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# Differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status: The REGARDS study

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# Differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status: The REGARDS study

**Running Title:** depressive symptoms and mortality

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## Abstract

**Objective:** To assess the association between time varying depressive symptoms with all-cause

**Design:** The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a national, population-based longitudinal study conducted from 2003-2007.

**Setting**: General continental U.S. communities

**Participants**: 29,491 black and white U.S. adults ≥45 years randomly sampled within race-sex-geographic strata.

**Exposure**: Elevated depressive symptoms (CES-D-4 ≥ 4) measured at baseline and on average 5 and 7 years later.

**Main Outcome Measures**: Cox proportional hazard regression models assessed cancer, non-cardiovascular (CVD), CVD and all-cause mortality.

**Results:** The average age was 64.9 years; 55% were female; 41% black; 11.0% had elevated depressive symptoms; 54% had poor, fair or good health. Time-varying depressive symptoms were significantly associated with nonCVD (aHR=1.29, 95% CI 1.16-1.44) and all-cause (aHR=1.24, 95%CI 1.14-1.39), but not cancer (aHR=1.15, 95%CI 0.96-1.38) or CVD (aHR=1.13, 95%CI 0.98-1.32) death adjusting for demographics, chronic clinical diseases, behavioral risk factors, and physiologic factors. Depressive symptoms were related to all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death in those who reported excellent or very good health. Baseline analyses yielded similar results.

**Conclusions:** Time varying depressive symptoms confer an increased risk for all-cause mortality, CVD, non-CVD death and cancer death, particularly in those with excellent or very good health. These findings may have implications for timely treatment, regardless of health status.

## Article summary

*Strengths and limitations of this study*:

- Our study is one of the first to use several measures of time varying depressive symptoms to show that depression confers a proximal risk for mortality, including cancer mortality.
- We are the first to demonstrate that depressive symptoms are an early modifiable risk factor for mortality in those with excellent or very good reported health who may be less likely to be recognized and treated.
- This is a large cohort of nearly 30,000 individuals, allowing for adjustment of multiple covariates that were not included in prior studies.
- Regional specificity may limit generalizability
- We use the short form CES-D, though this has demonstrated good specificity and sensitivity in prior literature.

**Introduction**

It is well known that elevated depressive symptoms predict all-cause mortality,[1] both in high-risk individuals with chronic illnesses like cardiovascular disease (CVD), and in general populations.[2-4 5,6] More recently, several studies have shown that depressive symptoms both preceding and following cancer diagnosis may confer an increased risk of cancer death as well.[7,8]

However, depressive symptoms relapse and remit, and prior studies on the relationship between depressive symptoms and mortality have been limited by one measurement of depressive symptoms.[1] In addition, prior literature has often been marked by inadequate adjustment for important covariates, such as behavioral risk factors. To our knowledge, few if any prior studies have examined the time varying association between depressive symptoms and excess causes of death. In addition, self-perceived health status may predict mortality[9] and complicate the relationship between depressive symptoms and poor outcomes.[10] It is unknown whether depressive symptoms confer an increased risk of excess mortality equally in those with self-reported excellent/very good (in whom depression may be less likely to be recognized) and good/fair/poor health.

The purpose of our study is to examine the association between time varying depressive symptoms with cancer, CVD, nonCVD and all-cause mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a broad, diverse population cohort with repeat measurements of depressive symptoms. We stratify by self-reported baseline health status (very good or excellent vs. poor, fair or good) to further isolate the association between depressive symptoms and excess mortality.

## Methods

The REGARDS study is a national cohort study of stroke incidence and cognitive decline in black and white community dwelling adults ≥ 45 years living in the United States stratified to reflect specific race-sex-geographic strata.[11] Coronary heart disease (CHD) outcomes are ascertained from a REGARDS-MI ancillary study. Participants were recruited by mail using commercially available lists of U.S. residents, followed by a computer-assisted telephone interview and subsequent home visit at which time individuals were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white adults were enrolled. Of these, 489 (1.6%) were lost to follow up and 208 (0.7%) were missing baseline depressive symptom measurements **(Figure 1)**. The REGARDS study protocol was approved by institutional review boards at participating centers.

### *Study Procedures*

Baseline data were collected through computer-assisted telephone interviews, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data, medical history and behavioral risk factors. Following the telephone interview, individuals had an in-home visit during which physical measurements, a resting electrocardiogram, medication inventory, phlebotomy and urine were collected.

### *Primary Outcomes*

The primary outcomes for these analyses were (1) cancer mortality (all body sites) (2) CVD death defined as death from CHD, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes (3) non-CVD death and (4) all-cause mortality. Living participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for

reported hospitalizations or physician visits. Deaths were detected by report of next-of-kin or through online services (e.g., Social Security Death Index) or the National Death Index.[11] Death certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and CVDoutcomes.

*Depressive symptoms*

The primary predictor was baseline depressive symptoms. The 4-item Center for Epidemiologic Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. This scale asks participants to rate the number of days over the last week in which they had: 1) felt depressed; 2) felt lonely; 3) had crying spells; and 4) felt sad. Response options included <1 day, 1 to 2 days, 3 to 4 days, and 5-7 days (0, 1, 2 3 points, respectively). Cronbach's α for the CES-D in the total sample was 0.80. Elevated depressive symptoms were defined as a summed score of ≥4.[12] The reliability and validity of the CES-D 4 is similar to the original 20-item instrument.[13]

*Covariates*

Demographic data included self-reported age, gender, race (black or white), education (less than high school, high school graduate, some college, and college graduate and above), annual income (less than $20,000, $20,000-$34,999, $35,000-$74,999, $75,000 and above), insurance status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk factors included (1) diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR) (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total

cholesterol, (7) history of CVD: coronary heart disease (self report history of myocardial infarction or coronary revascularization procedure or evidence of myocardial infarction on the study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8) cognitive impairment on the 6-item screener of global cognitive function[14,15] (9) chronic lung disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin, antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors included (1) self-reported pack-years of cigarette smoking; (2) physical activity ("How many times per week do you engage in intense physical activity, enough to work up a sweat?" with response options of "none", "1-3 times per week" and "4 or more times per week"); (3) alcohol use ("How many alcoholic beverages do you drink?": none, moderate [1 drink per day for women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2 drinks per day for men]);[11] (4) medication non-adherence assessed with the 4-item Morisky Medication Adherence Scale (>= 1).[16] Potential physiologic risk factors included high-sensitivity C-reactive protein, self-reported health status based on the physical component of the 12-item Short-Form Health Survey (SF 12),[17] and perceived stress, measured by the 4-item version of the Perceived Stress Scale (score of $\geq 5$ vs. <5).[18]

*Statistical Analyses*

Baseline characteristics of participants with and without elevated depressive symptoms at baseline were compared using chi-square tests (for categorical variables), Student t tests (for

continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous measures).

Cox proportional hazard regression models were constructed to separately analyze the association between time varying depressive symptoms (CES-D≥4) and mortality from cancer (from all body sites, a subset of nonCVD death), CVD death, nonCVD death and all-cause. The end date of follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the CES-D scale: 1) at baseline (initial telephone call) 2) on average five years after baseline measurement, and 3) on average two years after the second measurement. In the analyses, we considered depressive symptoms (CES-D≥4 vs. <4) as a time-varying exposure, with updates of exposure at 5-year and 7-year follow-up. Therefore each participant contributed up to 3 measures of CES-D (≥4 vs. <4) over the follow-up. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, end of follow-up or next CES-D. CES-D scores measured after the end of follow-up were not eligible for inclusion in the time-varying analysis. We additionally graphically plotted unadjusted cumulative incidence of mortality endpoints over follow-up for participants with elevated vs. nonelevated time-varying depressive symptoms using Kaplan-Meier curves.

Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were estimated for those with vs. without elevated depressive symptoms. Adjusted modeling proceeded in stages, starting with demographic (Model 1) and traditional CVDrisk factors (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential explanatory (Model 4) factors. We also conducted a formal test for interaction between

depressive symptoms and self-reported health (defined as excellent or very good vs. good, fair or poor health) in the fully-adjusted models. As such, all analyses were conducted overall as well as stratified by baseline self-reported health.

*Sensitivity Analyses*

Sensitivity analyses constructed in parallel to the main analyses examined association of baseline CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, or end of follow-up.

Missing data in covariates were imputed using chained equations and derived by bootstrapping across the 5 imputed datasets. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).

## Results

*Participant Characteristics*

Overall, 1.6% were lost to follow up and 0.7% were missing baseline depressive symptoms, leaving 29,491 eligible participants (**Figure 1)** of whom 3,254 (11.0%) had elevated depressive symptoms at baseline (CES-D≥4). The average age was 64.9 (9.4) years; 55.1% were female and 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease and 23.1% CVD. Nearly 33% of individuals were physically inactive, 29.2% non-adherent to their medication regimen and 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless

of health status, participants with elevated (vs. non-elevated) depressive symptoms were more likely to be female, African-American, low income, have more chronic diseases, low physical health, and more behavioral risk factors (**Table 1A-B**).

*Mortality*

A total of 4,581 (15.5%) participants died during the follow up period ending in 2012. Of these, 1,551 (33.9%) were attributed to CVD and 3,030 (66.1%) to nonCVD disease death. Of nonCVD deaths, 1,226 (44.3%) were due to cancer death (eTable 2). Overall, there were only 3 cases of mortality due to suicide.

For the time-varying analyses, depressive symptoms were measured at baseline and on average 4.8 years (SD = 1.5) years following the baseline measurement, the third measurement occurring on average 2.1 (SD = 0.4) years after the second measurement (eFigure 1). The mean follow-up time of the second and third measurement of CES-D measures did not differ by self-reported health (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8% had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 05% CI 0.98-1.32), even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-fatal CVD events (**Table 2, Figure 2**). The results appeared to be particularly robust amongst those with excellent or very good self-reported general health (**Table 2**): all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the

depressive symptoms x health status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death), and 0.20 (cancer death).

*Sensitivity Analyses:*

The mean follow-up time was 6.5 (SD = 2.3) years. Baseline depressive symptoms were significantly associated with all-cause mortality (aHR 1.18, 95%CI 1.07-1.29) and nonCVD death (aHR 1.21, 95%CI 1.08-1.36) and approached significance for CVD death (aHR 1.10, 95%CI 0.94-1.29) and cancer death (aHR 1.12, 95%CI 0.93-1.36), even in the exploratory models (Model 3) (**Table 3).** The results appeared to be particularly robust amongst those with excellent or very good health: cancer death (aHR 1.49, 95%CI 1.03-2.13), CVD death (aHR 1.63, 95%CI 1.16-2.30), nonCVD death (aHR 1.48, 95%CI 1.15-1.89) and all-cause mortality (aHR 1.53, 95% CI 1.25-1.88). In Model 4, the p values for depressive symptoms x health status interaction term was 0.003 (all cause mortality), 0.01 (CVD death), 0.06 (nonCVD death), and 0.07 (cancer death).

**Discussion**

To our knowledge, this is the largest study to date to examine the timing of the relationship between depressive symptoms and all-cause and cause-specific mortality in non-institutionalized middle to older aged adults. In this diverse cohort with an average follow up of 6.5 years, we found that time-varying depressive symptoms significantly increased the risk of nonCVD and all-cause mortality in fully adjusted models. In fully adjusted models, depressive symptoms increased the risk of cause-specific and all-cause mortality by 36% to 54% in those with a very good/excellent state of health.

Given that depression is a relapsing/remitting disease,[19] this study markedly adds to the literature by demonstrating a short-term relationship between elevated depressive symptoms and mortality, including cancer death. Major study strengths include the use 3 measurements of depressive symptoms and stringent physician adjudication outcomes. We are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and mortality. Many have long asked whether depression leads to mortality or whether individuals are depressed because they are dying. Our findings in those who report excellent states of health is striking and supports the former argument. It may also be that the effect of chronic illness burden on mortality in those with poor health overwhelms the effects of depressive symptoms. Those with excellent health may also fail to recognize/present for depression. In fact, our depressed excellent health individuals were less likely to be on an antidepressant.

The results have a coherence consistent with prior studies that suggest that depressive symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as cancer death.[20] While prior literature suggests that depressive symptoms confer mortality in those with active cancer, [21] our study excluded active cancer diagnoses confirming a possible relationship to incident cancer mortality. Prior studies have also been limited by inadequate covariate control, and our results for cancer persisted after adjusting for numerous traditional and behavioral risk factors, such as smoking, and approached significance even in models that included physiologic factors. We were however, unable to adjust for time varying covariates. It may be that changes in physical health (e.g., number of debilitating conditions) may mediate the relationship between depressive symptoms and mortality.[22]

This study also supports comprehensive evidence-based depression care management in primary care practices, which have been shown to lower mortality risk.[23] Nonetheless, depression treatment remains suboptimal in the general population,[24] despite decades of efforts. We too demonstrate that over time, nearly 40% of patients with elevated depressive symptoms at baseline were still depressed on average 5 and 7 years later. Given the potentially short-term relationship between depressive symptoms and mortality, our results suggest the importance of timely and effective treatment of depressive symptoms to prevent adverse consequences of depressive symptoms on physical health and mortality.

Limitations of our study include the regional specificity, limiting generalizability, and use of the short form of the CES-D, which measures only emotional and not somatic symptoms of depression. However, CES-D scales are one of the most widely used scales in baseline depression to outcome studies (the results of which do not appear to differ according to clinical diagnosis vs. use of continuous scales) and have good sensitivity and specificity.[7,12,13] We may also have been underpowered to examine CVD and cancer mortality, though the directionality of the estimates remained consistent. The exclusion of active/treated cancer participants, unlike prior studies, may also have contributed to lack of power. We were unable to adjust for family history of malignancy or CVD or definitively exclude subclinical disease.

Give our results of a relationship between time varying depressive symptoms and mortality, further research is warranted to test the long-term efficacy of and adherence to depression treatment and to explore preventive approaches to decreasing premature mortality risk.[25] To our knowledge, the finding of a relationship between depressive symptoms and mortality in those with excellent or very good self-reported health is a new finding and should be further studied.

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**Author Contributions:** Drs. Yulia Khodneva and Joshua Richman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford; *Analysis and interpretation of data:* Khodneva, Moise, Richman, Kronish, Shaffer, Safford; *Drafting of the manuscript:* Moise, Khodneva *Critical revision of manuscript for important*

*intellectual content:* Moise, Khodneva, Richman, Kronish, Davidson, Shaffer, Safford; *Statistical analysis*: Khodneva; *Obtained funding:* Safford; *Study supervision:* Safford

**Conflict of Interest:** None



**Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are available if deemed important by reviewers with open access by Monika Safford at Weill Cornell, Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised and risk of identification is low.

**What is already known on this subject**

- Prior studies on the relationship between depressive symptoms and all cause mortality thought to be secondary to CVD mortality and increasingly there is a ink to cancer mortality
- However, depressive symptoms often relapse and remit, and prior studies have been limited by one measurement of depression, inadequate assessment of the complex role of health status, and inadequate covariate adjustment.

**What this study adds**

- Our study is the first to show that depression confers a proximal risk for mortality, including cancer mortality, particularly in those with excellent or very good reported health.
- Our study suggests that depression is an early modifiable risk factor for mortality, including cancer mortality

**Table 1A. Overall baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D)**

| Characteristics | Overall (n=29,491) | CES-D < 4 (n=26,817) | CES-D ≥4 (n=3,254) | *p* |
|---|---|---|---|---|
| ***Socio-demographics*** | | | | |
| Age, *M* (SD) | 64.9 (9.4) | 65.1 (9.4) | 63.2 (9.8) | <.001 |
| Female, n (%) | 16245 (55.1) | 13988 (53.3) | 2257 (69.4) | <.001 |
| African American, n (%) | 12129 (41.1) | 10427 (39.7) | 1702 (52.3) | <.001 |
| Less than high school education, n (%) | 3696 (12.5) | 2916 (11.1) | 780 (24.0) | <.001 |
| Annual household income, n (%) | | | | |
| Less than $20,000 | 5322 (18.0) | 4148 (15.8) | 1174 (36.1) | <.001 |
| No health insurance, n (%) | 1926 (6.5) | 1532 (5.8) | 394 (12.1) | <.001 |
| Region, n (%) | | | | <.001 |
| Stroke belt[a] | 10193 (34.6) | 8973 (34.2) | 1220 (37.5) | |
| Stroke buckle[b] | 6188 (21.0) | 5437 (20.7) | 751 (23.1) | |
| Non-stroke belt or buckle | 13110 (44.5) | 11827 (45.1) | 1283 (39.4) | |
| ***General health and medical conditions*** | | | | |
| Self-reported general health, n (%) | | | | <.001 |
| Poor, fair, good | 15742 (53.5) | 13219 (50.5) | 2523 (77.7) | |
| Excellent, very good | 13690 (46.5) | 12965 (49.5) | 725 (22.3) | |
| Cardiovascular disease, n (%)[c] | 6825 (23.1) | 5838 (22.3) | 987 (30.3) | <.001 |
| Diabetes, n (%)[d] | 6252 (22.0) | 5305 (21.0) | 947 (30.2) | <.001 |
| COPD, n (%) | 2710 (9.2) | 2307 (8.8) | 403 (12.4) | <.001 |
| Physical component score on SF-12 scale, *M* (SD) | 46.4 (10.6) | 47.1 (10.2) | 40.7 (12.2) | <.001 |
| ***Physiological risk factors*** | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.3 (6.2) | 29.2 (6.1) | 30.6 (7.1) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 127.6 (16.7) | 127.5 (16.5) | 128.7 (18.1) | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.1 (40.1) | 191.7 (39.8) | 194.6 (43.0) | <0.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.8 (16.2) | 51.7 (16.2) | 52.5 (16.3) | 0.02 |
| QT Interval, corrected for heart rate, ms, M (SD) | 407.5 (23.6) | 407.2 (23.5) | 410.0 (24.1) | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.2[1.0-5.0] | 2.1[0.9-4.8] | 3.0[1.2-6.9] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.4[4.7-6.2] | 7.3[4.6-15.8] | 8.2[5.1-19.8] | <.001 |
| **Medications** | | | | |
| Antihypertensive medication use, n (%) | 15197 (52.1) | 13290 (51.2) | 1907 (59.4) | <.001 |
| Statin use, n (%) | 9295 (31.6) | 8248 (31.5) | 1047 (32.3) | 0.38 |

| | | | | |
|---|---|---|---|---|
| Aspirin use, n (%) | 12790 (43.4) | 11376 (43.4) | 1414 (43.5) | 0.91 |
| Antidepressant use, n (%) | 4086 (13.9) | 3164 (12.1) | 922 (28.4) | <.001 |
| ***Behavioral risk factors*** | | | | |
| Self-reported smoking, pack years, *M* (SD) | 13.5 ( 23.1 | 13.3 ( 22.8 | 15.5 ( 24.9 | <.001 |
| Current Smoking, n(%) | 4263(14.5) | 3463(13.3) | 800(24.7) | <.001 |
| Alcohol use, n (%) | | | | <.001 |
| Heavy | 1172 (4.1) | 1043 (4.0) | 129 (4.1) | |
| Moderate | 9626 (33.3) | 8786 (34.1) | 840 (26.6) | |
| None | 18116 (62.7) | 15925 (61.8) | 2191 (69.3) | |
| Physical inactivity, n (%) | 10004 (34.4) | 8500 (32.9) | 1504 (46.9) | <0.001 |
| Medication non-adherence, n (%) | 7959 (29.7) | 6820 (28.7) | 1139 (37.8) | <.001 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1888 (7.9) | 1542 (7.3) | 346 (12.6) | <.001 |
| Elevated perceived stress (PSS≥5) | 8591 (29.1) | 6283 (23.9) | 2308 (70.9) | <.001 |

**Table 1B. Baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D) and self-reported health**

| | *Self-reported general health as "excellent or very good"* | | | *Self-reported general health as "poor, fair or good"* | | |
|---|---|---|---|---|---|---|
| Characteristics | CES-D < 4 (n=12965) | CES-D ≥4 (n=725) | *p* | CES-D < 4 (n=13219) | CES-D ≥4 (n=2523) | *p* |
| ***Socio-demographics*** | | | | | | |
| Age, *M* (SD) | 64.8 (9.4) | 64.5 (10.2) | 0.47 | 65.5 (9.3) | 62.8 (9.6) | <.001 |
| Female, n (%) | 6600 (50.9) | 501 (69.1) | <.001 | 7357 (55.7) | 1751 (69.4) | <.001 |
| African American, n (%) | 3726 (28.7) | 295 (40.7) | <.001 | 6677 (50.5) | 1404 (55.6) | <.001 |
| Less than high school education, n (%) | 845 (6.5) | 119 (16.4) | <.001 | 2059 (15.6) | 658 (26.1) | <.001 |
| Annual household income, n (%) | | | | | | |
| Less than $20,000 | 1304 (10.1) | 190 (26.2) | <.001 | 2832 (21.4) | 983 (39.0) | <.001 |
| No health insurance, n (%) | 644 (5.0) | 70 (9.7) | <.001 | 884 (6.7) | 324 (12.9) | <.001 |
| Region, n (%) | | | 0.37 | | | <.001 |
| Stroke belt[a] | 4282 (33.0) | 256 (35.3) | | 4668 (35.3) | 963 (38.2) | |
| Stroke buckle[b] | 2619 (20.2) | 148 (20.4) | | 2807 (21.2) | 601 (23.8) | |
| Non-stroke belt or buckle | 6064 (46.8) | 321 (44.3) | | 5744 (43.5) | 959 (38.0) | |
| ***General health and medical conditions*** | | | | | | |
| Self-reported general health, n (%) | | | | | | |
| Poor, fair, good | -- | -- | | --- | -- | |
| Excellent, very good | -- | -- | | --- | --- | |
| Cardiovascular disease, n (%)[c] | 1948 (15.0) | 144 (19.9) | 0.004 | 3874 (29.3) | 840 (33.3) | <.001 |
| Diabetes, n (%)[d] | 1443 (11.6) | 93 (13.3) | 0.16 | 3840 (30.2) | 853 (35.1) | <.001 |
| COPD, n (%) | 796 (6.2) | 55 (7.6) | 0.11 | 1507 (11.4) | 347 (13.8) | 0.007 |
| Physical component score on SF-12 scale, *M* (SD) | 52.0 (6.5) | 51.3 (9.1) | 0.008 | 42.0 (10.7) | 37.7 (11.3) | <.001 |
| ***Physiological risk factors*** | | | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 27.8 (5.1) | 28.4 (5.7) | 0.006 | 30.5 (6.6) | 31.2 (7.3) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 125.3 (15.7) | 126.0 (17.2) | 0.27 | 129.6 (16.9) | 129.5 (18.3) | 0.91 |
| Total Cholesterol, mg/dL, *M* (SD) | 193.8 (38.2) | 195.5 (38.6) | 0.26 | 189.7 (41.2) | 194.4 (44.2) | <.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 53.1 (16.4) | 55.8 (16.6) | <.001 | 50.4 (15.8) | 51.5 (16.1) | 0.002 |
| QT Interval, corrected for heart rate, ms, M (SD) | 405.6 (22.6) | 407.2 (23.5) | 0.06 | 408.7 (24.3) | 410.8 (24.2) | <0.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 1.7[0.8-3.8] | 1.9[0.9-4.9] | 0.004 | 2.7[1.2-6.1] | 3.4[1.3-7.7] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 6.6[4.3-12.3] | 6.9[4.7-14.0] | 0.005 | 8.4[5.0-20.7] | 8.7[5.1-22.2] | 0.18 |
| **Medications** | 4916 (38.3) | 297 (41.7) | 0.06 | 8344 (63.9) | 1606 (64.5) | 0.57 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Antihypertensive medication use, n (%) | | | | | | |
| Statin use, n (%) | 3407 (26.4) | 176 (24.4) | 0.24 | 4822 (36.5) | 870 (34.6) | 0.06 |
| Aspirin use, n (%) | 5254 (40.5) | 273 (37.7) | 0.13 | 6100 (46.2) | 1140 (45.2) | 0.36 |
| | | | | | | <.001 |
| Antidepressant use, n (%) | 1224 (9.5) | 144 (19.9) | <.001 | 1933 (14.6) | 774 (30.8) | |
| ***Behavioral risk factors*** | | | | | | |
| Self-reported smoking, pack years, *M* (SD) | 11.2 ( 20.5) | 12.1 ( 21.6) | 0.24 | 15.3 ( 24.7) | 16.5 ( 25.6) | 0.03 |
| Current Smoking, n(%) | 1344 (10.4) | 114 (15.8) | <.001 | 2110 (16.0) | 684 (27.2) | <.001 |
| Alcohol use, n (%) | | | 0.01 | | | <.001 |
| Heavy | 634 (5.0) | 38 (5.4) | | 409 (3.2) | 91 (3.7) | |
| Moderate | 5034 (39.4) | 238 (33.8) | | 3746 (29.0) | 600 (24.5) | |
| None | 7103 (55.6) | 429 (60.9) | | 8779 (67.9) | 1758 (71.8) | |
| Physical inactivity, n (%) | 3107 (24.3) | 259 (36.0) | <.001 | 5372 (41.3) | 1242 (50.0) | <.001 |
| Medication non-adherence, n (%) | 2997 (26.2) | 211 (33.1) | <.001 | 3809 (31.0) | 926 (39.1) | <.001 |
| Impaired cognitive status | | | <.001 | | | <.001 |
| (Cognitive score ≤ 4) | 587 (5.6) | 61 (10.1) | | 947 (8.9) | 285 (13.3) | |
| Elevated perceived stress (PSS≥5) | 2219 (17.1) | 404 (55.7) | <.001 | 4048 (30.6) | 1900 (75.3) | <.001 |

**Table 2. Association of time-variant elevated depressive symptoms with mortality outcomes.** Each participant contributes to up to 3 time-variant CES-D measures. End of follow-up December 31, 2012.

| | Overall (N=29,491) | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | ***HR (95%CI) for time-variant categorical CES-D (Score =>4 v. < 4)*** | | |
| **All-cause mortality** | | | |
| Events, n | 4581 | 1392 | 3189 |
| Crude | **1.66(1.54-1.80)** | **1.97(1.66-2.33)** | **1.30(1.19-1.42)** |
| Model 1[a] | **1.63(1.50-1.76)** | **1.74(1.46-2.07)** | **1.42(1.29-1.55)** |
| Model 2[b] | **1.42(1.31-1.54)** | **1.60(1.34-1.90)** | **1.30(1.19-1.43)** |
| Model 3[c] | **1.38(1.27-1.49)** | **1.57(1.32-1.87)** | **1.27(1.16-1.39)** |
| Model 4[d] | **1.24(1.13-1.35)** | **1.53(1.27-1.83)** | **1.16(1.05-1.28)** |
| Model 5[e] | **1.24(1.14-1.36)** | **1.48(1.27-1.78)** | **1.17(1.06-1.30)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.005** | | |
| **CVD Death** | | | |
| Events, n | 1551 | 437 | 1114 |
| Crude | **1.61(1.41-1.85)** | **2.01(1.49-2.72)** | **1.23(1.05-1.43)** |
| Model 1[a] | **1.58(1.37-1.81)** | **1.76(1.29-2.40)** | **1.35(1.15-1.58)** |
| Model 2[b] | **1.31(1.13-1.51)** | **1.52(1.12-2.08)** | **1.20(1.03-1.41)** |
| Model 3[c] | **1.27(1.10-1.46)** | **1.53(1.12-2.09)** | 1.17(1.00-1.37) |
| Model 4[d] | 1.15(0.98-1.33) | **1.47(1.07-2.04)** | 1.06(0.90-1.26) |
| Model 5[e] | 1.13(0.98-1.32) | 1.37(0.99-1.91) p=0.06 | 1.07(0.90-1.27) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| **NonCVD Death** | | | |
| Events, n | 3030 | 955 | 2075 |
| Crude | **1.69(1.53-1.86)** | **1.95(1.58-2.39)** | **1.34(1.20-1.50)** |
| Model 1[a] | **1.65(1.50-1.83)** | **1.73(1.40-2.14)** | **1.45(1.30-1.63)** |
| Model 2[b] | **1.48(1.34-1.64)** | **1.63(1.32-2.02)** | **1.35(1.23-1.51)** |
| Model 3[c] | **1.44(1.30-1.59)** | **1.59(1.29-1.97)** | **1.33(1.18-1.49)** |
| Model 4[d] | **1.30(1.17-1.48)** | **1.58(1.27 -2.24)** | **1.22(1.08-1.38)** |
| Model 5 + intervening non-fatal CVD event[e] | **1.29(1.16-1.44)** | **1.54(1.24-1.92)** | **1.22(1.08-1.38)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.03** | | |
| **Cancer Death (a subset of nonCVD death)** | | | |
| Events, n | 1226 | 475 | 751 |
| Crude | **1.27(1.09-1.53)** | **1.53(1.11-2.12)** | 1.06(0.87-1.29) |
| Model 1[a] | **1.29(1.09-1.53)** | **1.45(1.04-2.01)** | 1.16(0.95-1.42) |
| Model 2[b] | **1.25(1.05-1.48)** | **1.40(1.01-1.95)** | 1.14(0.93-1.40) |
| Model 3[c] | **1.20(1.01-1.43)** | 1.35(0.97-1.88) | 1.11(0.91-1.36) |
| Model 4[d] | 1.16(0.96-1.39) | 1.37(0.97-1.92) | 1.08(0.87-1.33) |
| Model 5 + intervening non-fatal CVD event[e] | 1.15(0.96-1.38) | 1.36(0.97-1.91) | 1.08(0.90-1.34) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - 0.20 | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)

[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
[e]Model 5 adds non-fatal CVD event – first nonfatal myocardial infarction or stroke since baseline.
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
**Bold p-value < 0.05;** Missing data in covariates imputed using chained equations.

**Table 3. Association of baseline elevated depressive symptoms (CES-D≥4) with mortality outcomes. Each participant contributes 1 measure of CES-D at baseline.**

| | Overall n=29,491 | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| All-cause mortality | 4581 | 1392 | 3189 |
| Crude | **1.54(1.42-1.68)** | **1.91(1.59-2.31)** | **1.18(1.07-1.30)** |
| Model 1[a] | **1.57(1.44-1.72)** | **1.76(1.45-2.12)** | **1.34(1.21-1.47)** |
| Model 2[b] | **1.32(1.25-1.49)** | **1.61(1.33-1.96)** | **1.22(1.11-1.35)** |
| Model 3[c] | **1.32(1.27-1.44)** | **1.56(1.29-1.90)** | **1.20(1.09-1.32)** |
| Model 4[d] | **1.18(1.07-1.29)** | **1.53(1.25-1.88)** | 1.09(0.98-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.002** | | |
| CVD Death | 1551 | 437 | 1114 |
| Crude | **1.55(1.34-1.78)** | **2.16(1.58-2.96)** | **1.13(0.97-1.33)** |
| Model 1[a] | **1.57(1.35-1.81)** | **1.96(1.42-2.71)** | **1.29(1.10-1.52)** |
| Model 2[b] | **1.28(1.10-1.48)** | **1.71(1.23-2.38)** | 1.14(0.97-1.34) |
| Model 3[c] | **1.24(1.07-1.44)** | **1.70(1.22-2.36)** | 1.11(0.94-1.31) |
| Model 4[d] | 1.10(0.94-1.29) | **1.63(1.16-2.30)** | 1.00(0.84-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.01** | | |
| NonCVD Death | 3030 | 955 | 2075 |
| Crude | **1.54(1.39-1.71)** | **1.80(1.42-2.26)** | **1.21(1.08-1.35)** |
| Model 1[a] | **1.57(1.42-1.75)** | **1.66(1.31-2.10)** | **1.36(1.21-1.53)** |
| Model 2[b] | **1.41(1.26-1.56)** | **1.56(1.29-1.98)** | **1.27(1.13-1.43)** |
| Model 3[c] | **1.36(1.22-1.51)** | **1.49(1.17-1.90)** | **1.25(1.11-1.41)** |
| Model 4[d] | **1.21(1.08-1.36)** | **1.48(1.15-1.89)** | **1.14(1.00-1.29)** |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| Cancer Death (a subset of nonCVD death) | 1226 | 475 | 751 |
| Crude | **1.21(1.02-1.44)** | **1.63(1.16-2.30)** | 0.97(0.79-1.19) |
| Model 1[a] | **1.27(1.06-1.52)** | **1.58(1.12-2.23)** | 1.09(0.89-1.35) |
| Model 2[b] | **1.22(1.02-1.47)** | **1.53(1.08-2.17)** | 1.07(0.87-1.33) |
| Model 3[c] | 1.17(0.98-1.41) | **1.45(1.02-2.05)** | 1.05(0.85-1.30) |
| Model 4[d] | 1.12(0.93-1.36) | **1.49(1.03-2.13)** | 1.01(0.81-1.27) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.07** | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
HR and 95% CI were estimated by Cox proportional hazard regression models. Bold p-value < 0.05; Missing data in covariates imputed using chained equations.

## Figure Legend

**Figure 1.** Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

**Figure 2.** Kaplan Meier Curves of Time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.

Figure 1. Cohort Flow Diagram: Exclusion cascade of Depressive symptoms to Mortality Endpoints analysis.

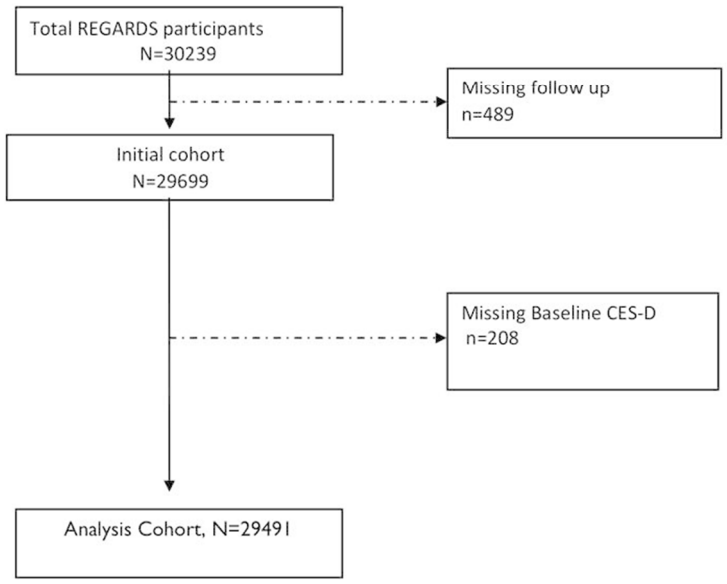



Figure 1. Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

254x190mm (96 x 96 DPI)

**Figure 2. Kaplan Meier Curves of Time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer.**

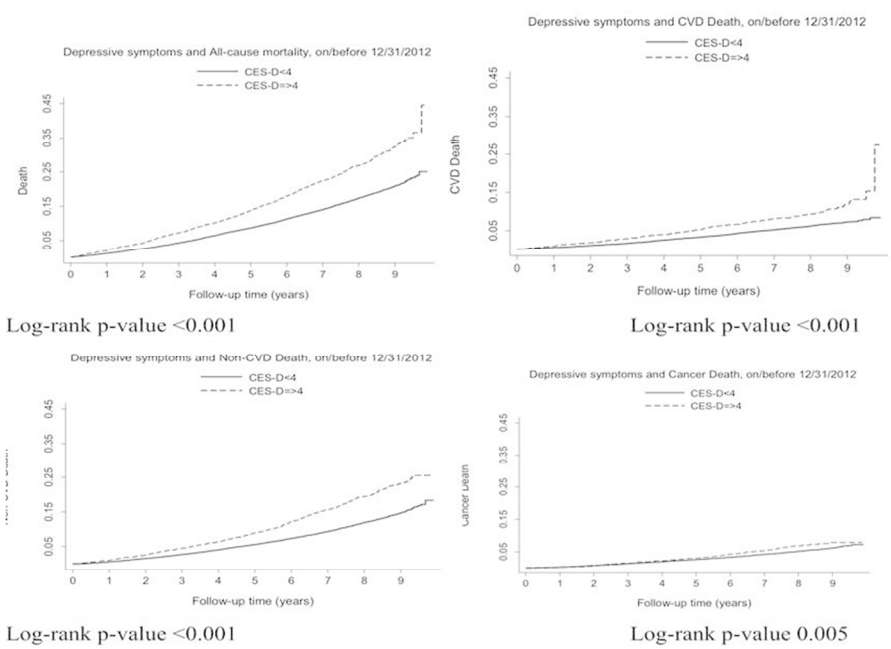
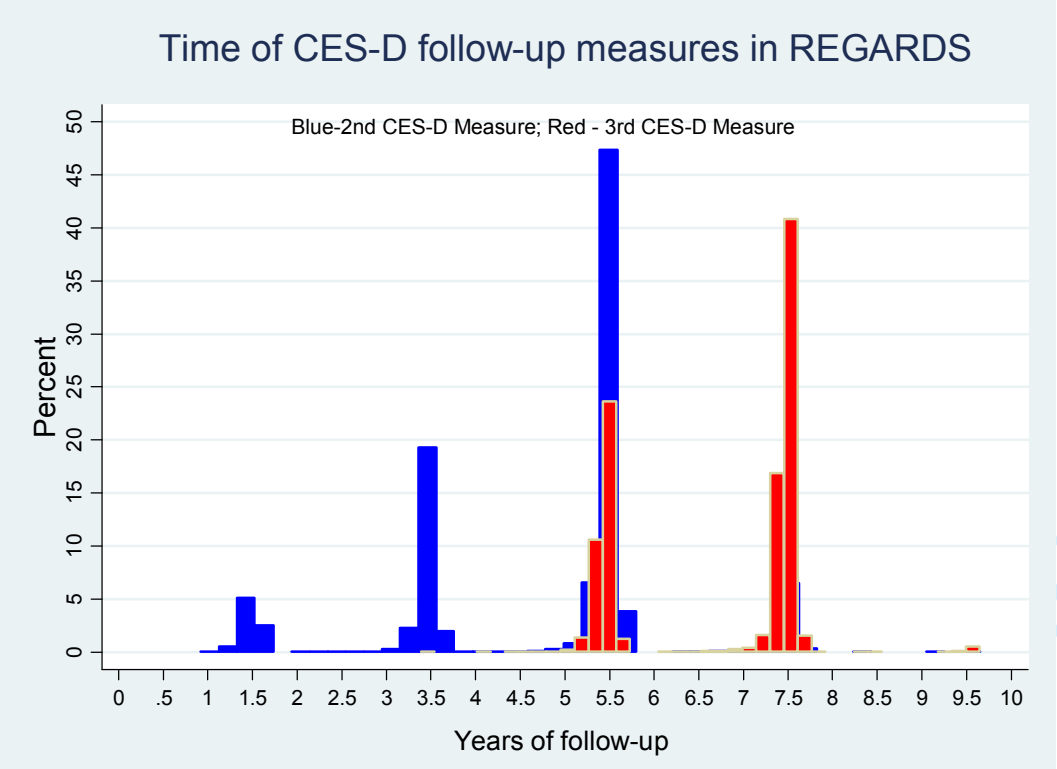



Figure 2. Kaplan Meier Curves of Time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.

