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Mental health conditions and cardiovascular diseases: associations and risk stratification based on genetics, lifestyle, and biomarkers



Shinya Nakada
MPH

Submitted in fulfilment of the requirement for the
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University of Glasgow

School of Health and Wellbeing
College of Medical, Veterinary & Life Sciences
University of Glasgow
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Abstract

Multimorbidity involving a common mental health condition (MHC) such as anxiety or depression and a concomitant cardiovascular disease (CVD) poses a high public health burden globally. However, health services and research are largely structured around single systems, rather than adopting a holistic approach. Given the emerging evidence that MHCs could increase the risk of CVD, understanding the roles of MHCs in developing CVD could inform preventive strategies and, thereby, may help to reduce burden.

UK Biobank is a very large-scale population cohort study, designed to investigate extensive environmental, lifestyle, and genetic risk factors related to a wide range of health conditions in adults. Utilising the UK Biobank, it is possible to undertake a systematic investigation of MHC-CVD clustering using various types of data and epidemiological approaches.

My thesis aimed to investigate the roles of anxiety and depression in developing CVD in middle-aged and older adults using data from UK Biobank. Specific objectives were to: (1) examine the individual and joint associations of anxiety and depression with a range of incident CVD outcomes; (2) examine the associations of anxiety and depression with CVD stratified by CVD genetic susceptibility; (3) examine the extent to which lifestyle, physical, and metabolic factors mediate the associations between anxiety and depression and incident CVD; and (4) examine whether including anxiety and depression in an existing CVD risk score improves the prediction of CVD risk.

To achieve the aim, my thesis included four published manuscripts, each addressing one objective. Collectively, my findings contributed to the elucidation of the roles of anxiety and depression in developing CVD and identified actionable pathways. Therefore, the findings generated not only advance current understanding but also have direct clinical and public health relevance.

Firstly, I found that having anxiety contributed the same relative excess risk of CVD regardless of the presence of depression, and vice versa, suggesting that

anxiety and depression operate independently and therefore both warrant attention in CVD risk management. Secondly, CVD genetic susceptibility partly contributed to the clustering of depression and CVD but did not provide a full explanation, nor did it explain the association between anxiety and CVD. Therefore, the increased risk of CVD in these patients should be addressed regardless of CVD genetic susceptibility. Thirdly, smoking and central obesity were the strongest lifestyle and physical mediators of CVD for both anxiety and depression. However, high systolic blood pressure was the strongest metabolic mediator for anxiety whilst C-reactive protein was the strongest metabolic mediator for depression. The findings inform a more personalised risk management among people with anxiety or depression. Lastly, I found that incorporating measures of anxiety and depression into an existing CVD risk score significantly, but only modestly, improved prediction of CVD onset. Whether to integrate MHCs into CVD risk scores should be carefully considered, especially when it attracts additional costs, and investigating broader MHCs using established tools or diagnostic interview data could be the focus of future studies.

Overall, these findings highlight the need to assess and manage CVD risk factors among people living with anxiety and depression in order to reduce their burden from CVD.

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Publications

Manuscripts included in this thesis

Nakada S et al. Individual and joint associations of anxiety disorder and depression with cardiovascular disease: A UK Biobank prospective cohort study. European Psychiatry 2023. DOI: 10.1192/j.eurpsy.2023.2425

Nakada S et al. Anxiety disorder, depression and coronary artery disease: associations and modification by genetic susceptibility. BMC Medicine 2025. DOI: 10.1186/s12916-025-03915-4

Nakada S et al. Shared and distinct pathways from anxiety disorder and depression to cardiovascular disease: a mediation analysis of the UK Biobank prospective cohort study. European Journal of Preventive Cardiology 2025. DOI: 10.1093/eurjpc/zwaf110

Nakada S et al. Refining PREVENT prediction models for 10-year risk of cardiovascular disease using measures of anxiety and depression. Canadian Medical Association Journal 2025. DOI: 10.1503/cmaj.240996

Other selected manuscripts published during the PhD period

Nakada S et al. Hospital admissions for anxiety disorder, depression, and bipolar disorder and venous thromboembolism: A UK biobank prospective cohort study, Journal of Affect Disorders 2024. DOI: 10.1016/j.jad.2024.12.060

Nakada S et al. Schizophrenia and Types of Stroke: A Mendelian Randomization Study. Journal of the American Heart Association 2024. DOI: 10.1161/JAHA.123.032011

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Lastly, I would like to give my special thanks to my wife. She has always believed in me and supported my student life.

Author's Declaration

I declare that this thesis is the result of my own work. Published work of others have been cited where used. The papers presented in each chapter have been published in peer-reviewed journals.

The text of each chapter is identical to the text of the published paper, except that tables and figures have been inserted at their points of citation within the text and their numbering have followed the sequence of the entire thesis. This has been done to fulfil the University of Glasgow guidelines on preparation of a thesis by 'alternate' format.

The contents of this thesis have not been submitted for any other degree at the University of Glasgow or any other Institution.

Shinya Nakada

March 2026

Main Abbreviations

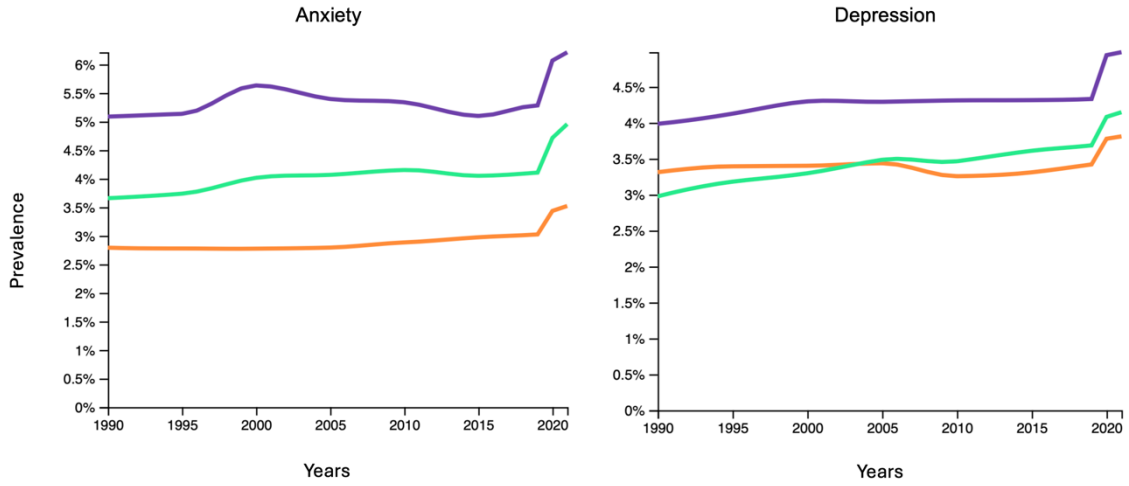
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HbA1c	Haemoglobin A1c
HDL-c	High-density-lipoprotein cholesterol
HR	Hazard ratio
ICD	International Classification of Diseases
LDL-c	Low-density-lipoprotein cholesterol
MET	Metabolic equivalent minute
MHC	Mental health condition
MI	Myocardial infarction
NIE	Natural indirect effect
PHQ-9	Patient Health Questionnaire-9
PRS	Polygenic risk score
PREVENT	American Heart Association Predicting Risk of Cardiovascular Disease Events
RERI	Relative excess risk due to interaction
SNP	Single nucleotide polymorphisms
TIA	Transient ischemic attack

Chapter 1 Introduction

1.1 Epidemiology of Anxiety and Depression

Anxiety and depression are the two most common mental health conditions (MHCs), each affecting 300 million people globally in 2019 (GBD 2019 Mental Disorders Collaborators, 2022). According to a large study that collated data from surveys conducted in 29 countries, approximately 20% of men and 30% of women had experienced anxiety or depression by the age of 75 years (McGrath et al., 2023). The prevalence is higher in developed countries compared to middle- and low-development countries, but is increasing in all three (Figure 1) (Global Burden of Disease Collaborative Network, 2019).

Figure 1. Global prevalence of anxiety and depression between 1990 and 2020



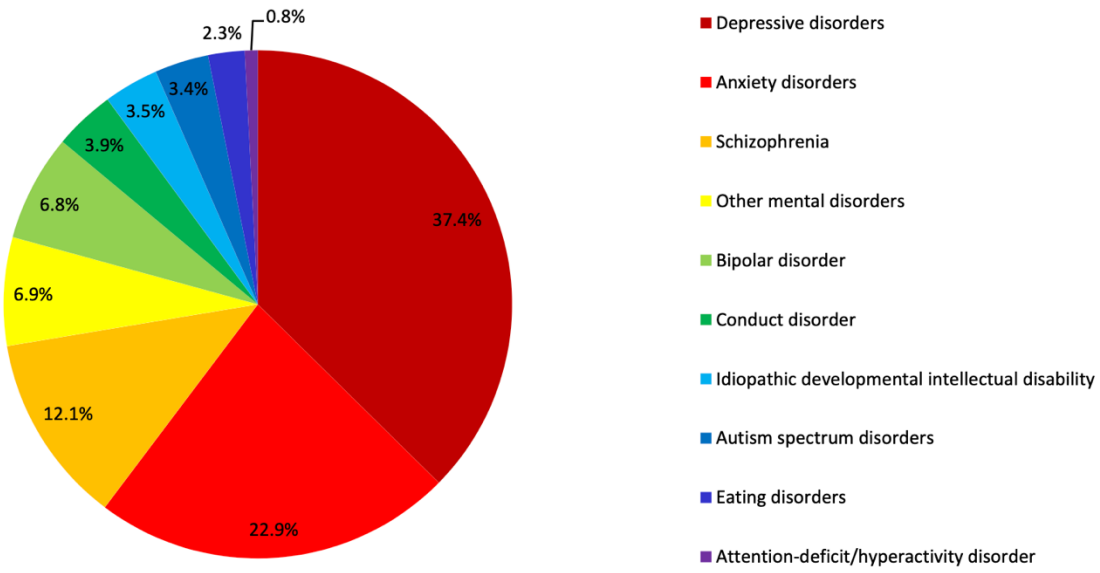
Purple: High-development countries, Green: Middle-development countries, Orange: Low-development countries

Adapted from Global Burden of Disease Collaborative Network, 2019

Anxiety and depression are leading contributors to the individual, economic and societal burden of MHCs. People with anxiety or depression have mortality rates approximately 40% and 70% higher than those of the general population, respectively (Walker et al., 2015). People living with these conditions suffer not only from persistent or recurring mental health symptoms but also cognitive decline and medical comorbidities (Craske et al., 2017, Marx et al., 2023, Kessler et al., 2009). They are more likely to experience school failure, academic underachievement, unemployment, reduced working hours, and lower household income, resulting in reduced quality of life (Craske et al., 2017, Marx et al., 2023, Kessler et al., 2009).

The annual societal costs of anxiety and depression in Europe were estimated at €74 billion and €113 billion, respectively, in 2010 (Gustavsson et al., 2011). Approximately 60% of the cost of depression arose from economic impact due to reduced working hours and productivity (Greenberg et al., 2003), whilst 60% of the cost of anxiety arose from healthcare including goods and services related to prevention, diagnosis and treatment (Gustavsson et al., 2011). At the global level, anxiety and depression were the top two leading causes of years lived with disability from MHCs across almost all age groups in 2019 (GBD 2019 Mental Disorders Collaborators, 2022). Reflecting this, they accounted for 23% and 37% of the total disability-adjusted life-years attributed to MHCs, respectively (Figure 2) (GBD 2019 Mental Disorders Collaborators, 2022).

Figure 2. Proportion of global mental disorder disability-adjusted life-years attributable to each disorder for both sexes and all ages in 2019



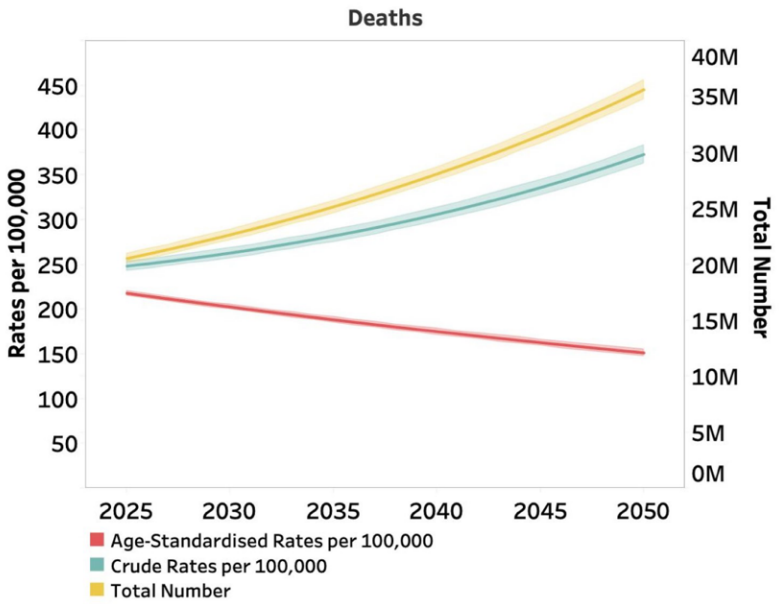
Adapted from GBD 2019 Mental Disorders Collaborators, 2022

1.2 Epidemiology of Cardiovascular Disease

Cardiovascular disease (CVD), including coronary artery disease (CAD), stroke, and heart failure, remains a major public health issue. CVD is the top ranking cause of disability-adjusted life-years in middle- and old-age groups globally, reflecting its substantial impact on both years lived with disability and

premature deaths (GBD 2019 Diseases and Injuries Collaborators, 2020). In 2022, more than 500 million people were affected and 20 million people died from CVD, equating to one third of all global deaths (Mensah et al., 2023). Although the age-standardised CVD mortality rate is expected to decline by 36% by 2050, the annual number of cases and deaths are projected to reach one billion and 36 billion, respectively due, in part, to the aging global population (Chong et al., 2024) (Figure 3). The highest age-standardised mortality rates in 2050 will be observed in Central Europe, Eastern Europe, and Central Asia, with a persistent gap compared to high-income countries (Chong et al., 2024).

Figure 3. Projected global number of deaths and age-standardised and crude mortality rates from cardiovascular disease.



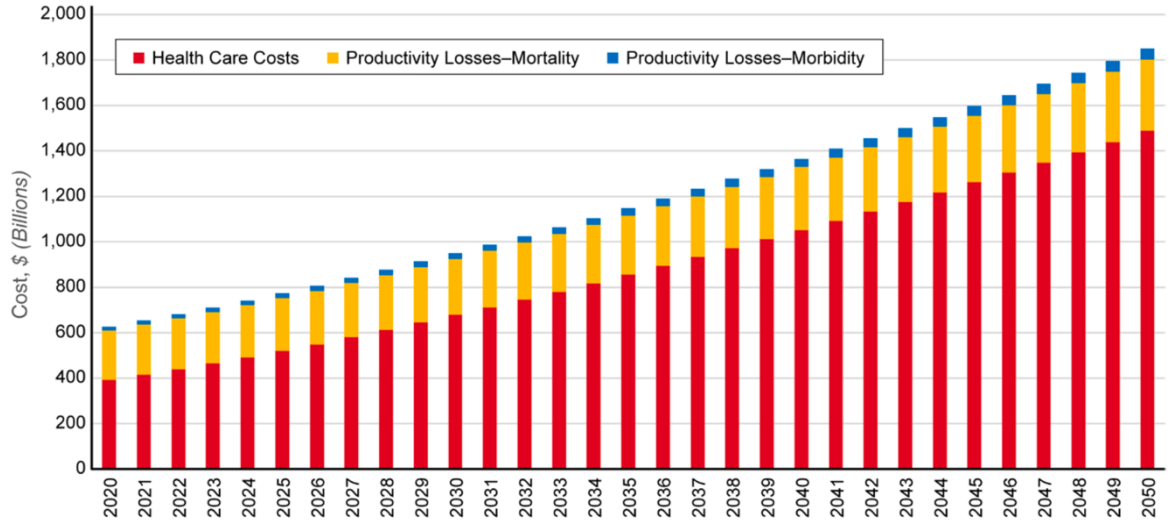
Adapted from Chong et al., 2024

Survivors of CVD experience lower quality of life compared with the general population (Luengo-Fernandez et al., 2013, Brown et al., 1999, Lewis et al., 2014). A British cohort study using the Short Form 36 found lower quality of life in all domains including physical functioning, social functioning, role limitations, mental health, energy/vitality, body pain, and general health perception (Brown et al., 1999). Inability to return to work was most strongly associated with the overall quality of life score.

Finally, the economic burden of CVD was estimated at €282 billion for European Union countries in 2021 and £21 billion for England in the United Kingdom (UK) in

2018 with healthcare expenditure accounting for approximately half of the total cost in both cases (Luengo-Fernandez et al., 2023, Landeiro et al., 2024). Notably, in the United States of America (USA), the total cost of CVD is projected to triple from 2020 to 2050, mainly driven by a near quadrupling of healthcare expenditure (Figure 4) (Kazi et al., 2024).

Figure 4. Projected economic burden of cardiovascular disease and stroke in the USA



Adapted from Kazi et al., 2024

1.3 Multimorbidity

1.3.1 Epidemiology of Multimorbidity

Multimorbidity, defined as the coexistence of two or more chronic conditions in the same individual, is a growing health issue, partly driven by the aging population (Mercer et al., 2016). Although comparing different studies is challenging due to varying definitions, existing evidence has shown a clear trend. Globally, one-third of adults and half of adults aged above 60 years have multimorbidity with a gradual increase among adults over the past two decades (Nguyen et al., 2019, Chowdhury et al., 2023). Those who are older or live in deprived areas are more likely to experience multimorbidity (Skou et al., 2022). A British study projected that the prevalence of severe multimorbidity (four or

more chronic conditions) will increase to 17% by 2035 and, two-thirds of those with multimorbidity will have MHCs (Kingston et al., 2018).

Multimorbidity increases individual, health care, and economic burden. People with multimorbidity require a complex treatment plan including multiple drugs, lifestyle changes, and frequent hospital admissions and appointments and have a higher risk of premature death than those with a single condition (Skou et al., 2022). Healthcare professionals, such as general practitioners, also experience challenges to managing multimorbidity. A systematic review of qualitative studies identified four areas of difficulty: disorganisation and fragmentation of healthcare; inadequacy of guidelines and evidence-based medicine; challenges in delivering patient-centred care; and barriers to shared decision-making (Sinnott et al., 2013). Finally, multimorbidity increases health care utilisation including physician and hospital attendances and admissions, and medication use, resulting in an increase in healthcare cost with expenditure approximately doubling for each additional chronic condition (Lehnert et al., 2011).

1.3.2 Clustering of Mental Health Conditions and Cardiovascular Disease

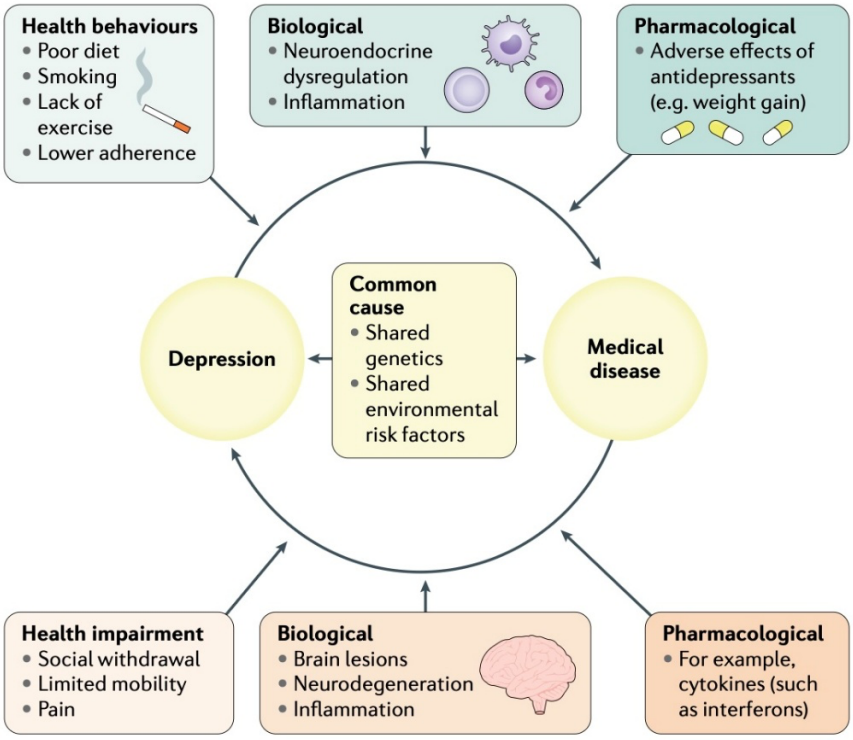
MHCs and CVD often co-occur, posing a substantial health burden (Sinnige et al., 2013). Anxiety and depression have been observed in 30% and 15% of patients with CVD, respectively (Todaro et al., 2007, Colquhoun et al., 2013). Whilst people with a MHC (e.g., depression) or CVD each have a moderately higher risk of premature death with a mortality ratio of 1.7, co-existence of these conditions is associated with a disproportionately higher mortality ratio of 4.63, suggesting a potential interaction (Momen et al., 2022). Furthermore, the economic burden associated with clustering of MHCs and CVD is substantially greater than the sum of each condition (Brilleman et al., 2013).

1.3.3 Theoretical frameworks of the Interrelationship between Mental Health Conditions and Cardiovascular Disease

There are two theoretical frameworks that help explain co-occurring MHCs and CVD: multimorbidity and the brain–heart axis. The framework of multimorbidity

explains why MHCs and CVD co-occur through bidirectional pathways (e.g., MHCs affect CVD via inflammation and vice versa) as well as through both conditions being consequences of upstream factors (e.g., sociodemographic factors affect both MHCs and CVD) (Figure 5) (Gold et al., 2020, The Academy of Medical Sciences, 2018).

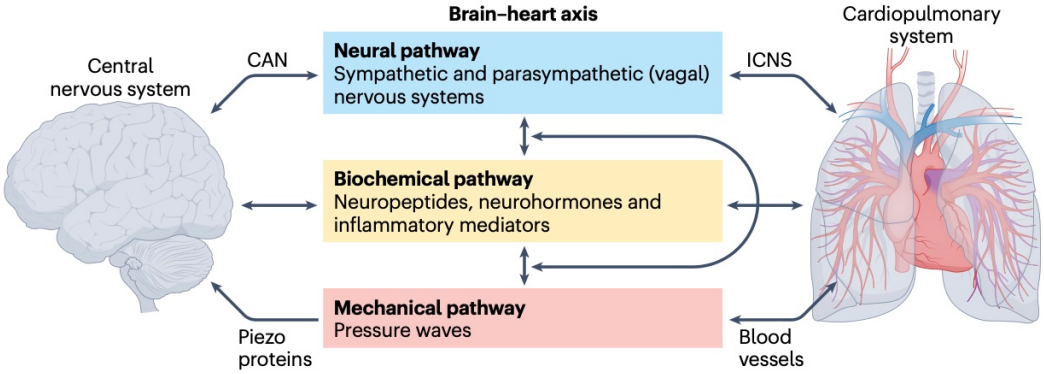
Figure 5. Theoretical framework of multimorbidity



Adapted from The Academy of Medical Science et al., 2018

The brain–heart axis framework explains the biological connections between the central nervous system and the cardiopulmonary system through neural pathways (e.g., the sympathetic nervous system), biochemical pathways (e.g., inflammation), and mechanical pathways (e.g., blood pressure) (Figure 6) (Valenza et al., 2025).

Figure 6. Theoretical framework of the brain-heart axis



Adapted from Valenza et al., 2025

The two frameworks are complementary to each other as the multimorbidity framework postulates the epidemiological explanations (e.g. via confounding of common causes) and more behavioural level mechanisms whilst the brain-heart axis focuses on more biological and physiological changes that might explain the co-occurrence. Together, these frameworks provide a basis for understanding why and how MHCs and CVD co-occur.

1.3.4 Empirical Evidence on the Interrelationship Between Mental Health Conditions and Cardiovascular Disease

There is well-established evidence that MHCs are associated with increased risk of CVD. For example, in 2007, a systematic review with meta-analyses included 28 longitudinal cohort and case-control studies that examined the associations between depression and incident CVD and reported pooled odds ratios ranging from 1.40 to 1.60 (Van der Kooy et al., 2007). In 2019, a larger systematic review meta-analysed 53 cohort studies that examined the association between depression and CVD mortality, yielding a pooled risk ratio of 1.31 (Wei et al., 2019). These findings have been well corroborated by Mendelian randomisation studies that showed an association between genetic susceptibility to depression and incident CVD (Tang et al., 2020). Additionally, a longitudinal matched cohort study including sibling analyses found an association between MHCs including depression and CVD (Shen et al., 2023), further increasing confidence of causality.

There is also some evidence of a bidirectional association, whereby CVD may also increase the risk of developing MHCs. For example, an experimental study using a mouse model demonstrated that tachycardia induced anxiety-like behaviour (Hsueh et al., 2023). Another murine study found an increased density of both sensory and sympathetic nerve fibres in arteries containing plaques (Mohanta et al., 2022). However, human epidemiological studies have shown inconsistent results. Whilst cohort studies showed that CVD was associated with increased risk of subsequent depression (Ziwei et al., 2023, Wium-Andersen et al., 2020), Mendelian randomisation studies did not find such associations or

reported relatively small effects, compared to those between genetic instruments of MHCs and risk of CVD (Tang et al., 2020, Bergstedt et al., 2024).

Overall, given the accumulating evidence that MHCs are associated with increased risk of CVD, understanding the roles of MHCs in developing CVD could inform preventive strategies and, thereby, potentially help to reduce burden.

1.4 Overall Aims and Specific Objectives

I conducted a systematic investigation into whether and how anxiety and depression are associated with CVD, with the overall aim of understanding their roles in the development of CVD in middle-aged and older adults. My specific objectives were:

(1) to examine the individual and joint associations of anxiety and depression with a range of incident CVD outcomes,
(2) to examine the associations of anxiety and depression with CVD stratified by CVD genetic susceptibility,
(3) to examine the extent to which lifestyle, physical, and metabolic factors mediate the associations between anxiety and depression and incident CVD, and
(4) to examine whether including anxiety and depression in an existing CVD risk score improves the prediction of CVD risk.

1.5 Data Source

I used data from the UK Biobank cohort to conduct all studies included in this thesis. UK Biobank is a very large-scale population cohort study conducted in the UK. UK Biobank was designed to complement existing cohorts that were limited by small sample size or incomplete measures of risk factors. UK Biobank enables investigation of various environmental, lifestyle, and genetic risk factors related to a wide range of health conditions in middle-aged and older adults through large scale and extensive baseline data collection (Sudlow et al., 2015, UK Biobank, 2007).

1.5.1 Recruitment and Measurements

UK Biobank aimed to recruit 500,000 participants, which was calculated, a priori, to be a sufficient number to investigate the factors associated with a wide range of health events. Potential participants were identified through National Health Service (NHS) central registers as nearly all UK residents are registered with an NHS general practitioner (UK Biobank, 2007). Recruitment was conducted by sending invitation letters to nine million people aged from 40 to 69 years who lived within reasonable travel distances of the 21 assessment centres run across England, Scotland, and Wales (UK Biobank, 2007). The response rate was approximately 5% and over 500,000 participants were successfully recruited.

Participants underwent the baseline assessment between 2006 and 2010 at one of the 21 assessment centres. The baseline assessment included a self-administrated touch-screen questionnaire (e.g., sociodemographic information), computer-assisted interview (e.g., medical history), physical measurements (e.g., body weight), and biological sample collection (e.g., blood sample). The interview, physical measurements, and biological sample collection were conducted by trained nurses and staff based on standardised protocols to ensure the quality of measurements. The baseline data were linked by UK Biobank staff to routine NHS databases including hospitalisations, primary care records, death certificates and cancer registrations to provide medical history and follow-up information on a wide range of health events (Sudlow et al., 2015, UK Biobank, 2007).

1.5.2 Consent and Ethical Approval

At the assessment centre, participants provided their electronically-signed consent to participate in UK Biobank. Participants were informed that they could withdraw from the study at any time without reason or penalty.

UK Biobank received approval from the NHS Northwest Multicentre Research Ethics Committee (Ref: 11/NW/0382). I registered with UK Biobank and was

approved to access their data. All studies in this thesis were conducted as a part of approved UK Biobank projects (application numbers 7155/71392).

1.6 Structure of the Thesis

My thesis follows an alternative format, wherein each chapter addresses a specific objective outlined in section 1.4 and consists of an original manuscript that has been already published in a peer-reviewed journal.

My thesis is comprised of six chapters including this chapter, with subsequent chapters as follows: Chapter 2 addressing objective 1 and including paper 1 entitled “Individual and joint associations of anxiety disorder and depression with cardiovascular disease: A UK Biobank prospective cohort study”; Chapter 3 addressing objective 2 and including paper 2 entitled “Anxiety disorder, depression and coronary artery disease: associations and modification by genetic susceptibility”; Chapter 4 addressing objective 3 and including paper 3 entitled “Shared and distinct pathways from anxiety disorder and depression to cardiovascular disease: a UK Biobank prospective cohort study”; and Chapter 5 addressing objective 4 and including paper 4 entitled “Refining PREVENT prediction models for 10-year risk of cardiovascular disease using measures of anxiety and depression”. Although each chapter addresses a specific objective, the chapters are interconnected through findings that build upon one another. In order to facilitate the narrative and readability of my thesis, I have included a preface at the beginning of each chapter. Lastly, Chapter 6 summarises the implications of the research findings contained in the preceding chapters and presents potential directions for future research.

