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Clinicopathological correlates of depression in early Alzheimer's disease in the NACC

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Abstract

Objective—Depression may be a prodrome to Alzheimer's disease (AD). We assessed whether AD neuropathology is associated with depression in mild cognitive impairment (MCI) and mild dementia (dAD).

Methods—All clinical and neuropathological data for this study came from the National Alzheimer's Coordinating Center (NACC). Healthy control (HC, n=120), MCI (n=77), and mild dAD (n=93) patients who underwent brain autopsy were included. In regression models with Geriatric Depression Scale (GDS) as the outcome, neuritic plaque (NP) score or Braak Stages of neurofibrillary (NF) pathology were covariates.

Results—GDS was not associated with cognitive status, NP score, Braak Stages, or their interaction. In both models, a history of TIAs, depression within the last 2 years, current benzodiazepine use, and greater severity of neuropsychiatric symptoms were associated with greater depression. In the Braak Stages model, less education was another significant predictor.

Conclusions—Depression in early AD appears to be independent of NP and NF pathology. Studies are needed to investigate other mechanisms that may be responsible for depression in MCI and dAD.

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Conflict of interest

With respect to a perceived duality of interest, we disclose financial support from the National Institute of Health. Dr. Leoutsakos is an unpaid statistical consultant for Lilly. Dr. Lyketsos reports additional grant support (research or CME) from the Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis, National Football League, Elan, and Functional Neuromodulation. He has served as a consultant or advisor for Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda,Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, Abvie, Janssen, Orion, Otsuka, Servier, and Astellas. Dr. Lyketsos has received honorarium or travel support from Pfizer, Forest, Glaxo-Smith Kline, and Health Monitor. Dr. Albert is currently a consultant to Lilly and Biogen. The other authors have no conflicts of interest to report.

Keywords

Alzheimer's disease; late-life depression; neuropsychiatric symptoms; dementia; mild cognitive impairment; neuropathology

Introduction

Clinically significant depression occurs in up to 50% of individuals with dementia because of Alzheimer's disease (dAD) (Lyketsos and Olin, 2002; Di Iulio et al., 2010) and 44% of those with mild cognitive impairment (MCI) (Di Iulio et al., 2010). Depression is linked to greater functional impairment (Garre-Olmo et al., 2003), earlier institutionalization (Steele et al., 1990), and worse quality of life for patients (Leon-Salas et al., 2013). Depression is an important risk factor for the transition from MCI to dAD (Modrego and Ferrandez, 2004). Standard antidepressants are not effective at treating depression in dAD (Rosenberg et al., 2010; Banerjee et al., 2011) and are associated with more rapid cognitive and functional decline (Rosenberg et al., 2012). Thus, the development of new treatments for depressed MCI and dAD patients is urgently needed. Critical to this is an improved understanding of the pathophysiology of depression along the AD continuum.

Converging evidence suggests that late-life depression (LLD) is an AD prodrome. LLD is associated with increased risk of MCI (Barnes et al., 2006; Steenland et al., 2012) and dAD (Barnes et al., 2012; Rosenberg et al., 2013). A recent meta-analysis estimated that LLD confers a 1.65 increase in odds of incident dAD (Diniz et al., 2013). Elders with amyloid-associated depression, defined by a high plasma beta-amyloid (Aβ) peptide 40 (Aβ40)/Aβ42 ratio, were more likely to develop AD than those with non-amyloid associated depression (Qiu et al., 2015). A post-mortem study found a predominance of AD neuropathology in individuals with LLD and dementia (Sweet et al., 2004). In another study, depression increased the odds for neurofibrillary tangle (NFT) neuropathology in AD patients (Rapp et al., 2008). Using Pittsburgh Compound B positron emission tomography, Butters and colleagues demonstrated that approximately one-half of individuals with MCI and remitted major depression had a retention pattern similar to early AD (Butters et al., 2008). Additional support comes from magnetic resonance imaging studies linking depression to greater atrophy in AD-affected regions (Zahodne et al., 2013; Dhikav et al., 2014). In the Alzheimer's Disease Neuroimaging Initiative, depressive symptoms in MCI were associated with cortical atrophy in AD-affected regions, faster cognitive decline, and increased likelihood of conversion to AD (Lee et al., 2012).

We queried data from the National Alzheimer's Coordinating Center (NACC) to assess whether measures of AD neuropathology are associated with depressive symptomatology in MCI and early dAD. Unlike prior studies biased in favor of end-stage AD, we focus on individuals who died with MCI and mild dAD where the neurodegenerative process is less advanced and less likely to confound statistical inferences. Based on the prior neuropathological findings of Rapp and colleagues, we hypothesize that NFT pathology, but not neuritic plaque (NP) pathology, will be associated with greater depressive symptoms in MCI and early dAD.