254x190mm (96 x 96 DPI)

**Supplementary Material**

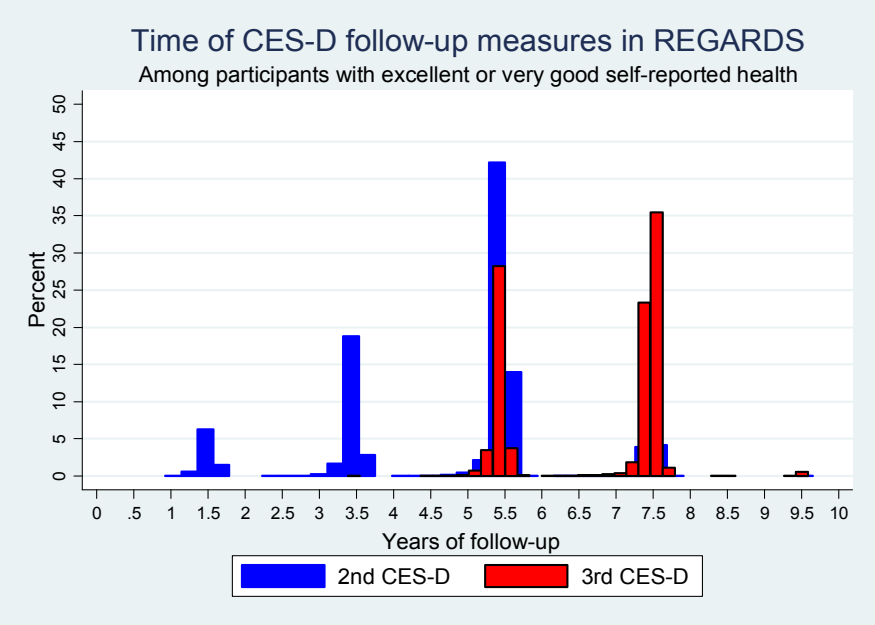
**eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.**

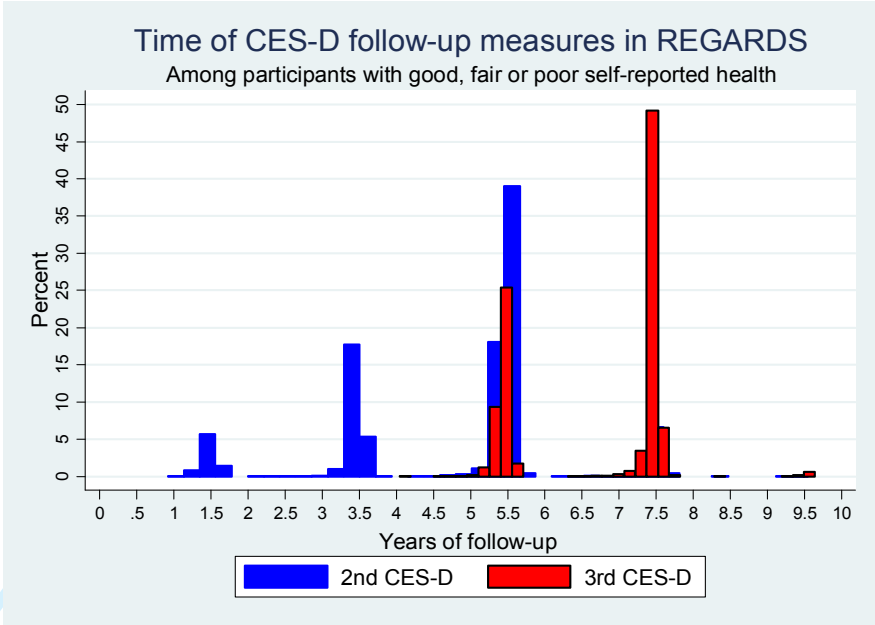



*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| | Time since preceding measurement (baseline or second follow-up), years | | | | |
|---|---|---|---|---|---|
| | Participants, n | Mean | SD | Minimum | Maximum |
| Second CES-D | 20934 | 4.8 | 1.5 | 0.9 | 9.7 |
| Third CES-D | 12451 | 2.1 | 0.4 | 1.0 | 4.2 |

**eFigure 2. Timing of CES-D follow up measures in REGARDS by self reported health at baseline.**




*"Percent" is a proportion of participants reporting CES-D scores at certain times, of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| Self-reported general health as "excellent or very good" | | | | | | Self-reported general health as "poor, fair or good" | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | |
| | N | Mean | SD | Minimum | Maximum | N | Mean | SD | Minimum | Maximum |
| Second CES-D | 10448 | 4.8 | 1.5 | 0.9 | 9.7 | 10448 | 4.8 | 1.5 | 0.9 | 9.5 |
| Third CES-D | 6472 | 2.1 | 0.4 | 1.7 | 4.2 | 5959 | 2.1 | 0.5 | 1.0 | 4.2 |

**eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).**

| Self-reported general health | Baseline | | | Second CES-D | | | Third CES-D | | |
|---|---|---|---|---|---|---|---|---|---|
| | CES-D<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n |
| **Excellent** | 4515<br>95.9 % | 195<br>4.1% | 4710 | 3444<br>94.7% | 194<br>5.3% | 3638 | 2109<br>94.6% | 120<br>5.4% | 2229 |
| **Very good** | 8450<br>94.1% | 530<br>5.9% | 8980 | 6332<br>93.0% | 478<br>7.0% | 6810 | 3938<br>92.8% | 305<br>7.2% | 4243 |
| **Good** | 9181<br>89.1% | 1124<br>10.9% | 10305 | 6363<br>88.6% | 818<br>11.4% | 7181 | 3717<br>88.9% | 464<br>11.1% | 4181 |
| **Fair** | 3424<br>77.8 % | 975<br>22.2 % | 4399 | 2185<br>79.7% | 556<br>20.3% | 2741 | 1236<br>82.0% | 271<br>18.0% | 1507 |
| **Poor** | 614<br>59.2% | 424<br>40.9% | 1038 | 322<br>61.2% | 204<br>38.8% | 526 | 177<br>65.3% | 94<br>34.7% | 271 |
| | | | 29432 | | | 20896 | | | 12431 |
| | **Frequency Missing = 59** | | | **Frequency Missing = 8595** | | | **Frequency Missing = 17060** | | |

**eTable 2. Reasons for non-cardiovascular disease death in the REGARDS study**

| | Overall | | Self-reported general health as **"excellent or very good"** n=13,711 | | Self-reported general health as **"poor, fair or good"** n=15,780 | |
|---|---|---|---|---|---|---|
| *Causes of Death* | n | Percent | Frequency | Percent | Frequency | Percent |
| Cancer | 1226 | 44.3 | 474 | 54.0 | 747 | 39.7 |
| Accidents/Injury/Suicide/Homicide | 164 | 5.9 | 52 | 5.9 | 111 | 5.9 |
| Suicide | 3 | 0.1 | 2 | 0.2 | 1 | 0.05 |
| Liver disease | 56 | 2.0 | 14 | 1.6 | 42 | 2.2 |
| Infection | 498 | 18.0 | 132 | 15.0 | 365 | 19.4 |
| ESRD | 119 | 4.3 | 23 | 2.6 | 95 | 5.1 |
| Dementia | 187 | 6.8 | 74 | 8.4 | 112 | 6.0 |
| COPD | 247 | 8.9 | 43 | 4.9 | 204 | 10.9 |
| Pulmonary Embolism | 38 | 1.34 | 11 | 1.3 | 27 | 1.4 |
| Other | 232 | 8.4 | 55 | 6.3 | 177 | 9.4 |
| | Frequency Missing = 263 | | | | Frequency Missing = 272 | |

**eTable 3. Baseline characteristics of REGARDS participants, who had all 3 CES-D measures vs. those with 1 or 2 CES-D measures**

| Characteristics | 1 or 2 CES-D measures (n=17,040) | All 3 CES-D measures (n=12, 451) | *p* value |
|---|---|---|---|
| ***Socio-demographics*** | | | |
| Age, *M* (SD) | 65.0 +- 10.0 | 64.7 +- 8.5 | 0.0069 |
| Female, n (%) | 9300 (54.6) | 6945 (55.8) | 0.04 |
| African American, n (%) | 7709 (45.2) | 4420 (35.5) | <.001 |
| Less than high school education, n (%) | 2583 (15.2) | 1113 (8.9) | <.001 |
| Annual Household Income, n (%) | | | <.001 |
| Less than $20,000 | 3549 (20.8) | 1773 (14.2) | |
| No Health Insurance, n (%) | 1290 (7.6) | 636 (5.1) | <.001 |
| Region, n (%) | | | <.001 |
| Stroke belt | 5806 (34.1) | 4387 (35.2) | |
| Stroke buckle | 3887 (22.8) | 2301 (18.5) | |
| Non-stroke belt or buckle | 7347 (43.1) | 5763 (46.3) | |
| ***General health and medical conditions*** | | | |
| Self-reported general health, n (%) | | | <.001 |
| Poor, fair, good | 9783 (57.5) | 5959 (47.9) | |
| Excellent, very good | 7218 (42.5) | 6472 (52.1) | |
| Cardiovascular disease (CHD, stroke, PAD, AA), n (%) | 4379 (25.7) | 2446 (19.6) | <.001 |
| Diabetes, n (%) | 4083 (25.0) | 2169 (18.0) | <.001 |
| COPD, n (%) | 1612 (9.5) | 1098 (8.8) | 0.05 |
| Physical component score on SF-12 scale, *M* (SD) | 45.5 +- 11.0 | 47.6 +- 9.9 | <.001 |
| ***Physiological risk factors*** | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.4 +- 6.3 | 29.2 +- 6.0 | 0.0024 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 128.0 +- 17.2 | 127.0 +- 15.9 | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.2 +- 41.0 | 191.9 +- 39.0 | 0.5732 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.4 +- 16.1 | 52.4 +- 16.3 | <.001 |
| QT Interval, corrected for heart rate, ms, M (SD) | 408.4 +- 24.2 | 406.3 +- 22.7 | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.3[1.0-5.4] | 2.1[0.9-4.7] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.9[4.8-18.7] | 6.9[4.5-13.5] | <.001 |

| | | | |
|---|---|---|---|
| ***Medications*** | | | |
| Antihypertensive medication use, n (%) | 9079 (53.9) | 6118 (49.7) | <.001 |
| Statin use, n (%) | 5344 (31.4) | 3951 (31.8) | 0.53 |
| Aspirin use, n (%) | 7297 (42.8) | 5493 (44.1) | 0.03 |
| Antidepressant use, n (%) | 2440 (14.4) | 1646 (13.2) | 0.006 |
| ***Behavioral risk factors*** | | | |
| Self-reported smoking, pack years, *M* (SD) | 14.5 +- 24.4 | 12.2 +- 21.0 | <.001 |
| Current Smoking, n(%) | 2786 (16.4) | 1477 (11.9) | <.001 |
| Alcohol use, n (%) | | | <.001 |
| Heavy | 652 (3.9) | 520 (4.2) | |
| Moderate | 5180 (31.1) | 4446 (36.3) | |
| None | 10822 (65.0) | 7294 (59.5) | |
| Physical inactivity, n (%) | 6150 (36.7) | 3854 (31.3) | <.001 |
| Medication non-adherence, n (%) | 4548 (29.6) | 3411 (29.9) | 0.59 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1300 (9.4) | 588 (5.9) | <.001 |
| Elevated perceived stress (PSS≥5) | 5437 (31.9) | 3154 (25.3) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.
Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use. CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No/Page # | Recommendation |
|---|---|---|
| **Title and abstract** | 1 (page 1) | (*a*) Indicate the study's design with a commonly used term in the title or the **abstract** |
| | (Page 2) | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 (Page 3) | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 (pages 3) | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 (Page 3 and 4) | Present key elements of study design early in the paper |
| Setting | 5 (page 4-7), | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 (page 4, 8) | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| | n/a | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 (page 4-6) | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8 (pages4-6) | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one |

| | | |
|---|---|---|
| | | group |
| Bias | 9 (page 12) | Describe any efforts to address potential sources of bias |
| Study size | 10 (page 8) | Explain how the study size was arrived at |
| Quantitative variables | 11 (page 4-7) | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 (page 6-8) | (*a*) Describe all statistical methods, including those used to control for confounding |
| | Pages 7-8 | (*b*) Describe any methods used to examine subgroups and interactions |
| | Page 8 | (*c*) Explain how missing data were addressed |
| | Page 7 | (*d*) If applicable, explain how loss to follow-up was addressed |
| | Page 8 | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13 (page 8) | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | Page 8 | (b) Give reasons for non-participation at each stage |
| | Figure 1 | (c) Consider use of a flow diagram |
| Descriptive data | 14 (page 8-9) | (a) Give characteristics of study participants (eg demographic, clinical, social) cand information on exposures and potential confounders |
| | Page 8 | (b) Indicate number of participants with missing data for each variable of interest |
| | Pages 9 | (c) Summarise follow-up time (eg, average and total amount) |

| | | |
|---|---|---|
| Outcome data | 15 (page 9) | Report numbers of outcome events or summary measures over time |
| Main results | 16 (pages 9-10) | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | Page 6, 8, 19-20 | (*b*) Report category boundaries when continuous variables were categorized |
| | n/a | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 (pages 10) | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 (page 10) | Summarise key results with reference to study objectives |
| Limitations | 19 (pages 12) | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 (page 11-12) | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 (page 12) | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 (page 16) | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present |

| | | |
|---|---|---|
| | | article is based |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study



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# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study

**Running Title:** depressive symptoms and mortality

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**Abstract**

**Objective:** To assess the association between time-varying depressive symptoms with all-cause and cause-specific mortality

**Design:** The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a national, population-based longitudinal study conducted from 2003-2007.

**Setting**: General continental U.S. communities

**Participants**: 29,491 black and white U.S. adults ≥45 years randomly sampled within race-sex-geographic strata

**Exposure**: Elevated depressive symptoms (CES-D-4 ≥ 4) measured at baseline and on average 5 and 7 years later

**Main Outcome Measures**: Cox proportional hazard regression models assessed cancer, non-cardiovascular (CVD), CVD and all-cause mortality.

**Results:** The average age was 64.9 years; 55% were female; 41% black; 11.0% had elevated depressive symptoms; 54% had poor, fair or good health. Time-varying depressive symptoms were significantly associated with nonCVD (aHR=1.29, 95% CI 1.16-1.44) and all-cause (aHR=1.24, 95%CI 1.14-1.39), but not cancer (aHR=1.15, 95%CI 0.96-1.38) or CVD (aHR=1.13, 95%CI 0.98-1.32) death adjusting for demographics, chronic clinical diseases, behavioral risk factors, and physiologic factors. Depressive symptoms were related to all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death in those who reported excellent or very good health. The analyses of the association between one measure of baseline depressive symptoms and mortality analyses yielded similar results.

**Conclusions:** Time-varying depressive symptoms confer an increased risk for all-cause mortality, CVD, non-CVD death and cancer death, particularly in those with excellent or very good health. These findings may have implications for timely treatment, regardless of health status.

**Strengths and limitations of this study.**

- Depression is a relapsing/remitting disease and our study is one of the first to use multiple measurements of depression to demonstrate a time varying relationship between depression and mortality, including cancer mortality, in a large, diverse cohort.
- To our knowledge, we are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and cause-specific mortality, with depression predicting mortality particularly in those with excellent or very good reported health.
- Our analyses were limited by the use of the short form of the CES-D scale
- The REGARDS cohort is regionally specific, limiting generalizability.

## Introduction

It is well known that elevated depressive symptoms predict mortality,[1] both in high-risk individuals with chronic illnesses like cardiovascular disease (CVD), and in general populations.[2-4] [5-8] More recently, several studies have shown that depressive symptoms both preceding and following cancer diagnosis may confer an increased risk of cancer death as well.[9,10]

However, depressive symptoms relapse and remit, and prior studies on the relationship between depressive symptoms and mortality have been limited by one measurement of depressive symptoms.[1] Recently, Lasserre et al. (2016) found that current but not remitted depressive symptoms predict all-cause mortality, but again depression diagnoses and history were ascertained at one time point.[11] In addition, prior literature has often been marked by inadequate adjustment for important covariates, such as behavioral risk factors. To our knowledge, few if any prior studies have examined the time-varying association between depressive symptoms and excess causes of death, including all-cause and cause specific mortality. In addition, self-perceived health status may predict mortality[12] and complicate the relationship between depressive symptoms and poor outcomes.[13] It is unknown whether depressive symptoms confer an increased risk of excess mortality equally in those with self-reported excellent/very good (in whom depression may be less likely to be recognized) and good/fair/poor health.

The purpose of our study is to examine the association between time-varying depressive symptoms with cancer, CVD, nonCVD and all-cause mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a broad, diverse population cohort with repeat measurements of depressive symptoms. We stratify by self-reported baseline health status

(very good or excellent vs. poor, fair or good) to further isolate the association between depressive symptoms and excess mortality.

## Methods

The REGARDS study is a national cohort study of stroke incidence and cognitive decline in black and white community dwelling adults ≥ 45 years living in the United States stratified to reflect specific race-sex-geographic strata.[14] Inclusion and exclusion criteria have been previously described; of note, those with active cancer were excluded from the original study.[14] Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study. Participants were recruited by mail using commercially available lists of U.S. residents, followed by a computer-assisted telephone interview and subsequent home visit at which time individuals were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing baseline depressive symptom measurements **(Figure 1)**. The REGARDS study protocol was approved by institutional review boards at participating centers.

### *Study Procedures*

Baseline data were collected through computer-assisted telephone interviews, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data, medical history and behavioral risk factors. Following the telephone interview, individuals had an in-home visit during which physical measurements, a resting electrocardiogram, medication inventory, phlebotomy and urine were collected. The median time between the initial phone interview and in-home examination was 28.0 (interquartile range = 21.0) days.

*Primary Outcomes*

The primary outcomes for these analyses were (1) cancer mortality (all body sites) (2) CVD death defined as death from CHD, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes (3) non-CVD death and (4) all-cause mortality. Living participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for reported hospitalizations or physician visits. Deaths were detected by report of next-of-kin or through online services (e.g., Social Security Death Index) or the National Death Index.[14] Death certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and CVD outcomes.

*Depressive symptoms*

The primary predictor was baseline depressive symptoms. The 4-item Center for Epidemiologic Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. This scale asks participants to rate the number of days over the last week in which they had: 1) felt depressed; 2) felt lonely; 3) had crying spells; and 4) felt sad. Response options included <1 day, 1 to 2 days, 3 to 4 days, and 5-7 days (0, 1, 2 3 points, respectively). Cronbach's α for the CES-D in the total sample was 0.80. Elevated depressive symptoms were defined as a summed score of ≥4.[15] The reliability and validity of the CES-D 4 is similar to the original 20-item instrument.[16]

*Covariates*

Demographic data included self-reported age, gender, race (black or white), education (less than high school, high school graduate, some college, and college graduate and above), annual income (less than $20,000, $20,000-$34,999, $35,000-$74,999, $75,000 and above), insurance

status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk factors included (1) diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR) (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial infarction or coronary revascularization procedure or evidence of myocardial infarction on the study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8) cognitive impairment on the 6-item screener of global cognitive function[17,18] (9) chronic lung disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin, antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors included (1) self-reported pack-years of cigarette smoking; (2) physical activity ("How many times per week do you engage in intense physical activity, enough to work up a sweat?" with response options of "none", "1-3 times per week" and "4 or more times per week"); (3) alcohol use ("How many alcoholic beverages do you drink?": none, moderate [1 drink per day for women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2 drinks per day for men]);[14] (4) medication non-adherence assessed with the 4-item Morisky Medication Adherence Scale (>= 1).[19] Potential physiologic risk factors included high-sensitivity C-reactive protein, self-reported health status based on the physical component of the 12-item

Short-Form Health Survey (SF 12),[20] and perceived stress, measured by the 4-item version of the Perceived Stress Scale (score of ≥ 5 vs. <5).[21]

*Statistical Analyses*

Baseline characteristics of participants with and without elevated depressive symptoms at baseline were compared using chi-square tests (for categorical variables), Student t tests (for continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous measures).

Cox proportional hazard regression models were constructed to separately analyze the association between depressive symptoms (CES-D≥4) and cancer death (from all body sites, a subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline measurement, and 3) on average two years after the second measurement. In the analyses, we considered depressive symptoms (CES-D≥4 vs. <4) as a time-varying exposure, with updates of exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3 measures of CES-D (≥4 vs. <4) with a broken-up follow-up time. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive symptoms using the Simon-Makuch method,[22] a modification of the Kaplan-Meier method. In this context, depression status is treated as a binary time-dependent covariate and study cohorts are continually updated to contribute to either the CES-D≥4 or CES-D <4 groups.

Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were estimated for those with vs. without elevated depressive symptoms. Adjusted modeling proceeded in stages, starting with demographic (Model 1) and traditional CVDrisk factors (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5), which considered intervening first non-fatal stroke and/or myocardial infarction as a time-dependent covariate in CVD death outcomes. All analyses were conducted overall as well as stratified. We also conducted a formal test for interaction between depressive symptoms and self-reported health (defined as excellent or very good vs. good, fair or poor health) in the fully-adjusted models. As such, all analyses were conducted overall as well as stratified by baseline self-reported health. To test the proportional hazards assumptions, we performed the chi-squared test for the Schoenfeld residuals and all the models resulted in a violation of the proportional hazards assumptions, indicating that time-varying covariates were appropriate The proportionality assumption for time varying depressive symptoms was tested by assessing the interaction of depressive symptoms*log of follow-up time and was satisfied for all mortality endpoints.

*Sensitivity Analyses*

Sensitivity analyses constructed in parallel to the main analyses examined association of baseline CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, or end of follow-up.

Missing data in covariates were imputed using chained equations and derived by bootstrapping across the 5 imputed datasets. Of the 29,491 participants, 2768 (9%) were missing income data, 59 (0.2%) health status, 9 (<0.1%) education, 26 (0.1%) health insurance, 1087 (4%) diabetes, 16 (0.1%) aspirin use, 70 (0.2%) statin use, 70 (0.2%) antidepressant use, 333 (1%) anti-hypertension meds use, 439 (2%) physical activity, 2705 (9%) medication adherence, 213 (0.7%) BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912 (3.1%) pack years, 84 (0.3%) SBP, 1394 (5%) renal function, 381 (1%) QTc, 5681 (19.3%) cognitive status, 4 (<0.1%) stress, 1425 (4%) SF-12 and 1881 (6%) CRP. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).

## Results

*Participant Characteristics*

Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms, leaving 29,491 eligible participants (**Figure 1)** of whom 3,254 (11.0%) had elevated depressive symptoms at baseline (CES-D≥4). The average age was 64.9 (9.4) years; 55.1% were female and 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33% of individuals were physically inactive, 29.2% non-adherent to their medication regimen and 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless of health status, participants with elevated (vs. non-elevated) depressive symptoms were more likely to be female, African-American, low income, have more chronic diseases, low physical health, and more behavioral risk factors (**Table 1A-B)**.

**Table 1A. Overall baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D)**

| Characteristics | Overall (n=29,491) | CES-D < 4 (n=26,817) | CES-D ≥4 (n=3,254) | *p* |
|---|---|---|---|---|
| ***Socio-demographics*** | | | | |
| Age, *M* (SD) | 64.9 (9.4) | 65.1 (9.4) | 63.2 (9.8) | <.001 |
| Female, n (%) | 16245 (55.1) | 13988 (53.3) | 2257 (69.4) | <.001 |
| African American, n (%) | 12129 (41.1) | 10427 (39.7) | 1702 (52.3) | <.001 |
| Less than high school education, n (%) | 3696 (12.5) | 2916 (11.1) | 780 (24.0) | <.001 |
| Annual household income, n (%) | | | | |
| Less than $20,000 | 5322 (18.0) | 4148 (15.8) | 1174 (36.1) | <.001 |
| No health insurance, n (%) | 1926 (6.5) | 1532 (5.8) | 394 (12.1) | <.001 |
| Region, n (%) | | | | <.001 |
| Stroke belt[a] | 10193 (34.6) | 8973 (34.2) | 1220 (37.5) | |
| Stroke buckle[b] | 6188 (21.0) | 5437 (20.7) | 751 (23.1) | |
| Non-stroke belt or buckle | 13110 (44.5) | 11827 (45.1) | 1283 (39.4) | |
| ***General health and medical conditions*** | | | | |
| Self-reported general health, n (%) | | | | <.001 |
| Poor, fair, good | 15742 (53.5) | 13219 (50.5) | 2523 (77.7) | |
| Excellent, very good | 13690 (46.5) | 12965 (49.5) | 725 (22.3) | |
| Cardiovascular disease, n (%)[c] | 6825 (23.1) | 5838 (22.3) | 987 (30.3) | <.001 |
| Diabetes, n (%)[d] | 6252 (22.0) | 5305 (21.0) | 947 (30.2) | <.001 |
| COPD, n (%) | 2710 (9.2) | 2307 (8.8) | 403 (12.4) | <.001 |
| Physical component score on SF-12 scale, *M* (SD) | 46.4 (10.6) | 47.1 (10.2) | 40.7 (12.2) | <.001 |
| ***Physiological risk factors*** | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.3 (6.2) | 29.2 (6.1) | 30.6 (7.1) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 127.6 (16.7) | 127.5 (16.5) | 128.7 (18.1) | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.1 (40.1) | 191.7 (39.8) | 194.6 (43.0) | <0.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.8 (16.2) | 51.7 (16.2) | 52.5 (16.3) | 0.02 |
| QT Interval, corrected for heart rate, ms, M (SD) | 407.5 (23.6) | 407.2 (23.5) | 410.0 (24.1) | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.2[1.0-5.0] | 2.1[0.9-4.8] | 3.0[1.2-6.9] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.4[4.7-6.2] | 7.3[4.6-15.8] | 8.2[5.1-19.8] | <.001 |
| **Medications** | | | | |
| Antihypertensive medication use, n (%) | 15197 (52.1) | 13290 (51.2) | 1907 (59.4) | <.001 |
| Statin use, n (%) | 9295 (31.6) | 8248 (31.5) | 1047 (32.3) | 0.38 |

| | | | | |
|---|---|---|---|---|
| Aspirin use, n (%) | 12790 (43.4) | 11376 (43.4) | 1414 (43.5) | 0.91 |
| Antidepressant use, n (%) | 4086 (13.9) | 3164 (12.1) | 922 (28.4) | <.001 |
| ***Behavioral risk factors*** | | | | |
| Self-reported smoking, pack years, *M* (SD) | 13.5 ( 23.1 | 13.3 ( 22.8 | 15.5 ( 24.9 | <.001 |
| Current Smoking, n(%) | 4263(14.5) | 3463(13.3) | 800(24.7) | <.001 |
| Alcohol use, n (%) | | | | <.001 |
| Heavy | 1172 (4.1) | 1043 (4.0) | 129 (4.1) | |
| Moderate | 9626 (33.3) | 8786 (34.1) | 840 (26.6) | |
| " None | 18116 (62.7) | 15925 (61.8) | 2191 (69.3) | |
| Physical inactivity, n (%) | 10004 (34.4) | 8500 (32.9) | 1504 (46.9) | <0.001 |
| Medication non-adherence, n (%) | 7959 (29.7) | 6820 (28.7) | 1139 (37.8) | <.001 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1888 (7.9) | 1542 (7.3) | 346 (12.6) | <.001 |
| Elevated perceived stress (PSS≥5) | 8591 (29.1) | 6283 (23.9) | 2308 (70.9) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease

[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.

[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

**Table 1B. Baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D) and self-reported health**

| | *Self-reported general health as "excellent or very good"* | | | *Self-reported general health as "poor, fair or good"* | | |
|---|---|---|---|---|---|---|
| Characteristics | CES-D < 4 (n=12965) | CES-D ≥4 (n=725) | *p* | CES-D < 4 (n=13219) | CES-D ≥4 (n=2523) | *p* |
| ***Socio-demographics*** | | | | | | |
| Age, *M* (SD) | 64.8 (9.4) | 64.5 (10.2) | 0.47 | 65.5 (9.3) | 62.8 (9.6) | <.001 |
| Female, n (%) | 6600 (50.9) | 501 (69.1) | <.001 | 7357 (55.7) | 1751 (69.4) | <.001 |
| African American, n (%) | 3726 (28.7) | 295 (40.7) | <.001 | 6677 (50.5) | 1404 (55.6) | <.001 |
| Less than high school education, n (%) | 845 (6.5) | 119 (16.4) | <.001 | 2059 (15.6) | 658 (26.1) | <.001 |
| Annual household income, n (%) | | | | | | |
| Less than $20,000 | 1304 (10.1) | 190 (26.2) | <.001 | 2832 (21.4) | 983 (39.0) | <.001 |
| No health insurance, n (%) | 644 (5.0) | 70 (9.7) | <.001 | 884 (6.7) | 324 (12.9) | <.001 |
| Region, n (%) | | | 0.37 | | | <.001 |
| Stroke belt[a] | 4282 (33.0) | 256 (35.3) | | 4668 (35.3) | 963 (38.2) | |
| Stroke buckle[b] | 2619 (20.2) | 148 (20.4) | | 2807 (21.2) | 601 (23.8) | |
| Non-stroke belt or buckle | 6064 (46.8) | 321 (44.3) | | 5744 (43.5) | 959 (38.0) | |
| ***General health and medical conditions*** | | | | | | |
| Self-reported general health, n (%) | | | | | | |
| Poor, fair, good | -- | -- | | --- | -- | |
| Excellent, very good | -- | -- | | --- | --- | |
| Cardiovascular disease, n (%)[c] | 1948 (15.0) | 144 (19.9) | 0.004 | 3874 (29.3) | 840 (33.3) | <.001 |
| Diabetes, n (%)[d] | 1443 (11.6) | 93 (13.3) | 0.16 | 3840 (30.2) | 853 (35.1) | <.001 |
| COPD, n (%) | 796 (6.2) | 55 (7.6) | 0.11 | 1507 (11.4) | 347 (13.8) | 0.007 |
| Physical component score on SF-12 scale, *M* (SD) | 52.0 (6.5) | 51.3 (9.1) | 0.008 | 42.0 (10.7) | 37.7 (11.3) | <.001 |
| ***Physiological risk factors*** | | | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 27.8 (5.1) | 28.4 (5.7) | 0.006 | 30.5 (6.6) | 31.2 (7.3) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 125.3 (15.7) | 126.0 (17.2) | 0.27 | 129.6 (16.9) | 129.5 (18.3) | 0.91 |
| Total Cholesterol, mg/dL, *M* (SD) | 193.8 (38.2) | 195.5 (38.6) | 0.26 | 189.7 (41.2) | 194.4 (44.2) | <.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 53.1 (16.4) | 55.8 (16.6) | <.001 | 50.4 (15.8) | 51.5 (16.1) | 0.002 |
| QT Interval, corrected for heart rate, ms, M (SD) | 405.6 (22.6) | 407.2 (23.5) | 0.06 | 408.7 (24.3) | 410.8 (24.2) | <0.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 1.7[0.8-3.8] | 1.9[0.9-4.9] | 0.004 | 2.7[1.2-6.1] | 3.4[1.3-7.7] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 6.6[4.3-12.3] | 6.9[4.7-14.0] | 0.005 | 8.4[5.0-20.7] | 8.7[5.1-22.2] | 0.18 |
| | 4916 (38.3) | 297 (41.7) | 0.06 | 8344 (63.9) | 1606 (64.5) | 0.57 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Medications** | | | | | | |
| Antihypertensive medication use, n (%) | | | | | | |
| Statin use, n (%) | 3407 (26.4) | 176 (24.4) | 0.24 | 4822 (36.5) | 870 (34.6) | 0.06 |
| Aspirin use, n (%) | 5254 (40.5) | 273 (37.7) | 0.13 | 6100 (46.2) | 1140 (45.2) | 0.36 |
| | | | | | | <.001 |
| Antidepressant use, n (%) | 1224 (9.5) | 144 (19.9) | <.001 | 1933 (14.6) | 774 (30.8) | |
| ***Behavioral risk factors*** | | | | | | |
| Self-reported smoking, pack years, *M* (SD) | 11.2 ( 20.5) | 12.1 ( 21.6) | 0.24 | 15.3 ( 24.7) | 16.5 ( 25.6) | 0.03 |
| Current Smoking, n(%) | 1344 (10.4) | 114 (15.8) | <.001 | 2110 (16.0) | 684 (27.2) | <.001 |
| Alcohol use, n (%) | | | 0.01 | | | <.001 |
| Heavy | 634 (5.0) | 38 (5.4) | | 409 (3.2) | 91 (3.7) | |
| Moderate | 5034 (39.4) | 238 (33.8) | | 3746 (29.0) | 600 (24.5) | |
| None | 7103 (55.6) | 429 (60.9) | | 8779 (67.9) | 1758 (71.8) | |
| Physical inactivity, n (%) | 3107 (24.3) | 259 (36.0) | <.001 | 5372 (41.3) | 1242 (50.0) | <.001 |
| Medication non-adherence, n (%) | 2997 (26.2) | 211 (33.1) | <.001 | 3809 (31.0) | 926 (39.1) | <.001 |
| Impaired cognitive status | | | <.001 | | | <.001 |
| (Cognitive score ≤ 4) | 587 (5.6) | 61 (10.1) | | 947 (8.9) | 285 (13.3) | |
| Elevated perceived stress (PSS≥5) | 2219 (17.1) | 404 (55.7) | <.001 | 4048 (30.6) | 1900 (75.3) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease

[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.

