Project Details	
Project Code	CMD27Ex Pilling
Title	Genetic and Therapeutic Determinants of Adverse Drug Reactions in Cardio-Renal Diseases
Research Theme	Cardiometabolic Disease
Project Type	Dry lab
Summary	Why do people with cardiometabolic diseases experience different health trajectories despite similar treatment? This interdisciplinary PhD project will investigate how genetic variation, prescribing, and patient characteristics influence treatment response, drug safety, and health. Leveraging health data science techniques developed by Exeter AGE Group, you will analyse linked genomic and clinical records data from cohorts of millions of people (including UK Biobank and Our Future Health) to, with embedded training and career development. Focusing on cutting-edge therapies like SGLT2 inhibitors and DOACs, your discoveries could help prevent adverse outcomes like falls and kidney injury, informing precision medicine and NHS clinical guidance.
Description	Background and Rationale Cardiometabolic diseases including heart failure, diabetes, and hypertension, are a leading cause of death globally (DOI:10.1016/j.jacc.2022.11.005). Individual health trajectories are shaped by a complex interplay of genetic susceptibility, medication use, and patient factors, leading to substantial variation in treatment response, adverse effects, frailty, and progression to cardiovascular and renal complications. Uniform treatment strategies often fail to account for individual heterogeneity in treatment response. Understanding how these factors interact is essential for improving risk prediction and developing more personalised approaches to prevention and treatment. For example, intensive blood pressure management is recommended to reduce stroke risk. However, our researchers demonstrated that blood pressure below 130/80 mmHg in adults aged 75+ was associated with excess mortality (DOI:10.1093/ageing/afaa028). To further our understanding of adverse effects and frailty, particularly within older, multi-morbid populations, this project will examine how genetic variation influences trajectories of cardiovascular frailty, including treatment-related effects on blood pressure, falls risk, and other ageing-related adverse outcomes. Our pharmacogenetics research has demonstrated that genetic variants in the CYP2C19 enzyme influence the risk of myocardial infarction and stroke among patients prescribed the antiplatelet drug clopidogrel in a large population-based cohort study (DOI:10.1136/bmjopen-2021-053905). These findings informed NHS clinical guidance. We extended this work by developing a robust statistical framework for estimating medication adverse events attributable to pharmacogenetic variants (TWIST, DOI:10.1371/journal.pgen.1009783). By leveraging naturally occurring genetic variation, TWIST provides a powerful framework for quantifying treatment heterogeneity and advancing precision medicine in cardiometabolic disease. We applied TWIST to common drugs in cardiovascular prevention (statins DOI:10.1111/bcp.15245 and antihypertensives DOI:10.1038/s41397-024-00333-2), and have also

	estimated the impact of medication non-adherence to statin tolerance and effectiveness (DOI:10.1186/s12916-025-04228-2). Less is known about the effect of genetics on newer treatments such as Sodium-glucose cotransporter 2 (SGLT2) inhibitors, used in diabetes and heart failure, and direct oral anti-coagulants (DOACs) used in prevention of stroke and thromboembolic disease. Our GW4 supervisory team have published on DOAC risk versus benefit (DOI:10.1007/s41999-023-00811-z; DOI:10.1186/s12916-021-02067-5). However, research is limited on how genomic factors may affect response to treatment (DOI:10.3389/fgene.2025.1571032). Building on our previous pharmacogenetic research and extending the TWIST framework, this PhD project will investigate genetically modified treatment effects for these treatments using large-scale linked healthcare and genetic data. The project will seek to identify genetic factors associated with variation in treatment response in different cardiometabolic diseases, and adverse effects such as falls, bleeding, and acute kidney injury. Ultimately, heterogeneity in treatment response may influence not only short-term outcomes but also long-term cardiovascular and renal disease trajectories. Cardiometabolic diseases frequently cluster and interact, with the development of one condition contributing to the progression of another; for example, hypertension increases the risk of heart failure and chronic kidney disease (DOI:10.1016/j.ebiom.2025.105584). Recent work from our group has further demonstrated that obesity is a shared causal risk factor underlying these conditions, highlighting the interconnected nature of cardiometabolic multimorbidity (DOI:10.1038/s43856-025-01347-y). Building on our ongoing Medical Research Council-funded research investigating how cardiometabolic diseases evolve over time, this PhD project will examine how genetic susceptibility, pharmacogenetic factors, and medication adherence contribute to individual differences in disease progression, cardiometabolic multimorbidity, frailty, and long-term cardiovascular and renal outcomes. Key Research Questions 1. How do genetic susceptibility and cardiovascular medication use interact to influence long-term blood pressure trajectories, falls risk, and cardiovascular frailty in older adults? 2. Does genetic variation modify the efficacy and safety profiles of DOACs and SGLT2 inhibitors in diverse primary care populations? 3. To what extent do pharmacogenetic variants, polygenic scores, and medication adherence interact to drive the progression of cardio-renal multi-morbidity? This health data science project will use UK Biobank (half a million participants) and Our Future Health (up to 5 million participants), two of the world's largest population cohorts with linked electronic medical records and genetic data. Breakdown of Objectives 1. Genetics, blood pressure regulation, and cardiovascular frailty: The study will apply epidemiological methods to investigate how genetic variation and cardiovascular medication use influence blood pressure trajectories, falls risk, and frailty-related outcomes in older adults.

	2. Pharmacogenetic effects of newer therapies: Utilizing the TWIST frame, the student will determine whether genetic variation modifies the effectiveness and safety of DOACs and SGLT2 inhibitors, identifying genetically defined subgroups with differential treatment response, bleeding risks, and acute kidney injury, to inform precision treatment strategies. 3. Cardio-renal disease trajectories, treatment heterogeneity, and multimorbidity: The student will integrate genetic susceptibility (polygenic risk scores) with medication adherence, and longitudinally model individual trajectories contribute to progression of cardiometabolic multimorbidity and long-term cardiovascular and renal outcomes. Student Ownership The project proposal and supervisory team provide a structured epidemiological and clinical framework yet leave plenty of opportunity for the student to take ownership of the project. The final objectives (medication and outcomes to focus on) will be decided in collaboration with the student, aligned to their scientific interests and the most up-to-date literature when the PhD starts.
Can be completed part time?	Yes
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