Study Report

P4-C3-005

DARWIN EU® - Assessing the potential association between venlafaxine and heart failure among adults

07/07/2026

Version 4.0

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Public

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Study title	DARWIN EU® - Assessing the potential association between venlafaxine and heart failure among adults.
Study report version	V4.0
Date	07/07/2026
EUPAS number	EUPAS1000000974
Active substance	Venlafaxine ATC-code: N06AX16
Medicinal product	NA
Research question and objectives	The study aimed to assess the potential association between venlafaxine and heart failure among adults. Specific objectives were: 1) To assess the risk of incident heart failure and incident cardiomyopathy between new users of venlafaxine versus new users of mirtazapine. 2) To assess the risk of heart failure exacerbation between new users of venlafaxine versus new users of mirtazapine who have been diagnosed with heart failure before treatment initiation. 3) To characterise both new venlafaxine and new mirtazapine users at the time of treatment start (in terms of demographics, pre-defined comorbidities/comedication/conditions of interest, and drug utilisation) for contextualisation of Objectives 1+2. Analyses were conducted overall and stratified for condition of interest, age group, sex, history of CV disease, and previous SSRI use.
Countries of study	Denmark, Finland, Spain, Sweden, the United Kingdom
Authors	Martí Català Sabaté, m.catalasabate@darwin-eu.org Annika Jödicke, a.jodicke@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical
ATT	Average treatment effects in the treated
BIFAP	Pharmacoepidemiological Research Database for Public Health Systems
CC	Coordination Centre
CCB	Calcium Channel Blocker
CDM	Common Data Model
CI	Confidence Interval
CPRD GOLD	Clinical Practice Research Datalink GOLD
CV	Cardiovascular
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FAERS	FDA Adverse Event Reporting System
FinOMOP-THL	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
HF	Heart Failure
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischaemic Heart Disease
IR	Incidence Rates
IRB	Institutional Review Board
IRR	Incidence Rate Ratios
IQR	Interquartile Range
ITT	Intention to treat
LASSO	Least Absolute Shrinkage and Selection Operator [LASSO]
LOINC	Logical Observation Identifiers Names and Codes
MAO	Monoamine Oxidase
MDRR	Minimum detectable relative risk

Acronyms/term	Description
MI	Myocardial infarction
NCO	Negative control outcomes
N	Number
NA	Not applicable
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PP	Per protocol
PS	Propensity score
PY	Person years
RAAS	Renin-Angiotensin-Aldosterone System
RxNorm	Medical prescription normalised
SD	Standard deviation
SIDIAP	The Information System for Research in Primary Care
(A)SMD	(absolute) Standardised mean difference
SmPC	Summaries of product characteristics
SNOMED	Systematized Nomenclature of Medicine
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Assessing the potential association between venlafaxine and heart failure among adults.

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Annika Jödicke	University of Oxford
Data Scientists	Marti Catala Sabate Cecilia Campanile Xintong Li	University of Oxford
Epidemiologists	Wanning Wang Marti Catala Sabate Xintong Li	University of Oxford
Clinical Domain Experts	Daniel Prieto-Alhambra Annika Jödicke Anna Camps Vilaro Anna Saura Lazaro Alejandro Ballve	University of Oxford
Study Manager	Natasha Yefimenko	Erasmus Medical Center
Data source	**Names**	**Data Source name***
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Data Health Registries
FinOMOP-THL	Toni Lehtonen	Finnish Care Register for Health Care
BIFAP	Belén Castillo Cano Cristina Justo Astorgano Alicia Peñaranda Navazo Ana Llorente Garcia Miguel Angel Macia Martinez	Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público
SIDIAP	Elena Roel Herranz Agustina Giuliodori Picco Laura Granés Irene López Sánchez Anna Palomar Cros	The Information System for Research in Primary Care
HI-SPEED	Marcel Ballin Huiqi Li Fredrik Nyberg Mats Talbäck Rickard Ljung	Health Impact - Swedish Population Evidence Enabling Data-linkage
CPRD GOLD	Antonella Delmestri	Clinical Practice Research Datalink GOLD

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Assessing the potential association between venlafaxine and heart failure in adults.

Rationale and background

Venlafaxine is a dual-acting serotonin and norepinephrine reuptake inhibitor (SNRI). A case series and spontaneously reported cases suggest an association between venlafaxine and heart failure (HF) and cardiomyopathy other than Takotsubo. Therefore, a study was requested to estimate the association between venlafaxine and heart failure/cardiomyopathy, using mirtazapine as an active comparator.

Research question and objectives

Research questions

Was new use of venlafaxine associated with an increased risk of incident HF compared to new use of mirtazapine?

Was new use of venlafaxine associated with exacerbation of pre-existing HF compared to new use of mirtazapine?

Objectives

The study aimed to assess the potential association between venlafaxine and HF among adults. The specific objectives of this study were:

1) To assess the risk of incident HF and incident cardiomyopathy between new users of venlafaxine versus new users of mirtazapine.
2) To assess the risk of HF exacerbation between new users of venlafaxine versus new users of mirtazapine who have been diagnosed with HF before treatment initiation.
3) To characterise both new venlafaxine and new mirtazapine users at the time of treatment start (in terms of demographics, pre-defined comorbidities/comedication/conditions of interest, and drug utilisation) for contextualisation of Objectives 1+2.

Methods

Study design

- New user active comparator cohort studies (Objectives 1+2)
- Patient-level characterisation (Objective 3)

Index date was the date of first prescription of venlafaxine or mirtazapine, and individuals were followed up until date of last data availability, drug discontinuation, outcome occurrence, death, or end of study period.

Population

The study population included all adults with a recorded first prescription for venlafaxine or mirtazapine within the study period, from 01/01/2010 up to the end of data availability, who met the eligibility criteria at study entry.

Variables

Exposure and comparator: Venlafaxine (exposure) [ATC-code: N06AX16] and Mirtazapine (active comparator) [ATC-code: N06AX11]

Outcomes:

Objective 1: Primary outcome: Incident HF (broad definition); Secondary outcomes: narrow definitions for incident HF; incident cardiomyopathy (broad and narrow definition), HF hospitalisation

Objective 2: Primary outcome: HF hospitalisation; Secondary outcomes: Acute pulmonary oedema, recurrent HF recording (broad)

Objective 3: Summarised patient characteristics at index date (venlafaxine/mirtazapine initiation).

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Spain: Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP)
4. Spain: The Information System for Research in Primary Care (SIDIAP)
5. Sweden: Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)
6. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

HF hospitalisation was only conducted in DK-DHR, FinOMOP-THL, SIDIAP, and HI-SPEED, where hospital data were available.

Statistical analysis

Objectives 1–2:

We used large-scale propensity score (PS) matching to address confounding from observed covariates and to match venlafaxine with mirtazapine patients. Among the PS-matched cohorts, Poisson regression was used to estimate incidence rates for the outcomes of interest among the two treatment groups.

Cox proportional hazards modelling was used to estimate hazard ratios (HRs) for all outcomes, using an "on treatment" estimand as the primary treatment strategy analysis and "ever exposed" as secondary treatment strategy analysis. The proportional hazards assumption was tested using visual inspection of log-log plots. Incidence Rate Ratios (IRR) were calculated using Poisson regression (which does not rely on the proportional hazards assumption) and presented alongside the HR. Results were stratified for age, sex, history of CV disease, previous SSRI use, and condition of interest (depression/anxiety).

To detect residual confounding, Negative Control Outcome (NCO) analyses were conducted for each outcome. Sensitivity analyses with a population restricted to having at least 5 years of data source history prior to index date (instead of two years) was conducted. Random-effects meta-analyses were conducted to pool results.

Objective 3:

Patient-level characterisation analyses of all new venlafaxine and mirtazapine were conducted. Covariates of interest were also reported as counts and proportions.

Results

Objective 1

A total of 514,210 adults initiating venlafaxine were matched to adults initiating mirtazapine (151,787 from BIFAP; 44,952 from CPRD GOLD; 60,058 from DK-DHR; 57,706 from FinOMOP-THL; 125,609 from HI-SPEED; and 74,098 from SIDIAP).

The meta-analytic HR_{meta} for incident heart failure associated with venlafaxine initiation (compared to mirtazapine) was 0.9 [95% Confidence Interval (CI) 0.81 – 0.99]. Data source-specific HRs ranged between

0.72 (95%CI 0.45 – 1.17) in FinOMOP-THL and 1.00 (95%CI 0.91 – 1.09) in HI-SPEED. Results from secondary outcome definitions for heart failure and secondary/sensitivity analyses (including "ever exposed") were largely consistent with the main findings. Point estimates for incident cardiomyopathy were higher than for incident heart failure, with meta-analytic HR_{meta} of 1.18 (95%CI 0.93 – 1.50) for the broad definition (including Takotsubo) and HR_{meta} 1.13 (95%CI 0.89 – 1.45) for cardiomyopathy excluding Takotsubo.

The proportion of NCOs associated with venlafaxine use ranged from 4.9% in BIFAP to 34.3% in HI-SPEED, suggesting possible residual bias. When estimates were calibrated, the calibrated meta-analytic $HR_{meta,cal}$ for incident HF (broad) was 0.86 (95%CI 0.78 – 0.96). HR_{cal} ranged from 0.77 (95%CI 0.44 – 1.35) in CPRD GOLD to 0.98 (95%CI 0.71 – 1.35) in DK-DHR, with CIs across all data sources including 1. The meta-analytic calibrated estimate for incident cardiomyopathy (broad) was $HR_{meta,cal}$ 1.14 (95%CI 0.91 – 1.43).

Objective 2

A total of 3,465 matched venlafaxine and mirtazapine users were included (1,644 from HI-SPEED; and 1,821 from SIDIAP).

Covariate imbalance was present despite PS matching in all data sources (as defined by absolute standardised mean differences (ASMD)>0.1). HRs are only reported for HI-SPEED and SIDIAP, where covariate imbalance was less. For the primary outcome of hospitalisation due to HF, HR were 0.93 [95%CI 0.81 – 1.07] and 0.91 [95%CI 0.79 – 1.05], respectively. Results from secondary outcome analyses were in line with these findings. The proportion of NCOs associated with venlafaxine initiation were 15.6% in HI-SPEED and 0% in SIDIAP. Calibrated HR for hospitalisation for HF was HR_{cal} 1.04 (95%CI 0.64 – 1.70) in HI-SPEED and HR_{cal} 0.94 (95%CI 0.81 – 1.08) in SIDIAP. Results from analyses based on "ever exposed" status were in line with "on treatment" estimands.

Objective 3

The median age of adult venlafaxine initiators ranged from 42 to 53 years. Individuals prescribed mirtazapine were on average older with greater comorbidity, with hypertension being the most prevalent comorbidity. Females were more commonly prescribed both venlafaxine and mirtazapine across data sources. Depression was the most common indication for venlafaxine, followed by anxiety. The proportion of adults previously prescribed SSRIs (suggesting second-line use) varied across data sources, ranging from 12.9% to 69%.

Discussion

No significant association was observed between venlafaxine exposure and incident heart failure compared to mirtazapine. Results from sensitivity analyses, secondary outcomes, and different causal estimands were largely consistent with the main results. Negative control outcome analyses suggested potential residual confounding, although calibrated effect estimates remained consistent with the main (uncalibrated) estimates.

Small sample size and residual covariate imbalance following PS matching limited the analysis for Objective 2. For the two data sources that could be analysed (with reservations regarding confounding), no differential risks of heart failure exacerbation with venlafaxine were identified.

These findings need to be interpreted together with all other available evidence and considering the study specific limitations.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned*)	Timelines (actual)
Final Study Protocol	28 February 2026	27 March 2026
Creation of Analytical code	February – March 2026	March 2026
Execution of Analytical Code on the data	End of March – beginning of April 2026	April 2026
Study Report (submitted to EMA)	Early May 2026	13 May 2026
Final Study Report	May 2026	16 June 2026

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources and deliverables review rounds.

6. RATIONALE AND BACKGROUND

Venlafaxine is a dual-acting serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of depression, prevention of relapse and prevention of recurrence of depression, anxiety or generalized anxiety disorder, social anxiety disorder, and panic disorder. Mirtazapine is indicated for the treatment of depression.

Venlafaxine has a dose-dependent pharmacodynamic profile. At lower doses it primarily inhibits serotonin reuptake, while at higher doses (≥150 mg/day), it additionally inhibits norepinephrine reuptake and exerts weak inhibitory effects on dopamine reuptake.

Several cardiovascular effects are already labelled in section 4.8 of the Summaries of product characteristics (SmPC) in Europe, e.g. tachycardia and hypertension, Torsade de pointes, ventricular tachycardia, ventricular fibrillation, prolonged QT, and stress cardiomyopathy (Takotsubo cardiomyopathy).

A published case series and spontaneously reported cases (e.g. EudraVigilance, Vigibase, US FDA Adverse Event Reporting System (FAERS), company global pharmacovigilance safety database) suggest an association between venlafaxine and cardiotoxicity (heart failure (HF), cardiomyopathy, Ischaemic heart disease).[1,2] In addition, serious cardiac events were reported with venlafaxine overdose. However, a previous observational study did not find an increased risk of adverse cardiac events with low-to-moderate dose venlafaxine compared to sertraline.[3]

An observational study from the DARWIN EU® network could add important further evidence to evaluate the potential association. A study was therefore requested to estimate the association between venlafaxine and heart failure/cardiomyopathy, using mirtazapine, which is indicated for the treatment of depression, as an active comparator.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

Was new use of venlafaxine associated with an increased risk of incident HF compared to new use of mirtazapine?

Was new use of venlafaxine associated with worsening of pre-existing HF compared to new use of mirtazapine?

Objectives

The study aimed to assess the potential association between venlafaxine and HF among adults.

The specific objectives of this study were:

1. To assess the risk of incident HF and incident cardiomyopathy between new users of venlafaxine versus new users of mirtazapine.
2. To assess the risk of HF exacerbation between new users of venlafaxine versus new users of mirtazapine who have been diagnosed with HF before treatment initiation.
3. To characterise both new venlafaxine and new mirtazapine users at the time of treatment start (in terms of demographics, pre-defined comorbidities/comedication/conditions of interest, and drug utilisation) for contextualisation of Objectives 1+2.

Analyses were conducted overall and stratified for condition of interest, age group, sex, history of cardiovascular (CV) disease, and previous Selective Serotonin Reuptake Inhibitor (SSRI) use.

8. RESEARCH METHODS

8.1. Study design

The study comprised two new user active comparator cohort studies (Objectives 1+2) and a patient-level characterisation (Objective 3).

All studies were conducted using routinely collected health data from 6 data sources from 5 countries across Europe and in 4 European Union (EU) member states.

8.1.1. Objectives 1+2

A new user active comparator cohort study design was used to assess

1) The risk of incident heart failure and incident cardiomyopathy between new users of venlafaxine versus new users of mirtazapine.
2) The risk of heart failure exacerbation between new users of venlafaxine versus new users of mirtazapine who have been diagnosed with heart failure before treatment initiation.

This study design was recognised as a gold standard method in the ENCEPP Methodological guidelines and proposed as a standard analysis in the DARWIN EU® Catalogue of Standard Analyses (https://darwin-eu.org/index.php/methods/standardised-analytics).

The studies were designed using the Target trial emulation framework, with the target trial and plan for emulation in DARWIN EU® data sources provided in **Table 1** below. An illustration of the study design is provided in **Figures 1 and 2** below.

Table 1. Study Design Specification for Objectives 1 and 2.

	Target trial	Emulation of target trial in DARWIN EU® data sources
Population		
Inclusion	• Patient consents to participate • Aged ≥18 years at study inclusion/randomisation • Prior history of heart failure [Objective 2 only]	• Aged ≥18 years at index date • At least 730 days of data source history prior to the date of treatment initiation with venlafaxine or mirtazapine (index date) • Index date occurred between 01/01/2010 and date of last data availability in the respective data source • Diagnosis or record of heart failure or cardiomyopathy ever recorded in the data source before index date [Objective 2 only]
Exclusion	• Use of other antidepressants in the year before study start, except SSRIs, which are permitted • Prior history of heart failure or cardiomyopathy [Objective 1 only]	• Prescription/dispensation of other antidepressants recorded in the data source in the year before index date, except SSRIs, which were permitted • Prescription/dispensation record of both venlafaxine and mirtazapine at index date • Diagnosis or record of heart failure or cardiomyopathy ever recorded in the data source before index date [Objective 1 only]
Intervention		
Target	Venlafaxine	Prescription/dispensation record of venlafaxine
Comparator	Mirtazapine	Prescription/dispensation record of mirtazapine
Treatment Assignment	Randomisation to either venlafaxine or mirtazapine.	Participants were classified according to the treatment strategy that their data was compatible at baseline (first prescription of venlafaxine or mirtazapine). Randomisation was emulated using PS matching
Outcome		
Time of outcome	First heart failure (or cardiomyopathy) event after drug therapy has started [Objective 1] Hospitalisation for exacerbation of pre-existing heart failure, acute pulmonary oedema, or recurrent heart failure after drug therapy has started. [Objective 2]	First heart failure (or cardiomyopathy) diagnosis recorded in the data source after index date [Objective 1] Hospitalisation for heart failure, acute pulmonary oedema, or recurrent heart failure recorded in the data source after index date [Objective 2]
Causal estimands		
Censoring	Treated continuously until the earliest occurrence of either an outcome event, death, end of study (24 months), or consent withdrawal	Follow-up ended on the earliest of loss to follow-up, death, end of observation period (the latest available data) or occurrence of outcome of interest (“on treatment” analysis)

	Target trial	Emulation of target trial in DARWIN EU® data sources
		Follow-up ended on the earliest of loss to follow-up, death, end of observation period (the latest available data), occurrence of outcome of interest, or 24 months after index date ("ever exposed" and "on treatment" analysis)
Intercurrent events	• Treatment discontinuation (due to adverse events or resolution of depression) • Treatment switch (due to adverse events or lack of efficacy) • Treatment escalation/add-on treatments were allowed	• Treatment discontinuation (end of first continuous drug era) • Treatment switch, defined as a first record of prescription/dispensation of another antidepressant without continuation of venlafaxine/mirtazapine, as well as a first record of prescription/dispensation of mirtazapine among venlafaxine new users or a first record of prescription/dispensation of venlafaxine among mirtazapine new users • Treatment escalation was allowed (added on of any additional antidepressants or dose escalation) If an individual in the matched pair got censored for any of the reasons above, follow-up for the matched pair was censored. A sensitivity analysis without pair censoring was conducted
Artificial Censoring	NA	Treatment discontinuation and switching were handled through artificial censoring at their occurrence
Causal contrast	1) Per-protocol (PP) analysis, based on the treatment that was received 2) Intention-to-treat (ITT) analysis, based on the treatment that was assigned*	1) Observational analogue of the per-protocol analysis ("on treatment"). Artificial censoring occurred for treatment discontinuation and switching 2) Analysis based on venlafaxine/mirtazapine "ever exposure", with maximum follow-up of 24 months from index date. No artificial censoring for treatment discontinuation and switching*
Statistical analyses		
Statistical analyses	Survival analysis in randomised groups	Among the PS-matched population, we estimated average treatment effects in the treated (ATT) Poisson regression was used to estimate incidence rates of the outcome events in each treatment group Cox proportional hazard models estimated HRs for the outcome events, overall and stratified by age, sex, CV history, previous SSRI use, and condition of interest (depression/anxiety). In addition, incidence rate ratios estimated through Poisson regression analyses were used (in case proportional hazard assumptions were violated) and presented alongside HR NCO and calibrated HRs were used to detect residual confounding, for the overall population,

	Target trial	Emulation of target trial in DARWIN EU® data sources
		previous SSRI use, and condition of interest subgroups were reported in addition Random effect meta-analyses to pool results from individual data sources. I^2 was reported to assess heterogeneity
Sensitivity analyses		Sensitivity analyses were conducted for each outcome: • Restricted to patients with at least 5 years of prior observation prior to index date instead of 730 days • Extending the maximum gap between subsequent prescriptions to be combined to a treatment era from 90 days to 365 days

SSRIs = Selective serotonin reuptake inhibitors; NA = Not applicable; ITT = Intention to treat; ATT = average treatment effects in the treated; HRs = Hazard ratios; CV = Cardiovascular; NCO = Negative control outcomes; I^2 = measure of heterogeneity.
*Details on the causal contrast are provided in **Section 8.6.3.**

Choice of active comparator:

We expected venlafaxine to be predominantly prescribed as a second-line treatment, potentially following treatment with SSRIs as first line treatment for depression. Mirtazapine was considered the most likely alternative treatment option for venlafaxine for treatment of depression and chosen as the active comparator for the comparative safety study. Mirtazapine does not have warnings on heart failure/cardiomyopathy in the SmPC. However, peripheral oedema is labelled as side effect.

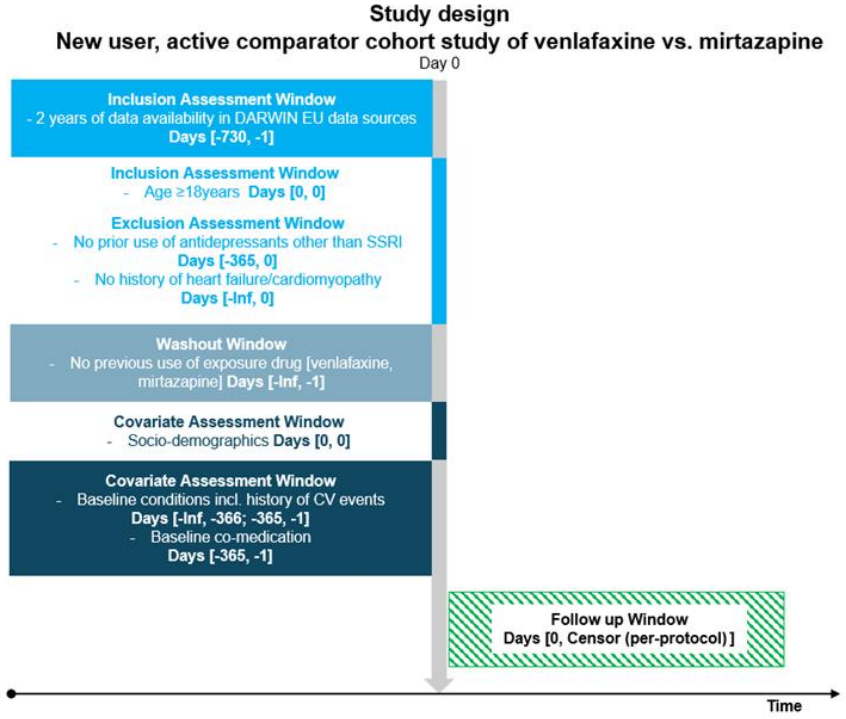

Figure 1. Graphical depiction of the study design for Objective 1.

SSRIs = Selective serotonin reuptake inhibitors; CV = Cardiovascular.

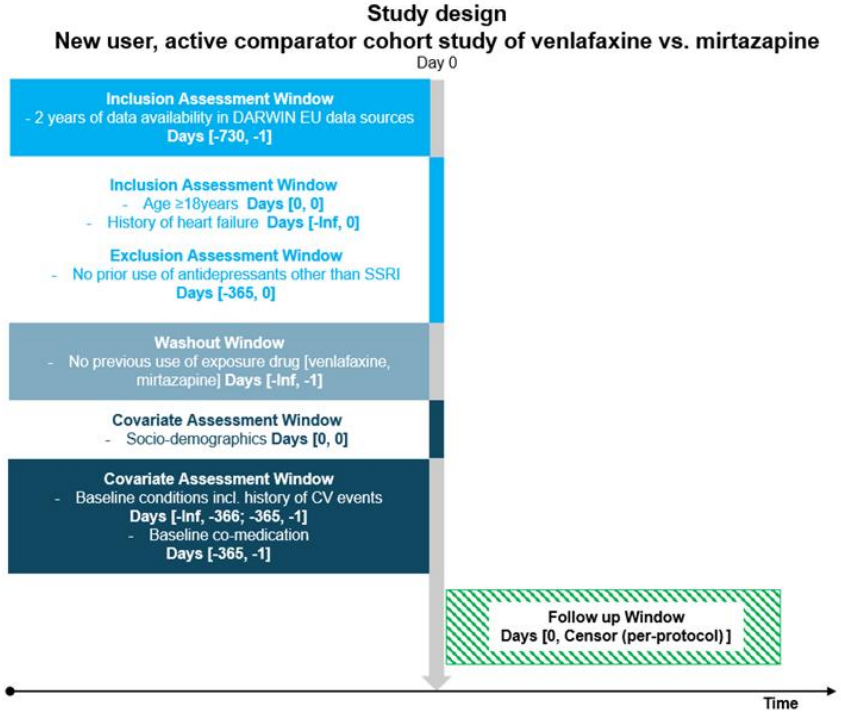

Figure 2. Graphical depiction of the study design for Objective 2.

SSRIs = Selective serotonin reuptake inhibitors; CV = Cardiovascular.

8.1.2. Objective 3

We summarised patient characteristics for new venlafaxine and new mirtazapine users, respectively. Patient-level characterisation included:

- Demographics
- Pre-defined comorbidities (e.g. cardiovascular diseases/history of outcomes)
- Comedication (e.g. previous use of antidepressants)
- Utilisation of venlafaxine and mirtazapine (e.g. time to treatment from depression/anxiety diagnosis, treatment dose, and duration)

Stratifications were conducted for condition of interest/indication (depression/anxiety), age groups, sex, history of CV disease (yes/no), and previous SSRI use (yes/no).

8.2. Follow-up

For characterisation, baseline characteristics were assessed for venlafaxine or mirtazapine users in pre-defined time windows before/at index date.

Follow-up for the new user active comparator cohort studies started on the date of first prescription of venlafaxine or mirtazapine. Follow-up ended on the earliest of

- Loss to follow-up
- Death
- Outcome occurrence
- End of observation period (the latest available data).

In addition, for "on treatment" analyses follow-up was artificially censored at the time of treatment discontinuation (either stopping of treatment or switching to a different treatment).

"Ever exposed" analyses had a maximum follow-up of 24 month after index date. Similarly, in addition to the overall analysis, follow-up was also restricted to 24 months for an "on treatment" analysis.

8.3. Study population with inclusion and exclusion criteria

The study population included all individuals with a recorded first prescription for venlafaxine or mirtazapine within the study period from 01/01/2010 up to the end of data availability who met the eligibility criteria at study entry.

Other eligibility criteria were:

Inclusion criteria

- At least 730 days of data source history prior to index date.
- Aged ≥18 years at index date
- At least one record/diagnosis of heart failure recorded in the data source before index date (Objective 2 only).

Exclusion criteria

- Prescription/dispensation of other antidepressants recorded in the data source in the year before index date, except SSRIs, which were permitted.
- Prescription/dispensation record of both venlafaxine and mirtazapine at index date.
- Diagnosis or record of heart failure or cardiomyopathy ever recorded in the data source before index date (Objective 1 only).

For Objectives 1 – 3, a sensitivity analysis was conducted requiring 5 years of data source history prior to index date.

8.4. Study setting and data sources

This study was conducted using routinely collected data from 6 primary/secondary care data sources in the DARWIN EU® network of data partners from 5 European countries, of which 4 are EU member states. All data were *a priori* mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Spain: Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP)
4. Spain: The Information System for Research in Primary Care (SIDIAP)
5. Sweden: Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)
6. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

An overview of the 6 data sources is provided in **Table 2** below.

Table 2. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals	Calendar period covered by each data source	Contributing to Objectives
Denmark	DK-DHR	Community pharmacists, secondary Care and Hospital in-patient care	National Registry	6M	1995 – 2025	1, 2, 3
Finland	FinOMOP-THL	Primary care, secondary care, hospital inpatient care	EHR, registries	5.7M	2016 – 2023	1, 2, 3
Spain	BIFAP	Primary care, no use of hospital linkage	Insurance claims, EHR, registries	23M	2005 – 2024	1, 2, 3
Spain	SIDIAP	Primary care, hospital inpatient care	EHR	8M	2006 – 2025	1, 2, 3
Sweden	HI-SPEED	Primary care, secondary care, hospital inpatient care	National Registry	4.5M	2015 – 2025	1, 2, 3
The United Kingdom	CPRD GOLD	Primary Care	EHR	17M	1987 – 2025	1, 2, 3

DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; CPRD GOLD = Clinical Practice Research Datalink GOLD; EHR = Electronic Health Records.

Data sources selection

Out of 40 data partners onboarded into the DARWIN EU® network as of November 2025, 10 covered the required setting for the study, namely population-level (regional or national) coverage of primary care, and where available, linked to secondary care or registries. Six data sources had an acceptable estimated size of study population, fulfilled data source recency/lookback period requirements, and covered key variables.

The 6 selected data sources therefore fulfilled the criteria required in terms of data quality, completeness, timeliness, and representativeness for a new user active comparator cohort study while covering different regions of Europe. Additional details on the data sources are provided in **Annex II**.

As CPRD GOLD and BIFAP did not have inpatient data, these data sources did not assess the outcome of heart failure hospitalisation in Objectives 1 and 2.

8.5. Study period

The study period ranged from 01/01/2010 to the most recent data available for each contributing data source (see **Table 2**).

It was noted that the availability of the accurate data ends in 12/2023 in FinOMOP-THL, as prescription records were only available until the end of 2023. Therefore, the study period was restricted to between 2016 – 2023. For HI-SPEED, data availability started in 2015.

8.6. Variables

8.6.1. Exposure

Exposure:

- Venlafaxine (exposure) [ATC-code: N06AX16]
- Mirtazapine (active comparator) [ATC-code: N06AX11]

In this study, venlafaxine or mirtazapine were identified as the first prescription/dispensing recorded (defined as no previous exposure to venlafaxine or mirtazapine in an individual's history) using RxNorm codes for the respective ingredient. The standard ingredient concepts used for the identification of venlafaxine and mirtazapine were 743670 and 725131, respectively. Desvenlafaxine was not included in the venlafaxine cohort.

Drug eras were defined as follows: Exposure starts at the date of the first prescription, e.g. the index date the individual entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the Common Data Model (CDM), using start and end date of the respective prescription. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications: Treatment episodes of sequential prescriptions (i.e. drug era) had a maximum of 90 days between the end date of one prescription and the start date of the next prescription (i.e. definition of gap). The drug era therefore accounted for all periods when the individual was likely to be continuously using venlafaxine or mirtazapine, starting from the day of their first prescription ("index date").

8.6.2. Outcome

Objective 1:

The outcomes for Objective 1 were separated into primary and secondary outcomes:

Heart failure and cardiomyopathy were defined as described in the DARWIN EU® study P3-C3-001 Adverse Events of Special Interest , with the first ever event/diagnosis in the patient history being used as the event date for incident outcomes.

The heart failure (broad) definition included all terms directly related to heart failure, with high sensitivity and moderate specificity, which would reasonably be included in notes for a patient with a clinical diagnosis of heart failure.

Concepts included in the code list for cardiomyopathy (broad) included both codes related to primary and secondary causes, whereas cardiomyopathy (primary) excludes diagnoses related to secondary causes.

Code lists for these conditions are available in **Annex IV.** These definitions were developed following the DARWIN EU® phenotyping standard processes, which involve the development of a clinical description, the review of code lists by clinical experts, and the review of phenotypes after their execution in the participating data sources (of which CPRD GOLD and SIDIAP were included in the present study). We conducted large-scale diagnostics to test the definition in all data sources. Cohort code use for each data source was reported as part of the study results.

Primary outcome: incident heart failure

The following definitions were used:

- Incident heart failure (HF) (broad)

  Cohort inclusion event was the first ever record of heart failure.

Secondary outcomes: broad/narrow definitions for incident heart failure; incident cardiomyopathy

The following definitions were used:

- Incident heart failure (broad), *without* a preceding alternative cause of heart failure

  We used the "Incident heart failure (broad)" definition. Cohort inclusion event was the first ever record of heart failure. In the case that any of the redefined cardiac conditions (Ischaemic heart disease, valvular disease, pulmonary heart disease) were recorded in the month before the respective first ever record of heart failure, we did not consider the event as outcome.

- Incident heart failure (narrow)

  Building on the definition of heart failure (broad), we excluded heart failure cases with a clearly identified primary cause unrelated to cardiomyopathy or acquired drug-related effect ("narrow definition"). Cohort inclusion event was the first ever record of heart failure.

- Incident heart failure (narrow, *without* a preceding alternative cause of heart failure)

  We used the narrow definition of heart failure. Cohort inclusion event was the first ever record of heart failure (narrow). In the case that any of the redefined cardiac conditions (Ischaemic heart disease, valvular disease, pulmonary heart disease) were recorded in the month before the respective first ever record of heart failure, we did not consider the event as outcome.

- Incident cardiomyopathy (broad)

  A broad definition of cardiomyopathy, including both primary and secondary causes (including Takotsubo), were used. Cohort inclusion event was the first ever record of cardiomyopathy.

- Incident cardiomyopathy (narrow)

  We used a definition restricted to records of primary cardiomyopathies, which were typically those where the condition is predominantly confined to the heart muscle. This definition does not include Takotsubo cardiomyopathy. Cohort inclusion event was the first ever record of cardiomyopathy.

- Hospitalisation with heart failure

  Heart failure hospitalisation was defined as a record of heart failure (broad definition) with an inpatient visit (HI-SPEED, FinOMOP-THL, DK-DHR) or a record of heart failure identified from linked hospital records (SIDIAP).

Objective 2:

Proxies for exacerbation of previously diagnosed heart failure were assessed. The following definition was used:

Primary outcome: Hospitalisation with heart failure

- Hospitalisation with heart failure

  Heart failure hospitalisation was defined as a record of heart failure (broad definition) with an inpatient visit (HI-SPEED, FinOMOP-THL, DK-DHR) or a record of heart failure identified from linked hospital records (SIDIAP).

Secondary outcomes: Acute pulmonary oedema, repeated event of heart failure

- Acute pulmonary oedema

  Acute pulmonary oedema was defined as a (first or recurrent) record of acute pulmonary oedema

- Recurrent heart failure (broad)

  We defined recurrent heart failure as a subsequent record of heart failure (broad) diagnosis following the incident diagnosis.

The outcome of recurrent HF diagnosis was assessed carefully at the diagnostic stage due to a high risk of re-recordings of diagnosis which might not accurately reflect a worsening of the condition. The inclusion of secondary outcome was conditional on the results from diagnostics review, e.g. plausibility based on prescriptions/procedures in the immediate time around re-recordings of heart failure.

Objective 3:

The outcome for the patient-level characterisation was summarised patient characteristics, including

- Demographics, including age, sex, previous observation time in the data source
- Conditions of interest, defined as potential indications including depression, anxiety, and other conditions, such as insomnia
- Pre-defined comorbidities, including cardiovascular diseases, CV outcomes, and hypertension
- Comedication, including previous use of antidepressants
- Utilisation of venlafaxine/mirtazapine,
    - time between new treatment from last depression/anxiety diagnosis, respectively
    - treatment dose (initial, cumulative)
    - treatment duration

Analyses for Objective 3 were stratified by condition of interest (for depression/anxiety), sex, age group, history of CV events, and previous SSRI use, respectively.

8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

8.6.3.1. Covariates

Objectives 1+2

Covariates included in the large-scale PS were selected from comedications and comorbidities recorded prior to index date using a data-driven approach (LASSO regression). Pre-defined key variables were used for exact matching, namely age, sex, calendar year, history of CV disease, previous SSRI use, and conditions of interest.

History of CV disease was defined as history of CV events, namely ischaemic heart disease, atrial fibrillation, valvular heart disease, myocardial infarction, and stroke.

Analyses were conducted overall and stratified for age groups (18 – 39, 40 – 59, 60 – 79, 80+), sex, history of CV disease (yes/no), previous SSRI use (yes/no), and clinical indication of interest (depression, anxiety).