[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

*Mortality*

A total of 4,581 (15.5%) participants died during the follow-up period ending in 2012. Of these, 1,551 (33.9%) were attributed to CVD and 3,030 (66.1%) to nonCVD disease death. Of nonCVD deaths, 1,226 (44.3%) were due to cancer death (eTable 2**)**. Overall, there were only 3 cases of mortality due to suicide.

For the time-varying analyses, depressive symptoms were measured at baseline and on average 4.8 years (SD = 1.5) years following the baseline measurement, the third measurement occurring on average 2.1 (SD = 0.4) years after the second measurement (eFigure 1). The mean follow-up time of the second and third measurement of CES-D measures did not differ by self-reported health

(eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8% had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 05% CI 0.98-1.32), even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-fatal CVD events (**Table 2,** eFigure 3). The results appeared to be particularly robust amongst those with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death), and 0.20 (cancer death) (**Table 2**).

**Table 2. Association of time-variant elevated depressive symptoms with mortality outcomes.** Each participant contributes to up to 3 time-variant CES-D measures. End of follow-up December 31, 2012.

| | Overall (N=29,491) | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | ***HR (95%CI) for time-variant categorical CES-D (Score =>4 v. < 4)*** | | |
| **All-cause mortality** | | | |
| Events, n | 4581 | 1392 | 3189 |
| Crude | **1.66(1.54-1.80)** | **1.97(1.66-2.33)** | **1.30(1.19-1.42)** |
| Model 1[a] | **1.63(1.50-1.76)** | **1.74(1.46-2.07)** | **1.42(1.29-1.55)** |
| Model 2[b] | **1.42(1.31-1.54)** | **1.60(1.34-1.90)** | **1.30(1.19-1.43)** |
| Model 3[c] | **1.38(1.27-1.49)** | **1.57(1.32-1.87)** | **1.27(1.16-1.39)** |
| Model 4[d] | **1.24(1.13-1.35)** | **1.53(1.27-1.83)** | **1.16(1.05-1.28)** |
| Model 5[e] | **1.24(1.14-1.36)** | **1.48(1.27-1.78)** | **1.17(1.06-1.30)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.005** | | |
| **CVD Death** | | | |
| Events, n | 1551 | 437 | 1114 |
| Crude | **1.61(1.41-1.85)** | **2.01(1.49-2.72)** | **1.23(1.05-1.43)** |
| Model 1[a] | **1.58(1.37-1.81)** | **1.76(1.29-2.40)** | **1.35(1.15-1.58)** |
| Model 2[b] | **1.31(1.13-1.51)** | **1.52(1.12-2.08)** | **1.20(1.03-1.41)** |
| Model 3[c] | **1.27(1.10-1.46)** | **1.53(1.12-2.09)** | 1.17(1.00-1.37) |
| Model 4[d] | 1.15(0.98-1.33) | **1.47(1.07-2.04)** | 1.06(0.90-1.26) |
| Model 5[e] | 1.13(0.98-1.32) | 1.37(0.99-1.91) p=0.06 | 1.07(0.90-1.27) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| **NonCVD Death** | | | |
| Events, n | 3030 | 955 | 2075 |
| Crude | **1.69(1.53-1.86)** | **1.95(1.58-2.39)** | **1.34(1.20-1.50)** |
| Model 1[a] | **1.65(1.50-1.83)** | **1.73(1.40-2.14)** | **1.45(1.30-1.63)** |
| Model 2[b] | **1.48(1.34-1.64)** | **1.63(1.32-2.02)** | **1.35(1.23-1.51)** |
| Model 3[c] | **1.44(1.30-1.59)** | **1.59(1.29-1.97)** | **1.33(1.18-1.49)** |
| Model 4[d] | **1.30(1.17-1.48)** | **1.58(1.27 -2.24)** | **1.22(1.08-1.38)** |
| Model 5 + intervening non-fatal CVD event[e] | **1.29(1.16-1.44)** | **1.54(1.24-1.92)** | **1.22(1.08-1.38)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.03** | | |
| **Cancer Death (a subset of nonCVD death)** | | | |
| Events, n | 1226 | 475 | 751 |
| Crude | **1.27(1.09-1.53)** | **1.53(1.11-2.12)** | 1.06(0.87-1.29) |
| Model 1[a] | **1.29(1.09-1.53)** | **1.45(1.04-2.01)** | 1.16(0.95-1.42) |
| Model 2[b] | **1.25(1.05-1.48)** | **1.40(1.01-1.95)** | 1.14(0.93-1.40) |
| Model 3[c] | **1.20(1.01-1.43)** | 1.35(0.97-1.88) | 1.11(0.91-1.36) |
| Model 4[d] | 1.16(0.96-1.39) | 1.37(0.97-1.92) | 1.08(0.87-1.33) |
| Model 5 + intervening non-fatal CVD event[e] | 1.15(0.96-1.38) | 1.36(0.97-1.91) | 1.08(0.90-1.34) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - 0.20 | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)

[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
[e]Model 5 adds non-fatal CVD event – first nonfatal myocardial infarction or stroke since baseline.
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
**Bold p-value < 0.05;** Missing data in covariates imputed using chained equations.

*Sensitivity Analyses:*

The mean follow-up time was 6.5 (SD = 2.3) years, with a median [interquartile range] of 6.9 [5.4-8.3] years. Baseline depressive symptoms were significantly associated with all-cause mortality (aHR 1.18, 95%CI 1.07-1.29) and nonCVD death (aHR 1.21, 95%CI 1.08-1.36) and approached significance for CVD death (aHR 1.10, 95%CI 0.94-1.29) and cancer death (aHR 1.12, 95%CI 0.93-1.36), even in the exploratory models (Model 3**).** The results appeared to be particularly robust amongst those with excellent or very good health: cancer death (aHR 1.49, 95%CI 1.03-2.13), CVD death (aHR 1.63, 95%CI 1.16-2.30), nonCVD death (aHR 1.48, 95%CI 1.15-1.89) and all-cause mortality (aHR 1.53, 95% CI 1.25-1.88). In Model 4, the p values for depressive symptoms x health status interaction term was 0.003 (all-cause mortality), 0.01 (CVD death), 0.06 (nonCVD death), and 0.07 (cancer death). Results were similar without multiple imputations within 2 decimal places (**Table 3**)

**Table 3. Association of baseline elevated depressive symptoms (CES-D≥4) with mortality outcomes. Each participant contributes 1 measure of CES-D at baseline.**

| | Overall n=29,491 | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| All-cause mortality | 4581 | 1392 | 3189 |
| Crude | **1.54(1.42-1.68)** | **1.91(1.59-2.31)** | **1.18(1.07-1.30)** |
| Model 1[a] | **1.57(1.44-1.72)** | **1.76(1.45-2.12)** | **1.34(1.21-1.47)** |
| Model 2[b] | **1.32(1.25-1.49)** | **1.61(1.33-1.96)** | **1.22(1.11-1.35)** |
| Model 3[c] | **1.32(1.27-1.44)** | **1.56(1.29-1.90)** | **1.20(1.09-1.32)** |
| Model 4[d] | **1.18(1.07-1.29)** | **1.53(1.25-1.88)** | 1.09(0.98-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.002** | | |
| CVD Death | 1551 | 437 | 1114 |
| Crude | **1.55(1.34-1.78)** | **2.16(1.58-2.96)** | **1.13(0.97-1.33)** |
| Model 1[a] | **1.57(1.35-1.81)** | **1.96(1.42-2.71)** | **1.29(1.10-1.52)** |
| Model 2[b] | **1.28(1.10-1.48)** | **1.71(1.23-2.38)** | 1.14(0.97-1.34) |
| Model 3[c] | **1.24(1.07-1.44)** | **1.70(1.22-2.36)** | 1.11(0.94-1.31) |
| Model 4[d] | 1.10(0.94-1.29) | **1.63(1.16-2.30)** | 1.00(0.84-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.01** | | |
| NonCVD Death | 3030 | 955 | 2075 |
| Crude | **1.54(1.39-1.71)** | **1.80(1.42-2.26)** | **1.21(1.08-1.35)** |
| Model 1[a] | **1.57(1.42-1.75)** | **1.66(1.31-2.10)** | **1.36(1.21-1.53)** |
| Model 2[b] | **1.41(1.26-1.56)** | **1.56(1.29-1.98)** | **1.27(1.13-1.43)** |
| Model 3[c] | **1.36(1.22-1.51)** | **1.49(1.17-1.90)** | **1.25(1.11-1.41)** |
| Model 4[d] | **1.21(1.08-1.36)** | **1.48(1.15-1.89)** | **1.14(1.00-1.29)** |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| Cancer Death (a subset of nonCVD death) | 1226 | 475 | 751 |
| Crude | **1.21(1.02-1.44)** | **1.63(1.16-2.30)** | 0.97(0.79-1.19) |
| Model 1[a] | **1.27(1.06-1.52)** | **1.58(1.12-2.23)** | 1.09(0.89-1.35) |
| Model 2[b] | **1.22(1.02-1.47)** | **1.53(1.08-2.17)** | 1.07(0.87-1.33) |
| Model 3[c] | 1.17(0.98-1.41) | **1.45(1.02-2.05)** | 1.05(0.85-1.30) |
| Model 4[d] | 1.12(0.93-1.36) | **1.49(1.03-2.13)** | 1.01(0.81-1.27) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.07** | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression

HR and 95% CI were estimated by Cox proportional hazard regression models. Bold p-value < 0.05; Missing data in covariates imputed using chained equations.

## Discussion

To our knowledge, this is the largest study to date to examine the timing of the relationship between depressive symptoms and all-cause and cause-specific mortality in non-institutionalized middle to older aged adults. In this diverse cohort, we found that time-varying depressive symptoms significantly increased the risk of nonCVD and all-cause mortality in fully adjusted models. In fully adjusted models, depressive symptoms increased the risk of cause-specific and all-cause mortality by 36% to 54% in those with a very good/excellent state of health.

Given that depression is a relapsing/remitting disease,[23] this study markedly adds to the literature by demonstrating a time-varying relationship between elevated depressive symptoms and mortality, including cancer death. Major study strengths include the use of 3 measurements of depressive symptoms and stringent physician adjudication of outcomes. We are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and mortality. Many have long asked whether depression leads to mortality or whether individuals are depressed because they are dying. Our findings in those who report excellent states of health is striking and supports the former argument. It may also be that the effect of chronic illness burden on mortality in those with poor health overwhelms the effects of depressive

symptoms. Those with excellent health may also fail to recognize/present for depression. In fact, depressed excellent health individuals in our cohort were less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future studies.

The results have a coherence consistent with prior studies that suggest that depressive symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as cancer death.[24] While prior literature suggests that depressive symptoms confer mortality in those with active cancer, [25] our study excluded active cancer diagnoses confirming a possible relationship between depressive symptoms and incident cancer mortality. Prior studies have also been limited by inadequate covariate control, and our results for cancer persisted after adjusting for numerous traditional and behavioral risk factors, such as smoking, and approached significance even in models that included physiologic factors. We were, however, unable to adjust for other time-varying covariates. For example, prior research suggests that changes in physical health (e.g., number of debilitating conditions) over time mediates the relationship between depressive symptoms and mortality.[26]

This study also supports comprehensive evidence-based depression care management in primary care practices, which have been shown to lower mortality risk.[27] Nonetheless, depression treatment remains suboptimal in the general population,[28] despite decades of efforts. We too demonstrate that over time, nearly 40% of patients with elevated depressive symptoms at baseline were still depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both time-varying analyses (by virtue of follow-up times being broken up by repeat depression measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend

greater urgency to the importance of timely and effective treatment of depressive symptoms to prevent adverse consequences of depressive symptoms on physical health and mortality.

Limitations of our study include the regional specificity, limiting generalizability, and use of the short form of the CES-D, which measures only emotional and not somatic symptoms of depression. Schultz (2002) demonstrated variance between studies using scales and interviews,[29] and others have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).[30] However, CES-D scales are one of the most widely used scales in clinical practice and in baseline depression to outcome studies and have good sensitivity and specificity.[9,15,16] We may also have been underpowered to examine CVD and cancer mortality, though the directionality of the estimates remained consistent. The exclusion of active cancer participants as part of the overall REGARDS study criteria, the rationale of which has previously been described, [14] may also have contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically excluded, which is in line with prior depression to mortality studies.[1,9] Nonetheless, our previously published study, which excluded those with a history of CVD, similarly found a strong relationship between time-varying depressive symptoms and CVD death.[31]

We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5 years) was relatively short compared to other studies with even shorter follow-up times between CES-D measures in time-varying analyses, suggesting a short-term effect on mortality. Our results support prior literature suggesting that shorter follow-up time is associated with greater excess mortality.[9,30] However, we did not formally compare short-term to long-term follow-up nor persistent to fluctuating depressive symptoms.

Given our results of a relationship between time-varying depressive symptoms and mortality, further research is warranted to test the long-term efficacy of and adherence to depression treatment and to explore preventive approaches to decreasing premature mortality risk.[32] To our knowledge, the finding of a relationship between depressive symptoms and mortality in those with excellent or very good self-reported health is a new finding and should be further studied.

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**Disclosures:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Author Contributions:** Drs. Yulia Khodneva and Joshua Richman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford; *Analysis and interpretation of data:* Khodneva, Moise, Jannat-Khah, Richman, Kronish, Shaffer, Safford; *Drafting of the manuscript:* Moise, Khodneva *Critical revision of manuscript for important intellectual content:* Moise, Khodneva, Jannat-Khah, Richman, Kronish, Davidson,

Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding:* Safford; *Study supervision:* Safford

**Conflict of Interest:** None



**Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are available if deemed important by reviewers with open access by Monika Safford at Weill Cornell, Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised and risk of identification is low.

## Figure Legend

**Figure 1.** Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

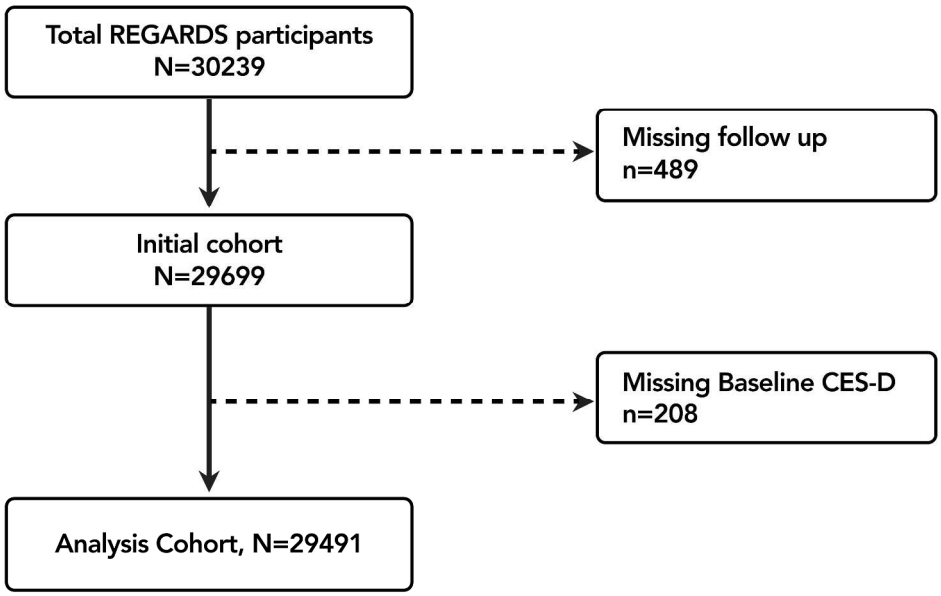



Figure 1. Consort Diagram

279x215mm (300 x 300 DPI)

**Supplementary Material**

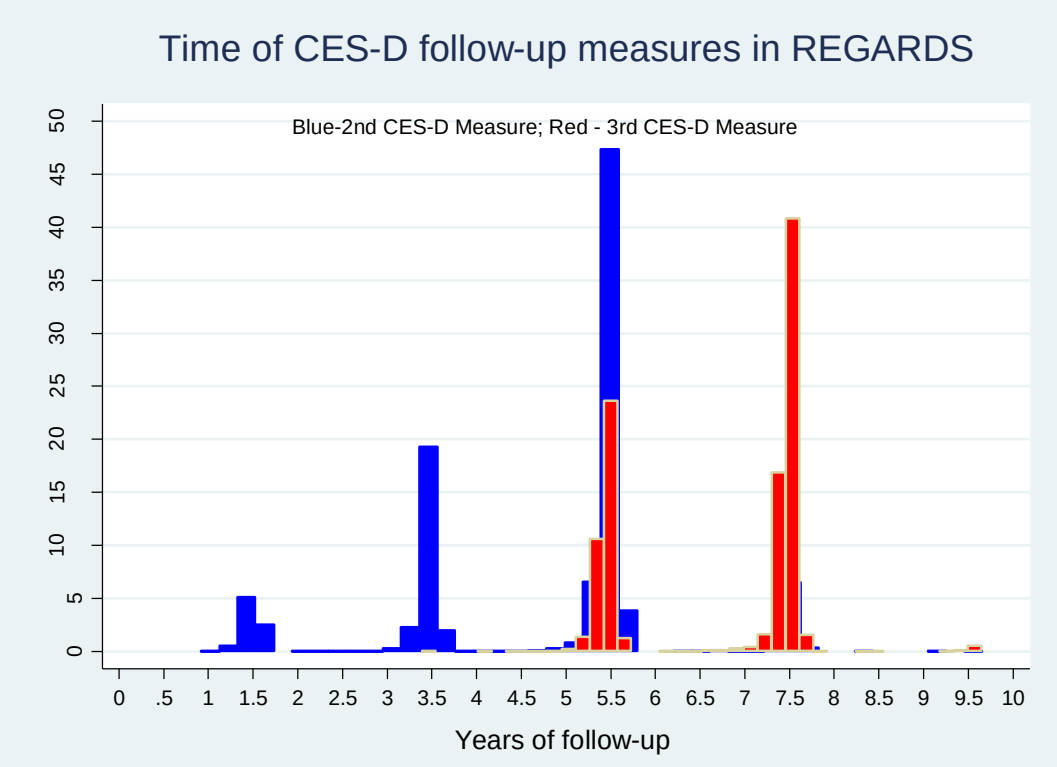
**eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).**

| Self-reported general health | Baseline | | | Second CES-D | | | Third CES-D | | |
|---|---|---|---|---|---|---|---|---|---|
| | CES-D<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n |
| **Excellent** | 4515<br>95.9 % | 195<br>4.1% | 4710 | 3444<br>94.7% | 194<br>5.3% | 3638 | 2109<br>94.6% | 120<br>5.4% | 2229 |
| **Very good** | 8450<br>94.1% | 530<br>5.9% | 8980 | 6332<br>93.0% | 478<br>7.0% | 6810 | 3938<br>92.8% | 305<br>7.2% | 4243 |
| **Good** | 9181<br>89.1% | 1124<br>10.9% | 10305 | 6363<br>88.6% | 818<br>11.4% | 7181 | 3717<br>88.9% | 464<br>11.1% | 4181 |
| **Fair** | 3424<br>77.8 % | 975<br>22.2 % | 4399 | 2185<br>79.7% | 556<br>20.3% | 2741 | 1236<br>82.0% | 271<br>18.0% | 1507 |
| **Poor** | 614<br>59.2% | 424<br>40.9% | 1038 | 322<br>61.2% | 204<br>38.8% | 526 | 177<br>65.3% | 94<br>34.7% | 271 |
| | | | 29432 | | | 20896 | | | 12431 |
| | **Frequency Missing = 59** | | | **Frequency Missing = 8595** | | | **Frequency Missing = 17060** | | |

**eTable 2. Reasons for non-cardiovascular disease death in the REGARDS study**

| | Overall | | Self-reported general health as **"excellent or very good"** n=13,711 | | Self-reported general health as **"poor, fair or good"** n=15,780 | |
|---|---|---|---|---|---|---|
| *Causes of Death* | n | Percent | Frequency | Percent | Frequency | Percent |
| Cancer | 1226 | 44.3 | 474 | 54.0 | 747 | 39.7 |
| Accidents/Injury/Suicide/Homicide | 164 | 5.9 | 52 | 5.9 | 111 | 5.9 |
| Suicide | 3 | 0.1 | 2 | 0.2 | 1 | 0.05 |
| Liver disease | 56 | 2.0 | 14 | 1.6 | 42 | 2.2 |
| Infection | 498 | 18.0 | 132 | 15.0 | 365 | 19.4 |
| ESRD | 119 | 4.3 | 23 | 2.6 | 95 | 5.1 |
| Dementia | 187 | 6.8 | 74 | 8.4 | 112 | 6.0 |
| COPD | 247 | 8.9 | 43 | 4.9 | 204 | 10.9 |
| Pulmonary Embolism | 38 | 1.34 | 11 | 1.3 | 27 | 1.4 |
| Other | 232 | 8.4 | 55 | 6.3 | 177 | 9.4 |
| | Frequency Missing = 263 | | | | Frequency Missing = 272 | |

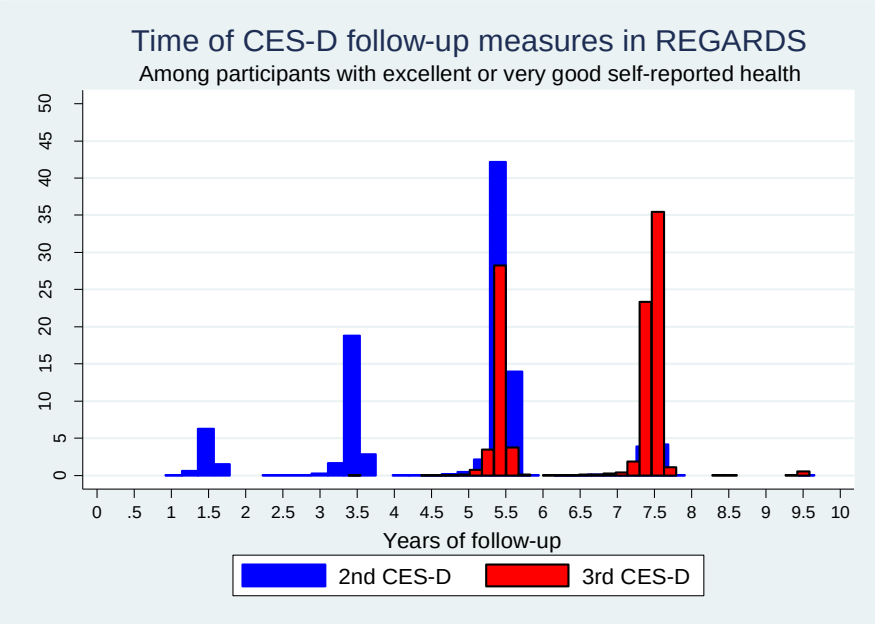
**eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.**

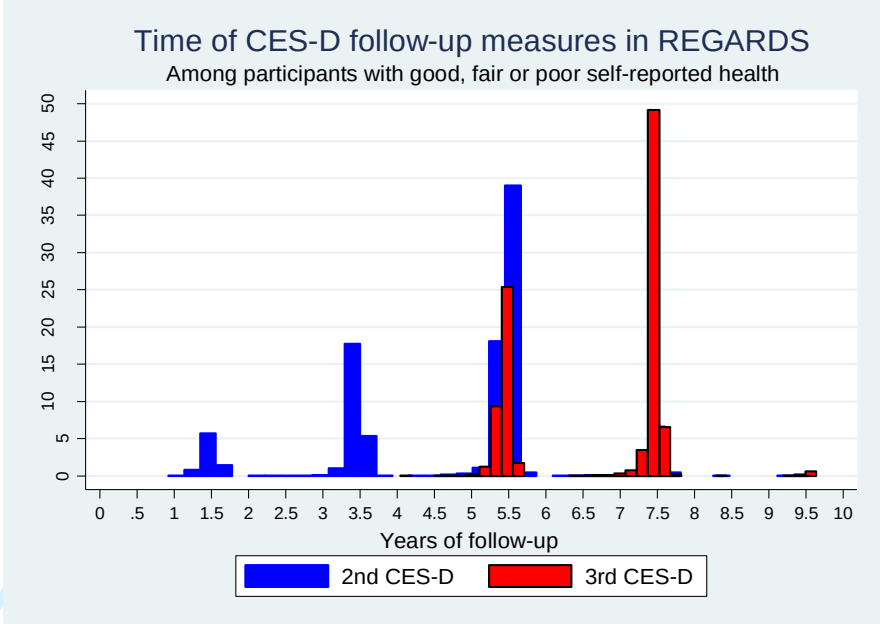



*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| | Time since preceding measurement (baseline or second follow-up), years | | | | |
|---|---|---|---|---|---|
| | Participants, n | Mean | SD | Minimum | Maximum |
| Second CES-D | 20934 | 4.8 | 1.5 | 0.9 | 9.7 |
| Third CES-D | 12451 | 2.1 | 0.4 | 1.0 | 4.2 |

**eFigure 2. Timing of CES-D follow up measures in REGARDS by self reported health at baseline.**




*"Percent" is a proportion of participants reporting CES-D scores at certain times, of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| Self-reported general health as "excellent or very good" | | | | | | Self-reported general health as "poor, fair or good" | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | |
| | N | Mean | SD | Minimum | Maximum | N | Mean | SD | Minimum | Maximum |
| Second CES-D | 10448 | 4.8 | 1.5 | 0.9 | 9.7 | 10448 | 4.8 | 1.5 | 0.9 | 9.5 |
| Third CES-D | 6472 | 2.1 | 0.4 | 1.7 | 4.2 | 5959 | 2.1 | 0.5 | 1.0 | 4.2 |

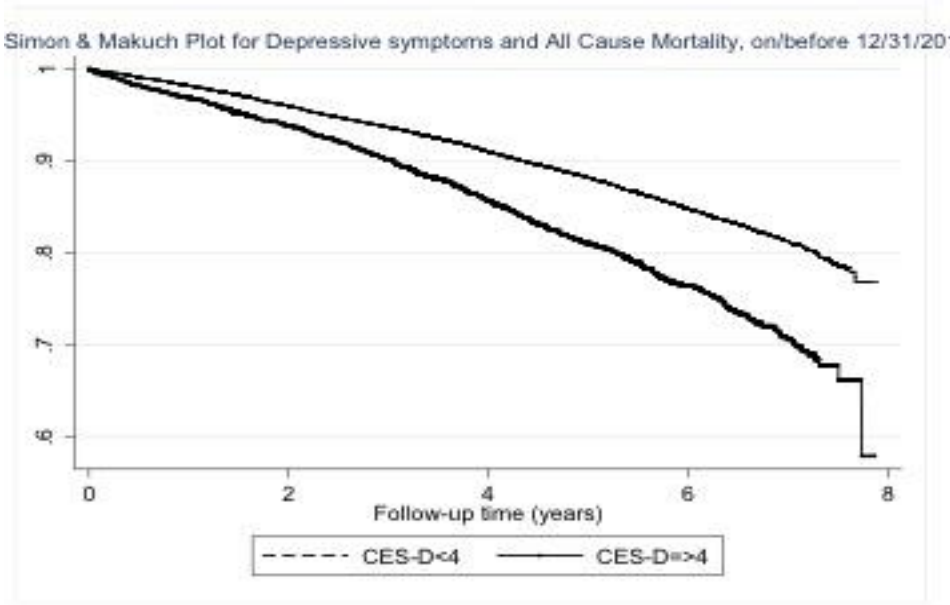
**eTable 3. Baseline characteristics of REGARDS participants who had all 3 CES-D measures vs. those with 1 or 2 CES-D measures**

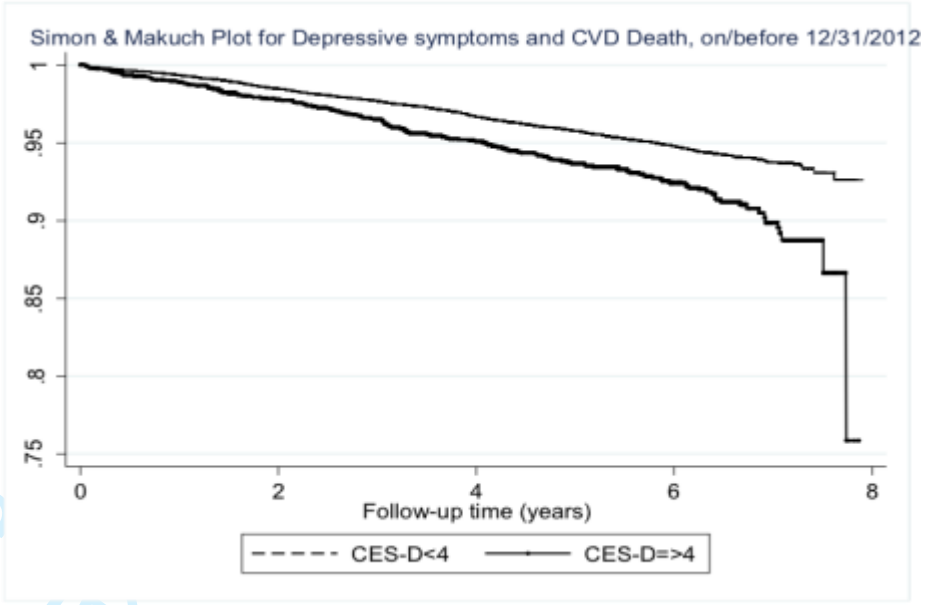
| Characteristics | 1 or 2 CES-D measures (n=17,040) | All 3 CES-D measures (n=12, 451) | *p* value |
|---|---|---|---|
| ***Socio-demographics*** | | | |
| Age, *M* (SD) | 65.0 +- 10.0 | 64.7 +- 8.5 | 0.0069 |
| Female, n (%) | 9300 (54.6) | 6945 (55.8) | 0.04 |
| African American, n (%) | 7709 (45.2) | 4420 (35.5) | <.001 |
| Less than high school education, n (%) | 2583 (15.2) | 1113 (8.9) | <.001 |
| Annual Household Income, n (%) | | | <.001 |
| Less than $20,000 | 3549 (20.8) | 1773 (14.2) | |
| No Health Insurance, n (%) | 1290 (7.6) | 636 (5.1) | <.001 |
| Region, n (%) | | | <.001 |
| Stroke belt | 5806 (34.1) | 4387 (35.2) | |
| Stroke buckle | 3887 (22.8) | 2301 (18.5) | |
| Non-stroke belt or buckle | 7347 (43.1) | 5763 (46.3) | |
| ***General health and medical conditions*** | | | |
| Self-reported general health, n (%) | | | <.001 |
| Poor, fair, good | 9783 (57.5) | 5959 (47.9) | |
| Excellent, very good | 7218 (42.5) | 6472 (52.1) | |
| Cardiovascular disease (CHD, stroke, PAD, AA), n (%) | 4379 (25.7) | 2446 (19.6) | <.001 |
| Diabetes, n (%) | 4083 (25.0) | 2169 (18.0) | <.001 |
| COPD, n (%) | 1612 (9.5) | 1098 (8.8) | 0.05 |
| Physical component score on SF-12 scale, *M* (SD) | 45.5 +- 11.0 | 47.6 +- 9.9 | <.001 |
| ***Physiological risk factors*** | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.4 +- 6.3 | 29.2 +- 6.0 | 0.0024 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 128.0 +- 17.2 | 127.0 +- 15.9 | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.2 +- 41.0 | 191.9 +- 39.0 | 0.5732 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.4 +- 16.1 | 52.4 +- 16.3 | <.001 |
| QT Interval, corrected for heart rate, ms, M (SD) | 408.4 +- 24.2 | 406.3 +- 22.7 | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.3[1.0-5.4] | 2.1[0.9-4.7] | <.001 |

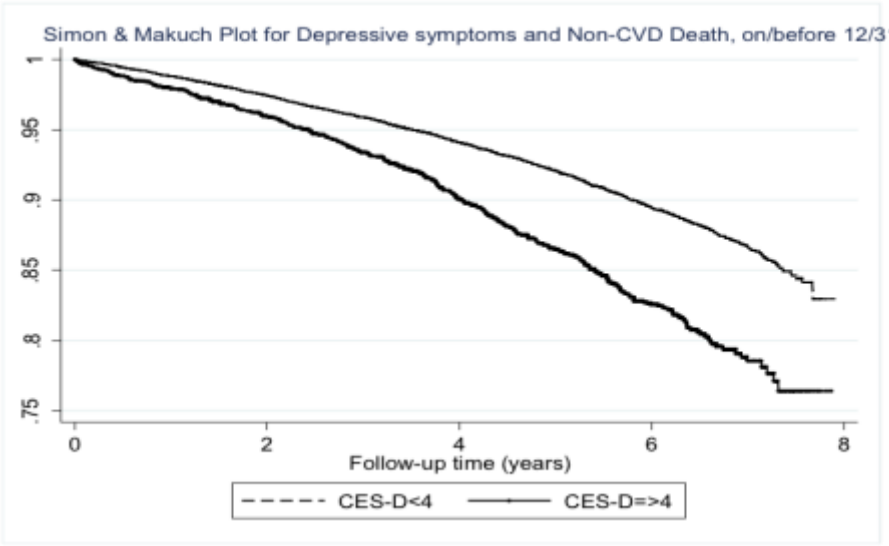
| | | | |
|---|---|---|---|
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.9[4.8-18.7] | 6.9[4.5-13.5] | <.001 |
| ***Medications*** | | | |
| Antihypertensive medication use, n (%) | 9079 (53.9) | 6118 (49.7) | <.001 |
| Statin use, n (%) | 5344 (31.4) | 3951 (31.8) | 0.53 |
| Aspirin use, n (%) | 7297 (42.8) | 5493 (44.1) | 0.03 |
| Antidepressant use, n (%) | 2440 (14.4) | 1646 (13.2) | 0.006 |
| ***Behavioral risk factors*** | | | |
| Self-reported smoking, pack years, *M* (SD) | 14.5 +- 24.4 | 12.2 +- 21.0 | <.001 |
| Current Smoking, n(%) | 2786 (16.4) | 1477 (11.9) | <.001 |
| Alcohol use, n (%) | | | <.001 |
| Heavy | 652 (3.9) | 520 (4.2) | |
| Moderate | 5180 (31.1) | 4446 (36.3) | |
| None | 10822 (65.0) | 7294 (59.5) | |
| Physical inactivity, n (%) | 6150 (36.7) | 3854 (31.3) | <.001 |
| Medication non-adherence, n (%) | 4548 (29.6) | 3411 (29.9) | 0.59 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1300 (9.4) | 588 (5.9) | <.001 |
| Elevated perceived stress (PSS≥5) | 5437 (31.9) | 3154 (25.3) | <.001 |

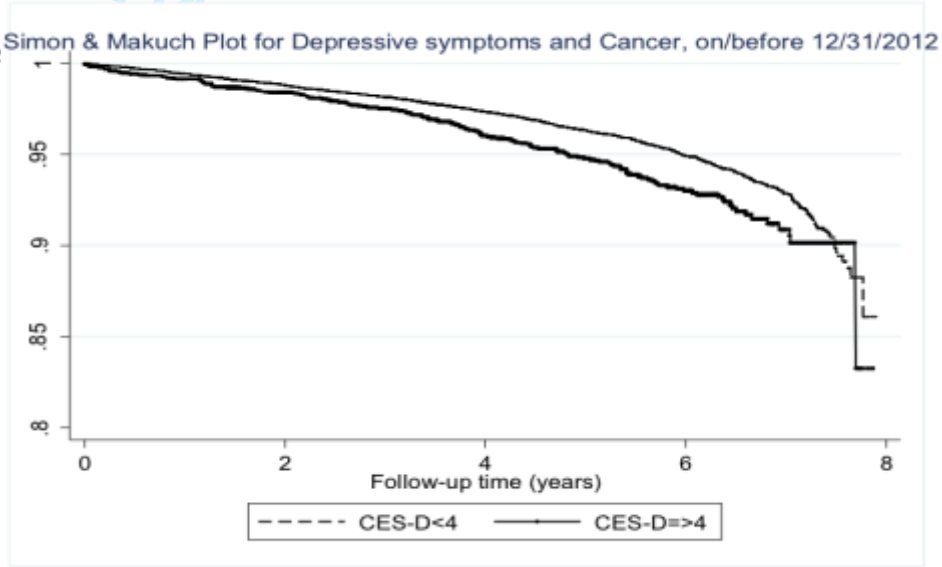
*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.
Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use. CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

**eFigure 3. Simon and Makuch plots of time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.**



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No/Page # | Recommendation |
|---|---|---|
| **Title and abstract** | 1 (page 1-3) | (*a*) Indicate the study's design with a commonly used term in the title or the **abstract** |
| | (Page 2-3) | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 (Page 4) | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 (pages 4-5) | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 (Page 5 and 6) | Present key elements of study design early in the paper |
| Setting | 5 (page 5-10), | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 (page 5-6, 8-9) | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| | n/a | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 (page 6-8) | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8 (pages 6-9) | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one |

| | | |
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| | | group |
| Bias | 9 (page 8-10) | Describe any efforts to address potential sources of bias |
| Study size | 10 (page 10) | Explain how the study size was arrived at |
| Quantitative variables | 11 (page 6-10) | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 (page 8-10) | (*a*) Describe all statistical methods, including those used to control for confounding |
| | Pages 9 | (*b*) Describe any methods used to examine subgroups and interactions |
| | Page 10 | (*c*) Explain how missing data were addressed |
| | Page 9 | (*d*) If applicable, explain how loss to follow-up was addressed |
| | Page 9-10 | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13 (page 10) | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | Page 10 | (b) Give reasons for non-participation at each stage |
| | Figure 1 | (c) Consider use of a flow diagram |
| Descriptive data | 14 (page 10-11) | (a) Give characteristics of study participants (eg demographic, clinical, social) cand information on exposures and potential confounders |
| | Page 10 | (b) Indicate number of participants with missing data for each variable of interest |
| | Pages 12 | (c) Summarise follow-up time (eg, average and total amount) |

| | | |
|---|---|---|
| Outcome data | 15 (page 11) | Report numbers of outcome events or summary measures over time |
| Main results | 16 (pages 11-12) | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | Page 7-8, 23-27 | (*b*) Report category boundaries when continuous variables were categorized |
| | n/a | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 (pages 12) | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 (page 12) | Summarise key results with reference to study objectives |
| Limitations | 19 (pages 14-15) | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 (page 12-13) | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 (page 14) | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 (page 20) | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present |

| | | |
|---|---|---|
| | | article is based |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study



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# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study

**Running Title:** depressive symptoms and mortality

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**Abstract**

**Objective:** To assess the association between time-varying depressive symptoms with all-cause and cause-specific mortality

**Design:** The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a national, population-based longitudinal study conducted from 2003-2007.

