the UCL Genomics Facility, according to the manufacturer's instructions. After DNA extraction, the concentration of DNA was assessed using the Broad Range DNA protocol; only samples with concentrations over 30 ng/µl were processed. Genotyping and phenotype assignment was conducted externally by an industry-based facility in Houston, USA, and an NHS laboratory in Birmingham, UK. The industry facility used the Agena VeriDose Core and CYP2D6 Copy Number Variant Panel, available on the Agena MassARRAY® platform. The panel comprised of a total of 68 variants across 20 genes, and 5 CYP2D6 copy number variant assays. The NHS laboratory used a modified version of the Agena panel, the Inagene® Personalized Insights™ panel, which includes 117 variants across 34 genes. Participants' metaboliser phenotypes for CYP2D6 were assigned according to their activity score, in which an activity score of 0 indicate poor metaboliser status, 0.25-1 indicated intermediate metaboliser status, 1.25-2.25 indicated normal metaboliser status, and greater than 2.25 indicated ultrarapid metaboliser status, in accordance with the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenomics Working Group guidelines[60].

4.3.2 Costing

In this study, a healthcare (NHS) perspective was adopted to be consistent with the methodology followed by Herbild at al[105] and to ensure comparability of results. Indeed, a direct comparison of findings would be misleading if different perspectives were used. At baseline, the study collected data on the following resource use categories: inpatient

hospital services, outpatient hospital services, accident and emergency attendances, and primary and community care contacts. Costs were valued using published literature and national databases, including the National Cost Collection for the NHS[185] and Personal Social Services Research Unit's unit costs[186] (Table 4.1). All costs were reported in 2022 GBP. Where unit costs for 2022 were not available, costs from previous years were inflated to 2022 costs using the Office for National Statistics consumer price index[187].

Table 4.1: Unit costs of inpatient and outpatient hospital services, accident and emergency usage, and primary and community care contacts.

Service	Unit cost (GBP 2022)	Source
Inpatient hospital services		
Acute psychiatric ward	341 (per bed day)	PSSRU, 2022[186]
Psychiatric rehabilitation ward	341 (per bed day)	PSSRU, 2022[186]
Long-stay ward	341 (per bed day)	PSSRU, 2022[186]
Crisis centre	341 (per bed day)	PSSRU, 2022[186]
Psychiatric intensive care unit	814 (per patient day; inflated to 2022)	PSSRU, 2010[188]
Psychiatric decision unit	1600 (per visit; costs inflated to 2022)	Gillard et al, 2023[189]
General medical ward (long stay)	4409 (per episode)	NHS England, 2023[185]
General medical ward (short stay)	801 (per episode)	NHS England, 2023[185]
Outpatient hospital services		
Psychiatric outpatient visit	295 (per attendance at an adult mental health service)	NHS England, 2023[185]

Service	Unit cost (GBP 2022)	Source
Perinatal mental health outpatient visit	180 (per attendance)	NHS England, 2023[185]
Depot clinic	28 (per attendance)	PSSRU, 2022[186]
Clozapine clinic	41 (per attendance)	Jin et al, 2019[190]
General outpatient visit	235 (per attendance, weighted average of all outpatient attendances)	PSSRU, 2022[186]
Day hospital	1224 (per episode)	PSSRU, 2022[186]
Dental appointment	192 (per attendance)	NHS England, 2023[185]
Drug services outpatient visit	122 (per attendance)	PSSRU, 2022[186]
Accident and emergency usage		
Crisis resolution team	11 (per call)	Turner et al, 2021[191]
A&E for physical health	242 (per attendance, average emergency care cost)	NHS England, 2023[185]
A&E/place of safety for mental health	304 (per care contact at A&E mental health liaison services)	PSSRU, 2022[186]
Ambulance	276 (per attendance, average of all ambulance usage, including hear and treat; see and treat and refer; and see and treat and convey)	PSSRU, 2022[186]
111 Telephone	11 (per call)	Turner et al, 2021[191]
Primary and community care contacts		
Psychiatrist	145 (per hour, including qualifications; assume 1 hour duration of contact)	PSSRU, 2022[186]

Service	Unit cost (GBP 2022)	Source
Psychologist	64 (per hour for band 7 clinical psychologist; assume 1 hour duration of contact)	PSSRU, 2022[186]
Assistant psychologist	37 (per hour for band 4 clinical psychology assistant practitioner, assume 1 hour duration of contact)	PSSRU, 2022[186]
GP	41 (per surgery consultation lasting 9.22 minutes, including qualifications and direct care staff costs)	PSSRU, 2022[186]
GP nurse	52 (per hour, assume 30 minutes duration of contact)	PSSRU, 2022[186]
Crisis resolution team or home treatment team	228 (mean average cost for a crisis resolution team for adults per team contact; inflated to 2022)	PSSRU, 2015[192]
District nurse	54 (per hour; assume 30 minutes duration of contact)	NHS England, 2023[185]
Community psychiatric nurse	76 (per hour for community nurse specialist, assume 30 minutes duration of contact)	NHS England, 2023[185]
Occupational therapist	50 (per hour, including qualification costs, assume 1 hour duration of contact)	PSSRU, 2022[186]
Social worker	50 (per hour, including qualification costs, assume 1 hour duration of contact)	PSSRU, 2022[186]
Home help/care worker	23 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Physiotherapist	144 (per one-to-one session)	PSSRU, 2022[186]
Counsellor	55 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]

Service	Unit cost (GBP 2022)	Source
Mental health and well-being practitioner	42 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Trainee mental health and wellbeing practitioner	37 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Support worker	37 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Community navigator	37 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Care coordinator	55 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Pharmacist (specialist)	66 (per hour, assume 30 minutes duration of contact)	PSSRU, 2022[186]
Pharmacist (advanced)	75 (per hour, assume 30 minutes duration of contact)	PSSRU, 2022[186]
Pharmacist (consultant)	86 (per hour, assume 30 minutes duration of contact)	PSSRU, 2022[186]
Art therapist	64 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Music therapist	64 (per hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Speech and language therapist	130 (per one-to-one session)	PSSRU, 2022[186]
Drug services community contact	110 (per contact)	PSSRU, 2022[186]
Psychotherapist	64 (per working hour, assume 1 hour duration of contact)	PSSRU, 2022[186]
Dietician	100 (per one-to-one session)	PSSRU, 2022[186]
Duty worker	55 (per working hour, assume 1 hour duration of contact)	PSSRU, 2022[186]

4.3.3 Model exposures

The main exposure in this study was CYP2D6 metaboliser status; poor and ultrarapid metabolisers were regrouped into a single category as "extreme metabolisers", because this group was shown by Herbild et al. [105] to incur significantly higher healthcare costs. In addition, I included age, sex, ethnicity, diagnosis, duration of illness and use of CYP2D6 strong inhibitors as covariates.

Covariates

Firstly, sex was included as a covariate, as there are sex differences in the metabolism of drugs. Indeed, previous studies have reported differences in pharmacokinetic pathways, such as pharmacokinetics of CYP450, potentially due to hormonal fluctuations, oral contraceptives, and hormonal therapy. Females have higher CYP3A4 and CYP2D6 enzyme activity, while males have higher CYP1A family enzyme activity. As a result, females are more likely to experience certain adverse effects of antipsychotics, such as weight gain, hyperprolactinemia and cardiac effects, such as a higher risk of induced long QT syndrome[193]. Age was also included as a covariate, as ageing is associated with reduced CYP enzyme activity and subsequently reduced drug clearance and higher plasma concentrations[120].

Participants who were taking antipsychotics may have been co-prescribed other psychotropics which were CYP2D6 inhibitors, such as paroxetine or fluoxetine[103], decreasing enzyme activity such that genotypically normal metabolisers were converted phenotypically to poor or intermediate metabolisers[194]. The discordance between an individual's genotype-predicted metaboliser status and clinically observed metaboliser status is referred to as phenoconversion[194]. Thus, I identified strong inhibitors of CYP2D6 using the Flockhart Table™ which reports nine CYP450 enzymes that metabolise the majority of medications prescribed by primary care physicians, and the substrates, inhibitors, and

inducers of these enzymes[103]. CYP2D6 inhibitors are classified as strong, moderate, and weak, causing an increase in plasma drug concentration by $\geq$5-fold, $\geq$2 to $<$5-fold, and $\geq$1.25 to $<$2-fold, respectively[194]; moderate and weak inhibitors of CYP2D6 were not adjusted for in this study due to the variability of inhibition observed[177].

Ethnicity was regrouped from 19 categories used by the 2021 UK census to the following two categories: “White” (including English, Welsh, Scottish, Northern Irish, Irish, and any other White background), or "BAME", (including Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; Black, Black British, Black Welsh, Caribbean and African; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; and any other ethnic group). This approach was taken because the majority of the sample self-identified as English, Welsh, Scottish, Northern Irish, Irish, and any other White background (65%, n=303). The remaining participants self-identified as one of the remaining 14 groups. The mean number of patients in these 14 groups was 11 participants (±4), which was too small to include individually. As this variable was a covariate in the model, and not a primary variable of interest, I therefore collapsed the individual groups to "White" and "BAME".

Diagnoses were also regrouped to broader categories, in which individuals with any subtype of schizophrenia (e.g., paranoid, hebephrenic, and unspecified schizophrenia) were categorised as “schizophrenia”; any subtype of bipolar disorder (type 1, unspecified) were categorised as “bipolar disorder”, and “other psychoses” included schizophrenia spectrum disorders (schizotypal disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, acute and transient psychotic disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, schizoid personality disorder, and other unspecified nonorganic psychosis). I also included individuals with reactive depressive psychosis or major depressive disorder with psychosis, and post-traumatic stress disor-

der with psychosis, in the "other psychoses" category.

Finally, duration of illness was a continuous variable that was calculated by subtracting the participants' age at diagnosis from their age at baseline.

4.3.4 Model outcomes

In this study, I focused on the following outcomes: (1) total healthcare costs, (2) psychiatric care costs, (3) nonpsychiatric costs, and (4) primary care costs. The services and contacts included in cost calculations for each outcome is summarised in Table 4.2.

Table 4.2: Summary of the services and contacts included in cost calculations for each outcome.

Outcome	Services and contacts included
Total healthcare costs	• Inpatient hospital services: acute psychiatric ward, psychiatric rehabilitation ward, long-stay ward, crisis centre, psychiatric intensive care unit, psychiatric decision unit, and general medical ward • Outpatient services: psychiatric visits, drug services outpatient visit, perinatal mental health outpatient visit, depot clinic, clozapine clinic, day hospital, physical health outpatient attendances • Emergency attendances: 111 telephone calls, A&E for physical health, A&E/place of safety for mental health, ambulance usage, crisis resolution team • Care contacts: psychiatrist, psychologist, assistant psychologist, GP, GP nurse, crisis resolution team or home treatment team, district nurse, community psychiatric nurse, occupational therapist, social worker, home help/care worker, counsellor, mental health and well-being practitioner, trainee mental health and wellbeing practitioner, support worker, community navigator, care coordinator, pharmacists, physiotherapists, psychotherapist, duty worker, speech and language therapist, art therapist, music therapist, drug services community contact, dietician

Outcome	Services and contacts included
Psychiatric care costs	• Inpatient hospital services: acute psychiatric ward, psychiatric rehabilitation ward, long-stay ward, crisis centre, psychiatric intensive care unit, and psychiatric decision unit • Outpatient services: psychiatric visits, drug services outpatient visit, perinatal mental health outpatient visit, depot clinic, clozapine clinic, day hospital • Emergency attendances: 111 telephone, A&E/place of safety for mental health, ambulance usage, crisis resolution team • Care contacts: psychiatrist, psychologist, assistant psychologist, GP, GP nurse, crisis resolution team or home treatment team, district nurse, community psychiatric nurse, occupational therapist, social worker, home help/care worker, counsellor, mental health and wellbeing practitioner, trainee mental health and wellbeing practitioner, support worker, community navigator, care coordinator, pharmacists, psychotherapist, duty worker, speech and language therapist, art therapist, music therapist, drug services community contact
Nonpsychiatric care costs	• General medical ward stays • Outpatient services: physical health outpatient attendance, drug services outpatient visit • Emergency attendances: 111 telephone calls, ambulance usage, and A&E for physical health • Care contacts: GP, GP nurse, paramedic nurse, phlebotomist, physiotherapist, pharmacists, drug services community contact, dietician
Primary care costs	• GP attendances • GP nurse contacts • Dental appointments • Physiotherapist contacts • Pharmacist contacts

4.3.5 Statistical analysis

Although the most common multivariable regression method is Ordinary Least Squares (OLS), this method assumes that the dependent variable is normally distributed and that the errors are independent. Cost data typically tends to be characterised by a positively skewed distribution, with 5% of the population accounting for the majority of health costs[195]. The assumptions of OLS were therefore unlikely to be met, and this method would not provide the best estimates and inferences would have been potentially misleading. In addition, cost data typically has many observations with zero expenditures. Thus, in this study, I conducted a two-part model. In the first part, a logit model was constructed using the full sample to estimate whether any participant had any non-zero healthcare expenditures. In the second part, a generalised linear model (GLM) was conducted on the subset of patients who had any healthcare expenditures, to evaluate the impact of CYP2D6 metaboliser status on healthcare costs. A GLM model was employed in this study to overcome the limitations of OLS, as it allows for non-normal distributions and therefore more flexible modelling of costs. There are two defining characteristics: the conditional distribution of the response variable (normal, Poisson, gamma, binomial, and gaussian), and the link function (identity, logarithmic, square root, logistic, and power links) which maps the mean of the non-linear response variable to the linear predictors[195]. In this study, a gamma distribution and log link were used as it has been found to be the most appropriate for modelling healthcare expenditure. The two-part model has been employed by Herbild et al. [105], as well as in a variety of empirical work in health services research[195]. Following the analyses, I conducted the Pregibon link test to determine if the model was properly specified. All statistical analyses were conducted using R 4.2.2 in RStudio v2022.07.2.

4.3.6 Missing data

My analyses was conducted on an imputed dataset using a random forest machine learning model with the missForest package[196]. This is a highly accurate method of imputation and has shown to outperform other imputation techniques[196]. This method assumed that the data was either missing completely at random (MCAR), i.e., there are no systematic differences between the participants with missing and complete data, or that the data was missing at random (MAR), i.e., the missing data is systematically related to the observed data, but not the unobserved data[197]. These assumptions were evaluated by observing missing data patterns and comparing attributes with and without missing cost data.

In the imputation model, I included the variables that would be investigated in the analyses regardless of whether they had missing data, including the outcome variables and predictors of interest. If any variables were excluded, relationships that exist would be biased towards the null, because the imputations would be generated assuming those variables were independent[198]. However, for an outcome variable with missing values, previous literature have suggested that the "multiple imputation, then deletion" (MID) strategy provides the most efficient estimates. The MID strategy involves including the outcome variable in the imputation model and allowing all missing observations in the outcome be imputed but excluding them from the analysis. This method is robust against poor imputation in the outcome[198].

The analysis model included variables that were derived from other variables. These included duration of illness, total costs, psychiatric care costs, nonpsychiatric care costs, and primary care costs. For duration of illness, I calculated the derived variable and included it in the imputation model to be imputed directly. This approach avoided negative values for duration of illness and had the additional benefit of incorporating the compo-

nents as well as the derived variable in the imputation model. For cost-related variables, I imputed the missing component variables first (i.e., resource use) and created the cost-related variables after all variables were imputed. The benefit of this approach was that it led to derived variables that were consistent with the derivation rule. Previous literature has indicated that neither strategy uniformly performs better than the other, and the strategy used requires tailoring to each variable[198].

4.3.7 Sensitivity analysis

Although CYP2D6 is a metabolizing enzyme for many antipsychotics, there are some which are metabolised by other CYP enzymes, such as CYP3A4 and CYP1A2[173]. Thus, making conclusions based on a sample of individuals taking a variety of antipsychotic medications with different metabolic pathways may be misleading. As a result, I restricted analyses to patients taking a medication that is a substrate of CYP2D6 in the sensitivity analysis. I used the Flockhart Table™ to identify CYP2D6 substrates[103]. As pregnancy can incur additional costs, I conducted a separate sensitivity analysis excluding pregnant women from the sample.

4.4 Results

A total of 466 patients were initially recruited in the study. However, 67 patients were excluded from the analysis for not having a diagnosis of a psychotic disorder and an additional 71 patients were excluded for not having information on their *CYP2D6* metaboliser status. Thus, statistical analysis was performed using a total sample of 328 individuals; the characteristics of the sample can be found in Table 4.3. The mean age in the sample was 43.5 (±14.6), and the sample was almost evenly distributed in regard to sex, with 47% of the sample comprised of females and 52% comprised of men. The majority of the sample was white (62%), and the remaining were of a Black, Asian, and minority eth-

nic background (35%). The average duration of illness in the sample was 11.3 (±11.2) years. Only 4% of the sample (n=12) reported taking a CYP2D6 strong inhibitor concomitantly with their prescribed antipsychotic. The most frequently prescribed medication was aripiprazole, which was prescribed to 24% of the sample (n=92), followed by clozapine which was prescribed to 17% of the sample (n=66), and olanzapine, which was also prescribed to 17% of the sample (n=64). Over half of the sample were characterised as normal metabolisers (n=180), 37% were intermediate metabolisers (n=121), and 8% were extreme metabolisers (i.e., poor and ultrarapid metabolisers, n=27).

Regarding missing data, duration of illness was the variable with the highest number of missing values (n=66), followed by age (n=26), and ethnicity (n=8). I compared the sample characteristics between individuals with complete and incomplete data on the primary outcome, total healthcare costs; I did not find any significant associations between age, sex, ethnicity and duration of illness and the missingness in total healthcare costs (Appendix C, Table C1). However, primary diagnosis was found to be significantly associated with missingness in total healthcare costs (P = 0.04), as individuals with a diagnosis of an "other psychotic disorder" had significantly increased levels of missingness (28%) compared to schizophrenia (16%) and bipolar disorder (18%).

The mean resource use for normal, intermediate, and extreme metabolisers, are presented in Table 4.4, demonstrating the variation in resource use across the sample. Psychiatric hospital services comprised the majority of healthcare costs, which included admission to an acute psychiatric ward, psychiatric rehabilitation ward, and long-stay ward. Resource use was greatest for the acute psychiatric ward, where the average patient required 0.29 (±0.93) admissions, and 8.99 (±22.46) inpatient days, over 3 months (Table 4.4). Overall, psychiatric hospital services amounted to an average cost of £5,753 (±10,335) per patient (Table 4.5).

Mean total healthcare costs for normal, intermediate, and extreme metabolisers over a 3-month time horizon were £7,594 (±12,350), £6,635 (±10,004), £12,043 (±13,744), respectively. However, healthcare cost data were skewed by a few patients with very high healthcare costs. Indeed, median costs for normal, intermediate, and extreme metabolisers were £1,820 (£0-83,210), £1,136 (£0-35,504), and £3,102 (£145-33,328), respectively. Histograms for total, psychiatric, physical health, and primary care costs are shown in Figure 4.2, where all plots show a positive right-skewed distribution.

Table 4.3: Baseline demographic characteristics for the sample. BAME, Black, Asian, and Minority Ethnic; SD, standard deviation.

	Missing n (%)	Extreme metabolisers† (n=27)	Intermediate metabolisers (n=121)	Normal metabolisers (n=180)	Full sample (n=328)
Age (Mean, SD)	26 (8)	42.2 (14.1)	44.0 (14.4)	43.3 (14.9)	43.5 (14.6)
Sex, n (%)					
Male	2 (1)	14.0 (52)	60.0 (50)	98.0 (54)	172.0 (52)
Female		13.0 (48)	61.0 (50)	80.0 (44)	154.0 (47)
Ethnicity, n (%)					
White	8 (2)	18.0 (67)	81.0 (67)	105.0 (58)	204.0 (62)
BAME‡		9.0 (33)	36.0 (30)	71.0 (39)	116.0 (35)
Primary diagnosis, n (%)					
Schizophrenia	0 (0)	9.0 (33)	35.0 (29)	53.0 (29)	97.0 (30)
Bipolar disorder		7.0 (26)	31.0 (26)	65.0 (36)	103.0 (31)
Other psychotic disorders		11.0 (41)	55.0 (45)	62.0 (34)	128.0 (39)
Duration of illness (Mean, SD)	66 (20)	9.6 (11.4)	13.9 (12.5)	9.8 (10.1)	11.3 (11.2)
CYP2D6 inhibitor use, n (%)	0 (0)	3.0 (11)	2.0 (2)	7.0 (4)	12 (4)
Medication, n (%)					
Amisulpride	0 (0)	1 (3)	10 (7)	8 (4)	19 (5)
Aripiprazole		8 (27)	35 (24)	49 (24)	92 (24)
Cariprazine		0 (0)	0 (0)	1 (0)	1 (0)
Clozapine		7 (23)	24 (16)	35 (17)	66 (17)
Flupentixol		0 (0)	6 (4)	7 (3)	13 (3)
Haloperidol		1 (3)	3 (2)	5 (2)	9 (2)
Lurasidone		0 (0)	5 (3)	8 (4)	13 (3)
Olanzapine		6 (20)	27 (18)	31 (15)	64 (17)
Paliperidone		2 (7)	5 (3)	12 (6)	19 (5)
Quetiapine		3 (10)	10 (7)	23 (11)	36 (9)
Risperidone		2 (7)	11 (7)	15 (7)	28 (7)
Zuclopenthixol		0 (0)	11 (7)	13 (6)	24 (6)

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

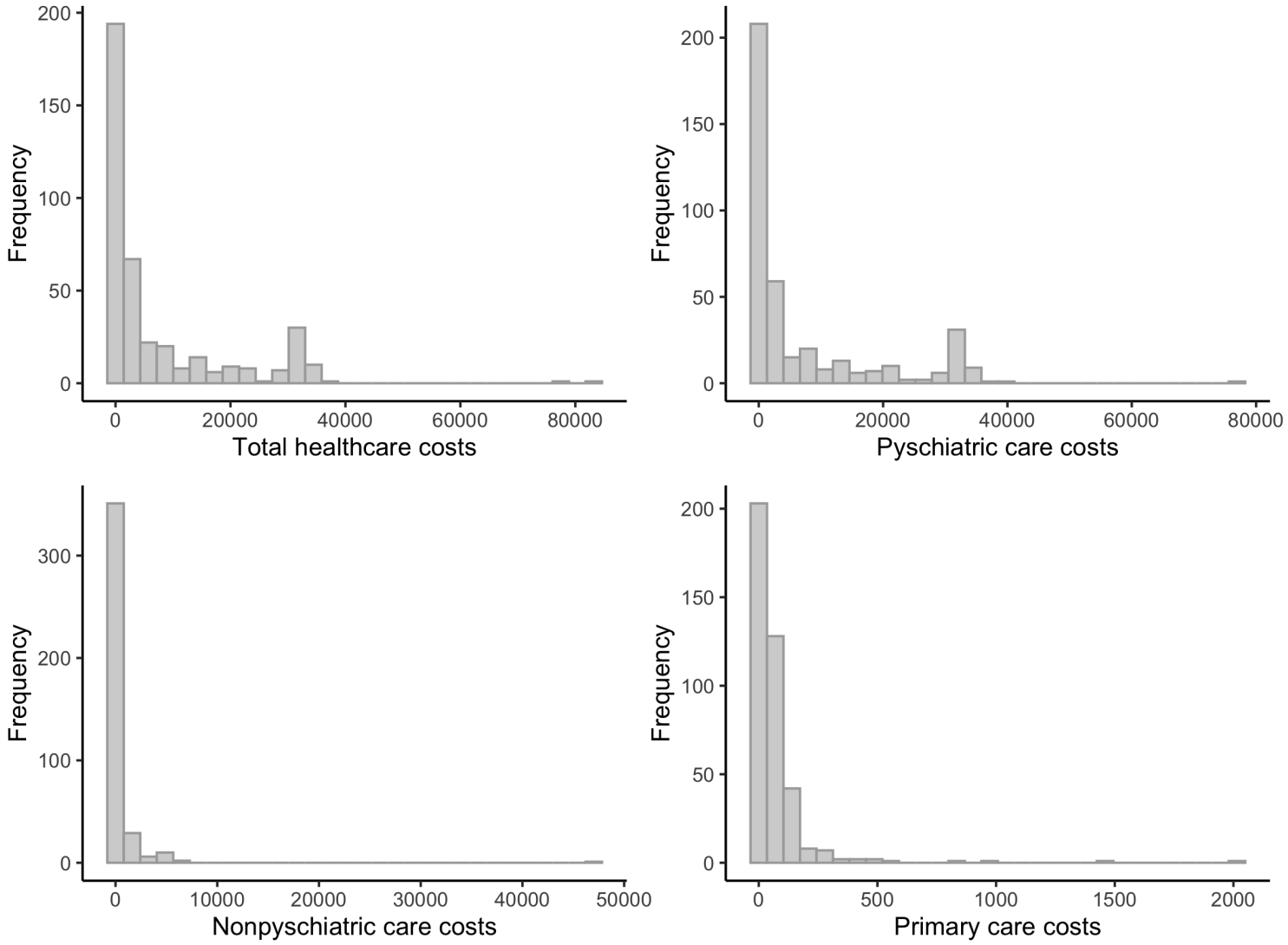


Figure 4.2: Histograms of total, psychiatric, nonpsychiatric (physical health) and primary care costs (GBP).

Extreme metabolisers† (mean, SD)	Intermediate metabolisers (mean, SD)	Normal metabolisers (mean, SD)	Full sample (mean, SD)	
Inpatient hospital services				
Acute psychiatric ward (admissions)	0.26 (±0.45)	0.30 (±0.56)	0.28 (±0.52)	0.29 (±0.93)
Acute psychiatric ward (number of inpatient days)	12.52 (±29.98)	8.95 (±20.86)	10.83 (±24.89)	8.99 (±22.46)
Psychiatric rehabilitation ward (admissions)	0.04 (±0.19)	0.08 (±0.28)	0.07 (±0.27)	0.07 (±0.26)
Psychiatric rehabilitation ward (number of inpatient days)	3.33 (±17.32)	5.11 (±19.6)	2.30 (±13.25)	3.05 (±15.4)
Long-stay ward (admissions)	0.15 (±0.46)	0.02 (±0.16)	0.03 (±0.16)	0.04 (±0.21)
Long-stay ward (number of inpatient days)	10 (±28.82)	2.23 (±14.05)	2.23 (±13.64)	3.27 (±16.72)
Crisis centre (admissions)	0.15 (±0.6)	0.09 (±0.58)	0.07 (±0.31)	0.07 (±0.41)
Crisis centre (number of inpatient days)	0.27 (±1.37)	0.55 (±4.31)	0.73 (±3.79)	0.52 (±3.5)
General medical ward (admissions)	0 (±0)	0.05 (±0.25)	0.09 (±0.77)	0.07 (±0.54)
General medical ward (number of inpatient days)	0 (±0)	0.20 (±1.14)	0.47 (±3.64)	0.45 (±3.45)

Outpatient services				
Psychiatric outpatient visit	0.48 (±0.89)	0.66 (±2.39)	1.51 (±7.35)	1.1 (±5.2)
Outpatient visit for physical health	0.07 (±0.27)	0.45 (±1.39)	0.54 (±1.47)	0.50 (±1.39)
Day hospital	0 (±0)	0.04 (±0.30)	0.04 (±0.3)	0.03 (±0.26)
Primary and community care contacts				
Psychiatrist	2.26 (±3.3)	1.29 (±2.15)	1.72 (±3.26)	1.52 (±2.77)
Psychologist	2.04 (±4.43)	0.83 (±2.45)	1.13 (±2.81)	0.95 (±2.69)
GP	1.22 (±3.15)	1.23 (±3.61)	1.06 (±1.51)	1.21 (±2.66)
Crisis Resolution Team or Home Treatment Team	0.17 (±0.64)	0.5 (±2.3)	1.08 (±4.06)	0.70 (±3.06)
District nurse	0.04 (±0.19)	0.36 (±2.81)	0.56 (±6.72)	0.40 (±4.81)
Community psychiatric nurse/case manager	0.85 (±2.33)	0.87 (±2.63)	1.07 (±4.03)	1.01 (±3.32)
Social worker	0.85 (±2.44)	0.43 (±1.33)	0.44 (±1.5)	0.42 (±1.43)
Occupational therapist	1.3 (±4.06)	0.68 (±3.41)	0.88 (±3.48)	0.84 (±4.04)
Home help/care worker	3.59 (±17.32)	3.38 (±15.37)	2.67 (±12.4)	3.97 (±19.02)
Accident and Emergency				
111 Telephone calls	0.12 (±0.33)	0.21 (±1.05)	0.14 (±0.67)	0.19 (±0.78)
Crisis Resolution Team calls (mental health)	0.24 (±0.72)	0.26 (±1.15)	0.25 (±1.11)	0.29 (±1.3)
A&E for physical health	0.28 (±1.21)	0.18 (±0.59)	0.20 (±0.78)	0.20 (±0.72)

A&E/place of safety for mental health	0.20 (±0.41)	0.13 (±0.66)	0.26 (±1.05)	0.19 (±0.81)
Ambulance	0.08 (±0.28)	0.15 (±0.54)	0.20 (±0.84)	0.17 (±0.65)

Table 4.5: Mean healthcare costs (GBP) per patient over 3 months, by CYP2D6 metaboliser status. SD, standard deviation.

Service	Extreme metabolisers mean (SD)	Intermediate metabolisers mean (SD)	Normal metabolisers mean (SD)	Full sample mean (SD)
Psychiatric hospital costs	10,628 (±13,906)	5,281 (±9,847)	5229 (±9,962)	5,653 (±10,335)
Physical health hospital costs	0 (±0)	135 (±742)	348 (±3,016)	246 (±2,318)
Other hospital costs†	213 (±1,168)	22 (±258)	323 (±4,863)	207 (±3,684)
Psychiatric outpatient costs	138 (±254)	197 (±652)	430 (±1,957)	325 (±1,531)
Physical health outpatient costs	24 (±72)	109 (±317)	135 (±349)	117 (±326)
Day hospital costs	0 (±0)	43 (±339)	43 (±323)	40 (±316)
Other outpatient costs†	52 (±263)	9 (±55)	22 (±154)	20 (±140)
A&E costs	158 (±426)	148 (±333)	180 (±576)	167 (±491)
Primary and community care contacts costs	768 (±830)	616 (±1,000)	809 (±1,342)	737 (±1,198)
Other contacts costs†	63 (±184)	74 (±245)	75 (±275)	74 (±258)

† Other costs refer to additional services used beyond the services specified in the resource use questionnaire.

The majority of these costs were from psychiatric services, which were used by 97% (n=317) of participants. On average, normal metabolisers incurred psychiatric costs of £7,055 (±11,463), intermediate metabolisers incurred costs of £6,315 (±9,937), and extreme metabolisers incurred costs of £11,907 (±13,757). Nonpsychiatric services were used by 57% (n=188) of participants, and subsequently comprised a considerably smaller amount of the total costs, as normal metabolisers incurred average costs of £638 (±3,253), intermediate metabolisers incurred costs of £431 (±1,006), and extreme metabolisers incurred costs of £226 (±437). Only 38% (n=125) of the sample used primary care services, and it subsequently made up the smallest amount of the total healthcare costs, with normal metabolisers incurring an average cost of £50 (±75), intermediate metabolisers incurring costs of £78 (±237), and extreme metabolisers incurring costs of £60 (±139).

The results for the two-part analyses are shown in Tables 4.6 and 4.7; the reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. Table 4.6 shows the probability of healthcare resource utilisation (i.e., positive expenditures); the coefficients for this model are in log-odd units, and indicates whether having positive healthcare expenditures is a more likely (log-odds > 0) or less likely (log-odds <0) event. We found no significant difference in the probability of positive expenditures in individuals of different metaboliser groups. Table 4.7 shows the results of the generalised linear model, which represents increases or decreases in healthcare costs, conditional on having positive expenditures. In the GLM, coefficients can be interpreted as a percentage change regarding the reference level. There was weak evidence suggesting that extreme metabolisers had 72% higher psychiatric care costs than normal metabolisers although this was not statistically significant (P=0.08). There was also evidence suggesting that intermediate metabolisers had 75% higher primary care costs compared to normal metabolisers (P<0.001).

Table 4.6: Part 1 of the two-part model: probability of positive expenditures. The reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. BAME, Black, Asian, and Minority Ethnic; CI, confidence interval.

