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Late-life Depressive Symptoms as Partial Mediators in the Associations between Subclinical Cardiovascular Disease with Onset of Mild Cognitive Impairment and Dementia

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Abstract

Objective—Depression may contribute to the association between subclinical cardiovascular disease (CVD) and dementia, yet the contribution's magnitude remains unclear.

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Author Contributions: Armstrong wrote the manuscript and analyzed data. All authors made substantial contributions to the conception and design. Carlson, Rosano, Chaves, and Carnethon acquired the data. All authors assisted with the interpretation of the data. All authors were involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Methods—Among participants from the Cardiovascular Health Study Cognition Study who did not have baseline CVD-related events (N=2,450), causal mediation methodology was implemented to examine whether late-life depressive symptoms, defined as 10-item Center for Epidemiologic Studies-Depression Scale scores 8 from 2–3 years after baseline, partially mediated the association of baseline subclinical CVD (CAC, carotid intimal medial thickness, stenosis, and ankle brachial index) with mild cognitive impairment (MCI)/dementia onset occurring between 5–10 years from baseline. The total effect was decomposed into direct and indirect effects (via late-life depressive symptoms), obtained from an accelerated failure time model with weights derived from multivariable logistic regression of late-life depressive symptoms on subclinical CVD. Analyses were adjusted by baseline covariates: age, race, sex, poverty status, marital status, BMI, smoking status, ApoE4 status, and mCES-D.

Results—Participants contributed 20,994 person-years of follow-up with a median follow-up time of 9.4 years. Subclinical CVD was associated with 12% faster time to MCI/dementia (Time Ratio, [TR]=0.88, 95% Confidence Interval, [CI]: 0.83, 0.93). The total effect of subclinical CVD on MCI/dementia onset was decomposed into a direct effect (TR=0.95, 95% CI: 0.92, 0.98) and indirect effect (TR=0.92, 95% CI: 0.88, 0.97). 64.5% of the total effect was mediated by late-life depressive symptoms.

Conclusions—These data suggest late-life depressive symptoms partially mediate the association of subclinical CVD with MCI/dementia onset.

Key Terms

depressive symptoms; subclinical cardiovascular disease; mild cognitive impairment; dementia

Introduction

Cerebrovascular changes and depression are independent risk factors of cognitive decline and all-cause dementia.^{1–4} Previous research suggests that older adults with cardiovascular disease (CVD), such as coronary heart disease (CHD), may also have late-life depressive symptoms,^{5,6} and that 22% of community-dwelling older adults with depressive symptoms have CHD.⁵ Moreover, late-life depressive symptoms are linked to cognitive decline, with evidence of a two-fold increase in the risk of developing mild cognitive impairment (MCI) and dementia among those with late-life depressive symptoms, compared to those who are asymptomatic.⁷ Although there are associations among cerebrovascular changes, depression and cognitive decline, the mechanism connecting these conditions is unclear.

One possible explanation of the relationship among cerebrovascular changes, depression and neurodegeneration is the vascular depression hypothesis, which postulates that CVD leads to, maintains, and/or exacerbates depression in older adults.⁸ Subclinical CVD is an independent predictor of both CVD and dementia.⁹ CVD contributes to pathology of white matter hyperintensities (WMH) in the brain.¹⁰ The occurrence of WMH is generally higher in individuals with late-life depression, compared to healthy older adults.¹¹ Such findings indicate a link between vascular pathology and late-life depression,^{12,13} which may in turn lower the effect of cognitive reserve and result in earlier manifestation of dementia symptoms.¹⁴ Previous studies reported that depression and dementia may arise from

common neuropathologic processes when depression onset occurs shortly before dementia diagnosis.^{15,16} Since CVD and depression may have a bidirectional relationship^{17,18}, examining subclinical CVD prior to the development of CVD could elucidate the associations among vascular pathway, depression and neurodegeneration.