**Setting**: General continental U.S. communities

**Participants**: 29,491 black and white U.S. adults ≥45 years randomly sampled within race-sex-geographic strata

**Exposure**: Elevated depressive symptoms (CES-D-4 ≥ 4) measured at baseline and on average 5 and 7 years later

**Main Outcome Measures**: Cox proportional hazard regression models assessed cancer, non-cardiovascular (CVD), CVD and all-cause mortality.

**Results:** The average age was 64.9 years; 55% were female; 41% black; 11.0% had elevated depressive symptoms; 54% had poor, fair or good health. Time-varying depressive symptoms were significantly associated with nonCVD (aHR=1.29, 95% CI 1.16-1.44) and all-cause (aHR=1.24, 95%CI 1.14-1.39), but not cancer (aHR=1.15, 95%CI 0.96-1.38) or CVD (aHR=1.13, 95%CI 0.98-1.32) death adjusting for demographics, chronic clinical diseases, behavioral risk factors, and physiologic factors. Depressive symptoms were related to all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death in those who reported excellent or very good health. The analyses of the association between one measure of baseline depressive symptoms and mortality analyses yielded similar results.

**Conclusions:** Time-varying depressive symptoms confer an increased risk for all-cause mortality, CVD, non-CVD death and cancer death, particularly in those with excellent or very good health. These findings may have implications for timely treatment, regardless of health status.

**Strengths and limitations of this study.**

- Depression is a relapsing/remitting disease and our study is one of the first to use multiple measurements of depression to demonstrate a time varying relationship between depression and mortality, including cancer mortality, in a large, diverse cohort.
- To our knowledge, we are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and cause-specific mortality, with depression predicting mortality particularly in those with excellent or very good reported health.
- Our analyses were limited by the use of the short form of the CES-D scale
- The REGARDS cohort is regionally specific, limiting generalizability.

## Introduction

It is well known that elevated depressive symptoms predict mortality,[1] both in high-risk individuals with chronic illnesses like cardiovascular disease (CVD), and in general populations.[2-4] [5-8] More recently, several studies have shown that depressive symptoms both preceding and following cancer diagnosis may confer an increased risk of cancer death as well.[9,10]

However, depressive symptoms relapse and remit, and prior studies on the relationship between depressive symptoms and mortality have been limited by one measurement of depressive symptoms.[1] Recently, Lasserre et al. (2016) found that current but not remitted depressive symptoms predict all-cause mortality, but again depression diagnoses and history were ascertained at one time point.[11] In addition, prior literature has often been marked by inadequate adjustment for important covariates, such as behavioral risk factors. To our knowledge, few if any prior studies have examined the time-varying association between depressive symptoms and excess causes of death, including all-cause and cause specific mortality. In addition, self-perceived health status may predict mortality[12] and complicate the relationship between depressive symptoms and poor outcomes.[13] It is unknown whether depressive symptoms confer an increased risk of excess mortality equally in those with self-reported excellent/very good (in whom depression may be less likely to be recognized) and good/fair/poor health.

The purpose of our study is to examine the association between time-varying depressive symptoms with cancer, CVD, nonCVD and all-cause mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a broad, diverse population cohort with repeat measurements of depressive symptoms. We stratify by self-reported baseline health status

(very good or excellent vs. poor, fair or good) to further isolate the association between depressive symptoms and excess mortality.

## Methods

The REGARDS study is a national cohort study of stroke incidence and cognitive decline in black and white community dwelling adults ≥ 45 years living in the United States stratified to reflect specific race-sex-geographic strata.[14] Inclusion and exclusion criteria have been previously described; of note, those with active cancer were excluded from the original study.[14] Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study. Participants were recruited by mail using commercially available lists of U.S. residents, followed by a computer-assisted telephone interview and subsequent home visit at which time individuals were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing baseline depressive symptom measurements **(Figure 1)**. The REGARDS study protocol was approved by institutional review boards at participating centers.

### *Study Procedures*

Baseline data were collected through computer-assisted telephone interviews, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data, medical history and behavioral risk factors. Following the telephone interview, individuals had an in-home visit during which physical measurements, a resting electrocardiogram, medication inventory, phlebotomy and urine were collected. The median time between the initial phone interview and in-home examination was 28.0 (interquartile range = 21.0) days.

*Primary Outcomes*

The primary outcomes for these analyses were (1) cancer mortality (all body sites) (2) CVD death defined as death from CHD, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes (3) non-CVD death and (4) all-cause mortality. Living participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for reported hospitalizations or physician visits. Deaths were detected by report of next-of-kin or through online services (e.g., Social Security Death Index) or the National Death Index.[14] Death certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and CVD outcomes.

*Depressive symptoms*

The primary predictor was baseline depressive symptoms. The 4-item Center for Epidemiologic Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. This scale asks participants to rate the number of days over the last week in which they had: 1) felt depressed; 2) felt lonely; 3) had crying spells; and 4) felt sad. Response options included <1 day, 1 to 2 days, 3 to 4 days, and 5-7 days (0, 1, 2 3 points, respectively). Cronbach's α for the CES-D in the total sample was 0.80. Elevated depressive symptoms were defined as a summed score of ≥4.[15] The reliability and validity of the CES-D 4 is similar to the original 20-item instrument.[16]

*Covariates*

Demographic data included self-reported age, gender, race (black or white), education (less than high school, high school graduate, some college, and college graduate and above), annual income (less than $20,000, $20,000-$34,999, $35,000-$74,999, $75,000 and above), insurance

status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk factors included (1) diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR) (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial infarction or coronary revascularization procedure or evidence of myocardial infarction on the study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8) cognitive impairment on the 6-item screener of global cognitive function[17,18] (9) chronic lung disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin, antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors included (1) self-reported pack-years of cigarette smoking; (2) physical activity ("How many times per week do you engage in intense physical activity, enough to work up a sweat?" with response options of "none", "1-3 times per week" and "4 or more times per week"); (3) alcohol use ("How many alcoholic beverages do you drink?": none, moderate [1 drink per day for women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2 drinks per day for men]);[14] (4) medication non-adherence assessed with the 4-item Morisky Medication Adherence Scale (>= 1).[19] Potential physiologic risk factors included high-sensitivity C-reactive protein, self-reported health status based on the physical component of the 12-item Short-Form Health Survey (SF 12),[20] and perceived stress, measured by the 4-item version of the

Perceived Stress Scale (score of ≥ 5 vs. <5).[21] Other than depressive symptoms, no other covariate was assessed more than once.

*Statistical Analyses*

Baseline characteristics of participants with and without elevated depressive symptoms at baseline were compared using chi-square tests (for categorical variables), Student t tests (for continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous measures).

Cox proportional hazard regression models were constructed to separately analyze the association between depressive symptoms (CES-D≥4) and cancer death (from all body sites, a subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline measurement, and 3) on average two years after the second measurement. In the analyses, we considered depressive symptoms (CES-D≥4 vs. <4) as a time-varying exposure, with updates of exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3 measures of CES-D (≥4 vs. <4) with a broken-up follow-up time. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive symptoms using the Simon-Makuch method,[22] a modification of the Kaplan-Meier method. In this context, depression status is treated as a binary time-dependent covariate and study cohorts are continually updated to contribute to either the CES-D≥4 or CES-D <4 groups.

Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were estimated for those with vs. without elevated depressive symptoms. Adjusted modeling proceeded in stages (adjusting for baseline covariates), starting with demographic (Model 1) and traditional CVDrisk factors (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5), which considered intervening first non-fatal stroke and/or myocardial infarction as a time-dependent covariate in CVD death outcomes. All analyses were conducted overall as well as stratified. We also conducted a formal test for interaction between time-varying depressive symptoms and self-reported health (defined as excellent or very good vs. good, fair or poor health) in model 4. As such, all analyses were conducted overall as well as stratified by baseline self-reported health. To test the proportional hazards assumptions, we performed the chi-squared test for the Schoenfeld residuals and all the models resulted in a violation of the proportional hazards assumptions, indicating that time-varying depressive symptoms were appropriate. The proportionality assumption for time varying depressive symptoms was also tested by assessing the interaction of depressive symptoms*log of follow-up time and was satisfied for all mortality endpoints.

Missing data in covariates were imputed using chained equations and derived by bootstrapping across the 5 imputed datasets. Of the 29,491 participants, 2768 (9%) were missing income data, 59 (0.2%) health status, 9 (<0.1%) education, 26 (0.1%) health insurance, 1087 (4%) diabetes, 16 (0.1%) aspirin use, 70 (0.2%) statin use, 70 (0.2%) antidepressant use, 333 (1%) anti-hypertension meds use, 439 (2%) physical activity, 2705 (9%) medication adherence, 213 (0.7%) BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912 (3.1%) pack years, 84 (0.3%) SBP, 1394

(5%) renal function, 381 (1%) QTc, 5681 (19.3%) cognitive status, 4 (<0.1%) stress, 1425 (4%) SF-12 and 1881 (6%) CRP. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).

*Sensitivity Analyses*

Sensitivity analyses constructed in parallel to the main analyses examined association of baseline CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, or end of follow-up.

**Results**

*Participant Characteristics*

Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms, leaving 29,491 eligible participants (**Figure 1)** of whom 3,254 (11.0%) had elevated depressive symptoms at baseline (CES-D≥4). The average age was 64.9 (9.4) years; 55.1% were female and 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33% of individuals were physically inactive, 29.2% non-adherent to their medication regimen and 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless of health status, participants with elevated (vs. non-elevated) depressive symptoms were more likely to be female, African-American, low income, have more chronic diseases, low physical health, and more behavioral risk factors (**Table 1A-B)**.

**Table 1A. Overall baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D)**

| Characteristics | Overall (n=29,491) | CES-D < 4 (n=26,817) | CES-D ≥4 (n=3,254) | *p* |
|---|---|---|---|---|
| ***Socio-demographics*** | | | | |
| Age, *M* (SD) | 64.9 (9.4) | 65.1 (9.4) | 63.2 (9.8) | <.001 |
| Female, n (%) | 16245 (55.1) | 13988 (53.3) | 2257 (69.4) | <.001 |
| African American, n (%) | 12129 (41.1) | 10427 (39.7) | 1702 (52.3) | <.001 |
| Less than high school education, n (%) | 3696 (12.5) | 2916 (11.1) | 780 (24.0) | <.001 |
| Annual household income, n (%) | | | | |
| Less than $20,000 | 5322 (18.0) | 4148 (15.8) | 1174 (36.1) | <.001 |
| No health insurance, n (%) | 1926 (6.5) | 1532 (5.8) | 394 (12.1) | <.001 |
| Region, n (%) | | | | <.001 |
| Stroke belt[a] | 10193 (34.6) | 8973 (34.2) | 1220 (37.5) | |
| Stroke buckle[b] | 6188 (21.0) | 5437 (20.7) | 751 (23.1) | |
| Non-stroke belt or buckle | 13110 (44.5) | 11827 (45.1) | 1283 (39.4) | |
| ***General health and medical conditions*** | | | | |
| Self-reported general health, n (%) | | | | <.001 |
| Poor, fair, good | 15742 (53.5) | 13219 (50.5) | 2523 (77.7) | |
| Excellent, very good | 13690 (46.5) | 12965 (49.5) | 725 (22.3) | |
| Cardiovascular disease, n (%)[c] | 6825 (23.1) | 5838 (22.3) | 987 (30.3) | <.001 |
| Diabetes, n (%)[d] | 6252 (22.0) | 5305 (21.0) | 947 (30.2) | <.001 |
| COPD, n (%) | 2710 (9.2) | 2307 (8.8) | 403 (12.4) | <.001 |
| Physical component score on SF-12 scale, *M* (SD) | 46.4 (10.6) | 47.1 (10.2) | 40.7 (12.2) | <.001 |
| ***Physiological risk factors*** | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.3 (6.2) | 29.2 (6.1) | 30.6 (7.1) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 127.6 (16.7) | 127.5 (16.5) | 128.7 (18.1) | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.1 (40.1) | 191.7 (39.8) | 194.6 (43.0) | <0.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.8 (16.2) | 51.7 (16.2) | 52.5 (16.3) | 0.02 |
| QT Interval, corrected for heart rate, ms, M (SD) | 407.5 (23.6) | 407.2 (23.5) | 410.0 (24.1) | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.2[1.0-5.0] | 2.1[0.9-4.8] | 3.0[1.2-6.9] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.4[4.7-6.2] | 7.3[4.6-15.8] | 8.2[5.1-19.8] | <.001 |
| **Medications** | | | | |
| Antihypertensive medication use, n (%) | 15197 (52.1) | 13290 (51.2) | 1907 (59.4) | <.001 |
| Statin use, n (%) | 9295 (31.6) | 8248 (31.5) | 1047 (32.3) | 0.38 |

| | | | | |
|---|---|---|---|---|
| Aspirin use, n (%) | 12790 (43.4) | 11376 (43.4) | 1414 (43.5) | 0.91 |
| Antidepressant use, n (%) | 4086 (13.9) | 3164 (12.1) | 922 (28.4) | <.001 |
| ***Behavioral risk factors*** | | | | |
| Self-reported smoking, pack years, *M* (SD) | 13.5 ( 23.1 | 13.3 ( 22.8 | 15.5 ( 24.9 | <.001 |
| Current Smoking, n(%) | 4263(14.5) | 3463(13.3) | 800(24.7) | <.001 |
| Alcohol use, n (%) | | | | <.001 |
| Heavy | 1172 (4.1) | 1043 (4.0) | 129 (4.1) | |
| Moderate | 9626 (33.3) | 8786 (34.1) | 840 (26.6) | |
| " None | 18116 (62.7) | 15925 (61.8) | 2191 (69.3) | |
| Physical inactivity, n (%) | 10004 (34.4) | 8500 (32.9) | 1504 (46.9) | <0.001 |
| Medication non-adherence, n (%) | 7959 (29.7) | 6820 (28.7) | 1139 (37.8) | <.001 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1888 (7.9) | 1542 (7.3) | 346 (12.6) | <.001 |
| Elevated perceived stress (PSS≥5) | 8591 (29.1) | 6283 (23.9) | 2308 (70.9) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease
n= total number assuming no missing data
[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.
[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.
[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

**Table 1B. Baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D) and self-reported health**

| | *Self-reported general health as "excellent or very good"* | | | *Self-reported general health as "poor, fair or good"* | | |
|---|---|---|---|---|---|---|
| Characteristics | CES-D < 4 (n=12965) | CES-D ≥4 (n=725) | *p* | CES-D < 4 (n=13219) | CES-D ≥4 (n=2523) | *p* |
| ***Socio-demographics*** | | | | | | |
| Age, *M* (SD) | 64.8 (9.4) | 64.5 (10.2) | 0.47 | 65.5 (9.3) | 62.8 (9.6) | <.001 |
| Female, n (%) | 6600 (50.9) | 501 (69.1) | <.001 | 7357 (55.7) | 1751 (69.4) | <.001 |
| African American, n (%) | 3726 (28.7) | 295 (40.7) | <.001 | 6677 (50.5) | 1404 (55.6) | <.001 |
| Less than high school education, n (%) | 845 (6.5) | 119 (16.4) | <.001 | 2059 (15.6) | 658 (26.1) | <.001 |
| Annual household income, n (%) | | | | | | |
| Less than $20,000 | 1304 (10.1) | 190 (26.2) | <.001 | 2832 (21.4) | 983 (39.0) | <.001 |
| No health insurance, n (%) | 644 (5.0) | 70 (9.7) | <.001 | 884 (6.7) | 324 (12.9) | <.001 |
| Region, n (%) | | | 0.37 | | | <.001 |
| Stroke belt[a] | 4282 (33.0) | 256 (35.3) | | 4668 (35.3) | 963 (38.2) | |
| Stroke buckle[b] | 2619 (20.2) | 148 (20.4) | | 2807 (21.2) | 601 (23.8) | |
| Non-stroke belt or buckle | 6064 (46.8) | 321 (44.3) | | 5744 (43.5) | 959 (38.0) | |
| ***General health and medical conditions*** | | | | | | |
| Self-reported general health, n (%) | | | | | | |
| Poor, fair, good | -- | -- | | --- | -- | |
| Excellent, very good | -- | -- | | --- | --- | |
| Cardiovascular disease, n (%)[c] | 1948 (15.0) | 144 (19.9) | 0.004 | 3874 (29.3) | 840 (33.3) | <.001 |
| Diabetes, n (%)[d] | 1443 (11.6) | 93 (13.3) | 0.16 | 3840 (30.2) | 853 (35.1) | <.001 |
| COPD, n (%) | 796 (6.2) | 55 (7.6) | 0.11 | 1507 (11.4) | 347 (13.8) | 0.007 |
| Physical component score on SF-12 scale, *M* (SD) | 52.0 (6.5) | 51.3 (9.1) | 0.008 | 42.0 (10.7) | 37.7 (11.3) | <.001 |
| ***Physiological risk factors*** | | | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 27.8 (5.1) | 28.4 (5.7) | 0.006 | 30.5 (6.6) | 31.2 (7.3) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 125.3 (15.7) | 126.0 (17.2) | 0.27 | 129.6 (16.9) | 129.5 (18.3) | 0.91 |
| Total Cholesterol, mg/dL, *M* (SD) | 193.8 (38.2) | 195.5 (38.6) | 0.26 | 189.7 (41.2) | 194.4 (44.2) | <.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 53.1 (16.4) | 55.8 (16.6) | <.001 | 50.4 (15.8) | 51.5 (16.1) | 0.002 |
| QT Interval, corrected for heart rate, ms, M (SD) | 405.6 (22.6) | 407.2 (23.5) | 0.06 | 408.7 (24.3) | 410.8 (24.2) | <0.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 1.7[0.8-3.8] | 1.9[0.9-4.9] | 0.004 | 2.7[1.2-6.1] | 3.4[1.3-7.7] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 6.6[4.3-12.3] | 6.9[4.7-14.0] | 0.005 | 8.4[5.0-20.7] | 8.7[5.1-22.2] | 0.18 |
| | 4916 (38.3) | 297 (41.7) | 0.06 | 8344 (63.9) | 1606 (64.5) | 0.57 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Medications** | | | | | | |
| Antihypertensive medication use, n (%) | | | | | | |
| Statin use, n (%) | 3407 (26.4) | 176 (24.4) | 0.24 | 4822 (36.5) | 870 (34.6) | 0.06 |
| Aspirin use, n (%) | 5254 (40.5) | 273 (37.7) | 0.13 | 6100 (46.2) | 1140 (45.2) | 0.36 |
| | | | | | | <.001 |
| Antidepressant use, n (%) | 1224 (9.5) | 144 (19.9) | <.001 | 1933 (14.6) | 774 (30.8) | |
| ***Behavioral risk factors*** | | | | | | |
| Self-reported smoking, pack years, *M* (SD) | 11.2 ( 20.5) | 12.1 ( 21.6) | 0.24 | 15.3 ( 24.7) | 16.5 ( 25.6) | 0.03 |
| Current Smoking, n(%) | 1344 (10.4) | 114 (15.8) | <.001 | 2110 (16.0) | 684 (27.2) | <.001 |
| Alcohol use, n (%) | | | 0.01 | | | <.001 |
| Heavy | 634 (5.0) | 38 (5.4) | | 409 (3.2) | 91 (3.7) | |
| Moderate | 5034 (39.4) | 238 (33.8) | | 3746 (29.0) | 600 (24.5) | |
| None | 7103 (55.6) | 429 (60.9) | | 8779 (67.9) | 1758 (71.8) | |
| Physical inactivity, n (%) | 3107 (24.3) | 259 (36.0) | <.001 | 5372 (41.3) | 1242 (50.0) | <.001 |
| Medication non-adherence, n (%) | 2997 (26.2) | 211 (33.1) | <.001 | 3809 (31.0) | 926 (39.1) | <.001 |
| Impaired cognitive status | | | <.001 | | | <.001 |
| (Cognitive score ≤ 4) | 587 (5.6) | 61 (10.1) | | 947 (8.9) | 285 (13.3) | |
| Elevated perceived stress (PSS≥5) | 2219 (17.1) | 404 (55.7) | <.001 | 4048 (30.6) | 1900 (75.3) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease
n= total number assuming no missing data
[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.
[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.
[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

*Mortality*

A total of 4,581 (15.5%) participants died during the follow-up period ending in 2012. Of these, 1,551 (33.9%) were attributed to CVD and 3,030 (66.1%) to nonCVD disease death. Of nonCVD deaths, 1,226 (44.3%) were due to cancer death (eTable 2**)**. Overall, there were only 3 cases of mortality due to suicide.

For the time-varying analyses, depressive symptoms were measured at baseline and on average 4.8 years (SD = 1.5) years following the baseline measurement, the third measurement occurring on average 2.1 (SD = 0.4) years after the second measurement (eFigure 1). The mean follow-up time

of the second and third measurement of CES-D measures did not differ by self-reported health (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8% had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 05% CI 0.98-1.32), even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-fatal CVD events (**Table 2,** eFigure 3). The results appeared to be particularly robust amongst those with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death), and 0.20 (cancer death) (**Table 2**).

**Table 2. Association of time-variant elevated depressive symptoms with mortality outcomes.** Each participant contributes to up to 3 time-variant CES-D measures. End of follow-up December 31, 2012.

| | Overall (N=29,491) | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | ***HR (95%CI) for time-variant categorical CES-D (Score =>4 v. < 4)*** | | |
| **All-cause mortality** | | | |
| Events, n | 4581 | 1392 | 3189 |
| Crude | **1.66(1.54-1.80)** | **1.97(1.66-2.33)** | **1.30(1.19-1.42)** |
| Model 1[a] | **1.63(1.50-1.76)** | **1.74(1.46-2.07)** | **1.42(1.29-1.55)** |
| Model 2[b] | **1.42(1.31-1.54)** | **1.60(1.34-1.90)** | **1.30(1.19-1.43)** |
| Model 3[c] | **1.38(1.27-1.49)** | **1.57(1.32-1.87)** | **1.27(1.16-1.39)** |
| Model 4[d] | **1.24(1.13-1.35)** | **1.53(1.27-1.83)** | **1.16(1.05-1.28)** |
| Model 5[e] | **1.24(1.14-1.36)** | **1.48(1.27-1.78)** | **1.17(1.06-1.30)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.005** | | |
| **CVD Death** | | | |
| Events, n | 1551 | 437 | 1114 |
| Crude | **1.61(1.41-1.85)** | **2.01(1.49-2.72)** | **1.23(1.05-1.43)** |
| Model 1[a] | **1.58(1.37-1.81)** | **1.76(1.29-2.40)** | **1.35(1.15-1.58)** |
| Model 2[b] | **1.31(1.13-1.51)** | **1.52(1.12-2.08)** | **1.20(1.03-1.41)** |
| Model 3[c] | **1.27(1.10-1.46)** | **1.53(1.12-2.09)** | 1.17(1.00-1.37) |
| Model 4[d] | 1.15(0.98-1.33) | **1.47(1.07-2.04)** | 1.06(0.90-1.26) |
| Model 5[e] | 1.13(0.98-1.32) | 1.37(0.99-1.91) p=0.06 | 1.07(0.90-1.27) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| **NonCVD Death** | | | |
| Events, n | 3030 | 955 | 2075 |
| Crude | **1.69(1.53-1.86)** | **1.95(1.58-2.39)** | **1.34(1.20-1.50)** |
| Model 1[a] | **1.65(1.50-1.83)** | **1.73(1.40-2.14)** | **1.45(1.30-1.63)** |
| Model 2[b] | **1.48(1.34-1.64)** | **1.63(1.32-2.02)** | **1.35(1.23-1.51)** |
| Model 3[c] | **1.44(1.30-1.59)** | **1.59(1.29-1.97)** | **1.33(1.18-1.49)** |
| Model 4[d] | **1.30(1.17-1.48)** | **1.58(1.27 -2.24)** | **1.22(1.08-1.38)** |
| Model 5[e] | **1.29(1.16-1.44)** | **1.54(1.24-1.92)** | **1.22(1.08-1.38)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.03** | | |
| **Cancer Death (a subset of nonCVD death)** | | | |
| Events, n | 1226 | 475 | 751 |
| Crude | **1.27(1.09-1.53)** | **1.53(1.11-2.12)** | 1.06(0.87-1.29) |
| Model 1[a] | **1.29(1.09-1.53)** | **1.45(1.04-2.01)** | 1.16(0.95-1.42) |
| Model 2[b] | **1.25(1.05-1.48)** | **1.40(1.01-1.95)** | 1.14(0.93-1.40) |
| Model 3[c] | **1.20(1.01-1.43)** | 1.35(0.97-1.88) | 1.11(0.91-1.36) |
| Model 4[d] | 1.16(0.96-1.39) | 1.37(0.97-1.92) | 1.08(0.87-1.33) |
| Model 5[e] | 1.15(0.96-1.38) | 1.36(0.97-1.91) | 1.08(0.90-1.34) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - 0.20 | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).

[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
[e]Model 5 adds non-fatal CVD event – first nonfatal myocardial infarction or stroke since baseline.
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
**Bold p-value < 0.05;** Missing data in covariates imputed using chained equations.

*Sensitivity Analyses:*

The mean follow-up time was 6.5 (SD = 2.3) years, with a median [interquartile range] of 6.9 [5.4-8.3] years. Baseline depressive symptoms were significantly associated with all-cause mortality (aHR 1.18, 95%CI 1.07-1.29) and nonCVD death (aHR 1.21, 95%CI 1.08-1.36) and approached significance for CVD death (aHR 1.10, 95%CI 0.94-1.29) and cancer death (aHR 1.12, 95%CI 0.93-1.36), even in the exploratory models (Model 3**).** The results appeared to be particularly robust amongst those with excellent or very good health: cancer death (aHR 1.49, 95%CI 1.03-2.13), CVD death (aHR 1.63, 95%CI 1.16-2.30), nonCVD death (aHR 1.48, 95%CI 1.15-1.89) and all-cause mortality (aHR 1.53, 95% CI 1.25-1.88). In Model 4, the p values for depressive symptoms x health status interaction term was 0.003 (all-cause mortality), 0.01 (CVD death), 0.06 (nonCVD death), and 0.07 (cancer death). Results were similar without multiple imputations within 2 decimal places (**Table 3**)

**Table 3. Association of baseline elevated depressive symptoms (CES-D≥4) with mortality outcomes. Each participant contributes 1 measure of CES-D at baseline.**

| | Overall n=29,491 | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| All-cause mortality | 4581 | 1392 | 3189 |
| Crude | **1.54(1.42-1.68)** | **1.91(1.59-2.31)** | **1.18(1.07-1.30)** |
| Model 1[a] | **1.57(1.44-1.72)** | **1.76(1.45-2.12)** | **1.34(1.21-1.47)** |
| Model 2[b] | **1.32(1.25-1.49)** | **1.61(1.33-1.96)** | **1.22(1.11-1.35)** |
| Model 3[c] | **1.32(1.27-1.44)** | **1.56(1.29-1.90)** | **1.20(1.09-1.32)** |
| Model 4[d] | **1.18(1.07-1.29)** | **1.53(1.25-1.88)** | 1.09(0.98-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.002** | | |
| CVD Death | 1551 | 437 | 1114 |
| Crude | **1.55(1.34-1.78)** | **2.16(1.58-2.96)** | **1.13(0.97-1.33)** |
| Model 1[a] | **1.57(1.35-1.81)** | **1.96(1.42-2.71)** | **1.29(1.10-1.52)** |
| Model 2[b] | **1.28(1.10-1.48)** | **1.71(1.23-2.38)** | 1.14(0.97-1.34) |
| Model 3[c] | **1.24(1.07-1.44)** | **1.70(1.22-2.36)** | 1.11(0.94-1.31) |
| Model 4[d] | 1.10(0.94-1.29) | **1.63(1.16-2.30)** | 1.00(0.84-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.01** | | |
| NonCVD Death | 3030 | 955 | 2075 |
| Crude | **1.54(1.39-1.71)** | **1.80(1.42-2.26)** | **1.21(1.08-1.35)** |
| Model 1[a] | **1.57(1.42-1.75)** | **1.66(1.31-2.10)** | **1.36(1.21-1.53)** |
| Model 2[b] | **1.41(1.26-1.56)** | **1.56(1.29-1.98)** | **1.27(1.13-1.43)** |
| Model 3[c] | **1.36(1.22-1.51)** | **1.49(1.17-1.90)** | **1.25(1.11-1.41)** |
| Model 4[d] | **1.21(1.08-1.36)** | **1.48(1.15-1.89)** | **1.14(1.00-1.29)** |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| Cancer Death (a subset of nonCVD death) | 1226 | 475 | 751 |
| Crude | **1.21(1.02-1.44)** | **1.63(1.16-2.30)** | 0.97(0.79-1.19) |
| Model 1[a] | **1.27(1.06-1.52)** | **1.58(1.12-2.23)** | 1.09(0.89-1.35) |
| Model 2[b] | **1.22(1.02-1.47)** | **1.53(1.08-2.17)** | 1.07(0.87-1.33) |
| Model 3[c] | 1.17(0.98-1.41) | **1.45(1.02-2.05)** | 1.05(0.85-1.30) |
| Model 4[d] | 1.12(0.93-1.36) | **1.49(1.03-2.13)** | 1.01(0.81-1.27) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.07** | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression

HR and 95% CI were estimated by Cox proportional hazard regression models. Bold p-value < 0.05; Missing data in covariates imputed using chained equations.

## Discussion

To our knowledge, this is the largest study to date to examine the timing of the relationship between depressive symptoms and all-cause and cause-specific mortality in non-institutionalized middle to older aged adults. In this diverse cohort, we found that time-varying depressive symptoms significantly increased the risk of nonCVD and all-cause mortality in fully adjusted models. In fully adjusted models, depressive symptoms increased the risk of cause-specific and all-cause mortality by 36% to 54% in those with a very good/excellent state of health.

Given that depression is a relapsing/remitting disease,[23] this study markedly adds to the literature by demonstrating a time-varying relationship between elevated depressive symptoms and mortality, including cancer death. Major study strengths include the use of 3 measurements of depressive symptoms and stringent physician adjudication of outcomes. We were, however, unable to adjust for other time-varying covariates, which should be addressed in future research. For example, prior research suggests that changes in physical health (e.g., number of debilitating conditions) over time may mediate the relationship between depressive symptoms and mortality.[24]

We are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and mortality. Many have long asked whether depression leads to mortality or whether individuals are depressed because they are dying. Our findings in those who report excellent states of health is striking and supports the former argument. It may also be that the effect of chronic illness burden on mortality in those with poor health overwhelms the effects of depressive symptoms. Those with excellent health may also fail to

recognize/present for depression. In fact, depressed excellent health individuals in our cohort were less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future studies.

The overall results also have a coherence consistent with prior studies that suggest that depressive symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as cancer death.[25] While prior literature suggests that depressive symptoms confer mortality in those with active cancer, [26] our study excluded active cancer diagnoses confirming a possible relationship between depressive symptoms and incident cancer mortality. Prior studies have also been limited by inadequate covariate control, and our results for cancer persisted after adjusting for numerous traditional and behavioral risk factors, such as smoking, and approached significance even in models that included physiologic factors.

Overall, baseline and time varying analyses were similar. However, while our baseline analyses suggest that depressive symptoms significantly contribute to cancer death in those with excellent/very good health, time varying analyses allowed for more accurate analyses in line with expectations, suggesting a weaker interaction by health status for proximal cancer mortality in this cohort that excluded those with active malignancy.

This study also supports comprehensive evidence-based depression care management in primary care practices, which have been shown to lower mortality risk.[27] Nonetheless, depression treatment remains suboptimal in the general population,[28] despite decades of efforts. We too demonstrate that over time, nearly 40% of patients with elevated depressive symptoms at baseline were still depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both

time-varying analyses (by virtue of follow-up times being broken up by repeat depression measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend greater urgency to the importance of timely and effective treatment of depressive symptoms to prevent adverse consequences of depressive symptoms on physical health and mortality.

Limitations of our study include the regional specificity, limiting generalizability, and use of the short form of the CES-D, which measures only emotional and not somatic symptoms of depression. Schultz (2002) demonstrated variance between studies using scales and interviews,[29] and others have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).[30] However, CES-D scales are one of the most widely used scales in clinical practice and in baseline depression to outcome studies and have good sensitivity and specificity.[9,15,16] We may also have been underpowered to examine CVD and cancer mortality, though the directionality of the estimates remained consistent. The exclusion of active cancer participants as part of the overall REGARDS study criteria, the rationale of which has previously been described, [14] may also have contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically excluded, which is in line with prior depression to mortality studies.[1,9] Nonetheless, our previously published study, which excluded those with a history of CVD, similarly found a strong relationship between time-varying depressive symptoms and CVD death.[31]

We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5 years) was relatively short compared to other studies with even shorter follow-up times between CES-D measures in time-varying analyses, suggesting a short-term effect on mortality. Our results support prior literature suggesting that shorter follow-up time is associated with greater excess

mortality.[9,30] However, we did not formally compare short-term to long-term follow-up nor persistent to fluctuating depressive symptoms.

Given our results of a relationship between time-varying depressive symptoms and mortality, further research is warranted to test the long-term efficacy of and adherence to depression treatment and to explore preventive approaches to decreasing premature mortality risk.[32] To our knowledge, the finding of a relationship between depressive symptoms and mortality in those with excellent or very good self-reported health is a new finding and should be further studied.

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**32.** Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. *JAMA Psychiatry.* 2016;73:565-574.

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**Author Contributions:** Drs. Yulia Khodneva and Joshua Richman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford; *Analysis and interpretation of data:* Khodneva, Moise, Jannat-Khah, Richman, Kronish, Shaffer, Safford; *Drafting of the manuscript:* Moise, Khodneva *Critical revision of manuscript for important intellectual content:* Moise, Khodneva, Jannat-Khah, Richman, Kronish, Davidson,

Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding:* Safford; *Study supervision:* Safford

**Conflict of Interest:** None



**Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are available if deemed important by reviewers with open access by Monika Safford at Weill Cornell, Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised and risk of identification is low.

