Cerebrovascular Burden and Depression: Examining a Process Model of Geriatric Developmental Psychopathology

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CEREBROVASCULAR BURDEN AND DEPRESSION: EXAMINING A PROCESS MODEL OF GERIATRIC DEVELOPMENTAL PSYCHOPATHOLOGY

by

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the Department of Psychology in the College of Sciences at the University of Central Florida Orlando, Florida

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ABSTRACT

Depression is the second leading cause of disability worldwide, and is associated with substantial functional impairment and poor health implications in older adults. These adverse outcomes are exacerbated in older adults who exhibit comorbid depression and cerebrovascular burden (CVB). Given that the population of older adults is projected to double by year 2050, a process model of the development of depression in later-life and a subsequent clear delineation of the relationship between CVB and depression is paramount. One explanation of this process of disease development is the vascular depression theory, however alternative hypotheses have not been exhaustively falsified and the literature consists of methodological barriers that produce potentially unreliable results. The goals of this thesis are (1) to examine the interrelationship between CVB and depressive symptomatology from mid-life to later-life, and (2) to assess a potential genetic modifier of the CVB/depressive symptomatology relationship. Participants were drawn from the Wisconsin Longitudinal Study, which represents the 1957 graduating class from Wisconsin high schools. Data was drawn from three waves (1993, 2004, and 2011), spanning 18 years. Study 1 utilized a dual-change model to evaluate the relationship between CVB and depressive symptomatology from mid-life to later-life. Results indicated that depressive symptomatology at both follow-up waves was predicted by earlier depressive symptomatology. Prior CVB significantly predicted future depressive symptomatology in both 2004 and 2011. Depressive symptomatology in 2004 significantly predicted CVB in 2011. Thus, CVB significantly predicted future depressive symptomatology even after accounting for prior depressive symptomatology. Study 2 utilized a repeated-measures ANOVA and a moderated path structural model to evaluate the moderating effect of ApoE carriage on the relationship...
between CVB and depressive symptomatology. Results indicated that ApoE carriage has no
significant main effect on depressive symptomatology, nor is it a significant moderator of the
relationship between CVB and depressive symptomatology. Overall findings strongly support
the vascular depression theory, and do not implicate ApoE carriage in the manifestation of
depressive symptomatology. Future research should longitudinally evaluate the relationship
between CVB and depressive symptomatology across a greater number of defined time points
and with a more diverse sample. Lastly, future research should continue to identify genetic risk
factors that influence the development of detrimental disease processes.
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CHAPTER 1: INTRODUCTION

Depression is the second leading cause of disability worldwide, and is associated with significant functional impairment and poor health implications in older adults (Bruce, Seeman, Merrill, & Blazer, 1994; Ferrari et al., 2013; Lichtenberg, Gibbons, Nanna, & Blumenthal, 1993). When combined with comorbid cerebrovascular burden (CVB), the detrimental effects of depression in later-life are exacerbated (Yochim, Mast, & Lichtenberg, 2003). The number of adults over the age of 65 in the United States is projected to double by year 2050, comprising 20% of the total U.S. population. This imminent increase in the proportion of older adults prioritizes the pursuit to effectively predict, prevent, and treat detrimental disease processes (i.e., comorbid CVB and depression).

Past efforts to conceptualize the development of depressive symptomatology in later-life have generated the vascular depression theory, whereby vascular disease may “predispose, precipitate, or perpetuate” depressive symptoms among older adults (Alexopoulos et al., 1997, p. 915). Vascular depression theory posits a temporal sequence of disease development such that depressive symptomatology develops as a consequence of CVB, however two contrary hypotheses are evident in the literature. First, depression is episodic in nature, with past depression being among the strongest predictors of future depression (Djernes, 2006; Lewinsohn, Zeiss, & Duncan, 1989). Second, a review of the health psychology literature broadly concludes depression as the antecedent to a subsequent increase in vascular load, suggesting a directly opposite system of comorbid CVB and depressive symptomatology development to that proposed in the vascular depression theory. Without adequate examination of these alternative
hypotheses, CVB cannot be conclusively identified as the catalyst of increased depressive symptomatology in later-life.

A second avenue through which researchers are attempting to delineate the development of depressive symptomatology in later-life is through the identification of neurobiological correlates. One meta-analysis identified apolipoprotein E (ApoE) as one of the most strongly associated genes with major depressive disorder (MDD; Lopez-Leon et al., 2008). ApoE is most prominently recognized as a determinant in the development of Alzheimer’s disease (AD), however it has also been implicated in the manifestation of Parkinson’s disease and Wilson’s disease (Li et al., 2004; Liu, Kanekiyo, Xu, & Bu, 2013; Schiefermeier et al., 2000). Specifically, the presence of the ApoE-4 allele has been related to detrimental health outcomes, such as greater risk of developing, and lower age of onset for, certain neurodegenerative diseases (Blacker et al., 1997; Farrer et al., 1997; Li et al., 2004; Schiefermeier et al., 2000). Given the neurobiological correlates of disordered mood and CVB, it is logical to assume a similar effect of ApoE carriage on the development of depressive symptomatology, whether it is a direct effect on the development of depressive symptoms or a moderating effect on the relationship between CVB and depressive symptomatology. However, a review of the literature reflects inconsistent findings, such that some studies show a detrimental effect of ApoE-4 on depressive symptomatology (Butters et al., 2003; Rigaud et al., 2001; Skoog et al., 2015), while other studies show no association between the two constructs (Cervilla, Prince, Joels, Russ, & Lovestone, 2004; Surtees et al., 2009).
Goals of this thesis are to examine the relationship between CVB and depressive symptomatology from mid-life to later-life (Study 1), and to examine whether ApoE carriage moderates the effect that CVB has on the development of depressive symptomatology (Study 2). The present thesis addresses common methodological barriers (i.e., small sample sizes and samples that are too young for an apparent relationship, listwise deletion of participants with missing data, and cross-sectional designs) to most effectively evaluate the relationships between CVB, depressive symptomatology, and ApoE. Results of this thesis may improve our understanding of interrelated disease processes, thus informing integrated healthcare delivery.
CHAPTER 2: THE IMPACT OF CEREBROVASCULAR BURDEN ON DEPRESSIVE SYMPTOMATOLOGY FROM ADULTHOOD TO LATER-LIFE