Chapter 2 Individual and joint associations of anxiety disorder and depression with cardiovascular disease: A UK Biobank prospective cohort study

2.1 Preface

In Chapter 1, I described the evidence that MHCs are associated with higher risk of CVD (Van der Kooy et al., 2007, Wei et al., 2019, Tang et al., 2020, Shen et al., 2023). Compared with depression, fewer studies have investigated associations between anxiety and CVD, particularly in relation to different types of CVD. In 2016, a systematic review with meta-analyses of between 3 and 28 cohort studies reported associations between anxiety and incident CVD subtypes including myocardial infarction, stroke, and heart failure (Emdin et al., 2016). A recent systematic review in 2019 with meta-analyses of 14 cohorts, of which 9 provided data on men and 10 on women, reported that anxiety was associated with incident CVD in both sexes (Smaardijk et al., 2019).

Whilst these studies suggest a likely association between anxiety and increased risk of CVD and its subtypes, they did not examine anxiety jointly and independently of depression, which is important since these conditions often co-exist within one individual. A previous study reported that over 60% of those with anxiety had co-existing depression, and vice versa (Lamers et al., 2011). Studying both anxiety and depression may provide mechanistic insights into their associations with CVD and enhance preventive strategies accordingly.

Therefore, in this chapter, I examine the individual and joint associations of anxiety and co-existing depression with CVD and its subtypes.

2.2 Published Manuscript

ABSTRACT

Background: Growing evidence suggests that individuals with anxiety disorder have an elevated risk of cardiovascular disease (CVD) but few studies have assessed this association independently of or jointly with depression.

Methods: We conducted a prospective cohort study using UK Biobank. Diagnoses of anxiety disorder, depression, and CVDs were ascertained through linked hospital admission and mortality data. Individual and joint associations between

anxiety disorder and depression and CVD overall, as well as each of myocardial infarction, stroke/transient ischemic attack, and heart failure, were analyzed using Cox proportional hazard models and interaction tests.

Results: Among the 431,973 participants, the risk of CVD was higher among those who had been diagnosed with anxiety disorder only (hazard ratio [HR] 1.72; 95% confidence interval [CI] 1.32–2.24), depression only (HR 2.07; 95% CI 1.79–2.40), and both conditions (HR 2.89; 95% CI 2.03–4.11) compared to those without these conditions, respectively. There was very little evidence of multiplicative or additive interaction. Results were similar for myocardial infarction, stroke/transient ischemic attack, and heart failure.

Conclusions: Having anxiety is associated with the same magnitude of increased risk of CVD among people who do not have depression and those who do. Anxiety disorder should be considered for inclusion in CVD risk prediction and stratification, in addition to depression.

INTRODUCTION

Mental health disorders and cardiovascular disease (CVD) affect more than 600 and 400 million people worldwide, respectively (GBD 2019 Mental Disorders Collaborators, 2022, Roth et al., 2017). One of the most common mental health disorders is anxiety disorder. Over the past 20 years, annual incident cases of anxiety disorder have increased globally by almost 50%, from 31 to 45 million (Xiong et al., 2022). Those with anxiety disorder are more likely to have CVD risk factors, such as hypertension and diabetes (Lim et al., 2021, Mersha et al., 2022). A meta-analysis found a 40% excess risk of hypertension among those with anxiety disorder (Lim et al., 2021). Further evidence has suggested an association between anxiety disorder and CVD. A meta-analysis reported 29 and 42% higher risk of incident CVD among women and men with anxiety disorder, respectively (Smaardijk et al., 2019). Single prospective cohort studies also showed associations between anxiety disorder and myocardial infarction (MI) (hazard ratio [HR] 2.51; 95% confidence interval [CI] 1.38–4.55) (Janszky et al., 2010), and stroke (HR 1.14; 95% CI 1.03–1.25) specifically (Lambiase et al., 2014).

However, these studies did not assess the association of anxiety disorder with CVDs independently of and jointly with depression. Existing evidence has shown both that depression is associated with CVD (Van der Kooy et al., 2007, Harshfield et al., 2020, Wei et al., 2019) and that, based on Mendelian randomization studies, the association is likely to be causal (Li et al., 2022, Tang et al., 2020). Since anxiety disorder and depression often co-exist and may have shared or overlapping etiology (Lamers et al., 2011, Etkin and Schatzberg, 2011, Goodkind et al., 2015, McTeague et al., 2017), the mechanism by which they are associated with CVD may be common to both conditions.

To that end, our study aimed to examine the individual and joint associations of anxiety disorder and co-existing depression with a range of incident CVD (MI, stroke/transient ischemic attack [TIA], or heart failure) using the UK Biobank population cohort.

METHODS

Study design and participants: We conducted a prospective cohort study using data from UK Biobank. UK Biobank recruited over 500,000 participants between 2007 and 2010 from the general population, aged 40 to 69 years. Participants visited one of the 22 assessment centers across England, Scotland, and Wales to provide their information and biological samples. We excluded participants who had experienced CVD, MI, stroke/TIA, or heart failure before the baseline assessment ascertained through either self-report or linkage to medical records and who were first admitted for anxiety disorder or depression after the baseline assessment.

Measurements: The exposures of interest were anxiety disorder and depression diagnosed before the baseline assessment and were obtained through record linkage to hospital admission data: Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). We defined anxiety disorder as F40–43 and depression as F32–33, using the International Classification of Diseases, 10th revision (ICD-10).

The outcomes of interest were incident (fatal or non-fatal) CVD, MI, stroke/TIA, and heart failure. The death certificate data were obtained from the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland) and were available up to September 2021 in England and Wales, and October 2021 in Scotland. The hospital admission data were available up to September 2021 in England, July 2021 in Scotland, and February 2018 in Wales. Follow-up was censored at the date of relevant hospitalization or date of death, whichever occurred first. We defined CVD as an ICD-code of I20–25, I42.0, I42.6, I42.7, I42.9, I50, I60–64, and I110; MI as I21; stroke/TIA as I60–64 or G45, and heart failure as I42.0, I42.6, I42.7, I42.9, I50, or I110.

Covariates included sociodemographic (age, sex, ethnicity, and deprivation level) and lifestyle (alcohol intake, smoking status, sleep duration, TV viewing duration, physical activity, and body mass index [BMI]) factors. Age, sex, and ethnic group were self-reported by participants using a touchscreen questionnaire at baseline. Deprivation level was based on tertiles of the Townsend area deprivation index, which was derived from the postcode of residence using aggregated data on unemployment, car and home ownership, and household overcrowding (Townsend et al., 2023). Alcohol intake, smoking status, sleep, and TV viewing duration were self-reported using the touchscreen questionnaire at baseline. Physical activity was based on tertiles of metabolic equivalent minutes per week, which were derived from the self-completed, validated International Physical Activity Questionnaire (Craig et al., 2003). BMI was calculated as weight/height^2; height was measured to the nearest centimeter, using a Seca 202 stadiometer, and body weight was measured to the nearest 0.1 kg, using a Tanita BC-418 body composition analyzer by trained staff.

Statistical analyses: Cox proportional hazard models were used to estimate the associations between anxiety disorder and depression and CVD outcomes, and the results expressed as HR and 95% CIs. Proportional hazard assumptions were checked by statistical tests based on Schoenfeld residuals. Separate models were run for each CVD outcome: overall CVD, MI, stroke/TIA, and heart failure. The main analyses comprised two stages. Firstly, the associations of each anxiety disorder and depression with CVD outcomes were analyzed by (1) univariable

models, (2) multivariable models adjusted for sociodemographic confounders (age, sex, ethnic group, and deprivation level), and (3) multivariable models adjusted for both sociodemographic confounders and lifestyle factors (alcohol intake, smoking status, sleep duration, TV viewing duration, physical activity, and BMI). Because we could not establish the temporality between exposures and lifestyle factors, which could follow the exposure onset, we used models adjusted for sociodemographic confounders in the following analyses. Secondly, the individual and joint associations of anxiety disorder and depression with each of CVD, MI, stroke/TIA, and heart failure were determined, and multiplicative and additive interactions were tested. CVD outcomes were regressed on anxiety disorder, depression, their product term, and sociodemographic confounders. The HRs of anxiety disorders, depression, and their product term were used to estimate the individual and joint associations. The product term, and the relative excess risk due to interaction (RERI), were used to investigate the presence of multiplicative and additive interactions respectively. Missing values were < 5% and all analyses were complete case analyses.

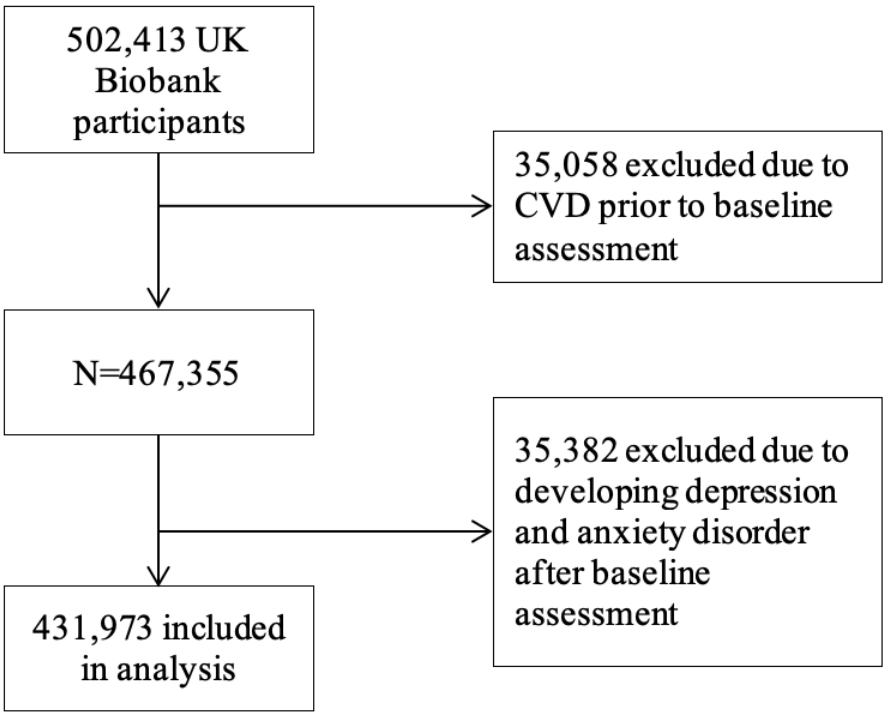
Two different sensitivity analyses were performed to assess whether the additional use of self-reported exposures or primary care-diagnosed exposures and outcomes (available for 45% of the participants) affected the results. The case ascertainment in primary care settings was based on the UK Biobank Read codes mapping (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=592) (Supplementary Table 1). All analyses were conducted using R (version 3.5.3) with packages survival (version 3.2-7) and interactionR (version 0.1.5).

Ethical considerations: UK Biobank was approved by the North-West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). The investigation conforms to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. This work was conducted under the UK Biobank application number 7155.

RESULTS

Of the 502,413 UK Biobank participants who had not withdrawn from the study and could be linked to hospital admission/death data, 35,058 were excluded because they had CVD before the baseline assessment and 35,382 were excluded because they developed depression or anxiety disorder after the baseline assessment. Consequently, 431,973 participants were included in the analyses (Figure 7).

Figure 7. Flowchart of the participant selection process



Overall, 428,296 (99%) had no anxiety disorder or depression, 911 (0.2%) had anxiety disorder only, 2,427 (0.6%) had depression only and 399 (0.1%) had both anxiety disorder and depression (Table 1). Participants with either anxiety disorder or depression or both were more likely to be female and deprived than participants without either condition. They were also more likely to be a current smoker, inactive, and obese and to have longer sleep and TV viewing hours, but less likely to drink more alcohol than recommended. Those with both anxiety disorder and depression were more likely to have unhealthy lifestyles and develop CVDs than those with only anxiety disorder or depression (Table 1 and Supplementary Table 2).

Table 1. Characteristics of subjects by anxiety disorder and depression

	No anxiety disorder nor depression	Anxiety disorder only	Depression only	Anxiety disorder and depression
	N=428,296	N=911	N=2,427	N=339
Mean (SD) Age (years)	56.1 (8.09)	55.8 (8.11)	55.0 (7.95)	53.7 (8.08)
Missing	11	0	0	0
Sex:				
Female	235,675 (55.0%)	565 (62.0%)	1482 (61.1%)	208 (61.4%)
Male	192,610 (45.0%)	346 (38.0%)	945 (38.9%)	131 (38.6%)
Missing	11	0	0	0
Ethnicity:				
White	402,496 (94.5%)	855 (95.3%)	2,279 (94.8%)	320 (95.2%)
Non-white	23,496 (5.5%)	42 (4.7%)	126 (5.2%)	16 (4.8%)
Missing	2,304	14	22	3
Deprivation level:				
Most deprived	141,972 (33.2%)	398 (43.9%)	1,265 (52.2%)	171 (50.7%)
Middle	142,814 (33.4%)	269 (29.7%)	627 (25.9%)	97 (28.8%)
Least deprived	142,967 (33.4%)	240 (26.5%)	531 (21.9%)	69 (20.5%)
Missing	543	4	4	2
Alcohol intake ≥14 units/week	161,619 (41.4%)	278 (34.2%)	721 (32.5%)	85 (28.3%)
Missing	37522	97	207	339
Smoking status:				
Never	240,855 (56.5%)	479 (53.3%)	1,064 (44.3%)	171 (51.0%)
Previous	143,039 (33.6%)	283 (31.5%)	785 (32.7%)	81 (24.2%)
Current	42,068 (9.88%)	137 (15.2%)	551 (23.0%)	83 (24.8%)
Missing	2,334	12	27	4
Mean (SD) Sleep duration hours/day	7.15 (1.04)	7.17 (1.40)	7.23 (1.56)	7.33 (1.74)
Missing	3132	21	54	8
Mean (SD) TV hours/day	2.72 (1.54)	3.08 (2.03)	3.32 (2.18)	3.55 (2.43)
Missing	7609	30	85	10
Physical activity:				
High	110,861 (33.4%)	208 (32.9%)	538 (30.4%)	80 (32.5%)
Middle	110,952 (33.4%)	186 (29.4%)	483 (27.3%)	66 (26.8%)
Low	110,602 (33.3%)	238 (37.7%)	748 (42.3%)	100 (40.7%)
Missing	95,881	279	658	93
Mean (SD) BMI (kg/m2)	27.2 (4.65)	27.6 (5.12)	28.9 (6.15)	28.8 (6.32)
Missing	2,376	11	37	5

Abbreviations: BMI, body mass index; N, number; SD, standard deviation; TV, television.

When adjusted for sociodemographic factors, both anxiety disorder and depression were associated with increased risk of CVD, MI, stroke/TIA, and heart failure (Table 2). Additional adjustments for lifestyle factors attenuated most of the estimates but anxiety disorder remained associated with overall CVD and

stroke/TIA and depression remained associated with both of these and heart failure (Table 2).

Table 2. Associations of anxiety disorder and depression with cardiovascular disease, myocardial infarction, stroke/TIA, and heart failure

	Cardiovascular disease HR [95% CI]	Myocardial infarction HR [95% CI]	Stroke/TIA HR [95% CI]	Heart failure HR [95% CI]
Model 1 (n=431,973)				
Depression	1.92 [1.68, 2.20]	1.59 [1.29, 1.97]	1.73 [1.44, 2.09]	2.34 [1.98, 2.78]
Anxiety disorder	1.76 [1.43, 2.18]	1.59 [1.16, 2.18]	1.72 [1.31, 2.28]	1.62 [1.20, 2.18]
Model 2 (n=429,091)				
Depression	2.16 [1.88, 2.48]	1.79 [1.45, 2.22]	1.96 [1.62, 2.36]	2.69 [2.27, 3.19]
Anxiety disorder	2.00 [1.62, 2.47]	1.81 [1.32, 2.48]	1.91 [1.44, 2.52]	1.80 [1.34, 2.44]
Model 3 (n=302,373)				
Depression	1.83 [1.54, 2.18]	1.17 [0.87, 1.58]	1.97 [1.57, 2.46]	2.16 [1.74, 2.70]
Anxiety disorder	1.61 [1.21, 2.15]	1.38 [0.89, 2.15]	1.56 [1.06, 2.29]	1.47 [0.97, 2.24]

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number; TIA, transient ischemic attack. Note: Model 1: no adjustment. Model 2: adjusted for age, sex, ethnicity, and deprivation level. Model 3: adjusted for age, sex, ethnicity, deprivation level, alcohol intake, smoking status, sleep duration, television viewing, physical activity, and body mass index.

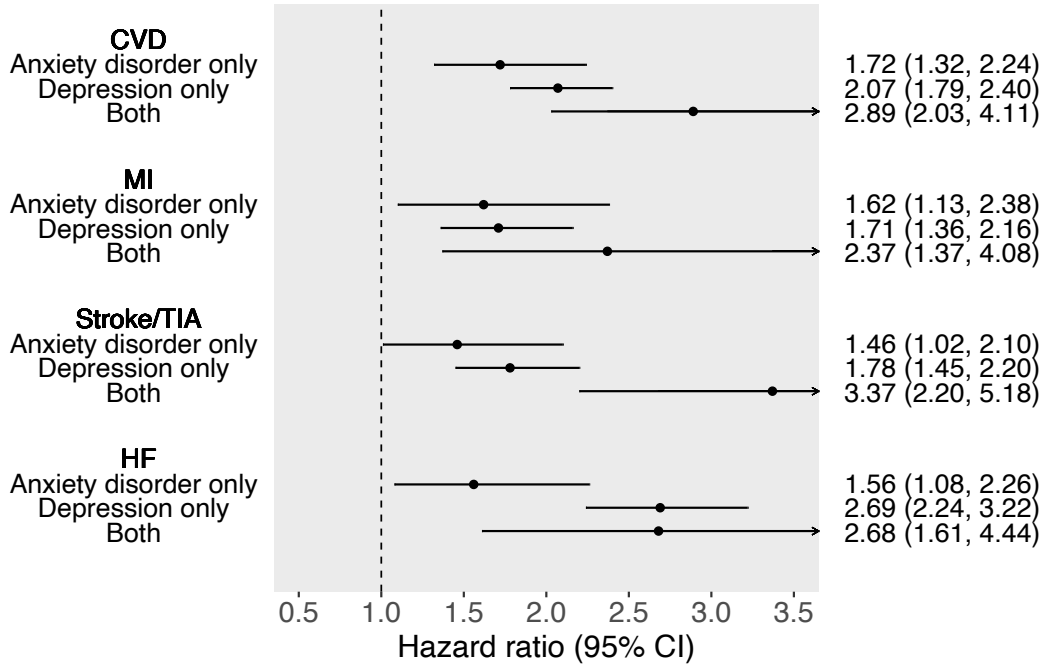
Anxiety disorder was associated with CVD, MI, stroke/TIA, and heart failure independently of and jointly with depression when adjusted for sociodemographic factors (Table 3 and Figure 8). The risk of CVD was higher for those who had been diagnosed with anxiety disorder only (HR 1.72; 95% CI 1.32-2.24), depression only (HR 2.07; 95% CI 1.79–2.40), and both conditions (HR 2.89; 95% CI 2.03–4.11) referent to those without these conditions, respectively (Table 3). There was very little evidence of interaction on the multiplicative scale with the RERI values close to null (Table 3). We found similar results for MI, stroke/TIA, and heart failure.

Table 3. Joint associations and interactions of depression and anxiety disorder with cardiovascular disease, myocardial infarction, stroke/TIA, and heart failure

	No anxiety disorder HR [95% CI]	Anxiety disorder HR [95% CI]	Multiplicative interaction	RERI
Cardiovascular disease			0.81 [0.51, 1.29]	0.10 [-0.96, 1.41]
No depression	Reference	1.72 [1.32, 2.24]		
Depression	2.07 [1.78, 2.40]	2.89 [2.03, 4.11]		
Myocardial infarction			0.85 [0.42, 1.72]	0.03 [-1.30, 1.85]
No depression	Reference	1.62 [1.10, 2.38]		
Depression	1.71 [1.36, 2.16]	2.37 [1.37, 4.08]		
Stroke/TIA			1.29 [0.71, 2.35]	1.13 [-0.27, 3.01]
No depression	Reference	1.46 [1.01, 2.1]		
Depression	1.78 [1.45, 2.20]	3.37 [2.20, 5.18]		
Heart failure			0.64 [0.33, 1.22]	-0.58 [-1.95, 1.30]
No depression	Reference	1.56 [1.08, 2.26]		
Depression	2.69 [2.24, 3.22]	2.68 [1.61, 4.44]		

Abbreviations: CI, confidence interval; HR, hazard ratio; RERI, relative risk due to interaction; TIA, transient ischemic attack. Note: All models were adjusted for anxiety disorder, depression, anxiety disorder × depression, age, sex, ethnicity, and deprivation level.

Figure 8. Individual and joint associations of anxiety disorder and depression with cardiovascular disease, myocardial infarction, stroke/TIA, and heart failure.



CI, confidence interval; CVD, cardiovascular diseases; HF, heart failure; MI, myocardial infarction; TIA, transient ischemic attack. All models were adjusted for age, sex, ethnicity, and deprivation level.

In the sensitivity analysis, the addition of self-reported anxiety disorder and depression attenuated overall associations but there were individual and joint associations of both conditions with overall CVD (Supplementary Table 3). Similarly, the addition of primary care data showed individual and joint associations with MI (Supplementary Table 4).

DISCUSSION

Primary findings: Our study examined the individual and joint associations of anxiety disorder and depression with incident CVD and its subtypes (MI, stroke/TIA, and heart failure) using the UK Biobank population cohort. Anxiety disorder and depression were associated with incident CVD independently of each other and their co-existence was associated with a higher risk than either condition in isolation. However, there was no evidence of interaction implying that the sum of their individual associations with CVD was almost identical to their joint association based on RERI. Therefore, having anxiety contributes to

the same relative excess risk of CVD regardless of whether depression is also present.

Comparison with the literature: Our findings would be consistent with different mechanisms by which anxiety disorder and depression potentially increase CVD risk. This would be biologically plausible based on previous studies suggesting different brain structures between these conditions (Serra-Blasco et al., 2021, van Tol et al., 2010, Lai and Wu, 2015). For example, a recent meta-analysis found lower gray matter volume in the superior temporal gyrus of people with anxiety disorder, compared with those with depression. This structural difference could affect reactions to stimuli, which could lead to distinctive behaviors associated with anxiety disorder (Serra-Blasco et al., 2021). Our findings are consistent with previous evidence that has suggested similar individual and joint associations of anxiety disorder and depression with CVD risks (Walters et al., 2008, Seldenrijk et al., 2015) but a few studies reported conflicting findings. A US prospective cohort study did not find an association between anxiety disorder and CVD, ascertained through self-reported symptoms, independent of depression (HR 1.06; 95% CI 0.80–1.39) (Karlsen et al., 2021). Their conflicting results may be explained by reporting bias or the inclusion of milder cases of anxiety disorder. Similarly, a German prospective cohort study did not show individual or joint associations for depression and sub-types of anxiety disorder (e.g., generalized anxiety disorder) (Tully and Baune, 2014). This finding might be explained by sub-types of anxiety disorders operating differently from composite anxiety disorder and highlights the need for future research powered to investigate sub-group differences.

Limitations: There are some limitations to our study. First, ascertainment of anxiety disorder and depression using hospital admission may be incomplete and less likely to include people with less severe conditions since they are often treated in primary care settings (Ansseau et al., 2004). However, we investigated how the additional use of self-reports or primary care data affected our findings in sensitivity analyses and still found individual and joint associations with CVD and MI. Second, we only ascertained whether anxiety disorder and depression had ever occurred over a time period. We could not record varying anxiety severity or remitting–relapsing fluctuations, and therefore

could not investigate the impact these may have on the relationship between anxiety and CVD (Peter et al., 2020). Third, our findings may not be generalizable to the whole UK population because UK Biobank participants are more likely to be white, affluent, and healthy than the national survey data (Fry et al., 2017).

Our findings suggest that anxiety disorder and depression may increase the risk of CVD independently of each other. As we are facing an increasing number of people living with anxiety disorder, their higher risk of CVD should be noted. In recent years, some CVD risk prediction algorithms (e.g., QRISK3) have included depression (Hippisley-Cox et al., 2017). Given the findings of our study, the added value of including anxiety disorder in risk prediction and stratification should be explored.

CONCLUSIONS

We examined the individual and joint associations of anxiety disorder and depression with incident CVD, MI, stroke/TIA, and heart failure among the middle- and old-aged UK population using the linkage of UK Biobank to hospital admission and mortality data. We found a higher risk of CVD among those with anxiety disorder only and depression only and the highest risk among those with both conditions, but no evidence of interaction on multiplicative or additive scales. This implies that the sum of their individual associations with CVD was almost identical to their joint association and therefore having anxiety contributes the same relative excess risk of CVD regardless of the presence of depression. One explanation is the existence of different mechanisms by which anxiety disorder and depression increase the CVD risk and this requires further research. Meanwhile, as has happened with depression, anxiety should be considered for inclusion in CVD risk prediction and stratification.

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2.3 Supplementary Materials

Supplementary Table 1. READ codes to ascertain depression and anxiety disorder

	READ2	READ3
Depression	Eu32., Eu320, Eu321, Eu322, Eu323, Eu324, Eu325, Eu326, Eu327, Eu328, Eu329, Eu32A, Eu32B, Eu32y, Eu32z, Eu33., Eu330, Eu331, Eu332, Eu333, Eu334, Eu33y, Eu33z	2257., E0043, E1121, E1122, E1123, E1124, E1126, E1131, E1132, E1133, E1134, E1135, E1136, E1137, E11y2, E130., E2B0., E2B1., Eu320, Eu321, Eu322, Eu323, Eu32y, Eu32z, Eu330, Eu331, Eu332, Eu333, Eu334, Eu33y, Eu33z, X00SO, X00SQ, X00SR, X00SS, X00SU, XE1Y0, XE1Y1, XE1YC, XE1ZY, XE1ZZ, XE1Za, XE1Zb, XE1Zc, XE1Zd, XE1Ze, XE1Zf, XM1GC, XSEGJ, XSGok, XSGol, XSGom, XSGon, Xa0wV, XaB9J, XaCHo, XaCHr, XaCHs, XaCIs, XaCIt, XaCIu, XaX53, XaX54, XaY2C
Anxiety disorder	Eu4.., Eu40., Eu400, Eu401, Eu402, Eu403, Eu40y, Eu40z, Eu41., Eu410, Eu411, Eu412, Eu413, Eu41y, Eu41z, Eu42., Eu420, Eu421, Eu422, Eu42y, Eu42z, Eu43., Eu430, Eu431, Eu432, Eu433, Eu434, Eu435, Eu43y, Eu43z	1B1L., 1BE.., E200., E2002, E2004, E2021, E2023, E2024, E2025, E2027, E2028, E2029, E202E, E203., E2030, E2031, E2753, E280., E281., E282., E2830, E2831, E284., E29.., E290., E291., E2924, E2925, E292y, E293., E2930, E2931, E2932, E294., E29y2, E29y4, Eu40., Eu400, Eu402, Eu40y, Eu40z, Eu41., Eu410, Eu413, Eu41y, Eu41z, Eu420, Eu421, Eu422, Eu42y, Eu42z, Eu430, Eu432, Eu43y, Eu43z, Ua18L, Ua18k, Ua1qS, Ua1qU, Ua1qV, Ua1qW, Ua1qX, Ua1qY, Ua1qa, Ua1qc, Ua1qd, Ua1qe, Ua1qf, Ua1qg, Ua1qh, Ua1qi, Ua1qj, Ua1qk, Ua1ql, Ua1qm, Ua1qn, Ua1qo, Ua1qp, Ua1qs, Ua1qt, X00SV, X00SW, X00SX, X00SY, X00SZ, X00Sa, X00Sb, X00Sc, X00Sd, X00Se, X00Sf, X00Sl, X00Sr, X50G3, X50GI, X75YV, X761d, X761n, X761q, X761t, X761u, X761y, X7627, X7628, X7629, X762A, X762C, X762E, X762F, X762G, X762H, X762T, X762c, X762d, X762e, X762f, X762g,

		X762h, X762i, X762j, X762l, X762m, X762n, X762p, X762q, X764L, X764N, X764O, X764P, X764Q, X78wp, XE0rb, XE1Y7, XE1YA, XE1Ym, XE1Yo, XE1Yp, XE1Zj, XM001, XM0Ak, XM0As, XM0At, XM1Q3, Xa00r, Xa00s, Xa02G, Xa02H, Xa02I, Xa03z, Xa18j, Xa18v, Xa1Ev, Xa1a8, Xa2kf, Xa3Vj, Xa3Vk, Xa3Vl, Xa3WH, Xa3WI, Xa3WJ, Xa7k9, Xa7kB, XaC2u, XaIo7, XaKVA, XaX55, XaX56, XaX58

Supplementary Table 2. Outcome summary by anxiety disorder and depression

	No anxiety disorder nor depression	Anxiety disorder only	Depression only	Anxiety disorder and depression	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
	42,8296 (99.1)	911 (0.2)	2,427 (0.6)	339 (0.08)	
CVD	17,205 (4.02)	56 (6.15)	177 (7.29)	31 (9.14)	17,469 (4.0)
MI	8,465 (1.98)	26 (2.85)	73 (3.01)	13 (3.83)	8,577 (2.0)
Stroke/TIA	10,077 (2.35)	29 (3.18)	90 (3.71)	21 (6.19)	10,217 (2.4)
HF	9,167 (2.14)	28 (3.07)	120 (4.94)	15 (4.42)	9,330 (2.2)

N, number; CVD, cardiovascular diseases; MI, myocardial infarction; TIA, transient ischaemic attack; HF, heart failure.