	Total costs		Psychiatric care costs		Nonpsychiatric care costs		Primary care costs	
	Coefficient (95% CI)	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**
Metaboliser group								
Extreme metabolisers†	15.47 (-3594.99-3625.94)	0.99	15.47 (-3594.99-3625.94)	0.99	-0.65 (-1.44-0.14)	0.11	-0.57 (-1.37-0.22)	0.16
Intermediate metabolisers	-0.14 (-1.43-1.14)	0.83	-0.14 (-1.43-1.14)	0.83	-0.15 (-0.61-0.31)	0.53	-0.28 (-0.72-0.17)	0.23
Age	0.01 (-0.05-0.07)	0.81	0.01 (-0.05-0.07)	0.81	0.00 (-0.02-0.01)	0.63	0.00 (-0.02-0.02)	0.84
Sex (female)	1.58 (-0.07-3.22)	0.06	1.58 (-0.07-3.22)	0.06	0.28 (-0.17-0.73)	0.23	0.38 (-0.05-0.82)	0.09
Ethnicity (BAME‡)	0.26 (-1.16-1.69)	0.72	0.26 (-1.16-1.69)	0.72	0.37 (-0.09-0.84)	0.12	0.64 (0.2-1.08)	0.00
Primary diagnosis								
Schizophrenia	0.16 (-1.62-1.95)	0.86	0.16 (-1.62-1.95)	0.86	-0.21 (-0.75-0.33)	0.44	-0.47 (-1-0.05)	0.08
Other psychotic disorder	-0.68 (-2.37-1.02)	0.43	-0.68 (-2.37-1.02)	0.43	0.06 (-0.5-0.61)	0.84	-0.36 (-0.89-0.17)	0.18
Duration of illness	-0.06 (-0.13-0.01)	0.07	-0.06 (-0.13-0.01)	0.07	0.01 (-0.02-0.03)	0.50	-0.01 (-0.03-0.02)	0.57
CYP2D6 inhibitor use	15.88 (-4343.78-4375.53)	0.99	15.88 (-4343.78-4375.53)	0.99	0.86 (-0.3-2.02)	0.15	0.48 (-0.49-1.45)	0.33
Constant	3.65 (0.86-6.45)	0.01	3.65 (0.86-6.45)	0.01	0.60 (-0.26-1.45)	0.17	-0.01 (-0.83-0.81)	0.99

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table 4.7: Part 2 of the two-part model: cost estimation (conditional on positive expenditures). The reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. BAME, Black, Asian, and Minority Ethnic; CI, confidence interval.

	Total costs		Psychiatric care costs		Nonpsychiatric care costs		Primary care costs	
	Coefficient (95% CI)	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**
Metaboliser group								
Extreme metabolisers†	0.64 (-0.09-1.93)	0.10	0.72 (-0.07-2.18)	0.08	-0.54 (-0.86-0.47)	0.19	0.03 (-0.48-1.02)	0.94
Intermediate metabolisers	-0.11 (-0.36-0.25)	0.51	-0.10 (-0.36-0.29)	0.58	-0.21 (-0.56-0.43)	0.44	0.75 (0.24-1.49)	0.00
Age	-0.01 (-0.02-0.00)	0.12	-0.01 (-0.02-0.00)	0.17	-0.01 (-0.04-0.01)	0.23	-0.01 (-0.02-0.00)	0.13
Sex (female)	-0.02 (-0.30-0.35)	0.88	-0.03 (-0.31-0.37)	0.87	-0.08 (-0.49-0.64)	0.77	0.17 (-0.16-0.64)	0.36
Ethnicity (BAME‡)	-0.30 (-0.50–0.02)	0.04	-0.29 (-0.50-0.01)	0.06	-0.42 (-0.67-0.04)	0.07	-0.26 (-0.47-0.02)	0.07
Primary diagnosis								
Schizophrenia	0.66 (0.12-1.46)	0.01	0.75 (0.16-1.65)	0.01	-0.30 (-0.66-0.44)	0.33	-0.27 (-0.52-0.10)	0.14
Other psychotic disorder	0.93 (0.30-1.87)	0.00	0.94 (0.28-1.95)	0.00	0.65 (-0.18-2.32)	0.16	-0.05 (-0.36-0.41)	0.81
Duration of illness	-0.01 (-0.03-0.01)	0.43	-0.01 (-0.03-0.01)	0.41	0.00 (-0.03-0.03)	0.90	-0.01 (-0.03-0.01)	0.37
CYP2D6 inhibitor use	-0.31 (-0.66-0.38)	0.29	-0.37 (-0.70-0.31)	0.21	0.90 (-0.40-5.04)	0.28	0.92 (-0.02-2.74)	0.06
Constant	£9,560 (£5,180-17,790)	0.00	£8,545 (£4,470-16,335)	0.00	£1,793 (£581-5,534)	0.00	£190 (98-370)	0.00

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table 4.8 reports the adjusted mean costs for the different outcomes (total, psychiatric, physical health, and primary care costs). Compared to normal metabolisers, extreme metabolisers had higher total costs (normal metabolisers, £7,530, 95% CI £5,495-8,592; extreme metabolisers, £12,692, 95% CI 4,555-8,132), and psychiatric care costs (normal metabolisers, £7,044, 95% CI £5,495-8,592; extreme metabolisers, £12,500, 95% CI £5,284-19,717). Marginal effects are illustrated in Table 4.8, and represent the change in healthcare costs per unit change in the exposure, while holding other variables constant. Compared to normal metabolisers, extreme metabolisers were associated with an increase in total costs and psychiatric care costs of £5,162 (£-1,953-12,277) and £5,457 (£-1,887-12,800), respectively, although confidence intervals were very wide. Intermediate metabolisers were associated with an increase in primary care costs of £28 (£-2-57).

I repeated the two-part model using a subset of the original sample, including only individuals who take medications metabolised by CYP2D6. The baseline demographic characteristics for individuals taking a CYP2D6 medication can be found in Appendix C, Tables C2. In total, 193 individuals reported taking a CYP2D6 medication; similar to the original sample, I did not find any significant differences in the probability of positive expenditures or in the cost of treating individuals of different metaboliser groups (Appendix C, Tables C3 and C4). There was weak evidence demonstrating that intermediate metabolisers had 50% higher primary care costs than normal metabolisers (P=0.04).

In addition, I repeated the two-part model excluding pregnant women. There were only 2 participants in the sample who reported being pregnant, thus, excluding these participants did not affect the overall conclusions of the study.

Table 4.8: The marginal effects and average adjusted predicted means for total, psychiatric, physical health, and primary care costs. Marginal effects represent the expected change in costs per unit change in the exposure of interest. Adjusted for age, sex, ethnicity, primary diagnosis, duration of illness, and CYP2D6 inhibitor use. AME, average marginal effects; CI, confidence interval.

	Marginal effect (GBP)	**95% CI**	**Adjusted mean cost (GBP)**	**95% CI**
Total costs				
Normal metabolisers			7,530	5,495-8,592
Intermediate Metaboliser	-829	-3,199-1,541	6,701	4,901-8,502
Extreme metaboliser	5,162	-1,953-12,277	12,692	5,717-19,667
Psychiatric costs				
Normal metabolisers			7,044	5,495-8,592
Intermediate Metaboliser	-700	-3,043-1,643	6,344	4,555-8,132
Extreme metaboliser	5,457	-1,887-12,800	12,500	5,284-19,717
Physical health costs				
Normal metabolisers			598	367-828
Intermediate Metaboliser	-146	-456-165	452	226-678
Extreme metaboliser	-384	-720–48	214	196-231
Primary care costs				
Normal metabolisers			52	39-64
Intermediate Metaboliser	28	-2-57	80	52-107
Extreme metaboliser	-12	-45-21	40	9-70

4.5 Discussion

In this chapter, I evaluated the impact of *CYP2D6* genetic variation on healthcare costs (including total costs, psychiatric care costs, nonpsychiatric/physical health care costs, and primary care costs) in individuals with psychosis. The two-part model did not find a significant difference in the likelihood of having healthcare expenditures between extreme and normal metabolisers. In this analysis, total healthcare costs and psychiatric costs had particularly wide confidence intervals as the vast majority of the sample had positive expenditures for these analyses. Indeed, 97% of participants had a positive expenditure for total and psychiatric care costs, compared to nonpsychiatric and primary care costs, where only 57% and 38% of participants had a positive expenditure, respectively. There was also no significant difference in the cost of treating extreme metabolisers compared to normal metabolisers. However, there was evidence indicating that intermediate metabolisers had 75% higher primary costs compared to normal metabolisers ($P<0.001$), which remained significant in the sensitivity analysis restricted to individuals taking CYP2D6 medications ($P=0.04$).

This study did not replicate the promising findings of higher healthcare costs in poor and ultrarapid CYP2D6 metabolisers reported by Herbild et al. [105]. I speculate that this is due to a number of reasons. Firstly, while my study had a larger total sample size (n=328) than Herbild et al. [105](n=207), I had a smaller number of extreme metabolisers (n=27) compared to their study (n=60). Herbild et al. [105] captured a larger number of extreme metabolisers through their sampling strategy: they identified 600 individuals diagnosed with schizophrenia and conducted *CYP2D6* genotyping, revealing 60 extreme metabolisers and 540 normal and intermediate metabolisers. They randomly excluded over 300 normal or intermediate metabolisers to increase the frequency of extreme metabolizers to 20%, leading to a high number of extreme metabolisers. A post-hoc power analysis using G*Power 3.1[199] indicated that this study had 50% power to detect sta-

tistically significant differences between the extreme and normal metaboliser groups. To achieve 80% power, which is the minimum power recommended by the literature[200], a sample of 410 normal metabolisers and 62 extreme metabolisers would be required. Furthermore, the period over which resource use data was collected differed. In my study, data was collected over a period of 3 months, whereas Herbild et al. [105] collected data over a year. A longer time horizon increases the power of the study and the chances of finding group differences. As a result, the differences in study designs and methodology could potentially explain the differences in results.

Secondly, these varying results could be the result of "winner's curse", a term used to describe the phenomena where an effect estimate in a small discovery trial is an overestimate and therefore cannot be replicated in subsequent studies[201]. This can be due to many reasons, for example, the initial trial may have been done in an ideal population group due to strict inclusion and exclusion criteria. It is possible that naturalistic studies that are conducted in the general population, such as this present study, are likely to have smaller effect estimates. Participants in this study were recruited from a variety of services, including hospital wards, community health services, and forensic services. Heterogeneity among study participants and between different NHS trusts and services may, therefore, have reduced the effect estimate. Another reason is that results that are statistically significant are more likely to be published, leading to publication bias. Due to these reasons as well as others, it is possible for published effect sizes get smaller over time.

Finally, the complexity of CY450-mediated metabolism and the antipsychotic drugs taken by the participants in the sample may explain my results. While CYP2D6 is the major metabolizing enzyme for many antipsychotics, there are several antipsychotics where CYP2D6 only plays a minor role in its metabolism, and other CYP enzymes play a larger

role. For example, clozapine, which was one of the most frequently prescribed antipsychotic for the extreme metabolisers in this study, is primarily metabolised by CYP3A4, CYP1A2 and CYP2C19, with CYP2D6 playing a minor role[202]. On the Flockhart Table™, it is not listed as a CYP2D6 substrate[103]. In fact, 63% of medications taken by the extreme metabolisers were not listed as a substrate, so for these participants, being an extreme metaboliser may have had little effect on their medication response and healthcare costs. Thus, broadening the study to include other CYP450 genes, such as *CYP1A2* and *CYP3A4*, might be more informative.

Although this study has focused on the economic burden of individuals with extremes in *CYP2D6* enzyme activity, it is worth considering that there are benefits to increased resource use and healthcare spending that must be considered. From an economist' perspective, spending more money in one therapeutic area could mean less to spend in other areas. Given the current financial constraints on the NHS, this perspective is understandable. Alternatively, from a psychiatrist' perspective, patients who engage with their treatment and regularly attend healthcare appointments may have better health outcomes long-term[203]. Indeed, several analyses of NHS programme budgeting data demonstrate an association between increased spending and improved health outcomes, with the cost of securing an extra quality-adjusted life year (QALY) ranging between £5000 to £15000, which is below the National Institute for Health and Care Excellence's threshold for new treatments of £20,000 per QALY[203]. Furthermore, a study spanning 35 countries, including the UK, found that a 10% increase in health spending was associated with a gain of 3.5 months of life expectancy between 1995 to 2015[203]. Thus, it can be argued that healthcare spending can be productive and may provide value for money.

4.5.1 Strengths and limitations

This study is the first and largest investigation of the influence of pharmacogenetics on healthcare expenditure in individuals with a psychotic disorder, specifically in the UK. One of the major strengths of this study is the diversity of the study sample, with 36% identifying as BAME. For context, the 2021 UK Census for England and Wales found that 82% identified as white, and 18% identified as BAME[204]. Previous studies in this field have not disclosed the racial and ethnic compositions of their sample[105][182]. Another strength of this study was the use of an array-based platform for *CYP2D6* genotyping, which was important given the diversity of the sample. This method provided sufficient coverage of *CYP2D6* genetic variation, including structural variation, and included variants common in European and North American populations, as well as variants that are more common in other ancestries.

However, there were several limitations to this study. As mentioned, statistical power and a short follow-up time period limited the ability to detect differences between metaboliser groups. Another limitation was the method used to collect resource use data. This study relied on self-reported data on resource utilisation over a 3-month period; the data may have been subject to recall bias, where there is error in the recall of information, such as forgetting to report an event or reporting an event that did not occur[205]. Events may also be recalled with an incorrect timeline, referred to as telescoping, such as recalling an event that actually occurred before the specified period[205]. Recall bias can be affected by poor memory, when a participant has an inability to recall when, and the exact number of times, an event took place, and this can be influenced by different demographic and methodological factors such as patient population and recall time frame. For example, an individual with poor health status may not have the capacity for accurate recall and may therefore under-report. Collecting resource data through electronic health records would be the optimal way to overcome recall bias and accurately collect resource data for future

studies. Electronic health record data was not available to me at the point of analysis but will become available in the near future. In addition, the study did not collect information regarding the duration of the appointments and contacts and assumed an average duration. Given the lack of information, these assumptions are appropriate, but for some patients, this may not be accurate. Thus, recording the duration of each appointment and contact would increase the accuracy of the data. When recording nonpsychiatric hospital resource utilisation, the study also did not collect specific data regarding the nature of the hospitalisation, such as whether the stay was elective or non-elective, and the reason for these stays. This could have had potentially impacted the results, as a complex surgical operation is likely to be much more costly than, for example, an infection. Finally, the use of a healthcare system perspective does not take into account patients' direct non-medical costs (such as accommodation or travel-related costs) and productivity costs. If these costs were taken into account, the costs incurred by extreme metabolisers may potentially have been higher, due to suboptimal treatment outcomes reported in this patient population[85].

For future studies, I make the following recommendations. Firstly, studies must include participants of BAME ancestry and be transparent about the racial and ethnic composition of their sample, as these populations have genetic variants that are less common than in individuals of European ancestry. Secondly, to increase the number of extreme metabolisers in the sample, it is recommended that researchers strategically enrich their sample with *CYP2D6* ultrarapid and poor metaboliser phenotypes as done by Herbild et al. [105]. Thirdly, it is recommended to increase the follow-up period over which resource use data is collected to at least 6 months, or ideally, 1 year. Ideally, this data would be collected through electronic health records to ensure accuracy of the data and prevent recall bias. Future studies should consider the role of phenoconversion when determining an individual's metaboliser status given the increasing rates of polypharmacy in real-world

practise. Finally, given the complexity of CYP450-mediated drug metabolism which may be mediated by different enzymes, researchers could investigate additional genes relevant to antipsychotic metabolism, such as *CYP1A2* and *CYP3A4*.

4.5.2 Conclusion

To conclude, while previous studies have suggested that poor and ultrarapid metabolisers would benefit from pharmacogenetic testing, this study was only about to demonstrate increased primary care costs in intermediate metabolisers. The limited evidence demonstrating the economic and clinical benefits of pharmacogenetic testing for psychosis has hindered its implementation in broader, clinical settings, thus, I would recommend studies that strategically enrich their sample with *CYP2D6* ultrarapid and poor metaboliser phenotypes with a time horizon of at least a year, to provide sufficient statistical power to detect differences between groups.

Chapter 5

Cost-effectiveness of pharmacogenetic testing to guide treatment in schizophrenia

5.1 Abstract

Antipsychotics are licensed to treat schizophrenia, bipolar disorder and other conditions with psychosis symptoms, but there is substantial interindividual variability in response and tolerability. Knowledge of an individual's genotype could potentially optimise the choice of drug and/or its dosing. I investigated the cost-effectiveness of pharmacogenetic testing to inform antipsychotic prescribing in people with schizophrenia compared to treatment as usual with antipsychotics. A decision analytic model comprised of a decision tree embedded with a Markov model was constructed, with a focus on treatment-naïve people with a diagnosis of schizophrenia. A healthcare provider (UK's National Health Service) payer perspective was adopted. This study found that the pharmacogenetics strategy saved £38,016.01 and gained 0.41 additional QALYs compared to TAU over an individual's

lifetime (incremental cost-effectiveness ratio, -£93,134.68 GBP per QALY). Pharmacogenetics' dominance over TAU was robust to all scenario analyses conducted. Probabilistic sensitivity analysis demonstrated that there was a 89% probability of the pharmacogenetic testing strategy being cost-effective within the willingness-to-pay threshold of £20,000. Overall, pharmacogenetic testing has the potential to optimise treatment for patients diagnosed with schizophrenia. Although I found evidence of cost-effectiveness over a lifetime period, there is inconsistent evidence that pharmacogenetic testing improves long-term clinical utility and further prospective studies investigating clinical benefits of pharmacogenetic testing are necessary to bring more certainty around the parameters used in the model.

5.2 Introduction

Pharmacogenetic testing is an emerging approach that could potentially improve health outcomes and reduce costs in schizophrenia, as knowledge of a patient's genotype could optimise treatment by guiding the choice of drug and/or its dose adjustments[105]. However, pharmacogenetics is currently not used in mental health settings in the UK's National Health Service (NHS) as there are currently several barriers which hinder its implementation, including funding, as pharmacogenetic testing is expected to incur additional costs associated with genotyping[206]. In the UK, pharmacogenetic testing is likely to be funded by the NHS, through existing commissioning pathways, thus, commissioners need evidence demonstrating whether pharmacogenetic testing will increase or reduce healthcare costs downstream before deciding to implement this in the NHS[206].

A full economic evaluation aims to inform decision making by comparing the costs and health outcomes of two or more treatment approaches[207]. The methods for conducting economic evaluations can be trial-based, model-based, or real-world based. Trial-based

evaluations collect resource use and health-related quality of life data over the duration of a randomised controlled trial, and provide strong evidence of cost-effectiveness[207]. Despite having high internal validity, trial-based evaluations have low external validity due to strict inclusion and exclusion criteria[208]. Evidence from randomised controlled trials may not be generalisable due to large heterogeneity of patients in clinical practise compared with randomised controlled trial populations[208]. They also have a limited time horizon (i.e., the start and end point over which costs and health effects are measured and valued), which is often too short to capture differences in outcomes and thus for differences in costs to be realised[209]. Real-world evidence, i.e., data collected outside of randomised controlled trials (electronic health records, registries, observational cohort studies, and administrative records), can fill evidence gaps where randomised controlled trials are not feasible[210]. However, there are reservations regarding the quality of real-world evidence, making them less optimal for decision making[210]. Model-based evaluations can overcome some of the limitations of both real-world evidence and trial-based evaluations. They use mathematical models (decision-analytic or state-transition computer stimulation models) and synthesise data from multiple sources, such as randomised controlled trials and real-world evidence, to evaluate more complex scenarios or long-term outcomes[207][208]. Model-based evaluations may have broader generalisability as they can simulate various patient populations, informing decision making across different contexts[208].

In Chapter 2, I conducted a systematic review and identified a total of 8 economic evaluations investigating the use of pharmacogenetic testing to guide treatment in schizophrenia. Of these, 3 were trial-based economic evaluations of pharmacogenetic testing for schizophrenia, and 2 found the intervention to be cost-saving. Skokou et al. [109] found no differences in cost and quality of life after pharmacogenetic testing. However, Carrascal-Laso et al. [112] found that total hospital costs and pharmaceutical costs decreased by

59% and 10% over 3 years, respectively, and Herbild et al. [105] found that total costs among extreme metabolizers (poor and ultrarapid metabolisers of *CYP2D6*) were significantly reduced by 28% over 1 year. These trial-based economic evaluations were based in Greece, Spain, and Denmark, respectively.

My systematic review also identified 5 decision analytic models evaluating the cost-effectiveness of pharmacogenetic testing to guide antipsychotic treatment. However, caution is generally advised when assessing the transferability of results across different healthcare settings due to the heterogeneity of cost-effectiveness analyses. Only 2 were conducted in a UK setting: firstly, a decision model investigating the cost-effectiveness of pharmacogenetic testing for antipsychotics was conducted by Rejon-Parrilla et al., [118]. This study provided evidence of cost-effectiveness at an incremental cost-effectiveness ratio (ICER) of £2,059 per QALY, which remained below the conventional decision threshold of £20,000-30,000 assigned by the National Institute for Health and Care Excellence (NICE)[84]. Their study was conducted in 2014, when there were no studies on the prospective use of genotyping tests in clinical practise, so data on clinical utility (i.e., the likelihood that pharmacogenetic testing can improve clinical outcomes, such as response or adverse drug reactions) was limited. Their model was, therefore, populated based on assumptions on clinical utility, rather than empirical evidence. As the study was conducted 10 years ago, their cost estimates are also outdated. A more recent decision model by Ninomiya et al., [115] found pharmacogenetic testing to be cost-effective for clozapine therapy at an ICER of £16,215 per QALY, which also remained below the decision threshold. Their study focused exclusively on genetic testing for HLA-DQB1, HLA-B and SLCO1B3-SLCO1B7 variants to reduce clozapine-induced agranulocytosis or granulocytopenia. Thus, they did not incorporate any non-clozapine antipsychotics in their model. Overall, there are very few decision analytic models evaluating the cost-effectiveness of pharmacogenetic testing to guide antipsychotic treatment in the UK. To

date, there has been limited information on input parameters, such as pharmacogenetic test cost and effect of pharmacogenetic testing on clinical outcomes. As a result, there is a lack of up-to-date cost-effectiveness data to support evidence-based implementation in the NHS.

To fill the evidence gap, this chapter utilised a decision analytic model to estimate the costs and health benefits associated with pharmacogenetic testing for all antipsychotic drugs in patients with schizophrenia and assess the potential cost-effectiveness in the UK NHS.

5.3 Methods

The research methods and analyses followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines[211], to improve standardisation and transparency of health economic evaluations, and the NICE reference case, to support decision making in the NHS. The NICE reference case were used to inform the choice of comparator, perspective, time horizon and discounting, and type of economic evaluation.[212].

5.3.1 Study population and perspective

The analysis focused on treatment-naïve patients with a diagnosis of schizophrenia. The starting age of the patients in this model was 25-years old, based on the median age of onset for schizophrenia, as reported by Solmi et al. [213]. A healthcare provider (UK's National Health Service) payer was adopted.

5.3.2 Model structure

Following the revised Brennan's taxonomy[214], a decision tree with a Markov process embedded was deemed to be the most appropriate modelling method for this project,

based on three reasons: the chronic and recurrent nature of schizophrenia; the likely impacts of using pharmacogenetic testing on patients' disease history; and the resources available for this study. The model structure for this study (Figure 5.1) was developed based on the structure of previously published models[215][216], especially those developed for the UK, such as the model developed by the NICE guidelines for schizophrenia [39] and the models developed by Jin et al. [190][217]. All the base-case input parameters in the model are evidence-based and provided in Section 5.3.3.

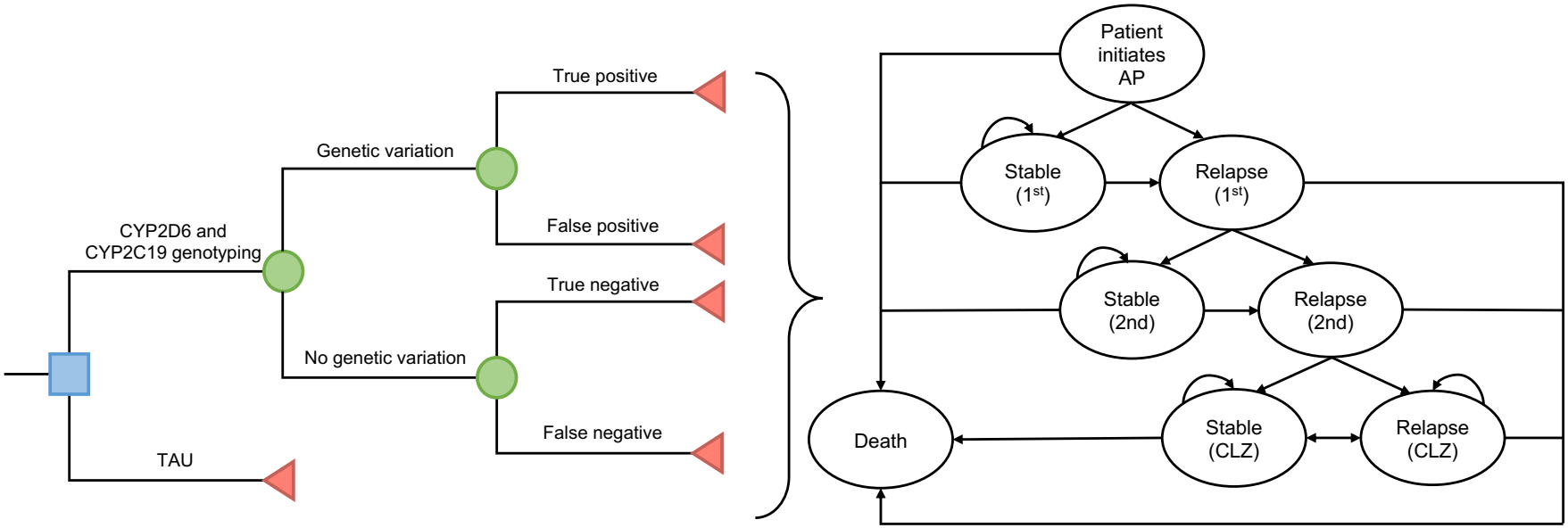


Figure 5.1: Decision analytical model comprised of a decision tree and Markov model for evaluating the cost-effectiveness of pharmacogenetic testing. AP, antipsychotic; CLZ, clozapine; TAU, treatment as usual.

In a decision tree, distinct branches are used to represent different outcomes for a patient[218]. The branches are connected by a node: either a decision node, which represents a decision regarding which intervention to use, or a chance node, which represents an event occurring or not occurring, as governed by chance, or finally, a terminal node, which is found at the end of each branch[218]. The likelihood of each outcome is expressed as a probability. Within the decision tree, the use of *CYP2D6* and *CYP2C19* genotyping strategy to inform antipsychotic treatment was compared to treatment as usual with antipsychotic medicines (TAU) to reflect current prescribing practices. According to the NICE guidelines, the standard choice and dose of medication is based on patient's personal preferences, medication history, symptomology, adverse drug reactions, co-prescribed medications, comorbidities, age and sex as main factors to consider[219].

In the genotyping strategy, treatment is based on all the factors and NICE recommendations, as well as the patients' genetic profile, which can further inform dosage and/or choice of medication, to identify the optimal treatment for the patient. Testing of *CYP2D6* and *CYP2C19* genes were chosen for inclusion in this model, because there is evidence that they are clinically actionable to inform the prescribing of antipsychotics by the Clinical Pharmacogenetics Implementation Consortium[220], the Dutch Pharmacogenetics Working Group[221], and by an expert group from the International Society of Psychiatric Genetics[222]. In the genotyping strategy pathway, patients undergo testing before initiating medication to guide therapy decisions (pre-emptive testing). In the pre-emptive approach, the test results are maintained in the patient's electronic health record and effectively informs all future prescribing decisions. With results available pre-emptively, turnaround time for returning results is also not an issue[223]. In comparison, a reactive approach, where testing is done after the patient has already begun medication, can be less efficient with respect to cost and time. Therefore, the model in this chapter is based on pre-emptive genetic testing. After undergoing genotyping, patients can either

be classified as an alternate metaboliser (i.e., they have a genetic variant in *CYP2D6* or *CYP2C19* affecting the rate of drug metabolism) or they can be a normal metaboliser (i.e., they have no genetic variants that require a treatment adjustment). The percentage of normal metabolisers varies ranges from 4% to 64%, depending on ethnicity and gene[224][225]. To capture test inaccuracy, a patient could be classified as a false negative, i.e., they were incorrectly detected as normal metabolisers when they harboured genetic variants associated with altered drug metabolism, or a false positive, i.e., they were incorrectly detected as an alternate metaboliser when they were, in fact, a normal metaboliser. False positives rates were very low (1%), according to a previous study[226] and expert opinion. False negatives varied between 11-29% depending on ethnicity, according to a study which evaluated the detection rate of 14 different pharmacogenetic tests[129]. For patients in the pharmacogenetic testing pathway, while the cost of testing was considered for all patients regardless of their diagnostic outcomes, the intervention effect was not explicitly modelled for false negatives and false positives, i.e., they have the same transition probabilities as patients in the TAU pathway. In the absence of data on treatment outcomes for false positives and false negatives, this approach was justified.

Within the Markov process, mutually exclusive health states are modelled as potential consequences of a health condition, and each state has an associated cost and health effect[219]. The movement from one state to another is represented by transition probabilities[219]. In the Markov model constructed for this study, the patient initiates a first-line non-clozapine antipsychotic. However, if the patient does not respond to a first-line antipsychotic, they are switched to a second-line antipsychotic. After not responding adequately to two lines of antipsychotic therapy, the patient is switched to clozapine, which would require mandatory white blood cell and absolute neutrophil count monitoring. After initiating the antipsychotic or clozapine, the patient can either enter the health states ‘stable’ (responder), or ‘relapse’ (non-responder); the patient can enter the state ‘death’

from any health state. In the Markov model, a few assumptions were made. Firstly, if a patient were to respond to a particular antipsychotic, they would continue to receive the same antipsychotic in the following cycles. Secondly, if a patient were to enter the Markov model from the *CYP2D6* and *CYP2C19* genotyping pathway, it was assumed that there was no turnaround time for the pharmacogenetic test, and that genotype information was known when the patient entered the cycle.

The model ran with a cycle length of 1 year and adopted a lifetime horizon with a maximum number of 70 cycles. A lifetime horizon was adopted because it accurately reflects the chronic and recurrent nature of schizophrenia, and it is long enough to reflect the key differences between the options regarding costs and outcomes.

5.3.3 Model inputs

The base-case input parameters of the model are evidence-based, and a summary is provided in Table 5.1. These parameters were identified using multiple different methods: I searched electronic databases, such as PubMed, using free-text keywords to identify literature for costs, utilities, mortality rate, and resource use. In addition, I used my systematic review in Chapter 2 to identify existing health economic models, of which I manually searched the reference lists to identify data for the aforementioned parameters. I also used my systematic review to identify clinical trials investigating the use of pharmacogenetic testing to inform clinical utility in the model. Where literature for a parameter was not available or was limited, I sought clinical input from a psychiatrist.

Table 5.1: Input parameters for the decision analytic model. *Estimate for pharmacogenetic test cost was based on the ongoing UK-based Pharmacogenetics in Mental Health study including cost of consultation with a clinician to discuss the results, costs of sample collection kits, sample shipments, DNA extractions, and multi-gene panel genotyping in a clinically-accredited laboratory[1]. GBP, Great British Pound; OWSA, one-way sensitivity analysis; NPV, negative predictive value; PPV, positive predictive value; PSA, probabilistic sensitivity analysis; RR, relative risk.

