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Depression and cardiovascular risk in primary care patients

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ABSTRACT

Objective: This study assessed the relationship of both depression diagnosis and clinically significant depressive symptoms with individual cardiovascular risk factors and estimated total cardiovascular risk in primary care patients.

Methods: This study used a cross-sectional and retrospective design. Patients who had a primary care encounter between January 2016 and September 2018 and completed depression screening (PHQ-9) during the year prior to their appointment ($N = 70,980$) were included in this study. Data examining estimated total cardiovascular risk, specific cardiovascular risk factors, and relevant clinical diagnoses (including depression diagnosis) were extracted from the electronic health record. Patients were categorized into three groups: no depression (PHQ-9 < 10 and no depression diagnosis), controlled depression (PHQ-9 < 10 with previous depression diagnosis), and current depression (PHQ-9 ≥ 10). Groups were compared on estimated total risk and specific cardiovascular risk factors (e.g., body mass index [BMI], smoking status, lipids, blood pressure, and glucose).

Results: In adjusted analyses, patients with current depression ($n = 18,267$) demonstrated significantly higher 10-year and 30-year cardiovascular risk compared to patients with controlled depression ($n = 33,383$; 10-year: b = 0.59 [95% CI = 0.44,0.74]; 30-year: OR = 1.32 [95% CI = 1.26,1.39]) and patients without depression ($n = 19,330$; 10-year: b = 0.55 [95% CI = 0.37,0.73]; 30-year: OR = 1.56 [95% CI = 1.48,1.65]). Except for low-density lipoprotein (LDL), patients with current depression had the greatest cardiovascular risk across specific risk factors.

Conclusions: Individuals who had a depression diagnosis and clinically significant depressive symptoms had the greatest cardiovascular risk. Pathways to prevent cardiovascular disease in those with depression might focus on treating depressive symptoms as well as specific uncontrolled cardiovascular risk factors.

1. Introduction

Depression affects approximately 10% of adults at some point in their lifetime [1] and is considered the leading cause of disability around the world [2]. In addition to being a debilitating chronic condition in its own right, depression is also a risk factor for cardiovascular disease (CVD) morbidity and mortality [3]. In several meta-analyses examining the rates of CVD among people with depression, patients with depression demonstrated an increased risk of CVD ranging from 30% to 80% [4].

Despite the robust association between depression and CVD, the mechanisms linking depression to increased risk for CVD are still unclear. Many hypotheses have been proposed, including shared biological pathways (e.g., inflammation, activation of the hypothalamic-pituitary-adrenal [HPA] axis) and suboptimal health behaviors (e.g., physical inactivity, smoking, medication non-adherence) [3]. To elucidate potential mechanisms, several studies have examined factors that may explain the relationship between depression and cardiovascular risk. For example, two large studies have demonstrated that depression did not enhance the impact of hypertension, dyslipidemia, or diabetes on

Acronyms: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, Body Mass Index; BP, Blood Pressure; CV, cardiovascular; CVD, Cardiovascular Disease; DBP, diastolic blood pressure; EHR, Electronic health record; HDL, high-density lipoprotein; HPA, hypothalamic-pituitary-adrenal; LDL, low-density lipoprotein; SBP, systolic blood pressure.

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cardiovascular events [5] nor was it related to medication non-adherence for the same conditions [6]. Many studies have examined factors that may account for the associations between depression and CVD among patients with clinically diagnosed depression or established CVD [7], yet more studies examining the associations between depression and cardiovascular risk in non-diseased populations are emerging [8]. Work needs to be done to further understand how depression is related to cardiovascular risk factors, ultimately elucidating mechanisms linking depression and CVD.

In addition to depression diagnosis, examining depression symptoms in relation to cardiovascular risk factors may be important for a disease that is variable in severity. Indeed, evidence suggests that individuals with elevated depressive symptoms, regardless of whether the person has a clinical diagnosis of depression, are at increased risk of cardiovascular events [9,10]. Thus, accounting for the presence of clinically significant depression symptoms may be helpful in further understanding the associations between depression and CVD.

Notably, studies have examined the presence of clinically significant depression symptoms in relation to cardiovascular risk factors. Kronish and colleagues [11] examined depressive symptoms in relation to cardiovascular health (measured by the American Heart Association's Life's Simple 7 [12], which includes measures of physical activity, smoking, diet, body mass index [BMI], blood pressure [BP], cholesterol, and glucose) in 20,093 adults ≥45 years old. They found that patients with clinically significant depressive symptoms had poorer overall cardiovascular health, with lower scores across six of the seven cardiovascular risk factors (BMI, physical activity, diet, BP, glucose, and smoking). Another study of Brazilians demonstrated that those with clinically significant depressive symptoms had poorer cardiovascular health (a composite of 5 cardiovascular risk factors: BMI, BP, smoking, lipids, and diabetes), and this effect was stronger in women than in men [13]. Two studies have demonstrated that greater depressive symptoms are associated with greater estimated cardiovascular risk, as measured by composite cardiovascular risk scores [14,15]. Song et al. [14] studied a national sample in Korea and categorized subjects based on depressive symptom severity. They found that greater depressive symptom severity was associated with greater estimated total cardiovascular risk, higher BMI (among women only), being a smoker, increased fasting blood sugar, and taking diabetes and antihypertensive medications. However, they found no association between depressive symptoms and waist circumference, BP, physical activity, or total cholesterol. Although these studies had some similar findings, neither took current or past depression diagnosis into account when considering the association between the presence of clinically significant depressive symptoms and cardiovascular risk.

To address this limitation of previous research, the purpose of this study was to examine both depression diagnosis and the presence of clinically significant depressive symptoms in relationship to estimated total cardiovascular risk and specific cardiovascular risk factors among primary care patients. We hypothesized that patients with current depression (those with elevated depression symptoms at the time of the encounter), compared to patients with controlled depression (those who had a previous diagnosis of depression but no clinically significant depressive symptoms) or no depression (no clinical diagnosis of depression and no clinically significant depressive symptoms), would have the highest estimated total cardiovascular risk (as measured by 10-year and 30-year risk equations) and elevation of specific risk factors (especially BMI and smoking status).

