

Progression of Coronary Artery Calcification by Depression and Social Support: A Longitudinal
Study from the Multiethnic Study of Atherosclerosis (MESA)

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Abstract

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Background: This study investigated the association between and the progression of coronary artery calcification (CAC) in a large, multiethnic sample using linear mixed effects models as well as the potential buffering role of social support in the association this association.

Methods: Data were drawn from the first five waves of the Multiethnic Study of Atherosclerosis (MESA) from 2000 to 2011. Depression was the covariate of interest and measured by the Center for Epidemiologic Studies Depression (CES-D) scale. The primary outcome, CAC progression, was measured at multiple time points across study waves using chest computed tomography (CT). Social support was measured using the ENRICH Social Support Instrument (ESSI) at baseline and individuals were characterized by ESSI quartile. A linear mixed effects model with random slope and intercept was utilized to evaluate the association of baseline

depression and the progression of repeated CAC measurements over time adjusted for relevant demographic and clinical covariates.

Results: A +1 SD difference in CES-D score was associated with a decrease in CAC progression of 1.5 Agatston units per year ($\beta = -1.5$, 95% CI = -2.9, -0.1). Estimates varied minimally when grouped by ESSI quartile (Q1: -1.0 [-3.2, 1.1], Q2: -3.7 [-6.8,-0.6], Q3: -0.1 [-3.5, 3.2], Q4: -2.1 [-7.8, 3.5]).

Discussion: We observed a small but clinically insignificant inverse association between baseline CES-D score and the progression of CAC overall, and no meaningful differences were observed by quartile of ESSI. This study was the first to use linear mixed effects modelling for the association between depression and CVD as well as the first to incorporate the potential buffering role of social support.

Introduction

Depression in older adults

As recent Census estimates illustrate, older adults are quickly becoming one of the largest demographic groups in the US¹, prompting considerable interest in the public health field. In the general population, depression is estimated to be one of the leading causes of overall disability, with the 3rd highest rate of years lost to disability (YLD)² and has been argued to be one of the most important determinants of health-related quality of life. Among older adults, recent estimates of depression prevalence vary by a variety of factors as well as definitions of both “older adults” and depression. One of the largest recent representative samples of the US population estimated that 14% percent of those 55 and older meet criteria for depression.³ Several community samples of adults 60 and older have provided estimates of depression prevalence ranging from 4% to 15%⁴⁻⁶. Estimates tend to be higher with older age cutoffs⁷ as well as in clinical samples⁸. Additionally, estimates appear to vary by depression instrument even in the same sample⁶, as older individuals experiencing depression may present with different types of symptoms compared to younger adults⁹.

A recent meta-analysis placed the risk of mortality associated with depression at approximately 50% higher than that in non-depressed comparison groups¹⁰, and some of the most recent Global Burden of Disease (GBD) estimates have suggested that depression may account for as many as 2.2 million deaths a year globally¹¹. This impact appears to be largely due to its role as a risk factor for a variety of other poor health outcomes including cardiovascular disease¹².

Depression and CVD

A meta-analysis investigating both the etiologic and prognostic implications of depression on coronary heart disease (CHD) found that on aggregate those with depression had a roughly 80% increased risk of fatal CHD or incident myocardial infarction compared to those with no depression¹³. Another meta-analysis of longitudinal studies investigating the etiologic contribution of depression to the burden and incidence of ischemic heart disease (IHD) showed a 56% higher likelihood of IHD in those with major depression vs. no major depression¹⁴. In a cohort of exclusively older adults (age ≥ 55 years old), van Marwijk et al. found that those with a diagnosis of depression at baseline using DSM-IV criteria had two and a half times the incidence of CVD in the 2 year follow-up period than did the non-depression comparison group¹⁵.

Subclinical measures of CVD are of increasing interest to researchers and clinicians due to their ability to communicate information about CVD risk before individuals become symptomatic.^{16,17} Depression has previously been shown to be associated with such subclinical measures. One study found that over a ten-year follow up period, individuals who endorsed depressive symptoms at more than one time point had considerably higher odds of high coronary artery calcification (CAC)¹⁸. A three year study found a significant association between baseline depression and progression of carotid intima-media thickness (CIMT)¹⁹. Additionally, individuals in a Dutch cohort with a DSM-IV diagnosed depressive disorder had considerably higher odds of developing a low ankle-brachial index score over a 6-year follow up²⁰. One potential limitation to these studies, however, is that by categorizing depression using traditional clinical cutoffs, rather than as existing on a continuum, some of the true depression-CVD relationship may be missed in those with subclinical or subsyndromal depressive symptoms^{21,22}.

To date two cross-sectional studies from the Multiethnic Study of Atherosclerosis (MESA) have investigated the association between depression and subclinical atherosclerosis measures, with one finding no association between depression and CAC ²³ and the other finding an association between depression and both heart rate and heart rate variability (HRV) ²⁴. To date, no MESA studies have investigated the association between depression and subclinical atherosclerosis longitudinally.

Previous work on the association between depression and the progression of CAC has been somewhat limited. A small study of 146 middle-aged women enrolled in the Study of Women's Health Across the Nation (SWAN) study found some association between depressive episodes and the progression of CAC ²⁵, and similarly, a slightly larger study also from the SWAN Heart cohort demonstrated a modest association between baseline CES-D score and the progression of CAC ²⁶. Both of these studies, however, used a simple dichotomous definition of progression based on fairly small change score. This methodology may not make full use of available data to model progression and may be more susceptible to bias such as regression to the mean. In another study using a similarly small cohort of middle-aged women, baseline CES-D score was not found to be associated with the progression of CAC, however their observation period (approximately 3 years) may not have allowed the researchers enough time to observe a change in CAC trajectory ²⁷.

Though far less has been written on the mechanisms thought to link depression and CVD, it is thought that the causal pathways are similar to that of chronic stress and CVD. Two broad categories of pathways are generally recognized as explaining observed depression

and CVD associations. *Behavioral* pathways describe behavioral risk factors that may mediate the association between depression and CVD. The most prominent of these are cigarette use, poor diet, excess alcohol use, and lack of exercise^{28,29}. Additionally, it is thought that several *physiologic* mechanisms may also explain part of the depression and CVD association, such as dysregulation of the autonomic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis²⁹ as well as increased inflammation and limited heart rate variability (HRV; Musselman, Evans, & Nemeroff, 1998).

Social support

Previous research suggests that social support may help buffer the negative impacts of aging on physical and mental health among older adults³¹, with perceived social support appearing to be a particularly important protective factor³². Specifically, social support has been shown to be potentially protective against depressive symptoms in older adults³³ with similar findings having been shown across various racial and socioeconomic populations.³⁴⁻³⁷ In one of the only meta-analyses on the topic to date, Garipey and colleagues³⁸ found considerable support for the protective effect of social support against the development of depression in older adults.

Social support itself has been linked to CVD in previous studies³⁹, though previous work in MESA found insufficient evidence for an association between social support and CVD events⁴⁰. Additionally, two cross-sectional studies in MESA found modest inverse associations between social support and biomarkers associated with CVD.^{41,42}

Within the stress literature, the *buffering hypothesis* has been put forth to incorporate social support in the study of stress and CVD. This hypothesis posits that the strength of the stress-CVD association will be attenuated or “buffered” in individuals with high social support. Some support has been shown for this relationship^{43,44}, which may identify social support as a potential point of intervention. As the pathways linking stress and CVD are thought to be similar to those linking depression and CVD, it is plausible that the association between depression and CVD may similarly be “buffered” by social support.

Current Study

We are unaware of any previous studies that have investigated the association between depression and subclinical CVD longitudinally in a large, diverse, and older cohort nor any that have examined the role social support may play on the depression-subclinical CVD relationship over time. This study seeks to analyze the degree to which depression is associated with the progression of CAC in a large, multiethnic sample using more sophisticated methodology to model the progression of CAC. Additionally, as a secondary aim, we set out to test the buffering role of social support in the association between depression and the progression of CAC.

STUDY DESIGN AND DATA SOURCES

Data were drawn from the Multiethnic Study of Atherosclerosis (MESA), a prospective cohort study of risk factors for sub-clinical atherosclerosis in an ethnically diverse sample of US adults age 45-84 years at baseline. Between 2000 and 2002, 6,814 participants were recruited from six communities across the United States: Baltimore, MD, Los Angeles, CA, Saint Paul, MN, Chicago, IL, Winston-Salem, NC, and New York, NY. Demographic data as well as cardiovascular disease (CVD) outcomes and risk factors were collected at 5 waves approximately every two years from 2000 to 2011 (Bild et al., 2002). Wave 1 included the most exhaustive battery of measures with subsequent waves repeating selected measures.

A roughly equal number of participants were recruited at each study site with roughly equal numbers of males and females. Sampling was conducted so as to ensure that at least two of the following race/ethnic groups were sampled at each site: Chinese Americans, Hispanic Americans, African Americans, and European Americans. The sampling protocol sought to ensure a roughly equal distribution of age up to 75 years old, with those 75 years of age sampled at lower frequencies.

