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# Mental illness and cardiovascular health: observational and polygenic score analyses in a population-based cohort study

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## Original Article

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## Abstract

**Background.** Individuals with serious mental illness have a markedly shorter life expectancy. A major contributor to premature death is cardiovascular disease (CVD). We investigated associations of (genetic liability for) depressive disorder, bipolar disorder and schizophrenia with a range of CVD traits and examined to what degree these were driven by important confounders.

**Methods.** We included participants of the Dutch Lifelines cohort ($N = 147\,337$) with information on self-reported lifetime diagnosis of depressive disorder, bipolar disorder, or schizophrenia and CVD traits. Employing linear mixed-effects models, we examined associations between mental illness diagnoses and CVD, correcting for psychotropic medication, demographic and lifestyle factors. In a subsample ($N = 73\,965$), we repeated these analyses using polygenic scores (PGSs) for the three mental illnesses.

**Results.** There was strong evidence that depressive disorder diagnosis is associated with increased arrhythmia and atherosclerosis risk and lower heart rate variability, even after confounder adjustment. Positive associations were also found for the depression PGSs with arrhythmia and atherosclerosis. Bipolar disorder was associated with a higher risk of nearly all CVD traits, though most diminished after adjustment. The bipolar disorder PGSs did not show any associations. While the schizophrenia PGSs was associated with increased arrhythmia risk and lower heart rate variability, schizophrenia diagnosis was not. All mental illness diagnoses were associated with lower blood pressure and a lower risk of hypertension.

**Conclusions.** Our study shows widespread associations of (genetic liability to) mental illness (primarily depressive disorder) with CVD, even after confounder adjustment. Future research should focus on clarifying potential causal pathways between mental illness and CVD.

## Introduction

Individuals diagnosed with serious mental illness – a definition that generally includes major depressive disorder, bipolar disorder, and schizophrenia – are associated with a significant reduction in life expectancy of up to 15 years, compared to the general population (Correll et al., 2017; Plana-Ripoll et al., 2019). An important driver of premature mortality among those with mental illness is cardiovascular disease (CVD). Having been diagnosed with a mental illness is associated with a range of unfavorable cardiovascular traits, including a higher blood pressure, higher risk of atherosclerosis, lower heart rate variability and higher risk of arrhythmic disorders (Blom et al., 2014; Nielsen, Banner, & Jensen, 2021; Rossom, Hooker, O'Connor, Crain, & Sperl-Hillen, 2022; Whooley & Wong, 2013). Knowing what drives these associations is crucial to increase quality and duration of life for people with mental illness, but currently our understanding is limited (de Hert, Detraux, & Vancampfort, 2018; Ladwig, Goette, Atasoy, & Johar, 2020).

One plausible explanation for increased CVD among individuals with mental illness is that psychiatric treatment often includes prescription of antidepressants, antipsychotics, or mood stabilizers, all of which have cardio-metabolic side effects such as weight gain, dyslipidemia, and arrhythmias (Grandjean & Aubry, 2009; Mazereel, Detraux, Vancampfort, van Winkel, & de Hert, 2020). Yet, psychotropic medication use does not considerably increase the risk of cardiovascular mortality and therefore should not be the only (or even primary) focus of

research (Goldstein et al., 2015; Khan, Faucett, Morrison, & Brown, 2013; Vermeulen et al., 2017). A second potential explanation is that having a mental illness is associated with poor health behaviors that are known risk factors for CVD (Firth et al., 2019), however, to what extent is unclear, since studies that include all relevant variables are scarce (Lambert et al., 2022). A third potential explanation is that there are causal effects of having mental illness on cardiovascular health, not mediated through medication use, health behaviors, or environmental factors. A growing body of evidence shows increased inflammation, oxidative stress, and autonomic dysfunction in patients with mental illness, all known to be involved in the pathophysiology of CVD (Dieset, Andreassen, & Haukvik, 2016; Goldstein et al., 2015; Sewell et al., 2021). Schizophrenia has even been described as a multisystem disorder (Pillinger, D'Ambrosio, McCutcheon, & Howes, 2019). An important aspect to consider is the role of sex – while both serious mental illnesses and CVD have a different prevalence and expression in women *v.* men, the question of how this affects their association has so far been overlooked (Goldstein, Handa, & Tobet, 2014; Hjorthøj, Stürup, McGrath, & Nordentoft, 2017).

