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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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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 mortality⁹ 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

1 reported hospitalizations or physician visits. Deaths were detected by report of next-of-kin or
2 through online services (e.g., Social Security Death Index) or the National Death Index.¹¹ Death
3 certificates, medical records, and autopsy reports were obtained to adjudicate cause of death and
4 CVD outcomes.
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10 11 12 *Depressive symptoms*

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14 The primary predictor was baseline depressive symptoms. The 4-item Center for Epidemiologic
15 Studies Depression (CES-D) scale was used to assess the presence of depressive symptoms. This
16 scale asks participants to rate the number of days over the last week in which they had: 1) felt
17 depressed; 2) felt lonely; 3) had crying spells; and 4) felt sad. Response options included <1 day,
18 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
19 in the total sample was 0.80. Elevated depressive symptoms were defined as a summed score of
20 ≥ 4 .¹² The reliability and validity of the CES-D 4 is similar to the original 20-item instrument.¹³
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33 *Covariates*

34 Demographic data included self-reported age, gender, race (black or white), education (less than
35 high school, high school graduate, some college, and college graduate and above), annual
36 income (less than \$20,000, \$20,000-\$34,999, \$35,000-\$74,999, \$75,000 and above), insurance
37 status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk
38 factors included (1) diabetes defined as fasting blood glucose ≥ 126 or random glucose > 200
39 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on
40 the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index
41 (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR)
42 (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total
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1 cholesterol, (7) history of CVD: coronary heart disease (self report history of myocardial
2 infarction or coronary revascularization procedure or evidence of myocardial infarction on the
3 study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8)
4 cognitive impairment on the 6-item screener of global cognitive function^{14,15} (9) chronic lung
5 disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled
6 corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium,
7 cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin,
8 antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake
9 inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors
10 included (1) self-reported pack-years of cigarette smoking; (2) physical activity (“How many
11 times per week do you engage in intense physical activity, enough to work up a sweat?” with
12 response options of “none”, “1-3 times per week” and “4 or more times per week”); (3) alcohol
13 use (“How many alcoholic beverages do you drink?": none, moderate [1 drink per day for
14 women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2
15 drinks per day for men]);¹¹ (4) medication non-adherence assessed with the 4-item Morisky
16 Medication Adherence Scale (≥ 1).¹⁶ Potential physiologic risk factors included high-sensitivity
17 C-reactive protein, self-reported health status based on the physical component of the 12-item
18 Short-Form Health Survey (SF 12),¹⁷ and perceived stress, measured by the 4-item version of the
19 Perceived Stress Scale (score of ≥ 5 vs. <5).¹⁸

20 *Statistical Analyses*

21 Baseline characteristics of participants with and without elevated depressive symptoms at
22 baseline were compared using chi-square tests (for categorical variables), Student t tests (for
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1 continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous
2 measures).
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8 Cox proportional hazard regression models were constructed to separately analyze the
9 association between time varying depressive symptoms (CES-D \geq 4) and mortality from cancer
10 (from all body sites, a subset of nonCVD death), CVD death, nonCVD death and all-cause. The
11 end date of follow-up for this analysis was December 31, 2012. Depressive symptoms were
12 measured on the CES-D scale: 1) at baseline (initial telephone call) 2) on average five years after
13 baseline measurement, and 3) on average two years after the second measurement. In the
14 analyses, we considered depressive symptoms (CES-D \geq 4 vs. <4) as a time-varying exposure,
15 with updates of exposure at 5-year and 7-year follow-up. Therefore each participant contributed
16 up to 3 measures of CES-D (\geq 4 vs. <4) over the follow-up. Follow-up time for each participant
17 was calculated from the date of the in-home visit to the date of the earliest of: death, last
18 telephone follow-up, end of follow-up or next CES-D. CES-D scores measured after the end of
19 follow-up were not eligible for inclusion in the time-varying analysis. We additionally
20 graphically plotted unadjusted cumulative incidence of mortality endpoints over follow-up for
21 participants with elevated vs. nonelevated time-varying depressive symptoms using Kaplan-
22 Meier curves.
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44 Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were
45 estimated for those with vs. without elevated depressive symptoms. Adjusted modeling
46 proceeded in stages, starting with demographic (Model 1) and traditional CVDrisk factors
47 (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential
48 explanatory (Model 4) factors. We also conducted a formal test for interaction between
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1 depressive symptoms and self-reported health (defined as excellent or very good vs. good, fair or
2 poor health) in the fully-adjusted models. As such, all analyses were conducted overall as well as
3 stratified by baseline self-reported health.
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10 *Sensitivity Analyses*

11 Sensitivity analyses constructed in parallel to the main analyses examined association of baseline
12 CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard
13 regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-
14 up time for each participant was calculated from the date of the in-home visit to the date of the
15 earliest of: death, last telephone follow-up, or end of follow-up.
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26 Missing data in covariates were imputed using chained equations and derived by bootstrapping
27 across the 5 imputed datasets. Analyses were conducted using SAS software version 9.4 (SAS
28 Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).
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34 **Results**

35 *Participant Characteristics*

36 Overall, 1.6% were lost to follow up and 0.7% were missing baseline depressive symptoms,
37 leaving 29,491 eligible participants (**Figure 1**) of whom 3,254 (11.0%) had elevated depressive
38 symptoms at baseline (CES-D \geq 4). The average age was 64.9 (9.4) years; 55.1% were female and
39 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease and 23.1% CVD. Nearly 33%
40 of individuals were physically inactive, 29.2% non-adherent to their medication regimen and
41 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be
42 poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of
43 whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless
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1 of health status, participants with elevated (vs. non-elevated) depressive symptoms were more
2 likely to be female, African-American, low income, have more chronic diseases, low physical
3 health, and more behavioral risk factors (**Table 1A-B**).

4 *Mortality*

5 A total of 4,581 (15.5%) participants died during the follow up period ending in 2012. Of these,
6 1,551 (33.9%) were attributed to CVD and 3,030 (66.1%) to nonCVD disease death. Of nonCVD
7 deaths, 1,226 (44.3%) were due to cancer death (eTable 2). Overall, there were only 3 cases of
8 mortality due to suicide.

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10 For the time-varying analyses, depressive symptoms were measured at baseline and on average
11 4.8 years (SD = 1.5) years following the baseline measurement, the third measurement occurring
12 on average 2.1 (SD = 0.4) years after the second measurement (eFigure 1). The mean follow-up
13 time of the second and third measurement of CES-D measures did not differ by self-reported
14 health (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and
15 36.8% had elevated depressive symptoms at the second and third measures, respectively (eTable
16 3). Time-varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29,
17 95% CI 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching
18 significance for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 95% CI
19 0.98-1.32), even after adjusting for demographic, clinical, behavioral physiologic factors and
20 time-varying non-fatal CVD events (**Table 2, Figure 2**). The results appeared to be particularly
21 robust amongst those with excellent or very good self-reported general health (**Table 2**): all-
22 cause (aHR=1.48, 95%CI 1.27-1.78), CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54,
23 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
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1 depressive symptoms x health status interaction term were 0.005 (all-cause mortality), 0.06
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3 (CVD death), 0.03 (nonCVD death), and 0.20 (cancer death).
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8 *Sensitivity Analyses:*

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10 The mean follow-up time was 6.5 (SD = 2.3) years. Baseline depressive symptoms were
11 significantly associated with all-cause mortality (aHR 1.18, 95%CI 1.07-1.29) and nonCVD
12 death (aHR 1.21, 95%CI 1.08-1.36) and approached significance for CVD death (aHR 1.10,
13 95%CI 0.94-1.29) and cancer death (aHR 1.12, 95%CI 0.93-1.36), even in the exploratory
14 models (Model 3) (**Table 3**). The results appeared to be particularly robust amongst those with
15 excellent or very good health: cancer death (aHR 1.49, 95%CI 1.03-2.13), CVD death (aHR
16 1.63, 95%CI 1.16-2.30), nonCVD death (aHR 1.48, 95%CI 1.15-1.89) and all-cause mortality
17 (aHR 1.53, 95% CI 1.25-1.88). In Model 4, the p values for depressive symptoms x health status
18 interaction term was 0.003 (all cause mortality), 0.01 (CVD death), 0.06 (nonCVD death), and
19 0.07 (cancer death).
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35 **Discussion**

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37 To our knowledge, this is the largest study to date to examine the timing of the relationship
38 between depressive symptoms and all-cause and cause-specific mortality in non-institutionalized
39 middle to older aged adults. In this diverse cohort with an average follow up of 6.5 years, we
40 found that time-varying depressive symptoms significantly increased the risk of nonCVD and
41 all-cause mortality in fully adjusted models. In fully adjusted models, depressive symptoms
42 increased the risk of cause-specific and all-cause mortality by 36% to 54% in those with a very
43 good/excellent state of health.
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1 Given that depression is a relapsing/remitting disease,¹⁹ this study markedly adds to the literature
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3 by demonstrating a short-term relationship between elevated depressive symptoms and mortality,
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5 including cancer death. Major study strengths include the use 3 measurements of depressive
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7 symptoms and stringent physician adjudication outcomes. We are also the first to report a
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9 significant moderating effect of self-reported health on the relationship between depressive
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11 symptoms and mortality. Many have long asked whether depression leads to mortality or
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13 whether individuals are depressed because they are dying. Our findings in those who report
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15 excellent states of health is striking and supports the former argument. It may also be that the
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17 effect of chronic illness burden on mortality in those with poor health overwhelms the effects of
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19 depressive symptoms. Those with excellent health may also fail to recognize/present for
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21 depression. In fact, our depressed excellent health individuals were less likely to be on an
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23 antidepressant.
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31 The results have a coherence consistent with prior studies that suggest that depressive symptoms
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33 don't solely predict suicide and CVD mortality, but also predict other causes such as cancer
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35 death.²⁰ While prior literature suggests that depressive symptoms confer mortality in those with
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37 active cancer,²¹ our study excluded active cancer diagnoses confirming a possible relationship to
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39 incident cancer mortality. Prior studies have also been limited by inadequate covariate control,
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41 and our results for cancer persisted after adjusting for numerous traditional and behavioral risk
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43 factors, such as smoking, and approached significance even in models that included physiologic
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45 factors. We were however, unable to adjust for time varying covariates. It may be that changes in
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47 physical health (e.g., number of debilitating conditions) may mediate the relationship between
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49 depressive symptoms and mortality.²²
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1 This study also supports comprehensive evidence-based depression care management in primary
2 care practices, which have been shown to lower mortality risk.²³ Nonetheless, depression
3 treatment remains suboptimal in the general population,²⁴ despite decades of efforts. We too
4 demonstrate that over time, nearly 40% of patients with elevated depressive symptoms at
5 baseline were still depressed on average 5 and 7 years later. Given the potentially short-term
6 relationship between depressive symptoms and mortality, our results suggest the importance of
7 timely and effective treatment of depressive symptoms to prevent adverse consequences of
8 depressive symptoms on physical health and mortality.
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10 Limitations of our study include the regional specificity, limiting generalizability, and use of the
11 short form of the CES-D, which measures only emotional and not somatic symptoms of
12 depression. However, CES-D scales are one of the most widely used scales in baseline
13 depression to outcome studies (the results of which do not appear to differ according to clinical
14 diagnosis vs. use of continuous scales) and have good sensitivity and specificity.^{7,12,13} We may
15 also have been underpowered to examine CVD and cancer mortality, though the directionality of
16 the estimates remained consistent. The exclusion of active/treated cancer participants, unlike
17 prior studies, may also have contributed to lack of power. We were unable to adjust for family
18 history of malignancy or CVD or definitively exclude subclinical disease.
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20 Give our results of a relationship between time varying depressive symptoms and mortality,
21 further research is warranted to test the long-term efficacy of and adherence to depression
22 treatment and to explore preventive approaches to decreasing premature mortality risk.²⁵ To our
23 knowledge, the finding of a relationship between depressive symptoms and mortality in those
24 with excellent or very good self-reported health is a new finding and should be further studied.
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Study concept and design: Moise, Khodneva, Safford; *Acquisition of data:* Khodneva, Safford;

Analysis and interpretation of data: Khodneva, Moise, Richman, Kronish, Shaffer, Safford;

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29 **Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent
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39 **Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are
40 available if deemed important by reviewers with open access by Monika Safford at Weill
41 Cornell, Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at
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43 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 link 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)	<i>p</i>
<i>Socio-demographics</i>				
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>				
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, <i>M</i> (SD)	46.4 (10.6)	47.1 (10.2)	40.7 (12.2)	<.001
<i>Physiological risk factors</i>				
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.3 (6.2)	29.2 (6.1)	30.6 (7.1)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	127.6 (16.7)	127.5 (16.5)	128.7 (18.1)	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.1 (40.1)	191.7 (39.8)	194.6 (43.0)	<0.001
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.8 (16.2)	51.7 (16.2)	52.5 (16.3)	0.02
QT Interval, corrected for heart rate, ms, <i>M</i> (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
<i>Medications</i>				
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

1	Aspirin use, n (%)	12790 (43.4)	11376 (43.4)	1414 (43.5)	0.91
2					
3	Antidepressant use, n (%)	4086 (13.9)	3164 (12.1)	922 (28.4)	<.001
4	Behavioral risk factors				
5	Self-reported smoking, pack years, <i>M</i>				
6	(SD)	13.5 (23.1)	13.3 (22.8)	15.5 (24.9)	<.001
7					
8	Current Smoking, n(%)	4263(14.5)	3463(13.3)	800(24.7)	<.001
9					
10	Alcohol use, n (%)				<.001
11	Heavy	1172 (4.1)	1043 (4.0)	129 (4.1)	
12	Moderate	9626 (33.3)	8786 (34.1)	840 (26.6)	
13	None	18116 (62.7)	15925 (61.8)	2191 (69.3)	
14	Physical inactivity, n (%)	10004 (34.4)	8500 (32.9)	1504 (46.9)	<0.001
15					
16	Medication non-adherence, n (%)	7959 (29.7)	6820 (28.7)	1139 (37.8)	<.001
17					
18	Impaired cognitive status	1888 (7.9)			
19	(Cognitive score \leq 4)		1542 (7.3)	346 (12.6)	<.001
20	Elevated perceived stress (PSS \geq 5)	8591 (29.1)	6283 (23.9)	2308 (70.9)	<.001

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

Characteristics	Self-reported general health as "excellent or very good"			Self-reported general health as "poor, fair or good"		
	CES-D < 4 (n=12965)	CES-D ≥4 (n=725)	<i>p</i>	CES-D < 4 (n=13219)	CES-D ≥4 (n=2523)	<i>p</i>
Socio-demographics						
Age, <i>M</i> (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, <i>M</i> (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 , <i>M</i> (SD)	27.8 (5.1)	28.4 (5.7)	0.006	30.5 (6.6)	31.2 (7.3)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (SD)	405.6 (22.6)	407.2 (23.5)	0.06	408.7 (24.3)	410.8 (24.2)	<.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

1	Antihypertensive medication use, n (%)						
2	Statin use, n (%)	3407 (26.4)	176 (24.4)	0.24	4822 (36.5)	870 (34.6)	0.06
3	Aspirin use, n (%)	5254 (40.5)	273 (37.7)	0.13	6100 (46.2)	1140 (45.2)	0.36
4							<.001
5	Antidepressant use, n (%)	1224 (9.5)	144 (19.9)	<.001	1933 (14.6)	774 (30.8)	
6	Behavioral risk factors						
7	Self-reported smoking, pack years, <i>M</i>						
8	(SD)	11.2 (20.5)	12.1 (21.6)	0.24	15.3 (24.7)	16.5 (25.6)	0.03
9							
10	Current Smoking, n(%)	1344 (10.4)	114 (15.8)	<.001	2110 (16.0)	684 (27.2)	<.001
11							
12	Alcohol use, n (%)			0.01			<.001
13	Heavy	634 (5.0)	38 (5.4)		409 (3.2)	91 (3.7)	
14	Moderate	5034 (39.4)	238 (33.8)		3746 (29.0)	600 (24.5)	
15	None	7103 (55.6)	429 (60.9)		8779 (67.9)	1758 (71.8)	
16	Physical inactivity, n (%)	3107 (24.3)	259 (36.0)	<.001	5372 (41.3)	1242 (50.0)	<.001
17							
18	Medication non-adherence, n (%)	2997 (26.2)	211 (33.1)	<.001	3809 (31.0)	926 (39.1)	<.001
19							
20	Impaired cognitive status			<.001			<.001
21	(Cognitive score \leq 4)	587 (5.6)	61 (10.1)		947 (8.9)	285 (13.3)	
22	Elevated perceived stress (PSS \geq 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
<i>HR (95%CI) for time-variant categorical CES-D (Score =>4 v. <4)</i>			
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 <i>socio-demographics</i> (age, gender, region, income, health insurance, education) ^b Model 2 adds to model 1 <i>medical conditions, physiological factors and medication use</i> (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)			

^cModel 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).

^dModel 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)

^eModel 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.

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Table 3. Association of baseline elevated depressive symptoms (CES-D \geq 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

^aModel 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
^bModel 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)
^cModel 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
^dModel 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.

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Figure Legend

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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.

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

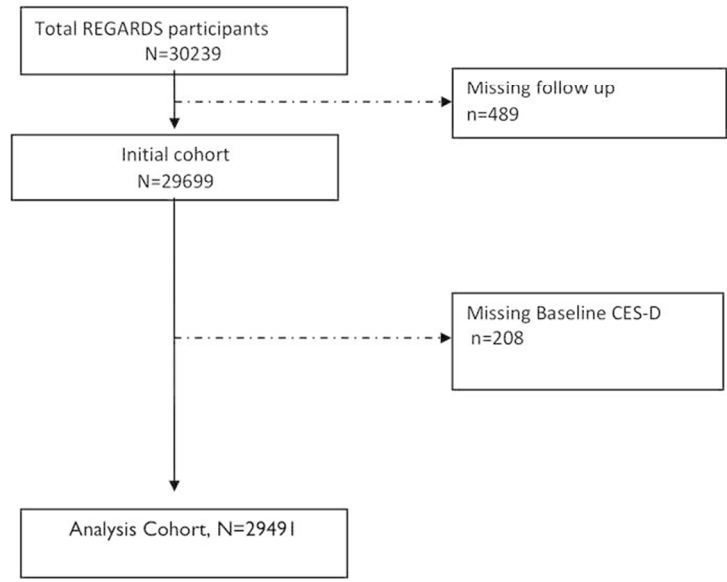


Figure 1. Cohort Flow Diagram: Exclusion cascade of depressive symptoms to mortality endpoints analysis.

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.