2. Methods

2.1. Study design and settings

Fifty-five primary care clinics in Minnesota and Wisconsin that are part of two healthcare delivery organizations (HealthPartners and Park Nicollet) participated in a larger trial of clinical decision support (CDS) to reduce cardiovascular risk in patients with serious mental illness [16]. The CDS system is a web-based tool embedded in the electronic health record (EHR) that collects relevant clinical data and uses clinical algorithms to provide clinicians evidence-based suggestions for addressing cardiovascular risk among patients with elevated risk. Study enrollment occurred between January 20, 2016 and September 19, 2018. For this study, data from all index (baseline) primary care encounters (not just those of patients with serious mental illness) at randomized clinics during the enrollment period were examined. The HealthPartners Institutional Review Board approved this study (#A13–154) with a waiver of informed consent.

2.2. Enrollment and eligibility

Eligible patients had an index encounter, defined as the first encounter at a randomized primary care clinic during the enrollment period that met the following criteria: (a) Aged 18 to 75 years, inclusive, at index encounter date; (b) Not pregnant; (c) No active cancer diagnosis; and (d) Not residing in a nursing home or receiving hospice care. Patients were retained for the secondary analyses presented here if they had completed the Patient Health Questionnaire-9 (PHQ-9) in the year prior to their index encounter. The PHQ-9 is the preferred depression screening tool in the health system, and it is also used to monitor depression in those with an existing depression diagnosis. In addition, patients who requested to be excluded from research studies at their healthcare systems (less than 1% of patients) were omitted from analyses.

2.3. Data sources

Much of the data collection was done by the CDS system itself, which harvested EHR data for each web service call. The CDS collected data on age, sex, race, vitals, medications, diagnoses, and orders. Data not routinely collected by the CDS (e.g., ethnicity, insurance status, PHQ-9 score) were retrieved from the EHR data repository.

2.4. Measures

2.4.1. Demographic characteristics

Age, race, ethnicity, sex, and insurance type were all extracted from the EHR. Age in years was calculated on the date of the index encounter. Race was categorized as American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, white, multiple races, other race, or unknown. Ethnicity was categorized as Hispanic or Latino/a, not Hispanic or Latino/a, or unknown. Sex was categorized as male or female. Insurance type was categorized as self-pay/uninsured, Medicare only, Medicaid only, commercial only, other only, Medicare and Medicaid, Medicare and commercial, or 2 or more insurance types.

2.4.2. Depressive symptoms

The PHQ-9 measures depressive symptoms based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for a major depressive episode [17]. Patients rate the frequency of their symptoms over the past two weeks on a scale from 0 (Not at all) to 3 (Nearly every day). Item scores are summed for a total score with a possible range of 0–27, with higher scores corresponding to more frequent and severe depressive symptoms. A cut-score of 10 is used as a positive screen for major depression and indicates clinically significant depressive symptoms. Evidence suggests that a cut-point of 10 has a sensitivity of 88% and a specificity of 88% for detecting major depressive disorder [17]. At these health care delivery organizations, the PHQ-9 is typically self-administered immediately prior to primary care and behavioral health encounters as a routine screening and monitoring instrument. The most recent PHQ-9 score in the year prior to the index encounter was used for analyses. In our sample, the internal consistency

reliability of the PHQ-9 was very high (Cronbach's α = 0.89).

2.4.3. Depression diagnosis

Patients were considered to have a diagnosis of depression if they had at least one diagnostic code on the problem list or two diagnostic codes at outpatient encounters documented in the EHR in the two years prior to index date. See Supplemental Table 1 for specific ICD-9 and ICD-10 codes used for depression classification.

2.4.4. Estimated total cardiovascular risk

Cardiovascular risk was calculated using two different equations. For patients aged 40–75 years without CVD, 10-year cardiovascular risk was estimated using the 10-year atherosclerotic CVD (ASCVD) risk score determined by the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Risk Equation [18,19]. This score theoretically ranges from 0 to 100% and corresponds to the percent likelihood of a fatal or nonfatal ASCVD event in the next 10 years. The risk equation takes the following risk factors into account: age, sex, race/ethnicity, total cholesterol, high-density lipoprotein (HDL), systolic BP (SBP), antihypertensive medication use, smoking status, and diabetes status. For patients aged 18–59 years without CVD, 30-year (sometimes referred to as lifetime) cardiovascular risk was estimated [20]. Patients were categorized into one of five groups based on risk factors (BP, lipids, diabetes status, and smoking status): (1) *risk factors optimal* (BP <120/<80 mmHg, total cholesterol <180 mg/dL, non-smoker, non-diabetic); (2) *1+ risk factor suboptimal* (SBP 120 to 139 mmHg, diastolic BP [DBP] 80 to 89 mmHg, total cholesterol 180 to 199 mg/dL, non-smoker, non-diabetic); (3) *1+ risk factor elevated* (total cholesterol 200 to 239 mg/dL, SBP 140 to 159 mmHg, DBP 90 to 99 mmHg, non-smoker, non-diabetic); (4) *1 major risk factor;* or (5) *2+ major risk factors* (total cholesterol ≥240 mg/dL, SBP ≥ 160 mmHg, DBP ≥ 100 mmHg, smoker, or diabetic). Patients with CVD were not included in the analyses examining either ASCVD risk or 30-year cardiovascular risk.

2.4.5. Cardiometabolic and mental health diagnoses

Patients were considered to have diagnoses for coronary heart disease (CHD), CVD, hypertension (HTN), diabetes mellitus (DM), anxiety, or insomnia if they had at least one diagnostic code on the problem list or two diagnostic codes at outpatient encounters documented in the EHR in the two years prior to index date. See Supplemental Table 1 for specific ICD-9 and ICD-10 codes used for each disease classification.