## Figure Legend

**Figure 1.** Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

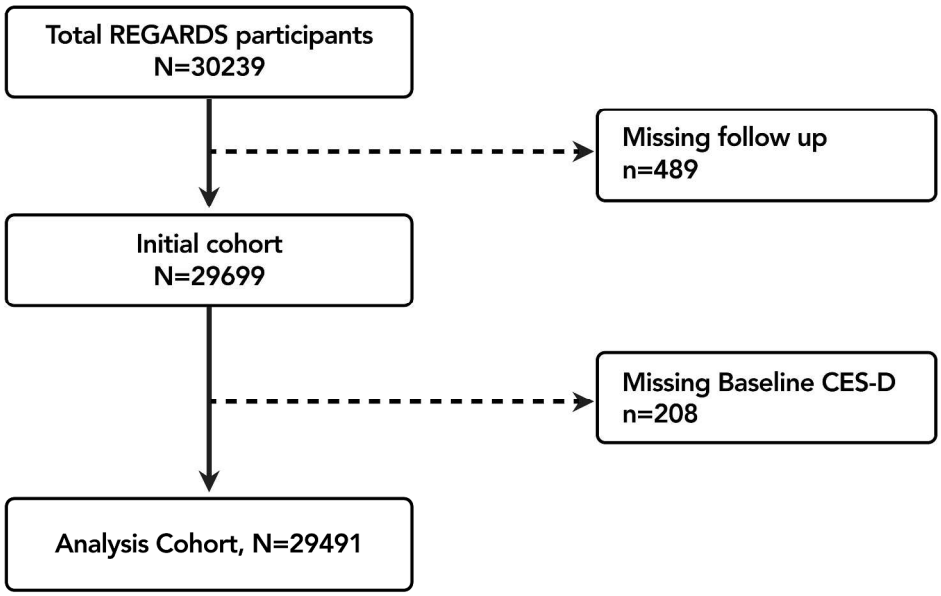



Figure 1. Consort Diagram

279x215mm (300 x 300 DPI)

**Supplementary Material**

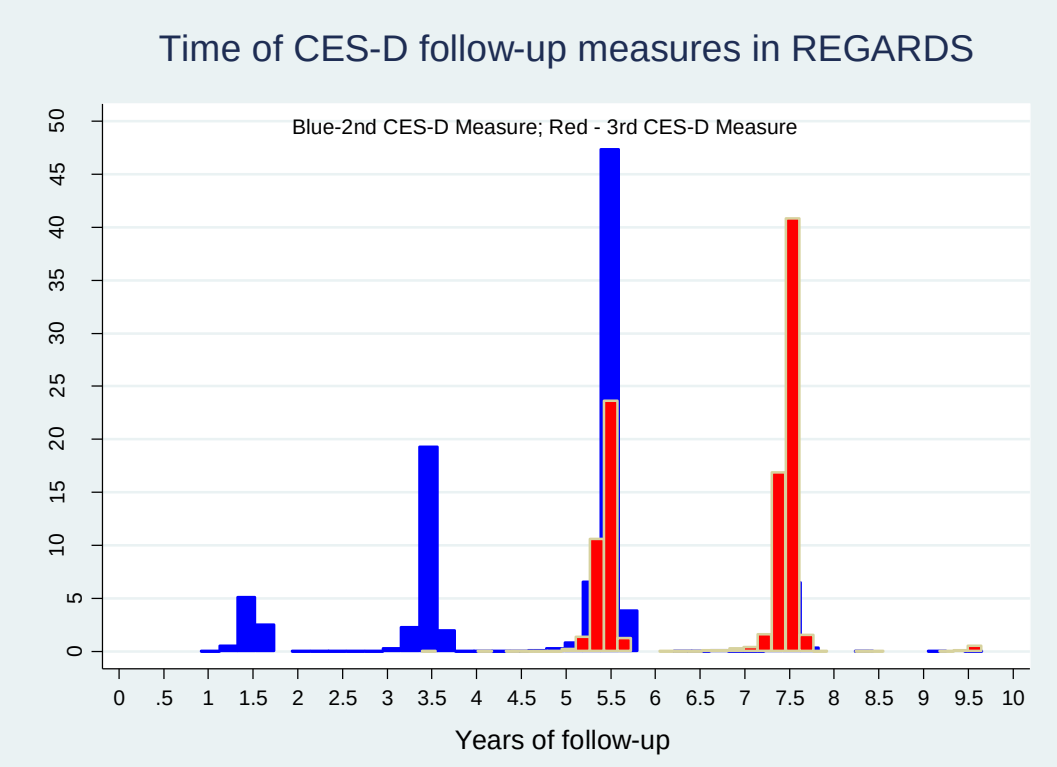
**eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).**

| Self-reported general health | Baseline | | | Second CES-D | | | Third CES-D | | |
|---|---|---|---|---|---|---|---|---|---|
| | CES-D<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n |
| **Excellent** | 4515<br>95.9 % | 195<br>4.1% | 4710 | 3444<br>94.7% | 194<br>5.3% | 3638 | 2109<br>94.6% | 120<br>5.4% | 2229 |
| **Very good** | 8450<br>94.1% | 530<br>5.9% | 8980 | 6332<br>93.0% | 478<br>7.0% | 6810 | 3938<br>92.8% | 305<br>7.2% | 4243 |
| **Good** | 9181<br>89.1% | 1124<br>10.9% | 10305 | 6363<br>88.6% | 818<br>11.4% | 7181 | 3717<br>88.9% | 464<br>11.1% | 4181 |
| **Fair** | 3424<br>77.8 % | 975<br>22.2 % | 4399 | 2185<br>79.7% | 556<br>20.3% | 2741 | 1236<br>82.0% | 271<br>18.0% | 1507 |
| **Poor** | 614<br>59.2% | 424<br>40.9% | 1038 | 322<br>61.2% | 204<br>38.8% | 526 | 177<br>65.3% | 94<br>34.7% | 271 |
| | | | 29432 | | | 20896 | | | 12431 |
| | **Frequency Missing = 59** | | | **Frequency Missing = 8595** | | | **Frequency Missing = 17060** | | |

**eTable 2. Reasons for non-cardiovascular disease death in the REGARDS study**

| | Overall | | Self-reported general health as **"excellent or very good"** n=13,711 | | Self-reported general health as **"poor, fair or good"** n=15,780 | |
|---|---|---|---|---|---|---|
| *Causes of Death* | n | Percent | Frequency | Percent | Frequency | Percent |
| Cancer | 1226 | 44.3 | 474 | 54.0 | 747 | 39.7 |
| Accidents/Injury/Suicide/Homicide | 164 | 5.9 | 52 | 5.9 | 111 | 5.9 |
| Suicide | 3 | 0.1 | 2 | 0.2 | 1 | 0.05 |
| Liver disease | 56 | 2.0 | 14 | 1.6 | 42 | 2.2 |
| Infection | 498 | 18.0 | 132 | 15.0 | 365 | 19.4 |
| ESRD | 119 | 4.3 | 23 | 2.6 | 95 | 5.1 |
| Dementia | 187 | 6.8 | 74 | 8.4 | 112 | 6.0 |
| COPD | 247 | 8.9 | 43 | 4.9 | 204 | 10.9 |
| Pulmonary Embolism | 38 | 1.34 | 11 | 1.3 | 27 | 1.4 |
| Other | 232 | 8.4 | 55 | 6.3 | 177 | 9.4 |
| | Frequency Missing = 263 | | | | Frequency Missing = 272 | |

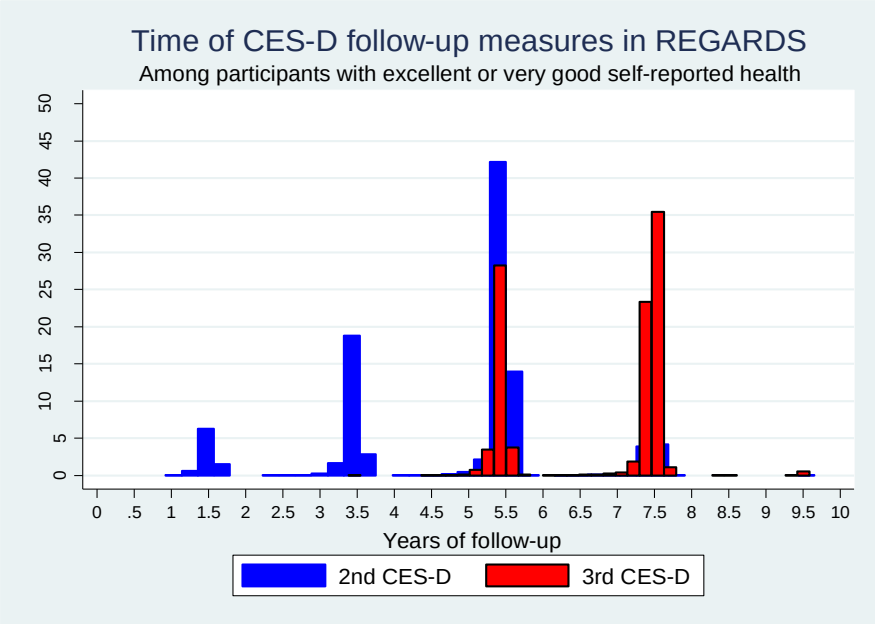
**eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.**

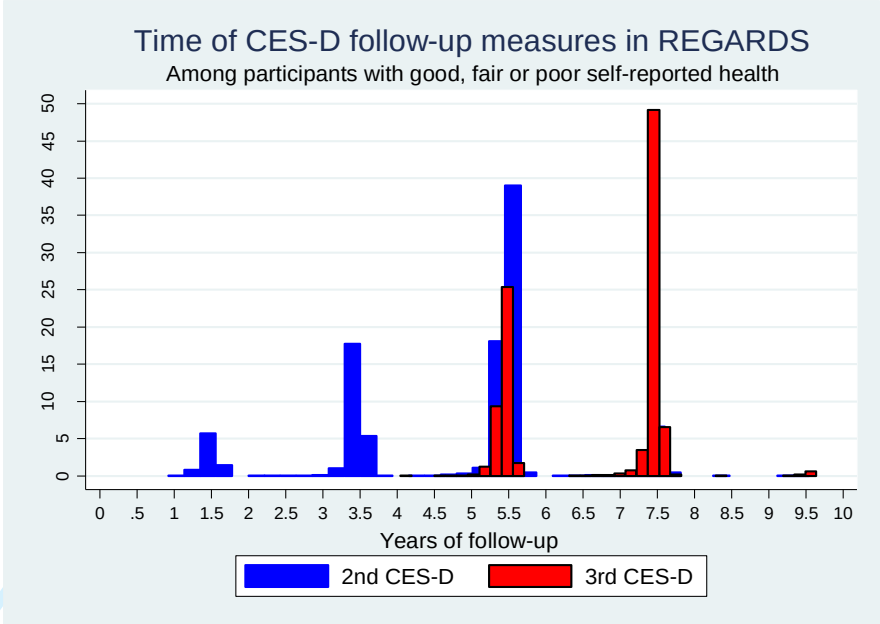



*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| | Time since preceding measurement (baseline or second follow-up), years | | | | |
|---|---|---|---|---|---|
| | Participants, n | Mean | SD | Minimum | Maximum |
| Second CES-D | 20934 | 4.8 | 1.5 | 0.9 | 9.7 |
| Third CES-D | 12451 | 2.1 | 0.4 | 1.0 | 4.2 |

**eFigure 2. Timing of CES-D follow up measures in REGARDS by self reported health at baseline.**




*"Percent" is a proportion of participants reporting CES-D scores at certain times, of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| Self-reported general health as "excellent or very good" | | | | | | Self-reported general health as "poor, fair or good" | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | |
| | N | Mean | SD | Minimum | Maximum | N | Mean | SD | Minimum | Maximum |
| Second CES-D | 10448 | 4.8 | 1.5 | 0.9 | 9.7 | 10448 | 4.8 | 1.5 | 0.9 | 9.5 |
| Third CES-D | 6472 | 2.1 | 0.4 | 1.7 | 4.2 | 5959 | 2.1 | 0.5 | 1.0 | 4.2 |

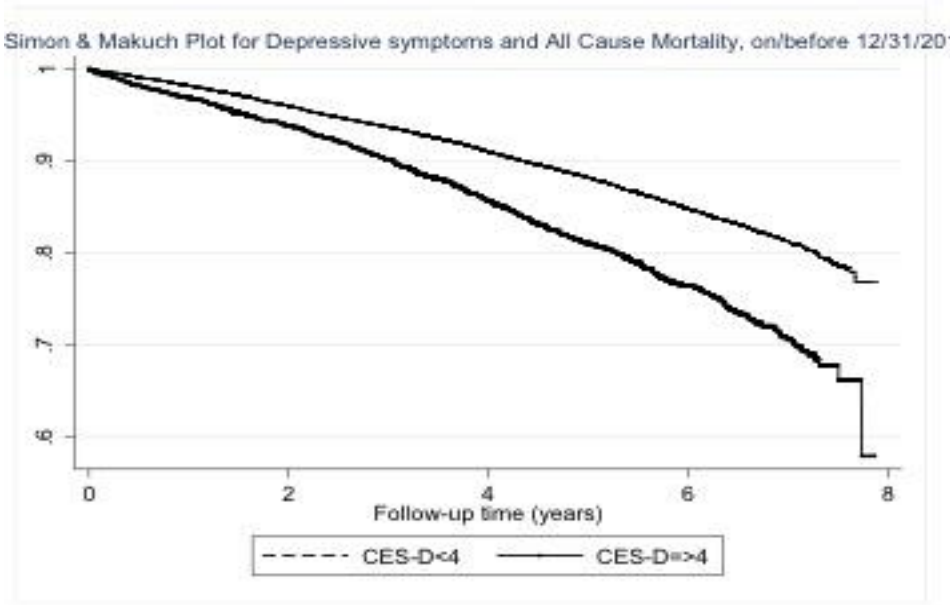
**eTable 3. Baseline characteristics of REGARDS participants who had all 3 CES-D measures vs. those with 1 or 2 CES-D measures**

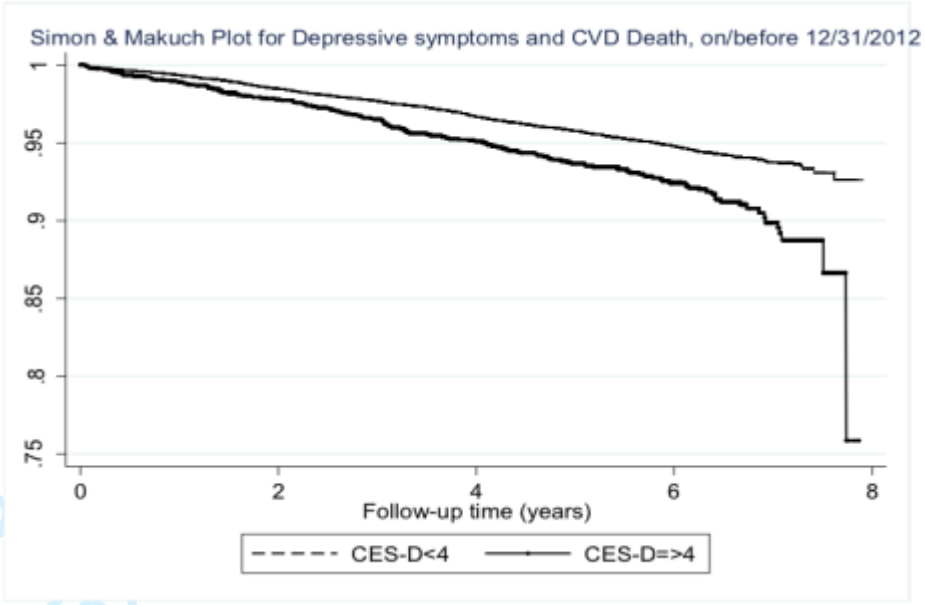
| Characteristics | 1 or 2 CES-D measures (n=17,040) | All 3 CES-D measures (n=12, 451) | *p* value |
|---|---|---|---|
| ***Socio-demographics*** | | | |
| Age, *M* (SD) | 65.0 +- 10.0 | 64.7 +- 8.5 | 0.0069 |
| Female, n (%) | 9300 (54.6) | 6945 (55.8) | 0.04 |
| African American, n (%) | 7709 (45.2) | 4420 (35.5) | <.001 |
| Less than high school education, n (%) | 2583 (15.2) | 1113 (8.9) | <.001 |
| Annual Household Income, n (%) | | | <.001 |
| Less than $20,000 | 3549 (20.8) | 1773 (14.2) | |
| No Health Insurance, n (%) | 1290 (7.6) | 636 (5.1) | <.001 |
| Region, n (%) | | | <.001 |
| Stroke belt | 5806 (34.1) | 4387 (35.2) | |
| Stroke buckle | 3887 (22.8) | 2301 (18.5) | |
| Non-stroke belt or buckle | 7347 (43.1) | 5763 (46.3) | |
| ***General health and medical conditions*** | | | |
| Self-reported general health, n (%) | | | <.001 |
| Poor, fair, good | 9783 (57.5) | 5959 (47.9) | |
| Excellent, very good | 7218 (42.5) | 6472 (52.1) | |
| Cardiovascular disease (CHD, stroke, PAD, AA), n (%) | 4379 (25.7) | 2446 (19.6) | <.001 |
| Diabetes, n (%) | 4083 (25.0) | 2169 (18.0) | <.001 |
| COPD, n (%) | 1612 (9.5) | 1098 (8.8) | 0.05 |
| Physical component score on SF-12 scale, *M* (SD) | 45.5 +- 11.0 | 47.6 +- 9.9 | <.001 |
| ***Physiological risk factors*** | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.4 +- 6.3 | 29.2 +- 6.0 | 0.0024 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 128.0 +- 17.2 | 127.0 +- 15.9 | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.2 +- 41.0 | 191.9 +- 39.0 | 0.5732 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.4 +- 16.1 | 52.4 +- 16.3 | <.001 |
| QT Interval, corrected for heart rate, ms, M (SD) | 408.4 +- 24.2 | 406.3 +- 22.7 | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.3[1.0-5.4] | 2.1[0.9-4.7] | <.001 |

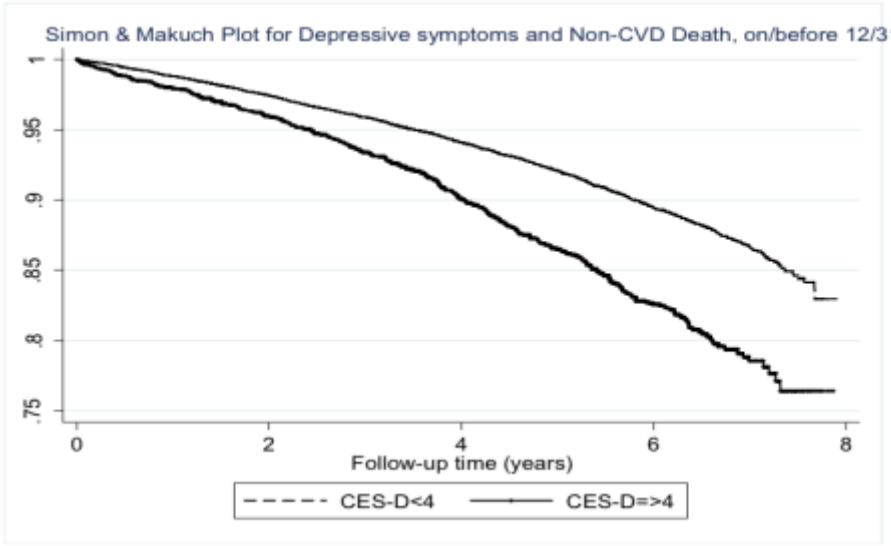
| | | | |
|---|---|---|---|
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.9[4.8-18.7] | 6.9[4.5-13.5] | <.001 |
| ***Medications*** | | | |
| Antihypertensive medication use, n (%) | 9079 (53.9) | 6118 (49.7) | <.001 |
| Statin use, n (%) | 5344 (31.4) | 3951 (31.8) | 0.53 |
| Aspirin use, n (%) | 7297 (42.8) | 5493 (44.1) | 0.03 |
| Antidepressant use, n (%) | 2440 (14.4) | 1646 (13.2) | 0.006 |
| ***Behavioral risk factors*** | | | |
| Self-reported smoking, pack years, *M* (SD) | 14.5 +- 24.4 | 12.2 +- 21.0 | <.001 |
| Current Smoking, n(%) | 2786 (16.4) | 1477 (11.9) | <.001 |
| Alcohol use, n (%) | | | <.001 |
| Heavy | 652 (3.9) | 520 (4.2) | |
| Moderate | 5180 (31.1) | 4446 (36.3) | |
| None | 10822 (65.0) | 7294 (59.5) | |
| Physical inactivity, n (%) | 6150 (36.7) | 3854 (31.3) | <.001 |
| Medication non-adherence, n (%) | 4548 (29.6) | 3411 (29.9) | 0.59 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1300 (9.4) | 588 (5.9) | <.001 |
| Elevated perceived stress (PSS≥5) | 5437 (31.9) | 3154 (25.3) | <.001 |

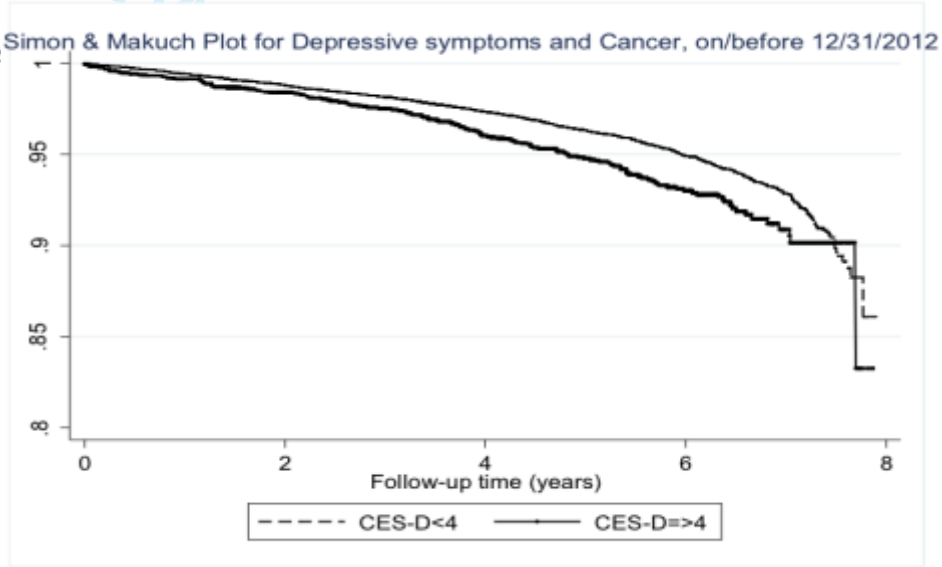
*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.
Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use. CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

**eFigure 3. Simon and Makuch plots of time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.**



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No/Page # | Recommendation |
|---|---|---|
| **Title and abstract** | 1 (page 1-3) | (*a*) Indicate the study's design with a commonly used term in the title or the **abstract** |
| | (Page 2-3) | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 (Page 4) | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 (pages 4-5) | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 (Page 5 and 6) | Present key elements of study design early in the paper |
| Setting | 5 (page 5-10), | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 (page 5-6, 8-9) | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| | n/a | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 (page 6-8) | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8 (pages 6-9) | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one |

| | | |
|---|---|---|
| | | group |
| Bias | 9 (page 8-10) | Describe any efforts to address potential sources of bias |
| Study size | 10 (page 10) | Explain how the study size was arrived at |
| Quantitative variables | 11 (page 6-10) | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 (page 8-10) | (*a*) Describe all statistical methods, including those used to control for confounding |
| | Pages 9 | (*b*) Describe any methods used to examine subgroups and interactions |
| | Page 10 | (*c*) Explain how missing data were addressed |
| | Page 9 | (*d*) If applicable, explain how loss to follow-up was addressed |
| | Page 9-10 | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13 (page 10) | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | Page 10 | (b) Give reasons for non-participation at each stage |
| | Figure 1 | (c) Consider use of a flow diagram |
| Descriptive data | 14 (page 10-11) | (a) Give characteristics of study participants (eg demographic, clinical, social) cand information on exposures and potential confounders |
| | Page 10 | (b) Indicate number of participants with missing data for each variable of interest |
| | Pages 12 | (c) Summarise follow-up time (eg, average and total amount) |

| | | |
|---|---|---|
| Outcome data | 15 (page 11) | Report numbers of outcome events or summary measures over time |
| Main results | 16 (pages 11-12) | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | Page 7-8, 23-27 | (*b*) Report category boundaries when continuous variables were categorized |
| | n/a | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 (pages 12) | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 (page 12) | Summarise key results with reference to study objectives |
| Limitations | 19 (pages 14-15) | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 (page 12-13) | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 (page 14) | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 (page 20) | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present |

| | | |
|---|---|---|
| | | article is based |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study



| | |
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| Primary Subject Heading: | Mental health |
| Secondary Subject Heading: | Mental health |
| Keywords: | mortality, health status, Depression & mood disorders < PSYCHIATRY |
| | |

# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study

**Running Title:** depressive symptoms and mortality

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**Journal Subject Codes: mortality, depression, health status**

**Total Document Text Count: 3063**

**Abstract: 240/300**

**Abstract**

**Objective:** To assess the association between time-varying depressive symptoms with all-cause and cause-specific mortality

**Design:** The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a national, population-based longitudinal study conducted from 2003-2007.

**Setting**: General continental U.S. communities

**Participants**: 29,491 black and white U.S. adults ≥45 years randomly sampled within race-sex-geographic strata

**Exposure**: Elevated depressive symptoms (CES-D-4 ≥ 4) measured at baseline and on average 5 and 7 years later

**Main Outcome Measures**: Cox proportional hazard regression models assessed cancer, non-cardiovascular (CVD), CVD and all-cause mortality.

**Results:** The average age was 64.9 years; 55% were female; 41% black; 11.0% had elevated depressive symptoms; 54% had poor, fair or good health. Time-varying depressive symptoms were significantly associated with nonCVD (aHR=1.29, 95% CI 1.16-1.44) and all-cause (aHR=1.24, 95%CI 1.14-1.39), but not cancer (aHR=1.15, 95%CI 0.96-1.38) or CVD (aHR=1.13, 95%CI 0.98-1.32) death adjusting for demographics, chronic clinical diseases, behavioral risk factors, and physiologic factors. Depressive symptoms were related to all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death in those who reported excellent or very good health. The analyses of the association between one measure of baseline depressive symptoms and mortality analyses yielded similar results.

**Conclusions:** Time-varying depressive symptoms confer an increased risk for all-cause mortality, CVD, non-CVD death and cancer death, particularly in those with excellent or very good health. These findings may have implications for timely treatment, regardless of health status.

**Strengths and limitations of this study.**

- Depression is a relapsing/remitting disease and our study is one of the first to use multiple measurements of depression to demonstrate a time varying relationship between depression and mortality, including cancer mortality, in a large, diverse cohort.
- To our knowledge, we are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and cause-specific mortality, with depression predicting mortality particularly in those with excellent or very good reported health.
- Our analyses were limited by the use of the short form of the CES-D scale
- The REGARDS cohort is regionally specific, limiting generalizability.

## Introduction

It is well known that elevated depressive symptoms predict mortality,[1] both in high-risk individuals with chronic illnesses like cardiovascular disease (CVD), and in general populations.[2-4] [5-8] More recently, several studies have shown that depressive symptoms both preceding and following cancer diagnosis may confer an increased risk of cancer death as well.[9,10]

However, depressive symptoms relapse and remit, and prior studies on the relationship between depressive symptoms and mortality have been limited by one measurement of depressive symptoms.[1] Recently, Lasserre et al. (2016) found that current but not remitted depressive symptoms predict all-cause mortality, but again depression diagnoses and history were ascertained at one time point.[11] In addition, prior literature has often been marked by inadequate adjustment for important covariates, such as behavioral risk factors. To our knowledge, few if any prior studies have examined the time-varying association between depressive symptoms and excess causes of death, including all-cause and cause specific mortality. In addition, self-perceived health status may predict mortality[12] and complicate the relationship between depressive symptoms and poor outcomes.[13] It is unknown whether depressive symptoms confer an increased risk of excess mortality equally in those with self-reported excellent/very good (in whom depression may be less likely to be recognized) and good/fair/poor health.

The purpose of our study is to examine the association between time-varying depressive symptoms with cancer, CVD, nonCVD and all-cause mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a broad, diverse population cohort with repeat measurements of depressive symptoms. We stratify by self-reported baseline health status

(very good or excellent vs. poor, fair or good) to further isolate the association between depressive symptoms and excess mortality.

## Methods

The REGARDS study is a national cohort study of stroke incidence and cognitive decline in black and white community dwelling adults ≥ 45 years living in the United States stratified to reflect specific race-sex-geographic strata.[14] Inclusion and exclusion criteria have been previously described; of note, those with active cancer were excluded from the original study.[14] Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study. Participants were recruited by mail using commercially available lists of U.S. residents, followed by a computer-assisted telephone interview and subsequent home visit at which time individuals were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing baseline depressive symptom measurements **(Figure 1)**. The REGARDS study protocol was approved by institutional review boards at participating centers.

### *Study Procedures*

Baseline data were collected through computer-assisted telephone interviews, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data, medical history and behavioral risk factors. Following the telephone interview, individuals had an in-home visit during which physical measurements, a resting electrocardiogram, medication inventory, phlebotomy and urine were collected. The median time between the initial phone interview and in-home examination was 28.0 (interquartile range = 21.0) days.

*Primary Outcomes*

The primary outcomes for these analyses were (1) cancer mortality (all body sites) (2) CVD death defined as death from CHD, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes (3) non-CVD death and (4) all-cause mortality. Living participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for reported hospitalizations or physician visits. Deaths were detected by report of next-of-kin or through online services (e.g., Social Security Death Index) or the National Death Index.[14] Death certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and CVD outcomes.

*Depressive symptoms*

The primary predictor was baseline depressive symptoms. The 4-item Center for Epidemiologic Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. This scale asks participants to rate the number of days over the last week in which they had: 1) felt depressed; 2) felt lonely; 3) had crying spells; and 4) felt sad. Response options included <1 day, 1 to 2 days, 3 to 4 days, and 5-7 days (0, 1, 2 3 points, respectively). Cronbach's α for the CES-D in the total sample was 0.80. Elevated depressive symptoms were defined as a summed score of ≥4.[15] The reliability and validity of the CES-D 4 is similar to the original 20-item instrument.[16]

*Covariates*

Demographic data included self-reported age, gender, race (black or white), education (less than high school, high school graduate, some college, and college graduate and above), annual income (less than $20,000, $20,000-$34,999, $35,000-$74,999, $75,000 and above), insurance

status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk factors included (1) diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR) (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial infarction or coronary revascularization procedure or evidence of myocardial infarction on the study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8) cognitive impairment on the 6-item screener of global cognitive function[17,18] (9) chronic lung disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin, antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors included (1) self-reported pack-years of cigarette smoking; (2) physical activity ("How many times per week do you engage in intense physical activity, enough to work up a sweat?" with response options of "none", "1-3 times per week" and "4 or more times per week"); (3) alcohol use ("How many alcoholic beverages do you drink?": none, moderate [1 drink per day for women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2 drinks per day for men]);[14] (4) medication non-adherence assessed with the 4-item Morisky Medication Adherence Scale (>= 1).[19] Potential physiologic risk factors included high-sensitivity C-reactive protein, self-reported health status based on the physical component of the 12-item Short-Form Health Survey (SF 12),[20] and perceived stress, measured by the 4-item version of the

Perceived Stress Scale (score of ≥ 5 vs. <5).[21] Other than depressive symptoms, no other covariate was assessed more than once.

*Statistical Analyses*

Baseline characteristics of participants with and without elevated depressive symptoms at baseline were compared using chi-square tests (for categorical variables), Student t tests (for continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous measures).

Cox proportional hazard regression models were constructed to separately analyze the association between depressive symptoms (CES-D≥4) and cancer death (from all body sites, a subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline measurement, and 3) on average two years after the second measurement. In the analyses, we considered depressive symptoms (CES-D≥4 vs. <4) as a time-varying exposure, with updates of exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3 measures of CES-D (≥4 vs. <4) with a broken-up follow-up time. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive symptoms using the Simon-Makuch method,[22] a modification of the Kaplan-Meier method. In this context, depression status is treated as a binary time-dependent covariate and study cohorts are continually updated to contribute to either the CES-D≥4 or CES-D <4 groups.

Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were estimated for those with vs. without elevated depressive symptoms. Adjusted modeling proceeded in stages (adjusting for baseline covariates), starting with demographic (Model 1) and traditional CVD risk factors (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5), which considered intervening first non-fatal stroke and/or myocardial infarction as a time-dependent covariate in CVD death outcomes. All analyses were conducted overall as well as stratified. We also conducted a formal test for interaction between depressive symptoms and self-reported health (defined as excellent or very good vs. good, fair or poor health) in model 4. As such, all analyses were conducted overall as well as stratified by baseline self-reported health. To evaluate the possibility of non-proportional hazards, we graphically inspected the log-log survival plots for depressive symptoms. We tested the Schoenfeld residuals for each model for a non-zero slope and all p values were greater than 0.05, indicating compatibility with the proportional hazards assumption.

*Sensitivity Analyses*

Sensitivity analyses constructed in parallel to the main analyses examined association of baseline CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, or end of follow-up.

Missing data in covariates were imputed using chained equations and derived by bootstrapping across the 5 imputed datasets. Multiple imputation was used for all analyses. Of the 29,491 participants, 2768 (9%) were missing income data, 59 (0.2%) health status, 9 (<0.1%) education, 26 (0.1%) health insurance, 1087 (4%) diabetes, 16 (0.1%) aspirin use, 70 (0.2%) statin use, 70 (0.2%) antidepressant use, 333 (1%) anti-hypertension meds use, 439 (2%) physical activity, 2705 (9%) medication adherence, 213 (0.7%) BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912 (3.1%) pack years, 84 (0.3%) SBP, 1394 (5%) renal function, 381 (1%) QTc, 5681 (19.3%) cognitive status, 4 (<0.1%) stress, 1425 (4%) SF-12 and 1881 (6%) CRP. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).

## Results

*Participant Characteristics*

Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms, leaving 29,491 eligible participants (**Figure 1)** of whom 3,254 (11.0%) had elevated depressive symptoms at baseline (CES-D≥4). The average age was 64.9 (9.4) years; 55.1% were female and 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33% of individuals were physically inactive, 29.2% non-adherent to their medication regimen and 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless of health status, participants with elevated (vs. non-elevated) depressive symptoms were more likely to be female, African-American, low income, have more chronic diseases, low physical health, and more behavioral risk factors (**Table 1A-B)**.