Methods

The NACC

Data analyzed are from the NACC. Established by the National Institute on Aging in 1999, the NACC is a standardized, large-scale dataset with clinical and neuropathological data from participants at 34 past and present Alzheimer's Disease Centers (ADCs). These data are available for a variety of AD topics (Morris et al., 2006).

Clinical assessments

NACC participants receive a comprehensive, inperson evaluation at one of the ADCs on a yearly basis until study withdrawal or death. This assessment includes medical, psychiatric, and neurologic histories; neuropsychological battery; psychiatric and neurological examinations; and the Clinical Dementia Rating (CDR) (Hughes et al., 1982). Before participation, subjects or their healthcare proxies provide informed consent under the oversight of the Institutional Review Board responsible for each ADC.

Following evaluation, each participant's cognitive status is determined by an experienced clinician or consensus conference at the ADC (Morris et al., 2006). MCI diagnoses are made according to the Petersen criteria (Petersen, 2004). During the period these data were collected, dAD was diagnosed according to the NINCDS/ADRDA criteria (McKhann et al., 1984). Autopsy for neuropathological diagnosis is offered to all participants. Neuropathological assessments are performed at each ADC using the NACC Neuropathology Data Set (NDS) manual (Beekly et al., 2004).

NACC Uniform Data Set (UDS) and NDS

Described in detail elsewhere (Beekly et al., 2004; Morris et al., 2006), all NACC data are stored without personal identifiers. The UDS captures clinical data including demographics; family, medical, neuropsychiatric, and dementia histories; neuropsychological test results; and clinical diagnosis of cognitive status. For those who receive an autopsy, the NDS contains date of death; APOE genotype; NP score according to Consortiumto Establish A Registry for Alzheimer's Disease (CERAD) standards (Mirra et al., 1991); Braak and Braak Neurofibrillary Stages (Braak and Braak, 1991); the presence of non-AD neuropathologies such as Lewy body pathology, hippocampal sclerosis, frontotemporal dementia, prion disease, and various forms of vascular pathology (e.g. amyloid angiopathy, ischemic pathology, etc.); and the primary and contributing neuropathological diagnoses assigned by the evaluating ADC neuropathologist. For these analyses, we examined data from the 1 March 2012 finalized NACC dataset.

Study participants

Analyses were restricted to NACC participants with an autopsy diagnosis and with one of the following clinical diagnoses at the last ADC visit before death: cognitively intact healthy controls (HCs), amnestic or non-amnestic MCI; and probable or possible dAD. Several exclusion criteria were applied. First, those with moderate or severe AD as defined by a CDR>1 were excluded. This yielded an initial sample size of 848 (HC=400, MCI=228, dAD=220). To specifically understand the relationship between AD pathology and

depression, we excluded individuals with neuropathological evidence of non-AD neurodegenerative disorders (i.e. Lewy Body, prion, frontotemporal dementias; hippocampal sclerosis) and other brain diseases (e.g. malignancy; infection; amyotrophic lateral sclerosis). Given its high occurrence in our sample and known association with LLD, we decided against the exclusion of individuals with a primary or contributing neuropathological diagnosis of vascular disease (Taylor et al., 2013). Based on guidance from the NACC, four subjects from one site were excluded because of problems with data collection. This yielded a final sample size of 290 (n=120 HCs; n=77 MCI; n=93 dAD).

Clinical Variables

All clinical data were from last ADC visit before death:

(1) Demographics: age at death; gender; race; marital status; education level; and time between last ADC visit and death;

(2) Medical history: hypertension; hypercholesterolemia; diabetes mellitus (DM); atrial fibrillation; coronary artery disease; transient ischemic attacks (TIAs); stroke; or depression within the past 2 years;

(3) Hachinski Ischemic Score (Rosen et al., 1980);

(4) Presence versus absence of APOE allele 4;

(5) Current use of 12 medications classes given that medication use serves as a proxy for various forms of pathology: benzodiazepines; sleep aids; antidepressants; mood stabilizers; antipsychotics; acetylcholinesterase inhibitors; memantine; lipid-lowering agents; non-steroidal anti-inflammatories; antihypertensives; blood thinners; and DM agents;

(6) Mini-mental state examination (MMSE) (Folstein et al., 1975), a measure of global cognitive impairment with scores ranging from 0 to 30 (higher scores suggest better cognition);

(7) CDR sumof boxes (O'Bryant et al., 2008), ameasure of dementia severity with scores ranging from 0 (no impairment) to 18 (severe cognitive impairment);

(8) Neuropsychiatric Inventory Questionnaire (NPI-Q) (Cummings et al., 1994), administered to a knowledgeable informant to evaluate the presence and severity of 12 neuropsychiatric symptoms (NPS) such as agitation or delusions. Scores range from 0 to 36 (higher scores indicate greater NPS occurrence and severity);

(9) Short form of the Geriatric Depression Scale (GDS) (Sheikh and Yesavage, 1986), a widely used measure of LLD. GDS was treated as a continuous variable ranging from zero to 15 where higher scores indicate more severe depression.