Objective 3

The covariates for the new venlafaxine/mirtazapine user characterisation were as follows:

- Demographics
    - Age [median, Interquartile Range (IQR), range, mean, standard deviation (SD)]
    - Sex [binary: female/male]
    - Calendar year [median, IQR, range, mean, SD]

  - Previous observation time in data source [median, IQR, range, mean, SD]
- Conditions of interest
  - Depression (with/without concomitant recording of anxiety)
  - Anxiety (without concomitant recording of depression)
  - Other (i.e. insomnia)
  - Assessment window before/at index date: [-Inf, -366; -365, 0]
- Medication prior to index date (comedication)
  - Previous antidepressant use, including SSRIs, Monoaminooxidase-(MAO)-inhibitors, and tricyclic antidepressants
  - Previous use of cardiovascular (CV) medication: anti-arrhythmic medications, diuretics (aldosterone antagonists), Renin-Angiotensin-Aldosterone-System (RAAS)-inhibitors, beta-blockers, calcium channel blockers (CCB).
  - Non-steroidal anti-Inflammatory drugs (NSAIDs), corticosteroids
  - Assessment window before index date: [-365, -1]
- Comorbidities
  - History of outcome events: heart failure, cardiomyopathy
  - History of CV events: ischaemic heart disease, atrial fibrillation and valvular heart disease, myocardial infarction (MI), stroke
  - Hypertension, diabetes mellitus, obesity, chronic kidney disease
  - Assessment window before index date: [-Inf, -366; -365, -1]
- Healthcare visits
  - Outpatient visits [primary care/outpatient specialised care] (where available in the respective data source)
  - Inpatient visits (where available in the respective data source)
  - Assessment window before index date: [-365, -1]
- Drug utilisation for venlafaxine/mirtazapine:
  - Time between new treatment (index date) and last record of depression diagnosis [median, IQR, range, mean, SD]
  - Time between new treatment (index date) and last record of anxiety diagnosis [median, IQR, range, mean, SD]
  - The number of records/episodes for depression/anxiety, with a washout of ≥365 days between repeated recordings (where possible) [median, IQR, range, mean, SD]
  - Initial treatment dose [median, IQR, range, mean, SD]
  - Number of prescriptions in the first treatment era [median, IQR, range, mean, SD]
  - Cumulative dose for first treatment era [median, IQR, range, mean, SD]
  - Duration of first continuous treatment era [median, IQR, range, mean, SD]

Analyses were conducted overall and stratified for age groups (18 – 39, 40 – 59, 60 – 79, 80+), sex, history of CV disease (yes/no), previous SSRI use (yes/no), and clinical indication of interest (depression, anxiety).

8.6.3.2. Intercurrent events/censoring

Intercurrent events were events that occurred after the start of follow-up (e.g. treatment initiation or cohort entry) and that may have affected the interpretation or the existence of the outcome of interest.

For Objectives 1 and 2, the primary estimand is the "on treatment" causal effect (i.e. the effect under full adherence), and the secondary estimand is the "ever exposed" effect (i.e. the effect of treatment assignment regardless of adherence). For both, we censored follow-up at the time of the following events:

Censoring:

- Loss to follow-up
- End of observation period (latest available data)
- Death
- Outcome occurrence
- 24 months (for "ever exposed" and "on treatment" analyses with restricted follow-up)

If an individual in the matched pair was censored for any of the reasons above, follow-up for the affected individual was ended but not for the matched counterpart.

Artificial censoring:

As per the "on treatment" approach, we censored follow-up at the time an individual discontinues treatments (i.e. end of the continuous treatment era) with venlafaxine and mirtazapine, respectively.

Artificial censoring was conducted at

- Treatment discontinuation (end of first continuous drug era)
- Treatment switch (defined as a first record of prescription/dispensation of another antidepressant without continuation of venlafaxine/mirtazapine, as well as a first record of prescription/dispensation of mirtazapine among venlafaxine new users or a first record of prescription/dispensation of venlafaxine among mirtazapine new users)

Treatment escalation was allowed, and no censoring was done in case of the addition of any additional antidepressant or dose escalation. If an individual in the matched pair got censored for any of the reasons above, follow-up for the matched pair was censored. Sensitivity analyses without censoring the pair were conducted.

8.6.4. Negative Control Outcomes

Negative control outcomes (NCO) are outcomes not causally associated with the exposure of interest,[4] here venlafaxine. However, their association with venlafaxine is ideally impacted by the same type of unmeasured confounding, e.g. healthcare-seeking behaviour, as the venlafaxine-outcome association.[5] NCO was used as an additional measure to identify any potential residual confounding.

A list of NCOs (**Annex IV**) is provided. Additional NCO were identified through large-scale characterisation at the study diagnostics stage: Among all venlafaxine/mirtazapine users in each data source, the 50 most commonly recorded conditions in the 180 days after treatment start were extracted. The list was then used by clinical experts to identify potential NCOs. This process was done to ensure sufficient counts of NCOs in the respective data source and study cohort.

8.7. Study size

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine in the data sources included in this study ranged from 184,600 (HI-SPEED) to 303,200 (CPRD GOLD). The expected number of person counts for mirtazapine in the data sources included in this study ranged from 266,900 (SIDIAP) to 1,088,000 (BIFAP). The expected number of person counts for heart failure in the data sources included in this study ranged from 252,200 (CPRD GOLD) to 936,600 (BIFAP).

In the DARWIN EU® P3-C3-001 (Adverse events of special interest) study, background rates of heart failure were estimated to be 138 per 100,000 person-years in CPRD GOLD and 386 per 100,000 person-years in SIDIAP.

Estimation of precision

Table 3 below shows the required number of events and sample size to estimate a HR of 1.25 with a relative precision of 5, 10, and 20%. Depending on the expected (difference in) event rates of incident heart failure outcomes in the venlafaxine and mirtazapine groups, the required sample size ranged between 13,697 and 573,793.

Table 3. Relative precision for HR incident heart failure.

Expected HR	Event rate venlafaxine	Event rate mirtazapine	Relative precision (%)	Lower limit 95%CI	Upper limit 95%CI	Events	Sample size
1.25	0.0125	0.01	5	1.19	1.31	6455	573,793
1.25	0.0125	0.01	10	1.14	1.38	1692	150,363
1.25	0.0125	0.01	20	1.04	1.50	462	41,091
1.25	0.025	0.02	5	1.19	1.31	6455	286,896
1.25	0.025	0.02	10	1.14	1.38	1692	75,182
1.25	0.025	0.02	20	1.04	1.50	462	20,545
1.25	0.0375	0.03	5	1.19	1.31	6455	191,264
1.25	0.0375	0.03	10	1.14	1.38	1692	50,121
1.25	0.0375	0.03	20	1.04	1.50	462	13,697

HRs = Hazard ratios; CI = 95% Confidence interval. Estimated based on Rothman KJ, Greenland S. Planning Study Size Based on Precision Rather Than Power. Epidemiology (Cambridge, Mass). 2018;29(5):599–603. and Schoenfeld D. Sample-size formula for the proportional-hazards regression model. Biometrics. 1983.

Table 4 shows the required number of events and sample size to estimate a HR of 1.25 with a relative precision of 5, 10, and 20%. Depending on the expected (difference in) event rates of heart failure (repeated events) outcomes in the venlafaxine and mirtazapine groups, the required sample size ranged between 1,370 and 57,379.

Table 4. Relative precision for HR heart failure.

Expected HR	Event rate venlafaxine	Event rate mirtazapine	Relative precision (%)	Lower limit 95%CI	Upper limit 95%CI	Events	Sample size
1.25	0.125	0.1	5	1.19	1.31	6,455	57,379
1.25	0.125	0.1	10	1.14	1.38	1,692	15,036
1.25	0.125	0.1	20	1.04	1.50	462	4,109
1.25	0.25	0.2	5	1.19	1.31	6,455	28,690
1.25	0.25	0.2	10	1.14	1.38	1,692	7,518
1.25	0.25	0.2	20	1.04	1.50	462	2,055
1.25	0.375	0.3	5	1.19	1.31	6,455	19,126
1.25	0.375	0.3	10	1.14	1.38	1,692	5,012
1.25	0.375	0.3	20	1.04	1.50	462	1,370

CI = 95% Confidence interval. Estimated based on Rothman KJ, Greenland S. Planning Study Size Based on Precision Rather Than Power. Epidemiology (Cambridge, Mass). 2018;29(5):599–603. and Schoenfeld D. Sample-size formula for the proportional-hazards regression model. Biometrics. 1983.

Minimum detectable relative risk (MDRR)

MDRRs estimated based on preliminary feasibility counts and event rate of 100/100,000 person years and/or 200/100,000 person years over a 5-year follow-up with an alpha of 0.05, power of 80%, are presented in **Table 5** below.

Table 5. MDRR.

Event rate		DK-DHR	FinOMOP-THL	BIFAP	SIDIAP	HI-SPEED	CPRD GOLD
100/100,000 person years	MDRR	<0.91; >1.10	<0.92; >1.10	<0.91; >1.10	<0.90; >1.13	<0.90; >1.11	<0.92; >1.09
200/100,000 person years	MDRR	<0.94; >1.07	<0.94; >1.08	<0.94; >1.08	<0.92; >1.10	<0.93; >1.09	<0.94; >1.06

DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; CPRD GOLD = Clinical Practice Research Datalink GOLD; MDRR = Minimum detectable relative risk.

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **Annex III**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main summary measures

Objectives 1 – 3

The patient-level characterisation analyses were calculated based on OMOP CDM mapped data.

Covariates of interest included demographics, conditions of interest, pre-defined comorbidities and previous medication, healthcare visits, as well as analyses on the utilisation of venlafaxine and mirtazapine.

Analyses were stratified separately by conditions of interest (depression/anxiety), age group, sex, history of CV disease (yes/no), and previous SSRI use (yes/no). For categorical variables, counts and proportions were reported. For numeric variables, median/IQR, mean/SD, and range were reported.

The R packages *CohortCharacteristics* [6] and *DrugUtilisation* [7], developed by DARWIN EU®, were used for these analyses.

Objectives 1 – 2

Following PS matching, we estimated incidence rates as events per 10,000 person-years and 95% confidence intervals for each of the outcomes of interest in the respective treatment group (venlafaxine/mirtazapine). Poisson regression was used.

In addition to the overall analyses, analysis with a pre-defined follow-up of up to 24 months after index date was conducted. This analysis was not stratified.

8.9.2. Main statistical methods

Objectives 1+2

The new user active comparator cohort studies were conducted using OMOP CDM mapped data.

Matching

All individuals meeting the eligibility criteria were included in the venlafaxine or mirtazapine group based on the first prescription they received, respectively. This prescription defined the “index date”, which was used for Propensity Score (PS) calculation. PS estimated the probability of receiving target treatment.

We used PS matching (ratio 1:1) to minimize observed confounding: venlafaxine versus mirtazapine users were matched based on a combination of 1) pre-defined key variables for exact matching, namely:

- Age (e.g. 5-year age bands)
- Sex (exact)
- Calendar time (+/- 365days from index date)
- Region (location identifier, exact) [BIFAP only]
- History of CV disease [yes/no] (exact) [-Inf, -1]
- Condition of interest [depression (yes/no), anxiety (yes/no)] (exact) [-365, 0]
- previous SSRI use [yes/no] (exact) [-365, -1]

In addition, 2) calliper matching (0.2 Standard Deviation) on large-scale PS were conducted: Covariates included in the large-scale PS were selected from comedications [assessment windows: -365, -31; -30, -1] and comorbidities recorded prior to index date [assessment windows: -Inf, -366; -365, -31; -30, -1]. Among those, covariates with a prevalence below 0.5% in the study population were omitted. Logistic regression with LASSO regularisation were used for variable selection. The list of selected covariates was manually

screened by 2 epidemiologists/clinical domain experts to exclude potential instrumental variables and variables already used for exact matching.

Propensity Scores: Diagnostics

Large-scale covariate balance was assessed before/after PS matching through visual inspection: For each data source, a plot was produced depicting the standardised mean differences between venlafaxine and mirtazapine cohorts for all available covariates before (x axis) and after PS matching (y axis).

Similarly, equipoise was assessed for each data source though plots of the distribution of the PS stratified by venlafaxine versus mirtazapine cohort.

Comparative Safety: Survival analyses

Cox proportional hazard models were used to estimate hazard ratios (HRs) for the outcomes of interest, respectively. Kaplan Meier plots and/or cumulative incidence plots were used to illustrate survival analyses. Corresponding 95% confidence intervals were provided.

"On treatment" analyses were conducted with artificial censoring at treatment discontinuation or switch to restrict the analyses to treatment-exposed times and avoid treatment exposure misclassification. In addition to the overall analyses, analysis with a pre-defined follow-up of up to 24 months after index date was conducted.

Analyses based on an individual's status of being "ever exposed" to venlafaxine/mirtazapine were conducted for a pre-defined follow-up of up to 24 months after index date without artificial censoring, allowing for capture of potential clinical complications/late cardiac effects following discontinuation of venlafaxine/mirtazapine.

HRs were calculated for each outcome overall and stratified by age group, sex, history of CV disease, previous SSRI use, and condition of interest (depression/anxiety).

The proportional hazard assumption was tested through visual investigation of log(-log) plots. Incidence rate ratios were calculated from Poisson regression (which does not rely on the proportional hazard assumption), and presented alongside the HR.

A list of NCOs was used to identify unmeasured confounding. Cox proportional hazard models were used to estimate HRs for NCOs, which were presented in forest plots. Additionally, calibrated HRs were provided for each outcome in the overall study population and in the stratified analyses of previous SSRI use and conditions of interest (depression/anxiety) to help understand whether unmeasured confounding was present.

Evidence synthesis: For Objectives 1+2, we reported all analyses separately for each data source and outcome. Additionally, pooled effect estimates across data sources were estimated using random effect meta-analyses for analyses for which at least 3 data sources have event counts ≥5. I^2 for heterogeneity will be reported. Forest plots were used to show results from meta-analyses.

Results from analyses described in Objective 3 were presented separately for each data source. No meta-analyses of results were conducted.

8.9.3. Missing values

We excluded individuals with missing sex and year of birth.

8.9.4. Sensitivity analysis

The following sensitivity analyses have been conducted:

- Restricting the study populations to individuals with at least 5 years of data availability prior to index date
- Extending the maximum gap between subsequent prescriptions to be combined to a treatment era from 90 days to 365 days

8.10. Deviations from the protocol

Table 6. Deviations from the protocol.

Deviation number	Protocol version	Section of study protocol	Deviation	Reason
1	V5	8.3: Study Population with inclusion and exclusion criteria: "For Objectives 1 – 2, a sensitivity analysis was conducted requiring 5 years of data source history prior to index date"	Sensitivity analysis was conducted for Objective 3 in addition	Allows for contextualisation of results from sensitivity analysis of Objectives 1 – 2
2	V5	8.9.2: Main statistical methods: "We used PS matching (ratio 1:1) to minimize observed confounding […] key variables for exact matching"	Region (location identifier) was added as criterion for exact matching for BIFAP	Control for potential bias due to differences of availability of linked data by region/time
3	V5	8.9.4: Sensitivity analyses	Extending the maximum gap between subsequent prescriptions to be combined to a treatment era from 90 days to 365 days	Prescriptions for chronic conditions in FinOMOP-THL are typically issued for 1 – 2 years. The 90 days gap period showed substantially shortened treatment duration for venlafaxine during diagnostics in FinOMOP-THL compared to other data sources
4	V5	8.9.2: Main statistical methods: Windows for exact matching	History of CV disease [-Inf, -1] instead of [-365, -1]; previous SSRI use [-365, -1] instead of [-365, 0]	Alignment with other criteria for matching

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; FinOMOP-THL = Finnish Care Register for Health Care; CV = Cardiovascular Disease; PS = Propensity Score.

9. RESULTS

The full set of results for this study is available in an interactive web-application ("Shiny app") at EUPAS1000000974.

9.1. Participants

Overall, we identified 1,800,000 initial records for new venlafaxine users and 4,242,548 initial records for new mirtazapine users from 6 European data sources. Of those, 581,858 initial records for venlafaxine users were from BIFAP; 303,198 from CPRD GOLD; 265,650 from DK-DHR; 240,041 from FinOMOP-THL; 196,891 from HI-SPEED; and 212,362 from SIDIAP.

After applying general eligibility criteria of: records within the study period; restricting to the first ever treatment record for venlafaxine or mirtazapine, respectively; age ≥18; excluding individuals receiving both treatments on the same day; and requiring 730 days of prior observation, we included 763,275 new venlafaxine users and 2,739,112 new mirtazapine users for Objective 3.

From these 2 new user cohorts, we subsequently applied additional eligibility criteria for inclusion to the causal inference studies in Objectives 1 and 2, respectively:

Objective 1: assessing the risk of incident heart failure

After PS matching, 514,210 new users of venlafaxine were matched to new users of mirtazapine (151,787 from BIFAP, 44,952 from CPRD GOLD, 60,058 from DK-DHR, 57,706 from FinOMOP-THL, 125,609 from HI-SPEED, and 74,098 from SIDIAP). The proportion of new eligible venlafaxine users who were matched ranged from 82.0% in DK-DHR to 95.6% in HI-SPEED.

Objective 2: assessing the risk of heart failure exacerbation

After PS matching, 4,627 new users of venlafaxine with a history of heart failure were matched to new users of mirtazapine (1,162 from FinOMOP-THL, 1,644 from HI-SPEED, and 1,821 from SIDIAP). As the counts of eligible venlafaxine users in BIFAP, CPRD GOLD and DK-DHR were below the required minimum sample size of <1370 individuals no analyses are reported for those data sources.

Table 7 provides the attrition rates for all 3 objectives.

Table 7. Number of individuals with venlafaxine or mirtazapine included for matching.

Reason	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Initial qualifying events	1,087,996	581,858	620,367	303,198	594,934	265,650	852,767	240,041	782,867	196,891	303,617	212,362
Record in observation	1,087,996	581,858	620,367	303,198	594,264	265,305	851,592	239,812	782,517	196,790	303,617	212,362
Collapse individual prescriptions to continuous treatment era (gap of 90 days)	1,087,996	581,858	620,367	303,198	594,264	265,305	851,592	239,812	782,517	196,790	303,617	212,362
First ever prescription (venlafaxine or mirtazapine)	1,087,996	581,858	620,367	303,198	594,264	265,305	851,592	239,812	782,517	196,790	303,617	212,362
Study period start date after 2010-01-01	980,439	466,074	456,548	136,436	346,105	131,128	NA	NA	NA	NA	269,421	158,882
Study period start date after 2015-01-01	NA	NA	NA	NA	NA	NA	NA	NA	782,517	196,790	NA	NA
Study period start date after 2016-01-01	NA	NA	NA	NA	NA	NA	586,981	150,929	NA	NA	NA	NA
Study period start date before 2023-12-31	NA	NA	NA	NA	NA	NA	552,619	142,310	NA	NA	NA	NA
Age requirement: >=18	972,430	462,305	455,364	136,233	344,202	130,171	541,420	138,627	771,142	195,234	267,015	157,842
Exclude individuals with a prior history (index date included)	873,546	383,584	419,204	90,720	310,757	90,899	500,982	87,650	732,279	154,377	229,738	129,859

Reason	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
of the alternative treatment												
Prior observation requirement: 730 days	685,023	251,547	305,328	59,390	304,780	88,318	494,658	86,177	726,803	152,618	222,520	125,225
ELIGIBLE for OBJECTIVE 3	685,023	251,547	305,328	59,390	304,780	88,318	494,658	86,177	726,803	152,618	222,520	125,225
Additional inclusion criteria for Objective 1 (from Objective 3 eligible population)												
No antidepressants (other than SSRI) in the year before index date	484,823	179,486	254,553	48,304	277,632	74,599	433,264	63,318	655,521	133,648	172,031	93,549
No prior history of heart failure or cardiomyopathy (any time before index date)	474,908	178,171	249,286	48,075	261,571	73,215	406,402	61,685	592,853	131,385	155,983	89,950
Restrict to matched individuals **(OBJECTIVE 1)**	151,787	151,787	44,952	44,952	60,058	60,058	57,706	57,706	125,609	125,609	74,098	74,098
Additional inclusion criteria for Objective 2 (from Objective 3 eligible population)												
No antidepressants (other than SSRI) in the year before index date	484,823	179,486	254,553	48,304	277,632	74,599	433,264	63,318	655,521	133,648	172,031	93,549

Reason	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Prior history of heart failure (any time before index date)	8,706	1,088	4,892	199	15,448	1,289	25,631	1,519	61,121	2,103	15,012	3,174
Restrict to matched individuals* **(OBJECTIVE 2)**	NA	NA	NA	NA	NA	NA	1,162	1,162	1,644	1,644	1,821	1,821

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; SSRI = Selective Serotonin Reuptake Inhibitors; NA = not applicable.
*As per the calculation of precision of 5, 10, and 20% in the study protocol (**Table 4**), the required sample size to estimate a HR of 1.25 ranged between 1,370 and 57,379. We therefore do not report analyses with n<1,370 for new venlafaxine users.

9.2. Descriptive data

9.2.1. Objective 1

9.2.1.1. Measured Confounding: Diagnostics of Propensity Score Matching

Propensity Score (PS) matching was applied to minimise measured confounding. **Figure 3** below shows a scatterplot of the absolute standardised mean differences (ASMDs) of covariates included in the large-scale PS. While several covariates were unbalanced with ASMD >0.1 prior to PS matching (x-axis), covariance balance was achieved after PS matching (y-axis), with all covariates having ASMD <0.1, except for anxiety with ASMD 0.101 in DK-DHR.

With covariance balance between matched cohorts being achieved, we report results of all data sources in the following sections.

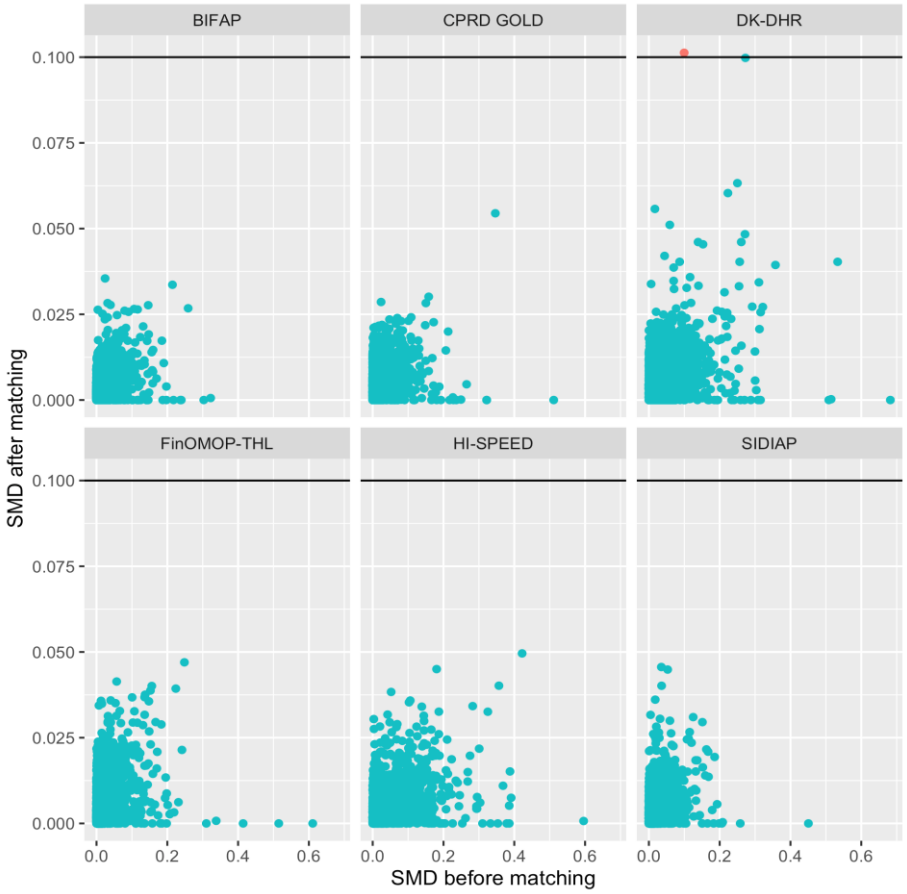

Figure 3. Diagnostics of Propensity Score Matching.

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; SIDIAP = The Information System for Research in Primary Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; CPRD GOLD = Clinical Practice Research Datalink GOLD. Covariates in green colour indicate (absolute) standardised mean differences ASMD <0.1 after matching, covariates in red colour indicate ASMD >0.1 after matching.

9.2.1.2. Baseline characteristics after matching

The median age of matched new users of venlafaxine and mirtazapine ranged from 39 years (IQR 26 – 56) in FINOMOP-THL to 52 years (IQR 41 – 66) in SIDIAP (**Table 8**).

New users in all data sources were more commonly female, with the proportion ranging between 59.45% in DK-DHR and 70.5% in BIFAP. The most common condition of interest (proxy for potential indication) recording in the year before treatment across data sources (except SIDIAP) was depression (ranging from 14.5% in BIFAP to 79.4% in DK-DHR). In SIDIAP, the most commonly recorded condition was anxiety (25.9%). Other conditions of interest were mostly balanced between venlafaxine and mirtazapine users. While SMDs were balanced in the PS for individual diagnosis codes of insomnia and sleep disorder prior to index date, a higher frequency of insomnia was observed in the mirtazapine group. This was due to a higher proportion of insomnia records on index date in mirtazapine users compared to venlafaxine users as seen in CPRD GOLD. Prior cardiovascular conditions, such as Ischaemic stroke, Ischaemic heart disease or myocardial infarction, and atrial fibrillation, were uncommon (<2%), and the prevalence of cardiovascular risk factors ranged between 3.2% – 7.6% for hypertension and 1.3% – 6.2% for diabetes.

The percentage of previous SSRI use ranged from 32.1% in HI-SPEED to 71.5% in CPRD GOLD, as a proxy for first- versus second-line use of venlafaxine and mirtazapine across the data sources. Individuals with a previous diagnosis of heart failure were excluded from Objective 1, and high ceiling diuretics (e.g. furosemide), which are often used for heart failure treatment, were only prescribed in 0.95% – 4.7% of individuals prior to index date.

The median initial daily dose in milligrams was 70 – 75mg for venlafaxine and 15mg for mirtazapine and was generally consistent across data sources. However, in DK-DHR, the median initial doses for venlafaxine and mirtazapine were higher, with 30mg and 100mg, respectively.

The median calculated treatment duration for venlafaxine allowing for a max. 90-day gap between prescriptions ranged from 42 days in FinOMOP-THL to 446 days in HI-SPEED, whilst treatment duration for mirtazapine ranged from 30 days (FinOMOP-THL) to 181 days (HI-SPEED). Extending the gap length to 365 days between prescriptions increased the calculated treatment duration for venlafaxine to a median of 87 in FinOMOP-THL.

Table 8. Patient baseline characteristics of matched venlafaxine and mirtazapine users with no history of HF.

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Demographics													
Number (subjects)	N	151,787	151,787	44,952	44,952	60,058	60,058	57,706	57,706	125,609	125,609	74,098	74,098
Age	Median [IQR]	51 [40 – 65]	51 [40 – 65]	43 [31 – 54]	43 [31 – 53]	43 [30 – 56]	43 [30 – 56]	39 [26 – 56]	39 [26 – 56]	44 [31 – 58]	44 [31 – 58]	52 [41 – 66]	52 [41 – 66]
	Mean (SD)	52.74 (17.23)	52.73 (17.20)	43.38 (15.47)	43.40 (15.44)	44.51 (17.58)	44.50 (17.54)	42.70 (18.81)	42.68 (18.79)	45.71 (17.42)	45.69 (17.34)	53.60 (17.22)	53.59 (17.17)
Sex: Female	N (%)	107,077 (70.54%)	107,077 (70.54%)	30,773 (68.46%)	30,773 (68.46%)	35,704 (59.45%)	35,704 (59.45%)	38,055 (65.95%)	38,055 (65.95%)	77,647 (61.82%)	77,647 (61.82%)	50,021 (67.51%)	50,021 (67.51%)
Duration of prior observation (days)	Median [IQR]	2,826 [1,833 – 4,439]	2,831 [1,842 – 4,464]	4,125 [2,510 – 5,859]	4,206 [2,501 – 5,941]	6,741 [5,884 – 8,073]	6,820 [5,966 – 8,143]	3,096 [2,431 – 3,883]	3,092 [2,441 – 3,903]	1,401 [1,145 – 2,237]	1,303 [1,139 – 2,276]	3,784 [2,539 – 5,402]	3,847 [2,593 – 5,470]
	Mean (SD)	3,220.89 (1,742.97)	3,236.41 (1,757.00)	4,287.20 (2,226.74)	4,320.34 (2,233.10)	6,840.21 (1,977.78)	6,965.92 (1,879.26)	3,148.15 (863.72)	3,164.31 (859.07)	1,765.77 (785.49)	1,759.94 (807.97)	3,944.74 (1,642.44)	3,993.43 (1,648.53)
Duration of future observation (days)	Median [IQR]	1,758 [719 – 3,512]	1,804 [753 – 3,535]	1,422 [592 – 2,752]	1,382 [597 – 2,660]	3,312 [1,606 – 4,518]	3,409 [1,741 – 4,553]	1,764 [992 – 2,478]	1,790 [986 – 2,486]	2,353 [1,353 – 2,727]	2,441 [1,386 – 2,744]	2,259 [967 – 3,757]	2,298 [1,005 – 3,828]
	Mean (SD)	2,143.96 (1,601.63)	2,174.65 (1,607.06)	1,806.63 (1,446.53)	1,761.79 (1,414.26)	3,043.93 (1,639.47)	3,109.64 (1,610.50)	1,727.81 (852.97)	1,738.72 (859.66)	1,988.94 (841.78)	2,028.24 (850.54)	2,403.42 (1,587.25)	2,447.83 (1,599.87)

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Treatment duration (days)	Median [IQR]	91 [31 – 282]	153 [31 – 507]	76 [28 – 272]	166 [30 – 617]	60 [30 – 179]	207 [73 – 631]	30 [30 – 30]	42 [30 – 114]	133 [61 – 523]	446 [121 – 1,402]	181 [59 – 537]	340 [91 – 959]
	Mean (SD)	313.89 (618.04)	476.07 (801.72)	323.78 (657.08)	538.52 (870.51)	224.99 (514.15)	580.17 (915.10)	50.22 (59.97)	87.32 (97.57)	512.38 (779.79)	881.31 (941.42)	521.01 (868.30)	784.94 (1,092.11)
Conditions of interest [-365, 0]													
Depression	N (%)	21,989 (14.49%)	21,989 (14.49%)	10,110 (22.49%)	10,110 (22.49%)	47,661 (79.36%)	47,661 (79.36%)	20,425 (35.39%)	20,425 (35.39%)	35,112 (27.95%)	35,112 (27.95%)	15,389 (20.77%)	15,389 (20.77%)
Anxiety	N (%)	17,188 (11.32%)	17,188 (11.32%)	6,933 (15.42%)	6,933 (15.42%)	10,902 (18.15%)	10,902 (18.15%)	12,043 (20.87%)	12,043 (20.87%)	21,326 (16.98%)	21,326 (16.98%)	19,182 (25.89%)	19,182 (25.89%)
Other													
- Insomnia	N (%)	10,478 (6.90%)	4,945 (3.26%)	1,751 (3.90%)	967 (2.15%)	10,610 (17.67%)	8,900 (14.82%)	5,969 (10.34%)	1,291 (2.24%)	948 (0.75%)	673 (0.54%)	6,494 (8.76%)	3,045 (4.11%)
- Menopausal symptoms	N (%)	1,013 (0.67%)	1,156 (0.76%)	508 (1.13%)	2,029 (4.51%)	15 (0.02%)	26 (0.04%)	889 (1.54%)	1,474 (2.55%)	1,150 (0.92%)	1,165 (0.93%)	1,107 (1.49%)	1,119 (1.51%)
- Migraine	N (%)	1,716 (1.13%)	1,734 (1.14%)	603 (1.34%)	614 (1.37%)	2,341 (3.90%)	2,316 (3.86%)	1,598 (2.77%)	1,540 (2.67%)	1,793 (1.43%)	1,703 (1.36%)	1,087 (1.47%)	1,053 (1.42%)
- Neuropathic pain	N (%)	3,808 (2.51%)	4,084 (2.69%)	457 (1.02%)	432 (0.96%)	767 (1.28%)	942 (1.57%)	1,380 (2.39%)	1,516 (2.63%)	1,502 (1.20%)	1,464 (1.17%)	3,995 (5.39%)	3,938 (5.31%)
Comorbidities [-365, -1]													

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Atrial fibrillation	N (%)	855 (0.56%)	801 (0.53%)	68 (0.15%)	55 (0.12%)	131 (0.22%)	135 (0.22%)	101 (0.18%)	86 (0.15%)	486 (0.39%)	501 (0.40%)	615 (0.83%)	619 (0.84%)
Chronic renal disease	N (%)	940 (0.62%)	902 (0.59%)	189 (0.42%)	185 (0.41%)	208 (0.35%)	198 (0.33%)	119 (0.21%)	144 (0.25%)	571 (0.45%)	514 (0.41%)	917 (1.24%)	1,001 (1.35%)
Diabetes mellitus	N (%)	1,961 (1.29%)	2,183 (1.44%)	562 (1.25%)	590 (1.31%)	2,840 (4.73%)	3,092 (5.15%)	2,779 (4.82%)	3,022 (5.24%)	6,955 (5.54%)	7,837 (6.24%)	2,275 (3.07%)	2,313 (3.12%)
Hypertension	N (%)	4,678 (3.08%)	4,787 (3.15%)	1,707 (3.80%)	1,671 (3.72%)	4,467 (7.44%)	4,821 (8.03%)	3,566 (6.18%)	3,920 (6.79%)	8,513 (6.78%)	9,586 (7.63%)	5,098 (6.88%)	4,925 (6.65%)
Ischaemic stroke	N (%)	346 (0.23%)	336 (0.22%)	114 (0.25%)	87 (0.19%)	613 (1.02%)	578 (0.96%)	566 (0.98%)	598 (1.04%)	921 (0.73%)	840 (0.67%)	741 (1.00%)	746 (1.01%)
Ischaemic heart disease	N (%)	556 (0.37%)	514 (0.34%)	105 (0.23%)	89 (0.20%)	748 (1.25%)	750 (1.25%)	727 (1.26%)	764 (1.32%)	1,383 (1.10%)	1,367 (1.09%)	718 (0.97%)	660 (0.89%)
Myocardial infarction	N (%)	304 (0.20%)	287 (0.19%)	44 (0.10%)	33 (0.07%)	189 (0.31%)	174 (0.29%)	154 (0.27%)	151 (0.26%)	738 (0.59%)	685 (0.55%)	262 (0.35%)	246 (0.33%)
Obesity	N (%)	1,903 (1.25%)	2,089 (1.38%)	362 (0.81%)	417 (0.93%)	1,357 (2.26%)	1,592 (2.65%)	905 (1.57%)	960 (1.66%)	2,441 (1.94%)	2,805 (2.23%)	2,670 (3.60%)	2,947 (3.98%)
Valvular heart disease	N (%)	114 (0.08%)	97 (0.06%)	28 (0.06%)	28 (0.06%)	239 (0.40%)	229 (0.38%)	223 (0.39%)	213 (0.37%)	299 (0.24%)	309 (0.25%)	226 (0.31%)	204 (0.28%)
Prior medications [-365, -1]													

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Aldosterone antagonists	N (%)	1,341 (0.88%)	1,254 (0.83%)	142 (0.32%)	123 (0.27%)	506 (0.84%)	507 (0.84%)	311 (0.54%)	365 (0.63%)	500 (0.40%)	540 (0.43%)	373 (0.50%)	368 (0.50%)
Antiarrhythmics	N (%)	888 (0.59%)	890 (0.59%)	617 (1.37%)	650 (1.45%)	80 (0.13%)	105 (0.17%)	254 (0.44%)	295 (0.51%)	1,080 (0.86%)	1,102 (0.88%)	510 (0.69%)	517 (0.70%)
Betablockers	N (%)	11,278 (7.43%)	11,527 (7.59%)	7,001 (15.57%)	6,902 (15.35%)	4,447 (7.40%)	4,611 (7.68%)	10,460 (18.13%)	10,572 (18.32%)	7,880 (6.27%)	8,681 (6.91%)	5,455 (7.36%)	5,476 (7.39%)
CCB	N (%)	8,459 (5.57%)	8,705 (5.74%)	2,426 (5.40%)	2,460 (5.47%)	4,627 (7.70%)	5,092 (8.48%)	3,593 (6.23%)	3,750 (6.50%)	5,275 (4.20%)	6,033 (4.80%)	4,826 (6.51%)	4,822 (6.51%)
Glucocorticoids	N (%)	22,049 (14.53%)	21,442 (14.13%)	3,311 (7.37%)	3,241 (7.21%)	4,202 (7.00%)	4,029 (6.71%)	7,874 (13.65%)	8,091 (14.02%)	12,475 (9.93%)	12,648 (10.07%)	8,910 (12.02%)	8,811 (11.89%)
High ceiling diuretics	N (%)	6,873 (4.53%)	7,177 (4.73%)	710 (1.58%)	774 (1.72%)	1,869 (3.11%)	1,980 (3.30%)	1,123 (1.95%)	1,289 (2.23%)	1,191 (0.95%)	1,343 (1.07%)	2,308 (3.11%)	2,449 (3.31%)
NSAIDs	N (%)	97,290 (64.10%)	95,032 (62.61%)	11,097 (24.69%)	10,647 (23.69%)	16,395 (27.30%)	16,256 (27.07%)	28,622 (49.60%)	27,927 (48.40%)	24,567 (19.56%)	24,104 (19.19%)	35,984 (48.56%)	34,489 (46.55%)
RAAS	N (%)	21,401 (14.10%)	22,030 (14.51%)	3,878 (8.63%)	4,143 (9.22%)	5,886 (9.80%)	6,297 (10.48%)	6,243 (10.82%)	6,728 (11.66%)	8,790 (7.00%)	10,340 (8.23%)	10,532 (14.21%)	10,486 (14.15%)
SSRI	N (%)	62,789 (41.37%)	62,789 (41.37%)	32,126 (71.47%)	32,126 (71.47%)	34,340 (57.18%)	34,340 (57.18%)	20,410 (35.37%)	20,410 (35.37%)	40,344 (32.12%)	40,344 (32.12%)	41,943 (56.60%)	41,943 (56.60%)
Healthcare visits [-365, -1]													