In this study, we investigated whether late-life depressive symptoms may affect the association between subclinical CVD and the known neurodegenerative process with the combination of MCI and dementia. To this end, we implemented the counterfactual approach to causal mediation with time-to-event data.¹⁹ We evaluated late-life depressive symptoms at two consecutive timepoints, as a single depressive episode can last for two years or more.²⁰ We examined the mediating role of late-life depressive symptoms in the association of subclinical CVD with MCI/dementia among those without CVD. We hypothesized that late-life depressive symptoms partially mediate the association of subclinical CVD with MCI/dementia onset.

Methods

Study Participants

The Cardiovascular Health Study (CHS) Cognition Study is an ancillary study of the Cardiovascular Health Study, an ongoing, prospective cohort of older adults across four sites that started in 1989.²¹ The CHS Cognition Study was initiated between 1992–1993 to identify dementia cases and followed participants at risk for developing dementia through 1999–2000. Additional details about the CHS Cognition Study are described in detail elsewhere.²¹ All participants provided informed consent for the CHS Cognition Study and Institutional Review Boards at each institution approved study procedures.

There were 3,602 participants enrolled in the CHS Cognition Study between 1992–1993. Participants contributed time from baseline until MCI/dementia onset, loss to follow-up, or administrative censoring in 1999–2000. For the current analysis, we excluded those with history of CVD-related events, e.g., myocardial infarction, coronary artery angioplasty, congestive heart failure (CHF), claudication, transient ischemic attack (TIA), and stroke, (N=783), prevalent dementia (N=145), those with MCI/dementia within five years of baseline (N=138), and those missing late-life depressive symptoms 2–3 years after baseline (N=86), resulting in 2,450 participants.

Subclinical Cardiovascular Disease

The baseline examination included a detailed medical history, list of current medications, blood, blood pressure, electrocardiogram, ultrasonography of carotid arteries, and an echocardiogram in 1989–1990.^{22,23} Baseline subclinical CVD was defined as having at least one of the following in the absence of an adjudicated history of clinically manifested CVD: (1) an ankle-arm-systolic blood pressure ratio ≥ 0.9 , (2) a percentage of stenosis of the internal carotid artery (based on ultrasonographic findings) of more than 25%, (3) intimal medial thickness of the internal or common carotid artery >80 th percentile of the CHS distribution, or (4) positive findings for angina or claudication on the Rose questionnaire

without history of angina or claudication.^{22,23} Methods for the development of the composite index of subclinical CVD are described elsewhere.²³

Late-life Depressive Symptoms

Late-life depressive symptoms were considered the potential mediators of the analysis. The 10-item Center for Epidemiologic Studies-Depression (mCES-D), a self-reported measure of depressive symptoms experienced in the past week, was used to quantify clinically relevant depressive symptoms approximately annually.²⁴ The 10 items are coded on a scale of 0 to 3 points, for a maximum of 30 points, and focus on mood (5 items), level of irritability (1 item), energy level (2 items), concentration (1 item), and sleep (1 item). A higher score indicates greater depressive symptoms.²⁴ We classified two consecutive mCES-D scores 8 between 2–3 years from baseline to determine whether participants had late-life depressive symptoms.²⁵ We chose two consecutive measures taken one year apart from 2–3 years after baseline, since a depressive episode can last for at least two years.²⁰ Diagnosis of clinical depression was unavailable.

Classification of Mild Cognitive Impairment and Dementia

Classification of MCI and dementia, the outcome, has been established in the CHS Cognition Study.²¹ Briefly, participants were stratified into high and low risk of possible dementia among the living and dead participants, based on evaluation of cognitive testing, changes in cognitive scores, nursing home admission, vital status, and history of stroke. Among living participants, high risk of possible dementia was defined if participants had one of the following: low 3MS score at one of the two most recent clinical visits, a 5-point decline in 3MS from MRI to last contact, a TICS score<28 and Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) score>3.6, history of incident stroke, history of dementia, or current residence in a nursing home.²¹ Among dead participants, participants were classified at high risk of dementia if they had at least one of the following: 3MS<80 within two years of death, 5-point decrease in 3MS from MRI to year closest to death, and TICS score<28, IQCODE score>3.6 within two years of death, diagnosis of dementia, or history of incident stroke, or non-white. High-risk whites and all African Americans (due to small sample size) were subjected to detailed evaluation of dementia diagnosis in three out of the four clinics.²¹ All participants at the Pittsburgh clinic were evaluated for MCI/dementia.