Neuropathological variables

The NACC does not record autopsy dates, although it recommends that ADCs perform autopsies as soon as possible following death. We used death dates to approximate date of

autopsy completion. Two measures of AD neuropathology, the NP score and Braak Stages of NFT pathology, were examined. Ranging from “no” to “frequent” NPs, the NP score is categorical according to CERAD standards (Mirra et al., 1991). A Braak Stages of 0 indicates no NFTs, while stages I through VI represent increasing severity of NFT pathology (Braak and Braak, 1991). We also included the following types of vascular pathology: large artery cerebral infarcts; microinfarcts; lacunes; single or multiple hemorrhages; and amyloid angiopathy.

Statistical analyses

Differences in demographic, medical, and neuropsychological characteristics across the three groups (HC, MCI, and dAD) were examined using descriptive statistics: ANOVA for continuous variables; Fisher’s exact test for dichotomous variables; and chi-squared for categorical variables. The relationship between AD pathology and depression severity was estimated with two multivariate linear regression models. In the first, NP score was the independent variable and collapsed into three categories: no or sparse NPs (reference group); moderate NPs; and frequent NPs. The independent variable in the second was Braak Stages: no NFT pathology (reference group); stages I–II; stages III–IV; and stages V–VI. The use of collapsed categories for measures of AD pathology has been described previously (Dolan et al., 2010; Hyman et al., 2012). To test the influence of vascular pathology on GDS, we modeled a dichotomous measure of clinically significant vascular neuropathology (CVP) as a covariate. CVP was considered present if vascular disease was deemed a contributing or primary cause of the cognitive impairment.

We fit univariate linear regression models with GDS as the outcome and relevant demographic, clinical, and neuropathological covariates. Next, we fit amodel with GDS as the outcome, and clinical diagnosis, NP score, and their interactions as covariates. We fit an analogous model for Braak Stages. Two models, one for NP score and one for Braak Stages, were estimated given that these measures might be collinear as both are measures of AD severity. Next, we fit two multivariate models. In the first, we included NP score, clinical diagnosis, the interaction between NP score and clinical diagnosis, and covariates that were significant at the 0.10 level in the univariate analyses (Alexopoulos, 2010).We fit an analogous model for Braak Stages. We assessed collinearity in our models by examining for dependent variables with a variance inflation factor greater than five. None met this criterion. For the multivariate analyses, the alpha was set at 0.05. All data analyses were performed using Stata 11 (2009, Stata Corporation, College Station, TX).

In addition to ruling out collinearity, we examined the correlation between NPI-Q and GDS to describe the relationship between these variables. Based on a Pearson correlation ($r=0.165$; $p=0.01$), the NPI-Q explains slightly less than 3% of the variance in GDS. Thus, we deemed the NPI-Q to be an appropriate covariate for our model. Further, we considered removing the depression domain from NPI-Q for our analyses. However, this one measure of depression from the NPI-Q is not expected to be as sensitive of a measure of depression as the GDS.

Results

Clinical characteristics

Demographic, medical, and neuropsychological characteristics are in Table 1. As a whole, the sample consisted of mostly white elders who died in their mid-to-late 80s. The proportion of male, married, and APOE allele 4 carriers was greater in the dAD group than the other groups. The proportion of individuals with a history of heart attack or cardiac arrest was lower among those with dAD. No significant between-group differences were found in vascular history. As expected, those within the dAD group had the most impaired scores on the CDR sum of boxes, MMSE, and NPI-Q, and were also more likely to be prescribed a cholinesterase inhibitor or memantine. No between-group differences for depression severity based on the GDS or history of prior depressive episodes were observed, but 31.2% of MCI and 33.3% of dAD participants were taking antidepressants in comparison to 17.5% of HCs ($p=0.015$). Between-group differences also existed for the use of benzodiazepines and DM medications, but no other classes.

Neuropathological characteristics

Table 2 shows the sample's neuropathological characteristics. On average, participants underwent brain autopsy within 1 year from last ADC visit. The proportion of individuals with amyloid angiopathy was higher in the dAD group, while the proportion of those with greater than one large artery infarct and CVP was higher in the MCI group. No other between group differences were observed in vascular pathology. As expected, the greatest proportion of individuals with frequent NPs, Braak Stages V and VI, and meeting CERAD or NIA/Reagan Institute criteria for definite AD or high likelihood of dAD, respectively, were in the dAD group. Nearly half of dAD participants met CERAD criteria for definite pathological AD, whereas only 4.2% and 10.4%fromthe HC and MCI groups, respectively, met these criteria ($p<0.01$). A similar pattern was observed among the groups for NIA/Reagan Institute criteria for the pathological diagnosis of dAD ($p<0.01$).

