### Title

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# The role of Alzheimer's and cerebrovascular pathology in mediating the effects of age, race, and apolipoprotein E genotype on dementia severity in pathologically confirmed Alzheimer's disease

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## Abstract

**Background—**Dementia severity can be modeled as the construct $\delta$, representing the "cognitive correlates of functional status."

**Objective—**We recently validated a model for estimating $\delta$ in the National Alzheimer's Coordinating Center's Uniform Data Set; however, $\delta$'s association with neuropathology remains untested.

**Methods—**We used data from 727 decedents evaluated at Alzheimer's Disease (AD) Centers nationwide. Participants spoke English, had no genetic abnormalities, and were pathologically diagnosed with AD as a primary or contributing etiology. Clinical data from participants' last visit prior to death were used to estimate dementia severity ($\delta$).

**Results—**A structural equation model using age, education, race, and apolipoprotein E (*APOE*) genotype (number of $\varepsilon 2$ and $\varepsilon 4$ alleles) as predictors and latent AD pathology and cerebrovascular disease (CVD) pathology as mediators fit the data well (RMSEA = 0.031; CFI = .957). AD pathology mediated the effects of age and *APOE* genotype on dementia severity. An older age at death and more $\varepsilon 2$ alleles were associated with less AD pathology and, in turn, with less severe dementia. In contrast, more $\varepsilon 4$ alleles were associated with more pathology and more severe dementia. Although age and race contributed to differences in CVD pathology, CVD pathology was not related to dementia severity in this sample of decedents with pathologically confirmed AD.

**Conclusions—**Using $\delta$ as an estimate of dementia severity fits well within a structural model in which AD pathology directly affects dementia severity and mediates the relationship between age and *APOE* genotype on dementia severity.

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**Keywords**

Alzheimer Disease; Dementia; Vascular Dementia; Aging; Apolipoprotein E2; Apolipoprotein E4

## Introduction

Accurate and valid measurement of dementia severity is important for characterizing the clinical manifestations of neurodegenerative disease, which is essential for diagnosis, intervention, and planning recommendations [1]. Latent variable modeling is one approach to quantifying the clinical changes in cognition and independent functioning caused by conditions such as Alzheimer's disease (AD) [2,3]. These methods have led to advances in understanding how measurable variables, such as neuropsychological test scores and rating scales for instrumental activities of daily living (IADL), allow for the estimation of dementia severity. Recently, Royall and colleagues identified a construct that they called $\delta$, which is designed to reflect "dementia-relevant variance in cognitive task performance" [4]. Royall's $\delta$ has been subject to a number of validation studies that indicate this construct may be invariant to the characteristics of the sample used to model $\delta$ as well as the specific cognitive and functional test scores used as indicators of $\delta$. For instance, Royall and colleagues' original model for $\delta$ was constructed in a cohort from the Texas Alzheimer's Research and Clinical Consortium (TARCC) and further validated in a diverse sample of independent living community-dwelling retirees, in a sample of Mexican Americans, and in Japanese persons presenting to a specialty memory center [4–7]. Our group has also shown that $\delta$ can be modeled in a large U.S. based sample of older adults with a variety of neurodegenerative pathologies, using a different set of indicator variables for $\delta$ than used by Royall et al. [8]. We also showed that $\delta$ possesses strong criterion validity both cross-sectionally (compared to clinical diagnosis and to the Clinical Dementia Rating Sum of Boxes; CDR-SB [9]) and longitudinally (compared to changes in CDR-SB over five years) [8].

Although $\delta$ has been subject to validation against clinical criteria, it is strengthened by validation against other data serving to mark neurodegenerative diseases like AD. Previous work by Royall and colleagues has demonstrated a relationship between $\delta$ and gray matter atrophy in the default mode network, apolipoprotein E (*APOE*) genotype, and serum biomarkers [10] of AD; further, the relationship between AD biomarkers and $\delta$ may be moderated by ethnicity [11–13]. Our group's previous work on this topic validated $\delta$ in a broad spectrum of dementia etiologies and was based on clinical diagnosis. Because $\delta$ has yet to be modeled in conjunction with autopsy-derived neuropathological data, its association with the pathophysiology of specific neurodegenerative disorders is unknown. The current study builds upon previous research by investigating $\delta$ in the context of the neuropathological, demographic, and genetic variables that play a role in determining clinical dementia severity. In particular, this study seeks to determine whether $\delta$ fits well within a model of AD that includes autopsy-based neuropathological outcomes for AD (i.e., amyloid plaques and neurofibrillary tangles [NFT]) and cerebrovascular disease (CVD; i.e., absence or presence of large arterial infarcts, cortical microinfarcts, lacunar infarcts, and hemorrhages), as well as demographic (age, education, race) and genetic (*APOE* genotype) risk factors. We selected age, education, race, and *APOE* genotype as predictors of dementia

severity based on the literature linking these variables with AD and CVD. Although CVD is not required for a diagnosis of AD, the two pathologies often co-occur and may share similar pathological mechanisms [14–16]. Education is included in the model not as a demographic risk factor but as a proxy for cognitive reserve, which may influence the effects of pathology on clinical outcomes. A brief summary of the literature on AD risk factors is described below.

## Age

Increasing age is the most prevalent risk factor for the development of AD; as such, both AD and CVD are classified as age-related diseases [17]. With increasing age, AD pathology increases [18] and changes occur in the cerebrospinal fluid biomarkers of AD (beta amyloid-42 [A$\beta_{42}$], total tau, phosphorylated tau, and tau/A$\beta_{42}$) [19]. These changes are evident not only in the case of suspected AD, but also within cognitively healthy older populations and those without clinical evidence of cognitive impairment [18, 19]. A recent autopsy study including participants with and without dementia, ranging in age at death from 77 to 87 years old, found that 100% of the brains examined showed neurofibrillary degeneration and 68.7% exhibited amyloid deposition [20]. In addition to the hallmark pathological signs of AD, age is associated with total brain volume loss [21] and studies have found associations between AD pathology, age, and declines in functioning [22]. Yu et al. [22] found that age predicted both non-episodic and episodic memory decline when mediated by amyloid plaques and neocortical tau.

Age is also associated with CVD pathology, including vascular lesions, infarcts, and white matter changes and serves as a risk factor for subsequent hemorrhage following an initial hemorrhagic stroke [23–26]. Kovacs et al. found that in addition to the AD pathology evident at autopsy, 48.9% of the brains examined had vascular lesions [20]. Another recent study found that 64% of autopsied cases exhibited microscopic infarcts, a pattern of CVD evident in the older group participants only [23]. White matter changes, likely driven by small vessel ischemic disease and often related to cognitive decline, are associated with advanced age [24,25].

