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MULTIPLE PROTEINOPATHIES AND THEIR ROLE IN COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES

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MULTIPLE PROTEINOPATHIES AND THEIR ROLE IN COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Public Health
at the University of Kentucky

By

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Lexington, Kentucky

Director: Dr. Erin L. Abner, Associate Professor of Epidemiology

Lexington, Kentucky

2021

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ABSTRACT OF DISSERTATION

MULTIPLE PROTEINOPATHIES AND THEIR ROLE IN COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES

Most age-related neurodegenerative disorders are associated with the aggregation of misfolded and aberrant proteins. Alzheimer's disease (AD) is one of the most common neurodegenerative disorders and is highly prevalent in older adults. Neuropathologically, AD is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs). Other misfolded proteins, including α-synuclein and transactive response DNA-binding protein 43 (TDP-43), are also commonly observed in aged brains. Aberrant α-synuclein has been associated with Parkinson's disease, Dementia with Lewy bodies, and multiple system atrophy, whereas TDP-43 has been associated with multiple neurological diseases, the most common of which was designated as limbic-predominant, age-related TDP-43 encephalopathy (LATE). Each neurodegenerative disorder exhibits aggregation of specific proteins, but very commonly there is an aggregation of multiple proteinopathies.

The three studies in this dissertation are focused on the co-existence of multiple proteinopathies. The primary data were drawn from the University of Kentucky Alzheimer's Disease research center (UK- ADRC), and additionally, for the second study, we used data drawn from the National Alzheimer's Coordinating Center (NACC). While in the third study, the participants from UK-ADRC were linked to the Kentucky Cancer Registry to obtain data regarding their history of cancer, along with additional details such as cancer site, stage, and treatment received.

In the first study, "Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults," using brain autopsy data from 375 older adults, quadruple misfolded proteins (tau, amyloid-β, α-synuclein, and transactive response DNA-binding protein 43) were commonly detected. Mild cognitive impairment transitioned to dementia most rapidly for those with all four proteinopathies, which were present in 19% of individuals with dementia. Overall, 12% of cases had QMP, while 38% had three proteinopathies. Dementia frequency was highest among those with QMP (89%), and

participants with QMP had the lowest final mean MMSE (Mean=13.4, SD=9.8). Adjusting for age and sex, ≥1 apolipoprotein ε4 (*APOE* ε4) allele was associated with higher odds of QMP (OR=2.55; 95% CI, 1.16, 5.62, P= 0.02). The QMP group had both the lowest probability of having normal MMSE, even 12 years before death and the highest probability of having severe impairment on the MMSE. In the second study, "Four common late-life cognitive trajectories patterns associate with replicable underlying neuropathologies," using group-based multi-trajectory models we found evidence that there are distinct, common trajectories that define the end of life cognition. The four distinct subgroups were determined by the shape of the trajectories using scores from the Mini-Mental State Examination, Logical Memory, and Animal Naming tests obtained in the last ten years of life; trajectories were labeled as No decline, Mild decline, Moderate decline, and Accelerated decline. The Accelerated and the Moderate decline groups were associated with lower age at death, lower educational attainment, higher Braak NFT stage, and more frequent hippocampal sclerosis and TDP-43 proteinopathy. Further, we validated the models using the NACC data. In the third study, "Cancer history associates with a lower burden of dementia and Alzheimer's-type neuropathology in autopsied research volunteers." History of cancer was reported in 190 (24.2%) participants. The prevalence of ≥1 *APOE* ε4 allele was lower among the participants with cancer history compared to cancer-free participants (32.6% vs 42.0%). Participants with cancer history had significantly lower odds of MCI/dementia at the last UK-ADRC visit (OR = 0.45; 95% CI, 0.31, 0.64; P < 0.0001), and had a reduced burden of AD neuropathological changes in the brain. Additionally, the change in cognitive test scores from baseline to the last available assessment showed relatively less decline in the participants with a cancer history. The examination of AD-associated genes showed that history of cancer was inversely associated with ≥1 *APOE* ε4 allele and higher odds of T allele of SNP rs11136000 located in the *CLU* gene on chromosome 8.

KEYWORDS: Alzheimer's Disease, Neurodegenerative diseases, Dementia, Multiple proteinopathies, Neuropsychological tests, Cognitive trajectories.

Shama Divakar Karanth

04/20/2021

Date

MULTIPLE PROTEINOPATHIES AND THEIR ROLE IN COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES

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CHAPTER ONE
Introduction

Major neurodegenerative diseases can be determined by the presence of one of four aggregated misfolded proteins each with distinct morphology and distribution.[1] In a healthy brain, these proteins are unstructured as a monomer, serving most likely as the physiological form.[2] In a disease state; the proteins namely amyloid-β (Aβ), tau, a-synuclein, and transactive response DNA-binding protein 43 (TDP-43) turn pathological and aggregate intracellularly, extracellularly, or both and are termed as "proteinopathies". However, proteinopathies also occur in individuals without any clinical presentation.[3] These aggregates have the potential to disturb proteostasis, compromising cell function.[4] Some of the etiological processes involved in misfolding are cellular aging, disease-related gene mutations, or proteotoxic stressors, like reactive oxygen species and toxins.[4] Each of the pure proteinopathies define various neurodegenerative diseases, but most commonly additional proteinopathies can accumulate as comorbid pathologies.[3,5-7]

Misfolded proteins

Tau

Tau proteins, ubiquitous in the adult brain, perform the function of stabilizing microtubules of the neural cells. The tau protein binds to microtubules in axons, but in certain neurodegenerative diseases, it is redistributed to the cell bodies.[8] The tau proteins that have become hyperphosphorylated insoluble aggregates are known as neurofibrillary tangles (NFTs) (**Figure 1.1)**. Neurodegenerative diseases characterized by the accumulation of NFTs are known as "tauopathies".[8] Tauopathies encompass more than 20 clinicopathological entities; including Alzheimer's disease (the most common

tauopathy), progressive supranuclear palsy, frontotemporal lobar degeneration (FTLD-tau), corticobasal degeneration, Pick's disease, chronic traumatic encephalopathy, argyrophilic grain disease (AGD), and primary age-related tauopathy.[9-12]

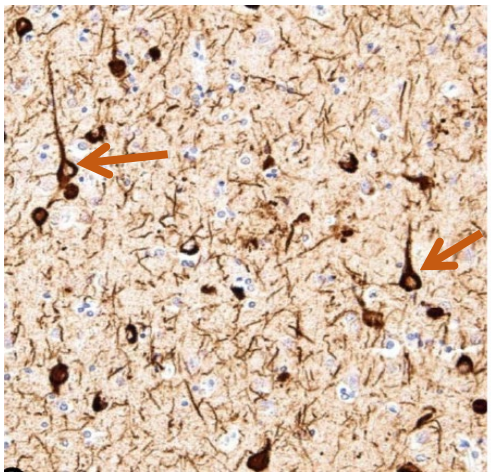
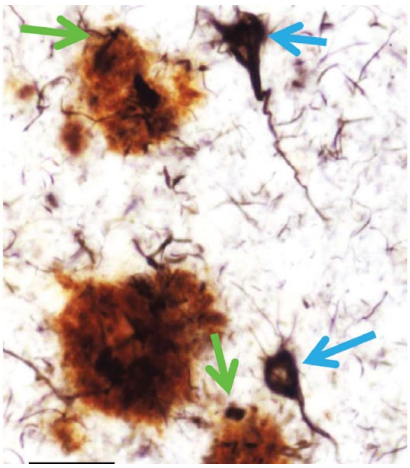
NFT distribution in Alzheimer's disease is defined by six Braak NFT stages (I-VI).[13] In Braak NFT stages I and II there is the involvement of the transentorhinal region of the brain; in NFT stages III and IV there is also the involvement of limbic regions such as the hippocampus, and in NFT stages V and VI there is widespread neocortical involvement.[13] Until recently, detection of tau deposition in the brain was only possible from invasive techniques such as biopsy or autopsy. The recent development of tau PET scan imaging provides a non-invasive detection of tau inclusions in the brain, which could become a biomarker to discover tauopathies in the near future.[14]

Amyloid-beta

Aβ peptides derive from the larger amyloid precursor protein (APP), which are cleaved by beta-secretase and gamma-secretase.[15] The cleavage of APP occurs at position 40 or 42, which gives rise to two major variants: Aβ40 (Aβ ending at residue 40) and Aβ42 (Aβ ending at residue 42).[15] The cleaved portions aggregate to form flexible soluble oligomers, which may exist in several forms and accumulate to form amyloid plaques. Thus, these Aβ peptides are the main component of the extracellular amyloid plaques found in the brains of people with Alzheimer's disease.[15] Amyloid plaques can be classified into two types: Neuritic plaques (NPs) and Diffuse plaques (DPs) (**Figure 1.1**). The NPs are extracellular amyloid deposits invested by swollen, degenerating neurites. Fibrillary polymers of the Aβ peptide comprise the structural core of NPs.[16] DPs also contain Aβ but lack the core and/or degenerating neurites.[17] Cerebral amyloid angiopathy

(CAA) is a condition in which amyloid peptides build up in the walls of the cerebral arteries.[18] The Aβ and plaques in the arteries first occur in neocortical areas and then expand into further brain regions.[18]

Figure 1.1: Photomicrographs of Alzheimer's disease proteinopathies

	
A: Photomicrograph: shows Immunohistochemical detection of neurofibrillary degeneration using phospho-tau antibody in the occipital cortex .[9]	B: Photomicrograph shows Aβ plaques (reddish-brown,). Neurofibrillary tau tangles (Black). Some of the Aβ plaques contain aberrant tau protein pathology (black marked by green arrows).[19]

Alpha-synuclein

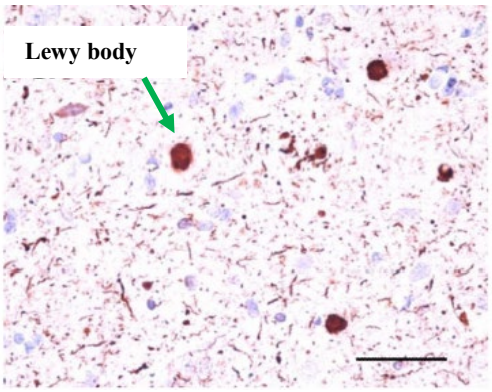
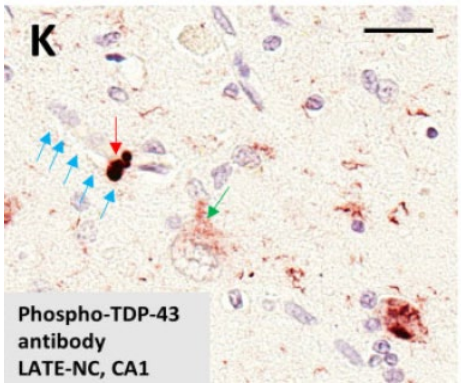
Alpha-synuclein (α-synuclein) protein is encoded by the *SNCA* gene in humans.[20] It is abundant in the brain, while smaller amounts are found in the heart, muscle, and other tissues. Misfolded abnormal accumulations of insoluble fibrils α-synuclein are characterized by Lewy bodies (**Figure 1.2**). The associated pathologies characterize "synucleinopathies" and cause Lewy body spectrum diseases,[3] like Parkinson's disease (PD), Dementia with Lewy bodies (DLB),[20] and multiple system atrophy.[6] DLB is the

second most common form of degenerative dementia following AD in older adults[21] and frequently co-occurs with other proteinopathies.[3,5,6,22,23]

TDP-43

TDP-43 protein in humans is encoded by the *TARDBP* gene. Pathological TDP-43 forms are observed as either neuronal cytoplasmic inclusions, neuronal intranuclear inclusions, and/or dystrophic neurites (**Figure 1.2**).[24] TDP-43 proteinopathy is associated with frontotemporal lobar degeneration (FTLD-TDP), amyotrophic lateral sclerosis (ALS), and more recently with limbic-predominant age-related TDP-43 encephalopathy (LATE) in persons older than 80 years of age.[25]

Figure 1.2: Lewy body and TDP-43 proteinopathies

	
A: Photomicrograph: shows detection of high concentrations of nitrated α-synuclein in the Lewy bodies (shown with green arrow).[9]	B: Photomicrograph: shows detection of intraneuronal phospho-TDP-43 inclusion (red arrow) and a phospho-TDP-43 deposit (green arrow) surrounding a capillary (shown with blue arrows).[25]

Mixed Pathologies

Aggregates of pathological/misfolded forms of tau, Aβ, α-synuclein, and TDP-43 in the brain combine in distinctive patterns in most neurodegenerative diseases.[7] Although each misfolded protein is known to cause certain neurodegenerative diseases, in many cases, there is an aggregation of multiple proteins). The existence of simultaneous aggregation has been increasingly reported and is of serious concern as we try to develop treatments for various neurodegenerative diseases, including AD. Treatment with monotherapies targeting Aβ and tau in Alzheimer's disease may not be helpful in treating the disease. Misfolded proteins may co-exist in varying degrees across all of the different neurodegenerative disorders[26] and increase the odds of developing dementia,[22] including the clinical type of Alzheimer's-type of dementia.[25] Additionally, presence cerebrovascular pathologies (infarcts, lacunes, arteriosclerosis, and atherosclerosis) are prevalent in the brains of advanced aged subjects. Hippocampal sclerosis (HS) pathologically characterized by neuronal cell loss and gliosis in the hippocampus (unilaterally or bilaterally) has clinical signs and symptoms similar to AD and can occur concurrently with other neurodegenerative diseases.[25,27]

Demographics, clinical presentation, and relevance of proteinopathies

The role of multiple proteinopathies and their association with clinical phenotypes and neuropsychological profiles is complex and requires further understanding in multiple aspects. Alzheimer's disease, the most common form of dementia, is characterized by progressive memory and cognitive decline. An estimated 5.8 million Americans age 65 and older are living with Alzheimer's dementia in 2020.[1] By 2025, the number is estimated to reach 7.1 million[28] and 86,000 in Kentucky.[29] Alzheimer's is the

sixth-leading cause of death in the U.S, while in 2018 there were 1,674 deaths in Kentucky attributable to the disease.[28,29] While extensive research has been conducted in understanding AD-type dementia, and other neurodegenerative diseases in terms of diagnosis, biomarkers, imaging techniques, risk factors, and genetics, there are no disease-modifying treatments or truly effective prevention methods. Diagnosis of dementia, AD, and other neurodegenerative diseases involves clinical examination, neuropsychological tests, brain-imaging studies using magnetic resonance imaging or positron emission tomography, and detection of proteins in cerebrospinal fluid. Clinical diagnosis of AD, which is the most common cause of dementia is classified into (1) Probable AD dementia, (2) Possible AD dementia[30] with a definite diagnosis established only by neuropathologic examination on performing an autopsy.

Multiple non–modifiable risk factors such as aging, sex, and genetics increase susceptibility to AD.[31] Several modifiable risk factors that may be altered by healthy lifestyle changes,[31] such as cardiovascular diseases, diabetes, traumatic brain injuries, and depression are also known to increase AD risk.[31] However, the association between these risk factors, dementia, and neuropathology may reflect a varied picture. Abner et al.[32] reported that diabetes is associated with cerebrovascular but not AD-type pathology, despite many large epidemiological studies reporting that diabetes increases the risk of AD.[33,34]

Several prior studies using autopsy data have enhanced our understanding of the association of risk factors with clinical AD, as well as the pathology present in the brain. Interestingly, the association of cancer with AD is unique; prior research studies have found strong evidence of an inverse association of cancer with AD.[35-38] While most of the

studies have examined the association with clinically diagnosed AD or Dementia, to date only two studies have used autopsy-confirmed brain diagnoses.[39,40]

Dissertation Outline

The purpose of the study is to expand on the understanding of the prevalence of multiple proteinopathies, the associated clinical phenotype, and their role in cognitive performance over time. In Chapter Two, the frequency and associated characteristics of multiple proteinopathies, focusing on quadruple misfolded proteins (QMP: Tau, Amyloid β, α-synuclein, TDP-43) among autopsied research volunteers were evaluated. Further, demographic and neuropathological characteristics were described. The cognitive diagnoses, duration of cognitive states, and longitudinal global cognition were evaluated in the last 12 years of life. In Chapter Three, patterns of longitudinal cognitive status in older adults using group-based multi-trajectory models were evaluated. Further, predictors and proteinopathies associated with the cognitive trajectories indicating cognitive status were evaluated. Additionally, random forest analyses were conducted to evaluate the association of clinicopathological characteristics with cognitive trajectory groups. We compared the results of the trajectory patterns and predictors to a larger study population using National Alzheimer's Coordinating Center (NACC) data. In Chapter Four, we expanded the understanding of cancer vs. AD relationship using autopsy data to evaluate whether the association of clinical AD diagnosis by prior studies is reflected by AD neuropathology, as well as other neuropathological variables in data drawn from the UK-ADRC community-based cohort. We applied causal inference methods (inverse probability weighting) to investigate the relationship between cancer history,

neuropathological features, and clinical diagnoses. The conclusion of the dissertation and future research directions are discussed in Chapter Five.

CHAPTER TWO

Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults

Abstract

Introduction: Quadruple misfolded proteins (tau neurofibrillary tangles, amyloid-β [Aβ], α-synuclein, and transactive response DNA-binding protein 43 [TDP-43]) in the same brain are relatively common in aging. However, the clinical presentation, associated factors, frequency in community-based cohorts, genetic characteristics, and cognitive trajectories associated with the quadruple misfolded proteins phenotype are not well understood. To describe the quadruple misfolded proteins phenotype, including the trajectories of global cognition, in an autopsy cohort.

Methods: This retrospective cohort study used brain autopsy data from the University of Kentucky Alzheimer Disease Center (UK-ADRC) Brain Bank. Participants were deceased individuals who were enrolled in a longitudinal community-based cohort study of aging and dementia in central Kentucky conducted by the UK-ADRC. Included participants were enrolled in the UK-ADRC cohort between January 1, 1989, and December 31, 2017; aged 55 years or older at baseline; and followed up for a mean duration of 10.4 years. The participants had Alzheimer disease pathology (tau and Aβ), α-synuclein, and TDP-43 data, along with Braak neurofibrillary tangle stage I to VI. Data analysis was conducted between February 1, 2019, and September 30, 2019.

Results: Frequency of quadruple misfolded proteins was estimated, and proteinopathy group characteristics and associations with global cognition were evaluated. Multinomial logistic regression was used to estimate the association of proteinopathy group with participant characteristics, including age at death, sex, and apolipoprotein ε4 (*APOE* ε4)

allele. Generalized estimating equations were used to estimate the probability of obtaining Mini-Mental State Examination (MMSE) scores within the normal cognition (27-30 points) and severe impairment (<13 points) ranges during the 12 years before death. The final sample included 375 individuals (mean [SD] age at death, 86.9 [8.0] years); 232 women [61.9%]). Quadruple misfolded proteins were detected in 41 of 214 individuals with dementia (19.2%). Overall, 46 individuals (12.3%) had quadruple misfolded proteins, whereas 143 individuals (38.1%) had 3 proteinopathies. Dementia frequency was highest among those with quadruple misfolded proteins (41 [89.1%]), and participants with quadruple misfolded proteins had the lowest final mean (SD) MMSE scores of 13.4 (9.8) points. Adjusting for age at death and sex, the *APOE* ε4 allele was associated with higher odds of quadruple misfolded proteins (adjusted odds ratio (OR)= 2.55; 95% CI, 1.16, 5.62; P = .02). The quadruple misfolded proteins group had both the lowest probability of obtaining MMSE scores in the normal cognition range, even 12 years before death and the highest probability of having MMSE scores in the severe impairment range.

Conclusions: Quadruple misfolded proteins appear to be a common substrate for cognitive impairment and to be associated with an aggressive course of disease that typically ends with severe dementia. The prevalence of comorbid α-synuclein and TDP-43 with Alzheimer disease pathology (tau and Aβ) may complicate efforts to identify therapies to treat and prevent Alzheimer disease.

Introduction

Amyloid-β (Aβ) plaques and tau neurofibrillary tangles (NFTs) define Alzheimer disease neuropathological change (ADNC).[9] Other misfolded proteins, including α-synuclein and transactive response DNA-binding protein 43 (TDP-43), also commonly occur in old age.[24,26,41] Aberrant α-synuclein has been associated with Parkinson disease, dementia with Lewy bodies, and multiple system atrophy,[20] whereas TDP-43 has been associated with multiple neurological diseases,[42] the most common of which was designated as limbic-predominant, age-related TDP-43 encephalopathy.[25,27]

Neuropathological studies report that all 4 proteinopathies (Aβ, tau, α-synuclein, and TDP-43) coexist in aged human brains.[3,6,7,22,24,26,29,41,43-47] We use the term quadruple misfolded proteins to describe this phenomenon. Other proteinopathies are associated with increased dementia risk.[22,46] For example, ADNC-associated cognitive impairment has been associated with neocortical NFT density.[9] The association of comorbid ADNC and α-synuclein with ADNC is well documented[6,48,49]: compared with ADNC and dementia with Lewy bodies pathology, pure dementia with Lewy bodies and ADNC were associated with improved memory and global cognition.[50,51] The TDP-43 proteinopathy with ADNC also occurs[5,24,25,52-54] and appears to be a factor in cognitive impairment.[5,24,42,52,54-56] In addition, TDP-43 is associated with memory loss and medial temporal atrophy in persons with ADNC,[57-59] and may preferentially change episodic and working memory.[55] Few studies have investigated the quadruple misfolded proteins phenotype.[3,24,26] Cognitive impairment is exacerbated by the presence of quadruple

misfolded proteins compared with the presence of 1 to 3 proteinopathies.[3,7,26] In this cohort study, we identified the prevalence and characteristics of the quadruple misfolded proteins phenotype in deceased research volunteers with brain autopsy data. We evaluated demographic and neuropathological characteristics, cognitive diagnoses, and global cognition trajectories in late life.

Methods

Study participants

We obtained brain autopsy data of long-term participants in a community-based cohort study of aging and dementia in central Kentucky conducted by the University of Kentucky Alzheimer Disease Research Center (UK-ADRC).[16,60] These research volunteers were recruited through community outreach, local press, or broadcast media; enrolled between January 1, 1989, and December 31, 2017; aged 55 years or older at baseline; followed up for a mean duration of 10.4 years; and autopsied. The UK-ADRC Brain Bank that we used also contains autopsy data from a non–UK-ADRC cohort. We included individuals with Braak NFT stage I or higher given the near-universal presence of tau pathology in older adults and its association with cognition.[9,61,62]

We excluded individuals with Down syndrome or frontotemporal lobar degeneration (FTLD); FTLD was excluded because of its rarity in the underlying population despite its relevance to protein misfolding.[25] Individuals with brain cancer were also excluded. In addition, available data were needed on all proteinopathies under study. Neuropathological assessments were performed with blinding of clinical information. The University of Kentucky Institutional Review Board approved the study procedures. Participants provided written informed consent.

Cognitive Diagnoses and Evaluations

Cognitive diagnoses were based on annual examinations and were described previously.[63,64] Participant cognition was classified as normal, mild cognitive impairment (MCI), impaired (but not MCI), or dementia. Normal cognition was defined as intact functional ability and performance on neurocognitive tests within expected ranges for age and years of education, and MCI was defined as objective cognitive impairment (score of >1.5 SD below the expected mean) or cognitive complaint, intact global cognition, no or minimal functional impairment, and no evidence of dementia.[65] Impaired cognition was defined according to the Uniform Data Set, a standard data protocol used by Alzheimer disease centers.[66] Participants with impaired cognition exhibited MCI features on clinical examination, but neurodegenerative or cerebrovascular disease was not suspected in these individuals. Standard criteria were used to determine dementia.[67]

Annual cognitive evaluations included the Mini-Mental State Examination (MMSE).[68] The MMSE scores, which have been consistently collected at UK-ADRC since 1989, range from 0 to 30 points.[68] For analysis, we classified MMSE scores as follows: 27-30 points as normal cognition and 13 points or less as severe impairment. These cutoff points were based on the guidelines published by Folstein et al[68] and on the cutoff points for severe dementia used in clinical trials.[69] Indicators for MMSE score of 13 points or less were imputed for 24 participants with missing scores for more than 3 years before death and with a last observed MMSE score of 16 points or less, assuming that the MMSE score decreased approximately 3 points per year.[70]

Neuropathological Assessments

Brain autopsies were performed as described previously.[16,71] Briefly, for autopsies performed before 2012 (n = 203), Bielschowsky silver stains were used to detect neuritic plaques (NPs) and diffuse plaques (DPs),and Gallyas silver stains[72] were used to detect NFTs in accordance with the 1997 National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease.[73] For autopsies performed beginning in 2012 (n = 172), immunohistochemical stains were used to detect Aβ deposits, and phospho–tau antibody ([PHF-1] a gift from Peter Davies, PhD, The Feinstein Institutes for Medical Research, Manhasset, New York) was used to visualize NPs and NFTs (per the 2012 National Institute on Aging–Alzheimer's Association guidelines), with digital pathological methods used for lesion detection and counting.[74]

Immunohistochemistry detection of α-synuclein aggregates, visualized with mouse monoclonal antibody (clone KM51,Novocastra; Leica Biosystems),were assessed using established diagnostic criteria.[5] Evaluation of TDP-43 immuno-reactive inclusions was performed on 5-μm-thick sections cut on slides (ProbeOn; Thermo Fisher Scientific). Rat anti-phospho TDP-43 (clone 1D3; Millipore) was used after antigen retrieval in a decloaking chamber and formic acid pretreatment. Secondary antibody reaction used the avidin-biotin complex kit (Vectastain ABC Kit; Vector Laboratories). Details were reported previously.[5]

Proteinopathy Groups

Participants were grouped on the basis of the presence of proteinopathies: Aβ, tau, α-synuclein, and TDP-43.Tau was considered present when Braak NFT stage was I or

higher, whereas Aβ was present when the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) ratings for DPs or NPs were at least sparse.[75] Meanwhile, α-synuclein was considered present if Lewy bodies were detected in the neocortex, medial temporal lobe, or amygdala. In defining proteinopathy groups, we did not consider Lewy bodies in the brainstem only (n = 7) as having α-synuclein. Previous work showed that brainstem-only Lewy bodies were not associated with cognitive impairment.[5] TDP-43 inclusion bodies were considered present for TDP-43 proteinopathy when detected in the left or right hippocampus. Previous work suggested that amygdala-only TDP-43 was not associated with odds of dementia or cognitive impairment.[58] In addition, we divided participants with pure ADNC into 2 groups according to Braak NFT stage (stage I to IV and stage V to VI).