**Table 1A. Overall baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D)**

| Characteristics | Overall (n=29,491) | CES-D < 4 (n=26,817) | CES-D ≥4 (n=3,254) | *p* |
|---|---|---|---|---|
| ***Socio-demographics*** | | | | |
| Age, *M* (SD) | 64.9 (9.4) | 65.1 (9.4) | 63.2 (9.8) | <.001 |
| Female, n (%) | 16245 (55.1) | 13988 (53.3) | 2257 (69.4) | <.001 |
| African American, n (%) | 12129 (41.1) | 10427 (39.7) | 1702 (52.3) | <.001 |
| Less than high school education, n (%) | 3696 (12.5) | 2916 (11.1) | 780 (24.0) | <.001 |
| Annual household income, n (%) | | | | |
| Less than $20,000 | 5322 (18.0) | 4148 (15.8) | 1174 (36.1) | <.001 |
| No health insurance, n (%) | 1926 (6.5) | 1532 (5.8) | 394 (12.1) | <.001 |
| Region, n (%) | | | | <.001 |
| Stroke belt[a] | 10193 (34.6) | 8973 (34.2) | 1220 (37.5) | |
| Stroke buckle[b] | 6188 (21.0) | 5437 (20.7) | 751 (23.1) | |
| Non-stroke belt or buckle | 13110 (44.5) | 11827 (45.1) | 1283 (39.4) | |
| ***General health and medical conditions*** | | | | |
| Self-reported general health, n (%) | | | | <.001 |
| Poor, fair, good | 15742 (53.5) | 13219 (50.5) | 2523 (77.7) | |
| Excellent, very good | 13690 (46.5) | 12965 (49.5) | 725 (22.3) | |
| Cardiovascular disease, n (%)[c] | 6825 (23.1) | 5838 (22.3) | 987 (30.3) | <.001 |
| Diabetes, n (%)[d] | 6252 (22.0) | 5305 (21.0) | 947 (30.2) | <.001 |
| COPD, n (%) | 2710 (9.2) | 2307 (8.8) | 403 (12.4) | <.001 |
| Physical component score on SF-12 scale, *M* (SD) | 46.4 (10.6) | 47.1 (10.2) | 40.7 (12.2) | <.001 |
| ***Physiological risk factors*** | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.3 (6.2) | 29.2 (6.1) | 30.6 (7.1) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 127.6 (16.7) | 127.5 (16.5) | 128.7 (18.1) | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.1 (40.1) | 191.7 (39.8) | 194.6 (43.0) | <0.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.8 (16.2) | 51.7 (16.2) | 52.5 (16.3) | 0.02 |
| QT Interval, corrected for heart rate, ms, M (SD) | 407.5 (23.6) | 407.2 (23.5) | 410.0 (24.1) | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.2[1.0-5.0] | 2.1[0.9-4.8] | 3.0[1.2-6.9] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.4[4.7-6.2] | 7.3[4.6-15.8] | 8.2[5.1-19.8] | <.001 |
| **Medications** | | | | |
| Antihypertensive medication use, n (%) | 15197 (52.1) | 13290 (51.2) | 1907 (59.4) | <.001 |
| Statin use, n (%) | 9295 (31.6) | 8248 (31.5) | 1047 (32.3) | 0.38 |

| | | | | |
|---|---|---|---|---|
| Aspirin use, n (%) | 12790 (43.4) | 11376 (43.4) | 1414 (43.5) | 0.91 |
| Antidepressant use, n (%) | 4086 (13.9) | 3164 (12.1) | 922 (28.4) | <.001 |
| ***Behavioral risk factors*** | | | | |
| Self-reported smoking, pack years, *M* (SD) | 13.5 ( 23.1 | 13.3 ( 22.8 | 15.5 ( 24.9 | <.001 |
| Current Smoking, n(%) | 4263(14.5) | 3463(13.3) | 800(24.7) | <.001 |
| Alcohol use, n (%) | | | | <.001 |
| Heavy | 1172 (4.1) | 1043 (4.0) | 129 (4.1) | |
| Moderate | 9626 (33.3) | 8786 (34.1) | 840 (26.6) | |
| " None | 18116 (62.7) | 15925 (61.8) | 2191 (69.3) | |
| Physical inactivity, n (%) | 10004 (34.4) | 8500 (32.9) | 1504 (46.9) | <0.001 |
| Medication non-adherence, n (%) | 7959 (29.7) | 6820 (28.7) | 1139 (37.8) | <.001 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1888 (7.9) | 1542 (7.3) | 346 (12.6) | <.001 |
| Elevated perceived stress (PSS≥5) | 8591 (29.1) | 6283 (23.9) | 2308 (70.9) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease
n= total number assuming no missing data
[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.
[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.
[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

**Table 1B. Baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D) and self-reported health**

| | *Self-reported general health as "excellent or very good"* | | | *Self-reported general health as "poor, fair or good"* | | |
|---|---|---|---|---|---|---|
| Characteristics | CES-D < 4 (n=12965) | CES-D ≥4 (n=725) | *p* | CES-D < 4 (n=13219) | CES-D ≥4 (n=2523) | *p* |
| ***Socio-demographics*** | | | | | | |
| Age, *M* (SD) | 64.8 (9.4) | 64.5 (10.2) | 0.47 | 65.5 (9.3) | 62.8 (9.6) | <.001 |
| Female, n (%) | 6600 (50.9) | 501 (69.1) | <.001 | 7357 (55.7) | 1751 (69.4) | <.001 |
| African American, n (%) | 3726 (28.7) | 295 (40.7) | <.001 | 6677 (50.5) | 1404 (55.6) | <.001 |
| Less than high school education, n (%) | 845 (6.5) | 119 (16.4) | <.001 | 2059 (15.6) | 658 (26.1) | <.001 |
| Annual household income, n (%) | | | | | | |
| Less than $20,000 | 1304 (10.1) | 190 (26.2) | <.001 | 2832 (21.4) | 983 (39.0) | <.001 |
| No health insurance, n (%) | 644 (5.0) | 70 (9.7) | <.001 | 884 (6.7) | 324 (12.9) | <.001 |
| Region, n (%) | | | 0.37 | | | <.001 |
| Stroke belt[a] | 4282 (33.0) | 256 (35.3) | | 4668 (35.3) | 963 (38.2) | |
| Stroke buckle[b] | 2619 (20.2) | 148 (20.4) | | 2807 (21.2) | 601 (23.8) | |
| Non-stroke belt or buckle | 6064 (46.8) | 321 (44.3) | | 5744 (43.5) | 959 (38.0) | |
| ***General health and medical conditions*** | | | | | | |
| Self-reported general health, n (%) | | | | | | |
| Poor, fair, good | -- | -- | | --- | -- | |
| Excellent, very good | -- | -- | | --- | --- | |
| Cardiovascular disease, n (%)[c] | 1948 (15.0) | 144 (19.9) | 0.004 | 3874 (29.3) | 840 (33.3) | <.001 |
| Diabetes, n (%)[d] | 1443 (11.6) | 93 (13.3) | 0.16 | 3840 (30.2) | 853 (35.1) | <.001 |
| COPD, n (%) | 796 (6.2) | 55 (7.6) | 0.11 | 1507 (11.4) | 347 (13.8) | 0.007 |
| Physical component score on SF-12 scale, *M* (SD) | 52.0 (6.5) | 51.3 (9.1) | 0.008 | 42.0 (10.7) | 37.7 (11.3) | <.001 |
| ***Physiological risk factors*** | | | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 27.8 (5.1) | 28.4 (5.7) | 0.006 | 30.5 (6.6) | 31.2 (7.3) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 125.3 (15.7) | 126.0 (17.2) | 0.27 | 129.6 (16.9) | 129.5 (18.3) | 0.91 |
| Total Cholesterol, mg/dL, *M* (SD) | 193.8 (38.2) | 195.5 (38.6) | 0.26 | 189.7 (41.2) | 194.4 (44.2) | <.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 53.1 (16.4) | 55.8 (16.6) | <.001 | 50.4 (15.8) | 51.5 (16.1) | 0.002 |
| QT Interval, corrected for heart rate, ms, M (SD) | 405.6 (22.6) | 407.2 (23.5) | 0.06 | 408.7 (24.3) | 410.8 (24.2) | <0.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 1.7[0.8-3.8] | 1.9[0.9-4.9] | 0.004 | 2.7[1.2-6.1] | 3.4[1.3-7.7] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 6.6[4.3-12.3] | 6.9[4.7-14.0] | 0.005 | 8.4[5.0-20.7] | 8.7[5.1-22.2] | 0.18 |
| | 4916 (38.3) | 297 (41.7) | 0.06 | 8344 (63.9) | 1606 (64.5) | 0.57 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Medications** | | | | | | |
| Antihypertensive medication use, n (%) | | | | | | |
| Statin use, n (%) | 3407 (26.4) | 176 (24.4) | 0.24 | 4822 (36.5) | 870 (34.6) | 0.06 |
| Aspirin use, n (%) | 5254 (40.5) | 273 (37.7) | 0.13 | 6100 (46.2) | 1140 (45.2) | 0.36 |
| | | | | | | <.001 |
| Antidepressant use, n (%) | 1224 (9.5) | 144 (19.9) | <.001 | 1933 (14.6) | 774 (30.8) | |
| ***Behavioral risk factors*** | | | | | | |
| Self-reported smoking, pack years, *M* (SD) | 11.2 ( 20.5) | 12.1 ( 21.6) | 0.24 | 15.3 ( 24.7) | 16.5 ( 25.6) | 0.03 |
| Current Smoking, n(%) | 1344 (10.4) | 114 (15.8) | <.001 | 2110 (16.0) | 684 (27.2) | <.001 |
| Alcohol use, n (%) | | | 0.01 | | | <.001 |
| Heavy | 634 (5.0) | 38 (5.4) | | 409 (3.2) | 91 (3.7) | |
| Moderate | 5034 (39.4) | 238 (33.8) | | 3746 (29.0) | 600 (24.5) | |
| None | 7103 (55.6) | 429 (60.9) | | 8779 (67.9) | 1758 (71.8) | |
| Physical inactivity, n (%) | 3107 (24.3) | 259 (36.0) | <.001 | 5372 (41.3) | 1242 (50.0) | <.001 |
| Medication non-adherence, n (%) | 2997 (26.2) | 211 (33.1) | <.001 | 3809 (31.0) | 926 (39.1) | <.001 |
| Impaired cognitive status | | | <.001 | | | <.001 |
| (Cognitive score ≤ 4) | 587 (5.6) | 61 (10.1) | | 947 (8.9) | 285 (13.3) | |
| Elevated perceived stress (PSS≥5) | 2219 (17.1) | 404 (55.7) | <.001 | 4048 (30.6) | 1900 (75.3) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease
n= total number assuming no missing data
[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.
[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.
[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

*Mortality*

A total of 4,581 (15.5%) participants died during the follow-up period ending in 2012. Of these, 1,551 (33.9%) were attributed to CVD and 3,030 (66.1%) to nonCVD disease death. Of nonCVD deaths, 1,226 (44.3%) were due to cancer death (eTable 2**)**. Overall, there were only 3 cases of mortality due to suicide.

For the time-varying analyses, depressive symptoms were measured at baseline and on average 4.8 years (SD = 1.5) years following the baseline measurement, the third measurement occurring on average 2.1 (SD = 0.4) years after the second measurement (eFigure 1). The mean follow-up time

of the second and third measurement of CES-D measures did not differ by self-reported health (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8% had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 05% CI 0.98-1.32), even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-fatal CVD events (**Table 2,** eFigure 3). The results appeared to be particularly robust amongst those with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death), and 0.20 (cancer death) (**Table 2**).

**Table 2. Association of elevated depressive symptoms with mortality outcomes.** Each participant contributes to up to 3 time-variant CES-D measures. End of follow-up December 31, 2012.

| | Overall (N=29,491) | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | ***HR (95%CI) for categorical CES-D (Score =>4 v. < 4)*** | | |
| **All-cause mortality** | | | |
| Events, n | 4581 | 1392 | 3189 |
| Crude | **1.66(1.54-1.80)** | **1.97(1.66-2.33)** | **1.30(1.19-1.42)** |
| Model 1[a] | **1.63(1.50-1.76)** | **1.74(1.46-2.07)** | **1.42(1.29-1.55)** |
| Model 2[b] | **1.42(1.31-1.54)** | **1.60(1.34-1.90)** | **1.30(1.19-1.43)** |
| Model 3[c] | **1.38(1.27-1.49)** | **1.57(1.32-1.87)** | **1.27(1.16-1.39)** |
| Model 4[d] | **1.24(1.13-1.35)** | **1.53(1.27-1.83)** | **1.16(1.05-1.28)** |
| Model 5[e] | **1.24(1.14-1.36)** | **1.48(1.27-1.78)** | **1.17(1.06-1.30)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.005** | | |
| **CVD Death** | | | |
| Events, n | 1551 | 437 | 1114 |
| Crude | **1.61(1.41-1.85)** | **2.01(1.49-2.72)** | **1.23(1.05-1.43)** |
| Model 1[a] | **1.58(1.37-1.81)** | **1.76(1.29-2.40)** | **1.35(1.15-1.58)** |
| Model 2[b] | **1.31(1.13-1.51)** | **1.52(1.12-2.08)** | **1.20(1.03-1.41)** |
| Model 3[c] | **1.27(1.10-1.46)** | **1.53(1.12-2.09)** | 1.17(1.00-1.37) |
| Model 4[d] | 1.15(0.98-1.33) | **1.47(1.07-2.04)** | 1.06(0.90-1.26) |
| Model 5[e] | 1.13(0.98-1.32) | 1.37(0.99-1.91) p=0.06 | 1.07(0.90-1.27) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| **NonCVD Death** | | | |
| Events, n | 3030 | 955 | 2075 |
| Crude | **1.69(1.53-1.86)** | **1.95(1.58-2.39)** | **1.34(1.20-1.50)** |
| Model 1[a] | **1.65(1.50-1.83)** | **1.73(1.40-2.14)** | **1.45(1.30-1.63)** |
| Model 2[b] | **1.48(1.34-1.64)** | **1.63(1.32-2.02)** | **1.35(1.23-1.51)** |
| Model 3[c] | **1.44(1.30-1.59)** | **1.59(1.29-1.97)** | **1.33(1.18-1.49)** |
| Model 4[d] | **1.30(1.17-1.48)** | **1.58(1.27 -2.24)** | **1.22(1.08-1.38)** |
| Model 5[e] | **1.29(1.16-1.44)** | **1.54(1.24-1.92)** | **1.22(1.08-1.38)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.03** | | |
| **Cancer Death (a subset of nonCVD death)** | | | |
| Events, n | 1226 | 475 | 751 |
| Crude | **1.27(1.09-1.53)** | **1.53(1.11-2.12)** | 1.06(0.87-1.29) |
| Model 1[a] | **1.29(1.09-1.53)** | **1.45(1.04-2.01)** | 1.16(0.95-1.42) |
| Model 2[b] | **1.25(1.05-1.48)** | **1.40(1.01-1.95)** | 1.14(0.93-1.40) |
| Model 3[c] | **1.20(1.01-1.43)** | 1.35(0.97-1.88) | 1.11(0.91-1.36) |
| Model 4[d] | 1.16(0.96-1.39) | 1.37(0.97-1.92) | 1.08(0.87-1.33) |
| Model 5[e] | 1.15(0.96-1.38) | 1.36(0.97-1.91) | 1.08(0.90-1.34) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - 0.20 | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).

[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
[e]Model 5 adds non-fatal CVD event – first nonfatal myocardial infarction or stroke since baseline.
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
**Bold p-value < 0.05;** Missing data in covariates imputed using chained equations.

*Sensitivity Analyses:*

The mean follow-up time was 6.5 (SD = 2.3) years, with a median [interquartile range] of 6.9 [5.4-8.3] years. Baseline depressive symptoms were significantly associated with all-cause mortality (aHR 1.18, 95%CI 1.07-1.29) and nonCVD death (aHR 1.21, 95%CI 1.08-1.36) and approached significance for CVD death (aHR 1.10, 95%CI 0.94-1.29) and cancer death (aHR 1.12, 95%CI 0.93-1.36), even in the exploratory models (Model 3**).** The results appeared to be particularly robust amongst those with excellent or very good health: cancer death (aHR 1.49, 95%CI 1.03-2.13), CVD death (aHR 1.63, 95%CI 1.16-2.30), nonCVD death (aHR 1.48, 95%CI 1.15-1.89) and all-cause mortality (aHR 1.53, 95% CI 1.25-1.88). In Model 4, the p values for depressive symptoms x health status interaction term was 0.003 (all-cause mortality), 0.01 (CVD death), 0.06 (nonCVD death), and 0.07 (cancer death). Results were similar without multiple imputations within 2 decimal places (**Table 3**)

**Table 3. Association of baseline only elevated depressive symptoms (CES-D≥4) with mortality outcomes. Each participant contributes 1 measure of CES-D at baseline.**

| | Overall n=29,491 | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| All-cause mortality | 4581 | 1392 | 3189 |
| Crude | **1.54(1.42-1.68)** | **1.91(1.59-2.31)** | **1.18(1.07-1.30)** |
| Model 1[a] | **1.57(1.44-1.72)** | **1.76(1.45-2.12)** | **1.34(1.21-1.47)** |
| Model 2[b] | **1.32(1.25-1.49)** | **1.61(1.33-1.96)** | **1.22(1.11-1.35)** |
| Model 3[c] | **1.32(1.27-1.44)** | **1.56(1.29-1.90)** | **1.20(1.09-1.32)** |
| Model 4[d] | **1.18(1.07-1.29)** | **1.53(1.25-1.88)** | 1.09(0.98-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.002** | | |
| CVD Death | 1551 | 437 | 1114 |
| Crude | **1.55(1.34-1.78)** | **2.16(1.58-2.96)** | **1.13(0.97-1.33)** |
| Model 1[a] | **1.57(1.35-1.81)** | **1.96(1.42-2.71)** | **1.29(1.10-1.52)** |
| Model 2[b] | **1.28(1.10-1.48)** | **1.71(1.23-2.38)** | 1.14(0.97-1.34) |
| Model 3[c] | **1.24(1.07-1.44)** | **1.70(1.22-2.36)** | 1.11(0.94-1.31) |
| Model 4[d] | 1.10(0.94-1.29) | **1.63(1.16-2.30)** | 1.00(0.84-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.01** | | |
| NonCVD Death | 3030 | 955 | 2075 |
| Crude | **1.54(1.39-1.71)** | **1.80(1.42-2.26)** | **1.21(1.08-1.35)** |
| Model 1[a] | **1.57(1.42-1.75)** | **1.66(1.31-2.10)** | **1.36(1.21-1.53)** |
| Model 2[b] | **1.41(1.26-1.56)** | **1.56(1.29-1.98)** | **1.27(1.13-1.43)** |
| Model 3[c] | **1.36(1.22-1.51)** | **1.49(1.17-1.90)** | **1.25(1.11-1.41)** |
| Model 4[d] | **1.21(1.08-1.36)** | **1.48(1.15-1.89)** | **1.14(1.00-1.29)** |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| Cancer Death (a subset of nonCVD death) | 1226 | 475 | 751 |
| Crude | **1.21(1.02-1.44)** | **1.63(1.16-2.30)** | 0.97(0.79-1.19) |
| Model 1[a] | **1.27(1.06-1.52)** | **1.58(1.12-2.23)** | 1.09(0.89-1.35) |
| Model 2[b] | **1.22(1.02-1.47)** | **1.53(1.08-2.17)** | 1.07(0.87-1.33) |
| Model 3[c] | 1.17(0.98-1.41) | **1.45(1.02-2.05)** | 1.05(0.85-1.30) |
| Model 4[d] | 1.12(0.93-1.36) | **1.49(1.03-2.13)** | 1.01(0.81-1.27) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.07** | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
HR and 95% CI were estimated by Cox proportional hazard regression models. Bold p-value < 0.05; Missing data in covariates imputed using chained equations.

## Discussion

To our knowledge, this is the largest study to date to examine the relationship between depressive symptoms and all-cause and cause-specific mortality in non-institutionalized middle to older aged adults using multiple measurements of depressive symptoms and examining the role of health status. In this diverse cohort, we found that time-varying depressive symptoms significantly increased the risk of nonCVD and all-cause mortality in fully adjusted models. In fully adjusted models, depressive symptoms increased the risk of cause-specific and all-cause mortality by 36% to 54% in those with a very good/excellent state of health.

Given that depression is a relapsing/remitting disease,[23] this study markedly adds to the literature by demonstrating a time-varying relationship between elevated depressive symptoms and mortality, including cancer death. Major study strengths include the use of 3 measurements of depressive symptoms and stringent physician adjudication of outcomes. We were, however, unable to adjust for other time-varying covariates, which should be addressed in future research. For example, prior research suggests that changes in physical health (e.g., number of debilitating conditions) over time may mediate the relationship between depressive symptoms and mortality.[24]

We are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and mortality. Many have long asked whether depression leads to mortality or whether individuals are depressed because they are dying. Our findings in those who report excellent states of health is striking and supports the former argument.

It may also be that the effect of chronic illness burden on mortality in those with poor health overwhelms the effects of depressive symptoms. Those with excellent health may also fail to recognize/present for depression. In fact, depressed excellent health individuals in our cohort were less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future studies.

The overall results also have a coherence consistent with prior studies that suggest that depressive symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as cancer death.[25] While prior literature suggests that depressive symptoms confer mortality in those with active cancer, [26] our study excluded active cancer diagnoses confirming a possible relationship between depressive symptoms and incident cancer mortality. Prior studies have also been limited by inadequate covariate control, and our results for cancer persisted after adjusting for numerous traditional and behavioral risk factors, such as smoking, and approached significance even in models that included physiologic factors.

Overall, baseline and time varying analyses were similar. However, while our baseline analyses suggest that depressive symptoms significantly contribute to cancer death in those with excellent/very good health, time varying analyses allowed for more accurate analyses in line with expectations, suggesting a weaker interaction by health status for proximal cancer mortality in this cohort that excluded those with active malignancy.

This study also supports comprehensive evidence-based depression care management in primary care practices, which have been shown to lower mortality risk.[27] Nonetheless, depression treatment remains suboptimal in the general population,[28] despite decades of efforts. We too demonstrate that

over time, nearly 40% of patients with elevated depressive symptoms at baseline were still depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both time-varying analyses (by virtue of follow-up times being broken up by repeat depression measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend greater urgency to the importance of timely and effective treatment of depressive symptoms to prevent adverse consequences of depressive symptoms on physical health and mortality.

Limitations of our study include the regional specificity, limiting generalizability, and use of the short form of the CES-D, which measures only emotional and not somatic symptoms of depression. Schultz (2002) demonstrated variance between studies using scales and interviews,[29] and others have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).[30] However, CES-D scales are one of the most widely used scales in clinical practice and in baseline depression to outcome studies and have good sensitivity and specificity.[9,15,16] We may also have been underpowered to examine CVD and cancer mortality, though the directionality of the estimates remained consistent. The exclusion of active cancer participants as part of the overall REGARDS study criteria, the rationale of which has previously been described, [14] may also have contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically excluded, which is in line with prior depression to mortality studies.[1,9] Nonetheless, our previously published study, which excluded those with a history of CVD, similarly found a strong relationship between time-varying depressive symptoms and CVD death.[31]

We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5 years) was relatively short compared to other studies and we saw even shorter follow-up times between CES-D measures in time-varying analyses, suggesting a short-term effect on mortality.

Our results support prior literature suggesting that shorter follow-up time is associated with greater excess mortality.[9,30] However, we did not formally compare short-term to long-term follow-up nor persistent to fluctuating depressive symptoms nor examine depression as a time-varying coefficient.

Given our results of a relationship between time-varying depressive symptoms and mortality, further research is warranted to test the long-term efficacy of and adherence to depression treatment and to explore preventive approaches to decreasing premature mortality risk.[32] To our knowledge, the finding of a relationship between depressive symptoms and mortality in those with excellent or very good self-reported health is a new finding and should be further studied.

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**Author Contributions:** Drs. Yulia Khodneva and Joshua Richman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford; *Analysis and interpretation of data:* Khodneva, Moise, Jannat-Khah, Richman, Kronish, Shaffer, Safford; *Drafting of the manuscript:* Moise, Khodneva *Critical revision of manuscript for important intellectual content:* Moise, Khodneva, Jannat-Khah, Richman, Kronish, Davidson,

Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding:* Safford; *Study supervision:* Safford

**Conflict of Interest:** None



**Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are available if deemed important by reviewers with open access by Monika Safford at Weill Cornell, Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised and risk of identification is low.

## Figure Legend

**Figure 1.** Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

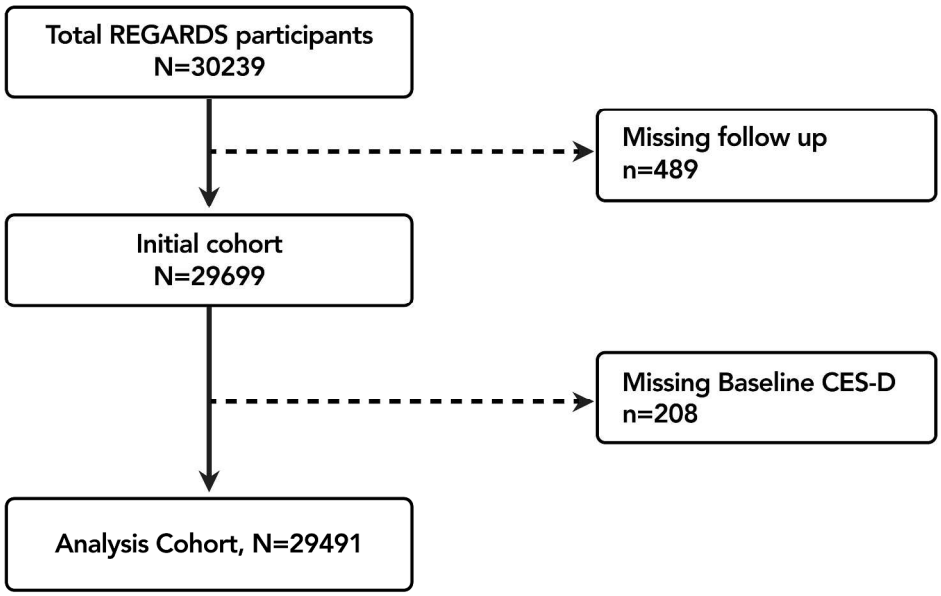



Figure 1. Consort Diagram

279x215mm (300 x 300 DPI)

**Supplementary Material**

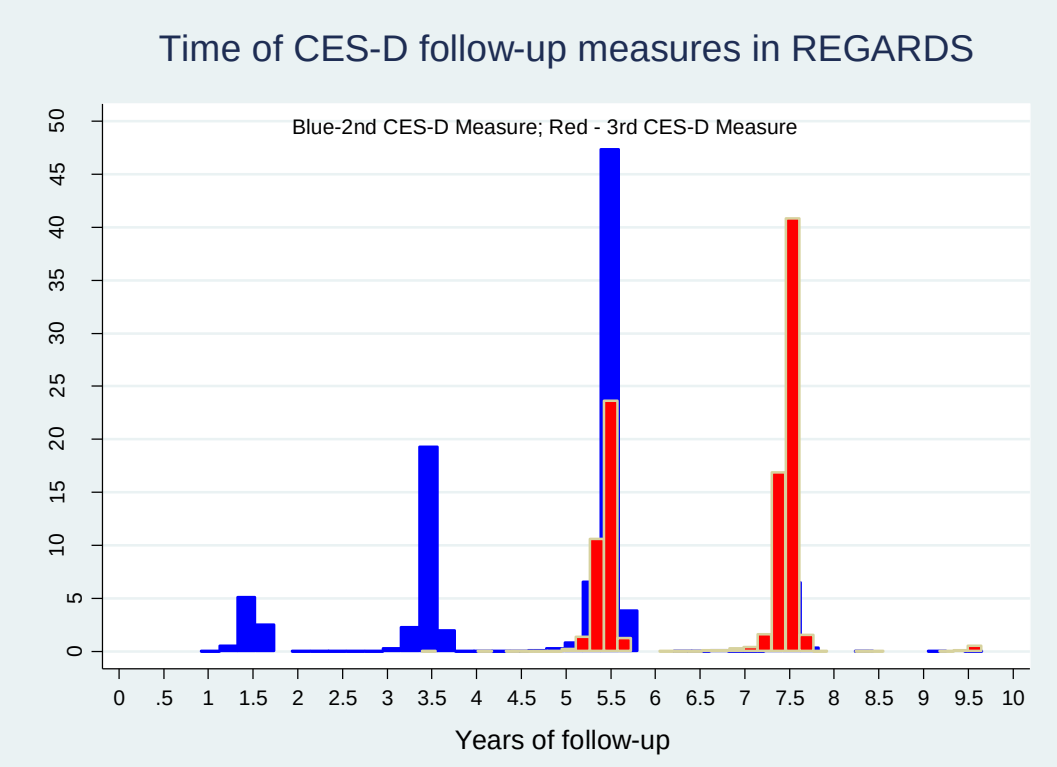
**eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).**

| Self-reported general health | Baseline | | | Second CES-D | | | Third CES-D | | |
|---|---|---|---|---|---|---|---|---|---|
| | CES-D<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n |
| **Excellent** | 4515<br>95.9 % | 195<br>4.1% | 4710 | 3444<br>94.7% | 194<br>5.3% | 3638 | 2109<br>94.6% | 120<br>5.4% | 2229 |
| **Very good** | 8450<br>94.1% | 530<br>5.9% | 8980 | 6332<br>93.0% | 478<br>7.0% | 6810 | 3938<br>92.8% | 305<br>7.2% | 4243 |
| **Good** | 9181<br>89.1% | 1124<br>10.9% | 10305 | 6363<br>88.6% | 818<br>11.4% | 7181 | 3717<br>88.9% | 464<br>11.1% | 4181 |
| **Fair** | 3424<br>77.8 % | 975<br>22.2 % | 4399 | 2185<br>79.7% | 556<br>20.3% | 2741 | 1236<br>82.0% | 271<br>18.0% | 1507 |
| **Poor** | 614<br>59.2% | 424<br>40.9% | 1038 | 322<br>61.2% | 204<br>38.8% | 526 | 177<br>65.3% | 94<br>34.7% | 271 |
| | | | 29432 | | | 20896 | | | 12431 |
| | **Frequency Missing = 59** | | | **Frequency Missing = 8595** | | | **Frequency Missing = 17060** | | |

**eTable 2. Reasons for non-cardiovascular disease death in the REGARDS study**

| | Overall | | Self-reported general health as **"excellent or very good"** n=13,711 | | Self-reported general health as **"poor, fair or good"** n=15,780 | |
|---|---|---|---|---|---|---|
| *Causes of Death* | n | Percent | Frequency | Percent | Frequency | Percent |
| Cancer | 1226 | 44.3 | 474 | 54.0 | 747 | 39.7 |
| Accidents/Injury/Suicide/Homicide | 164 | 5.9 | 52 | 5.9 | 111 | 5.9 |
| Suicide | 3 | 0.1 | 2 | 0.2 | 1 | 0.05 |
| Liver disease | 56 | 2.0 | 14 | 1.6 | 42 | 2.2 |
| Infection | 498 | 18.0 | 132 | 15.0 | 365 | 19.4 |
| ESRD | 119 | 4.3 | 23 | 2.6 | 95 | 5.1 |
| Dementia | 187 | 6.8 | 74 | 8.4 | 112 | 6.0 |
| COPD | 247 | 8.9 | 43 | 4.9 | 204 | 10.9 |
| Pulmonary Embolism | 38 | 1.34 | 11 | 1.3 | 27 | 1.4 |
| Other | 232 | 8.4 | 55 | 6.3 | 177 | 9.4 |
| | Frequency Missing = 263 | | | | Frequency Missing = 272 | |

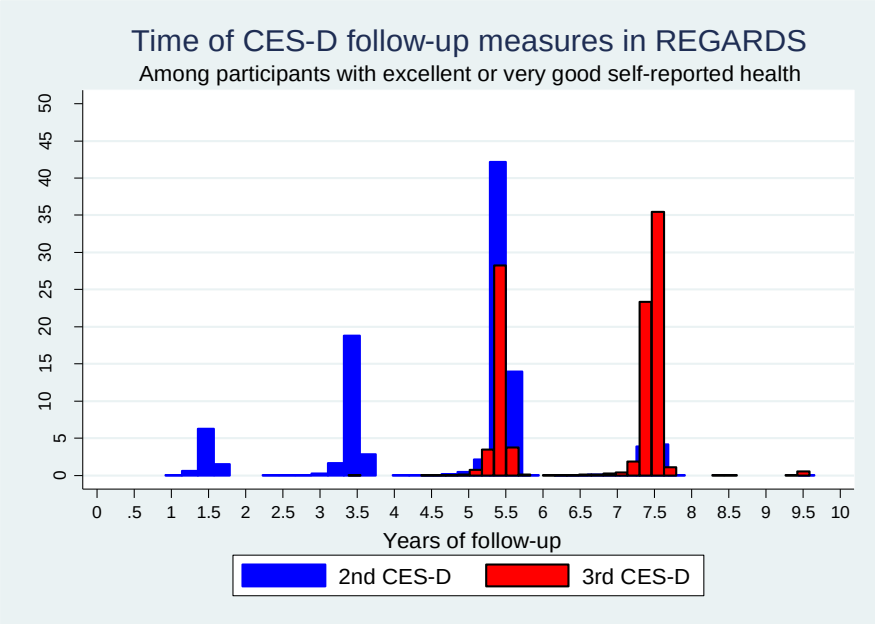
**eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.**

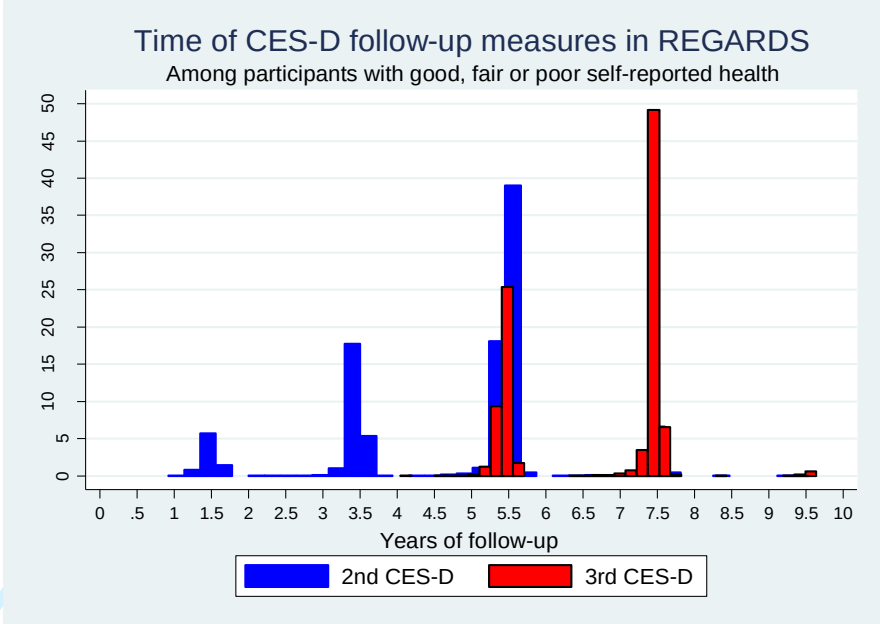



*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| | Time since preceding measurement (baseline or second follow-up), years | | | | |
|---|---|---|---|---|---|
| | Participants, n | Mean | SD | Minimum | Maximum |
| Second CES-D | 20934 | 4.8 | 1.5 | 0.9 | 9.7 |
| Third CES-D | 12451 | 2.1 | 0.4 | 1.0 | 4.2 |

**eFigure 2. Timing of CES-D follow up measures in REGARDS by self reported health at baseline.**




*"Percent" is a proportion of participants reporting CES-D scores at certain times, of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| Self-reported general health as "excellent or very good" | | | | | | Self-reported general health as "poor, fair or good" | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | |
| | N | Mean | SD | Minimum | Maximum | N | Mean | SD | Minimum | Maximum |
| Second CES-D | 10448 | 4.8 | 1.5 | 0.9 | 9.7 | 10448 | 4.8 | 1.5 | 0.9 | 9.5 |
| Third CES-D | 6472 | 2.1 | 0.4 | 1.7 | 4.2 | 5959 | 2.1 | 0.5 | 1.0 | 4.2 |

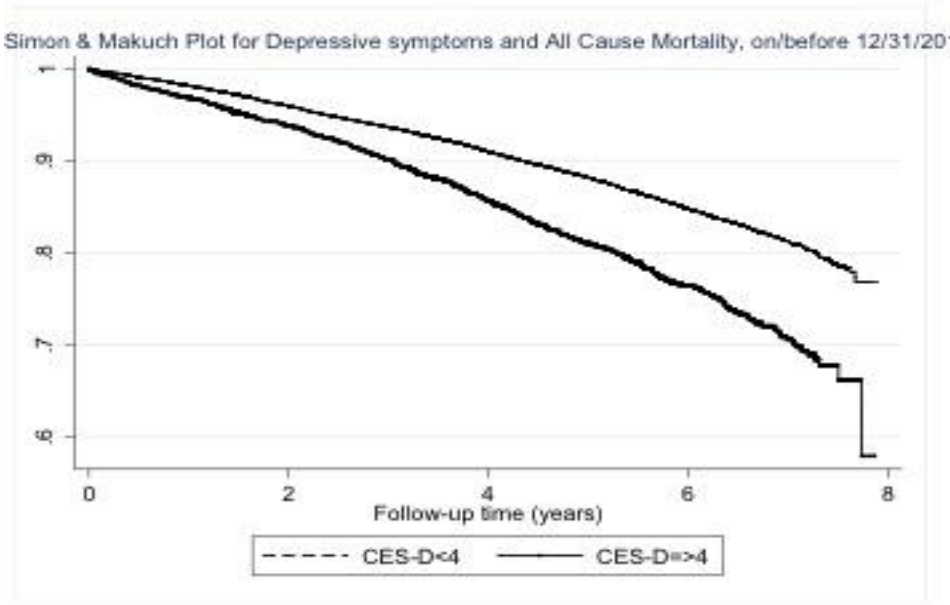
**eTable 3. Baseline characteristics of REGARDS participants who had all 3 CES-D measures vs. those with 1 or 2 CES-D measures**