All participants were free of CVD at baseline and had not previously experienced a cardiovascular event such as heart attack or stroke. Individuals were excluded if they were pregnant, weighed over 300 pounds, living in or on the waiting list for a nursing home, displayed

signs of cognitive inability, or had plans for relocation or long-term health issues which would have challenged long-term participation in the study.

MEASURES

Covariate of Interest – The exposure, depression level at baseline, was measured using the Center for Epidemiologic Studies Depression Scale (CES-D)⁴⁵. The CES-D is a 20 item instrument to evaluate depression symptoms in the general population. Each item asked respondents to express the frequency of a given symptom (e.g. “I felt hopeful about the future”) over the previous week using one of four responses (“Rarely or none of the time (less than 1 day),” “Some or a little of the time (1-2 days),” “Occasionally or a moderate amount of time (3-4 days),” or “Most or all of the time (5-7 days)”). Positive items indicating the lack of depressive symptoms (e.g. “I enjoyed life”) were reverse coded, and each item was scored on a 0-3 scale. Item scores were totaled to determine the overall score, which ranged from 0 to 60, with higher scores indicating more severe depression symptoms.

The CES-D demonstrated reasonable psychometric properties. Radloff⁴⁵ showed test-retest reliability estimates ranging from .32 to .60. The emphasis on recent symptoms is likely to explain the relatively low reliability of these estimates. To assess validity, the CES-D has been compared to other similar self-report depression instruments with correlations ranged from .43 to .61 depending on the instrument used for comparison. In a sample of psychiatric patients, the CES-D correlated modestly with two other depression scales at admission (.44, .54), though the correlations increased noticeably after 4 weeks of treatment (.69, .75). This may suggest that the

CES-D is less valid in individuals with more severe depression, as it was thought that the improvement in symptoms explained much of the increased correlation with other measures. The CES-D also demonstrated strong internal consistency with a Cronbach's Alpha of greater than .80 in all subgroups.

In order to make findings more interpretable for readers unfamiliar with the CES-D, baseline CES-D score was scaled so that the mean was 0 with a standard deviation of 1.

Outcome – The outcome measure, CAC, was measured in Agatston units using chest computed tomography (CT) scan using either a cardiac-gated electron-beam computed tomography scanner (Chicago, IL, New York, NY, and Los Angeles, CA) or a multidetector computed tomography system (Baltimore, MD and St. Paul, MN).^{46,47} Previous work found negligible differences measurement of CAC between the two methods.⁴⁸ All participants underwent CT scans at baseline. Scans were staggered in subsequent waves such that approximately 50 percent of participants were intended to receive a CT scan at exam 2, the other 50 percent at exam 3, and 25 percent at exam 4.⁴⁷ Approximately 50% of the sample underwent an additional CT scan at exam 5. As of exam 5 in our sample, 12% had received four scans, 42% had received three scans, 36% had received two scans, and 11% had received only the baseline scan.

Chest CT is a strong predictor of coronary calcium levels, with previous studies comparing chest CT scans to histologic measurements of coronary calcium having found correlations above 0.9.^{49,50}

Additional covariate selection – Confounders were defined as baseline variables which were likely associated with the exposure (baseline depression) and the outcome (progression of CAC), and not on the causal pathway between exposure and outcome. A preliminary literature review was conducted to identify a group of variables associated with either the exposure or the outcome. Additionally a causal diagram was created to conceptualize the interrelationships between exposure, outcome, and covariates (Figure 1). Variables were eliminated as potential confounders if they were likely to be a consequence of the exposure or if exclusion criteria were likely to block their role as potential confounder.

Preliminary analyses were conducted among the remaining variables of interest to evaluate the strength of their associations with both exposure and outcome. Based on the above criteria for confounding, the following baseline variables were included in the final adjusted model: age, gender, education level, race/ethnicity, income, self-reported general health, and chronic stress burden for greater than 6 months.

Chronic stress burden – Chronic stress burden was evaluated using a composite measure which assessed psychosocial stressors across multiple domains to characterize stressful life experiences⁵¹. Answers across domains were aggregated, and an overall score assigned on a scale of zero to five: zero representing no stress and five representing stress in all domains.

Age – As the minimum age for inclusion in MESA was 44, participant age was transformed to years from age 44 for the sake of interpretability of model intercepts.

Self-reported general health – Participants were asked to rate their general health on a scale of 1 to 5, with 1 being “poor” and 5 being “excellent.”

Social support – Baseline social support was measured using the ENRICH Social Support Instrument (ESSI), a short instrument developed to assess perceived social support in large scale, epidemiologic studies⁵². The ESSI consists of 6 questions in which participants were asked about the availability of social support (“Is there someone available to whom you can count on to listen to you when you need to talk?”) using a five point scale (“None of the time,” “A little of the time,” “Some of the time,” “Most of the time,” or “All of the time”). A seventh item asks whether the individual was married/living with a partner. Scores range from 0 to 30, with higher scores indicating higher levels of social support.

The ESSI has previously demonstrated strong internal consistency as well as test-retest reliability⁵³. Compared to assessments from the longer form Perceived Social Support Survey, individuals’ scores on the two instruments showed a correlation of $r = .63$, though there was considerable heterogeneity in correlation coefficients by both sex and race⁵².

Individuals were excluded from the sample if they were missing baseline data on any of the model covariates listed above with two exceptions. Missing baseline income was imputed from Exam 2 ($n = 149$). Additionally, chronic burden (6 months) was imputed from Exam 1 point-in-time chronic burden for individuals with data on the latter but not the former ($n = 67$). The point-in-time measure asked about stressors at the time of exam as opposed to in the six months previous. See the flow chart in Figure 2 for further information of exclusion and imputation.

ANALYSES

Primary

Linear mixed effects models were utilized to analyze the association between baseline CES-D and the progression of CAC across study waves. To account for clustering of CAC measurements across time points among participants, a random intercept and random effect for time were included at the participant level. All other covariates were treated as fixed effects. The association between baseline CES-D and the progression of CAC was evaluated by the coefficient of an interaction term between baseline CES-D and years from baseline exam as a continuous variable.

The fully adjusted model can be represented by the following form:

$$Y_{it} = \alpha_0 + X_{dep_{i0}} \alpha_1 + X_{ci0} \alpha_2 + a_i + t_{iv} \beta_0 + X_{dep_{i0}} t_i \gamma_1 + t_{iv} b_i + \epsilon_{iv}$$

Where:

Y_{it} { CAC for individual i at time t (years from baseline)

$X_{dep_{i0}}$ { baseline depression ($t = 0$), as measured by CES-D, for individual i .

X_{ci0} { Vector of time invariant covariates (C) measured at baseline.

t_{iv} { time in years from baseline for individual i at exam v .

α_0 = mean CAC level for individuals with baseline/0 value of all covariates

α_1 = coefficient for association between baseline depression and baseline CAC

α_2 = coefficient for associations between other baseline covariates (time invariant) and baseline CAC

a_i = individual level, random intercept

β_0 = represents the group averaged progression of CAC by time t in those with baseline/0 value of all covariates

γ_1 = coefficient for interaction between baseline CES-D and progression of CAC by year, *coefficient of primary interest*

b_i = deviation in slope of CAC progression over time for each individual i from the overall slope.

ϵ_{iv} = individual level error term for Y_{iv}

To determine whether this association differed by level of social support, the fully adjusted model was run separately by quartile of baseline ESSi score. Additionally, the fully adjusted model was run including a three-way interaction term for baseline CES-D score, time, and ESSi quartile, treated as a grouped linear (ordinal) variable, in order to assess statistical significance of the difference of the association between baseline CES-D and the progression of CAC across quartiles of social support.

To evaluate the difference in association by marital status, the fully adjusted model was run separately by marital status (“Married/Living as Married,” “Divorced/Separated,” “Never Married,” and “Widowed”), and the estimates for the interaction between CES-D and time since baseline were compared for clinically meaningful differences and trend.

Sensitivity analyses

In addition to treating baseline CES-D as a continuous variable, sensitivity analyses were run dichotomizing baseline CES-D score by the recommended clinical cutoff (16)⁴⁵, as well as a higher threshold of a score of 21 as suggested by Lyness and colleagues for use with older adults⁵⁴.

Social support was also evaluated by marital status at baseline categorized in four levels: “Married/Living as Married,” “Divorced/Separated,” “Widowed,” or “Never Married.” Individuals who responded “Prefer not to Answer” will be treated as missing.

Additionally, as previous research has suggested that the social support derived from marital status may differ between older males and females,⁵⁵ the fully adjusted model was run separately by level of a combined gender and marital status variable, and levels of marital status were collapsed in order to preserve sample size in subgroups (“married female,” “unmarried female,” “married male,” and “unmarried male”).