All models were adjusted for age, sex, ethnicity, and deprivation level.

Supplementary Table 3. Individual and joint associations of self-reported/hospitalised depression and anxiety disorder with cardiovascular disease, myocardial infarction, stroke/TIA, and heart failure

	No anxiety disorder HR [95% CI]	Anxiety disorder HR [95% CI]	Multiplicative interaction	RERI
Cardiovascular disease			1.01 [0.77, 1.32]	0.04 [-0.30, 0.42]
No depression	Reference	1.22 [1.07, 1.40]		
Depression	1.12 [1.04, 1.22]	1.38 [1.11, 1.73]		
Myocardial infarction			1.16 [0.78, 1.72]	0.18 [-0.28, 0.74]
No depression	Reference	1.13 [0.93, 1.38]		
Depression	1.01 [0.90, 1.14]	1.33 [0.96, 1.83]		
Stroke/TIA			1.16 [0.81, 1.66]	0.19 [-0.23, 0.70]
No depression	Reference	1.12 [0.93, 1.34]		
Depression	1.04 [0.94, 1.16]	1.35 [1.01, 1.81]		
Heart failure			1.09 [0.75, 1.57]	0.15 [-0.32, 0.72]
No depression	Reference	1.13 [0.93, 1.37]		
Depression	1.24 [1.11, 1.38]	1.52 [1.13, 2.04]		

HR, hazard ratio; CI, confidence interval; RERI, relative risk due to interaction; TIA, transient ischaemic attack.

All models were adjusted for anxiety disorder, depression, anxiety disorder*depression, age, sex, ethnicity, and deprivation level.

Supplementary Table 4. Individual and joint associations of depression and anxiety disorder with cardiovascular disease, myocardial infarction, stroke/TIA, and heart failure among participants with primary care data

	No anxiety disorder HR [95% CI]	Anxiety disorder HR [95% CI]	Multiplicative interaction	RERI
Cardiovascular disease			1.06 [0.90, 1.26]	0.12 [-0.11, 0.36]
No depression	Reference	1.09 [0.99, 1.20]		
Depression	1.35 [1.24, 1.47]	1.56 [1.39, 1.76]		
Myocardial infarction			1.0 [0.79, 1.28]	0.07 [-0.27, 0.42]
No depression	Reference	1.18 [1.04, 1.35]		
Depression	1.34 [1.19, 1.52]	1.59 [1.34, 1.89]		
Stroke/TIA			1.03 [0.84, 1.25]	0.07 [-0.19, 0.35]
No depression	Reference	1.09 [0.98, 1.22]		
Depression	1.36 [1.23, 1.50]	1.53 [1.33, 1.75]		
Heart failure			1.06 [0.83, 1.34]	0.11 [-0.22, 0.45]
No depression	Reference	1.06 [0.93, 1.21]		
Depression	1.43 [1.27, 1.60]	1.60 [1.36, 1.88]		

HR, hazard ratio; CI, confidence interval; RERI, relative risk due to interaction; TIA, transient ischaemic attack.

All models were adjusted for anxiety disorder, depression, anxiety disorder*depression, age, sex, ethnicity, and deprivation level.

Chapter 3 Anxiety disorder, depression and coronary artery disease: associations and modification by genetic susceptibility

3.1 Preface

In Chapter 2, I found that anxiety and depression were associated with CVD independently of each other and, therefore, hypothesised that they may have not only shared but also distinct mechanisms by which they predispose to the development of CVD. This chapter further investigates whether these associations vary according to genetic susceptibility to CVD.

Previous studies have suggested that associations between MHCs and CVD could be modified by individual lifestyle factors (Jin et al., 2022, Liu et al., 2022, Ladwig et al., 2005) whilst the modifying role of genetic predisposition remains unclear (Sun et al., 2022, Honigberg et al., 2022, Silventoinen et al., 2022). Genetic markers such as single nucleotide polymorphisms (SNPs) inform an individual's lifelong susceptibility to disease and utilising multiple SNPs is a better instrument to characterise CVD genetic susceptibility since CVD is polygenic.

In this chapter, I examine whether CVD genetic susceptibility modifies the associations of anxiety and depression with CVD and, if so, whether such modification differs between these two conditions, potentially reflecting differences in their underlying pathophysiological mechanisms.

3.2 Published Manuscript

ABSTRACT

Background: Associations of anxiety disorder and depression with coronary artery disease (CAD) are heterogeneous between populations. This study investigated how genetic susceptibility to CAD alters these associations with incident CAD, comparing and combining anxiety disorder and depression.

Methods: This is a prospective cohort study using UK Biobank. Diagnoses of anxiety disorder and depression were ascertained through linked hospital admission data. Incident CAD was ascertained through hospital admission and

death certificate data after baseline. CAD polygenic risk score (PRS_{CAD}) was obtained from CARDIoGRAMplus4 and categorised into low, intermediate, and high. Cox proportional hazard models were used to examine associations between anxiety disorder and depression and CAD.

Results: Both anxiety disorder (HR 2.31, 95% CI 1.92–2.78) and depression (HR 2.15, 95% CI 1.90–2.24) were associated with CAD after adjusting for sociodemographic confounders. There was an addictive interaction between depression and PRS_{CAD} (RERI 0.97, 95% CI 0.12–1.81) such that the association between depression and CAD was strongest among those with a high PRS_{CAD} whilst there was no such evidence for anxiety disorder. Anxiety disorder only (HR 1.68, 95% 1.16–2.44), depression only (HR 2.13, 95% CI 1.72–2.64), and concomitant anxiety disorder and depression (HR 3.85, 95% CI 2.48–5.98) were associated with CAD even among people with a low PRS_{CAD}. Adjusting for potential mediators attenuated all these associations across PRS categories.

Conclusions: CAD genetic susceptibility might partly contribute to the clustering of depression and CAD but does not provide a full explanation, nor does it explain the association between anxiety disorder and CAD. Therefore, other mechanisms should be explored.

BACKGROUND

Anxiety disorder and depression are the most common mental health conditions and substantial disease burdens globally (GBD 2019 Mental Disorders Collaborators, 2022). Comorbid anxiety disorder and/or depression with coronary artery disease (CAD) is common and associated with higher mortality (Hare et al., 2014). Previous studies reported that around one-third of patients with CAD suffered from anxiety disorder or depression (Bankier et al., 2004) and they experienced two-fold higher mortality than people without these conditions (Watkins et al., 2013). One explanation for this comorbidity is that both anxiety disorder and depression increase the risk of CAD via pathways such as obesity and hypertension, as supported by accumulating studies (Batelaan et al., 2016, Smaardijk et al., 2019, Cohen et al., 2015).

However, the risk estimates vary between different populations. For example, the largest UK study found a moderate association between diagnosed depression and incident CAD (hazard ratio [HR] 1.52, 95% confidence interval [CI] 1.34–1.73) after adjusting for sociodemographic factors (Mathur et al., 2016) whilst a Taiwanese study showed no association (HR 1.03, 95% CI 0.93–1.15) after similar adjustments (Chi et al., 2014). These heterogeneous findings may be due to effect modifiers such as lifestyle or genetic factors that vary between populations. Previous studies have demonstrated that this association was modified by various lifestyle factors such as sleep duration (Jin et al., 2022, Liu et al., 2022, Ladwig et al., 2005). CAD genetic variants could be associated with depression (Hagenaars et al., 2020), suggesting that pleiotropy could account for the clustering of CAD and these mental health conditions (Kendler et al., 2009). If so, the likelihood of people with one condition also developing the second could be stronger in the presence of genetic predisposition.

A previous cohort study found that the association of the psychological well-being score with incident CAD were consistent across CAD polygenic risk score (PRS_{CAD}) categories (Sun et al., 2022). Another cohort study found an interaction between self-reported depressive mood and PRS_{CAD} for incident CAD (Honigberg et al., 2022). There has been one cohort study into whether the association between depression and CAD was modified by PRS_{CAD} (Silventoinen et al., 2022). This study, based on 19,999 Finish participants, found no evidence of interaction. However, this could be due, in part, to being underpowered given its sample size. Furthermore, the focus of this study was on depression without considering anxiety disorder. Findings based on depression may not be fully applied to anxiety disorder. In addition, because these two mental health conditions can coexist, their joint conditions should be explored.

To this end, our study investigated the associations of anxiety disorder and/or depression with incident CAD overall and stratified by PRS_{CAD} in the UK Biobank cohort study.

METHODS

Study design: This is a prospective cohort study using the data from UK Biobank which recruited over 500,000 UK residents aged 40 to 69 years from 2007 to 2010. Participants visited one of the 22 assessment centres across England, Scotland, and Wales to provide their information and undergo a series of examinations (Sudlow et al., 2015, Collins, 2012). We excluded participants who reported a history of cardiovascular diseases before the baseline assessment to reduce reverse causation, who were first admitted for anxiety disorder or depression after the baseline assessment, or who had missing data on sociodemographic confounders. We included only participants who self-reported their ethnicity as white.

Measurements: Anxiety disorder and depression diagnosed before the baseline assessment were ascertained through record linkage to hospital admission data: Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). We defined anxiety disorder as F40–43 and depression as F32–33, using the International Classification of Diseases, 10th revision (ICD-10).

Incident CAD events after the baseline assessment were ascertained through linkage to the hospital admission data and death certificate data: the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). The hospital admission data were available up to October 2022 in England, August 2022 in Scotland, and May 2022 in Wales and the death certificate data were available up to November 2022 in England, Wales, and Scotland. Follow-up was censored at the date of relevant hospitalisation or date of death, whichever occurred first. We defined CAD as an ICD-10 code of I20–25.

Sociodemographic confounders included age at recruitment, sex, educational level, and area deprivation index. Age, sex, and educational level were self-reported by participants using a touchscreen questionnaire at baseline. Educational level was dichotomised as college/university degree or any other. Area deprivation index was measured using the Townsend area deprivation index, which was derived from the postcode of residence using aggregated data on unemployment, car and home ownership, and household overcrowding (Townsend et al., 2023).

Potential mediators included smoking status, body mass index (BMI), metabolic equivalent minutes (METs), diet quality, hypertension, low-density lipoprotein (LDL) cholesterol, hyperglycaemia, and C-reactive protein. We assumed that these factors measured at baseline lie on the path between anxiety disorder or depression and CAD. Smoking status was self-reported as current, previous, or never using the touchscreen questionnaire. METs per week were derived from the validated International Physical Activity Questionnaire. Diet quality was based on the cumulative dietary risk factors score, which has been reported previously (Craig et al., 2003). Participants were given 1 point for each of nine dietary recommendations met relating to processed meat, red meat, total fish, milk, spread type, cereal intake, salt added to food, water, and fruits and vegetables based on the touchscreen questionnaire at baseline. The overall score ranged from 0 (least healthy) to 9 (most healthy). BMI was calculated as weight(kg)/height(m)^2; height was measured to the nearest centimetre, using a Seca 202 stadiometer, and body weight was measured to the nearest 0.1 kg, using a Tanita BC-418 body composition analyser by trained staff. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or taking antihypertensive medication (Unger et al., 2020). Hyperglycaemia was defined as ≥ 48 mmol/mol or taking diabetic medication (World Health Organization, 2011a). Elevated LDL cholesterol was defined as ≥ 4.9 mmol/L or taking cholesterol-lowering medication (Arnett et al., 2019). Biomarker (LDL cholesterol, haemoglobin A1c, and C-reactive protein) measurements were performed at a central laboratory between 2014 and 2017 and details of these assay performances are available in the protocol (Daniel Fry, 2019).

PRS_{CAD} was based on summary-level genetic data from CARDIoGRAMplus4 (Nikpay et al., 2015, CARDIoGRAMplusC4D Consortium) which is independent of the UK Biobank cohort. Ambiguous single-nucleotide polymorphisms were excluded from our analysis. PRS was calculated by adding up the number of risk alleles for each individual participant, selected based on a clumping and thresholding approach (Choi et al., 2020), then stratifying into tertiles labelled as low, intermediate, and high genetic scores. For the UK Biobank participants, genotyping, imputation, and standard quality control procedures were conducted centrally by the UK Biobank team. Genotyping was performed using the UK Biobank Axiom

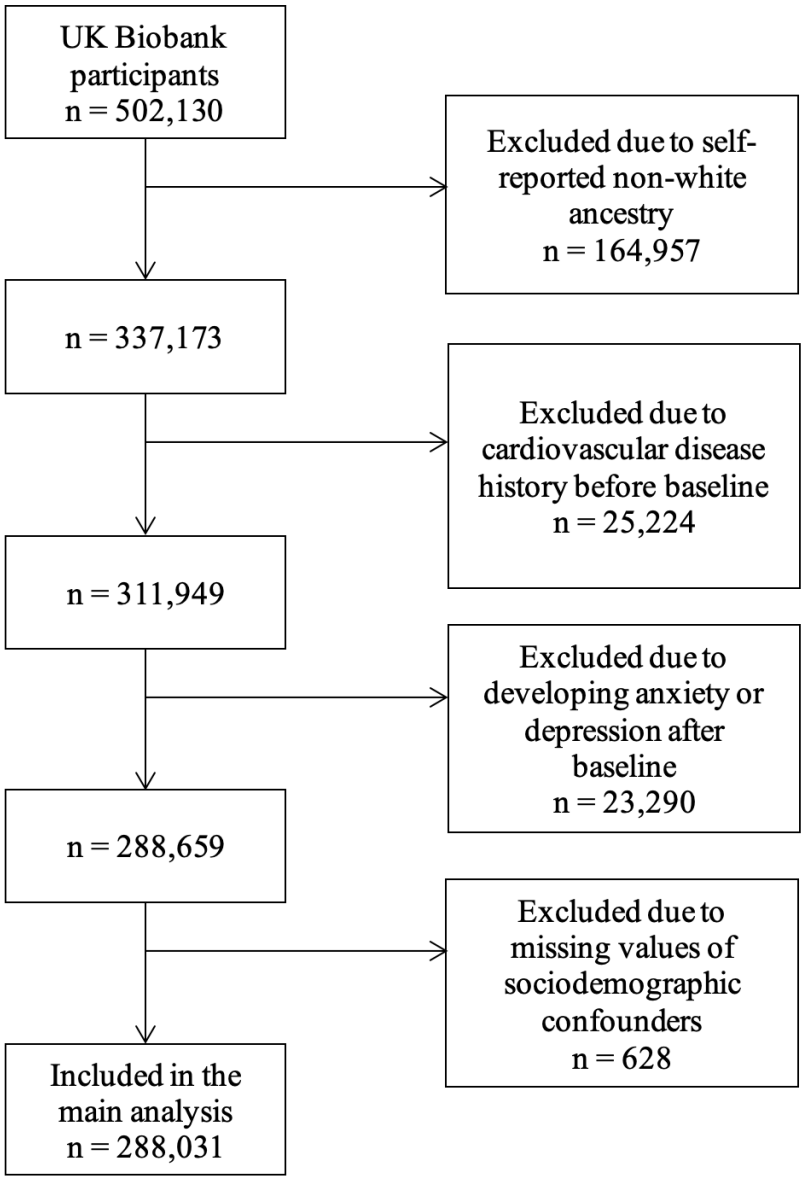
Array or UK BiLEVE Axiom Array and imputation was performed using a reference panel of HRC in combination with UK10K. All genetic quality control and computation of principal components of ancestry were undertaken by the central UK Biobank team (UK Biobank, 2017).

Statistical analyses: Participants' characteristics were summarised by anxiety disorder and depression and PRS_{CAD}, respectively, using frequency (percentage) for categorical data and mean (standard deviation) or median (interquartile range) for continuous data. All associations were estimated by Cox proportional hazard models, expressed as HRs and 95% CIs. Proportional hazard assumptions were checked using statistical tests based on Schoenfeld residuals. The main analyses were conducted in two stages. Firstly, the associations of anxiety disorder and/or depression with CAD were estimated conditional on sociodemographic confounders (age, sex, deprivation index, and educational level) and PRS_{CAD}, genotype array, and 10 principal components of ancestry in two models: separate models included anxiety disorder and depression without mutual adjustment and joint models included isolated anxiety disorder and depression and their joint condition. Secondly, the results of the first stage were stratified by low, intermediate, and high PRS_{CAD}. Multiplicative and additive interactions were tested by PRS_{CAD} tertiles and by extracting low and high PRS_{CAD} to examine whether the risk was different at extreme ends of the PRS_{CAD} distributions. Additional analyses were conducted to investigate whether including potential mediators (smoking status, BMI, METs, diet quality, hypertension, elevated LDL cholesterol, hyperglycaemia, and C-reactive protein) attenuated the associations across PRS_{CAD} categories. Sensitivity analyses were conducted by excluding those with severe mental health conditions, including schizophrenia and bipolar disorder and widening the definition of anxiety disorder and depression by including self-report of these conditions as the hospital admission record may not well capture milder cases. All analyses were conducted using R (version 3.5.3) with packages survival (version 3.2–7) and interactionR (version 0.1.5).

RESULTS

Of the over 500,000 UK Biobank participants recruited, 288,031 were eligible for inclusion after excluding those 164,957 who self-reported an ethnicity other than white, 25,224 who had a history of cardiovascular disease, 23,290 who developed anxiety disorder or depression after the baseline assessment, and 628 who did not provide data on sociodemographic confounders (Figure 9).

Figure 9. Flow chart of participant selection



Overall, 779 (0.3%) had anxiety disorder and 1788 (0.6%) had depression; 557 (0.2%) had isolated anxiety disorder, 1566 (0.5%) had isolated depression, and

222 (0.1%) had both conditions. Participants with anxiety disorder or depression were more likely to be younger, female, more deprived and less likely to attain higher education, compared with those without these conditions (Table 4). They were also more likely to experience a CAD event (Supplementary Figure 1, Supplementary Table 5); 112 (14.5%) of those with anxiety disorder and 21,212 (7.4%) of those without experienced an event over a median follow-up time of 13.4 and 13.6 years, respectively; 238 (13.4%) of those with depression and 21,086 (7.4%) of those without experienced an event over a median follow-up time of 13.3 and 13.6 years, respectively. Participants within the higher PRS_{CAD} categories were slightly more likely to be female and less likely to attain higher education (Supplementary Table 6) and they were more likely to experience a CAD event (Supplementary Figure 1).

In the univariable and multivariable models adjusted for sociodemographic confounders, both anxiety disorder and depression were associated with CAD with the strongest association for concomitant anxiety disorder and depression (Table 5). After additional adjustments for PRS_{CAD}, the strengths of these associations were only slightly reduced.

After stratifying by PRS_{CAD}, anxiety disorder was associated with CAD across low, intermediate, and high PRS_{CAD} categories with the strongest associations in the low PRS_{CAD} category (Table 6 and Figure 10). In contrast, the association between depression and CAD was strongest among those in the high PRS_{CAD} category with evidence of additive interaction (RERI 0.97, 95% CI 0.12–1.81).

Table 4. Participant characteristics by anxiety disorder and depression

	No. (%) of participants*			
	No anxiety disorder N = 287,252	Anxiety disorder N = 779	No depression N = 286,243	Depression N = 1,788
Age (years), mean (SD)	56.5 (7.98)	55.4 (8.17)	56.5 (7.98)	55.2 (7.88)
Sex				
Female	156,430 (54.46)	486 (62.39)	155,820 (54.44)	1,096 (61.30)
Male	130,822 (45.54)	293 (37.61)	130,423 (45.56)	692 (38.70)
Deprivation index, mean (SD)	-1.7 (2.87)	-0.6 (3.34)	-1.7 (2.86)	-0.1 (3.56)
With college or University degree	95,463 (33.23)	181 (23.23)	95,194 (33.26)	450 (25.17)
Polygenic risk score, mean (SD)	3,036 (47.46)	3,039 (46.40)	3,036 (47.45)	3,038 (48.30)
Polygenic risk score				
Low	95,769 (33.34)	242 (31.07)	95,409 (33.33)	602 (33.67)
Intermediate	95,750 (33.33)	260 (33.38)	95,438 (33.34)	572 (31.99)
High	95,733 (33.33)	277 (35.56)	95,396 (33.33)	614 (34.34)
Smoking				
Never	161,610 (56.43)	423 (54.44)	161,234 (56.50)	799 (44.96)
Previous	97,713 (34.12)	216 (27.80)	97,360 (34.11)	569 (32.02)
Current	27,066 (9.45)	138 (17.76)	26,795 (9.39)	409 (23.02)
Missing	863	2	854	11
MET-minutes/week, median (IQR)	1,848 (2,825)	1,864 (3,034)	1,850 (2,825)	1,518 (2,794)
Missing	60,677	215	60,416	476
Diet quality score, mean (SD)	4.4 (1.60)	4.4 (1.67)	4.4 (1.60)	4.2 (1.68)
Missing	33,563	97	33,419	241
Body mass index (kg/m^2), mean (SD)	27.2 (4.62)	27.7 (5.28)	27.2 (4.61)	28.8 (5.97)
Missing	778	7	771	14
SBP ≥140mmHg or medication	139,469 (49.79)	366 (48.48)	138,989 (49.79)	846 (48.79)
Missing	7,134	24	7,104	54
LDL-c ≥ 4.9 mmol/L or medication	55,293 (20.08)	173 (23.35)	54,997 (20.04)	469 (27.33)
Missing	11,875	38	11,841	72
HbA1c ≥ 48 mmol/mol or medication	8,086 (2.95)	32 (4.26)	8,025 (2.94)	93 (5.44)
Missing	13,056	27	13,005	78
C-reactive protein (mg/L), median (IQR)	1.28 (2.0)	1.65 (2.65)	1.28 (2.0)	1.96 (3.22)

Missing	13,376	43	13,331	88

SD Standard deviation, IQR Interquartile range, MET Metabolic equivalent, SBP Systolic blood pressure, HbA1c Haemoglobin A1c, LDL-c, Low-density lipoprotein cholesterol

*Unless indicated otherwise

Table 5. Associations between diagnosed anxiety disorder and depression and coronary artery disease

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Separate models* (n=288,031)			
Anxiety disorder (+/- depression)	2.09 (1.74–2.52)	2.31 (1.92–2.78)	2.28 (1.89–2.74)
Depression (+/- anxiety disorder)	1.97 (1.73–2.24)	2.15 (1.90–2.45)	2.14 (1.88–2.43)
Combined model (n=288,031)			
Anxiety disorder only	1.88 (1.50–2.36)	2.06 (1.64–2.59)	2.03 (1.61–2.55)
Depression only	1.87 (1.63–2.15)	2.04 (1.78–2.35)	2.03 (1.76–2.33)
Both anxiety disorder and depression	2.71 (1.98–3.70)	3.05 (2.23–4.17)	3.04 (2.22–4.16)

Model 1: no adjustment

Model 2: adjusted for age, sex, deprivation index, and education

Model 3: adjusted for age, sex, deprivation index, education, polygenic risk score, genotyping chip, and 10 principal components

n, number; HR, hazard ratio; CI, confidence interval

*Anxiety disorder and depression were not mutually adjusted

Table 6. Associations between diagnosed anxiety disorder and depression and coronary artery disease by polygenic risk score

	Low PRS	Intermediate PRS	High PRS	Multiplicative interaction	Additive interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RERI (95% CI)
Separate models* (n=288,031)					
Anxiety disorder (+/- depression)	2.46 (1.72–3.53)	2.26 (1.62–3.15)	2.18 (1.64–2.90)	0.87 (0.55–1.38)	0.31 (-0.99–1.60)
Depression (+/- anxiety disorder)	2.04 (1.60–2.61)	1.98 (1.56–2.51)	2.32 (1.92–2.82)	1.13 (0.83–1.54)	0.97 (0.12–1.81)
Combined model (n=288,031)					
Anxiety disorder only	2.30 (1.48–3.57)	2.33 (1.59–3.43)	1.68 (1.16–2.44)	0.71 (0.40–1.27)	-0.31 (-1.71–1.08)
Depression only	1.94 (1.49–2.53)	1.97 (1.53–2.54)	2.13 (1.72–2.64)	1.08 (0.77–1.52)	0.76 (-0.10–1.63)
Both anxiety disorder and depression	2.93 (1.58–5.46)	2.12 (1.10–4.07)	3.85 (2.48–5.98)	1.33 (0.62–2.84)	2.48 (-0.68–5.65)

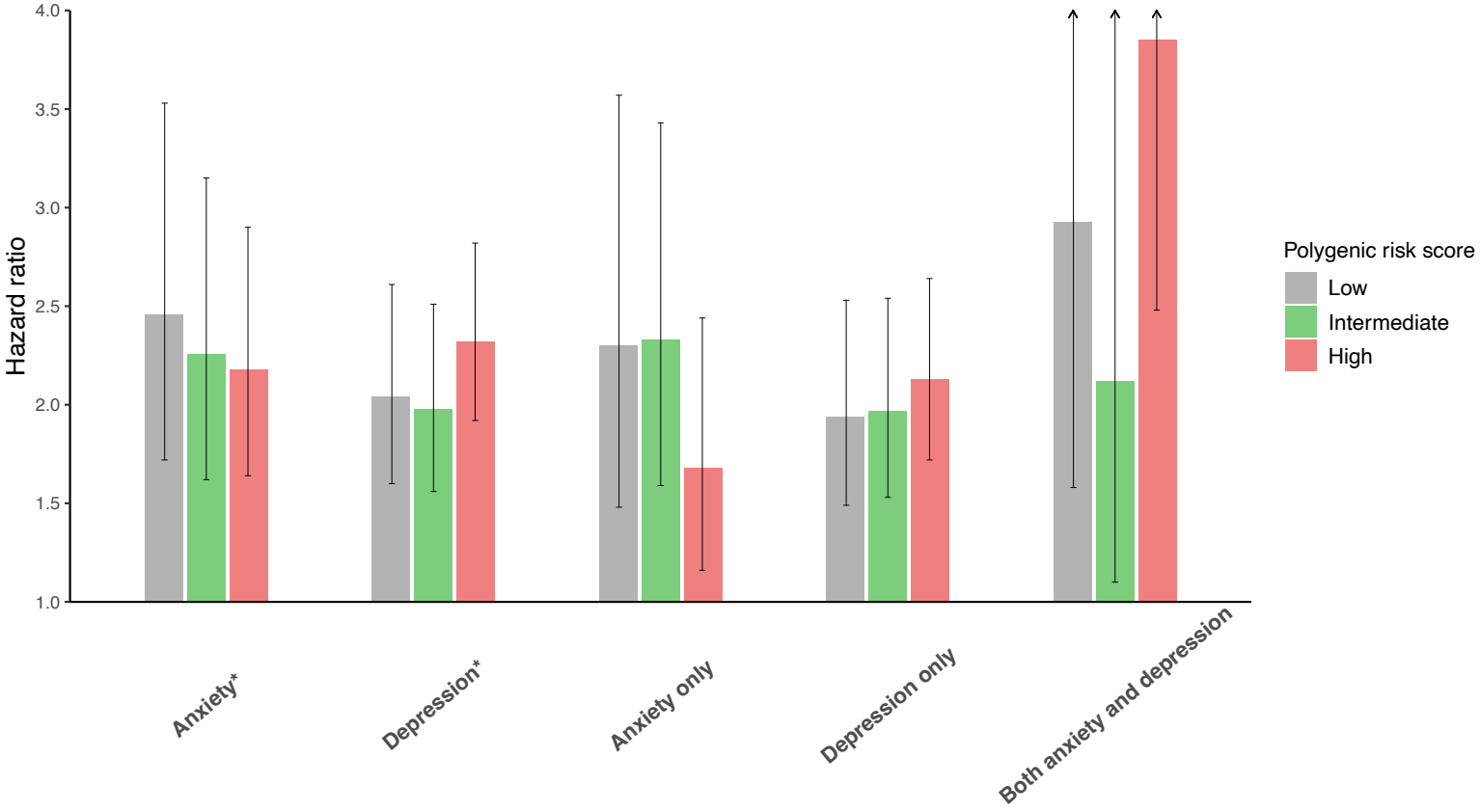
All models were adjusted for age, sex, deprivation index, education, genotyping chip, and 10 principal components

Interaction was calculated from low and high PRS categories

n number, HR Hazard ratio, CI Confidence interval, PRS Polygenic risk score, RERI Relative excess risk due to interaction

*Anxiety disorder and depression were not mutually adjusted

Figure 10. Associations between diagnosed anxiety disorder and depression and coronary artery disease by polygenic risk score.



*Anxiety disorder and depression were not mutually adjusted. All models were adjusted for age, sex, deprivation index, education, genotyping chip, and 10 principal components

The associations between concomitant anxiety disorder and depression and CAD were strong in both the high PRS_{CAD} category (HR 3.85, 95% CI 2.48–5.98) and low PRS_{CAD} category (HR 2.93, 95% CI 1.58–5.46). Repeating the analysis after excluding those with prevalent severe mental health conditions yielded consistent results (Supplementary Table 7). Additional adjustments for potential mediators attenuated the magnitude of the associations in both the separate and joint models and across PRS_{CAD} categories but the associations remained (Supplementary Table 8).

Expanding ascertainment of anxiety disorder and depression to include self-reported disease attenuated their associations with CAD and adjusting for PRS_{CAD} did not change the estimates (Supplementary Table 9). In both separate and joint models, as with anxiety disorder, the estimated effect sizes for depression varied little by PRS_{CAD} category (Supplementary Table 10). Overall, additional adjustments for potential mediators slightly attenuated the magnitude of associations across PRS_{CAD} categories (Supplementary Table 11).

DISCUSSION

Primary findings: Our findings demonstrated that the association between depression and CAD was stronger among those with a high PRS_{CAD}. In contrast, this pattern was not evident for anxiety disorder nor concomitant anxiety disorder and depression which were associated with CAD regardless of genetic predisposition to CAD. Adjusting for potential mediators attenuated these associations between anxiety disorder and/or depression and CAD, across PRS_{CAD} categories, consistent with them acting as mediators.

