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HANNA MARIA KARIIS

Improving pharmacotherapy outcomes in psychiatric and cardiovascular conditions

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Institute of Molecular and Cell Biology, Institute of Genomics, Faculty of Science and Technology, University of Tartu, Estonia, Estonia.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by Roman numerals (Ref. I to Ref. III):

I. Mattia Cordioli*, Andrea Corbetta*, **Hanna Maria Kariis***, Sakari Jukarainen, Pekka Vartiainen, Tuomo T. J. Kiiskinen, Matteo Ferro, Markus Perola, Mikko Niemi, Samuli Ripatti, Kelli Lehto, Lili Milani, Andrea Ganna. *Socio-demographic and genetic risk factors for drug adherence and persistence across 5 common medication classes*. Nature Communications, 15(1):9156, 2024. https://doi.org/10.1038/s41467-024-53556-z.

II. **Hanna Maria Kariis**, Silva Kasela, Tuuli Jürgenson, Aet Saar, Jana Lass, Kristi Krebs, Urmo Võsa, Elis Haan, the Estonian Biobank Research Team, Lili Milani, Kelli Lehto. *The role of depression and antidepressant treatment in antihypertensive medication adherence and persistence: Utilising electronic health record data*. Journal of Psychiatric Research, 168:269278, 2023. https://doi.org/10.1016/j.jpsychires.2023.10.018.

III. **Hanna Maria Kariis**, Dage Särg, Kristi Krebs, Maarja Jõeloo, Kadri Kõiv, Kairit Sirts, The Estonian Biobank Research Team, The Health Informatics Research Team, Maris Alver, Kelli Lehto, Lili Milani. *Genetic influences on antidepressant side effects: a CYP2C19 gene variation and polygenic risk study in the Estonian Biobank.* European Journal of Human Genetics (2025). https://doi.org/10.1038/s41431-025-01894-x.

∗ These authors contributed equally.
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My contributions to the listed publications are as follows:

I. Implemented the study design, participated in collaborator meetings, conducted data analysis, interpreted results, and prepared tables. Drafted the original manuscript sections related to the Estonian Biobank and took part in the critical review and revision of the final paper.

II. Led the study design and formulation of research questions. Performed data analysis, interpreted the results, and prepared all visual materials (figures and tables). Drafted the original manuscript and contributed to its critical review and refinement.

III. Designed the study and research questions, conducted data analysis, interpreted results, and prepared figures and tables. Drafted the original manuscript and participated in its critical review and revision.

LIST OF ABBREVIATIONS

ADEQ	Adverse Drug Events Questionnaire
AGDS	Australian Genetics of Depression Study
AHM	Antihypertensive Medication
ANX	Anxiety
ATC	Anatomical Therapeutic Chemical Classification
BIP	Bipolar Disorder
BMI	Body Mass Index
CAD	Coronary artery disease
CNV	Copy Number Variant
CPIC	Clinical Pharmacogenetics Implementation Consortium
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DPWG	Dutch Pharmacogenetics Working Group
EHR	Electronic Health Record
EstBB	Estonian Biobank
FDR	False Discovery Rate
GWAS	Genome-Wide Association Study
HTN	Hypertension
ICD-10	International Statistical Classification of Diseases 10th Revision
LDL	Low-Density Lipoprotein
MDD	Major Depressive Disorder
MHoS	Mental Health Online Survey
MPR	Medication Possession Ratio
NEUR	Neuroticism
NHIF	National Health Insurance Fund
NLP	Natural Language Processing
OR	Odds Ratio
PC	Principal Component
PDC	Proportion of Days Covered
PGS	Polygenic Score
RCT	Randomised Controlled Trial
SBP	Systolic Blood Pressure
SCZ	Schizophrenia

SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
WHO	World Health Organisation

1. INTRODUCTION

Psychiatric disorders and cardiovascular diseases (CVDs) are complex diseases that represent significant public health challenges globally. They frequently co-occur; for instance, the risk of developing a CVD is up to 75% higher in patients with depression compared to those without depression. Furthermore, mortality due to CVD is 2-3 times greater in patients with schizophrenia, major depressive disorder, or bipolar disorder than the general population. Conversely, patients with CVD often experience depressive symptoms, highlighting a bidirectional relationship. Despite the availability and increasing prescribing of effective cardiovascular medications, adherence to long-term CVD pharmacotherapies remains around 50%, preventing many patients from adequately reducing CVD risk factors. Adherence is the extent to which patients follow dosing recommendations, while persistence reflects the continuity of prescription refills over time. These patterns of medication use are particularly important in life-long treatments such as those for hypertension and hyperlipidaemia. Poor adherence to medications for these conditions can lead to uncontrolled blood pressure and elevated low-density lipoprotein (LDL) cholesterol levels, both major contributors to CVD onset and adverse outcomes. While behavioural and clinical determinants of medication use have been studied extensively, the role of genetic factors remains underexplored as only a few studies have examined adherence or persistence, and most relied on proxy measures. Furthermore, the association between psychiatric comorbidities and CVD medication use is inconsistent, with prior studies limited by small samples, short follow-up, and reliance on self-reported adherence.

In contrast to long-term CVD pharmacotherapies, antidepressant treatments are typically shorter in duration. Instead, one of the main barriers to persistence is the occurrence of side effects: around half of patients experiencing side effects discontinue treatment prematurely, delaying recovery. Since side effects are often underreported, alternative approaches such as extracting side effects from clinical notes using natural language processing (NLP) may improve the detection of side effects. Furthermore, few studies have investigated the genetic basis of side effects beyond variants in genes involved in how the body processes drugs. Given the associations between psychiatric disorders and CVD, discontinuation or non-adherence of psychiatric medications may indirectly influence cardiovascular risk.

Until recently, most evidence on medication use and side effects had relied on self-reported surveys or small randomised controlled trials (RCTs), limiting generalisability and long-term insight. The increasing availability of longitudinal electronic health records (EHRs), linked to centralised data sources such as genetic biobanks, now enables large-scale investigations under real-world conditions of medication usage patterns and side effect profiles. Genomic approaches have further advanced the study of treatment-related outcomes. Genome-wide association studies (GWAS) have identified thousands of variants associated with

complex traits and facilitated the development of polygenic scores (PGSs), which summarise genetic risk into a single quantitative measure. In parallel, pharmacogenetics has shown that variation in genes encoding drug-metabolising enzymes can influence drug plasma levels, efficacy, and side effect risk. This opens the possibility for a more personalised treatment where medication choice or dosage is guided based on an individual's genotype.

This thesis focuses on improving real-world pharmacotherapy-related outcomes for psychiatric and cardiovascular conditions by examining genetic determinants of CVD medication adherence, persistence, and antidepressant side effects. Using the Estonian Biobank, which combines genomic data with structured and unstructured EHRs as well as self-reported outcomes, this work aims to contribute to the advancement of personalised medicine, tailoring treatments to individuals to enhance efficacy and minimise harm.

2. REVIEW OF LITERATURE

2.1. Psychiatric and cardiovascular disease comorbidity

Major depressive disorder (MDD) and cardiovascular diseases (CVDs) are major public health concerns that lead to excess morbidity and mortality. MDD, commonly referred to as depression, is characterised by the persistence of low mood which affects 21% of individuals in Europe during their lifetime (Gutiérrez-Rojas et al. 2020). The prevalence has risen since the 1990s with 3.3% of the global adult population being diagnosed with major depressive disorder in 2019 (GBD 2019 Mental Disorders Collaborators 2022) which is expected to reach 4.5% by 2030 (Wang et al. 2025). The increase is most prominent among younger-old individuals (60-69 years) (Wang et al. 2025), however the COVID-19 pandemic exacerbated already growing mental health problems in young individuals (<19 years) (Thiha et al. 2025).

CVDs are even more widespread and a leading cause of mortality worldwide. Major forms of CVD include hypertension, coronary heart disease (ischaemic heart disease), heart failure, stroke, and atrial fibrillation (Roth et al. 2020). The American Heart Association reports that CVDs affect around 48.6% of individuals over the age of 20 (Martin et al. 2025) and their prevalence has nearly doubled from 271 million in 1990 to 523 million in 2019 (Roth et al. 2020). The prevalence of CVD rises with age: approximately 20–30% at 20–39 years, 55% at 40–59 years, 75% at 60–79 years, and 85% above 80 years (Martin et al. 2025). In the United States, CVDs claim more lives each year than cancer and chronic lower respiratory disease combined (Martin et al. 2025). In 2022, 206.8 per 100,000 people died of CVD (Martin et al. 2025) and the mortality has been increasing since the 2010s, followed by a decline between 1980-2010 (Martin et al. 2025).

The comorbidity of MDD and CVD is well-documented (Bergstedt et al. 2024; Tu et al. 2025). The risk of developing CVD is up to 75% higher in individuals with MDD compared to those without MDD (Correll et al. 2017). In addition, individuals with severe psychiatric disorders which include schizophrenia (SCZ), bipolar disorder (BIP), and MDD, have a life expectancy that is 15 to 25 years shorter than that of the general population, primarily due to premature deaths from cardiovascular disease (Goldfarb et al. 2022). Although cardiovascular conditions are the leading cause of death in both groups, people with severe psychiatric disorders have more than double the cardiovascular mortality rate compared to the general population (Goldfarb et al. 2022; Joukamaa et al. 2001). Furthermore, patients with CVD have higher depression scores compared to the general population (Zhang, Cao, and Baranova 2021). Despite advancements in CVD prevention and treatment, mortality in patients with severe psychiatric disorders has not declined in recent decades (Laursen, Munk-Olsen, and Gasse 2011).

The mechanism underlying the link between these two conditions is largely unknown. Previous studies have reported a range of factors associated with

MDD and CVD risk, including hormonal, inflammatory, neuroimmune, and behavioural factors (Nemeroff and Goldschmidt-Clermont 2012; Warriach et al. 2022; Goldfarb et al. 2022). Shared genetic factors have also been implicated, with Mendelian randomisation analyses suggesting a causal link between genetic liability to MDD and the development of coronary artery disease (CAD) and stroke (Zhang, Cao, and Baranova 2021; Lu et al. 2020). Studies have identified a plethora of genes that imply shared biological mechanisms linking MDD and CVD, including the activation of the hypothalamic-pituitary-adrenal (HPA) axis (Li et al. 2023; Hage et al. 2024), autonomic dysfunction e.g. reduced heart-rate variability (Mulle and Vaccarino 2013), activation of inflammation pathways (Torgersen et al. 2022; Bergstedt et al. 2024; Huang et al. 2022; Mulle and Vaccarino 2013), serotonergic signalling dysregulation (Amare et al. 2017; Fumeron et al. 2002; Mulle and Vaccarino 2013), metabolic pathways related to lipid metabolism (Kang et al. 2024; Torgersen et al. 2022; Bergstedt et al. 2024; Amare et al. 2017), greater platelet and endothelial dysfunction (Huang et al. 2022; Waclawovsky et al. 2025).

However, there are also secondary effects related to MDD or CVD that could contribute to this comorbidity, for example, treatment or inadequate treatment itself could increase the risk of CVD (van der Laan et al. 2017; Crawshaw et al. 2016; Behlke, Lenze, and Carney 2020; Biffi et al. 2020; Mortensen and Andersen 2022). Patients with MDD may be less likely to adhere to medication regimen than patients without MDD, which can increase their cardiovascular disease risks (van der Laan et al. 2017; Crawshaw et al. 2016). In addition, some antidepressants have cardiovascular side effects that may increase the risk of cardiac events (Behlke, Lenze, and Carney 2020; Biffi et al. 2020; Mortensen and Andersen 2022). For instance, tricyclic antidepressants (TCAs) can cause orthostatic hypotension, increased heart rate, and decreased heart rate variability (Behlke, Lenze, and Carney 2020) and some selective serotonin reuptake inhibitors (SSRIs) can prolong QT intervals in an electrocardiogram, meaning ventricle recovery from depolarisation to repolarisation takes longer, potentially leading to arrhythmias and exacerbating CVD progression (Mortensen and Andersen 2022).

2.1.1. Trends in the use of psychiatric and cardiovascular medications

The use of cardiovascular and psychiatric medications has increased in the recent decades (Kantor et al. 2015; Rouette et al. 2022; Sundbøll et al. 2017). A study of 2.7 million UK primary care adult patients found that antihypertensive prescriptions increased from 8% in 1988 to 22% in 2018 (Rouette et al. 2022). Similarly, in the United States, the use of statins increased by 10%, antihypertensive medications (AHMs) by 7% and antidepressants by 6% between 1999-2012 (Kantor et al. 2015). In Estonia, there has also been a marked increase in the use of psychiatric and cardiovascular medications, particularly antihypertensive med-

ications based on data from The National Health Insurance Fund (NHIF) since the start of data collection in 2004 (Figure 1). The increase in the use of CVD and psychiatric disorder medications is likely driven by the growing prevalence of CVDs and MDD (Roth et al. 2020; Proudman, Greenberg, and Nellesen 2021), demographic changes such as the aging population and population growth, as well as changes in clinical practice, earlier diagnosis, and greater awareness of psychiatric and cardiovascular conditions (Kantor et al. 2015).

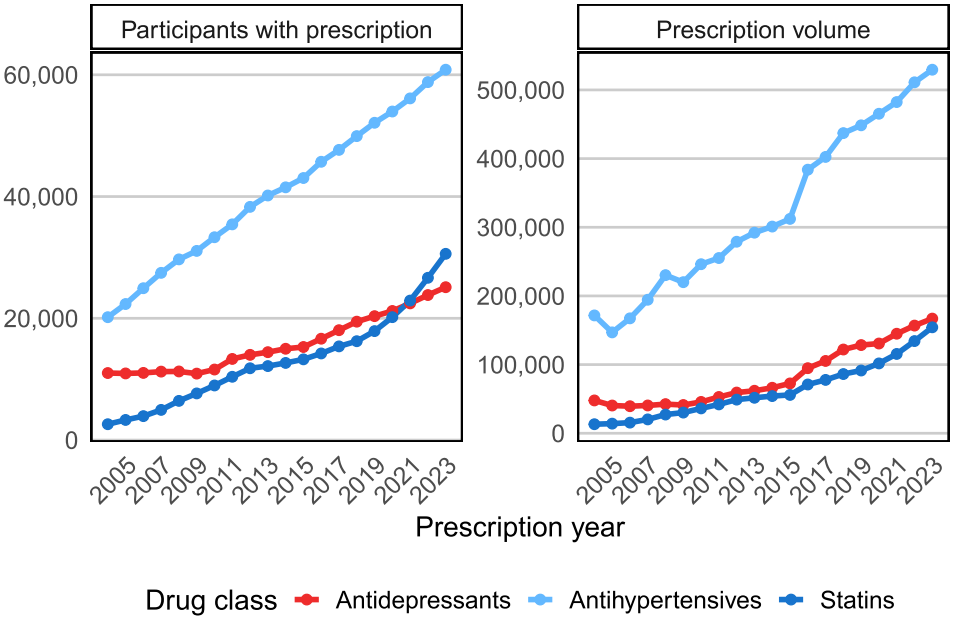

Figure 1. Number of individuals with a prescription and the total volume of prescriptions in the Estonian Biobank linked with the Estonian National Health Insurance Fund between 2004-2023. *Antidepressants (ATC N06A*), Statins (ATC C10AA), Antihypertensives (ATC CO3*,C07*,C08*,C09*)*

The increase in psychiatric and cardiovascular disorder medication use also underscores the need for a deeper understanding of medication use patterns, and safety under real-world conditions to mitigate associated risks and improve overall patient care. In addition, the prediction of medication use may be helpful for other studies where medication use is a common confounder which can lead to the underestimation of the extent of medication effects if not accounted for (Aasmets et al. 2024). Currently, Randomised Controlled Trials (RCTs) are considered the gold standard for evaluating medication safety and efficacy (Feinstein and Horwitz 1982). To minimise bias, they are conducted in controlled environments with strict eligibility criteria that often exclude underrepresented individuals, limiting generalisability to broader populations (Monti et al. 2018). Additionally, economic constraints restrict sample sizes and study duration, which may prevent the detection of rare or delayed side effects and limit the understanding of long-term

medication efficacy (Monti et al. 2018). Therefore, it is important to monitor the long-term use and safety of medications after they have been released to the market, in particular, for underrepresented populations such as individuals with comorbidities. Furthermore, longer observation periods enhance the detection of rare or delayed adverse effects (Monti et al. 2018).

2.1.2. Medication use patterns, associated outcomes, and influencing factors

Adherence and persistence characterise medication use behaviour. Adherence refers to the extent to which a patient follows the prescribed dosing and interval recommendations, while persistence focuses on the continuity of medication filling and refilling over a defined period (Lam and Fresco 2015). Long-term adherence to the prescribed treatment regimen is essential for achieving therapeutic and health outcomes. The World Health Organisation (WHO) stated in its 2003 report on medication adherence that increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment (Sabaté and World Health Organization 2003).

Real-world studies estimate non-adherence to be a widespread issue, with approximately 50% of patients with chronic diseases failing to adhere to prescribed treatment regimens (Lam and Fresco 2015; Sabaté and World Health Organization 2003; Rodriguez et al. 2019; Bosworth et al. 2011) which is lower than the estimates from RCTs (de Lemos et al. 2004; Hirsh et al. 2015). Despite the availability of well-tolerated and effective medications for CVDs, CVD medication use is low both among patients who are prescribed treatment to prevent a CVD (primary prevention) and those who take it after a CVD incident (secondary prevention). Up to 30% of prescriptions remain unfilled, and nearly 50% of medications are discontinued within the first year among patients taking it for CVD prevention (Naderi, Bestwick, and Wald 2012). For patients with a CVD, where the treatment is typically lifelong to manage chronic risk factors, adherence tends to decline over time. A study examining statin prescription data revealed that while 75% of nearly 60,000 patients with acute and chronic CAD adhered to statin therapy for six months, only 40% of acute and 36% of chronic CAD patients consistently refilled their prescriptions over two years (Jackevicius, Mamdani, and Tu 2002). Low long-term adherence is associated with poor health outcomes and mortality (Türkmen et al. 2025; Lam and Fresco 2015). Patients with low statin adherence have a 27% higher risk of coronary heart disease and a 50% increased risk of ischaemic stroke compared to those with high adherence (Türkmen et al. 2025). In addition, low adherence is also linked to increased healthcare costs due to avoidable CVD-related emergency department visits, inpatient care, and unused medications (Lam and Fresco 2015; Bansilal et al. 2016; Nelson, Pagidipati, and Bosworth 2024; Aubert et al. 2010).

Depression treatment typically lasts less than a year, although treatment is often extended to at least two years for those with recurrent depression (National Institute for Health and Care Excellence (NICE) 2022). Non-adherence to antidepressants is also common. Recent large-scale studies in the United States and five European countries found non-adherence rates of 42.9% in the US and 46.2% in Europe among adults prescribed antidepressants (Unni, Gupta, and Sternbach 2024). Antidepressants also have high discontinuity rates. A primary care research registry study in 673,177 depressed people found that 38.6% of patients discontinued treatment after two months and 87.7% discontinued after 12 months (De Crescenzo et al. 2024). The low antidepressant adherence has been associated with several negative outcomes, such as functional impairment, higher healthcare utilisation, relapse, hospitalisation, delays in remission, poor quality of life, substance abuse, premature mortality, and suicide (Unni, Gupta, and Sternbach 2024; Muhammad et al. 2023; Ta et al. 2021). For instance, a study in nearly 30,000 individuals over the age of 65 years who started antidepressant treatment after a CVD found that high adherence was associated with 9% lower mortality compared to low adherence (Biffi et al. 2018). Furthermore, the mortality reduction occurred in both individuals who received CVD co-medications and those without, suggesting that the reduction in mortality cannot be solely due to the confounding effect of CVD co-medications.

A range of factors have been reported to contribute to low medication adherence. The WHO has listed five categories of factors that have been reported to lead to poor medication adherence: patient-, therapy-, condition-, socioeconomic, and health system/health care team-related factors (Sabaté and World Health Organization 2003; Gast and Mathes 2019; Kvarnstrm et al. 2021). These factors can influence various stages of medication-taking: initiation, when the patient takes the first dose; implementation, the degree to which the patient adheres to the prescribed dosing schedule; and discontinuation, the conclusion of therapy, whether guided by the clinician or decided independently by the patient (Nelson, Pagidipati, and Bosworth 2024).

Patient-related factors such as age, sex, comorbidities, beliefs about medication, health literacy, motivation, forgetfulness, fear of adverse effects, and perceived necessity have been linked to lower medication adherence (Gast and Mathes 2019; Sabaté and World Health Organization 2003). Psychiatric comorbidities, particularly MDD, have been associated with reduced adherence to CVD medications. A recent study of 10,153 older patients with CVD showed that concomitant MDD was associated with up to 40% lower CVD medication adherence (Berimavandi et al. 2025), suggesting that psychological well-being may be important for CVD treatment success (Crawshaw et al. 2016; Gast and Mathes 2019), however, evidence for antihypertensive medications is inconsistent (van der Laan et al. 2017; Crawshaw et al. 2016). Previous research on the role of psychiatric comorbidities in CVD adherence has mostly included small sample sizes, short follow-up periods, self-reported measures which tend to overestimate adher-

ence (Spikes et al. 2019; Kulkarni et al. 2021; Lauder et al. 2021; Okunrinboye, Otakpor, and Ilesanmi 2019). Furthermore, the role of genetic factors in medication use is largely unexplored as the studies exploring medication use have mostly investigated proxies to adherence (Kiiskinen et al. 2023; Wu et al. 2019) and only a few have investigated adherence itself (Türkmen et al. 2024). Understanding patient-related barriers to medication adherence can help identify high-risk patients, reduce modifiable obstacles, and develop tailored interventions to improve adherence (Gast and Mathes 2019). For instance, patient-related factors may be addressed through targeted educational, behavioural, and psychological strategies (Gast and Mathes 2019).

There are also other factors that might have a negative influence on adherence such as therapy-related barriers, including regimen complexity and side effects (Sabaté and World Health Organization 2003). With regards to antidepressant treatment, side effects are a common reason for discontinuing medication, with 60-70% of patients experiencing them and approximately half discontinuing due to side effects (Campos et al. 2021; Garcia-Marin et al. 2023). Previous studies have identified that discontinuity due to side effects depends on the antidepressant medication (Cipriani et al. 2018; García-González et al. 2017), type of side effects (Garcia-Marin et al. 2023; Campos et al. 2021), side effect severity (Chanie et al. 2025) and burden (Braund et al. 2021). Yet, only a few studies have investigated the genetic determinants of antidepressant side effects (Campos et al. 2021; Fabbri et al. 2018).

Beyond patient- and therapy-related factors, adherence is influenced by condition-related factors, such as having asymptomatic or chronic illnesses. In addition, social and economic challenges such as poverty, unemployment, illiteracy, cultural beliefs, and poor access to healthcare services, as well as health system constraints, including overworked clinicians, short consultations, and inadequate follow-up appointments, can also influence adherence (Gast and Mathes 2019).

Taken together, poor adherence is common, linked to worse health outcomes, and increased costs. Understanding the patient-related factors associated with medication adherence or side effects may enable early identification of at-risk individuals, potentially reducing treatment failure, disease progression, and the broader economic burden of non-adherence.

2.2. The measurement of pharmacotherapy-related outcomes

Since psychiatric and cardiovascular conditions are increasing in prevalence and the use of medications for these conditions is rising, it is important to examine how patients use these medications in a real-world setting. In this section we focus on the adherence and persistence of CVD medications, since these medications are typically taken long-term and prolonged low adherence to these medications can worsen cardiovascular outcomes. In addition, we discuss side effects to antide-

pressant medications which are a common barrier to treatment persistence. Premature discontinuity or non-adherence may indirectly contribute to worse health outcomes among patients with psychiatric conditions.

