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ORIGINAL RESEARCH

Association Between ECG Abnormalities and Fatal Cardiovascular Disease Among Patients With and Without Severe Mental Illness

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BACKGROUND: ECG abnormalities are associated with adverse outcomes in the general population, but their prognostic significance in severe mental illness (SMI) remains unexplored. We investigated associations between no, minor, and major ECG abnormalities and fatal cardiovascular disease (CVD) among patients with SMI compared with controls without mental illness.

METHODS AND RESULTS: We cross-linked data from Danish nationwide registries and included primary care patients with digital ECGs from 2001 to 2015. Patients had SMI if they were diagnosed with schizophrenia, bipolar disorder, or severe depression before ECG recording. Controls were required to be without any prior mental illness or psychotropic medication use. Fatal CVD was assessed using hazard ratios (HRs) with 95% CIs and standardized 10-year absolute risks. Of 346 552 patients, 10 028 had SMI (3%; median age, 54 years; male, 45%), and 336 524 were controls (97%; median age, 56 years; male, 48%). We observed an interaction between SMI and ECG abnormalities on fatal CVD ($P<0.001$). Severe mental illness was associated with fatal CVD across no (HR, 2.17; 95% CI, 1.95–2.43), minor (HR, 1.90; 95% CI, 1.49–2.42), and major (HR, 1.40; 95% CI, 1.26–1.55) ECG abnormalities compared with controls. Across age- and sex-specific subgroups, SMI patients with ECG abnormalities but no CVD at baseline had highest standardized 10-year absolute risks of fatal CVD.

CONCLUSIONS: ECG abnormalities conferred a poorer prognosis among patients with SMI compared with controls without mental illness. SMI patients with ECG abnormalities but no CVD represent a high-risk population that may benefit from greater surveillance and risk management.

Key Words: ECG ■ primary care ■ risk prediction ■ severe mental illness

Patients with severe mental illness (SMI) comprising schizophrenia, bipolar disorder, and severe depression have excess cardiovascular risk and a reduced life expectancy of ≈20 years compared with the general population.[1–3] The mortality risk of cardiovascular disease (CVD), such as myocardial infarction, is 30% to 40% among these patients compared with 10% to 15% in the general population.[4] Although several reasons may explain differences in outcomes, patients with SMI are overall less likely to receive timely and proper medical care, including invasive coronary management, and tend to neglect cardiovascular symptoms such as chest pain, palpitations, or presyncope.[5,6] Therefore, there is a significant interest in early detection of subclinical CVD and its outcomes among patients with SMI.

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CLINICAL PERSPECTIVE

What Is New?

- Both minor (eg, QT prolongation) and major (eg, Q waves) ECG abnormalities conferred a poorer prognosis among patients with severe mental illness compared with controls without any prior mental illness or psychotropic medication use.
- Patients with severe mental illness and ECG abnormalities but no cardiovascular disease at baseline had a higher 10-year absolute risk of fatal cardiovascular disease relative to if the patient did not have either ECG abnormalities or severe mental illness.

What Are the Clinical Implications?

- Patients with severe mental illness have excess cardiovascular morbidity and mortality.
- Early detection of ECG abnormalities may offer a simple way to identify patients with severe mental illness at greater cardiovascular risk.

Nonstandard Abbreviations and Acronyms

SMI	severe mental illness

The ECG remains a readily available and inexpensive tool to assess cardiovascular risk and preexisting CVD. Although prior studies have demonstrated that commonly encountered ECG abnormalities predict adverse outcomes in the general population,[7–12] there are no published data on the prognostic significance of ECG abnormalities among patients with SMI. Recent work from our group suggests that these patients more often demonstrate elevated heart rate, corrected QT prolongation, and Q waves as a sign of prior myocardial infarction, and less left ventricular hypertrophy and atrial fibrillation/flutter on ECGs compared with background population controls.[13]

Therefore, using a large contemporary clinical laboratory database including nearly 1 million digital ECGs cross-linked with Danish nationwide administrative registries, we investigated the association between ECG abnormalities and fatal CVD among patients with SMI compared with controls without any prior mental illness or psychotropic medication use. Considering the higher prevalence of CVD and overrepresentation of certain ECG abnormalities among patients with SMI, we hypothesized that risk prediction incorporating the ECG may be useful in this vulnerable population.

METHODS

Data were obtained from Danish nationwide administrative registries, which were available on a Statistics Denmark server through remote access. The authors declare that all supporting data are available within the article and its online supplementary files.

Study Design and Population

This was a registry-based retrospective cohort study including patients with their latest available digital ECG recorded between January 1, 2001, and December 31, 2015, at the Copenhagen General Practitioners' Laboratory in Denmark. The index date was the day of ECG recording. The central core facility serviced primary care and specialty outpatient clinics including psychiatry, with various clinical examinations such as ECG recordings, as described previously.[14]

Patients were excluded in case of missing data on age or sex or if they were <16 years of age at the index date based on data obtained from the Danish Civil Registration System.[15] Data on vital status were obtained from the Danish Registry of Causes of Death.[16]

SMI Definition

We used the Danish Psychiatric Central Research Registry[17] to identify inpatient or outpatient encounters for schizophrenia (*International Classification of Diseases, Tenth Revision* [*ICD-10*] code: F20), bipolar disorder (*ICD-10* codes: F30–31), or severe depression (*ICD-10* codes: F32.2–.3 and F33.2–.3). If patients had more than one registered SMI diagnosis prior to the index date, patients were assigned to the lowest hierarchical diagnosis code regardless of the date of onset to comply with the diagnostic hierarchical order of the *ICD-10* system.

Patients were assigned as controls if they were without any prior mental illness (*ICD-10* code: F*) and had not filled any prescriptions for psychotropic medications within 180 days prior to the index date, which was identified using Anatomical Therapeutic Chemical codes in the Danish National Prescription Registry.[18]

ECG Abnormalities

All standard 12-lead ECGs were digitally recorded at rest and in the supine position, stored in the MUSE Cardiology Information System (GE Healthcare, Milwaukee, WI, USA), and processed using the Marquette 12SL algorithm version 23.[19] All ECGs have been over read by a consultant cardiologist. Using 12SL algorithm statements, we excluded ECGs of poor quality, ECGs with paced rhythms, or ECGs

unsuitable for further interpretation, as described previously.[13]

We reported data on continuous ECG measurements and defined corrected QT prolongation as >450 ms for males and >470 ms for females using the Fridericia formula.[20] Furthermore, ECG abnormalities were divided into minor (ie, first-degree atrioventricular, incomplete bundle branch, and left fascicular blocks or corrected QT prolongation) and major (ie, left ventricular hypertrophy, atrial fibrillation/flutter, bundle branch block, intraventricular conduction disturbance, Q waves, or ST-T deviations), in accordance with contemporary studies.[7,9] Moreover, we analyzed the heart rate based on cut offs of <60 and >90 beats per minute. When analyzing the association between ECG abnormalities and outcomes, patients with both minor and major ECG abnormalities were assigned as having major ECG abnormalities. Patients without any ECG abnormalities were considered to have no ECG abnormalities. See Table S1 for an overview of criteria used to define ECG abnormalities.

Covariates

We used the Danish National Patient Registry[21] to additionally exclude patients with a prior pacemaker or implantable cardioverter-defibrillator implantation based on either *ICD-10* or Nordic Medico-Statistical Committee Classification of Surgical Procedures codes, whichever came first. The Danish National Patient Registry was also used to identify prior diagnoses of heart failure, coronary artery disease including prior myocardial infarction, atrial fibrillation/flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease. Using Nordic Medico-Statistical Committee Classification of Surgical Procedures codes, we also identified percutaneous coronary intervention or coronary artery bypass grafting for coronary artery disease, ablation for atrial fibrillation/flutter, aortic or mitral valve surgery for valvular heart disease, and renal replacement therapy for chronic kidney disease. We further identified filled prescriptions for cardiovascular medications within 180 days prior to the index date based on Anatomical Therapeutic Chemical codes. Because hypertension, hyperlipidemia, diabetes mellitus, and chronic obstructive pulmonary disease are often managed in primary care, patients may not necessarily have *ICD* codes registered. Accordingly, prior filled prescriptions for antihypertensives (at least dual therapy), lipid-lowering medications, antidiabetics, and β-adrenergic or anticholinergic inhalants were also used to define these conditions. Finally, we used CredibleMeds, an internet-based registry of QT-prolonging medications, to identify medications associated with known or possible QT prolongation risk.[22] See Tables S2 and S3 for an overview of used *ICD*, Nordic Medico-Statistical Committee Classification of Surgical Procedures, and Anatomical Therapeutic Chemical codes.