	Base-case value	**Range tested in OWSA**	**Distribution in PSA**	**Reference**
Population parameters				
Age (years)	25	N/A	N/A	Solmi et al, 2022[213]
Race/ethnicity	European	N/A	N/A	N/A
Pharmacogenetic test parameters				
CYP2D6 normal metaboliser frequency per ethnicity				
European	0.49	N/A	Assume fixed	PharmGKB, [224]
African American/Afro-Caribbean	0.54	N/A	Assume fixed	PharmGKB, [224]
Sub-Saharan African	0.25	N/A	Assume fixed	PharmGKB, [224]
Central/South Asian	0.58	N/A	Assume fixed	PharmGKB, [224]
American	0.65	N/A	Assume fixed	PharmGKB, [224]
Latino	0.60	N/A	Assume fixed	PharmGKB, [224]
East Asian	0.54	N/A	Assume fixed	PharmGKB, [224]
Near Eastern	0.57	N/A	Assume fixed	PharmGKB, [224]
Oceanian	0.64	N/A	Assume fixed	PharmGKB, [224]
CYP2C19 normal metaboliser frequency per ethnicity				

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
European	0.40	N/A	Assume fixed	PharmGKB, [225]
African American/Afro-Caribbean	0.33	N/A	Assume fixed	PharmGKB, [225]
Sub-Saharan African	0.37	N/A	Assume fixed	PharmGKB, [225]
Central/South Asian	0.30	N/A	Assume fixed	PharmGKB, [225]
American	0.63	N/A	Assume fixed	PharmGKB, [225]
Latino	0.52	N/A	Assume fixed	PharmGKB, [225]
East Asian	0.38	N/A	Assume fixed	PharmGKB, [225]
Near Eastern	0.45	N/A	Assume fixed	PharmGKB, [225]
Oceanian	0.04	N/A	Assume fixed	PharmGKB, [225]
CYP2D6 NPV per ethnicity				
European	0.89	0.56-1.00	Beta (mean = 0.89, SE = 0.02)	Sayer et al, 2021[129]
African American/Afro-Caribbean	0.80	0.56-1.00		Sayer et al, 2021[129]
Sub-Saharan African	0.78	0.56-1.00		Sayer et al, 2021[129]
Central/South Asian	0.85	0.56-1.00		Sayer et al, 2021[129]
American	0.82	0.56-1.00		Sayer et al, 2021[129]

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
Latino	0.80	0.56-1.00		Sayer et al, 2021[129]
East Asian	0.71	0.56-1.00		Sayer et al, 2021[129]
Near Eastern	0.84	0.56-1.00		Sayer et al, 2021[129]
CYP2C19 NPV per ethnicity				
European	0.94	0.32-1.00	Beta (mean = 0.94, SE = 0.05)	Sayer et al, 2021[129]
African American/Afro-Caribbean	0.86	0.32-1.00		Sayer et al, 2021[129]
Sub-Saharan African	0.78	0.32-1.00		Sayer et al, 2021[129]
Central/South Asian	0.96	0.32-1.00		Sayer et al, 2021[129]
American	0.97	0.32-1.00		Sayer et al, 2021[129]
Latino	0.94	0.32-1.00		Sayer et al, 2021[129]
East Asian	0.94	0.32-1.00		Sayer et al, 2021[129]

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
Near Eastern	0.95	0.32-1.00		Sayer et al, 2021[129]
Oceanian	0.97	0.32-1.00		Sayer et al, 2021[129]
CYP2D6 and CYP2C19 PPV	0.99	0.80-1.00	Beta (1 event / 100 patients)	[226]
Clinical parameters				
Probability of first-line antipsychotic response	0.76	0.56-0.82	Beta (111 events / 146 patients)	Yoshimura et al, 2019[227]
Probability of second-line antipsychotic response	0.63	0.04-0.63	Beta (20 events / 32 patients)	Yoshimura et al, 2019[227]
Probability of clozapine response	0.67	0.28-0.75	Beta (6 events / 9 patients)	Yoshimura et al, 2019[227]
Probability of clozapine non-response (from clozapine response)	0.16	0.12-0.21	Beta (20 events / 132 patients)	Shah et al, 2020[228]
Probability of clozapine response (from clozapine non-response)	0.13	0.09-0.16	Beta (15 events / 119 patients)	Shah et al, 2020[228]
Probability of response to non-response for antipsychotics	0.28	0.20-0.34	Beta (42 events / 149 patients)	Schennach et al, 2020[229]

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
RR for response after genotyping strategy	1.27	1.07–1.50	Lognormal (μ = 0.24, σ = 0.09)	Kang et al, 2023 [106]
Age-specific mortality, males, 2021 (years)				
25-29	0.00	N/A	Assume fixed	ONS, 2023[230]
30-34	0.00	N/A	Assume fixed	ONS, 2023[230]
35-39	0.00	N/A	Assume fixed	ONS, 2023[230]
40-44	0.00	N/A	Assume fixed	ONS, 2023[230]
45-49	0.00	N/A	Assume fixed	ONS, 2023[230]
50-54	0.00	N/A	Assume fixed	ONS, 2023[230]
55-59	0.01	N/A	Assume fixed	ONS, 2023[230]
60-64	0.01	N/A	Assume fixed	ONS, 2023[230]
65-69	0.01	N/A	Assume fixed	ONS, 2023[230]
70-74	0.02	N/A	Assume fixed	ONS, 2023[230]
75-79	0.04	N/A	Assume fixed	ONS, 2023[230]
80-84	0.07	N/A	Assume fixed	ONS, 2023[230]
85+	0.15	N/A	Assume fixed	ONS, 2023[230]
Age-specific mortality, females, 2021 (years)				
25-29	0.00	N/A	Assume fixed	ONS, 2023[230]
30-34	0.00	N/A	Assume fixed	ONS, 2023[230]
35-39	0.00	N/A	Assume fixed	ONS, 2023[230]
40-44	0.00	N/A	Assume fixed	ONS, 2023[230]

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
45-49	0.00	N/A	Assume fixed	ONS, 2023[230]
50-54	0.00	N/A	Assume fixed	ONS, 2023[230]
55-59	0.00	N/A	Assume fixed	ONS, 2023[230]
60-64	0.01	N/A	Assume fixed	ONS, 2023[230]
65-69	0.01	N/A	Assume fixed	ONS, 2023[230]
70-74	0.01	N/A	Assume fixed	ONS, 2023[230]
75-79	0.05	N/A	Assume fixed	ONS, 2023[230]
85+	0.13	N/A	Assume fixed	ONS, 2023[230]
RR of all-cause mortality (schizophrenia vs general population) (<40 years old)	3.93	N/A	Assume fixed	Correll, 2022[29]
RR of all-cause mortality (schizophrenia vs general population) ($\geq$40 years old)	2.66	N/A	Assume fixed	Correll, 2022[29]
Costs (GBP)				
Pharmacogenetic test	276.92	100–1000	Gamma (mean = 276.92, SE = 193.84)	Estimate*
Annual cost of antipsychotic medication	257.33	N/A	Gamma (mean = 257.33, SE = 180.13)	NHSBSA, 2021[231]

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
Annual cost of clozapine	844.97	N/A	Gamma (mean = 844.97, SE = 591.48)	NHSBSA, 2021[231]
Switching between antipsychotics	123	N/A	Gamma (mean = 123, SE = 86.10)	NICE, 2014[39] ; PSSRU, 2021[232]
Monthly blood test for clozapine users	10.6	N/A	Gamma (mean = 10.6, SE = 89.04)	Ninomiya et al, 2022[115]
Annual cost of treating stable patients	19,848.61	14,872.83–25,122.68	Gamma (accommodation costs: mean = 12,744.16, SE = 8,920.91; resource costs: mean = 7,104.45, SE = 4,973.12)	NICE, 2014[39]; PSSRU, 2021[232]
Annual cost of treating relapsed patients	55,773.03	41,981.85–69,969.76	Gamma (acute episode costs: mean = 50,242.32, SE = 35,169.62; resource costs: mean = 5,530.71, SE = 3,871.50)	NICE, 2014[39]; PSSRU, 2021[232]
Utility				
Stable	0.87	0.87–0.92	Beta (mean = 0.87, SE = 0.02)	Briggs et al, 2008[233]
Relapse	0.48	0.19–0.60	Beta (mean = 0.48, SE = 0.03)	Briggs et al, 2008[233]

	Base-case value	Range tested in OWSA	Distribution in PSA	Reference
Other parameters				
Time horizon	Lifetime	N/A	Assume fixed	NICE, 2014[84]
Cycle length	1 year	N/A	Assume fixed	NICE, 2014[84]
Number of cycles	70	10–100	Assume fixed	NICE, 2014[84]
Discount rate for costs and outcomes (%)	3.50%	0–6%	Assume fixed	NICE, 2014[84]

5.3.4 Clinical parameters

Treatment response was the primary outcome in this study, as opposed to remission. According to the Andreasen criteria[234], remission is determined using the Positive and Negative Symptom Scale (PANSS), which includes 3 subscales: positive symptom scale which includes items P1-7, negative symptom scale which includes items N1-7, and a general psychopathology scale which includes items G1-16. Treatment remission is defined as a score of 3 or less on 8 specific symptom items across the subscales: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), N1 (blunted affect), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G5 (mannerisms and posturing), and G9 (unusual thought content)). This is a stringent criteria that indicates almost a complete absence of psychotic symptoms. Many patients experience moderate symptoms that are neither captured by remission nor relapse[235], thus, response was deemed more appropriate.

A retrospective study by Yoshimura et al., [227] was used to determine response rates after taking a first- and second-line antipsychotic and clozapine as a third-line medication. In their study, 160 individuals with first-episode schizophrenia spectrum disorders underwent antipsychotic therapy. Overall, 76% of patients responded adequately to the first-line antipsychotic trial (n=146); 62.5% responded to the second-line antipsychotic trial (n=32); and 66.7% responded to the clozapine trial as their third-line medication (n=9). Data regarding response to clozapine after initial non-response, or clozapine non-response after initial response, was determined by Shah et al. [228]. Where probabilities were not reported annually, I firstly converted these to a rate (r) using the aforementioned probability (p) and unit of time (t).

$$r = \frac{-ln[1 - P]}{t}$$

I subsequently converted the rate into a probability that aligned with the model cycle

(i.e., a one-year cycle) using the formula below, where *p* represents probability, *r* represents rate, and *t* represents time:

$$p = 1 - \exp(-rt)$$

The clinical utility of pharmacogenetic testing was identified using my systematic review in Chapter 2[235]. There were 4 relevant studies: (1) a double-blind RCT by Arranz et al. [110] (n=290), (2) a single-blind RCT by Jürgens et al. [104] (n=207), (3) a single-blind RCT by Qin et al. [107] (n=186), and a double-blind RCT by Kang et al. 2023 [106] (n=210), all comparing pharmacogenetic testing for patients with schizophrenia compared to treatment as usual. Although symptom severity was an outcome for all studies, they were reported differently in each study. Jürgens et al. [104] reported "improvement" or "non-improvement" in hallucinations or delusions using Scale for the Assessment of Positive Symptoms (SAPS) scale as their primary outcome, which does not take negative symptoms or general psychopathology into account and therefore may not best represent treatment response. The other three studies reported symptom severity using the Positive and Negative Syndrome Scale (PANSS), which assesses participants' positive and negative symptoms and severity of illness. Qin et al. [107] and Kang et al., [106] reported "response" as an outcome, defined as a percentage PANSS score change of 50% or more compared to baseline. In contrast, Arranz et al. [110], reported response as a continuous measure, using the PANSS score differences. Due to the continuous nature of the data reported by Arranz et al. [110], it was not possible for me to calculate a multiplicative intervention effect. Given that the study by Kang et al., [106] had a larger sample size and a more conservative treatment effect than Qin et al. [107], I proceeded to use data from Kang et al., [106] in the base-case analysis to calculate a relative risk (RR) for treatment response. I used the following formula, where P represents probability of response for treatment as usual and RR represents the relative risk for response in the pharmacogenetics group, to ensure the response rate for the pharmacogenetics group could not

exceed 100%[236].

$$p = 1 - (1 - p)^{(RR_{PGx})}$$

In the study by Kang et al. [106], a subgroup analysis was conducted, comparing treatment response in patients with first-episode schizophrenia and relapsed schizophrenia. They found a similar improvement in response in both groups after pharmacogenetic testing, thus, it was assumed that the therapeutic effect of pharmacogenetic testing was the same regardless of the patient's health state.

Mortality information in England and Wales was collected from the Office for National Statistics[230], and multiplied by the all-cause mortality rates for individuals with schizophrenia, collected from a recent meta-analysis. In this study, all-cause mortality for schizophrenia was 3.93 times higher than the general population for individuals under the age of 40, and 2.66 times higher for individuals older than 40 years old[29]. In this model, it was assumed that the mortality rate remained equal for patients in the "stable" and "relapse" health states due to limited availability of relevant data.

5.3.5 Pharmacogenetic testing parameters

Pharmacogenetic test accuracy varies greatly between laboratories due to differences in gene variant selection. Pharmacogenetic tests use targeted genotyping technologies which screen for specific variants with well-characterized drug-gene interactions. However, the variants interrogated are not currently standardised across labs, and the same alleles are not always tested typically due to cost considerations. If a specific genetic variant is not included in the test, then it cannot be detected and the individual would by default be assigned a normal metaboliser phenotype, leading to a false negative result. This can be problematic as allele frequencies vary greatly across different ancestries. To

capture negative predictive values of pharmacogenetic tests (i.e., false negatives), data by Sayer et al. [129] was used. This study evaluated the detection rate of 14 different pharmacogenetic tests and revealed variation in CYP2D6 and CYP2C19 detection rates across different ancestries. For example, for Europeans, the CYP2D6 detection rate was 87%, which was higher than the detection rate for Sub-Saharan Africans, which was 77%. The positive predictive value of the test (i.e., false positives) was low (1%), and was assumed based on expert opinion as well as previous literature[226]. Moreover, normal metaboliser frequency by race/ethnicity for CYP2D6 and CYP2C19 was captured using PharmGKB[224] [225]. For CYP2D6, it was assumed that individuals with an activity score between 1.25-2.25 were normal metabolisers, as recommended by guidance from the literature[60].

5.3.6 Costs and utilities

In this model, estimates on resource use associated with the health states “stable” and “relapse” were collected from the NICE schizophrenia guideline 2014[39] and adjusted to 2021 GBP using the Unit Costs of Health and Social Care 2021[232]. Where unit costs for 2021 were not available, costs from previous years were inflated to 2021 costs using the Office for National Statistics consumer price index[187]. Further information can be found in Appendix D, Tables D1 and D2. Medication cost data was collected from the Prescription Costs Analysis by NHS England[231]. Annual costs of antipsychotics were calculated based on a weighted daily cost of oral antipsychotics and weighted cost per injection for long-acting injectables. If patients relapsed after taking a first- or second-line antipsychotic, they were assumed to switch a second-line antipsychotic or clozapine, respectively. This would incur additional costs, including three visits to a consultant psychiatrist, each visit lasting 20 minutes. Pharmacogenetic test costs were estimated to be £276.92 per patient as a one-off cost in their lifetime. This was based on the ongoing UK-based Pharmacogenetics in Mental Health study including a 20 minute consultation with a

psychiatric to discuss results, costs of sample collection kits, sample shipments, DNA extractions, and multi-gene panel genotyping in a clinically-accredited laboratory[1]. Utilities were expressed as quality-adjusted life years (QALYs), the preferred outcome measure for NICE and thus for UK decision measures. QALYs combines quantity and quality of life to measure the health benefits of a new treatment[237]; it is measured on a scale of 0 to 1, where 0 and 1 represent the worst, and best possible health, respectively; thus, one QALY is equal to one year of perfect health. Such utility data was collected from Briggs et al. [233].

5.3.7 Analysis

The value of a new intervention can be assessed using the net monetary benefit. The main reason for using net monetary benefit was that it is easily interpreted, with a value > 0 indicating that the intervention is cost-effective compared to the alternative. When comparing the net monetary benefit of different scenarios, the scenario with the highest net monetary benefit is the most cost-effective scenario. In contrast, interpreting an incremental cost-effectiveness ratio (ICER) is less straightforward, as changes in the ICER does not necessarily indicate an increase or decrease in cost-effectiveness. The net monetary benefit is calculated using the following equation, where λ represents the willingness-to-pay threshold, $\Delta\overline{E}$ represents the incremental health effect, and $\Delta\overline{C}$ represents the incremental cost.

$$NMB = \lambda \cdot \Delta\overline{E} - \Delta\overline{C}$$

The validity of decision analytic models relies largely on the validity of the input data and are based on several assumptions. Thus, I conducted scenario and sensitivity analyses to determine the impact of changes in the input data on the results. In the scenario analysis, cost-effectiveness was assessed under different scenarios to demonstrate the

hypothetical outcomes that could be achieved for different patient populations. The parameters included in the scenario analysis were patients' age, sex, and race/ethnicity. Base-case and scenario analysis used a 3.50% annual discount rate for both costs and QALYs, in line with NICE[39]. The annual discount rate is used to account for the possibility that costs and health outcomes that occur in the future may be valued less than what they presently do[238].

Furthermore, deterministic one-way sensitivity analysis was conducted for transition probabilities, costs, utilities, positive and negative predictive values of the pharmacogenetic test, number of cycles, and discount rate, to evaluate the impact of uncertainty of a single parameter at a time. Where available, ranges were obtained from the literature; this was the case for transition probabilities, utilities, pharmacogenetic test sensitivity, number of cycles, and discount rates. Where ranges could not be retrieved, ranges were based on expert opinion (such as for specificity values) or values equal to ± 25% of the mean estimated value (such as for costs), as used in previous cost-effectiveness analyses[239][240][241]. If the results of the one-way sensitivity analyses were consistent with the base-case analysis, this would indicate that uncertainty of input data would have limited impact on the study conclusions. I then conducted probabilistic sensitivity analysis with 10,000 Monte Carlo simulations to assess joint uncertainty of multiple parameters and a cost-effectiveness acceptability curve was reported. The cost-effectiveness acceptability curve were introduced as an alternative to confidence intervals, and indicates the probability that the pharmacogenetic strategy will be cost-effective across a range of different willingness-to-pay thresholds, compared to TAU[242]. In the probabilistic sensitivity analysis, cost and utility values followed gamma distributions, probabilities followed beta distributions, and relative risk ratios followed lognormal distributions. The parameters, ranges tested, and distributions for the sensitivity analysis can be found in Table 5.1. The standard error of all costs were assumed to be 70% of the respective mean value. The

Table 5.2: Base-case results by treatment strategy, over a lifetime period. GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; PGx, pharmacogenetics; TAU, treatment as usual; QALYs, quality-adjusted life years.

	Cost	QALYs	Incremental cost (GBP)	Incremental QALYs	INMB (GBP)
Base-case analysis					
TAU	789,878.30	14.55	-	-	-
PGx	751,862.29	14.96	-38,016.01	0.41	46,179.67

model was constructed and analysed using RStudio v2021.09.0.

5.4 Results

The base-case estimates of costs and effects are presented in Table 5.2. Compared to TAU, pharmacogenetic testing incurred £38,016.01 lower costs and 0.41 additional QALYs per person over their lifetime. These results indicated that pharmacogenetics represented the dominant option, i.e., the less costly and more effective option. A further breakdown of costs and consequences are presented in Appendix D, Table D3.

I also conducted scenario analysis by adjusting input values for parameters such as age, sex, and ethnicity, and the results are also presented in Table 5.3. After increasing the starting age of the analysis by 10-year increments, I found that incremental costs and incremental QALYs both decreased compared to the base case. While a starting age of 35-years old could result in £33,617.25 lower costs and 0.36 additional QALYs, a starting age of 75-years old would result in £7,311.49 lower costs and 0.08 additional QALYs. Scenario analysis also identified a slightly higher costs saved and QALYs gained when sex in the model was changed to female, saving potentially £40,275.99 and gaining 0.43 additional QALYs. Finally, after adjusting ethnicity, there were small differences in incremental

costs and QALYs between different groups. Pharmacogenetic testing was the most cost-effective strategy for individuals of Oceanian ancestry, saving £39,043.12 and gaining 0.42 additional QALYs, and the least cost-effective strategy for individuals of American ancestry, saving £35,988.04 and gaining 0.39 additional QALYs. However, among all scenarios, pharmacogenetic testing remained the dominant option, and therefore did not change the study conclusions about cost-effectiveness.

Table 5.3: Scenario analysis results by treatment strategy. GBP, Great British Pound; PGx, pharmacogenetics; TAU, treatment as usual; QALYs, quality-adjusted life years.

	Cost (GBP)	QALYs	Incremental cost (GBP)	Incremental QALYs	INMB (GBP)
Base-case analysis					
TAU	789,878.30	14.55	-	-	-
PGx	751,862.29	14.96	-38,016.01	0.41	46,179.67
Age					
35					
TAU	695,257.83	13.03	-	-	-
PGX	661,640.59	13.40	-33,617.25	0.36	40,836.71
45					
TAU	577,313.31	11.13	-	-	-
PGX	549,218.55	11.43	-28,094.75	0.30	34,129.61
55					
TAU	437,760.01	8.82	-	-	-
PGX	416,298.36	9.05	-21,461.65	0.23	26,076.08
65					
TAU	289,874.82	6.25	-	-	-
PGX	275,617.01	6.40	-14,257.81	0.15	17,334.28
75					
TAU	151,674.13	3.63	-	-	-
PGX	144,362.64	3.71	-7,311.49	0.08	8,913.52
Sex					
Female					
TAU	838,355.91	15.33	-	-	-
PGX	798,079.92	15.76	-40,275.99	0.43	4,8924.61
Ethnicity					
African American/Afro-Caribbean					
TAU	789,878.30	14.55	-	-	-
PGX	752,807.47	14.95	-37,070.83	0.40	45,033.00

Sub-Saharan African					
TAU	789,878.30	14.55	-	-	-
PGX	752,066.31	14.95	-37,812.00	0.41	45,932.17
Central/South Asian					
TAU	789,878.30	14.55			
PGX	751,810.82	14.96	-38,067.48	0.41	46,242.12
American					
TAU	789,878.30	14.55	-	-	-
PGX	753,890.27	14.93	-35,988.04	0.39	43,719.36
Latino					
TAU	789,878.30	14.55	-	-	-
PGX	753,365.53	14.94	-36,512.77	0.39	44,355.96
East Asian					
TAU	789,878.30	14.55	-	-	-
PGX	753,301.61	14.94	-36,576.70	0.39	44,433.51
Near Eastern					
TAU	789,878.30	14.55	-	-	-
PGX	752,613.34	14.95	-37,264.96	0.40	45,268.51
Oceanian					
TAU	789,878.30	14.55	-	-	-
PGX	750,835.18	14.97	-39,043.12	0.42	47,425.75

I conducted one-way sensitivity analysis on parameters associated with costs, utilities, and probabilities (Figure 5.2, Appendix D Table D4). The net monetary benefit was most sensitive to changes in the annual discount rate and likelihood of achieving response for the genotyping strategy (i.e., clinical utility). When clinical utility was adjusted, the cost savings and gains in QALYs associated with pharmacogenetic testing changed substantially. If patients in the genotyping pathway have a 1.07 times greater likelihood of achieving treatment response relative to TAU, this strategy would save £10,900.57 and gain 0.12 additional QALYs. However, if patients in the genotyping pathway have a 1.50

times greater likelihood of achieving treatment response relative to TAU, the strategy would save £62,390.67 and gain 0.67 additional QALYs. Nonetheless, the results showed that even after adjusting each of the model parameters in its range, pharmacogenetics remained the dominant option. In addition, I conducted probabilistic sensitivity analysis, where the input parameters were varied simultaneously along to represent a real-world situation where each patient may have a different set of parameters that varies from one another. The incremental cost-effectiveness plane and cost-effectiveness acceptability curves are shown in Figure 5.3. The incremental cost-effectiveness plane is a scatter plot which represents the uncertainty in the surrounded by the estimates of incremental costs (in GBP) and incremental effect (QALYs gained) gained. The scatter plot is characterised by four quadrants which represent the four planes of cost-effectiveness, in which the northwest, northeast, southwest, and southeast quadrants represent neither effective nor cost-saving, effective but not cost-saving, not effective but cost-saving and both effective and cost-saving, respectfully. The majority of the points fell below the horizontal axis, indicating that the pharmacogenetics strategy is likely to be cost-saving, although there was considerable variation in the magnitude of cost-savings. However, the points were spread between the southwest and southeast quadrants, indicating uncertainty in the regarding the existence and extent of a health benefit associated with the pharmacogenetics strategy compared to TAU. The cost-effectiveness acceptability curve showed at a willingness-to-pay threshold of £20,000/QALY, pharmacogenetic testing was cost-effective 89% of the time.

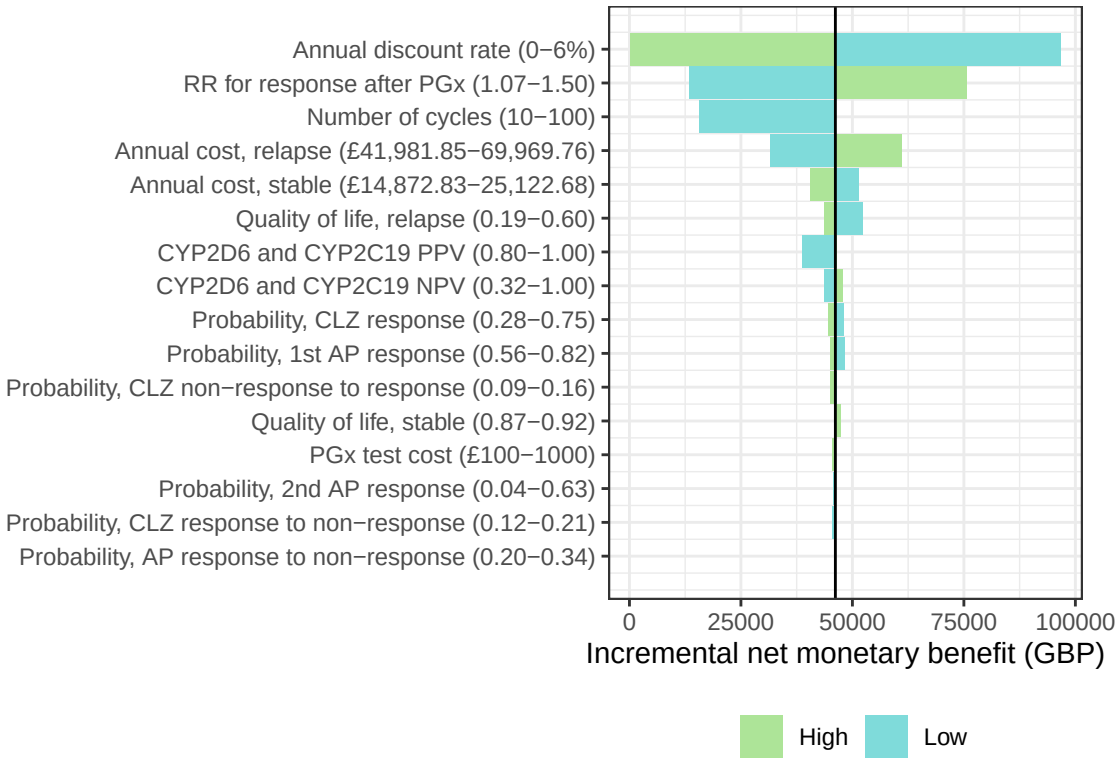


Figure 5.2: Tornado diagram showing the incremental net monetary benefit of the range of values tested for each variable in one-way sensitivity analysis. The variables with the most variation in incremental net monetary benefit are presented in descending order. "High" refers to the upper limit of the range and "low" refers to the lower limit of the range. The tails of each bar represent the minimum and maximum incremental net monetary benefit for each variable. The tornado diagram is centred at the base-case incremental net monetary benefit value (£46,179.67). CLZ, clozapine; PGx, pharmacogenetics; RR, relative risk.

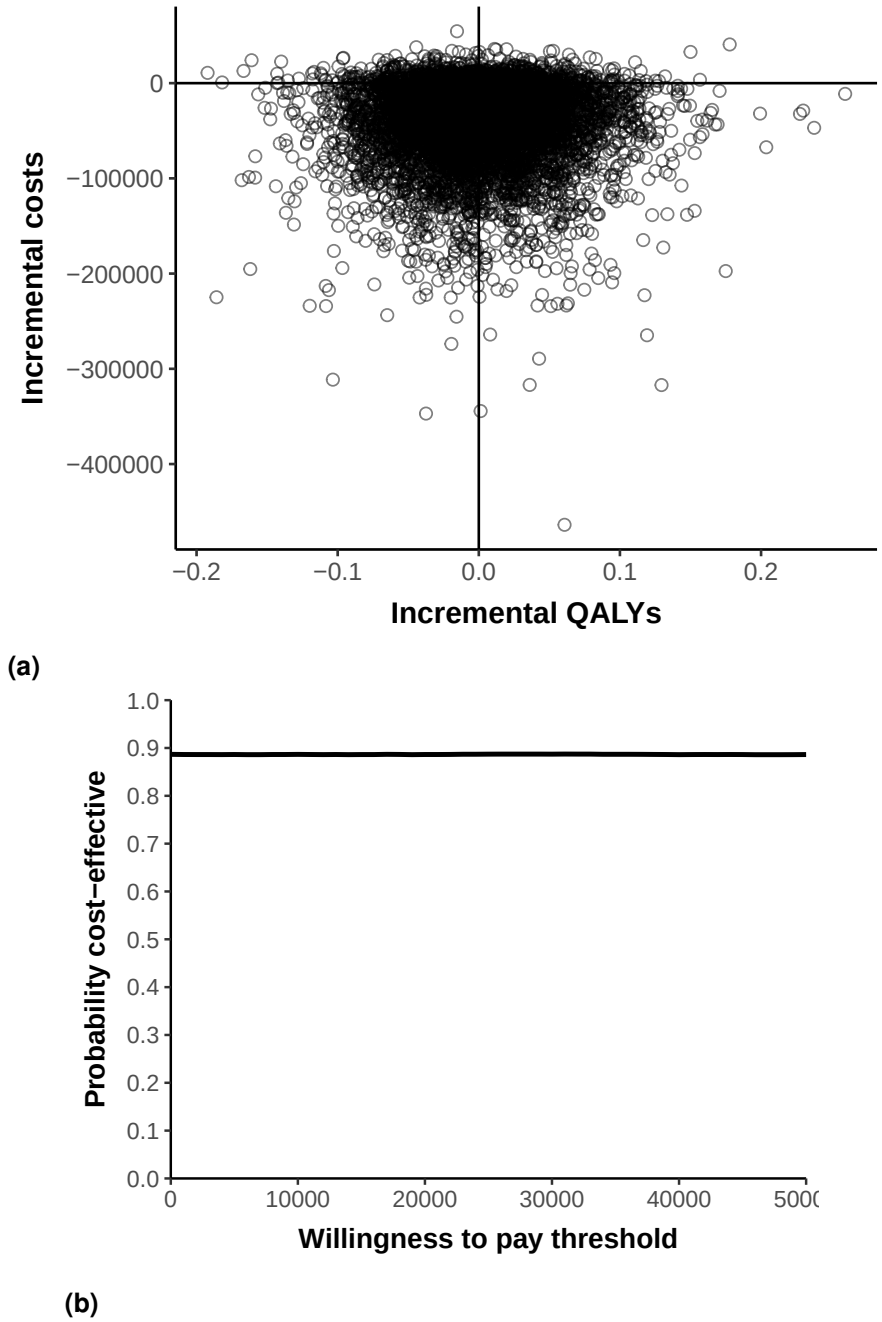


Figure 5.3: Probabilistic sensitivity analysis results, including (a) incremental cost-effectiveness plane and (b) cost-effectiveness acceptability curve. The northwest, northeast, southwest, and southeast quadrants of the cost-effectiveness plane represent neither effective nor cost-saving, effective but not cost-saving, not effective but cost-saving and both effective and cost-saving, respectfully. QALYs, quality-adjusted life years.

5.5 Discussion

In this chapter, I used a decision analytic model to evaluate the potential cost-effectiveness of the use of pre-emptive pharmacogenetic testing to guide antipsychotic treatment among people diagnosed with schizophrenia, over a lifetime horizon from a healthcare provider perspective. This study found that the pharmacogenetics strategy saved £38,016.01 and gained 0.41 additional QALYs compared to TAU. Pharmacogenetics' dominance over TAU was robust to all scenario analyses conducted. In the scenario analysis, there were three main findings. Firstly, the costs saved and QALYs gained reduced considerably with increased age. Thus, pre-emptive genotyping during early life is the most cost-effective approach. Secondly, pharmacogenetic testing was shown to be more cost-saving for women, although this is driven mainly by the differences in mortality rates between men and women. Finally, this study found that pharmacogenetic testing remained cost-effective for individuals of different ancestry. In one-way sensitivity analysis, the parameter that had the greatest impact on the model was annual discount rate, followed by clinical utility; when the response rate after pharmacogenetic testing took the lower limit, pharmacogenetic testing reduced costs by £10,900.57 and gained 0.12 additionally QALYs. Furthermore, probabilistic sensitivity analysis demonstrated that there was a 89% probability of the pharmacogenetic testing strategy being cost-effective within the willingness-to-pay threshold of £20,000.

In this study, I focused on two genes (*CYP2D6* and *CYP2C19*) selected for pharmacogenetic testing as they have evidence-based clinical guidelines for mental health drugs[220][222][60]. In addition to psychiatric medication, these genes have been characterised as clinically actionable for other drugs in multiple therapeutic areas. For example, antipsychotics, antidepressants, beta blockers, and analgesics are all substrates of CYP2D6[173]. Thus, testing for these genes may have further downstream health benefits beyond what has been addressed in this study, as patients with a severe mental

illness have an 84% greater odds of physical multimorbidity compared to those without, and may take multiple drugs as a result[243]. Furthermore, genotyping technologies now allow for simultaneous characterisation of multiple genes which are associated with drugs from multiple therapeutic areas[244]. Compared to testing for these two genes alone, it is likely that including *CYP2D6* and *CYP2C19* as part of a broader, multigene panel to guide prescribing for a variety of drugs may be more beneficial. Although this approach could be more expensive than a single-gene test[245], it has been consistently shown that more than 95% of all individuals carry at least one actionable genotype when tested using a multigene panel[244], which could increase the likelihood that the pharmacogenetics test will be cost-effective. In general, panel-based tests are performed pre-emptively, whereas single-gene tests are performed reactively. A previous decision analytic model comparing pre-emptive and reactive approaches demonstrated that pre-emptive testing was cost-effective compared to TAU, while reactive testing was not[246]. The PREDICT program conducted pre-emptive, panel-based pharmacogenetic testing of almost 10,000 patients and found that if they had opted for a reactive approach instead, 14,656 pharmacogenetic tests would have been required, thus concluded that pre-emptive testing was saving costs by reducing the number of tests required for their sample[247]. In addition, the Generation Study by Genomics England, which aims to sequence the genomes of 100,000 newborn babies to improve diagnosis and treatment for genetic conditions, has suggested that this strategy could be cost-effective when weighing up the costs of genomic testing for newborns against the long-term savings to the NHS and the benefits generated for patients and their families[248].