Participants were classified into 7 proteinopathy groups: (1) tau alone; (2) tau and TDP-43; (3) tau Braak stage I to IV and Aβ; (4) tau Braak stage V to VI and Aβ; (5) tau, Aβ, and α-synuclein; (6) tau, Aβ, and TDP-43; and (7) quadruple misfolded proteins (tau, Aβ, TDP-43, and α-synuclein). Cerebrovascular pathology was not considered in proteinopathy group definitions. We assessed gross diagnosis of atherosclerosis severity (all vessels ≥50% vs <50% occluded), microscopic diagnosis of brain arteriolosclerosis (moderate or severe vs none or mild), and brain infarcts (stage 0, none; stage 1, microinfarcts or lacunar or large infarcts; and stage 2, both microinfarcts and lacunar or large infarcts) within proteinopathy groups.[3] In addition, the right and left hippocampi were evaluated for hippocampal sclerosis.[76] Presence of argyrophilic grain disease was assessed in cornu ammonis, subiculum, and entorhinal regions.

Covariates

Age at death, sex (reference group: male), years of education, and apolipoprotein (*APOE*) ε4 allele were covariates of interest. The *APOE* (OMIM 107741) genotype was converted to a dummy indicator for 1 or more ε4 alleles.

Statistical Analysis

Characteristics of participants by proteinopathy group were assessed with analysis of variance or $\chi 2$ tests. Time in MCI and dementia states was calculated on the basis of the dates of clinical diagnosis. When a participant transitioned to a new diagnosis between annual visits, the diagnosis date was taken as the midpoint between the 2 visits. Time in cognitive state that was consistent throughout follow-up (e.g. dementia at baseline) was taken as the difference between the date of death and UK-ADRC study enrollment date. We repeated the analyses on restricted cohort of participants who began follow-up with normal cognition.

Multivariable multinomial logistic regression was used to estimate the association between demographic characteristics and proteinopathy groups. Tau Braak stage I to IV and Aβ was the largest proteinopathy group and served as the reference. Adjusted odds ratios (AORs) with 95% CIs were obtained from the logistic regression model, which included age at death, sex, and *APOE* ε4 allele indicator.

To evaluate the association of the proteinopathies with global cognition over time, we used multivariable logistic regression with generalized estimating equations with a first order autoregressive (AR[1]) working correlation structure. With this approach, we estimated the probability that individuals in the proteinopathy groups obtained MMSE scores within the normal range at each assessment in the 12 years before death (based on

data availability), adjusting for age at death, sex, *APOE* ε4 allele, and years of education. We used the same approach to estimate the probability that individuals would obtain MMSE scores in the severe impairment range. The reference group was, again, tau Braak stage I to IV and Aβ.

To assess potential misclassification owing to group definitions in the current study, we examined amygdalar TDP-43 proteinopathy in a convenience sample of 47 individuals (of 234 [20.1%]) without hippocampal TDP-43. In addition, because the definition of Aβ positivity could include individuals with low Aβ,we examined the joint distribution of NP and DP ratings to ascertain the frequency of individuals with sparse numbers of both NP and DP. All data were analyzed using SAS, version 9.4 (SAS Institute Inc). Statistical significance was set at $\alpha = .05$. Data analysis was conducted between February 1, 2019, to September 30, 2019.

Results

The final sample included 375 individuals (**Figure 2.1**). The mean (SD) age at death was 86.9 (8.0) years and ranged from 82.7 (10.3) years in the tau, Aβ, and α-synuclein proteinopathy group to 89.7 (6.7) years in the tau and TDP-43 group. Participants were predominantly women (232 [61.9%]); were predominantly white individuals (363 [96.8%]), which was consistent with the underlying population; and had a mean (SD) 15.6 (3.1) years of education (**Table 2.1**).

Presence of multiple proteinopathies was common, with just 24 individuals (6.4%) having tau alone (**Figure 2.2**). Two proteinopathies were detected in 162 of 375 individuals (43.2%), 3 proteinopathies in 143 individuals (38.1%), and quadruple misfolded proteins in 46 individuals (12.3%). Overall, α-synuclein was present in 117

individuals (31.2%), TDP-43 in 141 (37.6%), and tau and Aβ in 327 (87.2%). Individuals with quadruple misfolded proteins had a higher frequency of Braak stage VI (23 [50.0%), as did individuals with 3 proteinopathies (44 [approximately 30%]).

Dementia was diagnosed in 214 of 375 participants (57.1%), and 104 (27.7%) participants retained normal cognition (**Table 2.1**). Dementia prevalence was highest in the quadruple misfolded proteins group (41 [89.1%]), followed by tau, Aβ, and TDP-43 group (58 [81.7%]); tau Braak stage V to VI and Aβ group (41 [71.9%]); and tau, Aβ, and α-synuclein group (44 [61.1%]). Among all participants with dementia (**Figure 2.3**), quadruple misfolded proteins were present in 41 of 214 individuals (19.2%); tau, Aβ, and TDP-43 in 58 individuals (27.1%); tau, Aβ, and α-synuclein in 44 individuals (20.6%); and tau Braak stage V to VI and Aβ in 41 individuals (19.2%).

Among those with a final diagnosis of MCI (n = 45), none had quadruple misfolded proteins (although 5 participants died with normal cognition), whereas 14 (31.1%) had tau Braak stage I to IV and Aβ; 11 (24.4%) had tau, Aβ, and α-synuclein; 7 (15.6%) had tau Braak stage V to VI and Aβ; and 6 (13.3%) had tau, Aβ, and TDP-43 (**Figure 2.3**). Among participants with an initial diagnosis of normal cognition (n = 228), 14 of 83 individuals (16.9%) with a final diagnosis of dementia had quadruple misfolded proteins (**Figure 2.4**).

APOE ε4 allele was common in persons with quadruple misfolded proteins (23 of 46 [50.0%]), similar to those in the tau Braak stage V to VI and Aβ group (30 of 57 [52.6%]). In contrast, *APOE*ε4 allele was observed in a single participant (4.2%) in the tau alone group and in 3 of 24 participants (12.5%) in the tau and TDP-43 group. Mean (SD) time spent in the MCI state was shortest among those in the quadruple misfolded

proteins group (1.7 [0.6] years) (**Table 2.1**) and among those with initial normal cognition (1.8 [0.6] years) (**Table 2.2**). This finding suggests a more aggressive disease course for individuals with quadruple misfolded proteins (**Figure 2.5**).

Cerebrovascular burden (atherosclerosis, arteriolosclerosis, and infarcts) was similar across groups (**Table 2.1**), although atherosclerosis was most prevalent in the quadruple misfolded proteins group (30 of 46 [65.2%]) and in those who started follow-up with normal cognition (15 of 19 [79.0%]) (**Table 2.1; Table 2.2**). As expected, hippocampal sclerosis was most common in participants with TDP-43. The highest proportion of hippocampal sclerosis was in the quadruple misfolded proteins group (33 [71.7%) (**Table 2.1**). This finding may be relevant to a previous finding that more clinically severe cases of limbic-predominant age-related TDP-43 encephalopathy–neuropathological change are more likely to have hippocampal sclerosis pathology.[25]

The lowest final mean (SD) MMSE score was observed in the quadruple misfolded proteins group (13.4 [9.8] points), which was significantly lower than in any other group ($P < .001$). Although the final mean (SD) MMSE scores in the tau alone group (26.6 [4.2] points) and tau Braak stage I to IV and Aβ group (26.2 [5.1] points) indicated generally intact cognition at death, participants in all other groups had mean MMSE scores lower than 21, indicating moderate to severe dementia (**Table 2.1**). Among participants with initially normal cognition, the final mean (SD) MMSE score was also lowest among those in the quadruple misfolded proteins group (18.9 [9.0] points) (**Table 2.4**).

With a 5-year increase in age at death, participants were less likely to have quadruple misfolded proteins (AOR= 0.82; 95% CI, 0.63,1.08; $P = .15$) or tau, Aβ, and α-

synuclein (AOR=0.61; 95% CI, 0.48, 0.78; P < .001) compared with tau Braak stage I to IV and Aβ (reference). *APOE* ε4 allele was associated with higher odds of having quadruple misfolded proteins (AOR= 2.55; 95% CI, 1.16,5.62; P = .02); tau Braak stage V to VI and Aβ (AOR= 3.45; 95% CI, 1.61,7.39; P < .001); and tau, Aβ, and TDP-43 (AOR= 2.34; 95%CI, 1.15, 4.77; P = .02). Sex was not significantly associated with the proteinopathy groups (**Table 2.5**).

The estimated probabilities of obtaining MMSE scores categorized as normal cognition and severely impaired cognition are shown in **Figure 2.6**. For example, 6 years before death, the mean (SD) estimated probability of an MMSE score in the normal cognition range (27-30 points) was lowest in the quadruple misfolded proteins group (0.33 [0.24]), followed by tau, Aβ, and TDP-43 group (0.49 [0.12]); tau, Aβ, and α-synuclein group (0.57 [0.15]); and tau Braak stage V to VI and Aβ group (0.59 [0.16]; P < .001 for all proteinopathy group β coefficients). Moreover, 6 years before death, the mean [SD] probability of an MMSE score in the severe impairment range (≤13 points) was highest in the quadruple misfolded proteins group (0.16 [0.10]; P < .001), followed by tau, Aβ, and TDP-43 group (0.10 [0.05]; P < .001); tau, Aβ, and α-synuclein group (0.07 [0.09]; P = .04); and tau Braak stage V to VI and Aβ group (0.05 [0.05]; P = .004).

To assess how proteinopathy definitions may have altered the results, we performed 2 additional analyses. First, we assessed a convenience sample of 47 individuals without hippocampal TDP-43 proteinopathy, and TDP-43 was detected in the amygdala of 19 participants (40.4%). By proteinopathy group of the sampled cases, TDP-43 in the amygdala was detected in 12 of 23 participants (52.2%) in the tau, Aβ, and α-synuclein group; 3 of 8 participants (37.5%) in the tau Braak stage I to IV and Aβ group;

4 of 13 participants (30.8%) in the tau Braak stage V to VI and Aβ group; and none in 3 participants assessed in the tau group. Twelve of 327 participants (3.7%) with Aβ proteinopathy had only sparse numbers of both NPs and DPs: quadruple misfolded proteins (n = 3); tau, Aβ, and α-synuclein (n = 1); and tau Braak stage I to IV and Aβ (n = 8).

Discussion

In this cohort study, we investigated quadruple misfolded proteins and other proteinopathy combinations in a cohort of 375 deceased individuals with autopsy data. At least 3 proteinopathies were observed in 50% of brains. Quadruple misfolded proteins were observed in 19.2% of individuals with dementia, which was the same proportion of participants with dementia who had pure ADNC with Braak stage V to VI. In addition, quadruple misfolded proteins were associated with severe cognitive impairment at least 12 years before death.

Participants with 3 or more proteinopathies tended to have high Braak NFT stages (V-VI). Higher Braak stage in these groups complicates the interpretation of the association among risk factors, cognition, and comorbid brain pathologies because it raises the question of which primary factor (the Braak stage or the number and combination of proteinopathies) is associated with cognitive decline. Participants with 3 proteinopathies tended to have poorer global cognition earlier than with the presence of only tau and Aβ and were likely to have higher Braak stages.

Previous studies have reported cognitive decline associated with the presence of mixed pathologies,[24,26,3,46,54] with study-to-study differences in methods and proteinopathies,[24,26,46,52] the assessment and inclusion of cerebrovascular

pathologies,[3,44,46] and hippocampal sclerosis.[44,46] In the present sample, as in other community-based cohorts,[58] FTLD in old age was rare (with an estimated incidence of 8.9 of 100000 in individuals aged 60 to 69 years [77]; no incidence data are available for older age groups) and was not found in brains of individuals who began follow-up with normal cognition.[25] Individuals with FTLD-TDP with data in the UKADC Brain Bank were recruited from a dementia clinic. We excluded 6 individuals with FTLD-TDP in the study; none had the quadruple misfolded proteins phenotype. No discernible overlap in any FTLD feature was observed in these individuals other than presence of TDP-43 proteinopathy, which is now detected in many different neurological diseases outside of the amyotrophic lateral sclerosis–FTLD spectrum.[77]

Cognitive impairment was associated with quadruple misfolded proteins at autopsy, with 89.1% of participants developing dementia and some experiencing profound impairment (as measured by MMSE scores) up to 12 years before death. This finding suggests that quadruple misfolded proteins occur before end-stage ADNC (i.e., before high Braak stage). Consistent with this hypothesis, the MCI-to-dementia transition was, on average, fastest in the quadruple misfolded proteins group (Figure 3).

Estimation of the group cognitive trajectories was aided by the relatively long follow-up (mean duration of 10.4 years). These data provide the basis for a novel hypothesis that quadruple misfolded proteins have a more aggressive phenotype from the early stages of the disease rather than accruing additional pathologies only after ADNC has progressed to high levels. About 10% of these participants died with normal cognition, and previous research has shown quadruple misfolded proteins were present in persons with apparently normal cognition.[3] In the present study, all individuals with

quadruple misfolded proteins who had normal cognition at the last visit before death had lower Braak NFT stages (I-III), had no *APOE* ε4 allele, and were predominantly male (4 of 5 participants). These individuals may represent an early stage of quadruple misfolded proteins, but there are complexities: clinical presentation of proteinopathy combinations may be cohort specific and depend on other currently unknown factors. Older cohorts that survive into advanced old age, like those in the UK-ADRC study, may be more likely to experience multiple proteinopathies than younger cohorts.

As previously described,[3,26] *APOE* appeared to be associated with multiple proteinopathies in this study, particularly those proteinopathy combinations including Aβ plaques. Carriers of *APOE* ε4 allele not only had increased odds of tau and Aβ, an expected result, but also had higher odds of tau, Aβ, and α-synuclein; tau, Aβ, and TDP-43; and quadruple misfolded proteins. Unlike previous studies, this study did not find evidence that the ε4 allele was associated with tau or TDP-43 in the absence of Aβ,[56,78] but the sample size was relatively small.

The temporality of protein misfolding may play a clinically important and differentiating role in disease progression. Autopsy data, although cross-sectional by nature, are compatible with the hypothesis that Aβ aggregates precede, and perhaps stimulate or exacerbate, the widespread misfolding of tau, TDP-43, and α-synuclein.13 These results suggest that TDP-43 pathology may be associated with poor global cognition.

Limitations

This study has limitations. The cohort comprised primarily older adult, white, and well-educated participants, which limit generalizability of the findings. Some studies

have reported that black [79,80] and Hispanic [80] persons are more likely to have mixed ADNC. Furthermore, although the sample size was relatively large for an autopsy-based study, it underpowered some intergroup comparisons. The sample size also limited our ability to assess associations with other participant characteristics, such as medical history and environmental risk factors. In particular, the association of traumatic brain injury with quadruple misfolded proteins and multiple proteinopathies needs to be addressed in future research.

We did not use data on TDP-43 pathology in brain regions other than the hippocampus. In a future study, we will examine the role of limbic-predominant, age-related TDP-43 encephalopathy neuropathological change stages 1 and 3 in the disease course of individuals with mixed pathology. The convenience sample analyses suggest that 30% to 40%of individuals without hippocampal TDP-43 pathology may have TDP-43 in the amygdala, although the amygdalar TDP-43 pathology was often sparse. However, the convenience sample was about 5 years younger than the overall cohort but had a higher proportion of Braak stage V (similar in all other characteristics), which suggests that the true proportion of participants with amygdalar TDP-43 but without hippocampal TDP-43 is higher than the estimate. Furthermore, the definition of Aβ positivity could include individuals with little amyloid, and we did not include quantitative measures of amyloid in the analyses. The analyses showed few individuals in any group with lowβ; thus, we believe that adjusting for quantitative Aβ in the models would not change the results meaningfully.

Conclusions

The presence of multiple proteinopathies, particularly the quadruple misfolded proteins phenotype, appeared to have been associated with the cognitive decline in deceased individuals who participated in a longitudinal community-based study at the UK-ADRC. Most individuals who had quadruple misfolded proteins had dementia, and none died with MCI. These observations have potentially significant implications for clinical practice and public health, given that strategies to prevent or manage AD dementia may be complicated by the unrecognized presence of multiple additional neuropathologies.

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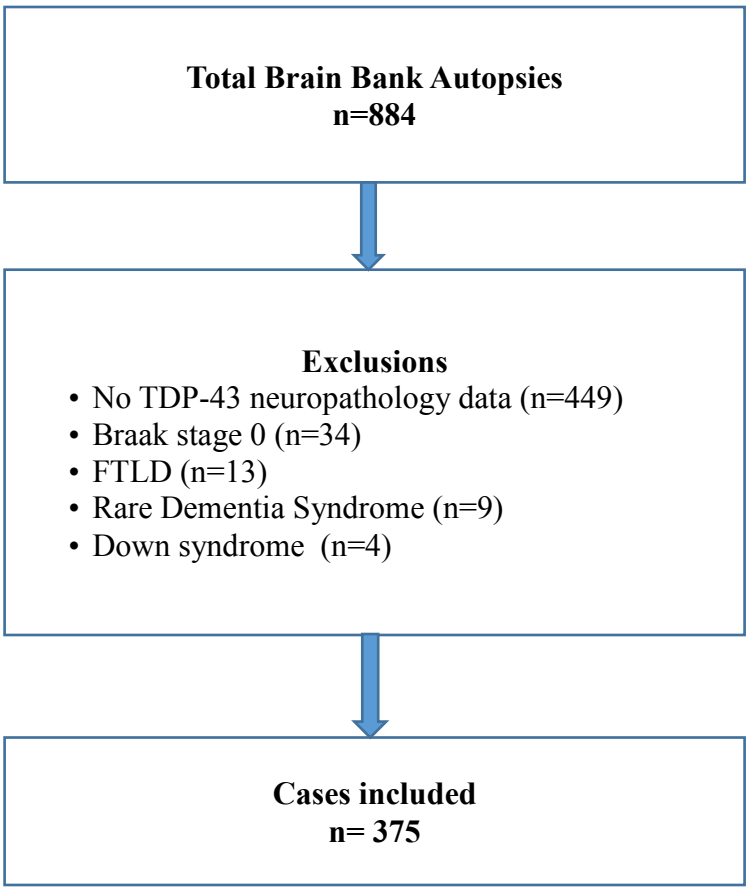
Figure 2.1: Flow diagram included cases



Abbreviation: TDP-43, transactive response DNA-binding protein of 43 kDa; FTLD, frontotemporal lobar degeneration

Table 2.1: Proteinopathy case group characteristics

Variable	Overall n=375	Tau n=24	$Tau_{Braak\ I-IV}$+Aβ n=81	$Tau_{Braak\ V-VI}$ + Aβ n=57	Tau +TDP-43 n=24	Tau+Aβ +α-Syn n=72	Tau+Aβ +TDP-43 n=71	QMP n=46
Age at death, y	86.9 (8.0)	87.0 (6.6)	88.7 (7.0)	86.1 (7.9)	89.7 (6.7)	82.7 (10.3)	89.2 (5.6)	86.3 (7.6)
Female sex	232 (61.9)	16 (66.7)	48 (59.3)	37 (64.9)	18 (75.0)	41 (56.9)	44 (61.9)	28 (60.9)
White race	363 (96.8)	24 (100.0)	78 (96.3)	56 (96.3)	23 (95.8)	69 (95.8)	70 (98.6)	42 (93.5)
Education, y	15.6 (3.1)	15.1 (2.6)	16.0 (2.9)	14.9 (3.5)	16.2 (2.3)	16.0 (2.9)	15.4 (3.4)	15.3 (3.4)
APOE ε4 (≥1 allele)	137 (36.5)	1 (4.2)	21 (25.9)	30 (52.6)	3 (12.5)	30 (41.7)	29 (40.8)	23 (50.0)
MMSE	20.0 (9.7)	26.6 (4.2)	26.2 (5.1)	17.4 (9.3)	20.5 (8.9)	19.4 (10.1)	15.7 (10.2)	13.4 (9.8)
Last Clinical Dx								
Normal	104 (27.7)	16 (66.7)	48 (59.3)	7 (12.3)	8 (33.3)	14 (19.4)	6 (8.5)	5 (10.9)
Impaired	10 (2.7)	3 (12.5)	3 (3.7)	1 (1.8)	0	3 (4.2)	0	0
MCI	45 (12.0)	2 (8.3)	14 (17.3)	7 (12.3)	5 (20.8)	11 (15.3)	6 (8.5)	0
Demented	214 (57.1)	3 (12.5)	16 (19.8)	41 (71.9)	11 (45.8)	44 (61.1)	58 (81.7)	41 (89.1)
Braak stage								
I	35 (9.3)	10 (41.7)	0	-	8 (33.3)	13 (18.1)	3 (4.2)	1 (2.2)
II	77 (20.5)	10 (41.7)	40 (49.4)	-	11 (45.8)	9 (12.5)	3 (4.2)	4 (8.7)
III	43 (11.5)	2 (8.3)	23 (28.4)	-	4 (16.7)	5 (6.9)	4 (5.6)	5 (10.9)
IV	36 (9.6)	2 (8.3)	18 (22.2)	-	1 (4.2)	4 (5.6)	7 (9.8)	4 (8.7)
V	87 (23.2)	0	-	27 (47.4)	0	20 (27.8)	31 (43.7)	9 (19.6)
VI	97 (25.9)	0	-	30 (52.6)	0	21 (29.2)	23 (32.4)	23 (50.0)
Atherosclerosis								
<50% occluded	149 (39.7)	12 (50.0)	29 (35.8)	27 (47.4)	11(45.8)	31 (43.1)	25 (35.2)	14 (30.4)
≥50% occluded	222 (59.2)	12 (50.0)	52 (64.2)	30 (52.6)	13 (54.2)	40 (55.6)	45 (63.4)	30 (65.2)
Arteriolosclerosis								
None/Mild	238 (64.5)	17 (70.8)	49 (60.5)	36 (63.2)	15 (62.5)	52 (72.2)	38 (53.5)	31 (67.4)
Moderate/Severe	92 (24.5)	5 (20.8)	24 (29.6)	12 (21.1)	6 (25.0)	18 (25.0)	16 (22.5)	11 (23.9)

Infarcts								
Stage 0	254 (67.7)	15 (62.5)	48 (59.3)	40 (70.2)	13 (54.2)	60 (83.3)	45 (63.4)	33 (71.7)
Stage 1	66 (17.6)	4 (16.7)	19 (23.4)	6 (10.5)	5 (20.8)	8 (11.1)	16 (22.5)	8 (17.4)
Stage 2	55 (14.7)	5 (20.8)	14 (17.3)	11 (19.3)	6 (25.0)	4 (5.6)	10 (14.1)	9 (10.9)
Time in state, y								
MCI	2.9 (2.4)	4.1 (3.6)	3.0 (2.4)	2.9 (2.0)	3.0 (1.9)	2.9 (3.2)	3.0 (2.4)	1.7 (0.6)
Dementia	5.3 (3.4)	8.9 (2.9)	4.7 (2.8)	3.9 (2.8)	4.9 (2.5)	5.3 (4.1)	5.8 (3.3)	6.2 (3.5)

Data are mean (SD) or n (%). Abbreviation: SD, standard deviation; MMSE, Mini-Mental State Examination; QMP, quadruple misfolded proteins; Aβ, Amyloid Beta; α-Syn, α-Synuclein; TDP-43, transactive response DNA-binding protein of 43 kDa; APOE ε4, Apolipoprotein ε4 allele; Dx, Diagnosis; Stage 0, none; Stage 1, microinfarcts or lacunar/large infarcts; Stage 2, both microinfarcts or lacunar/large infarcts; Missing data information is reported in Table 2.3 and Table 2.4

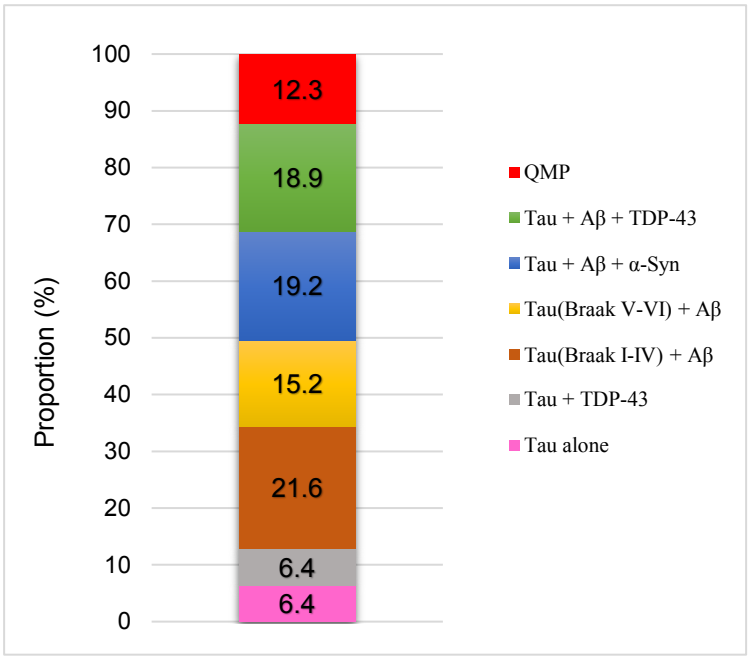
Table 2.2: Participant Characteristics by Proteinopathy Among Participants Who Started as Cognitively Normal at Baseline (n=228)

