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Research Article

Cardiovascular Disease Burden in Persons with Mental Illness: Comparison between a U.S. Psychiatry Outpatient Sample and a U.S. General Population Sample

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Background. Cardiovascular disease (CVD) and depression are the leading causes of disability in the U.S. Using electronic health record data, we describe the CVD burden among persons with mental illness enrolled in the Penn State Psychiatry Clinical Assessment and Rating Evaluation System (PCARES) Registry between 2015 and 2020. *Methods*. CVD burden assessment included prevalence of CVD conditions (any major CVD or individual CVD risk factors), indicated medication prescriptions for CVD risk factors, and mean levels of body mass index (BMI, kg/m^2), glycosylated hemoglobin (HbA1C, %), glucose (mg/dl), and lipids (mg/dl). We compared the CVD burden between the PCARES sample to a representative sample of adults from the U.S. general population (NHANES 2013-2016) using one-sample chi-square/t-tests for proportions/means. The CVD burden in NHANES participants was adjusted to PCARES age, race, and sex statistics. *Results*. The PCARES sample ($N = 3556$) had a mean (SE) age of 42.4 (0.3) years and comprised 63.0% women, 85.0% non-Hispanic Caucasians, and 41.0% with major depressive disorder. CVD burden was higher in the PCARES sample compared to NHANES participants for any major CVD (8.6% vs. 4.6%), diabetes (18.4% vs. 10.4%), BMI (30.3 vs. 28.3), HbA1C (6.1 vs. 5.6), cholesterol (185.6 vs. 181.7), triglycerides (153.3 vs. 136.1), and indicated antihypertensive (94.3% vs. 76.9%) and cholesterol-lowering (49.5% vs. 36.7%) medications (Bonferroni-corrected $p = 0.03$ for each outcome). The CVD burden was lower in the PCARES sample compared to NHANES participants for hypertension (45.9% vs. 50.4%), dyslipidemia (43.2% vs. 61.9%), HDL-C (48.4 vs. 41.4), and LDL-C (107.9 vs. 112.0) (Bonferroni-corrected $p = 0.03$ for each outcome). Glucose levels (110.9 vs. 111.9) and indicated antidiabetic medications (87.4% vs. 86.6%) were similar in the two samples ($p > 0.05$). *Conclusions*. The CVD burden was higher in persons with mental illness compared to the U.S. general population. Integrated mental and physical healthcare services could reduce long-term disability among persons with mental illness.

1. Introduction

Major depressive disorder (MDD) and anxiety disorders are the leading mental illnesses in the U.S. and are especially prevalent among young and middle-aged adults [1]. Due to shared socioeconomic, behavioral, and environmental risk factors, a bidirectional relationship has been hypothesized between depression and cardiovascular disease (CVD) [2]. With individual economic burdens ranging in billions of dollars [3, 4], depression and CVD are the leading causes of

disability in the U.S. [5]. In 2019, 21.0 million and 18.2 million U.S. adults suffered from depression and CVD, respectively [1, 3].

In the U.S. National Health Interview Survey, compared to U.S. adults without psychological distress, individuals with increasing levels of psychological distress had a linearly increasing risk of CVD mortality [6]. Similar findings were reported for the U.K. general population in the Health Survey for England [7]. Indeed, CVD is the leading cause of premature mortality among persons with mental illness [6, 8]. Recently, a Finnish study reported heritable CVD risk among individuals with mental illness, wherein children of parents with severe mental illness (SMI) were at 63% higher risk for CVD [9]. Given the premature mortality from CVD in persons with mental illness and the bidirectional relationship between mental illness and CVD, it is critical to understand the burden of CVD in persons with mental illness. Importantly, depression and anxiety disorders are modifiable risk factors, and their timely identification and treatment could prevent CVD onset and progression [10]. Lastly, our findings could have implications for supporting integrated healthcare systems, addressing preclinical CVD risk factors in individuals with mental illness, and developing specific protocols for mental illness in cardiovascular health programs to better address the collective morbidity from CVD and mental illness.

Studies that examined the relationship between mental illness and CVD using electronic health record (EHR) data have expectedly focused on specific populations, such as veterans [11, 12], women only [13], individuals with psychosis [14], and adults in the United Kingdom [15]. Although EHR data focuses on specific populations, it allows a better understanding of patient behavior and clinical care in real-world settings [16, 17]. Therefore, we conducted a cross-sectional study to assess the CVD burden in a clinical registry of persons with mental illness and compared it with the CVD burden among adults in the U.S. general population. Using the EHR data of this clinical registry, our goal was to corroborate existing evidence on the relationships between mental illness and CVD with greater validity using clinician-assigned diagnoses, prescribed medications, and lab values. We hypothesized that a greater CVD burden would be observed in our clinic-based sample of persons with mental illness as compared to the U.S. adult population sample.