## Race

While most studies have not found differences in plaques and tangles based on the race or ethnicity of the decedent (e.g., [27,28]), many studies show consistent ethnoracial differences in CVD pathology [29]. Koch et al. reported racial and ethnic differences in the incidence of lacunar infarcts for which non-Hispanic whites showed the lowest incidence, whereas Caribbean blacks had the highest rate [30]. Similarly, a study comparing the prevalence of lacunar infarcts, large-vessel disease, and small-vessel disease across ethnoracial groups showed fewer lacunar infarcts in white participants when compared to non-white participants. Large-vessel disease was more common in white participants, whereas small vessel disease was more common in black participants [31]. However, the ethnoracial differences in CVD risk are primarily related to differences in cardiovascular risk factors such as hypertension, diabetes, body mass index, socioeconomic status, and tobacco smoking [32].

### *APOE* genotype

Possession of the *APOE* ε4 allele is the most common genetic risk factor for sporadic AD, with risk of disease increasing fourfold or tenfold with inheritance of one or two copies of the allele, respectively [33,34]. The ε4 allele is most reliably linked to AD through its action on the deposition and accumulation of Aβ plaques, but other pathogenetic mechanisms, including atrophy, tau phosphorylation, lipid metabolism, synaptic plasticity, inflammation, and neurogenesis, are also linked to this allele [35]. While its exact contribution to pathology remains unknown, studies have continued to identify an isoform-dependent pattern for *APOE* ε4 in the accumulation of Aβ that is associated with dementia severity [34,36]. Evidence suggests that APOE plays a role in the clearance of Aβ and that the ε4 allele leads to a loss of function in the protein or an increase in its toxicity, dictating the rate and anatomical pattern of neuropathology [34,37,38]. Though evidence is mixed and potentially population dependent, cleavage and fragmentation of the APOE protein is associated with NFTs, implicating the ε4 allele's relationship to disease susceptibility [39].

The ε4 allele has also been associated with microstructural white matter differences [40] and pro-inflammatory responses [41], making it a relevant target for research on CVD pathology as well. This allele is associated with increased risk of vascular dementia in which loss of APOE function, through fragmentation of the protein, accelerates the progression of disease and the spread of immunoreactive pathology, particularly in the presence of other cerebrovascular risk factors [39]. The ε4 allele may also indirectly influence CVD pathology through mechanisms that increase risk of hypertension [42].

In contrast to the ε4 allele, the e2 isoform may confer protective effects against the development of AD [43,44]. The role of the ε2 allele in modifying the risk of CVD is less well known, but may be associated with an increased risk [45]. *APOE* ε2 homozygotes are at increased risk of type III hyperlipoproteinemia and ischemic stroke; ε2/ε3 carriers are at a decreased risk of ischemic stroke, while for ε2/ε4 carriers the risk is increased [46,47].

### Education

Several studies have suggested that low education is a risk factor for dementia, particularly Alzheimer's disease [48–52]. Education is often used as a proxy measure for cognitive reserve, a hypothesized mechanism explaining the differences seen in clinical dementia severity across individuals exhibiting the same degree of pathology [52]. Higher cognitive reserve can mask the clinical symptoms of dementia but may be associated with more rapid cognitive decline after neuropathological changes have reached a certain threshold [49]. It is unclear whether education increases cognitive reserve or whether education is a consequence of greater reserve, but it is likely that education exerts its effects by compensating for pathological burden and not by protecting against the accumulation of neuropathology [48,50]. Education is also reflective of other risk factors for dementia, including various socioeconomic, vascular, and lifestyle factors, but the effects of education on the clinical manifestations of dementia remain even after accounting for these variables [50]. Among the demographic variables reviewed here, education's effects on the clinical signs and symptoms of dementia are unique in that they are not believed to be mediated by neuropathology.

Therefore, education will be modeled differently than the other demographic predictors to account for the absence of indirect effects on $\delta$.

### The present study

There are two interrelated aims of the present study. First, we seek to test the hypothesis that, in a sample of decedents with pathologically confirmed AD, $\delta$ functions as expected as a measure of dementia severity in a comprehensive model of clinical AD severity. In other words, we hypothesize that the variability in $\delta$, measured at the visit just prior to death, can be explained by neuropathological burden (AD and CVD) along with the demographic and genetic risk factors reviewed above. Second, we aim to test the hypothesis that AD neuropathology and CVD neuropathology mediate the influence of age, race, and *APOE* genotype on dementia severity. In contrast, pathology is not expected to mediate the effects of education on cognition; instead, education is thought to modify the effects of pathology on clinical outcomes by serving as a proxy for cognitive reserve. To achieve these aims, we will use archival, de-identified clinical and pathological data curated by the National Alzheimer's Coordinating Center (NACC) and collected at Alzheimer's Disease Centers throughout the United States. We will use a model comparison approach to determine whether treating AD and CVD neuropathology as mediators of demographic and genetic variables improves model fit relative to simpler models that do not account for mediation effects or the effects of demographic and genetic variables altogether. If $\delta$ is found to fit well within our hypothesized models, then these results will provide additional evidence that it is a valid and clinically useful outcome measure for estimating dementia severity. A properly fitting model will also provide additional evidence that can help AD researchers and clinicians better understand the interrelationships between demographic variables, genetic variables, neuropathological variables, and clinical variables, including how these variables synergistically contribute to the cognitive and functional deficits seen in dementia.

## Materials and Methods

### Participants

Data were obtained from NACC through a request for pathological and clinical outcomes from participants at the 34 past and present ADCs. We began with data from 2987 decedents with data from at least one evaluation at an ADC between September 2005 and March 2014. All clinical data analyzed in this study were obtained from the last visit before death. Participants were excluded if they did not speak English as their primary language ($n$ = 146), did not have Functional Activities Questionnaire (FAQ) data needed to estimate $\delta$ ($n$ = 1157), had identified genetic or chromosomal abnormalities related to neurodegenerative disease (including APP, PS1, PS2, Tau, alpha-synuclein, Parkin, PRNP, Huntingtin, Notch 3, Trisomy 21, and other mutations; $n$ = 60), or if their last study visit occurred more than 1.5 years prior to death ($n$ = 785). If participants did not have a primary or contributing pathological diagnosis of AD, they were also excluded ($n$ = 68). After further excluding 111 participants with missing data on one or more exogenous covariates in our hypothesized model, we were left with a total sample size of 727 decedents, on which the analyses were based (some decedents met more than one of the exclusion criteria).