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Inpatient visit	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	15,017 (25.00%)	14,374 (23.93%)	7,692 (13.33%)	8,219 (14.24%)	20,599 (16.40%)	18,490 (14.72%)	11,521 (15.55%)	10,677 (14.41%)
Outpatient GP visit	N (%)	0 (0.00%)	0 (0.00%)	44,664 (99.36%)	44,670 (99.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Outpatient specialist visit	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	37,879 (63.07%)	37,660 (62.71%)	51,077 (88.51%)	51,518 (89.28%)	92,671 (73.78%)	91,780 (73.07%)	71,738 (96.82%)	70,676 (95.38%)
Prior anxiety/depression episodes [-Inf, 0]													
Depression	N (%)	41,188 (27.14%)	42,860 (28.24%)	22,998 (51.16%)	23,231 (51.68%)	50,947 (84.83%)	51,077 (85.05%)	26,328 (45.62%)	26,120 (45.26%)	47,572 (37.87%)	48,894 (38.93%)	27,467 (37.07%)	28,355 (38.27%)
Anxiety	N (%)	43,334 (28.55%)	42,702 (28.13%)	15,602 (34.71%)	15,693 (34.91%)	16,591 (27.62%)	16,176 (26.93%)	17,249 (29.89%)	16,911 (29.31%)	32,558 (25.92%)	32,714 (26.04%)	39,138 (52.82%)	38,539 (52.01%)
Days from last record of condition of interest until treatment initiation													
Depression	Median [IQR]	420 [5 – 1,835]	498 [2 – 1,846]	538 [50 – 1,770]	560 [58 – 1,757]	0 [0 – 0]	0 [0 – 0]	3 [0 – 284]	0 [0 – 221]	50 [1 – 400]	70 [3 – 442]	341 [33 – 1,506]	366 [24 – 1,494]
	Mean (SD)	1,136.84 (1,492.53)	1,152.93 (1,492.61)	1,171.04 (1,507.06)	1,166.87 (1,480.41)	132.76 (585.49)	128.88 (572.01)	357.02 (736.77)	330.76 (706.14)	306.93 (521.89)	319.11 (518.38)	979.04 (1,310.51)	961.64 (1,276.81)
Anxiety	Median [IQR]	866 [123 – 2,152]	861 [125 – 2,147]	510 [53 – 1,618]	510 [49 – 1,575]	97 [13 – 842]	27 [0 – 741]	51 [0 – 577]	16 [0 – 504]	130 [7 – 597]	136 [8 – 593]	574 [86 – 1,761]	575 [94 – 1,779]
	Mean (SD)	1,394.30 (1,533.83)	1,394.19 (1,537.28)	1,113.59 (1,468.58)	1,074.40 (1,411.46)	684.10 (1,179.48)	614.10 (1,138.51)	460.36 (778.13)	419.56 (759.68)	399.62 (575.33)	396.75 (570.03)	1,133.73 (1,352.94)	1,140.03 (1,353.60)

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
Drug utilisation		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Number of prescriptions in first treatment era	Median [IQR]	2 [1 – 7]	4 [1 – 15]	3 [1 – 8]	5 [1 – 19]	1 [1 – 3]	4 [1 – 11]	1 [1 – 2]	2 [1 – 4]	2 [1 – 7]	7 [2 – 22]	1 [1 – 3]	2 [1 – 4]
	Mean (SD)	8.65 (18.54)	14.87 (26.36)	10.54 (25.93)	18.86 (37.17)	4.66 (13.60)	11.07 (21.88)	1.84 (3.75)	3.26 (5.11)	12.77 (33.96)	18.71 (37.47)	2.33 (2.53)	3.56 (3.91)
Cumulative dose milligram	Median [IQR]	1,256.04 [450.00 – 4,050.00]	4,500.00 [1,162.50 – 21,525.00]	1,260.00 [420.00 – 5,700.00]	14,700.00 [2,250.00 – 68,100.00]	1,500.00 [450.00 – 3,600.00]	15,000.00 [2,547.00 – 55,650.00]	450.00 [420.00 – 900.00]	5,495.00 [1,036.00 – 13,909.00]	3,000.00 [1,500.00 – 14,400.00]	54,000.00 [13,500.00 – 195,375.00]	2,970.00 [915.00 – 10,575.00]	31,725.00 [7,125.00 – 111,818.75]
	Mean (SD)	5,670.87 (13,487.03)	28,396.89 (69,263.12)	8,756.23 (21,959.64)	76,168.65 (162,103.20)	5,221.89 (14,883.57)	67,082.71 (139,963.76)	841.08 (1,280.18)	9,683.42 (14,571.32)	164,880.44 (982,087.58)	179,689.45 (824,913.40)	11,266.39 (22,146.85)	101,244.24 (171,188.90)
Initial daily dose milligram	Median [IQR]	14.52 [14.52 – 28.12]	75.00 [36.89 – 75.00]	15.00 [15.00 – 15.00]	75.00 [75.00 – 75.00]	30.00 [30.00 – 30.00]	100.00 [84.90 – 113.33]	15.00 [14.00 – 15.00]	70.00 [34.53 – 245.00]	14.85 [14.52 – 29.70]	74.26 [72.58 – 148.48]	15.00 [15.00 – 15.00]	75.00 [75.00 – 150.00]
	Mean (SD)	19.99 (18.02)	67.34 (63.92)	18.22 (18.13)	89.53 (152.13)	27.51 (17.15)	112.33 (100.93)	19.05 (15.92)	120.06 (137.61)	88.38 (460.77)	204.88 (1,054.31)	17.96 (10.20)	97.72 (60.82)

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; CCB = Calcium Channel Blocker; GP = General Practitioner; MAO = Monoamine Oxidase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; RAAS = Renin-Angiotensin-Aldosterone System; SD = standard deviation; SSRI = Selective Serotonin Reuptake Inhibitors; IQR = interquartile range; NA = not applicable.
All ASMD were balanced after PS matching, except for anxiety in DK-DHR, with ASMD 0.101.

9.2.2. Objective 2

Compared to Objective 1, the figures of individuals in each data source meeting the eligibility criteria of a previous diagnosis of heart failure were substantially lower. A total of 1,088; 199; 1,289; 1,519; 2,103 and 3,174 eligible venlafaxine users were identified from BIFAP, CPRD GOLD, DK-DHR, FinOMOP-THL, and SIDIAP, respectively (**Table 9**).

As per the calculation of precision of 5, 10, and 20% in the study protocol (**Table 4**), the required sample size to estimate a HR of 1.25 ranged between 1,370 and 57,379. We therefore do not report analyses with n <1,370 for new venlafaxine users (BIFAP, CPRD GOLD, and DK-DHR).

9.2.2.1. Measured Confounding: Diagnostics of Propensity Score Matching

Following PS matching, the number of matched pairs in FinOMOP-THL, HI-SPEED, and SIDIAP were 1,162, 1,644, and 1,821, respectively.

Given the substantially smaller study population compared to Objective 1, covariate balance was much harder to achieve. **Figure 4** shows the scatterplot of the ASMDs of covariates included in the large-scale PS. As indicated in red, several of the covariates that were unbalanced with ASMD >0.1 prior to PS matching (x-axis) remained unbalanced after PS matching (y-axis).

Covariance balance between matched cohorts was not achieved in FinOMOP-THL, including some covariates that could potentially be confounders: SMDs showed that a few conditions were associated with a higher probability of being prescribed mirtazapine, such as Alzheimer's disease and dementia (FinOMOP-THL). In light of the failure to pass PS diagnostics and with sample size being below the required threshold, analyses for Objective 2 from FinOMOP-THL are not reported.

While incomplete covariate balance was achieved for HI-SPEED and SIDIAP, a smaller number of covariates remained unbalanced after matching. Covariates with SMD >0.1 for HI-SPEED, however, still included some potential cardiac confounders, including old myocardial infarction (SMD 0.127), acute kidney injury (SMD 0.107), and spontaneous cerebral haemorrhage (SMD 0.130). The two covariates with SMD >0.1 after matching in SIDIAP were amlodipine (SMD 0.117) and lormetazepam (SMD 0.114).

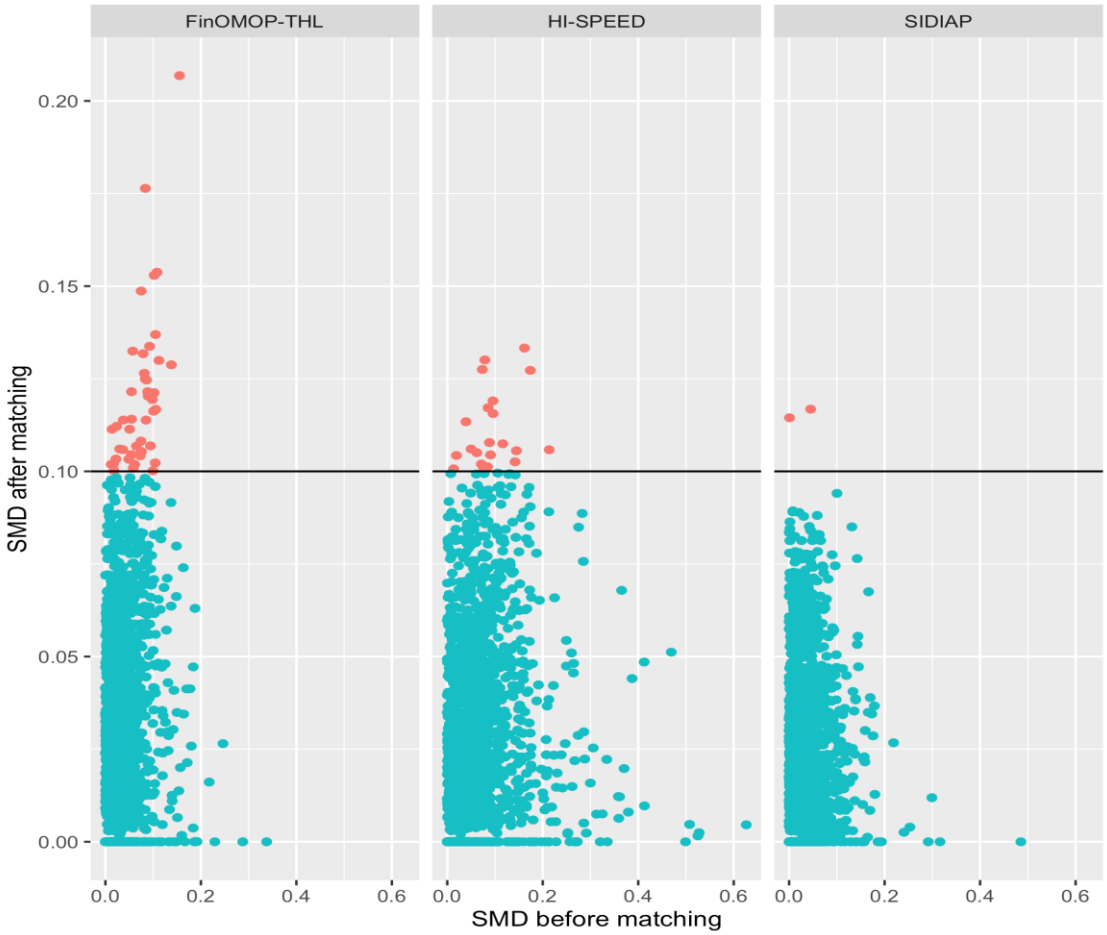

Figure 4. Diagnostics of Propensity Score Matching.

FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; SMD = Standardised mean differences.
Covariates in green colour indicate SMD <0.1 after matching, covariates in red colour indicate SMD >0.1 after matching.

9.2.2.2. Baseline characteristics after matching

Median age in new venlafaxine/mirtazapine users with a previous record of heart failure was high (**Table 9**), ranging from 75 years (IQR 67 – 83) in HI-SPEED to 82 years (IQR 77 – 87) in SIDIAP. The distribution of sex among the new users varied by data source: sex was largely balanced in HI-SPEED, while the proportion of new female users was higher in SIDIAP (69.7%).

Recording of a condition of interest (proxy for indication) was low in the year before initiation: Depression was the most common potential indication ranging around 20% in SIDIAP and HI-SPEED. A higher proportion of individuals with a recorded history of insomnia was seen in mirtazapine users.

The frequency of history of cardiovascular conditions and risk factors was highest for hypertension and diabetes mellitus, while history of cardiovascular conditions was relatively high across data sources, including Ischaemic heart disease (16.3% – 31.0%) and Ischaemic stroke (6.7% – 9.4%).

Notably, the proportion of prescriptions of high-ceiling diuretics (e.g. furosemide,) in the year prior to treatment initiation ranged between 27.6% in HI-SPEED and 60.5% in SIDIAP. Similarly, the proportion of prescription of RAAS inhibitors and betablockers is consistent with the expected treatments in a cohort of individuals with heart failure. The percentage of individuals with a prior history of SSRI prescription were 19.1% in HI-SPEED and 46% in SIDIAP. Notably, a substantial percentage of individuals had been prescribed NSAIDS in the previous year.

Median initial daily doses of 75mg for venlafaxine and 15mg for mirtazapine were generally consistent across data sources. The median treatment durations were 311 days (SIDIAP) and 450 days (HI-SPEED) for venlafaxine and 213 days (SIDIAP) to 295 days (HI-SPEED) for mirtazapine.

Table 9. Patient baseline characteristics of matched venlafaxine and mirtazapine users with a history of HF.

Variable level	Estimate name	HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine
Demographics					
Number (subjects)	N	1,644	1,644	1,821	1,821
Age	Median [IQR]	75 [67 – 83]	75 [67 – 83]	82 [77 – 87]	82 [77 – 87]
	Mean (SD)	74.22 (11.22)	74.14 (11.11)	81.11 (8.22)	80.97 (8.23)
Sex: Female	N (%)	826 (50.24%)	826 (50.24%)	1,269 (69.69%)	1,269 (69.69%)
Duration of prior observation (days)	Median [IQR]	1,186 [1,107 – 2,017]	1,176 [1,110 – 2,028]	3,939 [2,850 – 5,525]	3,861 [2,843 – 5,478]
	Mean (SD)	1,647.87 (785.61)	1,649.66 (803.94)	4,104.61 (1,530.36)	4,110.18 (1,529.55)
Duration of future observation (days)	Median [IQR]	1,052 [358 – 2,206]	1,368 [558 – 2,567]	874 [306 – 1,880]	966 [369 – 1,994]
	Mean (SD)	1,264.68 (970.28)	1,461.84 (979.43)	1,228.83 (1,143.60)	1,321.23 (1,189.67)
Treatment duration (days)	Median [IQR]	295 [101 – 901]	450 [117 – 1,238]	213 [54 – 652]	311 [73 – 914]
	Mean (SD)	649.48 (791.82)	808.40 (854.71)	508.49 (697.99)	646.11 (829.57)
Conditions of interest [-365, 0]					
Depression	N (%)	326 (19.83%)	326 (19.83%)	357 (19.60%)	357 (19.60%)
Anxiety	N (%)	141 (8.58%)	141 (8.58%)	138 (7.58%)	138 (7.58%)
Other					

Variable level	Estimate name	HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine
- Insomnia	N (%)	20 (1.22%)	12 (0.73%)	208 (11.42%)	118 (6.48%)
- Menopausal symptoms	N (%)	<5	6 (0.36%)	5 (0.27%)	6 (0.33%)
- Migraine	N (%)	9 (0.55%)	11 (0.67%)	5 (0.27%)	8 (0.44%)
- Neuropathic pain	N (%)	23 (1.40%)	36 (2.19%)	116 (6.37%)	131 (7.19%)
Comorbidities [-365, -1]					
Atrial fibrillation	N (%)	173 (10.52%)	147 (8.94%)	499 (27.40%)	476 (26.14%)
Cardiomyopathy broad	N (%)	69 (4.20%)	91 (5.54%)	80 (4.39%)	79 (4.34%)
Chronic renal disease	N (%)	210 (12.77%)	166 (10.10%)	415 (22.79%)	409 (22.46%)
Diabetes mellitus	N (%)	453 (27.55%)	466 (28.35%)	442 (24.27%)	399 (21.91%)
Heart failure	N (%)	1,076 (65.45%)	1,010 (61.44%)	895 (49.15%)	860 (47.23%)
Hypertension	N (%)	795 (48.36%)	776 (47.20%)	855 (46.95%)	807 (44.32%)
Ischaemic stroke	N (%)	155 (9.43%)	110 (6.69%)	124 (6.81%)	145 (7.96%)
Ischaemic heart disease	N (%)	509 (30.96%)	477 (29.01%)	332 (18.23%)	297 (16.31%)
Myocardial infarction	N (%)	357 (21.72%)	324 (19.71%)	138 (7.58%)	99 (5.44%)
Obesity	N (%)	97 (5.90%)	101 (6.14%)	225 (12.36%)	206 (11.31%)
Valvular heart disease	N (%)	155 (9.43%)	115 (7.00%)	165 (9.06%)	168 (9.23%)

Variable level	Estimate name	HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine
Prior medications [-365, -1]					
Aldosterone antagonists	N (%)	273 (16.61%)	276 (16.79%)	306 (16.80%)	308 (16.91%)
Antiarrhythmics	N (%)	61 (3.71%)	54 (3.28%)	147 (8.07%)	157 (8.62%)
Betablockers	N (%)	694 (42.21%)	729 (44.34%)	909 (49.92%)	885 (48.60%)
CCB	N (%)	236 (14.36%)	200 (12.17%)	544 (29.87%)	575 (31.58%)
Glucocorticoids	N (%)	308 (18.73%)	339 (20.62%)	475 (26.08%)	463 (25.43%)
High ceiling diuretics	N (%)	453 (27.55%)	462 (28.10%)	1,100 (60.41%)	1,102 (60.52%)
NSAIDs	N (%)	568 (34.55%)	573 (34.85%)	555 (30.48%)	529 (29.05%)
RAAS	N (%)	643 (39.11%)	616 (37.47%)	1,030 (56.56%)	986 (54.15%)
SSRI	N (%)	314 (19.10%)	314 (19.10%)	839 (46.07%)	839 (46.07%)
Healthcare visits [-365, -1]					
Inpatient visit	N (%)	1,030 (62.65%)	892 (54.26%)	1,050 (57.66%)	992 (54.48%)
Outpatient GP visit	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Outpatient specialist visit	N (%)	1,540 (93.67%)	1,514 (92.09%)	1,787 (98.13%)	1,777 (97.58%)
Prior anxiety/depression episodes [-Inf, 0]					
Depression	N (%)	493 (29.99%)	526 (32.00%)	725 (39.81%)	748 (41.08%)

Variable level	Estimate name	HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine
Anxiety	N (%)	268 (16.30%)	271 (16.48%)	435 (23.89%)	464 (25.48%)
Days from last record of condition of interest until treatment initiation					
Depression	Median [IQR]	148 [19 – 520]	202 [23 – 601]	420 [28 –1,419]	528 [10 –1,590]
	Mean (SD)	353.02 (484.49)	378.46 (478.32)	953.37 (1,245.97)	1,001.82 (1,260.95)
Anxiety	Median [IQR]	260 [27 – 723]	321 [38 – 714]	1,022 [303 –2,425]	1,088 [301 –2,282]
	Mean (SD)	461.25 (539.75)	461.46 (515.13)	1,529.50 (1,493.14)	1,460.51 (1,375.53)
Drug utilisation					
Number of prescriptions in first treatment era	Median [IQR]	8 [2 – 42]	11 [3 – 42]	2 [1 – 3]	2 [1 – 3]
	Mean (SD)	33.95 (52.38)	38.20 (61.56)	2.41 (2.14)	2.77 (2.51)
Cumulative dose milligram	Median [IQR]	11,934.00 [1,630.94 – 126,210.89]	64,228.95 [14,620.06 – 226,099.39]	3,825.00 [915.00 – 12,465.00]	24,225.00 [5,325.00 – 73,050.00]
	Mean (SD)	553,395.78 (1,464,655.10)	349,166.62 (1,316,142.48)	10,208.07 (16,302.30)	62,217.86 (103,886.70)
Initial daily dose milligram	Median [IQR]	14.85 [14.52 – 29.70]	74.26 [70.00 – 148.48]	15.00 [15.00 – 15.00]	75.00 [50.00 – 75.00]
	Mean (SD)	379.47 (953.40)	742.45 (2,517.50)	17.64 (6.12)	79.28 (45.07)

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; CCB = Calcium Channel Blocker; GP = General Practitioner; MAO = Monoamine Oxidase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; RAAS = Renin-Angiotensin-Aldosterone System; SD = standard deviation; SSRI = Selective Serotonin Reuptake Inhibitors; IQR = interquartile range; NA = not applicable.

9.2.3. Objective 3

A total of 685,023; 305,328; 304,780; 494,658; 726,803; and 222,520 new mirtazapine users and 251,547; 59,390; 88,318; 86,177; 152,618; and 125,225 new venlafaxine users were characterised from BIFAP, CPRD GOLD, DK-DHR, FinOMOP-THL, HI-SPEED, and SIDIAP, respectively.

Among all new users, individuals prescribed venlafaxine were younger than those prescribed mirtazapine, with median age differences ranging from 5 years in CPRD GOLD (44 vs 49 years) to 24 years in HI-SPEED (44 vs 68 years) (**Table 10**). While the general population of new users was generally older compared to the PS-matched population in Objective 1, the overall demographics of the PS-matched populations were more representative of the (overall and unmatched) venlafaxine group in terms of age and sex compared to the (overall and unmatched) mirtazapine users.

Before matching, depression was the most frequently recorded condition of interest in the 365 days before the index date across all data sources, and substantially more common in new venlafaxine users (FinOMOP-THL, HI-SPEED, SIDIAP) compared to new mirtazapine users. In the PS-matched population for Objective 1, depression rates were broadly representative of the overall venlafaxine new users for CPRD GOLD, DK-DHR, FinOMOP-THL, and HI-SPEED, and slightly lower for BIFAP and SIDIAP. Insomnia was more commonly recorded among overall new mirtazapine users compared to overall new venlafaxine users, with the lowest prevalence observed in HI-SPEED and the highest in DK-DHR. This pattern remained consistent in the PS-matched cohort in Objective 1.

Prevalence of common comorbidities, i.e. hypertension, diabetes mellitus, chronic renal disease, and Ischaemic heart disease, were substantially higher in (overall and unmatched) new mirtazapine users compared to new venlafaxine users across all data sources, whereas obesity was slightly more common in venlafaxine users. Following PS matching for Objective 1, the proportions of hypertension, diabetes, CKD, and obesity were slightly smaller than in the unmatched venlafaxine cohort.

Prior use of SSRIs was substantially more common in overall new venlafaxine users compared to mirtazapine users and broadly similar to the overall venlafaxine user cohort following PS matching. While previous users of non-SSRI antidepressant drugs were excluded for Objectives 1 and 2, the use of MAO inhibitors and other antidepressants was not uncommon in both overall new venlafaxine and mirtazapine users (4.2% – 13.8% and 3.9% – 22.8%). Overall, mirtazapine users more frequently received concomitant medications compared to the venlafaxine group. However, prior use of antidepressants was generally more common among venlafaxine users across data sources, suggesting that venlafaxine is commonly used for second line treatment.

Overall, the initial daily doses in milligrams was consistent between data sources. However, in DK-DHR, the median initial doses of venlafaxine and mirtazapine were higher, consistent with the PS-matched population from Objective 1.

Compared to overall new users of venlafaxine and mirtazapine, where records of HF diagnoses before treatment initiation were rare, the PS-matched population with previous heart failure in Objective 2 was substantially older, with higher rates of comorbidities and prescriptions of co-medication.

Table 10. Patient characteristics of new venlafaxine and mirtazapine users, overall.

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Demographics													
Number (subjects)	N	685,023	251,547	305,328	59,390	304,780	88,318	494,658	86,177	726,803	152,618	222,520	125,225
Age	Median [IQR]	62 [47 – 78]	52 [40 – 65]	49 [34 – 68]	44 [32 – 55]	60 [41 – 77]	42 [30 – 56]	53 [36 – 72]	42 [27 – 57]	68 [47 – 80]	44 [31 – 58]	62 [45 – 78]	53 [42 – 66]
	Mean (SD)	61.68 (19.44)	52.87 (17.03)	51.07 (20.52)	44.63 (15.53)	58.41 (21.13)	44.36 (17.42)	53.68 (21.03)	44.08 (18.94)	62.98 (21.11)	45.72 (17.23)	61.01 (19.84)	54.11 (16.93)
Sex: Female	N (%)	440,737 (64.34%)	177,455 (70.55%)	168,674 (55.24%)	41,588 (70.03%)	171,991 (56.43%)	53,628 (60.72%)	299,061 (60.46%)	56,696 (65.79%)	421,938 (58.05%)	96,254 (63.07%)	138,044 (62.04%)	86,113 (68.77%)
Duration of prior observation (days)	Median [IQR]	3,380 [1,914 – 5,159]	2,728 [1,780 – 4,424]	4,334 [2,635 – 6,073]	4,228 [2,522 – 5,953]	7,747 [6,366 – 9,244]	6,822 [5,974 – 8,113]	3,293 [2,566 – 3,999]	3,113 [2,454 – 3,918]	2,150 [1,371 – 2,990]	1,365 [1,142 – 2,351]	4,446 [2,997 – 5,776]	3,777 [2,544 – 5,413]
	Mean (SD)	3,608.51 (1,922.69)	3,192.13 (1,779.04)	4,450.58 (2,278.38)	4,337.99 (2,235.54)	7,670.98 (2,008.58)	6,967.07 (1,875.81)	3,278.58 (852.97)	3,177.61 (861.47)	2,226.45 (879.74)	1,796.37 (822.34)	4,339.62 (1,611.57)	3,949.37 (1,654.07)
Duration of future observation (days)	Median [IQR]	1,130 [451 – 2,360]	1,613 [682 – 3,427]	1,236 [481 – 2,472]	1,391 [597 – 2,669]	1,795 [664 – 3,458]	3,425 [1,736 – 4,545]	1,456 [785 – 2,218]	1,758 [960 – 2,462]	1,253 [543 – 2,150]	2,366 [1,311 – 2,740]	1,506 [594 – 2,933]	2,343 [1,005 – 3,883]
	Mean (SD)	1,560.84 (1,380.74)	2,084.88 (1,607.84)	1,628.66 (1,390.29)	1,766.35 (1,415.81)	2,119.46 (1,626.53)	3,108.78 (1,612.10)	1,526.93 (860.85)	1,716.06 (863.83)	1,345.45 (897.15)	1,989.01 (863.59)	1,870.42 (1,484.75)	2,478.69 (1,622.15)

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Treatment duration (days)	Median [IQR]	114 [31 – 357]	174 [46 – 545]	84 [28 – 319]	173 [34 – 643]	60 [30 – 213]	206 [73 – 649]	30 [30 – 30]	44 [30 – 117]	126 [56 – 475]	424 [113 – 1,335]	181 [57 – 544]	356 [93 – 1,020]
	Mean (SD)	344.45 (591.33)	491.59 (799.92)	349.48 (668.15)	553.21 (881.72)	243.16 (495.74)	598.30 (948.60)	50.18 (57.38)	89.42 (98.96)	422.70 (634.35)	855.57 (928.91)	489.15 (781.92)	816.14 (1,115.06)
Conditions of interest [-365, 0]													
Depression	N (%)	82,886 (12.10%)	44,661 (17.75%)	64,858 (21.24%)	13,221 (22.26%)	190,904 (62.64%)	64,866 (73.45%)	79,515 (16.07%)	32,421 (37.62%)	141,828 (19.51%)	47,072 (30.84%)	35,892 (16.13%)	32,570 (26.01%)
Anxiety	N (%)	81,010 (11.83%)	32,245 (12.82%)	40,760 (13.35%)	9,770 (16.45%)	27,002 (8.86%)	23,361 (26.45%)	40,931 (8.27%)	18,499 (21.47%)	91,505 (12.59%)	28,556 (18.71%)	50,391 (22.65%)	32,253 (25.76%)
Other													
- Insomnia	N (%)	75,382 (11.00%)	9,687 (3.85%)	19,222 (6.30%)	1,497 (2.52%)	79,522 (26.09%)	13,188 (14.93%)	68,079 (13.76%)	2,062 (2.39%)	6,658 (0.92%)	886 (0.58%)	27,890 (12.53%)	5,678 (4.53%)
- Menopausal symptoms	N (%)	3,598 (0.53%)	2,395 (0.95%)	1,726 (0.57%)	2,874 (4.84%)	139 (0.05%)	32 (0.04%)	5,025 (1.02%)	1,947 (2.26%)	5,340 (0.73%)	1,506 (0.99%)	2,336 (1.05%)	1,997 (1.59%)
- Migraine	N (%)	6,624 (0.97%)	3,655 (1.45%)	3,001 (0.98%)	1,091 (1.84%)	9,994 (3.28%)	3,935 (4.46%)	10,213 (2.06%)	3,126 (3.63%)	7,843 (1.08%)	2,614 (1.71%)	3,334 (1.50%)	2,360 (1.88%)
- Neuropathic pain	N (%)	19,802 (2.89%)	7,753 (3.08%)	4,730 (1.55%)	944 (1.59%)	9,658 (3.17%)	2,954 (3.34%)	10,370 (2.10%)	3,844 (4.46%)	11,003 (1.51%)	2,210 (1.45%)	12,617 (5.67%)	7,546 (6.03%)
Comorbidities [-365, -1]													

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Atrial fibrillation	N (%)	13,600 (1.99%)	1,759 (0.70%)	2,581 (0.85%)	93 (0.16%)	3,259 (1.07%)	255 (0.29%)	2,800 (0.57%)	158 (0.18%)	18,853 (2.59%)	792 (0.52%)	9,946 (4.47%)	2,041 (1.63%)
Cardiomyopathy broad	N (%)	636 (0.09%)	148 (0.06%)	165 (0.05%)	11 (0.02%)	870 (0.29%)	110 (0.12%)	1,831 (0.37%)	168 (0.19%)	3,155 (0.43%)	258 (0.17%)	1,625 (0.73%)	344 (0.27%)
Chronic renal disease	N (%)	10,510 (1.53%)	1,752 (0.70%)	3,214 (1.05%)	287 (0.48%)	3,939 (1.29%)	375 (0.42%)	4,209 (0.85%)	362 (0.42%)	23,373 (3.22%)	838 (0.55%)	11,597 (5.21%)	2,462 (1.97%)
Diabetes mellitus	N (%)	15,302 (2.23%)	4,241 (1.69%)	5,805 (1.90%)	927 (1.56%)	25,755 (8.45%)	4,905 (5.55%)	39,840 (8.05%)	5,601 (6.50%)	88,350 (12.16%)	10,095 (6.61%)	15,754 (7.08%)	5,012 (4.00%)
Heart failure	N (%)	4,739 (0.69%)	591 (0.23%)	1,997 (0.65%)	53 (0.09%)	8,969 (2.94%)	762 (0.86%)	16,512 (3.34%)	1,022 (1.19%)	45,431 (6.25%)	1,401 (0.92%)	10,813 (4.86%)	1,949 (1.56%)
Hypertension	N (%)	30,427 (4.44%)	9,028 (3.59%)	17,464 (5.72%)	2,500 (4.21%)	53,892 (17.68%)	7,497 (8.49%)	64,958 (13.13%)	7,089 (8.23%)	166,627 (22.93%)	12,579 (8.24%)	35,203 (15.82%)	10,436 (8.33%)
Ischaemic stroke	N (%)	5,138 (0.75%)	864 (0.34%)	2,710 (0.89%)	146 (0.25%)	8,695 (2.85%)	886 (1.00%)	12,705 (2.57%)	1,120 (1.30%)	27,020 (3.72%)	1,152 (0.75%)	5,819 (2.62%)	1,769 (1.41%)
Ischaemic heart disease	N (%)	7,155 (1.04%)	1,529 (0.61%)	2,707 (0.89%)	169 (0.28%)	12,615 (4.14%)	1,592 (1.80%)	22,981 (4.65%)	1,745 (2.02%)	47,337 (6.51%)	2,354 (1.54%)	8,025 (3.61%)	2,084 (1.66%)
Myocardial infarction	N (%)	3,785 (0.55%)	851 (0.34%)	1,389 (0.45%)	57 (0.10%)	3,220 (1.06%)	411 (0.47%)	5,959 (1.20%)	353 (0.41%)	26,880 (3.70%)	1,284 (0.84%)	3,239 (1.46%)	815 (0.65%)
Obesity	N (%)	8,450 (1.23%)	4,381 (1.74%)	1,789 (0.59%)	597 (1.01%)	4,848 (1.59%)	2,611 (2.96%)	6,318 (1.28%)	2,004 (2.33%)	13,726 (1.89%)	4,291 (2.81%)	10,248 (4.61%)	6,041 (4.82%)

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Valvular heart disease	N (%)	1,606 (0.23%)	293 (0.12%)	1,097 (0.36%)	62 (0.10%)	5,389 (1.77%)	442 (0.50%)	7,734 (1.56%)	530 (0.62%)	15,674 (2.16%)	559 (0.37%)	3,792 (1.70%)	787 (0.63%)
Prior medications [-365, -1]													
Aldosterone antagonists	N (%)	19,216 (2.81%)	2,697 (1.07%)	4,409 (1.44%)	271 (0.46%)	9,584 (3.14%)	1,104 (1.25%)	9,330 (1.89%)	904 (1.05%)	29,751 (4.09%)	1,165 (0.76%)	5,651 (2.54%)	1,392 (1.11%)
Antiarrhythmics	N (%)	9,811 (1.43%)	1,811 (0.72%)	5,489 (1.80%)	999 (1.68%)	2,254 (0.74%)	230 (0.26%)	3,933 (0.80%)	642 (0.74%)	15,853 (2.18%)	1,649 (1.08%)	3,968 (1.78%)	1,228 (0.98%)
Betablockers	N (%)	98,903 (14.44%)	22,746 (9.04%)	53,972 (17.68%)	10,215 (17.20%)	51,362 (16.85%)	7,884 (8.93%)	116,741 (23.60%)	18,426 (21.38%)	184,536 (25.39%)	12,547 (8.22%)	32,163 (14.45%)	12,252 (9.78%)
CCB	N (%)	73,201 (10.69%)	15,550 (6.18%)	34,697 (11.36%)	3,757 (6.33%)	52,539 (17.24%)	7,625 (8.63%)	60,914 (12.31%)	6,729 (7.81%)	126,961 (17.47%)	7,889 (5.17%)	26,202 (11.78%)	9,277 (7.41%)
Glucocorticoids	N (%)	134,998 (19.71%)	40,336 (16.04%)	31,398 (10.28%)	4,928 (8.30%)	33,477 (10.98%)	6,271 (7.10%)	78,363 (15.84%)	13,868 (16.09%)	152,857 (21.03%)	16,898 (11.07%)	36,975 (16.62%)	16,353 (13.06%)
High ceiling diuretics	N (%)	82,393 (12.03%)	14,084 (5.60%)	19,657 (6.44%)	1,471 (2.48%)	35,022 (11.49%)	3,721 (4.21%)	39,725 (8.03%)	3,282 (3.81%)	73,080 (10.05%)	2,453 (1.61%)	23,941 (10.76%)	6,474 (5.17%)
MAO inhibitors	N (%)	40,622 (5.93%)	16,909 (6.72%)	41,046 (13.44%)	8,177 (13.77%)	12,683 (4.16%)	5,391 (6.10%)	31,798 (6.43%)	10,655 (12.36%)	32,801 (4.51%)	5,859 (3.84%)	14,521 (6.53%)	9,868 (7.88%)
Other antidepressants	N (%)	156,169 (22.80%)	53,476 (21.26%)	11,837 (3.88%)	3,602 (6.06%)	14,567 (4.78%)	8,933 (10.11%)	26,562 (5.37%)	14,317 (16.61%)	35,824 (4.93%)	12,798 (8.39%)	35,295 (15.86%)	20,734 (16.56%)
NSAIDs	N (%)	472,881 (69.03%)	165,610 (65.84%)	78,959 (25.86%)	16,138 (27.17%)	81,244 (26.66%)	25,214 (28.55%)	246,644 (49.86%)	45,548 (52.85%)	289,826 (39.88%)	33,244 (21.78%)	99,453 (44.69%)	61,159 (48.84%)