Introduction

The number of adults over the age of 65 in the United States is projected to reach an estimated 88.5 million by year 2050, and will constitute 20% of the total United States population (Shrestha & Heisler, 2011). Depression is a common and multi-faceted late-life comorbidity in this growing population, and one that imposes significant functional impairment and physical health implications among older adults (Bruce et al., 1994; Lichtenberg et al., 1993; Yochim et al., 2003). Past efforts to conceptualize the phenomenon of late-life depression, particularly late-onset depression, have yielded the vascular depression theory. Alternate perspectives from the epidemiological and health psychology literatures call into question some core assumptions of the vascular depression theory. To our knowledge, those competing perspectives have not been directly contrasted using longitudinal data.

The empirical perspective reflects a consistent finding that depression has a chronic and recurrent trajectory, with past depression being among the strongest predictors of future depression (Djernes, 2006). For instance, past work has found that the probability of the recurrence of depressive episodes is positively associated with the number of previous episodes (Lewinsohn et al., 1989). Vascular depression theory, however, posits a temporal sequence such that depressive symptomatology emerges in later-life only after the development of significant cerebrovascular burden (CVB; Alexopoulos et al., 1997). The trajectory posited by vascular
depression theory neglects the influence of prior episodes of depression, and thus may confound
the effects of earlier CVB with prior depressive symptomatology.

The second alternative perspective to the vascular depression hypothesis is based on the
health psychology literature, and posits that depression has not only been identified as a
consequence of disordered health; a review of the health psychology literature broadly concludes
that depression is an antecedent to subsequent increases in vascular load, suggesting a hypothesis
that is directly contrary to vascular depression theory. For instance, depressed mood is positively
associated with medical noncompliance (Carney, Freedland, Eisen, Rich, & Jaffe, 1995; Glazer,
Emery, Frid, & Banyasz, 2002; Wang et al., 2002). In turn, substandard medical regimen
compliance engenders poor health outcomes, particularly for people with chronic comorbidities
that affect the brain such as hypertension, various heart problems, and diabetes. Depressed
individuals are more likely to smoke and to have ever smoked compared to their non-depressed
counterparts (Covey, Glassman, & Stetner, 1998; Glassman et al., 1990). Longitudinally,
depression has been consistently indicated as a predictor of CVB, as demonstrated with the
development of hypertension at 5-year follow-up (Davidson, Jonas, Dixon, & Markovitz, 2000),
the diagnosis of coronary heart disease during a 7-year study (Nabi et al., 2010), and incident
acute myocardial infarction and mortality in a 27-year follow-up (Barefoot & Schroll, 1996).
Depression has also been shown to increase an individual’s vulnerability to the onset of type 2
diabetes (Knol et al., 2006) as well as incident hypertension (Jonas, Franks, & Ingram, 1997).
Therefore, it may be premature to assume that CVB is the antecedent in the hypothesized CVB-
depression relationship.
Extant research has not examined how high CVB in mid-life predicts depressive symptomatology in later life over and above mid-life depressive symptomatology. Nor has past vascular depression research examined the competing and seemingly contradictory hypothesis (i.e., depression as the antecedent to CVB). The present study is an attempt to elucidate this apparent conflict by utilizing longitudinal data and a three-faceted hypothesis. Specifically, the longitudinal inter-relationships between CVB and depression will be examined across three waves spanning mid-life (age 53.20 years) to later-life (age 71.21 years). The temporal sequence between depressive symptomatology and the manifestation of CVB among aging adults will be examined using a dual change model. This model tests the hypotheses that (1) mid-life depressive symptomatology will predict later-life depressive symptomatology, and that (2) CVB in mid-life will positively predict future depressive symptomology even after controlling for past depressive symptomatology, as posited by the vascular depression theory (Alexopoulos et al., 1997). The inverse hypothesis suggested by Barefoot and Schroll (1996), Nabi et al. (2010), and Davidson et al. (2000), that (3) mid-life depressive symptomatology will predict later-life CVB, is also examined by this model. This dual change model will include both A) autoregressive pathways reflecting the hypothesized relationship between past CVB on future CVB and past depressive symptomatology on future depressive symptomatology, respectively; and B) cross-lagged pathways reflecting the hypothesized effect of past CVB on future depressive symptomatology and of past depressive symptomatology on future CVB, respectively (see examined model in Figure 2.1). Based on past work, sex, education, and income were selected a priori as control variables.
Method

Participants

The present study will utilize data collected through the Wisconsin Longitudinal Study (WLS). The WLS is a longitudinal cohort study that includes over 10,000 randomly selected representatives of the 1957 high school graduating class from Wisconsin. Participants were originally recruited in 1957 with an in-person questionnaire, then follow up data collections were gathered in 1964 (mail survey of parents), 1975 (telephone survey), 1993 (telephone and mail surveys), 2004 (telephone and mail surveys), and 2011 (in-person survey and mail survey; Herd, Carr, & Roan, 2014). The WLS includes a wide breadth of information on its participants, including demographics, mental health status, medical health status, genetic variables, and measures of cognition. The initial goals of the WLS were to assess the demand for post-high school education, to determine if promising high school students were attending college or university, and what circumstances contributed to these education plans via a state-sponsored questionnaire (Little, 1958). Follow up studies were originally conducted to examine the extent to which family background and childhood experiences and aspirations affected educational and occupational attainment (Herd et al., 2014). Since 1991, the WLS has been principally funded by the National Institutes for Health and National Institute on Aging, with additional support provided by the Vilas Estate Trust, the National Science Foundation, the Spencer Foundation, and the Graduate School of the University of Wisconsin-Madison (Herd et al., 2014).

The data relevant to this study is found in the 1993, 2004, and 2011 data collection waves. Participants who have missing data within the variables of interest were excluded from the study.
Measures

Demographic Variables. Age, sex, and income were self-reported by the participant. Education was assessed as self-reported years of formal schooling.