Variable	Overall n=228	Tau n=20	$Tau_{Braak\ II\text{-}IV}$+ Aβ n= 75	$Tau_{Braak\ V\text{-}VI}$ +Aβ n= 30	Tau+TDP-43 n= 17	Tau Aβ + α-Syn n= 32	Tau+Aβ + TDP-43 n=35	QMP n= 19
Age at death, y	89.1 (6.4)	85.6 (6.1)	88.8 (6.5)	89.0 (6.9)	90.9 (7.0)	87.5 (6.5)	91.7 (4.0)	90.2 (6.2)
Age on onset (MCI)	85.1 (6.7)	82.6 (3.7)	87.1 (5.6)	84.2 (7.2)	89.7 (4.7)	79.6 (7.9)	86.8 (3.8)	82.1 (9.4)
Age of onset, Dementia	86.1 (6.9)	82.0 (NA)	88.7 (5.4)	85.5 (8.6)	88.5 (6.2)	81.7 (7.0)	88.3 (4.3)	83.6 (8.4)
Female sex	149 (65.4)	13 (65.0)	44 (58.7)	20 (66.7)	15 (88.2)	24 (75.0)	21 (60.0)	12 (63.2)
White race	224 (98.3)	20(100.0)	73 (97.3)	30 (100.0)	16 (94.2)	31 (96.9)	35 (100.0)	19(100.0)
Education, y	16.1 (2.6)	15.2 (2.7)	15.9 (2.5)	16.0 (3.0)	16.7 (2.4)	15.9 (2.7)	16.5 (2.6)	16.4 (2.3)
APOE ε4 (present)	73 (32.0)	1 (5.0)	21 (28.0)	17 (56.7)	3 (17.7)	13 (40.6)	12 (34.3)	6 (31.6)
Final MMSE	23.7 (7.8)	27.9 (2.2)	26.7 (4.5)	21.2 (8.6)	22.2 (9.1)	23.7 (8.3)	19.6 (9.7)	18.9 (9.0)
Last Clinical Dx								
Normal	104 (45.6)	16 (80.0)	48 (64.0)	7 (23.3)	6 (35.3)	14 (43.8)	6 (17.1)	5 (26.3)
Impaired/Other	6 (2.6)	1 (5.0)	3 (4.0)	1 (3.3)	0	1 (3.1)	0	0
MCI	35 (15.4)	2 (10.0)	12 (16.0)	7 (23.3)	3 (17.7)	6 (18.8)	5 (14.3)	0
Demented	83 (36.4)	1 (5.0)	12 (16.0)	15 (50.0)	6 (47.1)	11 (34.4)	24 (68.6)	14 (73.7)
Braak NFT stage								
I	17 (7.5)	7 (35.0)	0	-	4 (23.5)	4 (12.5)	1 (2.9)	1 (5.3)
II	65 (28.5)	9 (45.0)	37 (49.3)	-	8 (47.1)	6 (18.8)	2 (5.7)	3 (15.8)
III	40 (17.5)	2 (10.0)	23 (30.7)	-	4 (23.5)	4 (12.5)	3 (8.6)	4 (21.1)
IV	30 (13.2)	2 (10.0)	15 (20.0)	-	1 (5.9)	4 (12.5)	6 (17.1)	2 (10.5)
V	54 (23.7)	0	-	20 (66.7)	0	10 (31.2)	20 (57.1)	4 (21.1)
VI	22 (9.6))	0	-	10 (33.3)	0	4 (12.5)	3 (8.6)	5 (26.3)
Atherosclerosis								
<50% occluded	86 (37.7)	12 (60.0)	28 (37.3)	12 (40.0)	8 (47.1)	12 (37.5)	10 (28.6)	4 (21.1)
≥50% occluded	142 (62.3)	8 (40.0)	47 (62.7)	18 (60.0)	9 (52.9)	20 (62.5)	25 (71.4)	15 (79.0)
Arteriolosclerosis								
None/Mild	145 (63.6)	16 (80.0)	46 (61.3)	20 (66.7)	10 (58.8)	21 (65.6)	22 (62.9)	10 (52.6)
Moderate/Severe	60 (26.3)	2 (10.0)	21 (28.0)	6 (20.0)	5 (29.4)	9 (28.1)	9 (25.7)	8 (42.1)
Infarcts								
Stage 0	114 (50.0)	12 (63.2)	39 (51.3)	11 (36.7)	8 (47.1)	19 (59.4)	15 (42.9)	10 (52.6)
Stage 1	78 (34.2)	2 (10.5)	21 (27.6)	11 (36.7)	8 (47.1)	11(34.4)	18 (51.4)	7 (36.8)

Stage 2	36 (15.8)	5 (26.3)	16 (21.1)	8 (26.7)	1 (5.9)	2 (6.3)	2 (5.7)	2 (10.5)
HS (present)	44 (19.3)	0	1 (1.3)	1 (3.3)	8 (47.1)	2 (6.3)	18 (51.4)	14 (73.7)
AGD (present)	35 (15.3)	4 (20.0)	14 (18.7)	3 (10.0)	2 (11.8)	1 (3.1)	8 (22.9)	3 (15.8)
Mean time in state, y								
MCI	2.9 (2.0)	3.1 (3.1)	3.0 (2.4)	3.0 (2.0)	3.3 (1.7)	2.7 (1.9)	3.1 (2.1)	1.8 (0.6)
Dementia	4.9 (3.1)	7.1 (NA)	3.9 (2.4)	4.6 (3.5)	4.9 (1.6)	6.2 (3.9)	4.8 (2.7)	5.7 (3.8)

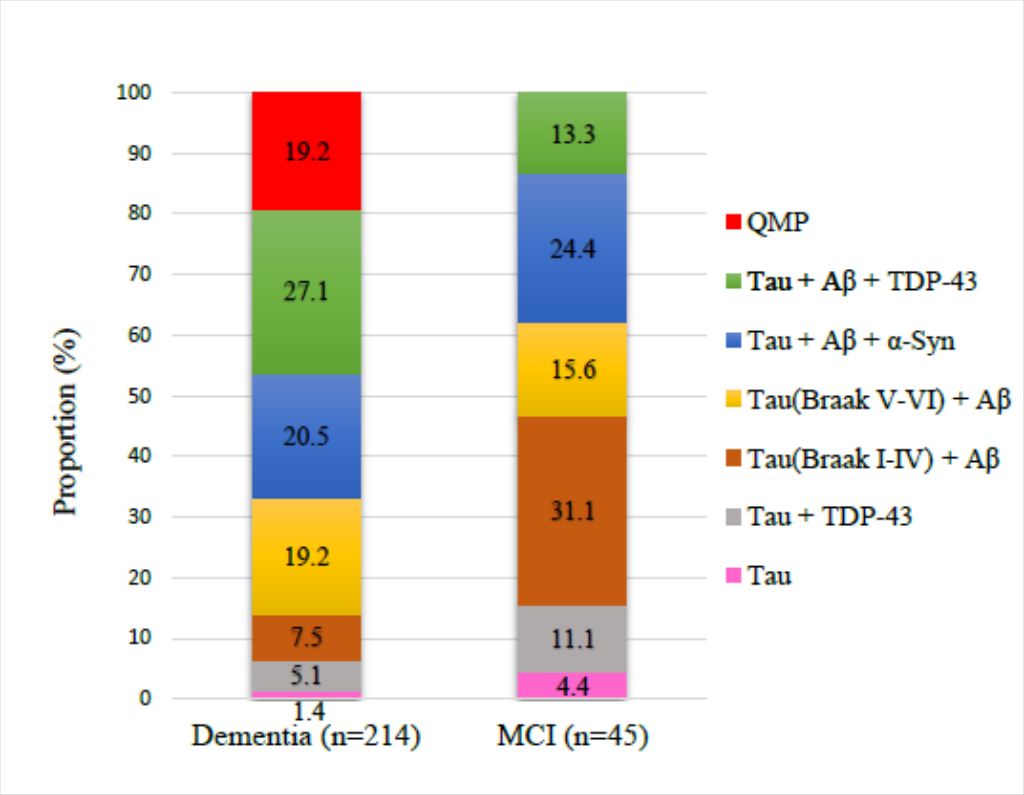
Data are mean (SD) or n (%). y, years; MMSE, Mini-Mental State Examination; ; QMP, quadruple misfolded proteins; Aβ, Amyloid Beta; α-Syn, α-Synuclein; TDP-43, transactive response DNA-binding protein of 43 kDa; *APOE* ε4 - Apolipoprotein ε4 allele; Dx, Diagnosis; MCI, Mild cognitive impairment; NA, SD could not be calculated, only one participant in the cell.; Stage 0, No infarcts; Stage 1, microinfarcts or lacunar/large infarcts; Stage 2,both microinfarcts and lacunar/larger infarcts; HS-Hippocampal Sclerosis; ; AGD- Argyrophilic grain disease. Missing data information can be found in Table 2.3 and 2.4.

Figure 2.2. Distribution of Proteinopathy Groups Among Participants



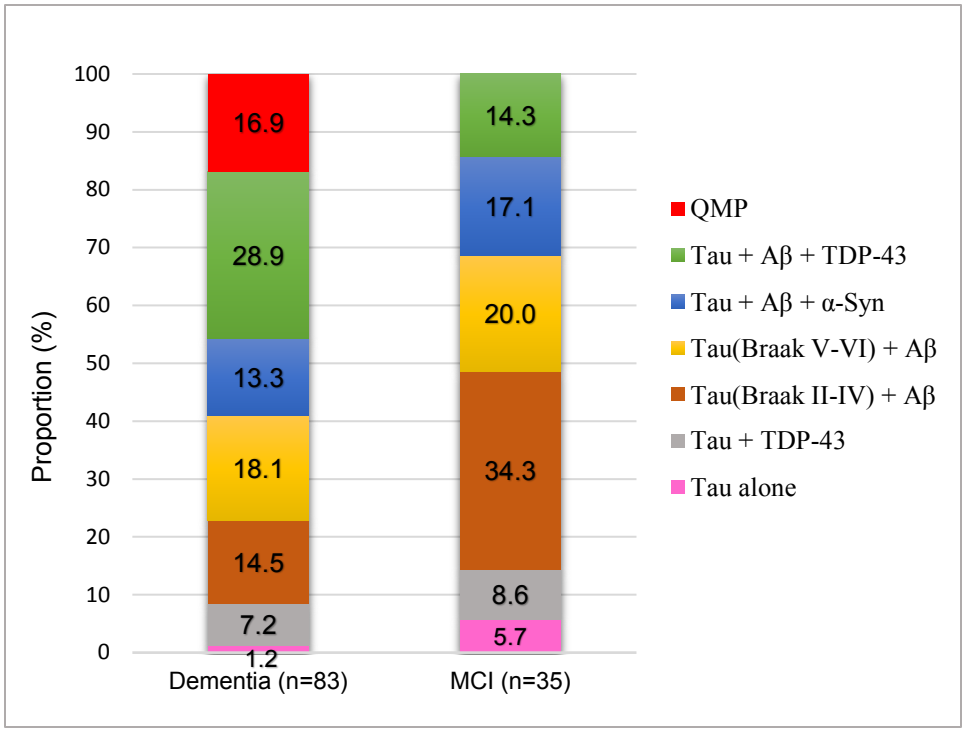
Abbreviation: QMP, quadruple misfolded proteins; Aβ, Amyloid Beta; α-Syn, α-Synuclein; TDP-43, transactive response DNA-binding protein of 43 kDa.

Figure 2.3. Distribution of Proteinopathy Groups Among Participants With Dementia and Participants With Mild Cognitive Impairment (MCI) Proximate to Death



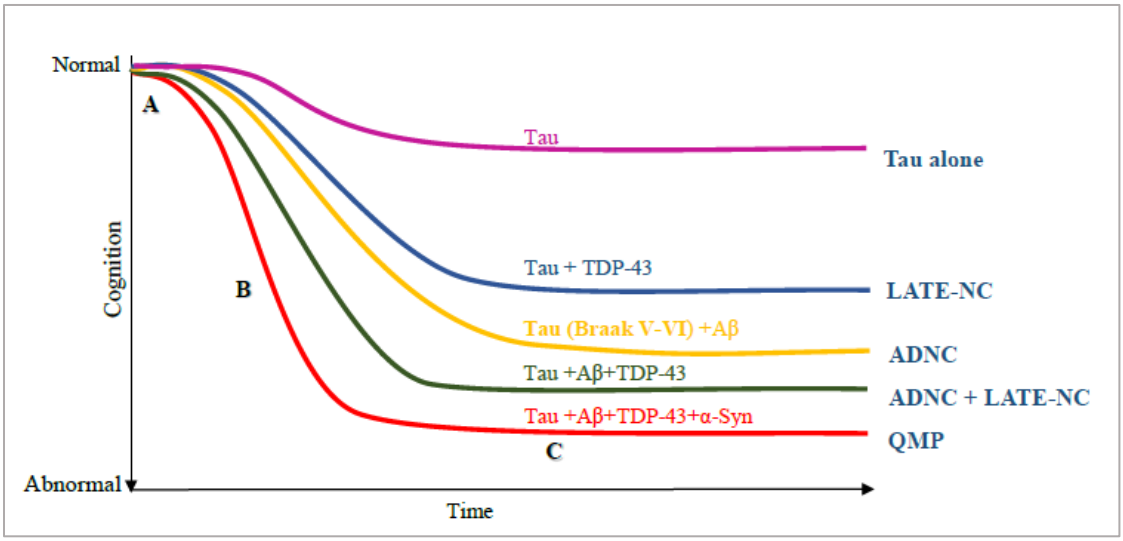
Abbreviations: Aβ indicates amyloid-β; αSyn, α-synuclein; QMP, quadruple misfolded protein; and TDP-43, transactive response DNA-binding protein 43.

Figure 2.4: Distribution of Proteinopathy Groups Among Participants with Dementia and Participants With Mild Cognitive Impairment (MCI) Proximate to Death Who Started as Cognitively Normal at Baseline (n=228)



Abbreviation: MCI, Mild cognitive impairment; QMP, quadruple misfolded proteins; Aβ, Amyloid Beta; α-Syn, α-Synuclein; TDP-43, transactive response DNA binding protein 43 kDa.

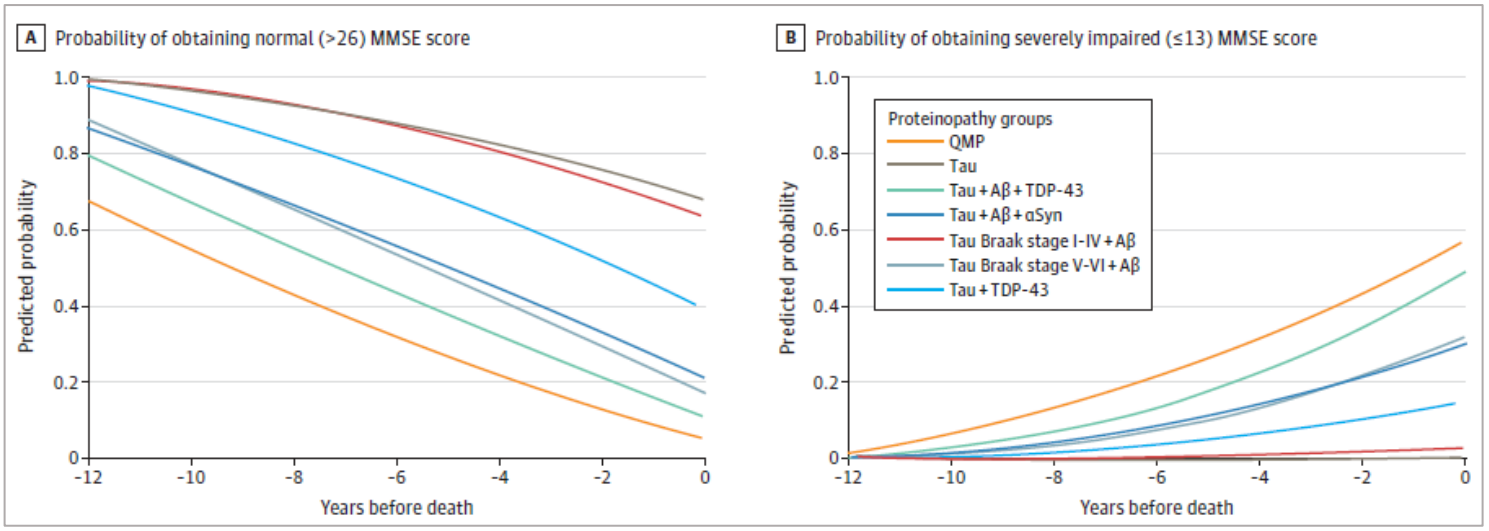
Figure 2.5. Hypothesized Patterns of Late-Life Cognitive Decline Associated With Specific Proteinopathies



Quadruple misfolded protein (QMP) is distinguished by early decline in cognition (A), fast transition through mild cognitive impairment of approximately 1.7 years (B), and long duration of severely abnormal cognition (C).

Abbreviation: Aβ indicates amyloid-β; ADNC, Alzheimer disease neuropathological change; αSyn, α-synuclein; LATE-NC, limbic-predominant, age-related TDP-43 encephalopathy neuropathological change; and TDP-43, transactive response DNA-binding protein 43.

Figure 2.6 Mean Estimated Probabilities of Obtaining Normal or Severely Impaired Mini-Mental State Examination (MMSE) Score Ranges in the 12 Years Before Death



Abbreviation: Aβ indicates amyloid-β; αSyn, α-synuclein; QMP, quadruple misfolded protein; and TDP-43, transactive response DNA-binding protein 43.

Table 2.3: Frequency of missing data in all participants (n=375)

Variable	Overall n=375	Tau n=24	$Tau_{Braak\ I-IV}$ + Aβ n=81	$Tau_{Braak\ V-VI}$ + Aβ n=57	Tau + TDP-43 n=24	Tau + Aβ + α-Syn n=72	Tau + Aβ + TDP-43 n=71	QMP n=46
Education	7	0	1	1	0	1	1	3
APOE ε4 (present)	19	0	2	5	1	5	5	1
MMSE	48	1	4	10	1	11	10	11
Last clinical Dx	2	0	1	0	0	0	1	0
Atherosclerosis	4	0	0	0	0	1	1	2
Arteriolosclerosis	45	2	8	9	3	2	17	4
HS	4	1	0	0	0	1	2	0
AGD	9	0	3	2	1	0	2	1

Table 2.4: Frequency of Missing Data in all Participants Who Started as Cognitively Normal at Baseline (n=228)

Variable	Overall n=228	Tau n=20	$Tau_{Braak\ I-IV}$ + Aβ n= 75	$Tau_{Braak\ V-VI}$ + Aβ n= 30	Tau +TDP-43 n= 17	Tau + Aβ + α-Syn n= 32	Tau +Aβ + TDP-43 n=35	QMP n= 19
Education	3	0	1	0	0	1	0	1
APOE ε4 (present)	2	0	2	0	0	0	0	0
MMSE	18	0	3	4	1	6	2	2
Arteriolosclerosis	23	2	8	4	2	2	4	1
HS	2	1	0	0	0	1	0	0
AGD	6	0	3	2	0	0	1	0

Abbreviation: MMSE, Mini-Mental State Examination; QMP, quadruple misfolded proteins; Aβ, Amyloid Beta; α-Syn, α-Synuclein; TDP-43, transactive response DNA-binding protein of 43 kDa; *APOE* ε4 - Apolipoprotein ε4 allele; Dx, Diagnosis; HS-Hippocampal Sclerosis; ; AGD- Argyrophilic grain disease; Variables not listed here are fully observed

Table 2.5: Adjusted odds ratios and 95% confidence intervals for odds of proteinopathy case group membership relative to Tau (Braak I-IV) + Aβ

Variable	Proteinopathy groups	Adjusted OR (95% CI)
Age at death (5 year increase)	Tau	0.71 (0.51-1.00)
	$Tau_{Braak\ V\text{-}VI}$ + Aβ	0.85 (0.66-1.11)
	Tau + TDP-43	1.02 (0.69-1.49)
	Tau + Aβ + α-Syn	**0.61 (0.48-0.78)**
	Tau+ Aβ + TDP-43	1.15 (0.89-1.50)
	QMP	0.82 (0.63-1.08)
Female sex	Tau	1.65 (0.60-4.51)
	$Tau_{Braak\ V\text{-}VI}$ + Aβ	1.48 (0.69-3.15)
	Tau + TDP-43	1.87 (0.65-5.38)
	Tau + Aβ + α-Syn	1.41 (0.70-2.87)
	Tau+ Aβ + TDP-43	1.00 (0.50-1.99)
	QMP	1.18 (0.55-2.57)
APOE ε4 allele ≥1 vs 0	Tau	**0.10 (0.01-0.77)**
	$Tau_{Braak\ V\text{-}VI}$ + Aβ	**3.45 (1.61-7.39)**
	Tau + TDP-43	0.43 (0.11-1.62)
	Tau + Aβ + α-Syn	1.53 (0.73-3.19)
	Tau+ Aβ + TDP-43	**2.34 (1.15-4.77)**
	QMP	**2.55 (1.16-5.62)**

Results are from multinomial logistic regression with age, sex and *APOE* ε4 as covariates. OR, odds ratio; CI, confidence interval; QMP, quadruple misfolded proteins; Aβ, Amyloid Beta; α-Syn, α-Synuclein; TDP-43, transactive response DNA-binding protein of 43 kDa; *APOE* ε4 - Apolipoprotein ε4 allele. 19 participants were excluded from this analysis due to missing data (Table 2.3).

CHAPTER THREE

Four common late-life cognitive trajectories patterns associate with replicable underlying neuropathologies

Abstract

Background: Late-life cognitive function is heterogeneous, ranging from no decline to severe dementia. Prior studies of cognitive trajectories have tended to focus on a single measure of global cognition or individual tests scores, rather than considering longitudinal performance on multiple tests simultaneously. The current study aimed to examine cognitive trajectories from two independent datasets to assess whether similar patterns might describe longitudinal cognition in the decade preceding death, as well as what participant characteristics were associated with trajectory membership.

Materials and Methods: Data were drawn from autopsied longitudinally followed participants of two cohorts (total N=1346), a community-based cohort at the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC) and National Alzheimer's Coordinating Center (NACC). We used group-based multi-trajectory models (GBMTM) to identify cognitive trajectories over the decade before death using Mini-Mental State Exam, Logical Memory-Immediate, and Animal Naming performance. Multinomial logistic and Random Forest (RF) analyses assessed characteristics associated with trajectory groups.

Results: There were 365 participants included from UK-ADRC and 981 participants from NACC. GBMTM identified four similar cognitive trajectories in each dataset. In multinomial models, death age, Braak NFT stage, TDP-43, and α-synuclein were associated with declining trajectories. RF results suggested most important trajectory

predictors were Braak NFT stage, cerebral atrophy, death age, and brain weight. Multiple pathologies were most common in trajectories with moderate or accelerated decline.

Conclusion: Cognitive trajectories are associated strongly with neuropathology, particularly Braak NFT stage. The high frequency of multiple pathologies in trajectories with cognitive decline suggests dementia treatment and prevention efforts must consider multiple diseases simultaneously.

Introduction

Cognitive impairment and dementia are associated with multiple brain pathologies in elderly persons,[5,23,26] particularly accumulation of tau neurofibrillary tangles (NFTs) with amyloid-β (Aβ) plaques, α-synuclein, and TAR-DNA binding protein 43 kDa (TDP-43).[5,26] Additionally, infarctions and other cerebrovascular pathologies are prevalent and deleterious for cognition.[5,32] Although prior studies have characterized cognitive status before death related to specific neurodegenerative diseases, fewer studies have evaluated trajectories of cognitive decline in the presence of multiple pathologies.[47,81-84]

Group-based trajectory models (GBTM) are a specialized application of finite mixture modeling developed to identify longitudinal patterns and distinctive trajectories.[85,86] GBTM allows visualization of cognitive trajectories, as well as classification of similar individuals into clinically meaningful groups.[85] Group-based multi-trajectory modeling (GBMTM), an extension of GBTM, identifies shared trajectories across multiple outcomes of interest [87] (e.g., cognitive function as measured by multiple cognitive tests). Prior studies seeking to identify distinct patterns of cognition[82,88-91] have relied on either cognitive test scores that are examined one test at a time,[88] or on a summary global cognition score derived from all tests.[83] Here, we used GBMTM to identify cognitive trajectories based simultaneously on three cognitive tests, representing global cognition, episodic memory, and category fluency.

Autopsied research volunteers from the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC), as well as a separate sample of autopsied research volunteers from various ADRCs contributing data to the National Alzheimer's

Coordinating Center (NACC) Neuropathology Data Set,[66] were included in the current study. The National Institute on Aging funds all ADRCs. While UK-ADRC research participants were mostly recruited from the community, many ADRCs recruit from memory disorders clinics. We examined cognitive trajectories to assess whether similar patterns might describe longitudinal cognition in the decade preceding death, as well as what characteristics were associated with trajectory group membership.