Most participants (91.06%) were clinically diagnosed with dementia at their last visit prior to death. However, a small number of participants were diagnosed as cognitively normal (1.93%) or with MCI (6.33%). Of those with MCI, the vast majority (91.30%) were diagnosed with the amnestic subtype. A very small fraction of participants was diagnosed with cognitive impairment not sufficient to meet criteria for MCI (0.69%). The majority of participants diagnosed with dementia were assigned a clinical diagnosis of probable AD (72.21%). Other clinical dementia diagnoses included possible AD (7.55%), dementia with Lewy Bodies (7.70%), frontotemporal dementia (2.72%), probable (1.06%) and possible (0.60%) vascular dementia, and other dementias (8.16%).

## Materials

The estimation of $\delta$ is based on ten cognitive test scores and one functional variable in the Uniform Data Set (UDS). The cognitive test scores include the Mini-Mental State Examination (MMSE) [53], animal and vegetable fluency, the Boston Naming Test (BNT) [54,55], Immediate (LM-I) and Delayed (LM-D) recall of Story A from the Wechsler Memory Scales Revised (WMS-R) Logical Memory subtest [56], Digit Span Forward (DS-F) and Backward (DS-B) [57], Digit Symbol Coding (DSC) [57], and the Trail Making Test Parts A (TMT-A) & B (TMT-B) [58]. The functional variable is derived from the FAQ [59]. A previous study has validated these variables as latent indicators of $\delta$ in the UDS; see [8] for more details.

## Procedure

Before examining the fit of $\delta$ within a model containing genetic, demographic, and pathological variables, we first sought to establish the model fit of correlated latent variables for AD and CVD pathology. These latent variables take into account the variance shared between the AD and CVD pathology indicators, as described below. We hypothesized that a continuous AD pathology factor could be measured by the severity of neuritic plaque (NP; as measured by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [60] rating system) and NFT (as measured by the Braak & Braak [61] system) pathology. The National Institute on Aging (NIA)-Reagan system [62], which is the most commonly used method to stage AD neuropathology, is based on the combination of the CERAD and Braak rating systems. NPs were rated as absent, sparse, moderate, or frequent and were coded ordinally as 1, 2, 3, and 4, respectively [60]. NFTs were rated in stages, I – VI, with higher stages reflective of greater NFT burden [61]. Abundance of NFT pathology was coded as 1–7, with 1 reflecting no NFT pathology and 7 reflecting a Braak and Braak stage VI rating. A continuous latent CVD pathology variable was indicated by four dichotomously rated (absent/present) CVD markers: large arterial infarcts, cortical microinfarcts, lacunar infarcts, and hemorrhages.

Once we established that the latent variable models for AD and CVD fit the data well, we used a model comparison approach to examine the fit of three nested models. In the first and most restrictive model (Model 1), we hypothesized that AD and CVD pathology have a direct effect on dementia severity as measured by the latent variable $\delta$ (Figure 1). In a second, less restrictive model (Model 2), we hypothesized that demographic (age, race, education) and genetic (frequency of *APOE* $\varepsilon$2 and *APOE* $\varepsilon$4 alleles) variables, in addition

to AD and CVD pathology, have a direct effect on dementia severity as measured by $\delta$ (Figure 2). The third, and least restrictive, model (Model 3) hypothesized that AD and CVD pathology mediate the relationship between age, race, and *APOE* genotype on dementia severity (Figure 3).

### Data Analysis

Models 1–3, shown in Figures 1–3, were tested using a robust weighted least squares estimator in Mplus version 6.11 [63]. Model fit was judged using the $\chi^2$ test of model fit, root mean square error of approximation (RMSEA), comparative fit index (CFI), and the Tucker-Lewis Index (TLI). Good model fit is supported by RMSEA values of 0.06 or less and CFI/TLI values of ≥ .95 [64]. Because the $\chi^2$ test is sensitive to large sample sizes, some have suggested that model fit is acceptable if $\chi^2/df$ is ≤ 3 [65]. The DIFFTEST function in Mplus was used to perform $\chi^2$ difference testing to compare the fit of the three competing models. After identifying the model that provided the best fit to the data, we examined the parameter estimates produced by the best fitting model to interpret the specific relationships between variables. Of note, standardized parameter estimates can be interpreted as partial regression coefficients. For the mediation analyses, bias-corrected bootstrap resampling with 10,000 replicates was used to generate 95% confidence intervals for the indirect effects [66–69].

## Results

The 727 decedents ranged in age at death from 48 to 105 years and in education from 1 to 24 years. Interval from the last UDS visit to death ranged from 0 to 547 days ($M$ = 227.27 days, $SD$ = 138.39). Additional demographic characteristics of the sample are shown in Table 1. Of the 662 (91.06%) decedents clinically diagnosed with dementia, AD was the primary pathology in 590 (89.12%) and a contributing pathology in 72 (10.88%). Other primary pathologies in the sample with dementia included Lewy Body pathology ($n$ = 44; 6.65%), CVD ($n$ = 12; 1.81%), frontotemporal lobar degeneration ($n$ = 5; 0.76%), hippocampal sclerosis ($n$ = 4; 0.60%), and other pathologies ($n$ = 7; 1.06%). In the 46 (6.33%) cases with MCI, AD was the primary pathology in 38 (82.61%) and a contributing pathology in 8 (17.39%). Other primary pathologies in the decedents with MCI included CVD ($n$ = 5, 10.87%), Lewy Body pathology ($n$ = 1; 2.17%), and hippocampal sclerosis ($n$ = 1; 2.17%). Of the 14 decedents who were cognitively normal at the last visit before death, AD was the primary pathology in all 14 (100%) but for one person, AD was coded as the contributing diagnosis because the pathology did not meet criteria for definite AD (i.e., very mild AD pathology). Additional clinical information pertaining to the sample is presented in Table 2.

The initial analyses investigating latent variable models for correlated AD and CVD pathology factors suggested that a model using Braak and CERAD staging as indicators of latent AD pathology and large vessel infarcts, lacunar infarcts, microvascular cerebral infarcts, and hemhorrages as indicators of latent CVD pathology fit the data well, $\chi^2$ (8) = 22.43, $p$ = .004; RMSEA = 0.050, 90% CI [0.026, 0.075]; CFI = .970; TLI = .944.

The results of $\chi^2$ difference testing revealed that Model 2, which regressed $\delta$ onto demographic, genetic, and neuropathological variables fit better than Model 1, which

regressed $\delta$ onto neuropathology only. However, the added indirect effects (mediation) of Model 3 further improved its fit relative to Model 2, which only included direct effects. These differences in model fit are further supported by the fit statistics for each model (Table 3). Therefore, all subsequent results presented are from Model 3.