Cerebrovascular Health Variables. All medical variables used in this study were collected by self-report. Participants were asked “Has a doctor ever told you that you have . . .” high blood pressure or hypertension; high blood sugar; diabetes; heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems; stroke. In this study, these comorbidities were grouped into three categories by organ system. Presence of hypertension was identified by endorsement of high blood pressure or hypertension. Presence of blood sugar dysregulation was identified by endorsement of high blood sugar or diabetes. Presence of cardiac disease was identified by endorsement of heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems. Participants endorsing a history of stroke were excluded, as these individuals have been shown to be more likely to experience subsequent mood dysregulation (Bour et al., 2009).

Total CVB. Total CVB is a continuous measure of cerebrovascular risk factors, comprising a participant’s scores on the hypertension, high blood sugar/diabetes, and heart disease measures and emitting a total score ranging from 0-3.

Outcome Variable

Depression. Depression was measured using the Center for Epidemiological Studies Depression (CES-D) measure (L.S. Radloff, 1977). The CES-D collapses ranges of scores (0, 1-2, 3-4, and 5-7, then recodes these ranges to 0, 1, 2, or 3), for an individual’s total score ranging
from 0-60. The internal consistency of the CES-D is high for older adults (coefficient alpha .85 to .90), as is the validity of the measure (Lenore S. Radloff & Teri, 1986). Although the CES-D has a suggested cutoff score for probable depression, the present study will utilize this measure as a continuous degree of depressive symptomatology.

Statistical Methods

A dual-change model was employed to represent the relationship between CVB and depressive symptomatology across three time points ranging from mid-life (year 1993, mean age 53.20 years) to later-life (year 2011, mean age 71.21 years; see Figure 2.1). This model includes autoregressive pathways modeling to demonstrate, for example, the effect of CVB at time 1 on CVB at time 2. This model also includes cross-lagged pathways representing the hypothesized causal effect of CVB on depressive symptomatology, and vice-versa, over time. Full information maximum likelihood estimation (FIML) was utilized to prevent listwise deletion and, in turn, to prevent the underrepresentation of at-risk respondents on variables associated with mortality-based attrition (e.g., those who are socially marginalized which may affect one’s access to healthcare, or those carrying greater medical burden). Data was prepared in SPSS and the structural equation model analysis was performed utilizing Mplus software program (Muthen & Muthen, 2012).

Results

The final sample consisted of 5,175 participants. Participant characteristics are provided in Table 1.1. Mean age of participants was 53 years in 1993, 64 years in 2004, and 71 years in 2011. The largest proportion of the sample that was estimated using FIML was for depressive
symptomatology; 19.1%, 17.3%, and 23.5% of participants’ depressive symptomatology data was estimated in 1993, 2004, and 2011, respectively. Participant CVB data was estimated less frequently, with 12.8%, 0.004%, and 0.006% of participant’s CVB data estimated in 1993, 2004, and 2011, respectively.

The temporal sequence between depressive symptomatology and the manifestation of CVB among aging adults was examined using a dual-change model, incorporating three waves of data (1993, 2004, and 2011; Figure 2.1). Overall, results suggest that the hypothesized model fit the data very well (RMSEA=0.047; Comparative Fit Index (CFI)=0.963, $\chi^2_{(57, N=5175)}=8573.411, p<.00005$). With respect to the model’s autoregressive pathways evaluating the relationship demonstrating how previous CVB effects future CVB, greater CVB in 1993 significantly predicted CVB in 2004 ($\beta=0.492, SE=0.011, p<.001$). Further, greater CVB in 2004 was significantly associated with greater CVB in 2011 ($\beta=0.699, SE=0.007, p<.001$). The autoregressive pathways demonstrating the relationship between prior and future depressive symptomatology revealed a similar relationship, whereby higher CES-D scores in 1993 were significantly associated with higher CES-D scores in 2004 ($\beta=0.546, SE=0.011, p<.001$), and higher CES-D scores in 2004 were significantly related to higher CES-D scores in 2011 ($\beta=0.603, SE=0.011, p<.001$). With respect to the cross-lagged pathways identifying the relationship between CVB and depressive symptomatology from previous waves to future waves, greater CVB in 1993 was significantly associated with higher CES-D scores in 2004 ($\beta=0.038, SE=0.013, p=.004$). Greater CVB in 2004 was also associated with higher CES-D scores in 2011 ($\beta=0.027, SE=0.013, p=.042$). Conversely, an effect of past CES-D scores on level of CVB at future waves was only evident in the last wave; higher CES-D scores in 2004
were significantly positively predictive of level of CVB in 2011 ($\beta=0.022$, $SE=0.011$, $p=.038$). Overall, the model accounted for 38.2% of the variance in depressive symptomatology in 2011.

To assess the pathway by which CVB in 1993 significantly predicts depressive symptomatology in 2011, two indirect pathways were analyzed in the model: (1) CVB in 1993 to depressive symptomatology in 2011 by way of CVB in 2004, and (2) CVB in 1993 to depressive symptomatology in 2011 by way of depressive symptomatology in 2004. Both indirect pathways were statistically significant, whereby CVB in 1993 significantly predicted depressive symptomatology in 2011 through CVB in 2004 ($\beta=0.013$, $SE=0.007$, $p=.042$) and CVB in 1993 significantly predicted depressive symptomatology in 2011 through depressive symptomatology in 2004 ($\beta=0.023$, $SE=0.008$, $p=.004$).