2. Materials and Methods

2.1. Study Populations

2.1.1. PCARES. The Penn State Psychiatry Clinical Assessment and Rating Evaluation System (PCARES) is a measurement-based care system and data registry which merges EHR data with patient-reported data [18]. The PCARES registry includes 3556 persons with mental illness, who received care at a psychiatry and behavioral health outpatient clinic or partial hospitalization program at an academic medical center based in Central Pennsylvania between February 17, 2015 and March 15, 2020. Individuals excluded from PCARES included those presenting with significant cognitive impairment (e.g., intellectual disability and dementia). On their first visit, individuals were evaluated by a board-certified psychiatrist or licensed clinical psychologist. Additionally, as part of their routine care, individuals were asked to self-report on their symptoms of mental illness via a battery of assessments [18]. For our study, the primary baseline study window ranged from February 1, 2015 to three months after each individual's first psychiatric assessment date (index date). For sensitivity analysis, we extended the three-month time window to one-year after the index date and used it as our secondary baseline study window. Our selection of the time windows was intended to maximize the time length to capture CVD prevalence. February 1, 2015, to three months after each individual's index visit date was selected as our primary study window to be consistent with our protocols for upcoming CVD-based longitudinal studies on the PCARES cohort, for which minimal overlap between the exposure and outcome was desired. Our study was conducted according to the ethical principles of the Declaration of Helsinki of 1975, as revised in 2008 and approved by the Institutional Review Board at the Penn State University College of Medicine (reference #19937). Our study used deidentified datasets, which were not considered human subjects research by our institution's IRB. Study data were collected and managed using REDCap electronic data capture [19] tools hosted at Penn State Health Milton S. Hershey Medical Center and Penn State University College of Medicine.

2.1.2. NHANES. The National Health and Nutrition Examination Survey (NHANES) is a continuous, cross-sectional surveillance program conducted biennially by the CDC to examine the health and nutritional status of civilian, noninstitutionalized children and adults in the U.S. [20]. The survey collects information based on a household interview, dietary recalls, and a clinical exam performed at the NHANES mobile examination center (MEC). Written informed consent is sought from all participants. The NHANES data are publicly available and provide well-representative samples of the U.S. general population [20]. Adults who participated in the 2013-14 and 2015-16 NHANES cycles were included in our study ($N = 12105$).

2.2. Study Variables

2.2.1. Sociodemographics. In the PCARES sample, demographic characteristics were obtained from the EHR and included patient-reported gender, race, ethnicity, marital status, insurance type, and date of birth to calculate age at index date. Using the patient's zip code from the EHR, education and income levels were extracted from the 2016 American Community Survey five-year estimates database [21]. Each patient's residential address was also used to determine their municipality as rural or urban using data from the Center for Rural Pennsylvania [22]. Commercial insurance included preferred provider organizations (PPO), Blue Cross/Blue Shield-related organizations, health maintenance organizations (HMO), and other commercial insurance payers. Public/self-pay insurance included state-funded Medicaid payers, Medicare, and self-pay. Among NHANES participants, demographic characteristics and insurance information were

participant-reported and obtained during the home interview. Information on municipality was not available [20]. As for education and income levels, these variables were collected in PCARES at the zip-code level and in NHANES at the individual level; hence, they were not directly comparable between the two study populations.

2.2.2. The Nine-Item Patient Health Questionnaire (PHQ-9). The PHQ-9 is a self-reported questionnaire, which assesses severity of depressive symptoms as "0" (not at all), "1" (several days), "2" (more than half the days), or "3" (nearly every day) over the past two weeks [23]. Among the PCARES sample, baseline PHQ-9 scores represented patient-reported scores on the index visit. Among NHANES participants, the PHQ-9 was administered in the MEC.

2.2.3. CVD Conditions and Medications. CVD conditions included coronary heart disease (CHD, which includes stable/unstable angina), stroke, and congestive heart failure (CHF), and cardiometabolic risk factors included type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia. In the PCARES sample, the diagnostic criteria for CVD conditions and risk factors were based on algorithms [16] that included only ICD-10 codes, or a combination of ICD-10 codes, relevant metabolic markers, or relevant medications (Table 1) [24–28]. Blood pressure (BP) measurements were not available in the EHR. In the PCARES sample, the 2020 International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) list was used as a reference [25] for all psychiatric and CVD diagnostic codes classified by coauthors, ES and DL, respectively. Electronic drug prescriptions associated with cardiometabolic conditions (i.e., indicated prescriptions) were classified into antihypertensive, antidiabetic, and cholesterol-lowering drug classes using the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System Drug, 2020-2021 version [29]. For combination drugs, each ingredient was counted as a separate medication. The earliest date of each electronic prescription was considered the baseline prescription date. For the diagnostic criteria of CVD conditions and risk factors among NHANES participants [20], see Table 1 in Supplementary Material.