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
RAAS	N (%)	159,008 (23.21%)	38,867 (15.45%)	51,166 (16.76%)	6,390 (10.76%)	66,068 (21.68%)	9,961 (11.28%)	98,264 (19.87%)	12,087 (14.03%)	203,939 (28.06%)	13,885 (9.10%)	51,167 (22.99%)	19,979 (15.95%)
SSRI	N (%)	217,075 (31.69%)	115,152 (45.78%)	139,944 (45.83%)	41,001 (69.04%)	83,233 (27.31%)	50,231 (56.88%)	63,840 (12.91%)	30,607 (35.52%)	169,455 (23.32%)	49,416 (32.38%)	86,454 (38.85%)	74,441 (59.45%)
Healthcare visits [-365, -1]													
Inpatient visit	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	103,197 (33.86%)	21,936 (24.84%)	81,629 (16.50%)	14,213 (16.49%)	221,233 (30.44%)	24,662 (16.16%)	59,519 (26.75%)	21,217 (16.94%)
Outpatient GP visit	N (%)	0 (0.00%)	0 (0.00%)	301,743 (98.83%)	59,098 (99.51%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Outpatient specialist visit	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	216,636 (71.08%)	57,670 (65.30%)	432,088 (87.35%)	78,512 (91.11%)	583,178 (80.24%)	115,098 (75.42%)	217,204 (97.61%)	120,775 (96.45%)
Prior anxiety/depression episodes [-Inf, 0]													
Depression	N (%)	168,192 (24.55%)	82,460 (32.78%)	128,900 (42.22%)	30,940 (52.10%)	211,682 (69.45%)	71,854 (81.36%)	117,250 (23.70%)	41,280 (47.90%)	196,985 (27.10%)	64,307 (42.14%)	70,301 (31.59%)	56,497 (45.12%)
Anxiety	N (%)	190,477 (27.81%)	74,707 (29.70%)	87,620 (28.70%)	21,644 (36.44%)	51,018 (16.74%)	30,942 (35.03%)	67,648 (13.68%)	25,997 (30.17%)	138,712 (19.09%)	43,360 (28.41%)	104,203 (46.83%)	66,177 (52.85%)
Days from last record of condition of interest until treatment initiation													
Depression	Median [IQR]	605 [34 – 2,193]	414 [15 – 1,686]	358 [0 – 1,742]	591 [64 – 1,850]	0 [0 – 0]	0 [0 – 0]	13 [0 –735]	1 [0 – 219]	37 [1 – 464]	64 [3 – 413]	483 [47 – 1,787]	316 [34 – 1,334]

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
	Mean (SD)	1,353.21 (1,673.05)	1,088.12 (1,446.50)	1,145.00 (1,620.20)	1,215.85 (1,523.95)	234.52 (861.12)	179.06 (658.84)	540.37 (919.66)	332.67 (712.24)	369.62 (642.81)	311.30 (519.18)	1,124.25 (1,404.64)	892.77 (1,222.80)
Anxiety	Median [IQR]	844 [129 – 2,343]	795 [151 – 2,029]	469 [26 – 1,698]	491 [52 – 1,584]	276 [21 – 1,618]	0 [0 – 341]	122 [0 – 986]	28 [0 – 507]	107 [5 – 634]	134 [9 – 581]	622 [83 – 1,961]	623 [121 – 1,806]
	Mean (SD)	1,492.32 (1,680.80)	1,349.07 (1,519.13)	1,158.02 (1,584.30)	1,082.50 (1,434.68)	1,058.91 (1,523.10)	462.26 (1,011.45)	638.91 (941.82)	428.72 (767.76)	444.82 (678.05)	395.73 (573.47)	1,230.71 (1,449.67)	1,168.54 (1,350.28)
Drug utilisation													
Number of prescriptions in first treatment era	Median [IQR]	3 [1 – 9]	5 [1 – 17]	3 [1 – 10]	6 [1 – 20]	2 [1 – 4]	4 [1 – 12]	1 [1 – 2]	2 [1 – 4]	2 [1 – 11]	7 [2 – 21]	1 [1 – 3]	2 [1 – 5]
	Mean (SD)	9.68 (17.85)	15.75 (26.90)	12.09 (28.25)	19.80 (39.78)	5.43 (14.96)	11.56 (23.10)	1.82 (3.07)	3.44 (6.33)	15.86 (34.60)	18.67 (37.91)	2.36 (2.43)	3.80 (4.20)
Cumulative dose milligram	Median [IQR]	1,504.92 [450.00 – 5,400.00]	4,575.00 [412.50 – 22,800.00]	1,545.00 [420.00 – 6,720.00]	14,700.00 [2,400.00 – 72,525.00]	1,500.00 [450.00 – 4,050.00]	15,000.00 [2,547.00 – 57,621.25]	450.00 [420.00 – 900.00]	6,300.00 [1,036.00 – 14,700.00]	3,000.00 [1,058.82 – 15,660.00]	52,500.00 [11,625.00 – 190,575.00]	2,940.00 [915.00 – 10,515.00]	35,475.00 [8,062.50 – 125,100.00]
	Mean (SD)	6,282.36 (12,877.78)	29,250.09 (71,082.90)	9,329.17 (22,116.94)	79,834.88 (167,701.04)	5,196.58 (13,098.96)	69,800.61 (146,237.68)	833.26 (1,131.52)	10,026.14 (15,167.53)	202,258.44 (885,742.73)	181,844.32 (877,960.33)	10,397.93 (19,744.11)	111,225.58 (185,202.73)
Initial daily dose milligram	Median [IQR]	14.52 [14.52 – 28.12]	75.00 [24.73 – 75.00]	15.00 [15.00 – 15.00]	75.00 [75.00 – 75.00]	30.00 [30.00 – 30.00]	100.00 [84.90 – 113.33]	15.00 [14.00 – 15.00]	70.00 [34.53 – 245.00]	14.85 [14.52 – 29.03]	74.26 [72.58 – 148.48]	15.00 [15.00 – 15.00]	75.00 [75.00 – 150.00]

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
	Mean (SD)	19.87 (17.81)	67.30 (64.80)	18.25 (20.24)	89.42 (147.12)	27.26 (14.34)	112.96 (102.02)	19.62 (16.38)	120.44 (138.58)	115.96 (516.18)	211.78 (1,085.27)	17.73 (8.73)	101.80 (61.55)

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; CCB = Calcium Channel Blocker; GP = General Practitioner; MAO = Monoamine Oxidase; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; RAAS = Renin-Angiotensin-Aldosterone System; SD = standard deviation; SSRI = Selective Serotonin Reuptake Inhibitors; IQR = interquartile range; NA = not applicable.

9.3. Main results

All analyses, including stratifications and sensitivity analyses, are reported in the Shiny app (EUPAS1000000974).

9.3.1. Objective 1

The following section includes the main results for Objective 1, with the primary analyses (on treatment effect, a maximum of 90 days gap period between subsequent prescriptions (treatment era), and a requirement of at least 2 years of data availability prior to the first venlafaxine or mirtazapine prescription [index date]) being reported, if not otherwise specified.

9.3.1.1. Number of outcome events and incidence rates

Over the course of the study, the number of incident heart failure (broad) events in new venlafaxine and mirtazapine users were 153 and 189 events in BIFAP, 30 and 37 in CPRD GOLD, 104 and 102 in DK-DHR, 29 and 40 events in FinOMOP-THL, 890 and 871 events in HI-SPEED, and 605 and 687 events in SIDIAP (**Table 11**).

Incidence rates of heart failure (broad) recording ranged from 19.5/10,000 person-years in venlafaxine users (CPRD GOLD) to 147.4/10,000 person-years in mirtazapine users (SIDIAP). For new venlafaxine users, lower incidence rates were seen in primary care data without hospital linkage (19.5 and 28.7/10,000 person-years in CPRD GOLD and BIFAP, respectively) compared to national registries (52.2, 60.8, and 94.7/10,000 person-years in FinOMOP-THL, DK-DHR, and HI-SPEED) and primary care data linked to hospital records (SIDIAP, 127/10,000 person-years). A similar trend was seen for matched mirtazapine users. In addition, differences in the demographics and characteristics of the PS-matched populations might contribute to heterogeneity in incidence rates.

The incidence rates of cardiomyopathy (broad) recording ranged from 3.8/10,000 person-years in BIFAP to 17.62/10,000 person-years in SIDIAP.

Stratified number of events and incidence rates in the venlafaxine and mirtazapine cohorts are available in the Shiny app. Briefly, and in line with the characteristics of heart failure, incidence rates increased with age, and higher incidence rates were observed in individuals with a previous history of cardiovascular (CV) disease compared to individuals without history of CV disease.

Table 11. Number of events and incidence rates of outcome events, overall.

Outcome	Estimate	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Incident HF (broad definition)	N (event)	189	153	37	30	102	104	40	29	871	890	687	605
	person-years	52,351.49	53,232.14	15,178.27	15,375.84	16,529.37	17,091.51	5,508.38	5,521.82	91,963.41	93,970.25	46,598.15	47,636.01
	IR per 10,000 [95%CI]	36.10 [31.14 – 41.43]	28.74 [24.37 – 33.47]	24.38 [17.16 – 32.84]	19.51 [13.16 – 27.09]	61.71 [50.32 – 74.25]	60.85 [49.72 – 73.09]	72.62 [51.88 – 96.79]	52.52 [35.17 – 73.29]	94.71 [88.53 – 101.10]	94.71 [88.59 – 101.03]	147.43 [136.61 – 158.66]	127.00 [117.08 – 137.32]
Incident HF (narrow definition)	N (event)	185	147	36	30	93	94	36	29	837	839	654	575
	person-years	52,358.23	53,235.85	15,180.10	15,375.84	16,538.25	17,098.55	5,508.52	5,521.84	92,005.49	94,039.82	46,649.61	47,678.14
	IR per 10,000 [95%CI]	35.33 [30.43 – 40.60]	27.61 [23.33 – 32.25]	23.72 [16.61 – 32.07]	19.51 [13.16 – 27.09]	56.23 [45.39 – 68.22]	54.98 [44.43 – 66.63]	65.35 [45.77 – 88.37]	52.52 [35.17 – 73.29]	90.97 [84.91 – 97.24]	89.22 [83.28 – 95.35]	140.19 [129.65 – 151.14]	120.60 [110.94 – 130.65]
Incident HF (broad, excl. alternative causes)	N (event)	183	144	33	25	67	66	29	26	554	552	518	466
	person-years	52,356.44	53,236.58	15,182.26	15,383.25	16,554.30	17,117.79	5,509.61	5,521.96	92,367.37	94,456.33	46,784.23	47,793.30
	IR per 10,000 [95%CI]	34.95 [30.07 – 40.20]	27.05 [22.81 – 31.64]	21.74 [14.96 – 29.75]	16.25 [10.52 – 23.21]	40.47 [31.37 – 50.72]	38.56 [29.82 – 48.40]	52.64 [35.25 – 73.45]	47.08 [30.76 – 66.83]	59.98 [55.09 – 65.07]	58.44 [53.67 – 63.41]	110.72 [101.39 – 120.46]	97.50 [88.85 – 106.55]
Incid en +	N (event)	180	139	33	25	65	64	29	26	553	544	511	456

Outcome	Estimate	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
	person-years	52,360.50	53,239.64	15,182.26	15,383.25	16,555.15	17,118.80	5,509.61	5,521.98	92,361.09	94,463.50	46,788.96	47,816.53
	IR per 10,000 [95%CI]	34.38 [29.54 – 39.58]	26.11 [21.95 – 30.62]	21.74 [14.96 – 29.75]	16.25 [10.52 – 23.21]	39.26 [30.30 – 49.37]	37.39 [28.79 – 47.09]	52.64 [35.25 – 73.45]	47.08 [30.76 – 66.83]	59.87 [54.99 – 64.97]	57.59 [52.85 – 62.53]	109.21 [99.95 – 118.88]	95.36 [86.81 – 104.31]
Cardiomyopathy (broad definition)	N (event)	20	21	NA	8	9	13	NA	NA	47	70	83	85
	person-years	52,540.30	53,376.59	15,221.93	15,396.96	16,591.46	17,173.41	5,511.18	5,523.34	92,887.62	94,957.64	47,374.16	48,245.06
	IR per 10,000 [95%CI]	3.81 [2.33 – 5.65]	3.93 [2.44 – 5.79]	NA	5.20 [2.24 – 9.37]	5.42 [2.48 – 9.50]	7.57 [4.03 – 12.21]	NA	NA	5.06 [3.72 – 6.61]	7.37 [5.75 – 9.20]	17.52 [13.95 – 21.49]	17.62 [14.07 – 21.56]
Cardiomyopathy (primary causes only)	N (event)	14	16	NA	7	8	12	NA	NA	38	50	52	51
	person-years	52,543.01	53,377.97	15,221.93	15,397.26	16,592.17	17,175.56	5,511.18	5,523.34	92,909.25	94,997.48	47,410.29	48,310.37
	IR per 10,000 [95%CI]	2.66 [1.46 – 4.23]	3.00 [1.71 – 4.63]	NA	4.55 [1.83 – 8.48]	4.82 [2.08 – 8.69]	6.99 [3.61 – 11.46]	NA	NA	4.09 [2.89 – 5.49]	5.26 [3.91 – 6.82]	10.97 [8.19 – 14.14]	10.56 [7.86 – 13.64]
Hospitalisation with HF	N (event)	NA	NA	NA	NA	59	72	17	7	570	608	509	446
	person-years	NA	NA	NA	NA	16,558.13	17,120.22	5,510.00	5,523.12	92,263.28	94,280.79	46,870.11	47,869.58

Outcome	Estimate	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine	mirtazapine	venlafaxine
	IR per 10,000 [95%CI]	NA	NA	NA	NA	35.63 [27.12 – 45.28]	42.06 [32.91 – 52.31]	30.85 [17.97 – 47.16]	12.67 [5.10 – 23.65]	61.78 [56.81 – 66.95]	64.49 [59.46 – 69.71]	108.60 [99.37 – 118.23]	93.17 [84.72 – 102.01]

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; N = Number; IR = Incidence Rate; 95%CI = 95% Confidence Interval; NA = not applicable; alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

9.3.1.2. Effect estimation: Hazard Ratios, Incidence Rate Ratios and Meta-Analyses

Analyses for the primary outcome of incident heart failure (broad definition) showed no increased hazard associated with venlafaxine compared to mirtazapine in the meta-analysis (HR_{meta} 0.90, 95%CI 0.81 – 0.99, IRR_{meta} 0.90, 95%CI 0.81 – 1.00, **Table 12**).

Point estimates for incident cardiomyopathy were higher than for incident heart failure, with meta-analytic HR_{meta} of 1.18 (95%CI 0.93 – 1.50) for the broad definition (including Takotsubo) and HR_{meta} 1.13 (95%CI 0.89 – 1.45) for the narrow definition of cardiomyopathy (excluding Takotsubo).

Table 13 shows effect estimates for the primary outcome of incident HF (broad) for each data source, with HR ranging between 0.72 (95%CI 0.45 – 1.17) in FinOMOP-THL to 1.0 (95%CI 0.91 – 1.09) in HI-SPEED. BIFAP and SIDIAP reported a HR of 0.79 (95%CI 0.64 – 0.98) and 0.86 (95%CI 0.77 – 0.96), respectively. Results from secondary outcome definitions for heart failure (narrow definition and excluding alternative causes) were similar to the broad definition, and results from IRRs were very similar to the respective HR.

HR for cardiomyopathy (broad) in individual data sources ranged from 0.50 (95%CI 0.09 – 2.72) in FinOMOP-THL to 2.63 (95%CI 0.70 – 9.90) in CPRD GOLD, with HR 1.45 (95%CI 1.0 – 2.10) reported for HI-SPEED. Results from IRRs were very similar to the HRs.

Compared to the overall analysis, no substantial differences regarding hazard for heart failure associated with venlafaxine were seen in meta-analytic estimates for stratified analyses (**Table 14)**, including between males (HR_{meta} 0.98, 95%CI 0.86 – 1.11) and females (HR_{meta} 0.87, 95%CI 0.79 – 0.96); between individuals with and without a history of cardiovascular events (HR_{meta} 0.84 [95%CI 0.70 – 1.01] and HR_{meta} 0.92 [95%CI 0.84 – 1.00], respectively); in individuals with or without previous use of SSRI (HR_{meta} 0.83 [95%CI 0.74 – 0.93] and HR_{meta} 0.96 [95%CI 0.89 – 1.04], respectively), and in subgroups of individuals with recorded depression and/or anxiety (HR_{meta} 0.95 [95%CI 0.83 – 1.09] and HR_{meta} 0.85 [95%CI 0.58 – 1.25]).

Stratified analyses for HR for each data source are presented in **Table 15**. In HI-SPEED, higher HR for cardiomyopathy (broad) were reported for males (HR 1.89, 95%CI 1.05 – 3.39) compared to females (HR 1.20, 95%CI 0.74 – 1.95), and among older age groups (age group 60–70: HR 1.70 95%CI 1.02 – 2.83) compared to younger age groups. However, these differences were not consistent across other data sources.

Table 12. Meta-analysis Hazard Ratios and Incidence Rate Ratios for outcomes of interest, overall.

Outcome	HR_{meta}	95%CI HR	I2	IRR_{meta}	95%CI IRR	I2
Incident HF (broad definition)	0.90	0.81 – 0.99	0.36	0.90	0.81 – 1.00	0.36
Incident HF (narrow definition)	0.89	0.81 – 0.98	0.15	0.90	0.82 – 0.99	0.15
Incident HF (broad, excl. alternative causes)	0.89	0.82 – 0.98	0.00	0.90	0.82 – 0.98	0.00
Incident HF (narrow, excl. alternative causes)	0.88	0.81 – 0.97	0.00	0.89	0.81 – 0.97	0.00
Cardiomyopathy (broad definition)	1.18	0.93 – 1.50	0.00	1.18	0.93 – 1.50	0.01
Cardiomyopathy (primary causes only)	1.13	0.89 – 1.45	0.00	1.13	0.89 – 1.45	0.00
Hospitalisation with HF	0.95	0.79 – 1.13	0.70	0.95	0.80 – 1.14	0.70

HF = Heart failure, HR = Hazard Ratio, HR_{meta} = meta-analytic Hazard Ratio, 95%CI = 95% Confidence Intervals, I^2 = measure of heterogeneity, IRR = Incidence Rate Ratio, IRR_{meta} = meta-analytic Incidence Rate Ratio, alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

Table 13. Hazard Ratios and Incidence Rate Ratios for outcomes of interest, for each data source.

Data source	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
BIFAP	0.79	0.64 – 0.98	0.78	0.63 – 0.97	0.77	0.62 – 0.96	0.76	0.61 – 0.94	1.04	0.56 – 1.92	1.13	0.55 – 2.31	NA	NA
CPRD GOLD	0.79	0.49 – 1.29	0.82	0.50 – 1.33	0.74	0.44 – 1.25	0.74	0.44 – 1.25	2.63	0.70 – 9.90	2.29	0.59 – 8.87	NA	NA
DK-DHR	0.99	0.75 – 1.29	0.98	0.73 – 1.30	0.94	0.67 – 1.33	0.94	0.67 – 1.33	1.41	0.60 – 3.30	1.46	0.60 – 3.57	1.18	0.83 – 1.66
FinOMOP-THL	0.72	0.45 – 1.17	0.80	0.49 – 1.31	0.89	0.53 – 1.52	0.89	0.53 – 1.52	0.50	0.09 – 2.72	0.50	0.09 – 2.72	0.41	0.17 – 0.99
HI-SPEED	1.00	0.91 – 1.09	0.98	0.89 – 1.07	0.97	0.86 – 1.09	0.96	0.85 – 1.08	1.45	1.00 – 2.10	1.28	0.84 – 1.96	1.04	0.93 – 1.16
SIDIAP	0.86	0.77 – 0.96	0.86	0.76 – 0.96	0.88	0.77 – 0.99	0.87	0.76 – 0.98	1.00	0.74 – 1.36	0.96	0.65 – 1.41	0.85	0.75 – 0.97

Data source	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
BIFAP	0.80	0.64 – 0.99	0.78	0.63 – 0.97	0.77	0.62 – 0.96	0.76	0.61 – 0.95	1.03	0.56 – 1.91	1.12	0.55 – 2.30	NA	NA

CPRD GOLD	0.80	0.49 – 1.30	0.82	0.51 – 1.34	0.75	0.44 – 1.26	0.75	0.44 – 1.26	2.64	0.70 – 9.94	2.31	0.60 – 8.92	NA	NA
DK-DHR	0.99	0.75 – 1.30	0.98	0.73 – 1.30	0.95	0.68 – 1.34	0.95	0.67 – 1.34	1.40	0.60 – 3.26	1.45	0.59 – 3.54	1.18	0.84 – 1.67
FinOMOP-THL	0.72	0.45 – 1.17	0.80	0.49 – 1.31	0.89	0.53 – 1.52	0.89	0.53 – 1.52	0.50	0.09 – 2.72	0.50	0.09 – 2.72	0.41	0.17 – 0.99

Data source	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
HI-SPEED	1.00	0.91 – 1.10	0.98	0.89 – 1.08	0.97	0.87 – 1.10	0.96	0.85 – 1.08	1.46	1.01 – 2.11	1.29	0.84 – 1.96	1.04	0.93 – 1.17
SIDIAP	0.86	0.77 – 0.96	0.86	0.77 – 0.96	0.88	0.78 – 1.00	0.87	0.77 – 0.99	1.01	0.74 – 1.36	0.96	0.65 – 1.42	0.86	0.76 – 0.97

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Table 14. Meta-analysis of uncalibrated Hazard Ratios for outcomes of interest, stratified.

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI
Meta-Analysis														
Overall	0.90	0.81 – 0.99	0.89	0.81 – 0.98	0.89	0.82 – 0.98	0.88	0.81 – 0.97	1.18	0.93 – 1.50	1.13	0.89 – 1.45	0.95	0.79 – 1.13
Sex: Female	0.87	0.79 – 0.96	0.87	0.80 – 0.94	0.86	0.79 – 0.95	0.85	0.78 – 0.93	1.14	0.87 – 1.49	1.14	0.82 – 1.58	0.89	0.80 – 0.98
Sex: Male	0.98	0.86 – 1.11	0.97	0.85 – 1.10	0.97	0.78 – 1.19	0.96	0.78 – 1.18	1.24	0.82 – 1.86	1.13	0.77 – 1.66	1.07	0.85 – 1.35
Age: 18 to 39	0.41	0.19 – 0.90	0.50	0.21 – 1.23	0.89	0.15 – 5.44	0.82	0.10 – 6.79	0.81	0.21 – 3.05	0.67	0.11 – 4.13	0.39	0.15 – 1.00
Age: 40 to 59	0.77	0.54 – 1.12	0.71	0.50 – 1.03	0.76	0.50 – 1.14	0.73	0.53 – 1.01	0.97	0.64 – 1.47	1.03	0.64 – 1.65	0.68	0.41 – 1.12
Age: 60 to 70	0.86	0.71 – 1.04	0.87	0.73 – 1.04	0.84	0.67 – 1.04	0.83	0.67 – 1.03	1.15	0.79 – 1.67	1.02	0.72 – 1.46	1.05	0.93 – 1.17
Age: 80 or above	0.92	0.78 – 1.09	0.92	0.78 – 1.09	0.91	0.82 – 1.02	0.91	0.81 – 1.02	1.48	0.89 – 2.46	1.72	0.88 – 3.33	0.91	0.74 – 1.11
CV history: No	0.92	0.84 – 1.00	0.91	0.84 – 0.99	0.90	0.82 – 0.98	0.88	0.81 – 0.97	1.08	0.80 – 1.47	1.04	0.78 – 1.39	0.98	0.84 – 1.13
CV history: Yes	0.84	0.70 – 1.01	0.86	0.73 – 1.01	0.88	0.72 – 1.07	0.87	0.71 – 1.07	1.64	1.03 – 2.59	1.54	0.90 – 2.62	0.89	0.70 – 1.13
Prior SSRI: No	0.96	0.89 – 1.04	0.95	0.88 – 1.03	0.95	0.86 – 1.04	0.94	0.85 – 1.03	1.28	0.97 – 1.67	1.22	0.89 – 1.68	0.99	0.86 – 1.15
Prior SSRI: Yes	0.83	0.74 – 0.93	0.83	0.74 – 0.93	0.82	0.72 – 0.93	0.81	0.71 – 0.92	1.04	0.75 – 1.43	1.02	0.69 – 1.51	0.86	0.74 – 0.99
Depression (w/ or w/o anxiety)	0.95	0.83 – 1.09	0.92	0.80 – 1.06	0.93	0.79 – 1.09	0.90	0.76 – 1.06	1.25	0.83 – 1.88	1.28	0.79 – 2.06	0.99	0.75 – 1.32

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI
Meta-Analysis														
Anxiety with no depression	0.85	0.58 – 1.25	0.86	0.61 – 1.22	0.74	0.55 – 0.99	0.72	0.54 – 0.97	1.23	0.65 – 2.33	1.24	0.49 – 3.16	1.04	0.68 – 1.59

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Table 15. Uncalibrated Hazard Ratios for outcomes of interest, stratified.

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
BIFAP														
Overall	0.79	0.64 – 0.98	0.78	0.63 – 0.97	0.77	0.62 – 0.96	0.76	0.61 – 0.94	1.04	0.56 – 1.92	1.13	0.55 – 2.31	NA	NA
Sex: Female	0.80	0.62 – 1.02	0.78	0.61 – 1.01	0.77	0.60 – 0.99	0.75	0.58 – 0.97	1.08	0.48 – 2.45	1.13	0.41 – 3.12	NA	NA
Sex: Male	0.79	0.52 – 1.19	0.76	0.50 – 1.16	0.77	0.50 – 1.19	0.77	0.50 – 1.19	0.98	0.39 – 2.48	1.12	0.41 – 3.10	NA	NA
Age: 18 to 39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Age: 40 to 59	1.14	0.41 – 3.13	0.85	0.29 – 2.53	1.16	0.39 – 3.45	0.99	0.32 – 3.08	0.66	0.19 – 2.35	0.99	0.25 – 3.98	NA	NA
Age: 60 to 70	0.60	0.41 – 0.87	0.61	0.42 – 0.89	0.60	0.41 – 0.89	0.61	0.41 – 0.90	0.90	0.38 – 2.11	0.74	0.26 – 2.13	NA	NA
Age: 80 or above	0.88	0.68 – 1.16	0.87	0.66 – 1.14	0.84	0.64 – 1.11	0.82	0.62 – 1.08	1.95	0.49 – 7.81	2.92	0.59 – 14.48	NA	NA
CV history: No	0.83	0.65 – 1.06	0.82	0.64 – 1.05	0.81	0.63 – 1.04	0.80	0.62 – 1.03	0.87	0.42 – 1.77	0.89	0.36 – 2.18	NA	NA
CV history: Yes	0.69	0.45 – 1.05	0.67	0.44 – 1.02	0.66	0.43 – 1.02	0.64	0.42 – 0.99	1.71	0.50 – 5.85	1.71	0.50 – 5.85	NA	NA
Prior SSRI: No	0.82	0.62 – 1.10	0.79	0.59 – 1.06	0.81	0.60 – 1.08	0.78	0.58 – 1.05	1.24	0.58 – 2.64	1.61	0.67 – 3.88	NA	NA
Prior SSRI: Yes	0.76	0.55 – 1.04	0.76	0.55 – 1.05	0.73	0.52 – 1.01	0.73	0.53 – 1.02	0.74	0.26 – 2.14	0.49	0.12 – 1.97	NA	NA
Depression (w/ or w/o anxiety)	0.99	0.60 – 1.64	0.89	0.53 – 1.50	0.92	0.55 – 1.55	0.82	0.48 – 1.40	0.99	0.14 – 7.03	1.98	0.18 – 21.79	NA	NA
Anxiety with no depression	0.67	0.24 – 1.89	0.67	0.24 – 1.89	0.76	0.26 – 2.18	0.76	0.26 – 2.18	0.33	0.03 – 3.20	NA	NA	NA	NA
CPRD GOLD														

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Overall	0.79	0.49 – 1.29	0.82	0.50 – 1.33	0.74	0.44 – 1.25	0.74	0.44 – 1.25	2.63	0.70 – 9.90	2.29	0.59 – 8.87	NA	NA
Sex: Female	0.72	0.36 – 1.43	0.72	0.36 – 1.43	0.62	0.30 – 1.27	0.62	0.30 – 1.27	2.43	0.47 – 12.53	1.93	0.35 – 10.57	NA	NA
Sex: Male	0.88	0.45 – 1.73	0.94	0.47 – 1.85	0.92	0.43 – 1.97	0.92	0.43 – 1.97	2.99	0.31 – 28.71	2.99	0.31 – 28.71	NA	NA
Age: 18 to 39	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Age: 40 to 59	1.41	0.54 – 3.71	1.41	0.54 – 3.71	1.65	0.60 – 4.54	1.65	0.60 – 4.54	3.95	0.44 – 35.30	3.95	0.44 – 35.30	NA	NA
Age: 60 to 70	0.43	0.21 – 0.92	0.45	0.21 – 0.97	0.35	0.15 – 0.84	0.35	0.15 – 0.84	0.49	0.04 – 5.43	0.49	0.04 – 5.43	NA	NA
Age: 80 or above	0.92	0.35 – 2.47	0.92	0.35 – 2.47	0.79	0.28 – 2.18	0.79	0.28 – 2.18	NA	NA	NA	NA	NA	NA
CV history: No	0.85	0.47 – 1.55	0.85	0.47 – 1.55	0.75	0.39 – 1.44	0.75	0.39 – 1.44	2.63	0.70 – 9.90	2.29	0.59 – 8.87	NA	NA
CV history: Yes	0.68	0.30 – 1.53	0.73	0.32 – 1.67	0.71	0.30 – 1.68	0.71	0.30 – 1.68	NA	NA	NA	NA	NA	NA
Prior SSRI: No	1.51	0.58 – 3.89	1.51	0.58 – 3.89	1.60	0.58 – 4.39	1.60	0.58 – 4.39	1.98	0.18 – 21.85	1.98	0.18 – 21.85	NA	NA

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Prior SSRI: Yes	0.63	0.35 – 1.12	0.65	0.37 – 1.16	0.55	0.29 – 1.04	0.55	0.29 – 1.04	2.97	0.60 – 14.69	2.47	0.48 – 12.72	NA	NA
Depression (w/ or w/o anxiety)	0.73	0.23 – 2.30	0.73	0.23 – 2.30	0.58	0.17 – 1.99	0.58	0.17 – 1.99	NA	NA	NA	NA	NA	NA
Anxiety with no depression	0.63	0.10 – 3.75	0.63	0.10 – 3.75	0.63	0.10 – 3.75	0.63	0.10 – 3.75	NA	NA	NA	NA	NA	NA
DK-DHR														
Overall	0.99	0.75 – 1.29	0.98	0.73 – 1.30	0.94	0.67 – 1.33	0.94	0.67 – 1.33	1.41	0.60 – 3.30	1.46	0.60 – 3.57	1.18	0.83 – 1.66
Sex: Female	0.83	0.56 – 1.24	0.78	0.52 – 1.19	0.70	0.43 – 1.14	0.74	0.45 – 1.20	1.94	0.58 – 6.43	2.56	0.68 – 9.65	1.01	0.63 – 1.64
Sex: Male	1.14	0.78 – 1.67	1.19	0.80 – 1.78	1.28	0.78 – 2.09	1.21	0.73 – 1.99	0.99	0.29 – 3.41	0.79	0.21 – 2.94	1.36	0.83 – 2.23
Age: 18 to 39	0.75	0.17 – 3.35	1.50	0.25 – 8.97	3.00	0.31 – 28.82	3.00	0.31 – 28.82	NA	NA	NA	NA	0.50	0.05 – 5.51
Age: 40 to 59	0.49	0.21 – 1.14	0.49	0.20 – 1.21	0.33	0.10 – 1.01	0.35	0.11 – 1.11	0.66	0.11 – 3.97	1.00	0.14 – 7.07	0.56	0.16 – 1.91
Age: 60 to 70	0.90	0.63 – 1.29	0.83	0.57 – 1.21	0.77	0.49 – 1.19	0.75	0.48 – 1.16	1.44	0.51 – 4.04	1.43	0.51 – 4.02	1.17	0.74 – 1.84

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Age: 80 or above	1.63	0.94 – 2.84	1.70	0.96 – 3.04	2.19	1.04 – 4.61	2.33	1.07 – 5.05	NA	NA	NA	NA	1.50	0.80 – 2.81
CV history: No	1.07	0.75 – 1.54	1.03	0.70 – 1.50	0.90	0.59 – 1.38	0.86	0.56 – 1.32	1.27	0.47 – 3.40	1.48	0.53 – 4.15	1.32	0.83 – 2.09
CV history: Yes	0.84	0.55 – 1.28	0.87	0.56 – 1.35	0.96	0.54 – 1.73	1.06	0.58 – 1.93	1.88	0.34 – 10.27	1.32	0.22 – 7.98	0.98	0.58 – 1.65
Prior SSRI: No	0.98	0.62 – 1.55	0.95	0.59 – 1.54	1.11	0.64 – 1.94	1.12	0.63 – 1.97	1.49	0.25 – 8.90	2.97	0.31 – 28.60	1.23	0.69 – 2.21
Prior SSRI: Yes	0.99	0.70 – 1.39	0.99	0.69 – 1.41	0.86	0.56 – 1.32	0.85	0.55 – 1.32	1.39	0.53 – 3.66	1.25	0.47 – 3.36	1.15	0.75 – 1.76
Depression (w/ or w/o anxiety)	1.02	0.76 – 1.38	0.99	0.72 – 1.35	0.97	0.67 – 1.41	0.95	0.65 – 1.39	1.47	0.60 – 3.60	1.54	0.60 – 3.96	1.27	0.87 – 1.85
Anxiety with no depression	0.63	0.22 – 1.76	0.70	0.24 – 2.02	0.58	0.19 – 1.79	0.58	0.19 – 1.79	0.98	0.06 – 15.66	0.98	0.06 – 15.66	0.62	0.17 – 2.20
FinOMOP-THL														
Overall	0.72	0.45 – 1.17	0.80	0.49 – 1.31	0.89	0.53 – 1.52	0.89	0.53 – 1.52	0.50	0.09 – 2.72	0.50	0.09 – 2.72	0.41	0.17 – 0.99
Sex: Female	0.71	0.40 – 1.26	0.83	0.46 – 1.50	0.90	0.47 – 1.70	0.90	0.47 – 1.70	0.66	0.11 – 3.98	0.66	0.11 – 3.98	0.33	0.11 – 1.03

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Sex: Male	0.75	0.32 – 1.78	0.75	0.32 – 1.78	0.89	0.34 – 2.30	0.89	0.34 – 2.30	NA	NA	NA	NA	0.60	0.14 – 2.50
Age: 18 to 39	NA	NA	NA	NA	NA	NA	NA	NA	0.50	0.05 – 5.50	0.50	0.05 – 5.50	NA	NA
Age: 40 to 59	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Age: 60 to 70	0.99	0.48 – 2.02	1.35	0.62 – 2.93	1.38	0.61 – 3.11	1.38	0.61 – 3.11	NA	NA	NA	NA	0.49	0.12 – 1.98
Age: 80 or above	0.54	0.28 – 1.07	0.54	0.28 – 1.07	0.58	0.28 – 1.22	0.58	0.28 – 1.22	NA	NA	NA	NA	0.30	0.08 – 1.09
CV history: No	1.00	0.49 – 2.04	1.15	0.55 – 2.42	1.36	0.62 – 2.96	1.36	0.62 – 2.96	0.50	0.09 – 2.72	0.50	0.09 – 2.72	0.60	0.14 – 2.50
CV history: Yes	0.56	0.29 – 1.07	0.61	0.31 – 1.18	0.61	0.29 – 1.29	0.61	0.29 – 1.29	NA	NA	NA	NA	0.33	0.11 – 1.03
Prior SSRI: No	0.73	0.42 – 1.27	0.81	0.46 – 1.43	0.91	0.50 – 1.66	0.91	0.50 – 1.66	0.50	0.09 – 2.72	0.50	0.09 – 2.72	0.54	0.20 – 1.47
Prior SSRI: Yes	0.70	0.26 – 1.83	0.77	0.29 – 2.08	0.85	0.29 – 2.53	0.85	0.29 – 2.53	NA	NA	NA	NA	0.17	0.02 – 1.38
Depression (w/ or w/o anxiety)	1.33	0.30 – 5.96	2.00	0.37 – 10.92	4.00	0.45 – 35.78	4.00	0.45 – 35.78	1.00	0.06 – 15.96	1.00	0.06 – 15.96	NA	NA