As discussed above, the model for latent AD and CVD pathology fit the data well when examined separately from the rest of the model. When incorporated into Model 3, the parameter estimates in Table 4 were produced. These estimates reveal that each of the pathological indicators contributed to the estimation of their respective latent pathology variables.

Table 5 shows the parameter estimates for direct effects of demographic and genetic variables on AD and CVD neuropathology. The variables that produced significant direct effects on AD neuropathology included *APOE* $\varepsilon$4 and *APOE* $\varepsilon$2 allele frequency as well as age at autopsy. Age at autopsy and frequency of *APOE* $\varepsilon$2 alleles were inversely related to AD pathology, such that people who were older and who had more *APOE* $\varepsilon$2 alleles had less AD pathology at death. In contrast, people with more *APOE* $\varepsilon$4 alleles had more AD pathology at death. Race did not exert a significant direct effect on AD pathology but did have a direct effect on CVD pathology; Caucasian race was associated with less CVD pathology relative to non-Caucasians. The only other variable to exert a significant direct effect on CVD pathology was age at autopsy, with older age associated with greater CVD pathology burden at death. *APOE* was not directly related to CVD pathology at death in this sample of decedents with AD.

The data in Table 6 show the direct effects of pathology, demographics, and genetics on $\delta$. AD pathology was the only one of these seven variables to exert a significant direct effect on this latent construct representing dementia severity. These results suggest that, in people with pathologically confirmed AD, plaque and tangle pathology, but not CVD pathology, is the primary driver of co-occurring cognitive and functional impairment. These results also suggest that if demographic and genetic variables have any influence on clinical outcomes, their impact is indirect (i.e., mediated by pathology) rather than direct.

The findings of the mediation analysis are presented in Table 7. A similar pattern was observed for age and the two genetic variables (frequency of *APOE* $\varepsilon$2 and *APOE* $\varepsilon$4 alleles). The influence of these three variables on $\delta$ was mediated by neuropathology, such that age and *APOE* $\varepsilon$2 allele frequency were associated with less pathology and, subsequently, less severe dementia. In contrast, *APOE* $\varepsilon$4 allele frequency was associated with more pathology and, subsequently, more severe dementia. The mediating influence of neuropathology on age and *APOE* genotype was almost exclusively accounted for by AD pathology (i.e., plaques and tangles); CVD pathology had a negligible influence in mediating the relationship between the predictor variables and $\delta$. These results also show that race, despite its direct effect on CVD pathology, is neither directly nor indirectly related to clinical dementia severity in decedents with AD. Overall, Model 3 accounted for 54.0% of the variance in $\delta$.

## Discussion

This study sought to determine whether a latent variable model for measuring "dementia-relevant variance in cognitive task performance" [4] fit well within a larger model examining the effects of demographic variables (age, education, and race), genetic variables (*APOE* ε2 and ε4 allele frequency), and neuropathology (AD and CVD) on dementia severity (δ). The best fitting model reflects the hypothesis that neuropathology mediates the effects of genetic and demographic (other than education) variables on δ (see Table 3 and Figure 3).

The results of this study lend further support for the latent construct δ as a measure of the co-occurring cognitive and functional deficits that are characteristic of dementia. Previous research has established that a model for δ provided a good fit to the cognitive and functional variables in the NACC UDS, both cross-sectionally and longitudinally [8], but the results of that study were derived from living individuals without pathological data. Royall et al. have demonstrated a relationship between δ and dementia-relevant biomarkers [11–13]. This study builds upon previous work by relating δ to the neuropathological changes seen in decedents with autopsy-confirmed AD and with varying degrees of comorbid cerebrovascular pathology. In fact, this is the first known study to describe the association of δ with neuropathology. Because δ performed as expected within a model accounting for variables known to influence the clinical manifestations of sporadic AD (i.e., age, *APOE* genotype, neuropathology), these results provide further evidence for its utility as a clinical marker of dementia severity. Latent variables have the potential to pose interpretive challenges due to their abstract nature. By demonstrating the association of the latent variable δ with important demographic, genetic, and pathological variables, this study may give clinicians more confidence about the validity of δ as a useful measure of dementia severity in patients with AD.

In addition to providing support for δ, the current results also tested a comprehensive model examining how dementia severity is influenced by the interrelations between neuropathological, demographic, and genetic variables. The parameter estimates obtained from Model 3 (Tables 4–7) can help elucidate the synergistic effects of age, education, race, *APOE* genotype, and neuropathology on dementia severity within a single model. This model explained a substantial proportion of the variance in dementia severity ($R^2$ = .54). The specific findings from this model are described in more detail below.

### Age, *APOE* ε2, and *APOE* ε4 allele frequency have direct effects on AD pathology

As discussed above, age is a known risk factor for AD [17]. However, the results of this study suggest that individuals with AD who die at an older age have less AD pathology than individuals with AD who die at a younger age. These findings corroborate previous data that suggest earlier age of onset is associated with more severe AD pathology [70,71] and have important implications for targeted interventions. Although it may not be possible to completely prevent incident AD, delaying its onset may reduce pathological burden and attenuate its debilitating cognitive and functional sequelae. Because older age at death is associated with less AD pathology and less severe dementia, other factors - such as lower general intellectual ability (i.e., g′) - may better predict a diagnosis of incident dementia than pathology or dementia severity (i.e., δ) in the oldest old. On the other hand, the inverse

association between age and AD pathology may be due to a selection bias; this potential limitation is discussed more fully below.

The effect of the *APOE* $\varepsilon 2$ allele is in the same direction as age. People with more *APOE* $\varepsilon 2$ alleles have less severe AD pathology at death. As expected, the *APOE* $\varepsilon 4$ allele has the opposite effect of the $\varepsilon 2$ allele. These genetic findings are consistent with an abundance of research suggesting that the *APOE* $\varepsilon 4$ allele is associated with increased risk of AD while the $\varepsilon 2$ allele is protective against AD [38,39,48,49].

### Age and race have direct effects on CVD pathology

Two variables were found to have a direct effect on CVD pathology in people with AD: age and race (Caucasian vs. non-Caucasian). These findings are consistent with previous literature suggesting that risk of CVD pathology increases with age [17,25] and that being a member of an ethnic or racial minority group is associated with increased risk of CVD [32,33]. One important limitation of this finding is the limited ethnic and racial heterogeneity in our sample. Due to small sample sizes, we grouped all non-Caucasians together rather than analyzing different ethnic and racial groups separately. Evidence suggests that pathological differences exist across different non-Caucasian groups [35], but our data were not sufficiently diverse to examine these potential differences. We did not observe a strong relationship between the *APOE* genotype and CVD pathology.