2.2.4. CVD Metabolic Markers. In the PCARES sample, body mass index (BMI) was extracted from the EHR, and the BMI value closest to the index date was used as baseline BMI. Similarly, values for CVD-relevant biomarkers including glucose, glycosylated hemoglobin (HbA1C), and lipids (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)) were extracted from the EHR. The lab value closest to the index date was used as baseline lab value. The EHR data did not clearly indicate the type of glucose lab (fasting or random). Thus, we combined all labs that indicated a glucose test, which required the use of a glucose cut-off of ≥200 mg/dl as a diagnostic criterion for T2DM [24]. We used the Friedewald formula to calculate LDL-C, and for individuals with TG > 400 mg/dl, the TG were winsorized at 400 mg/dl [30]. If a specific lab test was performed more than once on the same date, the mean of all lab tests was calculated to generate one lab value for that date. Among NHANES participants, anthropometric measurements were collected in the MEC. CVD lab tests, also performed in the MEC, included fasting plasma glucose (FPG), HbA1C, and lipids. FPG, TG, and LDL-C values were available only for participants with nonmissing and nonzero fasting weights, which indicated adequate length of fasting prior to the lab test [20, 31].

2.2.5. Tobacco Use. In the PCARES sample, information on tobacco use was ascertained from the DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure—Adult form, a self-report questionnaire that included a question assessing frequency of different types of tobacco use (e.g., chewing tobacco, cigarettes, and snuff) over the past two weeks [32]. Among NHANES participants, tobacco use was self-reported and based on cigarette consumption only [33]. As tobacco use in the PCARES sample and the NHANES sample referred to different information and was collected using different methods, it was not compared between the two study populations.

2.3. Statistical Analysis. The analyses for both study populations were performed on deidentified datasets. NHANES participants with missing or null MEC weights were excluded ($N = 446$); thus, our analytic NHANES dataset included 11659 participants. One-sample chi-square tests were used to compare the proportions of CVD conditions and medications between the PCARES sample and NHANES participants. One sample t-tests were used to compare the mean levels of metabolic markers between the PCARES sample and NHANES participants. The significance level (alpha) of 0.05 was adjusted for multiple comparisons using the Bonferroni correction [34]. There were ten binary and seven continuous CVD variables for comparison; thus, we adjusted our significance level to 0.003 (0.05/17) to account for multiple comparisons. We first calculated proportions, means, and standard deviations (SD) for all 17 CVD variables for NHANES participants using appropriate sample weights and standardized them to the demographic characteristics (age, race, and sex) of the PCARES sample. CVD medication prescription prevalence was calculated only for participants with that specific CVD (e.g., antidiabetic medications among those with T2DM, i.e., indicated prescriptions). Similarly, NHANES proportions for medications were standardized based on PCARES mean age and proportions of sex and race for that specific CVD. Second, we calculated the PCARES proportions, means, and SDs for all 17 CVD variables. Finally, we used one-sample tests to compare PCARES proportions and means to the corresponding multivariable-adjusted NHANES proportions and means [35].

3. Results

Table 2 shows baseline characteristics of both study populations. The PCARES sample had a mean (standard error (SE)) age of 42.4 (0.3) years and comprised 63.0% women and 85.0% non-Hispanic Caucasians. In this sample, 41%

Table 1: Algorithms for cardiovascular conditions and risk factors in the PCARES sample.