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Anxiety with no depression	0.25	0.03 – 2.23	0.50	0.05 – 5.50	0.50	0.05 – 5.50	0.50	0.05 – 5.50	NA	NA	NA	NA	NA	NA
HI-SPEED														
Overall	1.00	0.91 – 1.09	0.98	0.89 – 1.07	0.97	0.86 – 1.09	0.96	0.85 – 1.08	1.45	1.00 – 2.10	1.28	0.84 – 1.96	1.04	0.93 – 1.16
Sex: Female	0.95	0.84 – 1.08	0.93	0.82 – 1.05	0.88	0.76 – 1.02	0.86	0.75 – 1.00	1.20	0.74 – 1.95	1.14	0.66 – 1.97	0.94	0.81 – 1.09
Sex: Male	1.06	0.92 – 1.23	1.04	0.90 – 1.21	1.15	0.95 – 1.40	1.15	0.94 – 1.40	1.89	1.05 – 3.39	1.53	0.78 – 3.00	1.19	1.00 – 1.42
Age: 18 to 39	0.38	0.14 – 1.08	0.44	0.14 – 1.44	0.44	0.14 – 1.44	0.33	0.09 – 1.23	1.00	0.14 – 7.08	1.00	0.06 – 15.99	0.44	0.14 – 1.44
Age: 40 to 59	0.92	0.70 – 1.21	0.85	0.63 – 1.13	0.86	0.60 – 1.23	0.80	0.56 – 1.15	1.09	0.58 – 2.07	1.23	0.58 – 2.64	0.92	0.66 – 1.28
Age: 60 to 70	0.99	0.87 – 1.12	0.96	0.84 – 1.09	0.97	0.82 – 1.14	0.96	0.81 – 1.14	1.70	1.02 – 2.83	1.36	0.78 – 2.38	1.09	0.94 – 1.27
Age: 80 or above	1.02	0.87 – 1.20	1.03	0.87 – 1.21	1.00	0.82 – 1.21	0.99	0.82 – 1.20	1.71	0.50 – 5.83	0.97	0.24 – 3.90	0.98	0.80 – 1.20
CV history: No	0.97	0.87 – 1.08	0.96	0.86 – 1.07	0.93	0.82 – 1.07	0.92	0.81 – 1.05	1.40	0.94 – 2.09	1.24	0.79 – 1.96	1.03	0.90 – 1.17

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
CV history: Yes	1.05	0.88 – 1.26	1.02	0.85 – 1.22	1.12	0.86 – 1.45	1.10	0.85 – 1.43	1.79	0.66 – 4.83	1.56	0.51 – 4.78	1.07	0.86 – 1.33
Prior SSRI: No	1.00	0.91 – 1.10	0.98	0.89 – 1.09	0.98	0.87 – 1.11	0.98	0.86 – 1.11	1.44	0.98 – 2.11	1.28	0.83 – 1.99	1.06	0.94 – 1.19
Prior SSRI: Yes	0.95	0.71 – 1.28	0.91	0.67 – 1.24	0.87	0.60 – 1.26	0.80	0.55 – 1.17	1.64	0.39 – 6.87	1.31	0.29 – 5.85	0.88	0.60 – 1.29
Depression (w/ or w/o anxiety)	0.96	0.79 – 1.17	0.93	0.76 – 1.15	0.97	0.75 – 1.26	0.94	0.72 – 1.22	1.29	0.61 – 2.73	1.21	0.48 – 3.07	1.07	0.83 – 1.37
Anxiety with no depression	1.32	0.88 – 1.96	1.23	0.81 – 1.85	0.93	0.58 – 1.49	0.90	0.56 – 1.45	1.98	0.60 – 6.57	1.49	0.42 – 5.28	1.44	0.87 – 2.37
SIDIAP														
Overall	0.86	0.77 – 0.96	0.86	0.76 – 0.96	0.88	0.77 – 0.99	0.87	0.76 – 0.98	1.00	0.74 – 1.36	0.96	0.65 – 1.41	0.85	0.75 – 0.97
Sex: Female	0.85	0.74 – 0.96	0.85	0.74 – 0.97	0.90	0.78 – 1.04	0.89	0.77 – 1.03	1.03	0.70 – 1.52	1.01	0.61 – 1.68	0.84	0.73 – 0.98
Sex: Male	0.89	0.72 – 1.10	0.88	0.71 – 1.09	0.80	0.62 – 1.03	0.80	0.62 – 1.04	0.96	0.59 – 1.56	0.90	0.50 – 1.63	0.88	0.69 – 1.12
Age: 18 to 39	0.17	0.02 – 1.38	0.17	0.02 – 1.38	NA	NA	NA	NA	1.00	0.06 – 15.98	NA	NA	0.20	0.02 – 1.71

Strata	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Age: 40 to 59	0.52	0.33 – 0.82	0.48	0.29 – 0.77	0.53	0.32 – 0.88	0.54	0.33 – 0.90	0.88	0.45 – 1.72	0.72	0.33 – 1.57	0.48	0.28 – 0.84
Age: 60 to 70	0.97	0.82 – 1.15	0.97	0.82 – 1.16	0.97	0.80 – 1.18	0.95	0.78 – 1.16	0.91	0.60 – 1.38	0.81	0.47 – 1.39	0.97	0.80 – 1.18
Age: 80 or above	0.82	0.70 – 0.96	0.82	0.70 – 0.97	0.86	0.72 – 1.03	0.86	0.72 – 1.03	1.36	0.74 – 2.50	1.83	0.78 – 4.31	0.81	0.68 – 0.97
CV history: No	0.86	0.75 – 0.99	0.86	0.75 – 0.98	0.87	0.75 – 1.01	0.86	0.74 – 1.00	0.86	0.61 – 1.23	0.81	0.52 – 1.28	0.87	0.75 – 1.02
CV history: Yes	0.83	0.69 – 1.00	0.83	0.69 – 1.01	0.87	0.69 – 1.09	0.86	0.68 – 1.08	1.54	0.84 – 2.83	1.50	0.70 – 3.21	0.79	0.64 – 0.98
Prior SSRI: No	0.92	0.78 – 1.09	0.91	0.77 – 1.08	0.91	0.75 – 1.10	0.90	0.74 – 1.09	1.11	0.68 – 1.82	0.98	0.53 – 1.83	0.89	0.73 – 1.08
Prior SSRI: Yes	0.81	0.70 – 0.94	0.81	0.70 – 0.94	0.85	0.72 – 1.00	0.84	0.71 – 1.00	0.94	0.64 – 1.38	0.95	0.58 – 1.56	0.83	0.70 – 0.98
Depression (w/ or w/o anxiety)	0.88	0.68 – 1.14	0.87	0.67 – 1.13	0.84	0.62 – 1.15	0.83	0.61 – 1.13	1.16	0.62 – 2.18	1.15	0.55 – 2.41	0.76	0.57 – 1.02
Anxiety with no depression	0.76	0.52 – 1.10	0.74	0.51 – 1.08	0.64	0.41 – 0.99	0.63	0.41 – 0.97	1.19	0.52 – 2.76	1.00	0.20 – 4.94	0.88	0.57 – 1.35

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HF = Heart Failure, HR = Hazard Ratio; 95%CI = 95% Confidence Interval, CV = cardiovascular, SSRI = Selective Serotonin Reuptake Inhibitors; w/ or w/o = with or without; NA = not applicable, alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

9.3.1.3. Residual unmeasured confounding: Negative control outcomes and calibration

Residual unmeasured confounding was assessed through Negative Control Outcome analyses. As shown in **Figure 5** for the "on treatment" analysis, the proportion of NCOs associated with venlafaxine use ranged from 4.9% in BIFAP to 34.3% in HI-SPEED, with the latter indicating potential residual bias towards an increased risk of incident heart failure. To account for this, we calibrated the estimated HR and IRR. Forest plots in **Figures 6, 7, and 8** illustrate the effect of calibration on the HRs and IRRs, and **Table 16** provides calibrated HR for all outcomes, as well as meta-analytic estimates (**Table 17**).

Calibration moved the effect estimated for incident HF (broad) in CPRD GOLD and HI-SPEED slightly away from 1, whereas point estimates were moved closer towards protective effects for BIFAP and FinOMOP-THL. Following calibration, HR_{cal} ranged from 0.77 (95%CI 0.44 – 1.35) in CPRD GOLD to 0.98 (95%CI 0.71 – 1.35) in DK-DHR, with calibrated confidence intervals including 1 for all data sources.

For cardiomyopathy (broad), calibration moved the effect estimated in HI-SPEED from HR 1.45 (95%CI 1.00 – 2.10) to HR_{cal} 1.38 (95%CI 0.88 – 2.15).

Calibrates estimates for stratified analyses are included in the Shiny app.

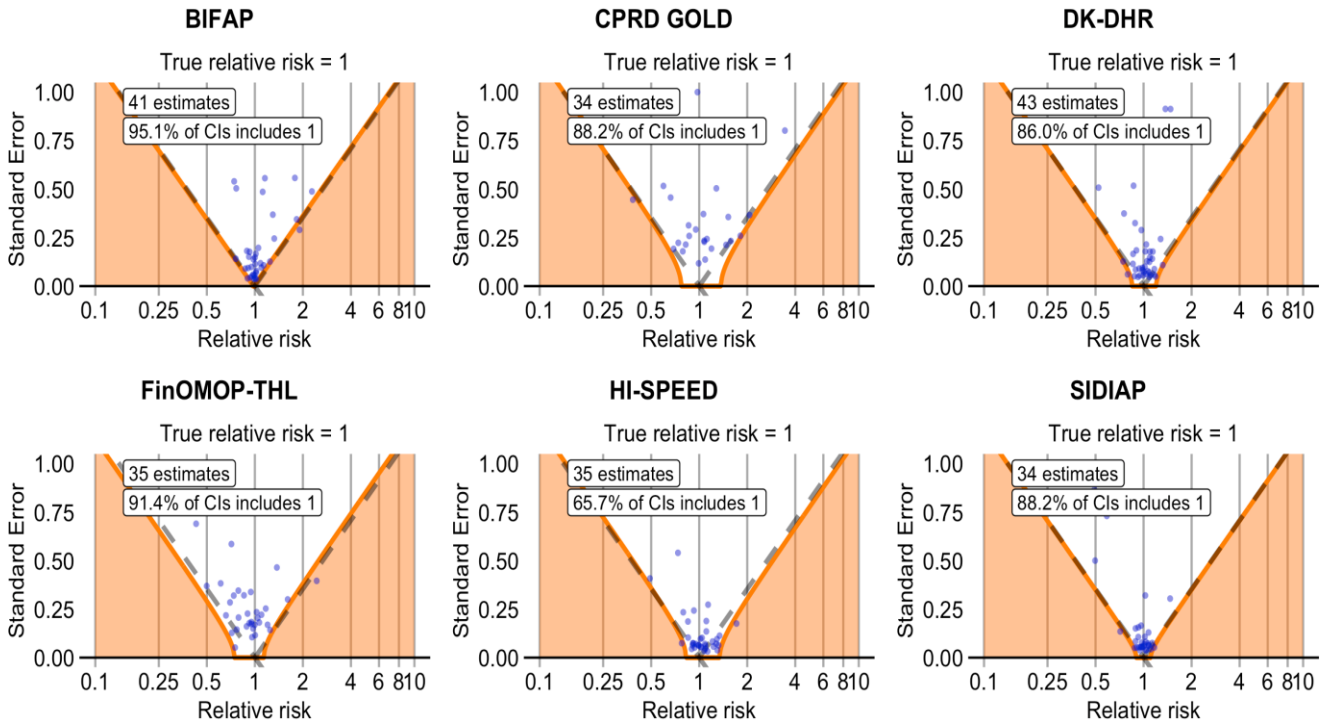

Figure 5. Negative control outcome analysis (overall).

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; 95%CI = 95% confidence intervals.
Note: Each blue dot in the plot represents a different NCO, which we expect not to be associated with venlafaxine (hence CI should include 1). The purple dashed lines indicate the significative threshold for the Negative Control Outcomes (NCO), indicating that they are positively correlated with venlafaxine if they are on the right of the dashed line (higher relative risk) and negatively correlated when on the left (reduced risk). Without significant associations, the spread should be symmetrical with most estimates for NCO in the middle. The orange lines mark the new significance thresholds after calibration, i.e. after adjustment according to the negative control outcome distribution.

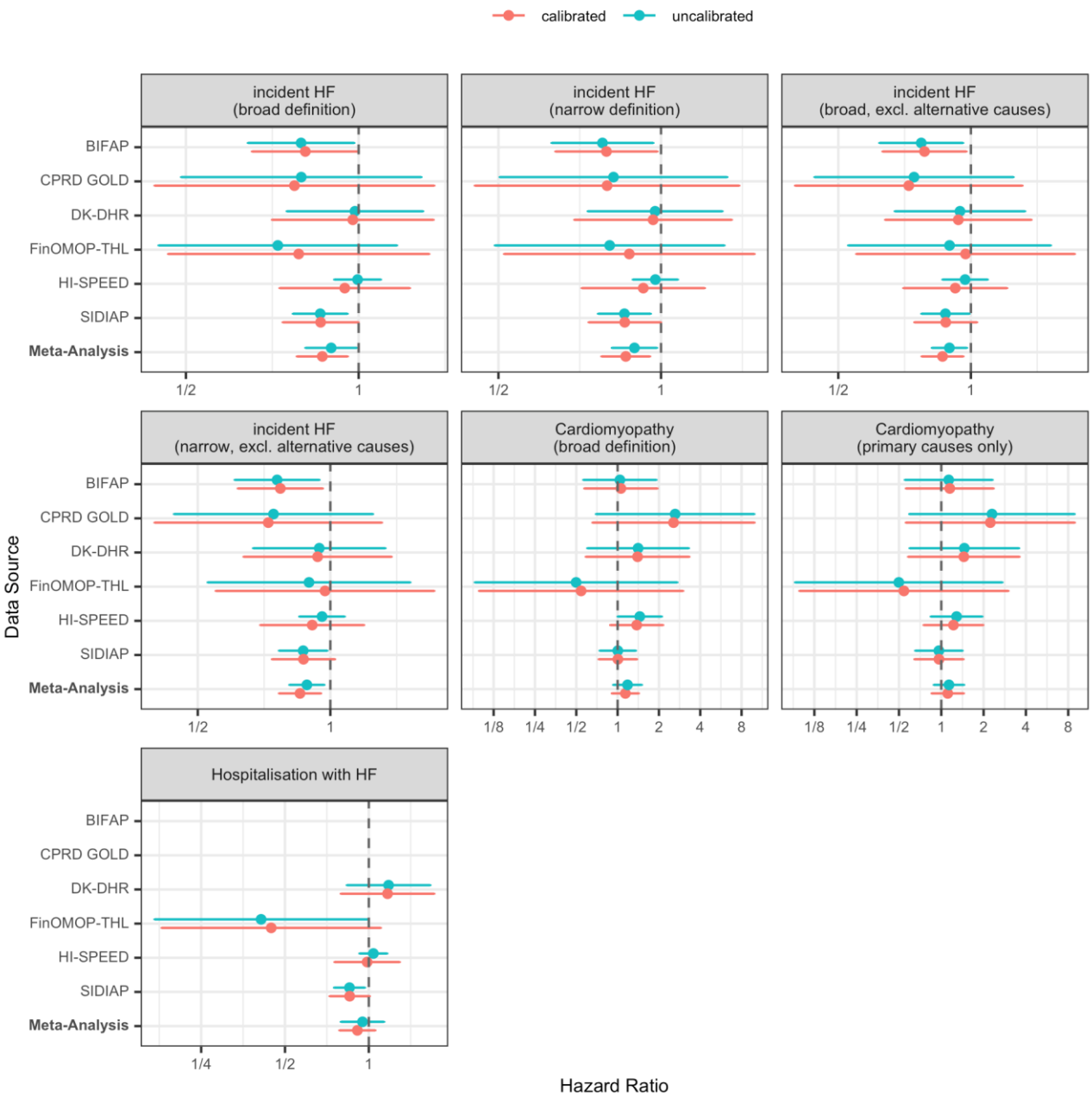

Figure 6. Calibrated and uncalibrated HRs, overall.

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR = Hazard Ratio, HF = heart failure, alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

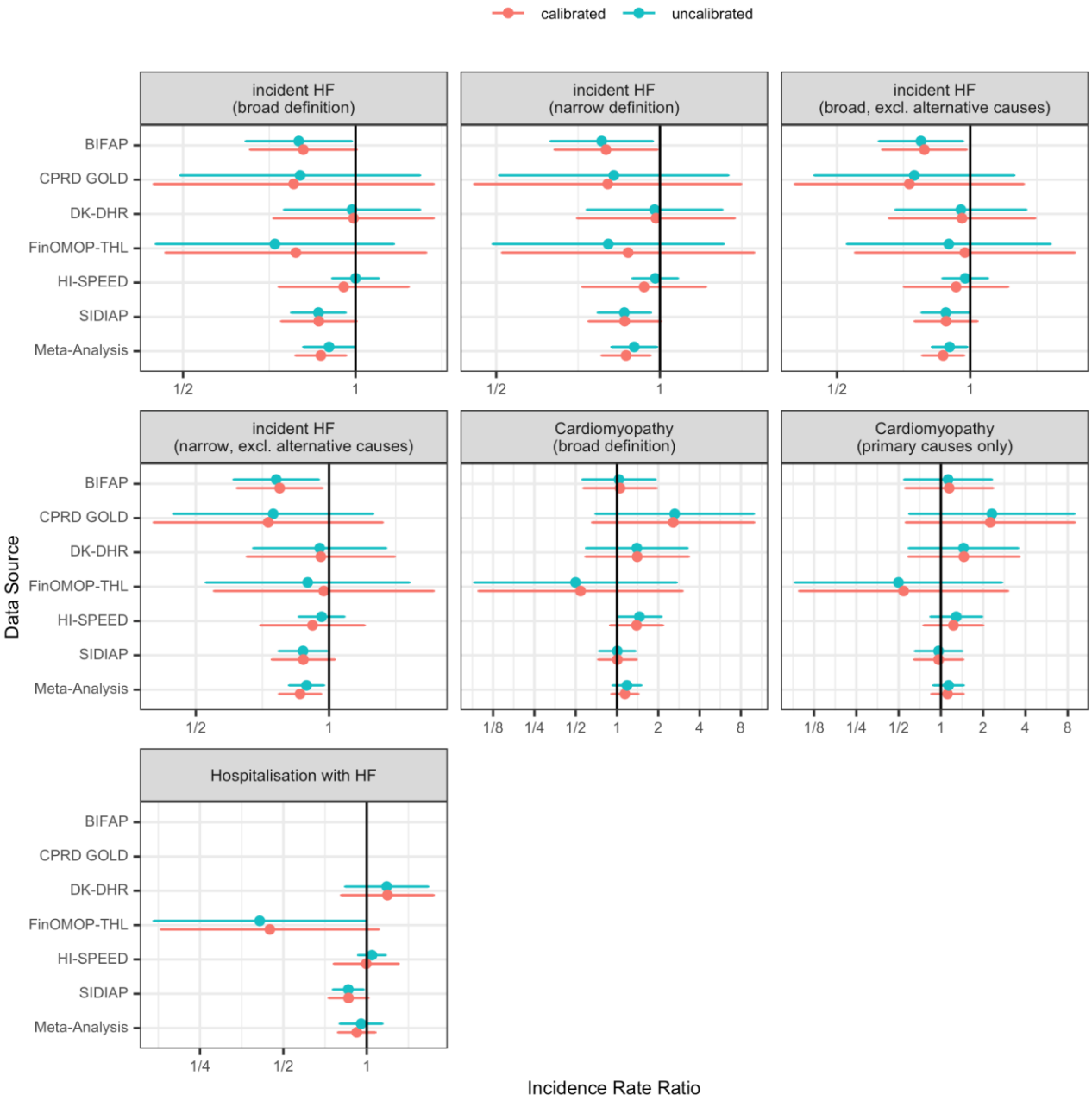

Figure 7. Calibrated and uncalibrated IRRs, overall.

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; IRR = Incidence Rate Ratio; HF = heart failure, alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

Table 16. Calibrated HRs for outcomes of interest, overall.

Data source	Incident HF (broad definition)		Incident HF (narrow definition)		Incident HF (broad, excl. alternative causes)		Incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR_{cal}	95%CI	HR_{cal}	95%CI	HR_{cal}	95%CI	HR_{cal}	95%CI	HR_{cal}	95%CI	HR_{cal}	95%CI	HR_{cal}	95%CI
BIFAP	0.81	0.65 – 1.00	0.79	0.64 – 0.98	0.78	0.63 – 0.98	0.77	0.62 – 0.96	1.06	0.57 – 1.95	1.15	0.56 – 2.35	NA	NA
CPRD GOLD	0.77	0.44 – 1.35	0.79	0.45 – 1.40	0.72	0.40 – 1.31	0.72	0.40 – 1.31	2.56	0.66 – 9.93	2.23	0.56 – 8.90	NA	NA
DK-DHR	0.98	0.71 – 1.35	0.97	0.69 – 1.35	0.94	0.64 – 1.37	0.94	0.64 – 1.38	1.40	0.59 – 3.33	1.45	0.58 – 3.60	1.17	0.79 – 1.72
FinOMOP-THL	0.79	0.47 – 1.33	0.87	0.51 – 1.49	0.97	0.55 – 1.72	0.97	0.55 – 1.72	0.54	0.10 – 3.00	0.54	0.10 – 3.00	0.45	0.18 – 1.10
HI-SPEED	0.95	0.73 – 1.23	0.93	0.71 – 1.20	0.92	0.70 – 1.21	0.91	0.69 – 1.19	1.38	0.88 – 2.15	1.22	0.75 – 1.99	0.99	0.75 – 1.29
SIDIAP	0.86	0.74 – 1.00	0.86	0.73 – 1.00	0.88	0.74 – 1.03	0.87	0.74 – 1.02	1.00	0.73 – 1.38	0.96	0.65 – 1.44	0.85	0.72 – 1.01

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HF = Heart Failure; HR = Hazard Ratio; 95%CI = 95% Confidence Interval; NA = not applicable, alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

Table 17. Meta-analysis of calibrated Hazard Ratios for outcomes of interest, overall.

Data Source	incident HF (broad definition)		incident HF (narrow definition)		incident HF (broad, excl. alternative causes)		incident HF (narrow, excl. alternative causes)		Cardiomyopathy (broad definition)		Cardiomyopathy (primary causes only)		Hospitalisation with HF	
	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI	HR_{meta}	95%CI
Meta-Analysis	0.86	0.78 – 0.96	0.86	0.78 – 0.95	0.86	0.77 – 0.96	0.85	0.76 – 0.95	1.14	0.91 – 1.43	1.11	0.85 – 1.45	0.91	0.78 – 1.05

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HF = Heart Failure, HR_{meta} = meta-analytic; Hazard Ratio; 95%CI = 95% Confidence Interval, alternative causes = Ischaemic heart disease, valvular disease, pulmonary heart disease.

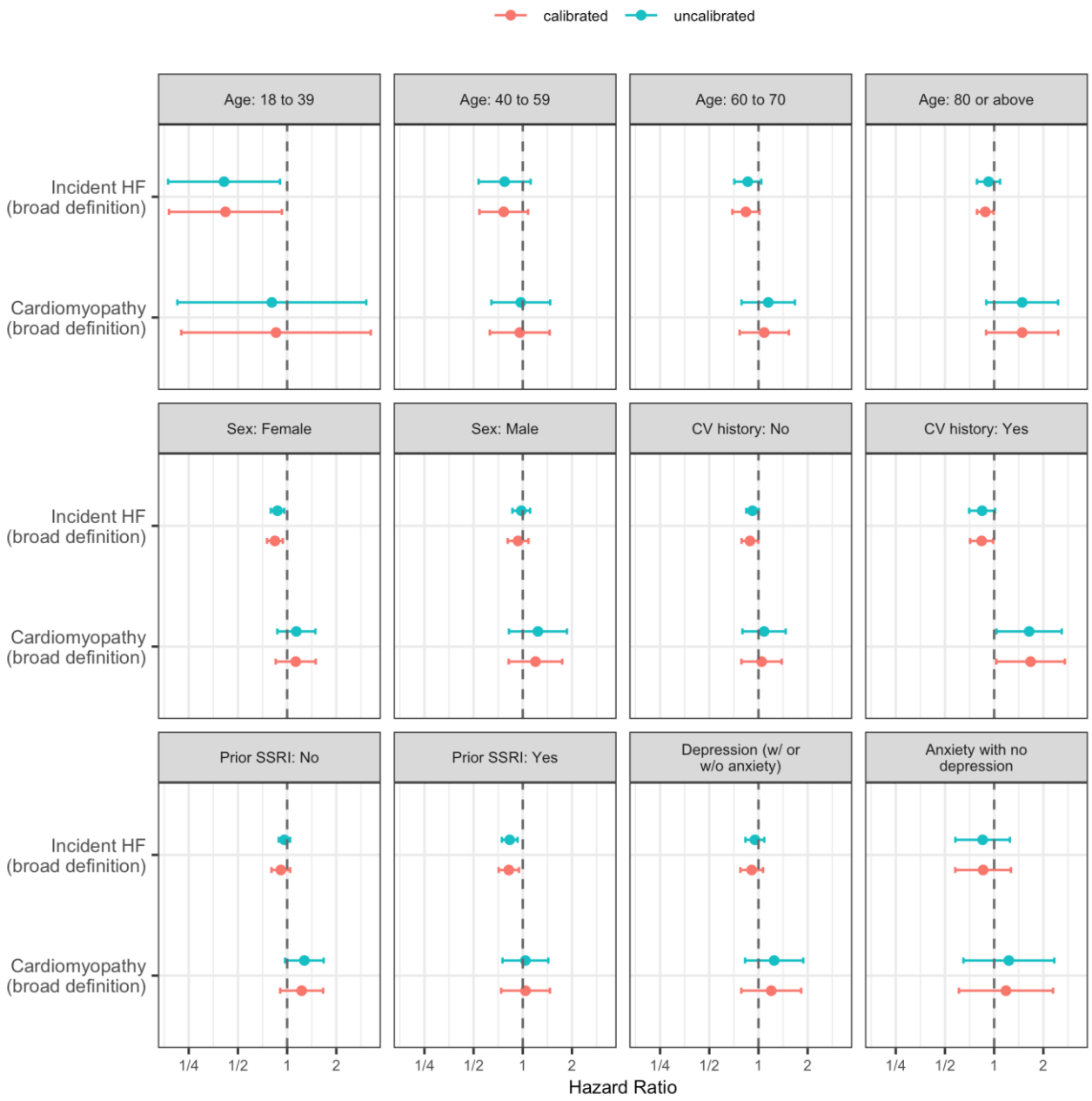

Figure 8. Calibrated and uncalibrated HR, stratified, for incident HF (broad) and cardiomyopathy (broad).

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; IRR = Incidence Rate Ratio; HF = heart failure.

9.3.1.4. Sensitivity analyses: Impact of causal estimate ("on treatment"/"ever exposed"), required data availability, and treatment duration estimation

Sensitivity analyses were conducted to test the robustness of our results related to study design choices, namely 1) the choice of the causal estimate and censoring modes, 2) the required data availability prior to index date, and 3) the impact of the length of allowed gap between individual prescriptions to be considered a continuous treatment episode.

Impact of the choice of the causal estimate

For the "on treatment" analysis, the duration of follow-up periods (in the venlafaxine cohort) was comparably short, with a median 32 days (IQR 30 – 114) of follow-up in BIFAP, 29 days (IQR 27 – 105) in CPRD GOLD, 44 days (IQR 21 – 94) in DK-DHR, and 29 days (IQR 29 – 29) in FinOMOP-THL. Follow-up in HI-SPEED and SIDIAP was slightly longer with a median of 100 days (IQR 36 – 232) and 86 days (IQR 30 – 235), respectively. The most common reasons were cessation of treatment (ranging from 30% in DK-DHR to 51% in FinOMOP-THL) and censoring of the matched pair (ranging from 46% in FinOMOP-THL to 66% in DK-DHR).

We added a post-hoc sensitivity analysis to remove the requirement of censoring the matched pair in case of treatment cessation or switching for one of the matched counterparts: While removing the pair censoring for "on treatment" analysis substantially increased the median follow-up time for venlafaxine in BIFAP (139 days instead of 32), CPRD GOLD (156 days instead of 29 days), DK-DHR (187 days instead of 44 days), HI-SPEED (376 days instead of 100 days), and SIDIAP (307 days instead of 86 days), 17% of NCO were associated with venlafaxine for BIFAP and CPRD GOLD, 44% for DK-DHR, 19% for FinOMOP-THL, 46% for HI-SPEED and 29% for SIDIAP, indicating potential residual bias towards protective venlafaxine effects in this analysis.

The analysis based on an "ever exposed" approach was commonly censored at 730 days for reaching the maximum follow-up (ranging from 70% in CPRD GOLD to 89% in DK-DHR), hence the median duration of follow-up was 730 days in all data sources. While the follow-up of individuals in the "on treatment" analysis was short, the longer follow-up time in the "ever exposed" analyses may include a substantial amount of unexposed follow-up time for some data sources.

Figure 9 and **Table 18** show uncalibrated and calibrated HR for the different causal contrasts and censoring definitions.

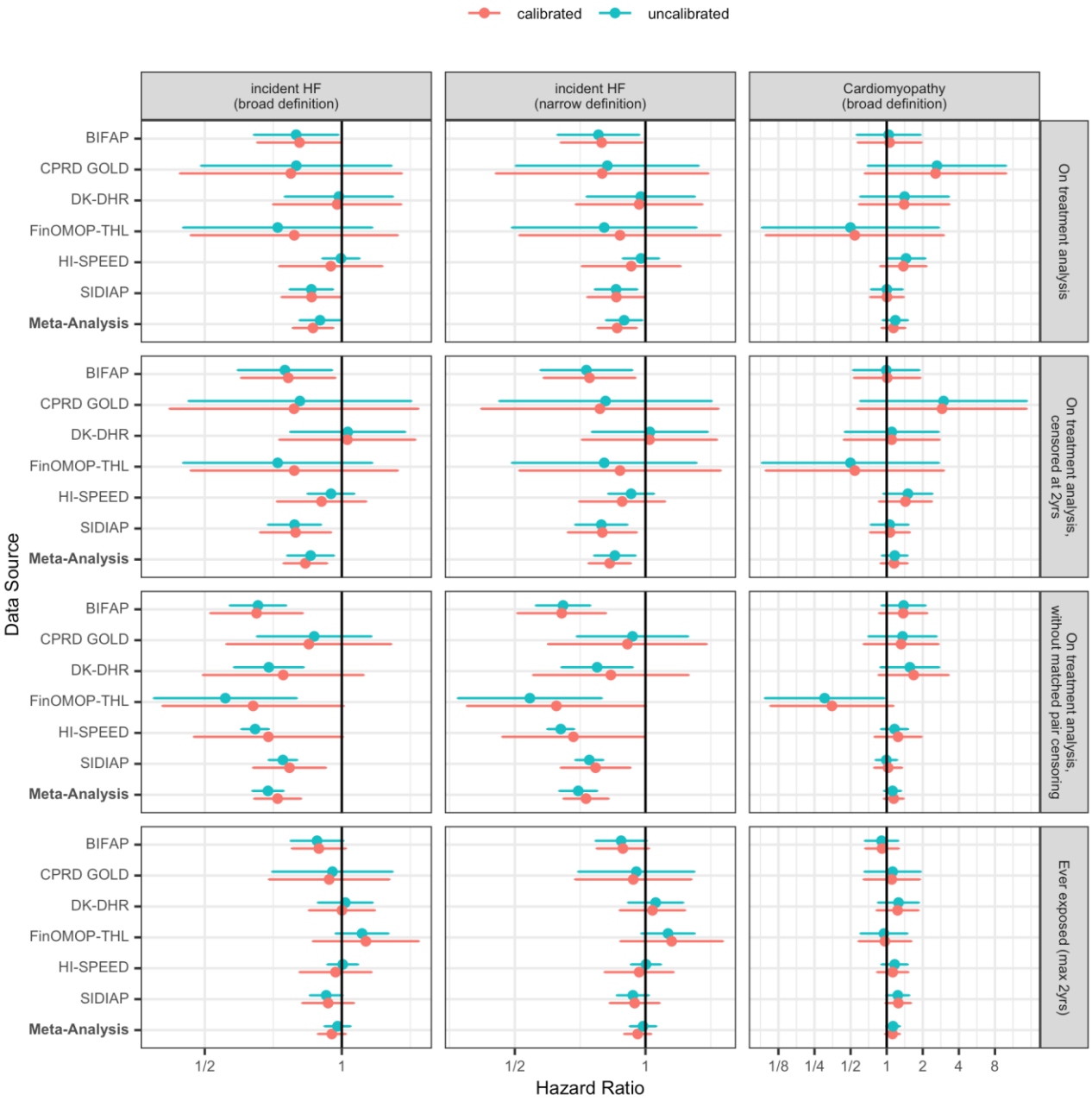

Figure 9. Comparison of causal estimands, uncalibrated and calibrated.

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR = Hazard Ratio.

Table 18. Comparison of causal estimands for incident HF (broad) and cardiomyopathy (broad).

Analysis	Estimate name	BIFAP	CPRD GOLD	DK-DHR	FinOMOP-THL	HI-SPEED	SIDIAP
Incident HR (broad)							
On treatment analysis	HR [95%CI]	0.79 [0.64 – 0.98]	0.79 [0.49 – 1.29]	0.99 [0.75 – 1.29]	0.72 [0.45 – 1.17]	1.00 [0.91 – 1.09]	0.86 [0.77 – 0.96]
	HR_{cal} [95%CI]	0.81 [0.65 – 1.00]	0.77 [0.44 – 1.35]	0.98 [0.71 – 1.35]	0.79 [0.47 – 1.33]	0.95 [0.73 – 1.23]	0.86 [0.74 – 1.00]
On treatment analysis, censored at 2yrs	HR [95%CI]	0.75 [0.59 – 0.95]	0.81 [0.46 – 1.42]	1.03 [0.77 – 1.38]	0.72 [0.45 – 1.17]	0.95 [0.84 – 1.06]	0.79 [0.69 – 0.90]
	HR_{cal} [95%CI]	0.76 [0.60 – 0.97]	0.79 [0.42 – 1.47]	1.03 [0.73 – 1.45]	0.79 [0.47 – 1.33]	0.90 [0.72 – 1.13]	0.79 [0.66 – 0.95]
On treatment analysis, without matched pair censoring	HR [95%CI]	0.65 [0.57 – 0.75]	0.87 [0.65 – 1.16]	0.69 [0.58 – 0.82]	0.55 [0.39 – 0.80]	0.65 [0.60 – 0.69]	0.74 [0.69 – 0.80]
	HR_{cal} [95%CI]	0.65 [0.51 – 0.82]	0.85 [0.56 – 1.28]	0.74 [0.50 – 1.12]	0.64 [0.40 – 1.01]	0.69 [0.47 – 1.00]	0.77 [0.64 – 0.92]
Ever exposed (max 2yrs)	HR [95%CI]	0.88 [0.77 – 1.01]	0.95 [0.70 – 1.29]	1.02 [0.89 – 1.17]	1.11 [0.97 – 1.27]	1.00 [0.93 – 1.08]	0.92 [0.85 – 1.00]
	HR_{cal} [95%CI]	0.89 [0.78 – 1.02]	0.94 [0.69 – 1.27]	1.00 [0.85 – 1.18]	1.13 [0.86 – 1.48]	0.97 [0.81 – 1.16]	0.93 [0.82 – 1.06]
Cardiomyopathy (broad)							
On treatment analysis	HR [95%CI]	1.04 [0.56 – 1.92]	2.63 [0.70 – 9.90]	1.41 [0.60 – 3.30]	0.50 [0.09 – 2.72]	1.45 [1.00 – 2.10]	1.00 [0.74 – 1.36]
	HR_{cal} [95%CI]	1.06 [0.57 – 1.95]	2.56 [0.66 – 9.93]	1.40 [0.59 – 3.33]	0.54 [0.10 – 3.00]	1.38 [0.88 – 2.15]	1.00 [0.73 – 1.38]
On treatment analysis, censored at 2yrs	HR [95%CI]	0.99 [0.53 – 1.87]	2.98 [0.60 – 14.78]	1.10 [0.45 – 2.72]	0.50 [0.09 – 2.72]	1.50 [0.94 – 2.40]	1.06 [0.74 – 1.52]
	HR_{cal} [95%CI]	1.01 [0.53 – 1.91]	2.90 [0.57 – 14.70]	1.10 [0.44 – 2.76]	0.54 [0.10 – 3.00]	1.43 [0.86 – 2.38]	1.06 [0.73 – 1.56]
On treatment analysis, without matched pair censoring	HR [95%CI]	1.38 [0.91 – 2.11]	1.36 [0.71 – 2.61]	1.56 [0.89 – 2.74]	0.30 [0.10 – 0.95]	1.16 [0.90 – 1.50]	0.99 [0.81 – 1.22]
	HR_{cal} [95%CI]	1.37 [0.87 – 2.18]	1.32 [0.64 – 2.71]	1.68 [0.86 – 3.29]	0.35 [0.11 – 1.14]	1.24 [0.79 – 1.95]	1.03 [0.79 – 1.34]

Analysis	Estimate name	BIFAP	CPRD GOLD	DK-DHR	FinOMOP-THL	HI-SPEED	SIDIAP
Incident HR (broad)							
Ever exposed (max 2yrs)	HR [95%CI]	0.91 [0.66 – 1.25]	1.12 [0.65 – 1.92]	1.25 [0.85 – 1.85]	0.95 [0.61 – 1.49]	1.17 [0.91 – 1.50]	1.24 [0.99 – 1.54]
	HR_{cal} [95%CI]	0.91 [0.66 – 1.26]	1.10 [0.64 – 1.89]	1.23 [0.83 – 1.84]	0.97 [0.58 – 1.60]	1.12 [0.83 – 1.52]	1.25 [0.98 – 1.59]

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR = Hazard Ratio; HR_{cal} = calibrated Hazard Ratio; 95%CI = 95% Confidence Interval.