2.2.1. Adherence to CVD medications

Measuring adherence is especially important for long-term therapies such as AHMs and statins used to lower blood pressure and low-density lipoprotein (LDL) cholesterol, respectively (Leslie, McCowan, and Pell 2019).

Various methods are available to measure medication adherence which can be categorised into prospective observational techniques, patient-reported measures, and objective retrospective measures. However, no single method is currently considered the gold standard (Shah, Touchette, and Marrs 2023; Lam and Fresco 2015). Prospective observational approaches include direct observation of medication-taking, devices, and therapeutic drug monitoring. Patient-reported methods include interviews, instruments, and diaries that are reported by a clinician or patient. Adherence metrics based on administrative data, including insurance claims, pharmacy dispensing or prescription databases are growing in popularity due to data availability, ability to retrospectively assess adherence in large populations for longer timeframes, their correlation with health outcomes and lack of recall bias (Sperber, Samarasinghe, and Lomax 2017). Retrospective methods such as the Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) are the most common objective measures when using administrative data, each capturing different aspects of adherence behaviour (Shah, Touchette, and Marrs 2023).

MPR is one of the most widely used methods for estimating the proportion of days within a specified timeframe that a patient has their prescribed medication:

$$\text{MPR} = \frac{\text{Total day's supply of medication}}{\text{Number of days in the observation period}}$$

MPR can exceed 100% if patients refill prescriptions early. There are many variants of MPR. Variants like modified MPR (MPRm) or capped MPR (cMPR) address overestimation by capping values at 100%, while fixed MPR (fMPR) uses a predefined observation period and truncates medication supply that extends beyond this period. In contrast, PDC focuses on the proportion of days a patient has access to medication based on days covered by prescriptions. It is capped at 100% to prevent overestimation due to overlapping refills. Even when studies rely on pharmacy dispensing data, there is no single standard metric. Further, each of the methods can have numerous variants due to methodological choices such as the observation window, handling of early refills, and grace periods (Sperber, Samarasinghe, and Lomax 2017). These methodological inconsistencies can

lead to significant differences in adherence estimates, even when analysing similar populations or medications (Sperber, Samarasinghe, and Lomax 2017). The appropriate measure depends on the research design, data availability, and study aims as well as the disease and treatment (Shah, Touchette, and Marrs 2023).

2.2.2. Persistence to CVD medications

Measuring persistence is important since most adherence measures do not account for the continuity of medication-taking or gaps between refills (Shah, Touchette, and Marrs 2023). Non-persistence refers to discontinuing or intermittently stopping medication before the treatment period ends (Shah, Touchette, and Marrs 2023). This distinction from adherence is important because patients can stop taking medications for various reasons, including medical advice, and these reasons are not always captured in claims data. Failing to account for non-persistence can lead to biased adherence metrics, making patients appear adherent despite intermittent use (Shah, Touchette, and Marrs 2023). To measure non-persistence, a "grace period" is often used, which is an interval after the last refill, during which if no new refill occurs, the patient is considered non-persistent. The length of the grace period depends on the prescribing patterns in a healthcare system and research goals. A shorter grace period is typically used when assessing continuous medication use, while a longer one is better suited for evaluating medication discontinuation (Shah, Touchette, and Marrs 2023).

Taken together, considering non-persistence alongside adherence provides a more complete understanding of medication use patterns and their impact on health outcomes, helping identify at-risk patients and reduce healthcare costs linked to non-persistence.

2.2.3. Side effects from antidepressant medications

Antidepressants are commonly prescribed for many psychiatric disorders, including MDD, anxiety (ANX) disorders, chronic pain (Bogowicz et al. 2021). Although there are several medications available, fewer than half of patients with MDD respond to the first medication they are prescribed (Ruhé, Huyser, and Schene 2006; Rush et al. 2006). Several studies report side effects to be the most common reason for antidepressant non-adherence globally (Chanie et al. 2025; Unni, Gupta, and Sternbach 2024). Non-adherence to antidepressants has been reported to lead to higher mortality among patients with psychiatric disorders (Biffi et al. 2018).

Antidepressant therapy typically comprises three distinct stages: the initiation or acute phase, lasting approximately 6-12 weeks, the continuation phase, which extends for 6 months after symptom remission, and the maintenance phase for people with recurrent MDD or high relapse risk, which extends to at least 2 years (National Institute for Health and Care Excellence (NICE) 2022). Antidepressants have a delayed onset of therapeutic effects of up to six weeks (Taylor et al. 2006).

During this initiation phase, side effects are common and are expected to diminish over time (Braund et al. 2021). However, a previous study has reported that over half of patients continue to experience side effects after 75–105 days of treatment (Kelly, Posternak, and Alpert 2008). The burden of side effects that are evident early in the treatment (as early as day four) has been shown to predict worse treatment outcomes in a clinical trial of 1008 participants with MDD (Braund et al. 2021). Side effects can significantly affect patients' quality of life and may also delay recovery, especially if lower doses are prescribed to minimise side effects instead of reaching the optimal therapeutic dose through titration.

Antidepressants are divided into several pharmacological classes based on the pharmacological mechanism, the most widely used antidepressant classes include Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. escitalopram), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (e.g. venlafaxine), and Tricyclic Antidepressants (TCAs) (e.g. amitriptyline) (National Institute for Health and Care Excellence (NICE) 2022). SSRIs are considered the first-line treatment for MDD (National Institute for Health and Care Excellence (NICE) 2022). The specific side effects often vary depending on the medication class, for instance, SSRIs and SNRIs are associated with anxiety, gastrointestinal symptoms, sexual dysfunction, sleep disturbances, dizziness, and headaches, while TCAs can cause dry mouth, constipation, sedation, and weight gain (Solmi et al. 2020).

Side effects can vary widely among individuals and are likely influenced by a combination of pharmacological, genetic, and environmental factors. Genetic differences can explain up to 42% of the variation in treatment response (Tansey et al. 2013), however, the role of genetic variation in antidepressant side effects is poorly understood. Genetic variation in cytochrome P450 gene *CYP2C19* has increasingly been recognised as a significant contributor to the variability in antidepressant response and side effects (Fabbri et al. 2018; Campos et al. 2022). In addition to pharmacogenetic variation, polygenic risk to MDD and SCZ has also been linked to treatment outcomes (Kamp et al. 2024; Li et al. 2024a). In Ref. III, we investigate these genetic factors on antidepressant side effects, specifically the genetic variation in a drug-metabolising gene *CYP2C19* and the broader polygenic risk to psychiatric and side effect-related traits.

Most of the research on side effects originates from clinical trials and post-marketing spontaneous case reports which are voluntary reports by patients or health care professionals that notify regulating authorities of suspected side effects (Strom, Kimmel, and PharmD 2019). However, most of the trials evaluating the effectiveness of antidepressants are not suited for assessing adverse outcomes, as they are typically of short duration and lack sufficient statistical power to detect many potential harms (Cipriani et al. 2018). Reporting systems for side effects exist in most countries but it is estimated that 90% of adverse drug reactions are underreported which affects all side effects, including life-threatening incidents (Hazell and Shakir 2006). Therefore, alternative sources of data, such as extracting side effects from clinical notes, could improve the detection of side effects. In

Ref. III, we use a multi-source approach to pool side effects reported by patients and doctors through self-reported questionnaires and clinical notes, respectively, to capture a wider range of side effects.

In conclusion, while antidepressants are a common treatment for MDD and other psychiatric conditions, their effectiveness is often limited by side effects. Current clinical trials and reporting systems also do not capture the full scope of side effects, therefore, expanding the use of real-world data sources, such as clinical notes, could help improve the detection of antidepressant side effects. A better understanding of the genetic factors underlying side effects could reduce treatment discontinuation and improve long-term recovery.

2.3. Real-world health data in pharmacoepidemiology

2.3.1. Electronic health records for studying medication use and side effects

In this section we discuss the sources of data to investigate medication use and side effects. Electronic Health Records (EHRs) are comprised of longitudinal datasets, including patient diagnosis, medication prescription, and purchase information. EHRs, among other sources such as biological samples and self-reported data can be stored in biobanks. Biobanks are valuable sources for research and enable the study of medication-related outcomes at scale.

Real-world data from EHRs and registries provide large datasets for pharmacoepidemiological studies including long-term medication use and tolerability (Tayefi et al. 2021). In addition to diagnostic codes, EHRs can contain information on symptoms, prescriptions, laboratory measurements, and procedures which can be in structured or unstructured form. The first EHR was developed in 1972 by the Regenstreif Institute in the United States, but it was more widely adopted in the 2000s (Honavar 2020). The health information system collecting EHRs was launched in Estonia in 2008 (Taal 2018) and in 2012 the adoption of EHRs in Australia, New Zealand, and northern Europe was nearly universal (Schoen et al. 2012).

Traditionally, self-reported data have been used, but with the increasing availability of administrative data, studies have started to use the latter source for exploring medication adherence and persistence. These data sources offer several strengths: they are easy to code, objective, readily available, reflect real-world adherence, and enable the analysis of larger sample sizes at lower costs compared to prospective and self-reported measures. There are also several weaknesses to measures based on administrative data, including potential errors in data, potential overestimation of adherence, and an uncertain link between refills and consumption (Shah, Touchette, and Marrs 2023; Lam and Fresco 2015) as well as creating reliable case and control groups from EHRs often requiring the input of clinical specialists (Zheng et al. 2020).

In addition to tracking medication use patterns, EHRs can be used to detect side effects from unstructured clinical notes. This has become available with the development of Natural Language Processing (NLP) techniques which involve identifying co-occurrences of medications and symptoms according to specific rules, manually verifying the side effects and then using the previously annotated data to fine-tune a pre-trained NLP model which can further extract side effects. However, this information is challenging to extract since it is associated with different contexts and contains uncertainty in medical reporting. For example, nausea in patient history can refer to a disease symptom or a medication side effect. In addition, clinical texts include complexities like grammatical and spelling errors, different languages, ambiguities, and abbreviations (Tayefi et al. 2021). Despite the challenges, methods like NLP can extract meaningful information for phenotyping and are becoming more widely used in research (Tayefi et al. 2021).

2.3.2. Biobanks as a source of health data

Along with the increase in large-scale health data, biobanks emerged which centralised collections of data including biological materials (such as genomic, proteomic, metabolomic), electronic health record, and questionnaire data (Annaratone et al. 2021).

Among those Estonian Biobank (EstBB), which is central to this thesis, was one of the first biobank initiatives, established in 2001 as part of the Estonian Genome Centre at the University of Tartu in Estonia. EstBB is a volunteer-based biobank that consists of approximately 212,000 participants, representing approximately 20% of the Estonian adult population (Leitsalu et al. 2015; Milani et al. 2025). EstBB includes genotype and other omics, electronic health record, and questionnaire data, additionally a participant portal *MinuGeenivaramu* (MyGenome Portal) was recently launched allowing participants to view their individual genomic research results (Milani et al. 2025). EstBB participants were recruited through medical practitioners and public campaigns; and the demographic is predominantly female, younger, and more highly educated than the general population (Leitsalu et al. 2015). EstBB also enables to contact participants for recall studies, carry out questionnaires among participants, and link the information to existing health information. In Ref. III we have taken advantage of this and pooled side effect information from several data layers of the EstBB, including two self-reported questionnaires and NLP-derived clinical notes.

FinnGen, another biobank used in this thesis, is a population-based biobank comprising 500,000 individuals and housed at the Institute for Molecular Medicine Finland at the University of Helsinki (Kurki et al. 2023). It was initiated in 2017 and is linked to FinRegistry, which includes data on approximately 7.2 million Finnish residents since 2010 (Viippola et al. 2023). FinRegistry covers public healthcare visits, medical conditions, medications, vaccinations, laboratory results, demographics, family relationships, and socioeconomic variables, with

decades of follow-up data. The integration of FinnGen and FinRegistry occurs without requiring additional consent forms from participants and offers diverse information that may not be available in other biobanks. The other advantage of FinnGen is that the Finnish population is an isolated population where multiple historical 'bottlenecks' have led to a unique genetic makeup. To a lesser extent, this is also the case in Estonia, which can present an advantage in genetic studies for the detection of population-specific or population-enriched alleles that are not common in older outbred populations (Kurki et al. 2023). For instance, even if the specific variant is population-specific, the underlying biological mechanism is likely to be conserved between populations and can help identify variants associated with disease (Kurki et al. 2023). FinnGen has also returned individual genomic research results to their participants through the GeneRISK study in Finland (Widén et al. 2022).

Biobanks are important to biomedical research and the development of personalised medicine. However, they have limitations such as lack of diversity and participation bias often resulting in the overrepresentation of healthier, more educated, and wealthier individuals (Schoeler et al. 2023). Data sharing across biobanks is challenging due to legal, ethical, and regulatory barriers. Informed consent and privacy concerns, particularly under the General Data Protection Regulation (GDPR), add complexity to national and international collaborations (Legido-Quigley et al. 2025). For example, in Estonia, EstBB cannot access some sociodemographic information as it is not classified as health data, necessitating additional consent forms, unlike FinnGen, which has broader access to sociodemographic data. Despite challenges, biobanks provide valuable resources for advancing genetic and epidemiological research.

2.4. Genetic variation in complex traits: polygenic scores

Biobanks have enabled researchers to investigate the genetic factors underlying psychiatric and cardiovascular traits, revealing their highly polygenic architecture. Here, we discuss some of the tools used to study common genetic variation in traits, including disease risk and treatment outcomes, as well as their limitations.

Genetic factors play an important role in the aetiology of psychiatric and cardiovascular traits. Family and twin studies of psychiatric conditions report a heritability (i.e. the inherited contribution of genetic variance to trait variance) ranging from 35% for MDD to over 60% for SCZ (Pettersson et al. 2018). Similarly, the heritability estimates reported in twin studies have been between 40-60% for fatal CAD, myocardial infarction, and atrial fibrillation (Aragam et al. 2022; Zdravkovic et al. 2002), indicating a strong genetic component. Non-genetic factors also influence the aetiology of psychiatric and cardiovascular disease and can perhaps explain most of the remaining variance in diseases (Pettersson et al. 2018). Genetic epidemiology has traditionally relied on twin studies, which compare genetic and environmental influences in twins, and candidate gene studies,

which examine specific genes hypothesised to influence a given trait (Fusar-Poli et al. 2022). Over the past two decades, advancements in technology and statistical methods, alongside a reduction in genotyping costs, particularly in microarray technology, have driven the rise of Genome-Wide Association Studies (GWASs). GWAS scans variations across the genome and identifies genetic variants (i.e. Single Nucleotide Polymorphisms (SNPs) associated with a quantitative trait or a disease phenotype (Fusar-Poli et al. 2022). A GWAS compares allele frequency differences across millions of SNPs between individuals affected by a given trait or disease (cases) and unaffected individuals (controls). From these studies, we know that most psychiatric and cardiovascular conditions are polygenic, meaning they are influenced by thousands of SNPs, each contributing only a small fraction of the total genetic variance. Since these genetic effects are small, large sample sizes are required to detect true associations (Choi, Mak, and OReilly 2020). However, GWAS only captures common genetic variants, most of which have small individual effects on complex traits and diseases. Over the years, increasing GWAS sample sizes have enhanced the statistical power to detect SNPs associated with complex traits. The GWAS Catalogue (Lambert et al. 2021) shows a number of studies with over a million participants such as the GWAS for height (Yengo et al. 2022), and blood pressure (Evangelou et al. 2018) as well as for MDD where the GWAS conducted in 5 million individuals identified nearly 700 genetic variants significantly associated with MDD (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. 2025).

2.4.1. The principles and construction of polygenic scores

The increasing availability of GWA-studies has led to the development of polygenic scores (PGSs), which aggregate genetic contributions of variants into a single predictive score to assess an individual's genetic susceptibility to a particular trait (Figure 2). Although nomenclature varies, polygenic risk score or genetic risk score typically refers to disease risk, while polygenic score encompasses both disease-related and non-disease traits, such as neuroticism; therefore, here we use the term PGS (Lambert et al. 2021). A PGS is a single value that summarises an individual's genetic predisposition to a phenotype based on the cumulative effect of multiple genetic variants. The calculation of PGS is based on the summary statistics of GWAS, which provide estimates of the association between SNPs and a given trait (Choi, Mak, and OReilly 2020). The discovery sample is derived from a GWAS in which the genotypes of an individual are weighted by the effect sizes of the relevant SNPs. The results of this analysis are presented as summary statistics which are then used to calculate PGSs in a separate target sample. To avoid inflated effect sizes and overfitting, discovery and target samples must be independent. The target sample consists of individual-level genotype data from a separate population, where the PGS is computed by summing the weighted genotypes of relevant SNPs. This approach assumes that genetic variants contribute

additively to the trait of interest (Choi, Mak, and OReilly 2020). PGSs can be constructed for both binary traits (e.g., presence or absence of disease) and continuous traits (e.g., height, body mass index (BMI)). PGS has a normal distribution in the general population; therefore, meaningful risk predictions can only be expected for extreme percentiles of PGS distributions (Fusar-Poli et al. 2022). Since GWAS typically tests associations between hundreds of thousands of genetic variants with a given phenotype, rigorous quality control is performed to ensure the effectiveness and accuracy of findings (Lewis and Vassos 2020).

Several methods have been developed for PGS construction, with the most widely used approaches including LDpred2 (Priv, Arbel, and Vilhjlmsson 2021), PRS-CS (Ge et al. 2019), PRSice-2 (Choi and O'Reilly 2019), and megaPRS (Zhang, Cao, and Baranova 2021), and SBayesR (Lloyd-Jones et al. 2019). There is no universally accepted methodology, as different methods vary in how they handle linkage disequilibrium, effect size shrinkage, and computational efficiency, however PRS-CS has been recommended for the investigation of complex traits (Pain et al. 2021a).

2.4.2. Evaluating the PGS performance, applications, and limitations

PGS have been shown to correlate with the case status in many complex diseases. A study by Howard *et al.* (2019), also cited in Ref. II as it was the largest GWAS on MDD at the time, reported that individuals in the 10th decile of the PGS for MDD had twice the odds of being a case (odds ratio (OR) = 2.0 per 1 standard deviation (SD) increase, 95% CI = 1.5–2.8) compared to those in the first decile (Howard et al. 2019). However, the prediction has improved over time as the PGS based on the most recent and largest MDD GWAS to date found a four-fold difference in MDD odds per SD between the highest and lowest decile (OR = 4.92, 95% CI = 4.57–5.29) (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. 2025). PGSs have similarly shown to predict CVD, with a UK Biobank study reporting that individuals within the highest 1–5% of the PGS for CAD had over 3-fold higher odds of developing CAD (Khera et al. 2018). The predictive accuracy of the PGS for CAD was also greater for younger individuals (under 50 years), specifically those with high PGS had a 3- to 4-fold increased associated risk of MI compared with those in the bottom 20% (Marston et al. 2023). The PGS based on a GWAS by Evangelou *et al*., also used in our study (Ref. III), found an association between the PGS for systolic blood pressure (SBP) and cardiovascular events, with odds ratios of 3.34 for hypertension, 1.47 for incident composite cardiovascular events, 1.50 for incident stroke, and 1.52 for incident myocardial infarction (Evangelou et al. 2018). Furthermore, individuals in the top 10% of the PGS for SBP had 12.9 mmHg higher SBP than the bottom decile (Evangelou et al. 2018).

In addition to predicting disease risk, PGSs are increasingly researched to help identify treatment outcomes for psychiatric and cardiovascular disorders (Xiang et al. 2024; Lewis et al. 2022; Klarin and Natarajan 2021; Schunkert et al. 2025).

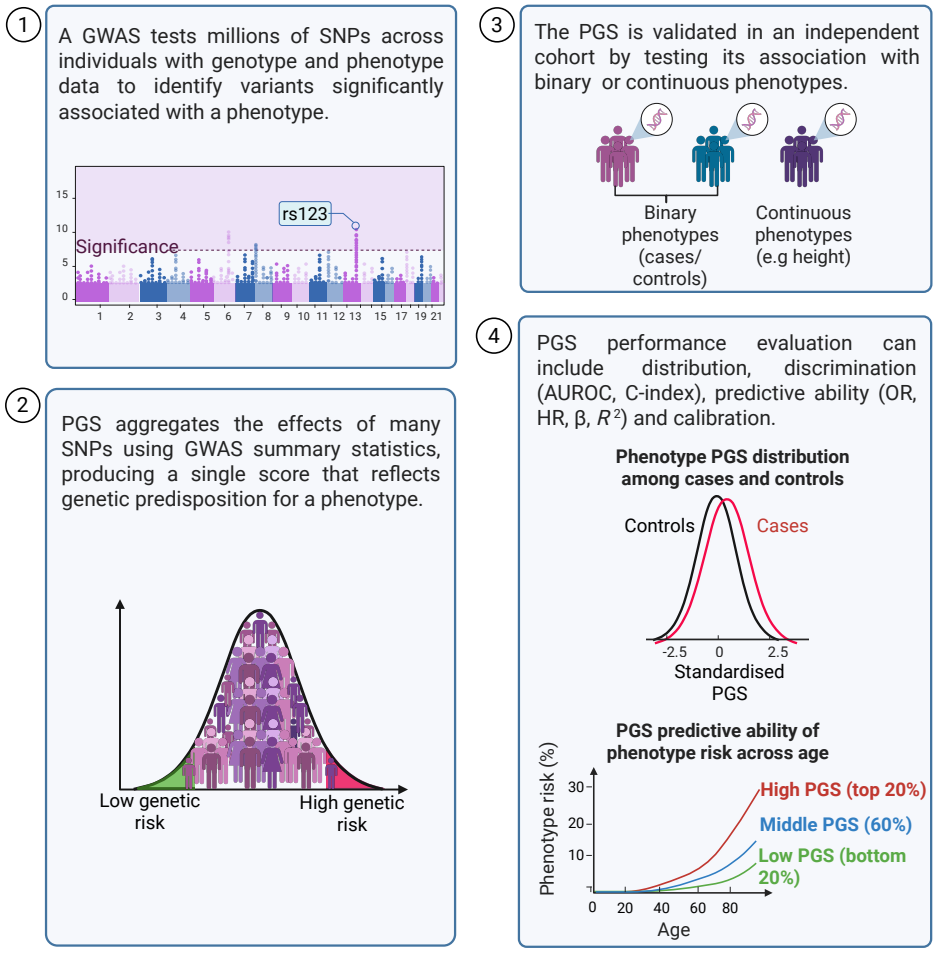

Figure 2. Workflow of PGS development and evaluation of performance. *GWAS is carried out for a phenotype on individuals with genotype and phenotype data (Step 1), where each genetic variant is tested for its association with a trait. Quality control (QC) steps are carried out, including sample QC (removing individuals with high missingness, relatedness or ancestry outliers), SNP QC (excluding variants with low call rate, low minor allele frequency, or Hardy-Weinberg disequilibrium), missing genotype information is imputed using a reference panel, and linkage disequilibrium pruning or clumping removes correlated SNPs that could cause overfitting. GWAS summary statistics are used to calculate a PGS by multiplying the individual's genotype dosage of each SNP (coded as 0, 1, or 2 copies of the risk allele) with the corresponding SNP effect size (β coefficient from GWAS). These weighted values are then summed across all selected SNPs to produce a score representing the individual's genetic predisposition to the trait (Step 2). The resulting PGS is then validated in an independent test cohort (Step 3), using either binary (e.g. disease status) or continuous traits (e.g. height). Performance is assessed using metrics such as discrimination, predictive ability and calibration (Step 4). Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism; PGS, polygenic score; HR, hazard ratio; OR, odds ratio; β, effect estimate; R^2, variance explained; AUROC, area under the receiver operating characteristic curve. Created in BioRender. Kariis, H. (2026) https://BioRender.com/78vzjsg.*

Several PGS for psychiatric disorders and CVDs have been associated with treatment response (Natarajan et al. 2017; Li et al. 2021; Fabbri et al. 2021; Pain et al. 2021b; Shao et al. 2025) and side effect prediction (Kamp et al. 2024; Li et al. 2024a; Campos et al. 2021), although the predictive accuracy is typically lower than for disease prediction. For instance, a meta-analysis of PGS for psychiatric disorders reported a result that individuals within the top 20% of the PGS had 50% higher odds of not achieving remission compared to those in the bottom 20% (OR = 1.5, 95% CI = 1.11–1.98) (Tapela et al. 2022). Some studies have investigated using PGSs to tailor specific treatment decisions. For example, PGSs could guide treatment selection (Campos et al. 2021; Loef et al. 2022), dose (Koch et al. 2024), disease progression (Liebers et al. 2021), age of treatment initiation (Natarajan et al. 2017; Mars et al. 2020; Marston et al. 2023). While many large-scale GWAS and PGS have been conducted on diseases and treatment outcomes, only a few GWA-studies have investigated medication use and calculated PGSs (Türkmen et al. 2025; Wu et al. 2019; Kiiskinen et al. 2023; Seo et al. 2014).

