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# Association Between Depressive Symptoms and Incident Cardiovascular Diseases

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**IMPORTANCE** It is uncertain whether depressive symptoms are independently associated with subsequent risk of cardiovascular diseases (CVDs).

**OBJECTIVE** To characterize the association between depressive symptoms and CVD incidence across the spectrum of lower mood.

**DESIGN, SETTING, AND PARTICIPANTS** A pooled analysis of individual-participant data from the Emerging Risk Factors Collaboration (ERFC; 162 036 participants; 21 cohorts; baseline surveys, 1960-2008; latest follow-up, March 2020) and the UK Biobank (401 219 participants; baseline surveys, 2006-2010; latest follow-up, March 2020). Eligible participants had information about self-reported depressive symptoms and no CVD history at baseline.

**EXPOSURES** Depressive symptoms were recorded using validated instruments. ERFC scores were harmonized across studies to a scale representative of the Center for Epidemiological Studies Depression (CES-D) scale (range, 0-60; ≥16 indicates possible depressive disorder). The UK Biobank recorded the 2-item Patient Health Questionnaire 2 (PHQ-2; range, 0-6; ≥3 indicates possible depressive disorder).

**MAIN OUTCOMES AND MEASURES** Primary outcomes were incident fatal or nonfatal coronary heart disease (CHD), stroke, and CVD (composite of the 2). Hazard ratios (HRs) per 1-SD higher log CES-D or PHQ-2 adjusted for age, sex, smoking, and diabetes were reported.

**RESULTS** Among 162 036 participants from the ERFC (73%, women; mean age at baseline, 63 years [SD, 9 years]), 5078 CHD and 3932 stroke events were recorded (median follow-up, 9.5 years). Associations with CHD, stroke, and CVD were log linear. The HR per 1-SD higher depression score for CHD was 1.07 (95% CI, 1.03-1.11); stroke, 1.05 (95% CI, 1.01-1.10); and CVD, 1.06 (95% CI, 1.04-1.08). The corresponding incidence rates per 10 000 person-years of follow-up in the highest vs the lowest quintile of (CES-D) score (geometric mean CES-D score, 19 vs 1) were 36.3 vs 29.0 for CHD events, 28.0 vs 24.7 for stroke events, and 62.8 vs 53.5 for CVD events. Among 401 219 participants from the UK Biobank (55% were women, mean age at baseline, 56 years [SD, 8 years]), 4607 CHD and 3253 stroke events were recorded (median follow-up, 8.1 years). The HR per 1-SD higher depression score for CHD was 1.11 (95% CI, 1.08-1.14); stroke, 1.10 (95% CI, 1.06-1.14); and CVD, 1.10 (95% CI, 1.08-1.13). The corresponding incidence rates per 10 000 person-years of follow-up among individuals with PHQ-2 scores of 4 or higher vs 0 were 20.9 vs 14.2 for CHD events, 15.3 vs 10.2 for stroke events, and for 36.2 vs 24.5 for CVD events. The magnitude and statistical significance of the HRs were not materially changed after adjustment for additional risk factors.

**CONCLUSIONS AND RELEVANCE** In a pooled analysis of 563 255 participants in 22 cohorts, baseline depressive symptoms were associated with CVD incidence, including at symptom levels lower than the threshold indicative of a depressive disorder. However, the magnitude of associations was modest.

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Supplemental content

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Depressive disorders are a leading and growing cause of disability, with more than an estimated 264 million people affected worldwide.[1] Previous studies have reported on potential links between depressive disorders, symptoms of lower mood, and cardiovascular disease (CVD).[2-13] Position papers of the American Heart Association and the European Society of Cardiology have acknowledged that depression may be a modifiable prognostic factor for coronary heart disease (CHD), encouraging improvement of its recognition and management.[14,15]

There are, however, uncertainties in the epidemiological evidence underpinning this possible link. First, several studies have used broad psychological measures of distress, leaving doubt about whether depressive symptoms per se are associated with CVD risk.[10,13] Second, most studies have had limited statistical power, preventing reliable characterization of the relationships across the spectrum of severity of depressive symptoms. Third, studies have used varying approaches to adjust for potential confounding factors, preventing robust inference about the independence of associations from established CVD risk factors.[3-7,9,11,12] Fourth, studies have used inconsistent disease definitions, preventing standardized analysis of CVD subtypes or direct comparisons of associations of depressive symptoms across multiple conditions.[2-7,10,12]

To help address these uncertainties, the present study pooled individual-participant data from multiple long-term prospective studies to evaluate the relationship between depressive symptoms and incident CVD.

### Key Points

**Question** Are depressive symptoms associated with incident cardiovascular diseases?

**Findings** In a pooled analysis of individual-participant data from 563 255 participants in 22 prospective cohorts, depressive symptoms (assessed by the Center for Epidemiologic Studies Depression [CES-D] scale and other validated scales) were significantly associated with incident cardiovascular disease, including scores lower than the threshold typically indicative of depressive disorders (CES-D ≥16; hazard ratio per 1-SD higher log CES-D, 1.06).

**Meaning** Depressive symptoms, even at levels lower than what is typically indicative of potential clinical depression, were associated with risk of incident cardiovascular disease although the magnitude of the association was modest.

## Methods

### Data Sources and Participant Inclusion

This study, which was approved by the Cambridgeshire Ethics Review Committee, was designed and conducted by the Emerging Risk Factors Collaboration (ERFC) academic coordinating center. Informed consent was obtained from participants in each contributing cohort. Data were analyzed from 2 sources: first the ERFC, a consortium of prospective cohort studies with information on a variety of cardiovascular risk factors; second, the UK Biobank, a single large prospective study. Both data sets involved a prospective cohort study design and have accessible individual-participant data, enabling standardized and detailed analyses using a common protocol.[16,17] Nevertheless, we conducted parallel analyses of the 2 data sources owing to potential differences in methods used to assess depressive symptoms.