To increase our knowledge about the connection between mental illness and CVD, more well-powered and well-designed studies are needed (Goldfarb et al., 2022). This is challenging due to the low prevalence of mental illness in the population at large (especially for schizophrenia and bipolar disorder). However, while the prevalence of *diagnosed* mental illnesses is low, a diagnosis can be seen as the extreme end of an underlying continuum of symptoms (Sullivan & Geschwind, 2019). Someone's 'position' on this continuum can be estimated by looking at their genetic liability. Twin studies have shown that depressive disorder, bipolar disorder, and schizophrenia are moderately to highly heritable (37, 75, and 81%, respectively) (Sullivan, Daly, & O'Donovan, 2012). In recent years, genome-wide association studies (GWASs) have estimated the association of genetic variants across the genome with various mental illnesses. While the effect sizes of individual variants are very small, all variants combined currently explain 9, 19, and 24% of the variance in depressive disorder, bipolar disorder, and schizophrenia, respectively (Howard et al., 2019; Mullins et al., 2021; Trubetskoy et al., 2022). Using summary-level GWAS data, a polygenic risk score (PGSs) can be computed, which estimates an individual's genetic liability to the disease in question. In this study, we compute PGSs for mental illness as 'proxies' (Bigdeli et al., 2022) and associate them with CVD traits. It should be noted that an association between mental illness PGSs and CVD could also be interpreted as a shared underlying pathophysiology (Sewell et al., 2021); however, so far there is no strong evidence for genetic correlations between mental illness and CVD (Perry et al., 2022; Veeneman et al., 2021).

The aim of this study was to investigate associations of depressive disorder, bipolar disorder, and schizophrenia diagnosis with a wide range of cardiovascular traits and examine to what degree these are driven by psychotropic medication use and other important confounders. We assessed mental illness diagnosis, as well as polygenic liability to these illnesses, in a large and well-phenotyped population cohort. We hypothesized (pre-registered: https://osf.io/8ey9m/) that: (1) having a mental illness diagnosis, or higher genetic liability, is associated with worse cardiovascular health, (2) these associations will be attenuated when correcting for psychotropic medication use, (3) these associations will be further attenuated when correcting for additional relevant confounders (age, sex, educational attainment, employment status, pack years of smoking, BMI, type-2 diabetes, physical activity), and (4) these associations differ between men and women.

## Method

### Data

#### Lifelines cohort

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design, including family members, the health and health-related behaviors of 152 632 adults living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. All participants signed informed consent and the Lifelines protocol was approved by the UMCG Medical Ethical Committee under number 2007/152. Detailed information on the study design and procedures is available elsewhere (Sijtsma et al., 2022).

#### Phenotype data

We used baseline data collected between 2006 and 2013. Participants completed self-report questionnaires in which they indicated whether they were ever diagnosed with depressive disorder, bipolar disorder, and/or schizophrenia (yes/no). Cardiovascular variables of interest were selected based on previous literature on the association between serious mental illness and CVD as well as practical considerations (i.e. sufficient prevalence in the Lifelines cohort). We included the following CVD traits: self-reported arrhythmia (yes/no), atherosclerosis (yes/no), and heart failure (yes/no), and physically measured systolic blood pressure (mmHg), diastolic blood pressure (mmHg), hypertension (yes/no), electrocardiogram (ECG) measured QTc interval (ms), QRS duration (ms), bundle branch block (yes/no), left ventricular hypertrophy (LVH; yes/no), and heart rate variability (root mean square of the successive differences of inter-beat intervals; RMSSD). Arrhythmia was defined as ever being ever diagnosed by a doctor and/or in the hospital with arrhythmia. Atherosclerosis was defined as reporting to have ever been diagnosed with one of the following conditions: atherosclerosis, high cholesterol, or myocardial infarction. These conditions share pathophysiological mechanisms such as cholesterol deposition, inflammation, and plaque formation, as well as risk factors and overlapping treatment options, which is why we have combined them as part of a unified disease process. Blood pressure was measured automatically using the DinaMap PRO100 or DinaMap PRO100V2, for those participants taking antihypertensive agents systolic and diastolic blood pressure were adjusted by adding 15 mm Hg and 10 mm Hg to their observed values, respectively. Hypertension was defined as systolic blood pressure $\geqslant$ 140 mm Hg and/or diastolic blood pressure $\geqslant$ 90 mm Hg, or use of antihypertensive medication. A variable on medication use was created to indicate whether individuals used any antihypertensive medication (the precise Anatomical Therapeutic Chemical (ATC) codes can be found in the Supplement). Twelve-lead ECG was done in all participants during rest, providing the QTc interval, QRS duration, and information on left ventricular mass indicating left ventricular hypertrophy and the presence of bundle branch block (left or right). The QTc interval represents the total time it takes for the

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electrical activity to move through the ventricles of the heart, including the time it takes for the ventricles to contract and relax (systole and diastole), corrected for heart rate. In extreme cases or susceptible individuals, prolongation of the QTc interval is associated with a condition called Torsades de pointes, which is a type of arrhythmia that can lead to sudden cardiac death (Haddad & Anderson, 2002). The QRS duration represents the time of ventricular depolarization, providing important information about the function of the conduction system of the heart. Heart rate variability was also calculated from ECG signals and expressed as RMSSD (Tegegne, Man, van Roon, Riese, & Snieder, 2018). Demographic (age, gender, educational attainment, and employment status) and lifestyle (psychotropic medication, BMI, physical activity, type 2 diabetes, smoking) variables were self-reported. A variable on medication use was created to indicate whether individuals used any of the following psychotropic medications: antidepressants, mood stabilizers, or antipsychotics (see the Supplement for the ATC codes). BMI was calculated from the measured height and weight. For physical activity, a compiled variable was created that includes the information from the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH), designed to give an indication of the habitual activity level. The SQUASH is composed of four domains: commuting, leisure time, household, and occupational activities. Results from the SQUASH were converted to time (minutes per week) spent in light, moderate, and vigorous activities as described elsewhere (Wendel-Vos, Schuit, Saris, & Kromhout, 2003). Prior to analysis, we standardized all continuous measures by calculating their *Z*-scores. Participants were excluded if they had missing data for the main psychiatric diagnosis variables or if they had missing data for sex.