Relationship between AD neuropathology and GDS by clinical diagnosis

Based on the univariate linear regression analyses (results not shown), years of education; histories of TIAs and depression within the last 2 years; current use of a benzodiazepine, antidepressant, or sleep aid; and NPI-Q score were associated with GDS and thus included in multivariate models. In the model of GDS as a function of NP score, clinical diagnosis, and their interaction, individuals with a clinical diagnosis of MCI and frequent NPs were expected on average to have a GDS score 1.89 greater than HCs with an NP score of no or sparse ($p=0.04$). There were no other significant relationships in this model. In the analogous model based on Braak Stages, none of these associations were statistically significant.

Table 3 shows the covariate-adjusted multivariate regression of GDS on NP score, clinical diagnosis, and their interaction. GDS was not associated with diagnostic category, NP score, or their interaction. However, a history of TIAs, depression within the last 2 years, current benzodiazepine use, and greater severity of comorbid NPS were associated with higher GDS. The results of the covariate-adjusted multivariate regression of GDS on Braak Stages,

clinical diagnosis, and their interaction are in Table 4. No significant relationships between Braak Stages and GDS, clinical diagnosis of cognitive status and GDS, or the interaction between Braak Stages and clinical diagnosis on GDS were observed. However, less education, history of TIAs, depression within the last 2 years, current benzodiazepine use, and greater severity of NPS were associated with greater GDS.

Discussion

Neither NP nor NFT pathology was associated with depression severity measured by GDS. In addition, clinical diagnosis of cognitive status was not related to depression and did not modify the relationship between NP or NFT pathology and depression severity. These results imply that a mechanism other than global burden of NP and NFT pathology is involved in the pathophysiology of depression in MCI and dAD. In both regression models, a history of TIAs, depression within the last 2 years, current benzodiazepine use, and severity of comorbid NPS were associated with depression. In the second model, less education was another significant predictor.

Prior studies of the neuropathological basis of depression in dAD have produced mixed results. In line with our results, a small study of 11 participants found no significant difference in measures of NP or NFT pathology between depressed elders with and without cognitive impairment (O'Brien et al., 2001). Results from the Religious Orders Study found no association between depressive symptoms and NP or NFT pathology (Wilson et al., 2003). Interestingly, depression severity increased the odds of a dAD clinical diagnosis. We observed a similar relationship, albeit at the trend level, whereby individuals with greater depressive symptoms but mild NFT burden (i.e. Braak Stages I or II) were diagnosed with clinical dAD. These findings suggest that depression has two possible effects on dAD clinical diagnosis. In the first, depression modifies the relationship between NFTs and diagnosis, such that a depressed individual needs fewer NFTs to receive a dAD diagnosis. In other words, such individuals have milder AD pathology. The second possibility is that depression causes a nondemented individual to receive a dAD diagnosis, previously referred to as "depressive pseudodementia." In the latter case, depression treatment may have important prognostic implications and may improve the cognitive impairment.

In contrast, Rapp and colleagues, studying 6500 NACC participants with pathological AD, reported that those with comorbid depression had greater NFT burden than those who were not depressed (Rapp et al., 2008). Although this study also uses data from the NACC, our findings may differ because of key methodological differences. First, the studies use different measures of depression. Rapp and co-investigators rated the presence or absence of depression according to the judgment of clinicians present at the ADC consensus conference. The study did not include standardized measures of depression, such as the GDS. Further, their depression assessment occurred at the time of study inclusion. Given that clinical assessments occur yearly at the ADCs, the presence and severity of depression may vary considerably in the time leading up to dementia diagnosis or death. In contrast, we choose to focus on the more temporally proximal relationship between depression and AD neuropathology in those with early AD.

Several mechanisms have been proposed to explain the neurobiology of depression in AD. Dysfunction of the monoamine system, critical for mood regulation, has been suggested, and the loss of monoaminergic cell bodies in AD has been documented (Lyness et al., 2003). In a transgenic AD mouse model of amyloid pathology, loss of monoaminergic axons and neurons preceded the onset of anxiety-associated behavior (Liu et al., 2008). Yet, other work has failed to show greater monoaminergic degeneration in depressed versus nondepressed AD participants (Hoogendijk et al., 1999). Given these mixed findings, the field is exploring alternative explanations, such as the role of alterations in glutamatergic neurotransmission, in the pathophysiology of depression in AD. (Khundakar and Thomas, 2015).