### AD pathology, but not CVD pathology, has a direct effect on $\delta$

The only variable found to exert a significant direct effect on dementia severity was level of AD pathology. This finding is not surprising in this sample of decedents with pathologically confirmed AD. What may be surprising, however, is that CVD did not exert a significant direct effect on $\delta$. Although the parameter estimate for $\delta$ regressed onto the latent CVD factor was non-significant, its direction was positive, which implies that more CVD pathology was associated with less severe dementia. There are several possible reasons for this non-significant finding. First, it may be the case that the local effects of cerebrovascular pathology are incongruent with the global nature of dementia and the latent variable $\delta$ [72]. It could also be the case that it is the variance that CVD pathology shares with AD pathology that influences dementia severity, not the variance that is unique to CVD pathology. Because we modeled the two types of pathology as correlated factors, we did not examine their independent effects. Finally, it is possible that $\delta$ - as currently constructed - is more specific to the cognitive and functional deficits caused by AD pathology and unable to capture the effects of CVD pathology. For instance, the indicators of $\delta$ in this study may be poorly suited to measure the cognitive abilities affected by CVD burden (e.g., processing speed) above and beyond what is accounted for by AD. Given the relatively small number of cases with CVD in the current sample, more research is needed to better estimate the effect of CVD on $\delta$.

None of the demographic or genetic variables were shown to exert direct effects on $\delta$, suggesting that, if these variables play a role in affecting dementia severity, their influence is mediated by other variables, such as neuropathology. The results of the mediation analyses are discussed below.

### AD pathology mediates the effects of age, *APOE ε2* allele frequency, and *APOE ε4* allele frequency on *δ*

Although demographic and genetic variables were not found to have any direct effects on *δ*, they did exhibit indirect effects (Table 7). We hypothesized that neuropathology would act as the mediating variable to explain the influence of age and *APOE* genotype on dementia severity. As discussed above, age at death and a greater frequency of *APOE ε2* alleles were associated with less AD pathology at death, whereas a greater frequency of *APOE ε4* alleles was associated with more AD pathology at death. In turn, more AD pathology at death was associated with more severe dementia (*δ*). These results indicate that the effects of age at death and *APOE* genotype on *δ* are indirect and are mediated by AD pathology. These results are consistent with recent evidence presented by Yu and colleagues, who found that age and *APOE* genotype indirectly, but not directly, affect cognitive functioning after accounting for the mediating influence of AD pathology [22].

CVD pathology was only directly affected by age and race, and it did not exert a direct effect on *δ*; it follows that CVD pathology did not serve to mediate the relationship between predictor variables and dementia severity. However, Yu et al. also found evidence to support the mediating effects of CVD, which stands in contrast to the results presented here. Our methods differ from Yu et al. in that we modeled AD and CVD pathology as latent factors rather than as manifest variables of specific neuropathological markers (e.g., NFTs, macroscopic infarcts). The inclusion of latent, rather than manifest, variables for AD and CVD pathology emphasizes the variance shared by the manifest variables, rather than their unique contributions, and could provide an explanation for the conflicting results. In addition, the results from Yu et al. were based on longitudinal trajectories of changes in episodic memory and executive functioning, whereas our results are based on cross-sectional data from a single combined latent variable representing cognitive and functional status [22]. Despite these differences, these results converge with those of Yu et al. [22] to strongly implicate AD pathology as a mediating influence relating the effects of age and *APOE* genotype on clinical dementia outcomes.

Other unmodeled variables may also serve to mediate the relationships discussed here. For instance, in vascular dementia, the relationship between CVD and *δ* may be mediated by ischemic sequelae (e.g., atrophy, white matter changes, loss of synaptic density, or functional metabolic changes). Future research should further explore the effects of additional neuropathological markers.

The results of this study do not disentangle the effects of AD and CVD pathology on dementia severity. Considering that AD pathology is commonly observed in non-demented individuals [18–20], and that our results show that AD, but not CVD, is the primary determinant of dementia severity, then it is possible that the dementing effects of CVD are indirect (i.e., mediated by AD or other neuropathology) rather than direct. It is noteworthy that race demonstrated a significant direct effect on CVD pathology in our sample, but because of the weak effects of CVD on dementia severity, there was no indirect effect of race on *δ*. Future research should explore alternative models, such as mediated mediation models, to clarify the basis for these unexpected findings.

The data, which were provided by NACC and compiled from the 34 past and present ADCs throughout the United States, represent both a strength and a potential limitation of the current study. The availability of such an extensive set of neuropathological data is clearly a strength. However, NACC data in general are not obtained through random sampling methods and may be influenced by a selection bias in terms of who chooses to participate in research at the National Institutes of Health-funded ADCs. This selection bias is further compounded in autopsy data, which obviously depends on generous donations from the decedents and their next of kin. Because autopsy data cannot be sampled at random, and because rates of organ donation tend to be influenced by factors that are complex and multiply determined, the results of this study may not generalize broadly [73–75]. For instance, the inverse association between age and AD pathology may be due in part to selection and survival biases. Especially at younger ages, the decedents in this study are likely different from their age-matched peers who are still alive – those still alive may have less AD pathology than those whose brains were donated for AD research. Similarly, these data only include cases where CVD occurs in the context of neuropathologically confirmed AD; future research should focus on the relationship between $\delta$ and CVD in those without AD. More broadly, the methods used by NACC to quantify CVD pathology may limit this study's ability to accurately characterize the role of CVD in these models. Because the pathological indicators of CVD pathology in this study are dichotomous (absent/present), they do not capture the continuous nature of cerebrovascular disease. Our use of a continuous latent variable model for CVD may mitigate this limitation to some degree, but it remains possible that the dichotomous coding schema for CVD pathology variables underestimates the prevalence of CVD in the current sample and reduces the statistical power to precisely estimate the effects of CVD pathology.

An additional limitation is related to the fact that this study focused exclusively on individuals with pathologically confirmed AD and the results are therefore not generalizable to individuals without pathological confirmation of AD. Other pathological species were not investigated, such as $\alpha$ synuclein or TDP-43. Similarly, other predictor variables, such as smoking history, markers of metabolic syndrome, and inflammatory markers were not investigated. Future research should attempt to model the influence of these variables along with those presented herein.

Although our sample includes a broad spectrum of AD neuropathology, these results may be limited by the relative paucity of mild and pre-clinical dementia cases in our sample. Out of 727 decedents whose data were analyzed, only 65 (8.94%) were non-demented at their last visit prior to death, compared to 324 (44.6%) with severe dementia (CDR = 3). However, when the analyses were repeated after excluding decedents with severe dementia (i.e., CDR = 3), the same pattern of results was observed (data not shown). Nevertheless, future research may wish to focus on modeling $\delta$ in pre-clinical cases with less pathology.