Methods

Study participants (UK-ADRC)

Data were drawn from the community-based cohort study of aging and dementia at the UK-ADRC.[60] Included participants were enrolled from 1989-2017 and were ≥ age 55 years at baseline (the usual age of eligibility for this cohort is age 70 and over). Inclusion criteria were available cognitive test data (see "Neuropsychological battery test scores"), Alzheimer's disease (AD) pathologies (Braak NFT stage, Aβ plaque rating), α-synuclein, and TDP-43 proteinopathies. We excluded participants with brain cancer, Down syndrome, frontotemporal lobar degeneration, and other rare dementia syndromes (given small numbers of cases for comparison between the datasets). FTLD cases are rare in old age, as were in the present sample, as in other community-based cohorts.[58,92]

Study participants (NACC)

Data were drawn from the NACC Uniform Data Set (UDS), and Neuropathology Data Set (NP), comprising participants enrolled at ADRCs throughout the United States (UK-ADRC). NACC maintains multicenter databases comprising standardized ADRC data protocols. Twenty-six ADRCs contributed data to both NACC UDS and NP through the September 2019 data freeze (https://www.alz.washington.edu/), when our data were

extracted. To generate an independent dataset comparable to UK-ADRC, we included participants based on the same criteria as above.

Neuropsychological battery test scores

At each clinical evaluation, participants were administered a battery of cognitive tests. To study their cognitive trajectories, we included tests measuring global cognition (Mini-Mental State Examination; MMSE),[68] episodic memory (Wechsler Memory Scale-Revised [WMS-R] Logical Memory Story A),[93] and category verbal fluency (Animal Naming Test)[94] as these were consistently measured across all participants.

The MMSE is frequently used to evaluate global cognition in older adults; scores range from 0-30.[68] Logical Memory measures the total number of story units recalled verbatim from a narrated short story; scores range from 0-25.[93] In the Animal Naming Test, participants name as many animals as they can in 60 seconds;[95] observed scores ranged from 0-41 (UK-ADRC) and 0-52 (NACC). We considered MMSE <27, Logical Memory <9, and Animal Naming <12 as abnormal scores, based on the baseline performance among the cognitively normal NACC study population.[94]

In March 2015, the NACC UDS changed to Version 3.0, wherein the MMSE was replaced by the Montreal Cognitive Assessment (MoCA),[96] and WMS-R Logical Memory IA-Immediate was replaced by Craft Story 21 Recall-Immediate.[97] NACC provides harmonized data crosswalks to researchers that bridge these scores.[97] Monsell et al. reported that the new tests (Version 3.0) were well correlated with the previous tests (Version 2.0) [97]. Hence, we used harmonized scores for all NACC participants from March 2015 onwards. UK-ADRC continued to obtain the MMSE, and so those scores were used, while the harmonized Logical Memory scores were used.

Cognitive status

Participants were evaluated clinically for cognitive impairment at each visit.[63,64] We used the last visit clinical diagnosis to define the cognitive status of the participants as normal cognition, impaired cognition (but not MCI; presence of medical comorbidities), MCI, or dementia.[98]

Neuropathological assessment

Details of neuropathological assessment at UK-ADRC [16,71] and NACC[99] have been described previously. Aβ was considered present when neuritic or diffuse plaques[9] were at least sparse. Braak NFT stages were dichotomized into an indicator for high Braak NFT stage V-VI vs. I-IV. TDP-43 proteinopathy was considered present if TDP-43 inclusion bodies were detected in the hippocampus, whereas α-synuclein proteinopathy was considered present when Lewy bodies were detected in the brain stem, neocortex, or the medial temporal lobe.

Cerebrovascular pathology included measures of cerebral amyloid angiopathy, categorized as moderate/severe vs. none/mild; atherosclerosis severity at Circle of Willis (all vessels ≥50% vs. <50% occluded); any infarcts/lacunes (yes vs. no); and, brain arteriolosclerosis (moderate/severe vs. none/mild). Cerebral atrophy was classified moderate/severe vs. none/mild. Additionally, both right and left hippocampi were evaluated for hippocampal sclerosis (HS) in UK-ADRC cases; the presence of HS on either side was considered as HS. For NACC, HS was considered present if right and/or left HS was reported, but not all ADRCs assess both sides of the hippocampal formation.[99]

Analyses and statistical methods

All analyses were first performed for UK-ADRC data, and then the same analyses were applied to the NACC data to attempt to replicate the results. We used GBMTM [100,101] to estimate latent trajectories in the decade before death and compared the trajectories and group membership characteristics to evaluate whether the trajectories were similar despite differences in recruitment and population characteristics.

To fit the GBMTM, we first fit separate GBTM for each test; we fit three, four, and five group models to determine the best-fitting number of trajectories. Four trajectories were selected for each of the three tests based on the Bayesian Information Criterion (BIC). A selection criterion was the mean maximum posterior probability in all trajectory groups being > 0.7, meaning on average every participant assigned to a trajectory has >70% probability of membership.[85] Age at death, sex, and education were included in the GBTM to account for their influence on group membership, but neuropathology and clinical diagnoses were not included.

Once we determined the best fitting number of trajectories for each measure, we fit a single GBMTM with four latent groups. Trajectory membership is probabilistic and based on the participant's performance on all three tests simultaneously. Each participant has an estimated probability of membership in each trajectory group, with a total probability equal to 1.0; maximum probability assignment was used to determine membership for post-hoc analyses. Further, once optimal GBMTM models were selected, we assessed trajectory face validity by examining the longitudinal mean scores of the participants assigned to each trajectory group.

Multinomial logistic regression was used to estimate the association of demographic characteristics and neuropathology with trajectory membership, with *No Decline* as the reference. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were obtained from the model, which included age at death, sex, education, *APOE* ε4 (indicator for any ε4 alleles vs. none), and indicators for the presence of Braak NFT stage V/VI, Aβ, TDP-43, atherosclerosis, arteriosclerosis, α-synuclein, and HS. While analyzing NACC data, indicator variables for ADRC were included as a fixed effect to account for center effects.

Because the multinomial logistic model requires the estimation of many parameters relative to other logistic models,[102] we could include only some variables of interest. To consider the relative importance of all variables of interest (**Table 3.1**) in explaining overall trajectory group membership; random forest (RF) and bagging ensemble algorithm,[103] which is a reliable variable selection method and produces unbiased variable importance were then applied.[104] As a sensitivity analysis, we repeated the analyses on the subgroups of participants who began the follow-up interval with normal cognition.

PROC TRAJ was used to estimate GBTM and GBMTM;[100] PROC LOGISTIC was used to fit the multinomial logistic regression (SAS:9.4®). RF was conducted using the cforest function in the "party" R package.[103] The reported results for multinomial and RF analysis are based on multiple imputation of missing neuropathological data (**Table 3.2**). The imputation was conducted by chained random forest using imputation with predictive mean matching with 5-iterations and 100 trees. The imputation was conducted using the "missRanger" R package.[105] The significance level was set at 0.05.

Results

Participants' characteristics

UK-ADRC included 365 autopsied participants (**Figure 3.1a**): mean (SD) age at death was 87.0 (8.0) years; educational attainment was 15.6 (3.0) years; median annual visit numbers was 9.9 (IQR: 5-14 visits); majority were female (n=228, 62.5%), and White race (n=354, 97.0%). Among autopsied NACC participants (n=981): mean age at death was 80.7 (9.6) years; education was 15.4 (3.1) years; median annual 5.0 visits (IQR: 3-7 visits); majority were male (n=527, 53.7%); and White race (n=911, 92.9%). A smaller proportion of UK-ADRC participants carried the *APOE*-ε4 allele (36.2% vs 45.8%) or had a dementia diagnosis at the time of death (56.2% vs 82.1%) versus NACC (**Table 3.1**).

Cognitive trajectories

Participants in the UK-ADRC and NACC overall showed similar cognitive trajectories (**Figure 3.2)**: we labeled the trajectories as "*No Decline"* (mean test scores remained normal during follow-up); "*Mild Decline*" (no decline in global cognition, slow decline in memory and fluency); "*Moderate Decline*" (decline from normal to abnormal global cognition, memory, and fluency); and, "*Accelerated Decline"* (decline from abnormal to severe impairment in global cognition, memory, and fluency). **Figure 3.2** and **Figure 3.3** (participants who started follow-up with normal cognition) show the observed means (dashed lines) and the estimated means (solid lines) with 95% CI for each trajectory.

Cognitive trajectories in the UK-ADRC

The No Decline group, comprising 27.9% of UK-ADRC participants (**Figure 3.2)**, had better mean cognitive scores throughout follow-up than the other groups across all tests. Mean MMSE scores remained relatively stable, while mean Logical Memory and Animal Naming scores showed a slight decline but remained normal throughout follow-up. The Mild Decline group (29.6%) declined marginally in the MMSE and Animal Naming trajectories, but the group was distinct from No Decline due to decreasing mean Logical Memory scores about 7-8 years before death. Moderate Decline (25.8%) started with normal mean MMSE scores but rapidly declined 6 to 7 years before death, while the Logical Memory trajectory started in the normal range and dropped to abnormal. However, Animal Naming scores were relatively better preserved. Accelerated Decline (16.7%) had abnormal scores 10 years before death. This group had low scores in all three cognitive scores, but Logical Memory scores were most affected.

Among UK-ADRC participants who started follow-up with normal cognition (n=228) (**Figure 3.3**), trajectory patterns were slightly different. MMSE trajectory for Accelerated Decline started with >26 mean MMSE and declined rapidly about 8 years before death. However, the mean Logical Memory and Animal Naming scores at baseline were 10.5, and 16.1, respectively, and declined rapidly, about 6 years before death. The Moderate Decline group also experienced decline in Logical Memory and Animal Naming scores about 6 years before death.

Table 3.3 presents participant characteristics by trajectories. Compared to the other groups, persons in the Accelerated Decline group on average died earlier, majority were female, diagnosed with dementia at the last visit (98.4%), and had higher

proportions of *APOE* ε4 allele (55.7%), Braak NFT stage V/VI (90.2%), TDP-43 proteinopathy (60.9%), HS (45.9%), moderate/severe Cerebral amyloid angiopathy (42.6%), and moderate/severe cerebral atrophy (67.2%). The Mild Decline and No Decline groups comparatively had a lower burden of *APOE* ε4 allele, proteinopathies, cerebral atrophy, and HS than the Moderate and Accelerated groups. Among the participants who began follow-up with normal cognition (n=228), those assigned to the Accelerated Decline and Moderate Decline groups were older than the No Decline and Mild Decline groups, and the burden of proteinopathies was higher (**Table 3.4)**.

Multinomial logistic regression estimated associations between participant characteristics and trajectory membership (**Table 3.7**). With a 5-year increase in age at death, participants were less likely to be in the Accelerated Decline group (aOR= 0.68; 95% CI, 0.51, 0.92). Braak NFT stage V/VI was strongly associated with higher odds of belonging to the Accelerated Decline (AOR =43.95; 95% CI, 12.00,163.98), Moderate Decline (AOR = 17.69; 95% CI, 7.69-44.10), and Mild Decline (AOR = 3.58; 95% CI, 1.66, 7.70) group membership compared to No Decline. Presence of TDP-43 proteinopathy had higher odds of being in the Accelerated Decline group (AOR = 3.52; 95% CI, 1.04, 12.87). While HS was significantly associated with group membership, this association was not significant in complete case analyses (**Table 3.8**). There was no significant association of α-synuclein, atherosclerosis, or *APOE* ε4 with group membership.

Cognitive trajectories in NACC

NACC included 981 autopsied participants (**Figure 3.1b**): On average, individuals in all NACC trajectory groups died younger (~6 years) than UK-ADRC

participants **(Table 3.5)**. Estimated cognitive trajectories in NACC were similar in shape to those in UK-ADRC (**Figure 3.2b**): No Decline (16.0%), Mild Decline (31.3%), Moderate Decline (38.3%), and Accelerated Decline (14.4%) groups, but the distribution of membership differed. In addition, estimated mean Logical Memory and Animal Naming scores were lower at the beginning of follow-up compared to the UK-ADRC participants. Participant characteristics of the NACC trajectory groups are presented in **Table 3.5** and **Table 3.6** (participants starting as normal).

Based on multinomial logistic regression (**Table 3.7),** a 5-year increase in age at death was associated with lower odds of Accelerated Decline (AOR = 0.57; 95% CI, 0.48, 0.67) and Moderate Decline (AOR = 0.69; 95% CI, 0.60, 0.79) membership versus No Decline. Braak NFT stage V/VI (AOR =26.18; 95% CI, 12.07, 56.82) and TDP-43 pathology (AOR = 4.32; 95% CI, 2.07, 8.99) were associated with Accelerated Decline. The Accelerated Decline (AOR =2.54; 95% CI, 1.37, 4.68), Moderate Decline (AOR = 3.36; 95% CI, 1.75, 6.44), and Mild Decline (AOR = 2.23; 95% CI, 1.19, 4.18) groups were associated with higher odds of having α-synuclein compared to the No Decline. Moderate/severe arteriosclerosis was associated with higher odds of membership in the Accelerated Decline (AOR = 3.05; 95% CI, 1.69, 5.49), Moderate Decline (AOR =1.92; 95% CI, 1.18, 3.12), and Mild Decline (AOR = 1.75; 95% CI, 1.11, 2.75). Complete case analyses are presented in **Table 3.8**.

Distribution of Multiple pathologies by trajectory groups

Figure 3.4 shows the frequencies of AD neuropathologic change (ADNC) and comorbid brain pathologies by trajectory groups. Over 80% of UK-ADRC cohort and >86% of NACC cohort brains had ADNC pathology with at least one comorbid

pathology. The Moderate Decline and Accelerated Decline groups had higher frequencies of quadruple misfolded proteins (QMP) i.e. presence of all four misfolded proteins,[23] as well as the presence of TDP-43 with cerebrovascular pathologies. The presence of ≥ 2 proteinopathies was also largely accompanied by moderate/severe cerebrovascular pathologies (**Figure 3.4**).

In the RF analysis, all 16 predictors (**Table 3.1**) were evaluated to assess their importance in classifying participants into trajectory groups (**Figure 3.6**). For UK-ADRC participants, the five most important variables were Braak NFT stage, cerebral atrophy, HS, brain weight, and age at death. Similarly, for NACC cases, Braak NFT stage, age at death, cerebral atrophy, brain weight, and α-synuclein were most important.

Discussion

We estimated cognitive trajectories among ADRC volunteers in their last decade of life based on longitudinal patterns of three cognitive test scores, considered simultaneously. GBMTM models identified four trajectories (we labeled as: No, Mild, Moderate, and Accelerated Decline) in both the UK-ADRC and NACC datasets. Although the NACC participants died younger and had, generally, worse cognitive status compared to the UK-ADRC participants, the trajectories during end of life, and the underlying pathologies, were quite similar.

The GBMTM approach allowed us to account for how longitudinal performance on each test was related to longitudinal performance on the other two tests. Importantly, the results have good face validity, which was assessed by mean scores in each trajectory groups (e.g., participants assigned to the No Decline group should have observed scores indicating normal cognition).

One of the strengths of the GBMTM method is the ability to characterize patterns of variation in longitudinal outcomes. In both cohorts, although the Moderate and the Accelerated Decline groups had a pronounced decline in the test scores before death, the trajectory patterns were dissimilar. Mean test scores in the Accelerated Decline group were lower at the start and showed a constant decline, and almost 100% of participants had dementia diagnoses. Accelerated Decline was associated with proportionally greater burden of proteinopathies and cerebrovascular pathologies than the other trajectory groups. The Moderate Decline trajectory scores rapidly decreased starting about 8 years before death, and >90% carried a dementia diagnosis. However, looking at the individual tests, the Logical Memory and Animal Naming scores were low a decade before death, whereas the Mild Decline group participants showed decline only in the last 4-5 years before death. These findings suggest that GBMTM models may be useful in recognizing the subpopulations of older adults that show varied patterns of cognitive performance and potentially disease burden.

Consistent with previous studies, neocortical tau proteinopathy (the pathology found in Braak NFT stages V/VI) was strongly associated with cognitive decline.[16] Results from both the multinomial logistic and RF analyses emphasized the importance of Braak NFT stages in trajectory membership probabilities. However, point estimates from the multinomial model should be interpreted with caution due to the wide confidence intervals, which arose primarily due to sparse cells in the Braak NFT stages I/II/III/IV in the Accelerated and the Moderate Decline groups. Even so, we consider the association very strong.

Also consistent with previous studies was the lack of a strong association between amyloid-β (in the absence of high Braak NFT stages) and cognitive trajectories.[16,106] Amyloid plaques were present in all trajectory groups and did not predict group membership in the multinomial analysis, and the RF analysis also showed amyloid was not important for group membership. Although the *APOE* ε4 carrier proportions were >40% in the Moderate and Accelerated decline groups, after controlling for the other proteinopathies there was no association with trajectory groups, except with the Moderate Decline group in the NACC cohort. The association between *APOE* ε4 and late-life cognitive decline appears to be mediated primarily by the relationship between *APOE* and ADNC, and once ADNC affects cognition, the association between *APOE* and cognition is diminished.[107]

TDP-43 proteinopathy was prevalent in Accelerated and Moderate Decline groups and was strongly associated with group membership. TDP-43 proteinopathy has a strong association with cognitive impairment,[23,25,26] and is associated independently with cognitive decline in the presence or absence of comorbid ADNC.[25,81] Presence of α-synuclein proteinopathy was strongly associated with group membership among the NACC participants but not among the UK-ADRC participants, perhaps due to age differences in the two cohorts, given that participants with α-synuclein proteinopathy die at a relatively younger age.[50] Moderate/severe atherosclerosis and arteriosclerosis were also strongly associated with the Accelerated Decline group. Furthermore, moderate/severe cerebral atrophy was proportionally higher in Accelerated and Moderate Decline and was one of the five of the most important variables in the RF analysis. The

confluence of proteinopathies, age at death, cerebrovascular pathologies, cerebral atrophy, HS, and brain weight appeared to play roles in the slopes of the trajectories.

This study has several strengths. First was the availability of longitudinal follow-up with both clinical and neuropathological data. Second, we were generally able to replicate UK-ADRC results with NACC data collected from different ADRCs. Third, careful assessment of missing data and performing multiple imputation increased the validity of our findings. Additionally, we performed a sensitivity analysis in participants who started follow-up with clinically normal cognition, allowing a basis for clinical inference with respect to a presumed normal baseline. Although there were differences in the cohorts in terms of age at death, proportions of *APOE* ε4 allele, TDP-43, α-synuclein, cerebrovascular diseases, and hippocampal sclerosis, multiple comorbidities were prevalent in Moderate and Accelerated Decline groups from both cohorts.

The study has some limitations, however. There is possible misclassification of the trajectory group membership due to missing data and the fact that group membership is probabilistic. Available genetic data were limited to *APOE* genotype. In addition, our results have limited generalizability, as our data were restricted to primarily white, well-educated, and autopsied participants. Future studies are needed that focus on living populations with more demographically diverse research volunteers. Finally, residual center effects may persist despite adjustment for the centers, though prior research has shown good to an excellent agreement in neuropathologic ratings across various ADRCs.[9]

Conclusion

In conclusion, this study provides evidence that older adults follow distinct trajectories of cognitive performance during end of life. The relationship between trajectory groups and cognitive performance correlated with both the number of proteinopathies and the burden of cerebrovascular pathology in the brain. Despite the younger age at death of the NACC participants compared to the UK-ADRC participants, strikingly similar neuropathologic profiles featuring multiple pathologies were associated with trajectories. Thus, the high burden of complex neuropathologies is not exclusively a phenomenon of extreme old age, and prevention and treatment strategies focused on a single disease may fail to decrease the dementia burden in the population.

Funding

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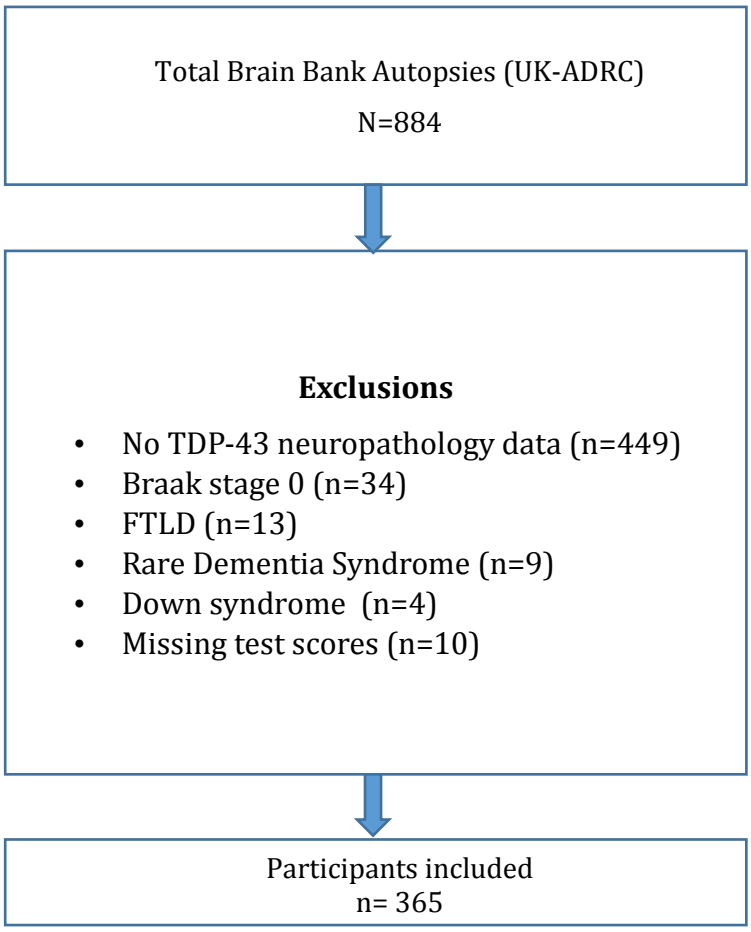
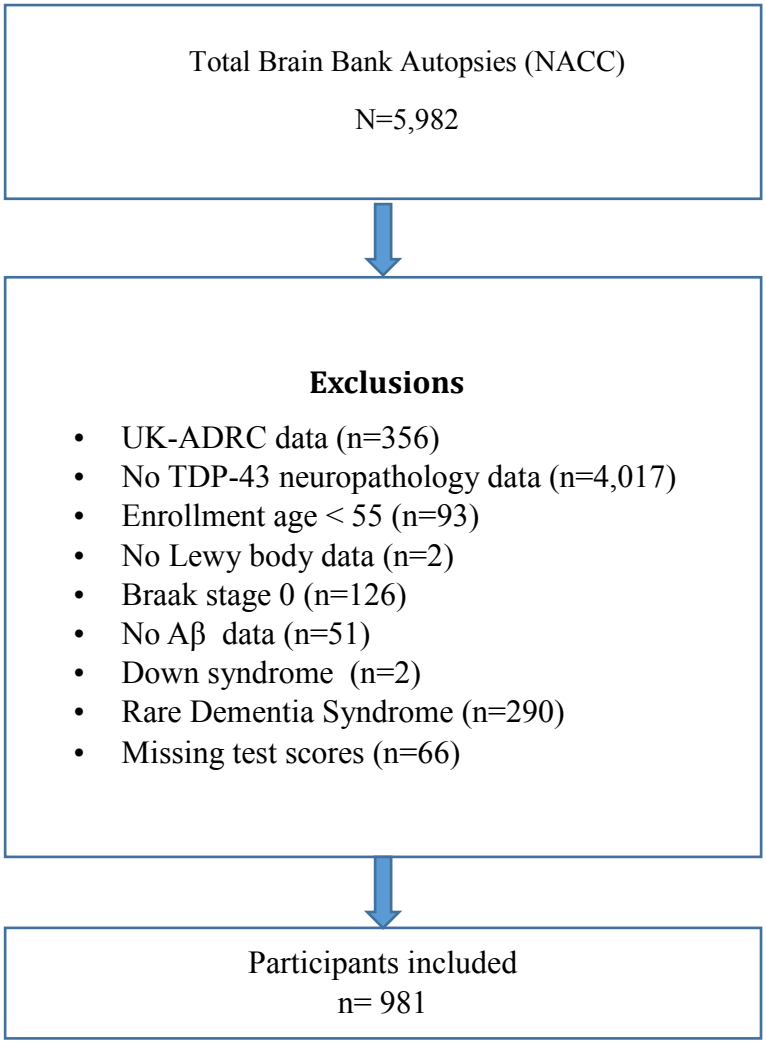
Figure 3.1a. Participant Inclusion Flow Diagram



UK-ADRC, University of Kentucky Alzheimer's Disease Research Center; TDP-43, transactive response DNA binding protein 43 kDa; FTLD, Frontotemporal lobar degeneration.

Figure 3.1b. Participant Inclusion Flow Diagram



NACC, National Alzheimer's Coordinating Center; TDP-43, transactive response DNA binding protein 43 kDa; FTLD, Frontotemporal lobar degeneration.