Those classified as either MCI or dementia cases were then reviewed by a dementia adjudication committee, which used standardized criteria for MCI and dementia diagnosis.²¹ In this present study, we combined MCI and dementia as an outcome, since both represent the same disease pathway leading to all-cause dementia and MCI predicts conversion to dementia.²⁶ Although MCI is a heterogeneous condition that could be reversible, the MCI criteria can identify a sample in the earliest clinical stages of dementia.

Adjustment Covariates

Baseline covariates included age, race, male sex, poverty status, marital status, education level, ApoE4 status, smoking status, body mass index (BMI), and baseline mCES-D continuous scores. Race was defined as either Caucasian or non-white. Poverty status was

defined using the income cut-off of \$11,770 per Federal Poverty Level Guidelines.²⁷ Marital status was defined as either being married or unmarried. Education level was defined as either high school graduate or not. ApoE4 status was categorized as having 1+ allele or not. Smoking status was characterized as current smoking status vs. not. BMI, a continuous measure, was defined as weight divided by height squared. Instead of restricting the sample to those with baseline mCES-D<8, we adjusted by baseline mCES-D scores to examine estimates of those with similar scores. All models were adjusted by baseline covariates.

Statistical Analysis

We evaluated differences between those with and without baseline subclinical CVD, using t-tests for continuous variables and χ^2 tests for categorical variables. Also, we examined the incidence and prevalence of MCI/dementia and late-life depressive symptoms.

We estimated Kaplan-Meier survival curves to show differences in the cumulative incidence of MCI/dementia by presence and absence of baseline subclinical CVD.²⁸ A log-rank test was used to test the difference of the cumulative proportions of MCI/dementia onset between presence and absence of baseline subclinical CVD.²⁹ Time from the first study visit (baseline) across 10 years was the time-scale. MCI diagnosis date was unavailable, so we assumed that MCI onset occurred at the end of the participant's follow-up period if the participant was assigned MCI. Only time to dementia onset was recorded in the CHS.

Schedule of Events

Figure 1 describes the framework for causal mediation to test whether the association of subclinical CVD with MCI/dementia onset was mediated by late-life depressive symptoms. Baseline subclinical CVD was the exposure of interest. Late-life depressive symptoms served as the mediators and were measured 2–3 years after baseline (Figure 1). A multivariable logistic regression model was used to examine the association between exposure-mediator relationship. The outcome, time to MCI/dementia onset, was measured, starting at five years from baseline up to 1999 (Figure 1).

Causal Mediation Analysis

Mediation analysis was performed using the approach proposed by Lange, Hansen¹⁹ and VanderWeele³⁰. We estimated direct and indirect effects by modeling weighted AFTM with a Weibull distribution, using a duplicated dataset with two replications of the values of the exposure. We used a parametric accelerated failure time model (AFTM), an alternative to Cox proportional hazards model³¹, using a Weibull distribution to determine the association between subclinical CVD and time to MCI/dementia onset, since the proportionality hazard assumption was not met. In AFTMs, time ratios (TRs) are reported. TR<1.0 indicates that the exposure had a faster time to onset of the outcome, while TR>1.0 indicates that the exposure had a slower time to onset of the outcome.