The full costs of implementing pharmacogenetics in the NHS are difficult to estimate, particularly as there are currently no national tariffs for the genetic tests that would be used. However, with regards to the cost of testing, there are two important considerations: firstly, genotyping technologies are becoming increasingly cheaper with time[94][249]; and

secondly, pharmacogenetic testing only has to be performed once, and is therefore a one-time fixed cost. Considering the results will not change during a patient's lifetime, the results can inform all future prescribing decisions. Nonetheless, the British Social Attitudes survey reported that 80% of respondents believed that the NHS is facing a "major" or "severe" funding crisis[250]. Furthermore, NICE guidelines indicate that recommendation of an intervention requires an ICER below £20,000-30,000 per QALY. An ICER above this threshold would require an increasingly stronger case for supporting the intervention[84]. Thus, implementation into clinical practise requires robust evidence of improvements in both clinical and economic outcomes to offset the costs associated with testing.

5.5.1 Strengths and limitations

In this study, I employed a modelling approach, populated using the most recent input data available, allowing us to synthesise data from multiple different sources to derive estimates of costs and health benefits over an individual's entire lifetime. Previous studies in this field have focused primarily on the use of pharmacogenetics for depression and the prescribing of antidepressants[95], thus, this study fills a necessary gap by focusing exclusively on the use pharmacogenetics for patients with schizophrenia taking antipsychotics. Furthermore, I consider the influence of ethnicity on cost-effectiveness as normal metaboliser frequency can vary between ethnic groups. This has not been previously explored by existing decision models on pharmacogenetic testing for schizophrenia[115][118].

However, there are several limitations to the decision model presented in this study. Firstly, the parameters in the model (costs, utilities, and mortality rates) may be outdated. I recommend future studies to conduct a systematic review of these parameters to inform an up-to-date health economic model investigating the cost-effectiveness of pharmacogenetic testing. Secondly, this model was highly sensitive to the effect of clinical utility, as

shown by a threshold analysis indicating that pharmacogenetic testing is no longer cost-effective at a relative risk of 1 (NMB, -£276). This sensitivity is due to limitations in the model structure: this study modelled false negatives and positives using transition probabilities consistent with the treatment as usual pathway (i.e., they do not incur additional costs or disutility), meaning that the model is driven by correct, actionable results. For a patient who is a false negative, their treatment regimen would not be disrupted. However, patients who are false positives may incur additional costs and may experience worse health outcomes due to additional medication switching. However, previous literature indicates that false positives are uncommon, and are unlikely to occur in clinical practice; in this chapter, we modelled a 1% false positive rate[226].

Another reason that the model was highly sensitive to the effect of clinical utility was that the model did not account for treatment adherence, assuming that patients who are in the "stable" state remain on the same medication and subsequently receive therapeutic benefit. This was largely due to a lack of available evidence at the time that the model was developed. I also did not incorporate the impact of adverse effects due to the uncertainty in the evidence, as pharmacogenetics has both the potential to increase and decrease adverse events, and therefore, increase or decrease costs. Treatment response is ultimately multifactorial, and pharmacogenetics does not guarantee absence of adverse effects, which can be caused by drug-drug interactions, comorbidities, or lifestyle factors. Thus, medication switching could lead to an increased adverse effects, which would have additional costs. On the other hand, some of the adverse events of antipsychotic medications, such as weight gain and diabetes, are chronic conditions that can have a life-time impact on individuals' health and cost outcomes[243]. Complications arising from such conditions, such as myocardial infarction and stroke, could further increase costs and increase disease burden. Thus, it is also possible that pharmacogenetics could prevent adverse drug reactions, which would increase cost-effectiveness

if incorporated. Indeed, the Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) study found that pharmacogenetic testing significantly reduced the incidence of developing an adverse drug reaction by 30%[86] for individuals who were prescribed any index drug (that is, any drug with recommendations in the guidelines of the Dutch Pharmacogenetics Working Group, including antipsychotics as well as other drugs, such as antidepressants, anticoagulants and analgesics, among others). Nonetheless, my systematic review, outlined in Chapter 2, showed that there was no difference in adverse drug reactions after pharmacogenetic testing to guide antipsychotic prescribing[110, 104, 108, 106]. In addition, the Mendelian randomisation analysis in chapter 3 indicated no causal relationship between schizophrenia and cardiometabolic abnormalities. Given this uncertainty, the impact of adverse events was not incorporated, and further research is required on aforementioned outcomes to provide evidence to be included into future models. Thus, while my study simplifies the complex patient journey, it provides a framework for future models.

For clinical utility, this study used data reported by Kang et al.[106], but there were several differences in their study and this present study. Firstly, their study was conducted in a Chinese Han population, so their findings may potentially not be generalisable to a UK population. They also used a multigene panel as part of their pharmacogenetic testing approach, consisting of the following genes: *CYP1A2*, *CYP2D6*, *CYP3A4*, *DRD2*, *EPM2A*, *HTR1A*, *HTR2A*, *HTR2C*, *MC4R*, *RGS4*, and *SH2B1*. Using a multigene panel could increase the number of actionable variants in their sample, which would increase the number of pharmacogenetic recommendations provided by the test. In contrast, only *CYP2D6* and *CYP2C19* were considered for pharmacogenetic testing in this study, as per clinical guidelines.

Finally, this study used a healthcare provider perspective and therefore focused on

direct costs, which do not fully capture all the costs associated with schizophrenia. For example, pharmacogenetics could help to reduce disease burden and other related costs, including loss of work productivity due to morbidity and mortality[251]. Thus, considering indirect costs that represent a wider societal perspective could make pharmacogenetic a more cost-effective option, as it could increase the difference in costs between the pharmacogenetic strategy and TAU.

5.5.2 Conformity to health economics best practice

This model followed principles outlined by the ISPOR-SMDM Modeling Good Research Practices Task Force[252]. Firstly, this study has provided and justified the perspective, target population, time horizon, and health outcomes. Regarding the time horizon, I applied a lifetime time horizon, which aligned with the task force, which state that the time horizon must be long enough to capture relevant differences in the intervention and control group. Furthermore, this study included uncertainty analysis in the form of both deterministic and probability sensitivity analysis; for probabilistic sensitivity analysis, the results were presented using a cost-effectiveness acceptability curve, and distributions of net monetary benefit. Validation of the model included black-box tests, i.e. checking if model calculations are in line with a priori expectations, and white-box testing, i.e. going through the program code details line by line, as recommended by Büyükkaramikli et al[253].
However, this study does deviate from some of the principles mentioned in the task force. The task force indicates that the model structure should be driven by the clinical decision problem or research question, rather than the data availability. However, in this study, conceptualisation of the model was data-driven; for instance, treatment adherence data was not available, and so it was not captured in the model. Furthermore, given that a systematic review was not conducted to parameterise the model (a systematic review was only conducted to identify data for clinical utility, and not the other parameters), it is possible that biases are present in the parameter estimates as I may not have incorporated all the

relevant evidence, as indicated by the task force.

5.5.3 Conclusion

Overall, pharmacogenetic testing has the potential to optimise treatment for individuals diagnosed with schizophrenia. From a healthcare provider perspective in the UK's NHS, this study evaluated the cost-effectiveness of pharmacogenetic testing for *CYP2D6* and *CYP2C19* and found evidence of cost-effectiveness over a lifetime period. However, given the inconsistent evidence on clinical utility, further prospective studies demonstrating clinical utility of pharmacogenetic testing are necessary to bring more certainty around the parameters used in the model.

Chapter 6

Discussion

Pharmacogenetic testing in mental health settings has been limited thus far, with very few examples of clinical implementation in the USA, Europe, and no examples in the UK. As mentioned in the introduction of the thesis (chapter 1), the NHS Genomic Medicine Service is helping to embed pharmacogenetics across the NHS for commonly prescribed drugs. However, there has been limited evidence supporting pharmacogenetic testing for psychosis in the UK. In addition to considering improvements in patient outcomes, it is important to consider the costs associated with this approach. The NHS is a single-payer healthcare system, and the NICE requires a high level of evidence, typically an incremental cost-effectiveness ratio below £20,000 per QALY, in order for a new intervention to be adopted by the NHS[84]. Thus, to be considered for NHS implementation, this thesis investigated the use of genomics to improve clinical and outcomes outcomes in psychosis using various study designs and methods. In this chapter, I discuss the main findings of my thesis, the clinical implications, and the main challenges in the field.

6.1 Main findings

Several bodies, including the Dutch Pharmacogenetics Working Group, Clinical Pharmacogenetics Implementation Consortium, and U.S. Food and Drug Administration, have developed evidence-based clinical guidelines providing drug and dose recommendations for gene-drug pairs[78]. While these guidelines are imperative in translating genetic laboratory test results into actionable prescribing decisions, they do not address whether pharmacogenetic tests should be implemented, and if so, which patients should be offered these tests and when. Thus, the application of pharmacogenetics in clinical practice is not well established. In chapter 2, I conducted a systematic review to determine whether pharmacogenetic testing in individuals undergoing antipsychotic treatment improved clinical and/or economic outcomes. The systematic search identified 16 eligible studies. There were 8 studies that explored clinical outcomes, and these studies reported adverse drug reactions; symptom severity; hospitalisation information; medication prescribing; quality of life; and clinicians opinions. Overall, clinical outcomes showed either no difference compared to treatment as usual or a benefit in favour of pharmacogenetics. In addition, there were 8 studies that reported economic outcomes. The majority of the studies (n=7) demonstrated that pharmacogenetic testing was cost-effective compared to treatment as usual. There were no RCTs or observational studies evaluating clinical or cost-effectiveness in the UK.

This systematic review had a broad scope due to the scarcity of studies in this field, which meant that there was substantial heterogeneity among the studies. Many studies included in the review were not directly comparable due to the differences in the outcomes measured. It was also common for studies to measure the same outcome using different clinical scales, for example, symptom severity was measured using the Scale for the Assessment of Positive Symptoms (SAPS), Positive and Negative Symptoms Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), as well as other scales. The review also

included different study designs, including randomised and nonrandomised trials; controlled and not controlled trials; modelling studies and trial-based economic evaluations. Finally, I observed a wide range of genes tested in each study, ranging from pharmacokinetic genes which are recommended by clinical guidelines, such as *CYP2D6*, to pharmacodynamic genes, such as *ABCB1*, *SLC6A4*, and *DRD2*, which currently have limited evidence for testing and are not yet supported by clinical guidelines. These differences could lead to different prescribing recommendations between each study.

Given the variation between the studies, this chapter demonstrated the importance of further research to support adoption into clinical practise. However, the level of evidence required to support the use of pharmacogenomics in routine clinical practice is controversial. While randomised control trials are at the top of the evidence hierarchy, there is growing support for for the confirmation of clinical utility through naturalistic studies[66]. In therapeutic areas outside of mental health, decisions about patient care are made based on a variety of evidence. For example, a systematic review by Glewis et al. [254], investigating the use of *DPYD* testing to reduce toxicity associated with fluoropyrimidine therapy, found that the evidence base consists only of observational studies, despite its adoption in the NHS since 2020[75]. RCTs also have limitations, such as cost, feasibility, and lack of generalisability for real-world use, as they tend to have stringent inclusion and exclusion criteria[66]. The use of naturalistic studies, such as the Pharmacogenetics in Mental Health study, are beneficial because they are more generalisable to everyday clinical practise, less costly, and easier to run than RCTs[1].

Furthermore, individuals with schizophrenia are at a higher risk of poor physical health and premature mortality compared to the general population, predominantly due to metabolic syndrome and cardiovascular disease[29]. It is possible that schizophrenia has an independent effect on metabolic and cardiovascular risk factors, but it is difficult to derive

causality using observational studies due to unmeasured confounding factors[140]. Thus, in chapter 3, I conducted a bidirectional genetic instrumental variable analysis, known as Mendelian randomisation, to assess the causal relationship between schizophrenia and cardiometabolic abnormalities (and vice versa). The results did not show a causal effect of schizophrenia on cardiometabolic traits, or of cardiometabolic traits on schizophrenia. These findings suggested that cardiometabolic abnormalities are not induced by schizophrenia *per se*, and is likely to be mediated by lifestyle factors (smoking, diet, physical activity), antipsychotic medication, among others factors which have been discussed in previous literature. A systematic review of 12 cohort studies found that reduced function or non-functional alleles for *CYP2D6* was significantly associated with increased antipsychotic-induced weight gain, suggesting that pharmacogenetic testing is, perhaps, a promising approach to optimise antipsychotic medication to each individual and reduce the burden of adverse effects, including cardiometabolic abnormalities[168]. In my systematic review, only 1 study explored the impact of pharmacogenetic testing on cardiometabolic outcomes in schizophrenia; Kang, et al. [106] did not identify a significant difference in metabolic profiles (triglycerides, LDL- and HDL-cholesterol, fasting plasma glucose) between the pharmacogenetics and treatment as usual group. The potential benefits of optimising antipsychotic medication using pharmacogenetic testing on cardiometabolic outcomes, such as BMI, waist-hip ratio, blood lipids, glycaemic traits, and blood pressure should be explored.

Chapter 2 revealed that there are currently no clinical studies conducting pharmacogenetic testing for psychosis in the UK. Thus, in chapter 4, I presented the findings from the Pharmacogenetics in Mental Health study, a clinical study investigating the use of pharmacogenetic testing to guide prescribing in individuals with psychosis[1]. This chapter utilised the results from baseline data, as follow-up data was not ready by the time of analysis. I conducted a two-part model to identify differences in total costs, psychi-

atric care costs, nonpsychiatric care costs, and primary care costs, between CYP2D6 extreme metabolisers, intermediate metabolisers, and normal metabolisers. There was considerable variation in costs among participants, thus, the two-part model did not find a significant difference in the likelihood of having healthcare expenditures between extreme, intermediate and normal metabolisers. There was also no significant difference in the cost of treating extreme metabolisers compared to normal metabolisers. However, intermediate metabolisers had 75% higher primary care costs compared to normal metabolisers. I identified several reasons that could explain my results: firstly, the study only had 27 extreme metabolisers, which which may have limited statistical power to detect a difference between groups; secondly, the time horizon was potentially too short (3 months) to fully capture resource utilisation; and finally, participants in the sample reported taking a variety of antipsychotics, many of which are not thought to be a major substrate of CYP2D6 by the Flockhart Table™[103]. In addition, this study relied on self-reported data. A systematic review of the challenges of resource use measurement in health economics found that personal characteristics, such as age, severity of illness, educational attainment, functional ability, and amount of resource use, may affect the accuracy of self-reported data. For resource use items with high unit costs, a small difference in the frequency of using this resource may cause great variation in total costs and vice versa[255]. Thus, the data collection methods used in this study may also have contributed to these results.

I used a diverse sample in this chapter, with 35% of the sample identifying as BAME; this was important because of the scarcity of genomic data from non-European populations. In general, pharmacogenetics research does not adequately address Black, Asian, and minority ethnic (BAME) populations, as well as admixed populations. This is exacerbated by the implicit biases present when referring patients from a BAME background to clinical trials, as healthcare providers assume that they are distrustful of genomics research and are unwilling to participate[256]. However, studies have shown that individuals

from these groups are as likely to participate as their white counterparts if they receive adequate information about the study, such as the benefits and risks[256]. Furthermore, conducting pharmacogenetics in one geographical region, or targeting a specific demographic, can be harmful and can lead to unequal access to improvements to care. For example, *CYP2C19* testing to guide clopidogrel use has been implemented by an NHS trust in Scotland. The burden of *CYP2C19* loss of function alleles varies greatly across ancestral groups, and is particularly high in Asian populations, with 57% identifying as intermediate or poor CYP2C19 metabolisers in a previous study[257]. Implementation in Tayside, where the population is 98% white, may not be cost-effective, whereas implementation in London, where the population is 21% Asian, is more likely to be cost-effective[258]. Thus, if ethnic minority groups are not considered during implementation, those who could benefit from the pharmacogenetic testing may be denied access. This could exacerbate existing health inequalities by promoting advances in personalised medicine for those who already enjoy the best health[258]. Nonetheless, there are ongoing efforts to improve capacity and capability in low- and middle-income countries to address this concern, through H3Africa, GenomeAsia 100K Project127, as well as other research initiatives[66].

Chapters 2 and 4 highlighted the need for further research to assess the cost-effectiveness of pharmacogenetic testing in the UK. Thus, in chapter 5, I constructed a decision analytic model to assess the cost-effectiveness of pharmacogenetic testing in people with schizophrenia compared to treatment as usual over a lifetime period. Focusing on treatment-naïve patients (pre-emptive pharmacogenetic testing) using a healthcare provider (NHS) payer perspective, I developed a decision tree and Markov model comparing *CYP2D6* and *CYP2C19* genotyping to treatment as usual. I found that the pharmacogenetic strategy saved £38,016.01 and gained 0.41 additional QALYs compared to TAU in the base-case analysis. I conducted scenario analysis by adjusting input values for parameters such as age, sex, and ethnicity, and one-way sensitivity analysis, and pharmacogenetics'

dominance over TAU was robust to all scenario analyses conducted. Probabilistic sensitivity analysis demonstrated that there was a 89% probability of the pharmacogenetic testing strategy being cost-effective within the willingness-to-pay threshold of £20,000. If a broader societal perspective was adopted, pharmacogenetic testing is likely to appear even more cost-effective. The results in this study echo the systematic review by Morris et al. [94], which investigated the cost-effectiveness of pharmacogenetic testing across multiple therapeutic areas, and found that majority (71%) of studies demonstrated cost-effectiveness. Although they did not find any studies on antipsychotics, they found that 9 of 11 antidepressant studies were cost-effective. They suggested that future economic evaluations are likely to consider pharmacogenetics to be cost-effective, given that genetic testing is becoming cheaper and more widely available.

In my model, I adopted a pre-emptive approach, where pharmacogenetic information is available at the point of prescribing. These is growing support for this approach compared to a reactive one, which refers to testing after an individual experiences an adverse drug reaction or treatment failure. Indeed, a qualitative study exploring service users' and clinicians' views on pre-emptive testing found that it was perceived as proactive for future health needs, and beneficial for expediting treatment and avoiding inconveniences[259][260]. Furthermore, a UK-based study reported that individuals in an early intervention psychosis cohort taking a "CYP2D6-PGx antipsychotic", i.e., an antipsychotic drug with dosing recommendations based on CYP2D6 genotype, were more likely to have 2 or more drug switches. A lack of therapeutic response (26%) and ADRs (42%) to antipsychotics were the most common reasons for drug switches, which could potentially be prevented if pharmacogenetic information was available at the point of prescribing. The two different approaches are, therefore, highly likely to impact cost outcomes. A model-based cost-effectiveness analysis compared pre-emptive and reactive pharmacogenomic panel testing in cardiovascular disease management and found pre-emptive testing to be

cost-effective compared to treatment as usual (ICER, $86,227/QALY), whereas reactive testing was not (ICER, $148,726/QALY)[246]. Pre-emptive pharmacogenetic testing has the potential to inform future prescribing decisions, which is important given that individuals with psychosis are at a greater risk of multi-morbidity[243]. Future studies could explore the use of pre-emptive pharmacogenetic testing in psychosis on downstream clinical outcomes, such as co-morbid conditions, and how this affects cost-effectiveness.

Although I did not include societal costs in this chapter, pharmacogenetic testing could have wider implications for patients. If pharmacogenetic testing leads to improvements in treatment outcomes, such as symptom severity, adverse drug reactions, and treatment adherence (among others), this could improve social, occupational, and school functioning. As a result, pharmacogenetics could reduce the need for carers, allow patients and carers to return to work, and have fewer contacts with the criminal justice system. The long-term and wider impacts of pharmacogenetics are largely unexplored and require further investigation.

Despite health benefits and costs saved downstream, pharmacogenetics will require a high upfront cost, depending on who and how many people are tested. Pharmacogenetic tests are estimated to cost £277, including a 20 minute consultation with a psychiatric to discuss results, costs of sample collection kits, sample shipments, DNA extractions, and multi-gene panel genotyping in a clinically-accredited laboratory[1]. Assuming a 1% prevalence rate of schizophrenia[15], if all patients were to be tested (criterion 1), this would mean that 692,300 tests would be required, incurring an estimated cost of £192 million. In contrast, a targeted approach would dramatically decrease the number of tests required. If only newly diagnosed patients were tested (criterion 2), this would only require 14,538 tests, amounting to an estimated cost of £4 million. If testing was restricted to those who do not respond to treatment, i.e., have had two or more drug trials, then 159,229 tests

Table 6.1: Estimated test numbers and cost of pharmacogenetic testing in the UK, per year.

	Number of people tested	Cost of test*	Estimated cost
Criterion 1: all patients with schizophrenia	692,300†	£277	£191,711,716
Criterion 2: newly diagnosed patients with schizophrenia (pre-emptive)	14,538‡	£277	£4,025,946
Criterion 3: those who do not respond to treatment (reactive)	159,229§	£277	£44,093,695

*Pharmacogenetic test costs were estimated to be £277, based on the ongoing UK-based Pharmacogenetics in Mental Health study. This estimate includes a 20 minute consultation with a psychiatric to discuss results, costs of sample collection kits, sample shipments, DNA extractions, and multi-gene panel genotyping in a clinically-accredited laboratory[1].

†Assuming a 1% prevalence of schizophrenia[15].

‡Using an incidence rate of 21 cases per 1,000 population per year[261].

§Assuming that 23% of patients do not respond to treatment and meet the criteria for reactive testing[262].

would be required, and this would cost £44 million. Thus, a targeted approach would be more feasible from a testing capacity and costing perspective.

6.2 Clinical implications

A qualitative study of clinicians and patients who participated in the Pharmacogenetics in Mental Health showed that the overall perception of pharmacogenetic testing was largely positive, with one participant suggesting that the study will "help so many people in the future"[260]. This sentiment was echoed by clinicians, one of whom said that the patients are "all glad to have done it", highlighting the importance of allocating resources to this area. Patients and clinicians suggested that this personalised approach improves col-

laborative care and increases patients' feelings of involvement in prescribing decisions. Patients and clinicians also agreed that pharmacogenetics has long-standing value, with the ability to inform future prescribing decisions; as a result, they believed that testing should be done at an earlier stage in the treatment journey, as treatment-naïve patients would benefit the most from this testing. Regarding clinical utility, the clinicians said that it could assist in reducing unnecessary medication changes. However, the findings from this study also highlighted the importance of managing patient and clinician expectations, as antipsychotic treatment response is a multifactorial process, and the clinicians said pharmacogenetics did not always match clinical presentations. One clinician said that "there were medications that had been relatively well tolerated, but actually they were a poor metabolizer and you maybe would have expected them to have had worse side effects." To avoid disappointment and dissatisfaction with the test, education surrounding pharmacogenetics should emphasise that prescribing decisions should attend to patients' holistic needs, in addition to their genetic profile.

While this thesis has demonstrated the potential of a genomics-guided approach in psychosis, there are implementation barriers that need to be addressed. Pharmacogenetic testing will be delivered through the seven Genomic Laboratory Hubs which deliver genomic tests included in the National Test Directory[263]. They provide genomic testing through a range of technologies, from single gene testing to large panels, whole exome sequencing and whole genome sequencing[263]. They currently deliver an estimated 650,000 genomic tests each year[263], and this figure is expected to increase substantially as pharmacogenetic testing becomes more widespread in the NHS. There is uncertainty regarding how to integrate pharmacogenetics into current workflow processes. The additional burden of obtaining samples for many thousands of pharmacogenetic tests may disrupt and overwhelm phlebotomy services without investment into testing infrastructure and workforce[264]. A self-sampling strategy, using cheek swabs and saliva samples, could

be adopted to alleviate the burden on phlebotomy services and improve test turnaround times as patients won't have to wait for an appointment to submit a sample[264]. Regarding turnaround times, there are also concerns that delays in receiving the results could lead to delays in prescribing. Dunbar et al. [265] reported an average turnaround time of 8 days, and an upper limit of 42 days, which makes it unsuitable for clinical scenarios where pharmacogenetic results are need to inform prescribing in an acute setting.

Once the samples have been been assigned a phenotype, it is uncertain how the pharmacogenetic results will be integrated in electronic health records to inform future prescribing. As part of the PROGRESS study led by NHS Manchester University NHS Foundation Trust and the NHS North West Genomic Medicine Service Alliance, ProgressRX was developed as a digital tool hosted in the NHS cloud to integrate pharmacogenomic data into existing clinical decision support systems[266]. Clinical decision support systems are digital tools that support clinicians in making evidence-based decisions, and can be used across specialities and pathways to improve healthcare delivery[266]. ProgressRX creates a genomic profile for each patient which can be managed and updated over a lifetime, and can inform prescribing within general practice, primary care, pharmacy, mental health trusts, and acute hospital settings[266]. The use of ProgressRX is being trialled in primary care as part of this study, and it will allow pharmacogenetics to be successfully embedded into NHS systems. Finally, there are concerns over increased consultation time, as clinicians would need to inform patients about pharmacogenetics and explain their results[206].

Misinterpretation of pharmacogenetic information is another concern. Typically, results are presented using a traffic light system, but mental health clinicians have suggested that this could be misleading[206]. Rather than being used as a guide to reflect the severity of drug-gene interactions, there is potential for drugs in the green category to be misinter-

preted as drugs that work and drugs in the red category as those that do not work[206]. Education and training of prescribing clinicians, as well as allied health professionals such as pharmacists, clinical pharmacologists, and nurse practitioners, is important to create multidisciplinary team approach to pharmacogenetic interpretation. As the test will inform future prescribing, healthcare professionals across various settings will encounter these results. Training will be provided through GeNotes, which is an educational resource for healthcare professionals working in the NHS, developed by the National Genomics Education programme[267]. GeNotes provides two types of educational materials, firstly "In the Clinic" articles which provides short clinical scenarios at the point of need (before or during a patient appointment), and secondly "Knowledge Hub", which is an encyclopaedia of learning resources to help clinicians develop their understanding of genomics[267]. GeNotes has a number of speciality collections, including cardiology, endocrinology, paediatrics, as well as pharmacogenomics[267]. The pharmacogenomics collection has been developed by clinical experts and will support the integration of pharmacogenetics into routine healthcare[267].

I have outlined several important barriers and challenges of implementing pharmacogenetics, mostly relating to impacts on the healthcare system, patients, and clinicians; addressing these challenges is essential for effective adoption in the NHS. Examples of pharmacogenetics centres or facilities where testing has been successfully rolled out, such as the Tanenbaum Centre for Pharmacogenetics, provide an optimal model for implementation and will help to overcome some of the challenges in the NHS. The future holds promise in advancing the use of genomic information in mainstream medicine and prescribing, but this will multidisciplinary collaboration with NHS England, NHS Digital, Royal College of Psychiatrists, Royal Pharmaceutical Society, and the UK Pharmacogenetics Stratified Medicines Network, to facilitate adoption[268].

6.3 Conclusion

This thesis has demonstrated that while there is potential for a genomics-guided approach to improve care and quality of life in psychosis, more robust evidence is required supporting the clinical utility and cost-effectiveness of pharmacogenetics before adoption in the NHS. Different study designs, including both RCTs and non-RCTs, should be employed, with sufficiently large sample sizes and long follow-up periods (1 year or longer) to evaluate whether the benefits of pharmacogenetic testing are sustained long-term. Studies should focus on using diverse samples to ensure results are generalisable across different age, sex and ethnic groups. In addition, studies exploring how pharmacogenomics can be embedded into clinical pathways is required; the PROGRESS trial is one of the first to do this in the UK, although they do not consider antipsychotics as part of their eligible medicine classes in their inclusion criteria[77]. This project, as well as the Pharmacogenetics in Mental Health study, will help to develop infrastructure to support healthcare professionals use pharmacogenetic testing. The Pharmacogenetics in Mental Health study is currently ongoing and the impact of pharmacogenetic testing on clinical outcomes in psychosis, such as treatment response, adverse effects, and quality of life, will also be evaluated in the future.

It is important to note that genetics is only one contributing factor to an individual's response to antipsychotics, and cannot be used in isolation. According to the International Society of Psychiatric Genetics genetic testing statement (available at `https://ispg.net/genetic-testing-statement/`), pharmacogenetics is a "decision-support tool to assist in thoughtful implementation of good clinical care, enhancing rather than offering an alternative to standard protocols". In an ideal constellation, a psychiatrist would take into account an individual's genetics, demographics, and medical history in combination, to choose the most optimal drug and dose at initiation of therapy for each individual patient. Thus, pharmacogenetics is a promising tool that provides an additional layer of information

to assist clinicians in prescribing safely and effectively.

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Appendix A

Appendices for chapter 2

Table A1: Characteristics of the excluded studies.

Study	Reason for exclusion	Identification method
Brixner, et al. [269]	Antipsychotics did not constitute the great majority of prescribed medications	Google Scholar
Ariefdjohan, et al. [270]	No intervention was provided	Citation search
Chou, et al. [271]	No intervention was provided	Citation search
Luke, et al. [272]	No intervention was provided	Citation search
Battersby [273]	Not yet recruiting/recruitment incomplete	Databases
Kennedy and Dechairo [274]	Unable to retrieve	Databases
Kahn [275]	No pharmacogenetic test conducted	Databases
Zhang [276]	Unable to retrieve	Databases
Su, et al. [277]	Not yet recruiting/recruitment incomplete	Databases

Study	Reason for exclusion	Identification method
Mueller, et al. [278]	Limited medication information	Databases
Loew [279]	Limited medication information	Databases
Tsermpini, et al. [280]	Not yet recruiting/recruitment incomplete	Databases
Daut, et al. [272]	Limited medication information	Databases
Cheema, et al. [281]	Limited medication information	Databases
McCarthy, et al. [282]	Antipsychotics did not constitute the great majority of prescribed medications	Databases
Winner, et al. [283]	No intervention was provided	Database
WHO International Clinical Trials Registry Platform [284]	Not yet recruiting/recruitment incomplete	Database
Laika, et al. [285]	No intervention was provided	Database
Ruaño, et al. [286]	Antipsychotics did not constitute the great majority of prescribed medications	Database
Winner, et al. [287]	Antipsychotics did not constitute the great majority of prescribed medications	Database
Fagerness, et al. [288]	Antipsychotics did not constitute the great majority of prescribed medications	Citation search

Study	Reason for exclusion	Identification method
Olson, et al. [289]	Antipsychotics did not constitute the great majority of prescribed medications	Citation search
Swen, et al. [86]	Antipsychotics did not constitute the great majority of prescribed medications	Database
Ramsey and Griffin [290]	Antipsychotics did not constitute the great majority of prescribed medications	Citation search
Espadaler, et al. [291]	Antipsychotics did not constitute the great majority of prescribed medications	Citation search
Breaux, et al. [292]	Antipsychotics did not constitute the great majority of prescribed medications	Database
Tanner, et al. [293]	Antipsychotics did not constitute the great majority of prescribed medications	Database
Rodieux, et al. [294]	Limited medication information	Database
Pelgrim, et al. [295]	Not yet recruiting/recruitment incomplete	Database
WHO International Clinical Trials Registry Platform [296]	Not yet recruiting/recruitment incomplete	Database

Table A2: A summary of the GRADE ranking for each outcome.

Author	Studies	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Final ranking
Clinical outcomes						
Adverse drug reactions	4	Minimal concerns	Minimal concerns	Serious	Serious	Low
Symptom severity	6	Serious	Serious	Serious	Serious	Very low
Clinicians' opinions	1	Serious	Serious	Serious	Very serious	Very low
Hospitalisation	3	Serious	Serious	Serious	Serious	Very low
Medication prescribing	2	Very serious	Minimal concerns	Minimal concerns	Serious	Very low
Quality of life	2	Serious	Serious	Serious	Very serious	Very low
Economic outcomes						
Overall costs	2	Serious	Minimal concerns	Minimal concerns	Serious	Low
Inpatient costs	3	Serious	Minimal concerns	Minimal concerns	Serious	Low
Non-inpatient costs	2	Very serious	Serious	Minimal concerns	Serious	Low
Incremental cost-effectiveness ratio	5	Serious	Serious	Minimal concerns	Serious	Low

Appendix B

Appendices for chapter 3

Table B1: Summary of the genetic variants used as instrumental variables in the Mendelian randomisation analysis. SE, standard error; SNP, single nucleotide polymorphism.