In addition to the primary variables of interest, all control variables used in the model had statistically significant pathways dependent upon the wave. Specifically, level of education was significantly inversely related to the level of CVB in 1993 ($\beta=-0.064$, $SE=0.015$, $p<.001$), 2004 ($\beta=-0.064$, $SE=0.013$, $p<.001$), and 2011 ($\beta=-0.042$, $SE=0.010$, $p<.001$). Level of education was also significantly inversely related to depressive symptomatology in 2004 ($\beta=-0.029$, $SE=0.013$, $p=.031$) and 2011 ($\beta=-0.042$, $SE=0.013$, $p=.002$). Participant income was significantly inversely associated with level of depressive symptomatology in 1993 ($\beta=-0.120$, $SE=0.016$, $p<.001$), 2004, ($\beta=-0.036$, $SE=0.014$, $p=.010$), and 2011 ($\beta=-0.051$, $SE=0.014$, $p<.001$). Sex of the participant was significantly associated with level of CVB in 1993 ($\beta=-0.059$, $SE=0.015$, $p<.001$), 2004 ($\beta=-0.088$, $SE=0.013$, $p<.001$), and 2011 ($\beta=-0.068$, $SE=0.010$, $p<.001$), suggesting that male sex is associated with higher levels of CVB. Lastly, sex of the participant was significantly associated with depressive symptomatology in 1993 ($\beta=0.082$, $SE=0.015$, $p<.001$).
and in 2004 ($\beta=0.039, SE=0.013, p=.004$), whereby female sex was associated with higher depressive symptomatology.

**Discussion**

Results support hypothesis 1 based on the epidemiological depression literature that past depressive symptomatology was a consistent predictor of future depressive symptomatology. Results also supported hypothesis 2 based on the vascular depression hypothesis that even after controlling for the effects of past depressive symptomatology, high CVB still predicted greater endorsement of depressive symptomatology later in life. Findings partially supported hypothesis 3 based on the health psychology literature that mid-life depressive symptomatology would predict later-life depressive symptomatology.

These findings address an unexamined assumption of the vascular depression theory. Past depression has been identified as one of the strongest predictors of future depression (Djernes, 2006; Lewinsohn et al., 1989), however the vascular depression theory assumes a temporal sequence that indicates CVB as the predecessor and catalyst to a subsequent increase in depressive symptomatology. Results of this study strongly support the vascular depression theory by indicating mid-life CVB as a significant risk factor for the development of depressive symptomatology in later-life above and beyond that associated with depressive symptomatology earlier in life.

The vascular depression theory focuses primarily on the unidirectional relationship between CVB and depressive symptomatology, a relationship for which the current results support. The inverse hypothesis, whereby greater depressive symptomatology at mid-life is significantly predictive of CVB in later-life, was partially supported in this study. Higher levels
of depressive symptomatology in 2004 were significantly related to increased CVB in 2011; this relationship was not evident from 1993 to 2004. This finding corroborates other results suggesting that depressive symptomatology is associated with subsequent development of cerebrovascular risk factors such as hypertension, diabetes, and heart disease (Barefoot & Schroll, 1996; Davidson et al., 2000; Knol et al., 2006; Nabi et al., 2010). This finding highlights the need for regular depression screening to allow for the identification of risk factors of, and the implementation of preventative measures for, cerebrovascular disease. Primary care clinics, where mental health screening and behavioral health specialists are becoming increasingly common, are one key setting where such interventions may be employed.

The twin indirect effects reflect the hypothesized effect through which CVB predisposes the development of depressive symptomatology; however, the rate at which CVB in mid-life precipitates the development of that depressive symptomatology is heterogeneous in its manifestation. The current results implicate this heterogeneity by reflecting multiple measured relationships leading to development of depressive symptomatology. One pathway indicated that CVB in mid-life (1993) precipitated the development of depressive symptomatology earlier (measured in 2004) in the observed 18-year span; this depressive symptomatology perpetuated throughout the observed epoch. A second pathway evidenced CVB in mid-life that was maintained or intensified during the observed 18-year span, from which depressive symptomatology was precipitated and perpetuated at a later time in the epoch (at the 2011 wave) compared to the first indirect effect. Given that the current model includes auto-regressive and cross-lagged pathways among three time points and two outcome variables (i.e., CVB and depressive symptomatology in 1993, 2004, and 2011), the two aforementioned indirect effects
were the only ones available to be tested. It is likely that these two measured trajectories reflect
the variable manifestation of vascular depression symptom development. Future research should
examine potential modifiers of which the rate of development of depressive symptomatology due
to CVB is a function.

The primary limitation of this study is the use of a racially homogeneous (Caucasian),
well-educated sample. Future research should seek to replicate these findings with a more
racially and socioeconomically diverse sample. A second limitation of this analysis is the use of
self-reported health data in creating the CVB variable. However, this practice is consistent with
past research on clinically defined vascular depression. Further, subjective accounts of medical
burden have yielded high concordance with objective measures (e.g., medical records and
examinations; Bush, Miller, Golden, & Hale, 1989; Psaty et al., 1995). A third limitation exists
in the assessment of chronological change that is imposed by using only three defined time
points over a long span of time (i.e., 18 years). To our knowledge, however, very few datasets
exist that represent such a large number of participants from mid-life to later-life. Thus,
feasibility of a more thorough analysis of these inter-relationships remains limited.

The findings of this study provide empirical evidence to address an assumption made by
the vascular depression theory that, to our knowledge, has not been adequately evaluated. A
primary question raised by these results is whether treatment of mid- to later-life depression can
prevent the development of chronic cerebrovascular comorbidities such as diabetes,
hypertension, and heart problems among aging adults. With the predicted significant increase in
the proportion of older adults over the upcoming decades, the need to identify risk factors for
disordered health in this aging population is paramount. By implementing preventative
interventions for depression in at-risk populations (i.e., individuals with high levels of CVB) earlier in the life span, it may reduce the prevalence of associated detrimental health outcomes and healthcare utilization.
CHAPTER 3: THE IMPACT OF APOE ON THE PREDISPOSITION AND PERPETUATION OF THE VASCULAR DEPRESSION EFFECT

Introduction

Depression in later-life is commonly undetected, despite its recognition as the second leading cause of disability worldwide, associated substantial functional impairment, and ominous physical health implications (Bruce et al., 1994; Ferrari et al., 2013; Lichtenberg et al., 1993). In conjunction with comorbid cerebrovascular burden (CVB), the effects of depression in later-life are exacerbated (Yochim et al., 2003). Currently the population of adults in the United States over the age of 65 years surpasses 44 million (U.S. Census Bureau Population Division, 2014). This number is projected to increase over the upcoming decades, reaching an estimated 88.5 million people by year 2050 and comprising 20% of the total U.S. population (Shrestha & Heisler, 2011). This surge in the population of older adults has led to a subsequent increase in scrutiny on the most effective way to predict, prevent, and treat detrimental disease processes. One avenue by which researchers are examining how best to provide healthcare to older adults is through the use of genetic sequencing, which has become more affordable in recent years. A strong emphasis has been placed on relating genetic diatheses with environmental and behavioral stressors on the development of life-limiting syndromes, allowing for individualized medicine which is more efficient, economical, and effective in the prevention and treatment of disease (Cortese, 2007).