Participants were eligible for inclusion in the current analysis if they met the following criteria: (1) had a documented assessment of depressive symptoms recorded at baseline using a validated or published questionnaire; (2) did not have a known baseline history of CVD (defined as CHD, other heart disease, stroke, transient ischemic attack, peripheral vascular disease, or cardiovascular surgery); and (3) had at least 1 year of follow-up after baseline. Details of contributing studies are presented in **Figure 1**, in eTables 1 and 2, and eAppendix 1 in the Supplement. In the ERFC, baseline assessments were conducted between 1974 and 2010, and the date of latest follow-up was March 2020; in the UK Biobank, the baseline assessment was conducted between 2006 and 2010, and the date of latest follow-up used for this analysis was March 2020.

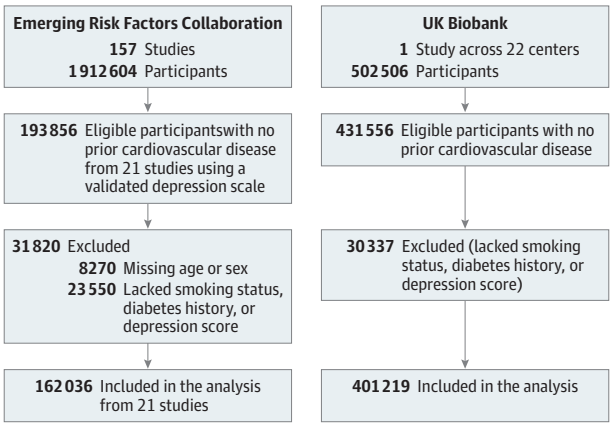
### Assessment of Depressive Symptoms

Twenty-one studies from the ERFC had relevant data and contributed to the present analysis. Seven used the Center for Epidemiological Studies Depression (CES-D) scale,[18] 5 used a modified or abbreviated version of the CES-D,[19] 3 used the Cohort of Norway Mental Health Index,[20] and 6 used the following study-specific questionnaires: the Beck Depression Inventory, the Hospital Anxiety and Depression Scale (depression-specific subscale), the Human Population Laboratory Depression scale, a modified version of the Minnesota Multiphasic Personality Inventory, a Mental Health Inventory derived from the 36-item Short Form Health Survey, and the Zung Self-Rating Depression Scale (eTable 3 and eAppendix 2 in the Supplement). Depression scores were harmonized across the cohorts to reflect the CES-D scale (eAppendix 3 in the Supplement), a 20-item scale designed to assess the frequency of depressive symptoms for the previous week. Items in the CES-D are evaluated on a 4-point scale from 0 (rarely) to 3 (most or all of the time). Thus, the CES-D score can range from 0 to 60. A score of 16 or higher is indicative of a possible depressive disorder.[18] To enhance validity of findings obtained using the transformed scale, results were directly compared between studies that used and did not originally use the full CES-D scale. In the UK Biobank, the Patient Health Questionnaire-2 (PHQ-2) was used to assess depressive symptoms at baseline. This 2-item instrument asks about the frequency of depressed mood and anhedonia over the past 2 weeks, with response options being "not at all," "several days," "more than half the days," and "nearly every day," scored as 0, 1, 2, and 3, respectively. Thus, the PHQ-2 score can range from 0 to 6; a score 3 of more is indicative of possible depressive disorder.[21]

### Outcomes

The primary end points were fatal or nonfatal CHD (defined as fatal CHD or nonfatal myocardial infarction), stroke, and their

Figure 1. Selection of Eligible Studies and Participants From the Emerging Risk Factors Collaboration and the UK Biobank




composite end point CVD. Participants contributed follow-up time to the first CVD outcome recorded (ie, CVD deaths preceded by nonfatal CVD outcomes were not included). Secondary end points were all-cause mortality, mortality due to CVD, mortality due to cancer, and mortality not attributable to either cancer or CVD. For the analysis of all-cause mortality, all deaths were included with no censoring for nonfatal events.

## Statistical Analysis

The CES-D score distribution was normalized using a natural log transformation before analysis. Cross-sectional correlates of depressive symptom scores were estimated using linear mixed models adjusted for age, sex, and cohort-level random effects and were presented by differences in depressive symptom scores per 1-SD higher level for continuous correlates or category for categorical correlates. To evaluate associations of depressive symptoms with primary and secondary outcomes, hazard ratios (HRs) were calculated separately within each study using Cox proportional hazards regression models with time on study as the timescale and stratified by sex. Hazard ratios were pooled across studies contributing to the ERFC using a random-effects meta-analysis.[22,23] Violation of the proportional hazards assumption was tested by including time interactions with depressive symptoms. To avoid model overfitting, studies with fewer than 10 incident cases of an outcome were excluded from analysis of that particular outcome.

To maximize the available data and to limit potential overadjustment for variables that could mediate associations between depressive symptoms and CVD, the basic models were stratified by sex and adjusted for age, smoking, and history of diabetes only (with only participants with complete data for these covariates included in the models). To evaluate the independence of the associations, HRs were further adjusted for systolic blood pressure, body mass index (BMI), total and high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), self-reported race (White; non-White), educational level (no schooling or primary; secondary; university or vocational), and alcohol consumption (current; former; never), which were defined by each study.