2.4.6. Cardiovascular risk factors

Six domains of cardiovascular risk were captured by the CDS system: BP (SBP and DBP), lipids (total cholesterol, low density lipoprotein cholesterol [LDL], high density lipoprotein cholesterol [HDL], triglycerides, and statin use), glucose (hemoglobin A1C), weight (BMI; kg/m^2), and smoking status (current, former, or nonsmoker). BP and weight were captured at the encounter. For smoking status, A1C, and lipids, the most recent value in the last 5 years was used for analyses. Although specific recommendations for cardiovascular risk vary based on a person's age and health status, in general recommended levels for optimal cardiovascular risk for these factors include: SBP < 130 mmHg, DBP < 80 mmHg, LDL < 100 mg/dL, HDL ≥ 60 mg/dL, triglycerides <150 mg/dL, A1C < 7.0% (up to 8.0% for some people with DM), BMI of 18.5–24.9 kg/m^2, and nonsmoker status.

2.5. Analysis

Data were cleaned and analyzed using SAS 9.4. Missing data were assumed to be missing at random (MAR). In an EHR data study that uses data collected as part of usual care, the absence of documentation of a laboratory test, prescription order, care process, or vital sign should not be interpreted as a missing value but rather as indicative of a care process or test that was not performed. Truly missing observations (e.g., lab test performed but not documented) are extremely rare, undetectable, and assumed to be MAR.

Participants were categorized into one of three groups based on depression diagnoses (based on EHR diagnosis) and PHQ-9 scores: (1) No Depression (no depression diagnosis and most recent PHQ-9 < 10); (2) Controlled Depression (depression diagnosis and most recent PHQ-9 < 10); and (3) Current Clinically Significant Depressive Symptoms (hereafter referred to as "Current Depression"; most recent PHQ-9 ≥ 10, regardless of depression diagnosis). Patients with PHQ-9 scores ≥10 who did not have a diagnosis of depression in the EHR were included in the current depression group because they were assumed to have a high likelihood of having a depression diagnosis that had not yet been documented.

Descriptive statistics were calculated to examine unadjusted differences in demographic characteristics (age, sex, race, ethnicity, and insurance coverage) and cardiovascular risk factors among the three groups. Given the large sample size, alpha was set to 0.01. General linear models were used to examine differences among the groups for continuous variables (e.g., 10-year ASCVD risk) and χ^2 analyses were used to examine differences among categorical variables (e.g., smoking status). Due to significant differences among groups in demographic characteristics, models were then adjusted for age, sex, race, ethnicity, and insurance type to examine differences in cardiovascular risk. These factors were chosen because they have been previously linked to cardiovascular risk, and insurance type was used as a proxy for socioeconomic status. General linear models were used for continuous variables (ASCVD risk, BP, lipids, BMI, and A1C), and logistic regression models were used for categorical variables. Different types of logistic regression were used for different variables: binary logistic regression was used for dichotomous dependent variables (presence or absence of diagnoses including CHD, CVD, DM, and HTN), ordinal regression was used for the ordinal dependent variable (30-year lifetime risk), and multinomial regression was used for the categorical dependent variable (smoking status).

For adjusted estimates, regression coefficients and adjusted marginal means or odds ratios (ORs) with 95% confidence intervals (CIs) and predicted percentages with 95% CIs were calculated based on the appropriate analysis (general linear regression or logistic regression, respectively). Adjusted marginal means and predicted percentages were calculated using observed margins for covariates. In secondary models, we examined whether the association between depression group and estimated cardiovascular risk (10-year ASCVD risk or 30-year lifetime risk) was moderated by age and sex by adding interaction terms to the adjusted models.

3. Results

A total of 655,129 unique adult patients had primary care encounters at a randomized clinic during the study period. After applying study eligibility criteria, 591,257 patients were considered for analyses. Of eligible patients, 70,980 (12%) had completed the PHQ-9 within the last year and were included in the main analyses. Patients with completed PHQ-9s were slightly older (M = 45.9 years, SD = 15.8 v. M = 45.2, SD = 15.7), were more likely to be female (70% v. 52%), were more likely to be white (86% v. 76%), were more likely to be non-Hispanic (85% v. 74%), had lower ASCVD (10-year) risk (M = 7.2%, SD = 8.0 v. M = 8.1, SD = 8.5), and had higher lifetime (30-year) cardiovascular risk (61% with ≥1 major risk factor v. 51% with ≥1 major risk factor) than patients who did not have a completed PHQ-9.

A total of 18,267 patients (24.1%) were categorized as having current depression, whereas 33,383 (47.0%) had controlled depression and 19,330 (27.2%) had no depression. Of the patients with clinically significant depressive symptoms at the encounter (PHQ-9 score ≥ 10), 79% had a prior diagnosis of depression. On average, patients with current depression were younger, more likely to be females and racial minorities, more likely to have Medicaid than commercial insurance, and more likely to have diagnoses of anxiety and insomnia (see Table 1)

Table 1
Differences by depression status: demographics, estimated total and specific cardiovascular risk in primary care patients (N = 70,980).