To summarize, the current results indicate that AD pathology (i.e., A$\beta_{42}$ plaques and NFTs) strongly influenced dementia severity, whereas CVD pathology was not strongly associated with clinical dementia in individuals with pathologically confirmed AD. Although age at death and *APOE* genotype also influenced dementia severity, their effects were indirect and mediated specifically by AD pathology. Education did not exert a direct effect on dementia

severity; as a proxy for cognitive reserve, education may interact with pathology to influence clinical outcomes, but this hypothesis was not supported in the current study (results not shown). Consistent with other research, racial differences in cerebrovascular pathology were observed, but these differences were not powerful enough to influence clinical dementia, primarily due to the limited influence CVD was found to exert on $\delta$. Also consistent with other studies, age and *APOE* genotype appear to be the most pronounced risk factors for AD pathology and clinical dementia. These results also provide strong support for the validity of the $\delta$ latent dementia phenotype; this construct appears to be an excellent marker of dementia severity in AD. The relationship between $\delta$ and other forms of neuropathology, including CVD, should be investigated further. Although $\delta$ has previously been shown to possess good longitudinal measurement properties [8], further validation efforts may wish to investigate the relationship between changes in $\delta$ and changes in pathological burden over the course of a neurodegenerative disease process.

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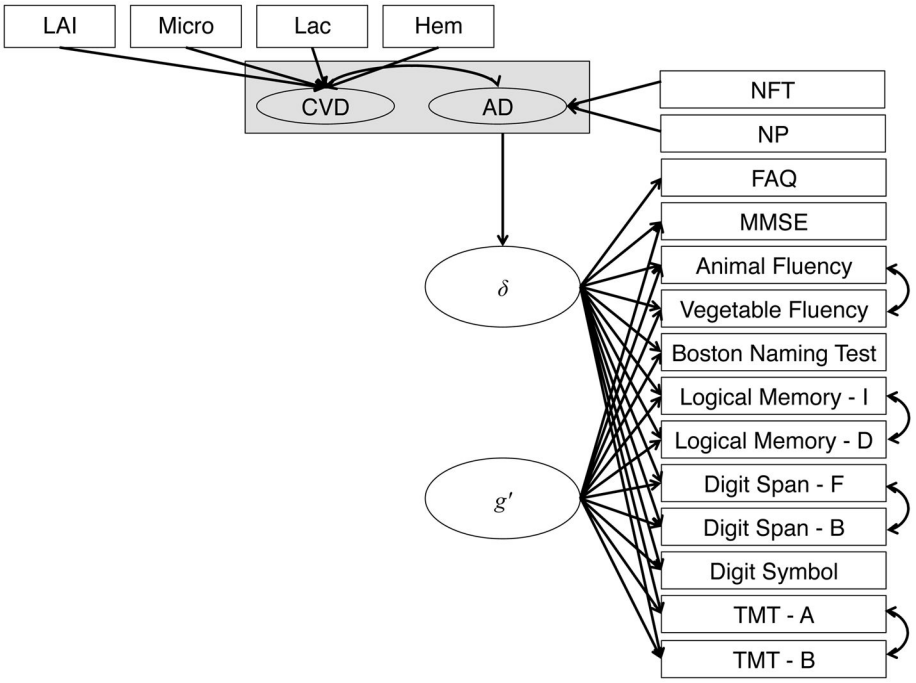


**Figure 1.**

Simplified graphical depiction of the direct effects of neuropathology on $\delta$ tested in Model 1. Arrows arising from the shaded gray box represent paths from both latent variables to $\delta$. LAI = Large arterial infarcts; Micro = cortical microinfarcts; Lac = lacunar infarcts, Hem = hemorrhages; NFT = neurofibrillary tangles; NP = neuritic plaques; CVD = cerebrovascular pathology; AD = Alzheimer's disease pathology; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; I = Immediate; D = Delayed; F = Forward; B = Backward; TMT = Trail Making Test.

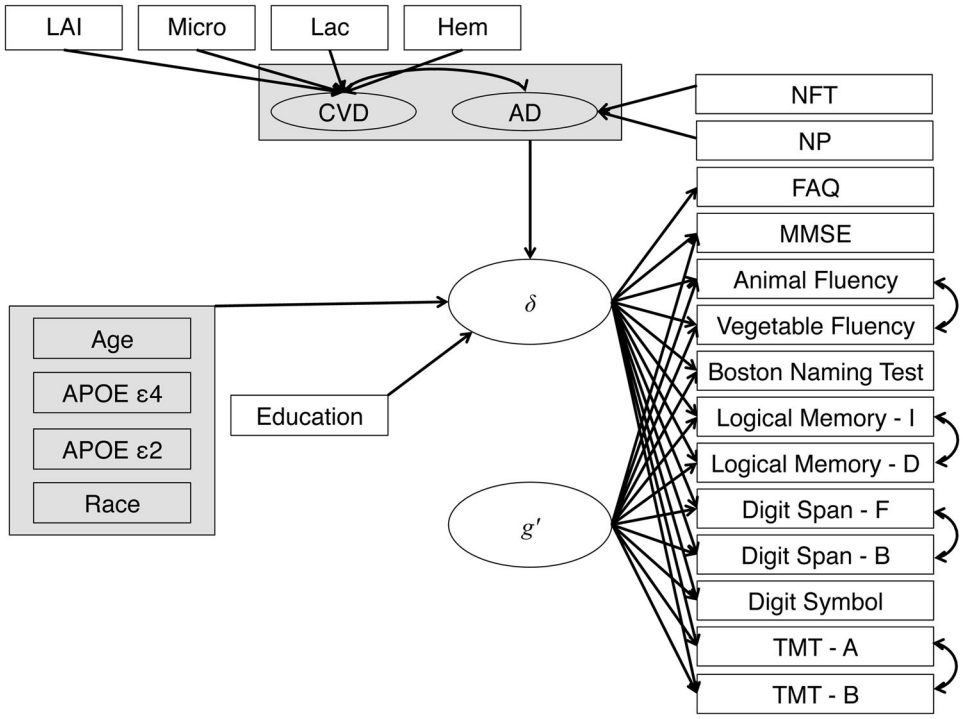


**Figure 2.**

Simplified graphical depiction of the direct effects of neuropathology, demographics, and genetics on $\delta$ tested in Model 2. Arrows arising from the shaded gray boxes represent paths from each of the variables contained in the boxes. LAI = Large arterial infarcts; Micro = cortical microinfarcts; Lac = lacunar infarcts, Hem = hemorrhages; NFT = neurofibrillary tangles; NP = neuritic plaques; CVD = cerebrovascular pathology; AD = Alzheimer's disease pathology; APOE = apolipoprotein E; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; I = Immediate; D = Delayed; F = Forward; B = Backward; TMT = Trail Making Test.