Table 3.1. Participant Characteristics by Cohort

Variable	UK-ADRC	NACC
N (%)	n=365	n=981
Number of visits mean ± SD	9.9 (5.7)	4.9 (2.7)
Age at death, y	87.0 (8.0)	80.7 (9.6)
Female sex	228 (62.5)	454 (46.3)
White race	354 (97.0)	911 (92.9)
Education, y , mean ± SD	15.6 (3.0)	15.4 (3.1)
APOE ε4 allele	132 (36.2)	449 (45.8)
Baseline Clinical Diagnosis		
Normal	228 (62.5)	163 (16.6)
Impaired	7 (1.9)	26 (2.6)
MCI	24 (6.6)	190 (19.4)
Demented	92 (25.2)	602 (61.4)
Last Clinical Diagnosis		
Normal	104 (28.5)	85 (8.6)
Impaired	10 (2.7)	18 (1.8)
MCI	45 (12.3)	73 (7.4)
Demented	205 (56.2)	805 (82.1)
Whole brain weight (g), mean ± SD	1146.7 (157.2)	1153.2 (169.7)
Braak NFT stage		
Braak I to IV	190 (52.0)	336 (34.2)
Braak V to VI	175 (48.0)	645 (65.8)
Cerebral atrophy		
None/Mild	253 (67.5)	557 (49.8)
Moderate/severe	122 (32.5)	488 (43.2)
Aβ plaques	317 (86.8)	910 (92.8)
α-synuclein	112 (30.7)	380 (38.7)
TDP-43 inclusion bodies	137 (37.5)	263 (26.8)
Hippocampal sclerosis	92 (24.5)	144 (14.8)
Cerebral amyloid angiopathy		
None/Mild	274 (63.3)	488 (49.8)
Moderate/severe	89 (24.7)	424 (43.2)
Atherosclerosis		
<50% Occluded	143 (39.2)	613 (62.5)
≥ 50% Occluded	218 (59.7)	362 (36.9)
Arteriosclerosis		
None/Mild	231 (63.3)	437 (44.6)
Moderate/Severe	90 (24.7)	535 (54.4)
Infarcts		
None	201 (55.1)	656 (66.8)
Present	164 (44.9)	322 (32.8)

UK-ADRC, University of Kentucky Alzheimer's Disease Research Center; NACC, National Alzheimer's Coordinating Center; *APOE*, Apolipoprotein E; Aβ, Amyloid-β; TDP-43, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangles.

Table 3.2: Frequency of Missing Data in all Participants

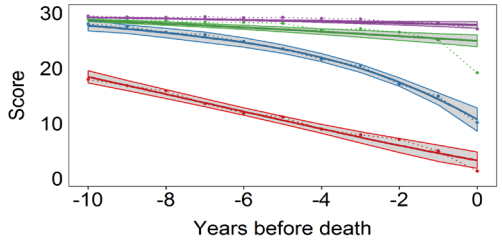
Variable	**UK-ADRC (n=365)**	**NACC (n=981)**
Education	5 (1.4)	9 (0.9)
APOE ε4 allele (≥1 allele)	16 (4.4)	103 (10.5)
Baseline Clinical Diagnosis	14 (3.8)	
Last Clinical Diagnosis (last visit)	1 (0.3)	-
Hippocampal sclerosis	4 (1.1)	5 (0.5)
Atherosclerosis	4 (1.1)	6 (0.6)
Arteriosclerosis	44 (12.1)	9 (0.9)
Infarcts/lacunes	-	11 (1.1)
Cerebral atrophy	4 (1.1)	(7.0)
Cerebral amyloid angiopathy	2 (0.5)	3 (0.3)
Whole brain weight	-	6 (0.6)

UK-ADRC, University of Kentucky Alzheimer's Disease Research Center; NACC, National Alzheimer's Coordinating Center.

Figure 3.2a: Group-based Multi-trajectory Modeling was used to Identify End-of-life Latent Cognitive Trajectories in Autopsied Research Volunteers (UK-ADRC). Within Each Cohort, there is a 1:1 Correspondence of Group Membership in the Plots

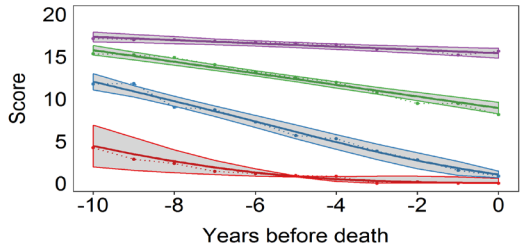
UK-ADRC

Mini-Mental State Examination



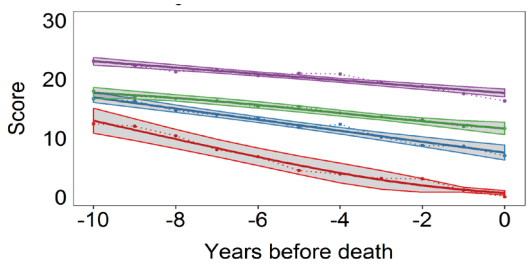
Years	No	Mild	Moderate	Accelerated
-10 yrs	29.2 (29.2-29.2)	28.6 (28.4-28.9)	27.7 (26.7-28.7)	18.4 (17.3-19.5)
-6 yrs	28.7 (28.6-28.8)	27.4 (27.0-27.7)	24.6 (23.8-25.5)	12.1 (11.4-12.8)
-3 yrs	28.3 (28.0-28.5)	26.2 (25.6-26.8)	19.9 (19.2-20.6)	7.4 (6.4-8.5)
< -1 yrs	27.8 (27.2-28.3)	24.9 (23.9-26.0)	10.6 (8.5-12.7)	3.3 (1.8-4.8)

Logical Memory (Immediate recall)



Years	No	Mild	Moderate	Accelerated
-10 yrs	17.3 (16.7-17.9)	15.7 (15.2-16.3)	12.0 (11.0-12.9)	4.4 (1.9-6.9)
-6 yrs	16.5 (16.2-16.8)	13.0 (12.7-13.3)	7.3 (6.6-8.0)	1.3 (0.8-1.7)
-3 yrs	16.0 (15.6-16.3)	10.9 (10.5-11.4)	3.7 (2.8-4.6)	0.3 (0.0-0.8)
< -1 yrs	15.4 (14.8-16.0)	8.9 (8.2-9.6)	1.0 (0.7-1.4)	0.0 (0.0-0.6)

Animal Naming Test



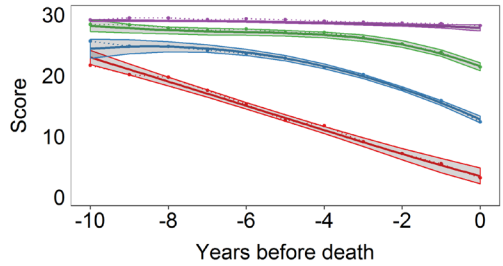
Years	No	Mild	Moderate	Accelerated
-10 yrs	23.0 (22.4-23.7)	17.6 (16.7-18.6)	16.9 (16.0-17.8)	12.9 (10.8-15.1)
-6 yrs	20.9 (20.5-21.2)	15.6 (15.0-16.2)	13.1 (16.0-13.6)	6.8 (5.3-8.3)
-3 yrs	19.3 (18.8-19.7)	13.5 (13.0-14.0)	10.3 (16.0-11.0)	2.9 (1.3-4.5)
< -1 yrs	17.6 (17.0-18.3)	11.6 (10.6-12.7)	7.5 (16.0-8.8)	0.7 (0.3-1.1)

Number of trajectory groups are based on most parsimonious multi-trajectory models. Trajectory groups: No Decline (purple), Mild Decline (green), Moderate decline (blue) and Accelerated Decline (red).Shaded areas are 95% CI. The tables present test scores 10, 6, 3, and in <1 year before death.

Figure 3.2b: Group-based Multi-trajectory Modeling was used to Identify End-of-life Latent Cognitive Trajectories in Autopsied Research Volunteers (NACC)

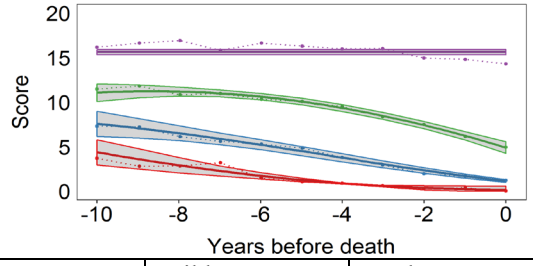
NACC

Mini-Mental State Examination



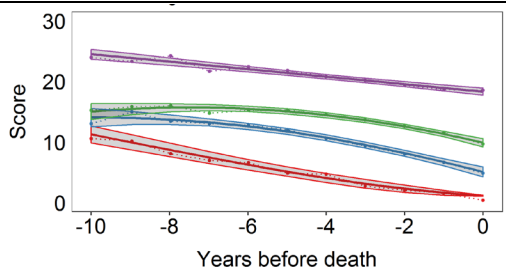
Years	No	Mild	Moderate	Accelerated
-10 yrs	29.0 (28.9-29.2)	28.2 (27.2-29.1)	24.3 (22.7-25.9)	22.9 (21.8-24.1)
-6 yrs	28.8 (28.7-28.9)	27.0 (26.5-29.3)	23.7 (23.2-24.2)	14.9 (14.4-15.5)
-3 yrs	28.5 (28.3-28.7)	26.0 (25.5-28.7)	19.7 (19.4-20.1)	8.9 (8.2-9.6)
< -1 yrs	27.8 (27.3-28.3)	21.2 (20.5-28.1)	12.7 (12.1-13.2)	3.4 (2.1-4.6)

Logical Memory (Immediate recall)



Years	No	Mild	Moderate	Accelerated
-10 yrs	17.3 (16.6-18.0)	11.1 (10.1-12.1)	7.4 (5.9-8.9)	4.4 (3.0-5.8)
-6 yrs	16.2 (15.8-16.5)	10.5 (10.2-10.9)	5.1 (4.5-5.7)	1.7 (1.4-2.1)
-3 yrs	15.3 (15.1-15.6)	8.3 (8.0-8.7)	3.0 (2.6-3.4)	0.6 (0.5-0.7)
< -1 yrs	14.5 (14.1-14.9)	4.8 (4.1-5.4)	1.1 (1.0-1.3)	0.1 (0.0-0.5)

Animal Naming Test



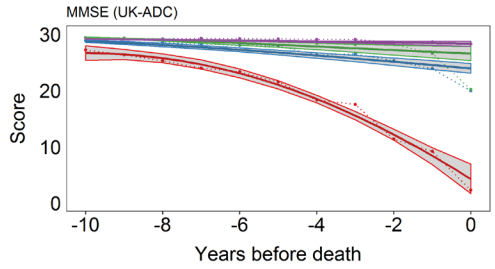
Years	No	Mild	Moderate	Accelerated
-10 yrs	24.5 (23.7-25.3)	15.0 (13.7-16.3)	14.0 (12.5-15.5)	11.3 (9.9-12.7)
-6 yrs	22.0 (21.5-22.4)	15.5 (15.0-15.9)	12.5 (12.0-13.1)	6.3 (5.4-7.1)
-3 yrs	20.1 (19.7-20.5)	13.6 (13.2-14.0)	9.5 (9.0-10.0)	3.2 (2.4-3.9)
< -1 yrs	18.2 (17.6-18.8)	9.8 (9.1-10.5)	5.1 (4.2-5.9)	1.1 (1.1-1.2)

Number of trajectory groups are based on most parsimonious multi-trajectory models. Trajectory groups: No Decline (purple), Mild Decline (green), Moderate decline (blue) and Accelerated Decline (red). Shaded areas are 95% CI. The tables present test scores 10, 6, 3, and in <1 year before death.

Figure 3.3a: Group-based Multi-trajectory Modeling was used to Identify End-of-life Latent Cognitive Trajectories in Autopsied Research Volunteers Who Started as Cognitively Normal.

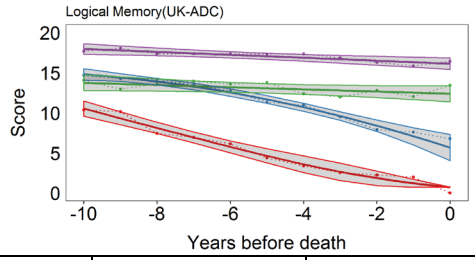
UK-ADRC

Mini-Mental State Examination



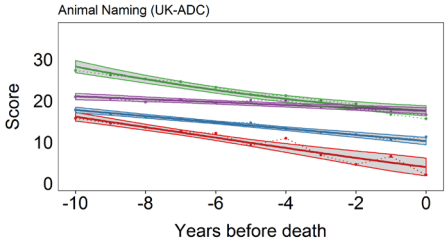
Years	No	Mild	Moderate	Accelerated
-10 yrs	29.1 (29.1-29.2)	29.4 (29.3-29.5)	28.8 (28.5-29.0)	26.6 (25.4-28.0)
-6 yrs	28.8 (28.7-29.0)	28.4 (28.1-28.8)	27.2 (26.9-27.6)	23.0 (22.2-23.8)
-3 yrs	28.6 (28.4-28.8)	27.4 (26.8-28.2)	25.7 (25.1-26.2)	15.5 (14.8-16.3)
< -1 yrs	28.3 (27.9-28.7)	26.5 (25.3-27.8)	23.9 (23.1-24.8)	4.3 (1.6-6.9)

Logical Memory (Immediate recall)



Years	No	Mild	Moderate	Accelerated
-10 yrs	18.0 (17.3-18.6)	13.7 (12.7-14.7)	14.8 (14.1-15.5)	10.5 (9.5-11.5)
-6 yrs	17.2 (16.8-17.6)	13.1 (12.6-13.8)	12.5 (12.1-13.0)	5.8 (5.0-6.5)
-3 yrs	16.7 (16.2-17.2)	12.8 (12.1-13.4)	9.5 (9.1-10.1)	2.6 (1.6-3.7)
< -1 yrs	16.1 (15.4-16.8)	12.4 (11.4-13.4)	4.7 (4.0-7.3)	0.7 (0.7-0.7)

Animal Naming test

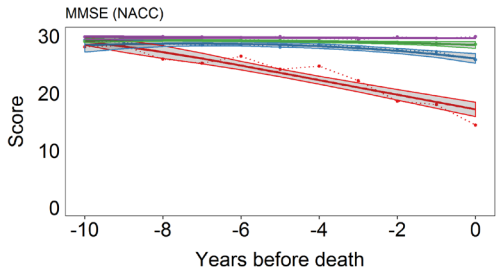


Years	No	Mild	Moderate	Accelerated
-10 yrs	21.0 (20.3-21.7)	28.2 (26.7-29.7)	17.7 (17.1-18.4)	16.1 (15.0-17.1)
-6 yrs	19.6 (19.2-20.1)	22.5 (21.8-23.3)	14.7 (14.4-15.1)	11.0 (10.4-11.7)
-3 yrs	18.6 (18.0-19.1)	19.5 (18.6-20.4)	12.5 (11.9-13.0)	7.3 (6.0-8.7)
< -1 yrs	17.5 (16.7-18.3)	17.5 (16.3-18.7)	10.2 (9.3-11.1)	3.9 (1.8-6.1)

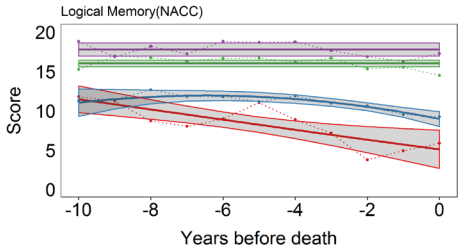
Number of trajectory groups are based on most parsimonious multi-trajectory models. Trajectory groups: No Decline (purple), Mild Decline (green), Moderate decline (blue) and Accelerated Decline (red). Shaded areas are 95% CI. The tables present test scores 10, 6, 3, and in < 1 year before death. UK-ADRC, University of Kentucky-Alzheimer's Disease Center.

Figure 3.3b: Group-based Multi-trajectory Modeling was used to Identify End-of-life Latent Cognitive Trajectories in Autopsied Research Volunteers Who Started as Cognitively Normal

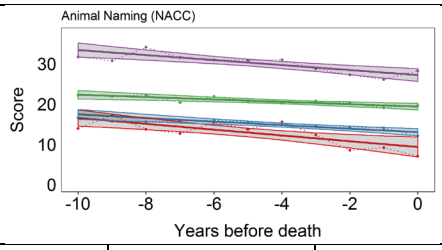
NACC



Years	No	Mild	Moderate	Accelerated
-10 yrs	29.7 (29.4-30.0)	29.2 (28.8-29.5)	28.4 (27.2-29.5)	29.0 (28.3-29.6)
-6 yrs	29.7 (29.5-29.8)	29.1 (29.0-29.3)	28.6 (28.2-28.9)	24.8 (24.0- 25.5)
-3 yrs	29.6 (29.5-297)	28.9 (28.7-29.1)	27.3 (27.4-28.3)	21.0 (20.2-21.8)
< -1 yrs	29.6 (29.5-29.7)	28.4 (27.8-29.0)	26.0 (25.2-26.9)	17.2 (15.9-18.4)



Years	No	Mild	Moderate	Accelerated
-10 yrs	17.8 (16.9-18.6)	16.0 (15.6-16.4)	11.0 (9.3-12.8)	11.5 (9.8-13.1)
-6 yrs	17.8 (16.9-18.6)	16.0 (15.6-16.4)	11.9 (11.3-12.5)	8.9 (7.9-9.8)
-3 yrs	17.8 (16.9-18.6)	16.0 (15.6-16.4)	11.1 (10.6-11.6)	6.9 (5.6-83)
< -1 yrs	17.8 (16.9-18.6)	16.0 (15.6-16.4)	8.9 (8.0-9.9)	5.1 (2.7-7.5)



Years	No	Mild	Moderate	Accelerated
-10 yrs	33.4 (31.6-35.1)	22.3 (21.2-23.3)	17.4 (16.1-18.7)	16.5 (14.5-18.5)
-6 yrs	30.9 (30.0-31.8)	21.1 (20.5-21.7)	15.6 (15.0-16.3)	13.6 (12.5-14.7)
-3 yrs	29.0 (28.0-30.0)	20.2 (19.7-20.7)	14.3 (13.8-14.8)	11.5 (10.1-12.8)
< -1 yrs	27.2 (25.6-28.8)	19.3 (18.5-20.1)	13.0 (12.1-13.9)	9.3 (6.8-11.8)

Number of trajectory groups are based on most parsimonious multi-trajectory models. Trajectory groups: No Decline (purple), Mild Decline (green), Moderate decline (blue) and Accelerated Decline (red).Shaded areas are 95% CI. The tables present test scores 10, 6, 3, and in < 1 year before death. NACC, National Alzheimer's Coordinating Center.

Table 3.3: UK-ADRC Participant Characteristics by Trajectory Group (N=365)

Variable	No Decline	Mild Decline	Moderate Decline	Accelerated Decline
N (%)	102 (27.9)	108 (29.6)	94 (25.8)	61 (16.7)
Age at death, y mean (SD)	87.1 (6.1)	89.0 (6.7)	87.6 (8.8)	82.4 (9.6)
Female sex	60 (58.8)	64 (59.3)	60 (63.8)	44 (72.1)
Race (White)	102 (100.0)	101 (93.5)	91 (96.8)	60 (98.4)
Education, y mean (SD)	16.7 (2.6)	15.7 (2.8)	15.1 (3.1)	14.4 (3.4)
APOE ε4 allele (≥1 allele)	28 (27.5)	32 (29.6)	38 (40.4)	34 (55.7)
Last Clinical Diagnosis				
Normal	72 (70.6)	30 (27.8)	2 (2.1)	0
Impaired/Other	5 (4.9)	4 (3.7)	1 (1.0)	0
MCI	15 (14.7)	27 (25.0)	3 (3.2)	0
Dementia	10 (9.8)	47 (43.5)	88 (93.6)	60 (98.4)
Whole brain weight (g) mean (SD)	1212.1 (134.2)	1164.9 (141.9)	1113.7 (174.3)	1056.1 (136.6)
Aβ Plaques (present)	81 (79.4)	92 (85.2)	85 (90.4)	59 (96.7)
α-synuclein (present)	24 (23.5)	27 (25.0)	32 (34.0)	29 (47.5)
TDP-43 inclusion bodies	20 (19.6)	35 (31.0)	48 (50.0)	39 (60.9)
Braak NFT stage				
I to IV	87 (85.3)	70 (64.8)	27 (28.7)	6 (9.8)
V to VI	15 (14.7)	38 (36.2)	67 (71.3)	55 (90.2)
Cerebral atrophy				
None/Mild	93 (91.2)	87 (80.6)	44 (46.8)	10 (31.2)
Moderate/Severe	8 (7.8)	20 (18.5)	49 (52.1)	41 (67.2)
Hippocampal Sclerosis	9 (8.8)	16 (14.8)	37 (39.4)	28 (45.9)
Cerebral amyloid angiopathy				
None/Mild	87 (85.3)	83 (76.8)	70 (74.5)	34 (55.7)
Moderate/severe	15 (14.7)	25 (23.2)	23 (24.5)	26 (42.6)
Atherosclerosis				
<50% Occluded	48 (47.1)	37 (34.3)	37 (39.4)	21 (34.4)
≥ 50% Occluded	54 (52.9)	71 (65.7)	56 (59.6)	37 (60.7)
Arteriosclerosis				
None/Mild	64 (62.8)	70 (64.8)	64 (68.1)	33 (54.1)
Moderate/Severe	26 (25.5)	28 (25.9)	23 (24.5)	13 (21.3)
Infarcts/Lacunes				
Yes	58 (56.9)	53 (49.1)	53 (56.4)	37 (60.7)
No	44 (43.1)	55 (50.9)	41 (43.6)	24 (39.3)

Mean (SD) or proportion as shown. SD, standard deviation; Abbreviations: UK-ADRC, University of Kentucky-Alzheimer's Disease Research Center; *.APOE,* Apolipoprotein; Aβ, Amyloid-β; TDP-43, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangles; HS, Hippocampal Sclerosis**.**
Missing data are reported in Table 3.2.

Table 3.4: UK-ADRC Participant Characteristics by Trajectory Group Among Participants Who Started as Cognitively Normal (n=228)

Variable	No Decline	Mild Decline	Moderate Decline	Accelerated Decline
N (%)	78 (34.2)	31 (13.6)	85 (37.3)	34 (14.9)
Age at death, y mean (SD)	87.0 (6.0)	87.5 (6.9)	91.0 (5.6)	90.8 (6.8)
Female sex	50 (64.1)	15 (48.4)	54 (63.5)	30 (88.2)
Race (White)	78 (100.0)	30 (96.8)	82 (96.5)	34 (100.0)
Education, y mean (SD)	16.3 (2.5)	17.3 (3.6)	15.2 (2.2)	16.2 (2.3)
APOE ≥ 1ε4 allele	16 (20.5)	12 (38.7)	30 (35.3)	15 (44.1)
Last Clinical Diagnosis				
Normal	66 (84.6)	17 (48.2)	22 (27.1)	0
Impaired/Other	2 (2.6)	1 (3.2)	3 (3.5)	0
MCI	7 (8.9)	8 (25.0)	19 (22.3)	1 (2.9)
Dementia	3 (3.9)	7 (22.6)	40 (47.1)	33 (97.1)
Whole brain weight (g) Mean (SD)	1201.2 (127.2)	1223.5 (157.2)	1145.5 (128.5)	1071.9 (106.2)
Aβ plaques (present)	61 (78.2)	25 (80.7)	75 (88.2)	30 (88.2)
α-synuclein (present)	16 (20.5)	5 (16.1)	16 (18.8)	14 (41.2)
TDP-43 inclusion bodies	15 (19.2)	7 (22.6)	29 (34.1)	20 (58.8)
Braak NFT stage				
I to IV	72 (92.3)	20 (64.5)	52 (61.2)	8 (22.5)
V to VI	6 (7.7)	11 (35.5)	33 (38.8)	26 (76.5)
Cerebral atrophy				
None/Mild	75 (96.2)	26 (83.9)	68 (80.0)	10 (29.4)
Moderate/Severe	2 (2.6)	5 (16.1)	16 (18.8)	24 (70.6)
HS (present)	4 (5.2)	6 (19.4)	15 (17.7)	19 (55.9)
Cerebral amyloid angiopathy				
None/Mild	68 (88.3)	23 (74.2)	60 (72.9)	26 (70.6)
Moderate/Severe	9 (11.5)	8 (27.1)	23 (27.1)	10 (29.4)
Atherosclerosis				
<50% Occluded	33 (42.3)	16 (51.6)	29 (34.1)	9 (26.5)
≥ 50% Occluded	45 (57.7)	15 (48.4)	56 (65.9)	25 (75.5)
Arteriosclerosis				
None/Mild	53 (68.0)	17 (54.8)	54 (63.5)	21 (61.8)
Moderate/Severe	15 (19.2)	11 (24.7)	21 (24.7)	13 (38.2)
Infarcts/Lacunes				
No	47 (60.3)	14 (45.2)	36 (42.4)	17 (50.0)
Yes	31 (39.7)	17 (54.8)	49 (57.6)	17 (50.0)

Mean (SD) or proportion as shown. SD, standard deviation; Abbreviations: UK-ADRC, University of Kentucky Alzheimer's Disease Research Center; .*APOE* Apolipoprotein E; Aβ, Amyloid-β; TDP-43, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangles; HS, Hippocampal Sclerosis**.**

Table 3.5: NACC Participant Characteristics by Trajectory Group (N=981)

Variable	No Decline	Mild Decline	Moderate Decline	Accelerated Decline
	157(16.0)	**307(31.3)**	**376(38.3)**	**141(14.4)**
Age at death, y, mean (SD)	85.1 (8.3)	82.2 (9.5)	79.1 (9.1)	76.9 (10.2)
Female sex	69 (44.0)	134 (43.7)	174 (46.3)	77 (54.6)
Race (White)	147 (93.6)	288 (93.8)	353 (93.9)	123 (87.2)
Education, y, mean (SD)	16.5 (2.9)	15.4 (3.1)	15.1 (3.1)	15.3 (3.3)
APOE ε4 allele (≥1 allele)	41 (26.1)	129 (42.0)	215 (57.2)	64 (45.4)
Last Clinical Diagnosis				
Normal	74 (47.1)	11 (3.6)	0	0
Impaired/Other	13 (8.3)	4 (1.3)	1 (0.3)	0
MCI	42 (26.8)	31 (10.1)	0	0
Dementia	28 (17.8)	261 (85.0)	375 (99.7)	141 (100.0)
Whole brain weight (g) Mean (SD)	1226.4 (137.8)	1193.6 (164.5)	1136.3 (148.6)	1029.2 (190.7)
Aβ Plaques	129 (82.2)	278 (90.6)	367 (97.6)	136 (96.5)
α-synuclein	31 (19.8)	124 (40.4)	157 (41.8)	68 (48.2)
TDP-43 inclusion bodies	20 (12.7)	70 (22.8)	121 (32.2)	52 (36.9)
Braak NFT stage				
I to IV	124 (79.0)	137 (44.6)	58 (15.4)	17 (12.1)
V to VI	33 (21.0)	170 (55.4)	318 (84.6)	124 (87.9)
Cerebral atrophy				
None/Mild	109 (69.4)	188 (61.2)	168 (44.7)	23 (16.3)
Moderate/Severe	28 (19.1)	99 (32.3)	189 (50.3)	106 (75.2)
Hippocampal Sclerosis	11 (7.0)	32 (10.4)	73 (19.4)	28 (19.9)
Cerebral amyloid angiopathy				
None/Mild	126 (82.9)	216 (70.8)	208 (54.5)	72 (50.7)
Moderate/Severe	25 (16.5)	88 (28.9)	173 (45.3)	70 (49.3)
Atherosclerosis				
<50% Occluded	95 (60.5)	200 (65.2)	241 (64.1)	77 (54.6)
≥ 50% Occluded	62 (39.5)	105 (34.2)	132 (35.1)	63 (44.7)
Arteriosclerosis				
None/Mild	91 (58.0)	137 (44.6)	163 (42.7)	48 (34.0)
Moderate/Severe	65 (41.4)	168 (54.7)	214 (56.0)	92 (65.3)
Infarcts/Lacunes				
No	99 (63.1)	200 (65.2)	251 (66.8)	106 (75.2)
Yes	57 (36.9)	106 (34.5)	123 (32.7)	35 (24.8)

Mean (SD) or proportion as shown. SD, standard deviation; Abbreviations: NACC, National Alzheimer's Coordinating Center. *APOE,* Apolipoprotein; Aβ, Amyloid-β; TDP, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangles. Missing data are reported in Table 3.2.