The primary models were run separately among subgroups of the sample grouped by age group (45-54, 55-64, 65-74, 75+) to rule out noticeable heterogeneity of effects by age group.

Body mass index (BMI) category was not initially included in the primary analyses due to a lack of observed association with baseline CES-D in preliminary analyses as well as concern about BMI at baseline being influenced by depression at a previous time point. Due to a considerable body of literature demonstrating associations between BMI and depression,⁵⁶⁻⁵⁸ we conducted additional sensitivity analyses including baseline BMI, categorized as normal, overweight or obese, as a covariate to evaluate whether its inclusion meaningfully affected our estimates.

HUMAN SUBJECTS/ ETHICAL REVIEW

This project was exempt from Institutional Review Board review as it does not involve intervention/interaction with participants or identifiable private information as per University of Washington's Institutional Review Board guidelines. Informed consent was received from participants at each study site at time of data collection.

Results

Sample Characteristics

We included 6,625 participants in our final sample after 188 participants were removed for missing CES-D, income, chronic burden, ESSI, or education data (Figure 2). Overall there were relatively low rates of attrition, with approximately 87% of individuals having participated in exam 4 or later (Figure 3).

Characteristics of the final sample can be found in Table 1. There was a slightly higher proportion of female than males overall. Mean age was 62.0 (SD = 10.2), with White/Caucasian the largest race/ethnic group (38.6%) followed by Black/African-American, Hispanic, and Chinese-American. The majority of participants were represented in one of the middle income groups (\$25k-\$75k) with the higher income (\geq \$75,000) and lower income (\leq \$25k) groups constituting roughly equal proportions of the remainder. Around a third of the sample had a Bachelor's degree or higher (35.6%) with a similar proportion having completed some college (28.5%). Those having a high-school education and those who did not complete high school constituted similarly sized groups (18.0%, 17.9%). The mean ESSI score for the full sample was 24.2 (SD = 5.3), and mean chronic burden score was 1.1 (SD = 1.2). Those reporting having an ongoing health problem made up 21% of the sample.

When grouping the sample by the CES-D clinical cutoff (\geq 16), the higher depression group was more likely to be female, Hispanic, and to have lower income and education. Mean ESSI was lower in the higher depression group (19.8 vs. 24.8) and chronic burden was higher (higher

depression: mean = 2.0, SD = 1.4 vs lower depression: mean = 1.0, SD = 1.1). Additionally, those reporting a serious ongoing health problem were more likely to be in the high depression group compared to those with low CES-D scores (25.6% vs. 9.5%).

At baseline, the distribution of CES-D was strongly positively skewed, with the majority of individuals having a score of zero (Figure 4). The maximum score was 53, and the mean was 7.6 (SD: 7.6). Distribution of Agatston Scores (CAC) were also similarly skewed at baseline, with the majority of participants having very low scores at or near zero (Figure 5). Mean baseline Agatston Score was 143 (SD: 412). Distribution of ESSi scores were heavily negatively skewed, with 17.6% having the maximum score (Figure 6).

Multivariate models

Table 2a shows the results of the primary linear mixed effects models. From the fully adjusted model, participants experienced on average an increase of 24.8 Agatston Units of CAC per year (95% CI = 23.4, 26.2), with an interclass correlation coefficient of .84, suggesting that most of the variability in CAC was found between rather than within participants. At baseline, CES-D was negligibly associated with CAC cross-sectionally ($\beta = -4.1$, 95% CI = -14.7, 6.4). When examining its association with progression of CAC, there was a statistically significant interaction between baseline depression and time, with a +1 SD difference in CES-D score associated with a decrease in CAC progression of 1.5 Agatston units per year ($\beta = -1.5$, 95% CI = -2.9, -0.1). This suggests that those with higher depression experienced a slightly attenuated progression of CAC.

Regarding effect modification by social support, the association between baseline CES-D and the progression of CAC varied minimally by quartile of baseline ESSI though there was no discernible pattern (Q1: -1.0 [-3.2, 1.1], Q2: -3.7 [-6.8,-0.6], Q3: -0.1 [-3.5, 3.2], Q4: -2.1 [-7.8, 3.5]; Table 2b). There was a modest difference in the association between baseline CES-D and CAC progression by marital status. A 1 SD higher CES-D score was associated with a lower progression of CAC by 3.1 Agatston units per year (95% CI = -5.1, -1.1) among married individuals and a 3.0 Agatston unit per year *higher* progression in widowed individuals (95% CI = -1.5, 7.5; Table 2c). By combined gender and marital status (married/unmarried), a 1 SD higher CES-D score was associated with a 2.7 Agatston unit (-6.3, 0.9) higher progression in married males and 1.1 Agatston unit (-4.0, 6.3) higher progression in unmarried males (Table 2d).

Sensitivity Analyses

Model results dichotomizing baseline CES-D scores are presented in Table 3a. In individuals who had a baseline CES-D score of ≥ 16 , the average progression of Agatston Units per year was 3.1 units lower than in those with a baseline CES-D of below 16 (95% CI = -7.3, 1.2).

Individuals with a baseline CES-D score of ≥ 21 had an average progression of Agatston Units per year 0.4 units lower than in the CES-D < 21 group (95% CI = -6.0, 5.2). Though qualitatively consistent with the estimates from our main models, neither of these differences were statistically significant.

Between ten year age groups, results of the association between baseline CES-D and the progression of CAC are shown in Table 3b. There were negligible differences between groups, with estimates ranging from -2.3 (-8.4, 3.9) in the oldest group [74-84) and 0.6 (-2.4, 3.6) in the [64-74) group, with no noticeable trend across groups.

Discussion

Our study found a modest inverse association between depression and the progression of CAC. In our sample, individuals with higher CES-D scores seemed to have a shallower slope of CAC over time, which was opposite to the hypothesized direction of this relationship. Additionally, there were only modest, though statistically significant, differences in estimates when stratifying by level of reported social support.

Previous work has found positive associations between depression and the progression of CAC.^{25,26} Janssen and colleagues²⁶ found depression to be positively associated with CAC progression in a smaller cohort of females (n = 346) within a smaller age range (42-52) than our study. When our analyses were stratified by sex (Table 2d), there was a very small positive association between baseline CES-D and the progression of CAC in unmarried females, though it was not statistically significant. There was essentially no difference in the association in married females. While there is some overlap between the Janssen study and ours, the larger and more

diverse sample in our study may explain some of the attenuation of the association in our study, however this still would not explain the difference in direction of the association especially as the overall association was still negative when we limited our analyses to a more comparable age range (44-54; Table 3b).

Both previous studies of depression and CAC progression measured progression using a simple change score. It is possible that the difference in our findings are at least in part due to our utilization of a linear mixed effects model, which uses data from multiple time points to fit a linear function for CAC progression. If the true progression of CAC were linear, the results of a change score ought to be similar to a linear model. However, if progression were non-linear, perhaps increasing exponentially over time, a linear model would likely provide a more conservative estimate than that of a change score (Figure 7). Therefore our use of a linear model as opposed to a change score is only likely to explain some of the attenuation of the progression compared to previous studies but not the difference in estimated direction of the association.

We know little about the dose-response relationship between depression and CVD. Though we measured depression at one time point, it is likely that the true risk for CVD associated with depression is a function of cumulative exposure over time. It is assumed, though, that cumulative lifetime depression would be reflected at least partially in the baseline depression measurement, and we would expect to see at least some association between baseline depression and CAC as a result. However we had little ability to distinguish episodic from chronic depression within our data, which may have attenuated the strength of a true relationship.

When incorporating baseline social support, there was little variability in the estimates of the association between baseline depression and CAC progression by ESSI quartile. The association was strongest amongst the second quartile (ESSI = 22-25) but was still in the opposite direction than hypothesized ($\beta = -3.7$, 95% CI = -6.8, -0.6). Estimates varied more by marital status, with the baseline depression associated with a modest flattening of CAC progression among married individuals ($\beta = -3.1$, 95% CI = -5.1, -1.1) and a slight increase in progression among widowed individuals ($\beta = 3.0$, 95% CI = -1.5, 7.5). Married males and females had modest negative associations between depression and CAC progression while their unmarried counterparts had modest positive associations. While none of the individual associations were statistically significant, the confidence intervals of the positive association in unmarried females and the negative association among married males only just covered the null. Overall, there was no meaningful trend when stratifying the sample by baseline ESSI quartiles, but the negative association between baseline depression and CAC progression seemed to be primarily driven by married males.

We conducted an additional post hoc analysis removing individuals with no detectable CAC (Agatston = 0) at baseline in order to lessen the skew of baseline CAC. After removing those with zero CAC at baseline, the association between depression and the progression of CAC was very small, positive, and not statistically significant. Similar results were found in the social support subgroups (ESSI quartiles, marital status, gender/marital status). Though some estimates were still negative, all were near zero and not statistically significant. It does appear that zero CAC individuals may have driven a considerable amount of the negative association seen in the

full sample. As depression likely represents a heterogeneous group of disorders, it is possible that in individuals with no CAC high depression represents a subtype with qualitative difference than that present in high depression individuals with higher levels of baseline CAC.