Impact of the requirement for data availability prior to index date

While the requirement for data availability prior to index date was 2 years for the main analysis, a sensitivity analysis was conducted requiring 5 years of data availability.

Table 19 shows that the number of subjects in most data sources was not substantially reduced when requiring a longer lookback period. The only exceptions were BIFAP and HI-SPEED, where the requirement of 5 years lookback period excluded 38,727 and 83,137 matched pairs, respectively. Given data availability only started in 2015 for the data cut available to DARWIN EU®, the number of matched venlafaxine users dropped from 125,609 to 42,742.

Table 19. Short summary demographics of matched venlafaxine users when requiring 2 or 5 years of data availability prior to index date, respectively.

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		2yrs	5yrs	2yrs	5yrs	2yrs	5yrs	2yrs	5yrs	2yrs	5yrs	2yrs	5yrs
Demographics													
Number (subjects)	N	151,787	113,060	44,952	37,400	60,058	58,500	57,706	56,967	125,609	42,742	74,098	66,189
Age	Median [IQR]	51 [40 – 65]	52 [40 – 65]	43 [31 – 53]	44 [31 – 54]	43 [30 – 56]	43 [30 – 57]	39 [26 – 56]	39 [26 – 56]	44 [31 – 58]	38 [28 – 52]	52 [41 – 66]	53 [41 – 67]
	Mean (SD)	52.73 (17.20)	53.02 (17.21)	43.40 (15.44)	44.01 (15.64)	44.50 (17.54)	44.72 (17.63)	42.68 (18.79)	42.76 (18.84)	45.69 (17.34)	40.93 (16.45)	53.59 (17.17)	53.78 (17.11)
Sex: Female	N (%)	107,077 (70.54%)	80,330 (71.05%)	30,773 (68.46%)	25,694 (68.70%)	35,704 (59.45%)	34,746 (59.39%)	38,055 (65.95%)	37,601 (66.00%)	77,647 (61.82%)	26,076 (61.01%)	50,021 (67.51%)	44,797 (67.68%)
Treatment duration (days)	Median [IQR]	153 [31 – 507]	153 [31 – 508]	166 [30 – 617]	169 [30 – 641]	207 [73 – 631]	208 [74 – 636]	42 [30 – 114]	41 [30 – 114]	446 [121 – 1,402]	224 [101 – 612]	340 [91 – 959]	336 [91 – 933]
	Mean (SD)	476.07 (801.72)	487.38 (819.28)	538.52 (870.51)	552.49 (885.07)	580.17 (915.10)	583.93 (920.16)	87.32 (97.57)	87.09 (97.14)	881.31 (941.42)	433.51 (479.01)	784.94 (1,092.11)	756.00 (1,033.53)
Comorbidities [-Inf, -366]													
Ischaemic heart disease	N (%)	2,039 (1.34%)	1,795 (1.59%)	625 (1.39%)	565 (1.51%)	2,410 (4.01%)	2,397 (4.10%)	1,596 (2.77%)	1,586 (2.78%)	1,929 (1.54%)	510 (1.19%)	1,537 (2.07%)	1,439 (2.17%)
Myocardial infarction	N (%)	1,124 (0.74%)	1,001 (0.89%)	223 (0.50%)	199 (0.53%)	714 (1.19%)	712 (1.22%)	445 (0.77%)	445 (0.78%)	1,031 (0.82%)	273 (0.64%)	497 (0.67%)	476 (0.72%)
Chronic renal disease	N (%)	2,765 (1.82%)	2,421 (2.14%)	983 (2.19%)	919 (2.46%)	282 (0.47%)	281 (0.48%)	231 (0.40%)	234 (0.41%)	600 (0.48%)	196 (0.46%)	2,460 (3.32%)	2,339 (3.53%)

Variable level	Estimate name	BIFAP		CPRD GOLD		DK-DHR		FinOMOP-THL		HI-SPEED		SIDIAP	
		2yrs	5yrs	2yrs	5yrs	2yrs	5yrs	2yrs	5yrs	2yrs	5yrs	2yrs	5yrs
Valvular heart disease	N (%)	338 (0.22%)	292 (0.26%)	116 (0.26%)	102 (0.27%)	412 (0.69%)	406 (0.69%)	456 (0.79%)	458 (0.80%)	485 (0.39%)	165 (0.39%)	746 (1.01%)	705 (1.07%)
Hypertension	N (%)	19,623 (12.93%)	15,974 (14.13%)	5,634 (12.53%)	5,188 (13.87%)	7,960 (13.25%)	7,917 (13.53%)	7,573 (13.12%)	7,541 (13.24%)	12,420 (9.89%)	3,395 (7.94%)	15,333 (20.69%)	14,459 (21.85%)
Ischaemic stroke	N (%)	708 (0.47%)	570 (0.50%)	259 (0.58%)	244 (0.65%)	1,139 (1.90%)	1,134 (1.94%)	791 (1.37%)	791 (1.39%)	1,124 (0.89%)	310 (0.73%)	1,058 (1.43%)	983 (1.49%)
Obesity	N (%)	11,064 (7.29%)	9,888 (8.75%)	3,536 (7.87%)	3,283 (8.78%)	6,018 (10.02%)	5,983 (10.23%)	2,794 (4.84%)	2,795 (4.91%)	5,709 (4.55%)	2,709 (6.34%)	10,973 (14.81%)	10,473 (15.82%)
Diabetes mellitus	N (%)	8,233 (5.42%)	6,664 (5.89%)	1,932 (4.30%)	1,724 (4.61%)	3,556 (5.92%)	3,483 (5.95%)	4,239 (7.35%)	4,230 (7.43%)	8,027 (6.39%)	2,110 (4.94%)	6,246 (8.43%)	5,866 (8.86%)
Atrial fibrillation	N (%)	2,148 (1.42%)	1,871 (1.65%)	216 (0.48%)	211 (0.56%)	175 (0.29%)	174 (0.30%)	53 (0.09%)	54 (0.09%)	675 (0.54%)	210 (0.49%)	1,195 (1.61%)	1,108 (1.67%)

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Variation in the requirement of the lookback periods had little impact on the effect estimate in some data sources (e.g. DK-DHR, SIDIAP), whereas differences in the point estimates were seen for other data sources (e.g. BIFAP, CPRD GOLD, FinOMOP-THL, and HI-SPEED) (**Table 20**).

Table 20. Impact of required duration of data availability prior to index date on Hazard Ratios for "on treatment" analyses, uncalibrated, for both incident HF (broad) and cardiomyopathy (broad).

Outcome	Lookback period	Estimate name	BIFAP	CPRD GOLD	DK-DHR	FinOMOP-THL	HI-SPEED	SIDIAP
Incident HF (broad definition)	2 years	HR [95%CI]	0.79 [0.64 – 0.98]	0.79 [0.49 – 1.29]	0.99 [0.75 – 1.29]	0.72 [0.45 – 1.17]	1.00 [0.91 – 1.09]	0.86 [0.77 – 0.96]
	5 years	HR [95%CI]	0.86 [0.66 – 1.12]	1.23 [0.72 – 2.10]	0.96 [0.74 – 1.26]	0.53 [0.34 – 0.84]	0.88 [0.65 – 1.18]	0.86 [0.77 – 0.97]
Cardiomyopathy (broad definition)	2 years	HR [95%CI]	1.04 [0.56 – 1.92]	2.63 [0.70 – 9.90]	1.41 [0.60 – 3.30]	0.50 [0.09 – 2.72]	1.45 [1.00 – 2.10]	1.00 [0.74 – 1.36]
	5 years	HR [95%CI]	1.54 [0.67 – 3.56]	3.99 [0.45 – 35.66]	2.81 [1.03 – 7.70]	0.50 [0.09 – 2.73]	0.74 [0.17 – 3.31]	1.10 [0.78 – 1.54]

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR = Hazard Ratio; 95%CI = 95% Confidence Interval.

Impact of the choice of length of allowed gap between individual prescriptions

While the length of allowed gap between individual prescriptions was defined as 90 days for the main analyses, drug exposure diagnostics showed that an extended gap might be needed for FinOMOP-THL to account for the local prescription pattern. A post-hoc sensitivity analysis was therefore added. **Table 21** below shows the impact on the different gap lengths.

Table 21. Impact of the choice of length of allowed gap between individual prescriptions on treatment duration.

Data source	Estimate name	Duration of first venlafaxine treatment episode	
		Allowed gap: 90 days	Allowed gap: 365 days
BIFAP	Median [IQR]	153 [31 – 507]	213 [50 – 733]
	Mean (SD)	476.07 (801.72)	635.27 (989.56)
CPRD GOLD	Median [IQR]	166 [30 – 617]	210 [43 – 759]
	Mean (SD)	538.52 (870.51)	626.00 (956.67)
DK-DHR	Median [IQR]	207 [73 – 631]	286 [75 – 968]
	Mean (SD)	580.17 (915.10)	814.37 (1,186.23)
FinOMOP-THL	Median [IQR]	42 [30 – 114]	87 [30 – 373]
	Mean (SD)	87.32 (97.57)	281.45 (414.82)

Data source	Estimate name	Duration of first venlafaxine treatment episode	
		Allowed gap: 90 days	Allowed gap: 365 days
HI-SPEED	Median [IQR]	446 [121 – 1,402]	698 [164 – 2,365]
	Mean (SD)	881.31 (941.42)	1,141.36 (1,060.00)
SIDIAP	Median [IQR]	340 [91 – 959]	385 [106 – 1,150]
	Mean (SD)	784.94 (1,092.11)	894.72 (1,180.13)

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; IQR = Interquartile range; SD = Standard Deviation; 95%CI = 95% Confidence Interval.

As shown in **Table 22**, an extended gap length of 365 days had little impact on the effect estimate for incident HF (broad) in BIFAP, DK-DHR, HI-SPEED, and SIDIAP. For CPRD GOLD and FinOMOP-THL, estimates were slightly shifted towards HR 1 in the analyses with extended gap lengths. For incident cardiomyopathy (broad), an extended gap length increased point estimates for HR in BIFAP, DK-DHR, FinOMOP-THL, and HI-SPEED, whereas no relevant impact was seen in SIDIAP, and HR was shifted towards 1 in CPRD GOLD.

Table 22. Impact of the choice of length of allowed gap between individual prescriptions on Hazard Ratios for "on treatment" analysis, uncalibrated, for incident HF (broad) and cardiomyopathy (broad).

Outcome	Allowed gap between prescriptions	Estimate name	BIFAP	CPRD GOLD	DK-DHR	FinOMOP-THL	HI-SPEED	SIDIAP
Incident HF (broad definition)	365 days	HR [95%CI]	0.78 [0.65 – 0.94]	0.92 [0.60 – 1.42]	1.06 [0.86 – 1.30]	0.98 [0.70 – 1.37]	0.96 [0.89 – 1.04]	0.85 [0.77 – 0.94]
	90 days	HR [95%CI]	0.79 [0.64 – 0.98]	0.79 [0.49 – 1.29]	0.99 [0.75 – 1.29]	0.72 [0.45 – 1.17]	1.00 [0.91 – 1.09]	0.86 [0.77 – 0.96]
Cardiomyopathy (broad definition)	365 days	HR [95%CI]	1.83 [0.93 – 3.59]	1.78 [0.60 – 5.31]	1.65 [0.83 – 3.27]	0.80 [0.21 – 2.96]	1.62 [1.20 – 2.18]	1.06 [0.79 – 1.41]
	90 days	HR [95%CI]	1.04 [0.56 – 1.92]	2.63 [0.70 – 9.90]	1.41 [0.60 – 3.30]	0.50 [0.09 – 2.72]	1.45 [1.00 – 2.10]	1.00 [0.74 – 1.36]

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR = Hazard Ratio; 95%CI = 95% Confidence Interval.

9.3.2. Objective 2

9.3.2.1. Number of outcome events and event rates

The number of hospitalisations with heart failure in venlafaxine and mirtazapine users were 398 and 399 (HI-SPEED), and 355 and 374 (SIDIAP), respectively (**Table 23**). Event rates per 10,000 person-years were slightly higher for new mirtazapine users compared to new venlafaxine users, with overlapping confidence intervals.

Repeated recordings of heart failure were more common in HI-SPEED compared to SIDIAP, with event rates of 6,718 and 6,314/10,000 person-years in mirtazapine and venlafaxine users respectively in HI-SPEED and

only 3,384 and 3,099/10,000 person-years respectively in SIDIAP. This could reflect local pattern of re-recordings of chronic diagnoses, which are less common in the Catalonian Health system (diagnoses are recorded as active and chronic conditions are not typically re-recorded). Acute pulmonary oedema was rarely recorded in either data source.

Event rates for heart failure hospitalisation were higher in older age groups in HI-SPEED and SIDIAP, and in individuals with a previous history of cardiovascular disease (other than heart failure) in SIDIAP (**Table 24**).

Table 23. Number of outcome events and incidence rates after matching, overall.

Outcome		HI-SPEED		SIDIAP	
	Estimate name	mirtazapine	venlafaxine	mirtazapine	venlafaxine
Hospitalisation with HF	N (event)	399	398	374	355
	person-years	1,328.59	1,450.50	1,130.55	1,181.87
	IR per 10,000 [95%CI]	3,003.17 [2,715.69 – 3,304.91]	2,743.88 [2,480.90 – 3,019.92]	3,308.11 [2,981.30 – 3,651.68]	3,003.71 [2,699.35 – 3,324.11]
Repeated HF (broad)	N (event)	658	666	368	355
	person-years	979.33	1,054.67	1,087.41	1,145.36
	IR per 10,000 [95%CI]	6,718.87 [6,215.23 – 7,241.84]	6,314.76 [5,844.21 – 6,803.26]	3,384.20 [3,047.23 – 3,738.59]	3,099.46 [2,785.39 – 3,430.07]
Acute Pulmonary Oedema	N (event)	14	18	8	5
	person-years	1,705.60	1,970.53	1,425.18	1,502.31
	IR per 10,000 [95%CI]	82.08 [44.88 – 130.34]	91.35 [54.14 – 138.13]	56.13 [24.23 – 101.20]	33.28 [10.81 – 68.17]

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HF = Heart Failure.

Table 24. Number of outcome events and incidence rates after matching, stratified.

Strata	venlafaxine						mirtazapine					
	Hospitalisation with HF			Repeated HF (broad)			Hospitalisation with HF			Repeated HF (broad)		
	N	PY	IR [95%CI]	N	PY	IR [95%CI]	N	PY	IR [95%CI]	N	PY	IR [95%CI]
HI-SPEED												
Sex: Female	205	795.31	2,577.60 [2,236.81 – 2,942.20]	344	578.36	5,947.88 [5,335.88 – 6,592.63]	208	715.46	2,907.24 [2,525.55 – 3,315.40]	352	526.21	6,689.32 [6,008.68 – 7,405.95]
Sex: Male	193	655.19	2,945.72 [2,544.78 – 3,375.57]	322	476.31	6,760.23 [6,041.93 – 7,518.30]	191	613.14	3,115.12 [2,688.98 – 3,572.14]	306	453.12	6,753.18 [6,017.64 – 7,530.51]
Age: 40 to 59	16	130.37	1,227.32 [701.52 – 1,897.76]	40	97.77	4,091.41 [2,922.96 – 5,453.26]	23	124.08	1,853.57 [1,175.00 – 2,684.31]	46	88.31	5,209.12 [3,813.73 – 6,818.69]
Age: 60 to 70	209	778.95	2,683.10 [2,331.65 – 3,058.86]	365	551.74	6,615.47 [5,954.12 – 7,311.14]	210	739.16	2,841.05 [2,469.77 – 3,237.96]	334	576.25	5,796.05 [5,191.05 – 6,433.91]
Age: 80 or above	173	533.06	3,245.42 [2,779.81 – 3,746.54]	259	400.55	6,466.10 [5,702.53 – 7,276.96]	164	455.21	3,602.70 [3,072.41 – 4,174.59]	275	310.64	8,852.79 [7,837.29 – 9,929.25]
CV history: No	142	549.37	2,584.77 [2,177.13 – 3,026.87]	254	390.43	6,505.72 [5,730.18 – 7,329.76]	138	511.06	2,700.28 [2,268.57 – 3,169.04]	259	345.08	7,505.53 [6,619.21 – 8,446.74]
CV history: Yes	256	901.13	2,840.88 [2,503.51 – 3,199.27]	412	664.25	6,202.52 [5,617.98 – 6,815.56]	261	817.54	3,192.52 [2,816.92 – 3,591.28]	399	634.25	6,290.86 [5,688.66 – 6,922.92]
Prior SSRI: No	347	1,270.33	2,731.58 [2,451.70 – 3,026.37]	570	902.87	6,313.23 [5,805.52 – 6,841.91]	339	1,169.61	2,898.40 [2,598.04 – 3,214.95]	562	843.49	6,662.83 [6,123.29 – 7,224.83]

Strata	venlafaxine						mirtazapine					
	Hospitalisation with HF			Repeated HF (broad)			Hospitalisation with HF			Repeated HF (broad)		
	N	PY	IR [95%CI]	N	PY	IR [95%CI]	N	PY	IR [95%CI]	N	PY	IR [95%CI]
Prior SSRI: Yes	51	180.17	2,830.62 [2,107.58 – 3,658.65]	96	151.81	6,323.88 [5,122.36 – 7,650.08]	60	158.98	3,774.02 [2,879.98 – 4,787.08]	96	135.85	7,066.79 [5,724.12 – 8,548.80]
Depression (w/ or w/o anxiety)	69	271.90	2,537.68 [1,974.47 – 3,170.49]	150	166.40	9,014.22 [7,629.40 – 10,512.81]	81	269.48	3,005.84 [2,387.07 – 3,694.84]	152	154.36	9,847.11 [8,343.91 – 11,472.97]
Anxiety	13	60.22	2,158.88 [1,149.51 – 3,481.05]	32	35.45	9,027.57 [6,174.85 – 12,413.49]	17	62.52	2,718.94 [1,583.88 – 4,155.66]	30	46.34	6,474.15 [4,368.08 – 8,988.03]
SIDIAP												
Sex: Female	252	905.87	2,781.86 [2,448.97 – 3,135.66]	249	872.23	2,854.74 [2,511.14 – 3,220.05]	258	850.71	3,032.77 [2,673.96 – 3,413.84]	258	814.85	3,166.24 [2,791.64 – 3,564.08]
Sex: Male	103	276.00	3,731.85 [3,046.05 – 4,486.23]	106	273.13	3,880.96 [3,177.42 – 4,653.82]	116	279.85	4,145.13 [3,425.20 – 4,932.70]	110	272.56	4,035.83 [3,316.96 – 4,824.15]
Age: 40 to 59	–	16.97	–	–	16.97	–	–	17.07	–	–	17.37	–
Age: 60 to 70	107	432.56	2,473.64 [2,027.21 – 2,963.83]	109	419.68	2,597.22 [2,132.59 – 3,106.96]	97	413.94	2,343.33 [1,900.28 – 2,832.10]	98	400.98	2,444.03 [1,984.18 – 2,951.08]
Age: 80 or above	247	732.33	3,372.78 [2,965.24 – 3,806.18]	245	708.71	3,457.00 [3,037.64 – 3,903.09]	274	699.55	3,916.81 [3,466.72 – 4,393.97]	268	669.06	4,005.61 [3,540.35 – 4,499.17]
CV history: No	63	336.76	1,870.78 [1,437.56 – 2,360.18]	63	325.95	1,932.78 [1,485.20 – 2,438.41]	74	321.58	2,301.14 [1,806.89 – 2,854.24]	74	308.51	2,398.65 [1,883.46 – 2,975.19]

Strata	venlafaxine						mirtazapine					
	Hospitalisation with HF			Repeated HF (broad)			Hospitalisation with HF			Repeated HF (broad)		
	N	PY	IR [95%CI]	N	PY	IR [95%CI]	N	PY	IR [95%CI]	N	PY	IR [95%CI]
CV history: Yes	292	845.11	3,455.17 [3,070.19 – 3,862.55]	292	819.41	3,563.56 [3,166.50 – 3,983.72]	300	808.97	3,708.40 [3,300.59 – 4,139.62]	294	778.90	3,774.56 [3,355.38 – 4,218.05]
Prior SSRI: No	188	563.16	3,338.29 [2,878.13 – 3,832.07]	182	548.31	3,319.28 [2,854.54 – 3,818.54]	193	542.01	3,560.84 [3,076.17 – 4,080.45]	180	534.64	3,366.76 [2,892.86 – 3,876.06]
Prior SSRI: Yes	167	618.71	2,699.17 [2,305.32 – 3,123.64]	173	597.05	2,897.59 [2,481.88 – 3,345.00]	181	588.55	3,075.37 [2,643.64 – 3,539.27]	188	552.77	3,401.07 [2,932.26 – 3,904.14]
Depression (w/ or w/o anxiety)	70	223.59	3,130.74 [2,440.57 – 3,905.55]	71	213.58	3,324.33 [2,596.33 – 4,140.93]	80	206.15	3,880.68 [3,077.14 – 4,776.03]	76	200.97	3,781.67 [2,979.53 – 4,677.99]
Anxiety	26	75.41	3,447.63 [2,252.11 – 4,893.64]	20	80.07	2,497.86 [1,525.76 – 3,705.69]	32	77.12	4,149.24 [2,838.08 – 5,705.47]	33	74.03	4,457.40 [3,068.27 – 6,101.83]

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; CV = Cardiovascular; HF = Heart Failure; SSRI = Selective Serotonin Reuptake Inhibitors; IR = Incidence Rate; PY = Person-years; N = Number; 95%CI = 95% Confidence Interval

9.3.2.2. Effect estimation: Hazard Ratios, Incidence Rate Ratios, and Negative control outcome analyses

Uncalibrated HR and IRR from "on treatment" analyses for hospitalisation with heart failure, repeated diagnosis, or acute pulmonary oedema showed no association increased risk associated with venlafaxine compared to mirtazapine (**Table 25**). Similarly, none of the stratified "on treatment" analyses were associated with an increased risk for the outcomes associated with venlafaxine.

Table 25. Uncalibrated HRs for outcomes of interest, overall.

Data source name	Hospitalisation with HF		Repeated HF (broad)		Acute Pulmonary Oedema	
	Uncalibrated					
	HR	95%CI	HR	95%CI	HR	95%CI
HI-SPEED	0.93	0.81 – 1.07	0.96	0.86 – 1.06	1.14	0.56 – 2.29
SIDIAP	0.91	0.79 – 1.05	0.92	0.79 – 1.06	0.58	0.19 – 1.79
	IRR	95%CI	IRR	95%CI	IRR	95%CI
HI-SPEED	0.91	0.80 – 1.05	0.94	0.84 – 1.05	1.11	0.55 – 2.24
SIDIAP	0.91	0.79 – 1.05	0.92	0.79 – 1.06	0.59	0.19 – 1.81

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; Hazard ratio = HR; 95%; HF = Heart Failure; IRR = Incidence Rate Ratio; CI = 95% Confidence Interval.

Negative control outcome analyses showed that 15.6% of NCO were associated with venlafaxine in HI-SPEED, indicating potential residual confounding towards a "protective" effect (**Figure 10**).

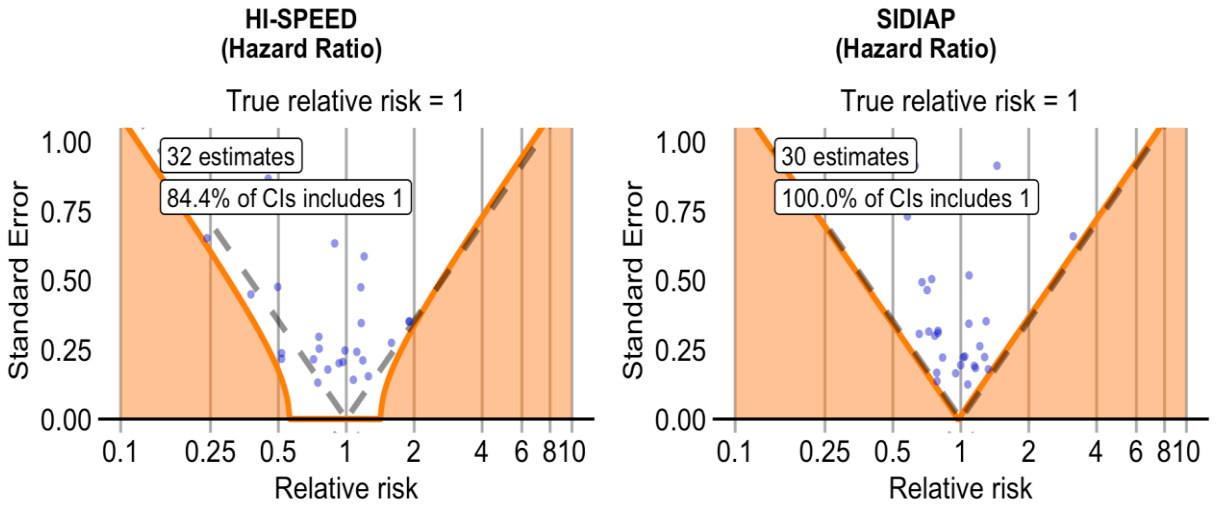


Figure 10. Negative Control outcomes.

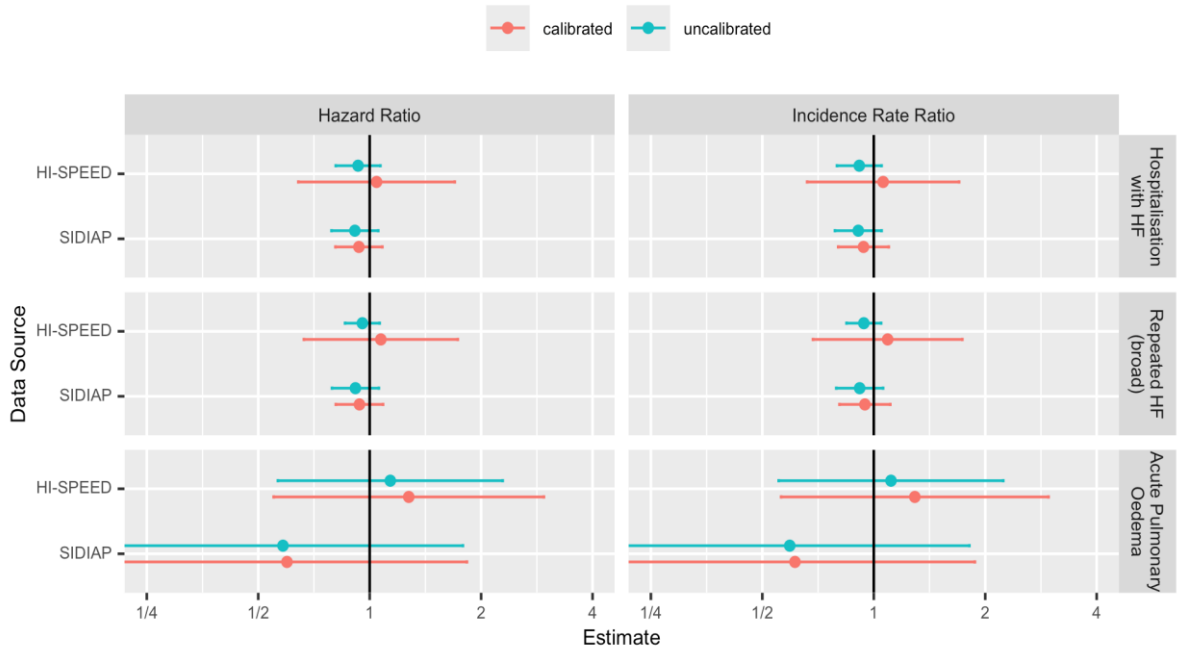
HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; CI = Confidence Intervals.
Note: Each blue dot in the plot represents a different Negative Control Outcomes (NCO), which we expect not to be associated with venlafaxine (hence CI should include 1). The purple dashed lines indicate the significative threshold for the NCO, indicating that they are positively correlated with venlafaxine if they are on the right of the dashed line (higher relative risk) and negatively correlated when on the left (reduced risk). Without significant associations, the spread should be symmetrical with most estimates for NCO in the middle. The orange lines mark the new significance thresholds after calibration, i.e. after adjustment according to the negative control outcome distribution.

Calibration shifted HR and IRR for all outcomes slightly upwards (Figures **11** and **12**). Similar to the uncalibrated estimates, no increased risk associated with venlafaxine compared to mirtazapine was seen (**Table 26**).

Table 26. Calibrated HRs for outcomes of interest, overall.

	Hospitalisation with HF		Repeated HF (broad)		Acute Pulmonary Oedema	
	HR_{cal}	95%CI	HR_{cal}	95%CI	HR_{cal}	95%CI
HI-SPEED	1.04	0.64 – 1.70	1.07	0.66 – 1.73	1.28	0.55 – 2.96
SIDIAP	0.94	0.81 – 1.08	0.94	0.81 – 1.09	0.60	0.20 – 1.83
	IRR_{cal}	95%CI	IRR_{cal}	95%CI	IRR_{cal}	95%CI
HI-SPEED	1.06	0.66 – 1.70	1.09	0.69 – 1.73	1.29	0.56 – 2.97
SIDIAP	0.94	0.80 – 1.10	0.95	0.81 – 1.11	0.61	0.20 – 1.88

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR_{cal} = HR calibrated; IRR_{cal} = Incidence rate ratio calibrated; 95%CI = 95% Confidence Interval.



Figures 11 and 12. Calibrated and uncalibrated HRs and IRRs for outcomes of interest, overall.

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HF = Heart Failure, HR = Hazard Ratio, IRR = Incidence Rate Ratio.

9.3.2.3. Sensitivity analyses: Impact of causal estimate ("on treatment"/ "ever exposed")

Impact of the choice of the causal estimate and follow-up duration

Uncalibrated and calibrated HR for the different causal estimands and follow-up definitions for the primary outcome of heart failure hospitalisation are provided in **Table 27.** No substantial differences between the estimands are seen, highlighting the robustness of the results.

For the "on treatment" analysis, the median duration of follow-up (in the venlafaxine cohort) was 146 days (IQR 60 – 561) in HI-SPEED and 90 days (IQR 30 – 363) in SIDIAP, respectively. The most common reasons for censoring were stop of treatment (37% and 43% in HI-SPEED and SIDIAP, respectively), censoring of the matched pair (35% and 42%, respectively), and death (17% and 12%, respectively).

While removing the pair censoring for "on treatment" analysis substantially increased the median follow-up time for the venlafaxine cohort in HI-SPEED (372 days instead of 90 days) and SIDIAP (279 days instead of 90 days), NCO analyses in HI-SPEED showed 20% of NCO to be associated with venlafaxine (compared to 15% in the analysis with pair censoring), indicating potential residual bias towards protective venlafaxine effects in this analysis.

Analyses based on an "ever exposed" approach were commonly censored at 730 days for reaching the maximum follow-up. Similar to Objective 1, the longer follow-up time in the "ever exposed" analyses might have included a substantial amount of unexposed follow-up time. However, this analysis included potential late effects after treatment cessation.

Table 27. Comparison of causal estimands, uncalibrated, using the primary outcome (heart failure hospitalisation).

		HI-SPEED	SIDIAP
On treatment analysis	HR [95%CI]	0.93 [0.81 – 1.07]	0.91 [0.79 – 1.05]
On treatment analysis, censored at 2yrs	HR [95%CI]	0.91 [0.78 – 1.06]	0.86 [0.73 – 1.00]
On treatment analysis, without matched pair censoring	HR [95%CI]	0.92 [0.81 – 1.03]	0.91 [0.81 – 1.02]
Ever exposed (max 2yrs)	HR [95%CI]	0.96 [0.86 – 1.08]	0.87 [0.78 – 0.98]
On treatment analysis	HR_{cal} [95%CI]	1.04 [0.64 – 1.70]	0.94 [0.81 – 1.08]
On treatment analysis, censored at 2yrs	HR_{cal} [95%CI]	1.09 [0.62 – 1.92]	0.89 [0.69 – 1.14]
On treatment analysis, without matched pair censoring	HR_{cal} [95%CI]	1.04 [0.73 – 1.49]	0.94 [0.83 – 1.06]
Ever exposed (max 2yrs)	HR_{cal} [95%CI]	1.05 [0.85 – 1.31]	0.89 [0.75 – 1.05]

HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; SIDIAP = The Information System for Research in Primary Care; HR=Hazard Ratio; HR_{cal} = HR calibrated; 95%CI = 95% Confidence Interval.

10. DISCUSSION

10.1. Key results

Based on data from 6 large European data sources, our study showed no association with an increased risk for either incident heart failure or hospitalisation with heart failure (in individuals with a prior heart failure diagnosis) associated with venlafaxine initiation compared to mirtazapine.

Results from sensitivity analyses, secondary outcome definitions, and different causal estimands ("on treatment" and "ever exposed") were largely consistent with the main results. Negative control outcome analyses suggested some residual confounding remained after propensity-score matching. However, calibrated estimates were in line with uncalibrated ones.

10.1.1. Objective 1

Data source-specific estimates were in line with the meta-analytic HR. Results from secondary outcome definitions for heart failure variations (narrow definition and excluding alternative causes) and secondary/sensitivity analyses (including analyses based on "ever exposed" status) were also largely consistent with the main findings.

Point estimates for incident cardiomyopathy (broad) were higher than for incident heart failure (HR_{meta} 1.18, 95%CI 0.93 – 1.50). Takotsubo cardiomyopathy is labelled as adverse event in the venlafaxine product information but was not assessed separately in this study.

The proportion of NCOs associated with venlafaxine use ranged from 7.9% in FinOMOP-THL to 34.3% in HI-SPEED, suggesting there might have been unmeasured confounding in some of the data sources. However, calibrated HRs remained in line with uncalibrated ones, with data source-specific estimates not suggesting an increased risk of either heart failure diagnosis or exacerbation associated with venlafaxine initiation.

10.1.2. Objective 2

Observed confounding was identified despite PS matching for Objective 2 in all data sources, significantly limiting the analysis. HRs are only reported for HI-SPEED and SIDIAP, where confounding was less notable.

No increased risk of hospitalisation with heart failure, recurrent heart failure diagnoses, or acute pulmonary oedema were associated with venlafaxine. The proportion of NCOs associated with venlafaxine initiation were 15.6% in HI-SPEED and 0% in SIDIAP. Calibrated HRs were in line with findings from uncalibrated HR, and results from "ever exposed" analyses were in line with "on treatment" estimands.

10.1.3. Objective 3

While the general population of new users was generally older compared to the PS-matched population in Objective 1, the overall demographics of the PS-matched populations were more representative of the (overall and unmatched) venlafaxine group in terms of age and sex compared to the (overall and unmatched) mirtazapine users. Before matching, depression was the most frequently recorded condition of interest in the 365 days before the index date across all data sources, and substantially more common in new venlafaxine users to new mirtazapine users. Hypertension was the most prevalent comorbidity. In the unmatched cohorts, differences between venlafaxine and mirtazapine users were related to comorbidities, including some related to the pharmacological profile of these medications, such as insomnia. The varying proportion of SSRI prescription history across data sources reflects that venlafaxine is not typically used as a first-line treatment.

10.2. Strengths and limitations of the research methods

The design of the study using the Target Trial Emulation framework, as well as its execution across multiple European data sources with similar findings, are major strengths. Following the Target Trial Emulation

approach ensured a structured documentation of the causal inference designs and helps to avoid self-inflicted biases in the study design. In addition to assessing both “on treatment” and “ever exposed” approaches as causal estimands, the study included several secondary and sensitivity analyses to assess the robustness of the findings. Further, confounding was minimised by applying large-scale Propensity Score matching, and residual confounding was measured and adjusted for using Negative Control Outcomes and empirical calibration. This allowed for the detection of potential residual confounding to help guide the reliability for decision making.

The present study using several, large real-world data sources from across Europe is particularly well-placed to assess a potential safety signal across different healthcare settings and geographies. Heart failure is a serious condition which is most likely coded in both primary and secondary care settings, and misdiagnosis rates are expected to be low. Given that several data sources covering both general practice and specialised and hospital data are included, the coverage of outcome diagnoses were increased.