SNP	Effect allele	Other allele	P value	β	SE
rs2332700	C	G	3.88x10^{-14}	0.075	0.009
rs167924	A	G	2.34x10^{-08}	-0.05	0.009
rs4575535	A	G	5.77x10^{-09}	-0.056	0.01
rs73292401	T	A	5.48x10^{-10}	-0.068	0.012
rs57433322	C	G	1.99x10^{-09}	0.083	0.013
rs2455415	C	T	1.69x10^{-08}	-0.049	0.009
rs39967	T	C	4.38x10^{-08}	-0.062	0.012
rs2333321	A	G	1.25x10^{-11}	0.071	0.01
rs61405217	C	T	7.03x10^{-09}	0.05	0.008
rs7191183	T	C	3.32x10^{-10}	-0.058	0.01
rs61786047	G	A	8.34x10^{-09}	0.078	0.012
rs6001259	C	T	3.70x10^{-08}	-0.191	0.04
rs11210892	G	A	2.68x10^{-12}	0.064	0.008
rs1604060	A	G	3.24x10^{-08}	-0.077	0.015
rs35734242	T	C	1.37x10^{-08}	-0.051	0.009

SNP	Effect allele	Other allele	P value	β	SE
rs9461856	G	A	5.71x10^{-13}	-0.062	0.009
rs2071277	T	C	2.64x10^{-14}	0.067	0.008
rs7830315	T	C	3.08x10^{-08}	-0.048	0.009
rs6984242	G	A	3.86x10^{-10}	0.055	0.008
rs60135207	G	T	1.53x10^{-08}	0.05	0.008
rs187557	C	T	2.03x10^{-08}	0.067	0.011
rs1901512	T	C	5.72x10^{-10}	0.058	0.009
rs61857878	A	T	4.44x10^{-09}	0.06	0.01
rs2909457	G	A	1.48x10^{-08}	0.049	0.008
rs113264400	T	C	2.87x10^{-08}	-0.112	0.022
rs331395	C	G	5.55x10^{-09}	-0.061	0.011
rs1914399	C	G	1.40x10^{-08}	0.049	0.008
rs4702	G	A	2.79x10^{-21}	0.084	0.008
rs2710323	T	C	1.23x10^{-19}	0.078	0.008
rs7647398	C	T	1.07x10^{-12}	0.077	0.01
rs6482437	A	C	3.33x10^{-12}	-0.099	0.015
rs3770754	C	G	5.35x10^{-09}	0.053	0.009
rs12303743	G	C	1.59x10^{-09}	-0.087	0.016
rs2456020	C	T	1.13x10^{-15}	0.082	0.009
rs56205728	G	A	1.01x10^{-10}	-0.063	0.01
rs2255663	C	T	8.40x10^{-10}	0.058	0.009
rs13107325	C	T	2.90x10^{-21}	-0.159	0.019
rs4766428	C	T	3.93x10^{-17}	-0.075	0.01
rs16851048	T	C	4.15x10^{-12}	-0.074	0.011
rs308697	C	A	8.83x10^{-09}	0.05	0.008
rs12877581	G	C	1.80x10^{-09}	-0.06	0.01
rs9318627	A	C	4.35x10^{-12}	0.061	0.008
rs17194490	G	T	1.80x10^{-11}	-0.078	0.012
rs12712510	T	C	5.14x10^{-11}	0.057	0.008
rs17571951	T	C	9.97x10^{-10}	-0.064	0.011

SNP	Effect allele	Other allele	P value	β	SE
rs12883788	C	T	1.86x10^{-12}	-0.061	0.009
rs778371	A	G	1.50x10^{-17}	-0.081	0.01
rs13011472	C	G	4.28x10^{-16}	-0.07	0.009
rs4779050	T	G	7.27x10^{-11}	0.058	0.008
rs11638554	T	G	7.58x10^{-12}	0.065	0.009
rs11680723	C	G	2.05x10^{-14}	-0.086	0.012
rs4812325	G	A	8.96x10^{-16}	-0.072	0.009
rs145071536	T	C	1.62x10^{-12}	-0.085	0.013
rs11090045	G	A	5.12x10^{-09}	-0.056	0.01
rs5995756	T	C	3.18x10^{-11}	0.057	0.008
rs5751191	T	C	3.00x10^{-14}	-0.066	0.009
rs500102	T	C	4.87x10^{-09}	0.052	0.008
rs113113059	T	C	4.89x10^{-08}	0.058	0.01
rs2078266	A	G	2.94x10^{-08}	0.07	0.012
rs9304548	C	A	1.59x10^{-08}	0.057	0.009
rs6673880	A	G	7.20x10^{-12}	-0.062	0.01
rs3795310	C	T	5.75x10^{-09}	0.051	0.008
rs3791710	T	C	3.02x10^{-08}	0.06	0.01
rs1384292	G	C	3.05x10^{-08}	-0.049	0.009
rs634940	G	T	1.78x10^{-11}	-0.066	0.01
rs6925964	A	T	3.11x10^{-08}	0.098	0.016
rs72974238	C	A	8.74x10^{-09}	0.053	0.009
rs4636654	G	A	4.89x10^{-08}	0.048	0.008
rs11027839	A	C	2.40x10^{-09}	-0.052	0.009
rs6798742	A	G	4.57x10^{-11}	-0.061	0.01
rs741896	C	G	2.17x10^{-09}	-0.054	0.01
rs3824451	T	C	2.54x10^{-08}	-0.066	0.012
rs6546857	A	G	2.74x10^{-09}	-0.06	0.011
rs17016552	C	G	1.20x10^{-08}	0.052	0.009
rs10861176	G	A	1.59x10^{-08}	-0.056	0.01

SNP	Effect allele	Other allele	P value	β	SE
rs16825349	A	G	7.72x10^{-10}	-0.069	0.012
rs13016542	T	C	8.28x10^{-12}	0.088	0.012
rs708228	C	T	6.56x10^{-09}	-0.053	0.01
rs11664298	G	A	8.94x10^{-13}	-0.077	0.012
rs76838079	C	T	1.53x10^{-08}	-0.078	0.015
rs498591	A	T	2.11x10^{-09}	-0.072	0.013
rs35351411	A	C	2.21x10^{-13}	-0.064	0.009
rs7515363	C	T	1.84x10^{-09}	0.054	0.008
rs10108980	C	T	2.73x10^{-09}	-0.063	0.011
rs11136325	G	A	3.05x10^{-09}	0.054	0.009
rs4129585	A	C	5.11x10^{-18}	0.075	0.008
rs79445414	T	C	2.80x10^{-08}	-0.123	0.025
rs7001340	T	C	3.17x10^{-08}	0.058	0.01
rs35531336	A	G	2.22x10^{-08}	0.074	0.012
rs728055	T	A	8.85x10^{-14}	0.067	0.008
rs7801375	A	G	7.56x10^{-10}	-0.073	0.013
rs77502336	G	C	1.25x10^{-08}	-0.053	0.01
rs12293670	A	G	1.56x10^{-14}	0.07	0.009
rs6125656	G	A	6.29x10^{-09}	-0.064	0.012
rs926288	A	G	2.50x10^{-08}	-0.061	0.012
rs12138231	T	A	7.99x10^{-09}	-0.067	0.012
rs58120505	T	C	2.24x10^{-24}	0.09	0.008
rs72943392	G	C	2.39x10^{-08}	-0.053	0.01
rs12969453	A	G	8.52x10^{-14}	0.065	0.008
rs1789595	A	T	4.04x10^{-11}	0.064	0.009
rs4632195	C	T	4.59x10^{-08}	-0.047	0.009
rs9636107	A	G	5.12x10^{-16}	-0.07	0.009
rs6974218	A	C	6.80x10^{-10}	0.055	0.008
rs7803571	C	T	1.27x10^{-12}	0.064	0.008
rs2514218	C	T	1.35x10^{-14}	0.07	0.009

SNP	Effect allele	Other allele	P value	β	SE
rs12771371	G	A	1.94x10^{-08}	0.052	0.009
rs1540840	G	C	2.21x10^{-09}	0.056	0.009
rs9876421	C	T	9.19x10^{-12}	-0.063	0.01
rs6549963	T	C	4.31x10^{-08}	0.048	0.008
rs10873538	T	G	3.01x10^{-13}	-0.067	0.01
rs10117	G	A	4.66x10^{-10}	0.055	0.008
rs9687282	T	G	7.33x10^{-09}	-0.053	0.01
rs1430894	C	T	6.15x10^{-10}	-0.053	0.009
rs12489270	T	C	7.47x10^{-11}	-0.058	0.009
rs699318	T	C	2.27x10^{-13}	0.067	0.009
rs1451488	A	G	4.47x10^{-16}	-0.071	0.009
rs11993663	C	A	3.32x10^{-08}	-0.05	0.009
rs4921741	A	G	1.21x10^{-08}	-0.056	0.01
rs1427633	G	C	4.10x10^{-08}	0.048	0.008
rs2238057	T	G	8.50x10^{-22}	-0.084	0.009
rs3814883	C	T	1.58x10^{-14}	0.067	0.008
rs215412	G	A	2.69x10^{-10}	-0.058	0.01
rs11693094	C	T	4.29x10^{-10}	0.054	0.008
rs62183855	A	C	2.66x10^{-09}	0.066	0.01
rs12129573	C	A	2.28x10^{-18}	-0.078	0.01
rs4700418	C	G	5.37x10^{-16}	-0.07	0.009
rs505061	C	A	5.80x10^{-10}	-0.053	0.009
rs7575796	A	G	2.07x10^{-08}	0.096	0.015
rs12310367	A	G	1.21x10^{-08}	-0.052	0.009
rs1615350	C	T	4.92x10^{-14}	0.074	0.009
rs79210963	T	C	4.14x10^{-10}	-0.086	0.015
rs8055219	G	A	5.69x10^{-11}	-0.067	0.011
rs1198588	A	T	1.73x10^{-21}	-0.103	0.012
rs6701322	A	G	6.15x10^{-12}	-0.069	0.011
rs1000237	T	A	2.80x10^{-16}	-0.073	0.009

SNP	Effect allele	Other allele	P value	β	SE
rs72986630	C	T	3.59x10^{-10}	-0.112	0.02
rs56335113	A	G	6.02x10^{-12}	0.065	0.009
rs11263861	G	A	2.02x10^{-08}	-0.052	0.01
rs246024	C	T	3.61x10^{-08}	0.048	0.008
rs117799466	G	C	1.28x10^{-10}	-0.062	0.01
rs7900775	T	C	3.82x10^{-08}	0.049	0.008
rs11191580	T	C	1.77x10^{-17}	0.132	0.013
rs79780963	C	T	3.39x10^{-17}	0.131	0.013
rs6715366	G	A	2.49x10^{-08}	-0.054	0.01
rs12285419	C	A	1.05x10^{-14}	-0.085	0.012
rs17731	G	A	4.37x10^{-09}	-0.052	0.009
rs2381411	T	C	1.25x10^{-08}	-0.05	0.009
rs6943762	T	C	1.57x10^{-15}	0.105	0.012
rs13233308	C	T	1.75x10^{-08}	0.049	0.008
rs10086619	A	G	4.97x10^{-10}	-0.072	0.012
rs9454727	A	G	3.35x10^{-08}	0.054	0.009
rs2815731	C	A	4.39x10^{-11}	0.06	0.008
rs217336	C	A	8.05x10^{-09}	0.05	0.008
rs6538539	G	T	4.43x10^{-11}	0.057	0.008
rs10777956	A	G	1.75x10^{-08}	-0.05	0.009
rs10894308	G	A	8.18x10^{-10}	0.054	0.008
rs7115692	G	A	6.32x10^{-10}	-0.062	0.01
rs4936215	A	G	1.87x10^{-14}	0.082	0.01
rs893949	C	T	1.64x10^{-12}	0.061	0.008
rs3016386	G	A	6.24x10^{-09}	0.05	0.008
rs2252074	T	G	6.19x10^{-15}	-0.069	0.009
rs10876446	G	C	1.03x10^{-08}	-0.054	0.01
rs61937595	C	T	1.15x10^{-15}	0.13	0.014
rs1881046	G	T	3.39x10^{-08}	0.051	0.009
rs13195636	A	C	6.55x10^{-40}	0.211	0.013

SNP	Effect allele	Other allele	P value	β	SE
rs1915019	A	G	6.57x10^{-09}	0.057	0.009
rs16867571	A	G	2.68x10^{-10}	0.066	0.01
rs4672366	A	T	2.80x10^{-08}	0.054	0.009
rs2053079	A	G	3.01x10^{-09}	-0.06	0.011
rs2532240	C	T	2.58x10^{-11}	0.061	0.008
rs55938136	A	G	1.23x10^{-08}	0.061	0.01
rs2999392	C	T	3.05x10^{-08}	-0.052	0.01
rs11941714	G	A	3.07x10^{-08}	0.052	0.009
rs7634476	A	G	5.46x10^{-11}	-0.058	0.009
rs1892346	T	A	3.56x10^{-08}	-0.048	0.009
rs11807834	G	A	2.98x10^{-08}	-0.055	0.01
rs11587347	C	G	1.53x10^{-12}	-0.104	0.016
rs149165	T	G	3.01x10^{-08}	0.048	0.008
rs10035564	A	G	4.38x10^{-13}	-0.067	0.01
rs713692	G	A	2.67x10^{-09}	-0.057	0.01
rs73229090	C	A	4.34x10^{-13}	0.103	0.013
rs7251	C	G	8.29x10^{-12}	0.064	0.009
rs11740474	A	T	1.13x10^{-09}	-0.054	0.009
rs72802868	G	T	4.55x10^{-13}	0.069	0.009
rs12652777	T	C	1.52x10^{-08}	0.049	0.008

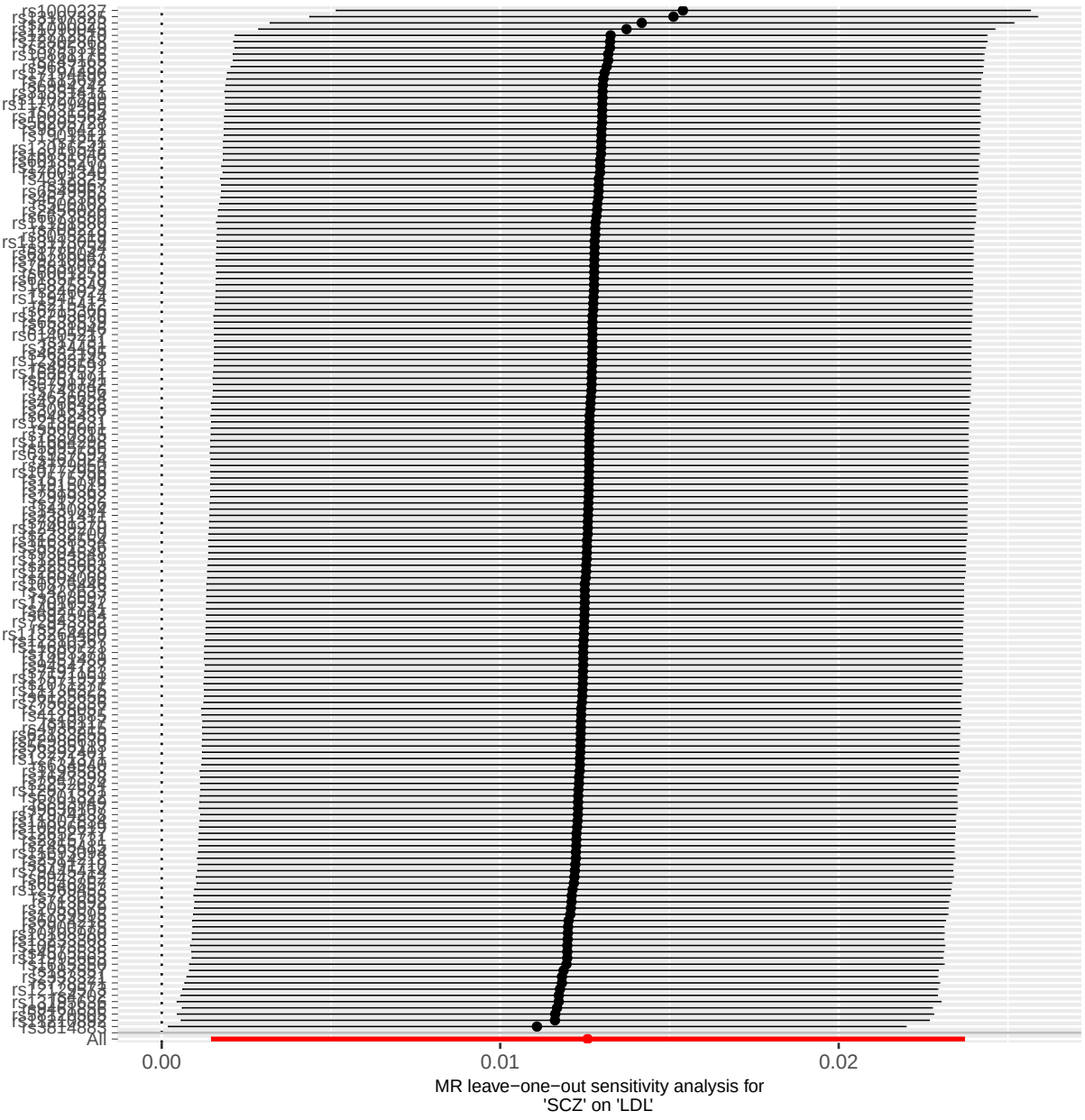

Figure B1: Leave-one-out analysis for schizophrenia on LDL. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. LDL, low-density lipoprotein; MR, Mendelian randomisation; SCZ, schizophrenia

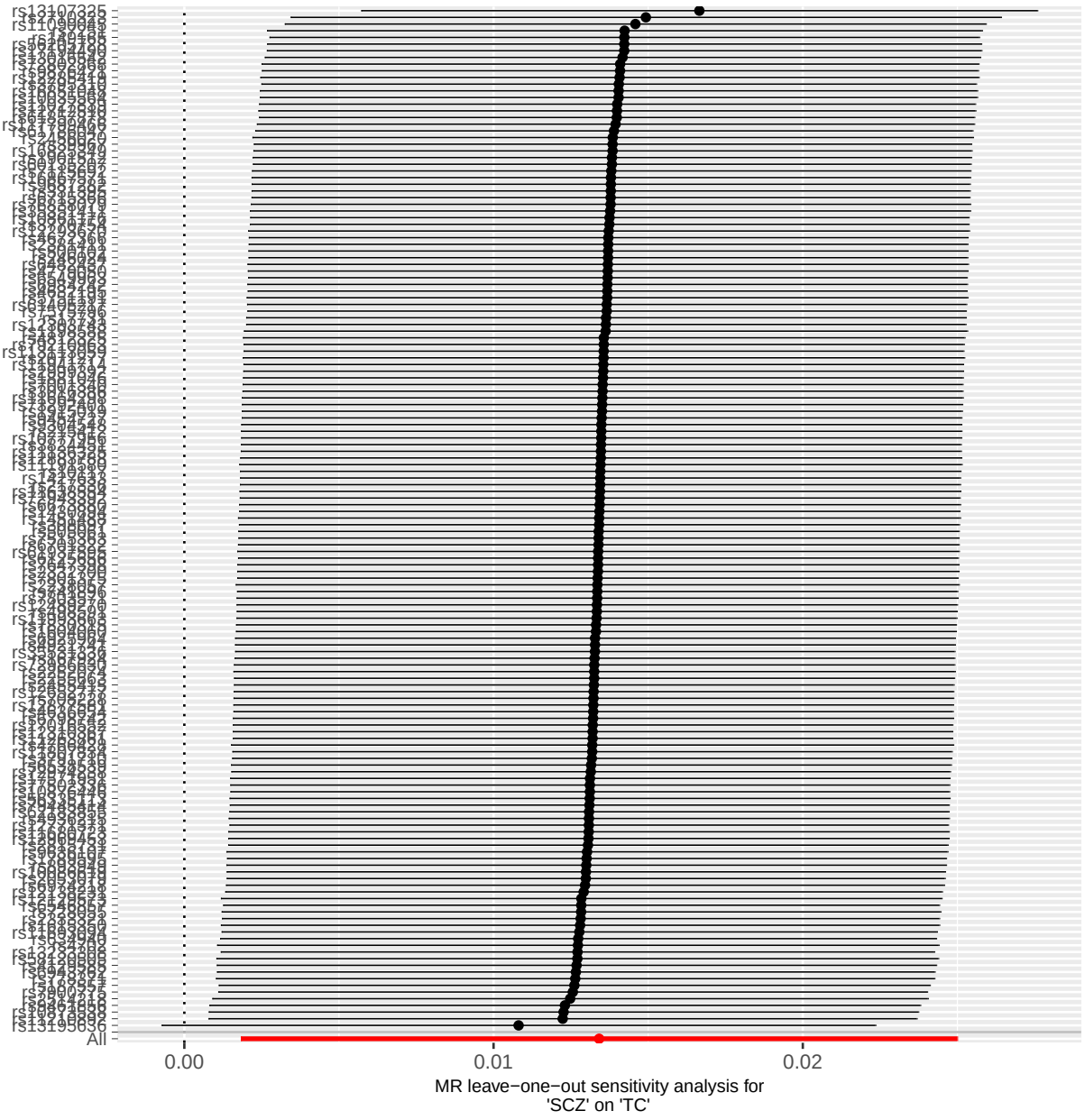

Figure B2: Leave-one-out analysis for schizophrenia on TC. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. MR, Mendelian randomisation; SCZ, schizophrenia, TC; total cholesterol

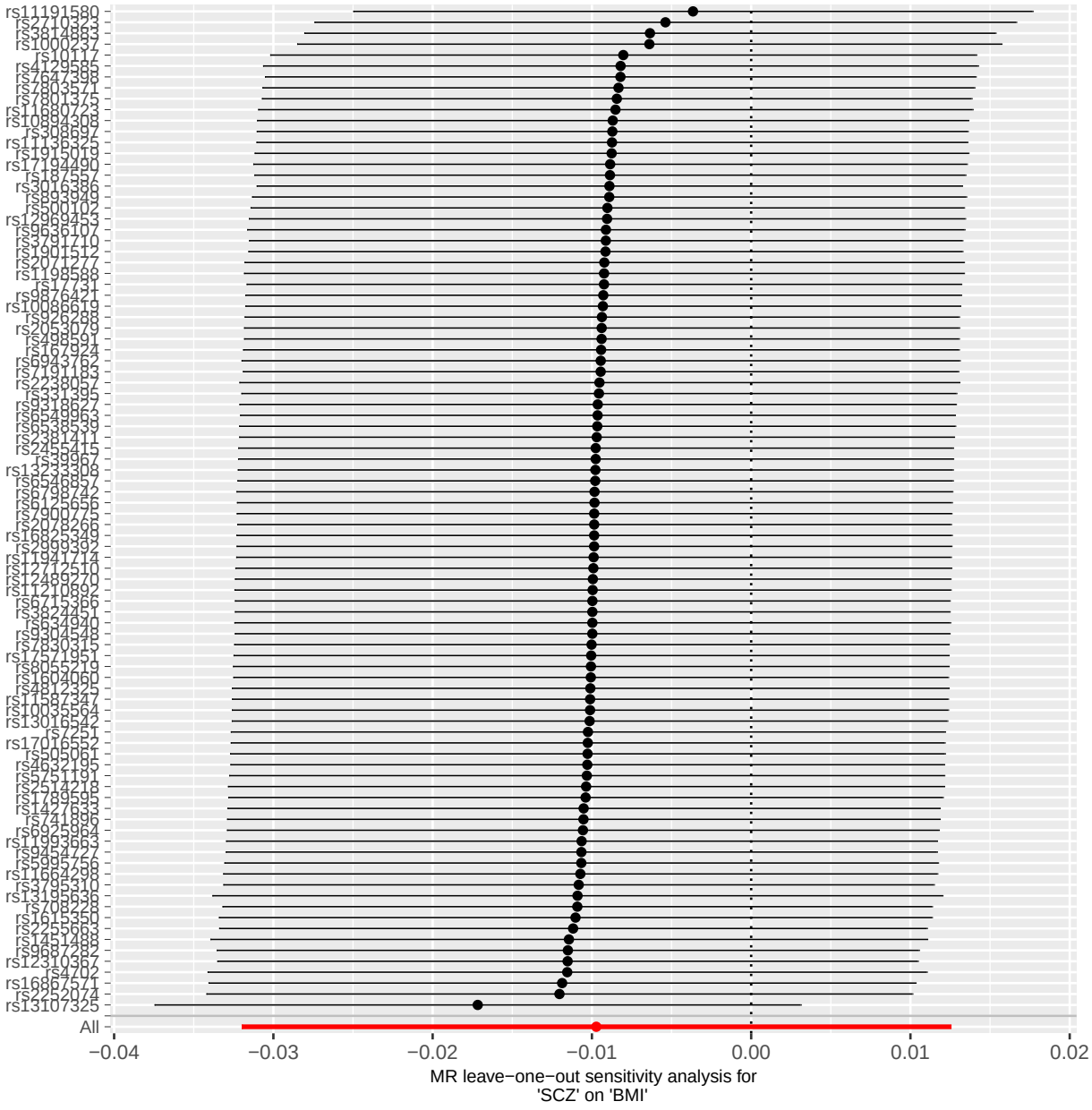

Figure B3: Leave-one-out analysis for schizophrenia on BMI. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. BMI, body mass index; MR, Mendelian randomisation; SCZ, schizophrenia

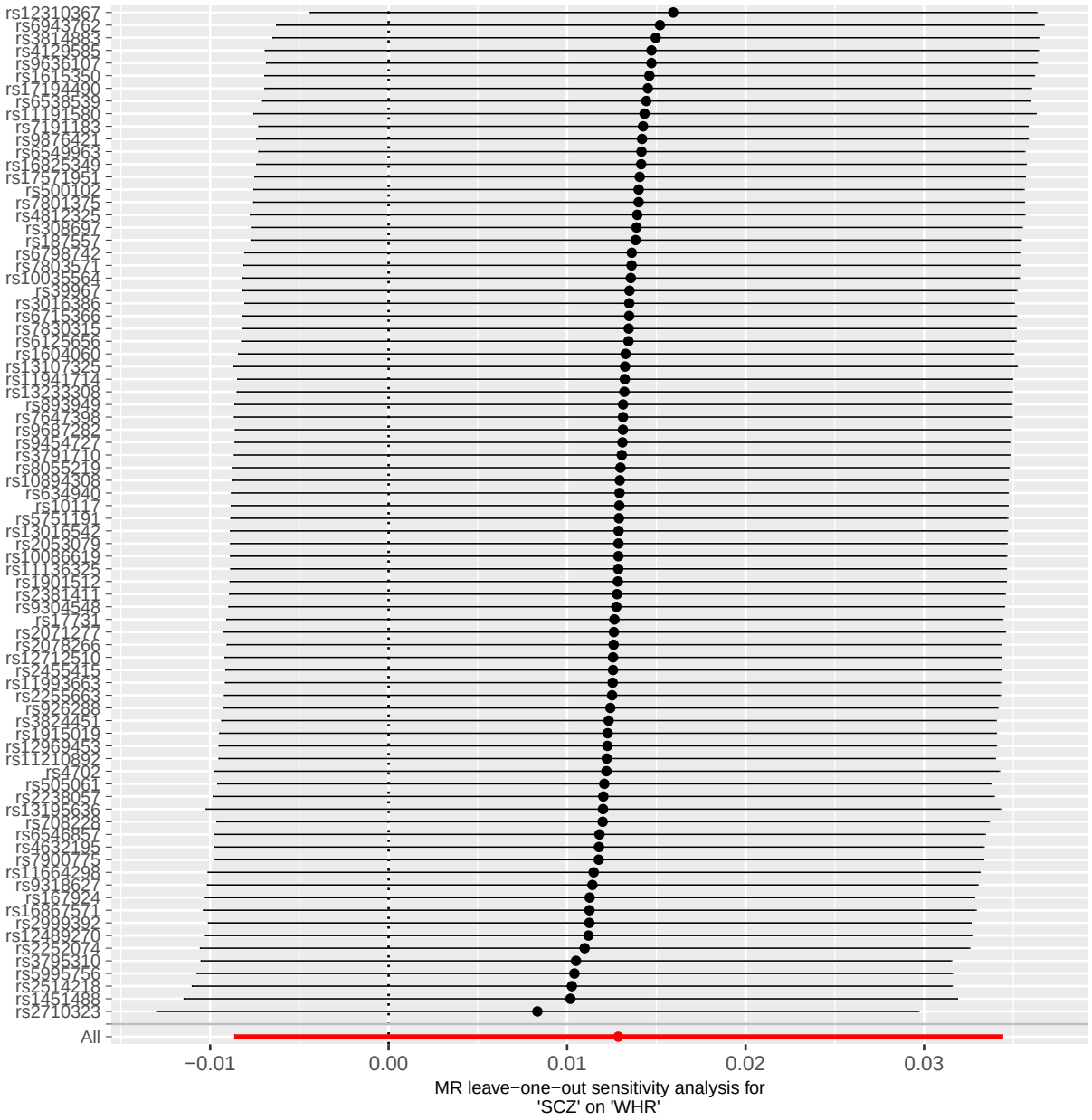

Figure B4: Leave-one-out analysis for schizophrenia on WHR. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. MR, Mendelian randomisation; SCZ, schizophrenia; WHR, waist-to-hip ratio

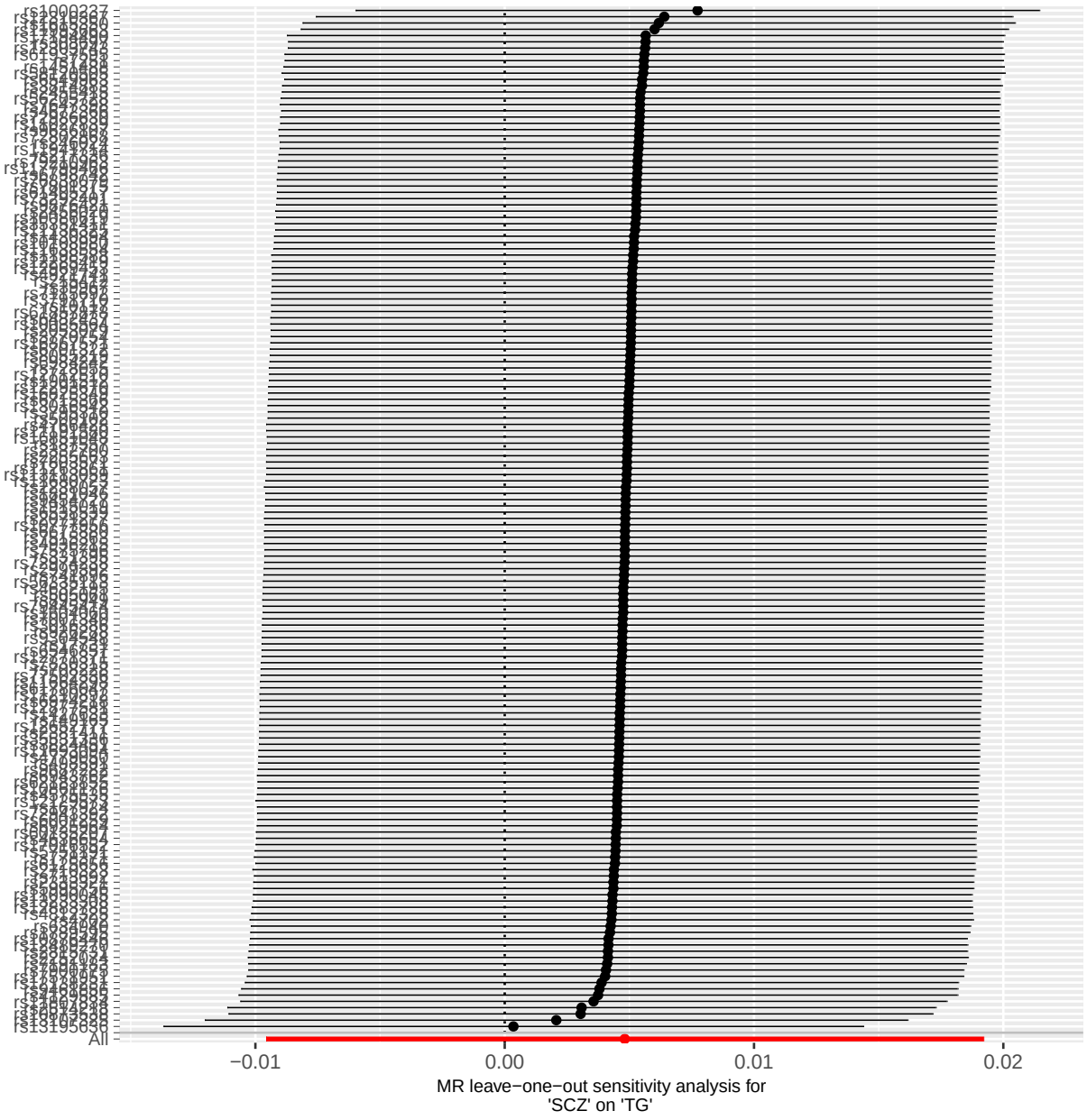

Figure B5: Leave-one-out analysis for schizophrenia on triglycerides. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. TG, triglycerides; MR, Mendelian randomisation; SCZ, schizophrenia