Comparisons with previous studies: We investigated the associations of anxiety disorder and depression with incident CAD and their modification by PRS_{CAD} in a single, very large, prospective, general population cohort study. We ascertained these mental health conditions through record linkage to hospital admission data as ICD-10 codes to obviate any reporting or recall bias. We also established the temporal order of these mental health conditions, potential mediators, and CAD to obviate reverse causation. A possible interaction between depression and PRS_{CAD} has been investigated in only one existing study (Silventoinen et al.,

2022). The non-significant finding of that study differ from ours and may be due to being underpowered by a much smaller sample size and testing for a multiplicative interaction alone. Furthermore, the authors acknowledged their potential measurement errors of depression due to the reliance on purchasing records of antidepressants, which is not specific to depression because of their broad indications.

Our findings offer several interpretations. Firstly, the stronger association between depression and CAD among those with genetic susceptibility would be consistent with pleiotropy contributing to the clustering of these conditions as shown by previous studies reporting the shared genetic architecture (Hagenaars et al., 2020, Kendler et al., 2009, Chen et al., 2023, Wray et al., 2018). For example, a recent UK study found a strong genetic correlation between depression and CAD (r_g=0.56) and similarly diabetes, hypertension, BMI, and waist-hip ratio (Chen et al., 2023). However, this did not fully explain the observed association between depression and CAD in those with low genetic predisposition, nor does it explain the associations between anxiety disorder and CAD, implying other mechanisms must play a role in the clustering of these mental health conditions and CAD. Adjustment for potential mediators attenuated the associations between these mental health conditions and CAD, consistent with previous studies (Kollia et al., 2017, Hiles et al., 2015, Atlantis et al., 2012). These findings are consistent with mediation contributing to the clustering, whereby these mental health conditions adversely impact lifestyle which, in turn, predisposes to CAD. This is supported by previous evidence, such that people with depression and anxiety disorder are more likely to smoke (Leventhal and Zvolensky, 2015).

Secondly, anxiety disorder and depression may respond to CAD genetic predisposition differently. This may be surprising given their genetic and phenotypic similarities. Anxiety disorder and depression have a strong genetic correlation (r_g=0.90) and have sometimes been classified in the same psychiatric group as internalising disorders (Derks et al., 2022, Grotzinger et al., 2022). In addition, they often co-exist and share similar symptoms. Around 40% of people with depression experienced anxiety disorder during 12-month follow-up and 45% over their lifetime (Kessler et al., 2015). They shared many symptoms such as

low energy and disturbed appetite, which could support their similar association strengths with CAD in our study (Hranov, 2007). On the other hand, there seem distinct mechanisms by which each of these mental health conditions increases CAD risk (Cohen et al., 2015). For example, whilst high blood pressure is more specific to anxiety disorder (Lim et al., 2021), inflammation is more associated with depression (particularly in the immunometabolic subtype) (Osimo et al., 2019), and this may result in our contrasting findings in relation to modification.

Thirdly, the role of depression in CAD development may be heterogeneous in that, overall, we found inconsistent results between diagnosed depression and additional use of self-reports. One reason is the varying severity between different measurements of depression: diagnosed depression in a hospital is probably more severe than self-reported depression which includes cases managed exclusively in the community. Interestingly, our study has suggested that the varying severity not only affects the size of the CAD risk but also affects the risk modification by CAD genetic susceptibility. This would encourage further studies to understand the underlying mechanisms and how to identify high-risk groups among those suffering from mental health disorders.

Limitations: Whilst there were several strengths in our study, the following limitations should be observed when interpreting the results. Firstly, remitting-relapsing fluctuations of these mental health conditions may affect our estimates. Because we only ascertained whether anxiety disorder and depression had ever occurred before the baseline assessment, it is unclear whether or not they remitted over follow-up and if so, how this attenuated our estimates (Peter et al., 2020). Secondly, our study based the diagnoses of these mental health conditions on the ICD-10 classification system, which cannot be directly mapped to the Diagnostic and Statistical Manual of Mental Disorders (DSM) classifications. Therefore, our findings may have limited applicability in settings that adopt the DSM system (Andrews et al., 1999). Thirdly, our main findings may not fully apply to milder cases of anxiety disorder and depression, as shown in the sensitivity analysis. Fourthly, because the original GWAS predominantly included those with European ancestry, our study was restricted to those reported as white. Therefore, our findings may not apply to other ethnic groups. Fifthly, residual confounding remains a concern due to unmeasured confounders as with

other observational studies. Lastly, anxiety disorder and depression in this study were less prevalent than in previous general population studies (Arias de la Torre et al., 2021), indicating that caution is required when applying the study findings outside UK Biobank. There are potentially two reasons for such discrepancies: (1) the UK Biobank participants do not fully represent the general population because they tend to be healthier (Fry et al., 2017), and (2) hospital admission data were used to ascertain these mental health conditions, which are mainly the more severe cases.

Implications: Because the prevalence of anxiety disorder, depression, and CAD are increasing (GBD 2019 Mental Disorders Collaborators, 2022, Roth et al., 2020), understanding the mechanism behind their mental health-cardiovascular comorbidity is needed to reduce the public health burden. Our findings suggest that CAD genetic susceptibility contributes to the clustering of depression and CAD by modifying their associations but does not provide the full explanation. Clustering is likely to also be due, in part, to poor mental health being associated with unhealthy lifestyle choices and their downstream biomarkers which predispose to CAD. The latter mechanism suggests that this form of multimorbidity could potentially be tackled by modifying those mediating factors in addition to treating and preventing anxiety disorder and depression.

CONCLUSIONS

CAD genetic susceptibility might partly contribute to the clustering of depression and CAD but does not provide a full explanation, nor does it explain the association between anxiety disorder and CAD. Therefore, other mechanisms should be explored.

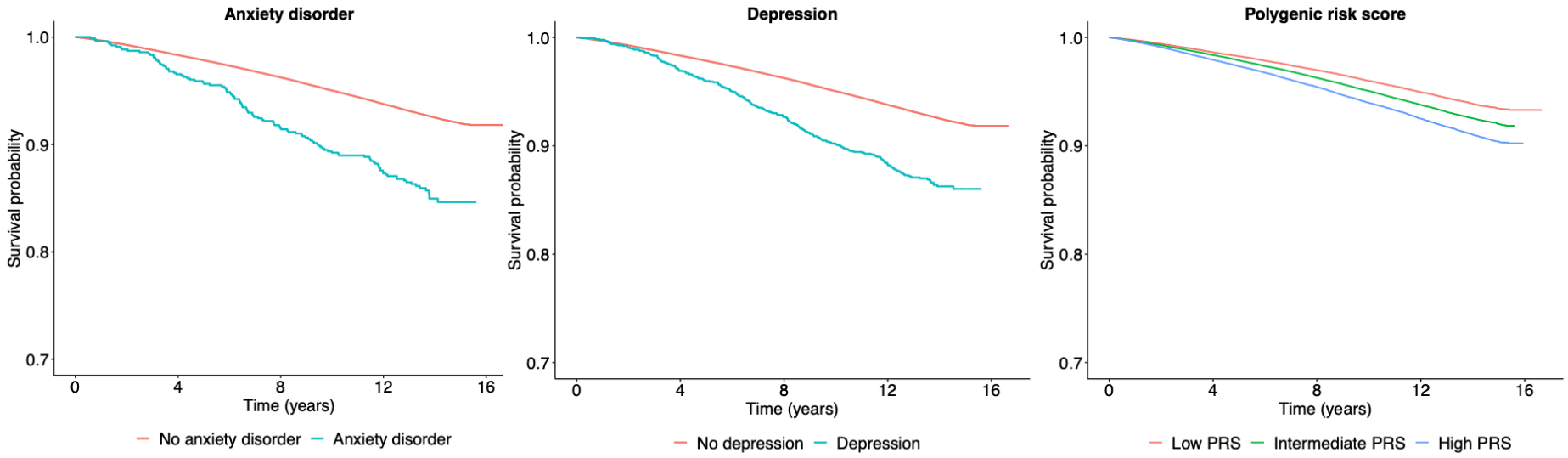
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3.3 Supplementary Materials

Supplementary Figure 1. Kaplan-Meier estimates of the survivor function for coronary artery disease comparing participants by anxiety disorder, depression, and polygenic risk score



Supplementary Table 5. Number of coronary artery disease events during the study period

	2 years	4 years	6 years	8 years	10 years	12 years	14 years	16 years	Total
No anxiety disorder	2,104	2,730	2,855	3,107	3,505	3,631	2,847	433	21,212
Anxiety disorder	9	18	13	26	18	15	13	0	112
No depression	2,096	2,710	2,834	3,091	3,478	3,612	2,832	433	21,086
Depression	17	38	34	42	45	34	28	0	238

Supplementary Table 6. Participant characteristics by coronary artery disease polygenic risk score

	Low PRS N = 96,011[1]	Intermediate PRS N = 96,010[1]	High PRS N = 96,010[1]
Age (years), mean (SD)	56.6 (7.98)	56.5 (7.98)	56.4 (7.98)
Sex			
Female	51,766 (53.92)	52,265 (54.44)	52,884 (55.08)
Male	44,245 (46.08)	43,745 (45.56)	43,126 (44.92)
Deprivation index, mean (SD)	-1.7 (2.86)	-1.7 (2.87)	-1.7 (2.87)
With college or University degree	32,719 (34.08)	31,793 (33.11)	31,131 (32.43)
Smoking			
Never	54,245 (56.67)	53,783 (56.18)	54,006 (56.42)
Previous	32,581 (34.04)	32,783 (34.25)	32,564 (34.02)
Current	8,895 (9.29)	9,164 (9.57)	9,145 (9.55)
Missing	290	280	295
MET-minutes/week, median (IQR)	1,830 (2,801)	1,855 (2,828)	1,860 (2,848)
Missing	19,997	20,270	20,625
Diet quality score, mean (SD)	4.4 (1.60)	4.4 (1.61)	4.4 (1.61)
Missing	11,422	11,123	11,115
Body mass index (kg/m2), mean (SD)	27.1 (4.58)	27.2 (4.63)	27.3 (4.66)
Missing	254	254	277
SBP ≥140mmHg or medication	44,898 (47.97)	46,719 (49.93)	48,219 (51.46)
Missing	2,409	2,433	2,316
LDL-c ≥ 4.9 mmol/L or medication	16,592 (18.03)	18,518 (20.14)	20,356 (22.10)
Missing	3,962	4,061	3,890
HbA1c ≥ 48 mmol/mol or medication	2,500 (2.73)	2,755 (3.01)	2,863 (3.12)
Missing	4,442	4,367	4,274
C-reactive protein (mg/L), median (IQR)	1.25 (1.97)	1.28 (2.01)	1.31 (2.04)
Missing	4,401	4,567	4,451

[1]Numbers presented are number (%) unless otherwise stated; SD, standard deviation; IQR, interquartile range; PRS, polygenic risk score; MET, metabolic equivalent; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol

Supplementary Table 7. Associations between diagnosed anxiety disorder and depression and coronary artery disease by polygenic risk score after excluding participants with severe mental health conditions

	Low PRS HR (95% CI)	Intermediate PRS HR (95% CI)	High PRS HR (95% CI)	Multiplicative interaction HR (95% CI)	Additive interaction RERI (95% CI)
Separate models* (n=287,608)					
Anxiety disorder (+/- depression)	2.50 (1.73–3.60)	2.25 (1.61–3.15)	2.11 (1.56–2.84)	0.83 (0.52–1.33)	0.15 (-1.18–1.48)
Depression (+/- anxiety disorder)	2.01 (1.55–2.59)	1.85 (1.44–2.39)	2.23 (1.82–2.73)	1.10 (0.79–1.52)	0.84 (-0.01–1.70)
Combined model (n=287,608)					
Anxiety disorder only	2.35 (1.51–3.65)	2.35 (1.60–3.45)	1.67 (1.15–2.44)	0.69 (0.39–1.24)	-0.39 (-1.81–1.04)
Depression only	1.90 (1.44–2.51)	1.84 (1.40–2.41)	2.05 (1.65–2.57)	1.06 (0.75–1.52)	0.68 (-0.19–1.56)
Both anxiety disorder and depression	2.97 (1.54–5.72)	2.01 (1.01–4.03)	3.87 (2.36–6.33)	1.31 (0.58–2.98)	2.44 (-1.04–5.92)

n, number; HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score; RERI: relative excess risk due to interaction

* Anxiety disorder and depression were not mutually adjusted.

All models were adjusted for age, sex, deprivation index, education, genotyping chip, and 10 principal components.

Interaction was calculated from Low and High PRS categories.

Supplementary Table 8. Associations between diagnosed anxiety disorder and depression and coronary artery disease by polygenic risk score, adjusted for potential mediators

	Low PRS HR (95% CI)	Intermediate PRS HR (95% CI)	High PRS HR (95% CI)
Separate models* (n=179,555)			
Anxiety disorder	1.69 (0.98–2.91)	2.10 (1.34–3.30)	1.97 (1.36–2.86)
Depression	1.68 (1.20–2.35)	1.73 (1.25–2.40)	1.75 (1.33–2.29)
Combined model (n=179,555)			
Anxiety disorder only	1.45 (0.72–2.91)	1.91 (1.08–3.38)	1.49 (0.91–2.44)
Depression only	1.61 (1.12–2.31)	1.61 (1.12–2.31)	1.53 (1.13–2.08)
Both anxiety disorder and depression	2.32 (0.96–5.58)	2.56 (1.22–5.38)	3.50 (1.98–6.19)

n, number; HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score

* Anxiety disorder and depression were not mutually adjusted.

Models were adjusted for age, sex, deprivation index, education, genotyping chip, 10 principal components, smoking status, MET, diet quality score, body mass index, hypertension, high low-density lipoprotein cholesterol, hyperglycaemia, and C-reactive protein.

Supplementary Table 9. Associations between diagnosed or self-reported anxiety disorder and depression and coronary artery disease

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Separate models* (n=288,031)			
Anxiety disorder (+/- depression)	1.13 (1.02–1.26)	1.25 (1.13–1.39)	1.26 (1.13–1.39)
Depression (+/- anxiety disorder)	1.02 (0.96–1.09)	1.25 (1.17–1.34)	1.25 (1.17–1.34)
Combined model (n=288,031)			
Anxiety disorder only	1.09 (0.97–1.23)	1.20 (1.06–1.35)	1.20 (1.06–1.35)
Depression only	1.00 (0.93–1.07)	1.23 (1.15–1.32)	1.23 (1.15–1.32)
Both anxiety disorder and depression	1.25 (1.03–1.52)	1.47 (1.21–1.78)	1.48 (1.22–1.79)

n, number; HR, hazard ratio; CI, confidence interval

* Anxiety disorder and depression were not mutually adjusted.

Model 1: no adjustment.

Model 2: adjusted for age, sex, deprivation index, and education.

Model 3: adjusted for age, sex, deprivation index, education, polygenic risk score, genotyping chip, and 10 principal components.

Supplementary Table 10. Associations between diagnosed or self-reported anxiety disorder and depression and coronary artery disease by polygenic risk score

	Low PRS	Intermediate PRS	High PRS	Multiplicative interaction	Additive interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RERI (95% CI)
Separate models* (n=288,031)					
Anxiety disorder (+/- depression)	1.29 (1.07–1.57)	1.24 (1.03–1.48)	1.25 (1.06–1.47)	0.97 (0.75, 1.24)	0.09 (-0.30, 0.49)
Depression (+/- anxiety disorder)	1.27 (1.12–1.44)	1.21 (1.08–1.36)	1.27 (1.15–1.41)	1 (0.85, 1.18)	0.15 (-0.1, 0.41)
Combined model (n=288,031)					
Anxiety disorder only	1.29 (1.03–1.61)	1.25 (1.01–1.53)	1.10 (0.91–1.34)	0.86 (0.63, 1.16)	-0.13 (-0.57, 0.32)
Depression only	1.27 (1.11–1.45)	1.21 (1.07–1.37)	1.23 (1.10–1.37)	0.97 (0.82, 1.15)	0.08 (-0.18, 0.35)
Both anxiety disorder and depression	1.36 (0.94–1.98)	1.24 (0.86–1.77)	1.80 (1.35–2.40)	1.32 (0.83, 2.12)	0.88 (-0.07, 1.82)

n, number; HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score

* Anxiety disorder and depression were not mutually adjusted.

All models were adjusted for age, sex, deprivation index, education, genotyping chip, and 10 principal components.

Supplementary Table 11. Associations between diagnosed or self-reported anxiety disorder and depression and coronary artery disease by polygenic risk score, adjusted for potential mediators

	Low PRS HR (95% CI)	Intermediate PRS HR (95% CI)	High PRS HR (95% CI)
Separate models* (n=179,555)			
Anxiety disorder	1.28 (0.99–1.66)	1.25 (0.99–1.58)	1.22 (0.99–1.50)
Depression	1.23 (1.05–1.45)	1.07 (0.91–1.25)	1.14 (0.99–1.31)
Crude model (n=179,555)			
Anxiety disorder only	1.25 (0.93–1.70)	1.23 (0.94–1.62)	1.10 (0.86–1.40)
Depression only	1.22 (1.03–1.44)	1.05 (0.89–1.24)	1.09 (0.94–1.26)
Both anxiety disorder and depression	1.41 (0.87–2.27)	1.31 (0.83–2.05)	1.74 (1.17–2.58)

n, number; HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score

* Anxiety disorder and depression were not mutually adjusted.

Models were adjusted for age, sex, deprivation index, education, genotyping chip, 10 principal components, smoking status, MET, diet quality score, body mass index, hypertension, high low-density lipoprotein cholesterol, hyperglycaemia, and C-reactive protein.

Chapter 4 Shared and distinct pathways from anxiety disorder and depression to cardiovascular disease: a UK Biobank prospective cohort study

4.1 Preface

In Chapter 3, CVD genetic susceptibility did not fully explain the clustering of anxiety and depression with CVD. However, traditional CVD risk factors appeared to mediate the associations across genetic risk categories. These findings suggest that identifying modifiable pathways between MHCs and CVD could enhance our understanding of MHC-CVD clustering and then inform CVD prevention strategies.

Although a few previous studies found plausible pathways for depression involving obesity and inflammatory markers (Kollia et al., 2017, Hiles et al., 2015), no studies have systematically investigated a wide range of potential mediators spanning lifestyle, physical, and metabolic factors. More importantly, few studies have investigated anxiety. My findings in Chapter 3 suggested that different mechanisms may be involved in developing CVD as a comorbid condition associated with depression or anxiety as genetic modification was observed only for depression. This indicates that findings for depression may not be generalisable to anxiety, highlighting the importance of comparing underlying CVD pathways between the two conditions.

This chapter investigates potential pathways between anxiety and depression and CVD using a broad range of lifestyle, physical, and metabolic factors.

4.2 Published Manuscript

ABSTRACT

Aims: Although anxiety disorder and depression increase the risk of cardiovascular disease (CVD), few studies have examined their underlying mechanisms systematically, particularly contrasting the difference between the two of them. Our study aimed to examine the extent to which lifestyle, physical, and metabolic factors mediate the associations of anxiety disorder and depression with incident CVD.

Methods and results: A prospective cohort study was conducted using UK Biobank. Anxiety disorder, depression, and incident CVD were ascertained

through linkage to hospital and death records. A causal mediation analysis was performed for anxiety disorder and depression, separately examining multiple potential lifestyle, physical, and metabolic mediators. Cox proportional hazard models and log-linear models were used to derive indirect effect estimates and proportions mediated. A total of 254 695 participants were included. Both anxiety disorder [hazard ratio (HR) 1.62, 95% confidence interval (CI) 1.15–2.30] and depression (HR 2.15, 95% CI 1.75–2.64) were associated with CVD after adjusting for sociodemographic confounders. Among lifestyle and physical factors, the strongest mediators were current smoking and higher waist–hip ratio which accounted for 11.9% and 13.4% of the excess risk from anxiety disorder, and 17.3% and 14.0% from depression, respectively. The strongest metabolic mediators were systolic blood pressure for anxiety disorder (10.4%) and C-reactive protein (10.8%) for depression. Systolic blood pressure was the weakest mediator for depression (4.3%).

Conclusion: Lifestyle and physical pathways to incident CVD may be common to both anxiety disorder and depression, but shared metabolic pathways seem unlikely. Our findings inform which risk factors to target among people with anxiety disorder or depression in order to reduce their higher risk of developing CVD.

INTRODUCTION

Anxiety disorder and depression often co-exist with cardiovascular disease (CVD). Previous studies reported that more than 30% of patients with CVD had anxiety disorder (Todaro et al., 2007) and 15% had depression (Colquhoun et al., 2013). These prevalences are more than two to three times that of the general population (Craske et al., 2017, Marx et al., 2023).

Whilst these mental health conditions could be affected by CVD, they would increase the risk of CVD. A meta-analysis found that people with anxiety disorder or depression had ~20% increased risk of incident CVD (Smaardijk et al., 2019). Since anxiety disorder and depression are common and increasing (GBD 2019 Mental Disorders Collaborators, 2022, Xiong et al., 2022), understanding the pathways to CVD could identify modifiable targets to reduce comorbidity.

Some previous studies have conducted mediation analyses. A cross-sectional study has demonstrated that lifestyle, metabolic syndrome, and inflammation mediated the association between distress and incident CVD (Kollia et al., 2017). Similarly, a prospective Australian study has demonstrated that each obesity and inflammation mediated ~10% of the association between depression and non-fatal CVD (Hiles et al., 2015). This is biologically plausible because obesity induced by depression can produce inflammatory markers, which in turn cause CVD (Yazıcı and Sezer, 2017). Conversely, it remained unclear whether diabetes and hypertension mediate such associations (Atlantis et al., 2012).

However, these studies have limitations. Firstly, they did not systematically assess and compare a broad range of potential mediators including lifestyle, physical, and metabolic factors. Understanding the relative importance of these potential pathways is key to targeting interventions. Secondly, these studies have focused on depression to the exclusion of anxiety disorder. Because anxiety disorder may have a different aetiology, the findings of studies based on depression cannot be automatically applied to anxiety disorder.

Therefore, we aimed to examine the extent to which lifestyle, physical, and metabolic factors mediate the associations between anxiety disorder and depression and incident CVD, contrasting the difference between the two of them.

METHODS

Study design and participants: Our study is a prospective cohort study using data from UK Biobank. Between 2007 and 2010, over 500 000 participants aged 37–73 years were enrolled. Participants visited one of the 22 assessment centres across England, Scotland, and Wales to provide their information and biological samples. We excluded participants who experienced CVD before the baseline assessment, those who developed depression or anxiety disorder <1 year before or after the baseline assessment to reduce the risk of reverse causation between the exposures and mediators, and those who had missing data in covariates or mediators.

Measurements: The exposures of interest were anxiety disorder and depression diagnosed at least 1 year before the baseline assessment and ascertained through record linkage to hospital admission data available from 2004: Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Anxiety disorder and depression were defined as an International Classification of Diseases, 10th revision (ICD-10) code of F40-43 and F32-33, respectively.

The outcome of interest was incident CVD (fatal or non-fatal) after baseline assessment ascertained from record linkage to hospital admission data and death certificates. Hospital admission data were available up to September 2021 in England, February 2018 in Wales, and July 2021 in Scotland. Death certificate data were obtained from the National Health Service Information Centre (England and Wales) and the National Health Service Central Register (Scotland) and were available up to September 2021 in England and Wales, and October 2021 in Scotland. Follow-up was censored at the date of hospitalization or death, whichever occurred first. Cardiovascular disease was defined as an ICD-10 code of I20-25, I42.0, I42.6, I42.7, I42.9, I50, I60-64, or I110.

The potential mediators of interest were lifestyle factors (physical activity, TV viewing, diet quality, smoking status and sleep duration), physical factors [waist–hip ratio, body mass index (BMI), and grip strength], and metabolic factors [systolic blood pressure, haemoglobin A1c (HbA1c), low-density lipoprotein-cholesterol (LDL-c), and C-reactive protein (CRP)]. Lifestyle factors were self-reported by participants using a touchscreen questionnaire at baseline. Physical activity was based on metabolic equivalent minutes (METs) per week derived from the validated International Physical Activity Questionnaire (Craig et al., 2003) and categorized into METs <1000 or ≥1000 per week (Jeong et al., 2019). TV viewing was categorized as <3 or ≥3 h per day, based on the median. Diet quality was based on the cumulative dietary risk factors score, which has been reported previously (Petermann-Rocha et al., 2021). In brief, participants were given one point for each of the nine dietary recommendations met relating to: processed meat, red meat, total fish, milk, spread type, cereal intake, salt added to food, water, and fruits and vegetables. Therefore, the overall score ranged from 0 (least healthy) to 9 (most healthy) but was categorized as ≥4 or <4

based on the median value. Smoking status was categorized as current smoker or not (never or former smoker). Sleep duration was categorized as <7 or ≥7 h per day, based on the median.

Physical factors were measured by trained staff at the baseline assessment and treated as binary variables. Waist–hip ratio was calculated as waist circumference/hip circumference, measured using a Wessex non-stretchable sprung tape and categorized as ≥0.90 or <0.90 for men and ≥0.85 or <0.85 for women (World Health Organization, 2011b). Body mass index was calculated as weight/height^2; height was measured by a Seca 202 stadiometer, and body weight was measured by a Tanita BC-418 body composition analyser. Body mass index was categorized as ≥30 kg/m^2 or <30 kg/m^2 (WHO Consultation on Obesity & World Health Organization, 2000). Grip strength was measured using a Jamar J00105 hydraulic hand 101 dynamometers and categorized as <36.0 kg or ≥36.0 kg for men and <21.0 kg or ≥21.0 kg for women, based on the median.

Metabolic factors were measured or samples were collected by trained staff at the baseline assessment and treated as binary variables. Systolic blood pressure was measured using an automated Omron device 0-255 and the use of anti hypertensive medication was self-reported. Systolic blood pressure was categorized as ≥140 mmHg or taking anti-hypertensive medication or not (Unger et al., 2020). HbA1c was categorized as ≥48 mmol/mol or taking diabetic medication or not (World Health Organization, 2011a). LDL-c was categorized as ≥4.9 mmol/L or taking cholesterol-lowering medication or not (Arnett et al., 2019). CRP was categorized as >3 mg/L or ≤3 mg/L (Jialal et al., 2004). All these factors were selected because they are risk factors for CVD and could be affected by anxiety disorder and depression.

Potential sociodemographic confounders were age, sex, ethnic group, and deprivation level. Age, sex, and ethnic group were self-reported by participants using the touchscreen questionnaire at baseline. Deprivation was based on tertiles of the Townsend area deprivation index, which was derived from the postcode of residence using aggregated data on unemployment, car and home ownership, and household overcrowding.

Statistical analyses: The main analyses were conducted in three stages: total effects were estimated; mediator models and outcome models were built; and a causal mediation analysis was performed. The total effects of anxiety disorder and depression on CVD were estimated using Cox proportional hazard models expressed as hazard ratios (HRs) adjusted for all sociodemographic confounders. In the mediator models, the associations of anxiety disorder and depression with each one of the mediators were estimated using log-linear models expressed as risk ratios adjusted for all sociodemographic confounders. In the outcome models, the associations between each one of the mediators and CVD were estimated using Cox proportional hazard models adjusted for all sociodemographic confounders and either anxiety disorder or depression. In the causal mediation, after testing for interactions between anxiety disorder/depression and the mediators, total natural indirect effects (NIEs) and proportions mediated were calculated using separate log-linear models and Cox proportional hazard models for each of the mediators, adjusted for the sociodemographic confounders. Standard errors and 95% confidence intervals (CIs) were derived from bootstrap procedures. Proportional hazard assumptions were checked by statistical tests based on Schoenfeld residuals. Participants with anxiety disorder were not excluded from the analysis of depression and vice versa.

A sensitivity analysis was conducted by stepwise adjustments for lifestyle and physical factors in addition to sociodemographic confounders to examine whether these affected any downstream associations (e.g. blood pressure and CVD). Particularly in this sensitivity analysis, adjustments were performed using the parametric g-formula approach because lifestyle and physical factors were considered to be affected by anxiety disorder and depression. We also assessed whether the additional use of self-reported anxiety disorder and depression at baseline affected the results. All analyses were conducted using R version 3.5.3 with a package CMAverse version 0.1.0.

Ethics statement: All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. UK Biobank was approved by the North-West Multi-Centre Research Ethics

Committee (Ref: 11/NW/0382). This work was conducted under the UK Biobank application number 7155.

Consent statement: Written informed consent was obtained from all individual participants included in the study.

RESULTS

Of more than 500 000 UK Biobank participants, 254 695 were eligible for inclusion in the analyses (Figure 11). Participants with anxiety disorder were more likely to have unfavourable lifestyle, physical, and metabolic factors except for diet quality (Table 7). They were also more likely to develop CVD; 32 (5.8%) of those with anxiety disorder and 9779 (3.9%) of those without experienced an event over a median follow-up time of 12.57 and 12.61 years, respectively. Similarly, participants with depression were more likely to have unfavourable lifestyle, physical, and metabolic factors, apart from systolic blood pressure, and were more likely to develop CVD; 92 (7.3%) of those with depression and 9719 (3.8%) of those without experienced an event over a median follow-up time of 12.50 and 12.61 years, respectively.