Coronary heart disease [28]	Composite variable formed by combining the ICD-10 diagnosis codes/subcodes: stable/unstable angina [I20], STEMI or NSTEMI [I21; I22], complications from MI [I23], acute ischemic heart disease [I24], atherosclerosis of coronary arteries or previous CABG [I25], atherosclerosis of aorta [I70.0], presence of aorto-coronary bypass graft [Z95.1], coronary angioplasty implant and graft [Z95.5], and coronary angioplasty [Z98.61]
Congestive heart failure [28]	Composite variable formed by combining the ICD-10 diagnosis codes/subcodes: I50
Stroke [28]	Composite variable formed by combining the ICD-10 diagnosis codes/subcodes: hemorrhagic stroke [I60, I61, I62]; ischemic stroke [I63, I65, I66]; cerebrovascular disease [I67, I68]; stroke sequelae [I69]
Type 2 diabetes mellitus [24]	The earliest occurrence of *any one* of the following criteria: (i) ICD-10 codes & subcodes for T2DM [E11; E13] (ii) Prescription of at least one antidiabetic medication; antidiabetic medications include oral hypoglycemic agents or insulin therapy (iii) Random plasma glucose levels ≥ 200 mg/dl or HbA1C ≥ 6.5 units
Hypertension [26]	The earliest occurrence of *any one* of the following criteria: (i) ICD-10 codes & subcodes for HTN [I10-I15]; or (ii) Prescription for at least one antihypertensive medication; antihypertensive medications include at least any one of the following medication classes: beta-blockers, angiotensin convertase enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and miscellaneous agents
Dyslipidemia [27]	The earliest occurrence of *any one* of the following criteria: (i) ICD-10 codes for dyslipidemia subtypes [E78] (ii) Prescription for at least one cholesterol-lowering medication; cholesterol-lowering medications include statins or nonstatins. (iii) Serum cholesterol ≥ 220 mg/dl, or serum triglycerides > 150 mg/dl, or (iv) Serum HDL-C (mg/dl) <50 in women, or <40 in men, or -LDL-C ≥ 130 mg/dl
Current smoking [32]	Individuals who scored ≥ 2 on item 22. "Smoking any cigarettes, a cigar, or pipe, or using snuff or chewing tobacco?" on the DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure—Adult

Abbreviations: MI: myocardial infarction; STEMI: ST-elevation MI; NSTEMI: non-ST elevation MI; CABG: coronary artery bypass graft. CVD diagnosis date: the diagnostic date for CVD conditions whose diagnoses are based only on ICD-10 diagnostic codes was the earliest date on which that particular ICD-10 code occurred. For CVD risk factors, whose diagnosis is based on specific criteria (ICD-10 code/medication prescription/higher lab test value), the diagnostic date was the earliest date on which one of the criteria was fulfilled.

of individuals were diagnosed with MDD, 37.0% with generalized anxiety disorder, and 10.0% with bipolar disorder. The mean (SE) PHQ-9 score in the PCARES sample was 10.6 (0.1), compared to the multivariable-adjusted mean (SE) PHQ-9 score in the U.S. population sample of 1.9 (0.1).

Table 3 shows the means and proportions of CVD variables with their 95% confidence limits (CL). The CVD burden was higher in the PCARES sample compared to the U.S. population sample for any CVD (8.6% vs. 4.6%), diabetes (18.4% vs. 10.4%), indicated antihypertensive (94.3% vs. 76.9%) and cholesterol-lowering medications (49.5% vs. 36.7%), BMI (30.3 kg/m^2 vs. 28.3 kg/m^2), HbA1C (6.1% vs. 5.6%), cholesterol (185.6 mg/dl vs. 181.7 mg/dl), and triglycerides (153.3 mg/dl vs. 136.1 mg/dl, $p = 0.03$ for each outcome). The CVD burden was lower in the PCARES sample compared to the U.S. population sample for hypertension (45.9% vs. 50.4%), dyslipidemia (43.2% vs. 61.9%), HDL-C (48.4 mg/dl vs. 41.4 mg/dl), and LDL-C (107.9 mg/dl vs. 112.0 mg/dl, $p = 0.03$ for each outcome). The CVD burden was similar between the PCARES sample and the U.S. population sample for glucose (110.9 mg/dl vs. 111.9 mg/dl) and indicated antidiabetic medications (87.4% vs. 86.6%, $p > 0.05$ for both outcomes). The p values of 0.03 for each outcome were originally all $p < 0.0001$ but were rescaled using the Bonferroni correction for 17 outcomes (0.0001/0.003). The sensitivity analyses, which are based on a longer baseline study window, showed similar trends for all CVD variables, except that HTN prevalence was no longer significantly different between the two populations (see Table 2 in Supplementary Material).

4. Discussion

Our clinic-based sample of persons with mental illness had a higher prevalence for most CVD conditions and risk factors compared to a sample of adults in the U.S. general population regardless of study window, thus, confirming our hypothesis.

4.1. CVD. Our estimate of 8.6% (95% CL: 7.7-9.5) CVD prevalence in the PCARES sample is comparable to the pooled CVD prevalence of 9.9% (7.4-13.3) from a large-scale meta-analysis of persons with SMI. After adjusting for traditional CVD risk factors and antipsychotic medication use, persons

Table 2: Baseline characteristics of the PCARES sample and the NHANES sample.