Our approach is similar to one used by Rochon, du Bois, Lange³² with the exception that we used AFTM, not a Cox Proportional Hazards model. For weighted causal mediation approaches for common outcomes, the dataset was duplicated. For the first replication, the value of baseline subclinical CVD, A^* , was set to the observed value, whereas for the

second replication, A^* was set to the opposite or “counterfactual” value of the subclinical CVD. Weights were determined by $W^c = P(M/A^*, C)/P(M/A, C)$, where M is the late-life depressive symptoms, A^* is baseline subclinical CVD, and C is the baseline covariates. The proportions for the weights were estimated from a multivariable logistic regression model of late-life depressive symptoms on subclinical CVD and baseline covariates.^{19,32} Standard errors and 95% confidence intervals were determined by 5,000 bootstrap simulations. The weighted AFT model analysis was performed in R version 3.1.2.³³ All other analyses were done in Stata 13.1.³⁴

As a secondary analysis, we examined whether late-life depressive symptoms would affect the association of any baseline CVD with MCI/dementia onset. Those with CVD-related events, e.g., myocardial infarction, coronary artery angioplasty, CHF, angina, claudication, stroke, and TIA, were included in this analysis.

Sensitivity Analyses

We conducted several sensitivity analyses. First, to test if we adequately adjusted by baseline covariates, we weighted models by propensity scores, since the distribution of exposed and unexposed groups was unequal.³⁵ Propensity scores were assigned to each participant, based on estimates from a multivariable logistic regression using demographic characteristics, (i.e., age, sex, race, poverty status, marital status, education level, BMI, smoking status), ApoE4 status, and baseline mCES-D scores. The analysis was further adjusted by baseline covariates to account for small differences.³⁶

Second, we examined incident dementia as a separate outcome and conducted the same analysis to determine whether inferences differed, since time to dementia onset was available in the CHS. Late-life depressive symptoms may account for more of the total effect of subclinical CVD on incident dementia.

Third, we evaluated possible bias due to non-linear relationships and interactions among exposure, baseline covariates, and mediator as well as allowance of 5%, 10%, and 15% misspecification of the mediator.

Results

Sample Characteristics

Table 1 shows the sample characteristics for each model for the mediating effect of late-life depressive symptoms on the association between subclinical CVD and MCI/dementia onset. Those with baseline subclinical CVD were likely to be older, male, current smokers, and impoverished as well as have diabetes, treated hypertension, higher systolic blood pressure, lower HDL cholesterol, and shorter time on study, as compared to those without baseline subclinical CVD (Table 1). Also, those with baseline subclinical CVD were less likely to be high school graduates than those without baseline subclinical CVD (Table 1). Those with and without baseline subclinical CVD were similar in terms of race, ethnicity, marital status, mCES-D, ApoE4 status, antidepressant medications, BMI, and total cholesterol (Table 1). Participants contributed 20,994.9 person-years to the study with mean follow-up time of 8.8 years (median=9.4 years).

Figure 2 shows Kaplan-Meier survival curves comparing the risk of MCI/dementia between those with and without baseline subclinical CVD. The cumulative proportion of MCI/dementia was higher among those with baseline subclinical CVD than those without baseline subclinical CVD.

Mediating Effect of Late-life Depressive Symptoms on the Association of Subclinical CVD with MCI/Dementia Onset

The total effect of subclinical CVD on MCI/dementia onset and its decomposition into indirect and direct effects is shown in Table 2. The TR for total effect for the association between subclinical CVD and MCI/dementia onset was 0.88 (95% Confidence Interval, [CI]: 0.83, 0.93). The time to MCI/dementia onset for those with baseline subclinical CVD was decreased by a factor of 0.83, as compared to those without baseline subclinical CVD (Table 3). The total effect was decomposed into a direct effect of subclinical CVD (TR=0.95, 95% CI: 0.92, 0.98) and indirect effect of late-life depressive symptoms (TR=0.92, 95% CI: 0.88, 0.97) (Table 2). The proportion mediated through late-life depressive symptoms was 64.5% on the log TR scale.

When evaluating the role of late-life depressive symptoms in the association between any baseline CVD and MCI/dementia onset, we found similar results (Table 2), suggesting that late-life depressive symptoms may underlie the association of a vascular pathway with neurodegenerative process.