Outcomes

Patients were followed from the index date until the occurrence of an outcome or censoring in case of emigration or end of study on December 31, 2017, whichever came first. The primary outcome fatal CVD was defined as death from any CVD (*ICD-10* code: I*). We also performed an additional analysis using all-cause mortality as a secondary outcome.

Statistical Analysis

Continuous variables were reported as medians with 25th to 75th percentiles and categorical variables as counts with percentages. Between-group differences were compared using Mann-Whitney *U* and χ^2 tests, as appropriate.

Outcomes were compared between patients with SMI and controls without mental illness, which served as the reference group, across similar levels of ECG abnormalities. Cumulative incidence curves of fatal CVD were generated using the Aalen-Johansen method, with death from other causes being accounted for as a competing risk event, and event distributions were compared using Gray's test. Multivariable Cox regression analysis was used to compute hazard ratios (HRs) with 95% CIs. Furthermore, we performed an additional analysis using a dummy variable that combined SMI status with ECG abnormalities, in which controls without mental illness demonstrating no ECG abnormalities served as the reference. We also performed stratified analyses of subtype of SMI diagnosis and individual ECG abnormalities.

All models were adjusted for age, sex, heart failure, coronary artery disease, atrial fibrillation/flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and QT-prolonging medications.

Due to nonlinearity, age was grouped by quartiles. The proportional hazards assumption was assessed using Martingale residuals and was not violated. Interaction testing was based on introducing an interaction term in a Cox regression model and using a likelihood ratio test to compare this model with another without an interaction term. Specifically, we tested for an interaction between SMI and ECG abnormalities on outcomes.

The time-dependent area under the receiver operating characteristics curve (AUC) was calculated to

assess the added discriminative value of ECG abnormalities to a conventional risk model for the purpose of 10-year risk prediction of fatal CVD.[23] The conventional risk model was based on age, sex, hypertension, hyperlipidemia, diabetes mellitus, and chronic obstructive pulmonary disease. Patients with SMI and controls without mental illness were stratified by the absence/presence of CVD at baseline, and data were split into training (63%) and test (37%) sets using bootstrap cross-validation with 1000 bootstrap samples. Brier scores were calculated to evaluate model calibration.[24] Furthermore, we calculated the standardized 10-year absolute risk of fatal CVD.[24]

Data management and analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A $P<0.05$ was considered statistically significant for all analyses except for during interaction testing where an a prior decision was made to use $P<0.01$ to account for multiple testing.

Ethics

In Denmark, registry-based studies do not require ethical committee approval or individual patient consent if the study is conducted for the sole purpose of statistics and scientific research, as defined in the Data Protection Act. Approval to use the data sources for research purposes was granted by the institute responsible for the data in the Capital Region of Denmark in accordance with the General Data Protection Regulation (approval number: P-2019-533).

RESULTS

Patients and Characteristics

A total of 346 552 patients with digital ECGs were included, of whom 10 028 (3%) had SMI, and 336 524 (97%) were controls without mental illness. See Figure S1 for the flowchart. Patient characteristics are shown in Table 1. The majority of patients with SMI had a diagnosis of schizophrenia (45%). The median age at the time of ECG recording was 54 years (25th–75th percentiles, 42–66 years) among patients with SMI and 56 years (25th–75th percentiles, 41–69 years) among controls without mental illness. Approximately 45% and 48% of patients with SMI and controls without mental illness were male, respectively. Overall, patients with SMI had a higher cardiovascular comorbidity burden and were less likely to fill prescriptions for cardiovascular medications compared with controls without mental illness. Furthermore, 68% of patients with SMI filled prescriptions for QT-prolonging medications,

Table 1. Baseline Characteristics

	Patients With SMI	Controls Without Mental Illness	*P* Value
n	10 028	336 524	NA
Age at ECG recording, y	54 [42–66]	56 [41–69]	<0.001
Male	4464 (44.5)	161 282 (47.9)	<0.001
Subtype of SMI diagnosis		NA	NA
Schizophrenia	4477 (44.6)		
Bipolar disorder	2571 (25.6)		
Severe depression	2980 (29.7)		
SMI duration, y	8 [3–13]	NA	NA
Heart failure	421 (4.2)	10 433 (3.1)	<0.001
Coronary artery disease	888 (8.9)	29 232 (8.7)	0.567
Atrial fibrillation/flutter	424 (4.2)	14 903 (4.4)	0.349
Valvular heart disease	123 (1.2)	3690 (1.1)	0.237
Hypertension	1479 (14.7)	50 432 (15.0)	0.521
Hyperlipidemia	1686 (16.8)	49 201 (14.6)	<0.001
Diabetes mellitus	1222 (12.2)	26 732 (7.9)	<0.001
Chronic obstructive pulmonary disease	1351 (13.5)	29 093 (8.6)	<0.001
Chronic kidney disease	311 (3.1)	6328 (1.9)	<0.001
ACEIs/ARBs	1401 (14.0)	64 743 (19.2)	<0.001
Beta-blockers	765 (7.6)	32 384 (9.6)	<0.001
Diuretics	1467 (14.6)	45 533 (13.5)	0.002
QT-prolonging medications	6819 (68.0)	44 377 (13.2)	<0.001

Data are reported as median (25th–75th percentiles) or n (%). *P* values based on Mann-Whitney *U* and χ^2 tests, as appropriate. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NA, not applicable; and SMI, severe mental illness.

which in most cases were antipsychotics or antidepressants (61%).

ECG characteristics are shown in Table 2. The distribution of ECG abnormalities was overall similar between patients with SMI (no, 73%; minor, 7%; major, 21%) and controls without mental illness (no, 71%; minor, 6%; major, 24%).

See Tables S4 and S5 for patient and ECG characteristics stratified by subtype of SMI diagnosis.

Associations Between SMI, ECG Abnormalities, and Adverse Outcomes

During a median follow-up of 6 years (25th–75th percentiles, 3–10 years), 23% of patients with SMI and 17% of controls without mental illness died, with fatal CVD accounting for 10% among patients with SMI and 8% among controls without mental illness. Across all levels of ECG abnormalities, patients with SMI had the highest rate of fatal CVD ($P<0.001$) (Figure 1).

We observed an interaction between SMI and ECG abnormalities on fatal CVD ($P<0.001$) as well as all-cause mortality ($P<0.001$). Severe mental illness was associated with fatal CVD across no (HR, 2.17; 95% CI, 1.95–2.43), minor (HR, 1.90; 95% CI, 1.49–2.42), and major (HR, 1.40; 95% CI, 1.26–1.55) ECG abnormalities compared with controls without mental illness (Figure 2A). Overall, similar results were observed with all-cause mortality (Figure 2B). Furthermore, when using a dummy variable that combined SMI status and ECG abnormalities,

Table 2. ECG Characteristics

	Patients With SMI	Controls Without Mental Illness	*P* Value
n	10 028	336 524	NA
Heart rate, bpm	75 [66–86]	69 [61–78]	<0.001
Missing	686	30 361	
P-wave duration, ms	108 [100–116]	108 [100–116]	<0.001
Missing	686	30 361	
PR interval, ms	156 [142–172]	156 [144–174]	0.604
Missing	686	30 361	
QRS duration, ms	90 [84–98]	92 [84–100]	<0.001
Missing	686	30 361	
QT interval, ms	388 [366–410]	396 [376–416]	<0.001
Missing	686	30 361	
QTcF interval, ms	417 [404–431]	414 [402–427]	<0.001
Missing	686	30 361	
No ECG abnormality	7295 (72.7)	237 397 (70.5)	<0.001
Minor ECG abnormality	660 (6.6)	18 541 (5.5)	<0.001
First-degree atrioventricular block	384 (3.8)	13 477 (4.0)	0.391
Incomplete bundle branch block	210 (2.1)	8504 (2.5)	0.007
Incomplete right bundle branch block	192 (1.9)	7680 (2.3)	0.016
Incomplete left bundle branch block	18 (0.2)	824 (0.2)	0.227
Left fascicular block	177 (1.8)	4504 (1.3)	<0.001
Left anterior fascicular block	102 (1.0)	2743 (0.8)	0.031
Left posterior fascicular block	75 (0.7)	1761 (0.5)	0.003
QTcF prolongation	324 (3.2)	5831 (1.7)	<0.001
Major ECG abnormality	2073 (20.7)	80 586 (23.9)	<0.001
Left ventricular hypertrophy	850 (8.5)	35 832 (10.6)	<0.001
Atrial fibrillation/flutter	234 (2.3)	12 561 (3.7)	<0.001
Bundle branch block	302 (3.0)	11 550 (3.4)	0.024
Right bundle branch block	217 (2.2)	7803 (2.3)	0.326
Left bundle branch block	85 (0.8)	3747 (1.1)	0.014
Intraventricular conduction disturbance	76 (0.8)	2786 (0.8)	0.479
Q waves	541 (5.4)	17 064 (5.1)	0.152
ST-T deviations	381 (3.8)	15 283 (4.5)	<0.001

Data are reported as median (25th–75th percentiles) or n (%). *P* values based on Mann-Whitney *U* and χ^2 tests, as appropriate. bpm indicates beats per minute; QTcF, Fridericia-corrected QT; and SMI, severe mental illness.