Characteristics	PCARES ($N = 3556$)*	NHANES ($N = 11659$)†
	Mean (SE)	
Age	42.36 (0.28)	46.84 (0.34)
BMI	30.38 (0.15)	29.17 (0.15)
PHQ-9 Score**	10.64 (0.13)	3.12 (0.06)
	N (%)	
Annual household income‡ (≥$75,000)	319 (9.00)	3008 (37.70)
≥ High school education‡ (%, SE for PCARES)	90.14 (0.07)	8929 (84.40)
Females	2251 (63.30)	6077 (51.84)
Residence in urban municipality	3008 (86.09)	N/A
Non-Hispanic White	2874 (84.45)	4330 (64.43)
Non-Hispanic Black	199 (5.85)	2450 (11.48)
Other race-including multiracial	330 (9.70)	4879 (24.07)
Single	1594 (46.19)	3000 (26.62)
Married	1383 (40.08)	5669 (54.84)
Widowed/divorced/separated	474 (13.74)	2388 (18.52)
Commercial/private insurance	2009 (56.67)	4771 (60.33)
Other insurance (Medicaid/Medicare)	1536 (43.33)	4551 (39.66)

*PCARES results reflect the primary baseline study window (February 1, 2015 to three months after the index date). **PHQ-9 score was available for only 2842 persons in the PCARES cohort. †NHANES results are weighted means or proportions and, in this table, are not adjusted to the demographic characteristics of the PCARES sample. ‡Education and income are at the zip code level for PCARES and individual level for NHANES. §Abbreviations: PCARES: Penn State Psychiatry Clinical Assessment and Rating Evaluation System; NHANES: National Health and Nutrition Examination Survey; SE: standard error; N/A: not available.

with SMI had significantly higher odds of CVD (odds ratio (OR) (95% CI): 1.5 (1.3-1.8)), CHD (1.5 (1.5-1.6)), and cerebrovascular disease (1.4 (1.2-1.7)) compared to controls [8]. Similarly, U.S. male veterans with bipolar disorder had significantly higher odds of being diagnosed with CHD and CVD risk factors [11]. A recent study reported that among SMI subtypes, patients with bipolar disorder had the highest 10-year cardiovascular risk, while patients with schizoaffective disorder had the highest 30-year cardiovascular risk [36]. Mental illness is associated with chronic stimulation of the autonomic nervous system and catecholamine production; over time, this leads to increased blood pressure, arterial stiffness, and thrombogenesis. These physiological disruptions can lead to microvascular endothelial dysfunction from oxidative stress [37], changes in peripheral vascular and cerebrovascular reactivity [38], dysregulated serotoninergic signaling [39], arrhythmogenesis, reduced heart rate variability, and impaired ventricular function [40]. Such physiologic alterations may also explain the significant association between CVDs and anxiety disorders [41].

Established behavioral risk factors for CVD, such as physical inactivity, poor diet quality, obesity, smoking, alcohol use, substance use, insomnia [2], and nonadherence to CVD medications [42], are also highly prevalent in individuals with mental illness. A U.S. population-based survey identified significant relationships between increasing depression severity and prevalence of smoking, obesity, and physical inactivity [43]. Similarly, U.S. veterans with bipolar disorder were more likely to report weight gain, physical inactivity, suboptimal diet, and lack of discussions about diet or exercise during clinical visits [44]. The increased CVD burden in persons with mental illness may also be contributed by certain sociodemographic factors. For example, mental illness may negatively affect people's ability to maintain a marital relationship [45, 46], which is protective against both mental illness [47] and CVD [48]. Low socioeconomic status is associated with poorer healthcare access, CVD, and mental illness [49]. Moreover, persons with mental illness have a greater likelihood of missing their primary care visits [50], which over time may lead to undetected and worsened CVD.

4.2. Metabolic Dysregulation. Possible links between metabolic dysregulation and depression include disturbances in the hypothalamic pituitary adrenal (HPA) axis [51, 52], reduced serotonin [53], abnormalities in brain-derived neurotrophic factor signaling [54], and neurostructural alterations in the prefrontal cortex [55]. Metabolic and immune-inflammatory dysregulations in depression are associated with insulin and leptin resistance and higher rates of obesity and metabolic syndrome (MetS) [56]. Indeed, the median (interquartile range (IQR)) BMI of 29.0 (24.6-35.0) kg/m^2 in the PCARES sample was comparable to Correll et al.'s [57] sample of persons with MDD, bipolar disorder, or schizophrenia, in whom the median (IQR) BMI was 30.4 (26.0-36.2) kg/m^2. Furthermore, there was a higher rate of obesity (BMI ≥ 30 kg/m^2) in the PCARES sample (46%) and Correll et al.'s [57] psychiatric patient sample (52%), compared to the obesity rate of 39.6% in the U.S. general population [58]. Obesity has also found its links with increased senescent cell burden, which is a major contributor to obesity-induced anxiety [59].

Table 3: Comparisons of the means and proportions (95% CL) of CVD metabolic markers, conditions, and risk factors in the PCARES sample to the age-, sex-, and race-adjusted means and proportions (95% CL) in the U.S. population sample (NHANES).