Sensitivity Analyses

Results were similar when we weighted models by propensity scores (Supplemental Table 1). TR for the total effect of subclinical CVD on MCI/dementia onset was 0.88 (95% CI: 0.83, 0.94). Among those with similar baseline characteristics, the time to MCI/dementia onset for those with subclinical CVD decreased by a factor of 0.88, as compared to those without baseline subclinical CVD. The total effect was decomposed into the direct effect (TR=0.96, 95% CI: 0.92, 0.99) and the indirect effect (TR=0.92, 95% CI: 0.88, 0.97) (Supplemental Table 1).

Additionally, we examined the indirect effect of late-life depressive symptoms on the association between subclinical CVD and onset of incident dementia. First, we evaluated survival curves from Kaplan-Meier plots to assess the association between subclinical CVD and incident dementia (Supplemental Figure 1). The cumulative proportion of incident dementia was higher among those with baseline subclinical CVD than those without baseline subclinical CVD ($p<0.01$).

Supplemental Table 2 shows the decomposition of the total effect of subclinical CVD and incident dementia into the direct and indirect effects. The time ratio for the total effect of subclinical CVD on incident dementia onset was 0.86 (95% CI: 0.73, 1.03) (Supplemental Table 2). The time to incident dementia onset for those with baseline subclinical CVD decreased by a factor of 0.86, as compared to those without baseline subclinical CVD. However, this estimate was not statistically significant. The total effect was decomposed into the direct effect (TR=0.88, 95% CI: 0.79, 0.96) and the indirect effect (TR=0.98, 95% CI: 0.85, 1.16). Only the direct effect was significant (Supplemental Table 2). Late-life

depressive symptoms mediated 11.0% of the association between subclinical CVD and incident dementia onset.

We also examined possible bias due to non-linear relationships and interactions between exposure, baseline variables and mediator. There were no statistically significant interactions and non-linear terms. When we introduced 5%, 10%, and 15% misclassification at random to the mediator, we found that the indirect effect was attenuated with each increase in misclassification (Supplemental Table 3).

Discussion

Subclinical CVD was associated with elevated risk of MCI/dementia. Late-life depressive symptoms partially mediated the association of subclinical CVD with MCI/dementia onset even after propensity score adjustment. Late-life depressive symptoms accounted for 64.5% of the total association between subclinical CVD and MCI/dementia onset. There was an indirect effect of late-life depressive symptoms on the association between any baseline CVD and MCI/dementia, and results were similar with models adjusted by propensity scores. These findings suggest that late-life depressive symptoms may potentially lie on the pathway between subclinical CVD and MCI/dementia onset, which are consistent with hypotheses that existing vascular disease may increase risk of depression and subsequent dementia.^{1,3} Because of the high percentage mediated by late-life depressive symptoms, early detection and possible treatment of late-life depressive symptoms could mitigate MCI/dementia onset among community-dwelling older adults with subclinical vascular damage.

These findings have some biological plausibility.^{1–3,8} One possible explanation of these findings is through the vascular depression hypothesis.⁸ As vascular damage progresses, late-life depression may occur via hypometabolism of dorsal cortical regions and hypermetabolism of the ventral limbic structures.^{1,37,38} As these cortical regions become affected by vascular damage and depression, frontolimbic structures become compromised, thus leading to neurodegenerative processes resulting in MCI and/or subsequent dementia.^{1,38}

Our study has several strengths. First, there was a large sample size of older adults with heterogeneity in demographic characteristics with up to 10 years of follow-up. When compared to Medicare beneficiaries residing in geographical regions of the CHS, DiMartino, Hammill, Curtis, Gottdiener, Manolio, Powe, Schulman³⁹ found that the overall cohort is comparable to the Medicare population in terms of comorbid conditions and resource use, so our findings could be generalizable to the Medicare population in the United States. Second, the CHS Cognition Study has a detailed evaluation of subclinical CVD and MCI/dementia. Third, the relative ordering of subclinical CVD, late-life depressive symptoms, and MCI/dementia onset was temporally intact for the mediation analysis, since late-life depressive symptoms occurred before MCI/dementia onset among those who had both late-life depressive symptoms and MCI/dementia. Also, there was minimal (3%) missingness for late-life depressive symptoms. All participants had measures on subclinical CVD and MCI/dementia onset.