Recent depression literature has advocated for depression to be studied and conceptualized by subtype.^{21,62} Of particular interest to our study is the distinction between atypical and melancholic subtypes of depression. The atypical subtype is most often associated with increased appetite, weight gain, excess sleep, fatigue, and interpersonal sensitivity as contrasted with the melancholic subtype which is characterized by loss of pleasure (anhedonia), mood non-reactivity, trouble sleeping, and loss of appetite^{63,64}. It may be important to distinguish between these subtypes, because previous work has found differences in physiologic impacts relevant to CVD. HPA axis dysregulation is thought to be more strongly associated with atypical depression than melancholic⁶³, and substance abuse is more common in atypical depression cases⁶⁴.

Perhaps not surprisingly, previous work has suggested that the association between depression and CVD may differ by depression subtype²¹. The largest scale study to date which used data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found individuals with atypical depression had considerably higher incidence of CVD than other non-atypical types⁶². It is possible that the CES-D is not the best instrument to capture the different subtypes. Though no previous work has explored the CES-D's performance in specific subtypes of depression, a cursory look at its specific items may suggest that it prioritizes melancholic rather than atypical depression. Several questions such as "my appetite was poor" and "I lost a lot of weight without trying to"⁴⁵ seem much more consistent with the melancholic subtype. As such the CES-D may not be capturing the most relevant aspects of depression associated with

CVD risk. Of additional concern is the suspicion that atypical depression may have an earlier onset than melancholic⁶⁵, which could have further complicated analysis in our sample of older adults.

The variability in the direction of the association between depression and CAC progression between our study subgroups (age, social support, marital status) may be partially explained by depression in those groups representing different subtypes. More moderate depression in the same group may represent atypical depression, which may be associated with a more rapid progression of CAC than melancholic depression, perhaps even when the melancholic depression is more severe. In this scenario, it is plausible that the overall association between depression and CAC progression than would be negative.

Beyond mechanistic explanations of the unexpected inverse associations we found, there are two plausible statistical explanations that are important to consider. First, the extreme skew of both CAC progression and baseline CES-D may have contributed to the inverse association between the two. Figure 8 shows the crude association between baseline CES-D and CAC progression (slope) to illustrate this phenomenon. As Agatston score progression (CAC) rarely dips below zero and CES-D score cannot dip below zero, the result is a wedge shaped distribution with considerably more variability in CAC slope at lower values of CES-D, due to the strong positive skew of the CES-D score distribution. Put another way, with the vast majority of individuals having very low CES-D scores, we would expect to see a greater range of CAC slopes at lower CES-D values, as there is more opportunity for extreme values by chance. Even in the absence of a true association, in which the true linear relationship would be horizontal, we might expect to

see a slight inverse association as an artifact of skewness. For example, if CAC progression slope were more normally distributed, slopes below zero would be expected to flatten the linear trend. In a post-hoc analysis, we log transformed both CES-D and Agatston score to reduce skew. The log transformed model still showed a slight inverse association between CES-D and CAC progression, but it was very small and not statistically significant ($p = .81$). This suggests that much, but not all, of the inverse association observed in our main models was a product of data skewness.

Second, it is plausible that individuals with high CAC progression and high baseline CES-D score had higher rates of attrition. This may essentially introduce a collider stratification bias, as we inherently conditioned on non-attrition, which might have been a collider of baseline CES-D and CAC progression (See Figure 9). It is unlikely, however, that this would explain the entirety of the negative association between baseline CES-D and CAC progression. Overall attrition was low in our sample, with only 5% of participants failing to contribute data past baseline and the vast majority having contributed data at waves four or five (87%; Figure 3). Additionally, a strength of the linear mixed effects model is its ability to compare the progression of an outcome variable between individuals with differing numbers of observations. Under the assumption that the trend is approximately linear, progression can be calculated for individuals with only two time points, limiting the potential bias of informative censoring in the presence of at least two time points. Such bias would only be present in the 11% of participants who received only one CT scan.

Contrary to convention in CVD literature, we opted not to include several traditional CVD risk factors in our model. This decision was due to a lack of observed association with baseline depression in our preliminary analyses and subsequent concerns that inclusion might thus introduce collider stratification bias,^{66,67} as many of these risk factors may be downstream from baseline depression. Inclusion in our models may have induced an artificial association between depression and CAC progression via unmeasured covariates associated with the cardiovascular risk factors and CAC progression by conditioning variables potentially affected by baseline depression.

Overall several important limitations ought to be noted in our study.

1. Little previous work is available to inform the selection of a relevant observation period between depression and CAC progression. It is possible that the latent period between depression and CAC progression is outside of the observation period for our study (e.g. depression may take 15 years to affect CAC when our observation period is only 10). It is also plausible that depression at certain ages is more salient to the progression of later life CAC, though sensitivity analyses in which comparisons were restricted to individuals within the same 10 year age range failed to demonstrate meaningful differences in our estimates from the larger sample.
2. We have limited information on the persistence of depression over time which may be an important factor in predicting CAC progression.²⁵ Persistence or recurrence of depression may also provide information about subtype of depression (e.g. atypical versus melancholic), and the association between depression and CAC may vary based across

subtypes.²¹ Perhaps most importantly, it is highly likely that cumulative “exposure” to depression may represent an important aspect of the depression-CAC progression link.

3. As with most instruments assessing psychosocial constructs, a degree of measurement error is likely inherent to the CES-D, as there is no objective standard by which to assess the underlying construct. There is some evidence in the literature that this measurement error may differ by race and immigration status⁶⁸, which may have attenuated any true association. Additionally, previous work has noted concern that CES-D score is associated with anxiety⁶⁹.
4. Consistent with some previous literature⁷⁰, we found a modest association between attrition and baseline depression (see Table 4), suggesting that the data is not missing completely at random. This association, however, is not expected to be large enough to meaningfully affect estimates, and a strength of the linear mixed effects model is its ability to yield valid estimates in the presence of missing data, assuming data are missing at random.

Despite its limitations, our study does make an important contribution to the literature on depression and cardiovascular disease, particularly in older adults. With the aging population, both depression and cardiovascular disease among older adults have independently been points of interest for public health professionals. Furthermore, understanding the role that social support may play in that dynamic may elucidate alternative approaches to prevention, as social support is likely influenced by a variety of social and structural factors such as the ability to age at home if culturally valued. Understanding the relationships between the depression, social support, and CVD has considerable potential impact to identify points of intervention. The lack of strong

positive association in our study may suggest that depression and social support do not represent as ideal of a point of intervention with CAC progression as they do with other health outcomes. Though some of our estimates were statistically significant, they were counterintuitive in direction as well as very small from a clinical perspective. While differences in CAC progression by clinical subtypes may explain some of the inverse association, it is highly likely that most, if not all, of the association is explained by statistical artifacts. As the previous literature on depression and CAC (progression and point-in-time) has been limited and yielded mixed results, our study built on previous findings through the following:

1. A larger and more diverse sample – Previous work has been limited to smaller samples which were overwhelmingly white and primarily female. Additionally, the inclusion of older adults helps to provide insight as to the hypothesized relationship in a population of particular public health interest.
2. More sophisticated analytic techniques – The use of linear mixed effect modeling allowed us to make use of outcome data across several time waves and compare individuals with CAC data measure during different combinations of visits. This provided us the ability to better model the entirety of the progression over the observation period (rather than a simple change score) as well as make fuller use of the data at hand.
3. Inclusion of social support – Though the lack of apparent association between depression and CAC progression did not provide evidence for effect modification by social support, to our knowledge, this is the first study to attempt to incorporate social support to the study of depression and CAC.