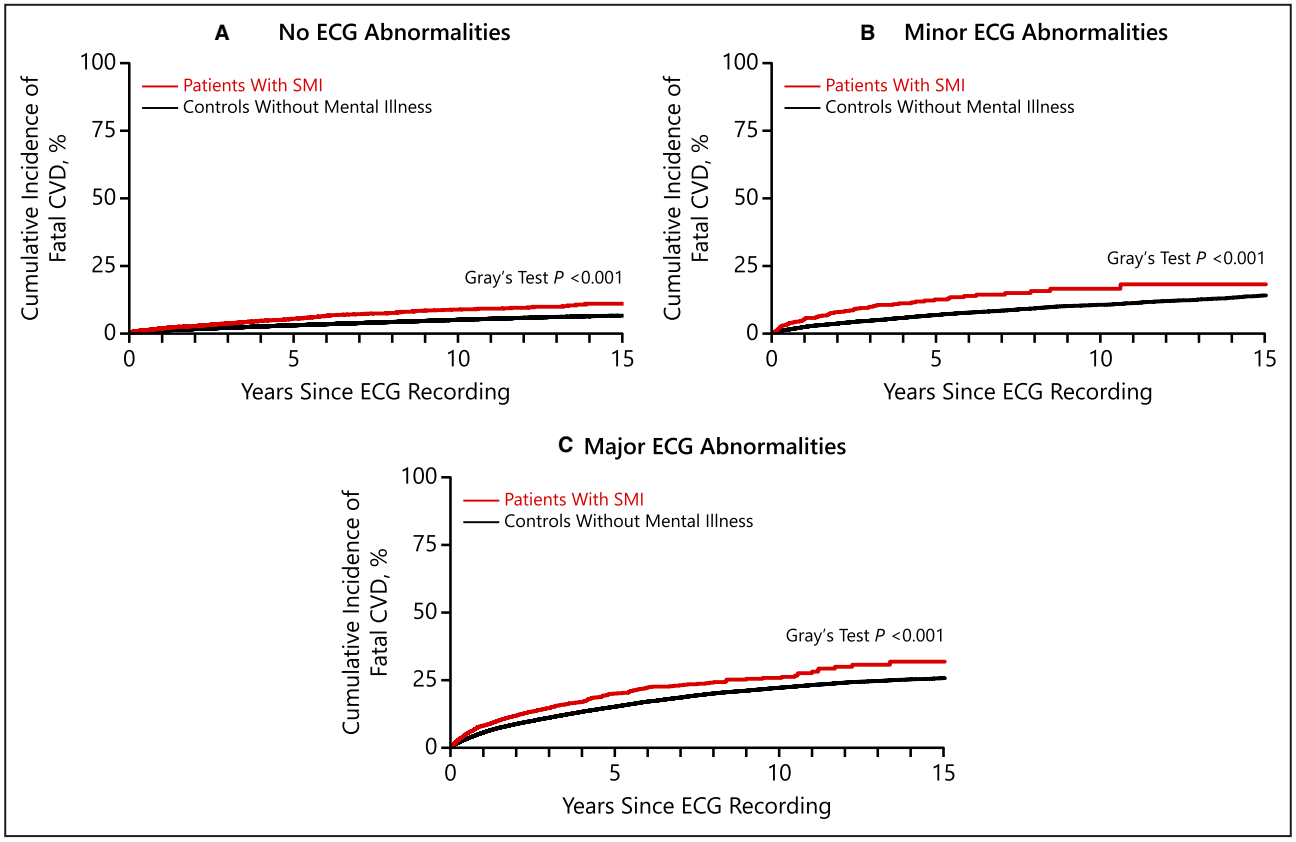

Figure 1. Cumulative incidence curves of fatal CVD among patients with SMI and controls without mental illness across no (A), minor (B), and major (C) ECG abnormalities.
CVD indicates cardiovascular disease; and SMI, severe mental illness.

fatal CVD rate was increased among patients with SMI demonstrating no (HR, 2.11; 95% CI, 1.89–2.35), minor (HR, 2.78; 95% CI, 2.22–3.48), or major (HR, 3.23; 95% CI, 2.91–3.58) ECG abnormalities compared with controls without mental illness demonstrating no ECG abnormalities. Similar but less pronounced rates were observed among controls without mental illness demonstrating minor (HR, 1.37; 95% CI, 1.30–1.45) or major (HR, 2.26; 95% CI, 2.20–2.33) ECG abnormalities (Figure S2A). As in the main analysis, similar results were obtained with all-cause mortality (Figure S2B).

When stratifying by subtype of SMI diagnosis, the interaction was driven by schizophrenia (P<0.001) rather than bipolar disorder (P=0.628) or severe depression (P=0.150), and patients with schizophrenia also had the worst prognosis (Figure S3).

Most of the individual minor and major ECG abnormalities as well as heart rate <60 or >90 beats per minute conferred a poorer prognosis among patients with SMI compared with controls without mental illness (Figure 3). In particular, an increased rate of fatal CVD was associated with patients with SMI demonstrating incomplete bundle branch block (HR, 2.29; 95% CI, 1.47–3.56), intraventricular conduction disturbance (HR, 2.00; 95% CI, 1.15–3.47), heart rate <60 beats per minute (HR, 1.64; 95% CI, 1.20–2.24), Q waves (HR, 1.57; 95% CI, 1.28–1.94), or heart rate >90 beats per minute (HR, 1.50; 95% CI, 1.25–1.79).

10-Year Risk Prediction

Adding ECG abnormalities to a conventional risk model increased the AUC for the 10-year risk prediction of fatal CVD only among the subset of patients with SMI without CVD at baseline (difference in AUC, 2.33%; 95% CI, 0.17%–4.18%). No model improvement was observed among the subset of patients with SMI and CVD at baseline. Contrarily, model improvement was observed among controls without mental illness regardless of baseline CVD status. See Figure S4 and Table S6 for AUC results including Brier scores.

As model improvement with ECG abnormalities was most pronounced in the non-CVD population, we calculated the standardized 10-year absolute risk of fatal CVD for levels of ECG abnormalities stratified by age groups, sex, and SMI status, as shown in Figure 4. Patterns of increasing risk with minor and major ECG abnormalities were observed among patients with SMI.