Newer approaches, particularly in CVD, have also made efforts to combine PGS with demographic and clinical factors to improve disease prediction (Figure 3). Although several studies have reported that the integration of PGS with traditional risk factors has enhanced cardiovascular disease prediction (Schunkert et al. 2025; O'Sullivan et al. 2022; Widén et al. 2022; Pirruccello et al. 2024; Riveros-Mckay et al. 2021; Sun et al. 2021), the improvements in prediction accuracy have been modest on a population level (Schunkert et al. 2025; Riveros-Mckay et al. 2021; Elliott et al. 2020). This is likely because most individuals have a similar number of risk alleles with the largest differences being in the individuals at the top and bottom PGS deciles since the effect sizes of risk alleles multiply each other (Pang et al. 2023). Therefore, integrating a PGS with clinical risk factors is likely to have a modest increase in the predictive accuracy at population level, however recent studies suggest that a targeted use of PGSs would be more efficient than population-wide use (Sun et al. 2021). For instance, PGSs can enhance risk stratification in individuals that are younger (Mars et al. 2020) , and have high (Khera et al. 2018; Natarajan et al. 2017) or intermediate risk (Sun et al. 2021). Furthermore, the inclusion of a higher number of SNPs and larger sample sizes for training sets is likely to improve the accuracy.

PGSs offer several advantages, particularly in psychiatric genetics, due to the absence of definitive biomarkers for psychiatric disorders (Andreassen et al. 2023). Furthermore, in current psychiatry practice, the selection of antidepressant treatment follows a trial-and-error approach, which can delay symptom remission (Fusar-Poli et al. 2022). While family history is commonly used to infer genetic risk, it is often incomplete, only reflects shared genetics and environment between family members, and tends to identify familial diseases linked to rare, highly penetrant genetic variants (Dineen et al. 2022; Xiang et al. 2024). Moreover, most people who experience psychiatric disorders have no family history (Wray et al. 2021).

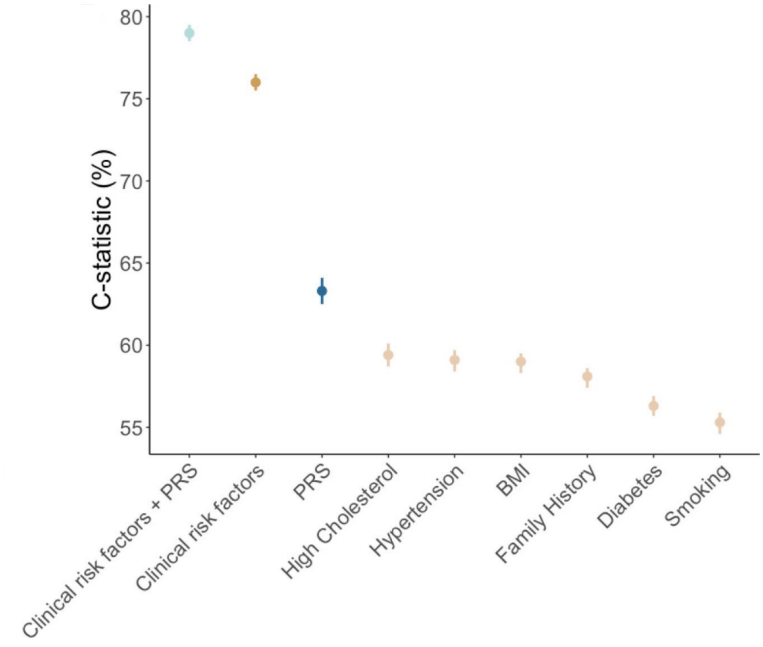

Figure 3. Predictive ability of clinical factors with and without the integration of polygenic score for coronary artery disease. *C-statistic describes the probability that the statistical model will correctly classify a participant who will go on to develop or not develop a disease (discrimination). Figure adapted from et al (O'Sullivan et al. 2022) (DOI: https://doi.org/10.1161/CIR.0000000000001077) under the terms of the Creative Commons CC-BY license. Copyright 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation.*

There are also wider applications of PGSs, for instance they have been proposed as a tool to motivate patients to change their lifestyle (Widén et al. 2022), raising the possibility that sharing genetic risk information with patients could enhance motivation to adhere to prescribed treatments, and other positive lifestyle changes. Furthermore, they could be used to improve the design of clinical trials by enrolling individuals at higher baseline risk of disease development, thereby increasing the chances of detecting an outcome (Fahed, Philippakis, and Khera 2022).

Despite the potential of PGS, there are limitations that need to be addressed. The predictive accuracy of PGS is contingent on the heritability, polygenicity, and GWAS discoverability (Jayasinghe et al. 2024). Most PGSs are derived from studies conducted in European populations, which limits their applicability to individuals of non-European descent. Even for diseases with high heritability, such as SCZ, the predictive accuracy is limited. The predictive accuracy reduces even further from 8.5% to 7.3% when non-European ancestry cohorts are included (Trubetskoy et al. 2022). Furthermore, there is no universally accepted methodology for PGS calculation, leading to inconsistencies between PGSs and complicating cross-study comparisons (Abramowitz et al. 2025). More transferable and accurate PGS can also be developed by increasing sample size and using improved statistical methods such as flexible SNP effect size modelling, incorporating pleiotropic association and SNP functional annotations, and considering multi-ethnic prediction (Ma and Zhou 2021).

Taken together, PGSs represent a valuable tool for understanding genetic contributions to complex traits and diseases. They hold a promise for early prediction of disease risk and treatment outcomes; however, their clinical utility remains limited due to modest predictive power, population biases, and methodological inconsistencies. Future research should focus on refining PGS methodologies, increasing GWAS diversity, and integrating genetic and environmental risk factors to improve prediction models. As the field advances, the responsible application of PGSs will also require careful consideration of ethical implications and clinical validity.

2.5. Genetic variation on medication effects: pharmacogenetics

In addition to common genetic variation, genetic variation in genes encoding enzymes can influence how individuals respond to medications, forming the basis of pharmacogenetics. Here, we discuss some of the genes involved in psychiatric or cardiovascular medication pharmacokinetic processes, their clinical relevance, and limitations.

2.5.1. Genetic variation and its effect on the pharmacokinetics of medications

Pharmacogenetics (PGx) focuses on understanding how genetic variation in drug-metabolising enzymes, drug transporters, and drug targets affects treatment efficacy, effectiveness, and adverse effects. PGx aims to personalise drug treatments based on an individual's genetic makeup, shifting from the traditional "one-size-fits-all" approach to tailored dosages and drug choices.

A drug undergoes both pharmacokinetic (ADME) and pharmacodynamic processes to exert its effects on the body (Roden et al. 2019). Pharmacokinetics refers to how the body absorbs, distributes, metabolises, and eliminates a drug (ADME), while pharmacodynamics describes how the drug interacts with its target molecules and receptors to produce therapeutic or adverse effects (Roden et al. 2019). Genetic variants that impact any of these processes can significantly influence treatment outcomes. It is estimated that approximately 20–30% of interindividual differences in drug response are due to variation in pharmacogenes that regulate ADME processes (Lauschke, Zhou, and Ingelman-Sundberg 2024). Most clinically relevant PGx interactions involve genes related to pharmacokinetics, such as those encoding cytochrome P-450 (CYP) enzymes, which are responsible for catalysing phase I reactions in drug metabolism (Kalman et al. 2015). With over 57 CYP enzymes identified, these enzymes account for approximately 90% of drug metabolism (Abdelmonem et al. 2024). Furthermore, over 2,000 mutations have been found in CYP P-450 genes, significantly affecting enzyme activity (Wrighton, VandenBranden, and Ring 1996). In addition, structural variations such as duplications and deletions of DNA segments can impact drug exposure and treatment outcomes (Roden et al. 2019). One such structural variation is Copy Number Variant (CNV), which involves changes in the number of copies of DNA segments. CNVs can involve deletions (a decrease in the number of copies) and duplications (an increase in the number of copies), thereby affecting drug exposure (Tansey et al. 2014).

In the current work, we mostly focus on variation in CYP-P450 genes which have a role in drug metabolism, including *CYP2C19* (antidepressants and clopidogrel), *CYP2D6* (tamoxifen), *CYP2C9* (fluvastatin) as well as other known transporter genes *ABCG2* (rosuvastatin), and *SLCO1B1* (all statins). For CYP2C19, we consider star alleles (Pratt et al. 2018), including a CNV with a partial deletion of CYP2C19*37. CYP2C19*37 marks a deletion of exons 1-5 and has been reported to lead to no enzyme function by CPIC but with limited evidence (ClinPGxCPIC 2025).

2.5.2. Nomenclature in pharmacogenetics

Haplotypes are combinations of genetic variants within a gene that are inherited together on a single chromosome (Kalman et al. 2015). Since pharmacogenes are often polymorphic, the pharmacogene haplotypes are classified using the

star (*) nomenclature system (Kalman et al. 2015). Each star allele (e.g., *1, *2, *3) represents a distinct set of genetic variants that may alter the function of the encoded enzyme or protein. These variations can include small genetic variations, including SNPs or short insertions/deletions (i.e. indels, typically <50 base pairs) as well as structural variations which are larger (typically 50 base pairs), including copy number variations.

The pair of haplotypes at a gene locus inherited from both parents are called diplotypes, and the metabolic capacity of a protein depends on the diplotype. Typically, wild-type alleles represent standard enzyme activity and are typically referred to as *1 haplotype. Individuals with two wild-type alleles are normal or extensive metabolisers (NM/EM) (Figure 4). Individuals with two loss-of-function alleles are called poor metabolisers (PM) and they have slower enzyme function which can lead to higher drug exposure. Intermediate metabolisers (IM) inherit one wild-type and one loss-of-function allele, leading to decreased enzyme function. Rapid metabolisers (RM) inherit one wild-type and one increased function allele and ultra-rapid metabolisers (UM) have two or more copies of the gene and typically have enzyme with increased activity, requiring higher doses to achieve a therapeutic effect (Kalman et al. 2015).

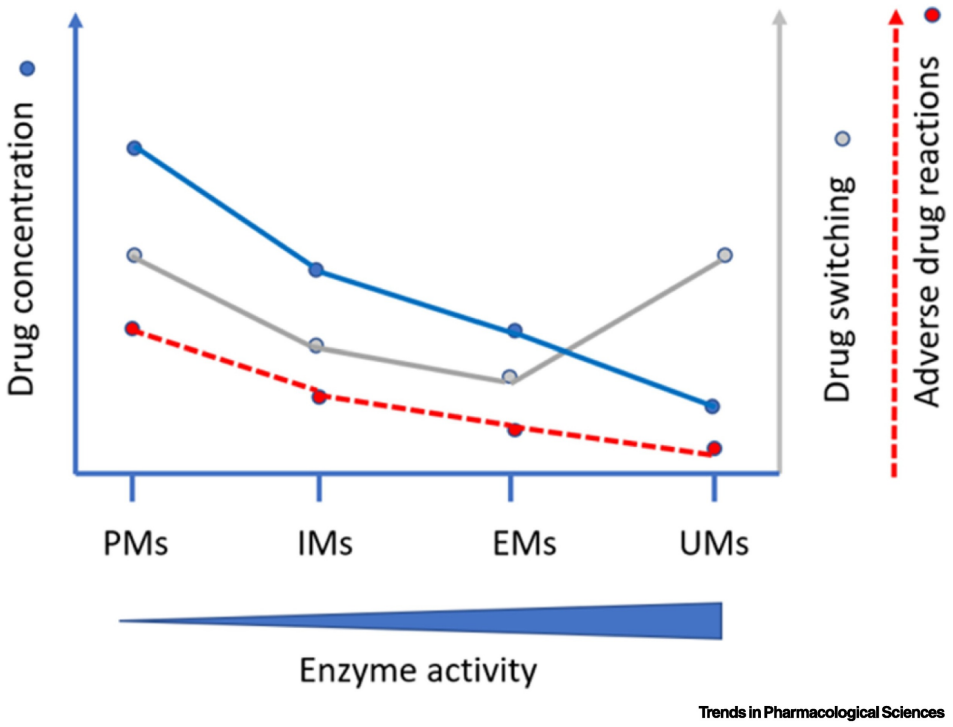

Figure 4. Effects of CYP2C19 phenotypes on drug metabolism. *Patients with inactive enzymes (PMs) have higher drug serum concentrations due to slower metabolism rate which may increase drug efficacy but can lead to an increased likelihood of side effects and drug switching. On the other hand, patients with excessive enzyme activity (RM, UMs) often experience low or no drug concentration, which makes the drug less effective, resulting in fewer side effects but more frequent medication adjustments. Abbreviations: EM (extensive metaboliser), IM (intermediate metaboliser), PM (poor metaboliser), UM (ultrarapid metaboliser). Figure reproduced from (Jukic et al. 2022) DOI: 10.1016/j.tips.2022.09.011. Published by Elsevier under the Creative Commons CC BY 4.0 license. No changes were made.*

Based on this classification, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) guidelines also provide dose recommendations for several genes and medications (Bousman et al. 2023; Hicks et al. 2015; Brouwer et al. 2022). For instance, the DPWG advises against using escitalopram in individuals who are *CYP2C19* UMs because its effectiveness may be reduced; instead, alternatives such as paroxetine or fluvoxamine are recommended (Brouwer et al. 2022). In contrast, PMs of *CYP2C19* have an increased risk of QT interval prolongation and potentially fatal arrhythmias like torsades de pointes tachycardia, requiring a reduction of escitalopram to 50% of the usual maximum dose. For IMs, a maximum of 75% of the standard dose is advised.

2.5.3. Clinical relevance and implementation

Although minor allele frequencies of specific variants in most common pharmacogenes are low and range from approximately 0.1-5% (Koopmans et al. 2021), approximately 99% of individuals have at least one actionable variant for a drug when classified according to the CPIC labels (Smith et al. 2020). Furthermore, nearly half of patients were taking a drug affected by genetic variation in a pharmacogene during the study, suggesting that the likelihood that an individual will be prescribed such a drug over their lifetime is even higher (Smith et al. 2020). The Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) RCT showed that genotype-guided prescribing reduced the incidence of clinically relevant adverse drug reactions by 30% in antidepressant users (Swen et al. 2023). In addition, antidepressant treatment guided by the highest CPIC evidence levels (A and B) has been reported to be either cost-effective or cost-saving (Morris et al. 2022).

Genetic variants of *CYP2C19* and *CYP2D6* are responsible for metabolising several antidepressants, including some SSRIs and TCAs, and are most clinically relevant to the pharmacokinetics of antidepressants. They are also involved in the metabolism of antiplatelet and cancer drugs clopidogrel and tamoxifen, respectively. The *CYP2C19*/*CYP2D6* genotypes have been associated with altered exposure to antidepressants (Hodgson et al. 2014; Milosavljevic et al. 2021; Jukic et al. 2018) and antipsychotics (Milosavljevic et al. 2021). However, the association between *CYP2C19* and drug response or side effects is inconsistent, with some studies finding links to drug response (Campos et al. 2022; Fabbri et al. 2018) and side effects (Campos et al. 2022; Calabrò et al. 2022; Mrazek et al. 2011), while others report no such link (Hodgson et al. 2014; Li et al. 2024b; Peters et al. 2008; Maggo et al. 2019).

The relationship between genetic variation and treatment response or side effects is complex, influenced by both genetic and non-genetic factors (Alomar 2014), such as dosage, drug mechanisms, interactions with other cytochrome P450 enzymes or modulating concomitant drugs, as well as age, sex, and other non-genetic and environmental factors such as diet, lifestyle, and comorbidities (Fornaro et al. 2019; Sang et al. 2025; Scherf-Clavel et al. 2024; Alomar 2014).

There are several challenges to implementing it in routine clinical care, including population diversity, lack of data interoperability, limited clinical guideline integration, and insufficient education for clinicians and patients (Yang et al. 2021; Pirmohamed 2023).

Two major European initiatives are actively addressing these barriers. The Ubiquitous Pharmacogenomics (U-PGx) project (Manson et al. 2017) is deploying pre-emptive PGx testing in seven countries by integrating genetic data into electronic health records and linking them to clinical decision support systems. This enables real-time, genetics-informed prescribing to reduce adverse drug reactions and improve efficacy. Meanwhile, the Beyond 1 Million Genomes (B1MG)

initiative (Beyond 1 Million Genomes Project 2022; Saunders et al. 2019) focuses on building the legal, technical, and infrastructural frameworks needed for cross-border genomic data sharing and aims to improve the representation of diverse ancestries in PGx research, supporting equitable and standardised implementation across Europe.

To support these goals, several genomic databases provide essential information on the function and population frequency of pharmacogenes. Resources such as GnomAD (Collins et al. 2020) and 1000 Genomes Project (Byrska-Bishop et al. 2022) for population-level genetic variation, ClinVar (Landrum and Kattman 2018) for clinical variant annotations, PharmVar (Gaedigk et al. 2018; Gaedigk et al. 2021) for standardised pharmacogene allele definitions and clinical guidelines help to translate research findings into clinical recommendations.

Taken together, genetic variation in PGx genes plays a role in interindividual variability in responses to medications. Pharmacogenetics enables the identification of actionable variants that influence drug efficacy and safety, thereby facilitating a shift towards personalised treatment strategies. Despite substantial evidence, supporting the clinical utility of PGx-guided prescribing in routine care remains limited. Several initiatives are ongoing to address these challenges by standardising allele nomenclature, enabling cross-border data sharing, and promoting equitable inclusion across diverse populations. As these efforts continue to mature, pharmacogenetics has the potential to improve therapeutic outcomes and reduce harm for patients across healthcare systems.

3. AIMS OF THE STUDY

This thesis investigates the influence of genetic factors on medication usage patterns and side effects in psychiatric and cardiovascular conditions.

3.1. Ref. I

The overarching aim of the study was to better understand the determinants of medication adherence and persistence across several medication classes using large-scale real-world health data from the FinnGen and the Estonian Biobank. Here, we focus on a subset of this study conducted using data from the Estonian Biobank with the aim to investigate the role of common genetic factors in long-term medication adherence and persistence to statin therapy, and to examine pharmacogenetic variation in genes affecting the pharmacokinetics of statins (pooled and individual agents fluvastatin and rosuvastatin), clopidogrel, and tamoxifen.

3.2. Ref. II

To assess the role of depression, its polygenic risk, and antidepressant treatment on the long-term adherence and persistence to antihypertensive medications using biobank data linked with electronic health records.

3.3. Ref. III

To investigate the influence of genetic factors in antidepressant side effects, leveraging side effect information from questionnaires and unstructured electronic health records extracted using natural language processing. The primary focus was to investigate the associations between the *CYP2C19* genetic variation and polygenic liability to complex traits in the experiencing of side effects from antidepressants. In addition, we meta-analysed our findings with an external cohort from the Australian Genetics of Depression Study (AGDS).

4. METHODS

4.1. Study design and population

4.1.1. Ref. I

Ref. I used a population-based cohort design using data from the Finnish national registry (FinRegistry) and genotype information from Finnish and Estonian biobanks (FinnGen, EstBB). The total study population consisted of 1,814,591 individuals with drug prescription and health records, of whom 217,005 had available genetic data (185,931 individuals in FinnGen and 31,074 in EstBB) (Figure 5). The cohorts included adults prescribed long-term medications from five medication classes including statins, blood pressure medications, antiplatelets, breast cancer medications, and direct oral anticoagulants. In EstBB, we included individuals who had used statins (Anatomical Therapeutic Chemical Classification (ATC) codes C10AA*) and for pharmacogenetic analyses, considered individuals taking the following individual medications: clopidogrel (ATC B01AC04), tamoxifen (L02BA01), fluvastatin (ATC C10AA04), and rosuvastatin (ATC C10AA07). The study population in EstBB consisted of individuals who initiated their treatment between 2007–2023 and were over the age of 18 at treatment initiation.

We constructed drug purchase trajectories in EstBB based on NHIF-derived EHRs. NHIF covers over 95% of the Estonian population as a result of universal health care in Estonia and thus provides information on diagnoses, prescribed and dispensed drugs since 2004 from primary and specialist care. Information on prescribed and dispensed drugs is collected from all pharmacies in Estonia. The NHIF database contains information on the prescribed and dispensed drug name, date of prescription and dispensing, International Statistical Classification of Diseases 10th Revision (ICD-10) diagnosis codes, ATC code of the drug, number of packs dispensed, number of dosage units (i.e. tablets, capsules or similar solid dosage forms) in each package, and the concentration of active ingredient in each unit. As most oral dosage units considered in this thesis are prescribed in tablet form, the term tablet will be used throughout this work as a shorthand for oral solid dosage forms. Since 2016, the NHIF also collects information on the daily drug dose prescribed by the clinician, although work is ongoing in the NHIF to improve the completeness of this data.