Patient characteristic	No Depression				Controlled Depression				Current Depression				*p*
	n = 19,330 (27.2%)				n = 33,383 (47.0%)				n = 18,267 (25.7%)				
	n	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	
Age			44.6*†	16.1			48.7†	15.3			42.4	15.3	<0.001
Female	12936*†	66.9			23,793	71.3			12,924	70.8			<0.001
Race													<0.001
White	16764*†	86.7			29,900†	89.6			14,663	80.3			
Black or African American	1110	5.7			1520	4.6			1857	10.2			
Asian	588	3.0			625	1.9			562	3.1			
Native American/Alaska Native	44	0.2			118	0.4			112	0.6			
Native Hawaiian/Pacific Islander	23	0.1			41	0.1			35	0.2			
Multiple	80	0.4			127	0.4			134	0.7			
Other	142	0.7			188	0.6			177	1.0			
Unknown	579	3.0			864	2.6			727	4.0			
Ethnicity													<0.001
Hispanic	463†	2.4			738†	2.2			676	3.7			
Non-Hispanic	16,466	85.2			28,344	84.9			15,293	83.7			
Unknown	2401	12.4			4301	12.9			2298	12.6			
Insurance Type													<0.001
Self-pay/Uninsured	280*†	1.5			546†	1.6			341	1.9			
Medicare Only	1704	8.8			4149	12.4			1355	7.5			
Medicaid Only	1803	9.3			3576	10.7			4039	22.1			
Commercial Only	11,754	60.8			17,281	51.8			7619	41.7			
Other Only	169	0.9			284	0.9			169	0.9			
Medicare + Medicaid	418	2.2			812	2.4			834	4.6			
Medicare + Commercial	724	3.8			1430	4.3			492	2.7			
2 or more insurances	2478	12.8			5305	15.9			3418	18.7			
10-year ASCVD risk‡			7.0*	8.1			7.3	7.8			7.1	8.1	0.010
30-year Lifetime risk§													<0.001
All optimal risk factors	1506*†	15.6			2061†	12.4			1066	11.4			
≥ 1 not optimal risk factors	2406	24.9			3619	21.8			1761	18.7			
≥ 1 elevated risk factors	549	5.7			768	4.6			354	3.8			
1 major risk factor	4007	41.4			7511	45.1			4264	45.4			
≥ 2 major risk factors	1209	12.5			2683	16.1			1950	20.8			
CHD	594*	3.1			1354†	4.1			635	3.5			<0.001
CVD	844*†	4.4			2000†	6.0			931	5.1			<0.001
Blood Pressure (BP)													
HTN	2751*†	14.2			5789†	17.3			2333	12.8			<0.001
SBP (mmHg)			121.6*†	15.5			122.1†	15.5			121.2	15.6	<0.001
DBP (mmHg)			75.4*†	10.8			75.9†	10.7			76.5	11.0	<0.001
Lipids													
LDL (statin only)			99.1	36.0			97.7†	34.8			100.3	38.0	0.002
LDL (non-statin only)			113.1*	30.9			115.9†	32.4			112.7	33.4	<0.001
HDL			53.9†	16.8			53.4†	17.0			51.2	16.4	<0.001
Triglycerides			126.6*†	93.7			134.5†	97.7			144.1	112.2	<0.001
Statin use	3597*†	18.6			8120†	24.3			3197	17.5			<0.001
Glucose													
DM	1506*†	7.8			3821†	11.5			1981	10.8			<0.001
A1c (DM only)‖			7.2†	1.4			7.2†	1.5			7.5	1.8	<0.001
Weight: BMI (kg/m^2)			28.6*†	6.8			30.2†	7.4			30.8	8.3	<0.001
Smoking status													<0.001
Current smoker	2248*†	11.6			4793†	14.4			4446	24.3			
Former smoker	4759	24.6			10,248	30.7			4901	26.8			
Nonsmoker	12,323	63.8			18,341	54.9			8920	48.8			
Mental Health Disorders													
Anxiety	10246*†	53.0			22,183†	66.5			14,112	77.3			<0.001
Insomnia	781*†	4.0			2516†	7.5			1717	9.4			<0.001

Note. *p*-values correspond to the omnibus test for depression group (no depression, controlled depression and current depression) in each analysis (*F* test for continuous variables or Wald χ^2 for categorical variables). ASCVD = 10-year atherosclerotic cardiovascular disease risk; BMI = Body mass index; CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; DBP = Diastolic blood pressure; DM = Diabetes Mellitus; HDL = high density lipoprotein; HTN = Hypertension; LDL = low density lipoprotein; SBP = Systolic blood pressure.

* Significantly different from Controlled Depression, $p < .01$.

† Significantly different from Uncontrolled Depression, $p < .01$.

‡ ASCVD risk is only calculated for patients age 40–75 without known CVD ($n = 36,328$).

§ 30-year lifetime risk of cardiovascular disease is only calculated for patients ages 18–59 without known CVD ($n = 35,714$).

‖ Calculated for patients with DM who have available A1c tests within the last 5 years ($n = 7157$).

compared to patients with no depression. Patients with controlled depression were older, more likely to be female and white, and to have Medicare than patients with no depression.

3.1. Unadjusted differences in cardiovascular risk between patients with no depression, controlled depression and current depression

In the unadjusted analyses, patients with controlled depression had the poorest cardiovascular risk profiles compared to patients with

current depression and no depression (see Table 1). Patients with controlled depression had higher 10-year cardiovascular risk; were more likely to be diagnosed with CHD, CVD, HTN, and DM; were more likely to be taking a statin; and had the highest SBP, DBP, and total cholesterol compared to patients with current depression or without depression (see Table 1). Conversely patients with current depression demonstrated the greatest lifetime risk (30-year) compared to patients with controlled depression or no depression, with a greater proportion of patients having ≥2 major risk factors than patients with current depression. This greater lifetime risk was reflected in specific cardiovascular risk factors, with patients in current depression having higher BMIs, being twice as likely to be current smokers, having the highest LDL (among those not taking statins) and triglycerides, and having the lowest HDL.

3.2. Adjusted differences in cardiovascular risk between patients with no depression, controlled depression and current depression

After adjusting for age, race, ethnicity, sex, and insurance type, patterns shifted so that patients with current depression had the poorest cardiovascular risk profiles, compared to patients without depression and those with controlled depression (see Tables 2 and 3 and Supplemental Table 2). Patients with current depression had significantly higher 10-year ASCVD risk compared to patients with controlled depression (b = 0.59, 95% CI = 0.44, 0.74) and patients without depression (b = 0.55, 95% CI = 0.37, 0.73). A similar pattern was seen for 30-year lifetime risk. Patients with current depression had greater odds of being in a higher risk factor category than patients with controlled depression (OR = 1.32, 95% CI = 1.26, 1.39) and patients without depression (OR = 1.56, 95% CI = 1.48, 1.65). There was no significant difference between patients with controlled depression and patients without depression on 10-year ASCVD risk; however, patients with controlled depression had greater odds of being in a higher risk factor category that patients without depression (OR = 1.18, 95% CI = 1.13, 1.24).