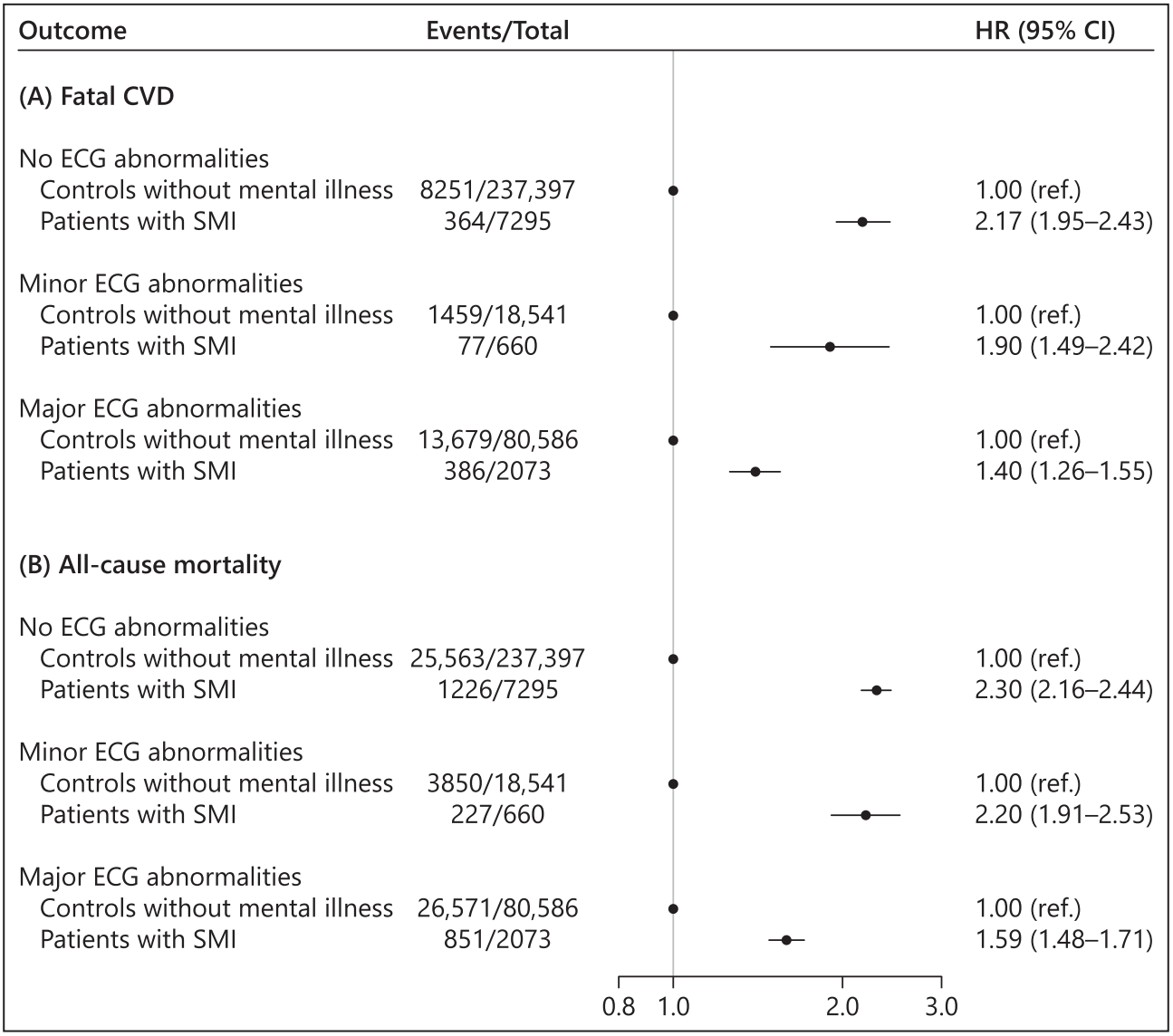

Figure 2. Multivariable Cox regression of the association between SMI and fatal CVD (A) and all-cause mortality (B) across no, minor, and major ECG abnormalities.

Adjusted for age, sex, heart failure, coronary artery disease, atrial fibrillation/flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and QT-prolonging medications. CVD indicates cardiovascular disease; HR, hazard ratio; and SMI, severe mental illness.

DISCUSSION

In this large-scale study, we report several key findings underscoring a differential association between ECG abnormalities and adverse outcomes among primary care patients with SMI compared with controls without mental illness. First, patients with SMI demonstrating minor or major ECG abnormalities had a poorer prognosis compared with the control group. Second, we observed clinically relevant differences in fatal CVD associated with individual ECG abnormalities among patients with SMI, where particularly incomplete bundle branch block, intraventricular conduction disturbance, and Q waves conferred a poorer prognosis. Finally, among patients with SMI but no CVD at baseline, adding ECG abnormalities to a conventional risk model improved 10-year risk prediction of fatal CVD.

Several prior studies have reported associations between minor and major ECG abnormalities and adverse outcomes,[7–12] and the magnitude of risk associated with abnormal ECGs varied across different populations. This is emphasized in clinical guideline recommendations for the utilization of the ECG as a screening tool among asymptomatic adults.[25,26] However, considering that the distribution of ECG abnormalities varies among

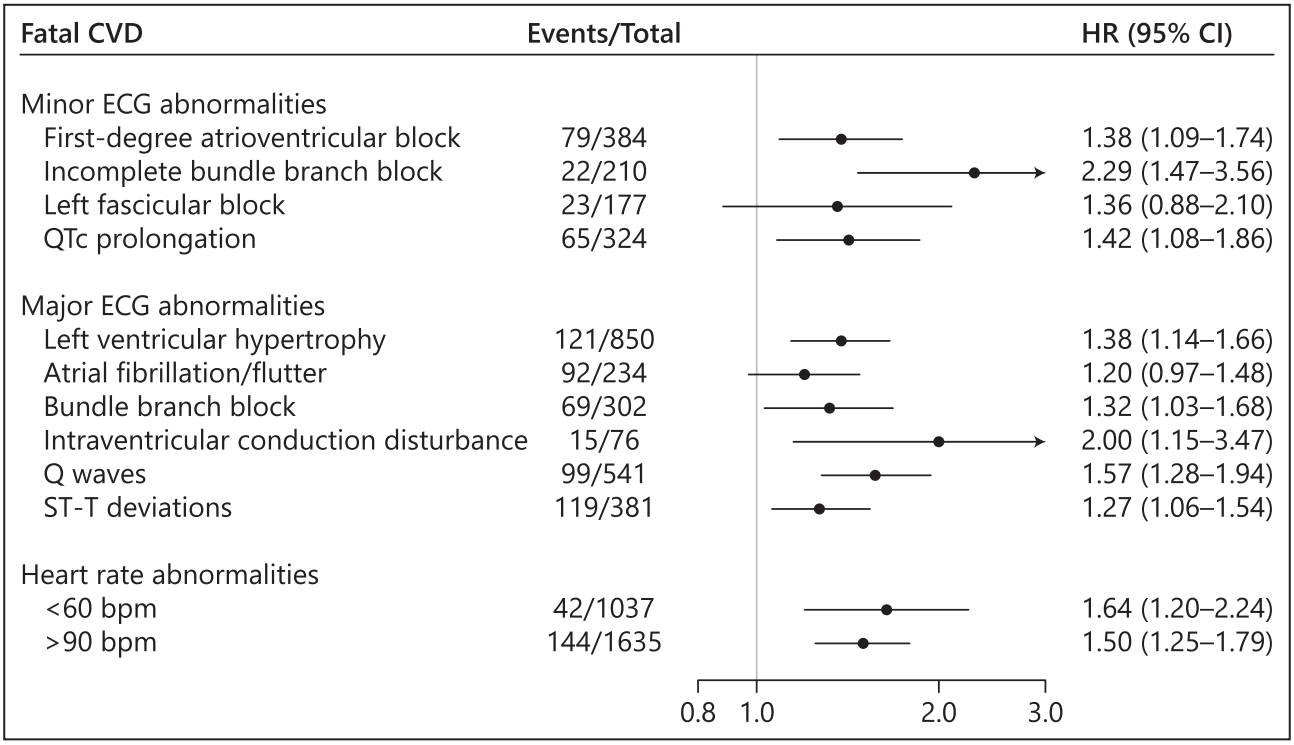

Figure 3. Multivariable Cox regression of the association between individual ECG abnormalities and fatal CVD for patients with SMI compared with controls without mental illness.
Adjusted for age, sex, heart failure, coronary artery disease, atrial fibrillation/flutter, valvular heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, and QT-prolonging medications. bpm indicates beats per minute; CVD, cardiovascular disease; HR, hazard ratio; QTc, corrected QT; and SMI, severe mental illness.

patients with SMI compared with a psychiatrically healthy population,[13] and that no studies have investigated their prognostic significance, evidence to suggest clear clinical ECG recommendations in the setting of SMI is lacking. This underscores the importance of our comprehensive study and adds to the evidence of the potential benefit of the ECG as a cardiovascular risk stratification tool among patients with SMI. However, the optimal frequency and cost-effectiveness of using the ECG to screen for CVD during routine clinical care of patients with SMI need to be explored.