4.1.2. Ref. II

The study leveraged EHR data from NHIF for participants in EstBB. The study sample included 20,724 individuals with newly diagnosed Hypertension (HTN) and who initiated AHMs between 2009 and 2017. HTN was defined as having at least two ICD-10 diagnosis codes (I10-I15) and two dispenses of AHMs during follow-up, including diuretics (ATC C03*), beta-blockers (C07*), calcium channel blockers (C08*), or renin-angiotensin system agents (C09*). Loop diuretics

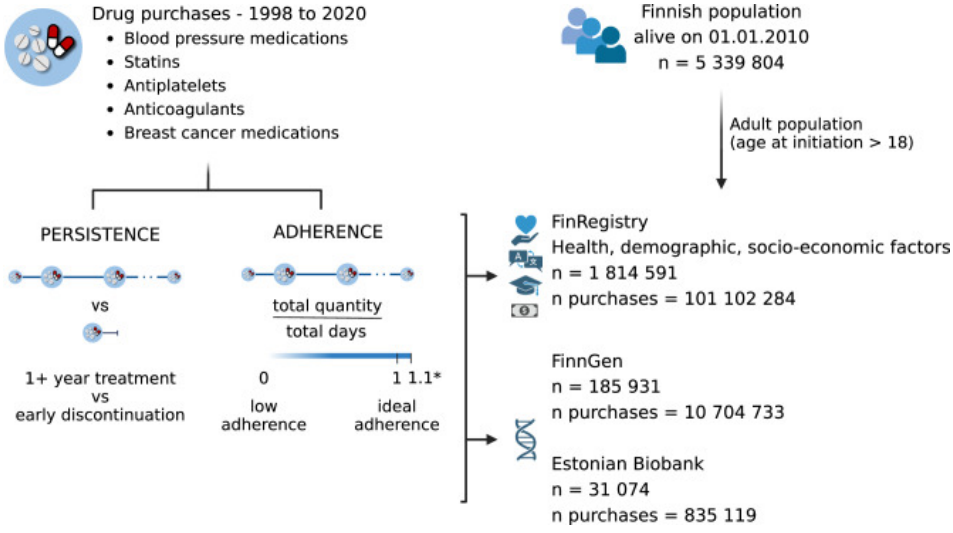

Figure 5. Ref. I study design overview. *Figure reproduced from (Cordioli et al. 2024) in accordance with Open Access terms. We included all individuals resident in Finland and alive on the first of January 2010 (N=5,339,804) and used information from the Finnish drug purchase register to identify individuals with at least one purchase for the following medication classes: blood pressure medications, statins, antiplatelets, direct oral anticoagulants, and breast cancer medications. We considered only the adult population, starting the treatment after age 18, and reconstructed individual medication purchase trajectories as a proxy to define the medication use phenotypes: persistence and adherence. Persistence was defined as continuing the treatment for at least 1 year versus discontinuing it after the first purchase. We defined adherence as the medication possession ratio (ratio of the quantity purchased in the observation period to the days in the observation period), for patients continuing the treatment for at least 1 year. Adherence is a continuous trait ranging from 0 (complete lack of adherence) to 1 (ideal adherence). *We excluded patients with adherence above 1.1, to exclude excessive stockpiling or overbuying behaviours, but still allowing for some variability. We then studied the association of these two medication-use phenotypes with health, demographic, and socioeconomic factors from nationwide registries (N = 1,814,591 with complete information) and with genetic information for a subset of the population from the FinnGen study (N = 185,931) and from Estonian Biobank (N = 31,074).*

furosemide and torasemide (C03C*) were excluded due to their short-term or as-needed use. Lifetime MDD was defined as having at least one ICD-10 code of F32*, F33*, or F41.2 over the EHR data availability period between 2004–2021. Despite the ICD-10 code F41.2 being grouped under anxiety disorders, it was included due to its common use to diagnose MDD with anxiety in Estonia. The sample included 6,294 cases of hypertension and MDD, as well as 14,430 controls with hypertension but without MDD. Patients were followed for three years from the first AHM dispense and those who died within four years of treatment initiation were excluded (n = 878).

For the secondary analysis to study the influence of antidepressant treatment on AHM adherence, the study population included a subset of patients with hypertension who had received their first MDD diagnosis at least six months before the end of follow-up and had made at least two purchases of antidepressants (ATC N06A*) on distinct days within six months of their first MDD diagnosis (n = 132).

4.1.3. Ref. III

We leveraged self-reported side effect data from the Adverse Drug Events Questionnaire (ADEQ) (N = 49,366) (Milani et al. 2025) and the Mental Health Online Survey (MHoS) (N = 86,244) (Ojalo et al. 2024) conducted in EstBB (Figure 6). Additionally, we extracted antidepressant side effects from unstructured EHRs of 206,066 EstBB participants using natural language processing. Side effect extraction from EHR free text was conducted in two rounds (2022 and 2024) and involved three stages: 1) construction of a library of drug names and symptoms, 2) relation classification, 3) manual verification by medical experts. In the first round, we created a library of drug and symptom lexicons, applied rule-based filtering to select relevant text snippets for approximately 50,000 participants, which were manually reviewed by clinical experts. In the second round, we included a larger sample of EstBB participants (N = 206,066) and used the EstRoberta model (EMBEDDIA 2021), fine-tuned on the data from round 1, using Huggingface (Hugging Face 2024) library, to classify snippets. The identified side effects of selected antidepressants were then manually verified and only the verified side effects were used in the study.

We pooled side effect information from questionnaires and clinical notes (Figure 6). Participants who had used at least one of the 16 most prescribed antidepressants and reported the presence or absence of side effects of any of the 23 most common side effects were included.

Given the broad use of antidepressants (e.g. for MDD, ANX, sleep disorders, chronic pain), we performed a subgroup analysis of participants with MDD diagnoses recorded in EHRs (ICD-10 F32*, F33*, F41.2) (79.5% of the study cohort, n = 10,914) between 2004 and March 2023, to reduce diagnostic and treatment heterogeneity.

We also analysed a subgroup treated with CYP2C19-metabolised antidepressants, given the enzyme's influence on drug exposure and side effect risk (n = 9,563).

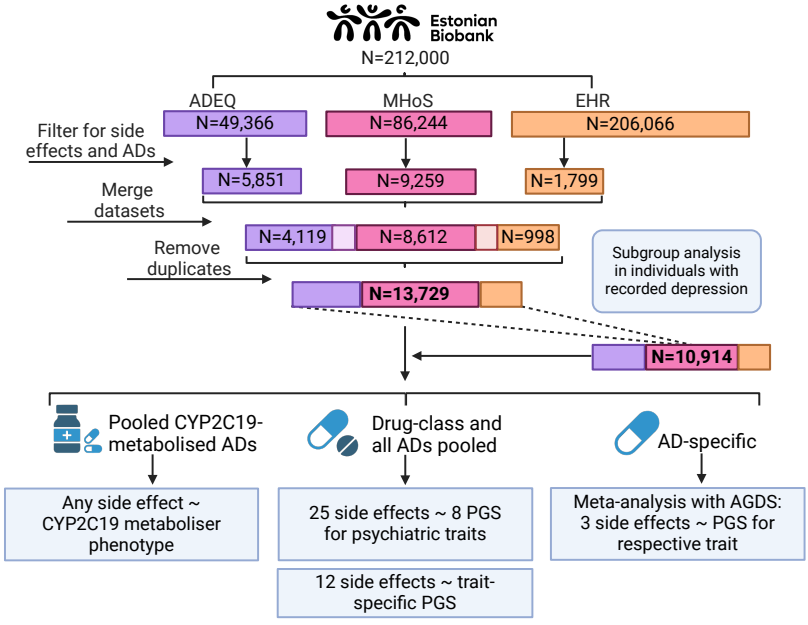

Figure 6. Ref. III study design overview. *Three data layers containing side effect information for the Estonian Biobank participants were used. The data layers ADEQ, MHoS, and EHR were merged and antidepressants users with distinct side effects and no side effects were retained. The sample was used to carry out analyses in different drug subgroups: 1) four drugs metabolised by CYP2C19 pooled for pharmacogenetic analysis; 2) all drugs combined and drug classes separately (SSRI; SNRI+Atyp.; TCA) for PGS analyses for psychiatric trait and trait-specific analyses; 3) meta-analysis with AGDS on individual drug-level. A subgroup analysis was carried out by restricting the sample to individuals with a recorded depression diagnosis. AD-antidepressant; PGS-polygenic score; MHoS-Estonian Biobank Mental Health online Survey; ADEQ-Estonian Biobank Adverse Drug Events Questionnaire (ADEQ); EHR-electronic health records; AGDS-Australian Genetics of Depression Study; TCA-tricyclic antidepressant; SSRI-selective serotonin reuptake inhibitor; SNRI+Atyp.-serotonin-norepinephrine reuptake inhibitor and atypical antidepressant. Created in BioRender. Kariis, H. (2024) https://BioRender.com/t02y173.*

4.2. Treatment-related phenotypes

4.2.1. CVD medication adherence

In Ref. I, we constructed drug purchasing trajectories for each individual, considering all purchases for each medication class (Figure 5). We then estimated adherence using the MPR measure:

$$\text{MPR} = \frac{\text{days of supply during observation period}}{\text{days in observation period}}$$

where:

- The days of supply during an observation period was the total number of tablets purchased in the time interval, normalised assuming drug-specific daily doses which was 1 tablet/day for statins, clopidogrel and tamoxifen.
- The days in the observation period was the sum of the intervals (in days) between all purchases considered in the trajectory.

The trajectory was constructed from the first purchase until the end of treatment, excluding the last purchase. In the FinRegistry, purchases with a 150-day interval between purchases without tablets were excluded as these were considered a break in treatment due to potential hospitalisation. In EstBB, we did not exclude the intervals with 150-day gaps in purchases since the hospital stays are typically short, therefore all refill gaps were treated as true treatment interruptions. When individuals switched to a different drug within the same medication class and the interval between purchases was shorter than the drug supply, we discarded the leftover tablets of the previous formulation. We included only individuals with at least one year of purchases that were based on purchases of at least 150 tablets, based on the assumption that they might have been taking half a tablet per day as prescribed. We further excluded individuals with adherence greater than 1.1, to exclude stockpiling.

In Ref. II the adherence to AHM was assessed using MPR based on previous recommendations for assessing AHM adherence (Vink et al. 2009; Halpern et al. 2006). As hypertension treatment is typically lifelong, the observation period was fixed to three years (1095 days). Adherence was estimated using MPR, which refers to the total days' supply divided by the number of days in the observation period (1095 days). Last refill was included if the supply could be used within the study timeframe, but supply beyond the time interval was truncated. No distinction was made between specific AHMs or AHM classes. New refills for AHM were assumed to start on the day after the previous drug supply ended. MPR values greater than 1.0 were truncated to 1.0, to limit assumed excess in the measure.

4.2.2. CVD medication persistence

In Ref. I we defined drug persistence as a binary phenotype, comparing individuals taking the statin or tamoxifen medications for at least 12 months (i.e. all individuals included in the adherence analysis) versus patients discontinuing the drug after one purchase, containing less than three packs and 100 tablets Figure 5. For antiplatelet clopidogrel, we did not analyse persistence, as this class of medications is frequently prescribed for temporary treatments of 6 to 12 months. We limited the drug supply that could be bought with one purchase to exclude indi-

viduals who may have stocked medications due to, for example, long travels. To avoid right censoring, only purchases made at least one year before the end of follow-up were considered. The end of follow-up date was either death date or the last date for which the data were available (28th of March 2023).

In Ref. II AHM persistence was defined using an anniversary method (Caetano, Lam, and Morgan 2006) where a patient was considered persistent if they refilled a prescription within 180 days of their last prescription or if their last refill was within 180 days from the end of the study follow-up period (Figure 7). The 180-day measure was based on the specifics of the Estonian medical system, where a repeat prescription is valid for six months.

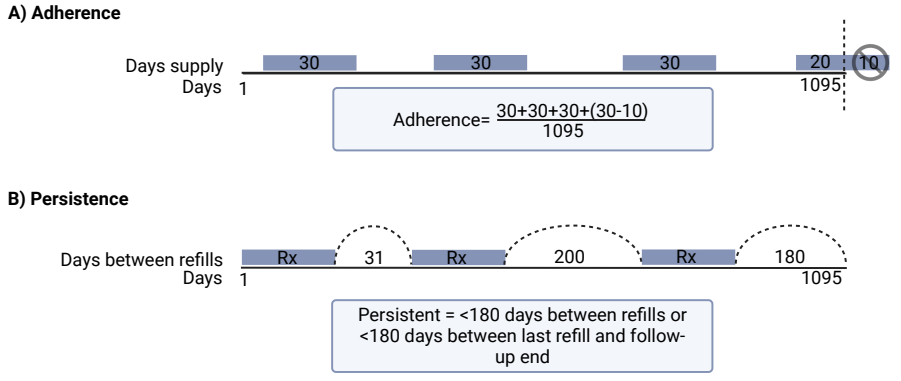

Figure 7. Measures of AHM medication adherence and persistence. ***A)*** *AHM adherence describes the total days of supply within a study period divided by the number of days in the study period.* ***B)*** *AHM persistence was defined as having less than 180 days between refills and between the last refill and follow-up end. Example of a non-persistent drug user. Created with BioRender.com.*

4.2.3. Antidepressant side effects

In Ref. III, we analysed 23 antidepressant side effects reported by at least 100 individuals, including sleepiness, mouth dryness, constipation, headache, weight gain, heart palpitations, sexual dysfunction, nausea, weight loss, blood pressure increase, blood pressure decrease, insomnia, agitation, allergic reaction, diarrhoea, sweating, mood change, irritability, dizziness, grogginess, anxiety, rash, and chills. Additionally, all side effects were pooled into "any side effect," while heart palpitations, weight gain, and increased blood pressure were grouped as "cardiometabolic side effects". Cases were defined as individuals reporting a specific side effect for a drug or drug class, while controls were antidepressant users without that specific side effect.

4.3. Genotyping and imputation

DNA samples from the Estonian Biobank were genotyped at the Core Facility of Genomics at the Institute of Genomics, University of Tartu. Genotyping was conducted using Illumina Global Screening Arrays. Standard quality control and imputation steps were carried out by the Bioinformatics Core Lab of the Institute of Genomics, University of Tartu. Briefly, genotype data were processed into PLINK format using Illumina GenomeStudio v2.0.4. Genotype data quality control was performed according to the best practices. Specifically, individuals with call rate <95%, who deviated $\pm$3SD from the samples' heterozygosity rate mean or showed mismatch between heterozygosity of the X chromosome and sex based on phenotype data were excluded; all AT and GC SNPs, invariable SNPs, SNPs showing potential traces of batch bias, poor cluster separation results and inconsistent allele frequency among any of the EstBB genotyping experiments were removed). Pre-phasing was conducted with Eagle v2.4.1 software (Loh et al. 2016). For imputation, the population-specific hg19 imputation reference panel of 2,695 WGS samples was used (Mitt et al. 2017). Imputation was done using Beagle (Browning and Browning 2007).

4.4. Polygenic scores

PGSs in Ref. II and III were computed using PGS-CS software, a Bayesian polygenic prediction method (Ge et al. 2019). PGS-CS infers posterior SNP weights using GWAS summary statistics and an external LD reference panel (1000 Genomes Project European) by placing a continuous shrinkage prior on SNP effect sizes (Ge et al. 2019). Genetic variants with minor allele frequency $< 1\%$, imputation info score of < 0.8, significant deviation ($p < 10^{-4}$) from Hardy-Weinberg equilibrium, and ambiguous strands (A/T and C/G) were removed from PGS calculations. In Ref. I, weights from trait-specific GWAS for 33 PGS were applied to all EstBB individuals using PLINK (Purcell et al. 2007).

The PGSs were transformed into z-scores. To control for the sample overlap between discovery and testing data, whenever possible leave-EstBB-out summary statistics were used. When leave-EstBB-out summary statistics were not available, individuals overlapping in the discovery and testing cohorts were excluded from the PGS analyses. The PGSs were based on the most recent GWAS for each trait.

4.5. Pharmacogene metaboliser phenotypes

Star alleles in Ref. I and III were called based on phased and imputed genotypes. In Ref. III the CNV data was called with PennCNV (Wang et al. 2007), while star alleles were determined using PharmCAT (Sangkuhl et al. 2020) and an in-house

pipeline (Reisberg et al. 2019), retaining only overlapping calls for downstream analyses.

In Ref. I, we selected variants based on the guidelines by the CPIC (Relling and Klein 2011; Cooper-DeHoff et al. 2022; Lee et al. 2022; Goetz et al. 2018), in the following genes: *ABCG2* for rosuvastatin, *CYP2C9* for fluvastatin, *SLCO1B1* for all statins, *CYP2C19* for clopidogrel, and *CYP2D6* for tamoxifen. For each gene, we defined individual diplotypes and grouped them into phenotypes defined based on each diplotype activity score. Patients were divided into groups reflecting the metabolic activity based on their diplotypes, including poor, decreased, normal, increased function for SLCO1B1 and ABCG2 as well as poor, intermediate, normal, ultrarapid metaboliser for CYP2D6, CYP2C9, and CYP2C19.

In Ref. III, we included tier 1–2 *CYP2C19* star alleles (Pratt et al. 2018) and the partial deletion of *CYP2C19**37. In EstBB, *CYP2C19**37 carriers were defined as individuals with ~61.8 kbp deletions overlapping *CYP2C19* exons 1–5. No *36 full gene deletion carriers were discovered. Individuals were divided into five metaboliser phenotypes based on their combination of *CYP2C19* star alleles and the presence of the *CYP2C19**37 partial deletion: normal (**1/*1, *1/*38, *38/*38*), rapid (*1/*17, *17/*38), ultrarapid (**17/*17*), intermediate (carrier of a deficient allele: *2,*3,*4,*8, *37), and poor (compound heterozygote or homozygote for deficient alleles).

4.6. Covariates

4.6.1. Ref. I

For analyses with PGS, we included the PGS for 33 major diseases, disease risk factors, and behavioural traits as well as first ten genotype Principal Components (PCs). For pharmacogenetic analyses, we considered pharmacogene metaboliser phenotypes were included with four levels, including poor, decreased, normal, increased function for SLCO1B1 and ABCG2, as well as poor, intermediate, normal, ultrarapid metaboliser for CYP2D6, CYP2C9, and CYP2C19.

4.6.2. Ref. II

Covariates were age at treatment initiation, sex, educational attainment, BMI, the first five genotype PCs, and the PGS for MDD, SBP, and diastolic blood pressure (DBP). The latter two PGSs were used as a proxy for HTN severity as these PGSs have been associated with uncontrolled and treatment-resistant hypertension (Tapela et al. 2022; Acosta et al. 2023).

4.6.3. Ref. III

Birth year, sex, and the first 10 genotype PCs were included as covariates. We created 19 psychiatric and trait-specific PGS. In pharmacogenetic analyses, CYP2C19 metaboliser phenotype was included, which contained five levels based

on the patients' combination of *CYP2C19* star alleles and the presence of the *CYP2C19**37 partial deletion: normal, rapid, ultrarapid, intermediate, and poor.

4.7. Statistical analyses

4.7.1. Ref. I

Statin use and PGS for 33 major diseases, disease risk factors, and behavioural traits

We tested the associations between 33 individual PGSs and statin adherence or persistence in EstBB using a linear or logistic regression model, adjusting for sex, age at initiation, and the first 10 genetic PCs. The PGS, age at treatment initiation, and PCs were standardised using z-score standardisation (mean = 0, SD = 1). Multiple testing was corrected for using Benjamini-Hochberg False Discovery Rate (FDR) (Benjamini and Hochberg 1995). The model results for adherence are reported as percentage change in adherence calculated by rescaling the log(OR) from the linear model by a factor of 1.1 (maximum adherence value).

Pharmacogene analyses in statins, clopidogrel and tamoxifen

We used a logistic or linear regression model to estimate the association of persistence or adherence, respectively, with the pharmacogene metaboliser phenotype. The analyses were adjusted for sex, age at initiation, and the first 10 genetic PCs. For *SLCO1B1* all statin users were considered, independent of the type, but for *ABCG2* and *CYP2D9* only rosuvastatin and fluvastatin users were considered, respectively. For *CYP2C19* we considered individuals taking clopidogrel, and for *CYP2D6* only those taking tamoxifen. Metaboliser phenotypes were tested when at least five individuals per metaboliser group were included in the adherence analysis, or if at least five persistent/non-persistent individuals were available for the persistence analysis. We used Bonferroni correction to correct for multiple testing of 25 phenotypes ($p < 0.002$). The results for adherence are reported as percentage change in adherence.

4.7.2. Ref. II

Depression diagnosis link to AHM use

Since the AHM adherence variable was a proportion in the range [0, 1], the associations between MDD and adherence were assessed using fractional logistic regression with robust standard errors to account for the proportional nature of the outcome variable. Logistic regression was used to assess the associations between MDD and persistence.

Four models were constructed, with MDD as the predictor and adherence or persistence as the outcome. Model 1, adjusted for age at AHM initiation and sex, was the primary model used to determine the strength of the association between MDD and adherence or persistence due to having the largest sample size and

therefore the largest power for the analysis. Subsequent models incorporated additional covariates, while including the covariates from the previous models: educational attainment and BMI (Model 2), PGS for MDD and the first five PCs of genetic variation for population stratification (Model 3), and the PGS for SBP and DBP (Model 4).

Depression treatment and AHM adherence

Secondary analyses used a linear mixed-effects model to explore the impact of antidepressant initiation on AHM adherence. We modelled AHM adherence six months after the first antidepressant purchase as a function of AHM adherence six months before the first purchase, adjusting for age at AHM initiation and sex. The first month after antidepressant initiation was excluded to account for an up to six-week delay in the onset of antidepressant therapeutic effects (Taylor et al. 2006). Significance was set at a P value of less than 0.05.

4.7.3. Ref. III

Side effect burden and CYP2C19 metaboliser phenotype analyses

The associations between CYP2C19 metaboliser phenotype and the presence of any antidepressant side effect were assessed in individuals taking antidepressants metabolised by CYP2C19 (escitalopram, citalopram, sertraline, or amitriptyline) using logistic regression. The models were adjusted for birth year, sex, and the first 10 PCs of the genotype. The CYP2C19 normal metaboliser phenotype was used as a reference.

Antidepressant side effects and their link to psychiatric and trait-specific polygenic score

The PGS analyses were divided into two main sub-analyses: psychiatric trait analyses, which examined the relationship between 25 antidepressant side effects and 8 PGS for psychiatric traits, as well as trait-specific analyses, focusing on 12 specific side effects and their respective PGSs.

In the psychiatric trait PGS analyses, all 25 side effects were included as outcome variables. Trait-specific PGSs were tested for 12 side effects: sleepiness, constipation, diarrhoea, headache, weight gain, palpitations, nausea, weight loss, blood pressure increase, blood pressure decrease, insomnia, and anxiety.

The analyses were carried out across the following drug classes based on the anatomical therapeutic chemical classification (ATC): i) selective serotonin-reuptake inhibitors (SSRIs, ATC: N06AB), including escitalopram, citalopram, sertraline, fluoxetine, and paroxetine; ii) serotonin and norepinephrine-reuptake inhibitors, including duloxetine and venlafaxine, combined with atypical antidepressants mirtazapine, bupropion, agomelatine, vortioxetine, trazodone, and tianeptine (SNRI & Atyp. ATC: N06AX); iii) tricyclic antidepressants (TCAs,

ATC: N06AA) including amitriptyline, clomipramine, nortriptyline; and iv) all antidepressants combined.

These analyses used logistic regression, with adjustments for birth year, sex, and first 10 genetic PCs. Multiple testing corrections were applied using the Benjamini-Hochberg FDR method (Benjamini and Hochberg 1995). Additionally, a forward stepwise regression was used to determine independent PGS effects of the PGSs for psychiatric traits due to collinearity between the predictors. We selected the FDR-significant associations from logistic regression models, and the PGS with the lowest p-value, when adjusted for covariates, was added to the baseline model first, followed by the next most significant predictor in the multivariate models. The process continued until no predictors met the $p < 0.05$ threshold. The models were then corrected for multiple testing using FDR-BH.

All analyses in Ref. III were also carried out among a restricted subset of participants with a recorded MDD diagnosis as antidepressants are prescribed for various psychiatric conditions, and this approach could reduce heterogeneity introduced by varying diagnoses, treatment, or symptomatology, and thus estimate whether the observed associations remained consistent within a more homogeneous population.

In addition, a sensitivity analysis was carried out in a subset of individuals taking antidepressants metabolised by CYP2C19, as variation in *CYP2C19* influences drug exposure, which in turn can affect side effects. The analyses for PGS for psychiatric and side effect-related traits were adjusted for the CYP2C19 metaboliser phenotype, adjusting for the same covariates as in the main analyses.