To assess the relationship between depressive symptoms and CVD, HRs for CVD outcomes within quintiles or categories of depressive symptom scores were plotted against the mean value within each quintile or category.[22] We estimated 95% CIs for each group (including the reference group) that corresponded to the amount of information underlying each group.[24] Deviance from log-linear associations was assessed using fractional polynomials,[25] and HRs were thereafter calculated per 1-SD higher depressive symptom scores (for log CES-D, this corresponds to a 2.7-fold increase in CES-D score). To investigate reverse causality, HRs were calculated with progressive exclusion of events recorded during the initial years of follow-up. Hazard ratios were also calculated using thresholds for depressive symptom scores typically indicative of a possible depressive disorder, ie, 16 or higher for the CES-D and 3 or higher for the PHQ-2 scores.

To place findings in context, HRs for depressive symptoms were compared with those for several established CVD risk factors. Effect modification was assessed using formal tests for interaction between depressive symptom scales and various individual- and study-level characteristics.[22] In ERFC, heterogeneity in HRs across studies was quantified using the $I^2$ statistic.[26]

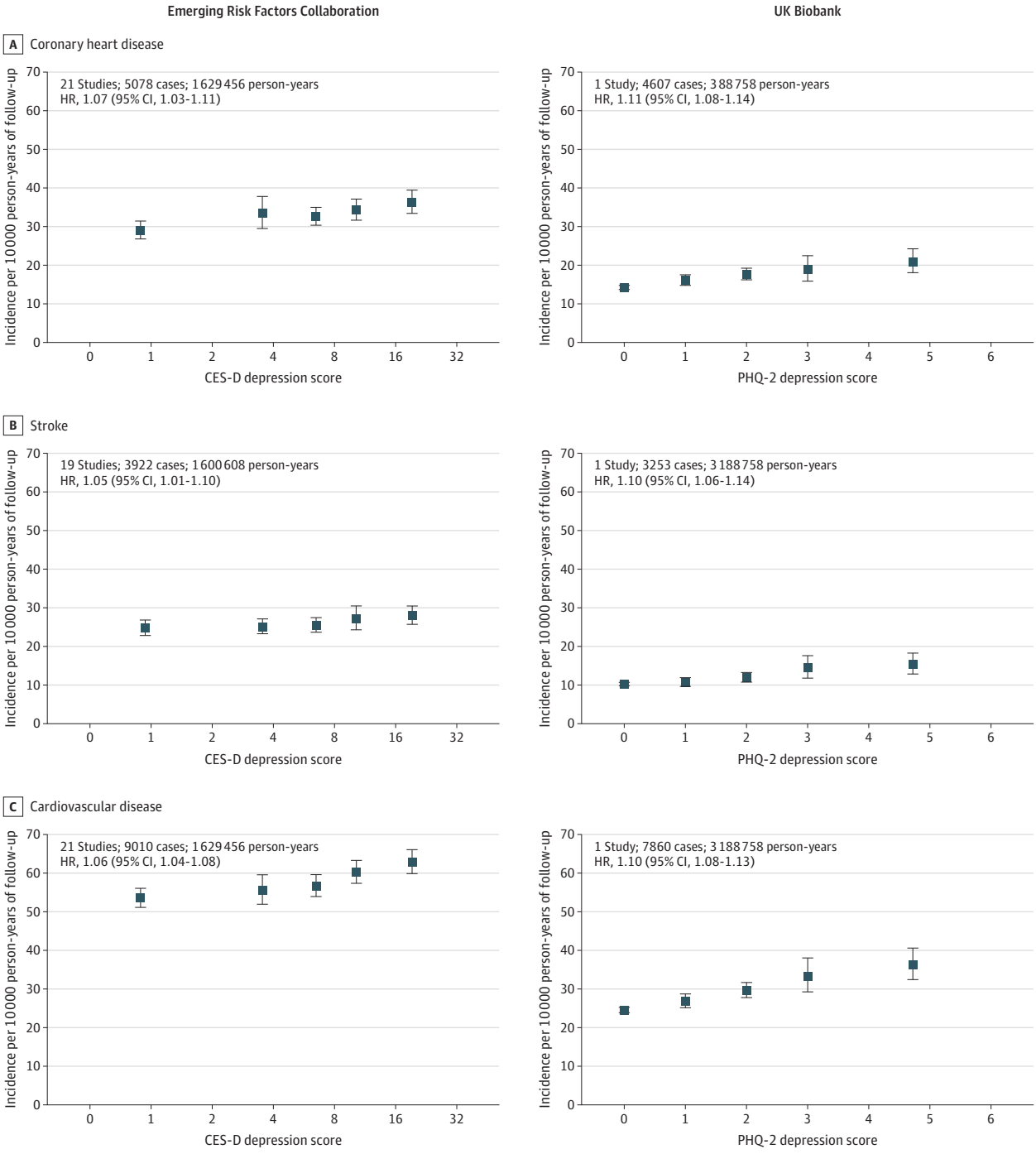
Analyses were performed using Stata version 16.1 (StataCorp) with 2-sided $P$ values. We used a significance level of $P < .05$, unless otherwise specified. Given the potential for type I error due to multiple comparisons, findings should be interpreted as exploratory.