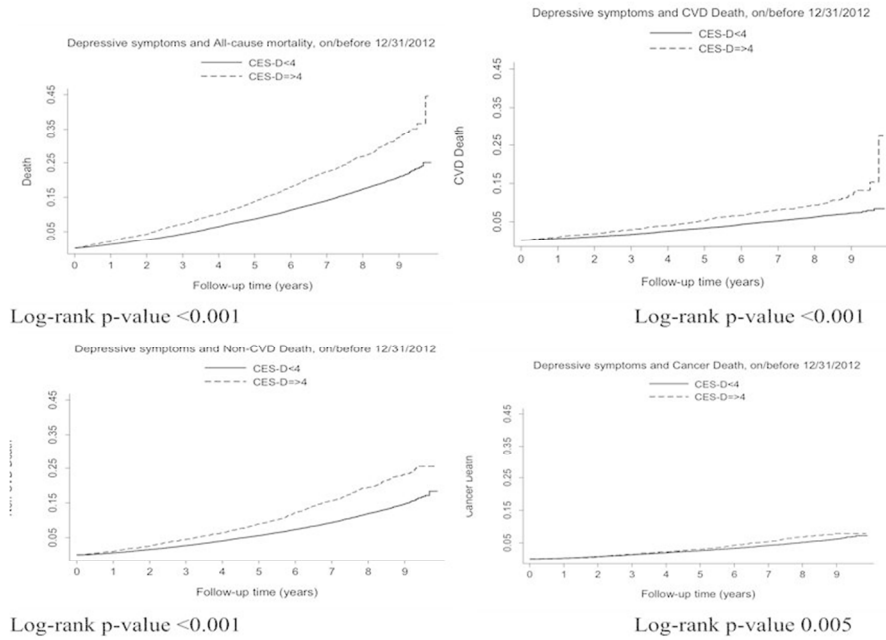
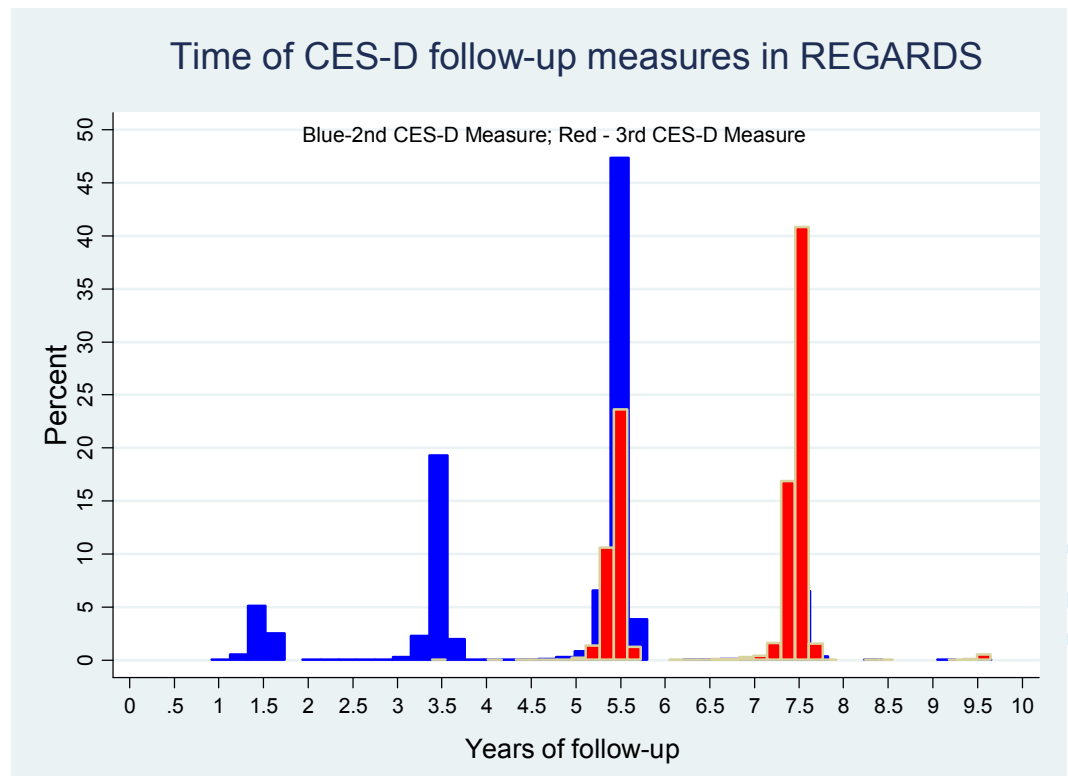


Figure 2. Kaplan Meier Curves of Time-varying depressive symptoms and all-cause mortality, cardiovascular disease death, noncardiovascular disease death and cancer death.

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Supplementary Material

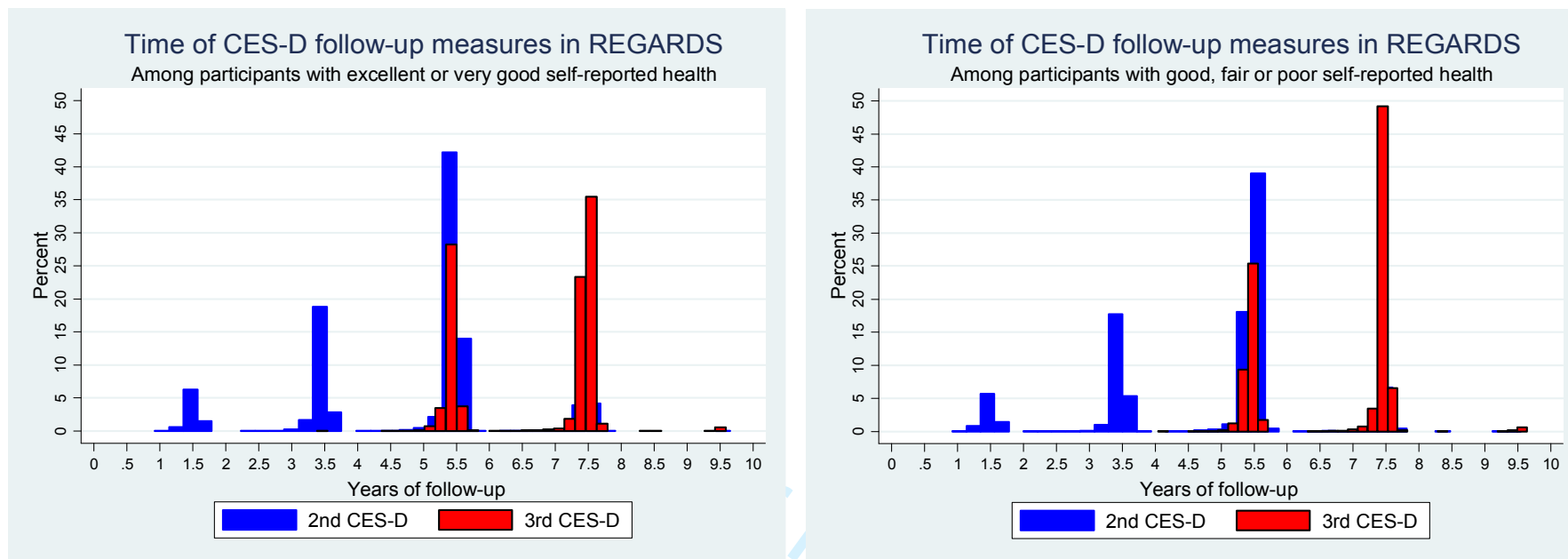
eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.



***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).

	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 95.9 %	195 4.1%	4710	3444 94.7%	194 5.3%	3638	2109 94.6%	120 5.4%	2229
Very good	8450 94.1%	530 5.9%	8980	6332 93.0%	478 7.0%	6810	3938 92.8%	305 7.2%	4243
Good	9181 89.1%	1124 10.9%	10305	6363 88.6%	818 11.4%	7181	3717 88.9%	464 11.1%	4181
Fair	3424 77.8 %	975 22.2 %	4399	2185 79.7%	556 20.3%	2741	1236 82.0%	271 18.0%	1507
Poor	614 59.2%	424 40.9%	1038	322 61.2%	204 38.8%	526	177 65.3%	94 34.7%	271
			29432			20896			12431
	Frequency Missing = 59			Frequency Missing = 8595			Frequency Missing = 17060		

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

<i>Causes of Death</i>	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	
	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)	<i>p</i> value
<i>Socio-demographics</i>			
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>			
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, <i>M</i> (SD)	45.5 +- 11.0	47.6 +- 9.9	<.001
<i>Physiological risk factors</i>			
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.4 +- 6.3	29.2 +- 6.0	0.0024
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	128.0 +- 17.2	127.0 +- 15.9	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.2 +- 41.0	191.9 +- 39.0	0.5732
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.4 +- 16.1	52.4 +- 16.3	<.001
QT Interval, corrected for heart rate, ms, <i>M</i> (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				
1	Antihypertensive medication use, n (%)	9079 (53.9)	6118 (49.7)	<.001
2	Statin use, n (%)	5344 (31.4)	3951 (31.8)	0.53
3	Aspirin use, n (%)	7297 (42.8)	5493 (44.1)	0.03
4	Antidepressant use, n (%)	2440 (14.4)	1646 (13.2)	0.006
5				
Behavioral risk factors				
6				
7	Self-reported smoking, pack years, <i>M</i> (SD)	14.5 +- 24.4	12.2 +- 21.0	<.001
8	Current Smoking, n(%)	2786 (16.4)	1477 (11.9)	<.001
9	Alcohol use, n (%)			<.001
10	Heavy	652 (3.9)	520 (4.2)	
11	Moderate	5180 (31.1)	4446 (36.3)	
12	None	10822 (65.0)	7294 (59.5)	
13	Physical inactivity, n (%)	6150 (36.7)	3854 (31.3)	<.001
14	Medication non-adherence, n (%)	4548 (29.6)	3411 (29.9)	0.59
15	Impaired cognitive status (Cognitive score ≤ 4)	1300 (9.4)	588 (5.9)	<.001
16	Elevated perceived stress (PSS≥5)	5437 (31.9)	3154 (25.3)	<.001
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20 *p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale.

21 CVD = cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.

22 Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the

23 noncoastal regions within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined

24 as coastal regions within the states of North Carolina, South Carolina and Georgia.

25 Diabetes defined as fasting blood glucose ≥126 or random glucose >200 mL/dL or oral hypoglycemic or

26 insulin use. CVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic

27 aneurism.

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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 (pages 4-6)	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) and 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
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*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>.

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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

Journal:	<i>BMJ Open</i>
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Complete List of Authors:	Moise, Nathalie; Columbia University Medical Center, Center for Behavioral Cardiovascular Health Khodneva, Yulia; University of Alabama School of Medicine Jannat-Khah, Deanna; NewYork-Presbyterian Hospital/Weill Cornell Medical Center Richman, Joshua; University of Alabama School of Medicine Davidson, Karina; Columbia University Medical Center, Medicine Kronish, Ian M. ; Columbia University Medical Center, Center Behavioral Cardiovascular Health Shaffer, Jonathan; University of Colorado Denver Department of Psychology Safford, Monika; Cornell University Joan and Sanford I Weill Medical College
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	mortality, health status, Depression & mood disorders < PSYCHIATRY

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Manuscripts

1 **An observational study of the differential impact of time-varying depressive symptoms on**
2
3 **all-cause and cause-specific mortality by health status in community dwelling adults: The**
4
5 **REGARDS study**

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7
8 **Running Title:** depressive symptoms and mortality

9
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37 **Journal Subject Codes:** mortality, depression, health status

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42 **Abstract:** 240/300
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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.

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

- 11 • Depression is a relapsing/remitting disease and our study is one of the first to use multiple
12 measurements of depression to demonstrate a time varying relationship between
13 depression and mortality, including cancer mortality, in a large, diverse cohort.
 - 14 • To our knowledge, we are also the first to report a significant moderating effect of self-
15 reported health on the relationship between depressive symptoms and cause-specific
16 mortality, with depression predicting mortality particularly in those with excellent or very
17 good reported health.
 - 18 • Our analyses were limited by the use of the short form of the CES-D scale
 - 19 • The REGARDS cohort is regionally specific, limiting generalizability.
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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 mortality¹² 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

1 (very good or excellent vs. poor, fair or good) to further isolate the association between
2
3 depressive symptoms and excess mortality.
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8 **Methods**

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10 The REGARDS study is a national cohort study of stroke incidence and cognitive decline in
11 black and white community dwelling adults ≥ 45 years living in the United States stratified to
12 reflect specific race-sex-geographic strata.¹⁴ Inclusion and exclusion criteria have been
13 previously described; of note, those with active cancer were excluded from the original study.¹⁴
14
15 Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study.
16
17 Participants were recruited by mail using commercially available lists of U.S. residents, followed
18 by a computer-assisted telephone interview and subsequent home visit at which time individuals
19 were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white
20 adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing
21 baseline depressive symptom measurements (**Figure 1**). The REGARDS study protocol was
22 approved by institutional review boards at participating centers.
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38 *Study Procedures*

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

1 status (yes/no), and stroke region (including the ‘stroke belt’ and ‘stroke buckle’). Clinical risk
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3 factors included (1) diabetes defined as fasting blood glucose ≥ 126 or random glucose >200
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5 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on
6
7 the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index
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9 (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR)
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11 (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total
12
13 cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial
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15 infarction or coronary revascularization procedure or evidence of myocardial infarction on the
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17 study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8)
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19 cognitive impairment on the 6-item screener of global cognitive function^{17,18} (9) chronic lung
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21 disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled
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23 corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium,
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25 cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin,
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27 antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake
28
29 inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors
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31 included (1) self-reported pack-years of cigarette smoking; (2) physical activity (“How many
32
33 times per week do you engage in intense physical activity, enough to work up a sweat?” with
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35 response options of “none”, “1-3 times per week” and “4 or more times per week”); (3) alcohol
36
37 use (“How many alcoholic beverages do you drink?": none, moderate [1 drink per day for
38
39 women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2
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41 drinks per day for men]);¹⁴ (4) medication non-adherence assessed with the 4-item Morisky
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43 Medication Adherence Scale (≥ 1).¹⁹ Potential physiologic risk factors included high-sensitivity
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45 C-reactive protein, self-reported health status based on the physical component of the 12-item
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1 Short-Form Health Survey (SF 12),²⁰ and perceived stress, measured by the 4-item version of the
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3 Perceived Stress Scale (score of ≥ 5 vs. <5).²¹
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8 *Statistical Analyses*

9

10 Baseline characteristics of participants with and without elevated depressive symptoms at
11
12 baseline were compared using chi-square tests (for categorical variables), Student t tests (for
13
14 continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous
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16 measures).
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21 Cox proportional hazard regression models were constructed to separately analyze the
22
23 association between depressive symptoms ($\text{CES-D} \geq 4$) and cancer death (from all body sites, a
24
25 subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of
26
27 follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the
28
29 CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline
30
31 measurement, and 3) on average two years after the second measurement. In the analyses, we
32
33 considered depressive symptoms ($\text{CES-D} \geq 4$ vs. <4) as a time-varying exposure, with updates of
34
35 exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3
36
37 measures of CES-D (≥ 4 vs. <4) with a broken-up follow-up time. Follow-up time for each
38
39 participant was calculated from the date of the in-home visit to the date of the earliest of: death,
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41 last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically
42
43 plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive
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45 symptoms using the Simon-Makuch method,²² a modification of the Kaplan-Meier method. In
46
47 this context, depression status is treated as a binary time-dependent covariate and study cohorts
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49 are continually updated to contribute to either the $\text{CES-D} \geq 4$ or $\text{CES-D} < 4$ groups.
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3 Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were
4
5 estimated for those with vs. without elevated depressive symptoms. Adjusted modeling
6
7 proceeded in stages, starting with demographic (Model 1) and traditional CVD risk factors
8
9 (Model 2) assessed in prior trials. We then added behavioral (Model 3) and other potential
10
11 explanatory (Model 4) factors. We also ran an additional model (Model 5), which considered
12
13 intervening first non-fatal stroke and/or myocardial infarction as a time-dependent covariate in
14
15 CVD death outcomes. All analyses were conducted overall as well as stratified. We also
16
17 conducted a formal test for interaction between depressive symptoms and self-reported health
18
19 (defined as excellent or very good vs. good, fair or poor health) in the fully-adjusted models. As
20
21 such, all analyses were conducted overall as well as stratified by baseline self-reported health. To
22
23 test the proportional hazards assumptions, we performed the chi-squared test for the Schoenfeld
24
25 residuals and all the models resulted in a violation of the proportional hazards assumptions,
26
27 indicating that time-varying covariates were appropriate. The proportionality assumption for time
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29 varying depressive symptoms was tested by assessing the interaction of depressive
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31 symptoms*log of follow-up time and was satisfied for all mortality endpoints.
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37 *Sensitivity Analyses*

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39 Sensitivity analyses constructed in parallel to the main analyses examined association of baseline
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41 CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard
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43 regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-
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45 up time for each participant was calculated from the date of the in-home visit to the date of the
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47 earliest of: death, last telephone follow-up, or end of follow-up.
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1 Missing data in covariates were imputed using chained equations and derived by bootstrapping
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3 across the 5 imputed datasets. Of the 29,491 participants, 2768 (9%) were missing income data,
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5 59 (0.2%) health status, 9 (<0.1%) education, 26 (0.1%) health insurance, 1087 (4%) diabetes, 16
6
7 (0.1%) aspirin use, 70 (0.2%) statin use, 70 (0.2%) antidepressant use, 333 (1%) anti-
8
9 hypertension meds use, 439 (2%) physical activity, 2705 (9%) medication adherence, 213 (0.7%)
10
11 BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912 (3.1%) pack years, 84 (0.3%) SBP, 1394
12
13 (5%) renal function, 381 (1%) QTc, 5681 (19.3%) cognitive status, 4 (<0.1%) stress, 1425 (4%)
14
15 SF-12 and 1881 (6%) CRP. Analyses were conducted using SAS software version 9.4 (SAS
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17 Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).
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23 Results

24 *Participant Characteristics*

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26 Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms,
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28 leaving 29,491 eligible participants (**Figure 1**) of whom 3,254 (11.0%) had elevated depressive
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30 symptoms at baseline (CES-D \geq 4). The average age was 64.9 (9.4) years; 55.1% were female and
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32 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33%
33
34 of individuals were physically inactive, 29.2% non-adherent to their medication regimen and
35
36 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be
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38 poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of
39
40 whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless
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42 of health status, participants with elevated (vs. non-elevated) depressive symptoms were more
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44 likely to be female, African-American, low income, have more chronic diseases, low physical
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46 health, and more behavioral risk factors (**Table 1A-B**).
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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)	<i>p</i>
<i>Socio-demographics</i>				
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>				
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, <i>M</i> (SD)	46.4 (10.6)	47.1 (10.2)	40.7 (12.2)	<.001
<i>Physiological risk factors</i>				
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.3 (6.2)	29.2 (6.1)	30.6 (7.1)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	127.6 (16.7)	127.5 (16.5)	128.7 (18.1)	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.1 (40.1)	191.7 (39.8)	194.6 (43.0)	<0.001
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.8 (16.2)	51.7 (16.2)	52.5 (16.3)	0.02
QT Interval, corrected for heart rate, ms, <i>M</i> (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
<i>Medications</i>				
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

1	Aspirin use, n (%)	12790 (43.4)	11376 (43.4)	1414 (43.5)	0.91
2					
3	Antidepressant use, n (%)	4086 (13.9)	3164 (12.1)	922 (28.4)	<.001
4	Behavioral risk factors				
5	Self-reported smoking, pack years, <i>M</i>				
6	(SD)	13.5 (23.1)	13.3 (22.8)	15.5 (24.9)	<.001
7					
8	Current Smoking, n(%)	4263(14.5)	3463(13.3)	800(24.7)	<.001
9					
10	Alcohol use, n (%)				<.001
11	Heavy	1172 (4.1)	1043 (4.0)	129 (4.1)	
12	Moderate	9626 (33.3)	8786 (34.1)	840 (26.6)	
13	None	18116 (62.7)	15925 (61.8)	2191 (69.3)	
14	Physical inactivity, n (%)	10004 (34.4)	8500 (32.9)	1504 (46.9)	<0.001
15					
16	Medication non-adherence, n (%)	7959 (29.7)	6820 (28.7)	1139 (37.8)	<.001
17					
18	Impaired cognitive status	1888 (7.9)			
19	(Cognitive score ≤ 4)		1542 (7.3)	346 (12.6)	<.001
20	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

^aStroke 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.

^bStroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

^cCVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

^dDiabetes 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

Characteristics	<i>Self-reported general health as "excellent or very good"</i>			<i>Self-reported general health as "poor, fair or good"</i>		
	CES-D < 4 (n=12965)	CES-D ≥4 (n=725)	<i>p</i>	CES-D < 4 (n=13219)	CES-D ≥4 (n=2523)	<i>p</i>
<i>Socio-demographics</i>						
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>						
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, <i>M</i> (SD)	52.0 (6.5)	51.3 (9.1)	0.008	42.0 (10.7)	37.7 (11.3)	<.001
<i>Physiological risk factors</i>						
Body Mass Index, kg/m ² , <i>M</i> (SD)	27.8 (5.1)	28.4 (5.7)	0.006	30.5 (6.6)	31.2 (7.3)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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 (Cognitive score \leq 4)	587 (5.6)	61 (10.1)	<.001	947 (8.9)	285 (13.3)	<.001
Elevated perceived stress (PSS \geq 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

^aStroke 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.

^bStroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

^cCVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

^dDiabetes defined as fasting blood glucose \geq 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, 95% 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 <i>socio-demographics</i> (age, gender, region, income, health insurance, education) ^b Model 2 adds to model 1 <i>medical conditions, physiological factors and medication use</i> (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)			

^cModel 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).

^dModel 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)

^eModel 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 \geq 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

^aModel 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
^bModel 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)
^cModel 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
^dModel 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

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

1 symptoms. Those with excellent health may also fail to recognize/present for depression. In fact,
2 depressed excellent health individuals in our cohort were less likely to be on an antidepressant.
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4 Nonetheless, this finding should be further explored in future studies.
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10 The results have a coherence consistent with prior studies that suggest that depressive symptoms
11 don't solely predict suicide and CVD mortality, but also predict other causes such as cancer death.²⁴
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13 While prior literature suggests that depressive symptoms confer mortality in those with active
14 cancer,²⁵ our study excluded active cancer diagnoses confirming a possible relationship between
15 depressive symptoms and incident cancer mortality. Prior studies have also been limited by
16 inadequate covariate control, and our results for cancer persisted after adjusting for numerous
17 traditional and behavioral risk factors, such as smoking, and approached significance even in
18 models that included physiologic factors. We were, however, unable to adjust for other time-
19 varying covariates. For example, prior research suggests that changes in physical health (e.g.,
20 number of debilitating conditions) over time mediates the relationship between depressive
21 symptoms and mortality.²⁶
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38 This study also supports comprehensive evidence-based depression care management in primary
39 care practices, which have been shown to lower mortality risk.²⁷ Nonetheless, depression treatment
40 remains suboptimal in the general population,²⁸ despite decades of efforts. We too demonstrate that
41 over time, nearly 40% of patients with elevated depressive symptoms at baseline were still
42 depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both
43 time-varying analyses (by virtue of follow-up times being broken up by repeat depression
44 measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend
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1 greater urgency to the importance of timely and effective treatment of depressive symptoms to
2 prevent adverse consequences of depressive symptoms on physical health and mortality.
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6 Limitations of our study include the regional specificity, limiting generalizability, and use of the
7 short form of the CES-D, which measures only emotional and not somatic symptoms of depression.
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9 Schultz (2002) demonstrated variance between studies using scales and interviews,²⁹ and others
10 have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).³⁰
11
12 However, CES-D scales are one of the most widely used scales in clinical practice and in baseline
13 depression to outcome studies and have good sensitivity and specificity.^{9,15,16} We may also have
14 been underpowered to examine CVD and cancer mortality, though the directionality of the
15 estimates remained consistent. The exclusion of active cancer participants as part of the overall
16 REGARDS study criteria, the rationale of which has previously been described,¹⁴ may also have
17 contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically
18 excluded, which is in line with prior depression to mortality studies.^{1,9} Nonetheless, our previously
19 published study, which excluded those with a history of CVD, similarly found a strong relationship
20 between time-varying depressive symptoms and CVD death.³¹
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39 We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we
40 included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5
41 years) was relatively short compared to other studies with even shorter follow-up times between
42 CES-D measures in time-varying analyses, suggesting a short-term effect on mortality. Our results
43 support prior literature suggesting that shorter follow-up time is associated with greater excess
44 mortality.^{9,30} However, we did not formally compare short-term to long-term follow-up nor
45 persistent to fluctuating depressive symptoms.
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1 Given our results of a relationship between time-varying depressive symptoms and mortality,
2 further research is warranted to test the long-term efficacy of and adherence to depression treatment
3 and to explore preventive approaches to decreasing premature mortality risk.³² To our knowledge,
4 the finding of a relationship between depressive symptoms and mortality in those with excellent or
5 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,

1 Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding*: Safford; *Study*
2
3 *supervision*: Safford
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5 **Conflict of Interest:** None
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20 **Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent
21 account of the study being reported; that no important aspects of the study have been omitted; and
22 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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25 **Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are
26 available if deemed important by reviewers with open access by Monika Safford at Weill Cornell,
27 Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of
28 Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised
29 and risk of identification is low.
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Figure Legend

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

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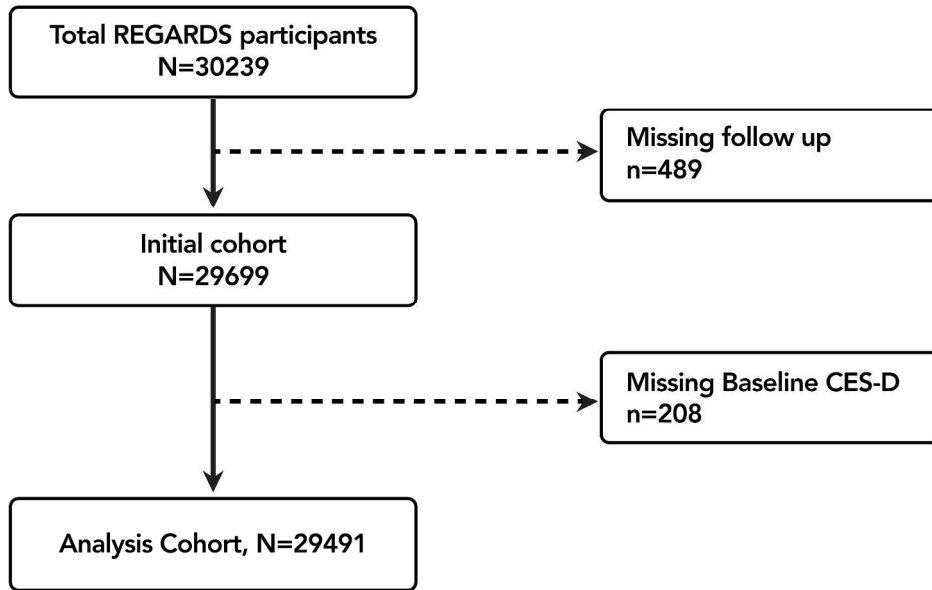


Figure 1. Consort Diagram

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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 95.9 %	195 4.1%	4710	3444 94.7%	194 5.3%	3638	2109 94.6%	120 5.4%	2229
Very good	8450 94.1%	530 5.9%	8980	6332 93.0%	478 7.0%	6810	3938 92.8%	305 7.2%	4243
Good	9181 89.1%	1124 10.9%	10305	6363 88.6%	818 11.4%	7181	3717 88.9%	464 11.1%	4181
Fair	3424 77.8 %	975 22.2 %	4399	2185 79.7%	556 20.3%	2741	1236 82.0%	271 18.0%	1507
Poor	614 59.2%	424 40.9%	1038	322 61.2%	204 38.8%	526	177 65.3%	94 34.7%	271
			29432			20896			12431
	Frequency Missing = 59			Frequency Missing = 8595			Frequency Missing = 17060		

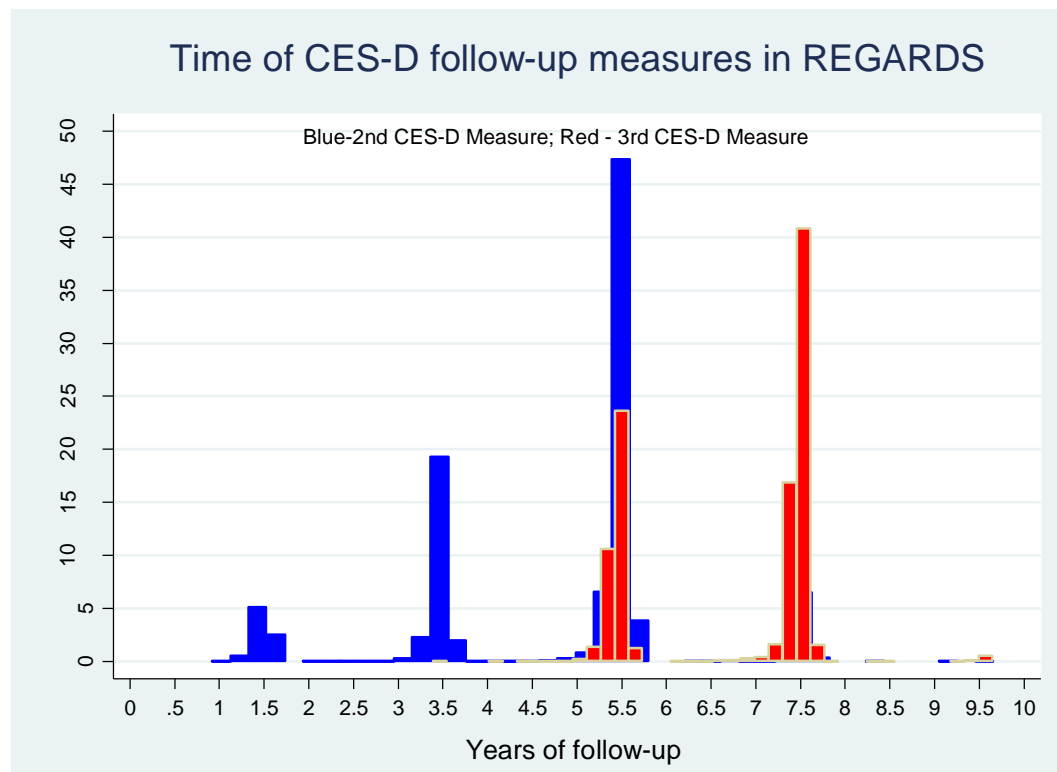
eTable 2. Reasons for non-cardiovascular disease death in the REGARDS study

<i>Causes of Death</i>	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	
	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.

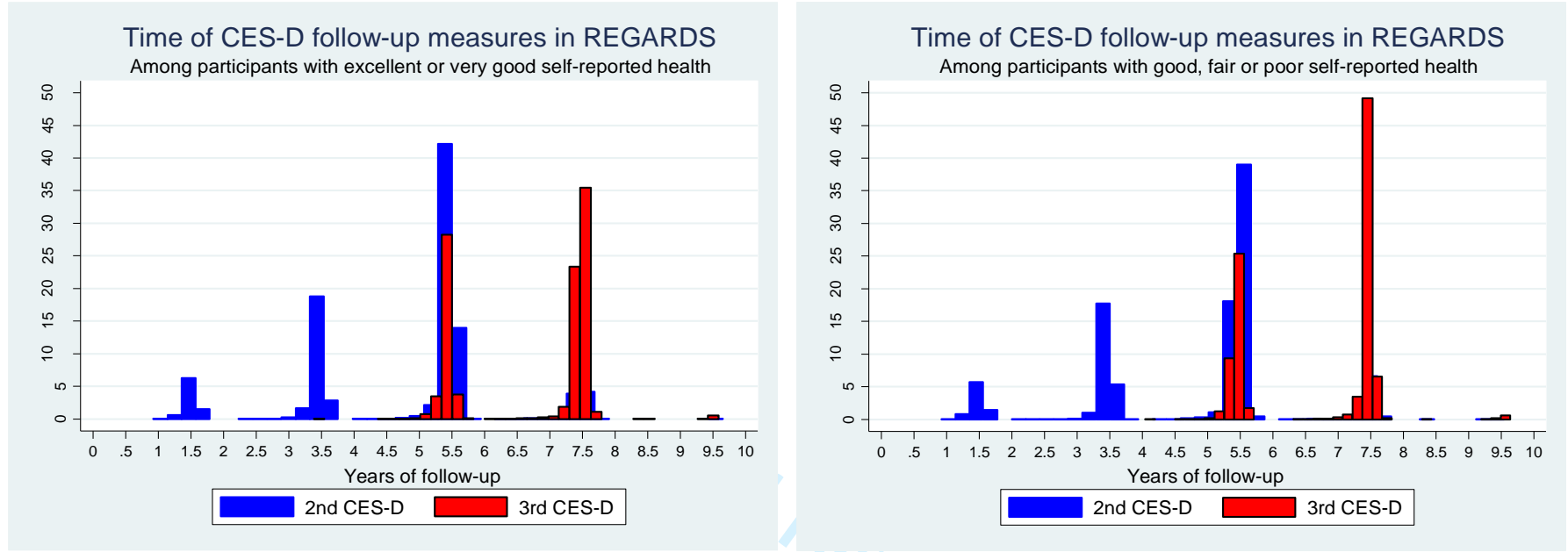


*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

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

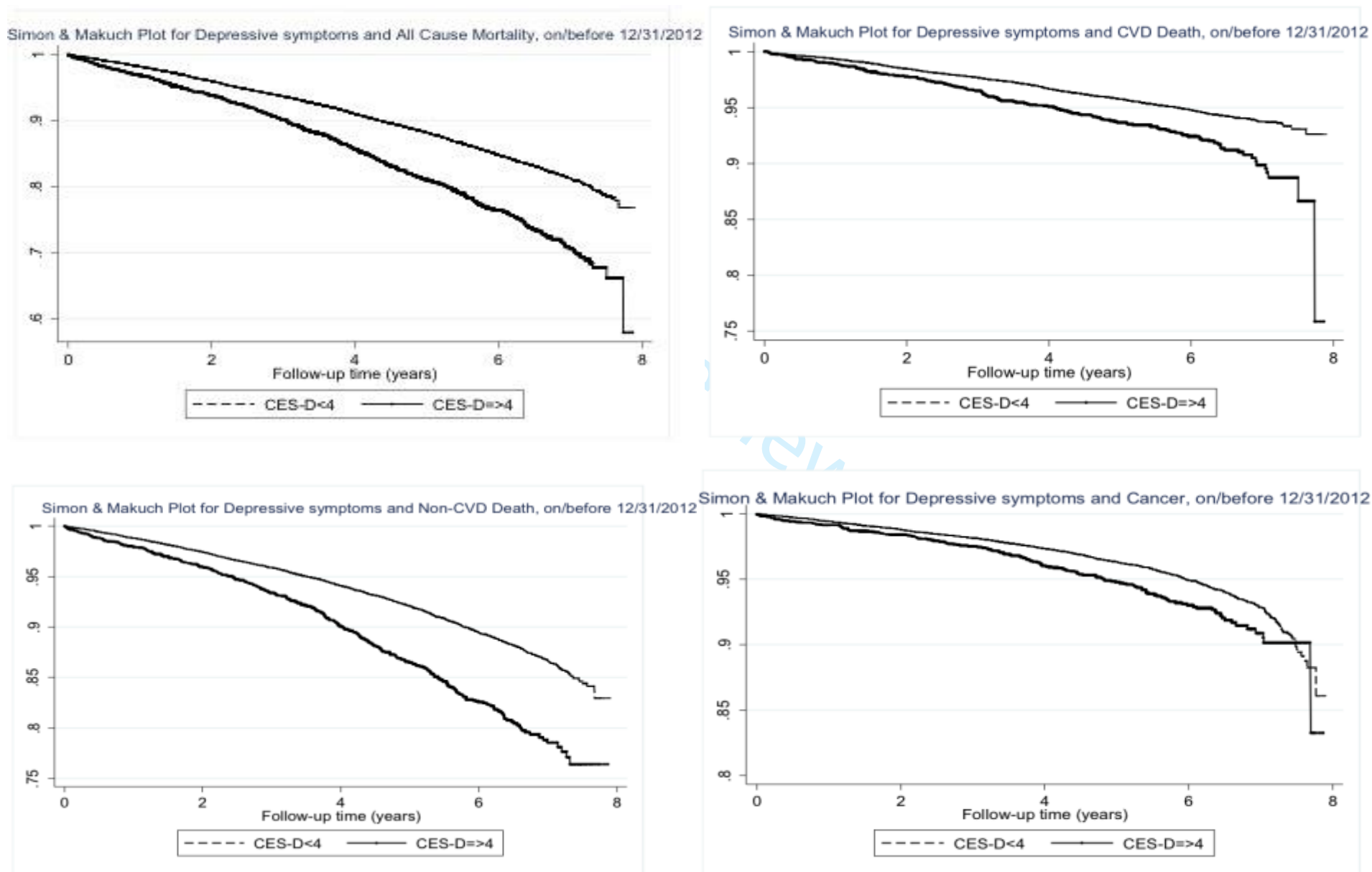
eTable 3. Baseline characteristics of REGARDS participants who had all 3 CES-D measures vs. those with 1 or 2 CES-D measures

Characteristics	1 or 2 CES-D measures (n=17,040)	All 3 CES-D measures (n=12, 451)	<i>p</i> value
<i>Socio-demographics</i>			
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>			
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, <i>M</i> (SD)	45.5 +- 11.0	47.6 +- 9.9	<.001
<i>Physiological risk factors</i>			
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.4 +- 6.3	29.2 +- 6.0	0.0024
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	128.0 +- 17.2	127.0 +- 15.9	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.2 +- 41.0	191.9 +- 39.0	0.5732
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.4 +- 16.1	52.4 +- 16.3	<.001
QT Interval, corrected for heart rate, ms, <i>M</i> (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

1	Albumin to Creatinine Ratio, mg/g, median,			
2	IQR	7.9[4.8-18.7]	6.9[4.5-13.5]	<.001
3	Medications			
4	Antihypertensive medication use, n (%)	9079 (53.9)	6118 (49.7)	<.001
5	Statin use, n (%)	5344 (31.4)	3951 (31.8)	0.53
6	Aspirin use, n (%)	7297 (42.8)	5493 (44.1)	0.03
7	Antidepressant use, n (%)	2440 (14.4)	1646 (13.2)	0.006
8	Behavioral risk factors			
9				
10	Self-reported smoking, pack years, <i>M</i> (SD)	14.5 +- 24.4	12.2 +- 21.0	<.001
11	Current Smoking, n(%)	2786 (16.4)	1477 (11.9)	<.001
12	Alcohol use, n (%)			<.001
13	Heavy	652 (3.9)	520 (4.2)	
14	Moderate	5180 (31.1)	4446 (36.3)	
15	None	10822 (65.0)	7294 (59.5)	
16	Physical inactivity, n (%)	6150 (36.7)	3854 (31.3)	<.001
17	Medication non-adherence, n (%)	4548 (29.6)	3411 (29.9)	0.59
18	Impaired cognitive status (Cognitive score \leq 4)	1300 (9.4)	588 (5.9)	<.001
19	Elevated perceived stress (PSS \geq 5)	5437 (31.9)	3154 (25.3)	<.001

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

For peer review only

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

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Manuscripts

1 **An observational study of the differential impact of time-varying depressive symptoms on**
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3 **all-cause and cause-specific mortality by health status in community dwelling adults: The**
4
5 **REGARDS study**

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7
8 **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.