For the sake of elucidating the true relationships between these factors, future research would benefit from targeting the following:

1. Further elucidation of demographic subgroups among which the association between depression and CAC progression may be stronger (e.g. newly widowed versus single long-time single males) and investigate the role social support plays in these groups
2. Better characterization of the temporal and dose-response relationship between depression and CAC progression
3. Distinguishing between subtypes of depression, particularly melancholic and atypical, as well as episodic versus chronic persistence
4. Longer term observation with more consistent psychosocial measures to better model dynamic relationships between variables with bidirectional associations (e.g. depression and BMI)

Figure 1 - Directed Acyclic Graph (DAG) of theorized covariate relationships

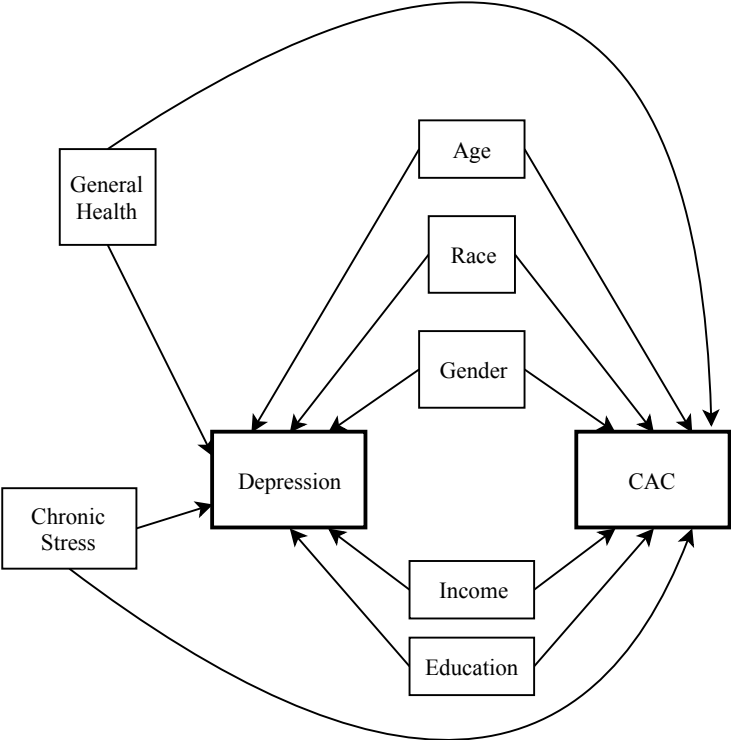


Figure 2: Study Exclusion and Imputation

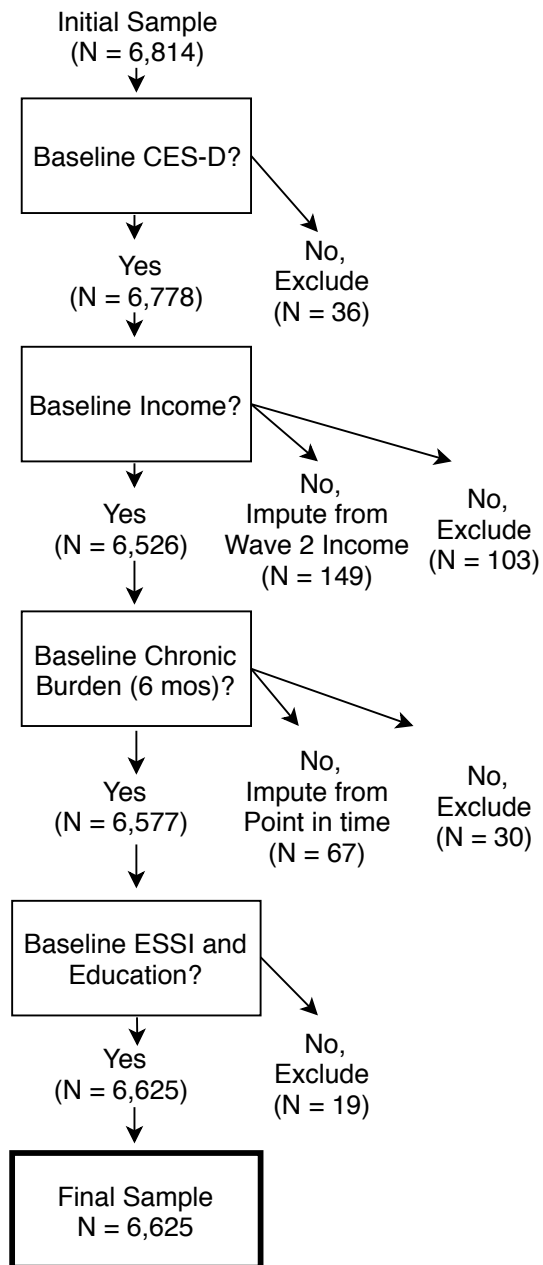


Figure 3: Distribution of Participants by Last Exam Completed

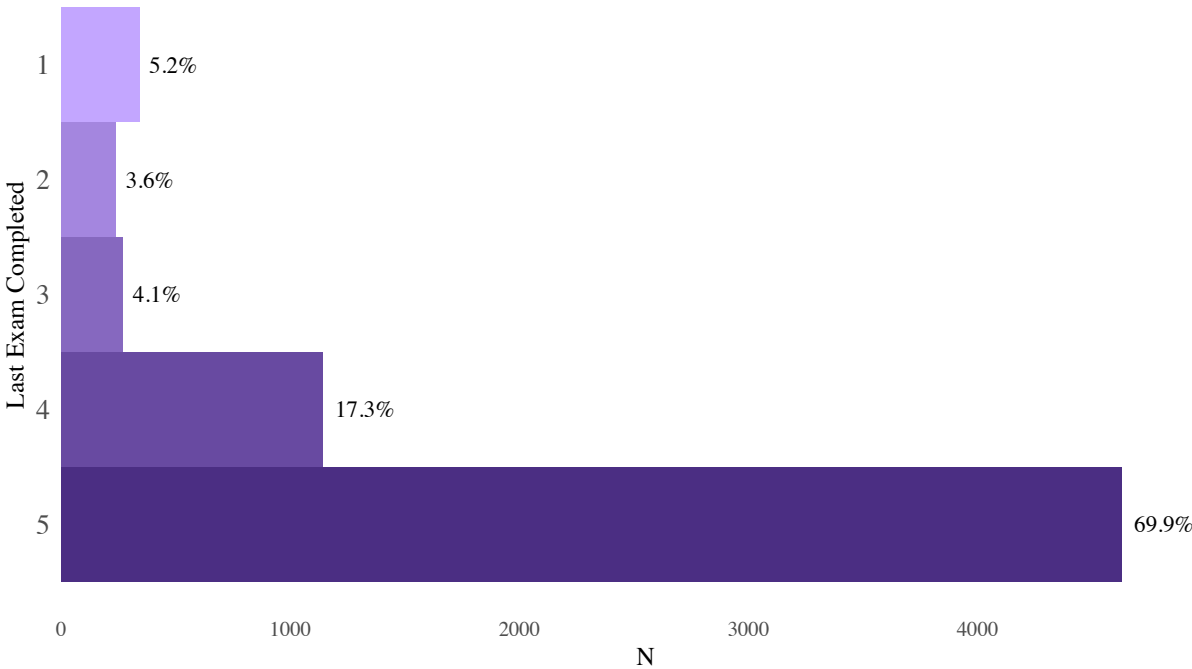


Table 1: Distribution of Baseline Variables Full Sample and By CES-D Clinical Cutoff (≥ 16)

Variable	Full Sample (N = 6,625) <i>N(%) or Mean(SD)</i>	Clinical Cutoff	
		CES-D < 16 (N = 5,768) <i>N(%) or Mean(SD)</i>	CES-D ≥ 16 (N = 857) <i>N(%) or Mean(SD)</i>
Gender			
Female	3510 (53.0%)	2919 (83.2%)	591 (16.8%)
Male	3115 (47.0%)	2849 (91.5%)	266 (8.5%)
Age	62.0 (10.2)	62.1 (10.1)	60.9 (10.6)
Race/Ethnicity			
White, Caucasian	2556 (38.6%)	2290 (89.6%)	266 (10.4%)
Chinese-American	803 (12.1%)	737 (91.8%)	66 (8.2%)
Black, African-American	1793 (27.1%)	1577 (88.0%)	216 (12.0%)
Hispanic	1473 (22.2%)	1164 (79.0%)	309 (21.0%)
Household Income			
< \$12k	796 (12.0%)	1083 (82.4%)	232 (17.6%)
\$12k -< \$25k	1315 (19.8%)	1074 (85.2%)	187 (14.8%)
\$25k -< \$40k	1261 (19.0%)	1592 (90.1%)	174 (9.9%)
\$40k -< \$75k	1766 (26.7%)	1395 (93.8%)	92 (6.2%)
\geq \$75k	1487 (22.4%)		
Education Level			
No High School	1185 (17.9%)	944 (79.7%)	241 (20.3%)
High School	1194 (18.0%)	1023 (85.7%)	171 (14.3%)
Some College	1889 (28.5%)	1654 (87.6%)	235 (12.4%)
Bachelors Degree or Higher	2357 (35.6%)	2147 (91.1%)	210 (8.9%)
Social Support (ESSI)	24.2 (5.3)	24.8 (4.8)	19.8 (6.1)
Chronic Burden (6 months)	1.1 (1.2)	1.0 (1.1)	2.0 (1.4)
Serious Ongoing Health Problem			
Yes	1400 (21.1%)	1041 (74.4%)	359 (25.6%)
No	5225 (87.9%)	4727 (90.5%)	498 (9.5%)