	PCARES* $N = 3556$	NHANES $N = 11659$	p-value†
Variable	*Mean (95% CL)*	*Mean (95% CL)*	
Age (years)	42.36 (41.81, 42.92)	—	—
BMI (kg/m^2)	30.38 (30.08, 30.67)	28.36 (27.95, 28.76)	0.03
Glucose (mg/dl)	110.85 (108.93, 112.77)	111.87 (109.13, 114.62)	0.21
Hemoglobin A1C (%)	6.09 (6.00, 6.17)	5.59 (5.53, 5.64)	0.03
Serum cholesterol (mg/dl)	185.61 (183.44, 187.79)	181.79 (179.01, 184.58)	0.03
Serum triglycerides (mg/dl)	153.30 (147.28, 159.32)	136.15 (126.37, 145.94)	0.03
Serum HDL-cholesterol (mg/dl)	48.44 (47.64, 49.23)	41.39 (40.36, 42.42)	0.03
Serum LDL-cholesterol (mg/dl)	107.89 (106.05, 109.73)	112.00 (108.54, 115.46)	0.03
Variable	*Proportion (95% CL)*	*Proportion (95% CL)*	*p value*†
Heart disease (CHD/angina)	4.89 (4.18, 5.60)	3.65 (2.79, 4.76)	0.03
Heart failure	2.42 (1.91, 2.92)	0.81 (0.55, 1.19)	0.03
Any CVD (CHD/stroke/CHF)	8.58 (7.66, 9.50)	4.65 (3.69, 5.86)	0.03
Stroke	3.63 (3.01, 4.24)	1.05 (0.68, 1.60)	0.03
Dyslipidemia	43.17 (41.54, 44.79)	61.91 (58.61, 65.10)	0.03
Cholesterol-lowering medications‡	49.51 (47.01, 52.01)	36.73 (32.60, 41.07)	0.03
Type 2 diabetes mellitus	18.39 (17.12, 19.66)	10.39 (8.70, 12.37)	0.03
Antidiabetic medications‡	87.46 (84.92, 90.00)	86.66 (80.17, 91.26)	0.16
Hypertension	45.89 (44.26, 47.53)	50.47 (46.68, 54.26)	0.03
Antihypertensive Medications‡	94.30 (93.18, 95.43)	76.96 (70.81, 82.15)	0.03
Smoking§	21.95 (20.27, 23.63)	25.05 (22.30, 28.01)	—

*PCARES results are based on the primary definition of the baseline study window (February 1, 2015 to three months after the index date). †p value is based on a one-sample t-test for means and a one-sample chi-square test for proportions. The significance level (alpha) of 0.05 was adjusted for multiple comparisons using the Bonferroni correction. For the 17 CVD outcomes above, we adjusted the significance level to 0.003 (0.05/17). Therefore, $p < 0.0001$ were scaled by dividing 0.0001 by 0.003, which is equal to 0.03. ‡Prescription medication prevalence includes only those persons with the diagnoses of that particular CVD risk factor. §Smoking is reported, but the proportions are not directly compared as smoking was ascertained through different instruments and different questions in the two study populations.

4.3. Diabetes. Despite no differences in the indicated antidiabetic medication prescription prevalence, T2DM prevalence among the PCARES sample was nearly twice that of adults in the U.S. general population. A previous study found a two-fold higher rate of depression in persons with diabetes [60]. Moreover, a meta-analysis reported that the pooled relative risk for incident diabetes associated with baseline depression was 1.6 (1.4-1.9) [61]. Kahn et al. [62] reported a statistically significant association ($r = 0.2$; $p = 0.01$) between FPG and PHQ-9 depression scores in a Medicaid sample of persons with mental illness and comorbid T2DM. Our finding of no differences in glucose levels between the two study samples could be due to the inability to differentiate between fasting and random glucose values in the PCARES sample or its highly indicated antidiabetic prescription rate. However, suboptimal glycemic control, as evidenced by the higher HbA1C levels in the PCARES sample, was in line with previous reports of significant diabetes treatment nonadherence, diminished self-efficacy, lack of dietary modification, physical inactivity, and increased micro- and macrovascular complications among persons with depression [63].