Second, AD pathology in key regions rather than its global burden may contribute to the pathophysiology of depression in AD. For instance, the anterior cingulate cortex (ACC) has been has been linked to LLD (Alexopoulos et al., 2008) and comorbid mood and cognitive impairment (Hirono et al., 1998; Tighe et al., 2012; Zahodne et al., 2013). Alternatively, the spread of AD pathology to key cortical and limbic regions may cause retrograde dysfunction and degeneration of monoamine neurons projecting to such regions (Koliatsos et al., 1988; Kitt et al., 1989).

Finally, a growing literature suggests that individuals with age-related cognitive impairment have neuropathological evidence of more than one neurodegenerative disorder (Armstrong et al., 2005). In a study of ten elders with LLD, Sweet and colleagues determined that AD was the predominant underlying neuropathology. However, this pathology did not occur in isolation, and all participants had evidence of either vascular or Lewy body pathology. Another study found higher rates of depression in individuals with comorbid AD and Lewy body pathologies compared to those with AD alone (Lopez et al., 2006). Despite the well-established relationship between LLD and vascular disease (Taylor et al., 2013), little is known about how vascular disease contributes to the pathologic basis of depression in dAD. Our results do not support a vascular contribution to depression in early AD.

Compared to other post-mortem studies, this study is unique in its large sample. By virtue of ADC protocols and the use of well-validated clinical scales, subjects included here have been well characterized clinically. Further, inclusion of participants in the earliest clinical stages of AD is novel.

Several limitations warrant mention. First, we examined cross-sectional relationships between AD neuropathology and depression before death. Thus, causal inferences cannot be drawn, and we cannot comment on the risk of an eventual diagnosis of dementia in HCs with depression. While our use of two different regression models may increase the risk of drawing false conclusions, we choose this approach to generate hypotheses for future studies. The GDS, our measure of LLD, relies on participants' abilities to recall their recent mood states. Given our inclusion of cognitively impaired elderly, the GDS is likely an imperfect measure. Further, we did not control for prior history of depression given the absence of reliable data across the ADCs about psychiatric history. Given the heterogeneity of LLD, individuals with recurrent depression may have a different neuropathological substrate than those with new onset depression occurring in close proximity to MCI or dAD diagnosis. Another limitation is that regionalspecific ratings of AD neuropathology are not

available. Therefore, the differential contribution of AD pathology in specific regions of interest cannot be explored. Third, the administration of psychotropic agents may obscure brain–behavior relationships. Given group differences for benzodiazepine, antidepressant, and memory enhancing agents in participants, medication effects might confound results. As we excluded participants with pathologic evidence of other neurodegenerative disorders, we are unable to comment whether other neuropathologies contribute to depression in this setting. Given the high occurrence of vascular disease across our study groups, we are unable to statistically test whether vascular pathology influences depression severity.

Conclusion

Depression in early AD appears to be independent of NP and NFT pathology. These results suggest that another mechanism is responsible for depression along the AD continuum. Future studies are needed to better understand the neuropathological substrate of depression in MCI and dAD. We recommend investigation of the relationship between AD pathology in key brain regions (e.g. ACC and monoaminergic nuclei) and depression. Further, the role of non-AD neurodegenerative processes should be considered. Such studies are critically needed to develop better treatments for depression in AD.

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Key points

- Depression may be an early clinical manifestation of Alzheimer's disease (AD).
- Using data from the National Alzheimer's Coordinating Center (NACC), we investigated whether measures of AD neuropathology are associated with depression in mild cognitive impairment (MCI) and mild dementia because of Alzheimer's disease (dAD).
- Based on a sample of 290 participants from the NACC, depression in early AD appears to be independent of neuritic plaque and neurofibrillary tangle pathology.
- Future studies are needed to evaluate other mechanisms that may contribute to depression in MCI and dAD.

Table 1

Demographic, medical, and neuropsychological characteristics by clinical diagnostic group at the last Alzheimer's Disease Center visit prior to death