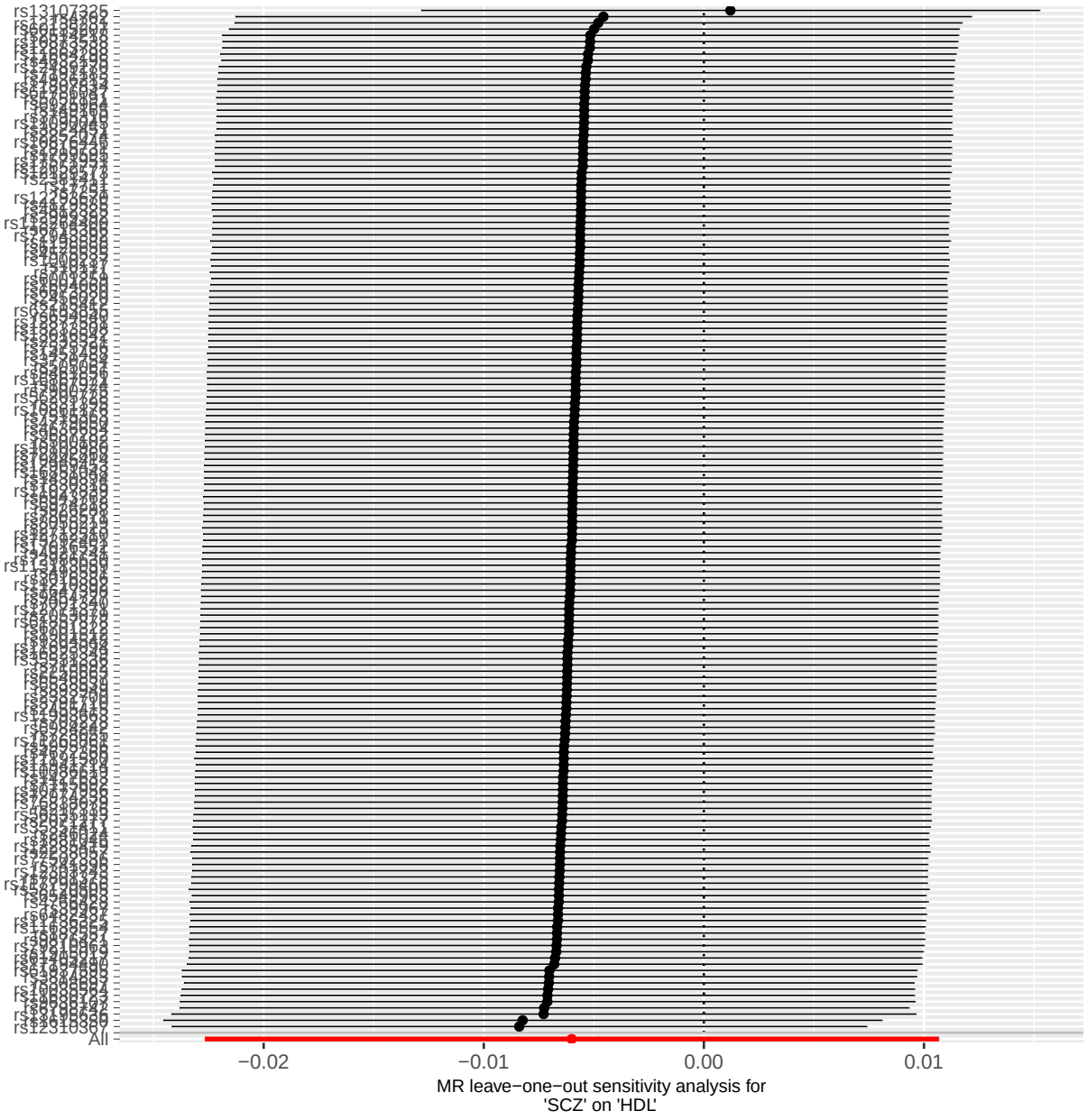

Figure B6: Leave-one-out analysis for schizophrenia on HDL. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. HDL, high-density lipoprotein; MR, Mendelian randomisation; SCZ, schizophrenia

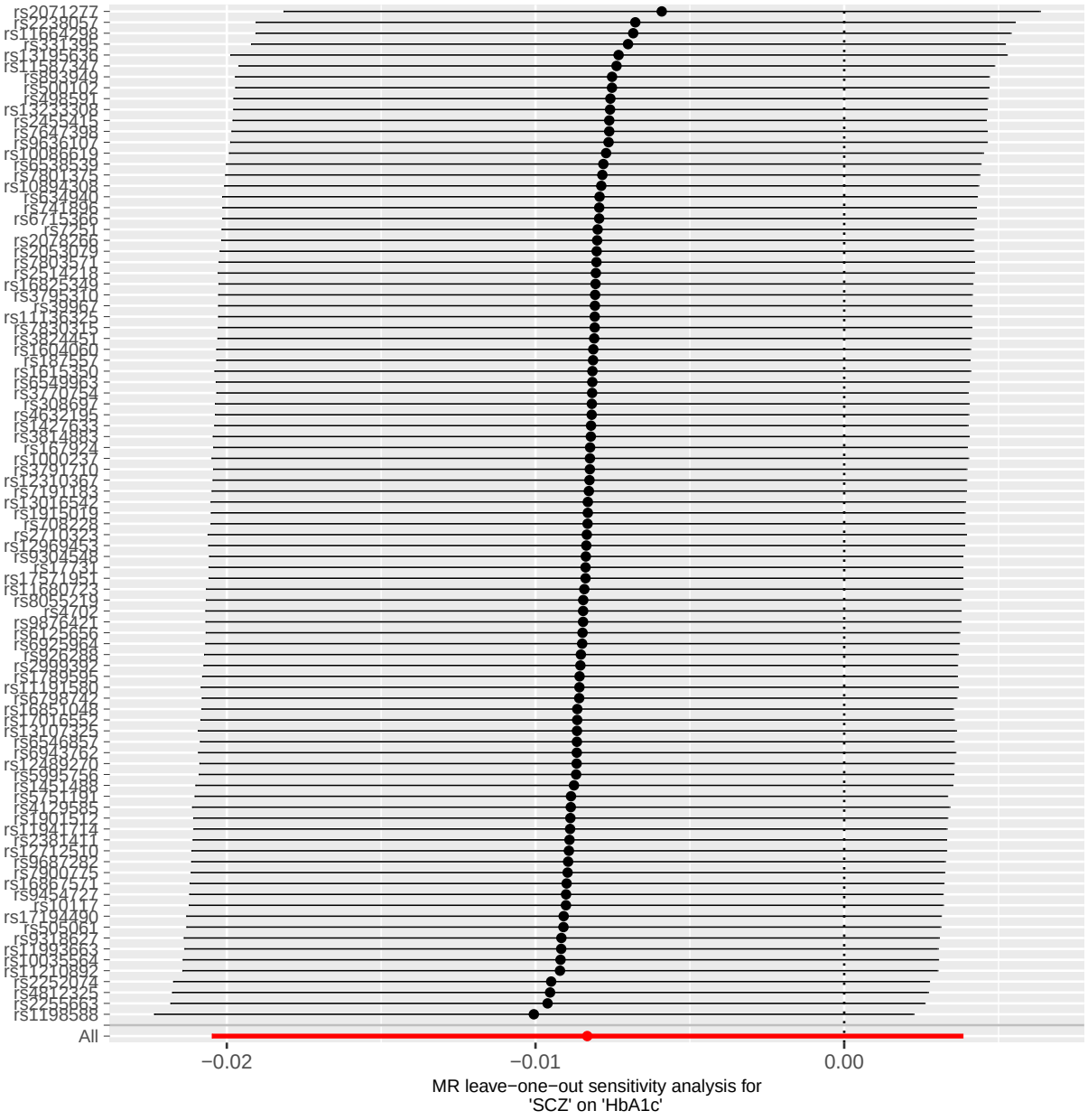

Figure B7: Leave-one-out analysis for schizophrenia on HbA1c. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. HbA1c, haemoglobin A1c; MR, Mendelian randomisation; SCZ, schizophrenia

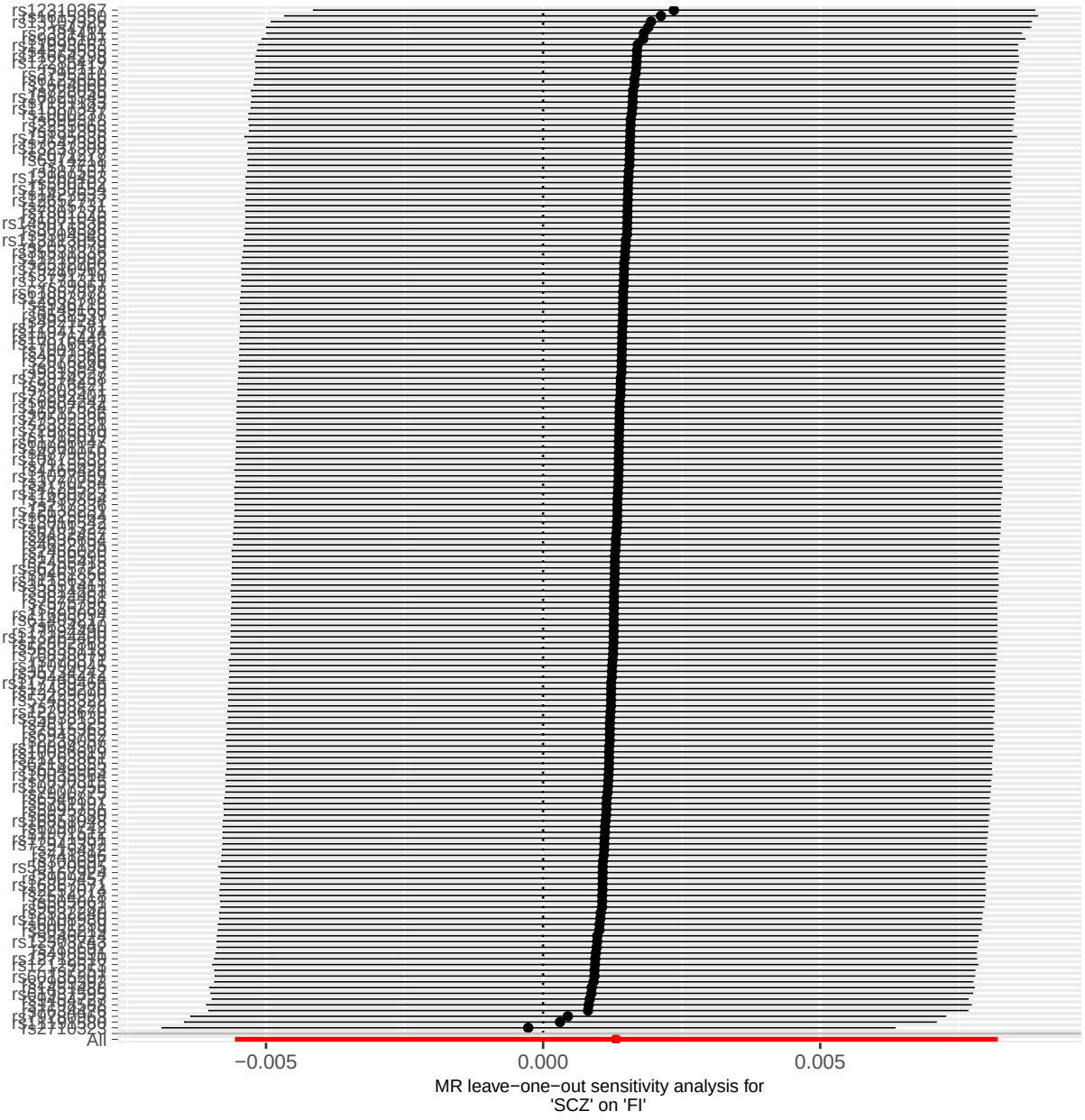

Figure B8: Leave-one-out analysis for schizophrenia on FI. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. FI, fasting insulin; MR, Mendelian randomisation; SCZ, schizophrenia

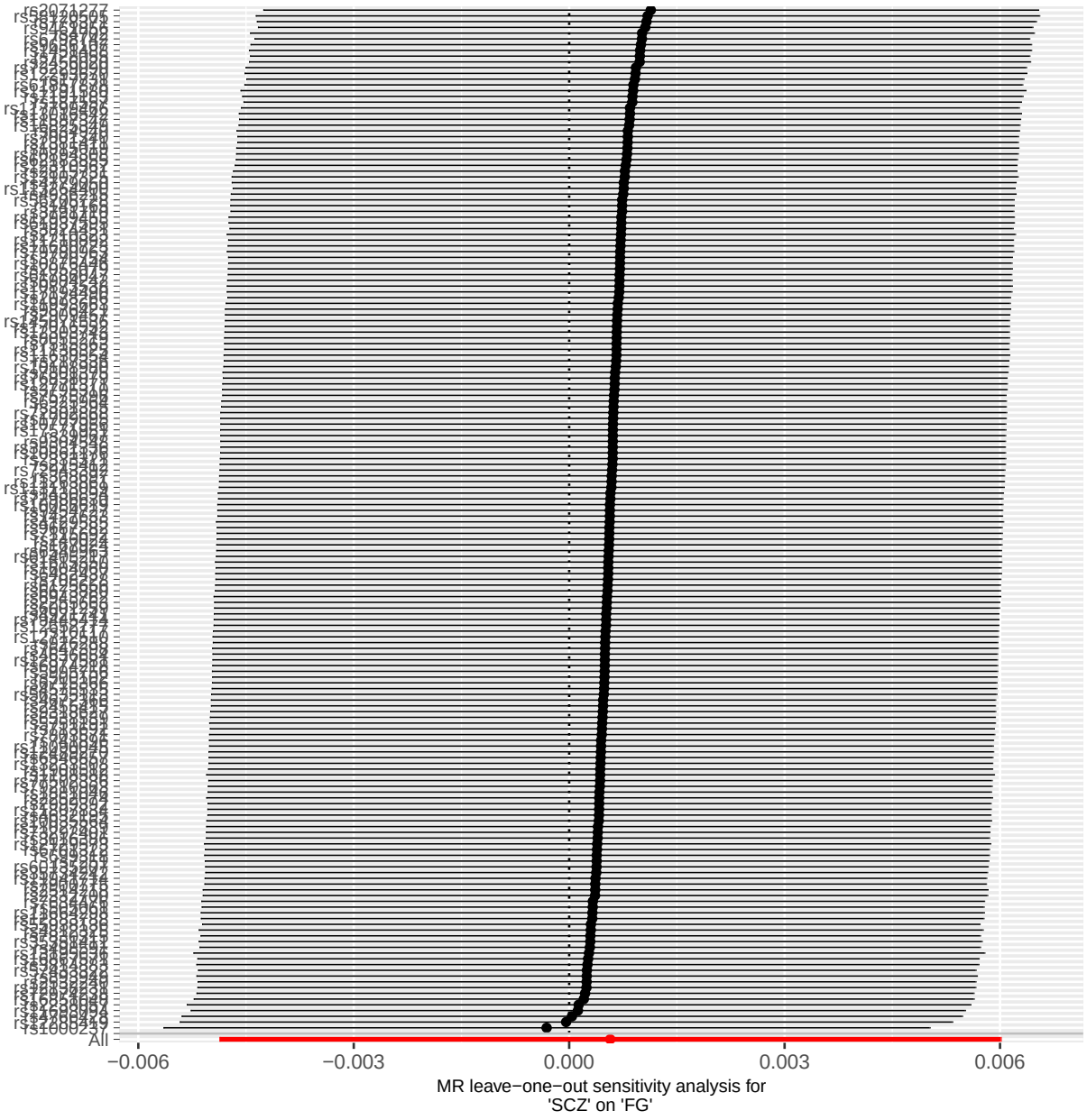

Figure B9: Leave-one-out analysis for schizophrenia on FG. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. FG, fasting glucose; MR, Mendelian randomisation; SCZ, schizophrenia

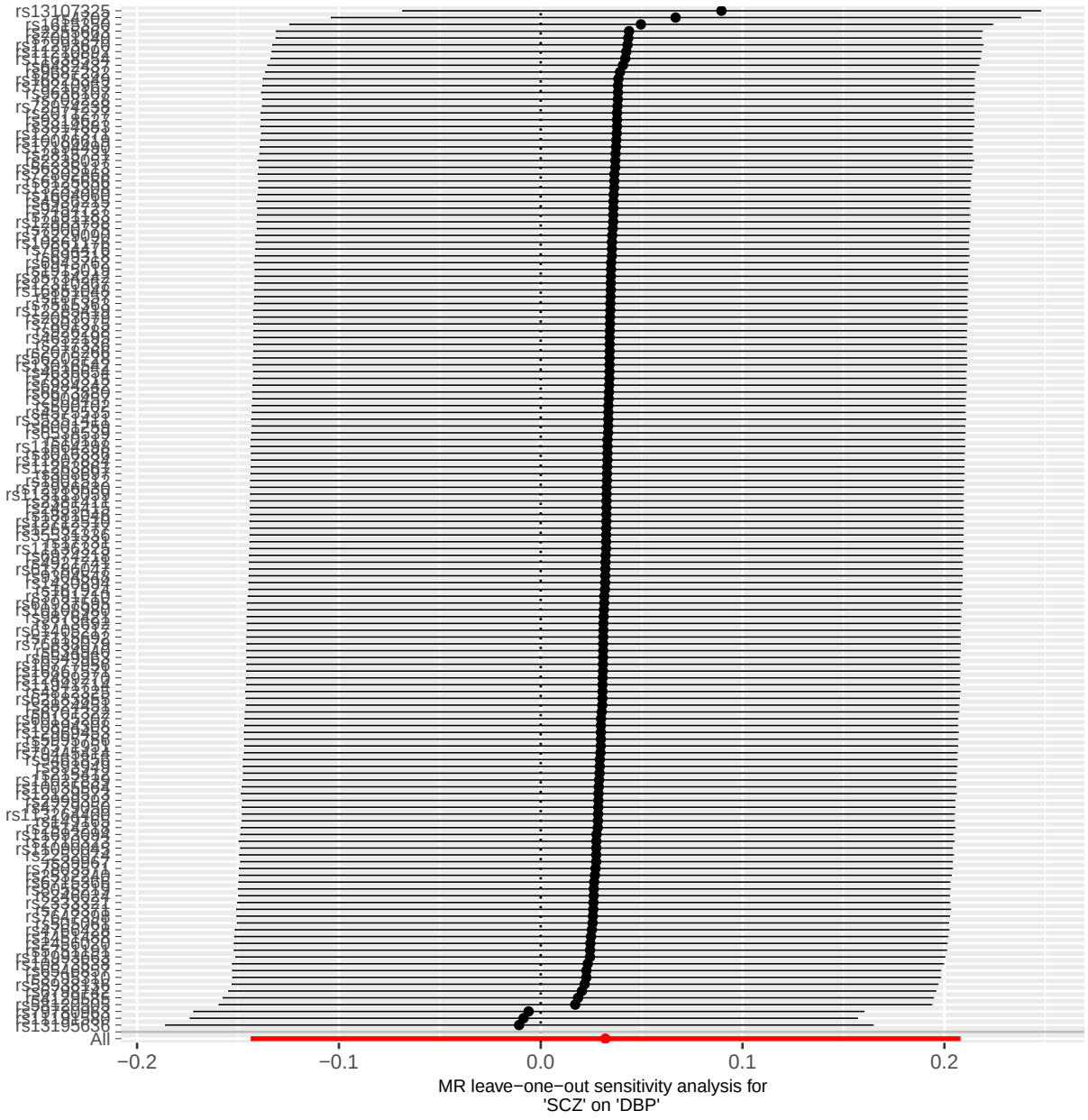

Figure B10: Leave-one-out analysis for schizophrenia on DBP. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. DBP, diastolic blood pressure; MR, Mendelian randomisation; SCZ, schizophrenia

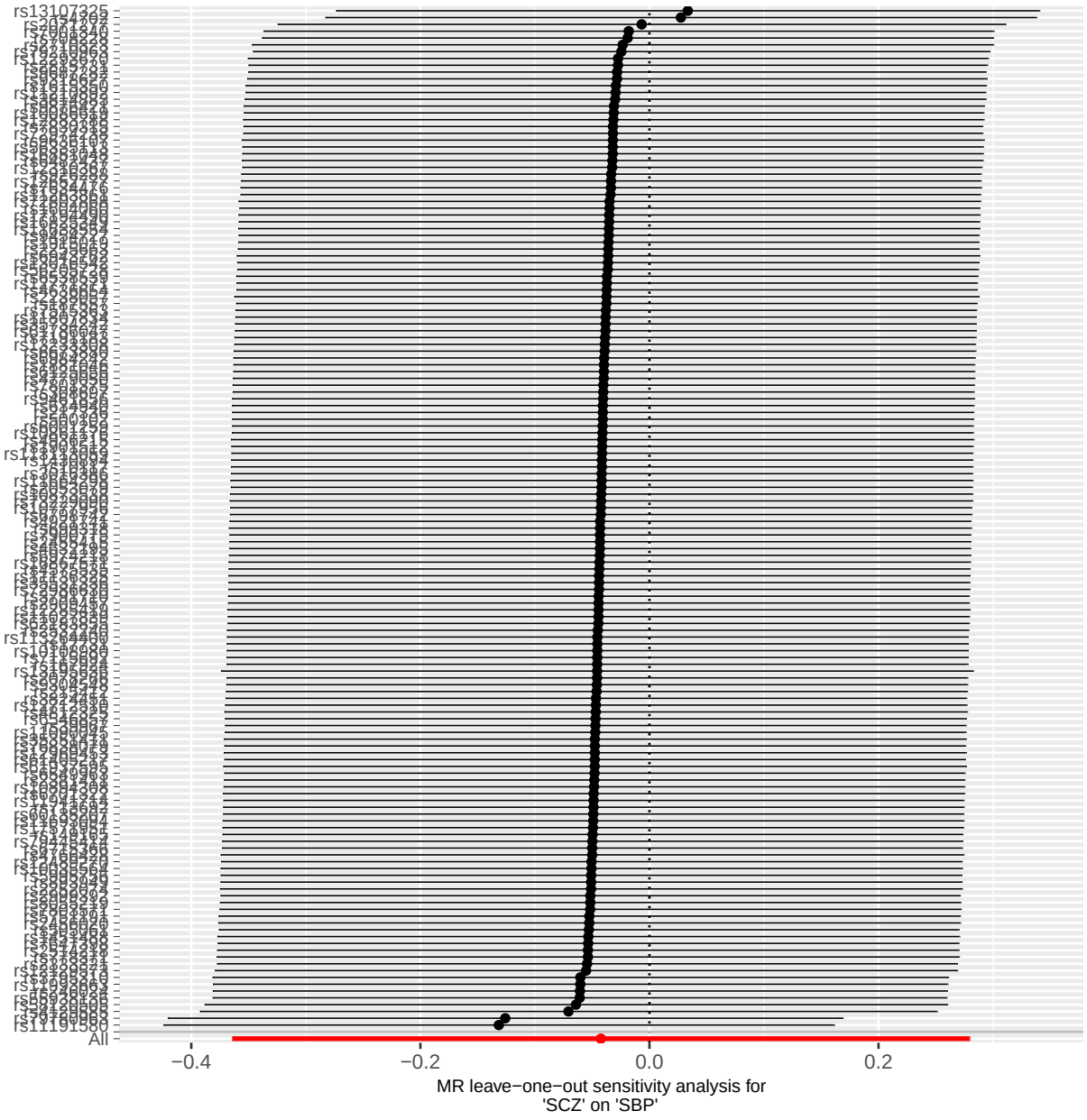

Figure B11: Leave-one-out analysis for schizophrenia on SBP. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. MR, Mendelian randomisation; SBP, systolic blood pressure; SCZ, schizophrenia

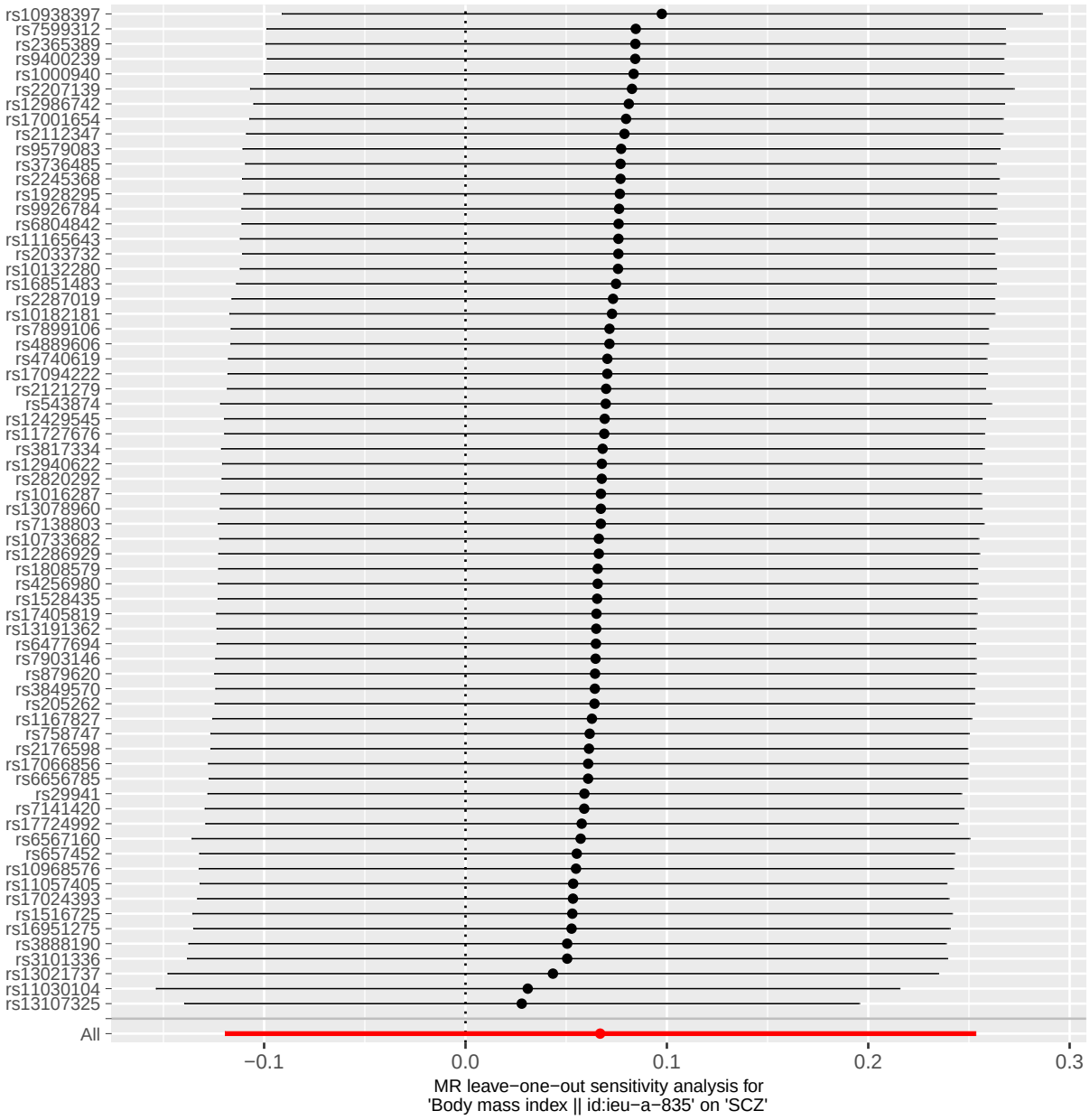

Figure B12: Leave-one-out analysis for BMI on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. BMI, body mass index; MR, Mendelian randomisation; SCZ, schizophrenia

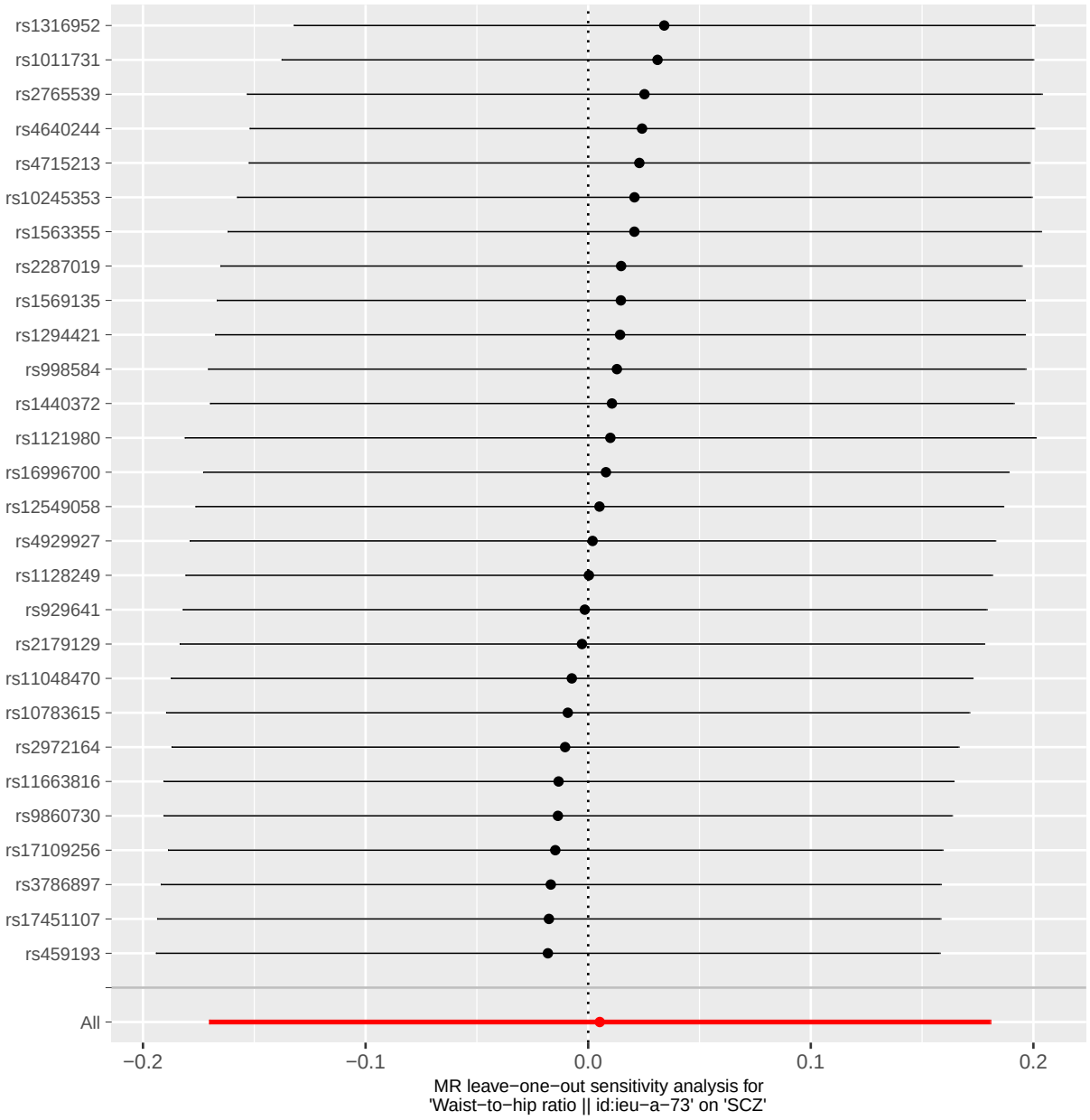

Figure B13: Leave-one-out analysis for WHR on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. MR, Mendelian randomisation; SCZ, schizophrenia; WHR, waist-to-hip ratio

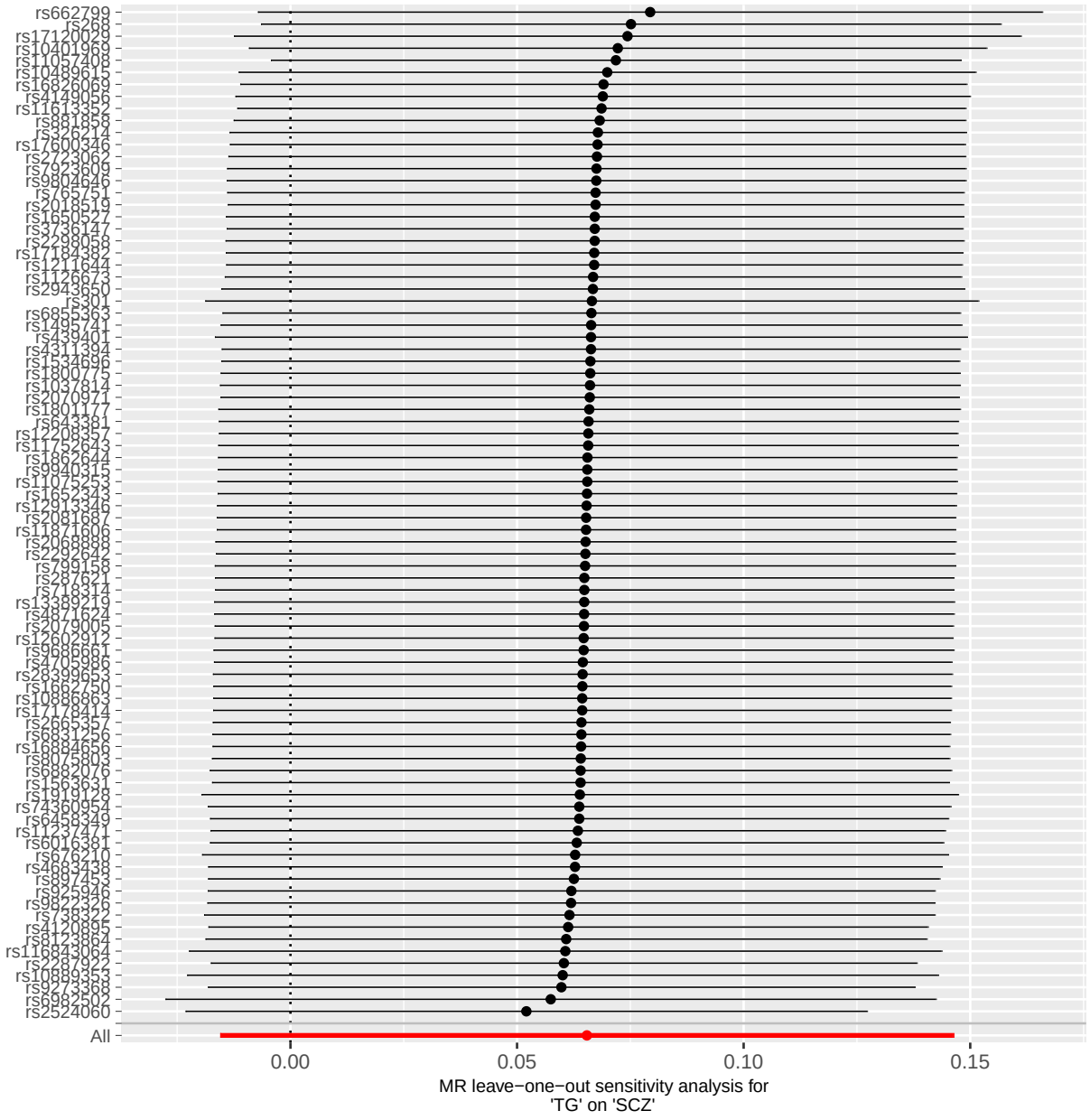

Figure B14: Leave-one-out analysis for triglycerides on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. TG, triglycerides; MR, Mendelian randomisation; SCZ, schizophrenia