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

- 11 • Depression is a relapsing/remitting disease and our study is one of the first to use multiple
12 measurements of depression to demonstrate a time varying relationship between
13 depression and mortality, including cancer mortality, in a large, diverse cohort.
 - 14 • To our knowledge, we are also the first to report a significant moderating effect of self-
15 reported health on the relationship between depressive symptoms and cause-specific
16 mortality, with depression predicting mortality particularly in those with excellent or very
17 good reported health.
 - 18 • Our analyses were limited by the use of the short form of the CES-D scale
 - 19 • The REGARDS cohort is regionally specific, limiting generalizability.
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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 mortality¹² 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

1 (very good or excellent vs. poor, fair or good) to further isolate the association between
2
3 depressive symptoms and excess mortality.
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8 **Methods**

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10 The REGARDS study is a national cohort study of stroke incidence and cognitive decline in
11 black and white community dwelling adults ≥ 45 years living in the United States stratified to
12 reflect specific race-sex-geographic strata.¹⁴ Inclusion and exclusion criteria have been
13 previously described; of note, those with active cancer were excluded from the original study.¹⁴
14
15 Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study.
16
17 Participants were recruited by mail using commercially available lists of U.S. residents, followed
18 by a computer-assisted telephone interview and subsequent home visit at which time individuals
19 were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white
20 adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing
21 baseline depressive symptom measurements (**Figure 1**). The REGARDS study protocol was
22 approved by institutional review boards at participating centers.
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38 *Study Procedures*

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

1 status (yes/no), and stroke region (including the ‘stroke belt’ and ‘stroke buckle’). Clinical risk
2
3 factors included (1) diabetes defined as fasting blood glucose ≥ 126 or random glucose >200
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5 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on
6
7 the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index
8
9 (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR)
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11 (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total
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13 cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial
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15 infarction or coronary revascularization procedure or evidence of myocardial infarction on the
16
17 study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8)
18
19 cognitive impairment on the 6-item screener of global cognitive function^{17,18} (9) chronic lung
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21 disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled
22
23 corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium,
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25 cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin,
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27 antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake
28
29 inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors
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31 included (1) self-reported pack-years of cigarette smoking; (2) physical activity (“How many
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33 times per week do you engage in intense physical activity, enough to work up a sweat?” with
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35 response options of “none”, “1-3 times per week” and “4 or more times per week”); (3) alcohol
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37 use (“How many alcoholic beverages do you drink?”: none, moderate [1 drink per day for
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39 women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2
40
41 drinks per day for men]);¹⁴ (4) medication non-adherence assessed with the 4-item Morisky
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43 Medication Adherence Scale (≥ 1).¹⁹ Potential physiologic risk factors included high-sensitivity
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45 C-reactive protein, self-reported health status based on the physical component of the 12-item
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47 Short-Form Health Survey (SF 12),²⁰ and perceived stress, measured by the 4-item version of the
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1 Perceived Stress Scale (score of ≥ 5 vs. <5).²¹ Other than depressive symptoms, no other
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3 covariate was assessed more than once.
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6 7 8 *Statistical Analyses* 9

10 Baseline characteristics of participants with and without elevated depressive symptoms at
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12 baseline were compared using chi-square tests (for categorical variables), Student t tests (for
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14 continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous
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16 measures).
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21 Cox proportional hazard regression models were constructed to separately analyze the
22
23 association between depressive symptoms ($\text{CES-D} \geq 4$) and cancer death (from all body sites, a
24
25 subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of
26
27 follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the
28
29 CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline
30
31 measurement, and 3) on average two years after the second measurement. In the analyses, we
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33 considered depressive symptoms ($\text{CES-D} \geq 4$ vs. <4) as a time-varying exposure, with updates of
34
35 exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3
36
37 measures of CES-D (≥ 4 vs. <4) with a broken-up follow-up time. Follow-up time for each
38
39 participant was calculated from the date of the in-home visit to the date of the earliest of: death,
40
41 last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically
42
43 plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive
44
45 symptoms using the Simon-Makuch method,²² a modification of the Kaplan-Meier method. In
46
47 this context, depression status is treated as a binary time-dependent covariate and study cohorts
48
49 are continually updated to contribute to either the $\text{CES-D} \geq 4$ or $\text{CES-D} < 4$ groups.
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3 Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were
4
5 estimated for those with vs. without elevated depressive symptoms. Adjusted modeling
6
7 proceeded in stages (adjusting for baseline covariates), starting with demographic (Model 1) and
8
9 traditional CVD risk factors (Model 2) assessed in prior trials. We then added behavioral (Model
10
11 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5),
12
13 which considered intervening first non-fatal stroke and/or myocardial infarction as a time-
14
15 dependent covariate in CVD death outcomes. All analyses were conducted overall as well as
16
17 stratified. We also conducted a formal test for interaction between time-varying depressive
18
19 symptoms and self-reported health (defined as excellent or very good vs. good, fair or poor
20
21 health) in model 4. As such, all analyses were conducted overall as well as stratified by baseline
22
23 self-reported health. To test the proportional hazards assumptions, we performed the chi-squared
24
25 test for the Schoenfeld residuals and all the models resulted in a violation of the proportional
26
27 hazards assumptions, indicating that time-varying depressive symptoms were appropriate. The
28
29 proportionality assumption for time varying depressive symptoms was also tested by assessing
30
31 the interaction of depressive symptoms*log of follow-up time and was satisfied for all mortality
32
33 endpoints.
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42 Missing data in covariates were imputed using chained equations and derived by bootstrapping
43
44 across the 5 imputed datasets. Of the 29,491 participants, 2768 (9%) were missing income data,
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46 59 (0.2%) health status, 9 (<0.1%) education, 26 (0.1%) health insurance, 1087 (4%) diabetes, 16
47
48 (0.1%) aspirin use, 70 (0.2%) statin use, 70 (0.2%) antidepressant use, 333 (1%) anti-
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50 hypertension meds use, 439 (2%) physical activity, 2705 (9%) medication adherence, 213 (0.7%)
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52 BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912 (3.1%) pack years, 84 (0.3%) SBP, 1394
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1 (5%) renal function, 381 (1%) QTc, 5681 (19.3%) cognitive status, 4 (<0.1%) stress, 1425 (4%)
2
3 SF-12 and 1881 (6%) CRP. Analyses were conducted using SAS software version 9.4 (SAS
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5 Institute, Cary, NC) and STATA version 12 (STATA incorporated, College Station, TX).
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10 *Sensitivity Analyses*

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12 Sensitivity analyses constructed in parallel to the main analyses examined association of baseline
13
14 CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard
15
16 regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-
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18 up time for each participant was calculated from the date of the in-home visit to the date of the
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20 earliest of: death, last telephone follow-up, or end of follow-up.
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27 **Results**

28 *Participant Characteristics*

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30 Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms,
31
32 leaving 29,491 eligible participants (**Figure 1**) of whom 3,254 (11.0%) had elevated depressive
33
34 symptoms at baseline (CES-D \geq 4). The average age was 64.9 (9.4) years; 55.1% were female and
35
36 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33%
37
38 of individuals were physically inactive, 29.2% non-adherent to their medication regimen and
39
40 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be
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42 poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of
43
44 whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless
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46 of health status, participants with elevated (vs. non-elevated) depressive symptoms were more
47
48 likely to be female, African-American, low income, have more chronic diseases, low physical
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50 health, and more behavioral risk factors (**Table 1A-B**).
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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)	<i>p</i>
<i>Socio-demographics</i>				
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>				
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, <i>M</i> (SD)	46.4 (10.6)	47.1 (10.2)	40.7 (12.2)	<.001
<i>Physiological risk factors</i>				
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.3 (6.2)	29.2 (6.1)	30.6 (7.1)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	127.6 (16.7)	127.5 (16.5)	128.7 (18.1)	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.1 (40.1)	191.7 (39.8)	194.6 (43.0)	<0.001
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.8 (16.2)	51.7 (16.2)	52.5 (16.3)	0.02
QT Interval, corrected for heart rate, ms, <i>M</i> (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
<i>Medications</i>				
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

1	Aspirin use, n (%)	12790 (43.4)	11376 (43.4)	1414 (43.5)	0.91
2					
3	Antidepressant use, n (%)	4086 (13.9)	3164 (12.1)	922 (28.4)	<.001
4	Behavioral risk factors				
5	Self-reported smoking, pack years, <i>M</i>				
6	(SD)	13.5 (23.1)	13.3 (22.8)	15.5 (24.9)	<.001
7					
8	Current Smoking, n(%)	4263(14.5)	3463(13.3)	800(24.7)	<.001
9					
10	Alcohol use, n (%)				<.001
11	Heavy	1172 (4.1)	1043 (4.0)	129 (4.1)	
12	Moderate	9626 (33.3)	8786 (34.1)	840 (26.6)	
13	None	18116 (62.7)	15925 (61.8)	2191 (69.3)	
14	Physical inactivity, n (%)	10004 (34.4)	8500 (32.9)	1504 (46.9)	<0.001
15					
16	Medication non-adherence, n (%)	7959 (29.7)	6820 (28.7)	1139 (37.8)	<.001
17					
18	Impaired cognitive status	1888 (7.9)			
19	(Cognitive score ≤ 4)		1542 (7.3)	346 (12.6)	<.001
20	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

^aStroke 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.

^bStroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

^cCVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

^dDiabetes 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

Characteristics	<i>Self-reported general health as "excellent or very good"</i>			<i>Self-reported general health as "poor, fair or good"</i>		
	CES-D < 4 (n=12965)	CES-D ≥4 (n=725)	<i>p</i>	CES-D < 4 (n=13219)	CES-D ≥4 (n=2523)	<i>p</i>
<i>Socio-demographics</i>						
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>						
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, <i>M</i> (SD)	52.0 (6.5)	51.3 (9.1)	0.008	42.0 (10.7)	37.7 (11.3)	<.001
<i>Physiological risk factors</i>						
Body Mass Index, kg/m ² , <i>M</i> (SD)	27.8 (5.1)	28.4 (5.7)	0.006	30.5 (6.6)	31.2 (7.3)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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 (Cognitive score \leq 4)	587 (5.6)	61 (10.1)	<.001	947 (8.9)	285 (13.3)	<.001
Elevated perceived stress (PSS \geq 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

^aStroke 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.

^bStroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

^cCVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

^dDiabetes defined as fasting blood glucose \geq 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

1 of the second and third measurement of CES-D measures did not differ by self-reported health
2
3 (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8%
4
5 had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-
6
7 varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI
8
9 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance
10
11 for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 95% CI 0.98-1.32),
12
13 even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-
14
15 fatal CVD events (**Table 2**, eFigure 3). The results appeared to be particularly robust amongst those
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17 with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78),
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19 CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer
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21 (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health
22
23 status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death),
24
25 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 <i>socio-demographics</i> (age, gender, region, income, health insurance, education)			
^b Model 2 adds to model 1 <i>medical conditions, physiological factors and medication use</i> (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 <i>behavioral risk factors</i> (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).			

^dModel 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)

^eModel 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 \geq 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

^aModel 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
^bModel 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)
^cModel 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
^dModel 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

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

1 recognize/present for depression. In fact, depressed excellent health individuals in our cohort were
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3 less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future
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5 studies.
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10 The overall results also have a coherence consistent with prior studies that suggest that depressive
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12 symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as
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14 cancer death.²⁵ While prior literature suggests that depressive symptoms confer mortality in those
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16 with active cancer,²⁶ our study excluded active cancer diagnoses confirming a possible relationship
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18 between depressive symptoms and incident cancer mortality. Prior studies have also been limited by
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20 inadequate covariate control, and our results for cancer persisted after adjusting for numerous
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22 traditional and behavioral risk factors, such as smoking, and approached significance even in
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24 models that included physiologic factors.
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31 Overall, baseline and time varying analyses were similar. However, while our baseline analyses
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33 suggest that depressive symptoms significantly contribute to cancer death in those with
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35 excellent/very good health, time varying analyses allowed for more accurate analyses in line with
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37 expectations, suggesting a weaker interaction by health status for proximal cancer mortality in this
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39 cohort that excluded those with active malignancy.
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45 This study also supports comprehensive evidence-based depression care management in primary
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47 care practices, which have been shown to lower mortality risk.²⁷ Nonetheless, depression treatment
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49 remains suboptimal in the general population,²⁸ despite decades of efforts. We too demonstrate that
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51 over time, nearly 40% of patients with elevated depressive symptoms at baseline were still
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53 depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both
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1 time-varying analyses (by virtue of follow-up times being broken up by repeat depression
2 measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend
3 greater urgency to the importance of timely and effective treatment of depressive symptoms to
4 prevent adverse consequences of depressive symptoms on physical health and mortality.
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11 Limitations of our study include the regional specificity, limiting generalizability, and use of the
12 short form of the CES-D, which measures only emotional and not somatic symptoms of depression.
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14 Schultz (2002) demonstrated variance between studies using scales and interviews,²⁹ and others
15 have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).³⁰
16
17 However, CES-D scales are one of the most widely used scales in clinical practice and in baseline
18 depression to outcome studies and have good sensitivity and specificity.^{9,15,16} We may also have
19
20 been underpowered to examine CVD and cancer mortality, though the directionality of the
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22 estimates remained consistent. The exclusion of active cancer participants as part of the overall
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24 REGARDS study criteria, the rationale of which has previously been described,¹⁴ may also have
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26 contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically
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28 excluded, which is in line with prior depression to mortality studies.^{1,9} Nonetheless, our previously
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30 published study, which excluded those with a history of CVD, similarly found a strong relationship
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32 between time-varying depressive symptoms and CVD death.³¹
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43 We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we
44 included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5
45 years) was relatively short compared to other studies with even shorter follow-up times between
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47 CES-D measures in time-varying analyses, suggesting a short-term effect on mortality. Our results
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49 support prior literature suggesting that shorter follow-up time is associated with greater excess
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1 mortality.^{9,30} However, we did not formally compare short-term to long-term follow-up nor
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3 persistent to fluctuating depressive symptoms.
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8 Given our results of a relationship between time-varying depressive symptoms and mortality,
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10 further research is warranted to test the long-term efficacy of and adherence to depression treatment
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12 and to explore preventive approaches to decreasing premature mortality risk.³² To our knowledge,
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14 the finding of a relationship between depressive symptoms and mortality in those with excellent or
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16 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,

1 Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding*: Safford; *Study*
2
3 *supervision*: Safford
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5 **Conflict of Interest:** None
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21 **Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent
22 account of the study being reported; that no important aspects of the study have been omitted; and
23 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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27 **Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are
28 available if deemed important by reviewers with open access by Monika Safford at Weill Cornell,
29 Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of
30 Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised
31 and risk of identification is low.
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Figure Legend

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

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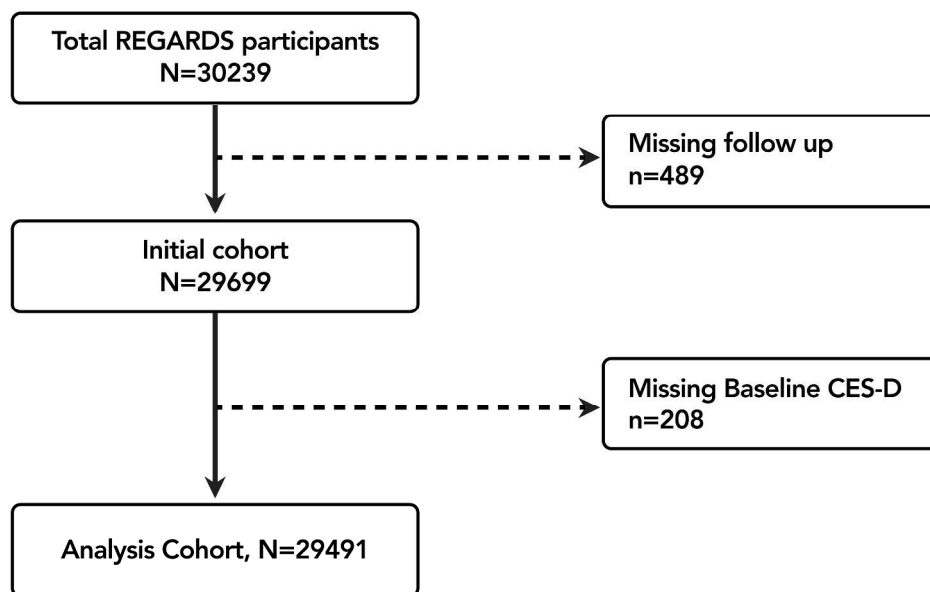


Figure 1. Consort Diagram

279x215mm (300 x 300 DPI)

Supplementary Material

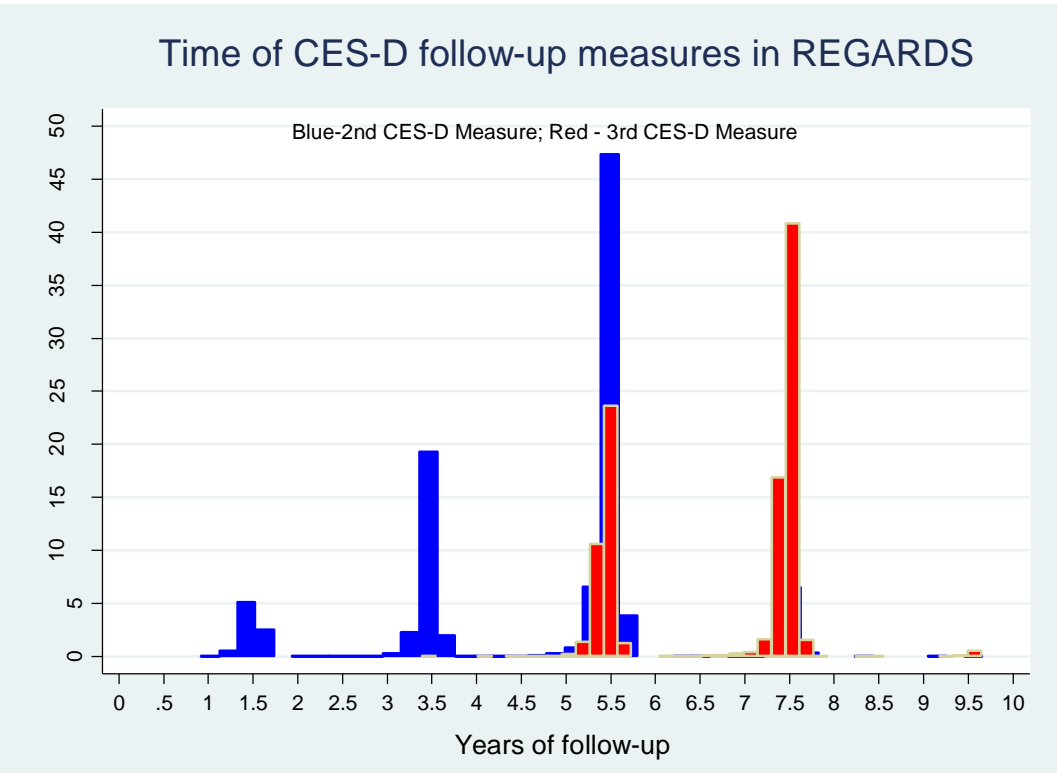
eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).