### Genotype data

DNA was genotyped on three different platforms: the Illumina HumanCytoSNP-12 BeadChip v2 array (GWAS; $n = 15\,011$ participants, European-ancestry), the Illumina global screening array (GSA) Beadchip-24 v1.0 (UGLI; $n = 32\,325$, European-ancestry) and the FinnGen Thermo Fisher Axiom custom array (UGLI2; $n = 29\,166$, European ancestry). If participants were included in more than one sample ($n = 1288$), UGLI2 was given priority over UGLI, and UGLI over GWAS, due to a larger number of SNPs. The total genotype sample was 73 965. A more detailed description can be found in the Supplement.

To compute PGSs we used summary-level data of the largest available GWASs (Howard et al., 2019; Mullins et al., 2021; Trubetskoy et al., 2022), sample sizes are presented in Table 1 and further details in the Supplement.

**Table 1.** Sample sizes of genome-wide association studies included to compute polygenic scores of depressive disorder, bipolar disorder and schizophrenia

| | | Sample size | | Effective sample size |
|---|---|---|---|---|
| | GWAS | *Cases* | *Controls* | |
| Depressive disorder | Howard et al. (2019) | 170 756 | 329 443 | 449 856 |
| Bipolar disorder | Mullins et al. (2021) | 41 917 | 371 549 | 150 670 |
| Schizophrenia | Trubetskoy et al. (2022) | 53 386 | 77 258 | 126 282 |

### Polygenic scores

PGSs were calculated as a weighted sum of the number of risk alleles carried by each individual in the Lifelines cohort; weights are based on effects estimated from the largest available GWASs for each serious mental illness. PGSs were computed in SBLUP, with the settlement under progressively exclusive relationship (SUPER) best linear unbiased prediction (BLUP) approach (Robinson et al., 2017), and expressed as beta/OR per S.D. increase of the PGS. This method maximizes the predictive power of the scores by including all SNPs accounting for linkage disequilibrium (LD) between SNPs. In order to obtain information on LD, we used a random sample of 10 000 unrelated individuals from UK Biobank, imputed using the Haplotype Reference Consortium reference panel (McCarthy et al., 2016). We conducted separate PGS analyses in the three genetic samples, corrected for principal components specific to each sample, to correct for population stratification. Subsequently, we conducted a meta-analysis using the inverse-variance weighted method to combine the results.

### Statistical analyses

We employed linear mixed models to assess associations between mental illness and cardiovascular traits (random intercept for family clusters). Analyses were performed in R version 4.1.2, using the *lme4* package (Bates, Mächler, Bolker, & Walker, 2015) for continuous outcomes and *glmer* for binary outcomes. In model 1a, we used mental illness diagnosis as the independent variable and ran separate analyses with the different cardiovascular traits as dependent variables. Model 1b was adjusted for psychotropic medication use and model 1c for psychotropic medication use plus other relevant confounders. Model 1d included an interaction term between sex and mental illness diagnosis to study sex differences. If there was evidence for interaction, we performed sex-stratified analyses. For the PGS analyses, we employed mixed effects models (models 2a–2d) with mental illness PGS as the independent variable. All models were fitted using restricted maximum likelihood (REML). We made the assumption that missingness was at random, made tenable by including a range of different confounders. For all scripts see https://osf.io/8ey9m/.

We describe findings as showing no clear evidence, weak evidence, evidence, or strong evidence against the null hypothesis, following the broad interpretation of *p* values described by Sterne and Davey Smith (Sterne, Smith, & Cox, 2001). We did not correct for multiple testing explicitly because we analyzed traits for which, a priori, there are plausible biological hypotheses why they are associated and want to avoid appraising the evidence based on an arbitrary threshold.

## Results

The total sample comprised 147 337 individuals (see Fig. 1 for exclusions), of which 132 366 reported never having been diagnosed with a mental illness, 14 735 being diagnosed with depressive disorder, 464 with bipolar disorder, and 130 with schizophrenia. It should be noted that individuals may belong to more than one group if they have multiple diagnoses of these mental disorders (for overlap see online Supplementary Table S1). Descriptive information per diagnosis group is presented in Table 2. The sample consisted of 69 526 family clusters