Figure 4: Distribution of Baseline CES-D Scores

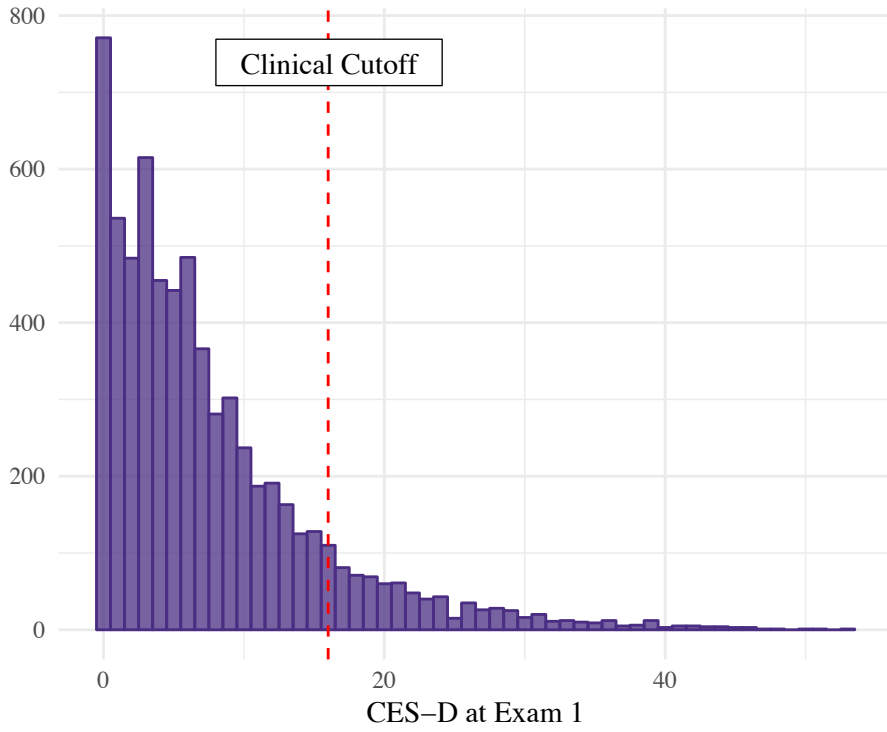
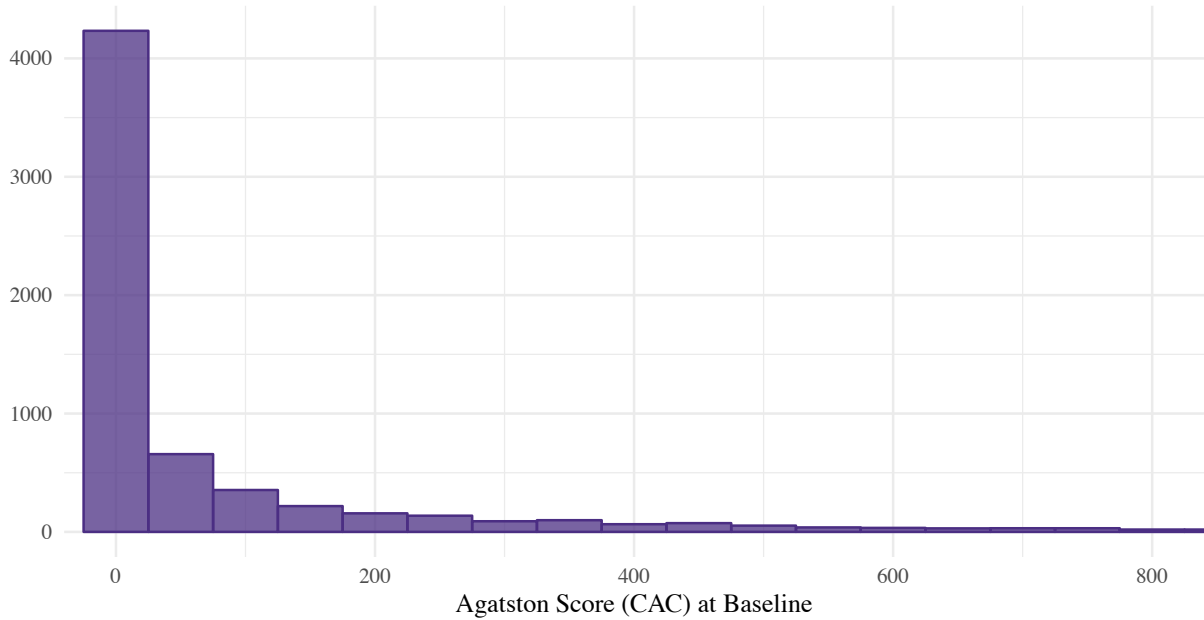
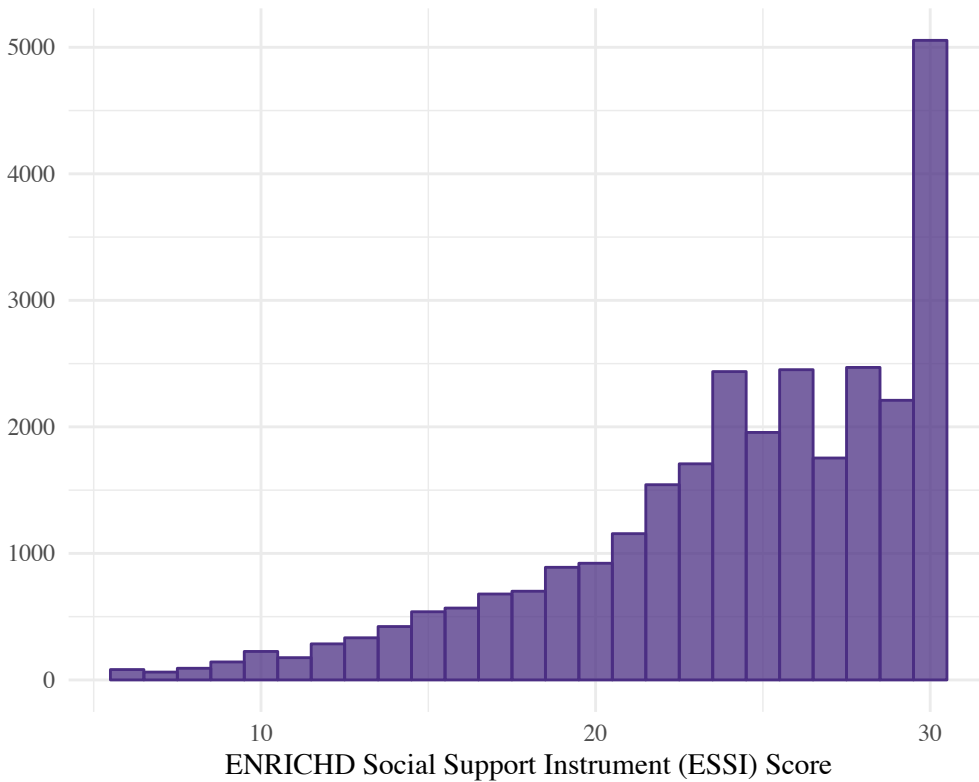


Figure 5: Distribution of Agatston Scores (CAC) at Baseline



Note: 314 participants with Agatston > 800 not shown

Figure 6: Distribution of ESSI Scores at Baseline



**Table 2a: Linear Mixed Effects Model for the Progression of CAC
(Agatston units/year from First Exam)**

	Coefficient (95% CI)
Intercept	40.1
Years from Baseline	24.8 (23.4, 26.2)
CES-D [†] (Baseline)	-4.1 (-14.7, 6.4)
Interaction: Years x CES-D [†] (Baseline)	-1.5 (-2.9, -0.1)

*Model included the following covariates: Age, Gender, Education Level, Race/Ethnicity, Household Income, Chronic Stress Burden, and presence of serious ongoing health problem

[†] CES-D scaled (mean = 0, sd = 1)

Table 2b: Adjusted* Linear Mixed Effects Models for the Progression of CAC by Baseline CES-D, Stratified by Quartile of Baseline ESSi

	Coefficient (95% CI)			
	Q1 (ESSi: < 21)	Q2 (ESSi: 22 – 25)	Q3 (ESSi: 26 – 29)	Q4 (ESSi: > 29)
Years from Baseline	24.3 (21.4, 27.2)	24.3 (21.6, 27.0)	23.7 (21.1, 26.3)	27.6 (23.1, 32.2)
CES-D† (Baseline)	-6.8 (-23.4, 9.9)	-11.2 (-32.3, 9.9)	16.8 (-7.4, 40.9)	-15.9 (-56.0, 24.6)
Years:CES-D† (Baseline)	-1.0 (-3.2, 1.1)	-3.7 (-6.8, -0.6)	-0.1 (-3.5, 3.2)	-2.1 (-7.8, 3.5)

*Models included the following covariates: Age, Gender, Education Level, Race/Ethnicity, Household Income, Chronic Stress Burden, Presence of Serious Ongoing Health Problem

† CES-D scaled (mean = 0, sd = 1)

Table 2c: Adjusted* Linear Mixed Effects Models for the Progression of CAC by Baseline CES-D, Stratified by Marital Status at Baseline