Meta-analysis with the Australian Genetics of Depression Study

A meta-analysis was conducted by pooling the study's results with publicly available summary statistics from AGDS for nine antidepressants, using inverse variance-weighted averaging. The following nine drugs were analysed separately: duloxetine, mirtazapine, escitalopram, fluoxetine, sertraline, citalopram, paroxetine, amitriptyline, and venlafaxine. Logistic regression was used to test associations between headache, insomnia, and weight gain side effects and the respective PGSs, adjusting for birth year, sex, and the first 10 PCs of the genotype. FDR correction was applied to account for multiple testing.

5. RESULTS

5.1. Ref. I: Genetic determinants of statin drug adherence and persistence

5.1.1. Sample overview

We identified 27,339 individuals using statin therapy who were eligible for the persistence analysis and 23,673 of these individuals (86.6%) were also eligible for the adherence analysis in EstBB (Table 2). In FinRegistry, there were 1,061,926 statin users out of whom 11% (n = 116,439) were also part of FinnGen and thus could be included in genetic analyses. Descriptive statistics and persistence for each class of medication are reported in (Table 2). In EstBB, early persistence was 87% for statins, while adherence averaged to 65% (SD = 0.28). Both adherence and persistence were lower in EstBB compared to FinRegistry with persistence of 95% and adherence of 89% (SD = 0.12) in FinRegistry. The mean statin treatment length was 8.8 years in EstBB and 9.2 in FinRegistry. The highest drug adherence was observed among 1,023 individuals taking breast cancer medication tamoxifen 82.9% (SD = 0.27), however only approximately half the individuals persisted on the treatment. Among the 2,712 individuals administering clopidogrel, the adherence was 66.3% (SD = 0.33).

Table 2. Descriptive statistics for three medication classes analysed in the EstBB and FinnGen cohorts (Ref. I).

Medication class	ATC codes	Cohort	N individuals	Total purchases	Proportion of persistent individuals	Mean adherence (SD)	Mean treatment length (years)
Statins	C10AA*	Estonian Biobank	27,339	792,839	0.866	0.648 (0.275)	8.815
		FinnGen	116,439	3,828,359	0.956	0.901 (0.118)	9.454
		FinRegistry	1,061,926	33,864,971	0.952	0.892 (0.123)	9.168
Antiplatelets (Clopidogrel)	B01AC04	Estonian Biobank	2,712	33,466	–	0.663 (0.325)	5.455
		FinnGen	12,618	285,902	–	0.933 (0.112)	5.572
Antiplatelets	B01AC04, B01AC30	FinRegistry	138,007	3,120,237	–	0.931 (0.114)	5.528
Breast cancer medications (Tamoxifen)	L02BA01	Estonian Biobank	1,023	8,814	0.58	0.829 (0.267)	3.973
		FinnGen	9,857	145,584	0.985	0.971 (0.067)	4.128
Breast cancer medications	L02BA01, L02BG04, L02BG06, L02BG03	FinRegistry	55,270	899,671	0.984	0.969 (0.067)	4.556

The statistics are shown for medication classes that were analysed in both cohorts. For each medication class, the ATC codes used to define the medication purchases of interest and other descriptive statistics are reported in the general Finnish population (FinRegistry), in the subset of the Finnish population with genetic data (FinnGen) and in the Estonian Biobank. Number of individuals is the total number of individuals included in the analysis, meaning the number of individuals considered for both the persistence and adherence analysis. Total purchases is the total number of purchases per each medication and each cohort considered in both analyses. Mean adherence (and its standard deviation) and the mean treatment length are reported for the individuals with at least one year long treatment (individuals considered in the adherence analysis).

5.1.2. Polygenic scores for cardiovascular and psychiatric traits linked to statin use

We next investigated associations between 33 PGSs for clinical traits and statin adherence or persistence in EstBB and FinnGen (Figure 8). Genetic predisposition to several cardiometabolic traits was linked to higher adherence in both cohorts, including the PGS for SBP, DBP, and BMI, while polygenic risk for psychiatric traits SCZ and chronic pain was linked to lower adherence. However, the effect sizes for the associations were modest. The most significant associations for adherence in EstBB was PGS for statin adherence, developed using FinnGen statin adherence GWAS, which was associated with less than 1% percent increase in statin adherence (EstBB percent change = 0.72%, SE = 1.7×10^{-3}). In FinnGen, the most significant association was with PGS for SBP that was associated with 0.28% change in adherence (SE = 3.7×10^{-4}).

For persistence, we observed similar associations with the PGS for cardiometabolic and psychiatric traits, but there were slightly more associations compared to adherence. Namely, PGS for SBP, DBP, LDL cholesterol, triglycerides, and CAD were linked to higher persistence and PGS for lifespan, SCZ and chronic pain were linked to lower persistence. The most significant effect was observed for the PGS for LDL, which was associated with 13% and 24% higher odds of statin persistence per 1 SD increase in the PGS, respectively in EstBB and FinnGen (EstBB: OR = 1.13, SE = 1.89×10^{-2}; FinnGen: OR = 1.24, SE = 1.5×10^{-2}).

We also observed that the genetic predisposition to psychiatric disorders was consistently linked to a lower effect direction for adherence and persistence to statins, although most did not reach FDR-significance.

These results suggest that individuals with a higher predisposition to underlying cardiometabolic disease or related risk factors may have higher treatment adherence and persistence, while those with genetic predisposition for psychiatric or neurological disorder may have lower medication adherence.

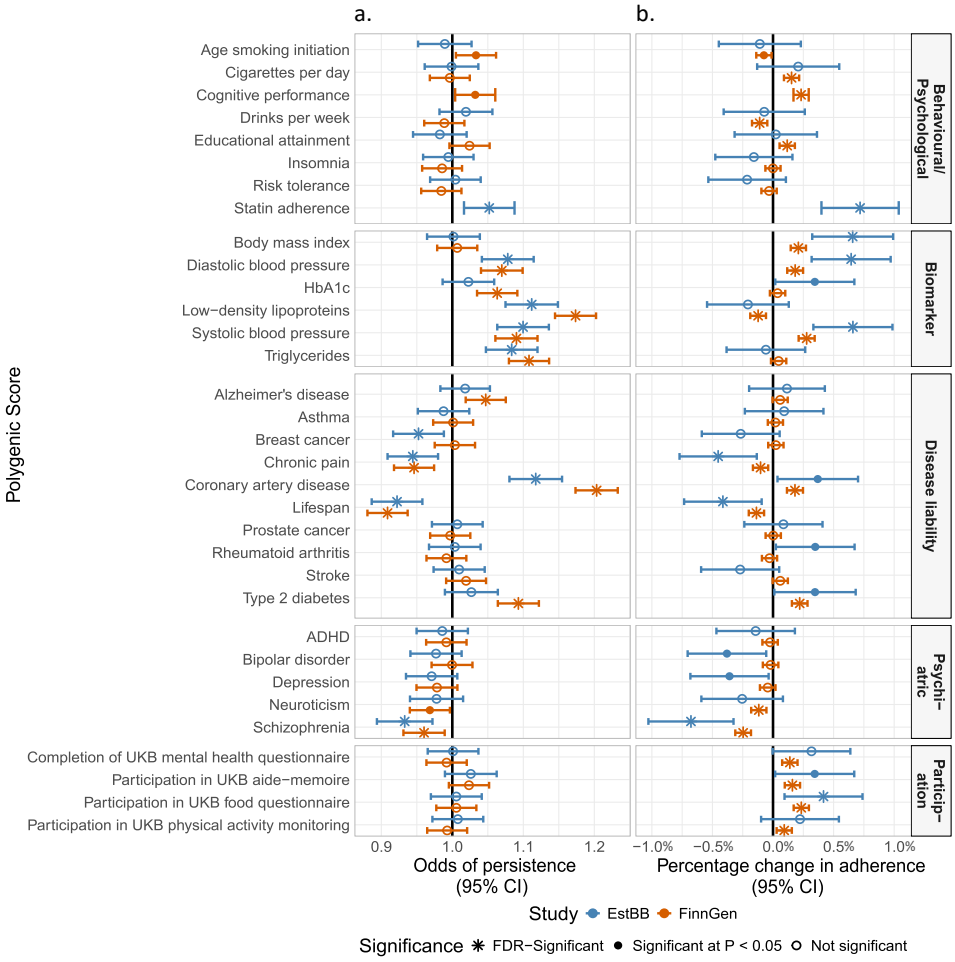

Figure 8. Associations between the PGS for 33 clinically relevant traits and statin persistence or adherence in EstBB and FinnGen biobank (Ref. I). ***a)*** *Results from a logistic regression model including the standardised PGS and adjusted for sex, age at initiation, first 10 genetic principal components (EstBB N = 27,339; FinnGen N = 116,439).* ***b)*** *Results from a linear regression model including the standardised PGS and adjusted for sex, age at initiation, first 10 genetic principal components (EstBB N = 23,673; FinnGen N = 111,315). The x-axis scale for adherence is shown as percentage change in adherence per 1-SD increase in trait PGS. Correction for multiple testing done using FDR-BH method. Figure created using data from Supplementary Tables S16–S19 of (Cordioli et al. 2024).*

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5.1.3. Pharmacogenetic variants in statin, tamoxifen and clopidogrel use patterns

To investigate whether genetic variation in pharmacogenes, contributing to the ADME processes of drugs, was associated with medication use patterns, we tested the effects of five pharmacogenes on persistence and adherence for statins,

clopidogrel, and tamoxifen (Figure 9). To this end, we considered star alleles in *ABCG2* for rosuvastatin, *CYP2C9* for fluvastatin, *SLCO1B1* for all statins, *CYP2C19* for clopidogrel, and *CYP2D6* for tamoxifen.

We observed nominal associations between the reduced metabolism of CYP2C9 and SLCO1B1 and lower persistence in both cohorts individually and in the meta-analysis. However, no association reached significance after multiple-testing correction ($P < 0.002$, Bonferroni correction for 19 phenotypes tested). More specifically, the CYP2C19 intermediate metaboliser phenotype was nominally associated with lower odds of persistence to fluvastatin (meta-analysis: OR = 0.6, 95% CI = 0.43–0.84, P = 0.003). Similarly, the decreased and poor function of SLCO1B1 was associated with lower odds of persistence to all statins (decreased function meta-analysis: OR = 0.92, 95% CI = 0.86–0.98, P = 0.009; poor function meta-analysis: OR = 0.94, 95% CI = 0.88–0.99, P = 0.04, respectively). The decreased SLCO1B1 function was also significantly associated with lower adherence, although with a marginal effect size (0.27% change in adherence, $P = 0.033$).

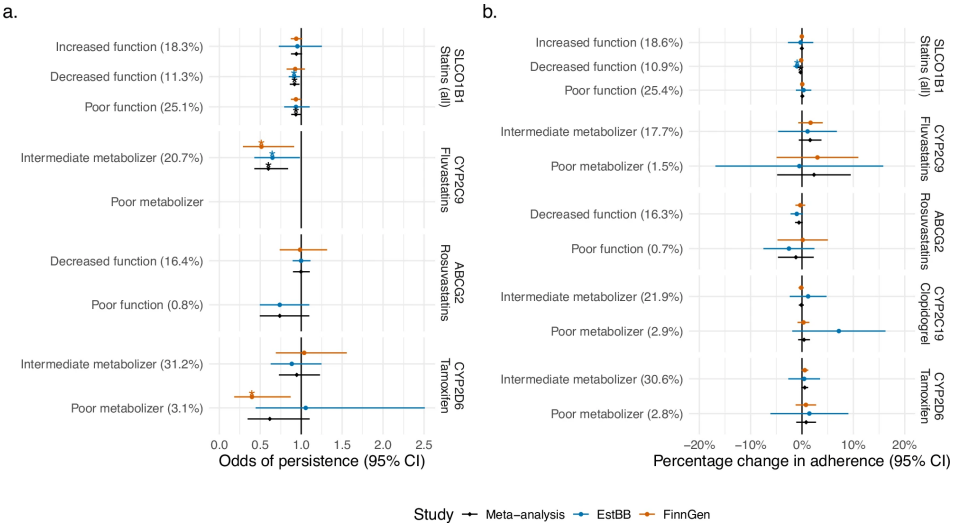

Figure 9. Association between clinically relevant pharmacogene phenotypes and persistence or adherence in the Estonian and FinnGen biobank (Ref. I) ***a)*** *ORs are estimated from a logistic regression model, separately for each gene/drug pair (N=83,305).* ***b)*** *Coefficients for percentage change in adherence are estimated from a linear regression model, separately for each gene/drug pair (N=81,902). Dots represent estimated odds of persistence/percentage change in adherence, error bars represent the 95% confidence interval for the estimate. Stars represent nominal ($P < 0.05$) statistical significance. Estimates are not reported for metaboliser phenotypes with $n < 5$. For each phenotype, the frequency within each drug user group is reported in parenthesis. Figure reproduced from (Cordioli et al. 2024) in accordance with Open Access terms.*

5.2. Ref. II: Depression, its polygenic risk and antidepressant treatment on antihypertensive medication adherence and persistence

5.2.1. Sample overview

We identified 20,724 patients with a first hypertension diagnosis between 2009 and 2017 in EstBB. Among these patients with HTN, 6,294 (30.3%) had a diagnosis of depression (cases) and 14,430 (69.6%) did not (controls).

The median three-year adherence to AHM therapy was 35% (SD = 0.29) in cases and 38% (SD = 0.29) in controls. Only 12.4% of cases and 13.0% of controls had drug supply for more than 80% of days over a three-year period, which is typically considered good adherence. Persistence to antihypertensive medication over three years was observed in 29.6% of cases and 32.5% of controls. We found that patients with depression were more likely to switch their antihypertensive drugs compared to those without depression since median different AHM drugs were 2 (SD = 1.2) and 1 (SD = 1.1) for cases and controls, respectively.

Table 3. Characteristics of the study sample (N = 20,724) (Ref. II)

Characteristic	Depression cases (6,294)	Controls (14,430)	p
Mean age (SD)	52.1 (12.1)	52.7 (13.3)	**
Sex [Female]	4,558 (72.4%)	7,940 (55.0%)	***
Education			ns
Primary	404 (6.4%)	888 (6.2%)	
Secondary	2,423 (38.5%)	5,402 (37.4%)	
Higher	1,526 (24.3%)	3,463 (24.0%)	
NA	1,941 (30.8%)	4,677 (32.4%)	
BMI			**
Underweight	21 (0.3%)	48 (0.3%)	
Normal weight	1,347 (21.4%)	2,811 (19.5%)	
Overweight	2,211 (35.1%)	5,394 (37.4%)	
Obese	2,226 (35.4%)	5,136 (35.6%)	
NA	489 (7.8%)	1,041 (7.2%)	
Median AHM adherence (SD)	0.35 (0.291)	0.38 (0.292)	***
AHM adherence >80%	777 (12.4%)	1,879 (13.0%)	
AHM persistence			***
Persistent	1,864 (29.6%)	4,692 (32.5%)	
Non-persistent	4,430 (70.4%)	9,738 (67.5%)	
Median different drugs	2 (1.2)	1 (1.1)	***
Median different drug classes	1 (0.7)	1 (0.7)	***

SD, Standard deviation; BMI, Body mass index; NA, Not available; AHM, Antihypertensive medication. P-values represent comparisons according to Student's t-test and chi-squared tests for continuous or categorical data, respectively; *** $p < 0.001$*;* ** $p < 0.01$*;* * $p < 0.05$*; ns, non-significant.*

5.2.2. Depression and its polygenic risk associated with reduced AHM adherence and persistence

We ran a series of fractional logistic (adherence) and logistic (persistence) regression models to investigate the effect of depression on AHM adherence and persistence, while adjusting for sociodemographic and genetic risk factors (Tables 4, 5). Depression diagnosis during the data availability period was linked to lower adherence and persistence (Tables 4, 5). Depression was associated with 6% lower probability of AHM adherence (OR = 0.94, 95%CI = 0.91–0.98) and 12% lower odds of AHM persistence (OR = 0.88, 95% CI = 0.82–0.94), while controlling for age and sex (Model 1). Adjusting for other sociodemographic, genetic, and health-related factors did not significantly influence these associations, suggesting that depression diagnosis was consistently associated with lower antihypertensive medication use.

Higher polygenetic risk for depression was independently associated with lower adherence and persistence, even when adjusting for depression diagnosis, sociodemographic and health-related covariates (Table 4, 5). However, the effect was small – approximately 3% lower odds of adherence and 4% lower odds of persistence (Model 3, adherence: OR = 0.97, 95% CI = 0.95–0.99); persistence: OR = 0.96, 95% CI = 0.93–0.10). Since both, the diagnosis and the PGS for depression were independently associated with lower medication use, it suggests that polygenic liability for depression may contribute to non-adherence, even in the absence of a confirmed diagnosis.

Table 4. Associations between depression and AHM adherence (Ref. II)

Characteristic	Model 1 (N = 20,724)		Model 2 (N = 14,088)		Model 3 (N = 13,968)		Model 4 (N = 13,968)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Depression diagnosis	0.943**	0.9090.979	0.94**	0.8990.982	0.935**	0.8950.978	0.939**	0.8980.982
Age	1.011***	1.011.012	1.01***	1.0091.012	1.01***	1.0081.011	1.011***	1.0091.012
Sex [Female]	0.922***	0.8910.955	0.906***	0.8690.946	0.919***	0.8810.959	0.913***	0.8740.953
Education level [Primary]	NA	NA	Reference	Reference	Reference	Reference	Reference	Reference
Education level [Secondary]	NA	NA	1.043	0.9671.125	1.049	0.9721.131	1.052	0.9751.134
Education level [Higher]	NA	NA	1.103*	1.021.192	1.098*	1.0161.188	1.102*	1.0191.192
BMI [Underweight]	NA	NA	0.881	0.6071.279	0.884	0.6081.285	0.881	0.6041.284
BMI [Normal weight]	NA	NA	Reference	Reference	Reference	Reference	Reference	Reference
BMI [Overweight]	NA	NA	1.129***	1.0711.191	1.128***	1.071.189	1.132***	1.0741.194
BMI [Obese]	NA	NA	1.326***	1.2571.4	1.313***	1.2441.386	1.331***	1.2611.405
Depression PGS	NA	NA	NA	NA	0.974*	0.9540.994	0.972**	0.9520.992
DBP PGS	NA	NA	NA	NA	NA	NA	1.024	0.991.06
SBP PGS	NA	NA	NA	NA	NA	NA	1.051**	1.0141.089

95% CI, 95% confidence interval; BMI, body mass index; PGS, polygenic score; DBP, diastolic blood pressure; SBP, systolic blood pressure; OR, odds ratio. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. *Primary exposure (depression) effect estimates are interpreted as conditional total effects. Covariate (age, sex, educational attainment, BMI, depression PGS, SBP PGS, DBP PGS) effect estimates are interpreted as controlled direct effects.*

Table 5. Associations between depression and AHM persistence (Ref. II)

Characteristic	Model 1 (N = 20,724) OR	Model 1 (N = 20,724) 95% CI	Model 2 (N = 14,088) OR	Model 2 (N = 14,088) 95% CI	Model 3 (N = 13,968) OR	Model 3 (N = 13,968) 95% CI	Model 4 (N = 13,968) OR	Model 4 (N = 13,968) 95% CI
Depression diagnosis	0.876***	0.8210.936	0.847***	0.7830.917	0.834***	0.7700.904	0.837***	0.7720.907
Age	1.013***	1.0111.015	1.012***	1.0091.015	1.011***	1.0081.014	1.012***	1.0091.015
Sex [Female]	1.024	0.9631.090	1.056	0.9801.139	1.093*	1.0131.180	1.088*	1.0081.175
Education level [Primary]	NA	NA	Reference	Reference	Reference	Reference	Reference	Reference
Education level [Secondary]	NA	NA	1.121	0.9851.277	1.138	0.9991.298	1.140	1.0001.300
Education level [Higher]	NA	NA	1.164*	0.0181.332	1.159*	1.0121.329	1.161*	1.0141.331
BMI [Underweight]	NA	NA	0.913	0.4651.683	0.910	0.4621.684	0.908	0.4611.682
BMI [Normal weight]	NA	NA	Reference	Reference	Reference	Reference	Reference	Reference
BMI [Overweight]	NA	NA	1.138**	1.0341.253	1.132*	1.0271.247	1.135*	1.0301.251
BMI [Obese]	NA	NA	1.431***	1.3001.577	1.400***	1.2701.544	1.415***	1.2841.561
Depression PGS	NA	NA	NA	NA	0.959*	0.9250.995	0.957*	0.9230.993
DBP PGS	NA	NA	NA	NA	NA	NA	1.022	0.9591.089
SBP PGS	NA	NA	NA	NA	NA	NA	1.037	0.9761.101

*95% CI, 95% confidence interval; BMI, body mass index; PGS, polygenic score; DBP, diastolic blood pressure; SBP, systolic blood pressure; OR, odds ratio.*** $p < 0.001$*; ** $p < 0.01$*; * $p < 0.05$. Primary exposure (depression) effect estimates are interpreted as conditional total effects. Covariate (age, sex, educational attainment, BMI, depression PGS, SBP PGS, DBP PGS) effect estimates are interpreted as controlled direct effects.*

5.2.3. Antidepressant treatment linked to improved AHM adherence

Next, we explored whether starting antidepressant treatment could improve AHM adherence (Figure 10). For this, we considered a subgroup of 132 individuals who had been diagnosed with depression and had initiated their antidepressant therapy during the AHM follow-up period. In a linear mixed-effects model adjusted for age and sex, we found that AHM adherence six months after initiating antidepressant therapy increased by 8% compared to AHM adherence six months before starting the antidepressant therapy (β= 0.08; 95% CI = 0.03–0.13). This suggests that the treatment of depression among patients with depression and hypertension comorbidity may improve the adherence to antihypertensive medication.

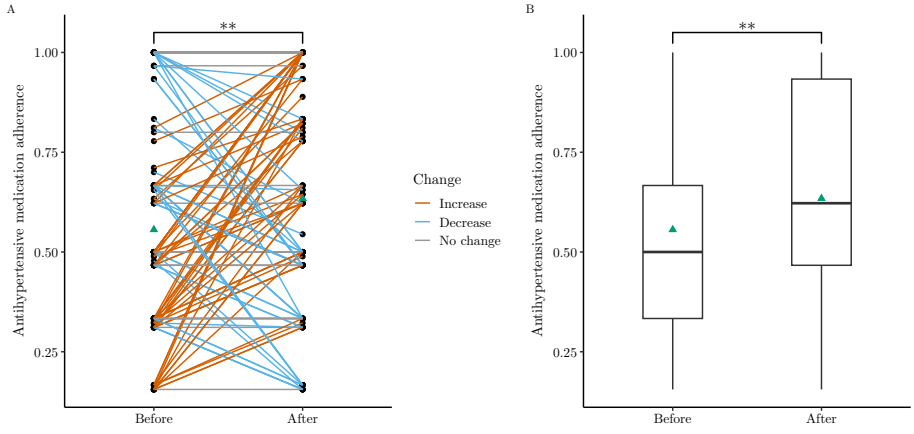

Figure 10. Change in AHM adherence after antidepressant therapy initiation. A) Intraindividual changes in AHM adherence six months after initiating antidepressant therapy (Ref. II). Red, blue, and grey lines show increase, decrease, and no change in AHM adherence, respectively. Green triangles show mean AHM adherence values. **B) Comparison of AHM adherence six months before and six months after antidepressant therapy initiation.** Green triangles show mean AHM adherence values. $***p < 0.001; **p < 0.01; *p < 0.05$.