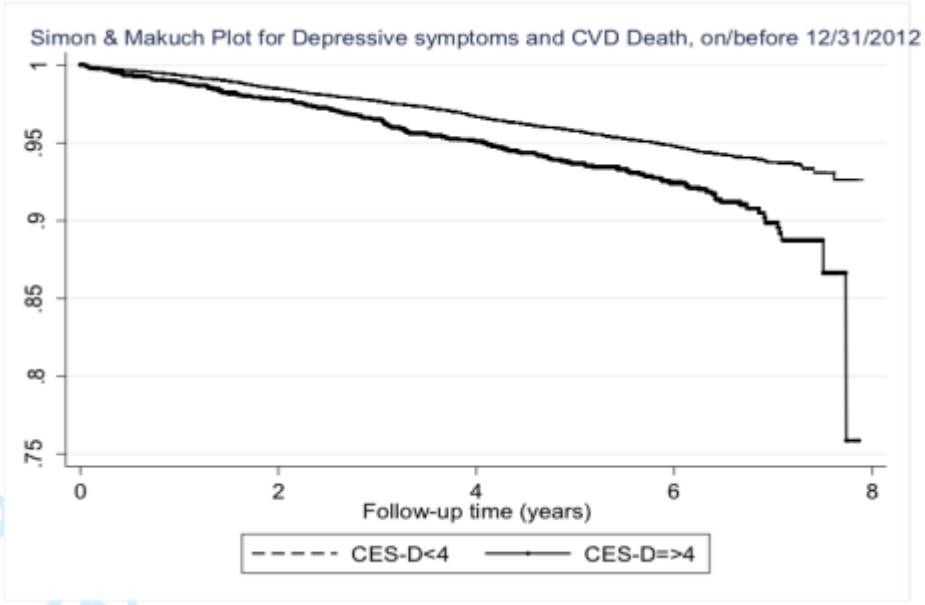
| Characteristics | 1 or 2 CES-D measures (n=17,040) | All 3 CES-D measures (n=12, 451) | *p* value |
|---|---|---|---|
| ***Socio-demographics*** | | | |
| Age, *M* (SD) | 65.0 +- 10.0 | 64.7 +- 8.5 | 0.0069 |
| Female, n (%) | 9300 (54.6) | 6945 (55.8) | 0.04 |
| African American, n (%) | 7709 (45.2) | 4420 (35.5) | <.001 |
| Less than high school education, n (%) | 2583 (15.2) | 1113 (8.9) | <.001 |
| Annual Household Income, n (%) | | | <.001 |
| Less than $20,000 | 3549 (20.8) | 1773 (14.2) | |
| No Health Insurance, n (%) | 1290 (7.6) | 636 (5.1) | <.001 |
| Region, n (%) | | | <.001 |
| Stroke belt | 5806 (34.1) | 4387 (35.2) | |
| Stroke buckle | 3887 (22.8) | 2301 (18.5) | |
| Non-stroke belt or buckle | 7347 (43.1) | 5763 (46.3) | |
| ***General health and medical conditions*** | | | |
| Self-reported general health, n (%) | | | <.001 |
| Poor, fair, good | 9783 (57.5) | 5959 (47.9) | |
| Excellent, very good | 7218 (42.5) | 6472 (52.1) | |
| Cardiovascular disease (CHD, stroke, PAD, AA), n (%) | 4379 (25.7) | 2446 (19.6) | <.001 |
| Diabetes, n (%) | 4083 (25.0) | 2169 (18.0) | <.001 |
| COPD, n (%) | 1612 (9.5) | 1098 (8.8) | 0.05 |
| Physical component score on SF-12 scale, *M* (SD) | 45.5 +- 11.0 | 47.6 +- 9.9 | <.001 |
| ***Physiological risk factors*** | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.4 +- 6.3 | 29.2 +- 6.0 | 0.0024 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 128.0 +- 17.2 | 127.0 +- 15.9 | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.2 +- 41.0 | 191.9 +- 39.0 | 0.5732 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.4 +- 16.1 | 52.4 +- 16.3 | <.001 |
| QT Interval, corrected for heart rate, ms, M (SD) | 408.4 +- 24.2 | 406.3 +- 22.7 | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.3[1.0-5.4] | 2.1[0.9-4.7] | <.001 |

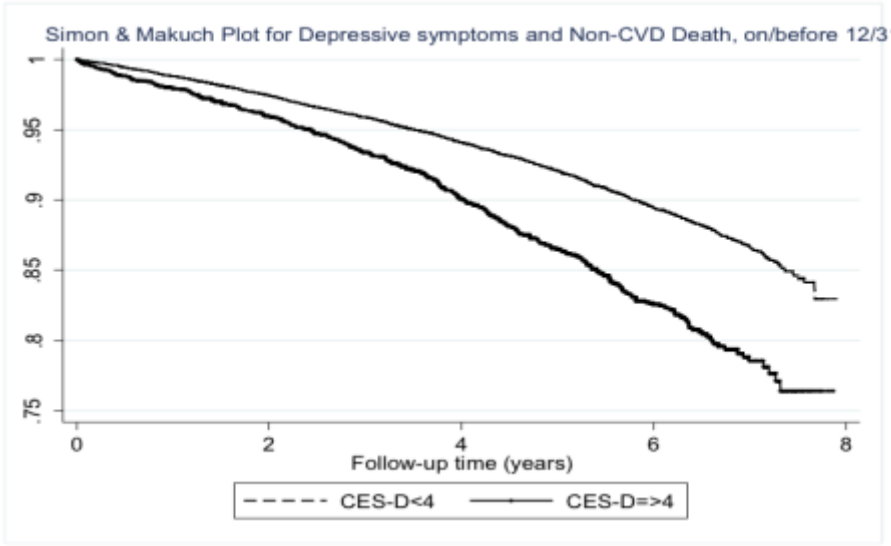
| | | | |
|---|---|---|---|
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.9[4.8-18.7] | 6.9[4.5-13.5] | <.001 |
| ***Medications*** | | | |
| Antihypertensive medication use, n (%) | 9079 (53.9) | 6118 (49.7) | <.001 |
| Statin use, n (%) | 5344 (31.4) | 3951 (31.8) | 0.53 |
| Aspirin use, n (%) | 7297 (42.8) | 5493 (44.1) | 0.03 |
| Antidepressant use, n (%) | 2440 (14.4) | 1646 (13.2) | 0.006 |
| ***Behavioral risk factors*** | | | |
| Self-reported smoking, pack years, *M* (SD) | 14.5 +- 24.4 | 12.2 +- 21.0 | <.001 |
| Current Smoking, n(%) | 2786 (16.4) | 1477 (11.9) | <.001 |
| Alcohol use, n (%) | | | <.001 |
| Heavy | 652 (3.9) | 520 (4.2) | |
| Moderate | 5180 (31.1) | 4446 (36.3) | |
| None | 10822 (65.0) | 7294 (59.5) | |
| Physical inactivity, n (%) | 6150 (36.7) | 3854 (31.3) | <.001 |
| Medication non-adherence, n (%) | 4548 (29.6) | 3411 (29.9) | 0.59 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1300 (9.4) | 588 (5.9) | <.001 |
| Elevated perceived stress (PSS≥5) | 5437 (31.9) | 3154 (25.3) | <.001 |

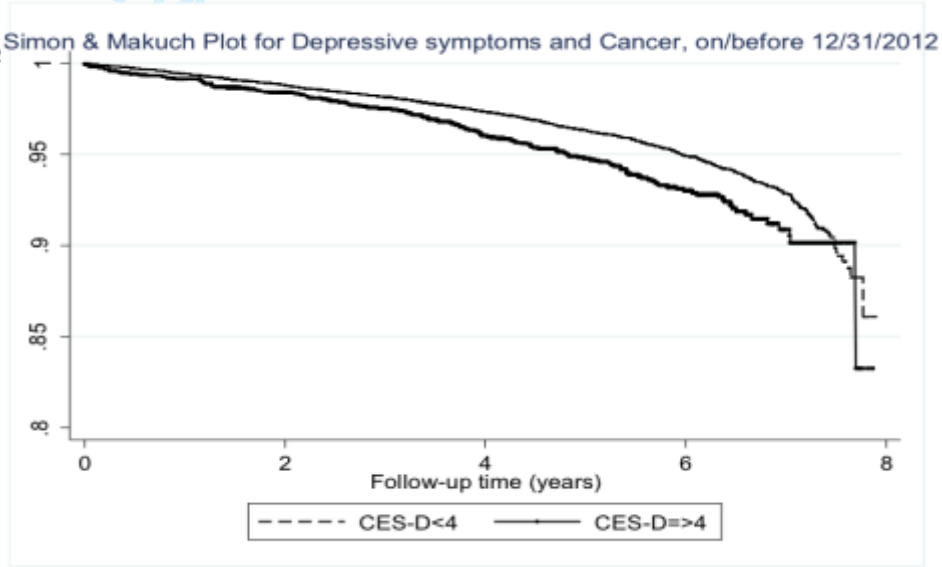
*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.
Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use. CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

**eFigure 3. Simon and Makuch plots of time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.**



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No/Page # | Recommendation |
|---|---|---|
| **Title and abstract** | 1 (page 1-3) | (*a*) Indicate the study's design with a commonly used term in the title or the **abstract** |
| | (Page 2-3) | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 (Page 4) | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 (pages 4-5) | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 (Page 5 and 6) | Present key elements of study design early in the paper |
| Setting | 5 (page 5-10), | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 (page 5-6, 8-9) | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| | n/a | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 (page 6-8) | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8 (pages 6-9) | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one |

| | | |
|---|---|---|
| | | group |
| Bias | 9 (page 8-10) | Describe any efforts to address potential sources of bias |
| Study size | 10 (page 10) | Explain how the study size was arrived at |
| Quantitative variables | 11 (page 6-10) | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 (page 8-10) | (*a*) Describe all statistical methods, including those used to control for confounding |
| | Pages 9 | (*b*) Describe any methods used to examine subgroups and interactions |
| | Page 10 | (*c*) Explain how missing data were addressed |
| | Page 9 | (*d*) If applicable, explain how loss to follow-up was addressed |
| | Page 9-10 | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13 (page 10) | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | Page 10 | (b) Give reasons for non-participation at each stage |
| | Figure 1 | (c) Consider use of a flow diagram |
| Descriptive data | 14 (page 10-11) | (a) Give characteristics of study participants (eg demographic, clinical, social) cand information on exposures and potential confounders |
| | Page 10 | (b) Indicate number of participants with missing data for each variable of interest |
| | Pages 12 | (c) Summarise follow-up time (eg, average and total amount) |

| | | |
|---|---|---|
| Outcome data | 15 (page 11) | Report numbers of outcome events or summary measures over time |
| Main results | 16 (pages 11-12) | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | Page 7-8, 23-27 | (*b*) Report category boundaries when continuous variables were categorized |
| | n/a | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 (pages 12) | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 (page 12) | Summarise key results with reference to study objectives |
| Limitations | 19 (pages 14-15) | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 (page 12-13) | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 (page 14) | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 (page 20) | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present |

| | | |
|---|---|---|
| | | article is based |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study



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| Secondary Subject Heading: | Mental health |
| Keywords: | mortality, health status, Depression & mood disorders < PSYCHIATRY |
| | |

# An observational study of the differential impact of time-varying depressive symptoms on all-cause and cause-specific mortality by health status in community dwelling adults: The REGARDS study

**Running Title:** depressive symptoms and mortality

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**Journal Subject Codes: mortality, depression, health status**

**Total Document Text Count: 3063**

**Abstract: 240/300**

**Abstract**

**Objective:** To assess the association between time-varying depressive symptoms with all-cause and cause-specific mortality

**Design:** The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a national, population-based longitudinal study conducted from 2003-2007.

**Setting**: General continental U.S. communities

**Participants**: 29,491 black and white U.S. adults ≥45 years randomly sampled within race-sex-geographic strata

**Exposure**: Elevated depressive symptoms (CES-D-4 ≥ 4) measured at baseline and on average 5 and 7 years later

**Main Outcome Measures**: Cox proportional hazard regression models assessed cancer, non-cardiovascular (CVD), CVD and all-cause mortality.

**Results:** The average age was 64.9 years; 55% were female; 41% black; 11.0% had elevated depressive symptoms; 54% had poor, fair or good health. Time-varying depressive symptoms were significantly associated with nonCVD (aHR=1.29, 95% CI 1.16-1.44) and all-cause (aHR=1.24, 95%CI 1.14-1.39), but not cancer (aHR=1.15, 95%CI 0.96-1.38) or CVD (aHR=1.13, 95%CI 0.98-1.32) death adjusting for demographics, chronic clinical diseases, behavioral risk factors, and physiologic factors. Depressive symptoms were related to all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death in those who reported excellent or very good health. The analyses of the association between one measure of baseline depressive symptoms and mortality analyses yielded similar results.

**Conclusions:** Time-varying depressive symptoms confer an increased risk for all-cause mortality, CVD, non-CVD death and cancer death, particularly in those with excellent or very good health. These findings may have implications for timely treatment, regardless of health status.

**Strengths and limitations of this study.**

- Depression is a relapsing/remitting disease and our study is one of the first to use multiple measurements of depression to demonstrate a time varying relationship between depression and mortality, including cancer mortality, in a large, diverse cohort.
- To our knowledge, we are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and cause-specific mortality, with depression predicting mortality particularly in those with excellent or very good reported health.
- Our analyses were limited by the use of the short form of the CES-D scale
- The REGARDS cohort is regionally specific, limiting generalizability.

## Introduction

It is well known that elevated depressive symptoms predict mortality,[1] both in high-risk individuals with chronic illnesses like cardiovascular disease (CVD), and in general populations.[2-4] [5-8] More recently, several studies have shown that depressive symptoms both preceding and following cancer diagnosis may confer an increased risk of cancer death as well.[9,10]

However, depressive symptoms relapse and remit, and prior studies on the relationship between depressive symptoms and mortality have been limited by one measurement of depressive symptoms.[1] Recently, Lasserre et al. (2016) found that current but not remitted depressive symptoms predict all-cause mortality, but again depression diagnoses and history were ascertained at one time point.[11] In addition, prior literature has often been marked by inadequate adjustment for important covariates, such as behavioral risk factors. To our knowledge, few if any prior studies have examined the time-varying association between depressive symptoms and excess causes of death, including all-cause and cause specific mortality. In addition, self-perceived health status may predict mortality[12] and complicate the relationship between depressive symptoms and poor outcomes.[13] It is unknown whether depressive symptoms confer an increased risk of excess mortality equally in those with self-reported excellent/very good (in whom depression may be less likely to be recognized) and good/fair/poor health.

The purpose of our study is to examine the association between time-varying depressive symptoms with cancer, CVD, nonCVD and all-cause mortality in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a broad, diverse population cohort with repeat measurements of depressive symptoms. We stratify by self-reported baseline health status

(very good or excellent vs. poor, fair or good) to further isolate the association between depressive symptoms and excess mortality.

## Methods

The REGARDS study is a national cohort study of stroke incidence and cognitive decline in black and white community dwelling adults ≥ 45 years living in the United States stratified to reflect specific race-sex-geographic strata.[14] Inclusion and exclusion criteria have been previously described; of note, those with active cancer were excluded from the original study.[14] Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study. Participants were recruited by mail using commercially available lists of U.S. residents, followed by a computer-assisted telephone interview and subsequent home visit at which time individuals were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing baseline depressive symptom measurements **(Figure 1)**. The REGARDS study protocol was approved by institutional review boards at participating centers.

### *Study Procedures*

Baseline data were collected through computer-assisted telephone interviews, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data, medical history and behavioral risk factors. Following the telephone interview, individuals had an in-home visit during which physical measurements, a resting electrocardiogram, medication inventory, phlebotomy and urine were collected. The median time between the initial phone interview and in-home examination was 28.0 (interquartile range = 21.0) days.

*Primary Outcomes*

The primary outcomes for these analyses were (1) cancer mortality (all body sites) (2) CVD death defined as death from CHD, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes (3) non-CVD death and (4) all-cause mortality. Living participants or their proxies were followed up every 6 months by telephone with retrieval of medical records for reported hospitalizations or physician visits. Deaths were detected by report of next-of-kin or through online services (e.g., Social Security Death Index) or the National Death Index.[14] Death certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and CVD outcomes.

*Depressive symptoms*

The primary predictor was baseline depressive symptoms. The 4-item Center for Epidemiologic Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. This scale asks participants to rate the number of days over the last week in which they had: 1) felt depressed; 2) felt lonely; 3) had crying spells; and 4) felt sad. Response options included <1 day, 1 to 2 days, 3 to 4 days, and 5-7 days (0, 1, 2 3 points, respectively). Cronbach's α for the CES-D in the total sample was 0.80. Elevated depressive symptoms were defined as a summed score of ≥4.[15] The reliability and validity of the CES-D 4 is similar to the original 20-item instrument.[16]

*Covariates*

Demographic data included self-reported age, gender, race (black or white), education (less than high school, high school graduate, some college, and college graduate and above), annual income (less than $20,000, $20,000-$34,999, $35,000-$74,999, $75,000 and above), insurance

status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk factors included (1) diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR) (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial infarction or coronary revascularization procedure or evidence of myocardial infarction on the study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8) cognitive impairment on the 6-item screener of global cognitive function[17,18] (9) chronic lung disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin, antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors included (1) self-reported pack-years of cigarette smoking; (2) physical activity ("How many times per week do you engage in intense physical activity, enough to work up a sweat?" with response options of "none", "1-3 times per week" and "4 or more times per week"); (3) alcohol use ("How many alcoholic beverages do you drink?": none, moderate [1 drink per day for women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2 drinks per day for men]);[14] (4) medication non-adherence assessed with the 4-item Morisky Medication Adherence Scale (>= 1).[19] Potential physiologic risk factors included high-sensitivity C-reactive protein, self-reported health status based on the physical component of the 12-item Short-Form Health Survey (SF 12),[20] and perceived stress, measured by the 4-item version of the

Perceived Stress Scale (score of ≥ 5 vs. <5).[21] Other than depressive symptoms, no other covariate was assessed more than once.

*Statistical Analyses*

Baseline characteristics of participants with and without elevated depressive symptoms at baseline were compared using chi-square tests (for categorical variables), Student t tests (for continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous measures).

Cox proportional hazard regression models were constructed to separately analyze the association between depressive symptoms (CES-D≥4) and cancer death (from all body sites, a subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline measurement, and 3) on average two years after the second measurement. In the analyses, we considered depressive symptoms (CES-D≥4 vs. <4) as a time-varying exposure, with updates of exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3 measures of CES-D (≥4 vs. <4) with a broken-up follow-up time. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive symptoms using the Simon-Makuch method,[22] a modification of the Kaplan-Meier method. In this context, depression status is treated as a binary time-dependent covariate and study cohorts are continually updated to contribute to either the CES-D≥4 or CES-D <4 groups.

Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were estimated for those with vs. without elevated depressive symptoms. Adjusted modeling proceeded in stages (adjusting for baseline covariates), starting with demographic (Model 1) and traditional CVD risk factors (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5), which considered intervening first non-fatal stroke and/or myocardial infarction as a time-dependent covariate in CVD death outcomes. All analyses were conducted overall as well as stratified. We also conducted a formal test for interaction between depressive symptoms and self-reported health (defined as excellent or very good vs. good, fair or poor health) in model 4. As such, all analyses were conducted overall as well as stratified by baseline self-reported health. To evaluate the possibility of non-proportional hazards, we graphically inspected the log-log survival plots for depressive symptoms. We tested the Schoenfeld residuals for each model for a non-zero slope and all p values were greater than 0.05, indicating compatibility with the proportional hazards assumption.

*Sensitivity Analyses*

Sensitivity analyses constructed in parallel to the main analyses examined association of baseline CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-up time for each participant was calculated from the date of the in-home visit to the date of the earliest of: death, last telephone follow-up, or end of follow-up.

Missing data in covariates were imputed using chained equations and derived by bootstrapping across the 5 imputed datasets. Multiple imputation was used for all analyses. Of the 29,491 participants, 2768 (9%) were missing income data, 59 (0.2%) health status, 9 (<0.1%) education, 26 (0.1%) health insurance, 1087 (4%) diabetes, 16 (0.1%) aspirin use, 70 (0.2%) statin use, 70 (0.2%) antidepressant use, 333 (1%) anti-hypertension meds use, 439 (2%) physical activity, 2705 (9%) medication adherence, 213 (0.7%) BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912 (3.1%) pack years, 84 (0.3%) SBP, 1394 (5%) renal function, 381 (1%) QTc, 5681 (19.3%) cognitive status, 4 (<0.1%) stress, 1425 (4%) SF-12 and 1881 (6%) CRP. Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).

## Results

*Participant Characteristics*

Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms, leaving 29,491 eligible participants (**Figure 1)** of whom 3,254 (11.0%) had elevated depressive symptoms at baseline (CES-D≥4). The average age was 64.9 (9.4) years; 55.1% were female and 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33% of individuals were physically inactive, 29.2% non-adherent to their medication regimen and 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless of health status, participants with elevated (vs. non-elevated) depressive symptoms were more likely to be female, African-American, low income, have more chronic diseases, low physical health, and more behavioral risk factors (**Table 1A-B)**.

**Table 1A. Overall baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D)**

| Characteristics | Overall (n=29,491) | CES-D < 4 (n=26,817) | CES-D ≥4 (n=3,254) | *p* |
|---|---|---|---|---|
| ***Socio-demographics*** | | | | |
| Age, *M* (SD) | 64.9 (9.4) | 65.1 (9.4) | 63.2 (9.8) | <.001 |
| Female, n (%) | 16245 (55.1) | 13988 (53.3) | 2257 (69.4) | <.001 |
| African American, n (%) | 12129 (41.1) | 10427 (39.7) | 1702 (52.3) | <.001 |
| Less than high school education, n (%) | 3696 (12.5) | 2916 (11.1) | 780 (24.0) | <.001 |
| Annual household income, n (%) | | | | |
| Less than $20,000 | 5322 (18.0) | 4148 (15.8) | 1174 (36.1) | <.001 |
| No health insurance, n (%) | 1926 (6.5) | 1532 (5.8) | 394 (12.1) | <.001 |
| Region, n (%) | | | | <.001 |
| Stroke belt[a] | 10193 (34.6) | 8973 (34.2) | 1220 (37.5) | |
| Stroke buckle[b] | 6188 (21.0) | 5437 (20.7) | 751 (23.1) | |
| Non-stroke belt or buckle | 13110 (44.5) | 11827 (45.1) | 1283 (39.4) | |
| ***General health and medical conditions*** | | | | |
| Self-reported general health, n (%) | | | | <.001 |
| Poor, fair, good | 15742 (53.5) | 13219 (50.5) | 2523 (77.7) | |
| Excellent, very good | 13690 (46.5) | 12965 (49.5) | 725 (22.3) | |
| Cardiovascular disease, n (%)[c] | 6825 (23.1) | 5838 (22.3) | 987 (30.3) | <.001 |
| Diabetes, n (%)[d] | 6252 (22.0) | 5305 (21.0) | 947 (30.2) | <.001 |
| COPD, n (%) | 2710 (9.2) | 2307 (8.8) | 403 (12.4) | <.001 |
| Physical component score on SF-12 scale, *M* (SD) | 46.4 (10.6) | 47.1 (10.2) | 40.7 (12.2) | <.001 |
| ***Physiological risk factors*** | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.3 (6.2) | 29.2 (6.1) | 30.6 (7.1) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 127.6 (16.7) | 127.5 (16.5) | 128.7 (18.1) | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.1 (40.1) | 191.7 (39.8) | 194.6 (43.0) | <0.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.8 (16.2) | 51.7 (16.2) | 52.5 (16.3) | 0.02 |
| QT Interval, corrected for heart rate, ms, M (SD) | 407.5 (23.6) | 407.2 (23.5) | 410.0 (24.1) | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.2[1.0-5.0] | 2.1[0.9-4.8] | 3.0[1.2-6.9] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.4[4.7-6.2] | 7.3[4.6-15.8] | 8.2[5.1-19.8] | <.001 |
| **Medications** | | | | |
| Antihypertensive medication use, n (%) | 15197 (52.1) | 13290 (51.2) | 1907 (59.4) | <.001 |
| Statin use, n (%) | 9295 (31.6) | 8248 (31.5) | 1047 (32.3) | 0.38 |

| | | | | |
|---|---|---|---|---|
| Aspirin use, n (%) | 12790 (43.4) | 11376 (43.4) | 1414 (43.5) | 0.91 |
| Antidepressant use, n (%) | 4086 (13.9) | 3164 (12.1) | 922 (28.4) | <.001 |
| ***Behavioral risk factors*** | | | | |
| Self-reported smoking, pack years, *M* (SD) | 13.5 ( 23.1 | 13.3 ( 22.8 | 15.5 ( 24.9 | <.001 |
| Current Smoking, n(%) | 4263(14.5) | 3463(13.3) | 800(24.7) | <.001 |
| Alcohol use, n (%) | | | | <.001 |
| Heavy | 1172 (4.1) | 1043 (4.0) | 129 (4.1) | |
| Moderate | 9626 (33.3) | 8786 (34.1) | 840 (26.6) | |
| " None | 18116 (62.7) | 15925 (61.8) | 2191 (69.3) | |
| Physical inactivity, n (%) | 10004 (34.4) | 8500 (32.9) | 1504 (46.9) | <0.001 |
| Medication non-adherence, n (%) | 7959 (29.7) | 6820 (28.7) | 1139 (37.8) | <.001 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1888 (7.9) | 1542 (7.3) | 346 (12.6) | <.001 |
| Elevated perceived stress (PSS≥5) | 8591 (29.1) | 6283 (23.9) | 2308 (70.9) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease
n= total number assuming no missing data
[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.
[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.
[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

**Table 1B. Baseline characteristics of REGARDS participants according to baseline depressive symptoms (CES-D) and self-reported health**

| | *Self-reported general health as "excellent or very good"* | | | *Self-reported general health as "poor, fair or good"* | | |
|---|---|---|---|---|---|---|
| Characteristics | CES-D < 4 (n=12965) | CES-D ≥4 (n=725) | *p* | CES-D < 4 (n=13219) | CES-D ≥4 (n=2523) | *p* |
| ***Socio-demographics*** | | | | | | |
| Age, *M* (SD) | 64.8 (9.4) | 64.5 (10.2) | 0.47 | 65.5 (9.3) | 62.8 (9.6) | <.001 |
| Female, n (%) | 6600 (50.9) | 501 (69.1) | <.001 | 7357 (55.7) | 1751 (69.4) | <.001 |
| African American, n (%) | 3726 (28.7) | 295 (40.7) | <.001 | 6677 (50.5) | 1404 (55.6) | <.001 |
| Less than high school education, n (%) | 845 (6.5) | 119 (16.4) | <.001 | 2059 (15.6) | 658 (26.1) | <.001 |
| Annual household income, n (%) | | | | | | |
| Less than $20,000 | 1304 (10.1) | 190 (26.2) | <.001 | 2832 (21.4) | 983 (39.0) | <.001 |
| No health insurance, n (%) | 644 (5.0) | 70 (9.7) | <.001 | 884 (6.7) | 324 (12.9) | <.001 |
| Region, n (%) | | | 0.37 | | | <.001 |
| Stroke belt[a] | 4282 (33.0) | 256 (35.3) | | 4668 (35.3) | 963 (38.2) | |
| Stroke buckle[b] | 2619 (20.2) | 148 (20.4) | | 2807 (21.2) | 601 (23.8) | |
| Non-stroke belt or buckle | 6064 (46.8) | 321 (44.3) | | 5744 (43.5) | 959 (38.0) | |
| ***General health and medical conditions*** | | | | | | |
| Self-reported general health, n (%) | | | | | | |
| Poor, fair, good | -- | -- | | --- | -- | |
| Excellent, very good | -- | -- | | --- | --- | |
| Cardiovascular disease, n (%)[c] | 1948 (15.0) | 144 (19.9) | 0.004 | 3874 (29.3) | 840 (33.3) | <.001 |
| Diabetes, n (%)[d] | 1443 (11.6) | 93 (13.3) | 0.16 | 3840 (30.2) | 853 (35.1) | <.001 |
| COPD, n (%) | 796 (6.2) | 55 (7.6) | 0.11 | 1507 (11.4) | 347 (13.8) | 0.007 |
| Physical component score on SF-12 scale, *M* (SD) | 52.0 (6.5) | 51.3 (9.1) | 0.008 | 42.0 (10.7) | 37.7 (11.3) | <.001 |
| ***Physiological risk factors*** | | | | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 27.8 (5.1) | 28.4 (5.7) | 0.006 | 30.5 (6.6) | 31.2 (7.3) | <.001 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 125.3 (15.7) | 126.0 (17.2) | 0.27 | 129.6 (16.9) | 129.5 (18.3) | 0.91 |
| Total Cholesterol, mg/dL, *M* (SD) | 193.8 (38.2) | 195.5 (38.6) | 0.26 | 189.7 (41.2) | 194.4 (44.2) | <.001 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 53.1 (16.4) | 55.8 (16.6) | <.001 | 50.4 (15.8) | 51.5 (16.1) | 0.002 |
| QT Interval, corrected for heart rate, ms, M (SD) | 405.6 (22.6) | 407.2 (23.5) | 0.06 | 408.7 (24.3) | 410.8 (24.2) | <0.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 1.7[0.8-3.8] | 1.9[0.9-4.9] | 0.004 | 2.7[1.2-6.1] | 3.4[1.3-7.7] | <.001 |
| Albumin to Creatinine Ratio, mg/g, median, IQR | 6.6[4.3-12.3] | 6.9[4.7-14.0] | 0.005 | 8.4[5.0-20.7] | 8.7[5.1-22.2] | 0.18 |
| | 4916 (38.3) | 297 (41.7) | 0.06 | 8344 (63.9) | 1606 (64.5) | 0.57 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Medications** | | | | | | |
| Antihypertensive medication use, n (%) | | | | | | |
| Statin use, n (%) | 3407 (26.4) | 176 (24.4) | 0.24 | 4822 (36.5) | 870 (34.6) | 0.06 |
| Aspirin use, n (%) | 5254 (40.5) | 273 (37.7) | 0.13 | 6100 (46.2) | 1140 (45.2) | 0.36 |
| | | | | | | <.001 |
| Antidepressant use, n (%) | 1224 (9.5) | 144 (19.9) | <.001 | 1933 (14.6) | 774 (30.8) | |
| ***Behavioral risk factors*** | | | | | | |
| Self-reported smoking, pack years, *M* (SD) | 11.2 ( 20.5) | 12.1 ( 21.6) | 0.24 | 15.3 ( 24.7) | 16.5 ( 25.6) | 0.03 |
| Current Smoking, n(%) | 1344 (10.4) | 114 (15.8) | <.001 | 2110 (16.0) | 684 (27.2) | <.001 |
| Alcohol use, n (%) | | | 0.01 | | | <.001 |
| Heavy | 634 (5.0) | 38 (5.4) | | 409 (3.2) | 91 (3.7) | |
| Moderate | 5034 (39.4) | 238 (33.8) | | 3746 (29.0) | 600 (24.5) | |
| None | 7103 (55.6) | 429 (60.9) | | 8779 (67.9) | 1758 (71.8) | |
| Physical inactivity, n (%) | 3107 (24.3) | 259 (36.0) | <.001 | 5372 (41.3) | 1242 (50.0) | <.001 |
| Medication non-adherence, n (%) | 2997 (26.2) | 211 (33.1) | <.001 | 3809 (31.0) | 926 (39.1) | <.001 |
| Impaired cognitive status | | | <.001 | | | <.001 |
| (Cognitive score ≤ 4) | 587 (5.6) | 61 (10.1) | | 947 (8.9) | 285 (13.3) | |
| Elevated perceived stress (PSS≥5) | 2219 (17.1) | 404 (55.7) | <.001 | 4048 (30.6) | 1900 (75.3) | <.001 |

*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation; PSS=Perceived stress scale; COPD=Chronic Obstructive Pulmonary Disease
n= total number assuming no missing data
[a]Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia.
[b]Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
[c] CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.
[d]Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use.

*Mortality*

A total of 4,581 (15.5%) participants died during the follow-up period ending in 2012. Of these, 1,551 (33.9%) were attributed to CVD and 3,030 (66.1%) to nonCVD disease death. Of nonCVD deaths, 1,226 (44.3%) were due to cancer death (eTable 2). Overall, there were only 3 cases of mortality due to suicide.

For the time-varying analyses, depressive symptoms were measured at baseline and on average 4.8 years (SD = 1.5) years following the baseline measurement, the third measurement occurring on average 2.1 (SD = 0.4) years after the second measurement (eFigure 1). The mean follow-up time

of the second and third measurement of CES-D measures did not differ by self-reported health (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8% had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 05% CI 0.98-1.32), even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-fatal CVD events (**Table 2,** eFigure 3). The results appeared to be particularly robust amongst those with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death), and 0.20 (cancer death). Results were similar without multiple imputations within 2 decimal places (**Table 2**).

**Table 2. Association of elevated depressive symptoms with mortality outcomes.** Each participant contributes to up to 3 time-variant CES-D measures. End of follow-up December 31, 2012.

| | Overall (N=29,491) | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | ***HR (95%CI) for categorical CES-D (Score =>4 v. < 4)*** | | |
| **All-cause mortality** | | | |
| Events, n | 4581 | 1392 | 3189 |
| Crude | **1.66(1.54-1.80)** | **1.97(1.66-2.33)** | **1.30(1.19-1.42)** |
| Model 1[a] | **1.63(1.50-1.76)** | **1.74(1.46-2.07)** | **1.42(1.29-1.55)** |
| Model 2[b] | **1.42(1.31-1.54)** | **1.60(1.34-1.90)** | **1.30(1.19-1.43)** |
| Model 3[c] | **1.38(1.27-1.49)** | **1.57(1.32-1.87)** | **1.27(1.16-1.39)** |
| Model 4[d] | **1.24(1.13-1.35)** | **1.53(1.27-1.83)** | **1.16(1.05-1.28)** |
| Model 5[e] | **1.24(1.14-1.36)** | **1.48(1.27-1.78)** | **1.17(1.06-1.30)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.005** | | |
| **CVD Death** | | | |
| Events, n | 1551 | 437 | 1114 |
| Crude | **1.61(1.41-1.85)** | **2.01(1.49-2.72)** | **1.23(1.05-1.43)** |
| Model 1[a] | **1.58(1.37-1.81)** | **1.76(1.29-2.40)** | **1.35(1.15-1.58)** |
| Model 2[b] | **1.31(1.13-1.51)** | **1.52(1.12-2.08)** | **1.20(1.03-1.41)** |
| Model 3[c] | **1.27(1.10-1.46)** | **1.53(1.12-2.09)** | 1.17(1.00-1.37) |
| Model 4[d] | 1.15(0.98-1.33) | **1.47(1.07-2.04)** | 1.06(0.90-1.26) |
| Model 5[e] | 1.13(0.98-1.32) | 1.37(0.99-1.91) p=0.06 | 1.07(0.90-1.27) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| **NonCVD Death** | | | |
| Events, n | 3030 | 955 | 2075 |
| Crude | **1.69(1.53-1.86)** | **1.95(1.58-2.39)** | **1.34(1.20-1.50)** |
| Model 1[a] | **1.65(1.50-1.83)** | **1.73(1.40-2.14)** | **1.45(1.30-1.63)** |
| Model 2[b] | **1.48(1.34-1.64)** | **1.63(1.32-2.02)** | **1.35(1.23-1.51)** |
| Model 3[c] | **1.44(1.30-1.59)** | **1.59(1.29-1.97)** | **1.33(1.18-1.49)** |
| Model 4[d] | **1.30(1.17-1.48)** | **1.58(1.27 -2.24)** | **1.22(1.08-1.38)** |
| Model 5[e] | **1.29(1.16-1.44)** | **1.54(1.24-1.92)** | **1.22(1.08-1.38)** |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - **0.03** | | |
| **Cancer Death (a subset of nonCVD death)** | | | |
| Events, n | 1226 | 475 | 751 |
| Crude | **1.27(1.09-1.53)** | **1.53(1.11-2.12)** | 1.06(0.87-1.29) |
| Model 1[a] | **1.29(1.09-1.53)** | **1.45(1.04-2.01)** | 1.16(0.95-1.42) |
| Model 2[b] | **1.25(1.05-1.48)** | **1.40(1.01-1.95)** | 1.14(0.93-1.40) |
| Model 3[c] | **1.20(1.01-1.43)** | 1.35(0.97-1.88) | 1.11(0.91-1.36) |
| Model 4[d] | 1.16(0.96-1.39) | 1.37(0.97-1.92) | 1.08(0.87-1.33) |
| Model 5[e] | 1.15(0.96-1.38) | 1.36(0.97-1.91) | 1.08(0.90-1.34) |
| Model 4 + CES-D x self-reported health | p-value for the interaction term - 0.20 | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).