In the movement toward identifying neurobiological correlates to physical and behavior disorders, one meta-analysis identified apolipoprotein E (ApoE) as one of the most strongly associated genes in terms of the odds ratio for adverse later-life health outcomes, including major
depressive disorder (MDD; Lopez-Leon et al., 2008). ApoE was first recognized for its implications in lipoprotein metabolism and cardiovascular disease, and has since become recognized for its role in cognitive function, immunoregulation, and the manifestation of Alzheimer’s disease (AD; Mahley & Huang, 1999). ApoE is a polymorphic protein arising from three alleles: e2, e3, and e4; thus, there are six possible combinations of ApoE carriage that, when displayed on a continuum, reflect a dimension of ApoE-conferred risk. Allelic frequencies of ApoE in Caucasian samples are approximately 7% e2, 77% e3, and 16% e4, with corresponding genotypic frequencies of 0.5% e2/e2, 11% e2/e3, 59% e3/e3, 2% e2/e4, 25% e3/e4, and 3% e4/e4 (Corder, Lannfelt, Bogdanovic, Fratiglioni, & Mori, 1998). Each allele combination implies varying substantial functional consequences. A broad review of the literature indicates e3 as most common in frequency and concomitant to normal functioning, whereas e2 and e4 are scarcer and have varying functional implications (Mahley & Huang, 1999).

ApoE is more prominently recognized in its relation to the development of AD. Extant research suggests a dose-dependent effect of ApoE isoforms on amyloid beta peptide clearance, aggregation, and deposition (Liu et al., 2013). When comparing across isoforms, the presence of an ApoE-4 allele puts individuals at significantly higher risk for developing AD (for e2/e4, OR = 2.6; for e3/e4, OR = 3.2; for e4/e4, OR = 14.9; Farrer et al., 1997). The presence of ApoE-4 has also been linked to an earlier onset of AD, such that individuals with the e4/e4 genotype have been shown to have a mean age of AD onset of 66.4 years compared to all other ApoE configurations, who show an average AD onset of 71.3 to 73.6 years (Blacker et al., 1997). Similar effects of ApoE-4 on hastened disease development have been indicated in Parkinson’s
disease and in Wilson’s disease (Li et al., 2004; Schiefermeier et al., 2000). By contrast, e2 has been shown to have a protective effect; in one study, individuals with genotypes e2/e2 and e2/e3 showed a 40% risk reduction in the development of AD (Farrer et al., 1997). This protective effect of ApoE on the development of AD was corroborated by Corder and colleagues (1994), whereby AD risk was lowest in individuals with the e2/e3 genotype. Further, 23% of AD cases in this meta-analysis were considered “attributable to the absence of an ApoE-2 allele” (Corder et al., 1994, p. 180).

Given that ApoE impacts the manifestation of various neurological diseases, it is logical to presume a similar effect exists by which ApoE carriage would affect the pathophysiology of depression in later-life. Concurrent with this hypothesis, extant depression literature reflects substantive parallels with the AD literature. Lopez-Leon and colleagues (2008) found that individuals who possessed an ApoE-2 allele, compared to the e3 allele, had a risk reduction of 49% in developing MDD; this effect mimics the protective effect seen between ApoE-2 and AD. Studies have also demonstrated the detrimental effect of ApoE-4, whereby ApoE-4 carriers exhibited a significantly higher risk of increased depressive symptomatology in older adults, with odds ratios ranging from 1.75 to 6.1 (Rigaud et al., 2001; Skoog et al., 2015). With regard to the onset of depression in later-life, the mean age of onset for ApoE-4 carriers was significantly lower than that for non-carriers (51.4±20.7 years and 58.8±16.8 years, respectively; Butters et al., 2003). Although results suggesting a link between ApoE and depression are compelling, the literature also includes studies within which no effect was apparent. For example, in a study of over 17,500 individuals aged 41 to 80 (mean age 60.9 years), there was no difference in MDD prevalence across ApoE genotypes (Surtees et al., 2009).
CVB, Depression, and ApoE: A Potential Intersection

The strongly supported relationship between the CVB and the development of depression in later life (for review, see Scott & Paulson (Under Review)), in conjunction with the effect that ApoE genotype has on lipoprotein metabolism and cardiovascular disease, suggests an intersection of these three constructs. Research examining the relationship between CVB, ApoE, and depression has been sparse. Some studies have yielded ApoE carriage as a significant moderator of CVB’s positive predictive effects on depressive symptomatology in older adults (Lavretsky et al., 2000; Nebes et al., 2001). Not only have ApoE-4 carriers with comorbid CVB been shown to have greater depressive symptomatology, but they also may experience a greater number of depressive episodes and have a lower mean age of depression onset (mean age of onset for ApoE-4 carriers = 50.8 ± 18.7 years; Lavretsky et al., 2000). However, the findings by Lavretsky et al. (2000) and Nebes et al. (2001) were generated from small sample sizes (16 and 92 participants, respectively), limiting the interpretation of their results.