Our finding of an association between ECG abnormalities and adverse outcomes that was particularly important among patients with SMI, as identified by interaction testing, has been underrecognized and not previously described. Moreover, considering the excess cardiovascular morbidity and mortality as well as poor cardiovascular care across other mental illnesses and patients treated with psychotropic medications only,[27] ECG abnormalities may also prove valuable in assessing cardiovascular risk among these patients. However, further studies are warranted to explore this. Although several common major ECG abnormalities conferred a poorer prognosis among patients with SMI in our study, clinicians should also pay attention to those who are demonstrating minor ECG abnormalities, as they are at high cardiovascular risk. Overall, this suggests that CVD may have a more severe course in the setting of SMI, which may be due to a multifactorial interplay of genetic risk, immune system alterations, unhealthy lifestyle, adverse effects of psychotropic medications, lack and neglect of timely cardiovascular care, cognitive impairment, and social deprivation.[1,28] Furthermore, a majority of patients with SMI experience sudden cardiac death as the first manifestation of CVD.[29] In most cases, this may be due to undetected or silent myocardial infarction, as identified by Q waves on the ECG, which occurs in up to 75% of patients with schizophrenia.[30] In our recent work, we observed an overrepresentation of Q waves among patients with SMI compared with a psychiatrically healthy population,[13] and the current study demonstrated that Q waves are not only more prevalent but also associated with an increase in mortality over time (HR of 1.57).

Contemporary risk prediction algorithms for CVD have been shown to underestimate the risk among patients with SMI.[31] Accordingly, to assess if ECG abnormalities improved risk prediction on an individual level compared with a conventional risk model, we calculated measures of discrimination of 10-year risk of fatal CVD and observed improvement with ECG abnormalities in the AUC by ≈2% points among patients with

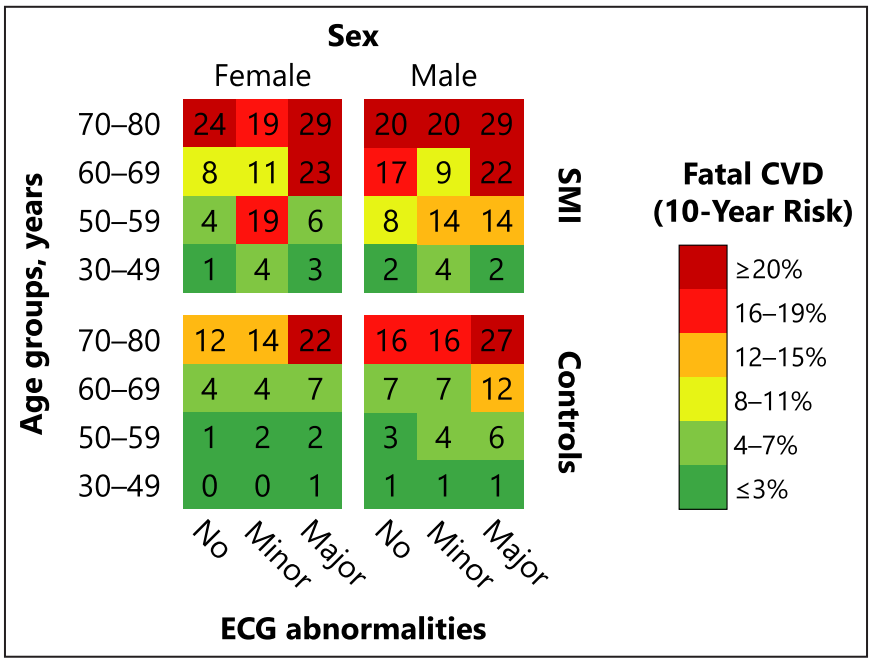

Figure 4. Risk chart showing the standardized 10-year absolute risk of fatal CVD among patients with SMI and controls without mental illness free of CVD at baseline across ECG abnormalities and age- and sex-specific subgroups.
CVD indicates cardiovascular disease; and SMI, severe mental illness.

SMI but no CVD at baseline. Furthermore, ECG abnormalities conferred very high standardized 10-year absolute risks of fatal CVD. For example, we predicted a 55-year-old female with SMI but no CVD at baseline who demonstrated a minor ECG abnormality to have a 19% 10-year absolute risk of fatal CVD compared with 4% if she had no ECG abnormality or 1% if she had no SMI. Based on our findings, we suggest that primary care patients with SMI, not already treated for or diagnosed with CVD, merit close monitoring and follow-up, and clinicians should incorporate a multidisciplinary approach to caring for patients with SMI and newly detected ECG abnormalities.

Limitations

Our study has several limitations. Both unmeasured and unknown confounding including cardiovascular symptoms, cardiovascular family history, and lifestyle factors including smoking may affect findings, but such data were not available in our registries. However, we indirectly accounted for smoking by adjusting analyses for a diagnosis of chronic obstructive pulmonary disease or filled prescriptions for inhalants. Furthermore, the use of large sample sizes may reduce variation in data, and by performing several between-group comparisons, statistically significant differences that are not necessarily clinically meaningful may appear. In particular, this was the case with most of the continuous ECG measurements. Although most patients with SMI undergo routine ECG examinations in primary care, particularly for screening for corrected QT prolongation, data on ECG indications were unfortunately not available. However, the proportional hazards assumption was not violated, indicating that the observed associations were not driven by accumulation of events in close proximity to the ECG recording. Finally, fatal CVD was used as our primary outcome, but the number of medicolegal autopsies has decreased over recent years in Denmark. Therefore, in some cases, the cause of death was based on a subjective judgement by clinicians, and caution should be taken when interpreting data. Therefore, we used all-cause mortality as a secondary outcome, which for no ECG abnormalities showed a comparable rate (HR of 2.30) to fatal CVD (HR of 2.17), suggesting that although patients with SMI do not have established risk factors or recognized CVD, they still have excess cardiovascular mortality. For minor and major ECG abnormalities, we observed increased rates of all-cause mortality compared with fatal CVD, suggesting that patients with ECG abnormalities may be more comorbid than if they had a normal ECG and thus have an overall poorer prognosis.

CONCLUSIONS

In a large contemporary primary care population, ECG abnormalities conferred a poorer prognosis among patients with SMI compared with controls without mental illness. SMI patients with ECG abnormalities but no

CVD at baseline represent a high-risk population that may benefit from greater surveillance and cardiovascular risk management.

ARTICLE INFORMATION

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SUPPLEMENTAL MATERIAL

Table S1. Overview of criteria used to define ECG abnormalities.

ECG Abnormalities	Criteria
LVH[32]	Sokolow-Lyon criteria: S wave in lead V1 and R wave in leads V5–V6 (largest) ≥35 mm Cornell voltage criteria: S wave in lead V3 and R wave in lead aVL >28 mm (male) or >20 mm (female) Requiring absence of: RBBB, LBBB, and IVCD
Atrial fibrillation/flutter[19]	Fibrillation or flutter waves with irregular or regular RR intervals, respectively
First-degree AV block[19]	PR interval >200 ms
RBBB[19]	QRS duration >120 ms rSR' pattern in leads V1–V2 S-wave duration >R-wave duration or >40 ms in leads I and V6 Normal R peak in leads V5–V6 but >50 ms in lead V1
Incomplete RBBB[19]	QRS duration <120 ms RBBB pattern
LBBB[19]	QRS duration >120 ms Absent Q waves in leads I and V5–V6 R-wave peak time >60 ms in leads V5–V6 Notched R wave in leads I, aVL, and V5–V6
Incomplete LBBB[19]	QRS duration <120 ms LBBB pattern
LAFB[19]	QRS duration <120 ms Frontal plane axis between –45 and –90 degrees qR pattern in lead aVL R-wave peak time in lead aVL >45 ms
LPFB[19]	QRS duration <120 ms Frontal plane axis between 90 and 180 degrees rS pattern in leads I and aVL qR pattern in leads III and aVF
IVCD	QRS duration >120 ms Requiring absence of: RBBB and LBBB
QTc prolongation[33]	Fridericia-corrected QT interval >450 ms (male) or >470 ms (female)
Q waves[34]	Any Q wave in leads V2–V3 >20 ms or QS complex in leads V2–V3 Q wave ≥30 ms and ≥1 mm or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF) R wave >40 ms in leads V1–V2 and R/S >1 with a concordant positive T wave Requiring absence of: LVH, RBBB, LBBB, and IVCD
ST depression or inverted T waves[34,35]	New horizontal or downsloping ST depression ≥0.5 mm in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF) T-wave inversion >1 mm in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF) with prominent R wave or R/S ratio >1 Requiring absence of (in leads V1–V3): RBBB, LBBB, and IVCD
ST elevation[34,35,36]	New ST elevation at the J point* in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF) with the cut-off levels:

	≥1 mm in all leads other than leads V2–V3, where the following cut-off levels apply: ≥2 mm in male ≥40 years ≥2.5 mm in male <40 years ≥1.5 mm in female regardless of age Requiring absence of (in leads V1–V3): RBBB, LBBB, IVCD

*Criteria for ST elevation were slightly modified as measurement of the ST segment was performed at QRS offset + 1/16 of the average RR interval, known as the STM point in the 12SL algorithm and equivalent to ~80 ms after QRS offset. STM was chosen instead of the J point as a notched or slurred appearance of the terminal QRS complex (i.e. early repolarization) can make it difficult to define the J point.