There are several limitations. First, a main assumption of the mediation analysis is that all relevant confounders are included in the analysis. We included all potential baseline confounders, such as demographic characteristics, mCES-D scores, and ApoE4 status. Moreover, when we used AFTM weighted by propensity scores, we obtained similar results. Second, we do not have information on life-long depression. We do not know if someone is depressed for many years or if someone has transient episodes prior to study enrollment. Third, we assumed that MCI onset occurred at the end of the participant's follow-up among participants with an MCI diagnosis, which could have led to an overestimation of direct and indirect effects. There was no indirect effect of late-life depressive symptoms on the association between subclinical CVD and all-cause dementia, which suggests that some MCI cases are resultant of depression and can be reversible with depression treatment. Fourth, mCES-D does not contain the full scale of depressive symptoms as the 20-item CES-D does, so it is not a descriptive classification of depressive symptoms. However, it performs similarly to the 20-item CES-D in terms of reliability and validity.²⁴

Another limitation is the assumption of no other variables that confound the mediator-outcome association after the exposure, but this is untestable in observational studies.¹⁹ For example, subclinical CVD can lead to a CVD-related event. This event, in turn, can lead to late-life depressive symptoms and subsequently MCI/dementia. Although we could not adjust for CVD-related events in the model, we evaluated late-life depressive symptoms as potential mediators in the association between any baseline CVD and MCI/dementia. We found similar results as our main findings.

These limitations notwithstanding, the partially mediating role of late-life depressive symptoms differs between the effects of subclinical CVD on MCI/dementia onset and dementia onset only. We observed no indirect effect of late-life depressive symptoms on the association between subclinical CVD and onset of incident dementia. Late-life depressive symptoms mediated 11% of the association between subclinical CVD and dementia onset. The discrepancy in these results could be two-fold. First, there were fewer cases of dementia than MCI, so the analysis might not have had enough power to detect an indirect effect. Second, our main analysis was conducted to allow for more follow-up time between visits during which a person with dementia may have progressed through MCI without being observed before they met dementia criteria, so we could detect more cases of cognitive impairment, a clinical representation of neurodegeneration.

There are several future directions to explore. First, we could examine the effect of CVD on MCI/dementia onset if we eliminated depression in older adults. Doing this could have important policy implications for incorporating screenings for depressive symptoms in Medicare wellness visits for older adults. Another future direction would be to examine the indirect effects of the different mCES-D domains, i.e., somatic complaints, interpersonal conflicts, depressed affect, and positive affect, on the association of early vascular damage and cognitive decline. We may further elucidate which mCES-D domain may affect the disease process leading from CVD to dementia.

These findings underscore the importance of mood disorders, like depression, in the association of subclinical CVD with MCI/dementia. Late-life depressive symptoms may

indirectly mediate the association between subclinical CVD and MCI/dementia onset. Interventions on late-life depressive symptoms may increase quality of life⁴⁰ and potentially delay MCI/dementia onset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Subclinical cardiovascular disease leads to earlier MCI/dementia onset.
- Late-life depressive symptoms partially mediate the association between subclinical cardiovascular disease and MCI/dementia onset.
- Subclinical cardiovascular disease, late-life depressive symptoms, and MCI/dementia may lie on same pathway.

Figure 1.

Hypothesized pathway linking cardiovascular disease, late-life depressive symptoms, Mild Cognitive Impairment, and dementia. This figure illustrates late-life depressive symptoms partially mediating the association between subclinical cardiovascular disease with onset of Mild Cognitive Impairment and dementia.

Number at risk						
No Subclinical CVD	1043	1006	887	844	819	34
Subclinical CVD	1348	1264	1060	982	928	33

Figure 2.

Kaplan-Meier plot for the association of baseline subclinical cardiovascular disease with onset of MCI/dementia five years after baseline.

Log-rank p-value pertains to the results from log-rank test for equality of survivor functions, which is a Pearson's chi-squared test with one degree of freedom.