Patients with current depression had greater odds of being diagnosed with CHD, CVD, and DM than patients with controlled depression (CHD: OR = 1.34, 95% CI = 1.20, 1.48; CVD: OR = 1.29, 95% CI = 1.18, 1.40; DM: OR = 1.19, 95% CI = 1.12, 1.27) or patients without depression (CHD: OR = 1.51, 95% CI = 1.33, 1.71; CVD: OR = 1.50, 95% CI = 1.35, 1.66; DM: OR = 1.55, 95% CI = 1.43, 1.67). Patients with controlled depression also had greater odds of being diagnosed with CVD (OR = 1.17, 95% CI = 1.07, 1.27) and DM (OR = 1.30, 95% CI = 1.22, 1.39) compared to people without depression. Among people with DM, patients with current depression had significantly higher A1Cs than people with controlled depression (b = 0.22, 95% CI = 0.13, 0.31) and people without depression (b = 0.26, 95% CI = 0.15, 0.37). There were no differences in HTN diagnosis based on depression status, yet patients with current depression had slightly higher SBP and DBP compared to patients with controlled depression (SBP: b = 0.79, 95% CI = 0.52, 1.06; DBP: b = 0.83, 95% CI = 0.63, 1.03) or without depression (SBP: b = 0.34, 95% CI = 0.05, 0.63; DBP: b = 1.22, 95% CI = 1.00, 1.43). Patients with controlled depression also had significantly higher DBP than patients without depression (b = 0.39, 95% CI = 0.20, 0.58).

Patients with current depression had significantly higher triglycerides and lower HDL than patients with controlled depression (triglycerides: b = 10.14, 95% CI = 7.93, 12.35; HDL: b = −1.21, 95% CI = −1.55, −0.87) and patients without depression (triglycerides: b = 17.83, 95% CI = 15.32, 20.33; HDL: b = −2.30, 95% CI = −2.69, −1.91). Further, patients with controlled depression also had significantly higher triglycerides and lower HDL than patients without depression (triglycerides: b = 7.69, 95% CI = 5.59, 9.79; HDL: b = −1.09, 95% CI = −1.42, −0.76). Among patients taking statins, there were no differences in LDL based on depression status; however, among patients not taking statins, patients with current depression had significantly higher LDL compared to patients without depression (b = 1.62, 95% CI = 0.70, 2.54).

As with the unadjusted analyses, patients with current depression had significantly higher BMIs and had greater odds of being current

Table 2
Adjusted models predicting estimated total and specific cardiovascular risk of patients with current or controlled depression compared patients without depression.

	Controlled Depression				Current Depression				
Dependent variable	B	OR	95% LL	95% UL	B	OR	95% LL	95% UL	p
10-year ASCVD risk‡	−0.04		−0.18	0.10	0.55		0.37	0.73	<0.001
30-year Lifetime risk§		1.18	1.13	1.24		1.56	1.48	1.65	<0.001
CHD		1.13	1.02	1.26		1.51	1.33	1.71	<0.001
CVD		1.17	1.07	1.27		1.50	1.35	1.66	<0.001
BP									
HTN		1.06	1.01	1.12		1.03	0.96	1.09	0.068
SBP (mmHg)	−0.45		−0.71	−0.19	0.34		0.05	0.63	<0.001
DBP (mmHg)	0.39		0.20	0.58	1.22		1.00	1.43	<0.001
Lipids									
LDL (statin only)	−1.85		−3.24	−0.45	−0.21		−1.95	1.53	0.012
LDL (non-statin only)	1.59		0.81	2.37	1.62		0.70	2.54	<0.001
HDL	−1.09		−1.42	−0.76	−2.30		−2.69	−1.91	<0.001
Triglycerides	7.69		5.59	9.79	17.83		15.32	20.33	<0.001
Glucose									
DM		1.30	1.22	1.39		1.55	1.43	1.67	<0.001
A1c (DM only)‖	0.04		−0.05	0.13	0.26		0.15	0.37	<0.001
Weight: BMI (kg/m^2)	1.23		1.09	1.37	2.12		1.96	2.28	<0.001
Smoking status									<0.001
Current smoker		1.35	1.28	1.43		2.23	2.10	2.40	
Former smoker		1.26	1.21	1.32		1.48	1.41	1.56	
Nonsmoker		REF				REF			

Note. Models adjusted for age, sex, race, ethnicity, and insurance type. No depression is the reference category. *p*-values correspond to the omnibus test for depression group (no depression, controlled depression and current depression) in each analysis (*F* test for continuous variables or Wald χ^2 for categorical variables). ASCVD = 10-year atherosclerotic cardiovascular disease risk; B = unstandardized regression coefficient; BMI = Body mass index; CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; DBP = Diastolic blood pressure; DM = Diabetes Mellitus; HDL = high density lipoprotein; HTN = Hypertension; LDL = low density lipoprotein; LL = Lower 95% Confidence Limit; M = Predicted Mean; OR = Odds ratio; P% = predicted percent; SBP = Systolic blood pressure; REF = Reference; UL = Upper 95% Confidence Limit.

‡ ASCVD risk is only calculated for patients age 40–75 without known CVD (n = 36,328).

§ 30-year lifetime risk of cardiovascular disease is only calculated for patients ages 18–59 without known CVD (n = 35,714).

‖ Calculated for patients with DM who have available A1c tests within the last 5 years (n = 7157).