# Results

Of the 162 036 participants (mean baseline age, 63 years [SD, 9 years]) from 21 studies in ERFC, 117 778 participants (73%) were women. Most participants were enrolled in either North America (67%) or Europe (26%). During a median follow-up of 9.5 years (5th-95th percentile, 1.9-16.9 years), 9010 incident CVD events (5078 CHD and 3932 stroke) and 23 660 deaths (including 4807 CHD or stroke and 7289 cancer deaths) were recorded. Of the 401 219 participants in the UK Biobank (mean baseline age, 56 years [SD, 8 years]), 221 660 participants (55%) were women. During a median follow-up of 8.1 years (5th-95th percentile, 6.7-9.4 years), 7860 incident CVD events (4607 CHD and 3253 stoke) and 18 516 deaths (2434 CVD, 11 440 cancer, and 4642 other causes) were recorded (eTable 1 in the Supplement). Study-specific distributions of baseline depressive symptom scores differed substantially across questionnaire types but were similar after transformation to the harmonized CES-D scale in the ERFC (eFigure 1 in the Supplement). Depressive symptom scales were positively correlated with age, female sex, history of diabetes, smoking status, measures of adiposity (ie, waist-hip ratio and BMI), triglyceride levels, and CRP, whereas they were inversely correlated with educational attainment and HDL-C levels (all $P < .01$; eTable 2, eTable 4, and eFigures 2-3 in the Supplement).

After adjustment for age, sex, smoking status, and history of diabetes, there were significant log-linear associations

Figure 2. Association of Depressive Symptoms With Coronary Heart Disease, Stroke, and Cardiovascular Disease



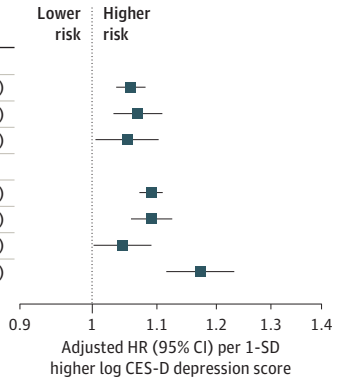

Hazard ratio (HR) reported is per 1-SD increase in depressive symptoms, adjusted for age, sex (stratified), smoking status, and history of diabetes. Values on the x-axis display the geometric mean Center for Epidemiological Studies Depression (CES-D) scale within quintiles across all studies (plotted on a log scale), or the 2-item Patient Health Questionnaire (PHQ-2) depression score. Floating absolute variances were used to derive 95% CIs (indicated by error bars) from the variances that corresponded to the amount of information underlying each group (including the reference group).

between depressive symptom scores and incidence of CHD, stroke, or CVD (**Figure 2** and eFigures 4-5 in the Supplement; models fit with fractional polynomials revealed no evidence for nonlinearity; all *P* values > .40). For the ERFC, the adjusted incidence rate per 10 000 person-years of follow-up in the highest vs lowest quintile of CES-D scores (geometric mean CES-D score, 19 vs 1) was 36.3 vs 29.0 for CHD events, 28.0 vs 24.7 for stroke events, and 62.8 vs 53.5 for CVD events (Figure 2 and eTable 5 in the Supplement). Adjusted HRs per 2.7-fold increase in CES-D score (ie, 1 SD) were 1.07 (95% CI, 1.03-1.11) for

Figure 3. Adjusted Hazard Ratios for Cause-Specific Mortality and Major Cardiovascular Disease Per 1-SD Higher Depression Score[a]

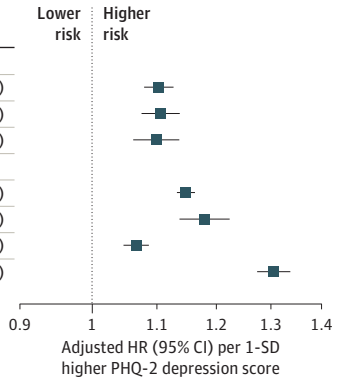
A Emerging Risk Factors Collaboration results (CES-D)

| End point or condition | No. of events | No. of person-years | HR (95% CI) |
|---|---|---|---|
| Vascular morbidity and mortality[b] | | | |
| CVD | 9010 | 1629450 | 1.06 (1.04-1.08) |
| CHD | 5078 | 1629450 | 1.07 (1.03-1.11) |
| Stroke | 3922 | 1600603 | 1.05 (1.01-1.10) |
| Mortality | | | |
| All-cause mortality | 23660 | 1810569 | 1.09 (1.07-1.11) |
| CVD mortality | 4800 | 1808619 | 1.09 (1.06-1.12) |
| Cancer mortality | 7280 | 1690271 | 1.05 (1.00-1.09) |
| Noncancer non-CVD mortality | 5677 | 1698407 | 1.17 (1.12-1.23) |




B UK Biobank results (PHQ-2)

| End point or condition | No. of events | No. of person-years | HR (95% CI) |
|---|---|---|---|
| Vascular morbidity and mortality[b] | | | |
| CVD | 7860 | 3188760 | 1.10 (1.08-1.13) |
| CHD | 4607 | 3188760 | 1.11 (1.08-1.14) |
| Stroke | 3253 | 3188760 | 1.10 (1.06-1.14) |
| Mortality | | | |
| All-cause mortality | 19555 | 4394342 | 1.15 (1.13-1.16) |
| CVD mortality | 2434 | 4394342 | 1.18 (1.14-1.22) |
| Cancer mortality | 11440 | 4394342 | 1.07 (1.05-1.09) |
| Noncancer non-CVD mortality | 4642 | 4394342 | 1.31 (1.27-1.34) |




[a] Adjusted for age, sex (stratified), smoking status, and history of diabetes. Studies with fewer than 10 events were excluded from the analysis of each outcome. A 1-SD increase in depression score corresponds to a 2.7-fold increase in the CES-D and 1-unit increase in the PHQ-2 scores.

[b] Includes fatal and nonfatal events.