4.4. Dyslipidemia. HPA axis disturbances and reduced adiponectin levels in depression may lead to visceral adipogenesis through proinflammatory cytokine secretions in adipose tissue [52, 64], which can result in a decrease in HDL-C and phospholipids and an increase in TGs [65]. In the Netherlands Study of Depression and Anxiety, subjects with severe depression had two times greater odds of having dyslipidemia [66]. Except for HDL-C levels, TC and TG levels in the PCARES sample were comparable to Correll et al.'s [57] subsample of psychiatry patients in whom the medians (IQRs) for TC, TG, and HDL-C were 184 mg/dl (158-213), 138 mg/dl (93-208), and 42 mg/dl (33-53), respectively. The low mean LDL-C levels and high mean HDL-C levels in the PCARES sample were consistent with findings from the Women's Health Initiative study [67] and some other studies [68–70] which reported that lower LDL-C levels and higher HDL-C levels were associated with increased risk/severity of depression. In a subsample of individuals with bipolar disorder, Fusar-Poli et al. [71], reported that patients experiencing a manic episode had significantly lower TC, HDL-C, and LDL-C as compared to euthymic patients. Moreover, the TC and LDL-C levels were significantly lower in individuals with hypomania than those with depression [71]. The relatively higher prevalence of indicated cholesterol-lowering medication prescriptions in the PCARES sample could also contribute to their lower mean

LDL-C levels. Conversely, the relatively lower prevalence of indicated cholesterol-lowering medication prescriptions among adults in the U.S. general population could contribute to their higher prevalence of dyslipidemia.

4.5. Hypertension. Increased sympathetic tone, disturbances in the HPA axis, and dopamine dysregulation are shared pathogenic pathways between depression and HTN. Meng et al. [72] reported a 42% increased risk for hypertension in patients with depression in a meta-analysis. Conversely, some studies reported inverse [73] or no association between HTN and depression [74, 75]. In the PCARES sample, the HTN prevalence estimates using shorter and longer study windows were comparable to the HTN prevalence rates among adults in the U.S. general population, as well as in Correll et al.'s [57] sample of persons with SMI. Since 2017, HTN prevalence has generally increased in the U.S. population, due to changes in diagnostic cut-offs for blood pressure measurements [76]. However, despite similar HTN prevalence, the PCARES sample had a higher rate of indicated antihypertensive prescriptions than adults in the U.S. general population.

4.6. Indicated CVD Medications. Compared to the U.S. population sample, the PCARES sample had higher indicated prescription rates for all three CVD medication classes. In prior research using EHR data, a higher underlying disease burden was positively associated with the number of days with medication orders and laboratory results [77]. A higher underlying disease burden and, possibly, an increased frequency of healthcare utilization could have increased the likelihood of receiving a CVD medication prescription in the PCARES sample [78]. Furthermore, persons with mental illness tend to have poor medication compliance and management of coexisting medical conditions [42]; this may lead to greater severity of CVD conditions and use of multiple treatments. Additionally, metabolic dysregulation due to certain antipsychotic and antidepressant medications could prompt a greater need for CVD treatment [57, 79]. Recent studies have also described that statins and antidiabetic medications may be added to antidepressant treatment regimens to target the frequent cooccurrence of CV risk factors and depression [80]. Importantly, the differences in the definitions of CVD risk factors between the PCARES sample and the U.S. population sample may also explain the increased indicated medication prevalence in the former. For example, in the PCARES sample, HTN was defined based on clinician diagnosis and/or indicated medication prescriptions, whereas the definition for the U.S. population sample additionally included blood pressure cut-offs [31], which might exclude those with HTN receiving antihypertensive treatment. Additionally, in the NHANES questionnaire [81], a single question was used to ascertain CVD medication use, and it was required to be answered by only those participants who answered yes to physician diagnosis of that particular CVD, possibly underestimating CVD medication prevalence. Conversely, in the PCARES sample, medication use for a particular CVD risk factor was calculated using the composite variable as the denominator. Certain attributes of EHR data also need to be considered when describing medication burden. First, the use of generic names for prescribing in the EHR can significantly overestimate generic drug prescriptions [82]; second, duplicate mentions of prescriptions in the EHR, due to inconsistent data collection processes, have been linked with prescription overestimation [83]; and finally, medications in the EHR represent written prescriptions, not filled prescriptions, and do not guarantee actual medication use [84].

Our study has several strengths. EHR data are clinician-documented and collected in near real-time, which minimized misclassification bias and recall bias. Combining diagnostic and therapeutic information increased the likelihood of CVD ascertainment [16]. Additionally, NHANES provided a representative U.S. population sample, and adjusting NHANES results to PCARES demographics enabled statistically rigorous and valid comparisons. Finally, two study windows ensured the reporting of CVD prevalence estimates with greater rigor.