Figure 11. Flow chart of the participant selection process

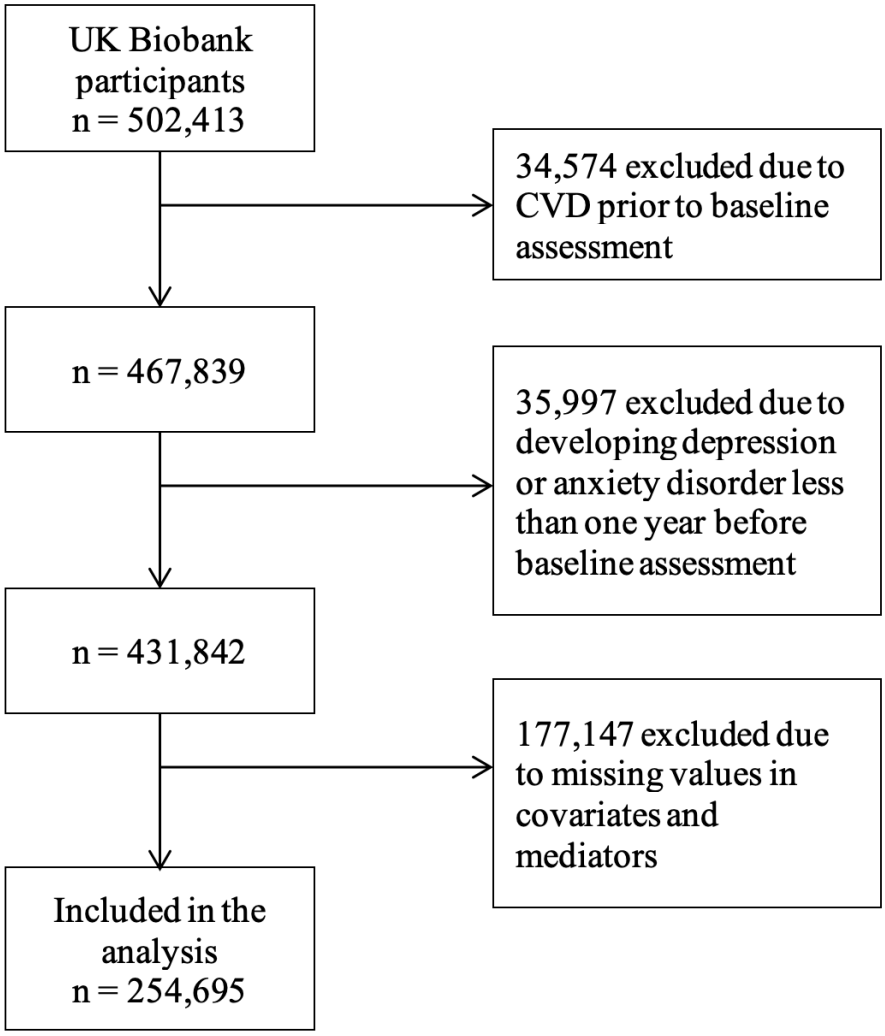


Table 7. Characteristics of participants by anxiety disorder and depression

	No anxiety disorder N=254,145 (%)	Anxiety disorder N=550 (%)	No depression N=253,437 (%)	Depression N=1,258 (%)
Mean (SD) Age (years)	55.8 (8.11)	55.4 (8.25)	55.8 (8.11)	54.9 (8.01)
Sex:				
Female	135,788 (53.4)	327 (59.5)	135,363 (53.4)	752 (59.8)
Male	118,357 (46.6)	223 (40.5)	118,074 (46.6)	506 (40.2)
Ethnic group:				
White	242,814 (95.5)	525 (95.5)	242,130 (95.5)	1,209 (96.1)
Non-white	11,331 (4.46)	25 (4.55)	11,307 (4.46)	49 (3.90)
Deprivation level:				
Least deprived	88,546 (34.8)	160 (29.1)	88,402 (34.9)	304 (24.2)
Middle	86,027 (33.8)	166 (30.2)	85,854 (33.9)	339 (26.9)
Most deprived	79,572 (31.3)	224 (40.7)	79,181 (31.2)	615 (48.9)
MET-minutes/week <1000	73,745 (29.0)	180 (32.7)	73,455 (29.0)	470 (37.4)
TV viewing ≥3 hours/day	122,642 (48.3)	288 (52.4)	122,213 (48.2)	717 (57.0)
Diet quality score <5	72,556 (28.5)	153 (27.8)	72,284 (28.5)	425 (33.8)
Current smoking	22,931 (9.02)	83 (15.1)	22,732 (8.97)	282 (22.4)
Sleep duration <7 hours/day	58,865 (23.2)	139 (25.3)	58,624 (23.1)	380 (30.2)
Waist-hip ratio ≥0.90 (male) ≥0.85 (female)	118,827 (46.8)	297 (54.0)	118,389 (46.7)	735 (58.4)
Body mass index ≥30kg/m^2	54,619 (21.5)	147 (26.7)	54,326 (21.4)	440 (35.0)
Grip strength <36 Kg (male) <21 Kg (female)	119,041 (46.8)	298 (54.2)	118,614 (46.8)	725 (57.6)
SBP ≥140mmHg or medication	120,996 (47.6)	278 (50.5)	120,682 (47.6)	592 (47.1)
HbA1c ≥ 48 mmol/mol or medication	7,845 (3.09)	28 (5.09)	7,802 (3.08)	71 (5.64)
LDL-c ≥ 4.9 mmol/L or medication	48,536 (19.1)	131 (23.8)	48,306 (19.1)	361 (28.7)

CRP >3mg/L	51,432 (20.2)	144 (26.2)	51,151 (20.2)	425 (33.8)

N, number; SD, standard deviation; MET, metabolic equivalent; TV, television; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP,

C-reactive protein

Both anxiety disorder (HR 1.62, 95% CI 1.15–2.30) and depression (HR 2.15, 95% CI 1.75–2.64) were associated with CVD after adjusting for sociodemographic confounders (Supplementary Figure 2). Anxiety disorder was associated with all potential mediators except for diet quality score and sleep duration and these mediators were associated with CVD. Similarly, depression was associated with all mediators but systolic blood pressure (Supplementary Tables 12 and 13).

Of the lifestyle and physical factors, current smoking (NIE HR 1.05, 95% CI 1.02–1.07) and high waist–hip ratio (NIE HR 1.06, 95% CI 1.04–1.08) were the strongest mediators of the association between anxiety disorder and CVD, mediating 11.9% and 13.4% of the association, respectively (Table 8 and Figure 12). All of the metabolic factors mediated this association with the largest contribution from systolic blood pressure (NIE HR 1.04, 95% CI 1.01–1.08) which mediated 10.4%. Similarly, smoking (NIE HR 1.10, 95% CI 1.08–1.13) and waist–hip ratio (NIE HR 1.08, 95% CI 1.07–1.10) were the strongest mediators of the association between depression and CVD, mediating 17.3% and 14.0% of the association, respectively. In contrast to anxiety disorder, CRP (NIE HR 1.06, 95% CI 1.05–1.08) made the largest contribution to mediation (10.8%) among the biomarkers and systolic blood pressure made the lowest (4.3%), whose CI crossed the null value.

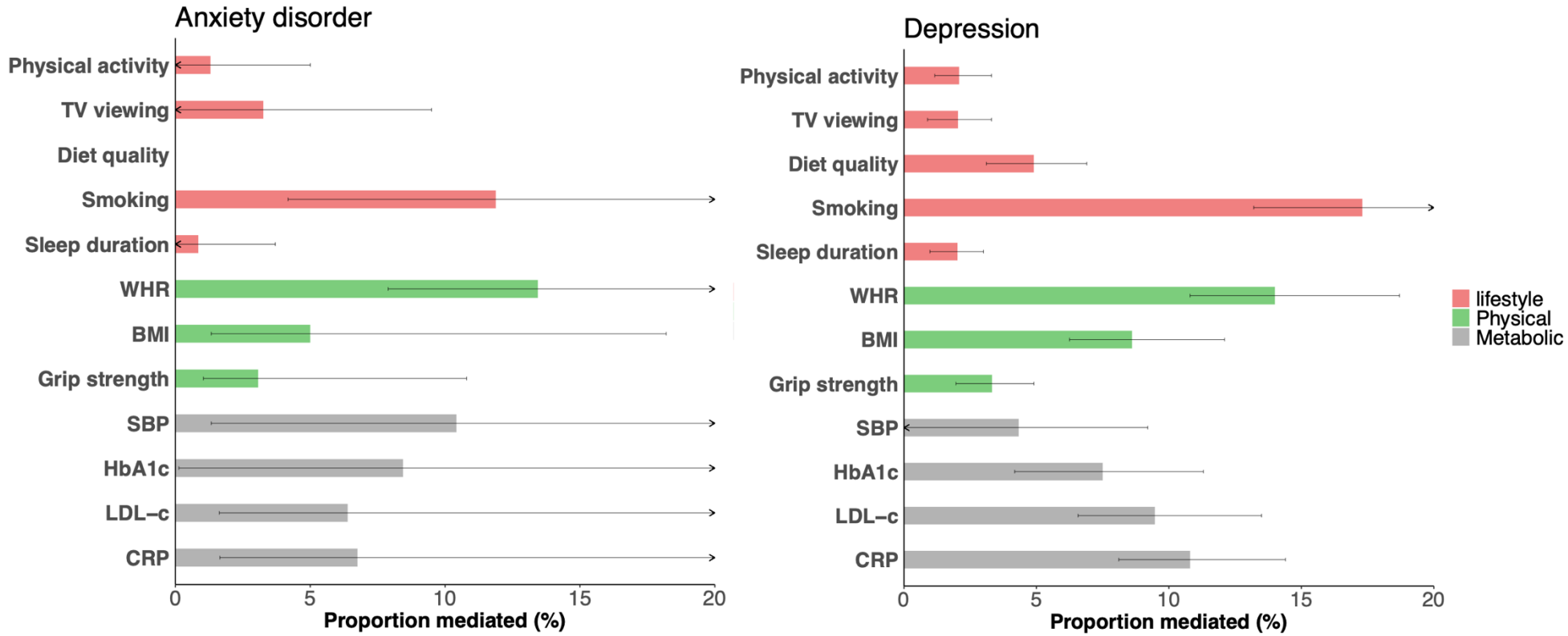
Table 8. Effect size estimates and proportions mediated via lifestyle, physical, and metabolic factors of the associations between anxiety disorder and depression and incident cardiovascular disease

	Anxiety disorder						Depression					
	Natural indirect effect			Proportion mediated			Natural indirect effect			Proportion mediated		
	HR	95% CI		%	95% CI		HR	95% CI		%	95% CI	
Lifestyle factors:												
Physical activity	1.01	1.00	1.01	1.30	-0.35	5.0	1.01	1.01	1.02	2.08	1.16	3.30
TV viewing	1.01	1.00	1.02	3.26	-1.35	9.50	1.01	1.00	1.02	2.04	0.89	3.30
Diet quality	1.00	0.99	1.01	Not estimable			1.03	1.02	1.04	4.90	3.11	6.90
Smoking	1.05	1.02	1.07	11.9	4.18	37.8	1.10	1.08	1.13	17.3	13.2	22.7
Sleep duration	1.00	1.00	1.01	0.85	-1.04	3.70	1.01	1.01	1.02	2.02	0.98	3.0
Physical factors:												
WHR	1.06	1.04	1.08	13.4	7.89	43.0	1.08	1.07	1.10	14.0	10.8	18.7
BMI	1.02	1.01	1.03	5.00	1.33	18.2	1.05	1.04	1.06	8.61	6.25	12.1
Grip strength	1.01	1.01	1.02	3.07	1.04	10.8	1.02	1.01	1.03	3.32	1.96	4.90
Metabolic factors:												
SBP	1.04	1.01	1.08	10.4	1.33	37.1	1.02	1.00	1.07	4.33	-0.21	9.20
HbA1c	1.03	1.01	1.07	8.35	0.13	29.4	1.04	1.02	1.07	7.50	4.18	11.3
LDL-c	1.03	1.01	1.04	6.39	1.63	21.4	1.05	1.04	1.07	9.47	6.57	13.5
CRP	1.03	1.01	1.04	6.75	1.65	24.3	1.06	1.05	1.08	10.8	8.11	14.4

All models were adjusted for sociodemographic confounders.

HR, hazard ratio; CI, confidence interval; TV, television; WHR, waist and hip ratio; BMI, body mass index; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein.

Figure 12. Proportions mediated by lifestyle, physical, and metabolic factors of the associations between anxiety disorder and depression and incident cardiovascular disease.



TV, television; WHR, waist-hip ratio; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein. All models were adjusted for sociodemographic confounders.

Adjusting for lifestyle factors in addition to sociodemographic confounders attenuated all indirect effects of anxiety disorder and depression, but associations remained mediated by physical and metabolic factors (Supplementary Tables 14 and 15). For example, the waist–hip ratio still mediated 8.6% and 9.4% of the associations of anxiety disorder and depression, respectively. Systolic blood pressure and CRP mediated 7.9% and 8.5% of associations of anxiety disorder and depression, respectively. Additional adjustments for physical factors did not meaningfully change the proportion mediated by systolic blood pressure of the association of anxiety disorder.

The results of sensitivity analysis by adding self-reported diagnoses were shown in Supplementary Figure 3 and Tables 16–20. Adding self-reported depression diagnosis showed similar trends of mediation with larger proportions mediated compared with our main findings. CRP still mediated the association after adjusting for lifestyle and physical factors in addition to the sociodemographic confounders. For self-reported anxiety disorder diagnosis, only LDL-c was a significant metabolic mediator (NIE HR 1.02, 95% CI 1.01–1.03), mediating 10.5% of the association, but this was attenuated to 6.8% after adjusting for lifestyle and physical factors.

DISCUSSION

Primary findings: Our study investigated and compared a wide range of the pathways linking anxiety disorder and depression with incident CVD. Among the lifestyle and physical factors investigated, the strongest mediators were smoking and waist–hip ratio for both anxiety disorder and depression. The strongest metabolic mediators were systolic blood pressure for anxiety disorder and CRP for depression. Systolic blood pressure was the weakest mediator for depression. These findings suggest that whilst smoking and central obesity would be common mediators of both anxiety disorder and depression, systolic blood pressure could be more specific to anxiety disorder and CRP to depression.

Whilst reverse causation has been reported between some of these relations (Hare et al., 2014, Wootton et al., 2020, Yuan et al., 2020, Tyrrell et al., 2019), we mitigated this risk by ensuring that anxiety disorder and depression had to be

recorded at least 1 year prior to the recruitment and anyone with any evidence of prevalent/historical CVD was excluded; thereby ensuring a temporal relationship of anxiety disorder and depression, mediators, and CVD as depicted in Supplementary Figure 4. Furthermore, in the sensitivity mediation analysis, we adjusted for exposure-induced lifestyle and physical factors. Importantly, upstream factors (e.g. smoking) would not fully involve the mediating roles of downstream factors (e.g. systolic blood pressure).

Comparisons with the literature: Existing evidence has suggested that anxiety disorder and depression would increase the risk of CVD (Smaardijk et al., 2019, Nakada et al., 2023, Shen et al., 2023, Tang et al., 2020) as well as traditional CVD risk factors consistent with our findings. Smoking would be a key mediator of the associations between anxiety disorder and depression and CVD based on their well-established associations and the broad impact on downstream CVD risk factors (e.g. inflammation, endothelial dysfunction, and platelet activity) (Centers for Disease et al., 2010). Indeed, when we additionally adjusted for lifestyle factors including smoking, indirect effects via downstream mediators were attenuated overall. The mediation by obesity is also important given the highly prevalent unhealthy lifestyles, such as poor diet quality and long sedentary time among those with mental health conditions (Carney and Freedland, 2017), as observed in our study that adjusting lifestyle factors attenuated the proportions mediated by obesity. However, this did not fully explain the mediating role of obesity, suggesting that other mechanisms would also remain to exist, such as the effects of antidepressants and antipsychotics (McIntyre et al., 2024).

The mediating role of high blood pressure in the association between anxiety disorder and CVD is plausible, given the accumulating evidence suggesting that anxiety disorder raises blood pressure in multiple ways: unhealthy lifestyle, stimulation of the sympathetic nervous system, and activation of the hypothalamic–pituitary–adrenal axis (Lim et al., 2021, al'Absi and Arnett, 2000). The latter two may be more predominant as we observed the remaining indirect effects via blood pressure after adjusting for lifestyle and physical factors. In our study, CRP still mediated the association of recorded/self-reported depression after adjusting for lifestyle and physical factors, highlighting more biological

inflammatory mechanisms. A systemic immune activation would be observed among those with depression (Beurel et al., 2020). Under severe mental stress, microglia and other central nervous system cells in the brain increase the production of cytokine, which has pro-inflammatory effects. However, CRP needs to be interpreted with causation because it is a proxy marker of other causal factors such as IL-6 rather than a causal risk factor itself (Zacho et al., 2008). It should be noted that although only LDL-c was a significant mediator for recorded/self-reported anxiety disorder, this would not invalidate our main findings. This may indicate that LDL-c is more specific to milder cases, whilst hypertension is more specific to severe cases. Some studies have reported that anxiety disorder is associated with elevated LDL-c concentration via emotional eating and subsequent body composition changes (Barbosa et al., 2022). Indeed, the proportion mediated by LDL-c was reduced after adjusting for lifestyle and physical factors in our study.

Limitations: There are several limitations to our study. Firstly, ascertainment of anxiety disorder and depression using hospital admission may be incomplete because it is less likely to include people with milder conditions. However, we assessed how this affected our main results through the inclusion of self-reports in the sensitivity analysis. Secondly, the baseline participant characteristics might have been modified by recent advancements in CVD risk factor management during the follow-up period. For example, obesity without diabetes is increasingly treated by glucagon-like peptide-1 agonists (Mahase, 2024). High-intensity statins are recommended and becoming common (Curtis et al., 2020). The use of tricyclic antidepressants is becoming less common (Bogowicz et al., 2021). Overall, these advancements might have diluted our estimates. Thirdly, some mediators could be on the same pathway, so interpreting each mediated effect needs care. For example, smoking could lead to CVD through elevated systolic blood pressure as well as other downstream factors. Therefore, the proportion mediated estimated in this study should not be summed but this does not necessarily invalidate the comparisons of the relative importance of mediators. Fourthly, the outcome of our study was restricted to composite incident CVD, which could not distinguish the subtype and severity of these cases. Additionally, ascertainment of CVD using hospital admission and death certificate data is less likely to include milder cases which are often managed in

primary care settings, such as angina. Lastly, UK Biobank participants are more likely to be white, affluent, and healthy than the national survey data, so applying our findings to the whole UK population may be limited.

CONCLUSIONS

Our study examined whether lifestyle, physical, and metabolic factors mediate the associations between anxiety disorder and depression and incident CVD and elucidated shared and distinct pathways. Among lifestyle and physical factors investigated, smoking and central adiposity were the strongest mediators for both anxiety disorder and depression. Systolic blood pressure was the strong metabolic mediator of anxiety disorder whilst CRP was a major mediator of depression. Our findings inform how best to target CVD prevention strategies among people with established anxiety disorder or depression.

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4.3 Supplementary Materials

Supplementary Table 12. Associations between anxiety disorder and depression and potential mediators

	Anxiety disorder N = 254,695		Depression N = 254,695	
	RR	95% CI	RR	95% CI
MET-minutes/week <1000	1.13	1.00, 1.27	1.29	1.20, 1.39
TV viewing ≥3 hours/day	1.09	1.01, 1.18	1.20	1.14, 1.26
Diet quality score <5	0.99	0.87, 1.13	1.18	1.09, 1.27
Current smoking	1.58	1.30, 1.92	2.21	2.00, 2.44
Sleep duration <7 hours/day	1.08	0.93, 1.24	1.27	1.17, 1.39
Waist-hip ratio ≥0.90 (male) ≥0.85 (female)	1.21	1.13, 1.30	1.32	1.27, 1.38
Body mass index ≥30kg/m2	1.23	1.07, 1.41	1.59	1.47, 1.71
Grip strength <36 Kg (male) <21 Kg (female)	1.16	1.08, 1.25	1.25	1.20, 1.31
SBP ≥140mmHg or medication	1.10	1.01, 1.19	1.05	0.99, 1.11
HbA1c ≥ 48 mmol/mol or medication	1.69	1.19, 2.41	1.89	1.50, 2.37
LDL-c ≥ 4.9 mmol/L or medication	1.28	1.11, 1.48	1.60	1.47, 1.74
CRP >3mg/L	1.26	1.10, 1.45	1.62	1.50, 1.75

N, number; RR, risk ratio; CI, confidence interval; MET, metabolic equivalent; TV, television; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for sociodemographic confounders.

Supplementary Table 13. Associations between potential mediators and incident cardiovascular disease adjusted for anxiety disorder or depression

	Anxiety disorder N = 254,695		Depression N = 254,695	
	HR	95% CI	HR	95% CI
MET-minutes/week <1000	1.05	1.00, 1.09	1.04	1.00, 1.09
TV viewing ≥3 hours/day	1.10	1.06, 1.15	1.10	1.06, 1.15
Diet quality score <5	1.08	1.03, 1.12	1.08	1.03, 1.12
Current smoking	1.81	1.71, 1.92	1.80	1.70, 1.91
Sleep duration <7 hours/day	1.13	1.08, 1.18	1.13	1.08, 1.18
Waist-hip ratio ≥0.90 (male) ≥0.85 (female)	1.15	1.10, 1.21	1.15	1.10, 1.21
Body mass index ≥30kg/m2	1.07	1.02, 1.12	1.07	1.02, 1.12
Grip strength <36 Kg (male) <21 Kg (female)	1.11	1.06, 1.16	1.11	1.06, 1.15
SBP ≥140mmHg or medication	1.53	1.46, 1.61	1.53	1.47, 1.61
HbA1c ≥ 48 mmol/mol or medication	1.62	1.50, 1.75	1.62	1.50, 1.75
LDL-c ≥ 4.9 mmol/L or medication	1.12	1.07, 1.18	1.12	1.07, 1.17
CRP >3mg/L	1.25	1.19, 1.31	1.25	1.19, 1.30

N, number; HR, hazard ratio; CI, confidence interval; MET, metabolic equivalent; TV, television; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for anxiety disorder/depression, sociodemographic confounders, and all mediators.

Supplementary Table 14. Effect size estimates and proportions mediated via physical and metabolic factors of the associations between anxiety disorder and depression and incident cardiovascular disease after adjusting for sociodemographic and lifestyle factors

	Anxiety disorder						Depression					
	Natural indirect effect			Proportion mediated			Natural indirect effect			Proportion mediated		
	HR	95% CI		%	95% CI		HR	95% CI		%	95% CI	
Physical factors:												
WHR	1.04	1.02	1.05	8.63	4.34	25.6	1.05	1.04	1.07	9.38	7.14	13.4
BMI	1.02	1.00	1.03	4.18	-0.02	14.5	1.05	1.03	1.06	8.04	5.64	11.2
Grip strength	1.01	1.00	1.02	2.27	0.65	6.70	1.01	1.01	1.02	2.57	1.23	3.90
Metabolic factors:												
SBP	1.03	1.01	1.07	7.91	0.22	32.3	1.02	1.00	1.04	3.47	-0.10	7.70
HbA1c	1.02	1.00	1.05	5.96	0.13	22.7	1.03	1.02	1.05	5.55	2.89	9.30
LDL-c	1.02	1.01	1.03	4.33	1.16	12.7	1.05	1.03	1.05	6.61	4.71	9.50
CRP	1.02	1.01	1.03	5.07	0.71	16.2	1.05	1.04	1.06	8.47	6.44	11.8

HR, hazard ratio; CI, confidence interval; WHR, waist and hip ratio; BMI, body mass index; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for sociodemographic confounders and exposure-affected lifestyle confounders (physical activity, television viewing, diet quality, smoking, and sleep duration).

Supplementary Table 15. Effect size estimates and proportions mediated via metabolic factors of the associations between anxiety disorder and depression and incident cardiovascular disease after adjusting for sociodemographic, lifestyle, and physical factors

	Anxiety disorder						Depression					
	Natural indirect effect			Proportion mediated			Natural indirect effect			Proportion mediated		
	HR	95% CI		%	95% CI		HR	95% CI		%	95% CI	
Metabolic factors:												
SBP	1.04	1.01	1.07	8.29	0.72	33.2	1.03	1.01	1.05	4.56	1.53	8.90
HbA1c	Not estimable			Not estimable			Not estimable			Not estimable		
LDL-c	1.02	1.01	1.03	4.37	1.23	15.0	1.04	1.03	1.34	6.48	4.45	37.5
CRP	1.02	1.01	1.51	5.02	1.51	93.4	Not estimable			Not estimable		

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein
All models were adjusted for sociodemographic confounders, exposure-affected lifestyle confounders (physical activity, television viewing, diet quality, smoking, and sleep duration), and exposure-affected physical confounders (waist and hip ratio, body mass index, and grip strength).

Supplementary Table 16. Associations between anxiety disorder and depression (ascertained through hospital admission data and self-reports) and potential mediators

	Anxiety disorder N = 254,695		Depression N = 254,695	
	RR	95% CI	RR	95% CI
MET-minutes/week <1000	1.12	1.07, 1.18	1.18	1.15, 1.21
TV viewing ≥3 hours/day	1.10	1.07, 1.14	1.09	1.07, 1.11
Diet quality score <5	1.01	0.96, 1.07	1.07	1.04, 1.10
Current smoking	1.34	1.23, 1.46	1.55	1.48, 1.63
Sleep duration <7 hours/day	1.12	1.06, 1.19	1.13	1.09, 1.17
Waist-hip ratio ≥0.90 (male) ≥0.85 (female)	1.10	1.07, 1.14	1.16	1.14, 1.18
Body mass index ≥30kg/m2	1.06	1.00, 1.13	1.31	1.27, 1.36
Grip strength <36 Kg (male) <21 Kg (female)	1.12	1.09, 1.16	1.12	1.10, 1.14
SBP ≥140mmHg or medication	1.02	0.99, 1.05	0.97	0.95, 0.99
HbA1c ≥ 48 mmol/mol or medication	1.04	0.87, 1.25	1.42	1.28, 1.57
LDL-c ≥ 4.9 mmol/L or medication	1.20	1.13, 1.28	1.28	1.24, 1.33
CRP >3mg/L	1.10	1.03, 1.17	1.28	1.24, 1.33

N, number; RR, risk ratio; CI, confidence interval; MET, metabolic equivalent; TV, television; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for sociodemographic confounders.

Supplementary Table 17. Associations between potential mediators and incident cardiovascular disease adjusted for anxiety disorder or depression (ascertained through hospital admission data and self-reports)

	Anxiety disorder N = 254,695		Depression N = 254,695	
	HR	95% CI	HR	95% CI
MET-minutes/week <1000	1.05	1.00, 1.09	1.05	1.00, 1.09
TV viewing ≥3 hours/day	1.10	1.06, 1.15	1.10	1.06, 1.15
Diet quality score <5	1.08	1.03, 1.12	1.08	1.03, 1.12
Current smoking	1.81	1.71, 1.92	1.81	1.71, 1.92
Sleep duration <7 hours/day	1.13	1.08, 1.18	1.13	1.08, 1.18
Waist-hip ratio ≥0.90 (male) ≥0.85 (female)	1.15	1.10, 1.21	1.15	1.10, 1.21
Body mass index ≥30kg/m2	1.07	1.02, 1.12	1.07	1.02, 1.12
Grip strength <36 Kg (male) <21 Kg (female)	1.11	1.06, 1.16	1.11	1.06, 1.16
SBP ≥140mmHg or medication	1.53	1.46, 1.61	1.53	1.46, 1.61
HbA1c ≥ 48 mmol/mol or medication	1.62	1.50, 1.75	1.62	1.50, 1.75
LDL-c ≥ 4.9 mmol/L or medication	1.12	1.07, 1.18	1.12	1.07, 1.18
CRP >3mg/L	1.25	1.19, 1.31	1.25	1.19, 1.31

N, number; HR, hazard ratio; CI, confidence interval; MET, metabolic equivalent; TV, television; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for anxiety disorder/depression (ascertained through hospital admission data and self-reports), sociodemographic confounders, and all mediators.

Supplementary Table 18. Effect size estimates and proportions mediated via lifestyle, physical and metabolic factors of the associations between anxiety disorder and depression (ascertained through hospital admission data and self-reports) and incident cardiovascular disease

	Anxiety disorder						Depression					
	Natural indirect effect			Proportion mediated			Natural indirect effect			Proportion mediated		
	HR	95% CI		%	95% CI		HR	95% CI		%	95% CI	
Lifestyle factors:												
Physical activity	1.00	1.00	1.01	2.88	0.97	11.5	1.01	1.00	1.01	5.13	2.02	18.3
TV viewing	1.01	1.01	1.02	8.27	2.30	26.5	1.00	1.00	1.01	3.03	1.07	13.2
Diet quality	1.00	1.00	1.00	0.53	-2.93	5.70	1.01	1.01	1.02	8.98	4.30	32.7
Smoking	1.03	1.02	1.04	16.1	5.23	56.6	1.05	1.04	1.05	Not estimable		
Sleep duration	1.01	1.00	1.01	2.96	0.46	11.4	1.01	1.00	1.01	3.92	1.66	14.4
Physical factors:												
WHR	1.03	1.02	1.05	14.9	7.08	47.7	1.04	1.03	1.05	26.7	15.2	75.8
BMI	1.01	1.00	1.01	3.21	-1.77	11.0	1.03	1.02	1.03	18.1	10.1	55.0
Grip strength	1.01	0.00	1.01	5.23	2.03	21.0	1.01	1.01	1.01	6.50	3.05	21.3
Metabolic factors:												
SBP	1.01	1.00	1.02	5.91	-6.23	23.1	0.99	0.98	1.00	Not estimable		
HbA1c	1.00	0.99	1.01	1.47	-8.82	11.9	1.02	1.01	1.03	13.9	6.28	47.3
LDL-c	1.02	1.01	1.03	10.5	3.76	37.2	1.03	1.02	1.03	17.4	9.34	54.3
CRP	1.01	1.00	1.02	6.08	-1.20	24.3	1.03	1.02	1.03	19.2	10.6	65.7

HR, hazard ratio; CI, confidence interval; TV, television; WHR, waist and hip ratio; BMI, body mass index; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for sociodemographic confounders.