CES-D indicates, Center for Epidemiological Studies Depression scale; CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio; and PHQ-2, 2-item Patient Health Questionnaire.

CHD, 1.05 (95% CI, 1.01-1.10) for stroke, and 1.06 (95% CI, 95% CI, 1.04-1.08) for CVD (**Figure 3** and **Table**). Likewise, for UK Biobank participants with PHQ-2 scores of 4 or higher vs 0, the incidence rate per 10 000 person-years was 20.9 vs 14.2 for CHD events, 15.3 vs 10.2 for stroke events, and 36.2 vs 24.5 for CVD events (Figure 2 and eTable 5 in the Supplement). Adjusted HRs per 1-unit increase in PHQ-2 score (ie, 1 SD) were 1.11 (95% CI, 1.08-1.14) for CHD, 1.10 (95% CI, 1.06-1.14) for stroke, and 1.10 (95% CI, 1.08-1.13) for CVD (Figure 3 and Table).

In comparison, among ERFC participants, the HR per 1-SD higher systolic blood pressure was 1.31 (95% CI, 1.28-1.34); non-HDL-C, 1.18 (95% CI, 1.14-1.22); and BMI, 1.17 (95% CI, 1.11-1.24), reflecting event rates per 10 000 person-years in the highest vs lowest quintile of 55.6 vs 24.2 for systolic blood pressure, 44.8 vs 31.2 for non-HDL-C, and 61.0 vs 43.5 for BMI. For the UK Biobank, these HRs were 1.32 (95% CI, 1.29-1.35) per 1-SD higher systolic blood pressure, 1.27 (95% CI, 1.24-1.30) for non-HDL-C, and 1.16 (95% CI, 1.13-1.18) for BMI, reflecting event rates per 10 000 person-years in the highest vs the lowest quintile of 23.7 vs 10.7 for systolic blood pressure, 39.6 vs 21.2 for non-HDL-C, and 24.5 vs 16.5 for BMI (**Figure 4**; eTable 5 in the Supplement).

The HRs did not vary in magnitude or statistical significance after further analyses, including additional adjustment for systolic blood pressure, BMI, total cholesterol, HDL-C, race, educational attainment, alcohol consumption, or CRP (Table; eTable 6 in the Supplement); after exploration for effect modification by baseline smoking status, sex, history of diabetes, use of antidepressant medications (or medical care related to depressive symptoms), symptom questionnaire, or geographical region (eFigures 6 and 7 in the Supplement); and after exclusion of events occurring during the initial years of follow-up (eTable 7 in the Supplement). Hazard ratios for CHD were smaller in magnitude at older ages in the ERFC (*P* value for interaction = .003, eFigure 6 in the Supplement). Furthermore, HRs did not vary in magnitude or statistical significance in sensitivity analyses that (1) used only studies that recorded depressive symptoms using a CES-D questionnaire; (2) used inverse normal rank-transformed depression scores rather than the harmonized CES-D scale; (3) excluded the largest study in the ERFC; and (4) excluded participants with a history of diabetes or other non-CVD comorbidities, such as rheumatoid arthritis or inflammatory bowel disease, at baseline (eFigures 8 through 13 in the Supplement). The extent of heterogeneity in HRs across studies contributing to the ERFC was moderate, with $I^2$ values of 15% (95% CI, 0%-49%) for CHD, 1% (95% CI, 0%-47%) for stroke, and 12% (95% CI, 0%,-48%) for CVD outcomes (eFigure 8 in the Supplement).

In a comparison of a depressive symptom score higher or lower than the threshold indicative of potential depressive

Table. Hazard Ratios per 1-SD Higher Depressive Symptoms Scores on Progressive Adjustment for Cardiovascular Disease Risk Markers