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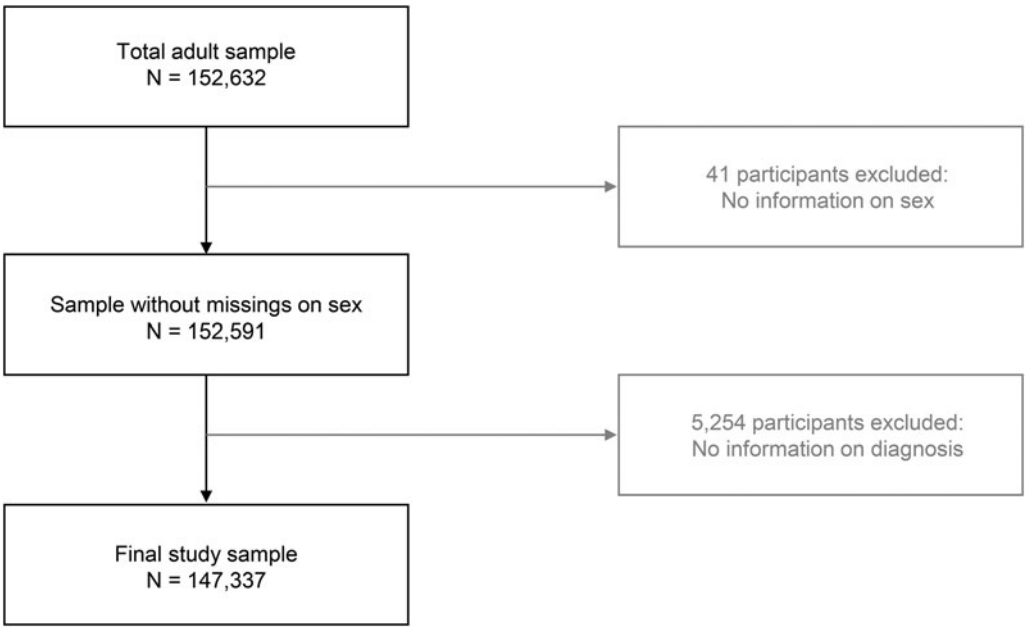


**Figure 1.** Flow diagram of exclusions. Participants without information on mental illness diagnosis or information on sex were excluded.

in total. To confirm the predictive value of the PGSs, we first associated these with all mental illness categories (online Supplementary Table S2). PGSs for depressive disorder, bipolar disorder and schizophrenia were significantly associated with their corresponding disorder (OR 1.30, 95% CI 1.3–1.4, $p = <2.0 \times 10^{-16}$; OR 1.83, 95% CI 1.5–2.2, $p = 1.8 \times 10^{-10}$; OR 2.14, 95% CI 1.4–3.2, $p = 2.1 \times 10^{-4}$, respectively).

Results of the analyses with mental illness diagnoses (models 1a–c) and mental illness PGSs (models 2a–c) are presented in Fig. 2, effect estimates in online Supplementary Tables S3 and S4. Low prevalence of heart failure, bundle branch block, and ECG-voltages LVH precluded us from including these. For the remaining models, the maximum number of missingness per variable was 10%. Some analyses were performed in non-related individuals only ($N = 69\,526$) due to fitting issues with the mixed models, see Supplement for further details.

### Depressive disorder

In the unadjusted analyses (model 1a), there was strong evidence that depressive disorder diagnosis is associated with a lower systolic and diastolic blood pressure (beta = −0.1, 95% CI −0.12 to −0.08, $p = <2.0 \times 10^{-16}$ and beta = −0.04, 95% CI −0.06 to −0.03, $p = 7.5 \times 10^{-7}$, respectively). The effect sizes were robust to correction for psychotropic medication use (model 1b), and other confounders (model 1c). There was strong evidence that depressive disorder is associated with lower heart variability, shorter QRS duration, and longer QTc interval in model 1a, but these associations were strongly attenuated in model 1b for heart rate variability and QTc interval, and in model 1c for QRS duration. Finally, there was strong evidence, across all models, that depressive disorder is associated with a lower risk of hypertension (model 1c OR 0.88, 95% CI 0.84–0.94, $p = 1.7 \times 10^{-5}$), and a higher risk of arrhythmia (OR 1.54, 95% CI 1.43–1.66, $p = <2.0 \times 10^{-16}$), and atherosclerosis (OR 1.23, 95% CI 1.15–1.31, $p = 1.6 \times 10^{-9}$).

For the analyses using a depressive disorder PGS, there was no clear evidence for association with any continuous cardiovascular trait. For the binary outcomes, the PGS analyses confirmed the diagnosis-based analyses with a similar pattern of associations, except for hypertension (model 2c OR 1.00, 95% CI 0.98–1.02, $p = 0.996$).

### Bipolar disorder

There was weak evidence that bipolar disorder diagnosis is associated with lower systolic blood pressure and heart rate variability in model 1a. After adjustment for medication use and other confounders (model 1c), statistical evidence increased for systolic blood pressure (beta = −0.19, 95% CI −0.28 to −0.10, $p = 4 \times 10^{-5}$), while for heart rate variability it disappeared (beta = 0.05, 95% CI −0.08 to 0.18, $p = 0.44$). There was weak evidence that bipolar disorder is associated with a higher QRS duration and QTc interval, which persisted across all models for the former but not for the latter. There was evidence that bipolar disorder is associated with a lower risk of hypertension in the fully adjusted model (OR 0.74, 95% CI 0.57–0.98, $p = 0.032$). Lastly, there was strong evidence that bipolar disorder is associated with arrhythmia (OR 1.72, 95% CI 1.26–2.33, $p = 5.3 \times 10^{-4}$) and atherosclerosis (OR 1.78, 95% CI 1.40–2.26, $p = 2.3 \times 10^{-6}$), but these associations were strongly attenuated in model 1b and (almost) disappeared in model 1c.