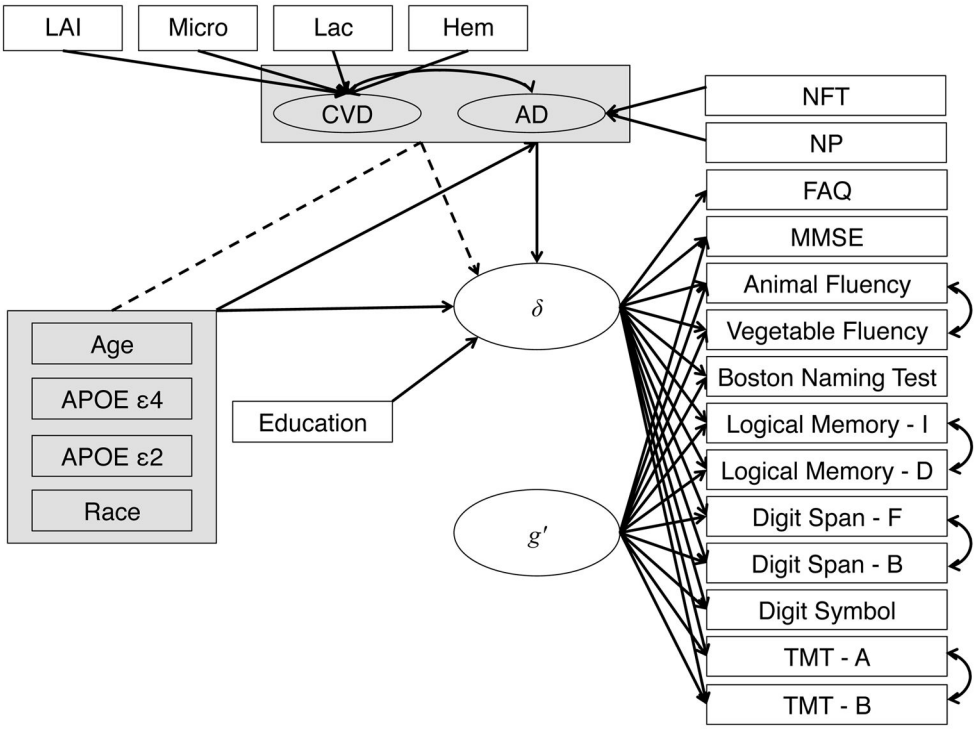


**Figure 3.**

Simplified graphical depiction of the direct and indirect effects of neuropathology, demographics, and genetics on $\delta$ tested in Model 3. Arrows arising from the shaded gray boxes represent paths from each of the variables contained in the boxes. LAI = Large arterial infarcts; Micro = cortical microinfarcts; Lac = lacunar infarcts, Hem = hemorrhages; NFT = neurofibrillary tangles; NP = neuritic plaques; CVD = cerebrovascular pathology; AD = Alzheimer's disease pathology; APOE = apolipoprotein E; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; I = Immediate; D = Delayed; F = Forward; B = Backward; TMT = Trail Making Test.

## Table 1

Demographic, genetic, and pathological characteristics of the decedents in the present study

| | | NIA-Reagan AD Staging | | |
|---|---|---|---|---|
| | **Total Sample** | **High** | **Intermediate** | **Low** |
| n | 727 | 532 | 166 | 22 |
| Interval[a]; *M* (*SD*) | 227.27 (138.39) | 229.77 (139.88) | 217.33 (132.43) | 211.68 (136.40) |
| Age at death; *M* (*SD*) | 81.59 (10.64) | 79.61 (10.44) | 87.74 (8.63) | 84.32 (10.24) |
| Education; *M* (*SD*) | 14.96 (3.22) | 15.00 (3.17) | 14.92 (3.43) | 14.32 (3.15) |
| Sex (% Female) | 46.6% | 45.1% | 53.0% | 27.3% |
| Race (% Caucasian) | 95.6% | 96.1% | 94.6% | 90.9% |
| *APOE ε*2 allele frequency (%) | | | | |
| 0 | 92.0% | 94.5% | 86.1% | 77.3% |
| 1 | 7.8% | 5.5% | 13.3% | 22.7% |
| 2 | 0.1% | 0.0% | 0.6% | 0% |
| *APOE ε*4 allele frequency (%) | | | | |
| 0 | 43.3% | 38.2% | 58.4% | 45.5% |
| 1 | 44.7% | 47.7% | 35.5% | 54.5% |
| 2 | 12.0% | 14.1% | 6.0% | 0% |
| CVD pathology frequency (%) | 32.1% | 27.9% | 42.2% | 50.0% |
| Large arterial infarcts | 8.4% | 6.6% | 13.9% | 13.6% |
| Cortical microinfarcts | 20.4% | 15.0% | 22.3% | 18.2% |
| Lacunar infarcts | 14.5% | 13.0% | 18.1% | 18.2% |
| Hemorrhages | 4.4% | 3.6% | 5.4% | 13.6% |

*Note*. NIA = National Institute of Aging; AD = Alzheimer's Disease. *APOE* = apolipoprotein E; CVD = cerebrovascular disease.

[a]Interval is the time in days from the last clinical assessment to death.

**Table 2**

Summary statistics for measures of dementia severity, by clinical diagnosis at last visit.

| | Total Sample (*n* = 727) | | | Dementia (*n* = 662) | | | MCI (*n* = 46) | | | NC (*n* = 14) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Test** | ***M*** | ***SD*** | **Range** | ***M*** | ***SD*** | **Range** | ***M*** | ***SD*** | **Range** | ***M*** | ***SD*** | **Range** |
| CDR Global | 2.10 | 0.95 | 0 – 3 | 2.26 | 0.83 | 0.5 – 3 | 0.49 | 0.07 | 0 – 0.5 | 0.07 | 0.18 | 0 – 0.5 |
| MMSE | 12.91 | 9.2 | 0 – 30 | 11.40 | 8.42 | 0 – 29 | 26.00 | 2.83 | 18 – 30 | 27.54 | 2.60 | 21 – 30 |
| FAQ | 25.43 | 8.01 | 0–30 | 27.29 | 5.05 | 0 – 30 | 8.07 | 7.95 | 0 – 26 | 1.29 | 2.87 | 0 – 8 |

*Note*. MCI = Mild cognitive impairment; NC = Normal control; CDR = Clinical Dementia Rating; MMSE = Mini-Mental Status Examination; FAQ = Functional Activities Questionnaire.