| | Emerging Risk Factors Collaboration results | | | UK Biobank results | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) per 1-SD higher log CES-D[a] | | | HR (95% CI) per 1-SD higher PHQ-2[b] | | |
| | CHD | Stroke | CVD | CHD | Stroke | CVD |
| Basic adjustment | | | | | | |
| No. of cohorts | 21 | 19 | 21 | 1 | 1 | 1 |
| Events | 5078 | 3922 | 9010 | 4607 | 3253 | 7860 |
| Person-years | 1 629 450 | 1 600 603 | 1 629 450 | 3 188 760 | 3 188 760 | 3 188 760 |
| Adjusted for age and sex | 1.09 (1.05-1.14) | 1.07 (1.02-1.12) | 1.08 (1.05-1.11) | 1.15 (1.12-1.18) | 1.13 (1.10-1.17) | 1.14 (1.12-1.17) |
| +Smoking status | 1.08 (1.04-1.12) | 1.06 (1.01-1.11) | 1.07 (1.05-1.09) | 1.11 (1.08-1.14) | 1.11 (1.07-1.15) | 1.11 (1.09-1.13) |
| +History of diabetes | 1.07 (1.03-1.11) | 1.05 (1.01-1.10) | 1.06 (1.04-1.08) | 1.11 (1.08-1.14) | 1.10 (1.06-1.14) | 1.10 (1.08-1.13) |
| Further adjustment | | | | | | |
| No. of cohorts | 9 | 9 | 10 | 1 | 1 | 1 |
| Events | 1390 | 897 | 2299 | 3903 | 2732 | 6635 |
| Person-years | 505 438 | 492 893 | 513 741 | 2 700 169 | 2 700 169 | 2 700 169 |
| Basic adjustment[c] | 1.10 (1.03-1.18) | 1.12 (1.04-1.20) | 1.10 (1.05-1.15) | 1.10 (1.06-1.13) | 1.10 (1.06-1.14) | 1.10 (1.07-1.12) |
| +Systolic blood pressure | 1.10 (1.03-1.18) | 1.12 (1.04-1.20) | 1.10 (1.05-1.15) | 1.11 (1.07-1.14) | 1.11 (1.07-1.15) | 1.11 (1.08-1.13) |
| +Body mass index | 1.09 (1.02-1.18) | 1.11 (1.03-1.19) | 1.09 (1.05-1.15) | 1.10 (1.07-1.13) | 1.10 (1.06-1.14) | 1.10 (1.08-1.13) |
| +Total cholesterol | 1.10 (1.02-1.18) | 1.11 (1.03-1.19) | 1.10 (1.05-1.15) | 1.10 (1.06-1.13) | 1.10 (1.06-1.15) | 1.10 (1.07-1.13) |
| +HDL cholesterol | 1.10 (1.02-1.18) | 1.11 (1.03-1.19) | 1.10 (1.05-1.15) | 1.09 (1.06-1.13) | 1.10 (1.06-1.14) | 1.10 (1.07-1.12) |
| +Educational level[d] | 1.09 (1.02-1.17) | 1.11 (1.03-1.19) | 1.09 (1.04-1.14) | 1.09 (1.06-1.12) | 1.10 (1.06-1.14) | 1.09 (1.07-1.12) |
| +Alcohol consumption status | 1.09 (1.02-1.17) | 1.11 (1.03-1.19) | 1.09 (1.04-1.14) | 1.08 (1.05-1.12) | 1.09 (1.05-1.13) | 1.09 (1.06-1.11) |
| Basic adjustment plus markers of inflammation | | | | | | |
| No. of cohorts | 5 | 5 | 6 | 1 | 1 | 1 |
| Events | 876 | 585 | 1472 | 4301 | 3031 | 7332 |
| Person-years | 158 448 | 162 382 | 169 509 | 2 975 605 | 2 975 605 | 2 975 605 |
| Basic adjustment[c] | 1.05 (0.98-1.13) | 1.06 (0.93-1.21) | 1.07 (1.01-1.13) | 1.10 (1.06-1.13) | 1.09 (1.06-1.13) | 1.10 (1.08-1.13) |
| +Log C-reactive protein | 1.04 (0.96-1.12) | 1.06 (0.93-1.20) | 1.06 (1.00-1.12) | 1.08 (1.05-1.12) | 1.08 (1.04-1.12) | 1.09 (1.07-1.11) |

Abbreviations: CES-D, Center for Epidemiological Studies Depression (CES-D) scale; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; PHQ-2, 2-item Patient Health Questionnaire.

[a] A 1-SD higher log CES-D depression score corresponds to a 2.7-fold higher CES-D depression score (range, 0-60; scores ≥16 indicate possible depressive disorder).

[b] 1-SD higher PHQ-2 depression score corresponds to a 1-unit higher PHQ-2 depression score (range, 0-6, ≥3 indicates possible depressive disorder).

[c] The basic adjustment consists of adjustment for age, sex (stratified), smoking status, and history of diabetes.

[d] Educational level is categorized as no schooling or primary, secondary, or vocational or university.

disorder (ie, CES-D ≥ 16 vs <16, and PHQ-2 ≥ 3 vs <3), HRs were 1.16 (95% CI, 1.00-1.35) for CHD, 1.07 (95% CI, 0.97-1.18) for stroke, and 1.10 (95% CI, 1.01-1.21) for CVD in ERFC. For the UK Biobank, the HRs were 1.34 (95% CI, 1.20-1.51) for CHD, 1.42 (95% CI, 1.24-1.63) for stroke, and 1.38 (95% CI, 1.26-1.50) for CVD (eFigures 14-15 in the Supplement).

When considering only individuals with depressive symptoms lower than the threshold indicative of depressive disorder HRs per 1-SD higher depressive symptoms score, CES-D were 1.07 (95% CI, 1.02-1.12) for CHD, 1.06 (95% CI, 1.00-1.12) for stroke, and 1.06 (95% CI, 1.03-1.09) for CVD in ERFC. For the UK Biobank, the HRs per 1-SD increase in PHQ-2 score were 1.12 (95% CI, 1.07-1.17) for CHD, 1.07 (95% CI, 1.02-1.13) for stroke, and 1.10 (95% CI, 1.06-1.14) for CVD (eFigure 16 in the Supplement). In an exploratory comparison in the UK Biobank of any episode of major depression reported over the life course vs none,[27] the HRs were 1.27 (95% CI, 1.09-1.47) for CHD, 0.99 (95% CI, 0.82-1.20) for stroke, and 1.15 (95% CI, 1.02-1.29) for CVD (eFigure 17 in the Supplement).

In analyses of secondary outcomes of the ERFC, HRs per 1-SD higher depressive symptom scores were 1.08 (95% CI, 1.05-1.11) for CVD mortality, 1.05 (95% CI, 1.00-1.09) for cancer mortality, and 1.17 (95% CI, 1.12-1.23) for noncancer or non-CVD mortality. The HRs in the UK Biobank were 1.17 (95% CI, 1.13-1.16) for CVD mortality, 1.07 (95% CI, 1.05-1.09) for cancer mortality, and 1.31 (95% CI, 1.27-1.34) for noncancer or non-CVD mortality (Figure 3). For the last category, HRs were highest for nervous system disorders (eg, Alzheimer disease), but data were sparse in this exploratory subanalysis (eFigures 18-19 in the Supplement). There was no evidence of publication bias or small studies effect in the current results (eFigure 20 in the Supplement).