There was no clear evidence that the bipolar disorder PGS is associated with any continuous cardiovascular trait. There was evidence that the PGS for bipolar disorder is associated with a higher risk of atherosclerosis (OR 1.04, 95% CI 1.01–1.06, $p = 0.010$), which was not markedly attenuated in models 2b and 2c.

### Schizophrenia

There was evidence that schizophrenia diagnosis is associated with lower systolic blood pressure in the fully adjusted model (beta = −0.24, 95% CI −0.41 to −0.06, $p = 0.008$). There was

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**Table 2.** Descriptive statistics for socio-demographic variables, life style related confounders, and cardiovascular disease (risk) outcomes, stratified on groups without any diagnosis, a diagnosis of depressive disorder, bipolar disorder, or schizophrenia

| | No diagnosis ($n$ = 132 366) | Depressive disorder ($n$ = 14 735) | Bipolar disorder ($n$ = 464) | Schizophrenia ($n$ = 130) |
|---|---|---|---|---|
| Socio-demographic variables | | | | |
| Age in years (mean (s.d.), min – max) | 44.2 (12.9), 18–93 | 44.4 (11.4), 18–88 | 46.4 (10.6), 19–83 | 41.9 (9.9), 19–74 |
| Gender ($n$ (%) female) | 75 590 (57%) | 10 610 (72%) | 289 (62%) | 49 (38%) |
| Educational attainment | | | | |
| Low ($n$ (%)) | 38 110 (30%) | 4817 (33%) | 154 (34%) | 57 (45%) |
| Middle ($n$ (%)) | 52 236 (40%) | 6087 (42%) | 188 (41%) | 47 (37%) |
| High ($n$ (%)) | 40 456 (31%) | 3657 (25%) | 117 (26%) | 24 (19%) |
| Employment status ($n$ (%) employed) | 104 899 (80%) | 10 015 (70%) | 231 (52%) | 47 (39%) |
| Lifestyle-related factors | | | | |
| BMI (mean (s.d.), min – max) | 26.0 (4.3), 13.4–66.3 | 26.5 (4.9), 14.4–73.6 | 27.2 (4.9), 17.0–48.7 | 27.8 (5.3), 17.2–44.8 |
| Minutes per week of moderate to vigorous physical activity (mean (s.d.), min – max) | 692.7 (839.5), 0–7170 | 588.7 (743.7), 0–6840 | 542.7 (696.9) 0–4155 | 522.1 (646.2), 0–3570 |
| Type 2 diabetes ($n$ (%)) | 3028 (2.3%) | 474 (3.2%) | 27 (5.8%) | <10 (<8%) |
| Current smokers ($n$ (%)) | 25 881 (19.6%) | 4219 (28.6%) | 168 (36.2%) | 55 (42.3%) |
| Ever smokers ($n$ (%)) | 66 539 (50.3%) | 8881 (60.2%) | 304 (65.6%) | 89 (68.5%) |
| Pack years of smoking (mean (s.d.), min – max) *all* | 5.9 (9.7), 0–150 | 8.8 (11.6), 0–97 | 11.9 (14.0), 0–73 | 15.0 (16.4), 0–80 |
| Pack years of smoking (mean (s.d.), min – max) *smokers only* | 11.5 (10.8), 0.03–150 | 14.0 (11.9), 0.03–97 | 17.6 (13.8), 0.05–73 | 20.7 (15.9), 0.9–80 |
| Antipsychotic use ($n$ (%)) | 170 (0.1%) | 491 (3.3%) | 126 (27%) | 96 (74%) |
| Lithium use ($n$ (%)) | 13 (0.01%) | 98 (0.6%) | 133 (29%) | <10 (<8%) |
| Antidepressant use ($n$ (%)) | 3102 (2.3%) | 4661 (32%) | 155 (33%) | 37 (29%) |
| Cardiovascular disease (risk) outcomes | | | | |
| Diastolic blood pressure in mmHg (mean (s.d.), min – max) | 74.8 (10.3), 35–153 | 74.4 (10.4), 47–130 | 75.6 (10.3), 53–122 | 75.5 (9.8), 54–110 |
| Systolic blood pressure in mmHg (mean (s.d.), min – max) | 127.2 (16.9), 71–258 | 125.5 (16.8), 79–233 | 126.3 (16.6), 94–205 | 125.6 (15.8), 94–191 |
| Hypertension ($n$ (%)) | 33 377 (25%) | 3599 (24%) | 127 (27%) | 26 (20%) |
| HRV (mean (s.d.), min – max) | 3.7 (2.9), 0.1–43.5 | 3.4 (2.8), 0.1–42.2 | 3.3 (2.7), 0.3–26.4 | 2.8 (2.4), 0.5–17.2 |
| Arrhythmia ($n$ (%)) | 9445 (7.1%) | 1636 (11%) | 56 (12.1%) | 13 (10%) |
| Atherosclerosis ($n$ (%)) | 17 391 (13%) | 2377 (16%) | 97 (21%) | 30 (23%) |
| Heart failure ($n$ (%)) | 910 (0.7%) | 121 (0.8%) | <10 (<2%) | <10 (<8%) |
| QTc interval (mean (s.d.), min – max) in ms | 409.1 (18.3), 256–609 | 409.6 (18.0), 343–576 | 411.2 (17.7), 356–476 | 409.2 (22.4), 366–490 |
| QRS duration (mean (s.d.), min – max) in ms | 94.7 (13.2), 57–298 | 93.1 (12.8), 54–219 | 95.7 (12.9), 71–167 | 96.2 (15.0), 65–190 |
| Bundle branch block, left or right ($n$ (%)) | 1403 (1.1%) | 138 (1.0%) | <10 (<2%) | <10 (<8%) |
| ECG – voltages LVH ($n$ (%)) | 780 (0.6%) | 74 (0.5%) | <10 (<2%) | 0 (0.0%) |