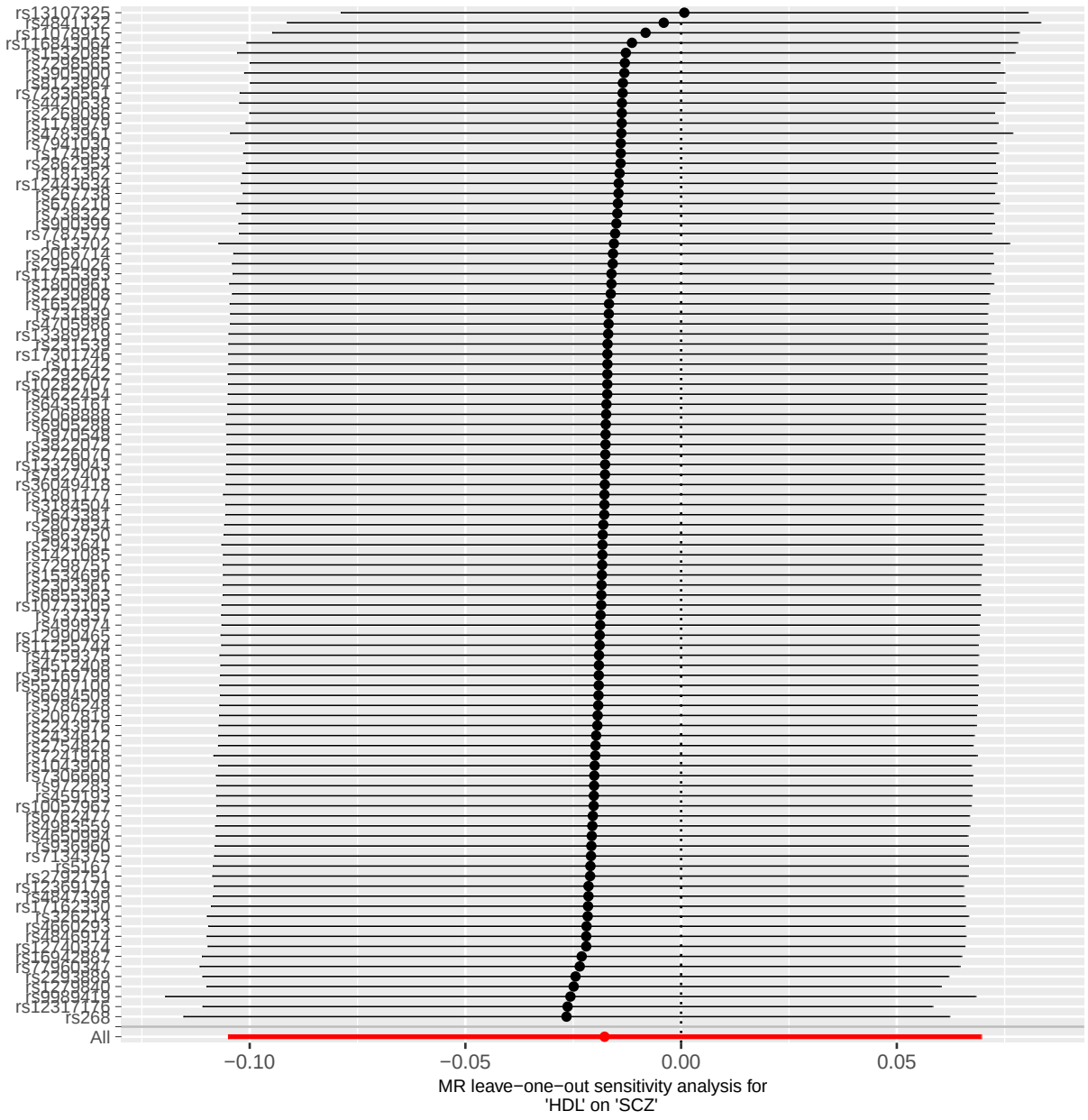

Figure B15: Leave-one-out analysis for HDL on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. HDL, high-density lipoprotein; MR, Mendelian randomisation; SCZ, schizophrenia

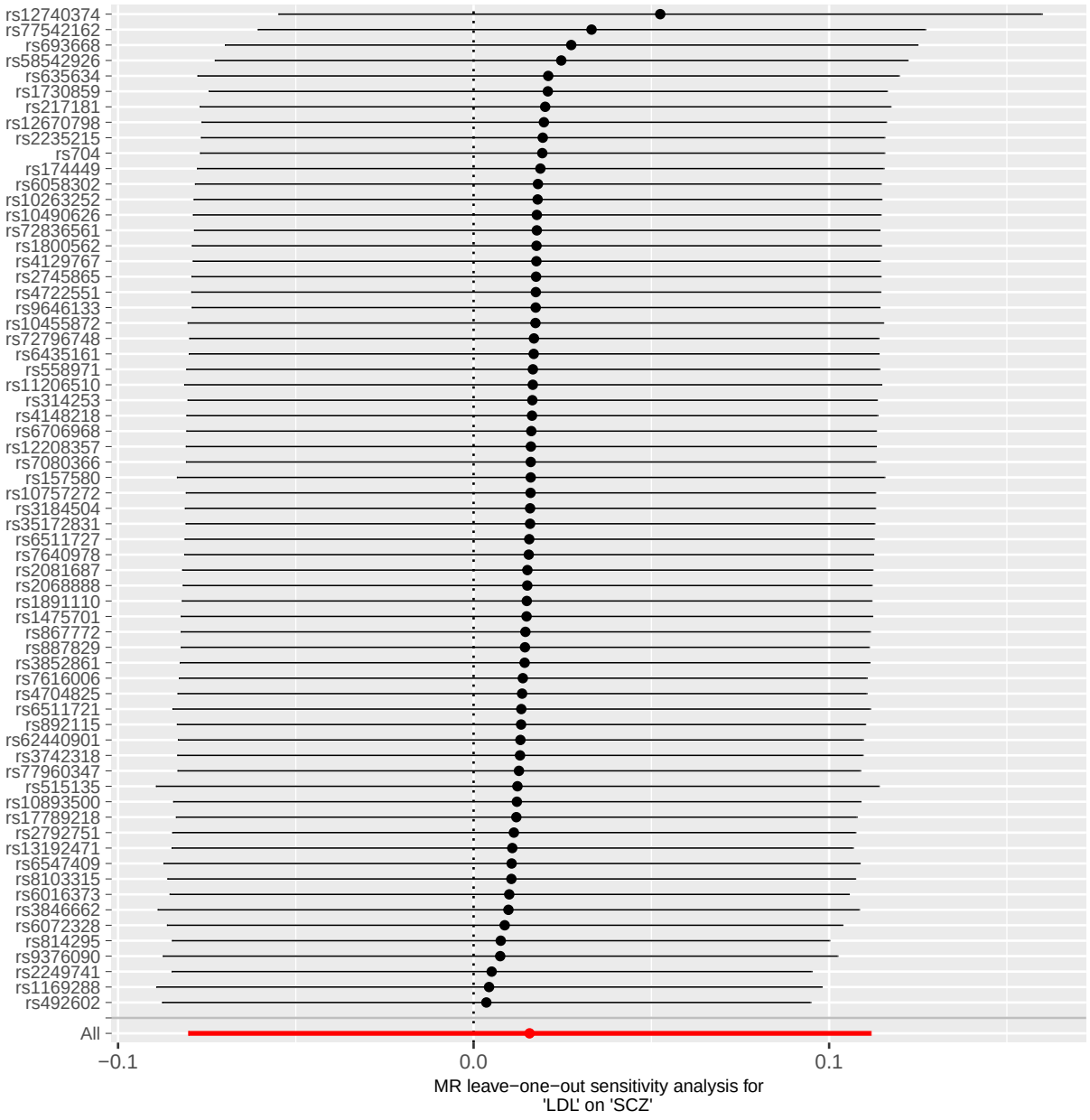

Figure B16: Leave-one-out analysis for LDL on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. LDL, low-density lipoprotein; MR, Mendelian randomisation; SCZ, schizophrenia

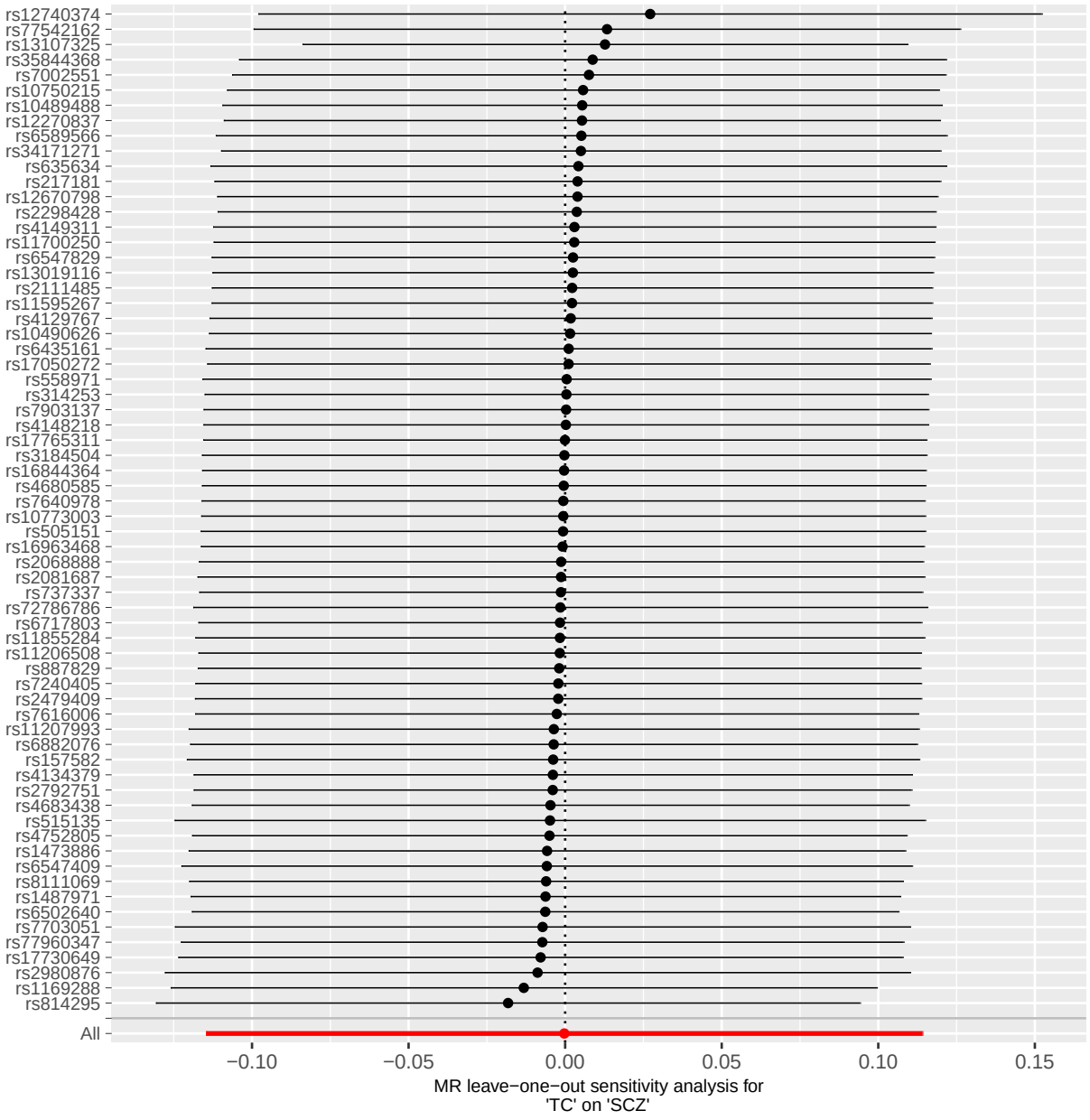

Figure B17: Leave-one-out analysis for TC on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. MR, Mendelian randomisation; SCZ, schizophrenia, TC; total cholesterol

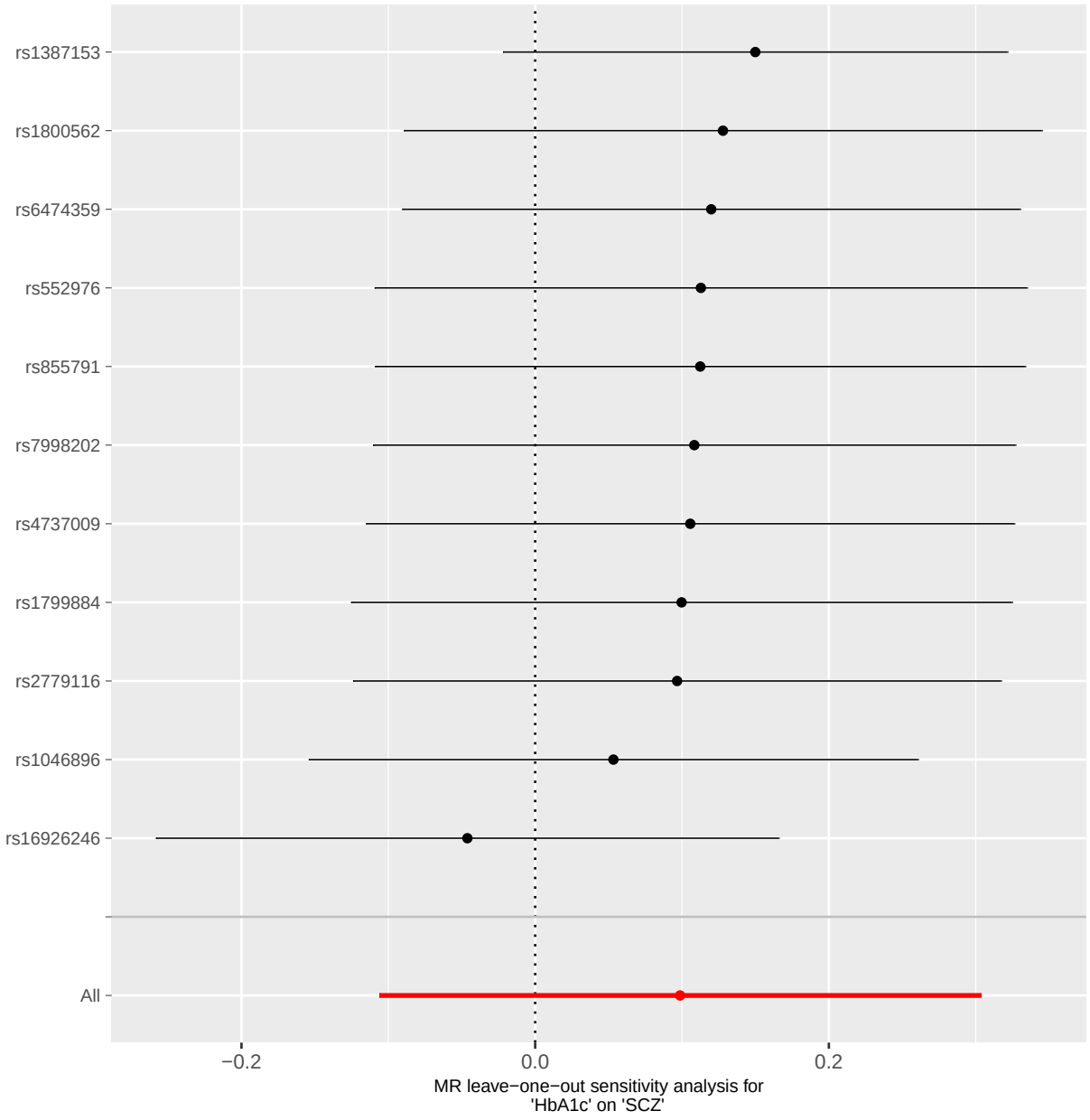

Figure B18: Leave-one-out analysis for HbA1c on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. HbA1c, haemoglobin A1c; MR, Mendelian randomisation; SCZ, schizophrenia

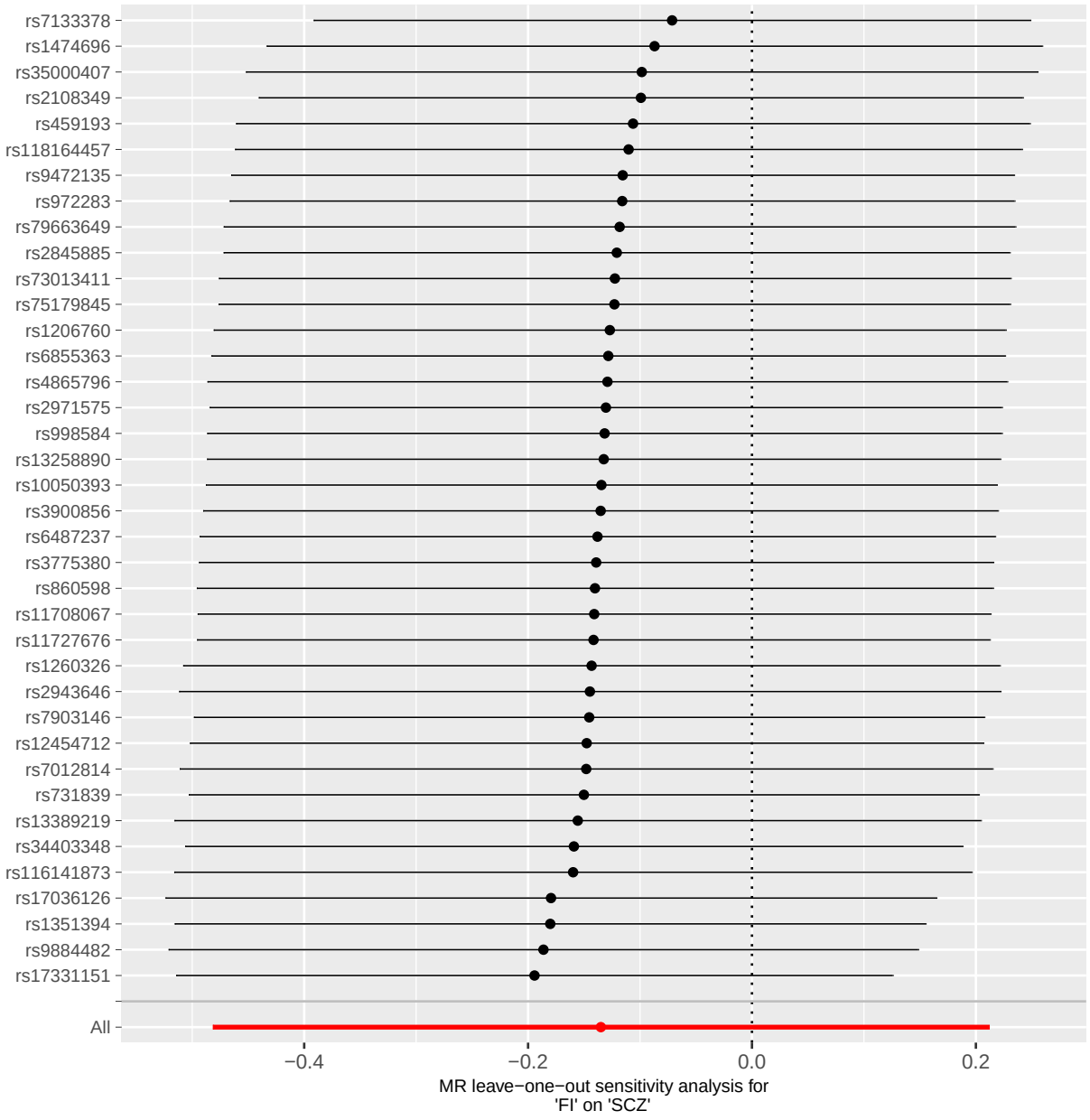

Figure B19: Leave-one-out analysis for FI on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. FI, fasting insulin; MR, Mendelian randomisation; SCZ, schizophrenia

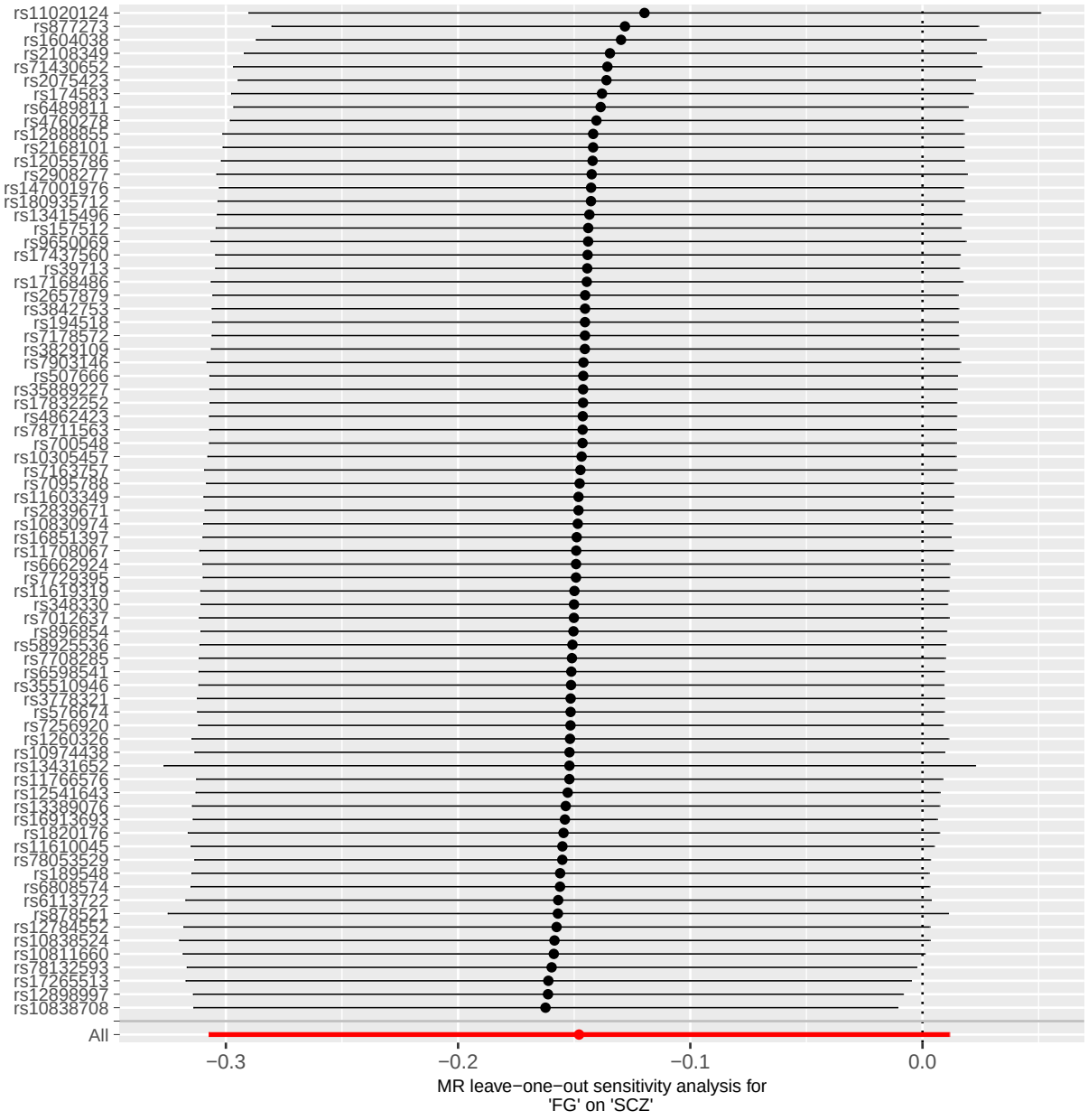

Figure B20: Leave-one-out analysis for FG on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. FG, fasting glucose; MR, Mendelian randomisation; SCZ, schizophrenia

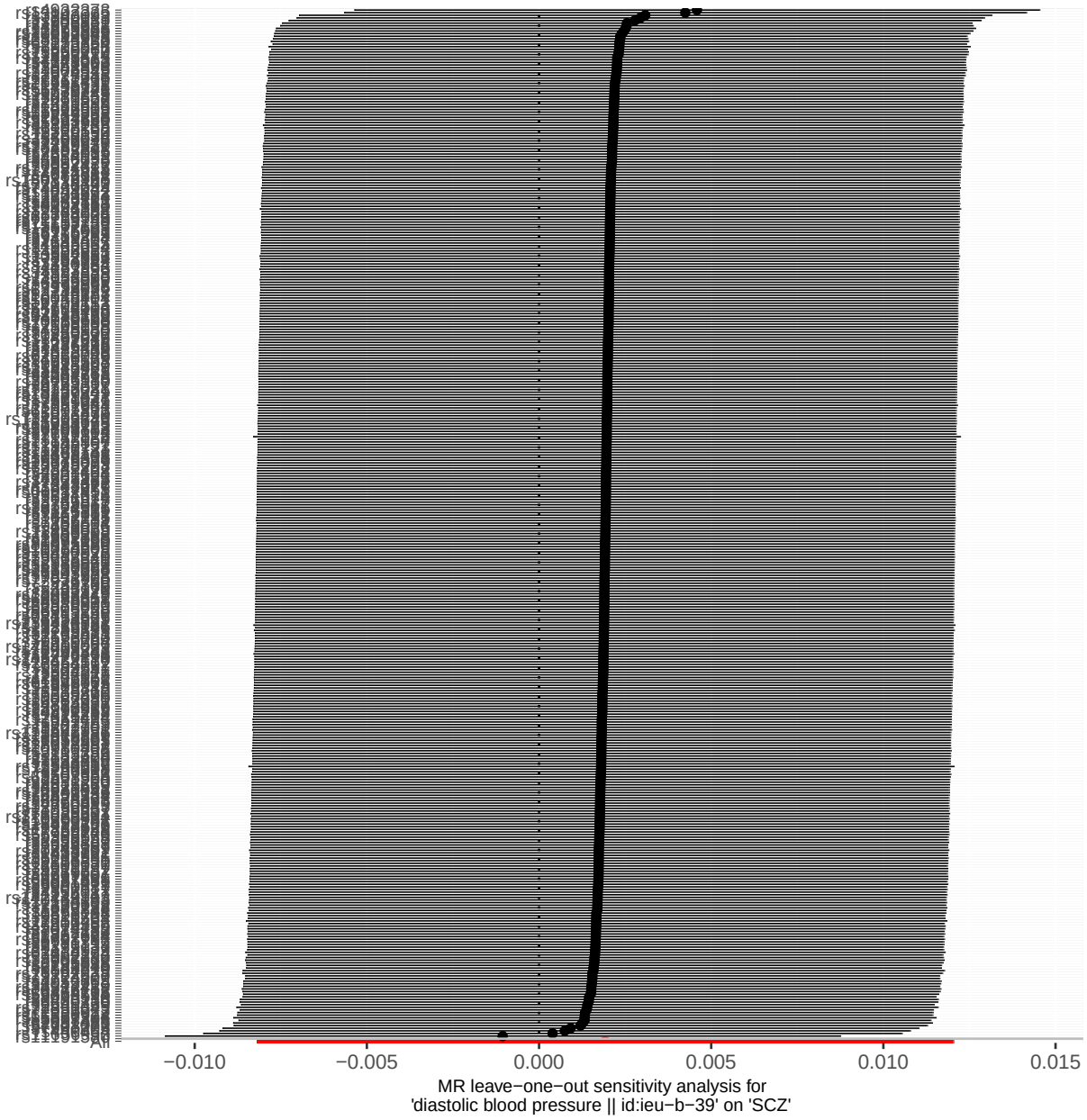

Figure B21: Leave-one-out analysis for DBP on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. DBP, diastolic blood pressure; MR, Mendelian randomisation; SCZ, schizophrenia

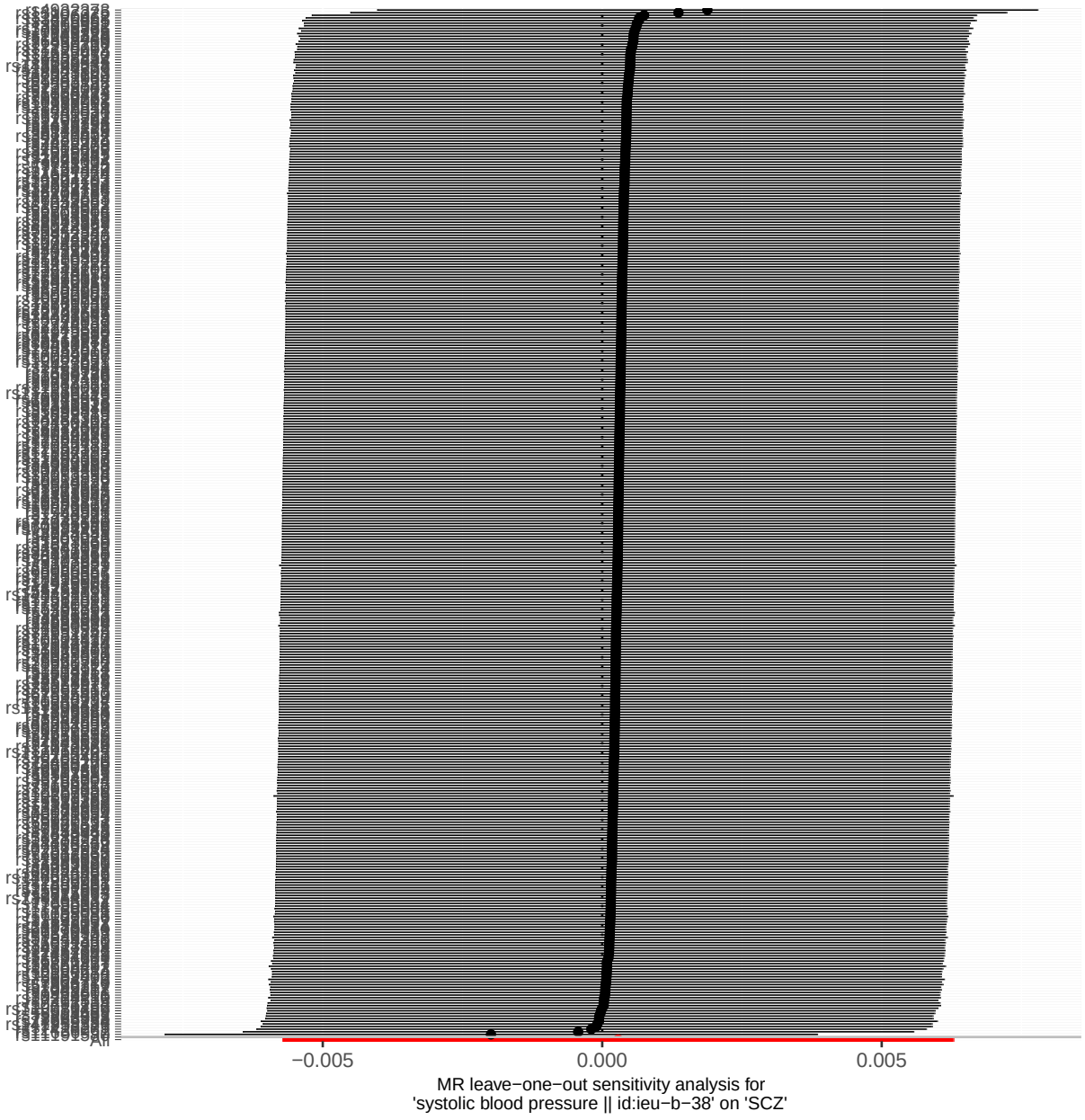

Figure B22: Leave-one-out analysis for SBP on schizophrenia. Circles represent the IVW estimate for schizophrenia on the cardiometabolic outcome and horizontal bars indicate 95% confidence intervals. MR, Mendelian randomisation; SBP, systolic blood pressure; SCZ, schizophrenia

Appendix C

Appendices for chapter 4

Pharmacogenetics: Genetics and environment in Mental Health Study (GEMS)
Questionnaire
Case Report Form (CRF) V1.7

We kindly ask that you do not leave any spaces blank.
If the answer if unknown please mark with NOT KNOWN and if the patient does not wish to disclose please mark with WITHHELD

Key questions: Participant:

Subject ID – **please attach study label here:**	Date of birth (day/month/year)	Age:
First name:		
Last name (family name):	Middle name if applicable:	

Key questions: Researcher:

Interviewer name:	Interviewer/team email:
Date of interview:	NHS Trust:
Clinician (that requested the genetic report):	
Location / service where participant was recruited:	
Reason for referral:	☐ Met criteria ☐ Side effects ☐ Lack of treatment response ☐ Other: _____

Participant contact details:

Email: Mobile phone: Home phone:	Home address:
Do we have a signed consent form?	☐ Yes ☐ No

Figure C1: Case report form used to collect data on patients' use of healthcare services at the baseline assessment. Continued on the next pages.