5.3. Ref. III: Polygenic and pharmacogenetic influences on antidepressant side effects

Non-persistence to therapy may indicate side effects causing individuals to discontinue treatment. However, genetic factors influencing the variability of antidepressant side effects remain inadequately explored. Research has primarily focused on drug-metabolising enzymes like CYP2C19, with few studies incorporating the broader genetic contribution. Given the observations in our previous study (Ref. II), that antidepressant treatment in patients with comorbid depression and hypertension may improve medication adherence, we aimed to investigate the role of genetic variation in *CYP2C19* and the PGSs for psychiatric and side effect-related phenotypes in experiencing antidepressant side effects since side effects are a common cause of treatment discontinuity.

5.3.1. Sample overview

We pooled data from two questionnaires and used a natural language processing model to extract side effects from EHRs. We identified 13,729 antidepressant users with side effect information, with the average age of 49.9 (SD = 14.3) years, of whom 80.2% were female (Table 6). Most had a record of depression diagnosis (N = 10,914, 79.5%). We also conducted a subgroup analysis on individuals with a recorded depression diagnosis to reduce heterogeneity introduced by varying diagnoses, treatment, or symptomatology; however, only the findings from the full sample are reported in the current thesis since the observed associations in the subgroup remained consistent with the full sample.

Table 6. Sample demographics (Ref. III).

Characteristic	Cases (%)	Controls (%)	Total (%)
Sex			
Female	5,932 (83.1%)	5,084 (71.2%)	11,016 (80.2%)
Male	1,209 (16.9%)	1,504 (21.1%)	2,713 (19.8%)
Age			
Mean age (years ± SD)	47.4±13.9	54.7±13.8	49.9±14.3
Metaboliser phenotype			
Poor	108 (2.2%)	73 (1.5%)	181 (1.9%)
Intermediate	1,221 (24.7%)	1,137 (23.0%)	2,358 (24.7%)
Normal	1,806 (36.5%)	1,690 (34.1%)	3,496 (36.6%)
Rapid	1,528 (30.9%)	1,379 (27.9%)	2,907 (30.4%)
Ultrarapid	288 (5.8%)	333 (6.7%)	621 (6.5%)
Subgroup			
Depression	5,923 (43.1%)	4,991 (32.7%)	10,914 (79.5%)

Percentages for cases and controls are calculated within each subcategory based on the total number of cases or controls for the characteristic. Total percentages are based on the entire study population ($N = 13{,}729$), except for the metaboliser phenotype where the percentages are calculated only for participants who took drugs metabolised by CYP2C19 ($N = 9{,}563$) and had complete CNV and star allele information. Cases were defined as individuals reporting a specific side effect for a drug or drug class, while controls were antidepressant users that did not report that specific side effect.

SSRIs were the most common antidepressants (N = 10,539, 76.8%), followed by SNRIs and atypical antidepressants (N = 5,589, 40.7%), and TCAs (N = 1,724, 12.6%) (Figure 11). Approximately half of the individuals (52.0%; n = 7,141) reported at least one antidepressant side effect, with the most reported individual side effects across all antidepressants being nausea (N = 2,155, 15.7%), weight gain (N = 2,099, 15.3%), and sleepiness (N = 2,055, 15.0%). The least reported side effects across all antidepressants were chills (N = 103, 0.8%), decreased

blood pressure (N = 134, 1.0%), and allergic reactions (N = 145, 1.1%) (Figure 11).

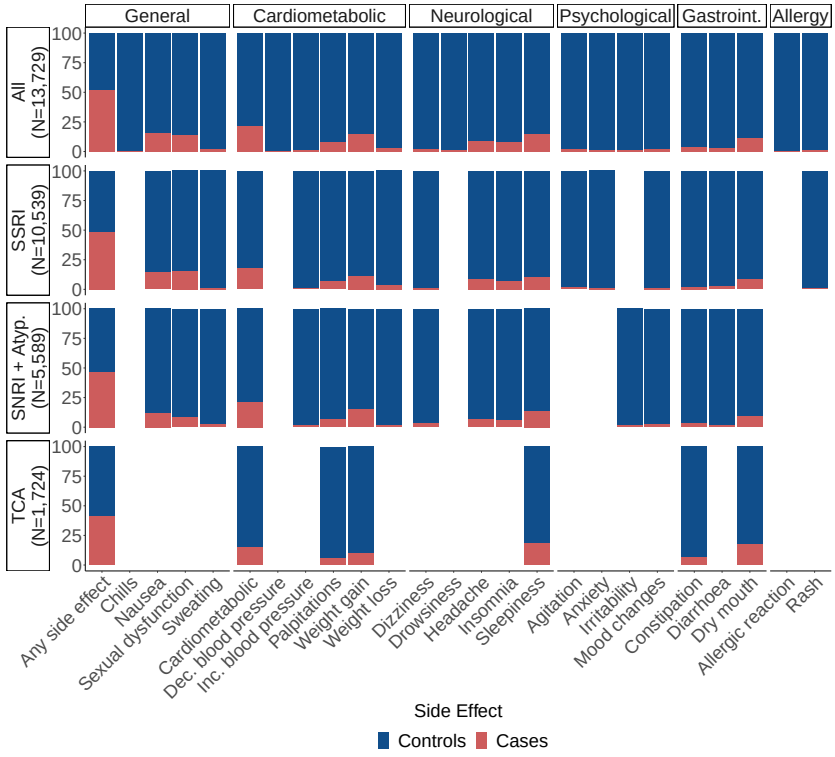

Figure 11. Proportion of cases reporting a side effect relative to total individuals in a drug class (Ref. III) Estimates are not reported for side effects with N < 100 cases for a given drug class (areas depicted in white). Inc.-increased; Dec.-decreased; Gastroint.-gastrointestinal; TCA-tricyclic antidepressant; SSRI-selective serotonin reuptake inhibitor; SNRI+Atyp.-serotonin-norepinephrine reuptake inhibitor and atypical antidepressant.

5.3.2. Genetic predisposition to psychiatric traits SCZ and MDD associated with increased side effects across all antidepressants

Next, we explored whether a higher genetic predisposition to psychiatric traits contributes to experiencing side effects across all antidepressants and within individual drug classes (Figure 12). Most associations were observed for all antidepressants pooled, with largely consistent findings for SSRIs, likely due to the larger sample sizes and the high prevalence of SSRI users in the cohort (76.8%).

The largest number of independent associations was found for the PGS for SCZ and MDD, both of which were consistently linked to increased odds of experiencing at least one side effect from all antidepressants pooled, SSRIs, SNRIs and atypical antidepressants; additionally, the PGS for SCZ was linked to the TCA class. The PGS for SCZ was the strongest predictor for side effect burden, identifying 26% higher odds of experiencing any side effect in TCAs per one SD

increase in the PGS for SCZ (95% CI = 1.14 – 1.37). Overall, the effect sizes were modest with the PGS for SCZ and MDD being respectively linked to 15% (95% CI = 1.11–1.19) and 14% (95% CI = 1.10–1.18) higher odds of side effects from all antidepressants pooled.

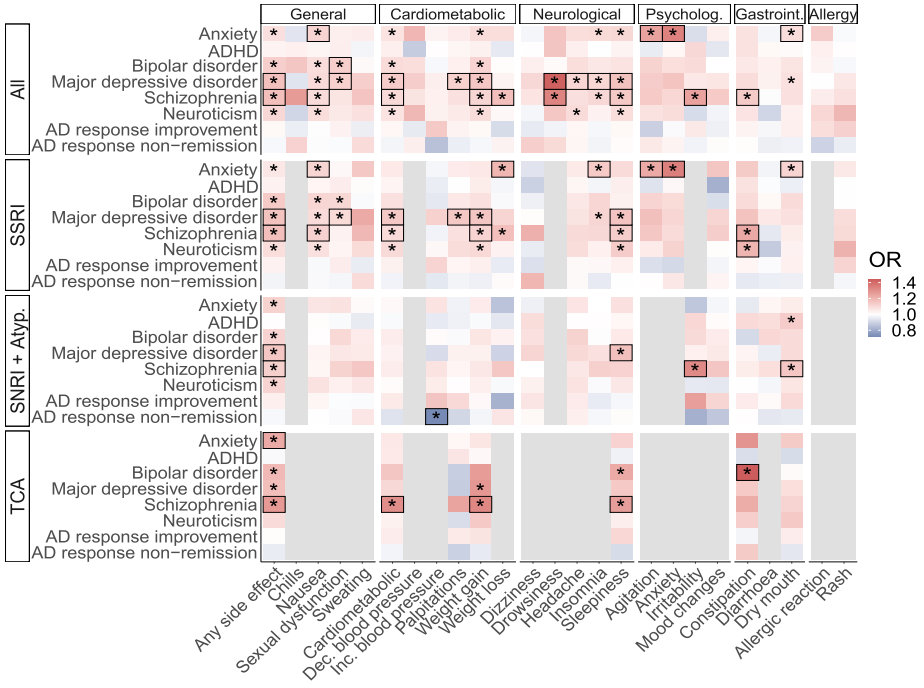

Figure 12. The associations between PGSs for psychiatric traits (y-axis) and side effects (x-axis) across antidepressant drug classes (Ref. III) Black boxes refer to independent signals in the forward regression model. AD-antidepressant; ADHD-Attention deficit/hyperactivity disorder; PGS-polygenic score; Inc.-increased; Dec.-decreased; OR-Odds ratio; Psycholog.-psychological; Gastroint.-gastrointestinal; TCA-tricyclic antidepressant; SSRI-selective serotonin reuptake inhibitor; SNRI+Atyp.-serotonin-norepinephrine reuptake inhibitor and atypical antidepressant. * FDR-corrected p.value < 0.05. Estimates are not reported for side effects with N < 100 cases for a given drug class (areas depicted in grey).

The PGS for SCZ and MDD were both associated with several individual side effects across symptom domains including, drowsiness, sleepiness, cardiometabolic side effects, and weight gain, while SCZ PGS alone was additionally linked to weight loss, constipation, irritability, and nausea across all antidepressants (Figure 12). MDD PGS was associated with palpitations, insomnia, headache, and sexual dysfunction across antidepressants. Genetic liability for other psychiatric disorders was also independently associated with side effects in all antidepressants pooled. The PGS for ANX was linked to nausea, agitation, anxiety symptoms, and dry mouth across all antidepressants and the PGS for BIP was associated with higher sexual dysfunction, mirroring the effect observed for MDD PGS. No ad-

ditional side effects remained significantly associated with the PGS for BIP and neuroticism (NEUR) in the forward stepwise model, indicating that their contribution to side effects may overlap with those captured by SCZ or MDD genetic liability.

Since our data did not include information on antidepressant dosage or the timing of side effect onset, we were unable to adjust for drug dose. Instead, we carried out a subgroup analysis, restricting our analyses to antidepressants metabolised by CYP2C19. In this subset, adjusting for the CYP2C19 metaboliser phenotype did not attenuate the associations between PGS and side effects. This suggests that differences in CYP2C19-mediated drug exposure did not explain the observed PGS associations.

5.3.3. Genetic predisposition to cardiometabolic and neurological traits linked to respective side effects

To explore whether individuals are genetically predisposed to experiencing specific side effects, we investigated links between trait-specific PGSs and the occurrence of respective traits as side effects. Higher PGS for ANX was significantly linked to reporting anxiety as a side effect (OR = 1.34, 95% CI = 1.17–1.50) across all antidepressants (Figure 13A). In addition, individuals with higher PGS for SBP and BMI were more likely to report respective traits (increased blood pressure and weight gain) as side effects across all antidepressants (OR = 1.27, 95% CI = 1.14–1.39 and OR = 1.10, 95% CI = 1.05–1.15, respectively).

Lastly, we conducted a meta-analysis to increase statistical power and assess the generalisability of findings between two independent cohorts. We used publicly available data from the AGDS for three side effects and conducted the analyses separately for each drug. Most effect directions were consistent between EstBB (N = 13,729) and the AGDS (N = 20,941) cohort; however in EstBB, escitalopram was the only antidepressant with a significant association between the PGS for BMI and weight gain (Figure 13B). The meta-analysis identified positive associations between the PGS for BMI and weight gain across all nine examined antidepressants (Figure 13B). Additionally, we identified an association between headaches and the PGS for headaches among sertraline users (OR = 1.12; 95% CI = 1.05–1.19). No significant association was observed between the PGS for insomnia and related symptoms.

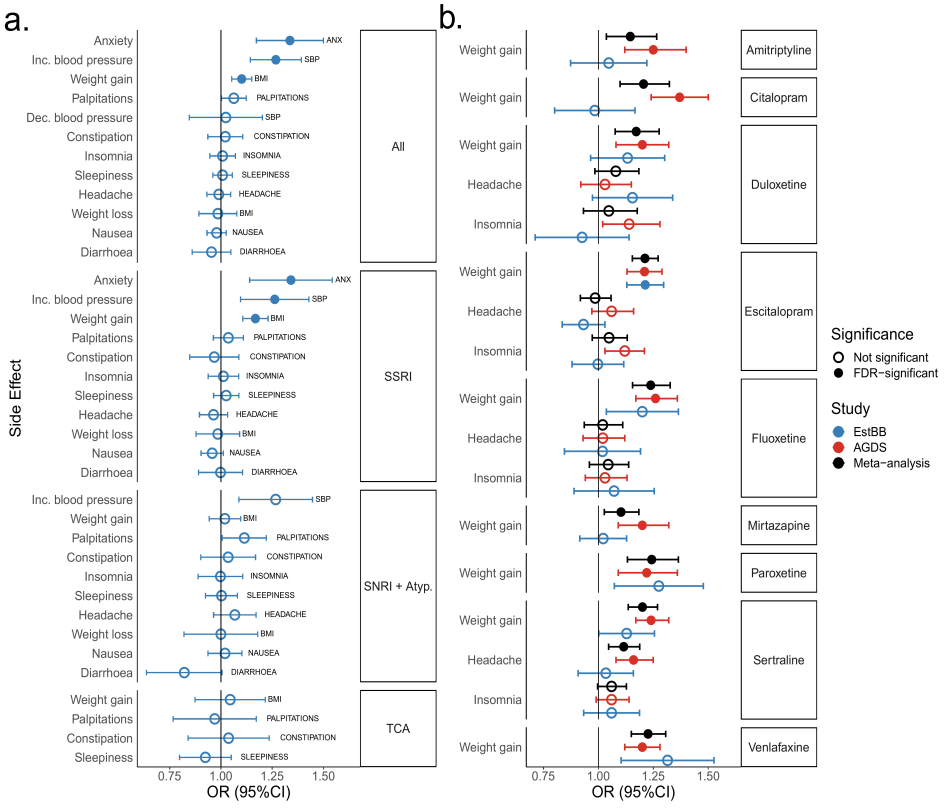

Figure 13. A) The associations between trait-specific PGSs and side effects across antidepressant classes in EstBB. B) Meta-analysis results between weight gain, headache, and insomnia and their respective PGSs in EstBB and AGDS across nine antidepressants (amitriptyline, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline and venlafaxine) (Ref. III). ANX-anxiety; AGDS-Australian Genetics of Depression Study; EstBB-Estonian Biobank; OR-odds ratio; SBP-systolic blood pressure; BMI-body mass index; PGS-polygenic score; TCA-tricyclic antidepressant; SSRI-selective serotonin reuptake inhibitor; SNRI+Atyp.-serotonin-norepinephrine reuptake inhibitor and atypical antidepressant. * FDR-corrected p.value < 0.05.

5.3.4. *CYP2C19* genetic variation linked to differences in the experiencing of antidepressant side effects

We then explored the influence of CYP2C19 metaboliser phenotypes on the overall side effect burden. The sample included 9,563 individuals who had taken CYP2C19-metabolised antidepressants and had complete CNV and star allele information. The most prevalent metaboliser phenotype was normal (n = 3,496, 36.6%), while poor (n = 181, 1.9%) and ultrarapid (n = 621, 6.5%) phenotypes were the least common (Table 7). Notably, the CYP2C19*37 partial gene deletion frequency in Estonia (1.5%) was ten times higher than in other European

subcohorts (0.16% in the 1000 Genomes Project (Byrska-Bishop et al. 2022) and 0.11%, in GnomAD v4 (Collins et al. 2020) (Table 7).

Table 7. CYP2C19 genotype and phenotype frequency distribution among 9,563 participants taking CYP2C19-metabolised antidepressants (Ref. III)

CYP2C19 Metaboliser phenotype	Genotype	n (%)	N (%)
Poor	*2/*2	168 (92.8%)	181 (1.9%)
	*2/*3	3 (1.7%)	
	*2/*37	3 (1.7%)	
	*2/*4	5 (2.8%)	
	*2/*8	2 (1.1%)	
Intermediate	*1/*2	1,362 (57.8%)	2,358 (27.7%)
	*1/*3	7 (0.3%)	
	*1/*37	103 (4.4%)	
	*1/*4	15 (0.6%)	
	*1/*8	15 (0.6%)	
	*17/*37	38 (1.6%)	
	*2/*17	667 (28.3%)	
	*2/*38	130 (5.5%)	
	*3/*17	4 (0.2%)	
	*3/*38	1 (0.0%)	
	*4/*17	7 (0.3%)	
	*4/*38	1 (0.0%)	
	*8/*17	6 (0.2%)	
	*8/*38	2 (0.1%)	
Normal	*1/*1	2,817 (80.6%)	3,496 (36.6%)
	*1/*38	638 (18.2%)	
	*38/*38	41 (1.2%)	
Rapid	*1/*17	2,579 (88.7%)	2,907 (30.4%)
	*17/*38	328 (11.3%)	
Ultrarapid	*17/*17	621 (100.0%)	621 (6.5%)

Calculated among participants taking CYP2C19-metabolised antidepressants ($N = 9{,}563$; escitalopram, citalopram, sertraline, amitriptyline) with complete CNV and star-allele information.

We found that poor metabolisers had 49% higher odds of experiencing a side effect (OR = 1.49, 95% CI = 1.09–2.04) while ultrarapid metabolisers were 17% less likely to experience a side effect (OR = 0.83, 95% CI = 0.70–0.99) compared to normal metabolisers (Figure 14).

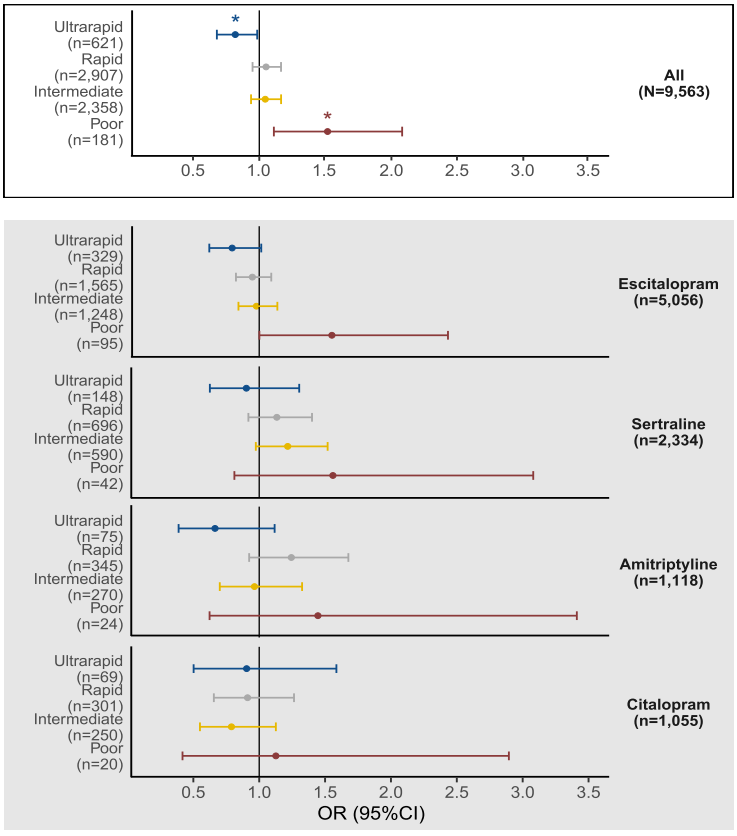

Figure 14. The association between CYP2C19 metaboliser status and the reporting of any side effect across escitalopram, citalopram, sertraline or amitriptyline antidepressant users (N = 9,563) (Ref. III) * $p.value < 0.05$. The normal metaboliser phenotype was used as reference. The primary analysis included all antidepressants pooled; drug-specific analyses were conducted to assess individual drug effects.

6. DISCUSSION

6.1. CVD medication adherence and persistence

6.1.1. Medication adherence to CVD medications in Estonia is low

Since CVD medications are typically prescribed for long-term use, maintaining high adherence is important to delay or prevent the onset of CVDs. High adherence to statins has been shown to lead to a greater reduction of LDL cholesterol (Türkmen et al. 2025) and cardiovascular events (Khunti et al. 2018). Further, high adherence also improves cost effectiveness by reducing preventable hospitalisations, unused medication costs, and delaying or preventing cardiovascular events (Lam and Fresco 2015; Bansilal et al. 2016; Nelson, Pagidipati, and Bosworth 2024; Aubert et al. 2010). Identifying subgroups of individuals such as those with comorbid conditions or genetic differences can help identify patients at risk of low adherence and develop targeted interventions to improve adherence.

In Ref. I and II, we identified that cardiovascular medication adherence is low in Estonia, with one study finding 65% adherence to statins (Ref. I) and another finding 38% adherence to antihypertensive medications among those without MDD comorbidity (Ref. II). Only 13.0% of individuals taking AHMs achieved an adherence of 80%, suggesting that most individuals are likely not achieving their blood pressure goals (Ref. II). Compared to Finland, where the adherence to statin medications was 89%, the adherence in Estonia was 24% lower (at 65%) (Ref. I). Early persistence was relatively similar between the two countries – the proportion of individuals who continued statin therapy after the first purchase was 86.6% in Estonia and 95.2% in Finland (Ref. I). Long-term persistence (three years) to antihypertensive medication was 32.5% among individuals without MDD comorbidity in Estonia (Ref. II).

These low adherence rates in Estonia may be partly due to differences in healthcare systems and clinical practices. For instance, Finnish pharmacies provide medication adherence counselling, focus on data collection and research, as well as have national policies promoting adherence support and education (Bell, Enlund, and Vainio 2010). Further, the clinical practice may differ in Estonia. For instance, it has been shown that post-myocardial infarction patients often did not receive statin prescriptions despite guideline recommendations, indicating potential systemic barriers in access to prescriptions (Lõiveke et al. 2021).

Real-world studies estimate non-adherence to be a widespread issue, with approximately 50% of individuals with chronic diseases failing to adhere to prescribed treatments (Lam and Fresco 2015; Sabaté and World Health Organization 2003; Rodriguez et al. 2019; Bosworth et al. 2011). Similar rates were also found in a recent study in Estonia which reported a 55.3% statin adherence in lipid-metabolism disorders and 57.4% adherence to antihypertensives, however,

different adherence definitions affect between-study comparison validity (Mooses et al. 2025).

Comparison of medication adherence studies is challenging. In our studies (Ref. I and Ref. II), adherence measures were selected based on the disease context, medication characteristics, stage of medication-taking, and healthcare system-related factors. We focused on cardiovascular diseases requiring long-term treatment to lower blood pressure and LDL cholesterol. We considered the implementation phase, meaning how closely patients follow dosing regimens (Ref. I, II) and persistence, measured both in the short term (discontinuity after a single purchase) (Ref. I) and long term (over three years), without excessive gaps in refills (Ref. II). To make our observations comparable between the Estonian and Finnish cohorts we used a consistent adherence definition in both Finland and Estonia but adjusted for healthcare system differences. In Finland, prescription refill gaps over 150 days were excluded from adherence trajectories to account for potential hospitalisations during which in-hospital dispensing is not recorded. In Estonia, where hospital stays are typically short, all refill gaps were treated as true treatment interruptions. Despite differences in healthcare systems, both countries have universal healthcare, ensuring that all prescriptions are recorded. This avoids issues common in insurance-based systems, where prescriptions obtained outside the network may not be captured (Lam and Fresco 2015).