Longitudinal relationships addressing the relationship between ApoE carriage, CVB, and later-life depression are relatively few among the literature. Support for the hypothesized model is dispersed across studies, though no single study has integrated variables into a single, coherent theoretical or empirical model with an adequately sized sample. An adequate evaluation of ApoE, CVB, and depressive symptomatology as it relates to aging requires a large sample of adults over the age of 65 and a longitudinal approach. The present study is the first of our knowledge to examine how ApoE carriage moderates the relationship between cerebrovascular health and depression longitudinally from mid-life to later-life.
Methods

Participants
The present study will utilize data collected through the Wisconsin Longitudinal Study (WLS). The WLS is a longitudinal cohort study that includes over 10,000 randomly selected representatives of the 1957 high school graduating class from Wisconsin. Participants were originally recruited in 1957 with an in-person questionnaire, then follow up data collections were gathered in 1964 (mail survey of parents), 1975 (telephone survey), 1993 (telephone and mail surveys), 2004 (telephone and mail surveys), and 2011 (in-person survey and mail survey; Herd et al., 2014). The WLS includes a wide breadth of information on its participants, including demographics, mental health status, medical health status, genetic variables, and measures of cognition. The initial goals of the WLS were to assess the demand for post-high school education, to determine if promising high school students were attending college or university, and what circumstances contributed to these education plans via a state-sponsored questionnaire (Little, 1958). Follow up studies were originally conducted to examine the extent to which family background and childhood experiences and aspirations affected educational and occupational attainment (Herd et al., 2014). Since 1991, the WLS has been principally funded by the National Institutes for Health and National Institute on Aging, with additional support provided by the Vilas Estate Trust, the National Science Foundation, the Spencer Foundation, and the Graduate School of the University of Wisconsin-Madison (Herd et al., 2014).

The data relevant to this study is found in the 1993, 2004, and 2011 waves. Participants who have missing data within the variables of interest were excluded from the study.
Measures

Demographic Variables. Age, sex, and income were self-reported by the participant. Education was assessed as self-reported years of formal schooling.

Cerebrovascular Health Variables. All medical variables used in this study were collected by self-report. Participants were asked “Has a doctor ever told you that you have . . .” high blood pressure or hypertension; high blood sugar; diabetes; heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems; stroke. In this study, these comorbidities were grouped into three categories by organ system. Presence of hypertension was identified by endorsement of high blood pressure or hypertension. Presence of blood sugar dysregulation was identified by endorsement of high blood sugar or diabetes. Presence of cardiac disease was identified by endorsement of heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems. Participants endorsing a history of stroke were excluded, as these individuals have been shown to be more likely to experience subsequent mood dysregulation (Bour et al., 2009).

Total CVB. Total CVB is a continuous measure of cerebrovascular risk factors, comprising a participant’s scores on the hypertension, high blood sugar/diabetes, and heart disease measures and emitting a total score ranging from 0-3.

Genetic Variable

Apolipoprotein E. Saliva samples were collected from participants in 2006-2007 using Oragene kits and a mail-back protocol (Herd et al., 2014). An additional consent form was completed for usage of returned saliva samples. DNA genotyping was performed by
K Bioscience in Hoddesdon, UK, using homogeneous fluorescent resonance energy transfer technology coupled to competitive allele-specific PCR (Roetker et al., 2012).

**Outcome Variable**

*Depression.* Depression was measured using the Center for Epidemiological Studies Depression measure (CES-D; L.S. Radloff, 1977). The CES-D collapses ranges of scores (0, 1-2, 3-4, and 5-7, then recodes these ranges to 0, 1, 2, or 3), for an individual’s total score ranging from 0-60. The internal consistency of the CES-D is high for older adults (coefficient alpha .85 to .90), as is the validity of the measure (Lenore S. Radloff & Teri, 1986). Although the CES-D has a suggested cutoff score for probable depression, the present study will utilize this measure as a continuous degree of depressive symptomatology.

**Statistical Methods**

A repeated-measures ANOVA (RM-ANOVA) was employed to evaluate the longitudinal effect that ApoE has on depressive symptomatology across three waves spanning mid-life (age 53.20 years) to later-life (age 71.21 years). This analysis included an evaluation of the main effect of ApoE-conferred risk on depressive symptomatology, as well as the interaction between ApoE-conferred risk and time to assess the change in the expression of ApoE-carriage on depressive symptomatology as participants age. Further, this analysis included the interaction of ApoE-conferred risk and CVB to test moderation effects. Baseline sex, education, income, and marital status were set as control variables. This analysis was run using SPSS Version 22, and alpha level is .05 unless otherwise stated.
To model the effect that ApoE-conferred risk has on the relationship between CVB and depressive symptomatology over time while concurrently addressing methodological barriers in past work (i.e., listwise deletion), a moderated path model was employed (Figure 2.2). This model includes autoregressive pathways modeling to demonstrate, for example, the effect of CVB at time 1 on CVB at time 2. This model also includes cross-lagged pathways representing the hypothesized causal effect of CVB on depressive symptomatology over time. Interaction terms representing the effect that ApoE-conferred risk has on the relationship between CVB and depressive symptomatology in 2004 and in 2011 were included. Full information maximum likelihood estimation (FIML) was utilized to prevent listwise deletion and, in turn, to prevent the underrepresentation of at-risk respondents on variables associated with mortality-based attrition (e.g., those who are social marginalized which may affect one’s access to healthcare, or those carrying greater medical burden). Based on past work, sex, education, and income were set as control variables. Data was prepared in SPSS and the structural equation model analysis was performed utilizing Mplus software program (Muthen & Muthen, 2012).

Results

The final sample consisted of 3,203 participants. Participant characteristics are provided in Table 1.2. Mean age of participants was 53 years in 1993, 64 years in 2004, and 71 years in 2011. Within the moderated path model, the largest proportion of missing data was depressive symptomatology; 6.6%, 11.4%, and 17.2% of participants’ depressive symptomatology data was estimated using FIML in 1993, 2004, and 2011, respectively. Only 0.6% of participants’ CVB data was missing in 2011. Participants with incomplete data were listwise deleted in the RM-ANOVA, resulting in a sample size of 2,350 participants.
Mauchly’s Test of sphericity for the RM-ANOVA was significant ($W = .989, \chi^2_{(2, N=2350)} = 26.730, p < .001$), suggesting that the observed matrix does not have approximately equal variances and equal covariances; therefore, degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\epsilon = .999$).