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 95.9 %	195 4.1%	4710	3444 94.7%	194 5.3%	3638	2109 94.6%	120 5.4%	2229
Very good	8450 94.1%	530 5.9%	8980	6332 93.0%	478 7.0%	6810	3938 92.8%	305 7.2%	4243
Good	9181 89.1%	1124 10.9%	10305	6363 88.6%	818 11.4%	7181	3717 88.9%	464 11.1%	4181
Fair	3424 77.8 %	975 22.2 %	4399	2185 79.7%	556 20.3%	2741	1236 82.0%	271 18.0%	1507
Poor	614 59.2%	424 40.9%	1038	322 61.2%	204 38.8%	526	177 65.3%	94 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

<i>Causes of Death</i>	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	
	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.

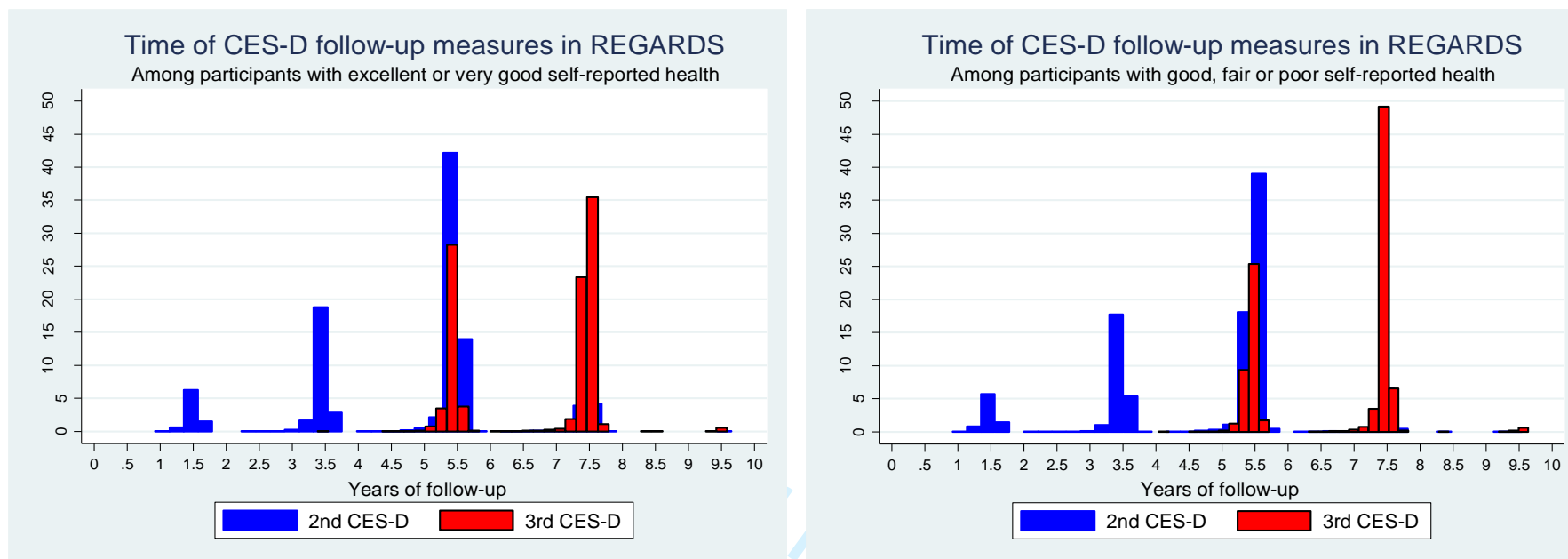


*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

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)	<i>p</i> value
<i>Socio-demographics</i>			
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>			
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, <i>M</i> (SD)	45.5 +- 11.0	47.6 +- 9.9	<.001
<i>Physiological risk factors</i>			
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.4 +- 6.3	29.2 +- 6.0	0.0024
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	128.0 +- 17.2	127.0 +- 15.9	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.2 +- 41.0	191.9 +- 39.0	0.5732
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.4 +- 16.1	52.4 +- 16.3	<.001
QT Interval, corrected for heart rate, ms, <i>M</i> (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

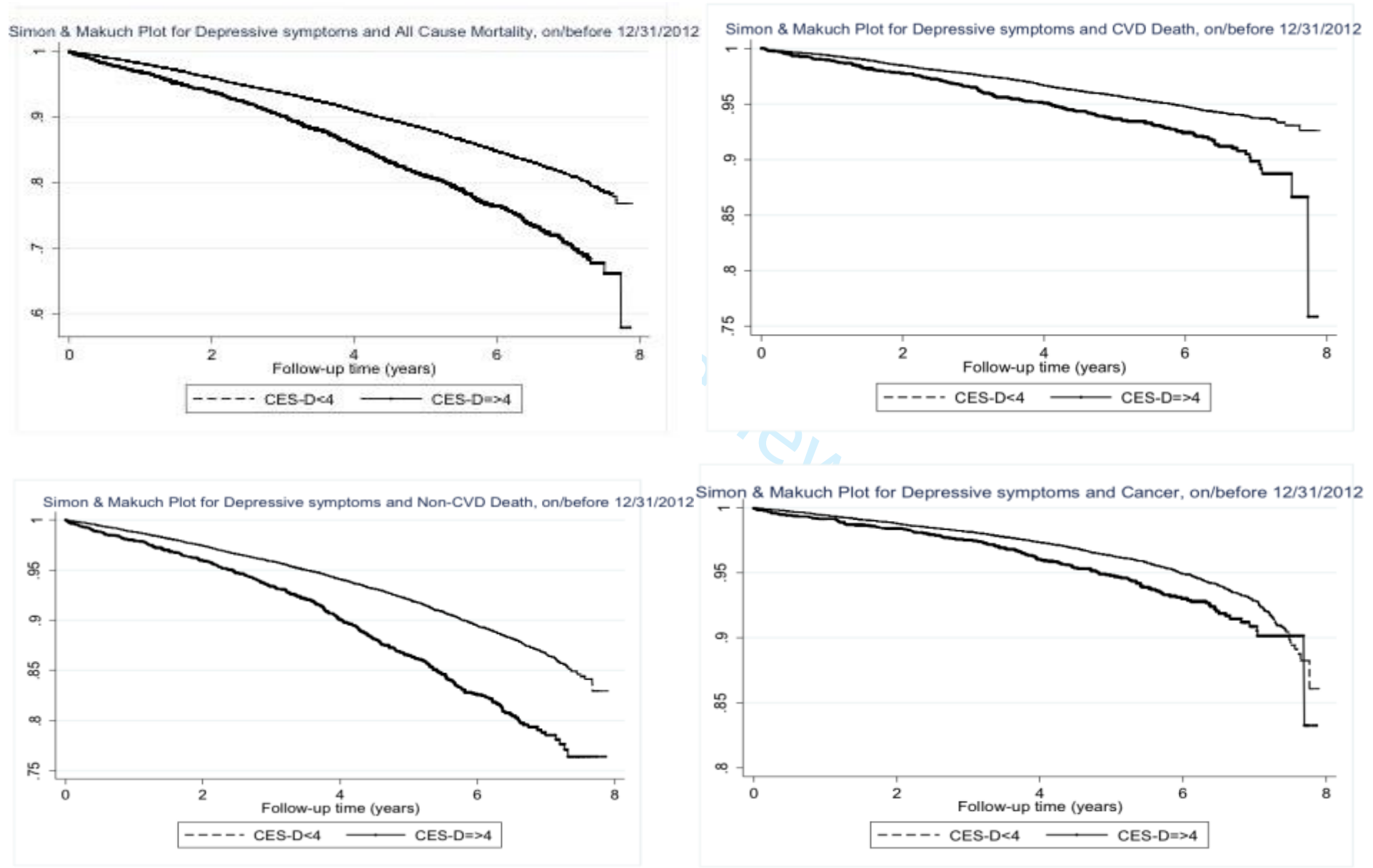
1	Albumin to Creatinine Ratio, mg/g, median,			
2	IQR	7.9[4.8-18.7]	6.9[4.5-13.5]	<.001
3	Medications			
4	Antihypertensive medication use, n (%)	9079 (53.9)	6118 (49.7)	<.001
5	Statin use, n (%)	5344 (31.4)	3951 (31.8)	0.53
6	Aspirin use, n (%)	7297 (42.8)	5493 (44.1)	0.03
7	Antidepressant use, n (%)	2440 (14.4)	1646 (13.2)	0.006
8	Behavioral risk factors			
9				
10	Self-reported smoking, pack years, <i>M</i> (SD)	14.5 +- 24.4	12.2 +- 21.0	<.001
11	Current Smoking, n(%)	2786 (16.4)	1477 (11.9)	<.001
12	Alcohol use, n (%)			<.001
13	Heavy	652 (3.9)	520 (4.2)	
14	Moderate	5180 (31.1)	4446 (36.3)	
15	None	10822 (65.0)	7294 (59.5)	
16	Physical inactivity, n (%)	6150 (36.7)	3854 (31.3)	<.001
17	Medication non-adherence, n (%)	4548 (29.6)	3411 (29.9)	0.59
18	Impaired cognitive status (Cognitive score \leq 4)	1300 (9.4)	588 (5.9)	<.001
19	Elevated perceived stress (PSS \geq 5)	5437 (31.9)	3154 (25.3)	<.001

22 *p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD =
 23 cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.

24 Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions
 25 within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states
 26 of North Carolina, South Carolina and Georgia.

27 Diabetes defined as fasting blood glucose \geq 126 or random glucose $>$ 200 mL/dL or oral hypoglycemic or insulin use. CVD
 28 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) and 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
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*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>.

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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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1 **An observational study of the differential impact of time-varying depressive symptoms on**
2
3 **all-cause and cause-specific mortality by health status in community dwelling adults: The**
4
5 **REGARDS study**
6

7 **Running Title:** depressive symptoms and mortality
8

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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.

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

- 14 • Depression is a relapsing/remitting disease and our study is one of the first to use multiple
15 measurements of depression to demonstrate a time varying relationship between
16 depression and mortality, including cancer mortality, in a large, diverse cohort.
17
18
 - 19 • To our knowledge, we are also the first to report a significant moderating effect of self-
20 reported health on the relationship between depressive symptoms and cause-specific
21 mortality, with depression predicting mortality particularly in those with excellent or very
22 good reported health.
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24
 - 25 • Our analyses were limited by the use of the short form of the CES-D scale
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 - 28 • The REGARDS cohort is regionally specific, limiting generalizability.
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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 mortality¹² 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

1 (very good or excellent vs. poor, fair or good) to further isolate the association between
2
3 depressive symptoms and excess mortality.
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6
7

8 **Methods**

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10 The REGARDS study is a national cohort study of stroke incidence and cognitive decline in
11 black and white community dwelling adults ≥ 45 years living in the United States stratified to
12 reflect specific race-sex-geographic strata.¹⁴ Inclusion and exclusion criteria have been
13 previously described; of note, those with active cancer were excluded from the original study.¹⁴
14
15 Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study.
16
17 Participants were recruited by mail using commercially available lists of U.S. residents, followed
18 by a computer-assisted telephone interview and subsequent home visit at which time individuals
19 were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white
20 adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing
21 baseline depressive symptom measurements (**Figure 1**). The REGARDS study protocol was
22 approved by institutional review boards at participating centers.
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38 *Study Procedures*

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

1 status (yes/no), and stroke region (including the ‘stroke belt’ and ‘stroke buckle’). Clinical risk
2
3 factors included (1) diabetes defined as fasting blood glucose ≥ 126 or random glucose > 200
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5 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on
6
7 the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index
8
9 (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR)
10
11 (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total
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13 cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial
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15 infarction or coronary revascularization procedure or evidence of myocardial infarction on the
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17 study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8)
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19 cognitive impairment on the 6-item screener of global cognitive function^{17,18} (9) chronic lung
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21 disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled
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23 corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium,
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25 cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin,
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27 antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake
28
29 inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors
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31 included (1) self-reported pack-years of cigarette smoking; (2) physical activity (“How many
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33 times per week do you engage in intense physical activity, enough to work up a sweat?” with
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35 response options of “none”, “1-3 times per week” and “4 or more times per week”); (3) alcohol
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37 use (“How many alcoholic beverages do you drink?”: none, moderate [1 drink per day for
38
39 women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2
40
41 drinks per day for men]);¹⁴ (4) medication non-adherence assessed with the 4-item Morisky
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43 Medication Adherence Scale (≥ 1).¹⁹ Potential physiologic risk factors included high-sensitivity
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45 C-reactive protein, self-reported health status based on the physical component of the 12-item
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47 Short-Form Health Survey (SF 12),²⁰ and perceived stress, measured by the 4-item version of the
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1 Perceived Stress Scale (score of ≥ 5 vs. <5).²¹ Other than depressive symptoms, no other
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3 covariate was assessed more than once.
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6 7 8 *Statistical Analyses* 9

10 Baseline characteristics of participants with and without elevated depressive symptoms at
11
12 baseline were compared using chi-square tests (for categorical variables), Student t tests (for
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14 continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous
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16 measures).
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20
21 Cox proportional hazard regression models were constructed to separately analyze the
22
23 association between depressive symptoms ($\text{CES-D} \geq 4$) and cancer death (from all body sites, a
24
25 subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of
26
27 follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the
28
29 CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline
30
31 measurement, and 3) on average two years after the second measurement. In the analyses, we
32
33 considered depressive symptoms ($\text{CES-D} \geq 4$ vs. <4) as a time-varying exposure, with updates of
34
35 exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3
36
37 measures of CES-D (≥ 4 vs. <4) with a broken-up follow-up time. Follow-up time for each
38
39 participant was calculated from the date of the in-home visit to the date of the earliest of: death,
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41 last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically
42
43 plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive
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45 symptoms using the Simon-Makuch method,²² a modification of the Kaplan-Meier method. In
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47 this context, depression status is treated as a binary time-dependent covariate and study cohorts
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49 are continually updated to contribute to either the $\text{CES-D} \geq 4$ or $\text{CES-D} < 4$ groups.
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3 Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were
4
5 estimated for those with vs. without elevated depressive symptoms. Adjusted modeling
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7 proceeded in stages (adjusting for baseline covariates), starting with demographic (Model 1) and
8
9 traditional CVD risk factors (Model 2) assessed in prior trials. We then added behavioral (Model
10
11 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5),
12
13 which considered intervening first non-fatal stroke and/or myocardial infarction as a time-
14
15 dependent covariate in CVD death outcomes. All analyses were conducted overall as well as
16
17 stratified. We also conducted a formal test for interaction between depressive symptoms and self-
18
19 reported health (defined as excellent or very good vs. good, fair or poor health) in model 4. As
20
21 such, all analyses were conducted overall as well as stratified by baseline self-reported health. To
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23 evaluate the possibility of non-proportional hazards, we graphically inspected the log-log
24
25 survival plots for depressive symptoms. We tested the Schoenfeld residuals for each model for a
26
27 non-zero slope and all p values were greater than 0.05, indicating compatibility with the
28
29 proportional hazards assumption.
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40 *Sensitivity Analyses*

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42 Sensitivity analyses constructed in parallel to the main analyses examined association of baseline
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44 CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard
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46 regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-
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48 up time for each participant was calculated from the date of the in-home visit to the date of the
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50 earliest of: death, last telephone follow-up, or end of follow-up.
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1 Missing data in covariates were imputed using chained equations and derived by bootstrapping
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3 across the 5 imputed datasets. Multiple imputation was used for all analyses. Of the 29,491
4
5 participants, 2768 (9%) were missing income data, 59 (0.2%) health status, 9 (<0.1%) education,
6
7 26 (0.1%) health insurance, 1087 (4%) diabetes, 16 (0.1%) aspirin use, 70 (0.2%) statin use, 70
8
9 (0.2%) antidepressant use, 333 (1%) anti-hypertension meds use, 439 (2%) physical activity,
10
11 2705 (9%) medication adherence, 213 (0.7%) BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912
12
13 (3.1%) pack years, 84 (0.3%) SBP, 1394 (5%) renal function, 381 (1%) QTc, 5681 (19.3%)
14
15 cognitive status, 4 (<0.1%) stress, 1425 (4%) SF-12 and 1881 (6%) CRP. Analyses were
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17 conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12
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19 (STATA incorporated, College Station, TX).
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27 **Results**

28 *Participant Characteristics*

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30 Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms,
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32 leaving 29,491 eligible participants (**Figure 1**) of whom 3,254 (11.0%) had elevated depressive
33
34 symptoms at baseline (CES-D \geq 4). The average age was 64.9 (9.4) years; 55.1% were female and
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36 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33%
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38 of individuals were physically inactive, 29.2% non-adherent to their medication regimen and
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40 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be
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42 poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of
43
44 whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless
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46 of health status, participants with elevated (vs. non-elevated) depressive symptoms were more
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48 likely to be female, African-American, low income, have more chronic diseases, low physical
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50 health, and more behavioral risk factors (**Table 1A-B**).
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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)	<i>p</i>
<i>Socio-demographics</i>				
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>				
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, <i>M</i> (SD)	46.4 (10.6)	47.1 (10.2)	40.7 (12.2)	<.001
<i>Physiological risk factors</i>				
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.3 (6.2)	29.2 (6.1)	30.6 (7.1)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	127.6 (16.7)	127.5 (16.5)	128.7 (18.1)	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.1 (40.1)	191.7 (39.8)	194.6 (43.0)	<0.001
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.8 (16.2)	51.7 (16.2)	52.5 (16.3)	0.02
QT Interval, corrected for heart rate, ms, <i>M</i> (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
<i>Medications</i>				
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

1	Aspirin use, n (%)	12790 (43.4)	11376 (43.4)	1414 (43.5)	0.91
2					
3	Antidepressant use, n (%)	4086 (13.9)	3164 (12.1)	922 (28.4)	<.001
4	Behavioral risk factors				
5	Self-reported smoking, pack years, <i>M</i>				
6	(SD)	13.5 (23.1)	13.3 (22.8)	15.5 (24.9)	<.001
7					
8	Current Smoking, n(%)	4263(14.5)	3463(13.3)	800(24.7)	<.001
9					
10	Alcohol use, n (%)				<.001
11	Heavy	1172 (4.1)	1043 (4.0)	129 (4.1)	
12	Moderate	9626 (33.3)	8786 (34.1)	840 (26.6)	
13	None	18116 (62.7)	15925 (61.8)	2191 (69.3)	
14	Physical inactivity, n (%)	10004 (34.4)	8500 (32.9)	1504 (46.9)	<0.001
15					
16	Medication non-adherence, n (%)	7959 (29.7)	6820 (28.7)	1139 (37.8)	<.001
17					
18	Impaired cognitive status	1888 (7.9)			
19	(Cognitive score ≤ 4)		1542 (7.3)	346 (12.6)	<.001
20	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

^aStroke 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.

^bStroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

^cCVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

^dDiabetes 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

Characteristics	<i>Self-reported general health as "excellent or very good"</i>			<i>Self-reported general health as "poor, fair or good"</i>		
	CES-D < 4 (n=12965)	CES-D ≥4 (n=725)	<i>p</i>	CES-D < 4 (n=13219)	CES-D ≥4 (n=2523)	<i>p</i>
<i>Socio-demographics</i>						
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>						
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, <i>M</i> (SD)	52.0 (6.5)	51.3 (9.1)	0.008	42.0 (10.7)	37.7 (11.3)	<.001
<i>Physiological risk factors</i>						
Body Mass Index, kg/m ² , <i>M</i> (SD)	27.8 (5.1)	28.4 (5.7)	0.006	30.5 (6.6)	31.2 (7.3)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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 (Cognitive score \leq 4)	587 (5.6)	61 (10.1)	<.001	947 (8.9)	285 (13.3)	<.001
Elevated perceived stress (PSS \geq 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

^aStroke 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.

^bStroke 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.

^dDiabetes defined as fasting blood glucose \geq 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

1 of the second and third measurement of CES-D measures did not differ by self-reported health
2
3 (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8%
4
5 had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-
6
7 varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI
8
9 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance
10
11 for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 95% CI 0.98-1.32),
12
13 even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-
14
15 fatal CVD events (**Table 2**, eFigure 3). The results appeared to be particularly robust amongst those
16
17 with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78),
18
19 CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer
20
21 (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health
22
23 status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death),
24
25 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 <i>socio-demographics</i> (age, gender, region, income, health insurance, education) ^b Model 2 adds to model 1 <i>medical conditions, physiological factors and medication use</i> (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 <i>behavioral risk factors</i> (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).			

^dModel 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)

^eModel 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 \geq 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 <i>socio-demographics</i> (age, gender, region, income, health insurance, education)			
^b Model 2 adds to model 1 <i>medical conditions, physiological factors and medication use</i> (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 <i>behavioral risk factors</i> (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).			
^d Model 4 adds to model 3 <i>other factors</i> (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.

1 It may also be that the effect of chronic illness burden on mortality in those with poor health
2 overwhelms the effects of depressive symptoms. Those with excellent health may also fail to
3 recognize/present for depression. In fact, depressed excellent health individuals in our cohort were
4 less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future
5 studies.
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14 The overall results also have a coherence consistent with prior studies that suggest that depressive
15 symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as
16 cancer death.²⁵ While prior literature suggests that depressive symptoms confer mortality in those
17 with active cancer,²⁶ our study excluded active cancer diagnoses confirming a possible relationship
18 between depressive symptoms and incident cancer mortality. Prior studies have also been limited by
19 inadequate covariate control, and our results for cancer persisted after adjusting for numerous
20 traditional and behavioral risk factors, such as smoking, and approached significance even in
21 models that included physiologic factors.
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35 Overall, baseline and time varying analyses were similar. However, while our baseline analyses
36 suggest that depressive symptoms significantly contribute to cancer death in those with
37 excellent/very good health, time varying analyses allowed for more accurate analyses in line with
38 expectations, suggesting a weaker interaction by health status for proximal cancer mortality in this
39 cohort that excluded those with active malignancy.
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49 This study also supports comprehensive evidence-based depression care management in primary
50 care practices, which have been shown to lower mortality risk.²⁷ Nonetheless, depression treatment
51 remains suboptimal in the general population,²⁸ despite decades of efforts. We too demonstrate that
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1 over time, nearly 40% of patients with elevated depressive symptoms at baseline were still
2 depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both
3 time-varying analyses (by virtue of follow-up times being broken up by repeat depression
4 measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend
5 greater urgency to the importance of timely and effective treatment of depressive symptoms to
6 prevent adverse consequences of depressive symptoms on physical health and mortality.
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16 Limitations of our study include the regional specificity, limiting generalizability, and use of the
17 short form of the CES-D, which measures only emotional and not somatic symptoms of depression.
18 Schultz (2002) demonstrated variance between studies using scales and interviews,²⁹ and others
19 have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).³⁰
20 However, CES-D scales are one of the most widely used scales in clinical practice and in baseline
21 depression to outcome studies and have good sensitivity and specificity.^{9,15,16} We may also have
22 been underpowered to examine CVD and cancer mortality, though the directionality of the
23 estimates remained consistent. The exclusion of active cancer participants as part of the overall
24 REGARDS study criteria, the rationale of which has previously been described,¹⁴ may also have
25 contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically
26 excluded, which is in line with prior depression to mortality studies.^{1,9} Nonetheless, our previously
27 published study, which excluded those with a history of CVD, similarly found a strong relationship
28 between time-varying depressive symptoms and CVD death.³¹
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48 We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we
49 included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5
50 years) was relatively short compared to other studies and we saw even shorter follow-up times
51 between CES-D measures in time-varying analyses, suggesting a short-term effect on mortality.
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1 Our results support prior literature suggesting that shorter follow-up time is associated with greater
2 excess mortality.^{9,30} However, we did not formally compare short-term to long-term follow-up nor
3 persistent to fluctuating depressive symptoms nor examine depression as a time-varying coefficient.
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10 Given our results of a relationship between time-varying depressive symptoms and mortality,
11 further research is warranted to test the long-term efficacy of and adherence to depression treatment
12 and to explore preventive approaches to decreasing premature mortality risk.³² To our knowledge,
13 the finding of a relationship between depressive symptoms and mortality in those with excellent or
14 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,

1 Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding*: Safford; *Study*
2
3 *supervision*: Safford
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5 **Conflict of Interest:** None
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21 **Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent
22 account of the study being reported; that no important aspects of the study have been omitted; and
23 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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27 **Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are
28 available if deemed important by reviewers with open access by Monika Safford at Weill Cornell,
29 Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of
30 Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised
31 and risk of identification is low.
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Figure Legend

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

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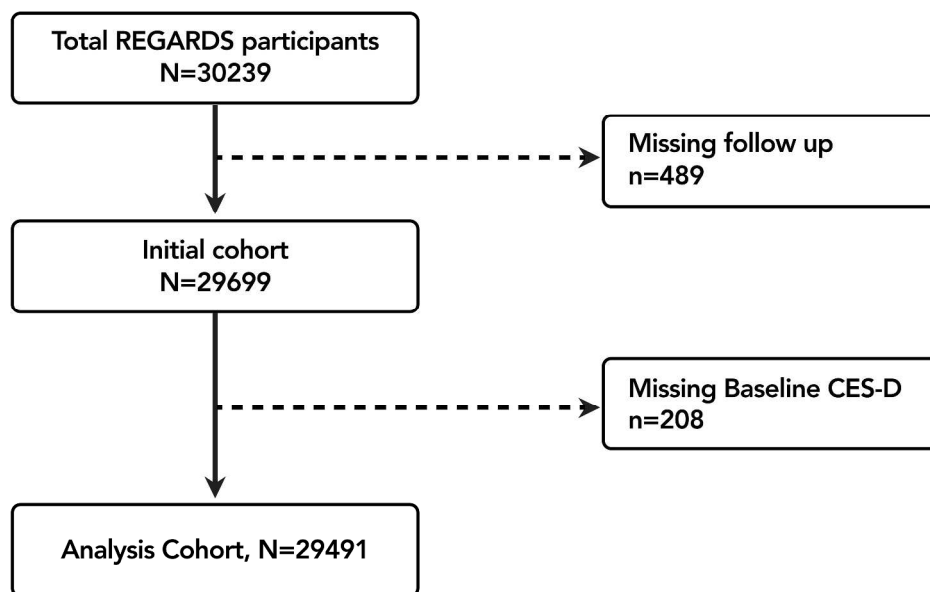


Figure 1. Consort Diagram

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Supplementary Material

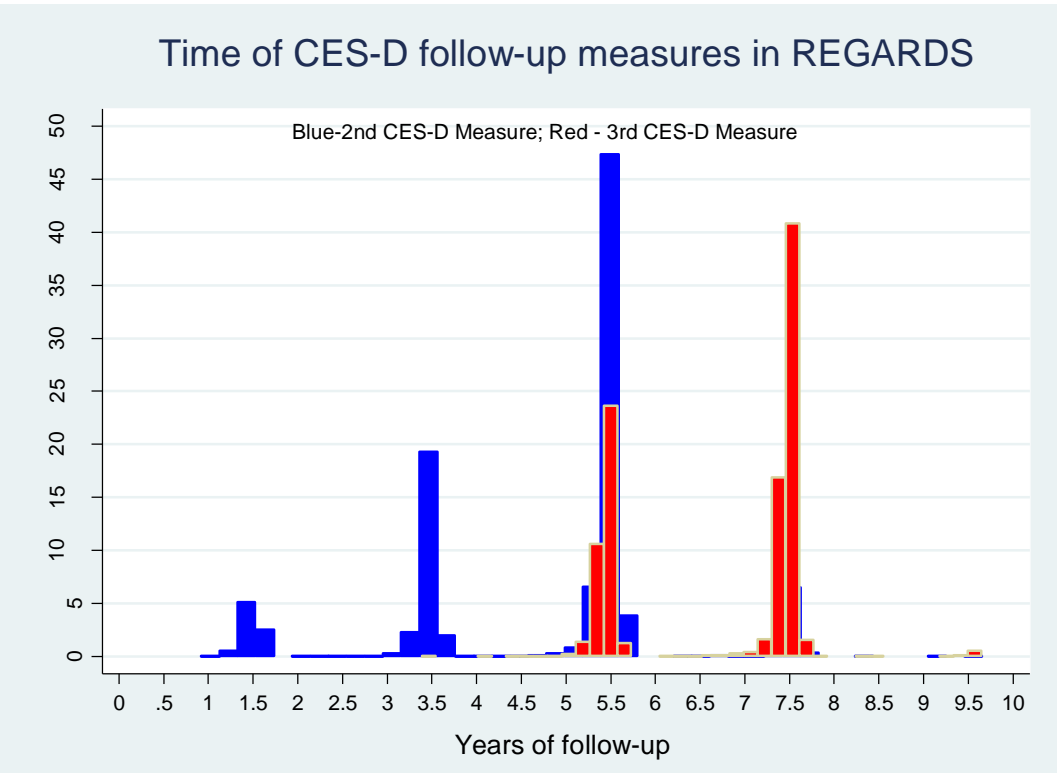
eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).

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 95.9 %	195 4.1%	4710	3444 94.7%	194 5.3%	3638	2109 94.6%	120 5.4%	2229
Very good	8450 94.1%	530 5.9%	8980	6332 93.0%	478 7.0%	6810	3938 92.8%	305 7.2%	4243
Good	9181 89.1%	1124 10.9%	10305	6363 88.6%	818 11.4%	7181	3717 88.9%	464 11.1%	4181
Fair	3424 77.8 %	975 22.2 %	4399	2185 79.7%	556 20.3%	2741	1236 82.0%	271 18.0%	1507
Poor	614 59.2%	424 40.9%	1038	322 61.2%	204 38.8%	526	177 65.3%	94 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

<i>Causes of Death</i>	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	
	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		

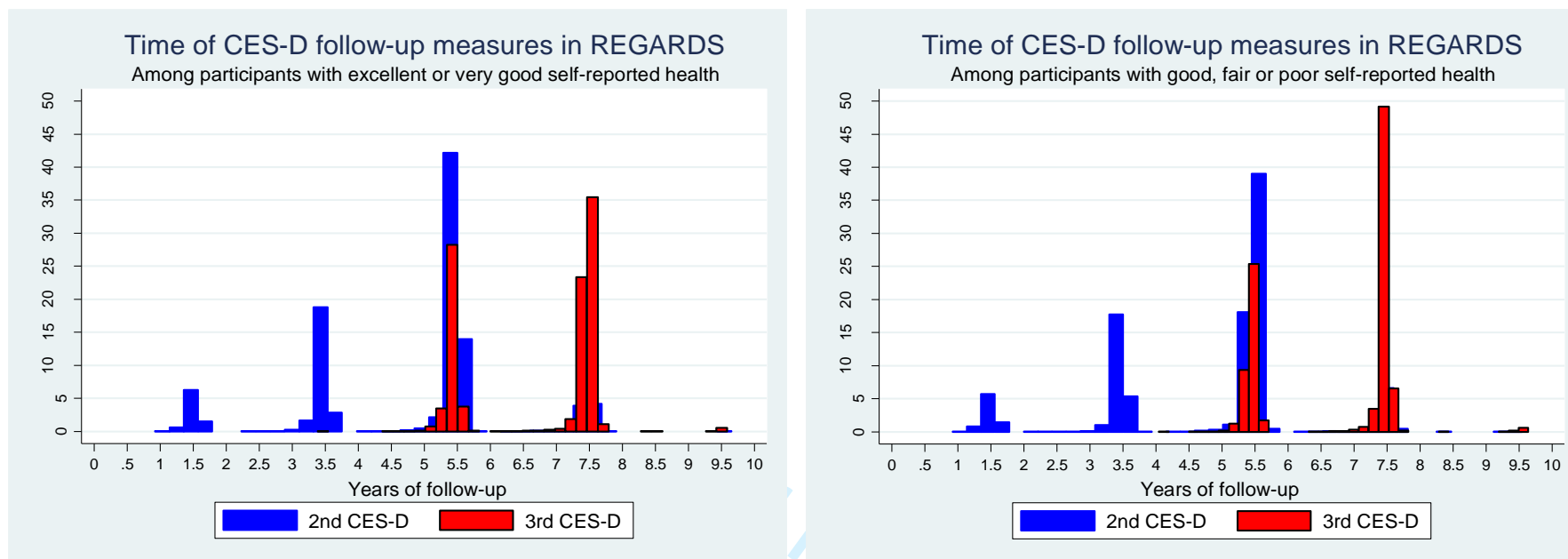
eFigure 1. Percent of participants with depression measured at baseline who had their second and third follow up measured by years of follow up.



*"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).

	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)	<i>p</i> value
<i>Socio-demographics</i>			
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>			
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, <i>M</i> (SD)	45.5 +- 11.0	47.6 +- 9.9	<.001
<i>Physiological risk factors</i>			
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.4 +- 6.3	29.2 +- 6.0	0.0024
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	128.0 +- 17.2	127.0 +- 15.9	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.2 +- 41.0	191.9 +- 39.0	0.5732
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.4 +- 16.1	52.4 +- 16.3	<.001
QT Interval, corrected for heart rate, ms, <i>M</i> (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

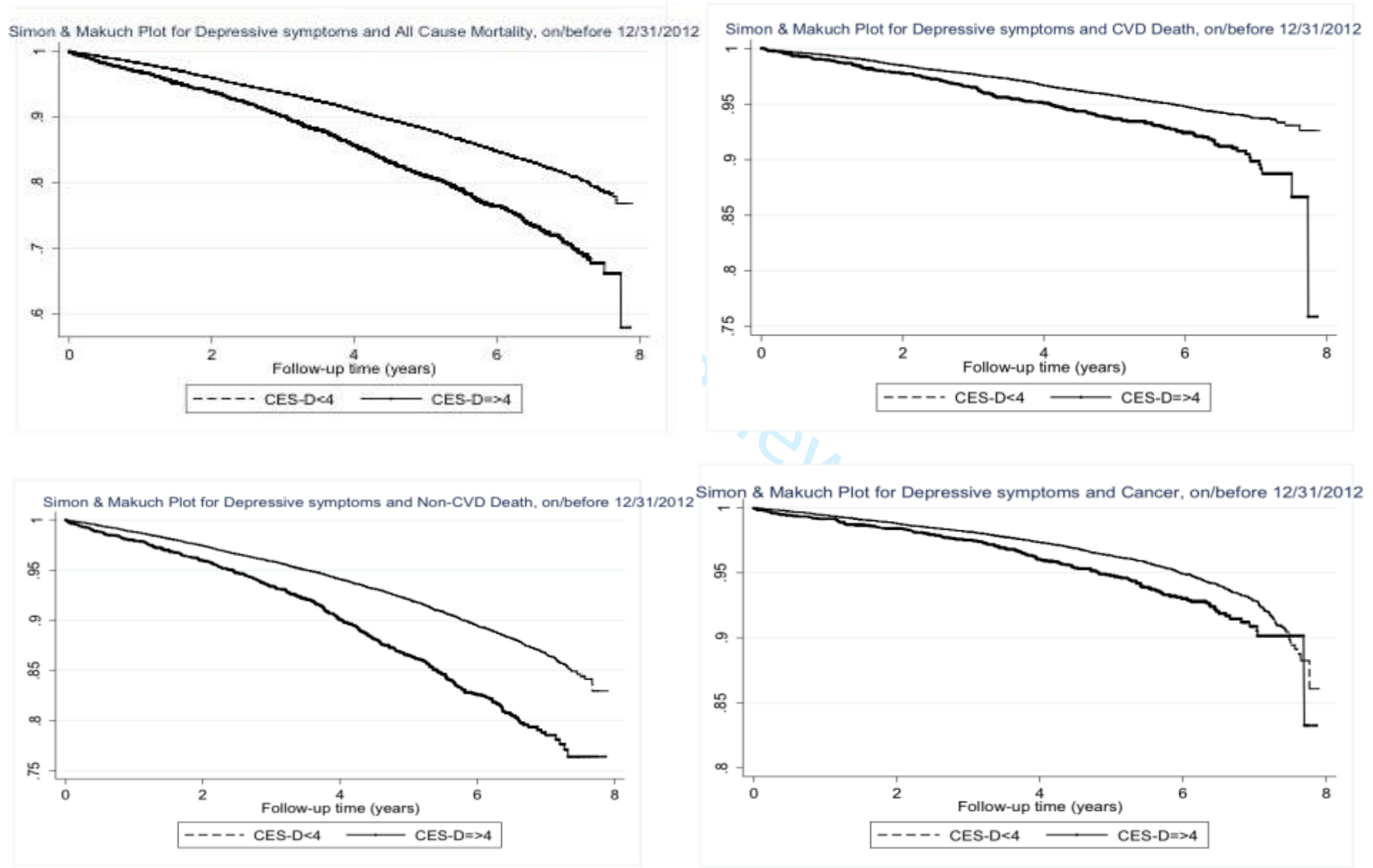
1	Albumin to Creatinine Ratio, mg/g, median,			
2	IQR	7.9[4.8-18.7]	6.9[4.5-13.5]	<.001
3	Medications			
4	Antihypertensive medication use, n (%)	9079 (53.9)	6118 (49.7)	<.001
5	Statin use, n (%)	5344 (31.4)	3951 (31.8)	0.53
6	Aspirin use, n (%)	7297 (42.8)	5493 (44.1)	0.03
7	Antidepressant use, n (%)	2440 (14.4)	1646 (13.2)	0.006
8	Behavioral risk factors			
9				
10	Self-reported smoking, pack years, <i>M</i> (SD)	14.5 +- 24.4	12.2 +- 21.0	<.001
11	Current Smoking, n(%)	2786 (16.4)	1477 (11.9)	<.001
12	Alcohol use, n (%)			<.001
13	Heavy	652 (3.9)	520 (4.2)	
14	Moderate	5180 (31.1)	4446 (36.3)	
15	None	10822 (65.0)	7294 (59.5)	
16	Physical inactivity, n (%)	6150 (36.7)	3854 (31.3)	<.001
17	Medication non-adherence, n (%)	4548 (29.6)	3411 (29.9)	0.59
18	Impaired cognitive status (Cognitive score \leq 4)	1300 (9.4)	588 (5.9)	<.001
19	Elevated perceived stress (PSS \geq 5)	5437 (31.9)	3154 (25.3)	<.001
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22 *p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD =
 23 cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.