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; IVCD, intraventricular conduction disturbance; LVH, left ventricular hypertrophy; QTc, corrected QT; RBBB, right bundle branch block; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block.

Table S2. Overview of ICD-8, ICD-10, NCSP, and ATC codes used to identify medical comorbidities, procedures, and cardiovascular medications.

Covariates	ICD-8/-10 Codes	NCSP Codes	ATC Codes
Pacemaker/implantable cardioverter-defibrillator	Z95.0	BFCA–B	
Heart failure	425, 427.0–.1; I11.0, I13.0, I13.2, I42, I50, J81		
Coronary artery disease including myocardial infarction	410–414; I20–25	KFNG0, KFNA–E	
Atrial fibrillation/flutter	427.93–.94; I48	BFFB03–04	
Valvular heart disease	394–396, 424.0–.1; I05–06, I34–35	KFK, KFM	
Hypertension	400–404; I10–15		C02–03, C07–09
Hyperlipidemia	279.00; E78.0–.5		C10
Diabetes	250; E10–14		A10
Chronic obstructive pulmonary disease	490–492; J40–44		R03AC, R03AL, R03AK, R03BB
Chronic kidney disease	250.02, 400.39, 403–404, 581–584, 590.09, 593.20, 753.10–.11, 753.19; I12.0, N02–08, N11–14, N15.8–.9, N16, N18–19, N26, N39.1, M32.1B, Q61, Z99.2	BJFD2	
Diuretics			C03A, C03C, C03EB
ACEIs/ARBs			C09A–D
Beta-blockers			C07

Table S3. Overview of QT-prolonging medications. From https://www.crediblemeds.org/. Up to date as of September 01, 2020.

Overall Classes	Individual Medications	ATC Codes
Alimentary tract and metabolism	Cisapride	A03FA02
	Domperidone	A03FA03
	Ondansetron	A04AA01
	Granisetron	A04AA02
	Tropisetron	A04AA03
	Dolasetron	A04AA04
	Palonosetron	A04AA05
	Eliglustat	A16AX10
Blood and blood-forming organs	Cilostazol	B01AC23
Cardiovascular system	Quinidine	C01BA01
	Procainamide	C01BA02
	Disopyramide	C01BA03
	Hydroquinidine	C01BA13
	Flecainide	C01BC04
	Amiodarone	C01BD01
	Dofetilide	C01BD04
	Ibutilide	C01BD05
	Dronedarone	C01BD07
	Ketanserin	C02KD01
	Sotalol	C07AA07
	Isradipine	C08CA03
	Nicardipine	C08CA04
	Lacidipine	C08CA09
	Bepridil	C08EA02
	Moexipril	C09AA13
	Probucol	C10AX02
Genitourinary system and sex hormones	Mifepristone	G03XB01
	Terodiline	G04BD05
	Tolterodine	G04BD07
	Mirabegron	G04BD12
	Vardenafil	G04BE09
	Alfuzosin	G04CA01
Systemic hormonal preparations	Terlipressin	H01BA04
	Oxytocin	H01BB02
	Carbetocin	H01BB03
	Pasireotide	H01CB05
	Osilodrostat	H02CA02
Antiinfectives	Erythromycin	J01FA01

	Roxithromycin	J01FA06
	Clarithromycin	J01FA09
	Azithromycin	J01FA10
	Telithromycin	J01FA15
	Ofloxacin	J01MA01
	Ciprofloxacin	J01MA02
	Norfloxacin	J01MA06
	Sparfloxacin	J01MA09
	Grepafloxacin	J01MA11
	Levofloxacin	J01MA12
	Moxifloxacin	J01MA14
	Gemifloxacin	J01MA15
	Gatifloxacin	J01MA16
	Telavancin	J01XA03
	Lefamulin	J01XX12
	Fluconazole	J02AC01
	Bedaquiline	J04AK05
	Delamanid	J04AK06
	Clofazimine	J04BA01
	Saquinavir	J05AE01
	Efavirenz	J05AG03
	Rilpivirine	J05AG05
	Lopinavir and ritonavir	J05AR10
Antineoplastic and immunomodulating agents	Fluorouracil	L01BC02
	Capecitabine	L01BC06
	Epirubicin	L01DB03
	Aclarubicin	L01DB04
	Oxaliplatin	L01XA03
	Necitumumab	L01XC22
	Inotuzumab ozogamicin	L01XC26
	Sunitinib	L01XE04
	Sorafenib	L01XE05
	Dasatinib	L01XE06
	Lapatinib	L01XE07
	Nilotinib	L01XE08
	Pazopanib	L01XE11
	Vandetanib	L01XE12
	Bosutinib	L01XE14
	Vemurafenib	L01XE15
	Crizotinib	L01XE16
	Dabrafenib	L01XE23
	Cabozantinib	L01XE26
	Ceritinib	L01XE28
	Lenvatinib	L01XE29
	Osimertinib	L01XE35
	Cobimetinib	L01XE38

	Midostaurin	L01XE39
	Ribociclib	L01XE42
	Encorafenib	L01XE46
	Entrectinib	L01XE56
	Arsenic trioxide	L01XX27
	Bortezomib	L01XX32
	Anagrelide	L01XX35
	Vorinostat	L01XX38
	Romidepsin	L01XX39
	Eribulin	L01XX41
	Panobinostat	L01XX42
	Rucaparib	L01XX55
	Bendamustine	L01AA09
	Leuprorelin	L02AE02
	Tamoxifen	L02BA01
	Toremifene	L02BA02
	Apalutamide	L02BB05
	Abarelix	L02BX01
	Degarelix	L02BX02
	Tacrolimus	L04AD02
	Fingolimod	L04AA27
	Siponimod	L04AA42
Musculoskeletal system	Tizanidine	M03BX02
	Nusinersen	M09AX07
Nervous system	Sevoflurane	N01AB08
	Propofol	N01AX10
	Cocaine	N01BC01
	Buprenorphine	N02AE01
	Tramadol	N02AX02
	Felbamate	N03AX10
	Retigabine	N03AX21
	Apomorphine	N04BC07
	Perphenazine	N05AB03
	Thioridazine	N05AC02
	Mesoridazine	N05AC03
	Haloperidol	N05AD01
	Melperone	N05AD03
	Pipamperone	N05AD05
	Benperidol	N05AD07
	Droperidol	N05AD08
	Sertindole	N05AE03
	Lurasidone	N05AE05
	Flupentixol	N05AF01
	Chlorprothixene	N05AF03
	Zuclopenthixol	N05AF05
	Pimozide	N05AG02

	Clozapine	N05AH02
	Asenapine	N05AH05
	Clotiapine	N05AH06
	Sulpiride	N05AL01
	Sultopride	N05AL02
	Tiapride	N05AL03
	Levosulpiride	N05AL07
	Lithium	N05AN01
	Prothipendyl	N05AX07
	Zotepine	N05AX11
	Aripiprazole	N05AX12
	Paliperidone	N05AX13
	Iloperidone	N05AX14
	Pimavanserin	N05AX17
	Dexmedetomidine	N05CM18
	Chlorpromazine	N05AA01
	Levomepromazine	N05AA02
	Cyamemazine	N05AA06
	Citalopram	N06AB04
	Escitalopram	N06AB10
	Mianserin	N06AX03
	Mirtazapine	N06AX11
	Venlafaxine	N06AX16
	Atomoxetine	N06BA09
	Donepezil	N06DA02
	Memantine	N06DX01
	Desipramine	N06AA01
	Imipramine	N06AA02
	Trimipramine	N06AA06
	Nortriptyline	N06AA10
	Maprotiline	N06AA21
	Methadone	N07BC02
	Levacetylmethadol	N07BC03
	Lofexidine	N07BC04
	Levomethadone	N07BC05
	Tetrabenazine	N07XX06
	Pitolisant	N07XX11
	Valbenazine	N07XX13
	Dextromethorphan	N07XX59
Antiparasitics, insecticides, and repellents	Chloroquine	P01BA01
	Hydroxychloroquine	P01BA02
	Primaquine phosphate	P01BA03
	Arthemether	P01BF01
	Artenimol and piperaquine	P01BF05
	Halofantrine	P01BX01
	Pentamidine	P01CX01

Respiratory system	Hydrocodone	R05DA03
	Alimemazine	R06AD01
	Promethazine	R06AD02
	Astemizole	R06AX11
	Terfenadine	R06AX12

Table S4. Patient characteristics stratified by subtype of SMI diagnosis.