	HC *n* = 120 Mean (SD)/*n*(%)	MCI *n* = 77 Mean (SD)/*n*(%)	dAD *n* = 93 Mean (SD)/*n*(%)	*p*-value
Age at death (yrs)	87.6 (8.2)	89.6 (6.9)	84.7 (10.7)	0.001
Sex				
Female	75 (62.5%)	43 (55.8%)	39 (41.9%)	0.011
Male	45 (37.5%)	34 (44.2%)	54 (58.1%)	
Race				
White	120 (100%)	72 (93.5%)	90 (96.8%)	0.010
Other	0 (0.0%)	5 (6.5%)	3 (3.2%)	
Education (yrs)	16.3 (8.1)	17.2 (13.7)	15.9 (9.3)	0.726
Marital Status				
Married	38 (31.7%)	24 (31.2%)	51 (54.8%)	0.001
Other	82 (68.3%)	53 (68.8%)	42 (45.2%)	
APOE genotype				
>1 copy of allele 4	10 (8.3%)	16 (20.8%)	34 (36.6%)	<0.001
No copies of allele 4	82 (68.3%)	45 (58.4%)	27 (29%)	
Hypertension				
Active[a]	74 (61.7%)	49 (63.6%)	51 (54.8%)	0.542
Inactive or no history[b]	45 (37.5%)	28 (36.4%)	42 (45.2%)	
Hypercholesterolemia				
Active	44 (36.7%)	31 (40.3%)	40 (43.0%)	0.645
Inactive or no history	74 (61.7%)	46 (59.7%)	53 (57%)	
Diabetes mellitus				
Active	17 (14.2%)	4 (5.2%)	10 (10.8%)	0.138
Inactive or no history	103 (85.8%)	73 (94.8%)	83 (89.3%)	
Atrial fibrillation				
Active	23 (19.2%)	13 (16.9%)	10 (10.8%)	0.380
Inactive or no history	96 (80.0%)	64 (83.1%)	82 (88.2%)	
History of angioplasty, endarterectomy, or stent for cardiovascular disease				
Recent[a]	4 (3.3%)	1 (1.3%)	3 (3.2%)	0.736
Remote or no history[b]	116 (96.7%)	76 (98.7%)	90 (96.8%)	
History of heart attack or cardiac arrest				
Recent	25 (20.8%)	17 (22.1%)	9 (9.7%)	0.042
Remote or no history	95 (79.2%)	60 (77.9%)	84 (90.3%)	
History of transient ischemic attack				
Recent	21 (17.5%)	14 (18.2%)	10 (10.8%)	0.516
Remote or no history	98 (81.7%)	62 (80.5%)	81 (87.1%)	

	HC *n* = 120 Mean (SD)/*n*(%)	MCI *n* = 77 Mean (SD)/*n*(%)	dAD *n* = 93 Mean (SD)/*n*(%)	*p*-value
History of stroke				
Recent	12 (10.0%)	10 (13.0%)	10 (10.8%)	0.472
Remote or no history	108 (90.0%)	67 (87.0%)	81 (87.1%)	
Hachinski Ischemic Score	1.3 (1.8)	1.6 (1.8)	1.3 (1.7)	0.596
CDR sum of boxes	0.1 (0.4)	1.6 (1.4)	6.4 (1.6)	<0.001
MMSE	28.4 (1.6)	26.6 (2.3)	20.4 (4.9)	<0.001
Depression, in last 2 years				
Yes	35 (29.2%)	24 (31.2%)	29 (31.2%)	0.730
No	85 (70.8%)	52 (67.5%)	64 (68.8%)	
Depression, prior episodes[c]				
Yes	28 (23.3%)	13 (16.9%)	19 (20.4%)	0.188
No	91 (75.8%)	63 (81.8%)	74 (79.6%)	
GDS score	3.1 (3.0)	3.1 (2.7)	2.9 (2.8)	0.770
Total NPI-Q score	1.7 (2.5)	1.9 (2.7)	5.0 (4.3)	<0.001
Current medication use by class:				
Benzodiazepines				
Yes	16 (13.3%)	11 (14.3%)	3 (3.2%)	0.014
No	104 (86.7%)	66 (85.7%)	90 (96.8%)	
Anti-depressants				
Yes	21 (17.5%)	24 (31.2%)	31 (33.3%)	0.015
No	99 (82.5%)	53 (68.8%)	62 (66.7%)	
Anti-psychotics				
Yes	7 (5.8%)	3 (3.9%)	5 (5.4%)	0.892
No	113 (94.2%)	74 (96.1%)	88 (94.6%)	
Mood stabilizers				
Yes	1 (0.8%)	0 (0%)	0 (0%)	1.000
No	119 (99.2%)	77 (100%)	93 (100%)	
Sleep aids				
Yes	12 (10%)	8 (10.4%)	7 (7.5%)	0.762
No	108 (90%)	69 (89.6%)	86 (92.5%)	
Cholinesterase inhibitors				
Yes	4 (3.3%)	12 (15.6%)	55 (59.1%)	<0.001
No	116 (96.7%)	65 (84.4%)	38 (40.9%)	
Memantine				
Yes	0 (0%)	5 (6.5%)	35 (37.6%)	<0.001
No	120 (100%)	72 (93.5%)	58 (62.4%)	
Anti-hypertensives				
Yes	80 (66.7%)	49 (63.6%)	48 (51.6%)	0.072
No	40 (33.3%)	28 (36.4%)	45 (48.4%)	
Diabetes mellitus medications				
Yes	13 (10.8%)	1 (1.3%)	4 (4.3%)	0.019