**Table 3**

Model comparison results

| Model | Description | Model Fit | | | | | | Difference Testing | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $\chi^2$ | *df* | RMSEA [90% CI] | CFI | TLI | WRMR | Test | $\chi^2$ | *df* | *p* |
| 1 | Pathology Only | 588.83 | 207 | 0.050 [0.046, 0.055] | .879 | .857 | 1.516 | -- | -- | -- | -- |
| 2 | PDG, no mediation | 432.11 | 202 | 0.040 [0.034, 0.045] | .927 | .912 | 1.099 | 1 v. 2 | 62.71 | 5 | < .001 |
| 3 | PDG, with mediation | 328.38 | 194 | 0.031 [0.025, 0.037] | .957 | .946 | 0.921 | 2 v. 3 | 72.48 | 8 | < .001 |

*Note*. PDG = pathology, demographics, and genetics; RMSEA = root mean square error of approximation; CI = confidence intervals; CFI = comparative fit index; TLI = Tucker-Lewis Index; WRMR = weighted root mean square residual.

**Table 4**

Parameter estimates for neuropathology latent variables

| Latent Variable | Indicator | *β* | *b* | SE | *b*/SE | *p* |
|---|---|---|---|---|---|---|
| AD Pathology | NFT pathology (Braak stage) | 0.794 | 1.000 | -- | -- | -- |
| | Neuritic plaques (CERAD stage) | 0.811 | 1.028 | 0.101 | 10.210 | 0.000 |
| Cerebrovascular Pathology | Large arterial infarcts | 0.733 | 1.000 | -- | -- | -- |
| | Cortical microinfarcts | 0.561 | 0.752 | 0.190 | 3.948 | 0.000 |
| | Lacunar infarcts | 0.421 | 0.559 | 0.191 | 2.930 | 0.003 |
| | Hemorrhage | 0.673 | 0.912 | 0.252 | 3.614 | 0.000 |

*Note.* $\beta$ = standardized regression coefficient; $b$ = unstandardized regression coefficient; SE = standard error (unstandardized); AD = Alzheimer's disease; NFT = neurofibrillary tangle; CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

**Table 5**

Direct effects of genetic and demographic variables on neuropathology

| Outcome Variable | Predictor Variable | *β* | *b* | SE | *b*/SE | *p* |
|---|---|---|---|---|---|---|
| Latent AD Pathology | *APOE ε*4 alleles (*n*) | 0.167 | 0.223 | 0.059 | 3.784 | 0.000 |
| | *APOE ε*2 alleles (*n*) | −0.179 | −0.578 | 0.125 | −4.634 | 0.000 |
| | Age at death (years) | −0.493 | −0.042 | 0.004 | −9.831 | 0.000 |
| | Race | 0.007 | 0.031 | 0.185 | 0.167 | 0.867 |
| Latent CVD Pathology | *APOE ε*4 alleles (*n*) | −0.008 | −0.009 | 0.077 | −0.115 | 0.908 |
| | *APOE ε*2 alleles (*n*) | 0.056 | 0.153 | 0.187 | 0.817 | 0.414 |
| | Age at death (years) | 0.333 | 0.024 | 0.006 | 3.997 | 0.000 |
| | Race | −0.171 | −0.635 | 0.231 | −2.752 | 0.006 |

*Note. β* = standardized regression coefficient; *b* = unstandardized regression coefficient; SE = standard error (unstandardized); *APOE* = apolipoprotein E; AD = Alzheimer's disease; CVD = cerebrovascular disease.

**Table 6**

Direct effects of pathological, genetic, and demographic variables on $\delta$

| Predictor Variable | $\beta$ | $b$ | SE | $b$/SE | $p$ |
|---|---|---|---|---|---|
| Latent AD Pathology | −0.691 | −1.131 | 0.179 | −6.325 | 0.000 |
| Latent CVD Pathology | 0.078 | 0.151 | 0.148 | 1.021 | 0.307 |
| *APOE* ε4 alleles (*n*) | 0.034 | 0.073 | 0.104 | 0.707 | 0.479 |
| *APOE* ε2 alleles (*n*) | 0.011 | 0.057 | 0.200 | 0.285 | 0.776 |
| Education (years) | 0.016 | 0.007 | 0.020 | 0.365 | 0.715 |
| Age at death (years) | 0.025 | 0.003 | 0.009 | 0.393 | 0.694 |
| Race | −0.016 | −0.117 | 0.333 | −0.351 | 0.725 |

*Note.* $\beta$ = standardized regression coefficient; $b$ = unstandardized regression coefficient; SE = standard error (unstandardized); AD = Alzheimer's disease; CVD = cerebrovascular disease; *APOE* = apolipoprotein E.

## Table 7

Indirect effects of genetic and demographic variables, mediated by pathology, on $\delta$

| Predictor Variable | Mediator Variable | $\beta$ | $b$ | 95% $CI_b$ |
|---|---|---|---|---|
| *APOE* ε4 allele (n) | Latent AD Pathology | −0.128 | −0.253 | [−0.437, −0.115] |
| | Latent CVD Pathology | −0.001 | −0.001 | [−0.058, 0.035] |
| | Total Indirect Effect | −0.129 | −0.254 | [−0.439, −0.099] |
| *APOE* ε2 allele (n) | Latent AD Pathology | 0.118 | 0.654 | [0.363, 1.045] |
| | Latent CVD Pathology | 0.005 | 0.023 | [−0.072, 0.641] |
| | Total Indirect Effect | 0.122 | 0.677 | [0.167, 1.107] |
| Age at death (years) | Latent AD Pathology | 0.338 | 0.047 | [0.031, 0.070] |
| | Latent CVD Pathology | 0.016 | 0.004 | [−0.005, 0.015] |
| | Total Indirect Effect | 0.354 | 0.051 | [0.034, 0.072] |
| Race | Latent AD Pathology | −0.013 | −0.035 | [−0.534, 0.459] |
| | Latent CVD Pathology | −0.009 | −0.096 | [−0.441, 0.097] |
| | Total Indirect Effect | −0.022 | −0.131 | [−0.709, 0.439] |

*Note.* $\beta$ = standardized regression coefficient; $b$ = unstandardized regression coefficient; $CI_b$ = bias-corrected bootstrap confidence interval for the unstandardized parameter estimate; *APOE* = apolipoprotein E; AD = Alzheimer's disease; CVD = cerebrovascular disease.