	Coefficient (95% CI)			
	Married	Divorced/ Separated	Never Married	Widowed
Years from Baseline	24.6 (22.8, 26.4)	20.4 (17.3, 23.5)	23.5 (19.3, 27.6)	31.8 (26.9, 36.6)
CES-D† (Baseline)	-11.2 (-26.0, 3.6)	5.0 (-14.9, 25.0)	22.4 (-8.3, 53.1)	-1.0 (-32.0, 30.0)
Years:CES-D† (Baseline)	-3.1 (-5.1, -1.1)	-1.1 (-3.9, 1.8)	-0.1 (-4.0, 3.75)	3.0 (-1.5, 7.5)

*Models included the following covariates: Age, Gender, Education Level, Race/Ethnicity, Household Income, Chronic Stress Burden, Presence of Serious Ongoing Health Problem

† CES-D scaled (mean = 0, sd = 1)

Table 2d: Adjusted* Linear Mixed Effects Models for the Progression of CAC by Baseline CES-D, Stratified by Marital Status and Gender

	Coefficient (95% CI)			
	Females		Males	
	Married	Unmarried	Married	Unmarried
Years from Baseline	12.7 (11.1, 14.3)	19.2 (16.9, 21.5)	34.0 (31.0, 37.0)	35.4 (30.4, 40.3)
CES-D† (Baseline)	1.5 (-6.9, 9.9)	9.6 (-3.7, 23.0)	-16.4 (-44.7, 11.9)	8.0 (-31.3, 47.3)
Years:CES-D† (Baseline)	-0.6 (-2.2, 1.0)	1.4 (-0.6, 3.4)	-2.7 (-6.3, 0.9)	1.1 (-4.0, 6.3)

*Models included the following covariates: Age, Gender, Education Level, Race/Ethnicity, Household Income, Chronic Stress Burden, Presence of Serious Ongoing Health Problem

† CES-D scaled (mean = 0, sd = 1)

Table 3a: Linear Mixed Effects Models for the Progression of CAC by Depression Cut-Off (≥ 16 , ≥ 21)

	Coefficient (95% CI)
CES-D ≥ 16	
Years from Baseline	25.2 (23.7, 26.7)
CES-D ≥ 16	4.6 (-25.8, 35.0)
Years:CES-D ≥ 16 (Baseline)	-3.1 (-7.3, 1.2)
CES-D ≥ 21	
Years from Baseline	24.8 (23.4, 26.3)
CES-D ≥ 21	-4.4 (-43.9, 35.1)
Years:CES-D ≥ 21 (Baseline)	-0.4 (-6.0, 5.2)

*Models included the following covariates: Age, Gender, Education Level, Race/Ethnicity, Household Income, Chronic Stress Burden, and presence of serious ongoing health problem

Table 3b: Adjusted* Linear Mixed Effects Models for the Progression of CAC by Baseline CES-D, Stratified by Age Group

	Age Group Coefficient (95% CI)			
	[44,54)	[54,64)	[64,74)	[74,85)
Years from Baseline	10.2 (8.3, 12.0)	18.4 (16.4, 20.3)	32.0 (29.2, 34.8)	52.1 (46.5, 57.7)
CES-D† (Baseline)	-1.4 (-6.6, 3.8)	-4.1 (-18.7, 10.5)	-8.9 (-33.7, 15.9)	5.7 (-36.9, 48.4)
Exam:CES-D† (Baseline)	-1.0 (-2.7, 0.7)	-0.9 (-3.0, 1.1)	0.6 (-2.4, 3.6)	-2.3 (-8.4, 3.9)

*Models included the following covariates: Age, Gender, Education Level, Race/Ethnicity, Household Income, Chronic Stress Burden, and presence of serious ongoing health problem

† CES-D scaled (mean = 0, sd = 1)

Table 4: CES-D Score by Exam Participation

Number of Exams w/ Data	N	CES-D	
		Mean	Median
5	4415	7.2	5
4	1151	7.8	5
3	404	8.2	6
2	313	9.3	7
1	342	9.2	7

Figure 7: Comparison of Linear Model and Change Score in Modelling Non-Linear Progression

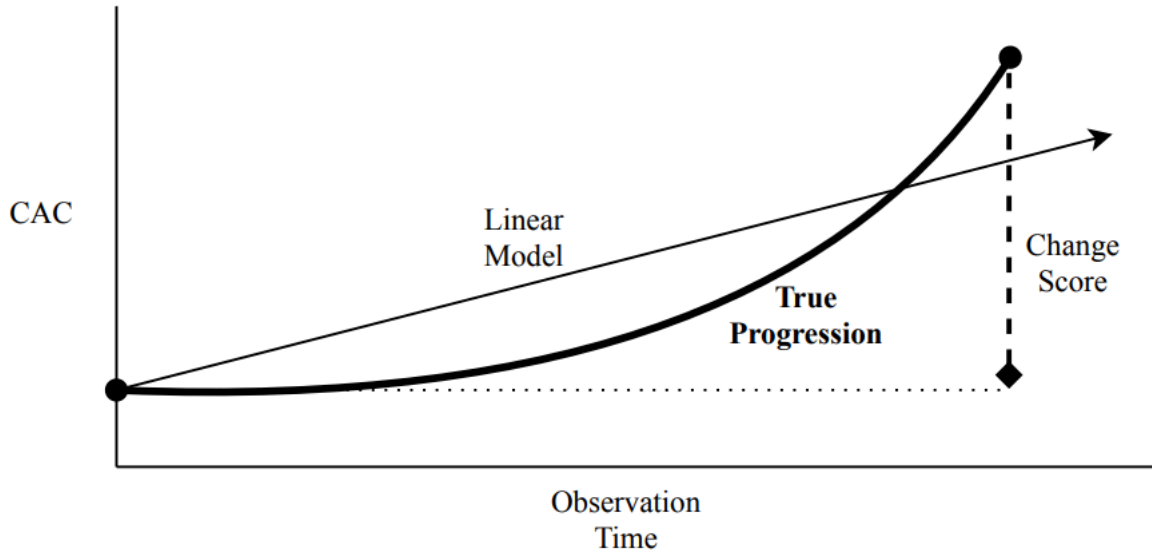


Figure 8: Crude Association of CAC Slope (Agatston Units/Yr) and Baseline CES-D Score (Scaled: Mean = 0, SD = 1)

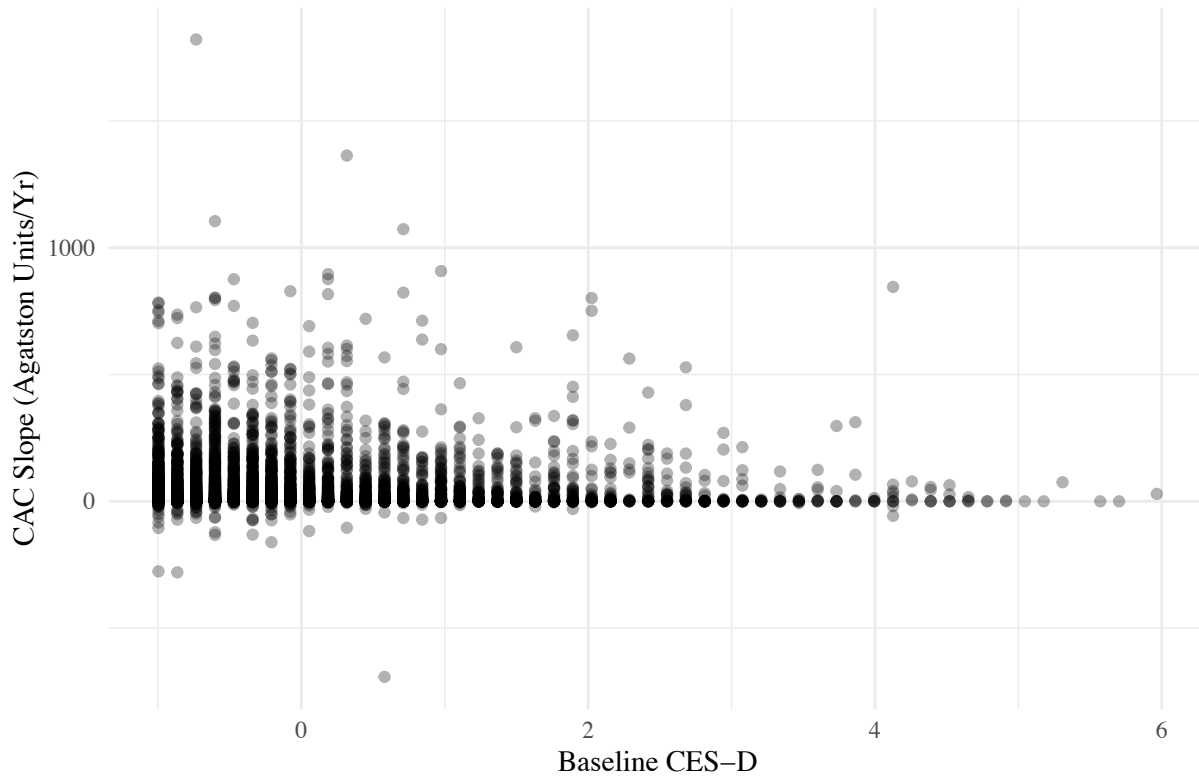
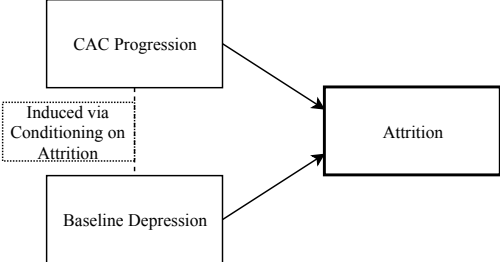