Health information:

NHS number:		GP's name (if known):	
GP surgery/practice name **in capitals**:			
Diagnoses **(mental health)** **Please provide F code if possible**	Age of diagnosis (mental health)	Diagnoses **(any other conditions):**	Age of diagnosis (any other conditions)

Pregnant or breast feeding?

☐ No	☐ Pregnant	☐ Breast feeding	☐ Not applicable

Medications: **Please list all medications you currently take (Include drugs for mental and physical health)**

Medication name **Please use capitals**	BNF section or medication group (see page 8)	Dose	Frequency e.g., 1 X daily	Tablet/Injection/Inhaler/Capsule

Medication name **Please use capitals**	BNF section or medication group (see page 8)	Dose	Frequency e.g., 1 X daily	Tablet/Injection/Inhaler/Capsule

Smoking

Q1. Do you currently smoke (anything that contains tobacco)?

☐ **YES** → **Go to Q3**

☐ **NO** → **Go to Q2**

Q2. Have you given up smoking in the last month?

☐ **YES** → **Go to Q3**

☐ **NO** → **Move to next section (body measurements)**

Q3. On average, how many do you currently / did you smoke a day?

_____ cigarettes / roll ups

Q4. Roughly, how many years have / had you been smoking?

_____ years

Body measurements:

If height or weight is unknown at the time of assessment please refer to hospital notes for latest measurements.

Height (inches or centimetres):	Weight (kilograms or pounds):

Demographic questions:

Sex (**this question asks for sex at birth, i.e., genetic sex. It is not a question about gender identity**)		☐ Female	☐ Male		☐ Prefer not to say
Marital status	☐ Single	☐ Married	☐ Separated or divorced	☐ Widow	☐ Not known
City/village/town of birth					
Country of birth / growing up					
Which is your first language	☐ English ☐ Other languages please list:				
Number of years of schooling / education					
Highest level of education	☐ Primary education ☐ Secondary education ☐ Tertiary (apprenticeships/vocational qualifications) ☐ Further education (university) ☐ Postgraduate ☐ Not known				
Where do you usually live?	<u>Domestic/family</u>	☐ Owner occupied flat or house ☐ Privately rented flat or house ☐ Rented from local authority/municipality or housing association/co-operative ☐ Student halls			
	<u>Community (non-hospital)</u>	☐ Overnight facility, 24-hour staffed ☐ Overnight facility, staffed (not 24-hour) ☐ Overnight facility, unstaffed always			
	<u>Hospital</u>	☐ Acute psychiatric ward ☐ Rehabilitation psychiatric ward ☐ Long-stay psychiatric ward ☐ General medical ward			
		☐ Homeless/roofless ☐ Other (please specify):			

Race and ethnicity:

Asian or Asian British	☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Chinese ☐ Any other Asian background
Black, Black British, Caribbean, or African	☐ Caribbean ☐ African ☐ Any other Black, Black British, Caribbean, or African background
Mixed or multiple ethnic groups	☐ White and Black Caribbean ☐ White and Black African ☐ White and Asian ☐ Any other Mixed or multiple ethnic background
White	☐ English, Welsh, Scottish, Northern Irish or British ☐ Irish ☐ Gypsy or Irish Traveller ☐ Roma ☐ Any other White background
Any other ethnic group	☐ Arab ☐ Any other ethnic group

Employment and income:

What is your employment status?	☐ Paid or self-employment ☐ Voluntary employment ☐ Sheltered employment ☐ Unemployed ☐ Student ☐ Housewife/husband ☐ Retired ☐ Other (please specify):	If employed, state occupation:	☐ Manager/administrator ☐ Professional (e.g health, teaching, legal) ☐ Associate professional (e.g technical, nursing) ☐ Clerical worker/secretary ☐ Skilled labourer (e.g building, electrical) ☐ Services/sales (e.g retail) ☐ Factory worker ☐ Other (please specify):
If unemployed, state the number of weeks unemployed within the **last 3 months:**			
Do you receive any state benefits?		☐ Yes	☐ No
If yes, what benefits are received?		<u>Unemployment/ income support</u> <u>Sickness/disability</u> <u>Housing</u> <u>Other</u>	☐ Income support ☐ Jobseeker's allowance ☐ PIP. ☐ Statutory sick pay ☐ Housing benefit ☐ State pension ☐ Child benefit
Please list any other benefits received.			
How many days have you been absent from work owing to illness within the **last 3 months**?			

Care Service Receipt:

We kindly ask that you do not leave any spaces blank. **If the answer if unknown please mark with NOT KNOWN or 0.**

Have you been admitted to hospital?
Please list any use of inpatient hospital services over the **last 3 months**

Service	Number of admissions	Total number of inpatient days
Acute psychiatric ward		
Psychiatric rehabilitation ward		
Long-stay ward		
Crisis centre or crisis house		
General medical ward or inpatient service for your physical health		
Other (please specify): _____		

Please list any use of outpatient services over the last 3 months:

Service	Number of appointments or day attendances
Psychiatric outpatient visit	
Outpatient visit for physical health (cardiology, respiratory physician, diabetes…)	
Day hospital	
Other (please specify): _____	

Please list any other primary and community care contacts over the last 3 months:

Service	Number of visits / appointments in the last 3 months
Psychiatrist	
Psychologist	
GP Primary care physician	
Crisis Resolution Team or Home Treatment Team	
District nurse	
Community psychiatric nurse/case manager	
Social worker	
Occupational therapist	
Home help/care worker	
Other (please specify): _____	

How many times have you attended an accident and emergency (A&E) in the last 3 months?

111 Telephone		Number of calls
Crisis Resolution Team (mental health)		Number of calls
A&E for physical health		Attendances
A&E / place of safety for mental health		Attendances
Ambulance		Contacts

BNF codes for medications

1. Gastro-Intestinal System
2. Cardiovascular System
3. Respiratory System
4. Central Nervous System
   - 4.1 Hypnotics and anxiolytics
   - 4.2 Drugs used in psychoses and related disorders
   - 4.3 Antidepressant drugs
   - 4.4 CNS stimulants and drugs used for ADHD
   - 4.5 Drugs used in the treatment of obesity
   - 4.6 Drugs used in nausea and vertigo
   - 4.7 Analgesics
   - 4.8 Antiepileptic drugs
   - 4.9 Drugs used in parkinsonism and related disorders
   - 4.10 Drugs used in substance dependence
   - 4.11 Drugs for dementia
5. Infections
6. Endocrine System
7. Obstetrics, Gynaecology and Urinary-Tract Disorders
8. Malignant Disease and Immunosuppression
9. Nutrition and Blood
10. Musculoskeletal and Joint Diseases
11. Eye
12. Ear, Nose and Oropharynx
13. Skin
14. Immunological Products and Vaccines

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)
The following scale is intended to be self-administered. Please indicate how much you have experienced each of the following symptoms in the **last month by ticking a box for each of the 53 items**.

	Not at all	Very little	A little	Quite a lot	Very much
1. Rash					
2. Difficulty staying awake during the day					
3. Runny nose					
4. Increased dreaming					
5. Headaches					
6. Dry mouth					
7. Swollen or tender chest					
8. Chilblains					
9. Difficulty in concentrating					
10. Constipation					
11. Hair-loss					
12. Urine darker than usual					
13. Period problems					
14. Tension					
15. Dizziness					
16. Feeling sick					
17. Increased sex drive					
18. Tiredness					
19. Muscle stiffness					
20. Palpitations					
21. Difficulty in remembering things					

	Not at all	Very little	A little	Quite a lot	Very much
22. Losing weight					
23. Lack of emotions					
24. Difficulty in achieving climax					
25. Weak fingernails					
26. Depression					
27. Increased sweating					
28. Mouth ulcers					
29. Slowing of movements					
30. Greasy skin					
31. Sleeping too much					
32. Difficulty passing water					
33. Flushing of face					
34. Muscle spasms					
35. Sensitivity to sun					
36. Diarrhoea					
37. Over-wet or drooling mouth					
38. Blurred vision					
39. Putting on weight					
40. Restlessness					
41. Difficulty getting to sleep					
42. Neck muscles aching					
43. Shakiness					
44. Pins and needles					
45. Painful joints					

	Not at all	Very little	A little	Quite a lot	Very Much
46. Reduced sex drive					
47. New or unusual skin marks					
48. Parts of body moving of their own accord e.g. foot moving up and down					
49. Itchy skin					
50. Periods less frequent					
51. Passing a lot of water					
52. Discharge from Nipples					
53. Seizures					
Other:					
Other:					
Other:					
Other:					
Other:					

EQ-5D-5L

Under each heading, please tick the ONE box that describes **your health TODAY**.

Mobility
I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

Self-care
I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual activities (e.g work, study, housework, family, or leisure activities)
I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

Pain/discomfort
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/depression
I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

We would like to know how good or bad your health is TODAY using a scale numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.

Please write a number to indicate how **your health is TODAY**.

YOUR HEALTH TODAY = _____

The Maudsley Environmental Risk Score for Psychosis

IGNORE: reminder to the UCL team to include ethnic minority when generating ERS.

PLEASE DO NOT LEAVE ANY ANSWERS BLANK – MARK WITH NK IF THE ANSWER IS NOT KNOWN.

Urbanicity (at your birth)

NOTE: high urbanicity would refer to living in a densely populated environment e.g., London, Paris; low urbanicity would refer to living in a sparsely populated rural environment.

Low ☐
Medium ☐
High ☐

Paternal age (at your birth)

<40 ☐
40-50 ☐
>50 ☐

Obstetric complications

No complications ☐
Birth weight <2.5kg ☐

Cannabis

No exposure ☐
Little to moderate exposure ☐
High exposure ☐

Childhood adversity

NOTE: Childhood adversity includes any form of child maltreatment (physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation), peer victimization (e.g. bullying), experiences of parental loss and separation, war-related trauma, natural disasters, and witnessing domestic or non-domestic violence.

No exposure ☐
Any exposure ☐

MARS Rating Scale:

Please can you mark your response with a X

Statements	YES	NO
Do you ever forget to take your medication?		
Are you careless at times about taking your medicine?		
When you feel better, do you sometimes stop taking your medication?		
Sometimes if you feel worse when you take the medicine, do you stop taking it?		
I take my medication only when I am sick.		
It is unnatural for my mind and body to be controlled by medication.		
My thoughts are clearer on medication.		
By staying on medication, I can prevent getting sick.		
I feel weird, like a 'zombie', on medication.		
Medication makes me feel tired and sluggish.		

Please ensure you have answered all questions.

If you leave anything blank we will have to contact you for the missing data.

- **If the answer if unknown please mark with NOT KNOWN**
- **If the participant does not wish to disclose please mark with WITHHELD**
- **If the question is not applicable please mark with NA**

Table C1: Comparison of those with complete and incomplete data on total healthcare costs. P-value represents chi-square test of the association between the missing data and the predictors of interest. BAME, Black, Asian, and Minority Ethnic; SD, standard deviation.

	Not missing	Missing	P value
Metaboliser group, n (%)			
Normal metaboliser	142 (78.9)	38 (21.1)	0.57
Intermediate metaboliser	90 (74.4)	31 (25.6)	
Extreme metaboliser†	22 (81.5)	5 (18.5)	
Age (Mean, SD)	44.0 (14.7)	42.2 (14.5)	0.33
Sex, n (%)			
Female	176 (79.6)	45 (20.4)	1
Male	141 (80.1)	35 (19.9)	
Ethnicity, n (%)			
White	208 (82.9)	43 (17.1)	0.36
BAME‡	110 (78.6)	30 (21.4)	
Primary diagnosis, n (%)			
Schizophrenia	95 (81.9)	21 (18.1)	0.04*
Bipolar disorder	91 (72.2)	35 (27.8)	
Other psychotic disorders	132 (84.1)	25 (15.9)	
Duration of illness (Mean, SD)	11.6 (11.1)	11.2 (11.0)	0.80
CYP2D6 inhibitor use, n (%)			
No use	300 (79.2)	29 (20.8)	0.37
Use of an inhibitor	319 (90)	2 (10)	

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table C2: Baseline demographic characteristics for a sample of individuals taking a medication that is a substrate of CYP2D6. BAME, Black, Asian, and Minority Ethnic; SD, standard deviation.

	Missing n	Extreme metabolisers† (n=20)	Intermediate metabolisers (n=67)	Normal metabolisers (n=106)	Full sample (n=193)
Age (Mean, SD)	15 (8)	43.8 (15.0)	46.0 (14.6)	43.6 (15.3)	44.4 (15.0)
Sex, n (%)					
Male	1 (1)	9.0 (45)	30.0 (45)	58.0 (55)	97.0 (50)
Female		11.0 (55)	37.0 (55)	47.0 (44)	95.0 (49)
(3) **Ethnicity, n (%)**					
White	6	14.0 (70)	42.0 (63)	63.0 (59)	119.0 (62)
BAME‡		6.0 (30)	22.0 (33)	40.0 (38)	68.0 (35)
Primary diagnosis, n (%)					
Schizophrenia	0 (0)	6.0 (30)	28.0 (42)	34.0 (32)	68.0 (35)
Bipolar disorder		7.0 (35)	19.0 (28)	32.0 (30)	58.0 (30)
Other psychotic disorders		7.0 (35)	20.0 (30)	40.0 (38)	67.0 (35)
Duration of illness (Mean, SD)	39 (20)	9.9 (12.6)	13.8 (12.1)	9.2 (9.8)	10.8 (11.1)
CYP2D6 inhibitor use, n (%)	0 (0)	3.0 (15)	1.0 (1)	7.0 (7)	11.0 (6)
Medication, n (%)					
Amisulpride	0 (0)	1 (3)	10 (7)	8 (4)	6 (3)
Aripiprazole		8 (27)	35 (24)	49 (24)	92 (40)
Cariprazine		0 (0)	0 (0)	1 (0)	1 (0)
Clozapine		7 (23)	24 (16)	35 (17)	16 (7)
Flupentixol		0 (0)	6 (4)	7 (3)	4 (2)
Haloperidol		1 (3)	3 (2)	5 (2)	9 (4)
Lurasidone		0 (0)	5 (3)	8 (4)	(4 (2)
Olanzapine		6 (20)	27 (18)	31 (15)	29 (13)
Paliperidone		2 (7)	5 (3)	12 (6)	8 (3)
Quetiapine		3 (10)	10 (7)	23 (11)	9 (4)
Risperidone		2 (7)	11 (7)	15 (7)	28 (12)
Zuclopenthixol		10 (7)	11 (7)	13 (6)	24 (10)

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table C3: Part 1 of the two-part model: probability of positive expenditures for individuals who take a CYP2D6 substrate. The The reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. BAME, Black, Asian, and Minority Ethnic; CI, confidence interval.

	Total costs		Psychiatric care costs		Nonpsychiatric care costs		Primary care costs	
	Coefficient (95% CI)	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**
Metaboliser group								
Extreme metabolisers†	16.79 (-10716.86-10750.43)	1.00	16.79 (-10716.86-10750.43)	1.00	-0.58 (-1.54-0.38)	0.24	-0.32 (-1.26-0.63)	0.51
Intermediate metabolisers	-0.93 (-2.85-0.98)	0.34	-0.93 (-2.85-0.98)	0.34	-0.15 (-0.76-0.46)	0.63	-0.22 (-0.81-0.36)	0.45
Age	-0.01 (-0.1-0.08)	0.81	-0.01 (-0.1-0.08)	0.81	-0.01 (-0.03-0.02)	0.63	0.00 (-0.03-0.02)	0.71
Sex (female)	1.17 (-0.97-3.3)	0.28	1.17 (-0.97-3.3)	0.28	0.33 (-0.26-0.93)	0.27	0.13 (-0.43-0.69)	0.65
Ethnicity (BAME‡)	-1.19 (-3.13-0.75)	0.23	-1.19 (-3.13-0.75)	0.23	0.12 (-0.48-0.73)	0.69	0.65 (0.07-1.23)	0.03
Primary diagnosis								
Schizophrenia	-16.83 (-6057.44-6023.78)	1.00	-16.83 (-6057.44-6023.78)	1.00	0.15 (-0.57-0.87)	0.68	-0.47 (-1.16-0.23)	0.19
Other psychotic disorder	-18.38 (-6058.99-6022.23)	1.00	-18.38 (-6058.99-6022.23)	1.00	0.02 (-0.68-0.73)	0.95	-0.55 (-1.23-0.12)	0.11
Duration of illness	-0.09 (-0.19-0.02)	0.10	-0.09 (-0.19-0.02)	0.10	0.01 (-0.02-0.05)	0.43	0.00 (-0.04-0.03)	0.78
CYP2D6 inhibitor use	18.01 (-10275.05-10311.06)	1.00	18.01 (-10275.05-10311.06)	1.00	0.74 (-0.45-1.93)	0.23	0.54 (-0.49-1.57)	0.30

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table C4: Part 2 of the two-part model: cost estimation (conditional on positive expenditures) for individuals who take a CYP2D6 substrate. The reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. BAME, Black, Asian, and Minority Ethnic; CI, confidence interval.

	Total costs		Psychiatric care costs		Nonpsychiatric care costs		Primary care costs	
	Coefficient (95% CI)	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**
Metaboliser group								
Extreme metabolisers†	0.46 (-0.26-1.86)	0.27	0.56 (-0.23-2.16)	0.22	-0.57 (-0.90-0.88)	0.26	0.31 (-0.32-1.52)	0.42
Intermediate metabolisers	-0.24 (-0.50-0.15)	0.19	-0.25 (-0.52-0.16)	0.20	-0.12 (-0.62-1.00)	0.75	0.50 (0.02-1.21)	0.04
Age	0.00 (-0.02-0.01)	0.66	0.00 (-0.02-0.01)	0.77	-0.01 (-0.04-0.03)	0.67	-0.01 (-0.02-0.01)	0.51
Sex (female)	-0.02 (-0.34-0.47)	0.94	-0.03 (-0.37-0.48)	0.88	0.03 (-0.55-1.34)	0.95	0.13 (-0.22-0.65)	0.51
Ethnicity (BAME‡)	-0.37 (-0.58–0.05)	0.03	-0.35 (-0.58-0.01)	0.06	-0.58 (-0.81–0.04)	0.04	-0.29(-0.51-0.03)	0.07
Primary diagnosis								
Schizophrenia	1.41 (0.48-2.94)	0.00	1.55 (0.52-3.28)	0.00	0.05 (-0.61-1.84)	0.93	-0.05 (-0.39-0.49)	0.82
Other psychotic disorder	1.58 (0.59-3.19)	0.00	1.62 (0.57-3.37)	0.00	1.11 (-0.20-4.59)	0.13	-0.13 (-0.43-0.34)	0.54
Duration of illness	-0.01 (-0.03-0.02)	0.64	-0.01 (-0.03-0.02)	0.61	-0.01 (-0.05-0.04)	0.75	-0.01 (-0.03-0.02)	0.61
CYP2D6 inhibitor use	-0.42 (-0.71-0.19)	0.14	-0.48 (-0.75-0.10)	0.09	0.58 (-0.58-5.05)	0.50	0.73 (-0.05-2.14)	0.08

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table C5: Part 1 of the two-part model: probability of positive expenditures, excluding women who are pregnant. The reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. BAME, Black, Asian, and Minority Ethnic; CI, confidence interval.

	Total costs		Psychiatric care costs		Nonpsychiatric care costs		Primary care costs	
	Coefficient (95% CI)	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**
Metaboliser group								
Extreme metaboliser†	15.48 (-3595.91-3626.88)	0.99	15.48 (-3595.91-3626.88)	0.99	-0.64 (-1.43-0.15)	0.11	-0.55 (-1.35-0.24)	0.17
Intermediate metaboliser	-0.14 (-1.42-1.15)	0.83	-0.14 (-1.42-1.15)	0.83	-0.13 (-0.59-0.33)	0.57	-0.25 (-0.7-0.19)	0.26
Age	0.01 (-0.05-0.07)	0.8	0.01 (-0.05-0.07)	0.8	0.00 (-0.02-0.01)	0.67	0.00 (-0.01-0.02)	0.78
Sex (female)	1.57 (-0.07-3.21)	0.06	1.57 (-0.07-3.21)	0.06	0.28 (-0.18-0.73)	0.23	0.38 (-0.06-0.81)	0.09
Ethnicity (BAME)‡	0.26 (-1.17-1.68)	0.72	0.26 (-1.17-1.68)	0.72	0.37 (-0.1-0.83)	0.12	0.64 (0.19-1.08)	0.01
Primary diagnosis								
Other psychotic disorder	-0.67 (-2.37-1.02)	0.44	-0.67 (-2.37-1.02)	0.44	0.07 (-0.48-0.63)	0.8	-0.34 (-0.87-0.18)	0.2
Schizophrenia	0.16 (-1.62-1.95)	0.86	0.16 (-1.62-1.95)	0.86	-0.21 (-0.75-0.33)	0.46	-0.47 (-0.99-0.06)	0.08
Duration of illness	-0.06 (-0.13-0.01)	0.07	-0.06 (-0.13-0.01)	0.07	0.01 (-0.02-0.03)	0.54	-0.01 (-0.03-0.02)	0.52
CYP2D6 Inhibitor use	15.88 (-4345.2-4376.96)	0.99	15.88 (-4345.2-4376.96)	0.99	0.87 (-0.29-2.03)	0.14	0.49 (-0.48-1.47)	0.32
Constant	3.63 (0.84-6.43)	0.01	3.63 (0.84-6.43)	0.01	0.57 (-0.29-1.42)	0.19	-0.05 (-0.87-0.78)	0.91

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Table C6: Part 2 of the two-part model: cost estimation (conditional on positive expenditures), excluding women who are pregnant. The reference group was a white male with a diagnosis of bipolar disorder who was not taking a CYP2D6 strong inhibitor and characterised as normal metaboliser status for *CYP2D6*. BAME, Black, Asian, and Minority Ethnic; CI, confidence interval.

	Total costs		Psychiatric care costs		Nonpsychiatric care costs		Primary care costs	
	Coefficient (95% CI)	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**	**Coefficient (95% CI)**	**P**
Metaboliser group								
Extreme metaboliser†	0.63 (-0.09-1.92)	0.10	0.71 (-0.07-2.16)	0.09	-0.54 (-0.86-0.47)	0.19	0.01 (-0.49-0.98)	0.98
Intermediate metaboliser	-0.11 (-0.37-0.24)	0.49	-0.1 (-0.37-0.28)	0.55	-0.21 (-0.56-0.43)	0.44	0.73 (0.22-1.46)	0.00
Age	-0.01 (-0.02-0)	0.11	-0.01 (-0.02-0)	0.16	-0.01 (-0.04-0.01)	0.23	-0.01 (-0.02-0)	0.11
Sex (female)	-0.02 (-0.29-0.36)	0.91	-0.02 (-0.3-0.38)	0.91	-0.09 (-0.49-0.64)	0.77	0.17 (-0.16-0.65)	0.35
Ethnicity (BAME)‡	-0.3 (-0.5–0.02)	0.04	-0.29 (-0.5-0)	0.05	-0.41 (-0.67-0.05)	0.07	-0.27 (-0.47-0.02)	0.07
Primary diagnosis								
Other psychotic disorder	0.92 (0.29-1.85)	0.00	0.93 (0.27-1.92)	0.00	0.65 (-0.18-2.31)	0.16	-0.06 (-0.37-0.39)	0.75
Schizophrenia	0.65 (0.12-1.45)	0.01	0.74 (0.15-1.63)	0.01	-0.3 (-0.66-0.44)	0.33	-0.28 (-0.52-0.09)	0.13
Duration of illness	-0.01 (-0.02-0.01)	0.45	-0.01 (-0.03-0.01)	0.43	0 (-0.03-0.03)	0.91	-0.01 (-0.03-0.01)	0.42
CYP2D6 Inhibitor use	-0.32 (-0.66-0.38)	0.29	-0.38 (-0.7-0.3)	0.21	0.9 (-0.4-5.04)	0.28	0.91 (-0.02-2.74)	0.06
Constant	9732.81 (5239.94-18073.54)	0.00	8682.06 (4533.75-16625.98)	0.00	1811.03 (581.47-5640.56)	0.00	197.95 (101.11-387.54)	0.00

† Includes poor and ultrarapid metabolisers of *CYP2D6*.

‡ Includes Indian, Pakistani, Bangladeshi, Chinese, and any other Asian background; White and Black African, White and Black Caribbean, White and Asian, and any other mixed or multiple ethnic groups; Arab, and any other ethnic group.

Appendix D

Appendices for chapter 5

Table D1: Resource use and unit costs associated with the health state "relapse". Resource use is obtained from National Institute for Health and Care Excellence[39]. Where qualification cost information was available, these were included in the unit costs.

Service	Mean usage per person	Unit cost (GBP)	Total cost (GBP)	Unit cost reference
Outpatient, primary and community care (over 6 months)				
Outpatient				
Psychiatric visits	2.1	137.00 (average outpatient attendance)	287.7	[232]
Other	0.3	137.00 (average outpatient attendance)	41.1	[232]
Day hospital	2.1	840.00 (average cost per episode)	1764	[232]
Community mental health centre visits	1.4	160.54 (inflated from 2008 to 2021 prices using consumer price index)	224.76	[39]

Day care centre visits	0.9	39.00 (per attendance in day care)	35.1	[232]
Group therapy	0.1	39.00 (per attendance in day care)	3.9	[232]
Sheltered workshop	0	63.44 (inflated from 2008 to 2021 prices using consumer price index)	0	[39]
Specialist education	0	39.00 (per attendance in day care)	0	[232]
Visits by				
Psychiatrist	2.3	41.00 (per patient contact, assume each appointment lasts 20 minutes)	94.3	[232]
General practitioner	1.6	39.23 (per patient contact lasting 9.22 minutes, including qualifications costs)	62.77	[232]
District nurse	0	52.00 (per face-to-face patient contact)	0	[297]
Community psychiatric nurse	5.2	30 (per face-to-face patient contact with specialist nurse, assume appointment lasts 20 minutes)	156	[297]
Social worker	0.4	17.33 (per patient contact, assume each appointment lasts 20 minutes, including qualification costs)	6.93	[232]
Occupational therapist	0.8	87.00 (per one-to-one session)	69.6	[232]
Home help/care worker	0.6	32.00 (per hour of face-to-face contact during the weekday)	19.2	[232]
Hospital, crisis resolution and home treatment teams				
Acute hospital (days)	111	428.00 (per bed day)	47508	[232]
Crisis resolution and home treatment team (weeks)	8	341.79 (inflated from 2008 to 2021 prices using consumer price index)	2734.32	[39]
Costs incurred by switching between antipsychotic medication (due to relapse)				

Psychiatrist	3	123.00 (per patient contact, assume each appointment lasts 20 minutes)	123	[232]

Table D2: Resource use and unit costs associated with the health state "relapse". Resource use is obtained from National Institute for Health and Care Excellence[39]. Where qualification cost information was available, these were included in the unit costs.

Service	Mean usage per person	Unit cost (GBP)	Total cost (GBP)	Unit cost reference
Outpatient, primary and community care				
Outpatient				
Psychiatric visits	1.4	137.00 (average outpatient attendance)	191.8	[232]
Other	0.1	137.00 (average outpatient attendance)	13.7	[232]
Day hospital	2.3	840.00 (average cost per episode)	1932	[232]
Community mental health centre visits	2.4	160.54 (inflated from 2008 to 2021 prices using consumer price index)	385.3	[39]
Day care centre visits	5.9	39.00 (per attendance in day care)	230.1	[232]
Group therapy	0.4	39.00 (per attendance in day care)	15.6	[232]
Sheltered workshop	1.1	63.44 (inflated from 2008 to 2021 prices using consumer price index)	69.78	[232]
Specialist education	2.9	39.00 (per attendance in day care)	113.1	[232]
Visits by				
Psychiatrist	2.5	41.00 (per patient contact, assume each appointment lasts 20 minutes)	102.5	[232]

General practitioner	1.8	39.23 (per patient contact lasting 9.22 minutes, including qualifications costs)	70.61	[232]
District nurse	0.1	52.00 (per face-to-face patient contact)	5.2	[297]
Community psychiatric nurse	12.6	30 (per face-to-face patient contact with specialist nurse, assume appointment lasts 20 minutes)	378	[297]
Social worker	0.1	17.33 (per patient contact, assume each appointment lasts 20 minutes, including qualification costs)	1.73	[232]
Occupational therapist	0	87.00 (per one-to-one session)	0	[232]
Home help/care worker	0.4	32.00 (per hour of face-to-face contact during the weekday; qualification costs not available)	12.8	[232]
Accommodation and costs of residential and long-term hospital care				
Private household	77.00%	0	0	N/A
Residential care	20.00%	776 (establishment cost plus personal living expenses and external services per permanent resident week)	8070.4	[232]
Long-term hospital care	3.00%	428 (per day)	4686.6	[232]

Table D3:

Breakdown of costs and consequences of the model. PGx, pharmacogenetics; TAU, treatment as usual; QALY, quality-adjusted life year. [39]. Where qualification cost information was available, these were included in the unit costs.

	TAU	**PGx**	**Incremental difference**
Costs			
Total costs	789,878.3	751,862.29	-38,016.01
PGx test	0	276.92	276.92
Medication (discounted, £)	16,464.04	16,163.12	-300.92
Relapse events (discounted, £)	493,162.77	440,030.02	-53,132.75
Stable events (discounted, £)	280,251.49	295,392.23	15,140.74
Consequences			
Total QALYs (discounted)	14.55	14.96	0.41
Total life years	43.17	43.17	0
Total stable years	21.45	23.67	2.21
Total relapse events (stable $\rightarrow$ relapse)	4.08	4.50	0.43
Total relapse events (relapse $\rightarrow$ relapse)	0.69	0.53	-0.16

Table D4: Results of the one-way sensitivity analysis. GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RR, relative risk.

Parameter	Value tested	Incremental cost (GBP)	Incremental QALY	NMB	Conclusion
Test parameters					
CYP2D6 and CYP2C19 sensitivity	0.56	-35,874.18	0.39	43,581.23	PGx dominates
	1.00	-39,316.38	0.42	47,757.27	PGx dominates
CYP2D6 and CYP2C19 specificity	0.80	-31,918.72	0.34	38,782.50	PGx dominates
	1.00	-38,336.92	0.41	46,569.00	PGx dominates
Clinical parameters					
RR for response after genotyping strategy	1.07	-10,900.57	0.12	13,283.49	PGx dominates
	1.50	-62,390.67	0.67	75,751.40	PGx dominates
Probability of first-line antipsychotic response	0.56	-39,757.76	0.43	48,290.48	PGx dominates
	0.82	-37,125.37	0.40	45,101.94	PGx dominates
Probability of second-line antipsychotic response	0.17	-37,544.37	0.40	45,634.33	PGx dominates
	0.63	-38,016.01	0.41	46,179.67	PGx dominates
Probability of clozapine response	0.28	-39,602.72	0.43	48,107.36	PGx dominates
	0.75	-36,746.73	0.39	44,637.63	PGx dominates
Probability of clozapine non-response (from clozapine response)	0.12	-37,434.33	0.40	45,473.00	PGx dominates
	0.21	-37,833.27	0.41	45,957.67	PGx dominates
Probability of clozapine response (from clozapine non-response)	0.09	-38,222.31	0.41	46,430.31	PGx dominates
	0.16	-36,960.08	0.40	44,896.83	PGx dominates
Probability of response to non-response for antipsychotics	0.35	-38,117.81	0.41	46,284.98	PGx dominates
	0.58	-37,923.48	0.41	46,077.05	PGx dominates
Costs (GBP)					
Annual cost, stable	14886.46	-43,277.75	0.41	51,441.41	PGx dominates
	24810.76	-32,438.84	0.41	40,602.51	PGx dominates

Annual cost, relapse	41829.77	-23,432.26	0.41	31,595.92	PGx dominates
	69716.29	-53,028.62	0.41	61,192.28	PGx dominates
Pharmacogenetic test cost	100	-38,192.93	0.41	46,356.59	PGx dominates
	1000	-37,292.93	0.41	45,456.59	PGx dominates
Utilities					
Quality of life, stable	0.799	-38,016.01	0.41	46,179.67	PGx dominates
	0.919	-38,016.01	0.47	47,342.89	PGx dominates
Quality of life, relapse	0.190	-38,016.01	0.71	52,291.85	PGx dominates
	0.674	-38,016.01	0.28	43,620.60	PGx dominates
Other parameters					
Number of cycles	10	-12,923.76	0.14	15,706.90	PGx dominates
	100	-38,016.29	0.41	46,180.01	PGx dominates
Discount rate	0	-79,622.52	0.85	96,707.73	PGx dominates
	10	-120.38	0.00	205.45	PGx dominates