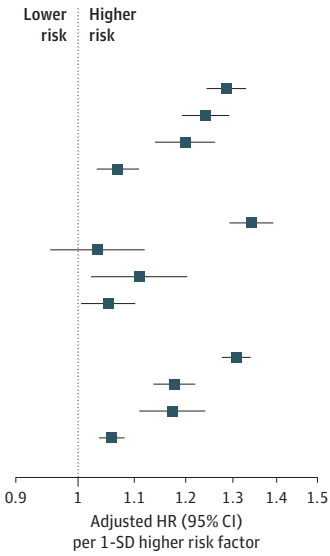
## Discussion

In an analysis of 563 255 participants in 22 prospective studies, baseline depressive symptoms were associated with CVD

Figure 4. Adjusted Hazard Ratios for Coronary Heart Disease, Stroke, and Cardiovascular Disease per 1-SD Higher Depressive Symptoms in Comparison With Established Cardiovascular Disease Risk Factors

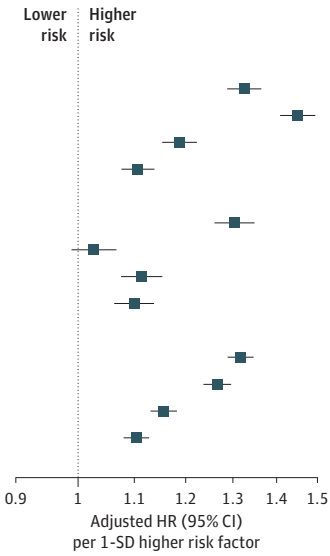
A Emerging Risk Factors Collaboration results (CES-D)

| Risk factor | No. of studies | No. of participants | No. of events | No. of person-years | Events per 10 000 person-years: First quintile | Events per 10 000 person-years: Second quintile | HR (95% CI) |
|---|---|---|---|---|---|---|---|
| CHD | | | | | | | |
| Systolic blood pressure | 18 | 158 234 | 4820 | 1 586 396 | 13.9 | 28.0 | 1.29 (1.24-1.33) |
| Non-HDL cholesterol | 13 | 64 115 | 1629 | 563 922 | 15.9 | 28.3 | 1.24 (1.19-1.29) |
| Body mass index | 15 | 151 388 | 4434 | 1 510 055 | 22.5 | 37.0 | 1.20 (1.14-1.26) |
| Depression score | 21 | 162 036 | 5078 | 1 629 450 | 29.0 | 36.3 | 1.07 (1.03-1.11) |
| Stroke | | | | | | | |
| Systolic blood pressure | 16 | 150 487 | 3666 | 1 558 980 | 10.4 | 28.0 | 1.34 (1.29-1.39) |
| Non-HDL cholesterol | 11 | 56 618 | 1099 | 537 929 | 15.5 | 15.7 | 1.03 (0.95-1.12) |
| Body mass index | 13 | 143 674 | 3386 | 1 482 630 | 21.2 | 24.3 | 1.11 (1.02-1.20) |
| Depression score | 19 | 154 099 | 3922 | 1 600 603 | 24.7 | 28.0 | 1.05 (1.01-1.10) |
| CVD | | | | | | | |
| Systolic blood pressure | 18 | 158 234 | 8496 | 1 586 396 | 24.2 | 55.6 | 1.31 (1.28-1.34) |
| Non-HDL cholesterol | 13 | 64 115 | 2737 | 563 922 | 31.2 | 44.8 | 1.18 (1.14-1.22) |
| Body mass index | 15 | 151 388 | 7830 | 1 510 055 | 43.5 | 61.0 | 1.17 (1.11-1.24) |
| Depression score | 21 | 162 036 | 9010 | 1 629 450 | 53.5 | 62.8 | 1.06 (1.04-1.08) |




B UK Biobank results (PHQ-2)

| Risk factor | No. of studies | No. of participants | No. of events | No. of person-years | Events per 10 000 person-years: First quintile | Events per 10 000 person-years: Second quintile | HR (95% CI) |
|---|---|---|---|---|---|---|---|
| CHD | | | | | | | |
| Systolic blood pressure | 1 | 400 534 | 4599 | 3 183 350 | 5.9 | 13.5 | 1.32 (1.29-1.36) |
| Non-HDL cholesterol | 1 | 343 673 | 3961 | 2 726 557 | 10.6 | 28.2 | 1.45 (1.41-1.49) |
| Body mass index | 1 | 399 429 | 4580 | 3 175 283 | 8.2 | 14.3 | 1.19 (1.15-1.22) |
| Depression score | 1 | 401 219 | 4607 | 3 188 760 | 14.2 | 20.9 | 1.11 (1.08-1.14) |
| Stroke | | | | | | | |
| Systolic blood pressure | 1 | 400 534 | 3243 | 3 183 350 | 4.8 | 10.1 | 1.30 (1.26-1.35) |
| Non-HDL cholesterol | 1 | 343 673 | 2782 | 2 726 557 | 10.6 | 11.8 | 1.03 (0.99-1.07) |
| Body mass index | 1 | 399 429 | 3223 | 3 175 283 | 8.3 | 10.1 | 1.11 (1.07-1.15) |
| Depression score | 1 | 401 219 | 3253 | 3,188,760 | 10.2 | 15.3 | 1.10 (1.06-1.14) |
| CVD | | | | | | | |
| Systolic blood pressure | 1 | 400 534 | 7842 | 3 183 350 | 10.7 | 23.7 | 1.32 (1.29-1.35) |
| Non-HDL cholesterol | 1 | 343 673 | 6743 | 2 726 557 | 21.2 | 39.6 | 1.27 (1.24-1.30) |
| Body mass index | 1 | 399 429 | 7803 | 3 175 283 | 16.5 | 24.5 | 1.16 (1.13-1.18) |
| Depression score | 1 | 401 219 | 7860 | 3 188 760 | 24.5 | 36.2 | 1.10 (1.08-1.13) |




Hazard ratios (HRs) for continuous variables are per 1-SD higher baseline values. Risk factors were adjusted for age, sex, smoking status, history of diabetes, and depression score.