With respect to tests of within-subjects effects, the effect of time on depressive symptomatology was not significant ($F(1.998, 4648.855) = 1.613, n.s.$), indicating that endorsement of depressive symptomatology was consistent across the period of the study. Within-subjects effects tests indicated a significant interaction between time and the sex of the participant ($F(1.998, 4648.855) = 5.493, p = .004$), suggesting a significant difference in depressive symptomatology between males and females across the period of the study. There was no significant interaction between time and CVB in 1993 on depressive symptomatology ($F(1.998, 4648.855) = 0.259, n.s.$), nor was there a significant interaction between time and ApoE-conferred risk on depressive symptomatology ($F(1.998, 4648.855) = 1.569, n.s.$), indicating no change in the effect that CVB or ApoE-conferred risk have on depressive symptomatology as participants age. With respect to tests of between-subjects effects that do not consider the effect of time, results indicated a significant main effect of education in 1993 ($F(1, 2327) = 5.253, p = .022$), CVB in 1993 ($F(1, 2327) = 16.274, p < .001$), sex ($F(1, 2327) = 4.787, p = .029$), income in 1993 ($F(4, 2327) = 4.476, p = .001$), and marital status in 1993 ($F(1, 2327) = 14.077, p < .001$) on depressive symptomatology. There was no significant between-subjects effect of ApoE-conferred risk on depressive symptomatology ($F(1, 2327) = 0.660, n.s.$), suggesting that ApoE-conferred risk has no effect on depressive symptomatology. LSD post-hoc comparisons indicated that females endorsed significantly greater depressive symptomatology
compared to males ($F(1, 2327) = 4.787, p = .029$), that married participants endorsed significantly less depressive symptomatology compared to non-married participants ($F(1, 2327) = 14.077, p < .001$), and that participants with higher income endorsed significantly less depressive symptomatology compared to participants with lower income ($F(4, 2327) = 4.476, p = .008$).

The longitudinal effect that ApoE-conferred risk has on the relationship between CVB and depressive symptomatology over time was modeled by a moderated path analysis (Figure 2.2). Overall, results suggest that the hypothesized model fit the data very well (RMSEA=0.041; Comparative Fit Index (CFI)=0.959, $\chi^2_{(44, N=3203)}=276.637, p<.00005$). With respect to the model’s autoregressive pathways evaluating the relationship demonstrating how previous CVB affects future CVB, greater CVB in 1993 significantly predicted CVB in 2004 ($\beta=0.498, SE=0.013, p<.001$). Further, greater CVB in 2004 was significantly associated with greater CVB in 2011 ($\beta=0.694, SE=0.009, p<.001$). The autoregressive pathways demonstrating the relationship between prior and future depressive symptomatology revealed a similar relationship, whereby higher CES-D scores in 1993 were significantly associated with higher CES-D scores in 2004 ($\beta=0.548, SE=0.013, p<.001$), and higher CES-D scores in 2004 were significantly related to higher CES-D scores in 2011 ($\beta=0.594, SE=0.013, p<.001$). With respect to the cross-lagged pathways identifying the relationship between CVB and depressive symptomatology from previous waves to future waves, greater CVB in 1993 was significantly associated with higher CES-D scores in 2004 ($\beta=0.037, SE=0.016, p=.018$). Greater CVB in 2004 was a marginally significant predictor of higher CES-D scores in 2011 ($\beta=0.030, SE=0.016, p=.067$). There was no significant main effect of ApoE-conferred risk on depressive symptomatology in 2004 or 2011.
The interaction between ApoE-conferred risk and CVB was not significant with respect to depressive symptomatology in 2004 or 2011, indicating that ApoE does not moderate the relationship between CVB and future depressive symptomatology. Overall, the model accounted for 37.1% of the variance in depressive symptomatology in 2011.

In addition to the primary variables of interest, all control variables used in the model has statistically significant pathways dependent upon the wave. Specifically, level of education was significantly inversely related to the level of CVB in 1993 ($\beta=-0.074$, $SE=0.019$, $p<.001$), 2004 ($\beta=-0.074$, $SE=0.016$, $p<.001$), and 2011 ($\beta=-0.033$, $SE=0.013$, $p=.012$). Level of education was also significantly inversely related to depressive symptomatology in 2004 ($\beta=-0.036$, $SE=0.016$, $p=.027$) and 2011 ($\beta=-0.039$, $SE=0.016$, $p=.017$). Participant income was significantly inversely associated with level of depressive symptomatology in 1993 ($\beta=-0.127$, $SE=0.019$, $p<.001$), 2004 ($\beta=-0.040$, $SE=0.017$, $p=.017$), and 2011 ($\beta=-0.043$, $SE=0.017$, $p=.012$). Sex of the participant was significantly inversely associated with level of CVB in 1993 ($\beta=-0.074$, $SE=0.018$, $p<.001$), 2004 ($\beta=-0.100$, $SE=0.016$, $p<.001$) and 2011 ($\beta=-0.064$, $SE=0.013$, $p<.001$), suggesting that male sex is associated with higher levels of CVB. Lastly, sex of the participant was significantly associated with depressive symptomatology in 1993 ($\beta=0.095$, $SE=0.018$, $p<.001$), and was marginally significantly associated with depressive symptomatology in 2004 ($\beta=0.030$, $SE=0.016$, $p=.061$), suggesting female sex was associated with higher depressive symptomatology.

**Discussion**

ApoE has inconsistently been identified as a genetic risk factor for vascular depression. The implication of ApoE carriage in various neurological diseases (e.g., AD, Wilson’s disease,
and Parkinson’s disease; Blacker et al., 1997; Farrer et al., 1997; Li et al., 2004; Liu et al., 2013; Schiefermeier et al., 2000) suggests a similar effect would exist for depression, given the neurobiological components of disordered mood. The present study is the first of our knowledge to evaluate the potential moderating effect of ApoE on the relationship between CVB and the development of depressive symptomatology, while concurrently addressing the methodological barriers identified in past work (e.g., small sample sizes, a sample younger than 65, and methods that underrepresent at-risk individuals with respect to characteristics related to mortality-based attrition, such as high depressive symptomatology, high CVB, and high levels of medical burden).