Table 1

Characteristics of the Cardiovascular Health Study Cognition sample (N=2,450)

Baseline Characteristics	No Subclinical CVD N=1,062	Subclinical CVD N=1,388	p-value for difference
Age, mean(SD) **	70.5 (4.0)	72.1 (4.8)	<0.01
White, n(%) ***	936 (88.1)	1,220 (87.9)	0.86
Hispanic, n(%) ***	9 (0.9)	14 (1.0)	0.27
Male, n(%) ***	345 (32.5)	575 (41.4)	<0.01
High School Graduate, n(%) ***	867 (81.6)	1,050 (75.7)	<0.01
Married, n(%) ***	745 (70.2)	947 (68.2)	0.31
mCES-D Score, mean (SD) **	3.9 (3.9)	4.2 (4.1)	0.06
Poverty, n(%) ***	168 (15.8)	288 (20.8)	<0.01
ApoE ε4, n(%) ***	243 (22.9)	285 (20.5)	0.22
Diabetes, n(%) ***	49 (4.6)	118 (8.5)	<0.01
Current Smokers, n(%) ***	88 (8.3)	186 (13.4)	<0.01
Hypertension, n(%) ***	302 (28.4)	591 (42.6)	<0.01
Antihypertensive Medications n(%) ***	306 (28.8)	571 (41.1)	<0.01
Antidepressant Medications, n(%) ***	32 (3.0)	51 (3.7)	0.51
BMI, mean (SD) **	26.2 (4.4)	26.6 (4.3)	0.06
SBP, mean (SD) **	130.7 (18.7)	136.8 (21.8)	<0.01
Total cholesterol, mean (SD) **	210.6 (35.6)	213.1 (39.0)	0.10
HDL cholesterol, mean (SD) **	57.9 (16.4)	54.6 (15.2)	<0.01
Time on Study, mean (SD) **	8.8 (1.4)	8.5 (1.6)	<0.01

SD=standard deviation, HDL=high density lipoprotein, mCES-D: modified Centers for Epidemiologic Studies: Depression Scale, SBP=systolic blood pressure, BMI=body mass index

** Two-sample t-tests with 2,448 degrees of freedom.

*** Pearson's chi-squared tests with one degree of freedom.

Table 2

Decomposition of total effect of cardiovascular disease with onset of Mild Cognitive Impairment and/or dementia onset into direct and indirect effects via late-life depressive symptoms using Accelerated Failure Time Models with a Weibull distribution

Effect (Baseline Subclinical CVD vs. no Baseline Subclinical CVD)	Time Ratio	95% Confidence Interval
Total Effect	0.88	(0.88, 0.90)
Direct Effect	0.96	(0.96, 0.98)
Indirect Effect (Through Late-life Depressive Symptoms)	0.92	(0.91, 0.92)
Percent Mediated on the Log TR Scale	65.85%	(63.97%, 65.85%)
Effect (Any Baseline CVD vs. No Baseline CVD)	Time Ratio	95% Confidence Interval
Total Effect	0.88	(0.84, 0.93)
Direct Effect	0.95	(0.92, 0.98)
Indirect Effect (Through Late-life Depressive Symptoms)	0.93	(0.89, 0.97)
Percent Mediated on the Log TR Scale	57.38%	(55.42%, 59.34%)

CVD – cardiovascular disease. Bolded values indicate $p < 0.05$ from Wald tests with 11 degrees of freedom. Weighted Accelerated Failure Time Models with Weibull distribution were adjusted by age, race, male sex, poverty status, marital status, education level, ApoE4 status, smoking status, body mass index, and 10-item Center for Epidemiologic Studies – Depression Scale scores at baseline. Time Ratio (TR), $TR < 1$, indicates a decrease in time without MCI/dementia and $TR > 1$ indicates a prolonged time without MCI/dementia. Percent mediated on the log TR scale was calculated by: $[\ln(TR_{indirect\ effect}) / \ln(TR_{total\ effect})] * 100$.