Future studies would benefit from a standardised measurement to quantify medication use. While no single adherence measure is universally optimal, adoption for a multi-measure approach could provide a more comprehensive and reliable assessment (Lam and Fresco 2015). For instance, combining objective and subjective measures, such as combining refill data in pharmacies to objectively quantify medication use with subjective self-report information, could allow to compensate for the limitations of current approaches and provide additional information about the reasons for discontinuity, motivations, and barriers.

6.1.2. Genetic liability to cardiovascular traits and medication use

The influence of common genetic variation in medication use patterns is largely unexplored. While some studies have investigated the genetic factors influencing medication use (Kiiskinen et al. 2023; Wu et al. 2019), they have investigated proxies to adherence but not adherence itself. To fill this gap, study Ref. I aimed to comprehensively assess the influence of polygenic and pharmacogenetic variation in adherence and persistence across statins medication class as well as pharmacogenetic variation for individual drugs including, statins fluvastatin and rosuvastatin, anticancer drug tamoxifen and antiplatelet medication clopidogrel, leveraging long-term follow-up and comprehensive phenotype and genotype-level data. We found that increased polygenic risk for cardiometabolic traits was associated with higher statin adherence and persistence in EstBB and FinnGen cohorts (Ref. I). More specifically, genetic predisposition for higher SBP and DBP was

linked to higher statin use. Additionally, higher adherence was linked to an increase in the PGS for BMI and higher persistence to PGS for CAD, LDL, and triglycerides. However, the effect sizes, particularly for adherence, were small, suggesting a limited role of common genetic factors in statin use.

These findings support previous and subsequent studies showing that genetic liability to cardiometabolic diseases is associated with greater CVD medication use and lower discontinuity rates (Türkmen et al. 2025; Kiiskinen et al. 2023; Wu et al. 2010). A recent study in 76,000 UK Biobank participants found that genetic liability to cardiovascular disease increased adherence for respective medications (Türkmen et al. 2025). A study in 193,933 FinnGen participants showed that the PGS for LDL, SBP, and type II diabetes were strongly associated with a higher number of drug purchases for respective traits (Kiiskinen et al. 2023). In Ref. II, we additionally found that the genetic predisposition to higher SBP was significantly associated with increased AHM adherence in hypertensive patients when controlling for sociodemographic and health-related factors. Furthermore, lower treatment discontinuation was also found in patients with high SBP PGS (Türkmen et al. 2025; Kiiskinen et al. 2023).

We suggest several reasons for the link between the PGS for cardiometabolic traits, higher medication adherence and lower discontinuity. The PGS captures the genetic risk for the cardiovascular risk factors and cardiovascular disease which are driving earlier initiation of the medication, a greater number of different medications used and treatment intensity (Kiiskinen et al. 2023). Furthermore, individuals with a higher genetic risk for cardiovascular disease are more likely to have a higher perceived risk due to more severe disease, family history, risk of complications which can motivate them to adhere better (Al-Noumani et al. 2019). Medical professionals may also be more motivated to seek alternative medications for high-risk patients experiencing side effects or wanting to stop treatment. Patients with high PGS for cardiometabolic traits may also have more treatment-resistant disease despite being on therapy (Tapela et al. 2022). Conversely, patients with lower polygenetic risk may reach their treatment goals easier and be able to discontinue treatment or lifestyle-related interventions may be sufficient to achieve treatment targets.

While many large-scale GWAS have been conducted on blood pressure (Evangelou et al. 2018; Surendran et al. 2020) and lipid levels (Sinnott-Armstrong et al. 2021; Tabassum et al. 2019; Ripatti et al. 2020) which have identified hundreds of associated loci, only a few GWA-studies have investigated medication use (Türkmen et al. 2025; Wu et al. 2019; Kiiskinen et al. 2023; Seo et al. 2014). These have mostly identified genetic variants that reflect the genetic predisposition to underlying diseases or risk factors for which the medications were prescribed, rather than medication-specific pathways or behaviour (Kiiskinen et al. 2023; Wu et al. 2019; Türkmen et al. 2025). The overlap between genetic factors influencing medication use with those driving disease risk is further supported by near-perfect genetic correlations (rg $\approx$ 0.9–1.0) between the use of medications for hyperlipidaemia,

hypertension, and type II diabetes and the respective conditions (Kiiskinen et al. 2023).

Taken together, previous evidence suggests that the genetic influence on medication use patterns is limited, with the underlying cardiometabolic genetic risk being the largest influence on medication use in cardiometabolic diseases.

6.2. Psychiatric disorders, their polygenic risk and treatment-related outcomes

6.2.1. Depression comorbidity and polygenetic risk to psychiatric traits linked to lower CVD medication use

MDD is known to contribute to lower adherence rates, but evidence linking these variables remains inconsistent (van der Laan et al. 2017). Prior studies, examining psychiatric comorbidities and AHM adherence, often suffer from small sample sizes (typically a few hundred participants) (Kulkarni et al. 2021; Lauder et al. 2021; Okunrinboye, Otakpor, and Ilesanmi 2019), limited follow-up (<2 years) (Caldern-Larraaga et al. 2016; Adams et al. 2013; Bailey et al. 2014; Kulkarni et al. 2021; Okunrinboye, Otakpor, and Ilesanmi 2019; Lauder et al. 2021), and reliance on self-reported measures (Okunrinboye, Otakpor, and Ilesanmi 2019; Spikes et al. 2019), which tends to overestimate adherence (Stirratt et al. 2015). While larger studies (N > 50,000) using pharmacy-refill data exist (Caldern-Larraaga et al. 2016; Adams et al. 2013; Bailey et al. 2014), they primarily assess short-term adherence and are largely US-based (Steiner et al. 2009; Adams et al. 2013; Bailey et al. 2014), limiting generalisability to Europe due to health insurance differences that may affect the completeness of data. In addition, to our knowledge, no prior study had examined whether genetic liability to MDD affects AHM use patterns. To address these gaps, we analysed three-year AHM adherence among over 20,000 individuals with hypertension using linked genetic information and longitudinal pharmacy-refill measures from EHRs in a real-world setting (Ref. II).

We sought to understand the role of MDD and its polygenetic risk on antihypertensive medication adherence and persistence. Our study observed lower AHM use in patients with recorded MDD compared to those without recorded MDD. Patients with the MDD diagnosis had a 6% lower probability of AHM adherence and 12% lower odds of persistence. One SD increase in the PGS for MDD was also significantly associated with a 3% lower AHM adherence probability and a 4% lower odds of persistence in hypertensive patients regardless of the MDD status. Although the effect size of the PGS was small, both MDD and its corresponding PGS remained significant when included in the model, suggesting that each independently contributes to the risk of non-adherence and non-persistence. In Ref. I, we observed a lower statin adherence and persistence among those with higher genetic predisposition to SCZ and chronic pain in both EstBB and FinnGen, sug-

gesting that genetic predisposition to some psychiatric and neurological traits may reduce CVD medication use. However, the PGS for MDD was only nominally significantly associated with reduced statin adherence in EstBB (Ref. I). The link between genetic liability for psychiatric disorders and medication use has not been widely studied but a recent UK Biobank study of 76,000 individuals also found an association between the PGS for SCZ and reduced statin adherence (Türkmen et al. 2025). This suggests that genetic risk for some psychiatric disorders may contribute to cardiovascular medication non-adherence, even if an individual has not been diagnosed with the disorder. One of the reasons for this may be that patients with high genetic liability to psychiatric disorder could be more susceptible to side effects which leads them to discontinue treatment early or miss doses (Campos et al. 2021).

Previous studies on MDD diagnosis have found MDD to reduce cardiovascular medication adherence (Crawshaw et al. 2016; Gast and Mathes 2019). A meta-analysis of 17 studies revealed that patients with acute coronary syndrome exhibiting MDD symptoms were twice as likely to be non-adherent to cardiovascular medications compared to patients without MDD (OR = 2.00, 95% CI = 1.57–3.33) (Crawshaw et al. 2016). But evidence specifically for hypertension medications is inconsistent (van der Laan et al. 2017; Crawshaw et al. 2016). A review of 18 studies on MDD and its link to AHM adherence found that 72% of the studies (13 out of 18) reported an adverse effect of MDD on AHM adherence (van der Laan et al. 2017). These inconsistencies are likely to be influenced by the differences in adherence measurements, MDD diagnosis, as well as differences in health care systems and care.

6.2.2. Depression treatment among HTN patients may improve AHM adherence

Given that both MDD and medication adherence are modifiable risk factors for CVD, we set out to investigate whether antidepressant therapy in patients with MDD and hypertension could improve AHM adherence (Ref. II). We found that hypertensive patients starting treatment for MDD during their three-year follow-up had an increase in AHM adherence six months after initiating antidepressants. This suggests that co-treatment may enhance adherence, though larger, long-term studies are needed for confirmation. Some previous studies have suggested that treating MDD might improve treatment outcomes among hypertensive patients (Wang et al. 2022) and CVD medication adherence or persistence (Bogner and de Vries 2008; Glozier et al. 2013; Xing et al. 2018; Schmittdiel et al. 2014; Berimavandi et al. 2025). Integrated care teams, including healthcare professionals of various specialities, which treat both psychiatric and cardiovascular conditions have been proposed as a strategy to improve adherence to treatment for these patients (Simon et al. 2021; Pomerantz et al. 2014). A meta-analysis of 27 RCTs in 2,606 patients reported substantial improvement in SBP, DBP, and antihyperten-

sive efficiency, suggesting that the integrated treatment of MDD and hypertension may improve health outcomes. Furthermore, a retrospective cohort study of 1,484 patients found that those diagnosed with MDD one year before starting AHM therapy and persistently taking antidepressants for at least six months were more likely to remain persistent in the first six months of AHM treatment compared to non-users (OR = 1.56, 95% CI = 1.04–2.38) (Schmittdiel et al. 2014). Although a smaller study in 629 patients with MDD and heart failure did not observe improvements in adherence with integrated care teams compared to standard care (Rollman et al. 2021). The success of integrated care teams likely depends on understanding individual barriers to adherence and tailoring interventions accordingly. MDD treatment alone may not improve adherence if the primary barrier is not related to MDD. Therefore, larger well-designed RCTs using standardised adherence measurement methods are needed to understand the effectiveness of integrated care interventions on the clinical outcomes and adherence of psychiatric and cardiovascular diseases.

Since MDD is often underdiagnosed (Faisal-Cury et al. 2022), clinicians should be aware of its potential impact on hypertensive patients' medication adherence and persistence as observed in Ref. II, as well as premature mortality (Tu et al. 2025). Routine screening, early detection, and effective management may help improve CVD prevention (Vaccarino et al. 2020).

6.2.3. Antidepressant side effects among participants with genetic liability for psychiatric or neurological disorders

In Ref. III, we aimed to investigate the polygenic and pharmacogenetic contributions to antidepressant side effects. Side effects are common in antidepressant treatment and the leading cause of treatment discontinuity (Garcia-Marin et al. 2023; Chanie et al. 2025; Unni, Gupta, and Sternbach 2024). Since side effects are often unreported (Hazell and Shakir 2006) we leveraged data from three distinct EstBB data layers – self-reported data from two questionnaires and natural language processing of unstructured clinical notes from EHRs (Ref. III). By combining unstructured EHR data with self-reported questionnaires, we show a comprehensive approach to characterising antidepressant side effects, as self-reported questionnaires can help capture subjective and milder side effects, while side effects reported in clinical notes enable the identification of potentially more severe or long-term effects (Legge et al. 2024). A multi-source approach also improves the validity by including more controls that may be underrepresented in clinical settings or targeted questionnaires. Therefore, questionnaires and unstructured EHRs were used for a more complete picture of side effects.

Most of the previous studies investigating the genetic factors underlying antidepressant side effects have involved pharmacogenes (Fabbri et al. 2021; Campos et al. 2022; Calabrò et al. 2022; Mrazek et al. 2011; Jokovic et al. 2022). A study by Campos *et al* conducted among 20,941 AGDS participants with MDD

explored polygenic contributions but included only a limited number of traits (n $x \leq 4$) and relied on a targeted MDD questionnaire, which can limit the inclusion of controls (Campos et al. 2021).

To advance knowledge on this, we investigated the role of 19 PGS for psychiatric and side effect-related phenotypes in experiencing side effects among 13,729 antidepressant users. We found that participants with higher genetic liability for several psychiatric traits, including SCZ, MDD, ANX, and BIP had a higher likelihood of reporting at least one side across antidepressant classes. The highest number and strongest associations were found for the PGS for SCZ and MDD, which were independently linked to 15% (95% CI = 1.11–1.19) and 14% (95% CI = 1.10–1.18) higher odds of experiencing a side effect from antidepressants, respectively. However, in specific drug classes, the odds of experiencing a side effect among those with high PGS for SCZ was even higher, namely – 26% in TCAs (95% CI = 1.14–1.37). TCAs are non-selective, inhibiting serotonin and norepinephrine reuptake as well binding to various other receptors such as muscarinic, histaminergic, and adrenergic ($\alpha 1$) receptors (McClure and Daniels 2021). Many of these neurotransmitters modulated by TCAs are also implicated in SCZ pathophysiology, including dopamine, glutamate, and acetylcholine (McCutcheon, Krystal, and Howes 2020). Therefore, individuals with high PGS for SCZ may have pre-existing vulnerabilities in these pathways, which TCAs may exacerbate, leading to increased side effects.

In addition, the PGS for SCZ was linked to specific side effects from multiple symptom domains, including fatigue-related symptoms (drowsiness, sleepiness), nausea, weight gain and weight loss, irritability, and constipation, while the PGS for MDD was associated with sexual dysfunction, palpitations, weight gain, and a broader range of neurological side effects (drowsiness, sleepiness, insomnia, headache) across all antidepressants. Similarly to this study (Ref. III), a study by Campos *et al* has also reported associations between the PGS for MDD and higher reporting of most side effects across all antidepressants (Campos et al. 2021). However, the study in Ref. III was the first to report a link between the PGS for SCZ and higher occurrence of antidepressant side effects. Individuals with high polygenic risk for MDD or SCZ often have worse treatment outcomes, possibly due to more severe or treatment-resistant symptoms (Fanelli et al. 2021; Kamp et al. 2024; Pain et al. 2021b). This in turn may prompt clinicians to prescribe higher doses of antidepressants that could amplify the risk of experiencing side effects. In addition, patients with psychiatric disorders may misattribute somatic or psychiatric symptoms as medication side effects. Additionally, patients with psychiatric disorders have also been suggested to have heightened sensitivity to physical discomfort (Tang et al. 2008). However, further investigation is required to understand the underlying mechanisms underlying the associations between the genetic predisposition to psychiatric disorders and increase side effects reporting.

The first meta-analysis to address this question further identified drug-specific side-effects for those with genetic predisposition to headaches. Individuals with

higher genetic predisposition to headaches had 12% higher odds of headache symptoms from sertraline (OR = 1.12; 95% CI = 1.05–1.19), suggesting that accounting for an individual's genetic predisposition to headaches when selecting antidepressants could help reduce the occurrence of this side effect.

6.2.4. Genetic predisposition to psychiatric and cardiometabolic traits linked to cardiometabolic antidepressant side effects

Cardiometabolic side effects of antidepressants are common and include mainly weight gain, increased blood pressure, and heart palpitations (Alonso-Pedrero, Bes-Rastrollo, and Marti 2019; Mortensen and Andersen 2022; Shi et al. 2017). We identified positive associations between PGS for SBP and increased blood pressure as well as PGS for BMI and increased weight gain across all antidepressants, with the blood pressure link being a novel finding. Meta-analysis results of EstBB and the AGDS cohort showed that the PGS for BMI was consistently associated with increased weight gain in all nine antidepressants under consideration in the analysis, indicating that genetic predisposition to the underlying trait, particularly some cardiometabolic traits, may increase the respective side effects.

In addition to trait-specific genetic liability, participants with a higher genetic risk to ANX, BIP, MDD, SCZ, and NEUR also reported more cardiometabolic side effects. The PGS for SCZ was linked to weight gain and weight loss across all antidepressants, while the PGS for MDD was also associated with weight gain and palpitations. SSRIs are generally well tolerated, but they have been linked with weight gain (Alonso-Pedrero, Bes-Rastrollo, and Marti 2019), and citalopram specifically, to QT interval prolongation, which can lead to palpitations (Mortensen and Andersen 2022). Furthermore, genetic risk for SCZ has previously been linked to worse cardiac function (Pillinger et al. 2023) and SCZ patients with high PGS for BMI were reported to gain more weight during antipsychotic treatment compared to those with lower genetic risk (Alver et al. 2024). Therefore, patients with polygenic risk for psychiatric disorders or underlying symptoms may experience more cardiometabolic side effects when taking antidepressants. These cardiovascular symptoms may be influenced not only by specific medications but also by the interaction of genetic risk, comorbid conditions, concurrent medications, and shared genetic pathways underlying psychiatric and cardiovascular traits (Pillinger et al. 2023; Rødevand et al. 2021; Solmi et al. 2019).

Cardiovascular symptoms during antidepressant treatment require careful monitoring, as overlapping physical symptoms, such as palpitations, between psychiatric and cardiovascular disorders complicate diagnosis and may lead to misattribution to treatment rather than an underlying cardiac condition. This can contribute to diagnostic errors which are more common in patients with psychiatric disorders (Okabe et al. 2015; Liberati et al. 2025). For instance, psychiatric patients had 48% higher odds of a missed myocardial infarction diagnosis in the emergency department (Sharp et al. 2022), and 20% of patients with palpitations

were misdiagnosed with anxiety instead of supraventricular tachycardia (Awlia et al. 2025). These findings are particularly concerning given the elevated CVD risk in psychiatric patients (Goldfarb et al. 2022).

Another reason for more careful monitoring of cardiovascular side effects is that safety evidence in high-risk groups remains limited. Despite the general safety of SSRI which are the first-line treatment of many psychiatric disorders, most RCTs focus on healthy individuals in short-term trials, often excluding older adults and those with comorbidities (Behlke, Lenze, and Carney 2020). Trials in high-risk populations are typically small, and randomisation may not ensure even distribution of all relevant confounding factors (Behlke, Lenze, and Carney 2020). Therefore, identifying patients at risk of side effects, especially cardiovascular symptoms that may mask heart disease, is likely to improve health outcomes.

6.2.5. Polygenic scores in pharmacotherapy-related outcomes

PGS could be useful in assessing the drug response, tolerability and in identifying those with the greatest benefit from pharmacological therapies. Most studies have used the PGS for the underlying disease to evaluate drug response and tolerability of respective medications. For example, the PGS for MDD and SCZ have been associated with antidepressant treatment response (Lewis et al. 2022; Meerman et al. 2022; Marshe et al. 2021; Fanelli et al. 2021; Loef et al. 2022; Fabbri et al. 2021; Pain et al. 2021b; Pardiñas et al. 2022; Pieri et al. 2024) and the occurrence of side effects (Kamp et al. 2024; Li et al. 2024a). Furthermore, PGS may also help identify patient groups most likely to benefit from pharmacological treatments. Retrospective analyses of clinical trials of CVD treatments have shown that individuals at high polygenic risk of CAD may receive the greatest risk reduction through statin (Natarajan et al. 2017) and alirocumab (Damask et al. 2020) treatment. Similarly, a study based on real-world data reported that individuals with the higher genetic risk for myocardial infarction could receive a 59% relative risk reduction, while those in lower risk could receive a 33% risk reduction (Oni-Orisan et al. 2022).

Although there are limitations to PGSs, they could function as the first biomarkers in clinical psychiatry when combined with other risk factors (Murray et al. 2021). Overall, PGS could prove useful for identifying patients at increased genetic risk of disorders, designing more efficient clinical trials as well as for identifying those most likely to benefit from specific treatments with high efficacy and tolerability. They can be accessed early in the patient trajectory and may help guide treatment decisions about drug selection, monitoring frequency, and dose. The evidence for the clinical utility of PGS is growing, and there have been several studies integrating PGS to conventional risk models which could be used in the clinic (Schunkert et al. 2025; Riveros-Mckay et al. 2021; Elliott et al. 2020). Although the incremental increase added by the PGS to the overall pre-

dictive accuracy currently is modest. Some of these limitations of PGSs can be overcome by improvements in method development (O'Sullivan et al. 2022).

Taken together, individuals with high genetic risk for MDD and SCZ could be at risk of lower CVD medication adherence, higher treatment discontinuity, and higher burden of antidepressant side effects. Cardiovascular symptoms during antidepressant treatment should be carefully monitored as they may be due to the treatment, psychiatric disorder or underlying cardiovascular disease which could lead to a diagnostic error. Cardiovascular symptoms are common in individuals with a high genetic predisposition to psychiatric disorders. However, these symptoms may be overlooked in psychiatric patients, which can result in life-threatening consequences. Polygenic scores may be useful in identifying those at higher risk of adverse treatment outcomes or disease and can help tailor treatment to the patient through drug selection, dose modification or screening frequency. Future research could prioritise real-world, longitudinal studies in diverse and high-risk populations to better inform safe and effective antidepressant use.

6.3. Pharmacogenetic variants in medication use and side effects

6.3.1. Pharmacogenetic variants not associated with statin adherence and persistence

Pharmacogenetic variants have been shown to influence the drug plasma concentration, thereby impacting drug response and side effects (Jukic et al. 2018). In Ref. I, we sought to understand whether differential metabolism resulting from genetic variation in pharmacogenes was associated with treatment discontinuity and changes in medication adherence. None of the associations remained significant after multiple testing correction, however, we observed trends of lower adherence or persistence with some medications. Reduced metabolism of CYP2C9 was nominally associated with lower persistence of fluvastatin, while the reduced metabolism of SLCO1B1 was nominally associated with lower statin adherence and persistence in EstBB and FinnGen cohorts. However, these associations did not pass multiple testing correction threshold, suggesting that larger studies are needed to confirm this hypothesis. The trend towards lower persistence among individuals with reduced enzyme function could indicate that individuals are potentially discontinuing treatment due to side effects. Statin-associated muscle symptoms are one of the most prevalent side effects and account for one of the principal reasons for statin discontinuation (Cohen et al. 2012; Stroes et al. 2015; Voora et al. 2022). The link between rs4149056 polymorphism in *SLCO1B1* and simvastatin-related muscle toxicity has been clearly established and is highly dose dependent (McClure et al. 2007; Ramsey et al. 2014). Statin-induced myopathy is dependent on a moderate intensity simvastatin treatment of at least 40mg daily (Ramsey et al. 2014). Therefore, the lack of significant associations af-

ter multiple-testing correction could indicate that most patients use lower doses which would not lead to strong myopathy symptoms, thereby underestimating the effect of the reduced metabolism of SLCO1B1 enzyme. Another reason could be that simvastatin-related muscle symptoms (SAMS) take longer to develop, therefore not leading to discontinuity after the first prescription. Discomfort and weakness in SAMS typically occur early (within 4–6 weeks after starting statin therapy) but may still occur after many years of treatment (Stroes et al. 2015).