24 Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions
 25 within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states
 26 of North Carolina, South Carolina and Georgia.

27 Diabetes defined as fasting blood glucose \geq 126 or random glucose $>$ 200 mL/dL or oral hypoglycemic or insulin use. CVD
 28 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) and 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
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*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>.

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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

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1 **An observational study of the differential impact of time-varying depressive symptoms on**
2
3 **all-cause and cause-specific mortality by health status in community dwelling adults: The**
4
5 **REGARDS study**

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7
8 **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.

1 **Conclusions:** Time-varying depressive symptoms confer an increased risk for all-cause
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3 mortality, CVD, non-CVD death and cancer death, particularly in those with excellent or very
4
5 good health. These findings may have implications for timely treatment, regardless of health
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7 status.
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9

10 11 12 **Strengths and limitations of this study.** 13

- 14 • Depression is a relapsing/remitting disease and our study is one of the first to use multiple
15 measurements of depression to demonstrate a time varying relationship between
16 depression and mortality, including cancer mortality, in a large, diverse cohort.
17
18
- 19 • To our knowledge, we are also the first to report a significant moderating effect of self-
20 reported health on the relationship between depressive symptoms and cause-specific
21 mortality, with depression predicting mortality particularly in those with excellent or very
22 good reported health.
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24
- 25 • Our analyses were limited by the use of the short form of the CES-D scale
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- 28 • The REGARDS cohort is regionally specific, limiting generalizability.
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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 mortality¹² 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

1 (very good or excellent vs. poor, fair or good) to further isolate the association between
2
3 depressive symptoms and excess mortality.
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7

8 **Methods**

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10 The REGARDS study is a national cohort study of stroke incidence and cognitive decline in
11 black and white community dwelling adults ≥ 45 years living in the United States stratified to
12 reflect specific race-sex-geographic strata.¹⁴ Inclusion and exclusion criteria have been
13 previously described; of note, those with active cancer were excluded from the original study.¹⁴
14
15 Coronary heart disease (CHD) outcomes were ascertained from a REGARDS-MI ancillary study.
16
17 Participants were recruited by mail using commercially available lists of U.S. residents, followed
18 by a computer-assisted telephone interview and subsequent home visit at which time individuals
19 were consented and enrolled. Between January 2003 and October 2007, 30,239 black and white
20 adults were enrolled. Of these, 489 (1.6%) were lost to follow-up and 208 (0.7%) were missing
21 baseline depressive symptom measurements (**Figure 1**). The REGARDS study protocol was
22 approved by institutional review boards at participating centers.
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38 *Study Procedures*

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

1 status (yes/no), and stroke region (including the 'stroke belt' and 'stroke buckle'). Clinical risk
2
3 factors included (1) diabetes defined as fasting blood glucose ≥ 126 or random glucose > 200
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5 mL/dL or oral hypoglycemic or insulin use, (2) systolic and diastolic blood pressures based on
6
7 the average of two standardized blood pressure measurements (in mm Hg) (3) body mass index
8
9 (BMI) based on measured height and weight (4) albumin-to-creatinine ratio (ACR)
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11 (logarithmically-transformed), (5) high-density lipoprotein (HDL)-cholesterol, (6) total
12
13 cholesterol, (7) history of CVD: coronary heart disease (self-reported history of myocardial
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15 infarction or coronary revascularization procedure or evidence of myocardial infarction on the
16
17 study electrocardiogram), self-reported stroke, peripheral vascular disease, or aneurysm, (8)
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19 cognitive impairment on the 6-item screener of global cognitive function^{17,18} (9) chronic lung
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21 disease defined as use of beta-2 adrenergic agonists, leukotriene inhibitors, inhaled
22
23 corticosteroids, combination inhalers, or other pulmonary medications such as ipratropium,
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25 cromolyn, aminophylline and theophylline. We also assessed self-reported (yes/no) aspirin,
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27 antidepressant (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake
28
29 inhibitors, tricyclic antidepressants), statin, and antihypertensive use. Behavioral risk factors
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31 included (1) self-reported pack-years of cigarette smoking; (2) physical activity ("How many
32
33 times per week do you engage in intense physical activity, enough to work up a sweat?" with
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35 response options of "none", "1-3 times per week" and "4 or more times per week"); (3) alcohol
36
37 use ("How many alcoholic beverages do you drink?": none, moderate [1 drink per day for
38
39 women or 2 drinks per day for men], and heavy [greater than 1 drink per day for women and 2
40
41 drinks per day for men]);¹⁴ (4) medication non-adherence assessed with the 4-item Morisky
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43 Medication Adherence Scale (≥ 1).¹⁹ Potential physiologic risk factors included high-sensitivity
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45 C-reactive protein, self-reported health status based on the physical component of the 12-item
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47 Short-Form Health Survey (SF 12),²⁰ and perceived stress, measured by the 4-item version of the
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1 Perceived Stress Scale (score of ≥ 5 vs. <5).²¹ Other than depressive symptoms, no other
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3 covariate was assessed more than once.
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8 *Statistical Analyses*

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10 Baseline characteristics of participants with and without elevated depressive symptoms at
11
12 baseline were compared using chi-square tests (for categorical variables), Student t tests (for
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14 continuous variables), and Wilcoxon rank sum tests (for non-normally distributed continuous
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16 measures).
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21 Cox proportional hazard regression models were constructed to separately analyze the
22
23 association between depressive symptoms ($\text{CES-D} \geq 4$) and cancer death (from all body sites, a
24
25 subset of nonCVD death), CVD death, nonCVD death and all-cause death. The end date of
26
27 follow-up for this analysis was December 31, 2012. Depressive symptoms were measured on the
28
29 CES-D scale: 1) at baseline (initial telephone call), 2) on average five years after baseline
30
31 measurement, and 3) on average two years after the second measurement. In the analyses, we
32
33 considered depressive symptoms ($\text{CES-D} \geq 4$ vs. <4) as a time-varying exposure, with updates of
34
35 exposure at 5-year and 7-year follow-up. Therefore, each participant contributed up to 3
36
37 measures of CES-D (≥ 4 vs. <4) with a broken-up follow-up time. Follow-up time for each
38
39 participant was calculated from the date of the in-home visit to the date of the earliest of: death,
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41 last telephone follow-up, end of follow-up or next CES-D measure. We additionally graphically
42
43 plotted unadjusted survival functions for participants with elevated vs. nonelevated depressive
44
45 symptoms using the Simon-Makuch method,²² a modification of the Kaplan-Meier method. In
46
47 this context, depression status is treated as a binary time-dependent covariate and study cohorts
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49 are continually updated to contribute to either the $\text{CES-D} \geq 4$ or $\text{CES-D} < 4$ groups.
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3 Unadjusted hazard ratios and 95% confidence intervals (CI) of mortality endpoints were
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5 estimated for those with vs. without elevated depressive symptoms. Adjusted modeling
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7 proceeded in stages (adjusting for baseline covariates), starting with demographic (Model 1) and
8
9 traditional CVD risk factors (Model 2) assessed in prior trials. We then added behavioral (Model
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11 3) and other potential explanatory (Model 4) factors. We also ran an additional model (Model 5),
12
13 which considered intervening first non-fatal stroke and/or myocardial infarction as a time-
14
15 dependent covariate in CVD death outcomes. All analyses were conducted overall as well as
16
17 stratified. We also conducted a formal test for interaction between depressive symptoms and self-
18
19 reported health (defined as excellent or very good vs. good, fair or poor health) in model 4. As
20
21 such, all analyses were conducted overall as well as stratified by baseline self-reported health. To
22
23 evaluate the possibility of non-proportional hazards, we graphically inspected the log-log
24
25 survival plots for depressive symptoms. We tested the Schoenfeld residuals for each model for a
26
27 non-zero slope and all p values were greater than 0.05, indicating compatibility with the
28
29 proportional hazards assumption.
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40 *Sensitivity Analyses*

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42 Sensitivity analyses constructed in parallel to the main analyses examined association of baseline
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44 CES-D measure with mortality endpoints in the sequentially-adjusted Cox proportional hazard
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46 regression models. The end date of follow-up for this analysis was December 31, 2012. Follow-
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48 up time for each participant was calculated from the date of the in-home visit to the date of the
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50 earliest of: death, last telephone follow-up, or end of follow-up.
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1 Missing data in covariates were imputed using chained equations and derived by bootstrapping
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3 across the 5 imputed datasets. Multiple imputation was used for all analyses. Of the 29,491
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5 participants, 2768 (9%) were missing income data, 59 (0.2%) health status, 9 (<0.1%) education,
6
7 26 (0.1%) health insurance, 1087 (4%) diabetes, 16 (0.1%) aspirin use, 70 (0.2%) statin use, 70
8
9 (0.2%) antidepressant use, 333 (1%) anti-hypertension meds use, 439 (2%) physical activity,
10
11 2705 (9%) medication adherence, 213 (0.7%) BMI, 1254 (4%) cholesterol, 1401 (5%) HDL, 912
12
13 (3.1%) pack years, 84 (0.3%) SBP, 1394 (5%) renal function, 381 (1%) QTc, 5681 (19.3%)
14
15 cognitive status, 4 (<0.1%) stress, 1425 (4%) SF-12 and 1881 (6%) CRP. Analyses were
16
17 conducted using SAS software version 9.4 (SAS Institute, Cary, NC) and STATA version 12
18
19 (STATA incorporated, College Station, TX).
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27 Results

28 *Participant Characteristics*

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30 Overall, 1.6% were lost to follow-up and 0.7% were missing baseline depressive symptoms,
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32 leaving 29,491 eligible participants (**Figure 1**) of whom 3,254 (11.0%) had elevated depressive
33
34 symptoms at baseline (CES-D \geq 4). The average age was 64.9 (9.4) years; 55.1% were female and
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36 41.1% were black, 22.0% had diabetes, 9.2% chronic lung disease, and 23.1% CVD. Nearly 33%
37
38 of individuals were physically inactive, 29.2% non-adherent to their medication regimen and
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40 14.5% current smokers. A total of 53.5% of participants self-reported their general health to be
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42 poor, fair, or good compared to 46.5% who reported their health to be excellent or very good, of
43
44 whom 16.0% and 5.3% had elevated depressive symptoms, respectively (eTable 1). Regardless
45
46 of health status, participants with elevated (vs. non-elevated) depressive symptoms were more
47
48 likely to be female, African-American, low income, have more chronic diseases, low physical
49
50 health, and more behavioral risk factors (**Table 1A-B**).
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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)	<i>p</i>
<i>Socio-demographics</i>				
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>				
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, <i>M</i> (SD)	46.4 (10.6)	47.1 (10.2)	40.7 (12.2)	<.001
<i>Physiological risk factors</i>				
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.3 (6.2)	29.2 (6.1)	30.6 (7.1)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	127.6 (16.7)	127.5 (16.5)	128.7 (18.1)	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.1 (40.1)	191.7 (39.8)	194.6 (43.0)	<0.001
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.8 (16.2)	51.7 (16.2)	52.5 (16.3)	0.02
QT Interval, corrected for heart rate, ms, <i>M</i> (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
<i>Medications</i>				
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

1	Aspirin use, n (%)	12790 (43.4)	11376 (43.4)	1414 (43.5)	0.91
2					
3	Antidepressant use, n (%)	4086 (13.9)	3164 (12.1)	922 (28.4)	<.001
4	Behavioral risk factors				
5	Self-reported smoking, pack years, <i>M</i>				
6	(SD)	13.5 (23.1)	13.3 (22.8)	15.5 (24.9)	<.001
7					
8	Current Smoking, n(%)	4263(14.5)	3463(13.3)	800(24.7)	<.001
9					
10	Alcohol use, n (%)				<.001
11	Heavy	1172 (4.1)	1043 (4.0)	129 (4.1)	
12	Moderate	9626 (33.3)	8786 (34.1)	840 (26.6)	
13	None	18116 (62.7)	15925 (61.8)	2191 (69.3)	
14	Physical inactivity, n (%)	10004 (34.4)	8500 (32.9)	1504 (46.9)	<0.001
15					
16	Medication non-adherence, n (%)	7959 (29.7)	6820 (28.7)	1139 (37.8)	<.001
17					
18	Impaired cognitive status	1888 (7.9)			
19	(Cognitive score ≤ 4)		1542 (7.3)	346 (12.6)	<.001
20	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

^aStroke 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.

^bStroke buckle defined as coastal regions within the states of North Carolina, South Carolina and Georgia.

^cCVD defined as baseline coronary heart disease, stroke, periphery artery disease or aortic aneurism.

^dDiabetes 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

Characteristics	Self-reported general health as "excellent or very good"			Self-reported general health as "poor, fair or good"		
	CES-D < 4 (n=12965)	CES-D ≥4 (n=725)	<i>p</i>	CES-D < 4 (n=13219)	CES-D ≥4 (n=2523)	<i>p</i>
Socio-demographics						
Age, <i>M</i> (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, <i>M</i> (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 , <i>M</i> (SD)	27.8 (5.1)	28.4 (5.7)	0.006	30.5 (6.6)	31.2 (7.3)	<.001
Systolic Blood Pressure, mmHg, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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, <i>M</i> (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 (Cognitive score \leq 4)	587 (5.6)	61 (10.1)	<.001	947 (8.9)	285 (13.3)	<.001
Elevated perceived stress (PSS \geq 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

^aStroke 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.

^bStroke 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.

^dDiabetes defined as fasting blood glucose \geq 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

1 of the second and third measurement of CES-D measures did not differ by self-reported health
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3 (eFigure 2). Of the participants with elevated depressive symptoms at baseline, 39.9% and 36.8%
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5 had elevated depressive symptoms at the second and third measures, respectively (eTable 3). Time-
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7 varying depressive symptoms significantly predicted nonCVD disease death (aHR 1.29, 95% CI
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9 1.16-1.44) and all-cause mortality (aHR 1.24, 95% CI 1.14-1.36), while approaching significance
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11 for cancer death (aHR 1.15, 95% CI 0.96-1.38) and CVD death (aHR 1.13, 95% CI 0.98-1.32),
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13 even after adjusting for demographic, clinical, behavioral physiologic factors and time-varying non-
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15 fatal CVD events (**Table 2**, eFigure 3). The results appeared to be particularly robust amongst those
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17 with excellent or very good self-reported general health: all-cause (aHR=1.48, 95%CI 1.27-1.78),
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19 CVD (aHR=1.37, 95%CI 0.99-1.91), nonCVD (aHR=1.54, 95%CI 1.24-1.92) and cancer
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21 (aHR=1.36 95% 0.97-1.91) death. In Model 4, the p-values for the depressive symptoms x health
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23 status interaction term were 0.005 (all-cause mortality), 0.06 (CVD death), 0.03 (nonCVD death),
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25 and 0.20 (cancer death). Results were similar without multiple imputations within 2 decimal places
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31 (**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 <i>socio-demographics</i> (age, gender, region, income, health insurance, education)			
^b Model 2 adds to model 1 <i>medical conditions, physiological factors and medication use</i> (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 <i>behavioral risk factors</i> (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).			

^dModel 4 adds to model 3 *other factors* (physical health component score of SF-12, log-transformed high sensitivity C-reactive protein and perceived stress)

^eModel 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 \geq 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

^aModel 1 adjusts for *socio-demographics* (age, gender, region, income, health insurance, education)
^bModel 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)
^cModel 3 adds to model 2 *behavioral risk factors* (pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication non-adherence).
^dModel 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.