We acknowledge the following important limitations to this study: The study was informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription or dispensation may not mean that the patient actually took the drug, and the extent of documentation of comorbidities may vary across data sources. In addition, assumptions around the duration of drug use were unavoidable. For instance, in FinOMOP-THL, the primary source dataset for prescriptions (Kanta Prescription Centre) included a prescription start date but no end date. For each prescription, the end date is therefore imputed using a standard value of 30 days given in the THEMIS conventions for the end date. While potential underestimation of treatment duration might limit follow-up time in the “on treatment” estimand, this would not affect the analysis of the “ever exposed” estimand, which, however, may instead include unexposed time.

Some adaptations had to be made to the study design to account for data source particularities: For FinOMOP-THL, as prescription records were only available until the end of 2023, and data on cardiovascular outcomes were only available until October 2024, the study period was restricted to 2016 – 2023. For BIFAP, the availability of linkage to hospital data varied by region and time. As bias might be introduced with the varying availability of HF inpatient diagnoses over time, we decided to not use linked hospital data in BIFAP for this study. Therefore, neither CPRD GOLD nor BIFAP used linkage to hospital data. While both the UK and Spain have general practitioners as gatekeepers in their national health systems, and hence heart failure admissions in hospitals are usually re-recorded in primary care, some degree of index date misclassification could not be excluded. However, this was not expected to be differential between venlafaxine and mirtazapine users.

Mirtazapine was selected as an active comparator to reduce potential confounding by indication and severity, under the assumption that it lacks significant similar cardiovascular effects. This is expected due to its differing pharmacological mechanism of action and lack of significant known cardiovascular adverse drug reactions. However, precisely due to its potentially safer cardiovascular profile, it might be a preferred medication in older and more fragile individuals (e.g. individuals with dementia). Frailty might be a confounding factor which is difficult to capture with the information available in electronic health records; however, several individual conditions related to frailty were included in the propensity score.

Previous studies have shown potential for index date misclassification for heart failure diagnosis (DARWIN EU® study P3-C3-001 (Adverse events of special interest)). Records of prescription of furosemide prior to index date despite excluding individuals with a record of HF/cardiomyopathy in Objective 1 across data sources suggests that index date misclassification might have been present in this study. However, among individuals without a heart failure diagnosis before index date in Objective 1, only few (between 1% in HI-SPEED and 3.3% in FinOMOP-THL/SIDIAP) had a prescription of high-ceiling diuretics, which also have other clinical indications for use. As a subgroup analysis, we have excluded individuals with a history of CV disease, in case index date misclassification is non-differential between the intervention and comparator

cohorts. No differences were seen in meta-analyses for when analyses were stratified for history of CV disease for incident heart failure, while an increased risk for incident cardiomyopathy was seen in individuals with CV history (no increased risk in individuals without CV history).

Worsening of pre-existing heart failure was assessed using hospitalisation of heart failure as the primary outcome to serve as a proxy for sudden worsening of cardiac function. However, changes in heart failure medication (add-on therapies, dose escalations) or measurements/procedures related to heart failure severity (e.g. ejection fraction) were not included in this study, because such data were not widely available. Characteristics of individuals with prior heart failure in Objective 2 showed a high percentage of prescriptions of high-ceiling diuretics, suggesting that prior to the start of the treatment with venlafaxine/mirtazapine there was at least some degree of congestion-decompensated heart failure. It was also notable the high percentages of NSAIDS and/or glucocorticoids prescribed in the year prior to the diagnostic record of heart failure, given that these medications might exacerbate this condition. However, for repeated heart failure diagnoses, there is a high risk that re-recordings of diagnosis might not actually reflect a worsening of the condition. Based on the expected high proportion of missingness measurements of ejection fractions and/or N-terminal pro brain natriuretic peptide in the data sources, such lab measurements were not considered for the study. This might have limited the information available on the severity of HF available in the respective data sources (e.g. for Objective 2, when selecting a study population with previous HF).

Heart failure can be caused by several other conditions, including Ischaemic heart disease (IHD), valvular dysfunction, and pulmonary disease. We included an outcome definition for heart failure without preceding alternative causes of heart failure and found consistent results. Moreover, the terminology of heart failure and cardiomyopathy might overlap: Heart failure as a functional diagnosis might be the presenting symptom for cardiomyopathy (structural diagnosis) and could hence be the diagnosis recorded. To address this uncertainty, we used 7 different variations of heart failure/cardiomyopathy phenotypes in this study.

We used large-scale propensity scores to minimize measured confounding and NCOs to assess potential residual confounding. However, given the observational nature of our data, we cannot fully rule out residual confounding, which could partially account for findings in this study.

Our study estimated a “on treatment” causal contrast as the main analysis, with censoring of follow-up time among the matched pair at treatment discontinuation or switching. Add-on treatments were allowed that might have an effect on the risk for outcome occurrence: The study built on the assumption of conditional exchangeability after PS matching, with no substantial difference in the occurrence of add-on therapies expected. We therefore did not account for add-on treatments as intercurrent events in this study. Similarly, we did not expect a high degree of venlafaxine to mirtazapine (or vice versa) switching. Outcomes recorded after treatment discontinuation (e.g. potential late effects) were not assessed in the “on treatment” effects. However, analyses based on an “ever exposed” approach were conducted to assess the impact of artificial censoring and include potential late effects in case of cumulative effects or delayed development/complication of the disease resulting from venlafaxine/mirtazapine treatment. Follow-up was limited to a maximum of 24 months to reduce bias from potential exposure misclassification, although our analyses showed that median treatment durations for venlafaxine typically only ranged between 1 month (FinOMOP-THL), 6 months (CPRD GOLD, DK-DHR), and 1 year (HI-SPEED, SIDIAP). Effect estimates from “on treatment” effect and “ever exposed” analyses were largely consistent, particularly after calibration to account for residual confounding.

Local prescription patterns had an impact on treatment duration: In FinOMOP-THL, prescriptions for chronic diseases are often issued for 1 – 2 years, with fillings of that prescription throughout the year not being recorded separately. The 90day gap length chosen to combine subsequent prescriptions into a continuous treatment era therefore did not adequately reflect the prescription pattern in Finland. An ad-

hoc sensitivity analysis was therefore added following the review of drug exposure diagnostic, to allow for an extended maximum gap between subsequent prescriptions (365 days instead of 90 days). As expected, this showed longer treatment durations for FinOMOP-THL and shifted the point estimate for incident heart failure towards HR 1 ("on treatment" analysis). The comparative safety studies did not consider venlafaxine or mirtazapine dose or changes in dose over time. Therefore, potential dose-dependent effects could not be assessed in this study.

10.3. Interpretation

Our study showed no significantly increased risk for incident heart failure associated with venlafaxine when compared to mirtazapine.

Results in context

Cardiovascular effects of venlafaxine have previously been described. These include effects on blood pressure (both hypertension and orthostatic hypotension), tachycardia, increases in QTc interval and stress cardiomyopathy (incl. Takotsubo cardiomyopathy) [1,8]. These have been labelled in the SmPC of the European Medicines Agency and have been described in case series and spontaneous reports.[1,2] A study which evaluated the FDA Event Reporting System database identified 132 individual case safety reports of stress cardiomyopathy associated with antidepressants, 48% of which were associated with venlafaxine,[9] and 80% of these cases occurred in females.

However, a systematic review of randomised clinical trials with meta-analysis of adverse effects of venlafaxine did not show differences with regards to placebo in these cardiovascular effects.[10] A nested case-control study using UK primary care electronic health records did not find an increased risk of tachyarrhythmia or sudden death as compared with citalopram or fluoxetine.[11] Another study using administrative health care databases in Canada did not show an increased risk of death or hospitalisation for acute myocardial infarction in elderly patients who were prescribed venlafaxine as compared with sertraline.[3] In short, there are conflicting results among studies that have addressed the issue of cardiovascular adverse effects of venlafaxine. Mentioned findings from large routinely collected and high-quality data in line with findings from our study suggest that, while spontaneous reports have reported cardiovascular adverse events associated with venlafaxine, when compared to other antidepressants (and accounting for potential confounding), no significant increase in risk for incident heart failure was observed.

10.4. Generalisability

This study included data sources from five European countries: United Kingdom, Denmark, Finland, Sweden, and Spain. As the analyses were based on populations captured within these specific data sources, the results reflect only the included populations and may not be generalisable to other countries or settings. In addition, some extent of heterogeneity is expected due to differences in the covered settings (primary care versus linkage to secondary care, national registries) and healthcare systems.

11. CONCLUSION

Based on data from 6 large European data sources, our study shows no association between venlafaxine and an increased risk for either incident heart failure or hospitalisation with heart failure (in individuals with a prior heart failure diagnosis) when compared to mirtazapine.

These findings need to be interpreted with attention to the study limitations and in combination with all other available evidence concerning potential effects of venlafaxine on the risk for heart failure.

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13. ANNEXES

ANNEX I. Description of data sources

Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Data source identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care-specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures (surgical and non-surgical hospital), and Sociodemographic information (sex and age only).
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, histologically confirmed incident cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have unique identifiers used to link datasets.
9	Quality control (data source specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g. non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.

#	Section	Description
12	Limitations	DK-DHR has the following limitations, which may be relevant confounders for certain complex Darwin EU studies: – We lack information on key socio-economic status (SES) factors, such as occupation, education, and income. These variables may be important for analysis in some studies. – We only have complete data on lifestyle factors (such as smoking status and weight) for pregnant women. – We have no information on patient contacts in primary care (visits to the GP). Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy. Stillborn children will not have any records in our CDM. This means that e.g. birth length of stillborns is not recorded.
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Finnish Care Register for Health Care (FinOMOP-THL)

#	Section	Description
1	Data source identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland
2	Data partner information section	Finnish Institute for Health and Welfare (THL) The Department of Data and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and other (specify). THL maintains health registers that cover both public and private, primary, and specialised inpatient, urgent and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. Since 1998, the Care Register for Health Care (TerveysHilmo) has covered both public outpatient and inpatient specialized care and private inpatient care. Since 2009, the Finnish National Vaccination Register has covered all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good to complete from 2020 onwards. Since 2011, the Register of Primary Health Care Visits (AvoHilmo) has covered public primary care. Since 2020, the register has also covered private outpatient care and occupational care. In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register. The register itself covers all laboratory confirmations for around 70 specific microbes from 1995 onwards, but only COVID-19 has currently been mapped to the CDM. The CDM also includes prescription records from multiple different sources. Both Care Register for Health Care and Register of Primary Health Care Visits contain very basic prescription data recorded during health care encounters that include just the ATC-code and trade name of medication. More comprehensive prescription data from Kanta Prescription Centre, maintained by Social Insurance Institution of Finland (Kela), has been integrated into the CDM since its 2024 release. The Kanta Prescription records are based electronic prescriptions, which were adopted by most public health care providers in 2010 and by most private providers by 2017.

#	Section	Description
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL (Kela in the case of Kanta Prescription Centre).
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates.
7	Data content /source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ICPC-2, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveydenhuollon erikoisalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.
9	Quality control (data source specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	All drug records in the CDM are currently based on prescriptions. Kanta Prescription Centre also includes information on drug dispensings, but these have not currently been converted into OMOP CDM. Depending on the type of the medication, a single prescription can be for up to two years dosage of the drug. This means a patient can have up to two-year breaks between observations while actively using the drug. Observation of a prescription also does not mean that the patient necessarily bought or used the medication. The CDM does not currently have meaningful end dates or days of supply for drug exposure. This information is not available for Care Register for Health Care or Register of Primary Health Care Visits, and for Kanta Prescription Centre it is only available in unstructured, free-form format that has not been converted into OMOP CDM. The source system for prescription drug data is only available to the DP until Dec-2023, therefore drug_exposure records from this source are only available in that time range. Not all private health care records are covered for the CDM's entire follow-up time from 2011 onwards. For Register of Primary Health Care Visits and Finnish National Vaccination Register, records from private health care have been available from 2020 onwards. For Kanta Prescription Centre, the coverage of private health care records has been good from 2017 onwards. The inclusion of private health care mainly presents itself as an increase in the number of observations, meaning that it has to be accounted for when interpreting any time series data from the CDM.
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveyden ja hyvinvoinnin laitos (2019):
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187;https://catalogues.ema.europa.eu/data-source/1111191 Website: https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions;https://www.kanta.fi/en/research-and-knowledge-management

Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP)

#	Section	Description
1	Data source identification and country	BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)) Spain
2	Data partner information section	AEMPS Pharmacoepidemiology and Pharmacovigilance Division - Medicines for human use Department
3	Coverage and timespan	Data collection since: 2001 Extent: Regional. Spanish National Health Service (SNS) from 9 of the 17 regions in Spain. The population currently included represents 36% of the total Spanish population.
4	Healthcare setting / type of data	Primary care – General Practitioner, and community pharmacists, and primary care specialists (e.g. paediatricians), and hospital inpatient care. BIFAP includes a collection of databases linked at individual patient level. The main one is the Primary care Database, given the central role of PCPs in the SNS. Linked, there are additional important structural databases, like the medicines dispensed at community pharmacies and the patients' hospital diagnosis at discharge. 7 out of the 9 regions have linkage to hospital data. However, hospital data is available for different time periods for each region. From 2014 onwards, linkage to hospital data is available for >68% of patients.
5	Data collection process	Insurance/administrative claims, and Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data in BIFAP is collected from Primary Care and Hospital EHR.
6	General representativeness	Spain has a SNS that provides universal access to health services through the Regional Healthcare Services. Primary care physicians (PCPs), both general practitioners and paediatricians, have a central role. They act as gatekeepers of the system and exchange information with other levels of care to ensure the continuity of care. Most of the population (98.9%) is registered with a PCP and, in addition, most drug prescriptions are written at the primary care level.
7	Data content /source coding	The BIFAP source data is coded in SNOMED, ICD, ICPC-2 (diagnoses), AEMPS (drugs), and local lab codes.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Pseudonymized ID numbers are generated at regional level. The Personal Identification Code for the Autonomous Community (CIPA) is used to perform the pseudonymisation procedure. Therefore, upon changing practice or de- and re-registration within the same region, (Autonomous Community) the patient in BIFAP is correctly identified as the same person with the same ID number. However, the same patient would obtain different ID numbers if the patient moves to a different region and is registered in a primary care practice in the new region. The percentage of people who are de-registered due to moving to other region in relation to the BIFAP population is, for example, 5% in Madrid and 4% Castilla y Leon. This situation would have a very limited impact on the data analysis due to the following: – The proportion is low (less than 5%) in relation to the overall population in BIFAP. – In BIFAP, only stable residents are included. This means that patients living in another region for a foreseen short time period and are provisionally assigned to a primary care practice are not included in BIFAP. – Medical events of those patients who have more than one ID do not overlap in time, since dates of events correspond to different periods. This means that counts of these events are never duplicated. – A number of study designs allows the same patient to be part of different cohorts or to be selected both as case and as control, provided that their person-time experience correspond to a different period of time. In all these cases, the impact in study analysis of duplicated IDs would be negligible.

#	Section	Description
9	Quality control (data source specific)	Patients who meet any of the following disability criteria are discarded: – Non-owners of the individual health card – Date of birth before 01/01/1801 – Active patients over 115 years of age – Patients without clinical records (only contains administrative information) – Patients marked as “fictitious” in the clinical history – Badly coded sex – Inactive without termination date – Start date = End date – Clinical records prior to date of birth
10	Linkage	The following data are also linked at individual patient level and available. For a subset of the BIFAP population (regions and/or periods of time): • Information on dispensation of medicines at hospital pharmacies from outpatients and inpatients. • Registration of Causes of Death by the National Institute for Statistics. From the start of the COVID-19 pandemic: • Vaccines COVID-19 Administration Registry linked to patients included in BIFAP. • Diagnosis Tests of COVID-19 linked to patients included in BIFAP, for some regions.
11	Vital status	Source for vital status unknown.
12	Limitations	Primary care is available from 2001 but is considered complete since 2005. Hospital discharge has different coverage periods per region Spain, with most starting between 2014–2016. This means that for different regions and different time periods there is a different coverage of healthcare events. In the release of July 2025, the laboratory results are not covered. These will be added again at the next release, expected at the end of 2025.
13	Main references	Maciá-Martínez MA, Gil M,Huerta C,Martín-Merino E,Álvarez A,Bryant V,Montero D "Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP): A data resource for pharmacoepidemiology in Spain." Pharmacoepidemiology and drug safety (2020): 32337840
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/21501 Website: http://www.bifap.org/index_EN.html

The Information System for Research in Primary Care (SIDIAP)

#	Section	Description
1	Data source identification and country	SIDIAP (The Information System for Research in Primary Care) Catalunya, Spain
2	Data partner information section	IDIAPJGol
3	Coverage and timespan	Data collection since: 2006 Extent: Regional. SIDIAP is a database of primary care electronic health records of the population of Catalonia, North-East Spain. It contains pseudo-anonymised records of more than 8 million people, of which 6.1 million are active as of 2022, representing around 76% of the Catalan population.
4	Healthcare setting / type of data	Primary care – General Practitioner, and hospital inpatient care. SIDIAP captured data includes routine visits, socio-demographics, diagnoses, laboratory tests, drugs (prescribed and dispensed), referrals, sick leaves and lifestyle information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records. Data is entered by primary care physicians upon healthcare contact, supplemented with

#	Section	Description
		hospital discharge records. The Institut Catala de la Salut (Catalan Health Institute) is the data controller.
6	General representativeness	It was previously shown that the captured SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions.
7	Data content /source coding	SIDIAP data covers all services that occur at the Primary Care Centres, as well as support services, such as sexual and reproductive health or home end-of-life care. Drugs are coded in ATC-WHO terminology in the source data. Health outcomes are captured in ICD-10CM codes. The SIDIAP contains all laboratory tests and results performed in primary health centres. Demographics, geographical, as well as socio-economic factors are recorded for each patient.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. A patient has a unique id, also upon changing practice or re-registration.
9	Quality control (data source specific)	Internal and external validation processes are carried out to determine the data quality of the SIDIAP information at each data update. These include stratifying the data by geographical regions and year in order to identify differences in data collection that need to be harmonized (e.g. recording of specific information under different codes). The measurement units of variables measuring one characteristic are also homogenized (e.g. transformation of the data from every laboratory that measures haemoglobin to grams per decilitre). Visual inspection of all data included in the database by week is also conducted, allowing one to see temporal patterns in the registry of a certain variable. With this information, the SIDIAP team can issue recommendations to researchers about the most common variable(s) where certain information is recorded (e.g. there are several variables with information concerning the women's menopausal status and with these visual inspection tools the SIDIAP team can inform the researchers about which related variables have the largest number of records and could be more helpful to capture menopause). Data availability (longitudinally and reliability), plausibility (range checks and unusual values), and consistency are inspected through visualisation tools. In addition, before accessing the data for a requested project, research teams have access to a quality-control report. This document contains counts, years, percentiles, maximums and minimums, incidences, and prevalence of the data requested for the project, allowing detection of inconsistencies in the data extraction prior to data delivery. External validation processes of the SIDIAP database mainly include assessing the data recorded in SIDIAP through linkage to external gold standard data sources, by analysing free text, or by sending questionnaires to health professionals.
10	Linkage	SIDIAP is linked to a hospital discharge database, pharmacy dispensation, and primary care laboratories. It can also be linked to other registries in Catalonia on a project by project basis.
11	Vital status	Mortality is fully captured in SIDIAP. The cause of death is not available but can be linked to the Spanish death registry on a project by project basis.
12	Limitations	The SIDIAP data is not representative of individuals not using public primary care, and conditions that are usually followed by specialist care might not be properly captured. In addition, there is limited information on lifestyle variables. Patients are followed until Death or when transferring to another primary health care centre that does not contribute to SIDIAP.
13	Main references	Recalde M, Rodríguez C,Burn E,Far M,García D,Carrere-Molina J,Benítez M,Moleras A,Pistillo A,Bolíbar B,Aragón M,Duarte-Salles T "Data Resource Profile: The Information System for Research in Primary Care (SIDIAP)." International journal of epidemiology (2022): 35415748
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry:-https://catalogues.ema.europa.eu/data-source/50190 Website: https://www.sidiap.org/index.php/en

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

#	Section	Description
1	Data source identification and country	HI-SPEED (Health Impact - Swedish Population Evidence Enabling Data-linkage) Sweden
2	Data partner information section	SMPA-GU, Pharmacoepidemiology and Analysis Department (FeA), Läkemedelsverket (SMPA), Box 26, 751 03 Uppsala, Sweden School of Public Health and Community Medicine, Institute of Medicine, Gothenburg University (GU), Box 469, 405 30 Gothenburg, Sweden
3	Coverage and timespan	Data collection since: 2015 Extent: Nation-wide. The catchment area includes the whole of Sweden, covering the full population of approximately 11.7 million.
4	Healthcare setting / type of data	Primary care – General Practitioner, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. Primary care (GPs) is available only for the 2 largest regions (~40% of national population) The following data elements are collected: Socio-demographics, dispensed drug prescriptions, cause of death, diagnoses and procedures from secondary (specialist) care and inpatient visits or clinical events, as well as from primary care visits (40%pop only).
5	Data collection process	Registries. The data is acquired from the relevant Swedish national and regional registries, only once all legislative, GDPR and ethical approvals have been granted. Therefore, only relevant data is passed on, which will then be entered and processed by the study team. The data are updated several times annually.
6	General representativeness	The coverage includes all patients of all sociodemographic characteristics. Therefore, it should mirror the source population to a very good extent.
7	Data content /source coding	Medicines are coded with ATC and NPLID (National Product ID), ICD10-SE is used for diagnoses, and the Swedish procedure coding system (KVA) is used for clinical procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have a uniquely id across datasets.
9	Quality control (data source specific)	The source data are obtained from the relevant Swedish National and Regional Registers. The registers perform some regular quality controls on their data. After receiving the data, we perform additional checks and cleaning. We also run regular quality checks on the data we manage.
10	Linkage	Data on specialist care is acquired from the National Patient Register; mortality information is provided by the Cause-Of-Death Registry. Drug data is provided by the Patient Drug Register. And similarly for other registers. Data are linked very accurately using the national personal ID number and pseudonymized before delivery to HI-SPEED. All data are updated 2–4 times per year.
11	Vital status	Data on death and underlying + contributing causes-of-death are extracted from the Cause-of-Death registry (i.e. based on death certificates).
12	Limitations	General limitations for the data type applicable. This is a research project where all studies require ethics approval. Data collection since: 2015 for most data, except prescribed drug register (from 2018), and some COVID-related data (tests, vaccination) from 2020 Primary care is only available for a subset.
13	Main references	Nyberg F, Franzén S, Lindh M, Vanfleteren L, Hammar N, Wettermark B, Sundström J, Santosa A, Björck S, Gisslén M "Swedish Covid-19 Investigation for Future Insights – A Population

#	Section	Description
		Epidemiology Approach Using Register Linkage (SCIFI-PEARL)." Clinical epidemiology (2021): 34354377
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/node/4463/ Website: https://www.gu.se/en/research/scifi-pearl

Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Data source identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) The United Kingdom
2	Data partner information section	University of Oxford NDORMS
3	Coverage and timespan	Data collection since: 1987 Extent: Nation-wide. CPRD GOLD consists of patients in contributing practices using Vision software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future, no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. CPRD GOLD data include patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications.
5	Data collection process	Outpatient electronic health records. Data are entered by clinicians into the EHR. Data is processed by CPRD that provides data releases for research.
6	General representativeness	In the last 10 years, the CPRD GOLD regional distribution of currently contributing general practitioner (GP) practices has significantly shifted, resulting in many new practices joining from Scotland, Wales, and Northern Ireland, and fewer participating from England. These changes have affected the CPRD GOLD population size, regional coverage, and eligibility for data linkages. CPRD GOLD January 2024 contains >21.3 million historical and current patients (12.9 in England, 3.1 in Wales, 4.7 in Scotland, 0.7 in Northern Ireland). Of these, nearly 3 million are currently registered in a GP practice and represent ~4.3% of the estimated current UK population (0.1% in England, 32.3% in Wales, 28.6% in Scotland, 16.2% in Northern Ireland). Patients currently registered in CPRD GOLD January 2024 are broadly representative of the UK population with respect to age and sex. Reference: https://doi.org/10.1093/ije/dyaf077
7	Data content /source coding	Gemscript, Read, dm+d
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In GOLD, a patient can be registered under different ID numbers upon changing practice or re-registration. Researchers are not able to identify these patients, as the data are anonymised. However, GOLD covers less than 5% of the current UK GP practices and it is unlikely that an individual who does change GP practice ends up in another GP practice which uses the Vision

#	Section	Description
		software and accepts the CPRD data collection agreement. The very small number of duplicated IDs will have different observation periods and should not have an impact on the data analyses.
9	Quality control (data source specific)	CPRD GOLD only includes practices whose data quality is assessed to be up-to-standard (UTS). Each practice is associated to an UTS date set when the data quality standards become satisfactory, and CPRD recommend using only longitudinal data starting from this UTS date. Every time CPRD collect the EHR from a practice, checks are run for the data quality standards, and if they are not adequate, the EHR is not accepted. When the data quality becomes acceptable again, CPRD updates the practice UTS date. CPRD also checks data quality standards at the patient level, and associates each patient with a flag, reporting if its data are acceptable for clinical research. Only patients with acceptable data quality are included in the population to be mapped to CDM.
10	Linkage	CPRD GOLD can be linked to several sources, however our Oxford OMOP CDM is only linked to the CPRD GOLD Ethnicity Record and to the CPRD Townsend Deprivation Index at the Practice Level.
11	Vital status	The date of death in CPRD GOLD has been validated against the Population registry (ONS) mortality data. Reference: https://doi.org/10.1002/pds.4747
12	Limitations	The main limitation is due to the fact that CPRD GOLD is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered.
13	Main references	Sanchez-Santos MT, Axson EL,Dedman D,Delmestri A "Data Resource Profile Update: CPRD GOLD." International journal of epidemiology (2025): 40499193
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111113 Website: https://www.cprd.com/data/primary-care-data/cprd-gold

ANNEX II. Fitness for use assessment

Data source justification for inclusion and key characteristics

Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP)

BIFAP was included in this study because it covers both the primary care and secondary care settings. For this study we did not use hospital linkage. The data source provides relevant information on venlafaxine and mirtazapine prescriptions in the general adult population and covers the settings in which heart failure and cardiomyopathies are diagnosed and treated.

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine and mirtazapine prescriptions were 229,200 and 1,088,000, respectively. 936,600 and 144300 individuals had a record of heart failure and/or cardiomyopathy.

Moreover, data availability and follow-up in BIFAP is currently available from the start of the study period (2010) until the date of the most recent data extraction, which is 06/2025.

The study needed Institutional Review Board (IRB) approval, which was obtained on the 27th of April 2026.

Danish Data Health Registries (DK-DHR)

DK-DHR, the Danish National Linked Health registries, was included in this study because it covers both the primary care (proxy for this using prescription retrievals) and secondary care settings, including hospital data. The data source provided relevant information on venlafaxine and mirtazapine prescriptions in the general adult population and covers the settings in which heart failure and cardiomyopathies are diagnosed and treated.

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine and mirtazapine prescriptions were 265,300 and 594,300, respectively. 415,400 and 48,000 individuals had a record of heart failure and/or cardiomyopathy.

Moreover, data availability and follow-up in DK-DHR are currently available from the start of the study period (2010) until the date of the most recent data extraction, which was 04/2025.

The study was covered by blanket IRB approvals for DARWIN EU® pharmacoepidemiology studies.

Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL was included in this study because it covers both the primary care and secondary care settings. The data source provides relevant information on venlafaxine and mirtazapine prescriptions in the general adult population and covers the settings in which heart failure and cardiomyopathies are diagnosed and treated.

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine and mirtazapine prescriptions were 239,900 and 851,600, respectively. 350,500 and 80,400 individuals had a record of heart failure and/or cardiomyopathy.

Moreover, data availability and follow-up in FinOMOP-THL are currently available from the start of the study period (2010) until the date of the most recent data extraction, which is 10/2024. As prescription data was only available until 2023, the study period was adapted accordingly for FinOMOP-THL.

The study needed IRB approval, which was obtained on the 3rd of March 2026.

The Information System for Research in Primary Care (SIDIAP)

SIDIAP was included in this study because it covers both the primary care and secondary care setting in Catalonia, Spain. Linkage to hospital data is available. The data source provides relevant information on

venlafaxine and mirtazapine prescriptions in the general adult population and covers the settings in which heart failure and cardiomyopathies are diagnosed and treated.

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine and mirtazapine prescriptions were 193,100 and 266,900, respectively. 381,100 and 79,300 individuals had a record of heart failure and/or cardiomyopathy.

Moreover, data availability and follow-up in SIDIAP are currently available from the start of the study period (2010) until the date of the most recent data extraction, which is end of 2024.

The study needed IRB approval, which was obtained 13th of April 2026.

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

HI-SPEED was included in this study because it is based on the Swedish National and Regional Health Registries, covering both the primary care and secondary care setting. The data source provides relevant information on venlafaxine and mirtazapine prescriptions in the general adult population and covers the settings in which heart failure and cardiomyopathies are diagnosed and treated.

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine and mirtazapine prescriptions were 184,600 and 706,100, respectively. 492,400 and 48,100 individuals had a record of heart failure and/or cardiomyopathy.

Moreover, data availability and follow-up in HI-SPEED was sufficient, as data availability starts in 2015, and the date of most recent data extraction is 2025.

The study needed IRB approval, which was obtained 17th of Marc 2026.

Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD was included in this study because it is a primary care data source that provides relevant information on venlafaxine and mirtazapine prescriptions in the general adult population and covers the settings in which heart failure and cardiomyopathies are diagnosed and treated.

Based on a preliminary feasibility assessment, the expected number of person counts for venlafaxine and mirtazapine prescriptions are 303,200 and 620,400, respectively. 252,200 and 23,100 individuals had a record of heart failure and/or cardiomyopathy.

Moreover, data availability and follow-up in CPRD GOLD are sufficient, as is availability to cover the study period from 2010 to the date of the most recent data extraction in 06/2025.

The study needed IRB approval, which was obtained 17th of March 2026.

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources had previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel/ and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it was important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

The output files were stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion was identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allowed the user to define a search strategy and used this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages were run to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code was based on DARWIN EU® R packages: *IncidencePrevalence* to estimate Incidence and Prevalence, *DrugUtilisation* to characterise the drug use, and *CohortCharacteristics* to characterise the

cohort by indication. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

ANNEX IV. List of stand-alone documents

Table S1. List of conditions definitions (cardiomyopathy, heart failure).