Supplementary Table 19. Effect size estimates and proportions mediated via physical and metabolic factors of the associations between anxiety disorder and depression (ascertained through hospital admission data and self-reports) and incident cardiovascular disease after adjusting for sociodemographic and lifestyle factors

	Anxiety disorder						Depression					
	Natural indirect effect			Proportion mediated			Natural indirect effect			Proportion mediated		
	HR	95% CI		%	95% CI		HR	95% CI		%	95% CI	
Physical factors:												
WHR	1.02	1.01	1.02	8.88	4.98	36.7	1.03	1.02	1.03	17.0	10.1	47.0
BMI	1.00	1.00	1.01	2.37	-0.13	12.6	1.02	1.02	1.03	15.3	9.33	46.4
Grip strength	1.01	1.00	1.01	3.74	1.83	15.9	1.01	1.00	1.01	4.67	2.33	13.2
Metabolic factors:												
SBP	1.01	1.00	1.02	3.89	-1.45	22.7	0.99	0.98	1.00	Not estimable		
HbA1c	1.00	1.00	1.01	0.46	-3.00	8.80	1.01	1.01	1.02	9.32	4.81	32.3
LDL-c	1.01	1.01	1.02	6.78	3.55	29.5	1.02	1.01	1.02	11.7	7.40	36.2
CRP	1.01	1.00	1.01	4.23	1.61	18.9	1.02	1.02	1.03	14.5	8.42	39.4

HR, hazard ratio; CI, confidence interval; WHR, waist and hip ratio; BMI, body mass index; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for sociodemographic confounders and exposure-affected lifestyle confounders (physical activity, television viewing, diet quality, smoking, and sleep duration).

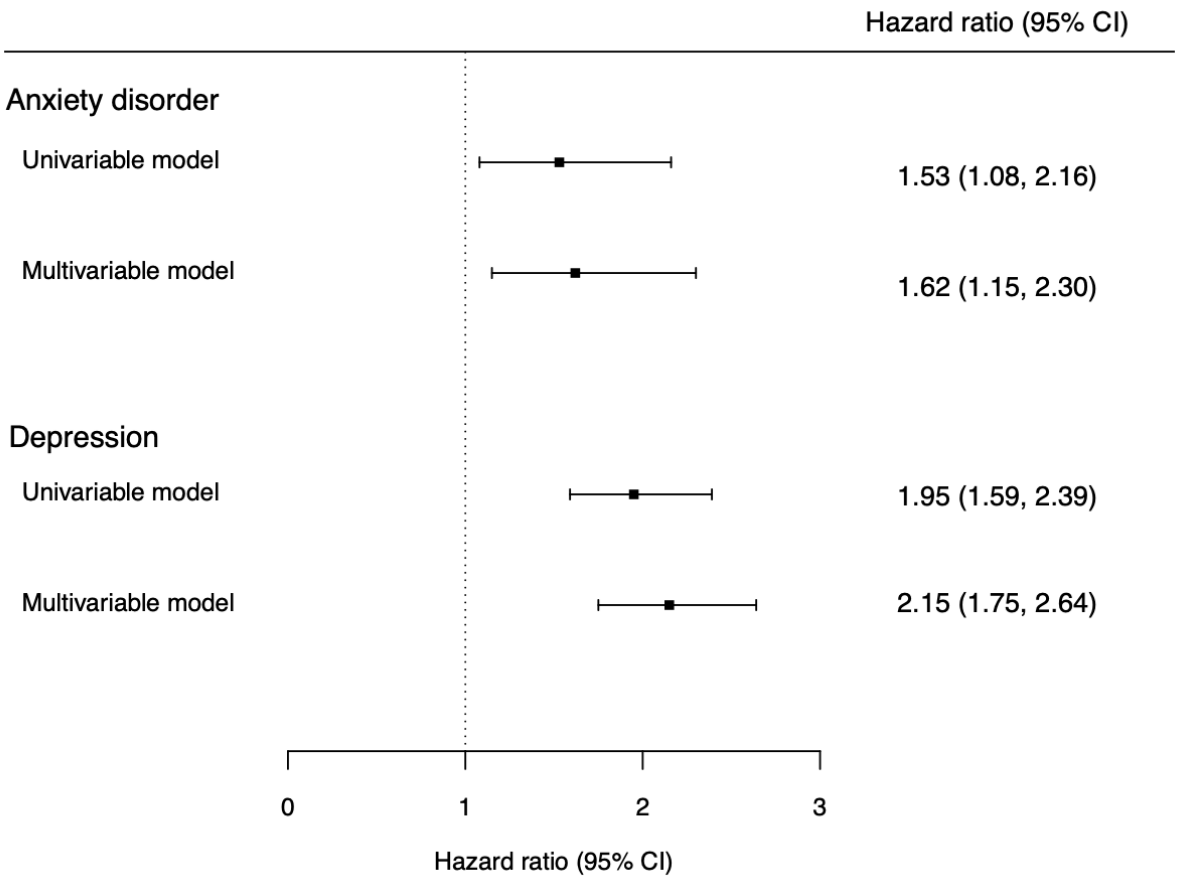
Supplementary Table 20. Effect size estimates and proportions mediated via metabolic factors of the associations between anxiety disorder and depression (ascertained through hospital admission data and self-reports) and incident cardiovascular disease after adjusting for sociodemographic, lifestyle, and physical factors

	Anxiety disorder						Depression					
	Natural indirect effect			Proportion mediated			Natural indirect effect			Proportion mediated		
	HR	95% CI		%	95% CI		HR	95% CI		%	95% CI	
Metabolic factors:												
SBP	1.01	1.00	1.02	3.22	-1.53	18.4	0.99	0.99	1.00	Not estimable		
HbA1c	Not estimable			Not estimable			Not estimable			Not estimable		
LDL-c	1.01	1.06	1.02	6.40	2.88	19.9	1.02	1.01	1.02	10.6	6.08	29.5
CRP	1.01	0.96	1.06	3.47	-7.02	63.4	1.02	1.01	1.60	13.7	7.48	95.3

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; CRP, C-reactive protein

All models were adjusted for sociodemographic confounders, exposure-affected lifestyle confounders (physical activity, television viewing, diet quality, smoking, and sleep duration), and exposure-affected physical confounders (waist and hip ratio, body mass index, and grip strength).

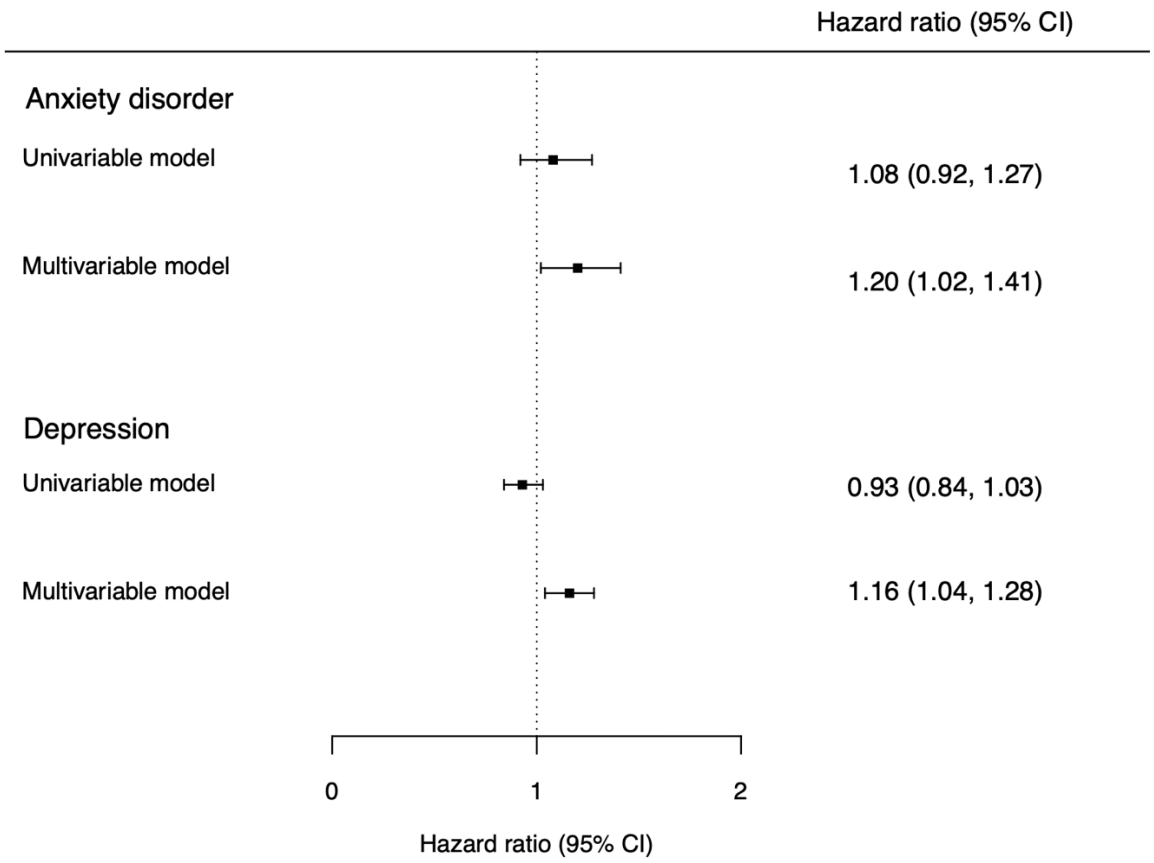
Supplementary Figure 2. Associations between anxiety disorder and depression and incident cardiovascular disease



CI, confidence interval

Multivariable models were adjusted for sociodemographic confounders.

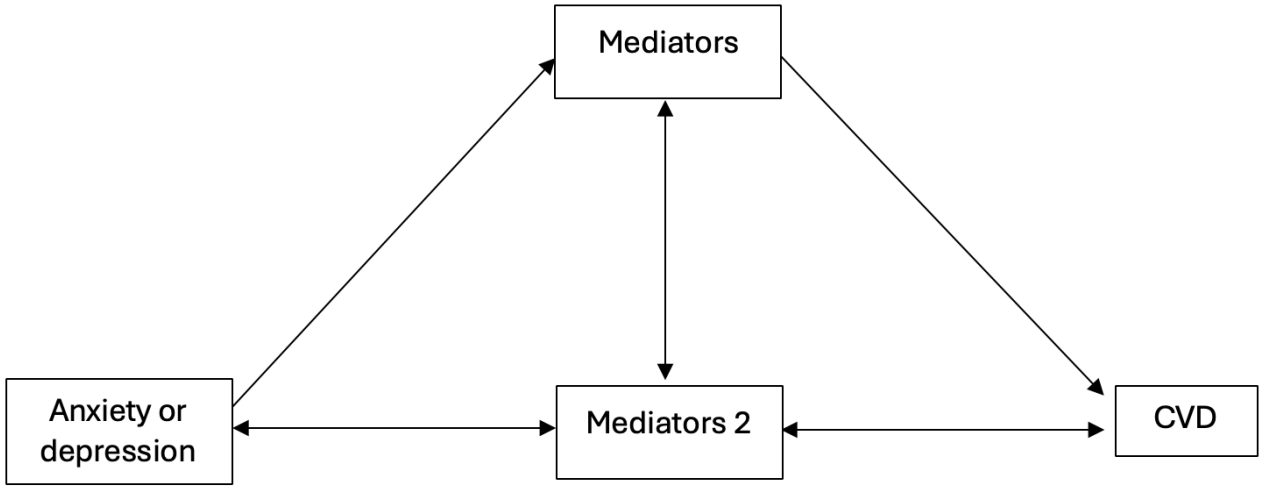
Supplementary Figure 3. Associations between anxiety disorder and depression (ascertained through hospital admission data and self-reports) and incident cardiovascular disease



CI, confidence interval

Multivariable models were adjusted for sociodemographic confounders.

Supplementary Figure 4. Potential pathways between anxiety disorder and depression and incident cardiovascular



CVD, cardiovascular disease

Mediators 2 are mediators that have any bidirectional associations with anxiety/depression, other mediators, or cardiovascular disease. Our mediation analyses assumed no such bidirectional associations, provided anxiety/depression, mediators (e.g., smoking), mediators 2 (e.g., blood pressure), and cardiovascular disease occurred in turn. The direct effect of anxiety/depression on cardiovascular disease was omitted from the diagram for simplicity.

Chapter 5 Refining PREVENT prediction models for 10-year risk of cardiovascular disease using measures of anxiety and depression

5.1 Preface

In Chapter 2, I found that anxiety and depression were associated with incident CVD, suggesting that these conditions may help predict CVD onset. This chapter extends this finding by investigating their additive predictive value to an existing CVD risk score. The ability to identify individuals at high risk of developing CVD enables physicians to target prevention. Therefore, inclusion of MHCs may not only improve overall identification of people of highest risk but also, specifically, mitigate the burden arising from clustering of MHCs and CVD.

There are several established CVD risk scores that are used to predict first onset of CVD, such as SCORE2 (SCORE2 working group and ESC Cardiovascular risk collaboration, 2021), QRISK3 (Hippisley-Cox et al., 2017), the American Heart Association (AHA) pooled cohort equation (Goff et al., 2014) and PREVENT (Khan et al., 2024) in the general population. However, few of these scores have included mental health predictors and the additive predictive value of anxiety and depression remains unknown. Only QRISK3 includes diagnosis of severe MHCs including psychosis, schizophrenia, and bipolar disorder although their additive predictive value is unclear. I selected PREVENT, which is the most recent CVD risk score developed by AHA in 2024, because of its key novelties. PREVENT predictors include a biomarker of kidney function, in addition to traditional metabolic biomarkers, and the outcomes it was developed to predict include both heart failure and atherosclerotic cardiovascular events. These key features are timely and increasingly important in the prevention of CVD given the growing burden of heart failure and expanding clinical application of sodium–glucose cotransporter-2 inhibitors.

Therefore, in this chapter, I investigate a range of measures of anxiety disorder and depression and their combinations with the aim of systematically examining whether including these improves the prediction performance of PREVENT.

5.2 Published Manuscript

ABSTRACT

Background: Anxiety and depression are associated with cardiovascular disease (CVD). We aimed to investigate whether adding measures of anxiety and depression to the American Heart Association Predicting Risk of Cardiovascular Disease Events (PREVENT) predictors improves the prediction of CVD risk.

Methods: We developed and internally validated risk prediction models using 60% and 40% of the cohort data from the UK Biobank, respectively. Mental health predictors included baseline depressive symptom score and self-reported and record-based history of anxiety and depression diagnoses before the baseline. We identified CVD events using hospital admission and death certificate data over a 10-year period from baseline. We determined incremental predictive values by adding the mental health predictors to the PREVENT predictors using Harrell's C-indices, sensitivity, specificity, and net reclassification improvement indices. We used a threshold of 10-year risk of incident CVD of greater than 5%.

Results: Of the 502 366 UK Biobank participants, we included 195 489 in the derivation set and 130 326 in the validation set. In the validation set, the inclusion of all mental health measures, except self-reported anxiety, produced a very modest increase in the C-index and specificity while sensitivity remained unchanged. Among these mental health predictors, depressive symptom score produced the greatest improvements in both C-index (difference of 0.005, 95% confidence interval 0.004–0.006) and specificity (difference of 0.89%). Depressive symptom score showed similar small improvements in female and male validation sets.

Interpretation: Our findings suggest that the inclusion of measures of depression and anxiety in PREVENT would have little additional effect on the risk classification of CVD at the population level and may not be worthwhile.

BACKGROUND

The global prevalence of cardiovascular disease (CVD) exceeded half a billion people in 2019 (Roth et al., 2020). Risk assessment plays a key role in targeting prevention to reduce this burden of disease. New CVD risk prediction equations — the American Heart Association Predicting Risk of Cardiovascular Disease

Events (PREVENT) equations — were developed by integrating predictors relevant to cardiovascular, kidney, and metabolic risks (e.g., obesity, diabetes, chronic kidney disease) (Khan et al., 2024, Khan et al., 2023) because these conditions increasingly cluster together and are associated with CVD development, including heart failure, especially in racial and ethnic minority groups (Khan et al., 2024, Khan et al., 2023).

Anxiety and depression are the most common mental health conditions worldwide (GBD 2019 Mental Disorders Collaborators, 2022). Each of these conditions has increased in prevalence by around 50% over the past 20 years and they are likely to increase the risk of CVD (GBD 2019 Mental Disorders Collaborators, 2022). Meta-analyses showed around 50% excess risk of incident CVD among people with anxiety or depression (Batelaan et al., 2016, Van der Kooy et al., 2007), which remained after adjusting for traditional CVD risk factors such as smoking, diabetes, and hypertension (Batelaan et al., 2016, Nicholson et al., 2006). We previously corroborated these findings using self-reported and record-based histories of anxiety and depression diagnoses and further showed that these 2 mental health conditions were independently associated with CVD (Nakada et al., 2023). Importantly, baseline depression symptoms were also associated with CVD (Harshfield et al., 2020).

Incorporating these various measures of anxiety and depression in PREVENT may detect high-risk groups that were overlooked by established predictors. We sought to determine whether including these mental health conditions with the PREVENT predictors improved the prediction of CVD risk.

METHODS

Study design: We developed and internally validated prediction models of 10 year risk of CVD to investigate whether adding measures of anxiety and depression to the PREVENT predictors improves performance.

In 2024, the American Heart Association's PREVENT equations were developed to predict the risk of first CVD event for the general adult population aged 30–79 years in the United States (Khan et al., 2024). The PREVENT equations were

based on a large contemporary sample and included heart failure and kidney function as a CVD outcome and predictor, respectively, unlike previous pooled cohort equations. Calculated risks from PREVENT are intended to inform risk discussions between patients and clinicians and help guide therapeutic strategies. Acceptable risk thresholds are expected to be defined by future guidelines (Khan et al., 2023). In addition to the total CVD prediction model and core predictors, the PREVENT equations include optional models (e.g., atherosclerotic CVD, heart failure) and predictors (e.g., social deprivation index, glycated hemoglobin A1c [HbA1c], urine albumin:creatinine ratio). Detailed information about the PREVENT equations can be found elsewhere (Khan et al., 2024, Khan et al., 2023).

Data sources: We developed prediction models using cohort data from the UK Biobank. Between 2007 and 2010, UK Biobank recruited more than 500 000 participants (a 5.5% response rate) from the general population aged 40–69 years (Sudlow et al., 2015, Fry et al., 2017). Participants were asked to undergo a baseline assessment at 1 of 22 centres across England, Scotland, and Wales. With the consent of participants, UK Biobank linked the baseline data to routine National Health Service databases to provide medical history and follow-up information on health events (UK Biobank, 2007, UK Biobank, 2020). The National Health Service Information Centre (England and Wales) and the National Health Service Central Register (Scotland) provided death certificate data; the Hospital Episode Statistics (England and Wales) and the Scottish Morbidity Records (Scotland) provided hospital admission data. Data were linked by UK Biobank staff using the National Health Service number (England and Wales) and Community Health number (Scotland).

In our study, we excluded participants if they had a history of CVD before the baseline assessment or missing values for the predictors. We also considered participants to have missing values if they had extreme clinical values for systolic blood pressure (< 90 mm Hg or > 200 mm Hg), total cholesterol (< 130 mg/dL or > 320 mg/dL), high-density-lipoprotein cholesterol (HDL-C, < 20 mg/dL or > 100 mg/dL), or estimated glomerular filtration rate (eGFR, < 0.1 or > 99.9 percentiles).

Outcome: The outcome was incident CVD, comprising coronary artery disease, stroke, and heart failure (International Classification of Diseases, 10th Revision [ICD-10] codes I20–25, I42.0, I42.6, I42.7, I42.9, I50, I60–64, or I110). Non-CVD death was a competing risk. Death certificate data were available up to November 2022. The hospital admission data were available up to October 2022 for England, May 2022 for Wales, and August 2022 for Scotland. Our analysis was restricted to a 10-year follow -up period. We censored participants at the end of the 10-year follow-up period unless they developed CVD or were censored earlier because of non-CVD death.

Predictors: We selected predictors for mental health conditions (depressive symptom score and self-reported and recorded history of anxiety and depression diagnoses) and those used in the PREVENT equations (age, sex, systolic blood pressure, HDL-C, non-HDL-C, eGFR, diabetes, current smoking, antihypertensive treatment, and statin treatment). Depressive symptom score was derived from the 4 items of the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001, Löwe et al., 2010), self-reported at the baseline assessment using a touchscreen. The questionnaire asked, “Over the past 2 weeks, how often have you felt down, depressed or hopeless?”; “Over the past 2 weeks, how often have you had little interest or pleasure in doing things?”; “Over the past 2 weeks, how often have you felt tense, fidgety or restless?”; and “Over the past 2 weeks, how often have you felt tired or had little energy?”. For each question, participants selected either “not at all” (scored 0), “several days” (scored 1), “more than half of the days” (scored 2), or “nearly every day” (scored 3). Finally, the answers were summed so that the total score ranged from 0 to 12, with higher scores indicating more severe conditions. Self-reported anxiety and depression diagnoses were confirmed during a verbal interview at the baseline assessment if participants responded to a touchscreen questionnaire that they had been told by a doctor that they had a serious illness or disability. In the interview, a trained nurse asked about past and current mental health conditions and coded these using an ICD-10 coding tree (UK Biobank, 2012). Recorded anxiety and depression diagnoses before the baseline assessment were ascertained through record linkage to hospital admission data and defined as an ICD-10 code of F40–43 and F32–33, respectively; therefore, this captured only people admitted to hospital for anxiety or depression.

Age, sex, and current smoking status were self-reported by participants using a touchscreen questionnaire at the baseline assessment. Age was treated as a continuous variable, while sex and current smoking were coded as binary variables (male or female and yes or no, respectively). A trained nurse measured systolic blood pressure at the baseline assessment. Total cholesterol and HDL-C were measured on baseline blood samples and non-HDL-C was calculated by subtracting HDL-C from total cholesterol. Creatinine level was measured using baseline blood samples and used to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation (Inker et al., 2021). Systolic blood pressure, HDL-C, non-HDL-C, and eGFR were continuous variables. Diabetes was defined as an HbA1c level of 6.5% or higher on baseline blood samples, self-reported use of glucose -lowering medication, or self-reported physician diagnosis, and was categorized as yes or no. Antihypertensive treatment and statin treatment were self-reported using the baseline touchscreen questionnaire and categorized as yes or no.

Statistical analyses: We randomly split our data set into the derivation set (60%) and the validation set (40%). In the derivation set, we evaluated the associations between the predictors and the outcome by single-predictor and multivariable models, including the PREVENT predictors with each of the mental health predictors. We also included anxiety, depression, and depressive symptom score together to assess whether associations remained after adjusting for other mental health predictors.

In the validation set, we evaluated and compared incremental predictive values of the mental health predictors with the PREVENT predictors using Harrell's C-index; sensitivity, specificity, and positive and negative predictive values; and net reclassification indices by applying the models developed in the derivation set (Supplementary Table 21). We estimated the 10-year CVD risk from these coefficients and 10-year baseline survival (Supplementary Table 21). We assessed calibration using the calibration slope and the expected:observed event probability ratio. We calculated all predictive performance measures (except the C-index, which does not require a risk threshold) by setting a threshold of 10-year risk of incident CVD greater than 5% because this is the minimum level

of risk at which to consider statin therapy initiation, as recommended by the 2019 American College of Cardiology and American Heart Association guideline (Arnett et al., 2019). We also evaluated incremental predictive values separately in male and female validation sets.

We used Cox proportional hazards models to calculate coefficients and 95% confidence intervals (CIs) associated with each predictor of CVD. We calculated the 95% CIs of the C-index and net reclassification improvement indices using the variance and percentile bootstrap method, respectively. In subsequent analyses, we used a penalized spline basis for depressive symptom scores to assess whether considering nonlinearity improved the predictive ability. We used interaction terms of anxiety and depression to assess their joint contribution to prediction. For descriptive purposes, we calculated events per parameter for both the derivation data set (n = 1052) and validation data set (n = 709) by including all predictors and confirmed these to well exceed the conventional threshold of 10.

We evaluated incremental predictive values of interaction between mental health and PREVENT predictors in 2 stages. First, a mental health predictor and each of the PREVENT predictors were used to create interaction terms. We compared models including these interaction terms and selected the one with the lowest Akaike Information Criterion (AIC) result. We then examined the predictive performance for those selected models.

In sensitivity analyses, we repeated the main analysis using another random split of participants between the derivation and validations sets and again using imputed data. Despite the small proportions of missing values of all data in our study (3.8%), we compared those included and excluded from our analysis and examined whether data imputation changed our main results using missForest (Stekhoven and Bühlmann, 2012, Li et al., 2024). Lastly, we evaluated the predictive performance of the publicly available PREVENT equations after logistic calibration and model revisions. We adjusted the intercept and all predictor regression coefficients of publicly available PREVENT equations by 1 overall adjustment factor (i.e., calibration slope) by fitting a new logistic regression model in our data set including the linear predictor as the only

predictor. We revised the model by fitting logistic regression models, including each of the mental health conditions in addition to the linear predictor. We conducted all analyses using R version 4.0.2 with the survival (3.3–1), compare (1.3.2), nricens (1.6), pROC (1.18.5), and missForest (1.5) packages.

Ethics approval: The original UK Biobank study was approved by the North-West Multi-Centre Research Ethics Committee (no. 11/NW/0382). The investigation conformed to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants included in the study. We conducted our study under the UK Biobank application number 71392.

RESULTS

Of the 502 366 UK Biobank participants, we excluded 176 551 participants: 164 803 because of missing predictor values and 11 748 because of history of CVD before the baseline assessment. Consequently, we included 325 815 participants in the analyses (Figure 11). In the derivation set, 195 489 participants had 15 787 CVD events over a mean follow-up time of 9.5 years. Participants who had a CVD event were older and more likely to be male and current smokers (Table 9). They had higher systolic blood pressure and lower eGFR and were more likely to have diabetes, take antihypertensive or statin treatment, and have mental health conditions. In the validation set, 130 326 participants had 10 639 CVD events over a mean follow-up time of 9.5 years. Overall, the baseline characteristics of participants in the validation set were similar to those of the derivation set.