1 It may also be that the effect of chronic illness burden on mortality in those with poor health
2 overwhelms the effects of depressive symptoms. Those with excellent health may also fail to
3 recognize/present for depression. In fact, depressed excellent health individuals in our cohort were
4 less likely to be on an antidepressant. Nonetheless, this finding should be further explored in future
5 studies.
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14 The overall results also have a coherence consistent with prior studies that suggest that depressive
15 symptoms don't solely predict suicide and CVD mortality, but also predict other causes such as
16 cancer death.²⁵ While prior literature suggests that depressive symptoms confer mortality in those
17 with active cancer,²⁶ our study excluded active cancer diagnoses confirming a possible relationship
18 between depressive symptoms and incident cancer mortality. Prior studies have also been limited by
19 inadequate covariate control, and our results for cancer persisted after adjusting for numerous
20 traditional and behavioral risk factors, such as smoking, and approached significance even in
21 models that included physiologic factors.
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35 Overall, baseline and time varying analyses were similar. However, while our baseline analyses
36 suggest that depressive symptoms significantly contribute to cancer death in those with
37 excellent/very good health, time varying analyses allowed for more accurate analyses in line with
38 expectations, suggesting a weaker interaction by health status for proximal cancer mortality in this
39 cohort that excluded those with active malignancy.
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49 This study also supports comprehensive evidence-based depression care management in primary
50 care practices, which have been shown to lower mortality risk.²⁷ Nonetheless, depression treatment
51 remains suboptimal in the general population,²⁸ despite decades of efforts. We too demonstrate that
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1 over time, nearly 40% of patients with elevated depressive symptoms at baseline were still
2 depressed on average 5 and 7 years later. Given the potentially shorter follow-up times in both
3 time-varying analyses (by virtue of follow-up times being broken up by repeat depression
4 measures) and baseline analyses (with 6.5 years of follow-up on average), these findings lend
5 greater urgency to the importance of timely and effective treatment of depressive symptoms to
6 prevent adverse consequences of depressive symptoms on physical health and mortality.
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16 Limitations of our study include the regional specificity, limiting generalizability, and use of the
17 short form of the CES-D, which measures only emotional and not somatic symptoms of depression.
18 Schultz (2002) demonstrated variance between studies using scales and interviews,²⁹ and others
19 have posited even stronger findings in studies with clinical diagnoses (vs. continuous measures).³⁰
20 However, CES-D scales are one of the most widely used scales in clinical practice and in baseline
21 depression to outcome studies and have good sensitivity and specificity.^{9,15,16} We may also have
22 been underpowered to examine CVD and cancer mortality, though the directionality of the
23 estimates remained consistent. The exclusion of active cancer participants as part of the overall
24 REGARDS study criteria, the rationale of which has previously been described,¹⁴ may also have
25 contributed to lack of power. Those with a *history* of malignancy or CVD were not specifically
26 excluded, which is in line with prior depression to mortality studies.^{1,9} Nonetheless, our previously
27 published study, which excluded those with a history of CVD, similarly found a strong relationship
28 between time-varying depressive symptoms and CVD death.³¹
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48 We were also unable to adjust for other psychiatric comorbidities, such as anxiety (though we
49 included stress) or account for subclinical CVD and/or cancer. In addition, the follow-up time (6.5
50 years) was relatively short compared to other studies and we saw even shorter follow-up times
51 between CES-D measures in time-varying analyses, suggesting a short-term effect on mortality.
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1 Our results support prior literature suggesting that shorter follow-up time is associated with greater
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3 excess mortality.^{9,30} However, we did not formally compare short-term to long-term follow-up nor
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5 persistent to fluctuating depressive symptoms nor examine depression as a time-varying coefficient.
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10 Given our results of a relationship between time-varying depressive symptoms and mortality,
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12 further research is warranted to test the long-term efficacy of and adherence to depression treatment
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14 and to explore preventive approaches to decreasing premature mortality risk.³² To our knowledge,
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16 the finding of a relationship between depressive symptoms and mortality in those with excellent or
17
18 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,

1 Shaffer, Safford; *Statistical analysis*: Khodneva, Jannat-Khah; *Obtained funding*: Safford; *Study*
2
3 *supervision*: Safford
4

5 **Conflict of Interest:** None
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21 **Transparency:** Dr. Moise affirms that the manuscript is an honest, accurate, and transparent
22 account of the study being reported; that no important aspects of the study have been omitted; and
23 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
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27 **Data Sharing:** Patient level data or full dataset or technical appendix or statistical code are
28 available if deemed important by reviewers with open access by Monika Safford at Weill Cornell,
29 Nathalie Moise at Columbia University Medical Center, and Yulia Khodneva at University of
30 Alabama at Birmingham. Patient consent was not obtained but the presented data are anonymised
31 and risk of identification is low.
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Figure Legend

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

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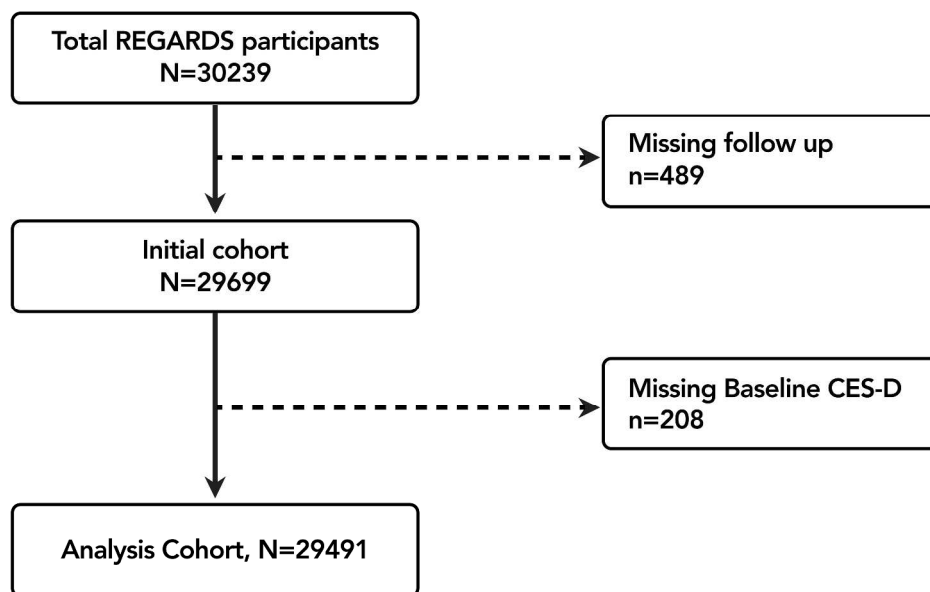


Figure 1. Consort Diagram

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Supplementary Material

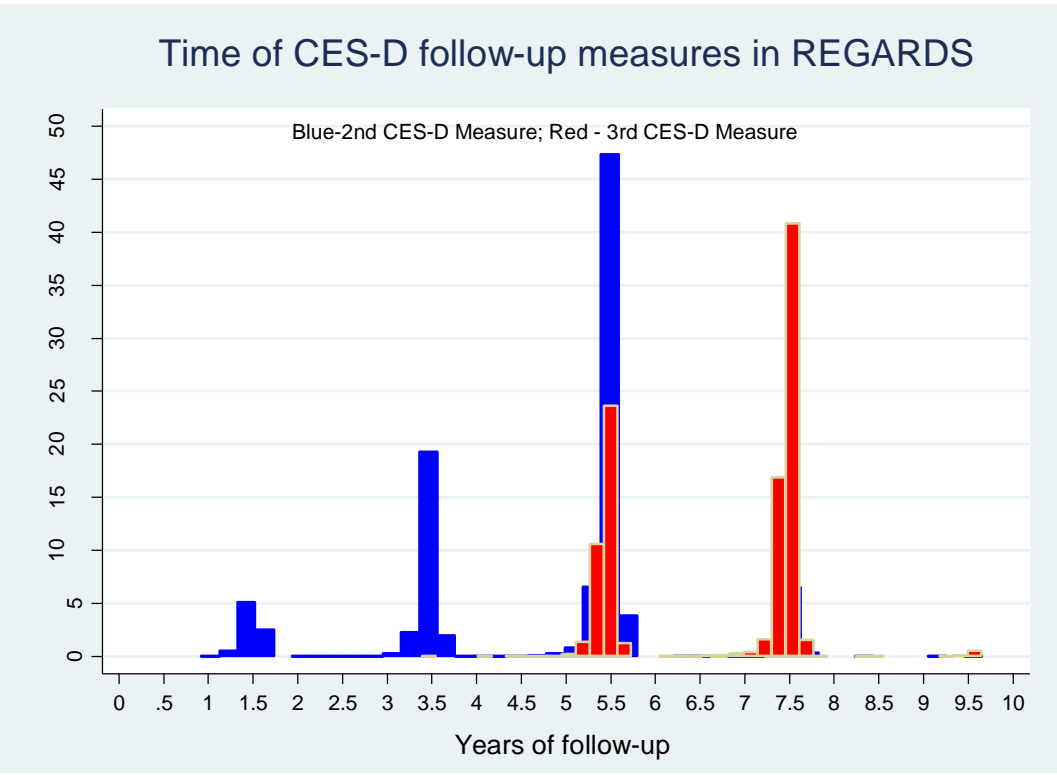
eTable 1. Proportion of persons with elevated depressive symptoms by baseline self-reported health status (original categories, without collapsing).

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 95.9 %	195 4.1%	4710	3444 94.7%	194 5.3%	3638	2109 94.6%	120 5.4%	2229
Very good	8450 94.1%	530 5.9%	8980	6332 93.0%	478 7.0%	6810	3938 92.8%	305 7.2%	4243
Good	9181 89.1%	1124 10.9%	10305	6363 88.6%	818 11.4%	7181	3717 88.9%	464 11.1%	4181
Fair	3424 77.8 %	975 22.2 %	4399	2185 79.7%	556 20.3%	2741	1236 82.0%	271 18.0%	1507
Poor	614 59.2%	424 40.9%	1038	322 61.2%	204 38.8%	526	177 65.3%	94 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

<i>Causes of Death</i>	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	
	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.

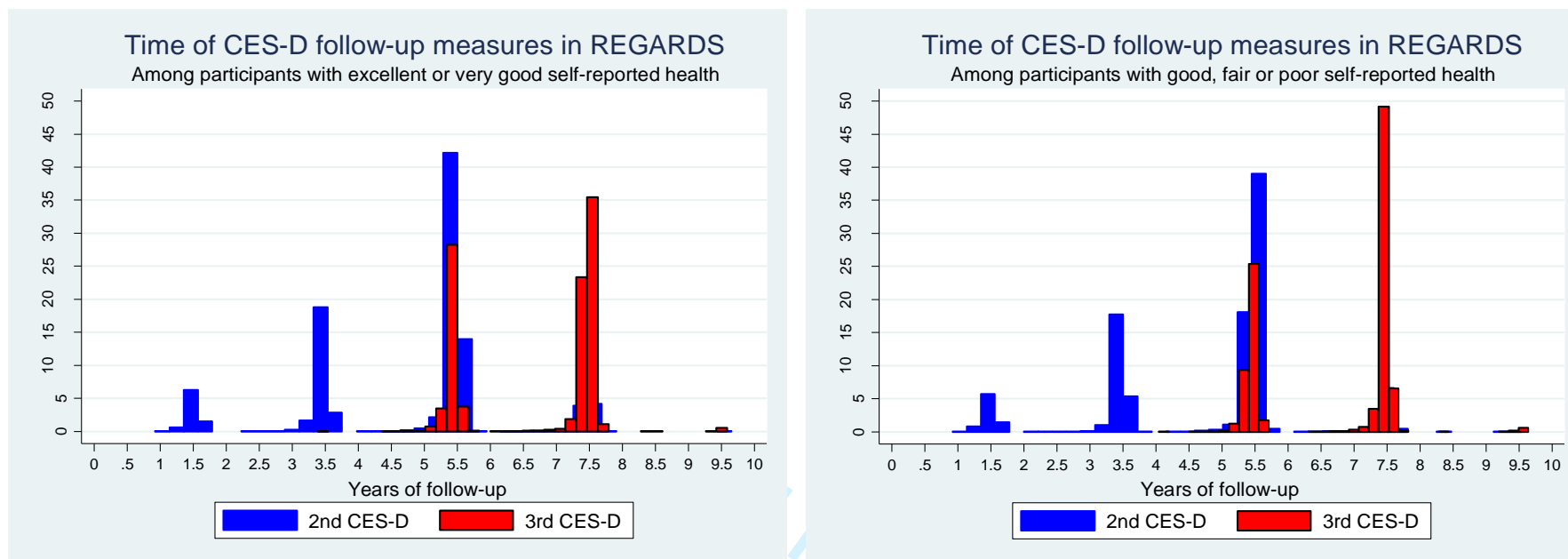


*"Percent" is a proportion of participants reporting CES-D scores at certain times of all participants available for either 2nd follow-up (blue) or 3rd follow-up (red).

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)	<i>p</i> value
<i>Socio-demographics</i>			
Age, <i>M</i> (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)	
<i>General health and medical conditions</i>			
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, <i>M</i> (SD)	45.5 +- 11.0	47.6 +- 9.9	<.001
<i>Physiological risk factors</i>			
Body Mass Index, kg/m ² , <i>M</i> (SD)	29.4 +- 6.3	29.2 +- 6.0	0.0024
Systolic Blood Pressure, mmHg, <i>M</i> (SD)	128.0 +- 17.2	127.0 +- 15.9	<.001
Total Cholesterol, mg/dL, <i>M</i> (SD)	192.2 +- 41.0	191.9 +- 39.0	0.5732
High-Density Lipoprotein, mg/dL, <i>M</i> (SD)	51.4 +- 16.1	52.4 +- 16.3	<.001
QT Interval, corrected for heart rate, ms, <i>M</i> (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

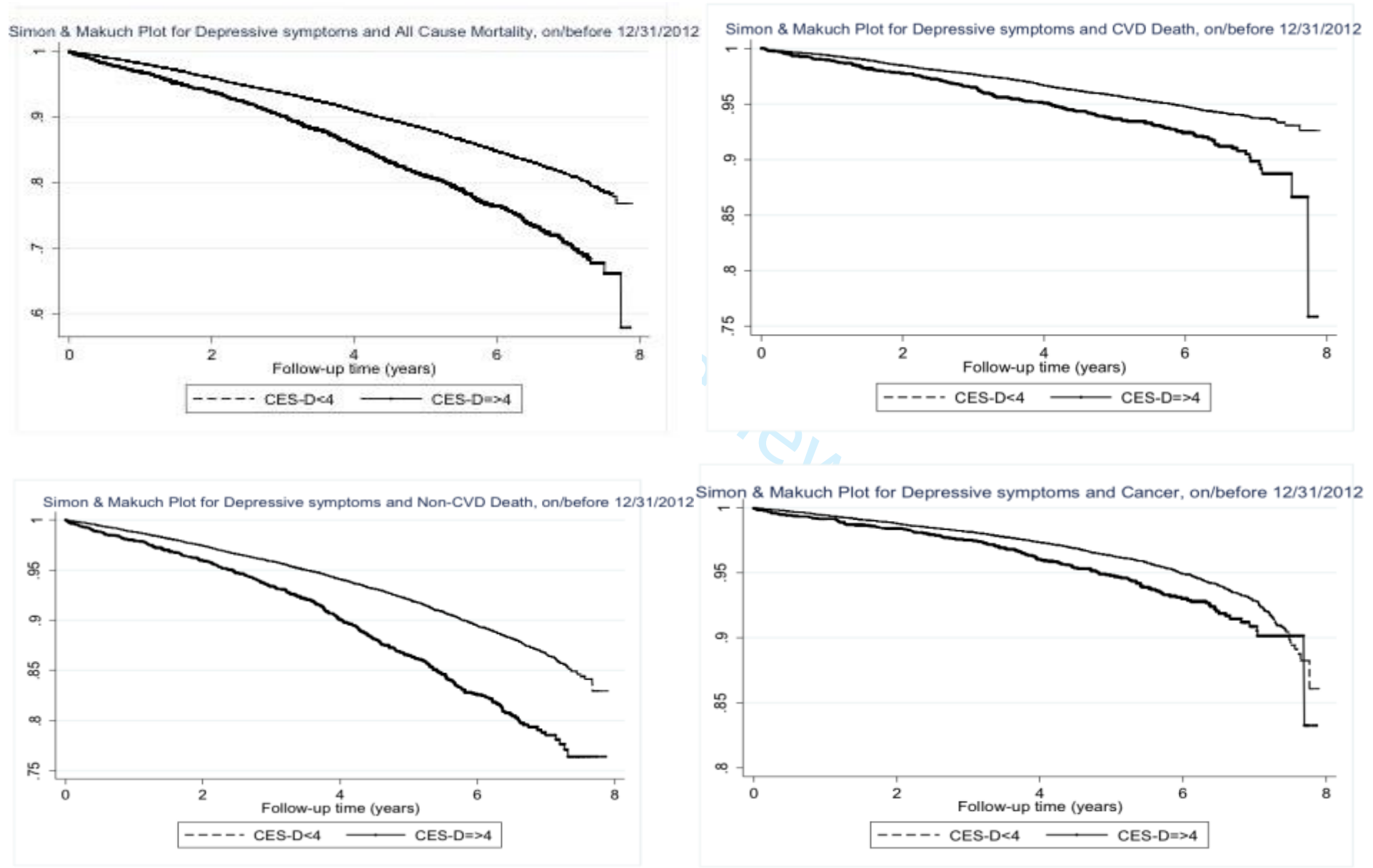
1	Albumin to Creatinine Ratio, mg/g, median,			
2	IQR	7.9[4.8-18.7]	6.9[4.5-13.5]	<.001
3	Medications			
4	Antihypertensive medication use, n (%)	9079 (53.9)	6118 (49.7)	<.001
5	Statin use, n (%)	5344 (31.4)	3951 (31.8)	0.53
6	Aspirin use, n (%)	7297 (42.8)	5493 (44.1)	0.03
7	Antidepressant use, n (%)	2440 (14.4)	1646 (13.2)	0.006
8	Behavioral risk factors			
9				
10	Self-reported smoking, pack years, <i>M</i> (SD)	14.5 +- 24.4	12.2 +- 21.0	<.001
11	Current Smoking, n(%)	2786 (16.4)	1477 (11.9)	<.001
12	Alcohol use, n (%)			<.001
13	Heavy	652 (3.9)	520 (4.2)	
14	Moderate	5180 (31.1)	4446 (36.3)	
15	None	10822 (65.0)	7294 (59.5)	
16	Physical inactivity, n (%)	6150 (36.7)	3854 (31.3)	<.001
17	Medication non-adherence, n (%)	4548 (29.6)	3411 (29.9)	0.59
18	Impaired cognitive status (Cognitive score \leq 4)	1300 (9.4)	588 (5.9)	<.001
19	Elevated perceived stress (PSS \geq 5)	5437 (31.9)	3154 (25.3)	<.001
20				
21				

22 *p* Values from chi square, Student t tests. CES-D = Centers for Epidemiology Studies – Depression scale. CVD =
 23 cardiovascular disease. IQR = interquartile range. *M* = mean. SD = standard deviation.

24 Stroke Belt defined as the states of Alabama, Arkansas, Louisiana, Mississippi, Tennessee and the noncoastal regions
 25 within the states of North Carolina, South Carolina and Georgia. Stroke buckle defined as coastal regions within the states
 26 of North Carolina, South Carolina and Georgia.

27 Diabetes defined as fasting blood glucose \geq 126 or random glucose $>$ 200 mL/dL or oral hypoglycemic or insulin use. CVD
 28 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) and 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
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*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>.

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