	Controls (*n*=336 524)	Schizophrenia (*n*=4477)	Bipolar disorder (*n*=2571)	Severe depression (*n*=2980)	*P*
Age at ECG recording, years	56 [41–69]	50 [39–61]	58 [44–70]	58 [45–72]	<0.001
Males	161 282 (47.9)	2443 (54.6)	987 (38.4)	1034 (34.7)	<0.001
SMI duration, years	NA	10 [5–16]	7 [3–12]	5 [2–9]	NA
Heart failure	10 433 (3.1)	158 (3.5)	117 (4.6)	146 (4.9)	<0.001
Coronary artery disease	29 232 (8.7)	304 (6.8)	250 (9.7)	334 (11.2)	<0.001
Atrial fibrillation/flutter	14 903 (4.4)	120 (2.7)	135 (5.3)	169 (5.7)	<0.001
Valvular heart disease	3690 (1.1)	36 (0.8)	36 (1.4)	51 (1.7)	0.001
Hypertension	50 432 (15.0)	490 (10.9)	420 (16.3)	569 (19.1)	<0.001
Hyperlipidemia	49 201 (14.6)	689 (15.4)	462 (18.0)	535 (18.0)	<0.001
Diabetes	26 732 (7.9)	644 (14.4)	288 (11.2)	290 (9.7)	<0.001
Chronic obstructive pulmonary disease	29 093 (8.6)	655 (14.6)	337 (13.1)	359 (12.0)	<0.001
Chronic kidney disease	6328 (1.9)	108 (2.4)	119 (4.6)	84 (2.8)	<0.001
ACEIs/ARBs	64 743 (19.2)	515 (11.5)	378 (14.7)	508 (17.0)	<0.001
Beta-blockers	32 384 (9.6)	290 (6.5)	200 (7.8)	275 (9.2)	<0.001
Diuretics	45 533 (13.5)	565 (12.6)	430 (16.7)	472 (15.8)	<0.001
QT-prolonging medications	44 377 (13.2)	2885 (64.4)	1878 (73.0)	2056 (69.0)	<0.001

Table S5. ECG characteristics stratified by subtype of SMI diagnosis.

	Controls (*n*=336 524)	Schizophrenia (*n*=4477)	Bipolar disorder (*n*=2571)	Severe depression (*n*=2980)	*P*
Heart rate, bpm	69 [61–78]	78 [68–89]	72 [64–82]	75 [66–85]	<0.001
Missing	30 361	219	228	239	
P-wave duration, ms	108 [100–116]	106 [98–114]	110 [102–118]	108 [100–116]	<0.001
Missing	30 361	219	228	239	
PR interval, ms	156 [144–174]	154 [140–168]	162 [146–178]	156 [142–172]	0.782
Missing	30 361	219	228	239	
QRS duration, ms	92 [84–100]	90 [84–98]	92 [84–100]	90 [84–98]	<0.001
Missing	30 361	219	228	239	
QT interval, ms	396 [376–416]	384 [362–404]	394 [374–416]	390 [370–410]	<0.001
Missing	30 361	219	228	239	
QTcF interval, ms	414 [402–427]	416 [402–430]	418 [404–431]	417 [405–431]	<0.001
Missing	30 361	219	228	239	
No ECG abnormality	237 397 (70.5)	3380 (75.5)	1789 (69.6)	2126 (71.3)	<0.001
Minor ECG abnormality	18 541 (5.5)	292 (6.5)	189 (7.4)	179 (6.0)	<0.001
First-degree atrioventricular block	13 477 (4.0)	107 (2.4)	144 (5.6)	133 (4.5)	<0.001
Incomplete bundle branch block	8504 (2.5)	97 (2.2)	58 (2.3)	55 (1.8)	0.036
Incomplete right bundle branch block	7680 (2.3)	92 (2.1)	49 (1.9)	51 (1.7)	0.076
Incomplete left bundle branch block	824 (0.2)	5 (0.1)	9 (0.4)	4 (0.1)	0.116
Left fascicular block	4504 (1.3)	85 (1.9)	42 (1.6)	50 (1.7)	0.002
Left anterior fascicular block	2743 (0.8)	40 (0.9)	30 (1.2)	32 (1.1)	0.088
Left posterior fascicular block	1761 (0.5)	45 (1.0)	12 (0.5)	18 (0.6)	<0.001
QTcF prolongation	5831 (1.7)	159 (3.6)	90 (3.5)	75 (2.5)	<0.001
Major ECG abnormality	80 586 (23.9)	805 (18.0)	593 (23.1)	675 (22.7)	<0.001
Left ventricular hypertrophy	35 832 (10.6)	322 (7.2)	242 (9.4)	286 (9.6)	<0.001
Atrial fibrillation/flutter	12 561 (3.7)	52 (1.2)	84 (3.3)	98 (3.3)	<0.001
Bundle branch block	11 550 (3.4)	104 (2.3)	97 (3.8)	101 (3.4)	<0.001
Right bundle branch block	7803 (2.3)	77 (1.7)	69 (2.7)	71 (2.4)	0.035
Left bundle branch block	3747 (1.1)	27 (0.6)	28 (1.1)	30 (1.0)	0.013
Intraventricular conduction disturbance	2786 (0.8)	29 (0.6)	23 (0.9)	24 (0.8)	0.590
Q waves	17 064 (5.1)	244 (5.5)	127 (4.9)	170 (5.7)	0.278
ST-T deviations	15 283 (4.5)	149 (3.3)	114 (4.4)	118 (4.0)	<0.001

Table S6. Brier scores.

Population	Brier Score (95% CI) For Conventional Model	Brier Score (95% CI) For ECG Abnormality Model
Controls		
Cardiovascular disease	0.186 (0.182–0.190)	0.182 (0.178–0.187)
No cardiovascular disease	0.053 (0.052–0.054)	0.052 (0.051–0.053)
SMI		
Cardiovascular disease	0.223 (0.198–0.251)	0.222 (0.194–0.253)
No cardiovascular disease	0.082 (0.072–0.093)	0.081 (0.071–0.092)

Figure S1. Flowchart.