Table 3.6: NACC Participant Characteristics by Trajectory Group Among Participants Who Started as Cognitively Normal (n=163)

Variable	No Decline	Mild Decline	Moderate Decline	Accelerated Decline
	15 (9.2%)	69 (42.3%)	67 (41.1%)	12 (7.4%)
Age at death, y mean (SD)	84.8 (6.2)	86.4 (8.3)	88.4 (6.6)	89.8 (11.8)
Female sex	12 (80.0)	32 (46.4)	43 (64.2)	11 (91.7)
Race (White)	15 (100.0)	67 (97.1)	57 (85.1)	11 (91.7)
Education, y mean (SD)	16.7 (3.0)	16.4 (3.1)	15.1 (2.8)	15.5 (3.0)
APOE ε4 allele (≥1 allele)	4 (26.7)	16 (23.2)	19 (28.4)	7 (58.3)
Last Clinical Diagnosis				
Normal	9 (60.0)	47 (68.1)	19 (28.4)	0
Impaired/Other	2 (13.3)	2 (2.9)	7 (10.4)	0
MCI	3 (20.0)	13 (18.8)	16 (23.9)	1 (8.3)
Dementia	1 (6.7)	7 (10.1)	25 (37.3)	11 (91.7)
Whole brain weight (g) mean (SD)	1215.9 (108.7)	1228.7 (148.8)	1159.0 (191.6)	1085.6 (83.0)
Aβ plaques	12 (80.0)	54 (78.3)	60 (89.6)	12 (100.0)
α-synuclein	2 (13.3)	12 (17.4)	12 (17.9)	1 (8.3)
TDP-43 inclusion bodies	2 (13.3)	7 (10.1)	8 (11.9)	3 (25.0)
Braak NFT stage				
I to IV	11 (73.3)	59 (85.5)	46 (68.7)	4 (33.3)
V to VI	4 (26.7)	10 (14.5)	21 (31.3)	8 (66.7)
Cerebral atrophy				
None/Mild	11 (73.3)	49 (71.0)	49 (73.1)	3 (25.0)
Moderate/Severe	1 (6.7)	13 (18.8)	15 (22.4)	9 (75.0)
HS	0 (0.0)	5 (7.3)	6 (8.9)	0 (0.0)
Cerebral amyloid angiopathy				
None	14 (93.3)	60 (87.0)	49 (73.1)	8 (66.7)
Moderate/Severe	1 (6.7)	9 (13.0)	18 (26.9)	4 (33.3)
Atherosclerosis				
<50% Occluded	9 (60.0)	40 (58.0)	37 (55.2)	6 (50.0)
≥ 50% Occluded	6 (40.0)	29 (42.0)	30 (44.8)	6 (50.0)
Arteriosclerosis				
None/Mild	9 (60.0)	41 (59.4)	30 (44.8)	5 (41.7)
Moderate/Severe	6 (40.0)	28 (40.6)	37 (55.2)	6 (50.0)
Infarcts /Lacunes				
No	14 (93.3)	62 (89.9)	52 (77.6)	11 (91.7)
Yes	1 (6.7)	7 (10.6)	15 (22.4)	1 (8.3)

Mean (SD) or proportion as shown. SD, standard deviation; Abbreviations: NACC, National Alzheimer's Coordinating Center. *APOE*, Apolipoprotein E; Aβ, Amyloid-β; TDP-43, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangles.

Table 3.7: Multinomial Logistic Regression was used to Estimate Adjusted Odds Ratios (AOR) of Membership in a Group with Cognitive Decline vs. No Decline Within Cohorts. Results are Based on Models Fully Adjusted for all Variables Listed

Variable	Accelerated vs No	Moderate vs No	Mild vs No
UK-ADRC (n=365)		**AOR (95%CI)**	
Age at death (5-yr increase)	**0.68 (0.51-0.92)**	1.14 (0.89-1.46)	1.24 (0.99-1.54)
Sex	1.98 (0.75-5.19)	0.80 (0.38-1.70)	0.71 (0.38-1.33)
Education	**0.71 (0.61-0.83)**	**0.77 (0.68-0.88)**	**0.83 (0.73-0.93)**
APOE ε4 allele ≥1 vs 0	1.17 (0.47-2.94)	0.91 (0.33-1.76)	0.84 (0.42; 1.75)
Braak NFT stage (V to VI) vs (I to IV)	**43.95 (12.00-163.98)**	**17.69 (7.63-44.10)**	**3.58 (1.66-7.70)**
TDP-43 Yes vs No	**3.52 (1.04-12.87)**	1.53 (0.55-4.14)	1.51 (0.63-3.63)
Aβ Yes vs No	1.10 (0.16-7.54)	0.84 (0.28-2.53)	1.20 (0.52-2.77)
α-Synuclein Yes vs No	1.61 (0.52-3.98)	1.50 (0.67-3.15)	1.14 (0.56-2.20)
Atherosclerosis >50% vs <50% Occluded	2.03 (0.80-5.54)	1.14 (0.66-2.75)	1.54 (0.84-2.93)
Arteriosclerosis Mod/Severe vs Mild/None	0.74 (0.28-2.19)	0.96 (0.33-1.74)	0.98 (0.40-1.82)
HS Yes vs No	**8.78 (2.25-33.28)**	**5.96 (1.89-20.86)**	1.34 (0.43-4.03)
NACC (n=981)		**AOR (95%CI)**	
Age at death (5yr increase)	**0.57 (0.48-0.67)**	**0.69 (0.60-0.79)**	**0.88 (0.77-1.00)**
Sex	1.14 (0.65-2.02)	0.79 (0.49-1.29)	0.79 (0.50-1.25)
Education	**0.82 (0.74-0.89)**	**0.81 (0.75-0.89)**	**0.86 (0.80-0.92)**
APOE ε4 allele ≥1 vs 0	1.70 (0.95-3.06)	**2.17 (1.31-3.58)**	1.55 (0.96-2.50)
Braak NFT stage (V to VI) vs (I to IV)	**26.18 (12.07-56.82)**	**14.48 (8.38-25.02)**	**3.93 (2.38-6.50)**
TDP-43 Yes vs No	**4.32 (2.07- 8.99)**	**3.36 (1.75-6.44)**	**2.23 (1.19-4.18)**
Aβ Yes vs No	0.65 (0.19-2.22)	1.53 (0.62-3.82)	0.96 (0.51-1.83)
α-synuclein Yes vs No	**2.54 (1.37- 4.68)**	**2.23 (1.30-3.82)**	**2.52 (1.51-4.21)**
Atherosclerosis >50% vs <50% occluded	1.65 (0.90-3.03)	1.02 (0.61-1.72)	0.80 (0.50-1.30)
Arteriosclerosis Mod/Severe vs Mild/None	**3.05 (1.69-5.49)**	**1.92 (1.18-3.12)**	**1.75 (1.11-2.75)**
HS Yes vs No	2.41 (0.95-6.16)	**2.56 (1.11-5.93)**	1.37 (0.60-3.13)

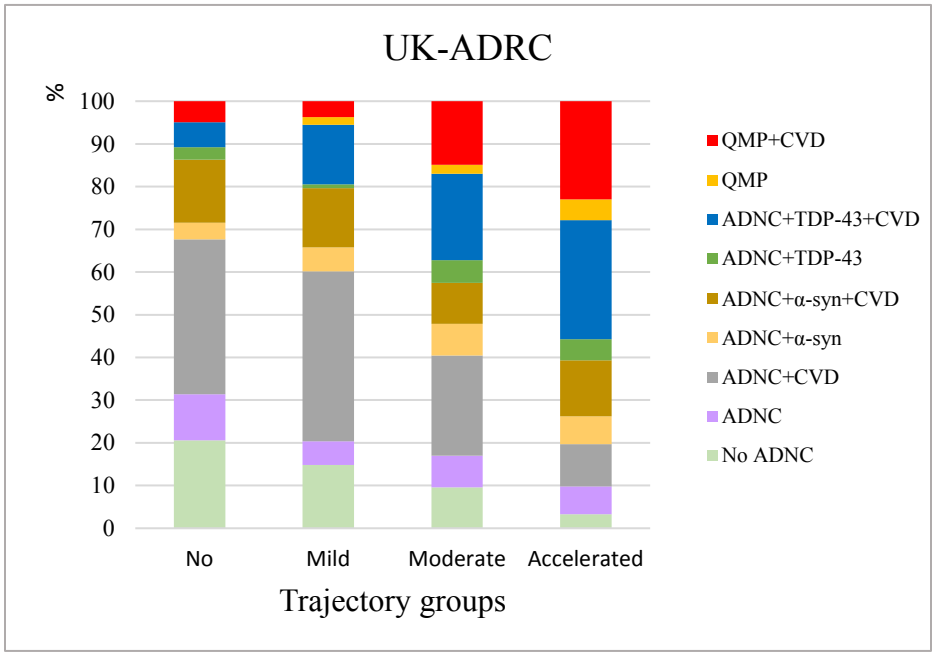
No Decline group was the reference; Abbreviations: AOR, adjusted odds ratio; CI, 95 % confidence intervals; *APOE*, Apolipoprotein E; Aβ, Amyloid-β; TDP, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangle; HS, Hippocampal Sclerosis.

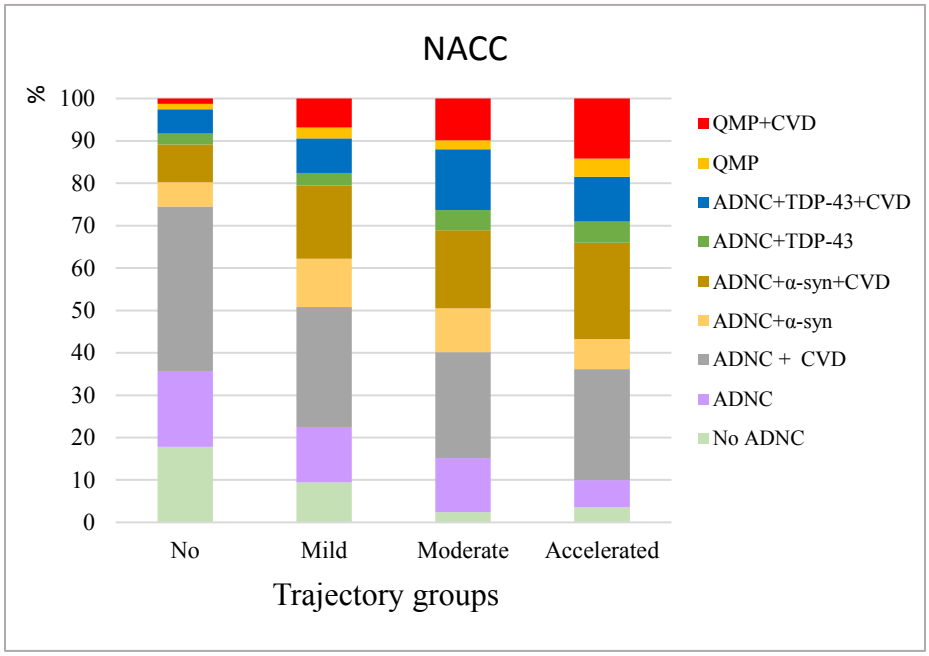
Table 3.8: Multinomial Logistic Regression based on Complete Case Analysis to Estimate Adjusted Odds Ratios (AOR) of Membership in a Group with Cognitive Decline vs. No Decline Within Cohorts. Results are Based on Models Fully Adjusted for all Variables Listed

Variable	Accelerated vs No	Moderate vs No	Mild vs No
UK-ADRC	**AOR (95%CI)**		
Age at death (5yr increase)	**0.68 (0.44 - 0.90)**	1.26 (0.97 - 1.64)	1.24 (98 - 1.57)
Sex Female vs Male	2.04 (0.63 – 6.59)	0.58 (0.26 -1.32)	0.60 (0.30 – 1.21)
Education	**0.70 (0.58 – 0.84)**	**0.79 (0.68 - 0.91)**	**0.82 (0.72 – 0.94)**
APOE ε4 allele ≥1 vs 0	0.83 (0.28 - 2.51)	1.05 (0.45 - 2.41)	0.96 (0.45 - 2.03)
Braak NFT stage (V to VI) vs (I to IV)	**35.92 (8.13-158.13)**	**19.26 (7.47 - 49.66)**	**3.18 (1.37 - 7.42)**
TDP-43 Yes vs No	**4.79 (1.08 - 21.34)**	2.13 (0.67 - 6.79)	2.61 (0.95 - 7.18)
Aβ Yes vs No	1.82 (0.15 - 22.63)	0.69 (0.22, 2.22)	1.50 (0.60, 3.75)
α-Synuclein Yes vs No	1.71 (0.57 - 5.10)	1.39 (0.57 - 3.23)	0.89 (0.41, 1.94)
Atherosclerosis >50% vs <50% Occluded	**6.44 (1.85 - 22.48)**	1.43 (0.65 - 3.18)	**1.99 (1.01 - 3.94)**
Arteriosclerosis Mod/Severe vs Mild/None	0.58 (0.18 - 1.82)	0.79 (0.34, 1.84)	0.87 (0.42, 1.79)
HS Yes vs No	4.26 (0.89 - 21.26)	2.85 (0.78 - 10.38)	0.81 (0.24 - 2.71)
NACC	**AOR (95%CI)**		
Age at death (5yr increase)	**0.53 (0.44 - 0.64)**	**0.67 (0.58 - 0.78)**	**0.85 (0.74 - 0.98)**
0Sex Female vs Male	**1.15 (0.61 - 2.14)**	**0.83 (0.50 – 1.38)**	**0.88 (0.54 - 1.41)**
Education	**0.85 (0.77 – 0.95)**	**0.82 (0.75 – 0.89)**	**0.88 (0.82 – 0.95)**
APOE ε4 allele ≥1 vs 0	1.73 (0.92 - 3.25)	**2.07 (1.23 - 3.48)**	1.56 (0.95 - 2.56)
Braak NFT stage (V to VI) vs (I to IV)	**28.45 (11.67-69.35)**	**15.40 (8.71 - 27.21)**	**3.48 (2.09- 5.81)**
TDP-43 Yes vs No	**4.18 (1.91 - 9.13)**	**3.20 (1.66 - 6.18)**	**2.11 (1.12 - 4.00)**
Aβ Yes vs No	0.98 (0.17 - 5.55)	1.38 (0.50 - 3.78)	0.81 (0.41 - 1.61)
α-synuclein Yes vs No	**2.34 (1.20 - 4.55)**	**2.16 (1.23 - 3.79)**	**2.62 (1.54 - 4.48)**
Atherosclerosis >50% vs <50% occluded	**1.97 (1.01 - 3.82)**	1.08 (0.63 - 1.86)	0.97 (0.58, 1.59)
Arteriosclerosis Mod/Severe vs Mild/None	**3.00 (1.58 - 5.70)**	**1.95 (1.17 - 3.25)**	**1.88 (1.17 - 3.03)**
HS Yes vs No	2.13 (0.78 - 5.75)	2.07 (0.87 - 4.92)	1.31 (0.57 - 3.03)

Results are from Multinomial logistic regression models, No Decline group was the reference. Abbreviations: AOR, adjusted odds ratio; CI, 95 % confidence intervals; *APOE,* Apolipoprotein E; Aβ, Amyloid-β; TDP, transactive response DNA binding protein 43 kDa; NFT, Neurofibrillary tangle; HS, Hippocampal Sclerosis.

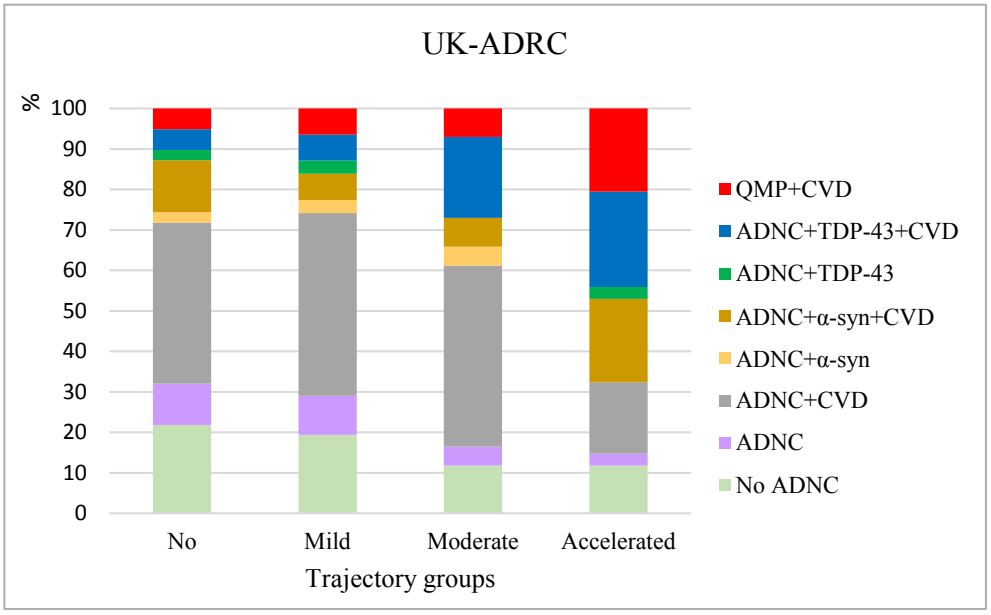
Figure 3.4: Distribution of Neuropathology Combinations by Trajectory Groups

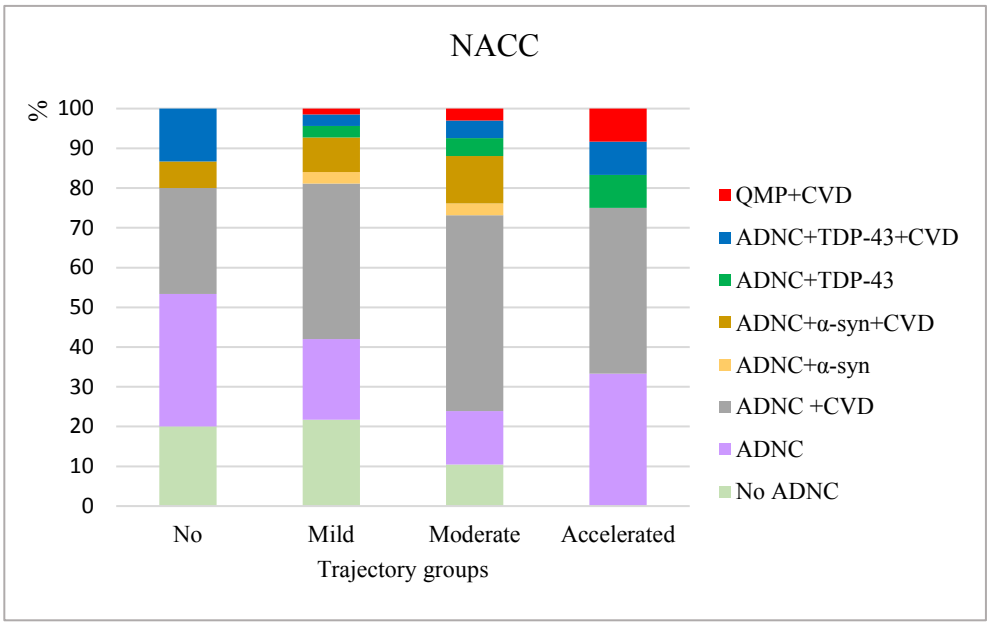




Abbreviations: ADNC, Alzheimer's disease neuropathologic change; No ADNC, Tau alone or Tau +CVD or Tau +TDP-43; Aβ, Amyloid-β; TDP, transactive response DNA binding protein 43 kDa; QMP, quadruple misfolded proteins, α-syn, α-synuclein; CVD, presence of at least one of the three: Atherosclerosis(>50% Occluded), Arteriosclerosis (Moderate/Severe) and presence of Infarcts/Lacunes.

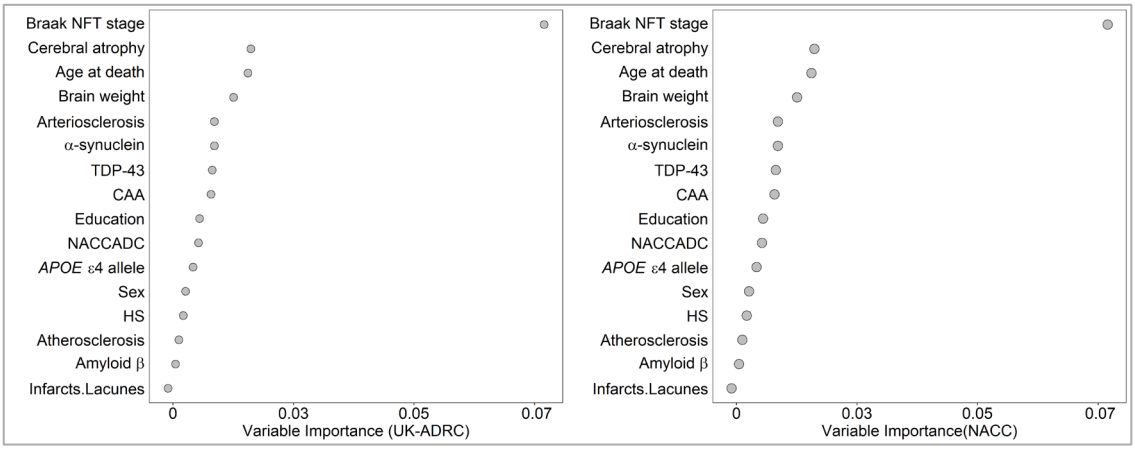
Figure 3.5: Distribution of Neuropathology Combinations by Trajectory Groups Among Participants Who Started as Cognitively Normal at Baseline





Abbreviations: ADNC, Alzheimer's disease neuropathologic change; No ADNC, Tau alone or Tau +CVD or Tau +TDP-43; Aβ, Amyloid-β; TDP, transactive response DNA binding protein 43 kDa; QMP, quadruple misfolded proteins, α-syn, α-synuclein; CVD, presence of at least one of the three: Atherosclerosis(>50% Occluded), Arteriosclerosis (Moderate/Severe) and presence of Infarcts/Lacunes.

Figure 3.6: Random Forest Results Indicate the Strength of Association for Each Variable With Overall Trajectory Membership Within Each Cohort



Variables ranked based on Mean Decrease Accuracy.
Abbreviations: NFT, Neurofibrillary tangle; *APOE*, Apolipoprotein E; Aβ, Amyloid-β; TDP-43, transactive response DNA binding protein 43 kDa; HS, Hippocampal Sclerosis; CAA, Cerebral amyloid angiopathy.

CHAPTER FOUR

Cancer history associates with a lower burden of dementia and Alzheimer's-type neuropathology in autopsied research volunteers

Abstract

Background

Cancer and Alzheimer's disease (AD) are common diseases in aging populations. Intriguingly, prior research has reported a lower incidence of AD dementia among individuals with a history of cancer. The current study was conducted to investigate the association of cancer history with neuropathological and cognitive features.

Methods

Data were drawn from elderly, longitudinally evaluated participants in a community-based cohort study of aging and dementia who came to autopsy at the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC). The UK-ADRC data were linked to the Kentucky Cancer Registry (KCR), which is a population-based state cancer surveillance system, to obtain cancer-related data. We examined the relationship between cancer history and neuropathological features and clinical diagnoses using inverse probability weighting to address confounding and selection bias. We investigated the relation between 20 putative risk single nucleotide polymorphisms that are associated with AD and cancer history.