Table 3
Differences by Depression Status: Adjusted estimates of estimated total and specific cardiovascular risk factors.

Patient characteristic	No Depression				Controlled Depression				Current Depression			
	n = 19,330 (27.2%)				n = 33,383 (47.0%)				*n* = 18,267 (25.7%)			
	M	P%	95% LL	95% UL	M	P%	95% LL	95% UL	M	P%	95% LL	95% UL
10-year ASCVD risk[‡]	7.05[†]		6.94	7.16	7.00[†]		6.93	7.08	7.60		7.47	7.71
30-year Lifetime risk[§]												
All optimal risk factors		12.82[*†]	12.33	13.33		11.07[†]	10.69	11.46		8.62	8.25	9.03
≥ 1 not optimal risk factors		24.66	24.16	25.16		22.95	22.21	29.97		19.15	18.77	19.53
≥ 1 elevated risk factors		5.40	4.49	6.31		5.19	4.50	5.88		4.72	3.90	5.54
1 major risk factor		45.25	44.30	46.20		47.42	46.69	48.15		50.15	49.26	51.04
≥ 2 major risk factors		11.87	11.87	12.34		13.73	13.30	14.17		17.36	16.74	17.99
CHD		0.91[†]	0.80	1.02		1.00[†]	0.93	1.13		1.36	1.22	1.52
CVD		1.64[*†]	1.49	1.80		1.90[†]	1.76	2.06		2.43	2.23	2.65
BP												
HTN		10.28	9.85	10.73		10.86	10.50	11.22		10.52	10.06	10.99
SBP (mmHg)	121.84[†]		121.64	122.05	121.39[†]		121.24	121.55	122.18		121.97	122.40
DBP (mmHg)	75.44[*†]		75.28	75.59	75.83[†]		75.71	75.94	76.66		76.50	76.82
Lipids												
LDL (statin only)	99.66		98.50	100.83	97.81		97.04	98.59	99.45		98.19	110.72
LDL (non-statin only)	113.41[*†]		112.78	114.04	115.00		114.54	115.49	115.03		114.37	115.70
HDL	54.18[*†]		53.92	54.45	53.09[†]		52.90	53.28	51.88		51.60	52.17
Triglycerides	126.73[*†]		125.01	128.44	134.41[†]		133.18	135.65	144.55		142.72	146.39
Glucose												
DM		5.15[*†]	4.86	5.46		6.61[†]	6.33	6.89		7.75	7.37	8.16
A1c (DM only)[‖]	7.20[†]		7.12	7.27	7.24[†]		7.19	7.29	7.46		7.39	7.53
Weight: BMI (kg/m^2)	28.78[*†]		28.67	28.89	30.01[†]		29.93	30.10	30.90		30.78	31.02
Smoking status												
Current smoker		11.73[*†]	11.26	12.19		14.35[†]	13.96	14.74		20.72	20.11	21.33
Former smoker		24.65	24.02	25.28		28.16	27.65	28.66		28.91	28.21	29.61
Nonsmoker		63.62	62.92	64.33		57.49	56.94	58.05		50.37	49.60	51.14

Note. Models adjusted for age, sex, race, ethnicity, and insurance type. ASCVD = 10-year atherosclerotic cardiovascular disease risk; BMI = Body mass index; CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; DBP = Diastolic blood pressure; DM = Diabetes Mellitus; HDL = high density lipoprotein; HTN = Hypertension; LDL = low density lipoprotein; LL = Lower 95% Confidence Limit; M = Predicted Mean; P% = predicted percent; SBP = Systolic blood pressure; UL = Upper 95% Confidence Limit.

[*] Significantly different from Controlled Depression, $p < .01$.

[†] Significantly different from Uncontrolled Depression, $p < .01$.

[‡] ASCVD risk is only calculated for patients age 40–75 without known CVD ($n = 36{,}328$).

[§] 30-year lifetime risk of cardiovascular disease is only calculated for patients ages 18–59 without known CVD ($n = 35{,}714$).

[‖] Calculated for patients with DM who have available A1c tests within the last 5 years ($n = 7157$).

smokers than patients with controlled depression (BMI: b = 0.89, 95% CI = 0.74, 1.04; OR [current smoker v. nonsmoker] = 1.65, 95% CI = 1.57, 1.73) and patients without depression (BMI: b = 2.12, 95% CI = 1.96, 2.28; OR [current smoker v. nonsmoker] = 2.23, 95% CI = 2.10, 2.40). Similarly, patients with controlled depression also had significantly higher BMIs and greater odds of being smokers compared to patients without depression (BMI: b = 1.23, 95% CI = 1.09, 1.37; OR [current smoker v. nonsmoker] = 1.35, 95% CI = 1.28, 1.43).

3.3. Moderator analyses

Because there was a 6-year age difference between patients with controlled depression and patients with current depression, we examined whether the relationship between estimated cardiovascular risk (as measured by 10-year ASCVD risk and 30-year lifetime risk) and depression group was moderated by age. There was a significant interaction between depression group and age on 10-year ASCVD risk, $F(2,36{,}305) = 5.06$, $p = .006$ (see Fig. 1). Specifically, across all ages, individuals with current depression had the highest 10-year ASCVD risk. At younger ages, such as age 40, individuals with controlled depression had higher ASCVD risk than those without depression, but this increased risk was attenuated at older ages. At age 70, individuals with controlled depression had lower 10-year ASCVD risk than those without depression. There was no significant interaction between age and depression group on 30-year lifetime risk, $\chi^2(2) = 0.33$, $p = .85$.

Because there are known sex differences in cardiovascular and depression risk, we examined whether the relationship between estimated cardiovascular risk and depression group was moderated by sex.