[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
[e]Model 5 adds non-fatal CVD event – first nonfatal myocardial infarction or stroke since baseline.
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
**Bold p-value < 0.05;** Missing data in covariates imputed using chained equations.

*Sensitivity Analyses:*

The mean follow-up time was 6.5 (SD = 2.3) years, with a median [interquartile range] of 6.9 [5.4-8.3] years. Baseline depressive symptoms were significantly associated with all-cause mortality (aHR 1.18, 95%CI 1.07-1.29) and nonCVD death (aHR 1.21, 95%CI 1.08-1.36) and approached significance for CVD death (aHR 1.10, 95%CI 0.94-1.29) and cancer death (aHR 1.12, 95%CI 0.93-1.36), even in the exploratory models (Model 3**).** The results appeared to be particularly robust amongst those with excellent or very good health: cancer death (aHR 1.49, 95%CI 1.03-2.13), CVD death (aHR 1.63, 95%CI 1.16-2.30), nonCVD death (aHR 1.48, 95%CI 1.15-1.89) and all-cause mortality (aHR 1.53, 95% CI 1.25-1.88). In Model 4, the p values for depressive symptoms x health status interaction term was 0.003 (all-cause mortality), 0.01 (CVD death), 0.06 (nonCVD death), and 0.07 (cancer death). Results were similar without multiple imputations within 2 decimal places (**Table 3**).

**Table 3. Association of baseline only elevated depressive symptoms (CES-D≥4) with mortality outcomes. Each participant contributes 1 measure of CES-D at baseline.**

| | Overall n=29,491 | Self-reported general health as "excellent or very good" n=13,711 | Self-reported general health as "poor, fair or good" n=15,780 |
|---|---|---|---|
| | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| All-cause mortality | 4581 | 1392 | 3189 |
| Crude | **1.54(1.42-1.68)** | **1.91(1.59-2.31)** | **1.18(1.07-1.30)** |
| Model 1[a] | **1.57(1.44-1.72)** | **1.76(1.45-2.12)** | **1.34(1.21-1.47)** |
| Model 2[b] | **1.32(1.25-1.49)** | **1.61(1.33-1.96)** | **1.22(1.11-1.35)** |
| Model 3[c] | **1.32(1.27-1.44)** | **1.56(1.29-1.90)** | **1.20(1.09-1.32)** |
| Model 4[d] | **1.18(1.07-1.29)** | **1.53(1.25-1.88)** | 1.09(0.98-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.002** | | |
| CVD Death | 1551 | 437 | 1114 |
| Crude | **1.55(1.34-1.78)** | **2.16(1.58-2.96)** | **1.13(0.97-1.33)** |
| Model 1[a] | **1.57(1.35-1.81)** | **1.96(1.42-2.71)** | **1.29(1.10-1.52)** |
| Model 2[b] | **1.28(1.10-1.48)** | **1.71(1.23-2.38)** | 1.14(0.97-1.34) |
| Model 3[c] | **1.24(1.07-1.44)** | **1.70(1.22-2.36)** | 1.11(0.94-1.31) |
| Model 4[d] | 1.10(0.94-1.29) | **1.63(1.16-2.30)** | 1.00(0.84-1.20) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.01** | | |
| NonCVD Death | 3030 | 955 | 2075 |
| Crude | **1.54(1.39-1.71)** | **1.80(1.42-2.26)** | **1.21(1.08-1.35)** |
| Model 1[a] | **1.57(1.42-1.75)** | **1.66(1.31-2.10)** | **1.36(1.21-1.53)** |
| Model 2[b] | **1.41(1.26-1.56)** | **1.56(1.29-1.98)** | **1.27(1.13-1.43)** |
| Model 3[c] | **1.36(1.22-1.51)** | **1.49(1.17-1.90)** | **1.25(1.11-1.41)** |
| Model 4[d] | **1.21(1.08-1.36)** | **1.48(1.15-1.89)** | **1.14(1.00-1.29)** |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.06** | | |
| Cancer Death (a subset of nonCVD death) | 1226 | 475 | 751 |
| Crude | **1.21(1.02-1.44)** | **1.63(1.16-2.30)** | 0.97(0.79-1.19) |
| Model 1[a] | **1.27(1.06-1.52)** | **1.58(1.12-2.23)** | 1.09(0.89-1.35) |
| Model 2[b] | **1.22(1.02-1.47)** | **1.53(1.08-2.17)** | 1.07(0.87-1.33) |
| Model 3[c] | 1.17(0.98-1.41) | **1.45(1.02-2.05)** | 1.05(0.85-1.30) |
| Model 4[d] | 1.12(0.93-1.36) | **1.49(1.03-2.13)** | 1.01(0.81-1.27) |
| Model 4 + baseline CES-D x self-reported health | p-value for the interaction term - **0.07** | | |

[a]Model 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
[b]Model 2 adds to model 1 *medical conditions, physiological factors and medication use* (systolic blood pressure, total cholesterol, high density lipoprotein-cholesterol, use of aspirin, statins, antihypertensives, antidepressants, body mass index, logarithmically transformed Albumin to Creatinine Ratio; diabetes, cardiovascular disease, medication use as a proxy for chronic obstructive pulmonary disease, and cognitive impairment)
[c]Model 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
[d]Model 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)
HR = hazard ratio; CVD cardiovascular disease; CES-D = Centers for Epidemiology Studies-Depression
HR and 95% CI were estimated by Cox proportional hazard regression models. Bold p-value < 0.05; Missing data in covariates imputed using chained equations.

## Discussion

To our knowledge, this is the largest study to date to examine the relationship between depressive symptoms and all-cause and cause-specific mortality in non-institutionalized middle to older aged adults using multiple measurements of depressive symptoms and examining the role of health status. In this diverse cohort, we found that time-varying depressive symptoms significantly increased the risk of nonCVD and all-cause mortality in fully adjusted models. In fully adjusted models, depressive symptoms increased the risk of cause-specific and all-cause mortality by 36% to 54% in those with a very good/excellent state of health.

Given that depression is a relapsing/remitting disease,[23] this study markedly adds to the literature by demonstrating a time-varying relationship between elevated depressive symptoms and mortality, including cancer death. Major study strengths include the use of 3 measurements of depressive symptoms and stringent physician adjudication of outcomes. We were, however, unable to adjust for other time-varying covariates, which should be addressed in future research. For example, prior research suggests that changes in physical health (e.g., number of debilitating conditions) over time may mediate the relationship between depressive symptoms and mortality.[24]

We are also the first to report a significant moderating effect of self-reported health on the relationship between depressive symptoms and mortality. Many have long asked whether depression leads to mortality or whether individuals are depressed because they are dying. Our findings in those who report excellent states of health is striking and supports the former argument.

It may also be that the effect of chronic illness burden on mortality in those with poor health overwhelms the effects of depressive symptoms. Those with excellent health may also fail to recognize/present for depression. In fact, depressed excellent health individuals in our cohort were less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future studies.

The overall results also have a coherence consistent with prior studies that suggest that depressive symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as cancer death.[25] While prior literature suggests that depressive symptoms confer mortality in those with active cancer, [26] our study excluded active cancer diagnoses confirming a possible relationship between depressive symptoms and incident cancer mortality. Prior studies have also been limited by inadequate covariate control, and our results for cancer persisted after adjusting for numerous traditional and behavioral risk factors, such as smoking, and approached significance even in models that included physiologic factors.

Overall, baseline and time varying analyses were similar. However, while our baseline analyses suggest that depressive symptoms significantly contribute to cancer death in those with excellent/very good health, time varying analyses allowed for more accurate analyses in line with expectations, suggesting a weaker interaction by health status for proximal cancer mortality in this cohort that excluded those with active malignancy.

This study also supports comprehensive evidence-based depression care management in primary care practices, which have been shown to lower mortality risk.[27] Nonetheless, depression treatment remains suboptimal in the general population,[28] despite decades of efforts. We too demonstrate that

over time, nearly 40% of patients with elevated depressive symptoms at baseline were still depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both time-varying analyses (by virtue of follow-up times being broken up by repeat depression measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend greater urgency to the importance of timely and effective treatment of depressive symptoms to prevent adverse consequences of depressive symptoms on physical health and mortality.

Limitations of our study include the regional specificity, limiting generalizability, and use of the short form of the CES-D, which measures only emotional and not somatic symptoms of depression. Schultz (2002) demonstrated variance between studies using scales and interviews,[29] and others have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).[30] However, CES-D scales are one of the most widely used scales in clinical practice and in baseline depression to outcome studies and have good sensitivity and specificity.[9,15,16] We may also have been underpowered to examine CVD and cancer mortality, though the directionality of the estimates remained consistent. The exclusion of active cancer participants as part of the overall REGARDS study criteria, the rationale of which has previously been described, [14] may also have contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically excluded, which is in line with prior depression to mortality studies.[1,9] Nonetheless, our previously published study, which excluded those with a history of CVD, similarly found a strong relationship between time-varying depressive symptoms and CVD death.[31]

We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5 years) was relatively short compared to other studies and we saw even shorter follow-up times between CES-D measures in time-varying analyses, suggesting a short-term effect on mortality.

Our results support prior literature suggesting that shorter follow-up time is associated with greater excess mortality.[9,30] However, we did not formally compare short-term to long-term follow-up nor persistent to fluctuating depressive symptoms nor examine depression as a time-varying coefficient.

Given our results of a relationship between time-varying depressive symptoms and mortality, further research is warranted to test the long-term efficacy of and adherence to depression treatment and to explore preventive approaches to decreasing premature mortality risk.[32] To our knowledge, the finding of a relationship between depressive symptoms and mortality in those with excellent or very good self-reported health is a new finding and should be further studied.

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**Author Contributions:** Drs. Yulia Khodneva and Joshua Richman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford; *Analysis and interpretation of data:* Khodneva, Moise, Jannat-Khah, Richman, Kronish, Shaffer, Safford; *Drafting of the manuscript:* Moise, Khodneva *Critical revision of manuscript for important intellectual content:* Moise, Khodneva, Jannat-Khah, Richman, Kronish, Davidson,

Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding:* Safford; *Study supervision:* Safford

**Conflict of Interest:** None



**Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are available if deemed important by reviewers with open access by Monika Safford at Weill Cornell, Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised and risk of identification is low.

## Figure Legend

**Figure 1.** Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

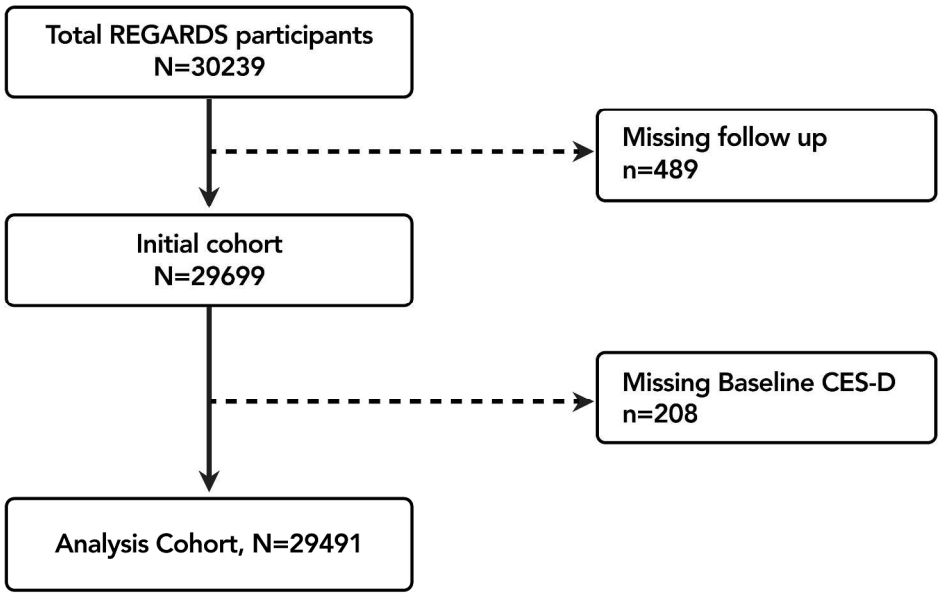



Figure 1. Consort Diagram

279x215mm (300 x 300 DPI)

**Supplementary Material**

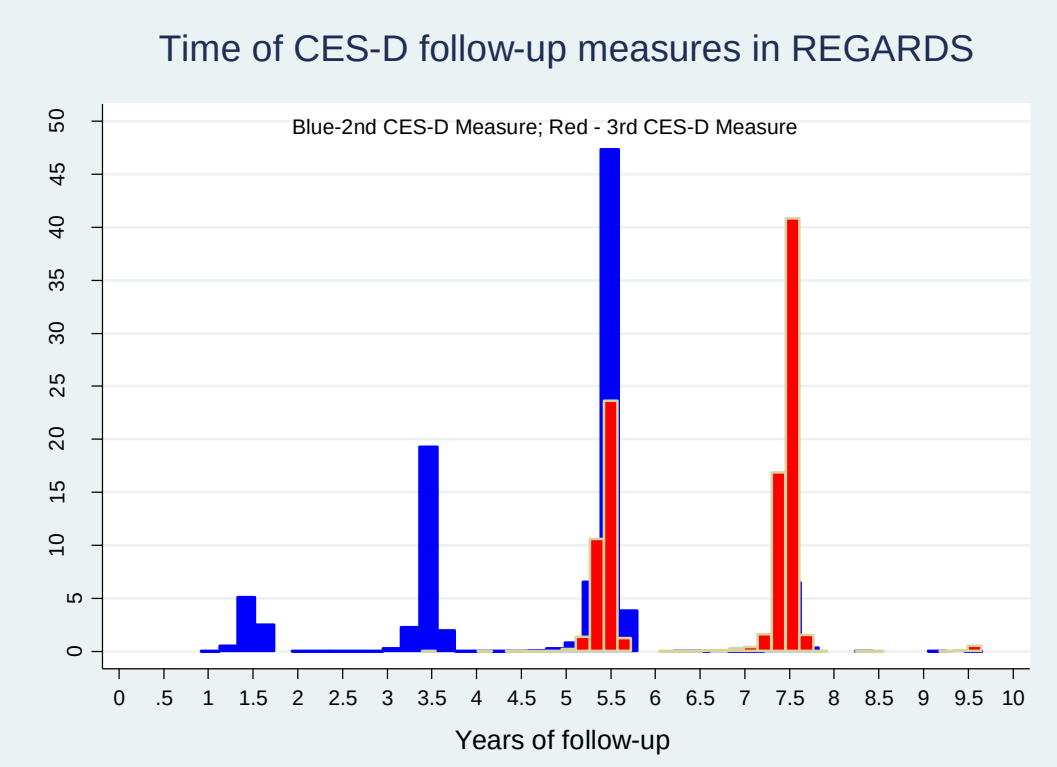
**eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).**

| Self-reported general health | Baseline | | | Second CES-D | | | Third CES-D | | |
|---|---|---|---|---|---|---|---|---|---|
| | CES-D<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n | CESD<4, n, % | CES-D≥4, n, % | Total, n |
| **Excellent** | 4515<br>95.9 % | 195<br>4.1% | 4710 | 3444<br>94.7% | 194<br>5.3% | 3638 | 2109<br>94.6% | 120<br>5.4% | 2229 |
| **Very good** | 8450<br>94.1% | 530<br>5.9% | 8980 | 6332<br>93.0% | 478<br>7.0% | 6810 | 3938<br>92.8% | 305<br>7.2% | 4243 |
| **Good** | 9181<br>89.1% | 1124<br>10.9% | 10305 | 6363<br>88.6% | 818<br>11.4% | 7181 | 3717<br>88.9% | 464<br>11.1% | 4181 |
| **Fair** | 3424<br>77.8 % | 975<br>22.2 % | 4399 | 2185<br>79.7% | 556<br>20.3% | 2741 | 1236<br>82.0% | 271<br>18.0% | 1507 |
| **Poor** | 614<br>59.2% | 424<br>40.9% | 1038 | 322<br>61.2% | 204<br>38.8% | 526 | 177<br>65.3% | 94<br>34.7% | 271 |
| | | | 29432 | | | 20896 | | | 12431 |
| | **Frequency Missing = 59** | | | **Frequency Missing = 8595** | | | **Frequency Missing = 17060** | | |

**eTable 2. Reasons for non-cardiovascular disease death in the REGARDS study**

| | Overall | | Self-reported general health as **"excellent or very good"** n=13,711 | | Self-reported general health as **"poor, fair or good"** n=15,780 | |
|---|---|---|---|---|---|---|
| *Causes of Death* | n | Percent | Frequency | Percent | Frequency | Percent |
| Cancer | 1226 | 44.3 | 474 | 54.0 | 747 | 39.7 |
| Accidents/Injury/Suicide/Homicide | 164 | 5.9 | 52 | 5.9 | 111 | 5.9 |
| Suicide | 3 | 0.1 | 2 | 0.2 | 1 | 0.05 |
| Liver disease | 56 | 2.0 | 14 | 1.6 | 42 | 2.2 |
| Infection | 498 | 18.0 | 132 | 15.0 | 365 | 19.4 |
| ESRD | 119 | 4.3 | 23 | 2.6 | 95 | 5.1 |
| Dementia | 187 | 6.8 | 74 | 8.4 | 112 | 6.0 |
| COPD | 247 | 8.9 | 43 | 4.9 | 204 | 10.9 |
| Pulmonary Embolism | 38 | 1.34 | 11 | 1.3 | 27 | 1.4 |
| Other | 232 | 8.4 | 55 | 6.3 | 177 | 9.4 |
| | Frequency Missing = 263 | | | | Frequency Missing = 272 | |

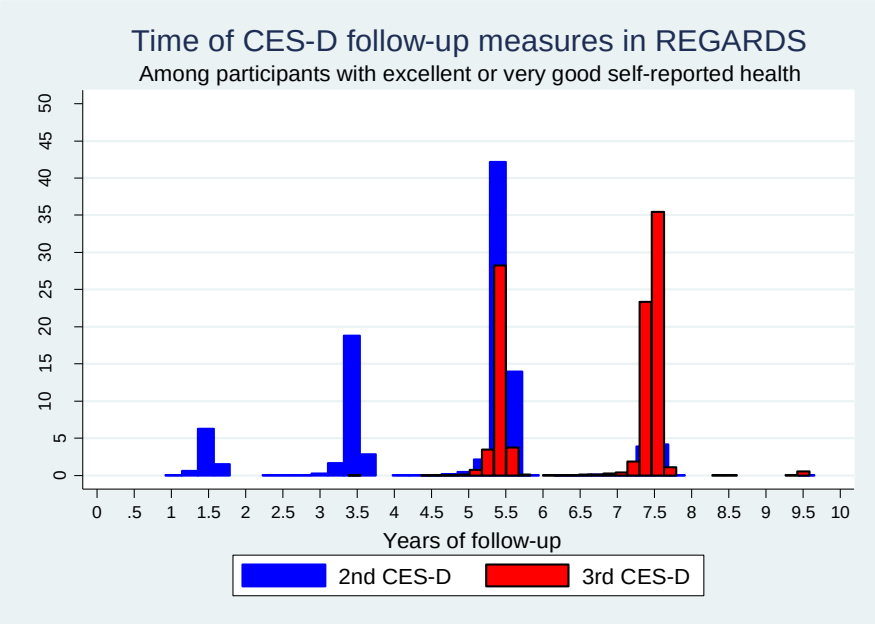
**eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.**

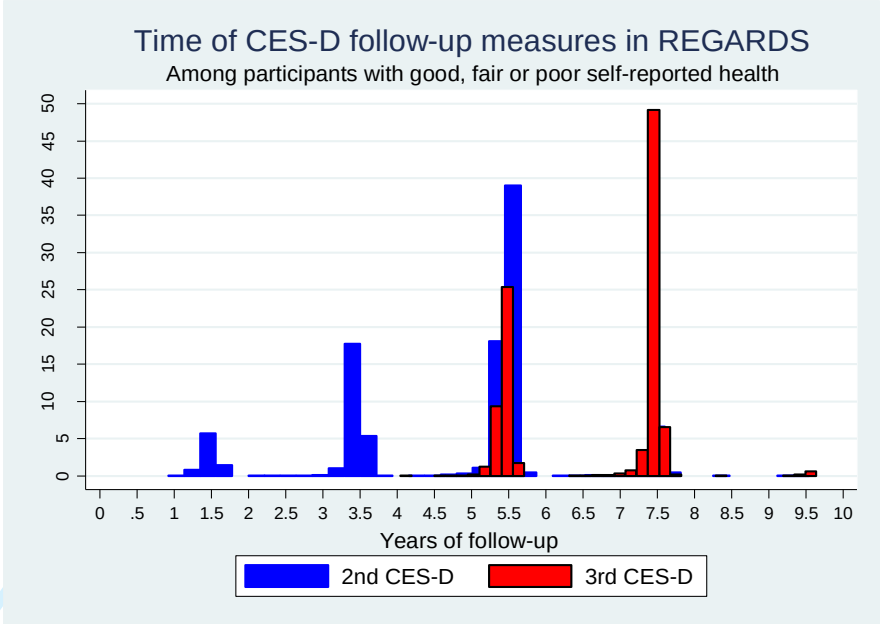



*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| | Time since preceding measurement (baseline or second follow-up), years | | | | |
|---|---|---|---|---|---|
| | Participants, n | Mean | SD | Minimum | Maximum |
| Second CES-D | 20934 | 4.8 | 1.5 | 0.9 | 9.7 |
| Third CES-D | 12451 | 2.1 | 0.4 | 1.0 | 4.2 |

**eFigure 2. Timing of CES-D follow up measures in REGARDS by self reported health at baseline.**




*"Percent" is a proportion of participants reporting CES-D scores at certain times, of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

| Self-reported general health as "excellent or very good" | | | | | | Self-reported general health as "poor, fair or good" | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | | | Time since preceding CES-D measurement (baseline or second follow-up), years | | | |
| | N | Mean | SD | Minimum | Maximum | N | Mean | SD | Minimum | Maximum |
| Second CES-D | 10448 | 4.8 | 1.5 | 0.9 | 9.7 | 10448 | 4.8 | 1.5 | 0.9 | 9.5 |
| Third CES-D | 6472 | 2.1 | 0.4 | 1.7 | 4.2 | 5959 | 2.1 | 0.5 | 1.0 | 4.2 |

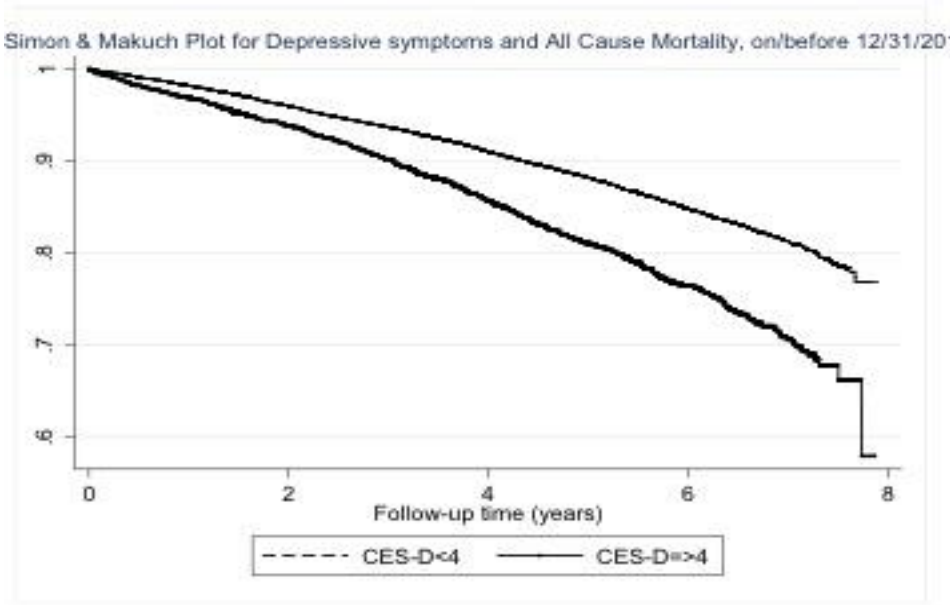
**eTable 3. Baseline characteristics of REGARDS participants who had all 3 CES-D measures vs. those with 1 or 2 CES-D measures**

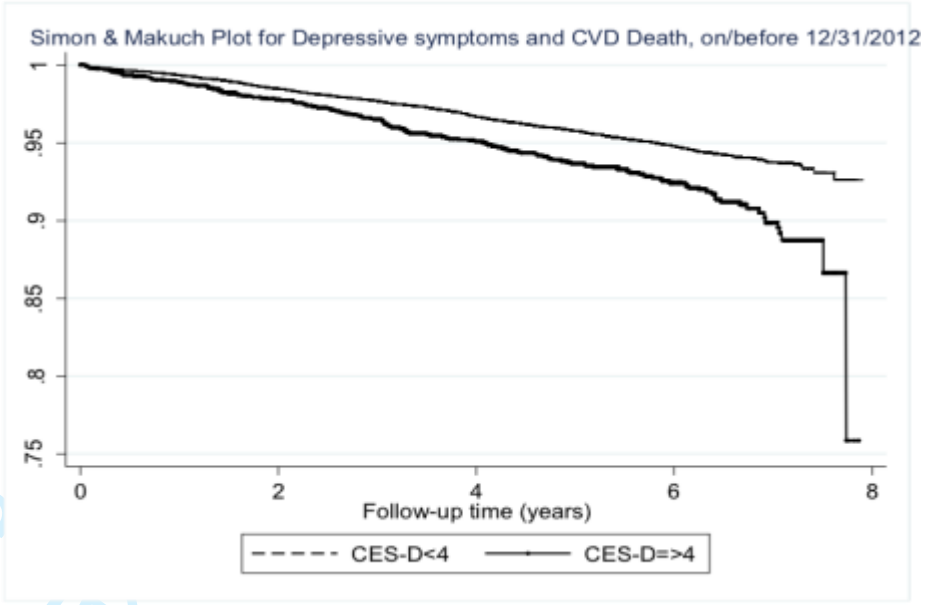
| Characteristics | 1 or 2 CES-D measures (n=17,040) | All 3 CES-D measures (n=12, 451) | *p* value |
|---|---|---|---|
| ***Socio-demographics*** | | | |
| Age, *M* (SD) | 65.0 +- 10.0 | 64.7 +- 8.5 | 0.0069 |
| Female, n (%) | 9300 (54.6) | 6945 (55.8) | 0.04 |
| African American, n (%) | 7709 (45.2) | 4420 (35.5) | <.001 |
| Less than high school education, n (%) | 2583 (15.2) | 1113 (8.9) | <.001 |
| Annual Household Income, n (%) | | | <.001 |
| Less than $20,000 | 3549 (20.8) | 1773 (14.2) | |
| No Health Insurance, n (%) | 1290 (7.6) | 636 (5.1) | <.001 |
| Region, n (%) | | | <.001 |
| Stroke belt | 5806 (34.1) | 4387 (35.2) | |
| Stroke buckle | 3887 (22.8) | 2301 (18.5) | |
| Non-stroke belt or buckle | 7347 (43.1) | 5763 (46.3) | |
| ***General health and medical conditions*** | | | |
| Self-reported general health, n (%) | | | <.001 |
| Poor, fair, good | 9783 (57.5) | 5959 (47.9) | |
| Excellent, very good | 7218 (42.5) | 6472 (52.1) | |
| Cardiovascular disease (CHD, stroke, PAD, AA), n (%) | 4379 (25.7) | 2446 (19.6) | <.001 |
| Diabetes, n (%) | 4083 (25.0) | 2169 (18.0) | <.001 |
| COPD, n (%) | 1612 (9.5) | 1098 (8.8) | 0.05 |
| Physical component score on SF-12 scale, *M* (SD) | 45.5 +- 11.0 | 47.6 +- 9.9 | <.001 |
| ***Physiological risk factors*** | | | |
| Body Mass Index, kg/m$^2$, *M* (SD) | 29.4 +- 6.3 | 29.2 +- 6.0 | 0.0024 |
| Systolic Blood Pressure, mmHg, *M* (SD) | 128.0 +- 17.2 | 127.0 +- 15.9 | <.001 |
| Total Cholesterol, mg/dL, *M* (SD) | 192.2 +- 41.0 | 191.9 +- 39.0 | 0.5732 |
| High-Density Lipoprotein, mg/dL, *M* (SD) | 51.4 +- 16.1 | 52.4 +- 16.3 | <.001 |
| QT Interval, corrected for heart rate, ms, M (SD) | 408.4 +- 24.2 | 406.3 +- 22.7 | <.001 |
| High-Sensitivity C-Reactive Protein, mg/L, median, IQR | 2.3[1.0-5.4] | 2.1[0.9-4.7] | <.001 |

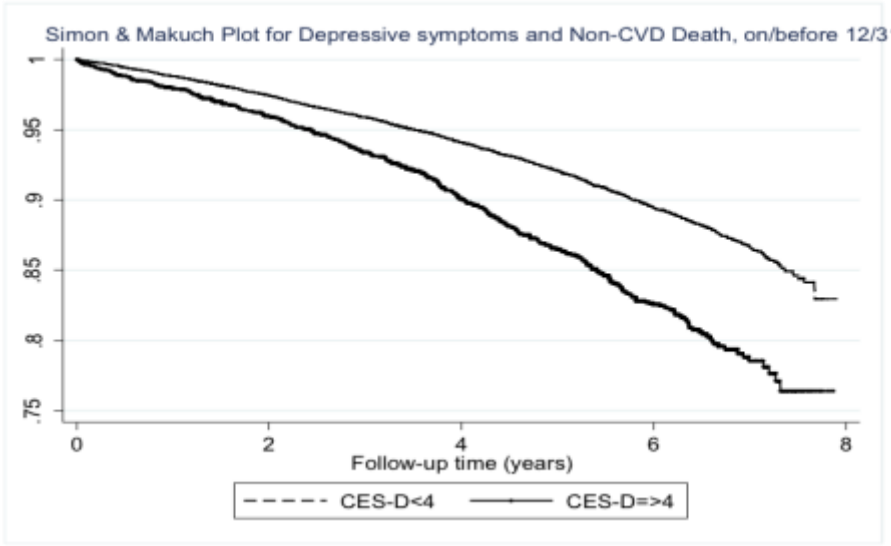
| | | | |
|---|---|---|---|
| Albumin to Creatinine Ratio, mg/g, median, IQR | 7.9[4.8-18.7] | 6.9[4.5-13.5] | <.001 |
| ***Medications*** | | | |
| Antihypertensive medication use, n (%) | 9079 (53.9) | 6118 (49.7) | <.001 |
| Statin use, n (%) | 5344 (31.4) | 3951 (31.8) | 0.53 |
| Aspirin use, n (%) | 7297 (42.8) | 5493 (44.1) | 0.03 |
| Antidepressant use, n (%) | 2440 (14.4) | 1646 (13.2) | 0.006 |
| ***Behavioral risk factors*** | | | |
| Self-reported smoking, pack years, *M* (SD) | 14.5 +- 24.4 | 12.2 +- 21.0 | <.001 |
| Current Smoking, n(%) | 2786 (16.4) | 1477 (11.9) | <.001 |
| Alcohol use, n (%) | | | <.001 |
| Heavy | 652 (3.9) | 520 (4.2) | |
| Moderate | 5180 (31.1) | 4446 (36.3) | |
| None | 10822 (65.0) | 7294 (59.5) | |
| Physical inactivity, n (%) | 6150 (36.7) | 3854 (31.3) | <.001 |
| Medication non-adherence, n (%) | 4548 (29.6) | 3411 (29.9) | 0.59 |
| Impaired cognitive status (Cognitive score ≤ 4) | 1300 (9.4) | 588 (5.9) | <.001 |
| Elevated perceived stress (PSS≥5) | 5437 (31.9) | 3154 (25.3) | <.001 |

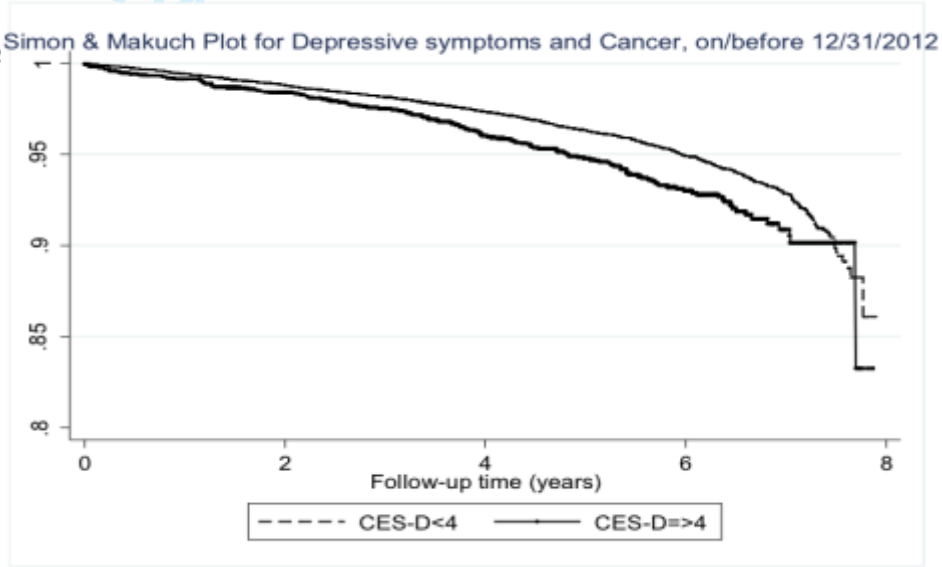
*p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.
Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.
Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or insulin use. CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

**eFigure 3. Simon and Makuch plots of time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.**



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No/Page # | Recommendation |
|---|---|---|
| **Title and abstract** | 1 (page 1-3) | (*a*) Indicate the study's design with a commonly used term in the title or the **abstract** |
| | (Page 2-3) | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 (Page 4) | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 (pages 4-5) | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 (Page 5 and 6) | Present key elements of study design early in the paper |
| Setting | 5 (page 5-10), | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 (page 5-6, 8-9) | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| | n/a | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 (page 6-8) | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8 (pages 6-9) | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one |

| | | |
|---|---|---|
| | | group |
| Bias | 9 (page 8-10) | Describe any efforts to address potential sources of bias |
| Study size | 10 (page 10) | Explain how the study size was arrived at |
| Quantitative variables | 11 (page 6-10) | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 (page 8-10) | (*a*) Describe all statistical methods, including those used to control for confounding |
| | Pages 9 | (*b*) Describe any methods used to examine subgroups and interactions |
| | Page 10 | (*c*) Explain how missing data were addressed |
| | Page 9 | (*d*) If applicable, explain how loss to follow-up was addressed |
| | Page 9-10 | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13 (page 10) | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | Page 10 | (b) Give reasons for non-participation at each stage |
| | Figure 1 | (c) Consider use of a flow diagram |
| Descriptive data | 14 (page 10-11) | (a) Give characteristics of study participants (eg demographic, clinical, social) cand information on exposures and potential confounders |
| | Page 10 | (b) Indicate number of participants with missing data for each variable of interest |
| | Pages 12 | (c) Summarise follow-up time (eg, average and total amount) |

| | | |
|---|---|---|
| Outcome data | 15 (page 11) | Report numbers of outcome events or summary measures over time |
| Main results | 16 (pages 11-12) | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | Page 7-8, 23-27 | (*b*) Report category boundaries when continuous variables were categorized |
| | n/a | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 (pages 12) | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 (page 12) | Summarise key results with reference to study objectives |
| Limitations | 19 (pages 14-15) | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 (page 12-13) | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 (page 14) | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 (page 20) | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present |

| | | |
|---|---|---|
| | | article is based |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.