Results

Included participants (n=785) had a mean (±SD) age of death of 83.8 (±8.6) years; 60.1% were female. History of cancer was ascertained in 190 (24.2%) participants. The prevalence of at least one *APOE* ε4 allele was lower among participants with cancer history compared to cancer-free participants (32.6% vs 42%). Participants with cancer

history had significantly lower odds of MCI/Dementia at the last UK-ADRC visit, as well as lower odds of Braak neurofibrillary tangle stages III/IV (OR=0.52; 95%CI, 0.34, 0.79; P = 0.0147) and V/VI (OR=0.38; 95%CI, 0.26, 0.55, P < 0.0001) vs. 0/I/II. Cancer history was also associated with reduced odds of moderate/frequent neuritic plaques, moderate/frequent diffuse plaques, and moderate/frequent cerebral amyloid angiopathy. TDP-43, α-synuclein, and cerebrovascular pathologies were not associated with cancer history. The investigation of AD-associated genes showed that history of cancer was inversely associated with *APOE* ε4 carrier status, and positively associated with T allele of SNP rs11136000 located in the *CLU* gene on chromosome 8.

Conclusion

In this study, we showed that cancer history was associated with a lower burden of AD pathology and have reduced burden of clinical dementia. These findings provide an additional basis of support for prior epidemiological research reporting a protective association between cancer and AD-type dementia.

Introduction

Cancer and Alzheimer's disease (AD) are common chronic diseases in aging populations. In the United States, over 5 million people currently have dementia, and its prevalence is expected to grow to 13.8 million by 2050.[25] Both cancer and AD have high morbidity and mortality and are leading causes of death among older adults.[108]

Cancer and AD share many reported risk factors, including age, education, sedentary behavior, smoking, and diet.[109,110] Yet, several studies[37,38,111-119] including a Mendelian randomization study[36] and meta-analysis studies[35,120,121] have reported a lower incidence of AD, Parkinson's disease, and other neurodegenerative disorders among individuals with a history of cancer compared with cancer-free controls. One study reported that the risk of dementia in patients with cancer was 21% lower compared to matched cancer-free controls; the risk of dementia was also lower in the cancer group prior to the diagnosis of cancer.[118] Another study reported that older individuals who developed cancer had better memory and slower memory decline than did similarly aged individuals who remained cancer-free.[122] A simulation study showed that the competing risk of death and selective survival after cancer could not fully explain the inverse cancer-dementia association.[123] In contrast, one large Danish study reported that the inverse association between cancer and AD is small and diminishes over time.[124]

While autopsy findings have been not reported extensively, the inverse association of cancer and AD was first suggested by a cross-sectional autopsy study.[40]A recent another autopsy-based study showed that individuals with a history of cancer have reduced odds of developing clinical AD and a lower burden of

neurofibrillary tangle deposition compared to individuals with no history of cancer, but similar levels of amyloid-β (Aβ).[39] No other neurodegenerative pathologies have been reported in prior literature.

Prior research suggests that a matrix of shared genetic factors may confer risks of cancer and neurodegenerative disease in opposing directions.[125,126] For example, the apolipoprotein E (*APOE*) gene is the foremost genetic risk-contributing factor for AD, with ≥ 1 ε4 allele conferring increased risk.[127,128] Yet, very few studies examining the association between cancer and AD have accounted for *APOE* ε4 carrier status.[39,112,129,130] While on the contrary, the *APOE* ε4 has been suggested to have a protective role in some cancers.[131,132]

Though several studies have examined the association of cancer and clinical outcomes of AD and dementia, the relation between cancer and AD is not well understood, but if the inverse association is real, it may lead to new preventive therapies for AD. The objective of the current study is to evaluate the relationships between cancer history, AD pathology and other neuropathologic changes, final syndromic cognitive diagnosis, as well as the association of *APOE* ε4 and other single nucleotide polymorphisms (SNPs) known to be associated with AD.

Methods

Study participants

Data were drawn from the community-based cohort study of aging and dementia at the UK-ADRC.[60,133] All included participants were enrolled from 1984-2017 and were ≥ 60 years at death. The University of Kentucky Institutional Review Board approved all study procedures and all participants provided written informed consent.

Cancer ascertainment

The Kentucky Cancer Registry (KCR) is a population-based central cancer registry for the Commonwealth of Kentucky.[24] KCR is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, regarded to be among the most comprehensive and accurate cancer registries in the world.[48] Kentucky law requires all health care facilities that either diagnose or treat cancer patients, as well as freestanding treatment centers, non-hospital (private) pathology laboratories, and physician offices to report every case of cancer to KCR.[54] KCR started collecting uniform, high-quality data in 1995, so we excluded UK-ADRC participants who died before 1995.[54]

The UK-ADRC autopsy data were linked to KCR data to identify cancer cases occurring in Kentucky from 1995 - 2017 and to acquire cancer-specific data on diagnosis, stage, treatment, and year at diagnosis. For the current study, only the first primary diagnosis identified by International Classification of Disease codes for Oncology 3rd Edition (ICD-O-3)[134] was considered a cancer case (i.e., each participant can count as only one cancer case but may have had multiple cancer diagnoses). The participants with an ICD code for cancer were considered as 1=cancer history and 0=no cancer history/cancer-free.

Cancer stage at diagnosis was categorized by the Summary Stage 2000 as in-situ (non-invasive malignant tumor), localized (tumor is confined to the organ of origin), regional (tumor has spread by direct extension to immediately adjacent tissues, organs, or lymph nodes) and distant (a tumor that has spread beyond the immediately adjacent

tissues and has developed secondary or metastatic tumors).[24] Treatment categorized into 3 levels as: 'No treatment', 'Surgery or Chemotherapy and with or without Radiotherapy', and 'Surgery with Radiotherapy and with or without other therapy'.[24] Additionally, to assess the timing of the cancer diagnosis relative to UK-ADRC participation, we categorized the cancer cases as 'diagnosis before ADRC enrollment,' 'during the ADRC follow-up period,' or 'diagnosed after the last recorded ADRC visit.' Because tobacco use is a leading risk factor for certain types of cancers,[135] dementia and death, we classified cancer cases into smoking-related (oropharynx, esophageal, liver, stomach, pancreas, lung, colorectal, kidney, and urinary bladder)[135] and non-smoking related cancers.

Neuropsychological testing

Cognitive functions were evaluated on an approximately annual basis as described previously[63,64] with neuropsychological tests including Mini-Mental State Examination (MMSE),[136] Logical Memory Immediate-Recall [137], and Animal Naming Test scores.[94] Participants were classified as having normal cognition, mild cognitive impairment (MCI), impaired cognition (but not MCI), or dementia at each annual visit based on cognitive test scores, co-participant reports, neurological examination, medical history, and physical examination.[98] Impaired cognition was defined as per the Uniform Data set (UDS) standard protocol[98] and includes mild impairment not suspected to be due to neurodegenerative or cerebrovascular disease. Normal cognition indicates intact functional ability[98] and performance within expected ranges for age and education on neurocognitive tests.[94] MCI indicates the presence of objective impairment (scores > 1.5 standard deviations below expected mean) in one or more cognitive domains, intact

global cognition, no or minimal functional impairment, and no evidence of dementia.[65] The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria were used to determine dementia status in the UDS.[138] Because of the smaller frequency in the MCI category at the last diagnosis (n=72), cognitive status was categorized into a binary variable as Normal vs. MCI/Dementia; we excluded participants with 'impaired' last clinical diagnosis (n=16) for analyses of this variable.

Neuropathological assessment

Details of neuropathological assessment at UK-ADRC have been described previously.[133,139,140] Neuropathological assessments were performed blind to clinical information. Braak neurofibrillary tangle (NFT) stages were categorized as 0/I/II, III/IV, and V/VI. Consortium to Establish a Registry in Alzheimer's Disease (CERAD) diffuse and neuritic plaque ratings were categorized into dichotomous variables as moderate/frequent vs. none/sparse.[141] Transactive response DNA binding protein 43 kDa (TDP-43) proteinopathy was considered present if TDP-43 inclusion bodies were detected in the hippocampus, whereas Lewy bodies (α-synuclein) were considered present if detected in the brain stem, medial temporal lobe, or the neocortex.

In addition to neurodegenerative pathology, cerebrovascular pathology included measures of cerebral amyloid angiopathy (CAA), categorized as moderate/severe vs. none/mild, atherosclerosis severity at Circle of Willis (all vessels ≥50% vs. <50% occluded), any infarcts/lacunes (yes vs. no), and brain arteriolosclerosis (moderate/severe vs. none/mild). Cerebral atrophy was classified as moderate/severe vs. none/mild. Additionally, both right and left hippocampi were evaluated for hippocampal sclerosis (HS); the presence of HS on either side was considered as the presence of HS.

Covariates

Covariates included age at death, sex (male/female), UK-ADRC follow-up time in years, education in years, *APOE* ε4 genotype converted to a dummy indicator for 1 or more ε4 alleles, self-reported medical history of diabetes (yes/no), hypertension (yes/no), myocardial infarction, congestive heart failure (yes/no), history of coronary artery bypass surgery, and history of angioplasty. **Figure 4.1** demonstrates relationship between cancer, cognitive impairment and neuropathological changes as well as associated covariates.

Genetics

Genetic data were obtained from the UK-ADRC database as described previously,[142] and linked to UK-ADRC clinical and neuropathological outcome data. The quality control methods were performed before and after imputation using TOPMed Imputation Server.[143,144] We used 21 single nucleotide polymorphisms (SNPs) that were reported to be associated with AD,[145] however we could not evaluate SNP rs8093731 (T) due to small cell sizes. We assumed that the disease followed a dominant mode of inheritance with penetrance, that is, we categorized 1 or 2 effect alleles as 1.

Statistical analyses

Two-group comparisons of demographic, neuropathological, and clinical variables for participants with and without a history of cancer were made using t-tests, χ^2 tests, and Wilcoxon-Mann-Whitney tests. To examine the association between cancer and outcomes (neuropathological and clinical diagnosis at the visit before death), we used binary and multinomial logistic regression models to estimate the adjusted odds ratios (OR) and 95% confidence intervals (CI). Thirteen dependent variables were evaluated in separate models. Statistical significance was set at 0.05, and we used the Holm-

Bonferroni procedure[146] to preserve the family-wise Type 1 error rate for multiple comparisons.

To account for confounding (i.e., shared causes of cancer and neuropathology), we applied stabilized inverse probability of treatment weights (SIPTW) to the logistic models[147]. SIPTW balances the distribution of measured confounding variables in the exposure groups (here cancer history vs. no cancer history) by creating a "pseudo-population"[147] where the probability of exposure (cancer) is conditionally independent of the confounding variables.

SIPTW were computed by fitting a logistic regression model to the data where the measured confounders age at death, sex, education, polynomial terms for age at death, education, and *APOE* ε4 were independent variables, and cancer history was the outcome, to obtain the conditional probability of having cancer (if the participant actually did have cancer) or the conditional probability of not having cancer (if the participant actually did not have cancer). The inverse of these conditional probabilities form the weight denominators. To stabilize the weights, the marginal probability of cancer (for those with cancer history) or no cancer (for those without cancer history) was multiplied by the inverse conditional probabilities. Because the application of the weights can cause underestimates of parameter variance, we used robust standard errors. Adequacy of covariate balance in the weighted pseudo-population was assessed by examining the distribution of weighted variables graphically and by standardized mean differences.[147]

To evaluate the association of cancer with TDP-43 and arteriosclerosis, which had a higher percentage of missing data due to administrative reasons (TDP-43 was not recognized as a biomarker of neurodegeneration until 2006, and arteriolosclerosis was not

systematically evaluated at UK-ADRC until 2002), we used joint stabilized inverse probability of treatment and censoring weighting.[147,148] Stabilized inverse probability of censoring weighting (SIPCW) was used under the assumption that data are missing at random. Like SIPTW, SIPCW is based on estimating the inverse of the probability of the data being observed for each participant in the dataset conditional on their confounders and cancer history, multiplied by the marginal probability of the data being observed. The final weights are the product of the SIPCW and SIPTW, which are applied only to the participants with complete data, who now represent a pseudo-population where the conditional probability of cancer is independent of the confounders *and* where the conditional probability of being included in the observed data is independent of the confounders and the exposure ("selection without selection bias")[147]. The joint weights were then used in the logistic models where TDP-43 and arteriolosclerosis were the outcomes, again with robust standard errors. The weighted sample was evaluated for robustness as described above.

To account for the possibility that dementia cases are overrepresented in the UK-ADRC due to selection bias, we we repeated all analyses on a restricted cohort of participants who began follow-up with normal cognition (n=404). To assess the influence of the timing of cancer diagnoses on the results, we repeated the analyses on a restricted cohort of participants excluding participants with prevalent cancers (n = 50).

The association of the SNPs and the outcomes of cancer and clinical diagnosis were evaluated using logistic regression with one SNP at a time along with covariates (age at death, sex) and weights derived using SIPTW method. As a sensitivity analyses, seven participants were excluded as ethnic outliers and reran logistic regression along

with the three principal components (PCs) and covariates The ethnic outliers were identified by performing principal component analysis (PCA) dimensionality reduction merged with 1000 Genomes Phase 3 data (**Figure 4.2**).[149] Analyses were conducted in SAS 9.4 (SAS, Inc., Cary, NC) and Forest plots were created in Stata/SE, version 14.2 (College Station, TX: StataCorp LP); ggplot2 package in R was used to generate the PCA plot.

Results

The final study sample included 785 autopsied participants with linkage to KCR (Figure 4.3). The data linkage with KCR identified 190 (24.2%) participants with cancer history. Participant characteristics are presented in **Table 4.1**. Overall, the mean (±standard deviation (SD) UK-ADRC follow-up time was 8.8 ±5.6 years (i.e., study baseline to death), the mean age at study entry was 75.1 ±8.2, the mean age of death was 83.8 ±8.6 years, more than 60.1% of the sample (n=472) were females, and 39.4% had at least one ε4 allele of the *APOE* genotype (n = 312). Participants with cancer history had significantly more years of education (15.8 vs. 14.8 years, P <0.001) and a lower prevalence of at least one *APOE* ε4 allele (32.6% vs. 42.0%, P = 0.0063) compared to cancer-free participants. Participants with cancer history had a higher prevalence (45.8%) of cognitively normal diagnosis at the last UK-ADRC assessment vs 23.5% of the cancer-free participants had a normal diagnosis, whereas MCI/Dementia prevalence (22.6%) was lower in the cancer history participants vs higher prevalence (48.2%) among the cancer-free participants, P <0.0001). Mean MMSE, Animal Naming, and Logical Memory Immediate-Recall scores (6 years before death) were higher among the participants with a cancer history (P <0.0001, P=0.045, and P=0.016, respectively), while closer to death (≤

2 years before death) only MMSE and Animal Naming scores were significantly higher among these participants (**Table 4.1**).

Among the participants who were cognitively normal at baseline (n=404) (**Table 4.2)**, participants with cancer history died younger (mean (SD), 85.3 (7.4)) compared to the cancer-free participants (mean (±SD) 87.9 ±2.2, P <0.001). Sex, educational attainment, *APOE* ε4 allele, and last visit clinical diagnosis were similar among those with and without cancer**.** Only MMSE (measured at 6 years before death), and Logical Memory Immediate-Recall (measured at ≤2 years before death) were significantly different (P = 0.0050, and P = 0.0289 respectively).

Cancer characteristics by cognitive diagnosis are provided in **Table 4.3**. At baseline 50 (26.3%) participants had a history of cancer before enrollment in the UK-ADRC, while 83 (43.7%) developed cancer during the UK-ADRC follow-up and 57 (30.0%) were diagnosed with cancer after the last visit. Breast cancer was diagnosed in 33 (17.4%) participants, gastrointestinal cancers in 32 (16.8%), lung cancer in 29 (15.2%), while other types of cancers were less common. Non-smoking-related cancers were diagnosed in 57.4%, and smoking-related in 42.6% of participants. 42.1% had localized stage of cancer and 60.0% of the participants were treated with a combination of treatments such as surgery and radiation and with/without other therapies, but not including chemotherapy. Further, the cancer characteristics were described by cognitive status.

The neuropathological outcome measures had only a small proportion of missing data except for TDP-43 (43.3%) and arteriosclerosis (18.5%) (**Table 4.4)**. Neuropathological characteristics are presented in **Table 4.5**. Participants with cancer

history were more likely to have lower frequencies of higher Braak NFT stages (III/IV and V/VI), moderate/frequent diffuse and neuritic plaques, Lewy bodies, moderate/severe cerebral atrophy, and moderate/severe CAA. While TDP-43, HS, and cerebrovascular pathologies were similar in distribution between the two groups. However, participants who were cognitively normal at baseline, lower frequencies were only seen in the higher Braak NFT stages (III/IV and V/VI), moderate/severe diffuse plaques, and presence of infarcts/lacunes among cancer history participants (**Table 4.6**).

In SIPTW multivariable logistic regression models using SIPTW, history of cancer was associated with approximately 55% lower odds (OR = 0.45; 95% CI, 0.31, 0.64; $P< 0.0001$) of MCI/Dementia. Participants with cancer history had an estimated 62% decreased odds (OR=0.38; 95% CI, 0.26, 0.56; $P <0.0001$) of having Braak NFT V/VI stages and 48% decreased odds (OR = 0.52; 95% CI, 0.34, 0.79; $P = 0.0147$) of Braak NFT III/IV stages vs. Braak NFT 0/I/II stages (**Figure 4.4a**). Cancer history was associated with lower odds of moderate/frequent diffuse (OR = 0.53; 95% CI, 0.36, 0.76; $P =0.0013$), neuritic plaques (OR = 0.53; 95%CI, 0.37, 0.76; $P = 0.0005$) and CAA (OR = 0.57; 95% CI, 0.37, 0.91; $P = 0.0165$). However, CAA and Braak NFT stage III/IV were not significant when the Holm-Bonferroni correction was applied. Among the participants who started as cognitively normal (**Figure 4.4b**), cancer history was only significantly associated with Braak NFT stages III/IV (OR= 0.56; 95%CI, 0.34, 0.91; $P = 0.0415$) and Infarcts/Lacunes (OR=0.57; 95%CI, 0.37, 0.87; $P = 0.0080$).

Finally, we examined genetic associations with history of cancer and cognitive diagnosis. Cancer history was associated with lower odds of ≥ 1 *APOE* ε4 allele (OR=0.63; 95% CI, 0.44, 0.90; P = 0.0115), while MCI/Dementia was significantly

associated with higher odds OR=2.73; 95% CI, 1.89, 3.95; P <0.0001). Of the 785 participants included in our study, 393 had SNP data (**Table 4.7**). Cancer history was associated with higher odds of the T allele of SNP rs11136000 located in the *CLU* gene on chromosome 8, with OR=1.79; 95% CI, 1.07, 3.00; P = 0.0276) while MCI/Dementia was associated with lower odds, OR=0.46; 95% CI, 0.25, 0.85; P = 0.0131), however sensitivity analysis using PCs as covariates resulted in similar estimates but a higher P-values (*P* = 0.0457 for cancer history and *P* = 0.0049 for MCI/Dementia)

Discussion

The current autopsy study based on UK-ADRC elderly participants (N=785) with and without cancer history supports prior findings that cancer diagnosis is significantly associated with a lower clinical all-cause dementia diagnosis, as well as a reduced burden of AD pathology. We also examined the association of cancer history with multiple neuropathological outcomes, which have not been extensively reported in prior research. AD pathology, as well as CAA, were notably lower in participants with a cancer history. These results remained unchanged even with incident cancers. Examination of cognitive test scores suggested that participants with cancer history had higher cognitive scores compared to cancer-free participants in the 6 years before death.

The perplexing inverse relationship between cancer and dementia has generated interest among researchers and has been increasingly reported by multiple studies.[9,35,37,39,111-113,115,117,118,122,124,150] But, to date, only two studies have reported on the association of cancer and neuropathology.[39,40] In the current study, cancer history participants had lower odds of AD neuropathology (NFT's, neuritic, and diffuse plaques), a plausible reason for higher MMSE, Animal Naming cognitive scores and a

lower percentage with clinical dementia. We did not find any significant association with the presence of Lewy bodies, TDP-43, other neuropathological disorders, and cerebrovascular pathologies.

The present study results were generally consistent with the previous studies. A recent multicenter cohort study found that among individuals with either mild or isolated cognitive complaints, incident cancer was associated with a reduced risk (~50%) of dementia, accounting for various biases.[129] A retrospective cohort of 3.5 million elderly veterans, survivors of most cancers had a reduced risk of AD, but increased risk of the alternative outcomes (non-AD dementia, osteoarthritis, stroke, and macular degeneration).[116] Driver et al., using data from the Framingham Heart Study, reported that the protective effect of previous cancer was greater for smoking-related cancers than for non-smoking-related cancers, accounting for competing risk of mortality.[37] While Ording et al., using a nationwide Danish cohort that included patients with dementia and Parkinson's disease, reported lower standardized incidence rate ratios and absolute reduction cancer risk during 10 years follow-up for AD, vascular dementia, and all-cause dementia.[119] While, in another study, Ording et al. analyzed individuals surviving cancer >10 years and reported that the standardized incidence rate ratios for incident diagnoses of AD after stratification by sex, age, and cancer stage, approached that of the general population.[124] Hanson et al., report that modeling cancer as a time-varying predictor mitigates the inverse relationship between cancer and AD.[151] However, a recently published study using Mendelian randomization to assess the causal relationship between cancer (data from Genome-Wide Association

Studies) and Alzheimer's disease (summary statistics from IGAP), found that genetically predicted cancer (lung, leukemia, breast), and smoking-related cancers were associated with lower odds of AD.[36]

This study results provide additional evidence for the inverse association of cancer history and AD-type pathology. Both diseases are characterized by a set of molecular determinants (such as p53, cyclin D, cyclin E, cyclin F, Pin1, and protein phosphatase 2A (PP2A)) that are either complementarily deregulated or share remarkably overlapping functional pathways.[152] The *PIN*1 gene (regulates Pin1 enzyme) is overexpressed in certain cancers but is downregulated in AD pathogenesis and neuronal degeneration.[153,154] An experimental study demonstrated that *PIN*1 knockout increases Aβ42 production, suggesting that it might favor amyloidogenic amyloid precursor protein (APP) processing and elevates Aβ42 in an age-dependent manner.[155] Transcription factor p53 (tumor suppressor) is reported to be downregulated in cancer but inversely upregulated in neurodegenerative diseases.[152,156]

APOE ε4 is one of the strongest risk factors for AD neuropathological changes,[127,128] and we found an inverse association of *APOE* ε4 and cancer history. We were not able to examine the three common isoforms[128] ε2, ε3, and ε4 of the *APOE* genotype individually due to small cell sizes. A recent mouse model study found that animals expressing the human *APOE ε*4 allele exhibited reduced melanoma progression and metastasis relative to *APOE ε*2 mice.[157] It is plausible that interaction of *APOE* ε4 genotype and Aβ, which plays a key role in aggregation and clearance and therefore directly influences the development of amyloid plaques,

cerebral amyloid angiopathy, and subsequent tau-related pathology,[158] and maybe partly responsible for the inverse association of cancer and AD. However, a study conducted using Alzheimer's disease Neuroimaging Initiative (ADNI) data found cancer survivors had a delay in the onset of AD independent of their *APOE* ε4 status.[159]

In an additional genetic analysis using 20 SNPs, we found the T allele of rs11136000 (located on the *CLU* gene in chromosome 8) had lower odds of MCI/Dementia. The T allele on this SNP has been reported to associate with a reduced risk for late-onset AD.[145,160] In a review article Foster et al., highlighted the role of Clusterin in a range of pathologies including cancer, cardiovascular disease, and neurodegeneration and suggested that the pathways may help to understand its biological function(s) in association with AD.[161] Clusterin protein encoded by the *CLU* gene is overexpressed in several metastatic cancer cells, such as colon, bladder, hepatocellular carcinoma, and renal cell carcinoma.[162,163]

The inverse association between cancer and AD-type dementia could also be due to non-biological pathways; for example, a cancer diagnosis may also bring about healthy lifestyle behavioral changes, such as increased exercise and better nutrition, which result in healthier brain aging.[39] Furthermore, cancer may be less often be screened and diagnosed in cognitively impaired individuals.[124] The role of survivor bias cannot be ruled out completely; however, a recently published simulation study demonstrated that selective survival was too small to explain the observed inverse cancer-dementia link, suggesting other mechanisms drive this

association.[123] In the current study, the average age at death of the participants was more than 83 years and similar among those with and without cancer.

Lower AD risk in cancer survivors is associated with chemotherapeutic drugs than those who receive radiation therapy.[116] A large study using a population-based cancer registry found that chemotherapy decreased the risk of AD death in white women diagnosed with breast cancer at the age of 65 or older.[38] Chemotherapeutic drugs such as taxanes are microtubule stabilizers, are investigated for their role in reducing tau pathology as a treatment for AD and related tauopathies.[164] In the current study, only 15% of the participants with cancer history received chemotherapy; however, we could not examine the effect of cancer treatment due to the small sample size.

A major strength of the study is that we linked the UK-ADRC data to the KCR, unlike other studies the cancer cases are confirmed by pathologists, and not self-reported. The KCR is a population-based registry, so it is less likely that we may have missed cancer diagnosis, although it is possible. The longitudinal cohort at the UK-ADRC with the availability of rich neuropathological data makes this study unique. Additionally, the availability and adjustment of *APOE* genotype status (not been commonly reported by prior research studies) while evaluating cancer and dementia association.[115,118,124] None of the prior research studies have included multiple aspects of evaluation i.e. clinical diagnosis, longitudinal cognitive scores, genetic, and neuropathological evaluations in reporting the association of cancer and dementia. Furthermore, we used inverse probability weighting to

examine the association to balance the measured confounding variables and multiple biases that are integral to observational and autopsy studies.[148]

The study had some limitations. Due to the relatively small sample size of participants with cancer (n=190), we could not investigate site-specific cancers, as well as the effect of the treatments, received stages of cancer, and comorbid heart diseases. Some studies have reported cancer chemotherapy treatments to decrease cognitive functions in cancer survivors,[38,130,165] the effect referred to as "chemobrain." Furthermore, our study included only participants age ≥ 60 years enrolled at the UK-ADRC; hence, it is unknown whether the inverse association would be relevant to the people who died of cancer before the age of 60. Other limitations are the unavailability of multiple cognitive test scores to examine specific cognitive domains, as well as the relatively limited generalizability of autopsy cohorts due to the nature of these studies.