Note: All results reporting numbers below 10 were not specified for privacy reasons, as this might identify certain participants. Note that sample sizes vary per variable due to missing data. For the relationships that we analyzed with linear mixed models, the maximum number of missingness per variable was 10%.

strong evidence that schizophrenia diagnosis is associated with a lower heart rate variability (beta = −0.31, 95% CI −0.53 to −0.08, $p = 0.007$) in model 1a, but correcting for psychotropic medication led to a strong attenuation of the association. None of the other continuous cardiovascular traits showed clear evidence for association. There was evidence that a diagnosis of schizophrenia is associated with a higher risk of atherosclerosis in model 1a (OR 1.99, 95% CI 1.28–3.08, $p = 0.002$), but the effect size was attenuated and statistical evidence weakened in model 1b.

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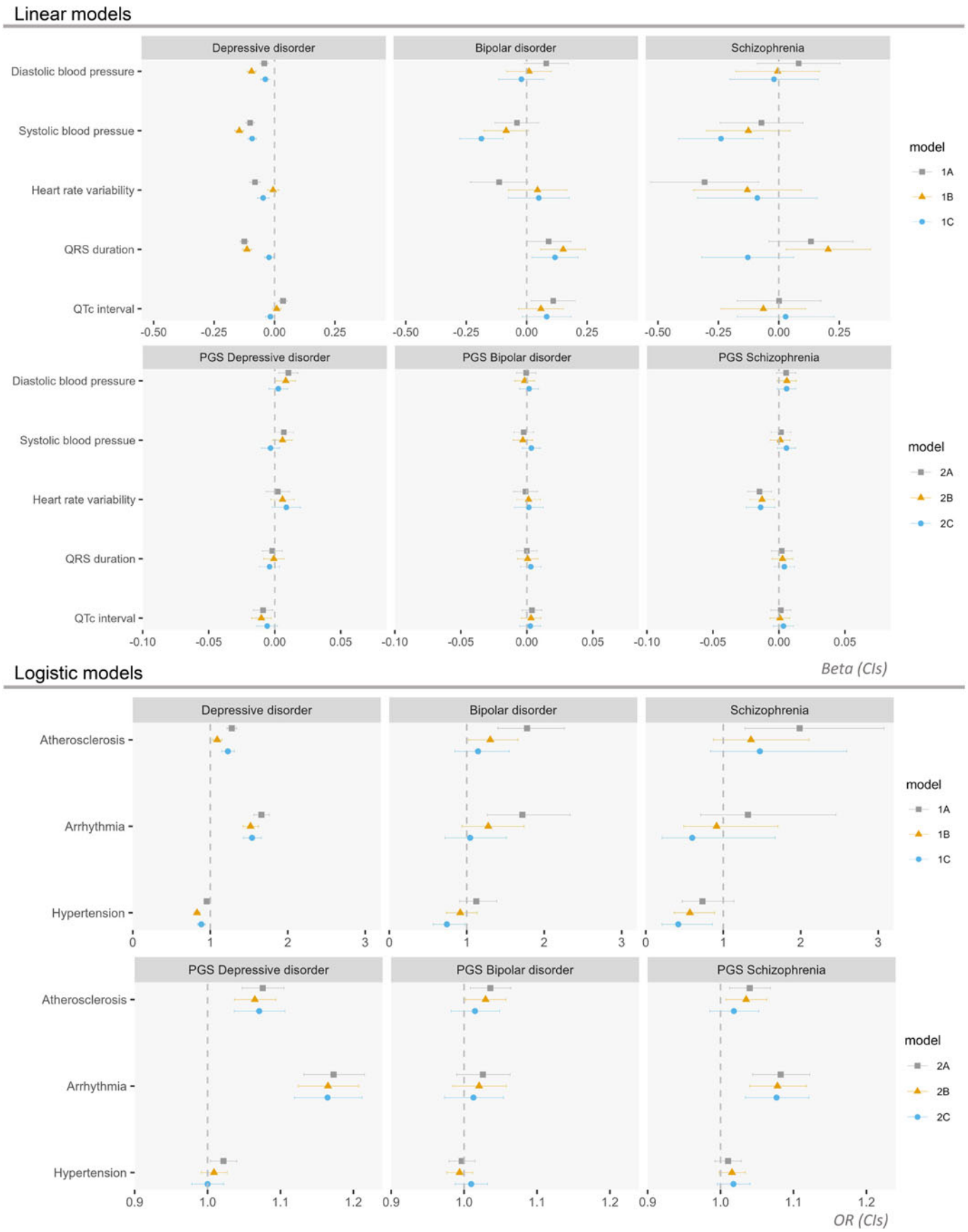