Taken together, the pharmacogenes considered in the analysis were not associated with reduced adherence and increased discontinuity of statins. However, we observed a trend towards lower statin use among participants with reduced function of CYP2C9 and SLCO1B1 enzymes. Larger studies are needed to clarify the role of pharmacogenetic variants in statin treatment discontinuation and adherence.

6.3.2. Pharmacogenetic variants linked to higher antidepressant side effect burden

In Ref. III, we investigated the role of a pharmacogene *CYP2C19* in antidepressant side effect load and found that poor metabolisers of CYP2C19 had 49% higher odds of experiencing a side effect while ultrarapid metabolisers had 17% lower odds of a side effect compared to normal metabolisers. This is in line with the biological mechanism where the reduced enzyme activity raises drug plasma concentration and consequently side effect risk, while increased enzyme activity lowers drug concentration, reducing side effects. The results agree with studies linking lower CYP2C19 enzyme activity to higher rates of side effects (Calabrò et al. 2022; Campos et al. 2022; Fabbri et al. 2018; Jokovic et al. 2022; Mrazek et al. 2011) and CPIC guideline-recommended dosage adjustments according to CYP2C19 metaboliser phenotype (Bousman et al. 2023; Hicks et al. 2015). Studies not finding any associations between decreased CYP2C19 enzyme activity and side effects (Brandl et al. 2014; Islam et al. 2022; Maggo et al. 2019; Peters et al. 2008) may have lacked statistical power due to smaller sample sizes (178–1,953 individuals). The larger cohort and the inclusion of structural variants enabled a more precise classification of CYP2C19 metaboliser phenotypes to detect associations. The inclusion of the partial deletion is particularly important since it is the first time it has been linked to a treatment outcome. A recent pharmacokinetics study from EstBB has validated the link between *37 and a loss of enzyme activity in participants, likely caused by the lack of exon 1 which carries the start codon and the membrane integration part of CYP2D6 (Krebs et al. 2025). Although CPIC considers this deletion to lead to a non-functional enzyme, the in vivo evidence is limited (ClinPGxCPIC 2025).

In addition, the *CYP2C19*37* has a higher frequency in specific European populations, including 1.9% in the Estonian population (EstBB) (Krebs et al. 2025) and 1.5% (gnomAD SV v4) in Finns (FinnGen), compared to a global frequency

of ~0.05% (Botton et al. 2019). This enforces the importance of population-specific analyses to fully characterise the function of variants.

In addition to the link between higher reporting of side effects among those with differential metabolism of CYP2C19, we also observed in our sensitivity analyses that the associations between side effects and the psychiatric or trait-specific polygenic scores were independent from CYP2C19 metaboliser phenotypes. This suggests that combining PGS and metaboliser phenotypes could improve predictions of adverse treatment effects. This is supported by a recent study among 32,000 UK Biobank participants which reported that combining PGS for disease with pharmacogenetic variants improved the prediction of calcium channel blocker treatment outcomes (Türkmen et al. 2024). Future studies could explore the interaction between between PGSs and CYP2C19 phenotypes to assess whether the strength of PGS effects differs across metaboliser subgroups compared to normal metabolisers.

In conclusion, the findings of this study suggest that pharmacogenetic information could help guide antidepressant prescribing through drug choice and dosage adjustments, which may improve treatment outcomes.

6.3.3. Perspectives of pharmacogenetics

One of the many clinical fields where pharmacogenetics has potential is in the treatment of psychiatric disorders. MDD is associated with high costs due to 65% of patients not responding to treatment, the trial-and-error process of selecting the appropriate medication, and patients often undergoing multiple medication trials (Pain et al. 2021b; Li et al. 2024b; Rush et al. 2006). Several studies have investigated the role of pharmacogenes in the treatment of MDD and SCZ (Jukic et al. 2022). Although implementing pharmacogenetics can be expensive, a recent pharmacoeconomic study suggests that it may lower overall healthcare costs due to a 37% reduction in cases of treatment-resistant MDD over a 20-year period when PGx-guided care is used (Ghanbarian et al. 2023). Furthermore, the initial cost of testing is recouped within approximately two years of use (Ghanbarian et al. 2023). Therefore, much work has already been done to investigate the function of variation in pharmacogenes and translate the genetics into actionable recommendations for clinicians.

Implementing PGx in routine clinical care faces several challenges, including population diversity, lack of data interoperability, limited clinical guideline integration, and insufficient education for clinicians and patients (Yang et al. 2021; Pirmohamed 2023).

On the scientific side, there are many advances in technologies that will help to improve our understanding of the function of pharmacogenes. Long-read sequencing can help to resolve complex genetic regions, identify novel variants, and improve haplotype phasing (Graansma et al. 2023). A PGS based on PGx variation has recently been used to predict drug response to clozapine and was

shown to explain 7.3% of the variance in clozapine metabolic ratios across ancestries (Pardiñas et al. 2023). However, PGS based on pharmacogenetic data typically includes fewer than 10 variations and could benefit from including more weakly associated variants as these have also been shown to increase predictive power (Lauschke, Zhou, and Ingelman-Sundberg 2024; International Schizophrenia Consortium et al. 2009). Computer algorithms trained on PGx datasets, such as activity prediction models, are being used to predict the functional consequences of rare variants (Zhou et al. 2019; Zhou and Lauschke 2021) along with the combination of in vitro gene expression combined with in-silico models, which have demonstrated protein-altering effects of rare variants (Johansson et al. 2025). In vivo impact has been further explored through probe-drug and targeted pharmacokinetic recall studies (Krebs et al. 2025). These approaches, alongside expanded biobank initiatives and real-world data, are expected to drive the PGx research and implementation.

6.4. Future prospects

One of the long-term goals of genomic research is to enhance patient treatment outcomes through personalised medicine, which uses genetic data to identify the most effective treatments for each individual. Although significant progress has been made in characterising the prevalence and genetic determinants of pharmacotherapy-related phenotypes, including medication use trajectories (Kiiskinen et al. 2023; Wu et al. 2019), response (Koch et al. 2024; Pain et al. 2021b), and side effects (Campos et al. 2021), substantial gaps remain in the mechanistic understanding, predictive capacity, and clinical translation.

One of the promising avenues involves the integration of different data sources to create more granular phenotypes of treatment outcomes. Traditional pharmacy refill-based adherence metrics are useful for large-scale inference but often fail to capture the nuanced behavioural and contextual factors that drive medication-taking behaviours. By linking genetic data from biobanks with clinical data, longitudinal prescription records, self-reported outcomes, and real-time behavioural inputs (e.g. from wearable devices), researchers can develop more detailed and dynamic phenotypes. Self-reported information can identify reasons for treatment discontinuation and provide details on the duration and intensity of adverse effects. Wearable data from smart watches, such as activity levels and heart rate variability, can help identify physiological correlates of adverse drug reactions, including early signs of cardiovascular side effects, monitor adherence or be used to monitor treatment outcomes, such as tracking heart rate responses to beta-blockers (Hughes et al. 2023; Cochran et al. 2022). Machine learning methods can help in analysing these data and some are being developed to understand medication-use behaviours with accuracies between 0.53–0.97 (Zakeri, Sansgiry, and Abughosh 2022). Furthermore, NLP techniques can help in enriching existing EHRs with relevant information on side effects and adherence behaviour from unstructured

clinical notes. Correct prediction of medication use is not only helpful for identifying risk factors of low adherence and improving treatment outcomes but also as part of other studies where medication use is a common confounder. Not accounting for medication adherence can lead to the underestimation of the extent of drug effects (Aasmets et al. 2024).

Another key direction involves advancing the understanding of the genetic underpinnings of medication use, response, and adverse effects. While most genetic studies to date have focused on disease risk (Evangelou et al. 2018; Surendran et al. 2020; Sinnott-Armstrong et al. 2021; Tabassum et al. 2019; Ripatti et al. 2020), recent GWA-studies have demonstrated that genetic factors also play a role in how individuals adhere to, respond to, or tolerate medications (Türkmen et al. 2025; Wu et al. 2019; Kiiskinen et al. 2023; Seo et al. 2014). Our findings suggest the underlying genetic risk is linked to the higher statin and antihypertensive medication use, but future studies could move beyond the intrinsic disease risk by accounting for the intrinsic genetic disease risk in the analyses. This may help identify medication-specific mechanisms that are independent of disease severity.

The development of a PGS to predict drug response, adverse effects, and medication use could help guide drug selection and dosage. Several studies have recently developed PGSs based on GWAS of disease (Natarajan et al. 2017; Zhang et al. 2019; Damask et al. 2020), pharmacogenetic (Pardiñas et al. 2023) or treatment response data (Koch et al. 2024) to understand common genetic variation in treatment outcomes. Future studies could investigate interactions and develop predictive models that integrate polygenic scores for disease and pharmacogenetic variants with clinical risk factors to estimate treatment outcomes. Such models could help personalise treatment regimens and follow-up intensity. The prediction of medication-related pharmacotherapy outcomes is particularly important among patients with psychiatric disorders who are at higher risk for CVD. Integrating polygenic scores for psychiatric disorders and CVD with other risk factors could help identify at-risk individuals and inform treatment plans that address both mental and physical health.

Studying medication use has methodological challenges due to the inconsistency and lack of harmonisation in how medication-related phenotypes are defined and measured (Hess et al. 2006). Many of these studies also do not take into account the dosage and polypharmacy. Standardising definitions for medication use across studies and the inclusion of additional information is essential to improve accuracy, reproducibility, and generalisability of findings. Another limitation in genetic research is the lack of inclusion of diverse ethnicities. GWA-studies should aim to include individuals with non-European ancestry to improve PGS predictive accuracy in non-European populations. Furthermore, studies with larger sample sizes are needed to improve the chances of identifying novel genetic variants with moderate or weak effect sizes on medication-related phenotypes.

Finally, the future of research in medication-related phenotypes must be shaped by policy and ethical considerations. The expansion of electronic health

record access, and linkage between biobank and registry data, have created unprecedented opportunities for research. However, data sharing remains constrained by regulatory differences, particularly with regard to the General Data Protection Regulation (GDPR) and data governance frameworks (Legido-Quigley et al. 2025). National and international collaboration will require harmonised legal interpretations, federated data infrastructures, and strong safeguards for privacy and participant trust (Legido-Quigley et al. 2025).

CONCLUSIONS

The studies in this thesis set out to better understand treatment-related outcomes of common pharmacotherapies. In our studies, we found that antihypertensive and cholesterol-lowering treatment adherence and persistence is low in Estonia and statin adherence is substantially lower in Estonia compared to Finland. The thesis underscores that medication adherence and persistence are complex multifactorial behaviours, influenced among others by psychiatric comorbidity and genetic factors. We observed that genetic factors have limited a role in statin usage patterns, however, genetic predisposition to the underlying cardiometabolic disease or its risk factors motivated higher statin medication use and increased respective side effects to antidepressants (BMI PGS and weight gain, SBP PGS and palpitations).

Polygenic risk for SCZ and MDD was associated with lower statin and AHM use, respectively, as well as a greater susceptibility to antidepressant side effects. In addition, clinical diagnosis of depression was linked to reduced use of AHM adherence and persistence. Importantly, we observed that the treatment of depression among patients with hypertension improved antihypertensive medication adherence. We also found that genetic predisposition to MDD, SCZ, BMI, SBP were linked to higher cardiometabolic side effect reporting across antidepressants. Extending this, we observed that genetic predisposition to headaches was specifically associated with increased headache symptoms from sertraline, suggesting a potential benefit of tailoring antidepressant choice to individual genotypes.

In addition to the broader genetic contribution of polygenic traits, we investigated the contribution of single PGx genes in statin medication use and antidepressant side effects. We found that genetic variation in pharmacogenes contributed to interindividual variability in antidepressant side effects, which was independent of PGS effects. However, the variation in PGx genes was not associated with medication adherence or persistence in statins, tamoxifen or clopidogrel. Therefore, our findings suggest that polygenic scores and pharmacogenetic information can be used to identify individuals at risk of antidepressant side effects. We also propose that combining the PGx and PGS information may help improve the prediction of antidepressant side effects.

The identification of the link between CYP2C19*37 partial deletion and increased side effects as well as its high prevalence specifically in the Estonian population highlights the importance of population-specific PGx analyses.

We observed that the integration of different data sources, including structured EHRs, unstructured clinical notes derived through NLP, and self-reported data improved side effect detection.

Collectively, this thesis highlights the utility of biobanks with longitudinal health records and genotype data for providing real-world evidence on pharmacotherapy-related outcomes.

Study-specific conclusions:

I.
- Statin medication adherence in Estonia was found to be low and considerably lower than in Finland.
- We reported a limited role of genetic factors in medication usage patterns, however genetic predisposition to cardiometabolic diseases was associated with higher statin adherence and persistence. Conversely, polygenic risk for SCZ and chronic pain reduced statin adherence and persistence.
- Genetic variation in pharmacogenes involved in the pharmacokinetic pathways of statins, tamoxifen, and clopidogrel was not associated with adherence or persistence to these medications.

II.
- Depression and its polygenetic risk were associated with lower antihypertensive medication adherence and persistence.
- The treatment of depression among patients with hypertension improved antihypertensive medication adherence.

III.
- Genetic factors were found to contribute to antidepressant side effects. More specifically, genetic predisposition to psychiatric traits, in particular MDD and SCZ, contributed to a higher burden of side effects across symptom domains.
- A drug-specific association was identified in a meta-analysis between the genetic predisposition to headaches and increased reporting of headache symptoms from sertraline.
- Genetic predisposition to some psychiatric and cardiometabolic traits, including the PGS for MDD, SCZ, BMI, and SBP was linked to higher cardiometabolic symptoms such as weight gain, increased blood pressure or heart palpitations.
- Antidepressant side effect burden varied by *CYP2C19* genotype, with poor metabolisers experiencing more and ultrarapid metabolisers experiencing fewer side effects from *CYP2C19*-metabolised antidepressants.
- CYP2C19*37 partial deletion was for the first time linked to an increase in side effects and it was identified to be approximately ten times more prevalent in the Estonian population compared to other European populations.
- The CYP2C19 metaboliser phenotype associations were independent of PGS for psychiatric and side-effect related traits.

SUMMARY IN ESTONIAN

Psühhiaatriliste ja kardiovaskulaarsete haiguste ravitulemuste parandamine

Psühhiaatriliste haigustega inimestel on suurem südame-veresoonkonna haigustesse (SVH) haigestumus ja suremus. Kuigi vererõhu- ja kolesterooliravimeid kirjutatakse üha enam välja, võtab vaid pool patsientidest ravimeid arsti ettekirjutuse järgi – käitumine, mida kirjeldab ravisoostumus ja -järjepidevus. Vähene SVH ravimite tarbimine suurendab SVH riski, seevastu kõrvaltoimed on psüühikahäirete ravimite võtmise katkestamise peapõhjus, mis aeglustab paranemist.

Käesolev doktoritöö uuris geneetilisi tegureid, mis mõjutavad SVH ravimite soostumust ja järjepidevust ning antidepressantide kõrvaltoimeid. Täpsemalt uuriti statiinide tarbimist Eesti Geenivaramu ja FinnGeni biopankade andmetel, depressiooni mõju vererõhuravimite tarbimisele ning antidepressantide kõrvaltoimeid.

Leidsime, et Eestis oli statiinide ravisoostumus (65%) oluliselt väiksem kui Soomes (89%). Geneetiliste tegurite mõju oli piiratud, kuid kõrgem südamehaiguste polügeenne risk, mis hindab paljude riskialleelide koondmõju, suurendas statiinide tarbimist, samal ajal kui psüühikahäirete polügeenne risk vähendas seda. Farmakogeenid, mis mõjutavad ravimite töötlemist organismis, ei selgitanud erinevusi SVH ega vähiravimite tarbimisel.

Depressioon ja selle polügeenne risk seostusid väiksema vererõhuravimite ravisoostumuse ja -järjepidevusega, kuid depressiooni ravimisel vererõhuravimite soostumus paranes.

Variatsioon farmakogeenis *CYP2C19* mõjutas selgelt kõrvaltoimete esinemist: aeglased metaboliseerijad kogesid 50% rohkem ja ultrakiired metaboliseerijad 17% vähem kõrvaltoimeid. Esmakordselt analüüsisime CYP2C19*37 geeni deletsiooni, mille tõttu on suur osa CYP2C19 geenist puudu ning leidsime, et deletsioonil on oluline mõju kõrvaltoimete tekkimisele. Samuti esineb seda eestlastel ligi kümme korda rohkem kui muudel Euroopa populatsioonidel. Psüühikahäirete ja kardiometaboolsete tunnuste polügeenne risk suurendas kardiometaboolsete kõrvaltoimete esinemise tõenäosust, sealhulgas südamepekslemise, kehakaalu ja vererõhu tõusu. Samuti esines sertraliini tarvitajatel peavalu sagedamini neil, kel oli geneetiline eelsoodumus peavalude tekkeks. Täheldasime, et erinevate andmeallikate, sealhulgas loomuliku keeletöötlusega (NLP) tuletatud struktureerimata haiguslugude ja eneseraporteeritud andmete kombineerimine parandas kõrvaltoimete tuvastamist.

Kokkuvõttes näitavad tulemused, et polügeenset ja farmakogeneetilist teavet saab kasutada antidepressantide kõrvaltoimete riski hindamiseks. Samuti võib depressiooni ravi parandada vererõhuravimite soostumust. Lisaks toob töö esile biopankade potentsiaali, mis koos tervise- ja genotüübiandmetega võimaldavad uurida ravimite pikaajalist tarbimist ja ravitulemusi väljaspool kliinilisi uuringuid nn reaalelu tingimustes.

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PUBLICATIONS

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29 Jul. 2025	University of Cambridge Pembroke International Summer School, *"Leveraging Large-Scale Health Data: Opportunities, Risks, and Ethical Imperatives"*, Cambridge, UK, Oral presentation
15 Jan. 2025	Annual Conference of the Institute of Molecular and Cell Biology and the Institute of Genomics, Tartu, Estonia, Poster presentation
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18 Jan. 2023	Annual Conference of the Institute of Molecular and Cell Biology and the Institute of Genomics, Tartu, Estonia, Poster presentation
03 Nov. 2022	Nordic Society of Human Genetics and Precision Medicine (NSHG-PM), Copenhagen, Denmark, Poster presentation
25 Jan. 2022	Annual Conference of the Institute of Molecular and Cell Biology and the Institute of Genomics, Tartu, Estonia, Oral presentation
11 Oct. 2021	World Congress of Psychiatric Genetics (WCPG), Virtual, Poster presentation

Teaching

Hanna Maria Kariis was invited in 2023, to Pembroke College, University of Cambridge, to mentor students from MIT, Harvard, Yale, Hong Kong Polytechnic, and other leading academic institutions as part of the International Summer School. She was responsible for leading discussions and mentoring students to enhance their knowledge of health data analytics.

Publications

Abner, E., Batool, K., Taba, N., Nikopensius, T., Läll, K., Alekseienko, A., Eriksson, A., Rämö, J., **Kariis, H. M.**, Haljasmägi, L., Haapaniemi, H., Tillmann, T., Ollila, H., Lehto, K., Kisand, K., Vainik, U., Võsa. U., Estonian Biobank Research Team & Esko, T. (2025). Characterization of prevalent genetic variants in Estonian Biobank body-mass index GWAS. Nature Communications. https://doi.org/10.21203/rs.3.rs-4708168/v1[1].

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Cordioli, M., Corbetta, A., **Kariis, H. M.**, Jukarainen, S., Vartiainen, P., Kiiskinen, T., Ferro, M., FinnGen, Estonian Biobank Research Team, Perola, M., Niemi, M., Ripatti, S., Lehto, K., Milani, L., & Ganna, A. (2024). Socio-demographic and genetic risk factors for drug adherence and persistence across 5 common medication classes. Nature Communications, 15(1), 9156. https://doi.org/10.1038/s41467-024-53556-z

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Warming, H., Pegasiou, C.-M., Pitera, A. P., **Kariis, H.**, Houghton, S. D., Kurbatskaya, K., Ahmed, A., Grundy, P., Vajramani, G., Bulters, D., Altafaj, X., Deinhardt, K., & Vargas-Caballero, M. (2019). A primate-specific short GluN2A-NMDA receptor isoform is expressed in the human brain. Molecular Brain, 12(1), 64. https://doi.org/10.1186/s13041-019-0485-9

ELULOOKIRJELDUS

Isikuandmed

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Haridus

2021–2025	PhD geenitehnoloogia, genoomika instituut, Tartu Ülikool (struktuuriüksuse muutus)
2020–2021	PhD geenitehnoloogia, molekulaar ja rakubioloogia instituut, Tartu Ülikool
2018–2019	MSc neuroteadus, Southamptoni Ülikool, Suurbritannia
2015–2018	BSc neuroteadus, Southamptoni Ülikool, Suurbritannia

Teenistuskäik

2021–...	Tartu Ülikool, Genoomika Instituut (psühhiaatrilise geneetika noorem teadur)
2020–2022	Tartu Ülikool, Genoomika Instituut (spetsialist)
2019-2021	Tervise Arengu Instituut (kopuvähi sõeluuringu projektijuht)

Ettekanded

31 Jul. 2025	Pharmacogenomics Global Research Network Psychiatry Special Interest Group Webinar, *"Genetic influences on antidepressant effects: a CYP2C19 gene variation and polygenic risk study in the Estonian Biobank"*, Virtuaalne, Suuline ettekanne
29 Jul. 2025	University of Cambridge Pembroke International Summer School, *"Leveraging Large-Scale Health Data: Opportunities, Risks, and Ethical Imperatives"*, Cambridge, UK, Suuline ettekanne
15 Jan. 2025	TÜ molekulaar- ja rakubioloogia instituudi ning TÜ genoomika instituudi aastakonverents, Tartu, Eesti, Stendiettekanne
24 Sep. 2024	Geenifoorum, Tartu, Eesti, Stendiettekanne
1 Jun. 2024	European Society of Human Genetics (ESHG), Berlin, Germany, Stendiettekanne
25 Aug. 2023	Geenifoorum, Tartu, Eesti, Stendiettekanne
19 Jun. 2023	NSHG-PM Precision Medicine Workshop, Tallinn, Eesti, Stendiettekanne
18 Jan. 2023	TÜ molekulaar- ja rakubioloogia instituudi ning TÜ genoomika instituudi aastakonverents, Tartu, Eesti, Stendiettekanne
03 Nov. 2022	Nordic Society of Human Genetics and Precision Medicine (NSHG-PM), Kopenhaagen, Taani, Stendiettekanne
25 Jan. 2022	TÜ molekulaar- ja rakubioloogia instituudi ning TÜ genoomika instituudi aastakonverents, Tartu, Eesti, Suuline ettekanne
11 Okt. 2021	World Congress of Psychiatric Genetics (WCPG), Virtuaalne, Stendiettekanne

Õpetamine

Hanna Maria Kariis kutsuti 2023. aastal mentoriks Pembroke kolledi suvekooli Cambridge'i Ülikoolis. Tema roll oli juhendada õpilasi MIT, Harvard, Yale, Hong Kong Polytechnic ülikoolidest seminaridel ja aidata neid terviseandmete mõistmise ja analüüsimisega seonduvates küsimustes.

Teaduspublikatsioonid

Abner, E., Batool, K., Taba, N., Nikopensius, T., Läll, K., Alekseienko, A., Eriksson, A., Rämö, J., **Kariis, H. M.**, Haljasmägi, L., Haapaniemi, H., Tillmann, T., Ollila, H., Lehto, K., Kisand, K., Vainik, U., Võsa. U., Estonian Biobank Research Team & Esko, T. (2025). Characterization of prevalent genetic vari-

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