CES-D indicates Center for Epidemiological Studies Depression scale; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; PHQ-2, 2-item Patient Health Questionnaire.

incidence, including at symptom levels lower than the threshold indicative of a potential depressive disorder. Associations persisted after adjustment for several cardiovascular risk factors and after attempts to limit the effects of reverse causality. The current data are consistent with the existence of associations between depressive symptoms across the spectrum of low mood and subsequent risk of major CVD outcomes.

This study extends previous work on this topic in several ways. First, the current data indicate that there are log-linear associations of depressive symptoms with CVD incidence, suggesting no clear evidence for a threshold level below which depressive symptoms are not associated with CVD risk. This observation supports the concept that prevention of CVD via addressing depressive symptoms could, in principle,

be amenable to population-wide, rather than targeted, approaches. At present, however, it is uncertain whether treatment of depression can reduce CVD risk.[15] Second, the current findings suggest that associations between depressive symptoms and CVD risk cannot be chiefly explained by several established or emerging cardiovascular risk factors, including systolic blood pressure, total cholesterol, HDL-C, BMI, diabetes, alcohol consumption, or CRP. Previous studies have proposed mechanisms including altered brain and neuronal function affecting neuroendocrine pathways, autonomic nerve dysfunction, immune responses, platelet activation and thrombosis, life behavior, and cardiac metabolic risk factors.[2,15]

Third, associations of depressive symptoms with CVD were considerably smaller in magnitude than those for systolic blood pressure, non-HDL-C, and BMI. An implication is that there is the need for studies of depressive symptoms and CVD to ensure adequate statistical power to enable reliable evaluation. Nevertheless, the population attributable risk of CVD due to lower mood could still be substantial because depressive symptoms are common. Further studies are needed, however, to determine whether there is a cause-and-effect relationship between depressive symptoms and CVD.[28] Fourth, this study showed that depressive symptoms were associated with a wide range of causes of death, including cancer and non-CVD or noncancer mortality. These findings reinforce previous observations, highlighting the potential need to investigate the presence of depression and depressive symptoms including among people who would not usually come to the attention of mental health services, and to monitor those expressing symptoms with increased vigilance.

This study had several strengths, including substantial statistical power, based on 16 870 incident CVD outcomes; focus on prospective cohort data; and use of information from 2 well-characterized studies that provided complementary sources of cohort data with respect to geographical region and calendar period of recruitment. The limitations of literature-based meta-analyses were avoided by accessing individual-participant data from cohorts, enabling detailed and standardized analyses. To limit potential effects of a CVD diagnosis on depressive symptoms (ie, reverse causality), analyses were restricted to individuals without a history of CVD at baseline and the initial years of follow-up were excluded. The generalizability of the findings, at least to populations in Western countries, was supported by broadly consistent results observed from 22 cohorts in 8 different countries, mainly in North America and Europe. The focus on populations in Western countries reduced the scope for bias due to different culturally determined mental health perceptions. Findings were broadly concordant across multiple subgroups and across different depressive symptom scales used.

### Limitations

This study had several limitations. First, it was not a systematic review: for pragmatic reasons, this study focused on the UK Biobank and 21 cohorts contributing to the ERFC with readily available individual-participant data. These findings do not, therefore, constitute a comprehensive synthesis of the available evidence. The results should, however, be based on a substantial and unbiased subset of relevant studies because cohorts in the ERFC were collated about a decade ago principally on the basis of availability of biochemical risk-factor data and not on the basis of depressive symptoms. Moreover, there was no evidence of publication bias in the current results. Second, contributing cohorts used a variety of depressive symptom questionnaires, potentially yielding inconsistencies. However, data across these scales were harmonized and, furthermore, were consistent across different questionnaires used.

Third, this analysis focused on depressive symptoms assessed at a single baseline examination, preventing investigation of cumulative depression burden, of incident depression, or of time-varying associations with outcomes. Such misclassification could have underestimated true associations, or even produced artifactual log-linear relationships. However, according to previous studies, depressive symptoms assessed by the CES-D are reasonably stable over adulthood,[29,30] and, moreover, in an analysis involving fractional polynomials, which should avoid selection of artificial cut points for continuous variables, the evidence for log-linear relationships persisted.[25]

Fourth, this study cannot exclude inadequate adjustment for unmeasured or imprecisely measured confounding factors, including various baseline comorbidities. Fifth, these analyses included only participants with complete information on risk factors, which could in principle have reduced efficiency and biased results. However, these analyses were well-powered and should be unbiased under the reasonable assumption that the probability of being a complete case was independent of CVD outcomes, given the variables included in the models. Sixth, the present analysis involved participants who were mostly of European continental ancestry, suggesting the need for well-powered studies in other ethnic and racial groups.

## Conclusions

In a pooled analysis of 563 255 participants in 22 prospective studies, baseline depressive symptoms were associated with CVD incidence, including at symptom levels lower than the threshold indicative of a depressive disorder. However, the magnitude of associations was modest.

ARTICLE INFORMATION

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**Correction:** This article was corrected December 21, 2020, to remove the word *log* from the x-axis in panel B of Figure 3.

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