	HC *n* = 120 Mean (SD)/*n*(%)	MCI *n* = 77 Mean (SD)/*n*(%)	dAD *n* = 93 Mean (SD)/*n*(%)	*p*-value
No	107 (89.2%)	76 (98.7%)	89 (95.7%)	
Cholesterol lowering medications				
Yes	26 (21.7%)	21 (27.3%)	28 (30.1%)	0.357
No	94 (78.3%)	56 (72.7%)	65 (69.9%)	
NSAIDs				
Yes	34 (28.3%)	23 (29.9%)	25 (26.9%)	0.918
No	86 (71.7%)	54 (70.1%)	68 (73.1%)	
Blood thinners				
Yes	28 (23.3%)	14 (18.2%)	14 (15.1%)	0.326
No	92 (76.7%)	63 (81.8%)	79 (85%)	

ADC, Alzheimer's Disease Center; CDR, Clinical Dementia Rating; dAD, dementia because of possible or probable Alzheimer's disease; GDS, Geriatric Depression Scale; HC, healthy control; MCI, mild cognitive impairment; MMSE, mini-mental state examination; NACC, National Alzheimer's Coordinating Center; NSAIDs, non-steroidal anti-inflammatory drugs; NPI-Q, Neuropsychiatric Inventory Questionnaire; SD, standard deviation; UDS, Uniform data set; yrs, years.

[a]Active or recent history: As per the NACC UDS Coding Guidebook, active or recent history of a condition is defined as a medical condition that has happened within the last year or still requires active management, and is consistent with information obtained from informant report, medical records and/or observation.

[b]Inactive or remote history: As per the NACC UDS Coding Guidebook, a condition should be considered inactive or remote if it existed or occurred in the past (greater than 1 year ago) but was resolved or there is no current treatment underway.

[c]Depressive episodes prior to the last 2 years.

Table 2

Neuropathological characteristics by clinical diagnostic group

	HC *n* = 120 Mean(SD)/*n*(%)	MCI *n* = 77 Mean(SD)/*n*(%)	dAD *n* = 93 Mean(SD)/*n*(%)	*p*-value
Duration between last ADC visit and death (years)	0.6 (0.8)	0.6 (0.8)	0.8 (1.2)	0.068
Presence of >1 large artery infarcts				
Yes	14 (11.7%)	21 (27.3%)	10 (10.8%)	0.006
No	106 (88.3%)	56 (72.7%)	83 (89.3%)	
Presence >1 cortical microinfarcts				
Yes	24 (20.0%)	20 (26.0%)	19 (20.4%)	0.570
No	96 (80.0%)	57 (74.0%)	74 (79.6%)	
Presence of >1 lacunes				
Yes	22 (18.3%)	18 (23.4%)	17 (18.3%)	0.644
No	98 (81.7%)	59 (76.6%)	76 (81.7%)	
Presence of >1 hemorrhages				
Yes	9 (7.5%)	8 (10.4%)	7 (7.5%)	0.741
No	111 (92.5%)	69 (89.6%)	86 (92.5%)	
Presence of amyloid angiopathy				
None	75 (62.5%)	39 (50.7%)	30 (32.3%)	
Mild	29 (24.2%)	20 (26.0%)	34 (36.6%)	0.003
Moderate	8 (6.7%)	10 (13.0%)	18 (19.4%)	
Severe	6 (5.0%)	6 (7.8%)	9 (9.7%)	
CVP				
Yes	37 (30.8%)	41 (53.3%)	39 (41.9%)	0.012
No	69 (57.5%)	25 (32.5%)	44 (47.3%)	
Braak Stages				
Not present	12 (10.0%)	0 (0.0%)	3 (3.2%)	
Stage I	29 (24.2%)	5 (6.5%)	2 (2.2%)	
Stage II	37 (30.8%)	12 (15.6%)	7 (7.5%)	<0.001
Stage III	21 (17.5%)	25 (32.5%)	14 (15.1%)	
Stage IV	18 (15.0%)	19 (24.7%)	27 (29.0%)	
Stage V	1 (0.8%)	9 (11.7%)	20 (21.5%)	
Stage VI	1 (0.8%)	6 (7.8%)	19 (20.4%)	
Neuritic plaque score				
None	53 (44.2%)	13 (16.9%)	11 (11.8%)	
Sparse	23 (19.2%)	22 (28.6%)	8 (8.6%)	<0.001
Moderate	30 (25.0%)	26 (33.8%)	30 (32.3%)	
Frequent	14 (11.7%)	16 (20.8%)	44 (47.3%)	
CERAD criteria				
Not met	59 (49.2%)	14 (18.2%)	9 (9.7%)	
Possible Alzheimer’s disease	24 (20.0%)	12 (15.6%)	7 (7.5%)	<0.001
Probable Alzheimer’s disease	7 (5.8%)	12 (15.6%)	17 (18.3%)	