Figure 13. Flowchart of the participant selection process

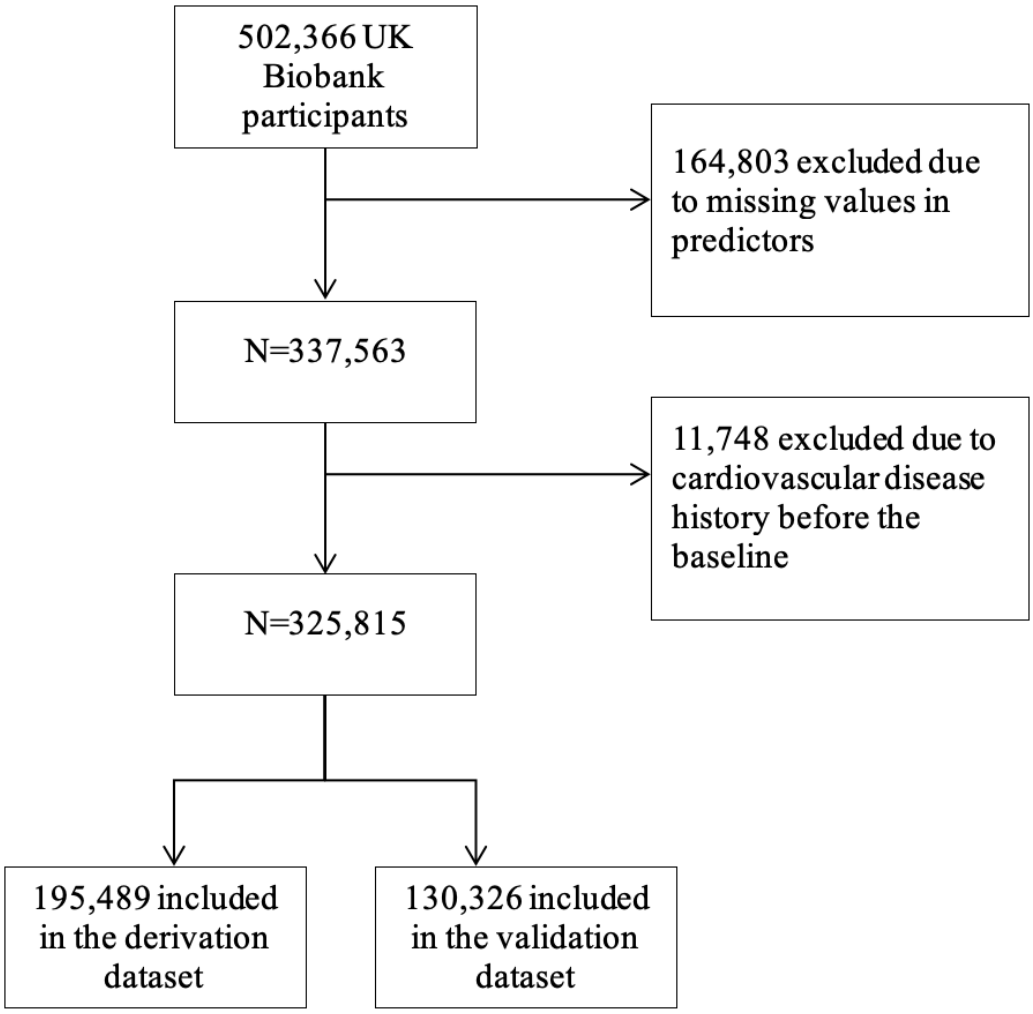


Table 9. Participant baseline characteristics

	Derivation set (60% of the participants)			Validation Set (40% of the participants)		
	Overall (N = 195,489) N (%)	No CVD (N = 179,702) N (%)	CVD (N = 15,787) N (%)	Overall (N = 130,326) N (%)	No CVD (N = 119,687) N (%)	CVD (N = 10,639) N (%)
Age (years), mean (SD)	56.2 (8.09)	56.0 (8.07)	61.8 (6.37)	56.3 (8.10)	55.9 (8.10)	60.6 (6.68)
Sex						
Female	105,472 (53.95)	99,601 (55.43)	5,871 (37.19)	69,934 (53.66)	66,062 (55.20)	3,872 (36.39)
Male	90,017 (46.05)	80,101 (44.57)	9,916 (62.81)	60,392 (46.34)	53,625 (44.80)	6,767 (63.61)
Systolic blood pressure (mmHg), mean (SD)	137.5 (18.08)	137.0 (18.00)	143.1 (18.11)	137.6 (18.13)	137.1 (18.03)	143.1 (18.36)
HDL-c (mmol/l), mean (SD)	1.4 (0.36)	1.5 (0.36)	1.3 (0.34)	1.4 (0.36)	1.5 (0.36)	1.3 (0.34)
Non-HDL-c (mmol/l), mean (SD)	4.3 (0.97)	4.3 (0.97)	4.2 (1.05)	4.3 (0.98)	4.3 (0.97)	4.2 (1.06)
eGFR (ml/min/1.73 m2), mean (SD)	94.5 (12.59)	94.8 (12.45)	91.0 (13.54)	94.5 (12.59)	94.9 (12.43)	90.8 (13.66)
Diabetes	9,531 (4.88)	7,677 (4.27)	1,854 (11.74)	6,430 (4.93)	5,159 (4.31)	1,271 (11.95)
Smoking	20,056 (10.26)	17,883 (9.95)	2,173 (13.76)	13,413 (10.29)	11,955 (9.99)	1,458 (13.70)
Anti-hypertensive treatment	36,163 (18.50)	30,212 (16.81)	5,951 (37.70)	24,175 (18.55)	20,074 (16.77)	4,101 (38.55)
Statin treatment	28,406 (14.53)	22,916 (12.75)	5,490 (34.78)	19,101 (14.66)	15,370 (12.84)	3,731 (35.07)
Depressive symptom score (0–12), mean (SD)	1.6 (2.08)	1.6 (2.05)	1.8 (2.33)	1.6 (2.08)	1.5 (2.06)	1.8 (2.36)
Self-reported anxiety disorder	3,301 (1.69)	2,967 (1.65)	334 (2.12)	2,311 (1.77)	2,068 (1.73)	243 (2.28)
Self-reported depression	10,767 (5.51)	9,735 (5.42)	1,032 (6.54)	7,205 (5.53)	6,495 (5.43)	710 (6.67)
Recorded anxiety disorder	585 (0.30)	495 (0.28)	90 (0.57)	471 (0.36)	395 (0.33)	76 (0.71)
Recorded depression	1,319 (0.67)	1,116 (0.62)	203 (1.29)	953 (0.73)	807 (0.67)	146 (1.37)

Note: CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-C = high density-lipoprotein cholesterol, SD = standard deviation.

All mental health predictors were associated with CVD in the single predictor models, and this association remained after adjusting for the PREVENT predictors (Table 10). When additionally adjusting for self-reported or recorded anxiety and depression and depressive symptom score together, the magnitude of the association between depressive symptom score and CVD changed little while the associations with anxiety and depression were attenuated. In the validation set, inclusion of all mental health predictors, except for self-reported anxiety, modestly increased the C-index compared with the original PREVENT predictors (Table 11 and Supplementary Table 22). The largest improvements were observed in models that included depressive symptom score, whether included in a linear (C-index difference 0.00502, 95% CI 0.00393–0.00611) or nonlinear (C-index difference 0.00516, 95% CI 0.00403–0.00629) model. This result was only slightly improved by adding histories of anxiety and depression together. The inclusion of depressive symptom score showed the largest, but nonetheless modest, improvement in specificity (0.89%); sensitivity remained unchanged with inclusion of any of the mental health predictors (Table 12). Consequently, the model including depressive symptom score yielded the largest overall (1.14, 95% CI 0.69–1.55) and nonevent (0.89, 95% CI 0.74–1.02) net reclassification indices (Table 13). Nonlinear modelling of depressive symptoms changed the results little (Supplementary Tables 23 and 24). All main models were well calibrated (Supplementary Table 25).

Table 10. Associations of Predicting Risk of Cardiovascular Disease Events (PREVENT) predictors and mental health conditions

	Single predictor models		PREVENT		PREVENT + self-reported or recorded anxiety and depression*		PREVENT + depressive symptom score + self-reported anxiety and depression		PREVENT + depressive symptom score + recorded anxiety and depression	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Depressive symptom score (0–12) †	1.06	1.05, 1.06	1.09	1.08, 1.10			1.09	1.08, 1.09	1.09	1.08, 1.09
Self-reported anxiety disorder	1.27	1.14, 1.42	1.34	1.20, 1.50	1.26	1.13, 1.40	1.14	1.02, 1.28		
Self-reported depression	1.21	1.14, 1.29	1.34	1.26, 1.43	1.32	1.24, 1.41	1.08	1.01, 1.15		
Recorded anxiety disorder	2.03	1.65, 2.50	2.00	1.62, 2.46	1.73	1.40, 2.14			1.53	1.24, 1.90
Recorded depression	2.03	1.77, 2.34	1.92	1.67, 2.21	1.81	1.57, 2.09			1.51	1.31, 1.74

Note: CI = confidence interval, HR = hazard ratio

*Self-reported conditions and recorded conditions were fitted separately (i.e., self-reported anxiety and depression included in 1 model, and recorded anxiety and depression in another model).

†Hazard ratio for depressive symptom score was expressed per 1-point increase.

Table 11. Comparisons of C-indices between Predicting Risk of Cardiovascular Disease Events (PREVENT) and models including mental health conditions in the validation set

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.736	0.732 to 0.741		
PREVENT + Depressive symptom score	0.741	0.737 to 0.746	0.00502	0.00393 to 0.00611
PREVENT + Self-reported anxiety disorder	0.737	0.732 to 0.741	0.00022	-0.00003 to 0.00046
PREVENT + Self-reported depression	0.737	0.733 to 0.742	0.00096	0.00052 to 0.00140
PREVENT + Self-reported anxiety disorder and depression	0.738	0.733 to 0.742	0.00110	0.00062 to 0.00157
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	0.742	0.737 to 0.746	0.00519	0.00409 to 0.00629
PREVENT + Recorded anxiety disorder	0.737	0.732 to 0.741	0.00031	0.00003 to 0.00059
PREVENT + Recorded depression	0.737	0.733 to 0.742	0.00079	0.00037 to 0.00120
PREVENT + Recorded anxiety disorder and depression	0.737	0.733 to 0.742	0.00101	0.00054 to 0.00147
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	0.742	0.738 to 0.746	0.00558	0.00444 to 0.00672

Note: CI = confidence interval.

*Table 12. Sensitivity, specificity, and positive and negative predictive values of Predicting Risk of Cardiovascular Disease Events (PREVENT) and models including mental health conditions in the validation set**

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	86.90	45.23	12.51	97.46
PREVENT + Depressive symptom score	87.14	46.13	12.73	97.55
PREVENT + Self-reported anxiety disorder	86.82	45.27	12.51	97.44
PREVENT + Self-reported depression	86.90	45.40	12.55	97.46
PREVENT + Self-reported anxiety disorder and depression	86.96	45.43	12.56	97.48
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	87.08	46.20	12.73	97.54
PREVENT + Recorded anxiety disorder	86.85	45.27	12.52	97.45
PREVENT + Recorded depression	86.92	45.32	12.53	97.46
PREVENT + Recorded anxiety disorder and depression	86.92	45.35	12.54	97.47
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	87.12	46.18	12.73	97.55

Note: NPV = negative predictive value, PPV = positive predictive value.

*We calculated these results using a 5% threshold of 10-year risk of cardiovascular disease.

Table 13. Net reclassification indices in the validation set for models including mental health conditions in addition to Predicting Risk of Cardiovascular Disease Events (PREVENT) predictors

	$NRI^{0.05*}$	95% CI	$NRI_e^{0.05*}$	95% CI	$NRI_{ne}^{0.05*}$	95% CI
PREVENT + Depressive symptom score	1.14	0.69 to 1.55	0.25	-0.14 to 0.60	0.89	0.74 to 1.02
PREVENT + Self-reported anxiety disorder	-0.04	-0.13 to 0.09	-0.07	-0.16 to 0.04	0.03	0.00 to 0.07
PREVENT + Self-reported depression	0.16	-0.03 to 0.37	0.00	-0.19 to 0.22	0.15	0.08 to 0.22
PREVENT + Self-reported anxiety disorder and depression	0.24	0.07 to 0.47	0.06	-0.12 to 0.30	0.18	0.11 to 0.25
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	1.13	0.69 to 1.56	0.18	-0.21 to 0.55	0.95	0.79 to 1.08
PREVENT + Recorded anxiety disorder	-0.01	-0.08 to 0.07	-0.05	-0.12 to 0.03	0.03	0.00 to 0.06
PREVENT + Recorded depression	0.10	-0.03 to 0.23	0.03	-0.10 to 0.15	0.07	0.03 to 0.11
PREVENT + Recorded anxiety disorder and depression	0.14	0.01 to 0.28	0.02	-0.11 to 0.16	0.11	0.07 to 0.15
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	1.15	0.71 to 1.58	0.22	-0.17 to 0.61	0.93	0.78 to 1.06

Note: e = event, ne = nonevent, CI = confidence interval, NRI = net reclassification index.

*We calculated NRIs using a 5% cut-off of 10-year cardiovascular disease risk.

The sex-specific prediction performance evaluations are shown in Supplementary Tables 26–31. Generally, the pattern was consistent, whereby the depressive symptom score, in either linear or nonlinear form, produced modest improvements in the C-index and specificity.

Based on the AIC, we selected 5 models that included an interaction term of mental health and PREVENT predictors (Supplementary Table 32). The predictive performance of these selected models were modest and similar to those without interaction terms (Supplementary Tables 33 and 34).

In sensitivity analyses, repeating the analysis with another random split yielded results consistent with those of our main analysis (Supplementary Tables 35–37). Comparing characteristics of included and excluded participants, we found that excluded participants were more likely to be female, have diabetes, be current smokers, and be taking antihypertensive and statin treatments (Supplementary Table 38). Predictors with the most missing data were total cholesterol (and therefore, non-HDL-C) and HDL-C (Supplementary Table 39). Overall, the analyses based on imputed data yielded results consistent with those of our main analysis (Supplementary Tables 40–43). Finally, adding mental health conditions to the PREVENT equations after logistic calibration led to modest improvements in the area under the curve overall, with the greatest improvement observed for the model with depressive symptom score (Supplementary Table 44).

INTERPRETATIONS

We found that the depressive symptom score was associated with CVD after adjusting for the PREVENT predictors, as well as history of anxiety and depression. Including the depressive symptom score showed the greatest, but still very modest, improvement in the performance of the model with PREVENT predictors across all validation sets (overall and by sex) in terms of C-index and specificity. From our findings, models including depressive symptom score were more likely to differentiate those at higher risk of CVD from those at lower risk and, in line with American College of Cardiology and American Heart Association prevention guideline, for every 1000 people at lower risk, about 9 would no longer be incorrectly classified as high risk. This suggests that the inclusion of

depression and anxiety in PREVENT equations would have relatively little additional effect on the risk classification of CVD at the population level and may not be worthwhile.

However, according to the American Heart Association, new CVD risk predictors should be specific markers that identify a targeted therapeutic pathway or actionable response and be routinely available in primary care settings (Khan et al., 2024, Khan et al., 2023). In keeping with this recommendation, the depressive symptom score can help identify previously undiagnosed depression and serves as a measure of the severity of the symptom; depression can be managed using a range of interventions such as antidepressants, psychotherapy, and physical exercise (Levkovitz et al., 2011, Cuijpers et al., 2014, Noetel et al., 2024). Importantly, the depressive symptom score could be readily available from reliable information, at relatively low cost and without requiring any invasive procedure, using the 4 items of PHQ-9, in keeping with guideline recommended routine screening in primary care (Barry et al., 2023) and could therefore be fairly easily considered when considering CVD risk prevention, despite its moderate contribution. Among many self-report tools (e.g., the Beck Depression Inventory), PHQ-9 has been validated most often (El-Den et al., 2018, Levis et al., 2019), and an ultra-short form of this tool, the 4-item PHQ, would be convenient and acceptable in primary care settings, given the demands on providers' time (Klinkman, 1997, Williams, 1998, Kroenke, 1997).

Although the lack of evidence for PREVENT hampers direct comparisons, 2 studies have given relatively consistent findings with our study by investigating the addition of common mental health conditions to CVD risk prediction. A score developed by machine learning using data from a single-centre survey of people with type 2 diabetes from 1 institution in China — which included self-rated anxiety and depression, as well as traditional CVD risk factors — showed high discrimination (Chu et al., 2021). This study also found that anxiety and depression ranked in the top 5 predictors based on mean impact values. A 2023 preprint study using UK Biobank data showed that some general mental health measures, such as anxious feeling and insomnia, were in the top 5 of 200 predictors of CVD risk based on a discrimination measure (Dziopa et al., 2023).

Limitations: We developed our models using the UK Biobank cohort data; participants in this cohort are more likely to be White, affluent, and healthy than the general population of the United Kingdom (Fry et al., 2017). Before generalizing our findings to the UK population or other populations, further validation should be conducted. We split data into derivation and validation sets, which reduced sample size. However, we confirmed that events per parameter exceeded the conventional threshold. We based results on the minimum risk threshold for considering statin therapy initiation as per the American College of Cardiology and American Heart Association prevention guideline because, to date, no guidelines have been tailored to the PREVENT equations. As these results are sensitive to the defined risk threshold, this should be re-evaluated in future guidelines. Using recorded anxiety and depression diagnoses identified only a small number of participants, likely because this captured only severe cases requiring hospital admission. However, we also used self-reported diagnoses and the depressive symptom score to include a broader range of these conditions. The measures used for this study may not identify people with anxiety or depression as well as other established mental health instruments, such as the Beck Depression Inventory or the Generalized Anxiety Disorder Scale, or diagnostic interviews, which could reduce their prediction performance. However, the measures used in this study were drawn from real-world settings (e.g., electronic health records, short self-reports), since they are of lower cost and can be implemented relatively easily. Lastly, we excluded participants with missing predictors, which could bias our results. However, the absolute differences in the characteristics between those included and excluded were small (a maximum of 4 percentage points). Because blood samples were taken routinely from all participants in the UK Biobank, the most likely reason for missing data for serum biomarkers such as HDL-C would be technical difficulties relating to the sample, which are likely to have happened randomly. The analysis based on imputed data did not meaningfully change our findings (UK Biobank).

CONCLUSION

Our findings suggest that the inclusion of measures of depression and anxiety in PREVENT would have little additional effect on the risk classification of CVD at

the population level and may not be worthwhile. Investigating broader mental health conditions using more established tools or diagnostic interview data could be the focus of future studies to further refine CVD risk classification.

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5.3 Supplementary Materials

Supplementary Table 21. Model coefficients estimated in the derivation set

	PREVENT	PREVENT + Depressive symptom score	PREVENT + Self-reported anxiety disorder	PREVENT + Self-reported depression	PREVENT + Recorded anxiety disorder	PREVENT + Recorded depression
	Log HR	Log HR	Log HR	Log HR	Log HR	Log HR
Age (years)	0.060	0.065	0.060	0.061	0.060	0.060
Sex, Male	0.450	0.488	0.453	0.459	0.451	0.452
SBP (mmHg)	0.004	0.005	0.004	0.004	0.004	0.004
HDL-c (mmol/l)	-0.536	-0.500	-0.534	-0.531	-0.535	-0.533
Non-HDL-c (mmol/l)	0.086	0.080	0.086	0.084	0.086	0.086
eGFR (ml/min/1.73 m2)	-0.004	-0.004	-0.004	-0.004	-0.004	-0.004
Diabetes	0.252	0.216	0.253	0.250	0.250	0.249
Smoking	0.416	0.365	0.414	0.406	0.413	0.410
Anti-hypertensive treatment	0.394	0.377	0.393	0.392	0.393	0.392
Statin treatment	0.637	0.619	0.635	0.631	0.636	0.634
Depressive symptom score		0.085				
Self-reported anxiety disorder			0.294			
Self-reported depression				0.296		
Recorded anxiety disorder					0.693	
Recorded depression						0.652
10-year baseline survival	0.960	0.961	0.960	0.961	0.960	0.960

HR, hazard ratio; SBP, systolic blood pressure; HDL-c, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

10-year cardiovascular disease risk based on each of the above models can be calculated using the equation below. Log HR and 10-year baseline survival can be obtained from the above table. Mental health condition can be selected from self-reported or recorded anxiety or depression.

10-year cardiovascular disease risk = 1 – 10-year baseline survival^exp((log HR_{age}*(age – 56.22007) + log HR_{sex}*(1 for male; 0 for female) + log HR_{SBP}*(SBP – 137.5314) + log $HR_{HDL\text{-}c}$*(HDL-c – 1.44788) + log $HR_{non\text{-}HDL\text{-}c}$*(non-HDL-c – 4.252748) + log HR_{eGFR} *(eGFR – 94.51684) + log $HR_{diabetes}$*(1 for yes; 0 for no) + log $HR_{smoking}$*(1 for yes; 0 for no) + log $HR_{anti\text{-}hypertensive\ treatment}$*(1 for yes; 0 for no) + log $HR_{statin\ treatment}$*(1 for yes; 0 for no) + log $HR_{depressive\ symptom\ score}$*(depressive symptom score – 1.57969) OR log $HR_{mental\ health\ condition}$*(1 for yes; 0 for no)).

Supplementary Table 22. Comparisons of C-indices between PREVENT and new models including interaction and non-linear terms of mental health conditions in the validation set

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.736	0.732 to 0.741		
PREVENT + Non-linear depressive symptom score	0.742	0.737 to 0.746	0.00516	0.00403 to 0.00629
PREVENT + Self-reported anxiety disorder and depression$	0.738	0.733 to 0.742	0.00111	0.00062 to 0.00160
PREVENT + Recorded anxiety disorder and depression$	0.738	0.733 to 0.742	0.00108	0.00059 to 0.00157
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	0.742	0.738 to 0.747	0.00573	0.00455 to 0.00691
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	0.742	0.738 to 0.747	0.00573	0.00455 to 0.00691

$ The model was fitted with an interaction term.

CI, confidence interval

Supplementary Table 23. Sensitivity, specificity, and positive and negative predictive values of PREVENT and new models including interaction and non-linear terms of mental health conditions in the validation set

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	86.90	45.23	12.51	97.46
PREVENT + Non-linear depressive symptom score	87.14	46.21	12.74	97.55
PREVENT + Self-reported anxiety disorder and depression$	86.87	45.43	12.55	97.46
PREVENT + Recorded anxiety disorder and depression$	86.90	45.36	12.54	97.46
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	87.17	46.25	12.76	97.56
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	87.15	46.27	12.76	97.56

These results were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

$ The model was fitted with an interaction term.

PPV, positive predictive values; NPV, negative predictive values

Supplementary Table 24. Net reclassification improvement in the validation set for mental health conditions with interaction and non-linear terms in addition to PREVENT predictors

	$NRI^{0.05}$	95% CI	$NRI_e^{0.05}$	95% CI	$NRI_{ne}^{0.05}$	95% CI
PREVENT + Non-linear depressive symptom score	1.21	0.73 to 1.66	0.25	-0.20 to 0.64	0.96	0.81 to 1.11
PREVENT + Self-reported anxiety disorder and depression$	0.16	-0.05 to 0.40	-0.02	-0.21 to 0.19	0.19	0.11 to 0.26
PREVENT + Recorded anxiety disorder and depression$	0.12	-0.04 to 0.26	0.01	-0.14 to 0.15	0.11	0.06 to 0.16
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	1.27	0.91 to 1.69	0.28	-0.06 to 0.66	0.99	0.84 to 1.13
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	1.28	0.87 to 1.68	0.27	-0.14 to 0.61	1.01	0.87 to 1.16

NRIs were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

$ The model was fitted with an interaction term.

NRI, net reclassification index; e, event; ne, non-event; CI, confidence interval

Supplementary Table 25. Calibration of prediction models in the validation set

	E/O ratio	Calibration slope
PREVENT	1.0007	1.0082
PREVENT + Depressive symptom score	1.0007	1.0112
PREVENT + Self-reported anxiety disorder	1.0011	1.0077
PREVENT + Self-reported depression	1.0010	1.0086
PREVENT + Self-reported anxiety disorder and depression	1.0013	1.0082
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	1.0010	1.0109
PREVENT + Recorded anxiety disorder	1.0014	1.0084
PREVENT + Recorded depression	1.0011	1.0089
PREVENT + Recorded anxiety disorder and depression	1.0016	1.0091
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	1.0014	1.0112

E/O, expected event probability to observed event probability

Supplementary Table 26. Comparisons of C-indices between PREVENT and new models including mental health conditions in the female validation set

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.731	0.724 to 0.739		
PREVENT + Depressive symptom score	0.739	0.731 to 0.746	0.00732	0.00523 to 0.00942
PREVENT + Non-linear depressive symptom score	0.739	0.732 to 0.746	0.00747	0.00532 to 0.00962
PREVENT + Self-reported anxiety disorder	0.732	0.724 to 0.739	0.00040	-0.00009 to 0.00089
PREVENT + Self-reported depression	0.734	0.726 to 0.741	0.00214	0.00121 to 0.00307
PREVENT + Self-reported anxiety disorder and depression	0.734	0.726 to 0.741	0.00239	0.00139 to 0.00339
PREVENT + Self-reported anxiety disorder and depression$	0.734	0.726 to 0.741	0.00238	0.00136 to 0.00340
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	0.739	0.732 to 0.747	0.00782	0.00569 to 0.00995
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	0.740	0.732 to 0.747	0.00824	0.00599 to 0.01050
PREVENT + Recorded anxiety disorder	0.732	0.724 to 0.739	0.00008	-0.00036 to 0.00052
PREVENT + Recorded depression	0.733	0.726 to 0.740	0.00151	0.00062 to 0.00240
PREVENT + Recorded anxiety disorder and depression	0.733	0.725 to 0.740	0.00147	0.00055 to 0.00240
PREVENT + Recorded anxiety disorder and depression$	0.733	0.725 to 0.740	0.00148	0.00053 to 0.00244
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	0.740	0.732 to 0.747	0.00809	0.00589 to 0.01029
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	0.740	0.732 to 0.747	0.00824	0.00599 to 0.01050

$ The model was fitted with an interaction term.

CI, confidence interval

Supplementary Table 27. Comparisons of C-indices between PREVENT and new models including mental health conditions in the male validation set

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.706	0.700 to 0.711		
PREVENT + Depressive symptom score	0.710	0.704 to 0.716	0.00416	0.00271 to 0.00561
PREVENT + Non-linear depressive symptom score	0.710	0.704 to 0.716	0.00433	0.00280 to 0.00587
PREVENT + Self-reported anxiety disorder	0.706	0.700 to 0.712	0.00007	-0.00025 to 0.00040
PREVENT + Self-reported depression	0.706	0.700 to 0.712	0.00020	-0.00033 to 0.00072
PREVENT + Self-reported anxiety disorder and depression	0.706	0.700 to 0.712	0.00025	-0.00033 to 0.00083
PREVENT + Self-reported anxiety disorder and depression$	0.706	0.700 to 0.712	0.00021	-0.00039 to 0.00082
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	0.710	0.704 to 0.716	0.00410	0.00264 to 0.00556
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	0.711	0.705 to 0.716	0.00488	0.00329 to 0.00648
PREVENT + Recorded anxiety disorder	0.706	0.700 to 0.712	0.00053	0.00010 to 0.00095
PREVENT + Recorded depression	0.706	0.700 to 0.712	0.00044	-0.00004 to 0.00093
PREVENT + Recorded anxiety disorder and depression	0.707	0.701 to 0.712	0.00088	0.00030 to 0.00146
PREVENT + Recorded anxiety disorder and depression$	0.707	0.701 to 0.712	0.00102	0.00039 to 0.00166
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	0.710	0.705 to 0.716	0.00470	0.00319 to 0.00621
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	0.711	0.705 to 0.716	0.00488	0.00329 to 0.00648

$ The model was fitted with an interaction term.

CI, confidence interval

Supplementary Table 28. Sensitivity, specificity, and positive and negative predictive values of PREVENT and new models including mental health conditions in the female validation set

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	74.38	60.05	9.94	97.53
PREVENT + Depressive symptom score	75.39	60.73	10.22	97.65
PREVENT + Non-linear depressive symptom score	75.39	60.88	10.25	97.66
PREVENT + Self-reported anxiety disorder	74.28	60.09	9.94	97.53
PREVENT + Self-reported depression	74.70	60.13	10.00	97.57
PREVENT + Self-reported anxiety disorder and depression	74.83	60.18	10.02	97.58
PREVENT + Self-reported anxiety disorder and depression$	74.54	60.17	9.99	97.55
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	75.34	60.78	10.22	97.65
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	75.52	60.93	10.28	97.67
PREVENT + Recorded anxiety disorder	74.31	60.08	9.94	97.53
PREVENT + Recorded depression	74.57	60.09	9.97	97.55
PREVENT + Recorded anxiety disorder and depression	74.51	60.13	9.97	97.55
PREVENT + Recorded anxiety disorder and depression$	74.54	60.13	9.98	97.55
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	75.39	60.72	10.22	97.65
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	75.50	60.90	10.27	97.67

These results were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

$ The model was fitted with an interaction term.

PPV, positive predictive values; NPV, negative predictive values

Supplementary Table 29. Sensitivity, specificity, and positive and negative predictive values of PREVENT and new models including mental health conditions in the male validation set

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	94.06	26.76	14.16	97.23
PREVENT + Depressive symptom score	93.87	27.94	14.33	97.26
PREVENT + Non-linear depressive symptom score	93.87	27.93	14.33	97.26
PREVENT + Self-reported anxiety disorder	94.00	26.80	14.16	97.21
PREVENT + Self-reported depression	93.88	27.03	14.18	97.18
PREVENT + Self-reported anxiety disorder and depression	93.90	27.04	14.18	97.18
PREVENT + Self-reported anxiety disorder and depression$	93.93	27.05	14.19	97.20
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	93.80	28.02	14.33	97.23
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	93.84	27.95	14.33	97.25
PREVENT + Recorded anxiety disorder	94.03	26.80	14.16	97.22
PREVENT + Recorded depression	93.99	26.90	14.17	97.21
PREVENT + Recorded anxiety disorder and depression	94.02	26.93	14.18	97.23
PREVENT + Recorded anxiety disorder and depression$	93.97	26.94	14.18	97.21
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	93.83	28.04	14.34	97.25
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	93.83	28.03	14.34	97.25

These results were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

$ The model was fitted with an interaction term.

PPV, positive predictive values; NPV, negative predictive values

Supplementary Table 30. Net reclassification improvement in the female validation set for mental health in addition to PREVENT predictors

	$NRI^{0.05}$	95% CI	$NRI_e^{0.05}$	95% CI	$NRI_{ne}^{0.05}$	95% CI
PREVENT + Depressive symptom score	1.69	0.90 to 2.45	1.02	0.33 to 1.70	0.67	0.47 to 0.87
PREVENT + Non-linear depressive symptom score	1.84	1.00 to 2.63	1.03	0.28 to 1.86	0.81	0.58 to 1.00
PREVENT + Self-reported anxiety disorder	-0.07	-0.28 to 0.15	-0.10	-0.30 to 0.12	0.03	-0.03 to 0.09
PREVENT + Self-reported depression	0.38	-0.04 to 0.78	0.31	-0.10 to 0.67	0.07	-0.03 to 0.19
PREVENT + Self-reported anxiety disorder and depression	0.56	0.08 to 0.99	0.44	0.03 to 0.87	0.12	0.00 to 0.23
PREVENT + Self-reported anxiety disorder and depression$	0.27	-0.22 to 0.74	0.16	-0.31 to 0.64	0.11	-0.01 to 0.23
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	1.69	0.91 to 2.39	0.97	0.27 to 1.63	0.72	0.53 to 0.94
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	2.02	1.18 to 2.80	1.16	0.40 to 1.96	0.86	0.64 to 1.05
PREVENT + Recorded anxiety disorder	-0.05	-0.21 to 0.11	-0.08	-0.22 to 0.08	0.02	-0.02 to 0.06
PREVENT + Recorded depression	0.22	-0.05 to 0.47	0.20	-0.07 to 0.46	0.03	-0.03 to 0.07
PREVENT + Recorded anxiety disorder and depression	0.21	-0.06 to 0.44	0.14	-0.10 to 0.40	0.07	0.00 to 0.13
PREVENT + Recorded anxiety disorder and depression$	0.23	-0.06 to 0.49	0.17	-0.09 to 0.45	0.06	0.00 to 0.12
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	1.68	0.84 to 2.36	1.03	0.28 to 1.68	0.66	0.46 to 0.86
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	1.97	1.05 to 2.81	1.14	0.22 to 1.97	0.83	0.63 to 1.05

NRIs were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

$ The model was fitted with an interaction term.