**Figure 2.** Results of linear mixed effects analyses with mental illness diagnosis (models 1) or mental illness PGS (models 2) as the independent variable and cardiovascular disease traits as the outcome variables. The effect estimates are provided as beta coefficients or odds ratios (OR) with 95% confidence intervals. The results are presented for models unadjusted for potential confounders (model a), adjusted for psychotropic medication use (model b), and adjusted for psychotropic medication use + other confounders (model c).

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There was evidence that the schizophrenia PGS is associated with a lower heart rate variability in model 2a (beta = −0.01, 95% CI −0.02 to −0.006, $p = 0.001$), persisting after correcting for all confounders. There was no clear evidence of association for any other continuous measure. Across all models, there was strong evidence that the schizophrenia PGS is associated with a higher risk of arrhythmia (model 2c: OR 1.08, 95% CI 1.03–1.12, $p = 3.3 \times 10^{-4}$). There was also evidence that the PGS for schizophrenia is associated with a higher risk of atherosclerosis in model 2a (OR 1.04, 95% CI 1.01–1.07, $p = 0.004$), which was not affected by adjustment for psychotropic medication use, but strongly attenuated after adjustment for other confounders. The PGS analyses did not confirm the diagnosis-based analyses for the association of schizophrenia with lower blood pressure and lower risk of hypertension.

### Sex differences

There was evidence for sex differences for the relationships of depressive disorder diagnosis with systolic blood pressure (negative), diastolic blood pressure (negative interaction), QTc interval (positive) and arrhythmia (negative; online Supplementary Table S5). A positive interaction indicates that the relationship is stronger for women than for men, a negative interaction the reverse. The most marked difference was seen for diastolic blood pressure, where the negative association with depressive disorder was only present in women (beta = −0.05, 95% CIs −0.07 to −0.03, $p = 2.7 \times 10^{-6}$) and not in men (beta = $-1.5 \times 10^{-3}$, 95% CI −0.04 to 0.03, $p = 0.933$); all stratified analyses are shown in online Supplementary Table S2.

## Discussion

We investigated associations of a diagnosis of depressive disorder, bipolar disorder, and schizophrenia, and a higher genetic liability, with a wide range of cardiovascular traits in a population-based cohort. Our results show that both a diagnosis of depressive disorder and a higher genetic liability were strongly associated with a higher risk of CVD, even after correcting for psychotropic medication use, demographics, and health behaviors. For diagnosed bipolar disorder there were fewer associations, most of which were attenuated after confounder adjustment, as was the case for genetic liability to bipolar disorder. Notably, all mental illness diagnoses were associated with a lower blood pressure and a lower risk of hypertension. While genetic liability to schizophrenia was strongly associated with a higher risk of arrhythmia, and associated with lower heart variability, self-reported diagnosis was not.

An important conclusion that can be made based on our study is that psychotropic medication use, demographics, and health behaviors contribute to the increased CVD risk in mental illness patients. For most relationships, psychotropic medication use alone greatly attenuated the association, with other confounders having little additional influence. This pattern was also seen in outcomes involved in cardiac electrical signaling (QRS duration, QTc interval, heart rate variability). There were some exceptions, like the association with arrhythmia that persisted after adjustment, particularly for depression. People with both a diagnosis of depressive disorder, as well as a higher genetic liability, also had a much higher risk of atherosclerosis, even after confounders were corrected for. This finding is in line with studies showing altered inflammatory markers (involved atherosclerosis development) among people with depression, independent of psychotropic medication use (Morch et al., 2019; Pillinger et al., 2019). While the analyses that we conducted cannot establish causality, we recently investigated the relation between schizophrenia and CVD using Mendelian randomization (MR), a causal inference method. We found robust evidence for a causal effect of schizophrenia on heart failure (Veeneman et al., 2021). Others found evidence for causal effects of depressive disorder on coronary artery disease and stroke (Zhang, Cao, & Baranova, 2021). Overall, these findings emphasize that we must look beyond psychotropic medication and health behaviors, and focus on potential causal pathways, such as dysfunction of the hypothalamic–pituitary–adrenal axis and autonomic nervous system activity, inflammation and oxidative stress (Bernardi, Aromolaran, & Aromolaran, 2021). If a causal relation is present, more effective treatment of mental illness will also benefit patients' cardiovascular health, which is sorely needed in order to lower cardiovascular mortality in this vulnerable population. To unravel the full causal pathway between mental illness and CVD additional causally-informative and (longitudinal) studies are needed.