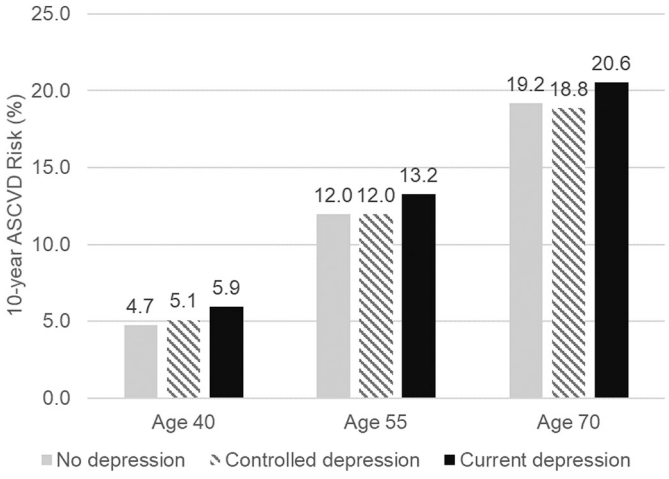

Fig. 1. Interaction between age and depression status on 10-year ASCVD risk.
Note. Estimated 10-year ASCVD risk using a general linear model with interaction terms between age and depression group. Equations were calculated to estimate risk for a white male with Medicaid insurance at age 40, 55, and 70.

There was no significant interaction effect on 10-year ASCVD risk between depression group and sex, $F(2,36{,}305) = 1.35$, $p = .26$. However, there was a significant interaction effect on 30-year lifetime risk between depression group and sex, $\chi^2(2) = 10.67$, $p = .005$ (see Fig. 2). Females with controlled depression had greater odds of being in higher

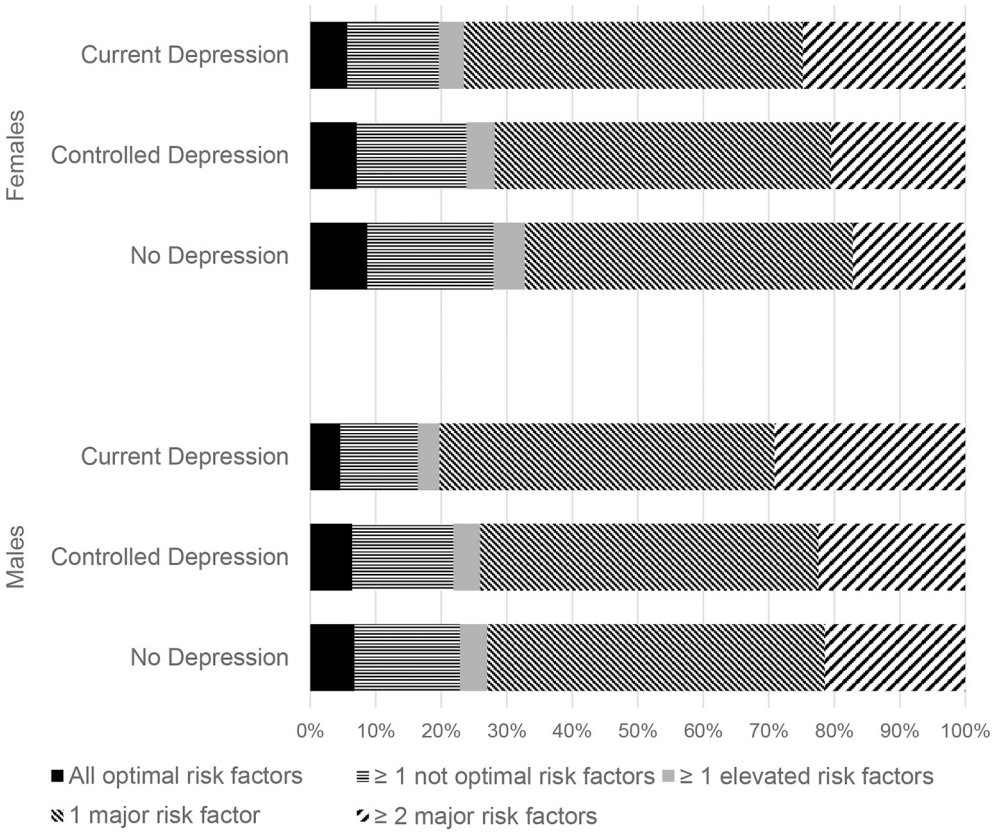

Fig. 2. Interaction between sex and depression status on 30-year lifetime risk: Estimated proportion in each 30-year lifetime risk category.
Note. Estimated proportion of participants that belong in each category of lifetime risk based on depression group and sex. Equations were calculated to estimate risk for a 45-year-old white person with Medicaid insurance.

risk categories compared to females without depression. Further, females with current depression had greater odds of being in a higher cardiovascular risk category than females with controlled depression or without depression. For males, however, there was almost no difference in odds between males without depression compared to males with controlled depression. However, males with current depression had greater odds of being in a higher cardiovascular risk category than both males with controlled depression and males without depression.

4. Discussion

The purpose of this study was to examine how both depression diagnosis and the presence of clinically significant depressive symptoms were related to estimated total and specific cardiovascular risk. After accounting for demographic differences, patients with current depression had greater cardiovascular risk, estimated total risk and across a variety of risk factors, than patients with controlled depression or patients without depression. Three risk factors - smoking status, BMI, and glucose control – demonstrated the largest differences among the groups. Patients with current depression were more likely to be smokers, had higher BMIs, and were more likely to have DM with poorer glucose control. Other risk factors, including lipids and BP, demonstrated small but perhaps not clinically significant differences among the groups, with patients with current depression having higher SBP, LDL (non-statin only), and triglycerides and lower HDL than patients with controlled depression or without depression. However, small differences across multiple cardiovascular risk factors may have added up to greater accumulated cardiovascular risk in patients with current depression. Further, patients with controlled depression had greater 30-year lifetime risk; had higher BMIs; were more likely to have DM, CVD, and CHD; and were more likely to be current smokers than patients without depression.