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
acute pulmonary oedema	Acute cardiac pulmonary edema	4235646	Condition	SNOMED	Inf
acute pulmonary oedema	Acute pulmonary edema	261600	Condition	SNOMED	Inf
acute pulmonary oedema	Acute pulmonary edema caused by fume	3654968	Condition	SNOMED	Inf
acute pulmonary oedema	Acute respiratory distress syndrome	4195694	Condition	SNOMED	Inf
acute pulmonary oedema	Acute respiratory distress syndrome due to COVID-19	3661406	Condition	SNOMED	Inf
acute pulmonary oedema	Acute respiratory distress syndrome due to dabbing	37171533	Condition	SNOMED	Inf
acute pulmonary oedema	Acute respiratory distress syndrome due to vaping	37171442	Condition	SNOMED	Inf
acute pulmonary oedema	Drug-induced acute pulmonary edema	4120268	Condition	SNOMED	Inf
acute pulmonary oedema	Exacerbation of pulmonary edema	1340450	Condition	OMOP Extension	Inf
acute pulmonary oedema	Exacerbation of pulmonary edema associated with pulmonary veno-occlusive disease	766260	Condition	OMOP Extension	Inf
acute pulmonary oedema	Fluid overload pulmonary edema	4119789	Condition	SNOMED	Inf
acute pulmonary oedema	Hemorrhagic pulmonary edema	4171119	Condition	SNOMED	Inf
acute pulmonary oedema	High altitude pulmonary edema	4119429	Condition	SNOMED	Inf
acute pulmonary oedema	Hypertension in the puerperium with pulmonary edema	44784484	Condition	SNOMED	Inf
acute pulmonary oedema	Malarial shock lung	4084955	Condition	SNOMED	Inf
acute pulmonary oedema	Negative pressure pulmonary edema	4225063	Condition	SNOMED	Inf
acute pulmonary oedema	Neurogenic pulmonary edema	4120267	Condition	SNOMED	Inf
acute pulmonary oedema	Non-cardiogenic pulmonary edema	4317285	Condition	SNOMED	Inf
acute pulmonary oedema	Oxygen-induced pulmonary edema	4119430	Condition	SNOMED	Inf
acute pulmonary oedema	Post-upper airway obstruction pulmonary edema	4119787	Condition	SNOMED	Inf
acute pulmonary oedema	Postimmersion-submersion syndrome	4232327	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
acute pulmonary oedema	Pregnancy induced hypertension with pulmonary edema	44784483	Condition	SNOMED	Inf
acute pulmonary oedema	Progression of acute respiratory distress syndrome	1340509	Condition	OMOP Extension	Inf
acute pulmonary oedema	Pulmonary edema	4078925	Condition	SNOMED	Inf
acute pulmonary oedema	Pulmonary edema associated with pulmonary veno-occlusive disease	766259	Condition	OMOP Extension	Inf
acute pulmonary oedema	Pulmonary edema caused by chemical fumes	46269768	Condition	SNOMED	Inf
acute pulmonary oedema	Pulmonary edema due to hypoproteinemia	45763920	Condition	SNOMED	Inf
acute pulmonary oedema	Toxic pulmonary edema	4119788	Condition	SNOMED	Inf
acute pulmonary oedema	Uremic lung	4046014	Condition	SNOMED	Inf
acute pulmonary oedema	Worsening pulmonary oedema	44805556	Condition	SNOMED	Inf
cardiomyopathy (broad)	3-methylglutaconic aciduria type 5	46272954	Condition	SNOMED	Inf
cardiomyopathy (broad)	Amyloid cardiomyopathy	44807892	Condition	SNOMED	Inf
cardiomyopathy (broad)	Arrhythmogenic right ventricular cardiomyopathy	4094188	Condition	SNOMED	Inf
cardiomyopathy (broad)	Arrhythmogenic right ventricular dysplasia	4101624	Condition	SNOMED	Inf
cardiomyopathy (broad)	Benign scapuloperoneal muscular dystrophy with cardiomyopathy	4345564	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiac glycogenosis	4111421	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy	321319	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy and renal anomaly syndrome	36715122	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy associated with another disorder	320746	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy caused by drug	35615148	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy co-occurrent with human immunodeficiency virus infection	37017276	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy due to diphtheria	46269894	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy due to hypertension	36712757	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Cardiomyopathy due to mucopolysaccharidosis	4108237	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy due to neuromuscular disorder	43021902	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy due to viral infection	45757557	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy in Duchenne muscular dystrophy	4154093	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy in Friedreich's ataxia	4111569	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy in myotonic dystrophy	4108238	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cardiomyopathy with cataract and hip spine disease syndrome	36715121	Condition	SNOMED	Inf
cardiomyopathy (broad)	Chagas' disease with heart involvement	321502	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cirrhotic cardiomyopathy	37110890	Condition	SNOMED	Inf
cardiomyopathy (broad)	Cobalt cardiomyopathy	4177188	Condition	SNOMED	Inf
cardiomyopathy (broad)	Combined oxidative phosphorylation defect type 17	36678496	Condition	SNOMED	Inf
cardiomyopathy (broad)	Congenital cataract, hypertrophic cardiomyopathy, mitochondrial myopathy syndrome	36713473	Condition	SNOMED	Inf
cardiomyopathy (broad)	Congestive heart failure due to cardiomyopathy	44782428	Condition	SNOMED	Inf
cardiomyopathy (broad)	Congestive heart failure stage B due to Ischaemic cardiomyopathy	36712928	Condition	SNOMED	Inf
cardiomyopathy (broad)	Congestive heart failure stage C due to Ischaemic cardiomyopathy	36712927	Condition	SNOMED	Inf
cardiomyopathy (broad)	Congestive obstructive cardiomyopathy	4124692	Condition	SNOMED	Inf
cardiomyopathy (broad)	Danish type familial amyloid cardiomyopathy	4097992	Condition	SNOMED	Inf
cardiomyopathy (broad)	Danon disease	4167868	Condition	SNOMED	Inf
cardiomyopathy (broad)	Diabetic cardiomyopathy	37312019	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy	4163710	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy 3B	45765475	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy caused by drug	4218771	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Dilated cardiomyopathy caused by radiation	4129399	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to Friedreich's ataxia	4177187	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to amyloidosis	4240233	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to bacterial myocarditis	4185379	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to dermatomyositis	4262911	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to familial storage disease	4245506	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to fungal myocarditis	4258681	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to glycogen storage disease	4243983	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to granuloma	4215284	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to hemochromatosis	4219376	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to infectious disease	4313305	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to infiltration	4273401	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to malignancy	4251051	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to metabolic disorder	4006292	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to mucopolysaccharidosis	4314400	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to muscular dystrophy	4103513	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to myotonic dystrophy	4101863	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to neuromuscular disorder	4195417	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to nutritional deficiency	4224935	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to phytanic acid storage disease	4006792	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to polyarteritis nodosa	4240306	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to protozoan myocarditis	4225077	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Dilated cardiomyopathy due to rheumatoid arthritis	4060405	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to sarcoidosis	4247261	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to systemic lupus erythematosus	4269448	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to systemic sclerosis	4147604	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to taurine deficiency	4189147	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy due to viral myocarditis	4147982	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy secondary to alcohol	318773	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy secondary to deficiency	4142185	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy secondary to electrolyte deficiency	4234537	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy secondary to metazoal myocarditis	4068262	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy secondary to toxic reaction	4023964	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy with connective tissue disorder	4185450	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy with genetic marker	43020659	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated cardiomyopathy with hypergonadotropic hypogonadism syndrome	36717720	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dilated peripartum cardiomyopathy	4037495	Condition	SNOMED	Inf
cardiomyopathy (broad)	Dystrophic cardiomyopathy	4108239	Condition	SNOMED	Inf
cardiomyopathy (broad)	Early onset myopathy with fatal cardiomyopathy	45765411	Condition	SNOMED	Inf
cardiomyopathy (broad)	Encephalopathy, hypertrophic cardiomyopathy, renal tubular disease syndrome	35621979	Condition	SNOMED	Inf
cardiomyopathy (broad)	Endomyocardial fibrosis	439399	Condition	SNOMED	Inf
cardiomyopathy (broad)	Familial cardiomyopathy	4261970	Condition	SNOMED	Inf
cardiomyopathy (broad)	Familial dilated cardiomyopathy with conduction defect due to LMNA mutation	35624231	Condition	SNOMED	Inf
cardiomyopathy (broad)	Familial isolated arrhythmogenic right ventricular dysplasia	37399476	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Familial restrictive cardiomyopathy	4119959	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fatal infantile mitochondrial cardiomyopathy	43020669	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fatty degeneration of heart	4321717	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fetal cardiomyopathy	43020781	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fetal dilated cardiomyopathy	43020785	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fetal hypertrophic cardiomyopathy	43020782	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fetal hypertrophic cardiomyopathy associated with renal disease	43020784	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fetal hypertrophic cardiomyopathy due to maternal diabetes mellitus	45766963	Condition	SNOMED	Inf
cardiomyopathy (broad)	Fetal hypertrophic cardiomyopathy due to twin to twin transfusion syndrome	43020783	Condition	SNOMED	Inf
cardiomyopathy (broad)	Generalised right ventricular dysfunction	44804845	Condition	SNOMED	Inf
cardiomyopathy (broad)	Glycogen storage disease with severe cardiomyopathy due to glycogenin deficiency	36713480	Condition	SNOMED	Inf
cardiomyopathy (broad)	Heart failure with reduced ejection fraction due to cardiomyopathy	45766167	Condition	SNOMED	Inf
cardiomyopathy (broad)	Heart-hand syndrome Slovenian type	36715371	Condition	SNOMED	Inf
cardiomyopathy (broad)	Histiocytoid mitochondrial cardiomyopathy	43020667	Condition	SNOMED	Inf
cardiomyopathy (broad)	Histiocytoid mitochondrial cardiomyopathy due to cytochrome aa3 deficiency	43021299	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy	4124693	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy and renal tubular disease due to mitochondrial DNA mutation	36675174	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy associated with another disorder	40483296	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy secondary to Friedreich's ataxia	4205593	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy secondary to hyperthyroidism	4246673	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy secondary to neuromuscular disorder	4223017	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy with genetic marker	43020658	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Hypertrophic cardiomyopathy with hypotonia and lactic acidosis syndrome	36713761	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic cardiomyopathy without obstruction	4108236	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic mitochondrial cardiomyopathy	43021905	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic mitochondrial cardiomyopathy associated with cataracts and lactic acidosis	43020668	Condition	SNOMED	Inf
cardiomyopathy (broad)	Hypertrophic obstructive cardiomyopathy	316428	Condition	SNOMED	Inf
cardiomyopathy (broad)	Infantile hypertrophic cardiomyopathy due to MRPL44 deficiency	36675178	Condition	SNOMED	Inf
cardiomyopathy (broad)	Inflammatory cardiomyopathy	43020652	Condition	SNOMED	Inf
cardiomyopathy (broad)	Ischaemic congestive cardiomyopathy	4145696	Condition	SNOMED	Inf
cardiomyopathy (broad)	Ischaemic dilated cardiomyopathy due to coronary artery disease	43020660	Condition	SNOMED	Inf
cardiomyopathy (broad)	Keshan disease	4264027	Condition	SNOMED	Inf
cardiomyopathy (broad)	Left ventricular myocardial noncompaction cardiomyopathy	40487105	Condition	SNOMED	Inf
cardiomyopathy (broad)	Maternally inherited cardiomyopathy and hearing loss syndrome	37119055	Condition	SNOMED	Inf
cardiomyopathy (broad)	Maternally inherited mitochondrial cardiomyopathy and myopathy	43021906	Condition	SNOMED	Inf
cardiomyopathy (broad)	Microcephalus cardiomyopathy syndrome	36714240	Condition	SNOMED	Inf
cardiomyopathy (broad)	Mitochondrial cardiomyopathy	43020666	Condition	SNOMED	Inf
cardiomyopathy (broad)	Mitochondrial hypertrophic cardiomyopathy with lactic acidosis due to MTO1 deficiency	36675150	Condition	SNOMED	Inf
cardiomyopathy (broad)	Mitral valve regurgitation due to cardiomyopathy	45771323	Condition	SNOMED	Inf
cardiomyopathy (broad)	Muscle and heart glycogen synthase deficiency	37110708	Condition	SNOMED	Inf
cardiomyopathy (broad)	Myocardial degeneration	321320	Condition	SNOMED	Inf
cardiomyopathy (broad)	Myocardial disease	4239975	Condition	SNOMED	Inf
cardiomyopathy (broad)	Naxos disease	37398927	Condition	SNOMED	Inf
cardiomyopathy (broad)	NonIschaemic congestive cardiomyopathy	42872390	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Nonobstructive cardiomyopathy	4288868	Condition	SNOMED	Inf
cardiomyopathy (broad)	Nutritional and metabolic cardiomyopathies	320122	Condition	SNOMED	Inf
cardiomyopathy (broad)	Pacing-induced cardiomyopathy	43020656	Condition	SNOMED	Inf
cardiomyopathy (broad)	Polyglucosan body myopathy type 1	36676853	Condition	SNOMED	Inf
cardiomyopathy (broad)	Post-myocarditic cardiomyopathy	4121474	Condition	SNOMED	Inf
cardiomyopathy (broad)	Postpartum cardiomyopathy	312383	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary cardiomyopathy	4232495	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary dilated cardiomyopathy	4108822	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary endomyocardial fibrosis cardiomyopathy	315560	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary endomyocardial fibrosis restrictive cardiomyopathy	4172641	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary eosinophilic endomyocardial cardiomyopathy	4204856	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary eosinophilic endomyocardial restrictive cardiomyopathy	4141588	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary familial dilated cardiomyopathy	4178584	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary familial hypertrophic cardiomyopathy	4222765	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary hypertrophic cardiomyopathy	44784145	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary idiopathic dilated cardiomyopathy	4203149	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary idiopathic hypertrophic cardiomyopathy	4270625	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary idiopathic restrictive cardiomyopathy	4274635	Condition	SNOMED	Inf
cardiomyopathy (broad)	Primary restrictive cardiomyopathy	4236332	Condition	SNOMED	Inf
cardiomyopathy (broad)	Progressive sensorineural hearing loss and hypertrophic cardiomyopathy syndrome	36714157	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy	4190773	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy due to mucopolysaccharidosis	4225117	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to amyloidosis	4197087	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to endocardial fibroelastosis	4139754	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to familial storage disease	4149725	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to glycogen storage disease	4273369	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to granulomas	4297316	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to hemochromatosis	4211517	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to infiltrations	4048268	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to malignancy	4076799	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy secondary to sarcoidosis	4191606	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy with endomyocardial fibrosis	4162674	Condition	SNOMED	Inf
cardiomyopathy (broad)	Restrictive cardiomyopathy without endomyocardial fibrosis	4119592	Condition	SNOMED	Inf
cardiomyopathy (broad)	Rheumatic cardiomyopathy	37312596	Condition	SNOMED	Inf
cardiomyopathy (broad)	Right ventricular myocardial noncompaction cardiomyopathy	40487104	Condition	SNOMED	Inf
cardiomyopathy (broad)	Secondary dilated cardiomyopathy	4071896	Condition	SNOMED	Inf
cardiomyopathy (broad)	Secondary nonIschaemic congestive cardiomyopathy	44783568	Condition	SNOMED	Inf
cardiomyopathy (broad)	Secondary restrictive cardiomyopathy	4217551	Condition	SNOMED	Inf
cardiomyopathy (broad)	Sensorineural deafness with dilated cardiomyopathy syndrome	37109990	Condition	SNOMED	Inf
cardiomyopathy (broad)	Severe scapuloperoneal muscular dystrophy with cardiomyopathy	4345565	Condition	SNOMED	Inf
cardiomyopathy (broad)	Systolic heart failure stage B due to Ischaemic cardiomyopathy	36717359	Condition	SNOMED	Inf
cardiomyopathy (broad)	Systolic heart failure stage C due to Ischaemic cardiomyopathy	36712929	Condition	SNOMED	Inf
cardiomyopathy (broad)	TMEM70 related mitochondrial encephalo-cardio-myopathy	37397548	Condition	SNOMED	Inf
cardiomyopathy (broad)	Tachycardia-induced cardiomyopathy	4144463	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (broad)	Takotsubo cardiomyopathy	40479589	Condition	SNOMED	Inf
cardiomyopathy (broad)	Transthyretin related familial amyloid cardiomyopathy	37396000	Condition	SNOMED	Inf
cardiomyopathy (broad)	Tropical endomyocardial fibrosis	37398931	Condition	SNOMED	Inf
cardiomyopathy (broad)	Tubular renal disease with cardiomyopathy syndrome	36717761	Condition	SNOMED	Inf
cardiomyopathy (broad)	Valvular cardiomyopathy	43020654	Condition	SNOMED	Inf
cardiomyopathy (broad)	Ventricular myocardial noncompaction cardiomyopathy	43021903	Condition	SNOMED	Inf
cardiomyopathy (broad)	Vici syndrome	36714540	Condition	SNOMED	Inf
cardiomyopathy (broad)	Wooly hair and palmoplantar keratoderma with dilated cardiomyopathy syndrome	36714549	Condition	SNOMED	Inf
cardiomyopathy (primary)	Cardiomyopathy	321319	Condition	SNOMED	Inf
cardiomyopathy (primary)	Cardiomyopathy and renal anomaly syndrome	36715122	Condition	SNOMED	Inf
cardiomyopathy (primary)	Cardiomyopathy caused by drug	35615148	Condition	SNOMED	Inf
cardiomyopathy (primary)	Cardiomyopathy with cataract and hip spine disease syndrome	36715121	Condition	SNOMED	Inf
cardiomyopathy (primary)	Congestive obstructive cardiomyopathy	4124692	Condition	SNOMED	Inf
cardiomyopathy (primary)	Dilated cardiomyopathy	4163710	Condition	SNOMED	Inf
cardiomyopathy (primary)	Dilated cardiomyopathy caused by drug	4218771	Condition	SNOMED	Inf
cardiomyopathy (primary)	Dilated cardiomyopathy with connective tissue disorder	4185450	Condition	SNOMED	Inf
cardiomyopathy (primary)	Generalised right ventricular dysfunction	44804845	Condition	SNOMED	Inf
cardiomyopathy (primary)	Myocardial degeneration	321320	Condition	SNOMED	Inf
cardiomyopathy (primary)	Myocardial disease	4239975	Condition	SNOMED	Inf
cardiomyopathy (primary)	NonIschaemic congestive cardiomyopathy	42872390	Condition	SNOMED	Inf
cardiomyopathy (primary)	Nonobstructive cardiomyopathy	4288868	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary cardiomyopathy	4232495	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
cardiomyopathy (primary)	Primary dilated cardiomyopathy	4108822	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary endomyocardial fibrosis cardiomyopathy	315560	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary endomyocardial fibrosis restrictive cardiomyopathy	4172641	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary eosinophilic endomyocardial cardiomyopathy	4204856	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary eosinophilic endomyocardial restrictive cardiomyopathy	4141588	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary idiopathic dilated cardiomyopathy	4203149	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary idiopathic restrictive cardiomyopathy	4274635	Condition	SNOMED	Inf
cardiomyopathy (primary)	Primary restrictive cardiomyopathy	4236332	Condition	SNOMED	Inf
cardiomyopathy (primary)	Restrictive cardiomyopathy	4190773	Condition	SNOMED	Inf
cardiomyopathy (primary)	Restrictive cardiomyopathy with endomyocardial fibrosis	4162674	Condition	SNOMED	Inf
heart failure (broad)	Acute combined systolic and diastolic heart failure	44782718	Condition	SNOMED	Inf
heart failure (broad)	Acute congestive heart failure	4023479	Condition	SNOMED	Inf
heart failure (broad)	Acute cor pulmonale	312927	Condition	SNOMED	Inf
heart failure (broad)	Acute diastolic heart failure	40481042	Condition	SNOMED	Inf
heart failure (broad)	Acute exacerbation of chronic congestive heart failure	44782655	Condition	SNOMED	Inf
heart failure (broad)	Acute heart failure	442310	Condition	SNOMED	Inf
heart failure (broad)	Acute heart failure co-occurrent with normal ejection fraction	764877	Condition	SNOMED	Inf
heart failure (broad)	Acute left ventricular failure	4108245	Condition	SNOMED	Inf
heart failure (broad)	Acute left-sided congestive heart failure	4327205	Condition	SNOMED	Inf
heart failure (broad)	Acute left-sided heart failure	4267800	Condition	SNOMED	Inf
heart failure (broad)	Acute on chronic combined systolic and diastolic heart failure	44782733	Condition	SNOMED	Inf
heart failure (broad)	Acute on chronic diastolic heart failure	40481043	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (broad)	Acute on chronic heart failure co-occurrent with normal ejection fraction	764874	Condition	SNOMED	Inf
heart failure (broad)	Acute on chronic right-sided congestive heart failure	37309625	Condition	SNOMED	Inf
heart failure (broad)	Acute on chronic systolic heart failure	40480602	Condition	SNOMED	Inf
heart failure (broad)	Acute right-sided congestive heart failure	4215446	Condition	SNOMED	Inf
heart failure (broad)	Acute right-sided heart failure	4233424	Condition	SNOMED	Inf
heart failure (broad)	Acute systolic heart failure	40480603	Condition	SNOMED	Inf
heart failure (broad)	Benign hypertensive heart disease with congestive cardiac failure	439698	Condition	SNOMED	Inf
heart failure (broad)	Biventricular congestive heart failure	4242669	Condition	SNOMED	Inf
heart failure (broad)	Cardiac failure after obstetrical surgery AND/OR other procedure including delivery	4205558	Condition	SNOMED	Inf
heart failure (broad)	Cardiac failure therapy	4146456	Procedure	SNOMED	Inf
heart failure (broad)	Cardiorenal syndrome	40482857	Condition	SNOMED	Inf
heart failure (broad)	Cardiorespiratory failure	4259490	Condition	SNOMED	Inf
heart failure (broad)	Chronic combined systolic and diastolic heart failure	44782719	Condition	SNOMED	Inf
heart failure (broad)	Chronic congestive heart failure	4229440	Condition	SNOMED	Inf
heart failure (broad)	Chronic cor pulmonale	4195892	Condition	SNOMED	Inf
heart failure (broad)	Chronic diastolic heart failure	40479576	Condition	SNOMED	Inf
heart failure (broad)	Chronic heart failure	444031	Condition	SNOMED	Inf
heart failure (broad)	Chronic heart failure co-occurrent with normal ejection fraction	764876	Condition	SNOMED	Inf
heart failure (broad)	Chronic left-sided congestive heart failure	4206009	Condition	SNOMED	Inf
heart failure (broad)	Chronic left-sided heart failure	4009047	Condition	SNOMED	Inf
heart failure (broad)	Chronic right-sided congestive heart failure	4284562	Condition	SNOMED	Inf
heart failure (broad)	Chronic right-sided heart failure	4014159	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (broad)	Chronic systolic heart failure	40479192	Condition	SNOMED	Inf
heart failure (broad)	Compensated cardiac failure	4108244	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure	319835	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure as early postoperative complication	44784345	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure as post-operative complication of cardiac surgery	762002	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure as post-operative complication of non-cardiac surgery	762003	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure due to cardiomyopathy	44782428	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure due to left ventricular systolic dysfunction	4139864	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure due to valvular disease	4142561	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure stage B due to Ischaemic cardiomyopathy	36712928	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure stage C	43021826	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure stage C due to Ischaemic cardiomyopathy	36712927	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure stage D	43021825	Condition	SNOMED	Inf
heart failure (broad)	Congestive heart failure with right heart failure	44782713	Condition	SNOMED	Inf
heart failure (broad)	Congestive rheumatic heart failure	315295	Condition	SNOMED	Inf
heart failure (broad)	Cor pulmonale	4307356	Condition	SNOMED	Inf
heart failure (broad)	Decompensated cardiac failure	4111554	Condition	SNOMED	Inf
heart failure (broad)	Decompensated chronic heart failure	4311437	Condition	SNOMED	Inf
heart failure (broad)	Diastolic heart failure	443587	Condition	SNOMED	Inf
heart failure (broad)	Diastolic heart failure stage C	43021842	Condition	SNOMED	Inf
heart failure (broad)	Diastolic heart failure stage D	43021841	Condition	SNOMED	Inf
heart failure (broad)	Discharge from heart failure nurse service	44805683	Observation	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (broad)	Emergency hospital admission for heart failure	4215511	Observation	SNOMED	Inf
heart failure (broad)	Exacerbation of congestive heart failure	43022068	Condition	SNOMED	Inf
heart failure (broad)	Felt discouraged or down in the dumps because of heart failure over the past 2 weeks [KCCQ]	36204172	Observation	LOINC	Inf
heart failure (broad)	H/O: heart failure	45478437	Observation	Read	Inf
heart failure (broad)	Has heart failure management plan	44813162	Observation	SNOMED	Inf
heart failure (broad)	Heart failure	316139	Condition	SNOMED	Inf
heart failure (broad)	Heart failure 6 month review	44790972	Observation	SNOMED	Inf
heart failure (broad)	Heart failure annual review	4193010	Observation	SNOMED	Inf
heart failure (broad)	Heart failure as a complication of care	4124705	Condition	SNOMED	Inf
heart failure (broad)	Heart failure clinical pathway	44808957	Observation	SNOMED	Inf
heart failure (broad)	Heart failure confirmed	4215689	Condition	SNOMED	Inf
heart failure (broad)	Heart failure due to end stage congenital heart disease	43020657	Condition	SNOMED	Inf
heart failure (broad)	Heart failure initial assessment	44808862	Observation	SNOMED	Inf
heart failure (broad)	Heart failure review completed	44789102	Observation	SNOMED	Inf
heart failure (broad)	Heart failure self-management plan agreed	44806371	Observation	SNOMED	Inf
heart failure (broad)	Heart failure self-management plan review	44806125	Procedure	SNOMED	Inf
heart failure (broad)	Heart failure with mid range ejection fraction	37311948	Condition	SNOMED	Inf
heart failure (broad)	Heart failure with normal ejection fraction	40486933	Condition	SNOMED	Inf
heart failure (broad)	Heart failure with reduced ejection fraction	45766164	Condition	SNOMED	Inf
heart failure (broad)	Heart failure with reduced ejection fraction due to cardiomyopathy	45766167	Condition	SNOMED	Inf
heart failure (broad)	Heart failure with reduced ejection fraction due to coronary artery disease	45766165	Condition	SNOMED	Inf
heart failure (broad)	Heart failure with reduced ejection fraction due to heart valve disease	45773075	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (broad)	Heart failure with reduced ejection fraction due to myocarditis	45766166	Condition	SNOMED	Inf
heart failure (broad)	High output heart failure	4004279	Condition	SNOMED	Inf
heart failure (broad)	History of Acute heart failure within 24 hours prior to procedure	36305423	Observation	LOINC	Inf
heart failure (broad)	How would you feel if you had to spend the rest of your life with your heart failure the way it is right now [KCCQ]	36204171	Observation	LOINC	Inf
heart failure (broad)	Hurrying or jogging (as if to catch a bus) was limited by heart failure over the past 2 weeks [KCCQ]	36204159	Observation	LOINC	Inf
heart failure (broad)	Hypertensive heart AND chronic kidney disease with congestive heart failure	44782728	Condition	SNOMED	Inf
heart failure (broad)	Hypertensive heart and chronic kidney disease	44784621	Condition	SNOMED	Inf
heart failure (broad)	Hypertensive heart and renal disease with (congestive) heart failure	439696	Condition	SNOMED	Inf
heart failure (broad)	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	439694	Condition	SNOMED	Inf
heart failure (broad)	Hypertensive heart disease NOS with congestive cardiac failure	45523365	Condition	Read	Inf
heart failure (broad)	Hypertensive heart disease with congestive heart failure	314378	Condition	SNOMED	Inf
heart failure (broad)	Hypertensive heart failure	444101	Condition	SNOMED	Inf
heart failure (broad)	Left heart failure	439846	Condition	SNOMED	Inf
heart failure (broad)	Low output heart failure	4103448	Condition	SNOMED	Inf
heart failure (broad)	Malignant hypertensive heart disease with congestive heart failure	316994	Condition	SNOMED	Inf
heart failure (broad)	Nutrition therapy for congestive heart failure	44782439	Procedure	SNOMED	Inf
heart failure (broad)	Nutritional therapy for congestive heart failure done	46269995	Observation	SNOMED	Inf
heart failure (broad)	On optimal heart failure therapy	44811840	Observation	SNOMED	Inf
heart failure (broad)	Participation in hobbies, recreational activities limited by heart failure over the past 2 weeks [KCCQ]	36204173	Observation	LOINC	Inf
heart failure (broad)	Participation in intimate relationships with loved ones limited by heart failure over the past 2 weeks [KCCQ]	36204176	Observation	LOINC	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (broad)	Participation in visiting family or friends out of your home limited by heart failure over the past 2 weeks [KCCQ]	36204175	Observation	LOINC	Inf
heart failure (broad)	Participation in working or doing household chores limited by heart failure over the past 2 weeks [KCCQ]	36204174	Observation	LOINC	Inf
heart failure (broad)	Pleural effusion due to congestive heart failure	4236658	Condition	SNOMED	Inf
heart failure (broad)	Pulmonary hypertension due to left heart disease	43020910	Condition	SNOMED	Inf
heart failure (broad)	Red half-moon nail in congestive heart failure	4293582	Condition	SNOMED	Inf
heart failure (broad)	Reduced ejection fraction co-occurrent and due to acute heart failure	764873	Condition	SNOMED	Inf
heart failure (broad)	Reduced ejection fraction co-occurrent and due to acute on chronic heart failure	764871	Condition	SNOMED	Inf
heart failure (broad)	Reduced ejection fraction co-occurrent and due to chronic heart failure	764872	Condition	SNOMED	Inf
heart failure (broad)	Refractory heart failure	4199500	Condition	SNOMED	Inf
heart failure (broad)	Rehabilitation for heart failure	44809279	Observation	SNOMED	Inf
heart failure (broad)	Rheumatic left ventricular failure	4184497	Condition	SNOMED	Inf
heart failure (broad)	Right heart failure due to pulmonary hypertension	4138307	Condition	SNOMED	Inf
heart failure (broad)	Right heart failure secondary to left heart failure	4195785	Condition	SNOMED	Inf
heart failure (broad)	Right ventricular failure	4273632	Condition	SNOMED	Inf
heart failure (broad)	Saddle embolus of pulmonary artery with acute cor pulmonale	35615055	Condition	SNOMED	Inf
heart failure (broad)	Sepsis-associated left ventricular failure	4079695	Condition	SNOMED	Inf
heart failure (broad)	Sepsis-associated right ventricular failure	4079296	Condition	SNOMED	Inf
heart failure (broad)	Symptomatic congestive heart failure	44784442	Condition	SNOMED	Inf
heart failure (broad)	Symptoms in heart failure patients during assessment period [CMS Assessment]	40760358	Observation	LOINC	Inf
heart failure (broad)	Systolic heart failure	443580	Condition	SNOMED	Inf
heart failure (broad)	Systolic heart failure stage C	43020421	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (broad)	Systolic heart failure stage C due to Ischaemic cardiomyopathy	36712929	Condition	SNOMED	Inf
heart failure (broad)	Systolic heart failure stage D	43021840	Condition	SNOMED	Inf
heart failure (broad)	X-linked intellectual disability, cardiomegaly, congestive heart failure syndrome	36676642	Condition	SNOMED	Inf
heart failure (narrow)	Acute combined systolic and diastolic heart failure	44782718	Condition	SNOMED	Inf
heart failure (narrow)	Acute congestive heart failure	4023479	Condition	SNOMED	Inf
heart failure (narrow)	Acute diastolic heart failure	40481042	Condition	SNOMED	Inf
heart failure (narrow)	Acute exacerbation of chronic congestive heart failure	44782655	Condition	SNOMED	Inf
heart failure (narrow)	Acute heart failure	442310	Condition	SNOMED	Inf
heart failure (narrow)	Acute heart failure co-occurrent with normal ejection fraction	764877	Condition	SNOMED	Inf
heart failure (narrow)	Acute left ventricular failure	4108245	Condition	SNOMED	Inf
heart failure (narrow)	Acute left-sided congestive heart failure	4327205	Condition	SNOMED	Inf
heart failure (narrow)	Acute left-sided heart failure	4267800	Condition	SNOMED	Inf
heart failure (narrow)	Acute on chronic combined systolic and diastolic heart failure	44782733	Condition	SNOMED	Inf
heart failure (narrow)	Acute on chronic diastolic heart failure	40481043	Condition	SNOMED	Inf
heart failure (narrow)	Acute on chronic heart failure co-occurrent with normal ejection fraction	764874	Condition	SNOMED	Inf
heart failure (narrow)	Acute on chronic right-sided congestive heart failure	37309625	Condition	SNOMED	Inf
heart failure (narrow)	Acute on chronic systolic heart failure	40480602	Condition	SNOMED	Inf
heart failure (narrow)	Acute right-sided congestive heart failure	4215446	Condition	SNOMED	Inf
heart failure (narrow)	Acute right-sided heart failure	4233424	Condition	SNOMED	Inf
heart failure (narrow)	Acute systolic heart failure	40480603	Condition	SNOMED	Inf
heart failure (narrow)	Biventricular congestive heart failure	4242669	Condition	SNOMED	Inf
heart failure (narrow)	Cardiac asthma	4215802	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (narrow)	Cardiorespiratory failure	4259490	Condition	SNOMED	Inf
heart failure (narrow)	Chronic combined systolic and diastolic heart failure	44782719	Condition	SNOMED	Inf
heart failure (narrow)	Chronic congestive heart failure	4229440	Condition	SNOMED	Inf
heart failure (narrow)	Chronic diastolic heart failure	40479576	Condition	SNOMED	Inf
heart failure (narrow)	Chronic heart failure	444031	Condition	SNOMED	Inf
heart failure (narrow)	Chronic heart failure co-occurrent with normal ejection fraction	764876	Condition	SNOMED	Inf
heart failure (narrow)	Chronic left-sided congestive heart failure	4206009	Condition	SNOMED	Inf
heart failure (narrow)	Chronic left-sided heart failure	4009047	Condition	SNOMED	Inf
heart failure (narrow)	Chronic right-sided congestive heart failure	4284562	Condition	SNOMED	Inf
heart failure (narrow)	Chronic right-sided heart failure	4014159	Condition	SNOMED	Inf
heart failure (narrow)	Chronic systolic heart failure	40479192	Condition	SNOMED	Inf
heart failure (narrow)	Compensated cardiac failure	4108244	Condition	SNOMED	Inf
heart failure (narrow)	Congestive heart failure	319835	Condition	SNOMED	Inf
heart failure (narrow)	Congestive heart failure due to cardiomyopathy	44782428	Condition	SNOMED	Inf
heart failure (narrow)	Congestive heart failure due to left ventricular systolic dysfunction	4139864	Condition	SNOMED	Inf
heart failure (narrow)	Congestive heart failure stage C	43021826	Condition	SNOMED	Inf
heart failure (narrow)	Congestive heart failure stage D	43021825	Condition	SNOMED	Inf
heart failure (narrow)	Congestive heart failure with right heart failure	44782713	Condition	SNOMED	Inf
heart failure (narrow)	Decompensated cardiac failure	4111554	Condition	SNOMED	Inf
heart failure (narrow)	Decompensated chronic heart failure	4311437	Condition	SNOMED	Inf
heart failure (narrow)	Diastolic heart failure	443587	Condition	SNOMED	Inf
heart failure (narrow)	Diastolic heart failure stage C	43021842	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (narrow)	Diastolic heart failure stage D	43021841	Condition	SNOMED	Inf
heart failure (narrow)	Discharge from heart failure nurse service	44805683	Observation	SNOMED	Inf
heart failure (narrow)	Emergency hospital admission for heart failure	4215511	Observation	SNOMED	Inf
heart failure (narrow)	Exacerbation of congestive heart failure	43022068	Condition	SNOMED	Inf
heart failure (narrow)	Felt discouraged or down in the dumps because of heart failure over the past 2 weeks [KCCQ]	36204172	Observation	LOINC	Inf
heart failure (narrow)	Heart failure	316139	Condition	SNOMED	Inf
heart failure (narrow)	Heart failure 6 month review	44790972	Observation	SNOMED	Inf
heart failure (narrow)	Heart failure annual review	4193010	Observation	SNOMED	Inf
heart failure (narrow)	Heart failure clinical pathway	44808957	Observation	SNOMED	Inf
heart failure (narrow)	Heart failure confirmed	4215689	Condition	SNOMED	Inf
heart failure (narrow)	Heart failure initial assessment	44808862	Observation	SNOMED	Inf
heart failure (narrow)	Heart failure review completed	44789102	Observation	SNOMED	Inf
heart failure (narrow)	Heart failure self-management plan agreed	44806371	Observation	SNOMED	Inf
heart failure (narrow)	Heart failure self-management plan review	44806125	Procedure	SNOMED	Inf
heart failure (narrow)	Heart failure with mid range ejection fraction	37311948	Condition	SNOMED	Inf
heart failure (narrow)	Heart failure with normal ejection fraction	40486933	Condition	SNOMED	Inf
heart failure (narrow)	Heart failure with reduced ejection fraction	45766164	Condition	SNOMED	Inf
heart failure (narrow)	Heart failure with reduced ejection fraction due to cardiomyopathy	45766167	Condition	SNOMED	Inf
heart failure (narrow)	High output heart failure	4004279	Condition	SNOMED	Inf
heart failure (narrow)	How would you feel if you had to spend the rest of your life with your heart failure the way it is right now [KCCQ]	36204171	Observation	LOINC	Inf
heart failure (narrow)	Hurrying or jogging (as if to catch a bus) was limited by heart failure over the past 2 weeks [KCCQ]	36204159	Observation	LOINC	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (narrow)	Left heart failure	439846	Condition	SNOMED	Inf
heart failure (narrow)	Low output heart failure	4103448	Condition	SNOMED	Inf
heart failure (narrow)	Nutrition therapy for congestive heart failure	44782439	Procedure	SNOMED	Inf
heart failure (narrow)	Nutritional therapy for congestive heart failure done	46269995	Observation	SNOMED	Inf
heart failure (narrow)	On optimal heart failure therapy	44811840	Observation	SNOMED	Inf
heart failure (narrow)	Participation in intimate relationships with loved ones limited by heart failure over the past 2 weeks [KCCQ]	36204176	Observation	LOINC	Inf
heart failure (narrow)	Participation in visiting family or friends out of your home limited by heart failure over the past 2 weeks [KCCQ]	36204175	Observation	LOINC	Inf
heart failure (narrow)	Participation in working or doing household chores limited by heart failure over the past 2 weeks [KCCQ]	36204174	Observation	LOINC	Inf
heart failure (narrow)	Pleural effusion due to congestive heart failure	4236658	Condition	SNOMED	Inf
heart failure (narrow)	Pulmonary hypertension due to left heart disease	43020910	Condition	SNOMED	Inf
heart failure (narrow)	Red half-moon nail in congestive heart failure	4293582	Condition	SNOMED	Inf
heart failure (narrow)	Reduced ejection fraction co-occurrent and due to acute heart failure	764873	Condition	SNOMED	Inf
heart failure (narrow)	Reduced ejection fraction co-occurrent and due to acute on chronic heart failure	764871	Condition	SNOMED	Inf
heart failure (narrow)	Reduced ejection fraction co-occurrent and due to chronic heart failure	764872	Condition	SNOMED	Inf
heart failure (narrow)	Refractory heart failure	4199500	Condition	SNOMED	Inf
heart failure (narrow)	Rehabilitation for heart failure	44809279	Observation	SNOMED	Inf
heart failure (narrow)	Right heart failure secondary to left heart failure	4195785	Condition	SNOMED	Inf
heart failure (narrow)	Right ventricular failure	4273632	Condition	SNOMED	Inf
heart failure (narrow)	Symptomatic congestive heart failure	44784442	Condition	SNOMED	Inf
heart failure (narrow)	Symptoms in heart failure patients during assessment period [CMS Assessment]	40760358	Observation	LOINC	Inf
heart failure (narrow)	Systolic heart failure	443580	Condition	SNOMED	Inf

Phenotype	Concept name	Concept ID	Domain	Vocabulary	Washout
heart failure (narrow)	Systolic heart failure stage C	43020421	Condition	SNOMED	Inf
heart failure (narrow)	Systolic heart failure stage D	43021840	Condition	SNOMED	Inf

Table S2. Preliminary list of medicines definitions.

Substance Name	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Venlafaxine	venlafaxine	SNRI	N06AX16	743670	Yes
Mirtazapine	mirtazapine	Tetracyclic antidepressants	N06AX11	725131	Yes

Table S3. Preliminary list of Negative Control Outcomes (NCO).

Phenotype	Codelist name	Concept ID
NCO	Acne	141095
NCO	Acute Maxillary Sinusitis	141323
NCO	Acute Pharyngitis	25297
NCO	Acute Tubulointerstitial Nephritis	4102631
NCO	Acute Upper Respiratory Infection	257011
NCO	Adrenal Cortical Hypofunction	435508
NCO	Allergic Conjunctivitis	43021807
NCO	Allergic Rhinitis	257007
NCO	Anemia	439777
NCO	Atrophic Vaginitis	201078
NCO	Benign Prostatic Hyperplasia	198803
NCO	Candidiasis Of Vagina	198363
NCO	Cobalamin Deficiency	4100822
NCO	Conjunctivitis	379019
NCO	Covid 19	37311061
NCO	Diaphragmatic Hernia	201061
NCO	Disorder Of Rotator Cuff	4212887
NCO	Disorder Of Teeth And Or Supporting Structures	201603
NCO	Diverticulosis Of Large Intestine Without Diverticulitis	4164898
NCO	Gastrointestinal Infection	37396146
NCO	Gout	440674
NCO	Hemorrhoids	195562
NCO	Hyperplasia Of Prostate	197032
NCO	Hyperthyroidism	4142479
NCO	Hypokalemia	437833

Phenotype	Codelist name	Concept ID
NCO	Hypothyroidism	140673
NCO	Impacted Cerumen	374375
NCO	Infective Otitis Externa	381859
NCO	Infiltrating Ductular Carcinoma Of Upper Outer Quadrant Of Breast	36544992
NCO	Iron Deficiency Anemia	436659
NCO	Mycosis	433701
NCO	Nuclear Senile Cataract	439297
NCO	Oral Mucosal Fungal Disease	4122211
NCO	Osteoporosis	80502
NCO	Pain In Throat	259153
NCO	Presbycusis	377574
NCO	Primary Malignant Neoplasm Of Breast	4162253
NCO	Primary Malignant Neoplasm Of Prostate	200962
NCO	Primary Malignant Neoplasm Of Respiratory Tract	4311499
NCO	Seasonal Allergic Rhinitis	4280726
NCO	Senile Cataract	381295
NCO	Sensorineural Hearing Loss Of Bilateral Ears	4110815
NCO	Sinusitis	4283893
NCO	Soft Tissue Infection	4320030
NCO	Vitamin D Deficiency	436070

ANNEX V. Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g. side effects).

Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g. its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.