A primary limitation of our study is that it uses a clinical sample of convenience, which limits the external generalizability and interpretation of our findings. Furthermore, the PCARES sample is a health service sample with a greater likelihood of receiving healthcare services and consequently having a greater CVD burden [78]. The extent to which our results may be impacted by the methodologic differences between the two study populations cannot be estimated. Existing studies reported a higher prevalence of chronic health conditions in medical records compared to administrative data or health surveys [85, 86]. Moreover, the prevalence of chronic health conditions in EHR data and health survey data significantly differs by gender and age [87]. In our study, we adjusted the CVD burden in the U.S. population to PCARES age, race, and sex statistics. Additionally, unmeasured and residual confounding is possible in PCARES data due to the lack of information on alcohol use, diet, physical activity, medication compliance, and severity of CVD or mental illness, among other factors. Misclassification bias is likely as individual chart reviews were not performed. Although antipsychotic and antidepressant medications can contribute to metabolic dysregulation, we did not assess their impact in our study. Thus, for accurate interpretation of our results, it is key to consider the purposes for which EHR data were initially collected [84].

4.7. Future Directions. Research describing the barriers and solutions towards the widespread implementation of integrated healthcare models is warranted. Additional studies are needed to confirm our findings, especially using EHR data, which is representative of real-world data and used for clinical decision-making.

5. Conclusions

We report a higher CVD burden in a sample of individuals seen in a psychiatric clinic compared to a sample of the U.S. general population. Our results have implications for various healthcare domains: (i) for healthcare systems, we corroborate existing evidence towards the long overdue need for integrated mental and physical healthcare services for

psychiatric patients [88]; (ii) for healthcare professionals, we recommend evaluating the risks and benefits of mental health screening in primary care and addressing preclinical CVD risk factors (e.g., physical inactivity) among psychiatric patients [44]; (iii) for researchers, we highlight the need to better understand the pathways between mental and physical health to address health disparities among vulnerable populations [89]; and (iv) for policy-makers, we urge special attention to persons with mental illness in cardiovascular health improvement programs [90]. Integrated mental and physical healthcare services and addressing preclinical CVD risk factors could improve quality of life and reduce healthcare costs, long-term disability, and premature mortality among persons with mental illness.

Abbreviations

AHFS: American Hospital Formulary Service
BMI: Body mass index
CDC: Centers for Disease Control and Prevention
CHD: Coronary heart disease
CHF: Congestive heart failure
CL: Confidence limits
CVD: Cardiovascular disease
EHR: Electronic health record
FPG: Fasting plasma glucose
HbA1C: Glycosylated hemoglobin
HDL-C: High-density lipoprotein cholesterol
HMO: Health maintenance organizations
HTN: Hypertension
ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification
LDL-C: Low-density lipoprotein cholesterol
MDD: Major depressive disorder
MEC: Mobile examination center
NHANES: National Health and Nutrition Examination Survey
PCARES: Penn State Psychiatry Clinical Assessment and Rating Evaluation System
PPO: Preferred provider organizations
PHQ-9: 9-item patient health questionnaire
SD: Standard deviation
SE: Standard error
SMI: Severe mental illness
T2DM: Type 2 diabetes mellitus
TC: Total cholesterol
TG: Triglycerides.

Data Availability

The datasets used for the current study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was conducted according to the ethical principles of the Declaration of Helsinki of 1975, as revised in 2008 and approved by the Institutional Review Board at the Penn State University College of Medicine (reference #19937). Our study used deidentified datasets, which were not considered human subject research by our institution's IRB.

Disclosure

Preliminary results of this study were submitted as an abstract and subsequently presented in an oral presentation at the American Heart Association's EPI/Lifestyle Meeting in May 2021 (Circulation. 2021; 143: A060. Available at doi:10.1161/circ.143.suppl_1.060).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

R.D was responsible for data management and analyses, preparation of tables, interpretation of results, writing the original draft, reviewing, and editing. F.H was responsible for data curation and management, supervision, interpretation of results, writing, reviewing, and editing. E.S., D.W., A.P., E.B., and A.S were responsible for project administration, interpretation of results, writing, reviewing, and editing. J.G., L.A., J.Y., and V.M were responsible for interpretation of results, supervision, writing, reviewing, and editing. D.L was responsible for conceptualization, supervision, interpretation of results, writing the original draft, reviewing, and editing. All authors reviewed the manuscript and approved the final version.

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Supplementary Materials

The information in supplementary table 1 describes the assessment of CVD conditions and risk factors for the U.S. population sample using NHANES data. Supplementary table 2 uses the secondary baseline study window to compare the CVD burden in the PCARES sample to the CVD burden in the U.S. population sample (NHANES sample). Supplementary Table 1: diagnostic criteria for cardiovascular conditions and risk factors in the NHANES sample. Supplementary Table 2: comparisons of the means and proportions (95% CL) of CVD metabolic markers, conditions, and risk factors in the PCARES* sample to the age-, sex-, and race-adjusted means and proportions (95% CL) in the U.S. population sample (NHANES). *(Supplementary Materials)*

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