	HC ***n*** **= 120** **Mean(SD)/*n*(%)**	**MCI** ***n*** **= 77** **Mean(SD)/*n*(%)**	**dAD** ***n*** **= 93** **Mean(SD)/*n*(%)**	***p*-value**
Definite Alzheimer's disease	5 (4.2%)	8 (10.4%)	42 (45.2%)	
NIA/Reagan Institute criteria				
Not met	60 (50.0%)	7 (9.1%)	7 (7.5%)	
Low likelihood of dAD	33 (27.5%)	17 (22.1%)	13 (14.0%)	<0.001
Intermediate likelihood of dAD	22 (18.3%)	40 (52.0%)	32 (34.4%)	
High likelihood of dAD	3 (2.5%)	12 (15.6%)	40 (43.0%)	

%, percentage; AD, dementia because of possible or probable Alzheimer's disease; ADC, Alzheimer's Disease Research Center; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CVP, contributing pathologic diagnosis of vascular pathology according to evaluating; ADC, neuropathologist; dAD, dementia because of Alzheimer's disease; HC, healthy control; MCI, mild cognitive impairment; NIA, National Institute on Aging; SD, standard deviation.

Table 3

Results of the covariate-adjusted multivariate linear regression model of the Geriatric Depression Scale as a function of neuritic plaque score, clinical diagnosis at the last Alzheimer's Disease Center visit prior to death, and their interaction

		β	95% CI	*p*-value
Clinical diagnostic category (HC as reference)	MCI	−0.69	(−1.73,0.35)	0.19
	dAD	0.80	(−0.53,2.13)	0.24
Neuritic plaque score (none or sparse as reference)	Moderate	0.39	(−0.72,1.5)	0.49
	Frequent	−0.28	(−1.82,1.27)	0.72
Interaction: MCI and neuritic plaque score	Moderate	0.52	(−1.3,2.34)	0.57
	Frequent	1.74	(−0.51,3.99)	0.13
Interaction: dAD and neuritic plaque score	Moderate	−1.53	(−3.37,0.32)	0.10
	Frequent	−1.13	(−3.22,0.96)	0.29
Education (years)		−0.04	(−0.07,0)	0.03
History of transient ischemic attack		1.68	(0.83,2.53)	<0.01
Depression, in last 2 years		2.12	(1.32,2.93)	<0.01
Current benzodiazepine use		1.93	(0.86,3.01)	<0.01
Current sleep aid use		0.97	(−0.13,2.06)	0.08
Current anti-depressant use		−0.81	(−1.64,0.03)	0.06
Total NPI-Q score		0.12	(0.02,0.23)	0.02
Intercept		2.26	(1.44,3.07)	<0.01

CI, confidence interval; dAD, dementia because of possible or probable Alzheimer's disease; HC, healthy control; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire.

Table 4

Results of the covariate-adjusted multivariate linear regression model of the Geriatric Depression Scale as a function of Braak Stages of neurofibrillary pathology, clinical diagnosis at the last Alzheimer's Disease Center visit prior to death, and their interaction

		β	95% CI	*p*-value
Diagnostic Category (HC as reference)	MCI	0.11	(−3.43,3.64)	0.95
	dAD	−0.88	(−4.03,2.27)	0.58
Braak Stages (0 as reference)	1/2	−1.15	(−2.79,0.49)	0.17
	3/4	−0.81	(−2.54,0.92)	0.36
	5/6	−0.6	(−3.49,2.28)	0.68
Interaction: MCI and Braak Stages (0 as reference)[a]	1/2	−0.56	(−4.41,3.29)	0.78
	3/4	−0.52	(−4.25,3.21)	0.78
Interaction: dAD and Braak Stages (0 as reference)[a]	1/2	2.61	(−100,6.22)	0.16
	3/4	0.23	(−3.11,3.57)	0.89
Education (years)		−0.04	(−0.07,0.00)	0.03
History of transient ischemic attack		1.72	(0.85,2.59)	<0.01
Depression, in last 2 years		2.11	(1.30,2.93)	<0.01
Current benzodiazepine use		1.75	(0.67,2.83)	<0.01
Current sleep aid use		0.89	(−0.22,2.00)	0.11
Current anti-depressant use		−0.59	(−1.43,0.24)	0.16
Total NPI-Q score		0.12	(0.02,0.23)	0.02
Intercept		3.21	(1.58,4.83)	<0.01

CI, confidence interval; dAD, dementia because of possible or probable Alzheimer's disease; HC, healthy control; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire.

[a]Too few individuals with Braak = 5/6 to fit interaction term.