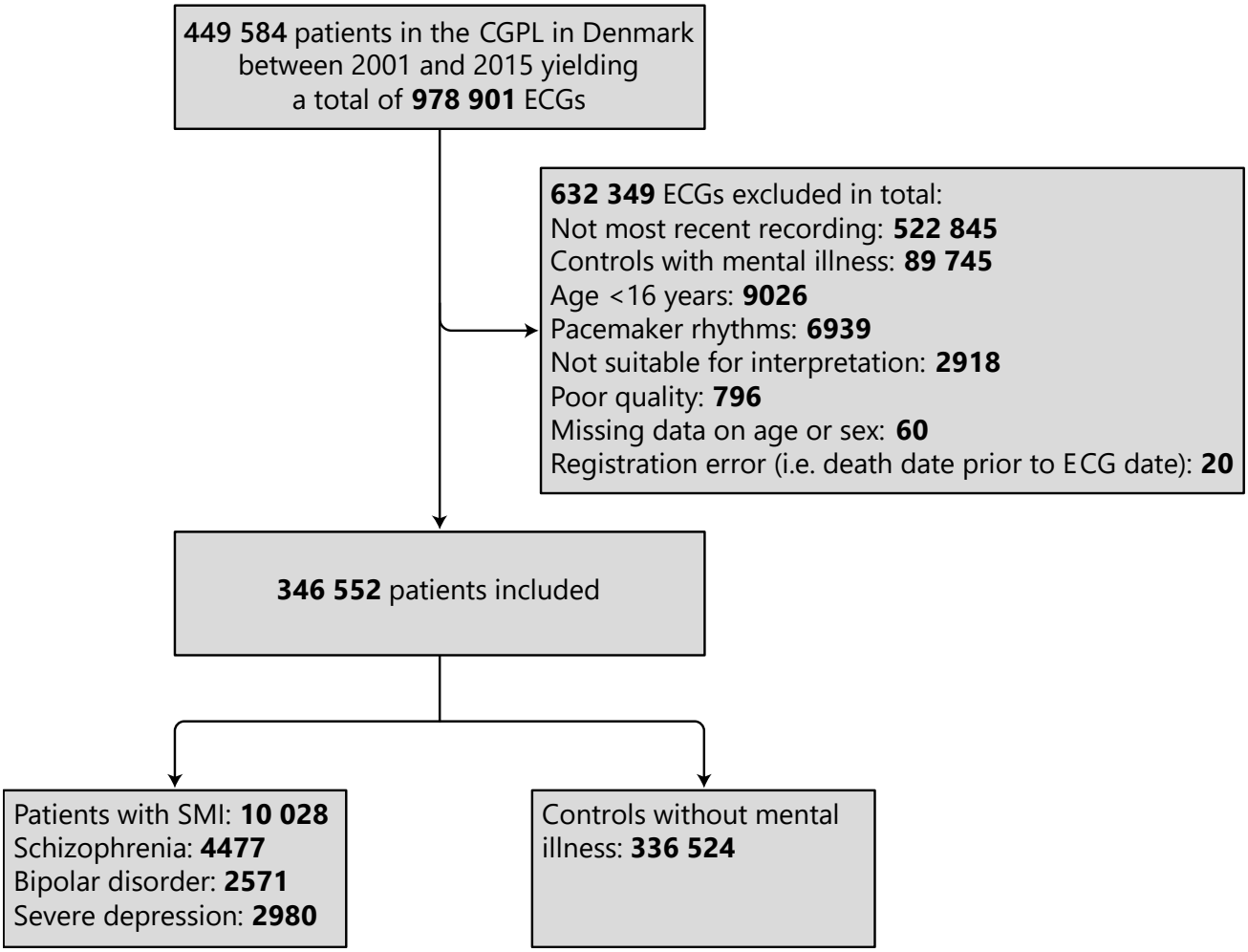

Figure S2. Association between SMI status and ECG abnormalities combined and long-term outcomes.

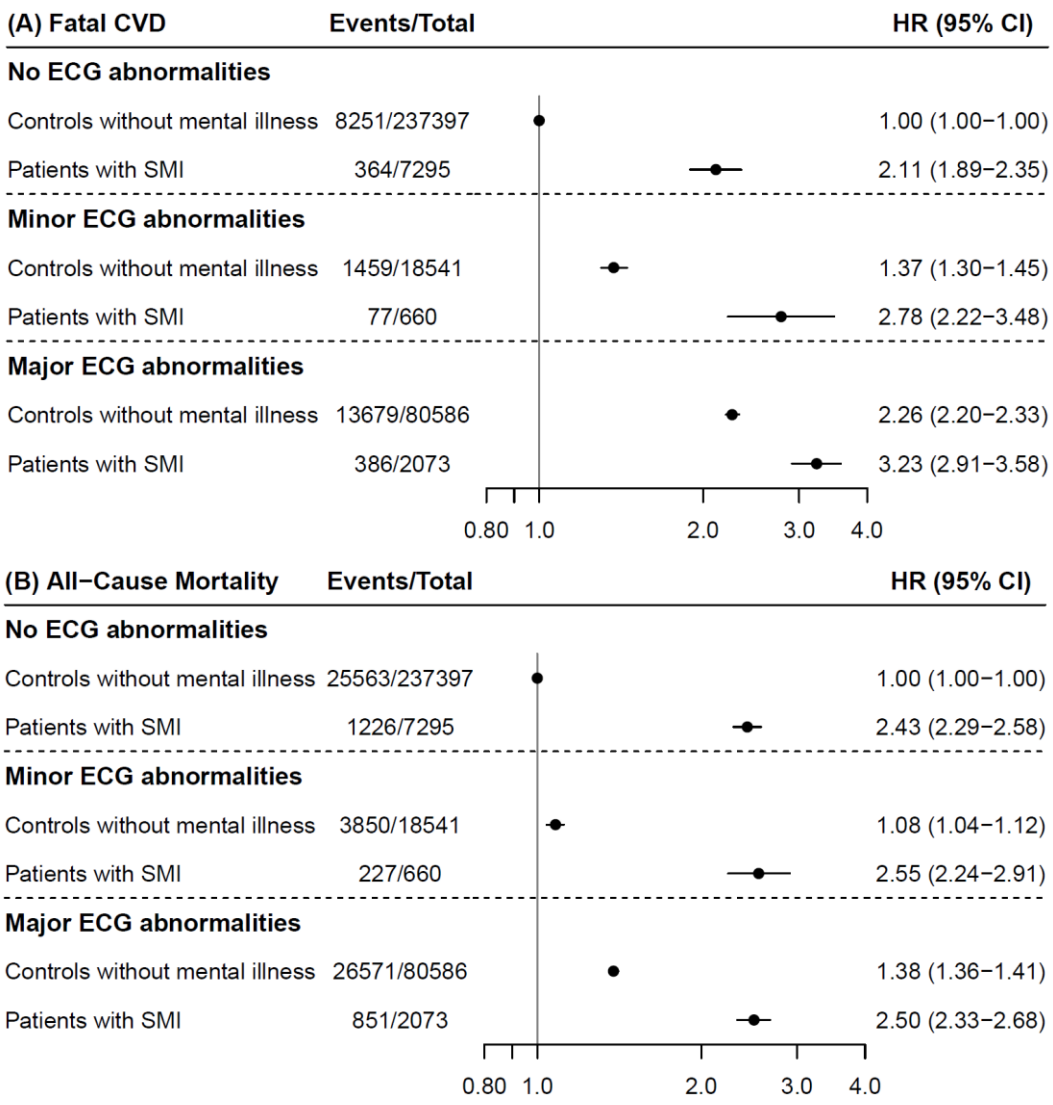

Figure S3. ECG abnormalities and fatal CVD risk stratified by subtype of SMI diagnosis.

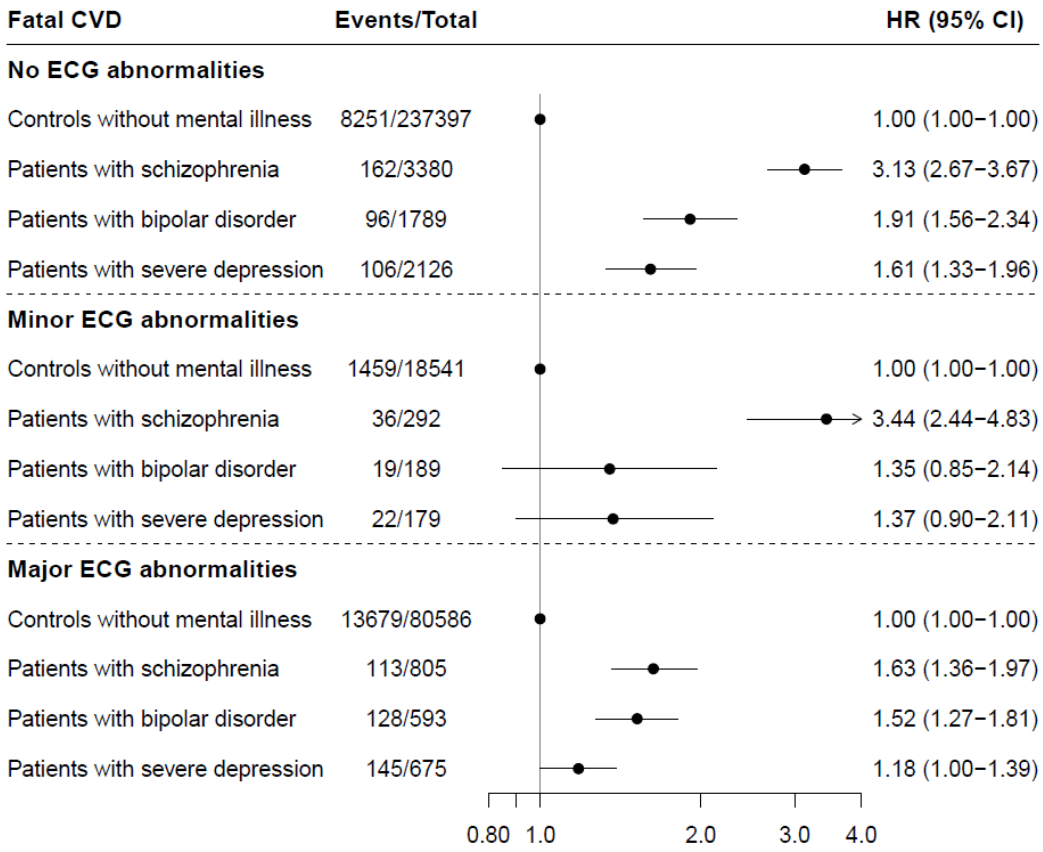

Figure S4. AUC values.