NRI, net reclassification index; e, event; ne, non-event; CI, confidence interval

Supplementary Table 31. Net reclassification improvement in the male validation set for mental health in addition to PREVENT predictors

	$NRI^{0.05}$	95% CI	$NRI_e^{0.05}$	95% CI	$NRI_{ne}^{0.05}$	95% CI
PREVENT + Depressive symptom score	0.97	0.59 to 1.44	-0.19	-0.58 to 0.24	1.16	0.99 to 1.35
PREVENT + Non-linear depressive symptom score	0.95	0.55 to 1.44	-0.19	-0.54 to 0.26	1.14	0.95 to 1.33
PREVENT + Self-reported anxiety disorder	-0.03	-0.15 to 0.10	-0.06	-0.17 to 0.06	0.03	-0.02 to 0.08
PREVENT + Self-reported depression	0.08	-0.12 to 0.27	-0.17	-0.38 to -0.01	0.25	0.15 to 0.34
PREVENT + Self-reported anxiety disorder and depression	0.11	-0.11 to 0.30	-0.16	-0.37 to 0.02	0.26	0.15 to 0.36
PREVENT + Self-reported anxiety disorder and depression$	0.15	-0.07 to 0.35	-0.13	-0.34 to 0.05	0.28	0.17 to 0.38
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	0.97	0.60 to 1.45	-0.26	-0.63 to 0.16	1.23	1.06 to 1.42
PREVENT + Self-reported anxiety disorder and depression and non-linear depressive symptom score	0.94	0.58 to 1.40	-0.22	-0.59 to 0.23	1.16	0.96 to 1.35
PREVENT + Recorded anxiety disorder	0.01	-0.07 to 0.10	-0.03	-0.12 to 0.04	0.04	0.01 to 0.08
PREVENT + Recorded depression	0.06	-0.05 to 0.20	-0.07	-0.17 to 0.07	0.13	0.08 to 0.18
PREVENT + Recorded anxiety disorder and depression	0.12	0.01 to 0.28	-0.04	-0.16 to 0.11	0.16	0.11 to 0.22
PREVENT + Recorded anxiety disorder and depression$	0.09	-0.05 to 0.25	-0.08	-0.22 to 0.07	0.17	0.11 to 0.23
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	1.02	0.65 to 1.49	-0.23	-0.58 0.19	1.26	1.07 to 1.45
PREVENT + Recorded anxiety disorder and depression and non-linear depressive symptom score	1.01	0.58 to 1.47	-0.23	-0.60 0.16	1.24	1.03 to 1.48

NRIs were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

$ The model was fitted with an interaction term.

NRI, net reclassification index; e, event; ne, non-event; CI, confidence interval

Supplementary Table 32. Akaike An Information Criterion for models including interaction terms between mental health and PREVENT predictors in the derivation set

PREVENT predictors used for an interaction term	Depressive symptom score	Self-reported anxiety	Self-reported depression	Recorded anxiety	Recorded depression
No interaction terms	371,372.5	371,896.7	371,845.7	371,887.8	371,852.9
Age	371,368.6	371,896.9	**371,835.0**	371,889.8	371,852.1
Sex	**371,363.6**	371,893.3	371,838.1	**371,880.6**	371,851.5
Systolic blood pressure	371,371.8	371,897.9	371,847.7	371,888.9	371,853.0
HDL-c	371,374.5	371,890.3	371,845.7	371,884.7	**371,847.0**
Non-HDL-c	371,366.7	371,898.7	371,841.8	371,888.0	371,851.0
eGFR	371,374.1	371,898.4	371,846.8	371,889.5	371,853.0
Diabetes	371,374.0	371,892.9	371,845.8	371,888.1	371,854.0
Smoking	371,374.0	371,898.6	371,845.5	371,889.5	371,854.8
Anti-hypertensive treatment	371,369.7	**371,885.9**	371,846.8	371,888.9	371,854.4
Statin treatment	371,371.5	371,892.0	371,847.7	371,888.1	371,852.6

HDL-c, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

All models included the PREVENT predictors and one of the mental health predictors with an interaction term indicated by a column and row.

The lowest Akaike An Information Criterion results were bolded.

Supplementary Table 33. Comparisons of C-indices between PREVENT and new models including interaction terms between mental health and PREVENT predictors in the validation set

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.736	0.732 to 0.741		
PREVENT + depressive symptom*sex	0.742	0.737 to 0.746	0.00506	0.00393 to 0.00619
PREVENT + Self-reported anxiety disorder*anti-hypertensive treatment	0.737	0.732 to 0.741	0.00014	-0.00018 to 0.00046
PREVENT + Self-reported depression*age	0.737	0.733 to 0.742	0.00087	0.00035 to 0.00139
PREVENT + Recorded anxiety disorder*sex	0.737	0.732 to 0.741	0.00016	-0.00012 to 0.00044
PREVENT + Recorded depression* HDL-c	0.737	0.733 to 0.742	0.00079	0.00032 to 0.00126

CI, confidence interval; HDL-c, high density lipoprotein cholesterol

Supplementary Table 34. Sensitivity, specificity, and positive and negative predictive values of PREVENT and new models including interaction terms between mental health and PREVENT predictors in the validation set

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	86.90	45.23	12.51	97.46
PREVENT + depressive symptom*sex	87.09	46.28	12.75	97.55
PREVENT + Self-reported anxiety disorder*anti-hypertensive treatment	86.83	45.31	12.52	97.45
PREVENT + Self-reported depression*age	86.95	45.33	12.54	97.47
PREVENT + Recorded anxiety disorder*sex	86.83	45.30	12.52	97.45
PREVENT + Recorded depression* HDL-c	86.92	45.37	12.54	97.47

These results were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

PPV, positive predictive values; NPV, negative predictive values; HDL-c, high density lipoprotein cholesterol

Supplementary Table 35. Associations of PREVENT predictors and mental health conditions with cardiovascular disease in the derivation set generated by a different random splitting

	Single predictor models		PREVENT + Each mental health predictor		PREVENT + Anxiety and depression#		PREVENT + Depressive symptom score and anxiety and depression		PREVENT + Depressive symptom score and anxiety and depression	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Depressive symptom score (0–12)	1.06	1.05, 1.06	1.09	1.08, 1.10			1.09	1.08, 1.09	1.09	1.08, 1.09
Self-reported anxiety disorder	1.34	1.20, 1.48	1.36	1.23, 1.51	1.24	1.11, 1.38	1.16	1.04, 1.29		
Self-reported depression	1.22	1.14, 1.29	1.32	1.24, 1.41	1.38	1.30, 1.47	1.06	0.99, 1.13		
Recorded anxiety disorder	2.03	1.66, 2.47	2.04	1.68, 2.48	1.80	1.48, 2.20			1.55	1.27, 1.89
Recorded depression	1.92	1.66, 2.21	1.88	1.63, 2.17	1.98	1.73, 2.27			1.43	1.24, 1.66

HR for depressive symptom score was expressed as per one-point increase.

Self-reported conditions and recorded conditions were fitted separately (i.e., self-reported anxiety and depression included in one model, and recorded anxiety and depression in another model.)

HR, hazard ratio; CI, confidence interval

Supplementary Table 36. Comparisons of C-indices between PREVENT and new models including mental health conditions in the validation set generated by a different random splitting

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.736	0.731 to 0.740		
PREVENT + Depressive symptom score	0.741	0.736 to 0.745	0.00529	0.00417 to 0.00640
PREVENT + Self-reported anxiety disorder	0.736	0.731 to 0.740	0.00016	-0.00011 to 0.00042
PREVENT + Self-reported depression	0.737	0.732 to 0.741	0.00096	0.00053 to 0.00139
PREVENT + Self-reported anxiety disorder and depression	0.737	0.732 to 0.741	0.00105	0.00057 to 0.00152
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	0.741	0.737 to 0.745	0.00538	0.00426 to 0.00651
PREVENT + Recorded anxiety disorder	0.736	0.731 to 0.740	0.00023	-0.00005 to 0.00050
PREVENT + Recorded depression	0.737	0.732 to 0.741	0.00104	0.00060 to 0.00147
PREVENT + Recorded anxiety disorder and depression	0.737	0.732 to 0.741	0.00114	0.00067 to 0.00162
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	0.741	0.737 to 0.746	0.00589	0.00473 to 0.00705

Supplementary Table 37. Sensitivity, specificity, and positive and negative predictive values of PREVENT and new models including mental health conditions in the validation set generated by a different random splitting

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	87.30	44.95	12.26	97.57
PREVENT + Depressive symptom score	87.34	45.80	12.44	97.62
PREVENT + Self-reported anxiety disorder	87.25	45.02	12.27	97.56
PREVENT + Self-reported depression	87.30	45.08	12.29	97.58
PREVENT + Self-reported anxiety disorder and depression	87.23	45.17	12.30	97.57
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	87.30	45.87	12.45	97.62
PREVENT + Recorded anxiety disorder	87.31	45.02	12.28	97.58
PREVENT + Recorded depression	87.38	45.07	12.30	97.59
PREVENT + Recorded anxiety disorder and depression	87.34	45.12	12.30	97.59
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	87.39	45.90	12.46	97.64

These results were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

PPV, positive predictive values; NPV, negative predictive values

Supplementary Table 38. Comparisons of characteristics of participants who were included in the analysis and excluded from the analysis due to missing values in predictors

	Participants included in the main analysis			Participants excluded from the main analysis due to missing values in predictors		
	Overall (N = 325,815) N (%)	No CVD (N = 299,389) N (%)	CVD (N = 26,426) N (%)	Overall (N = 157,795) N (%)	No CVD (N = 144,208) N (%)	CVD (N = 13,587) N (%)
Age (years), mean (SD)	56.2 (8.09)	55.9 (8.09)	60.5 (6.69)	56.6 (8.11)	56.2 (8.12)	60.6 (6.77)
Sex						
Female	175,406 (53.84)	165,663 (55.33)	9,743 (36.87)	91,883 (58.23)	86,350 (59.88)	5,533 (40.73)
Male	150,409 (46.16)	133,726 (44.67)	16,683 (63.13)	65,898 (41.77)	57,846 (40.12)	8,052 (59.27)
Systolic blood pressure (mmHg), mean (SD)	137.5 (18.10)	137.1 (18.01)	143.1 (18.21)	137.8 (18.45)	137.4 (18.36)	142.4 (18.74)
HDL-c (mmol/l), mean (SD)	1.4 (0.36)	1.5 (0.36)	1.3 (0.34)	1.4 (0.37)	1.4 (0.37)	1.3 (0.36)
Non-HDL-c (mmol/l), mean (SD)	4.3 (0.97)	4.3 (0.97)	4.2 (1.05)	4.3 (0.98)	4.3 (0.97)	4.2 (1.05)
eGFR (ml/min/1.73 m2), mean (SD)	94.5 (12.59)	94.8 (12.44)	90.9 (13.58)	94.1 (13.09)	94.4 (12.89)	90.4 (14.37)
Diabetes	15,961 (4.90)	12,836 (4.29)	3,125 (11.83)	9,492 (7.62)	7,572 (6.72)	1,920 (16.25)
Smoking	33,469 (10.27)	29,838 (9.97)	3,631 (13.74)	17,182 (11.08)	15,246 (10.76)	1,936 (14.56)
Anti-hypertensive treatment	60,338 (18.52)	50,286 (16.80)	10,052 (38.04)	31,272 (19.82)	25,696 (17.82)	5,576 (41.04)
Statin treatment	47,507 (14.58)	38,286 (12.79)	9,221 (34.89)	24,942 (15.81)	19,778 (13.71)	5,164 (38.01)
Depressive symptom score (0–12), mean (SD)	1.6 (2.08)	1.6 (2.05)	1.8 (2.34)	1.6 (2.15)	1.6 (2.12)	1.9 (2.39)
Self-reported anxiety disorder	5,612 (1.72)	5,035 (1.68)	577 (2.18)	3,059 (1.94)	2,775 (1.92)	284 (2.09)
Self-reported depression	17,972 (5.52)	16,230 (5.42)	1,742 (6.59)	9,268 (5.87)	8,236 (5.71)	1,032 (7.60)
Recorded anxiety disorder	1,056 (0.32)	890 (0.30)	166 (0.63)	661 (0.42)	548 (0.38)	113 (0.83)
Recorded depression	2,272 (0.70)	1,923 (0.64)	349 (1.32)	1,399 (0.89)	1,183 (0.82)	216 (1.59)

N, number; CVD, cardiovascular disease; SD, standard deviation; HDL-c, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

Supplementary Table 39. Summary of missing values in predictors

	Counts (%)
Non-HDL-c	85,702 (17.7)
HDL-c	73,660 (15.2)
Depressive symptom score	51,114 (10.6)
Diabetes	33,229 (6.87)
eGFR	33,072 (6.84)
Systolic blood pressure	17,659 (3.65)
Smoking	2,787 (0.58)
Age	14 (0.003)
Sex	14 (0.003)

HDL-c, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

Supplementary Table 40. Participant baseline characteristics by cardiovascular disease after data imputation

	Derivation set (60% of the participants)			Validation Set (40% of the participants)		
	Overall (N = 290,166) N (%)	No CVD (N = 266,046) N (%)	CVD (N = 24,120) N (%)	Overall (N = 193,444) N (%)	No CVD (N = 177,551) N (%)	CVD (N = 15,893) N (%)
Age (years), mean (SD)	56.3 (8.09)	55.9 (8.10)	60.6 (6.71)	56.3 (8.10)	56.0 (8.11)	60.6 (6.73)
Sex						
Female	160,257 (55.23)	151,078 (56.79)	9,179 (38.06)	107,038 (55.33)	100,940 (56.85)	6,098 (38.37)
Male	129,909 (44.77)	114,968 (43.21)	14,941 (61.94)	86,406 (44.67)	76,611 (43.15)	9,795 (61.63)
Systolic blood pressure (mmHg), mean (SD)	137.6 (17.92)	137.2 (17.82)	142.9 (18.10)	137.7 (18.00)	137.2 (17.93)	142.7 (18.06)
HDL-c (mmol/l), mean (SD)	1.4 (0.34)	1.5 (0.34)	1.3 (0.33)	1.4 (0.34)	1.5 (0.34)	1.3 (0.33)
Non-HDL-c (mmol/l), mean (SD)	4.3 (0.91)	4.3 (0.90)	4.2 (0.98)	4.3 (0.91)	4.3 (0.90)	4.2 (0.99)
eGFR (ml/min/1.73 m2), mean (SD)	94.4 (12.40)	94.7 (12.24)	90.7 (13.55)	94.4 (12.38)	94.7 (12.22)	90.8 (13.50)
Diabetes	15,904 (5.48)	12,782 (4.80)	3,122 (12.94)	10,471 (5.41)	8,371 (4.71)	2,100 (13.21)
Smoking	30,490 (10.51)	27,118 (10.19)	3,372 (13.98)	20,210 (10.45)	18,013 (10.15)	2,197 (13.82)
Anti-hypertensive treatment	55,123 (19.00)	45,697 (17.18)	9,426 (39.08)	36,487 (18.86)	30,285 (17.06)	6,202 (39.02)
Statin treatment	43,550 (15.01)	34,954 (13.14)	8,596 (35.64)	28,899 (14.94)	23,110 (13.02)	5,789 (36.42)
Depressive symptom score (0–12), mean (SD)	2.6 (2.14)	2.6 (2.12)	2.8 (2.35)	2.6 (2.14)	2.6 (2.12)	2.8 (2.39)
Self-reported anxiety disorder	5,170 (1.78)	4,655 (1.75)	515 (2.14)	3,501 (1.81)	3,155 (1.78)	346 (2.18)
Self-reported depression	16,321 (5.62)	14,670 (5.51)	1,651 (6.84)	10,919 (5.64)	9,796 (5.52)	1,123 (7.07)
Recorded anxiety disorder	1,011 (0.35)	843 (0.32)	168 (0.70)	706 (0.36)	595 (0.34)	111 (0.70)
Recorded depression	2,202 (0.76)	1,865 (0.70)	337 (1.40)	1,469 (0.76)	1,241 (0.70)	228 (1.43)

N, number; CVD, cardiovascular disease; SD, standard deviation; HDL-c, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

Supplementary Table 41. Associations of PREVENT predictors and mental health conditions with cardiovascular disease in the derivation set after data imputation

	Single predictor models		PREVENT + Each mental health predictor		PREVENT + Anxiety and depression#		PREVENT + Depressive symptom score and anxiety and depression		PREVENT + Depressive symptom score and anxiety and depression	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Depressive symptom score (0–12)	1.04	1.04, 1.05	1.08	1.08, 1.09			1.08	1.07, 1.09	1.08	1.07, 1.09
Self-reported anxiety disorder	1.22	1.11, 1.33	1.26	1.16, 1.38	1.18	1.08, 1.28	1.07	0.98, 1.17		
Self-reported depression	1.25	1.19, 1.31	1.38	1.31, 1.45	1.36	1.29, 1.43	1.11	1.05, 1.17		
Recorded anxiety disorder	2.17	1.86, 2.52	2.15	1.85, 2.50	1.87	1.60, 2.18			1.64	1.41, 1.92
Recorded depression	1.98	1.78, 2.21	1.93	1.73, 2.15	1.79	1.61, 2.00			1.50	1.34, 1.68

HR for depressive symptom score was expressed as per one-point increase.

Self-reported conditions and recorded conditions were fitted separately (i.e., self-reported anxiety and depression included in one model, and recorded anxiety and depression in another model.)

HR, hazard ratio; CI, confidence interval

Supplementary Table 42. Comparisons of C-indices between PREVENT and new models including mental health conditions in the validation set after data imputation

	C-index	95% CI	Change from PREVENT	95% CI
PREVENT	0.735	0.731 to 0.738		
PREVENT + Depressive symptom score	0.739	0.735 to 0.743	0.00420	0.00334 to 0.00505
PREVENT + Self-reported anxiety disorder	0.735	0.731 to 0.739	0.00022	0.00005 to 0.00039
PREVENT + Self-reported depression	0.736	0.732 to 0.740	0.00126	0.00086 to 0.00166
PREVENT + Self-reported anxiety disorder and depression	0.736	0.733 to 0.740	0.00137	0.00096 to 0.00179
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	0.739	0.736 to 0.743	0.00447	0.00361 to 0.00534
PREVENT + Recorded anxiety disorder	0.735	0.732 to 0.739	0.00040	0.00013 to 0.00067
PREVENT + Recorded depression	0.735	0.732 to 0.739	0.00066	0.00033 to 0.00099
PREVENT + Recorded anxiety disorder and depression	0.736	0.732 to 0.739	0.00095	0.00055 to 0.00135
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	0.740	0.736 to 0.743	0.00472	0.00383 to 0.00562

Supplementary Table 43. Sensitivity, specificity, and positive and negative predictive values of PREVENT and new models including mental health conditions in the validation set after data imputation

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PREVENT	87.10	44.21	12.42	97.42
PREVENT + Depressive symptom score	87.13	44.98	12.57	97.47
PREVENT + Self-reported anxiety disorder	87.14	44.23	12.43	97.43
PREVENT + Self-reported depression	87.04	44.39	12.44	97.42
PREVENT + Self-reported anxiety disorder and depression	87.03	44.39	12.44	97.41
PREVENT + Self-reported anxiety disorder and depression and depressive symptom score	87.15	45.01	12.58	97.47
PREVENT + Recorded anxiety disorder	87.10	44.30	12.43	97.42
PREVENT + Recorded depression	87.06	44.36	12.44	97.42
PREVENT + Recorded anxiety disorder and depression	87.04	44.41	12.45	97.42
PREVENT + Recorded anxiety disorder and depression and depressive symptom score	87.18	45.06	12.60	97.48

These results were calculated by a 5% cut-off of 10-year cardiovascular disease risk.

PPV, positive predictive values; NPV, negative predictive values

Supplementary Table 44. Performance of PREVENT at predicting 10-year cardiovascular disease risk in the validation set after logistic calibration and model revisions including mental health conditions

	AUC (95% CI)	D statistics (P-values) of differences from PREVENT*	Calibration in the large	Calibration slope
PREVENT	0.6345 (0.6293–0.6398)		0.0097	1.0146
PREVENT + Depressive symptom score	0.6371 (0.6319–0.6424)	4.71 (<0.0001)	0.0100	1.0150
PREVENT + Self-reported anxiety disorder	0.6349 (0.6297–0.6402)	1.60 (0.1103)	0.0093	1.0125
PREVENT + Self-reported depression	0.6353 (0.6301–0.6406)	2.76 (0.0055)	0.0096	1.0138
PREVENT + Recorded anxiety disorder	0.6350 (0.6297–0.6402)	1.72 (0.0854)	0.0092	1.0157
PREVENT + Recorded depression	0.6354 (0.6302–0.6407)	2.59 (0.0096)	0.0092	1.0124

AUC, area under the curve; CI, confidence interval

* Bootstrap test was used to compare the area under the curves between the models.

The intercept and all predictor regression coefficients of publicly available PREVENT equations were adjusted

by one overall adjustment factor (i.e., calibration slope) by fitting a new logistic regression model in our dataset including the linear predictor as the only predictor. The model was revised by fitting logistic regression models including each one of the mental health conditions in addition to the linear predictor.

Chapter 6 Research in a Wider Context

6.1 Summary of Key Findings

My PhD research has contributed to the elucidation of the roles of anxiety and depression in developing CVD, generating findings that not only advance current understanding but also have direct clinical and public health relevance. Chapter 2 found that having anxiety contributed the same relative excess risk of CVD regardless of the presence of depression, and vice versa. This suggests anxiety and depression operate independently in contributing to the development of CVD and therefore both warrant attention in CVD risk management. Chapter 3 found that genetic susceptibility to CVD partly contributed to the clustering of depression and CVD but did not provide a full explanation, nor did it explain the association between anxiety and CVD. Therefore, the increased risk of CVD in these patients should be addressed regardless of genetic susceptibility to CVD. Chapter 4 found that smoking and central obesity were the strongest lifestyle and physical mediators of CVD for both anxiety and depression. However, high systolic blood pressure was the strongest metabolic mediator for anxiety whilst C-reactive protein, a marker of inflammation, was the strongest metabolic mediator for depression. The findings inform which risk factors should be targeted among people with anxiety or depression. Lastly, Chapter 5 found that incorporating measures of anxiety and depression into the PREVENT risk score significantly, but only modestly, improved the prediction of CVD onset. Whether to integrate MHCs into CVD risk scores should be carefully considered, especially when it attracts additional costs, and investigating broader MHCs using more established tools or diagnostic interview data could be the focus of future studies.

6.2 Theoretical integration

Overall, my findings are consistent with the theoretical frameworks introduced in Chapter 1: multimorbidity and the brain–heart axis (Gold et al., 2020, The Academy of Medical Sciences, 2018, Valenza et al., 2025). This provides empirical support for these frameworks by showing that MHCs are prospectively associated with CVD development partly through multiple behavioural and clinical intermediates (including lifestyle, physical, and metabolic factors) in addition to genetic susceptibility to CVD. Since my studies lack the refined data

to characterise the brain-heart axis, the unexplained associations could be due in part to the factors postulated from the brain-heart axis. Nonetheless, the identified mediating effect of high systolic blood pressure may reflect increased activity of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system and CRP may reflect upstream biochemical pathways such as tumour necrosis factor-α and interleukin-6. Importantly, my findings offer additional insights into these frameworks by highlighting the potential role of anxiety in addition to depression in developing CVD and showing both similar and distinct mechanisms through which these MHCs operate. Taken together, these findings not only reinforce but also refine the existing frameworks, suggesting that future models of MHC-CVD clustering should explicitly incorporate the distinct roles of MHCs (e.g., anxiety and depression) in cardiovascular risk.

6.3 Clinical implications

Overall, my findings highlight the need to assess and manage traditional CVD risk factors among people living with anxiety and depression to reduce their burden from CVD. This would be increasingly feasible owing to the growing evidence base for effective pharmacological interventions and evolving healthcare systems (Otte et al., 2025, Mirzaei et al., 2021, Ganeshalingam et al., 2025, Hegde et al., 2024). For example, a double-blind, placebo-controlled, multicentre randomised controlled trial demonstrated that a 12-week course of simvastatin as an adjuvant treatment to escitalopram significantly reduced LDL cholesterol, total cholesterol, and C-reactive protein concentrations in patients with depression, compared with placebo (Otte et al., 2025). Blood glucose control and weight reduction using a glucagon-like peptide-1 receptor agonist could also be possible as demonstrated by a recent trial specifically targeted at patients with schizophrenia (Ganeshalingam et al., 2025). In the UK, an annual free health check is offered by NHS England to people with rare MHCs including schizophrenia, bipolar disorder, and psychotic disorder, and similar programmes are being piloted or implemented in other UK nations. Furthermore, the European Society of Cardiology Guidelines recommend greater attention be given to CVD risk management in populations with MHCs (Visseren et al., 2021), and a recent practice guideline has been developed to prevent antipsychotic-induced weight gain using metformin (Carolan et al., 2024).

However, care is needed when interpreting clinical implications of my findings. My findings suggest that, whilst people with severe anxiety and depression have an increased risk of CVD, those with milder cases have only a moderately increased risk. Given the high demands on primary care services, it may not be feasible to routinely manage CVD risk among all patients with these conditions and therefore, careful prioritisation based on the severity of MHCs may be warranted. Whilst I found that the association between depression and CVD varied according to genetic susceptibility to CVD, genetic screening for common diseases is not currently a part of the routine clinical practice due to cost and logistic concerns. Given the high risk of CVD even in the low PRS group, the CVD risk management should be implemented for those with MHCs regardless of genetic susceptibility to CVD. Although my findings from the PREVENT risk score showed little evidence that including MHCs provides additional predictive value at the population level, MHCs can contribute to the individual CVD risks and therefore, CVD risk management remains important alongside mental health care.

Lastly, there remain gaps in CVD risk management among people with MHCs. Patients with MHCs are less likely to attend screening for CVD risk factors, receive and adhere to pharmacological interventions (Nielsen et al., 2021), and achieve target levels for key risk factors such as LDL cholesterol (Ter Braake et al., 2024). Most trials, healthcare services, and health surveys tend to focus on rare MHCs such as schizophrenia, which can lead to the underrepresentation of more common conditions like depression and anxiety. Based on my research findings, there is a clear need to promote and broaden the focus of CVD risk management strategies to include people with common MHCs.

6.4 Future Research

Firstly, although I identified significant lifestyle, physical, and metabolic pathways linking MHCs and CVD, approximately half of the excess CVD risk in these high-risk patients remained unexplained. This highlights the need for future studies into residual molecular pathways. Recent technological advances have enabled high-resolution proteomics that could offer great potential to

elucidate novel mechanisms (Frantzi et al., 2019, Anderson and Anderson, 2002). Investigating circulating proteins would not only advance mechanistic understanding of MHC-CVD clustering but also identify potential intervention targets, informing drug repurposing and development.

Secondly, although observational studies and RCTs have demonstrated the associations between MHCs and CVD as well as the efficacy of managing CVD risk factors in those with MHCs (Otte et al., 2025), there is a clear research gap about whether and how treating MHCs prevents CVD development (Carney and Freedland, 2017). The increasing availability of large-scale clinical data and causal inference methods, such as target trial emulation, may enable the evaluation of a range of mental health treatments in relation to long-term CVD outcomes among these patients. This could provide actionable evidence to inform the design of future RCTs and to improve existing CVD risk prediction models (Osborn et al., 2015).

Thirdly, accumulating studies have found multimorbidity across diverse MHCs and CVDs and spanning life stages. For example, a large Danish population cohort study demonstrated that a wide range of neuropsychiatric disorders (such as developmental disorders, behavioural disorders, and personality disorders) were associated with circulatory disorders (Shen et al., 2023). The AHA has raised concerns about the elevated risk of early-onset CVD among children with depression (Kavey et al., 2006). My PhD research demonstrated that a collection of various epidemiological methods (including mediation analysis, genetic modification, and prediction modelling) could help disentangle complex multimorbidity. This framework could be extended to include different forms of MHC-CVD clustering and different life stages, aiming to provide a comprehensive picture of mechanisms and ultimately improve clinical practice.

6.5 What I Learned During My PhD

When I first enrolled in this programme, I could not clearly envision the researcher I would become and had only a narrow view of research. The Medical Research Council Doctoral Training Programme in Precision Medine, along with

my research project and supervisors, expanded my perspective and sharpened my research vision.

Through the Doctoral Training Programme, I undertook a personalised training programme including both internal and external training courses across diverse disciplines: epidemiology, statistics, data science, genetics, biology, cardiology, and precision medicine that reinforced my expertise and provided new knowledge. I also had multiple opportunities to present my research to diverse audiences, which developed my ability to communicate with people from different backgrounds. I was also exposed to a wide range of research fields pursued by my PhD student cohort. Although these differed from mine, I recognised them as good opportunities to identify transferable skills and insights, and to expand my own research ideas.

Throughout my research project, I benefited from a sufficient period of focused research, strong supervisory team and diverse collaborators. They allowed me to go through many trials and errors: conceptualising and designing studies; coding and analysing data; discussing and interpretating results; and disseminating findings. These plentiful experiences enabled me to connect practice with theory, providing a solid foundation in transferable research and problem-solving skills. One unique feature of my research project was to employ multiple epidemiological approaches. On completion of this project, I now understand how employing diverse approaches can disentangle complex multimorbidity by triangulating evidence obtained from different perspectives, offering a more comprehensive picture to address this health issue.

Overall, the Doctoral Training Programme, my research project, and the invaluable support of supervisors and collaborators have made my research vision more flexible, expansive, and clear. I believe that these provide a cornerstone to shape and lead a future comprehensive research programme of precision medicine and public health to tackle complex health issues.

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