Interestingly, the results of our study show associations of mental illness (most strongly depressive disorder) with a lower blood pressure and a lower risk of hypertension. While the most presumed hypothesis is that mental illness is associated with an increased blood pressure (Goldstein et al., 2015) some previous studies have found results similar to ours (Hildrum, Romild, & Holmen, 2011; Licht et al., 2009). One possible explanation is that the increased risk of depression and low blood pressure is due to a common underlying factor with opposing effects – a potential candidate being the central monoamine system and neuropeptide Y (associated with sympathetic activity and vascular regulation) (Hildrum et al., 2011; Licht et al., 2009). Another possibility is that chronic low blood pressure leads to psychological discomfort, through fatigue and somatic symptoms, and eventually depressive symptoms (Paterniti, Verdier-Taillefer, Geneste, Bisserbe, & Alpérovitch, 2000). Taken together, our findings suggest that higher blood pressure may not contribute to the increased CVD risk in serious mental illness patients, but, longitudinal research is needed to confirm this.

We demonstrated sex differences in the relationship between depressive disorder and CVD, mainly in detriment of women, confirming the importance of sex-specific prevention efforts among patients with serious mental illness (Ortiz et al., 2022). CVD and mental illness express differently in men and women, with differing patterns of side effects from psychotropic medication and prevalence of lifestyle factors (Gobinath, Choleris, & Galea, 2017). It should furthermore be noted that while genetic liability to depressive disorder and schizophrenia were associated with arrhythmia, genetic liability to bipolar disorder was not. This is remarkable considering the overlap in symptoms and PGSs (online Supplementary Table S4), but may be explained by the fact that the PGS for bipolar disorder was based on the GWAS with the smallest number of cases. Finally, there was a distinct association between the PGS for schizophrenia and lower heart rate variability, which is in line with previous research showing cardio-metabolic adversities (including lower heart rate variability) in first-episode, drug-naïve patients with schizophrenia (Ryan, Collins, & Thakore, 2003), and in their healthy first-degree relatives (Bär, 2015). The fact that the self-reported diagnosis was not associated with a higher risk of CVD, could be the result of low prevalence of schizophrenia diagnosis in the cohort, and thus insufficient power.

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Key strengths of our study are the large and richly phenotyped study population, our use of sophisticated mixed models incorporating a comprehensive list of relevant confounders, and our inclusion of both diagnosis-based and PGS-based analyses. There are also limitations to acknowledge. First, the cross-sectional design did not allow us to infer causality as inverse causation and residual confounding may be present. Second, since the total number of bipolar disorder and schizophrenia cases was low, we had insufficient power for certain analyses (heart failure, bundle branch block and ECG-voltages LVH, and sex interactions). Third, a potential limitation of our study is that the mental illness diagnoses and certain cardiovascular outcomes, such as arrhythmia, atherosclerosis, and heart failure, relied on self-reported data, which might introduce inaccuracies. Furthermore, the possibility of recall bias could have influenced the reporting of these outcomes. Fourth, the outcome arrhythmia was limited by its lack of specificity, as we were not able to identify different types of arrhythmias. Fifth, external validity may be compromised as patients who enrolled into Lifelines represent a biased selection of a relatively healthy subpopulation. This is a well-known limitation of population-based cohort studies (Schoeler et al., 2023). It may especially have impacted the analyses looking at schizophrenia, as the participants in this study who self-reported to have a schizophrenia diagnosis are likely to represent a high-functioning group with illness insight. Schizophrenia patients with more severe impairments in daily functioning are less likely to have participated. This limits the findings' generalizability for self-reported diagnosis outcomes, but less so for genetic vulnerability to schizophrenia. However, the impact of the recruitment strategy on the representativeness of the Lifelines population has been demonstrated to be minor (Klijs et al., 2015), indicating that the population is broadly representative for the adult population of the north of the Netherlands. Sixth, Lifelines mostly includes people of Dutch ancestry, limiting generalizable to other nationalities.

In summary, we present evidence for widespread associations between a diagnosis of mental illness (primarily depressive disorder), as well as genetic liability to mental illness, and CVD. While some associations are partly or fully attenuated when correcting for psychotropic medication use and health behaviors, others are consistent and robust to adjustment. This underlines the urgency of research focusing not only on modifiable risk factors, but also on potential causal effects between mental illness and CVD. This is acutely needed given the ongoing and serious challenge presented by the high CVD burden and mortality among patients with mental illness (Goldfarb et al., 2022).

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002635.

**Data availability statement.** Data are not publicly available as restrictions apply to the availability of these data, which were used under license for this study. The data that support the findings of this study are available on request from Lifelines (see: https://www.lifelines.nl/researcher). Full scripts are available (https://osf.io/8ey9m/).

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**Competing interest.** None.

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