The findings of the present study suggest that ApoE-conferred risk is not implicated in the predisposition or perpetuation of depressive symptomatology, nor do they suggest ApoE as a moderator of the effect of CVB on depressive symptomatology. These results exemplify the intersection of two lines of research: (1) genetic risk factors for depression, and (2) genetic risk factors for CVB, both of which have examined the influence of ApoE carriage. Our null findings are consistent with extant research showing no significant association between ApoE and depression, CVB, or their combination (Cervilla et al., 2004; Surtees et al., 2009). As importantly, these results contradict previous findings that ApoE-4 carriage is linked to increased risk for late-onset depression (Rigaud et al., 2001) as well as more severe depressive symptomatology and incident minor depression in elders who were non-depressed at baseline 5-years prior (Skoog et al., 2015).

The current study was pursued in the justifiable belief that ApoE would relate to depressive symptomatology in the absence of methodological barriers common within the
literature. The aforementioned methods included a longitudinal design, a large, appropriately aged sample, and a solution to missing data to ensure that effects are not underrepresented due to listwise deletion of individuals with missing data on variables associated with mortality-based attrition. Our null results offer one potential explanation not of a methodological nature, but of reporting bias: there may be a distorted portrayal of the influence of ApoE on depressive symptomatology in the literature due to the difficulty associated with publishing null findings. It is impossible to determine whether past findings of a relationship between ApoE carriage and depressive symptomatology reflect type I error. Given that meta-analyses typically employ published research, the underrepresentation of null findings in publicized literature may lead to an undue overrepresented effect in these studies. Yet even with a potential misrepresentation of the influence of ApoE on depressive symptomatology in the literature, one meta-analysis still failed to find a significant effect of ApoE-4 on depression (Lopez-Leon et al., 2008).

The primary limitation of this study is the use of a racially homogeneous, well-educated sample. The effect of ApoE on various neurological diseases such as AD has been shown to fluctuate between ethnic groups (Tang et al., 1998). Future research should seek to replicate these findings in a sample of greater racial and socioeconomic diversity. A second limitation of this analysis is the use of self-reported health data in measuring CVB. However, this approach is consistent with past research on clinically defined vascular depression, and subjective accounts of medical burden have yielded high concordance with objective measures (e.g., medical records and examinations; Bush et al., 1989; Psaty et al., 1995). A third limitation exists in the evaluation of chronological change that is imposed by using only three defined time points over an extended span of time (i.e., 18 years). To our knowledge, however, very few datasets exist that represent
such a large number of participants from midlife to later-life, limiting the feasibility of a more ideal analysis of these inter-relationships.

Future research should continue to examine the impact of ApoE on neurological disorders, in conjunction with identifying alternative genetic risk factors for disordered health. The imminent increase in the number of older adults over the next three decades makes the identification of idiographic risk factors for disorders more prevalent in later-life critical. A better understanding of the diatheses by which pathology develops will inherently lead to more effective individualized treatments and subsequent improved collaboration across healthcare providers.
Table 1.1. Description of Characteristics of Sample, $n = 5175$.

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<th>Variable</th>
<th>1993</th>
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<th>2011</th>
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<td></td>
<td>$M$ $(SD)$</td>
<td>$M$ $(SD)$</td>
<td>$M$ $(SD)$</td>
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<tr>
<td>Age</td>
<td>53.20 (0.62)</td>
<td>64.31 (0.68)</td>
<td>71.21 (0.93)</td>
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<tr>
<td>Education (years)</td>
<td>13.86 (2.37)</td>
<td>13.88 (2.39)</td>
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<td>CES-D</td>
<td>11.70 (6.98)</td>
<td>10.19 (6.14)</td>
<td>10.99 (6.69)</td>
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<td>CVB (range 0 to 3)</td>
<td>0.26 (0.50)</td>
<td>0.71 (0.78)</td>
<td>1.05 (0.89)</td>
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<tr>
<td>Household Income</td>
<td>$56,000$ ($50,800)</td>
<td>$48,944$ ($56,000)</td>
<td>$33,260$ ($35,930)</td>
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<table>
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<th>Percentage of Sample</th>
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<td>Female</td>
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<tr>
<td>Married</td>
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<td>White</td>
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<tr>
<td>Black</td>
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<tr>
<td>Other race or refused to answer</td>
<td>1.4</td>
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*Household income represented by median and IQR.
Table 1.2. Description of Characteristics of Sample, n = 3203.

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<th>Variable</th>
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<td>M (SD)</td>
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<td>M (SD)</td>
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<tr>
<td>Age</td>
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<td>CES-D</td>
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<td>10.78 (6.52)</td>
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<td>CVB (range 0 to 3)</td>
<td>0.25 (0.49)</td>
<td>0.69 (0.77)</td>
<td>1.03 (0.88)</td>
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<td>Household Income*</td>
<td>$59,230 ($49,555)</td>
<td>$53,144 ($55,440)</td>
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<td>Percentage of Sample</td>
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<td>Black</td>
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*Household income represented by median and IQR.
APPENDIX B: FIGURES
Figure 2.1. The relationship between CVB and depressive symptomatology from mid-life to later-life.

CVB = cerebrovascular burden.
D = depressive symptomatology.
§ denotes a significant relationship between the control variable and depressive symptomatology
φ denotes a significant relationship between the control variable and CVB.
--- denotes p<.05.
--- denotes a n.s. relationship.
Figure 2.2. The relationship between CVB and depressive symptomatology, and the moderating effect of ApoE on that relationship, from mid-life to later-life.

CVB = cerebrovascular burden.
D = depressive symptomatology.
ApoE = apolipoprotein E-conferred risk.
§ denotes a significant relationship between the control variable and depressive symptomatology
φ denotes a significant relationship between the control variable and CVB.
— denotes p<.05.
—- denotes a n.s. relationship.
—-— denotes marginal significance.
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