Figure 9: Directed Acyclic Graph Illustrating Potential Collider Stratification Bias from Attrition as a Consequence of CAC Progression and Baseline Depression



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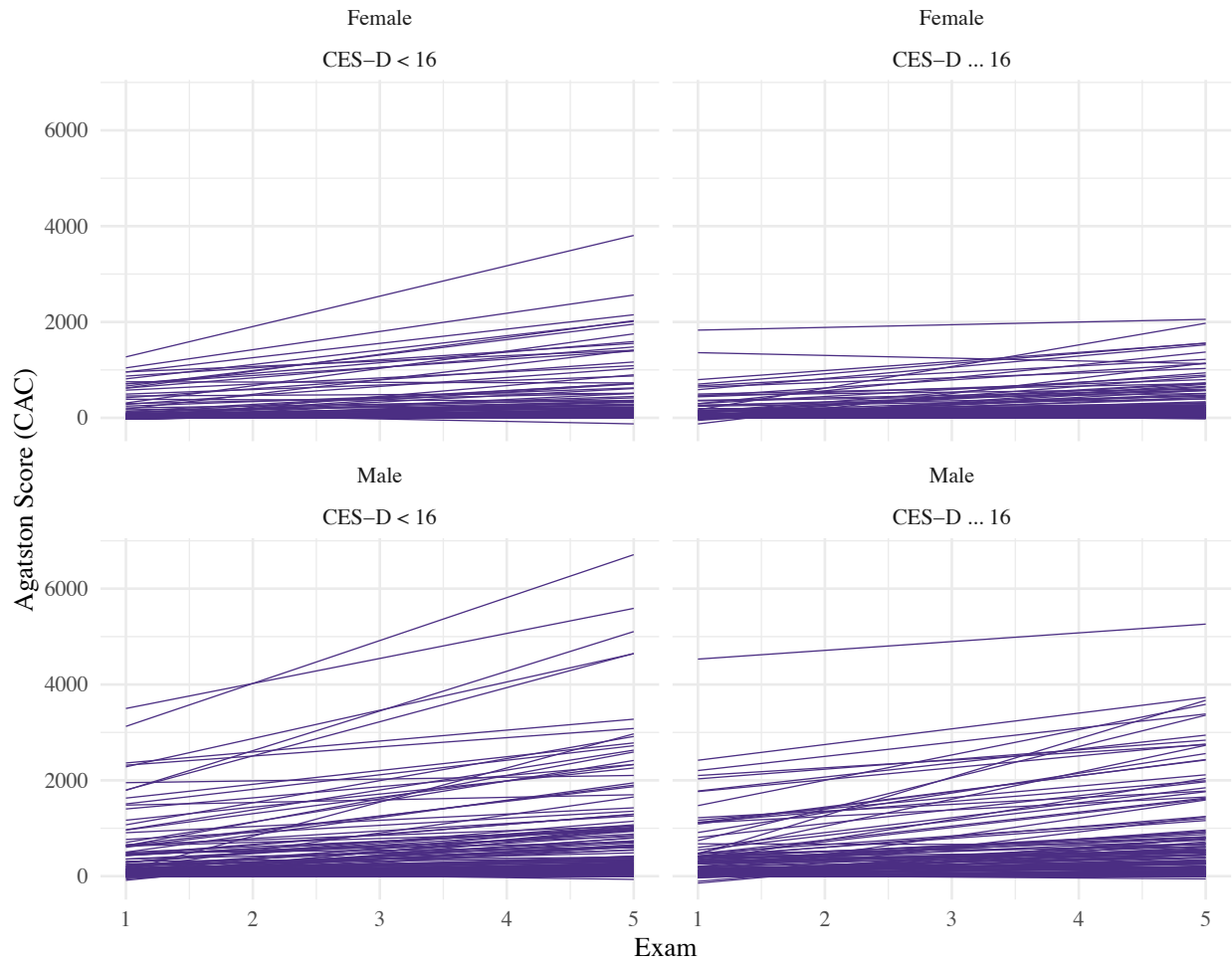
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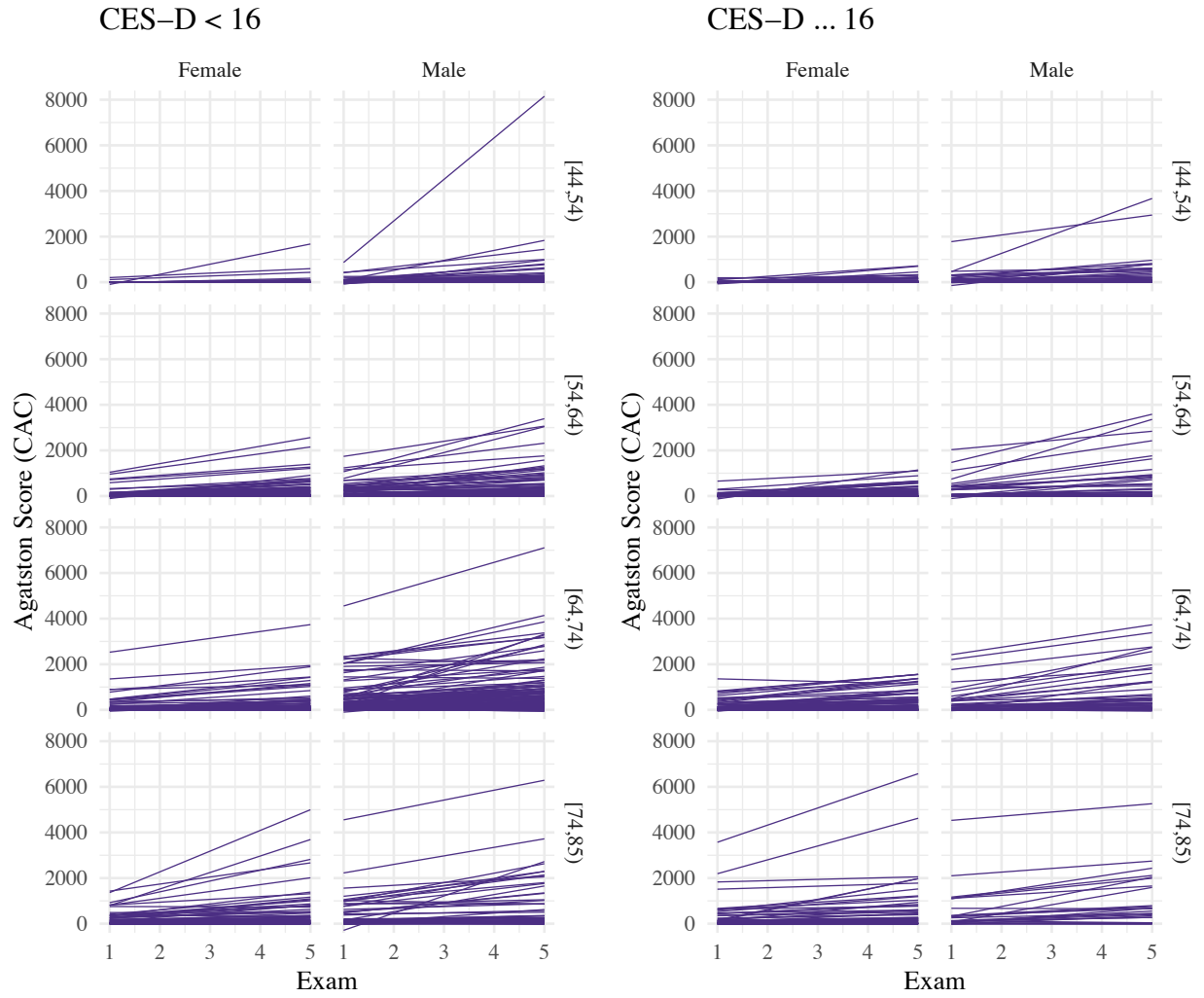
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SUPPLEMENTARY FIGURES

Progression of CAC by Gender and CES-D Cutoff: Sample of 1,000 Participants



Progression of CAC by Gender and Age Group: Sample of 2,000 Participants



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