The primary strength of this study was its inclusion of a large sample of adults seeking primary care and all eligible primary care encounters over the enrollment period. Data were systematically collected through the EHR, improving the reliability of lab values, vital signs, diagnoses, and current medications rather than relying on patient-reported values. However, this study does have notable limitations. This study is cross-sectional, and causality cannot be determined; thus, we do not know if greater depressive symptoms led to greater cardiovascular risk or vice versa or whether behavioral or physiologic factors contribute to both depression and cardiovascular risk. Participants were primary care patients, and results may not be generalizable to people not seeking primary care services. Further, each participant had to have one completed PHQ-9 survey to be included in this study, which excluded many patients. As a result, patients who were included were more likely to have a mental health diagnosis, including depression or anxiety. Thus, the patients without depression group may have been less healthy than the overall primary care population without depression, suggesting this study may underestimate the differences in cardiovascular risk between those without depression and people with current or controlled depression.

Additionally, the measures of estimated cardiovascular risk (10-year ASCVD risk and 30-year lifetime risk) were only validated for individuals within certain age ranges (i.e., 40–75 years and 18–59 years, respectively); thus, analyses using these variables were conducted on different subsamples, which may make it more difficult to draw conclusions about the relationship between depression and cardiovascular risk. In addition, a few participants were missing lab values (e.g., cholesterol) or vital signs (e.g., BMI). Missing data were treated MAR; we do not know if people with depression are more or less likely to have missing data. However, we do know that most people with depression

receive care for their depression in primary care settings [21–24], and some evidence suggests that people with depression have more frequent encounters and more laboratory tests than patients without depression [25–27]. Thus, because people with depression make more visits to primary care than people without depression, we suspect there would be more opportunities for them to have testing and treatment for cardiovascular risk as well. Finally, because data were restricted to that available in the EHR, there was no information on important psychosocial and behavioral factors, including physical activity, diet, or socioeconomic status, which are known to be related to cardiovascular risk and depression.

Depression likely influences cardiovascular risk factors and CVD development through multiple pathways, including behavioral, stress-related, or physiological pathways [3,4,28]. For example, patients with depression demonstrate dysregulation of the HPA axis, leading to elevated corticosteroids, which have been known to induce hypercholesterolemia, hypertriglyceridemia, and hypertension [29]. Further, as demonstrated in this study, patients with depression are more likely to be smokers. Other studies have demonstrated that patients with depression are less likely to engage in physical activity and more likely to eat unhealthy diets, which can contribute to higher BMIs, and thus, greater cardiovascular risk [11,30,31]. Because the results of this study indicate differences across a wide variety of risk factors, it is likely that these behavioral, stress-related, and physiological mechanisms all play a role in differences in cardiovascular risk among patients with current depression and those with controlled depression or without depression.

It is important to emphasize that although this study examines differences among groups based on depression status, the study is cross-sectional, and causality cannot be inferred. Thus, the reverse process of increased cardiovascular risk leading to depression should be considered. For example, there is evidence that cardiovascular risk factors, including smoking [32] and diabetes [33], are risk factors for depression. It has also possible that the vascular changes associated with CVD are risk factors for depression among geriatric populations [34]. Therefore, it may be that patients with elevated cardiovascular risk factors are more likely to fall into the current or controlled depression groups. Prospective longitudinal studies are needed to tease out the directionality of these effects.

Differences in unadjusted and adjusted analyses are likely attributable to age differences because patients with controlled depression were, on average, about 6 years older than patients with current depression. Further, in secondary moderation analyses, individuals with controlled depression had attenuated 10-year ASCVD risk at older ages, and their 10-year risk was comparable to individuals without depression at age 55 and lower than individuals without depression at age 70. These findings did not hold for 30-year lifetime risk, which is only applicable to a younger population (ages 18–59). Conversely, in analyses examined moderation by sex, females had elevated 30-year lifetime risk if they had controlled or current depression whereas males had elevated 30-year risk with only current depression. Sex did not impact the relationship between depression group and 10-year risk. Results in the adjusted analyses are consistent with the idea that treating depression may improve cardiovascular risk; however, these data do not provide direct evidence to support this hypothesis [35–37].

Regardless of the exact mechanisms, this study suggests that the negative associations between depression and cardiovascular risk may be minimized with depression treatment. There has been extensive investigation of this hypothesis with mixed results. Randomized clinical trials examining depression treatment (including antidepressants, cognitive behavioral therapy, or stepped care) among patients with established CVD have generally found that depression treatment does not reduce risk for future cardiac events; however, secondary analyses of those trials demonstrate that people with the greatest reductions in depressive symptoms do live longer than people whose depressive symptoms do not improve [4,38]. This may be because patients with depression have varying responses to treatments, including antidepressant medications and therapy, and among patients with existing CVD, it may be difficult to reverse the disease process. Furthermore, trials that delayed recruitment until at least 2 months after a cardiac event showed greater benefit, likely because included patients had more severe depression that did not spontaneously remit [39]. Fewer trials have examined the impact of depression treatment on cardiovascular risk in patients without established disease. One trial examined the impact of a collaborative care depression treatment in patients with DM and although the treatment improved depressive symptoms, there was no difference between the intervention and control groups on glucose control [40]. Given the known risk associated with current depression, research that develops and tests interventions that address cardiovascular risk factors and depression symptoms simultaneously in patients without existing disease is needed to determine if such treatments enhance CVD prevention efforts.

Patients with current depression had greater estimated total cardiovascular risk compared to patients with controlled depression and those without depression, which may be explained by differences in smoking status, glucose control, and weight. Clinical and research efforts are needed to ascertain mechanisms, determine causality, further examine moderators (such as age, sex, and socioeconomic status), and establish best approaches for reducing cardiovascular risk in patients with current depression. For example, clinical research studies may examine whether treating depression concurrently while simultaneously addressing multifactorial cardiovascular risk factors (e.g., managing hypertension, hyperlipidemia, BMI, and/or smoking) confers added benefits to reduced cardiovascular events over time.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2022.110920.

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