Conclusion

In conclusion, a persistent inverse association between cancer and dementia was evident in our study, and this study adds neuropathological evidence to the existing literature on epidemiological cohorts. We identified a possible mechanism for the inverse association with AD-type pathology, with genetically driven pathways acting in opposite directions, but the association of *APOE* ε4 and *CLU* with cancer needs further evaluation.

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Figure 4.1: Directed acyclic graph demonstrating the relationship between cancer, cognitive impairment, and neuropathological changes as well as associated covariates

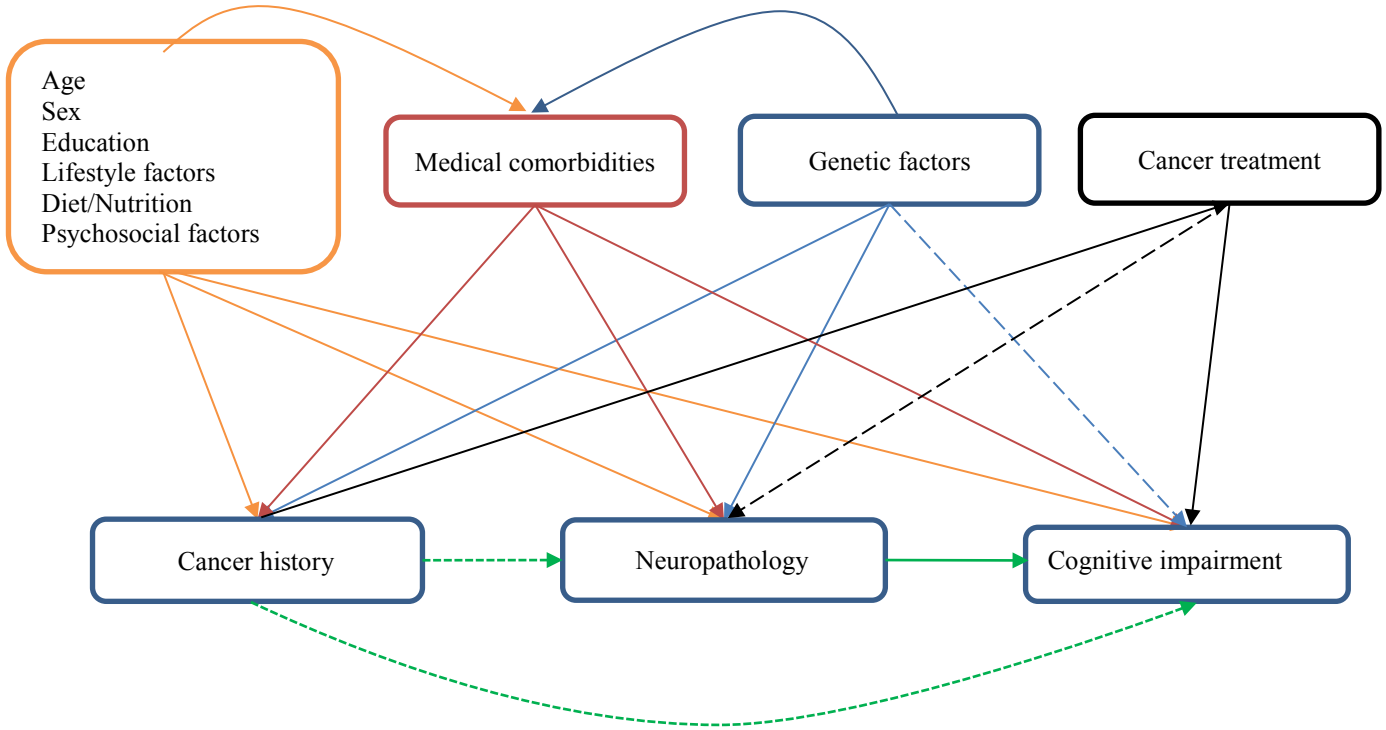
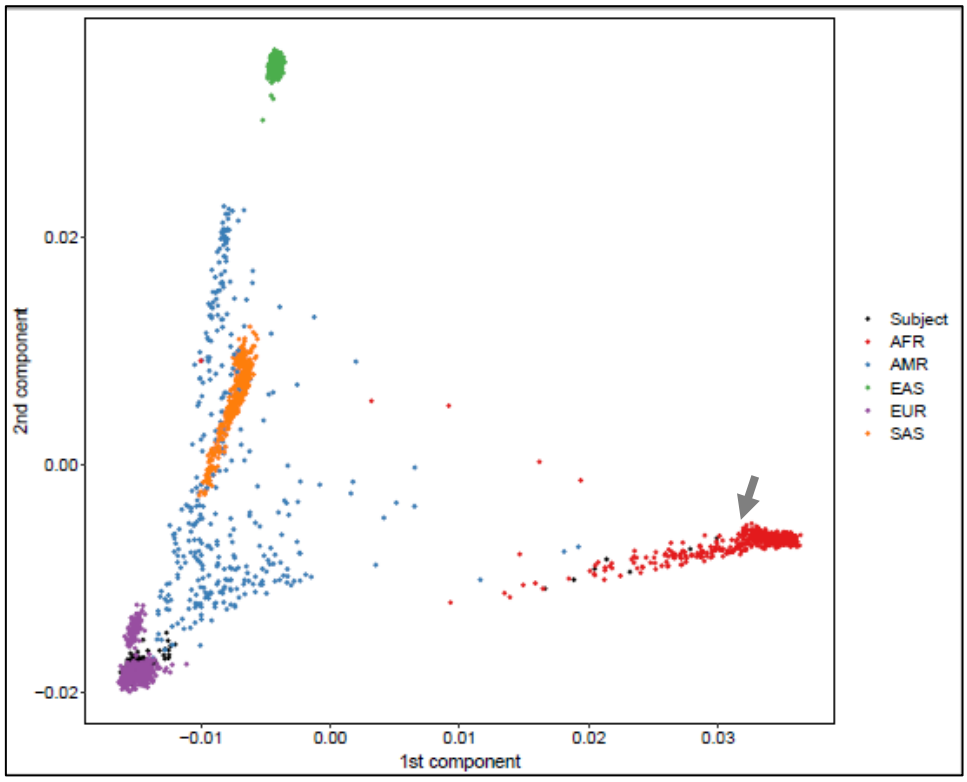
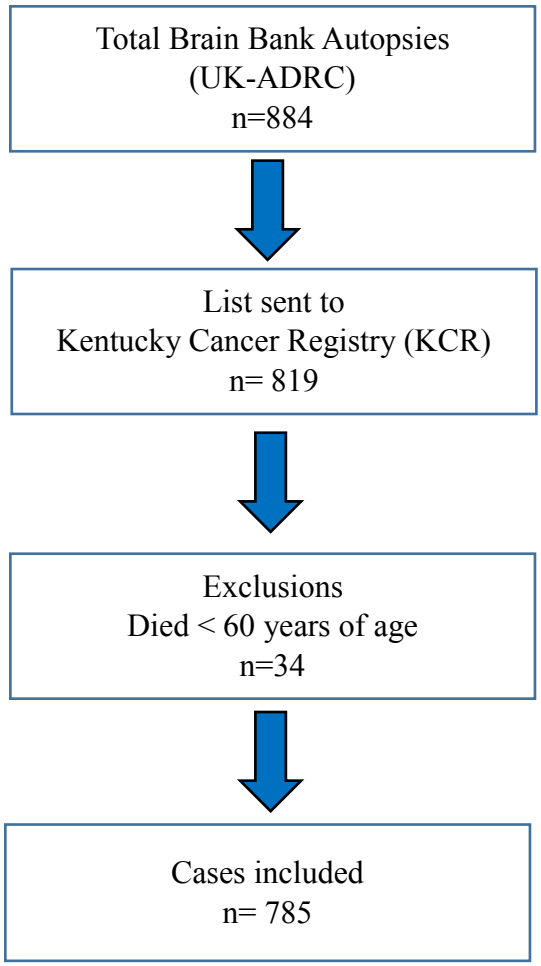


Figure 4.2: The First and Second Principal Components Plot Along With 1000 Genome Reference Samples



Black dots indicate individuals in this study. Gray arrow pointing to the seven participants, who were excluded in the sensitivity analysis. AFR = African; AMR = Admixed American; EAS = East Asian; EUR = European; SAS = South Asian

Figure 4.3: Participant Inclusion Flow Diagram



*KCR population-based state surveillance data available beginning in 1995

Table 4.1: Demographic and clinical characteristics of autopsied UK-ADRC participants by cancer history with known cancer status and available neuropathological data

Variable	All participants (n=785)	Cancer History (n=190)	No Cancer History (n=595)	P-value*
Age at baseline, mean (SD), y	75.1 (8.2)	74.7 (7.5)	75.3 (8.3)	0.345
Age at death, mean (SD) y	83.8 (8.6)	84.5 (7.8)	83.6 (8.9)	0.116
Follow-up time, mean (SD), y	9.2 (5.5)	10.0 (5.9)	8.9 (5.4)	0.019
Female sex	472 (60.1)	108 (56.8)	364 (61.2)	0.371
Race (White)	775 (98.7)	183 (96.3)	603 (98.7)	0.057
Education, y mean (SD)	15.0 (3.2)	15.8 (3.0)	14.8 (3.2)	<0.001
APOE ε4 allele				
None	429 (54.7)	123 (64.7)	306 (51.4)	
≥ 1 Alleles	312 (39.8)	62 (32.6)	250 (42.0)	0.006
Baseline clinical diagnosis				
Normal	404 (51.5)	144 (75.8)	260 (43.7)	
MCI /Dementia	330 (42.0)	43(22.6)	287 (48.2)	<0.001
Last Clinical Diagnosis**				
Normal	227 (31.0)	87 (45.8)	140 (23.5)	
MCI /Dementia	539 (68.7)	95 (50.0)	444 (74.6)	<0.001
Hypertension (present)	429 (54.7)	118 (62.1)	311 (52.3)	0.167
Diabetes (present)	104 (13.3)	26 (13.7)	78 (13.1)	0.741
Myocardial Infarction (present)	97 (12.4)	21 (11.1)	76 (12.8)	0.287
Congestive heart failure (present)	101 (12.9)	25 (13.2)	76 (12.8)	0.766
Angioplasty (present)	52 (6.6)	14 (7.4)	38 (6.4)	0.889
Coronary artery bypass surgery(present)	60 (7.6)	14 (7.4)	46 (7.7)	0.603
Cognitive test scores, mean (SD)				
MMSE, ≤2 years of death †	20.0(9.9)	24.0 (7.9)	18.4 (10.3)	<0.001
MMSE, 6 years prior to death††	25.3 (6.7)	27.5 (4.1)	24.3 (7.4)	<0.001
Animal naming, ≤2 years of death‡	13.4 (6.6)	14.8 (6.3)	12.6 (6.7)	0.002
Animal naming, 6 prior to death‡‡	17.0 (5.7)	17.9 (5.4)	16.5 (5.9)	0.046
Logical Memory (I), ≤2 years of death ℂ	10.9 (6.3)	11.4 (5.8)	10.6 (6.5)	0.309
Logical Memory (I), 6 prior to death ℂℂ	13.5 (5.13)	14.4 (5.0)	13.0 (5.2)	0.016

*Comparisons are Cancer history vs. No cancer history. **n= 766, participants with Impaired and missing clinical diagnosis are not reported here. Missing data are reported in Table 4.4.
† Cancer history n=155, No Cancer history n=382;†† Cancer history n=127, No Cancer history n=275
‡ Cancer history n=135, No Cancer history n=249; ‡ ‡ Cancer history n=121, No Cancer history n=219;
ℂ Cancer history n=125, No Cancer history n=213; ℂℂ Cancer history n=116, No Cancer history n=197;

Abbreviations**:** UK-ADRC =University of Kentucky Alzheimer's Disease Research Center; *APOE* ε4 allele = apolipoprotein ε4 allele**;** MMSE= Mini-Mental State Examination; Logical Memory (I)= Logical Memory Immediate Recall. SD=Standard deviation.

Table 4.2: Demographic and clinical characteristics of autopsied UK-ADRC participants who started as cognitively normal at baseline with known cancer status and available neuropathological data.

Variable	All participants (n=404)	Cancer History (n=144)	No History of cancer (n=260)	P-value*
Age at baseline	75.6 (7.3)	74.1 (6.9)	76.4 (7.4)	**0.0021**
Age at death, y mean (SD)	87.0 (7.4)	85.3 (7.4)	87.9 (2.2)	**0.0004**
Female sex	253 (62.6)	84 (58.3)	169 (65.0)	0.1847
Education, y mean (SD)	16.0 (2.6)	16.3 (2.8)	15.8 (2.5)	0.1193
APOE ε4 allele				
-/-	276 (68.3)	102 (70.8)	174 (66.9)	0.5207
≥ 1 ε4 Alleles	122 (30.2)	41 (28.5)	81 (31.2)	
Last Clinical Diagnosis**				
Normal	226 (58.9)	86 (62.8)	140 (54.9)	0.1326
MCI /Dementia	166 (41.1)	51 (37.2)	115 (45.1)	
Hypertension (present)	237 (58.7)	85 (59.0)	152 (58.5)	0.2423
Diabetes (present)	56 (13.9)	16 (11.1)	40 (15.4)	0.0854
Myocardial Infarction (present)	59 (14.6)	16 (11.1)	43 (16.5)	**0.0377**
Congestive heart failure (present)	76 (18.8)	20 (13.7)	56 (21.5)	**0.0166**
Angioplasty (present)	32 (7.9)	11 (7.6)	21 (8.1)	0.5679
Coronary artery bypass surgery(present)	35 (8.7)	9 (6.3)	26(10.0)	0.0646
Cognitive test scores (last visit) mean (SD)				
MMSE, ≤2 years of death †	25.1 (6.8)	26.3 (5.8)	24.5 (7.3)	**0.0050**
MMSE, 6 years prior to death††	28.2 (2.5)	28.6 (2.7)	28.0 (2.7)	0.2118
Animal Naming test, ≤2 years of death‡	15.0 (6.2)	15.6 (6.0)	14.5 (6.2)	0.1440
Animal Naming test, 6 prior to death‡‡	17.8 (5.4)	18.2 (5.1)	17.6 (5.5)	0.1674
Logical Memory (I), ≤2 years of death ₡	12.6 (5.4)	12.2 (5.4)	12.8 (5.3)	0.4353
Logical Memory (I), 6 prior to death ₡₡	14.3 (4.6)	15.3 (4.5)	13.8 (4.6)	**0.0289**

*Comparisons are Cancer history vs. No cancer history

** n= 392, 12 participants with Impaired and missing Clinical diagnosis were excluded

† Cancer history n=122, No Cancer history n=207; †† Cancer history n=109, No Cancer history n=191

‡ Cancer history n=115, No Cancer history n=179; ‡ ‡ Cancer history n=109, No Cancer history n=182

₡ Cancer history n=108, No Cancer history n=166; ₡₡ Cancer history n=106, No Cancer history n=177

Abbreviations: UK-ADRC, University of Kentucky Alzheimer's Disease Research Center; *APOE* ε4, apolipoprotein ε4 allele; MMSE, Mini-Mental State Examination score; Logical Memory (I), Logical Memory- Immediate recall test.

Table 4.3: Distribution of cancer case characteristics by final cognitive status

Cancer characteristics	All Cancer Cases (n=190)	Normal** (n= 87)	MCI / Dementia** (n=95)
Cancer diagnosis in relation to ADRC Enrollment period			
Diagnosis before ADRC enrollment	50 (26.3)	16 (18.4)	32 (33.7)
Diagnosis during ADRC follow-up	83 (43.7)	42 (48.3)	35 (36.8)
Diagnosis after last ADRC visit	57 (30.0)	29 (33.3)	28 (29.5)
Cancer types			
Breast	33 (17.4)	9 (10.3)	21 (22.1)
Colorectal/stomach/peritoneal /Pancreatic/Liver/Gallbladder	32 (16.8)	16 (18.4)	15 (15.8)
Lung	29 (15.2)	21 (24.1)	6 (6.3)
Prostate	26 (13.7)	9 (10.3)	15 (15.8)
Bladder/Kidney	18 (9.5)	6 (6.9)	10 (10.5)
Basal cell carcinoma/soft/connective tissue	16 (8.4)	8 (9.2)	7 (7.4)
Miscellaneous†	10 (5.3)	6 (6.9)	3 (3.2)
Unspecified Primary	10 (5.3)	5 (5.7)	5 (5.3)
Oropharyngeal/Esophageal	8 (4.2)	3 (3.4)	5 (5.3)
Ovary/ Uterus/Endometrium	8 (4.2)	3 (3.4)	5 (5.3)
Smoking related			
Smoking-related cancers*	81 (42.6)	47 (49.5)	34 (35.8)
Not smoking-related cancers	109 (57.4)	48 (50.5)	61 (64.2)
Cancer Stage			
In-situ	18 (9.5)	3 (3.5)	13 (13.7)
Localized	80 (42.1)	30 (34.5)	46 (48.4)
Regional	28 (14.7)	17 (19.5)	10 (19.5)
Distant	40 (21.1)	25 (28.7)	15 (15.8)
Unknown/Unstageable	24 (12.6)	12 (13.8)	11 (11.6)
Cancer Treatment			
No treatment	47 (24.7)	18 (20.7)	8 (8.4)
Chemo or Surgery and with/without Radiation therapy	29 (15.3)	23 (26.4)	22 (23.2)
Surgery and Radiation and with/without Other therapy	114 (60.0)	46 (52.9)	65 (68.4)

**8 participants with impaired diagnosis were excluded from the stratified analysis
*Smoking-related cancers (Lung, Bladder, oropharyngeal, pancreas, Stomach, Colorectal, Liver, Esophageal, Kidney); † Miscellaneous cancers: Brain, spinal cord, acoustic nerve, lymph nodes, cardiac; ADRC- Alzheimer's Disease Research Center; chemo- chemotherapy

Table 4.4: Frequency of Missing Data

Variable	All	Cancer history	No Cancer history
		No. (%)	
Education	18 (2.29)	1 (0.53)	17 (2.9)
Race	9 (1.15)	0	9 (1.51)
APOE ε4 allele	44 (5.6)	5 (2.6)	39 (6.6)
Clinical Diagnosis (Baseline)	51 (6.50)	3 (1.6)	48 (8.1)
Clinical Diagnosis Either missing/unknown or Impaired (last assessment)	19 (2.4)	8 (4.2)	11 (1.9)
Hypertension	138 (17.6)	23 (12.1)	115 (19.3)
Diabetes	188 (23.9)	33 (17.4)	155 (26.1)
Myocardial Infarction	181 (23.1)	33 (17.4)	148 (24.9)
Congestive heart failure	172 (21.9)	31 (16.3)	141 (23.7)
Angioplasty	203 (25.9)	38 (20.0)	165 (27.7)
Coronary artery bypass surgery	226 (28.8)	44 (23.2)	182 (30.6)
Braak NFT stage	18 (2.3)	1 (0.5)	17 (2.9)
Diffuse plaques	1 (0.1)	0	1 (0.2)
Neuritic plaques	1 (0.1)	0	1 (0.2)
TDP-43 inclusion bodies	340 (43.3)	66 (34.7)	274 (46.1)
Lewy bodies	5 (0.6)	3 (1.6)	2 (0.3)
Hippocampal sclerosis	10 (1.3)	4 (2.1)	6 (1.01)
Atherosclerosis	15 (1.9)	1 (0.5)	14 (2.4)
Arteriosclerosis	145(18.5)	16 (8.4)	129 (21.7)
Cerebral atrophy	10 (1.3)	0	10 (1.7)
Cerebral amyloid angiopathy	18 (2.3)	2 (1.1)	16 (2.7)
Argyrophilic grain disease	29 (3.7)	5 (2.6)	24 (4.0)

Abbreviations: *APOE* ε4, apolipoprotein ε4 allele; NFT, neurofibrillary tangle; TDP-43, transactive response DNA-binding protein 43 kDa.

Table 4.5: Neuropathological Characteristics of Autopsied UK-ADRC Participants by Cancer History (n=785)

Variable	All Participants (n=785)	Cancer History (n=190)	No Cancer History (n=595)	P-value
Brain weight, grams mean (SD)	1158.8 ±154.2	1187.6 ±163.9	1149.9 ±150.1	0.002
Braak NFT stage				
0/I/II	247 (31.5)	95 (50.3)	152 (26.3)	<0.0001
III/IV	133 (16.9)	33 (17.5)	100 (17.3)	
V/VI	387 (49.3)	61 (32.3)	326 (56.4)	
Diffuse Plaques				
None/Sparse	170 (21.7)	63 (33.2)	107 (18.0)	<0.0001
Moderate/Frequent	614 (66.8)	127 (66.8)	448 (82.0)	
Neuritic Plaques				
None/Sparse	255 (32.5)	90 (47.4)	165 (27.8)	<0.0001
Moderate/Frequent	529 (67.5)	100 (52.6)	316 (72.2)	
Lewy bodies (present)	264 (33.9)	51 (26.8)	213 (35.9)	0.0294
TDP-43 (present)	165 (20.0)	39 (20.5)	126 (20.3)	0.1267
Cerebral atrophy				
None/Mild	521 (67.2)	144 (75.8)	377 (63.4)	0.0038
Moderate/Severe	254 (32.8)	46 (24.2)	208 (35.0)	
Hippocampal Sclerosis (present)	133 (16.9)	27 (14.2)	106 (17.8)	0.2724
CAA				
None/Mild	553 (70.5)	153 (80.5)	400 (67.4)	0.0011
Moderate/severe	214 (27.3)	35 (18.4)	179 (29.8)	
Atherosclerosis				
<50% Occluded	370 (47.1)	91 (47.9)	279 (46.9)	0.9757
≥ 50% Occluded	400 (51.0)	98 (51.6)	302 (50.8)	
Arteriosclerosis				
None/Mild	495 (63.1)	131 (69.0)	364 (61.2)	0.4476
Moderate/Severe	145 (18.5)	43 (22.6)	102 (17.1)	
Brain Infarcts/Lacunes (Present)	348 (44.3)	78 (41.1)	270 (45.4)	0.2961
AGD (present)	113 (15.0)	25 (13.2)	88 (14.8)	0.5292

Missing data are reported in Table 4.4.
Abbreviations: NFT, neurofibrillary tangle; CAA, Cerebral amyloid angiopathy; AGD, Argyrophilic grain disease; TDP-43, transactive response DNA-binding protein 43 kDa.

Table 4.6: Neuropathological Characteristics of Autopsied UK-ADRC Participants Who Started as Cognitively Normal at Baseline by Cancer History (n=404)

Variable	All Participants (n=404)	Cancer History (n=144)	No Cancer History (n=260)	P-value
Brain weight, grams, mean (SD)	1191.6 ±137.3	1204.4 ±163.9	1149.9 ±150.1	0.1343
Braak NFT stage				
0/I/II	193 (47.8)	84 (58.3)	109 (41.9)	0.0064
III/IV	111 (27.5)	29 (20.1)	82 (31.5)	
V/VI	94 (23.3)	30 (20.8)	64 (24.6)	
Diffuse Plaques				
None/Sparse	131 (32.4)	57 (39.6)	74 (28.5)	0.0222
Moderate/Frequent	273 (67.6)	87 (60.4)	186 (71.5)	
Neuritic Plaques				
None/Sparse	196 (48.5)	79 (54.9)	117 (45.0)	0.0575
Moderate/Frequent	208 (51.5)	65 (45.1)	143 (55.0)	
Lewy bodies (present)	94 (23.3)	31 (21.5)	63 (24.2)	0.5730
TDP-43 (present)	82 (20.3)	28 (19.4)	54 (20.8)	0.8213
Cerebral atrophy				
None/Mild	331 (81.9)	121 (84.0)	210 (80.8)	0.6119
Moderate/Severe	69 (17.1)	23 (16.0)	46 (17.7)	
Hippocampal Sclerosis (present)	57 (14.1)	18 (12.5)	39 (15.0)	0.5488
Cerebral amyloid angiopathy				
None/Mild	320 (79.2)	201 (77.3)	119 (82.6)	0.1605
Moderate/severe	83 (20.5)	59 (22.7)	24 (16.7)	
Atherosclerosis				
<50% Occluded	190 (47.0)	70 (48.6)	120 (46.2)	0.6647
≥ 50% Occluded	210 (52.0)	73 (50.7)	137 (52.7)	
Arteriosclerosis				
None/Mild	264 (65.4)	99 (68.8)	165 (63.5)	0.7116
Moderate/Severe	83 (20.5)	43 (22.9)	50 (19.2)	
Brain Infarcts/Lacunes (present)	206 (51.0)	59 (41.0)	147 (56.5)	0.0027
AGD (present)	68 (16.8)	20 (13.9)	48 (18.5)	0.2152

Abbreviations: NFT, neurofibrillary tangle; AGD, Argyrophilic grain disease; TDP-43, transactive response DNA-binding protein 43 kDa.

Table 4.7: Weighted odds ratios for neuropathological features (Cancer history vs. No Cancer history)

Dependent variables	Weighted OR (95% CI) N= 785*	Weighted OR (95% CI) N=735**	Weighted OR (95% CI) N= 404***
Clinical diagnosis (last visit)			
MCI/Dementia vs Normal	0.47 (0.32 - 0.68)	0.35 (0.23 – 0.54)	0.90 (0.59 – 1.41)
Neuropathology			
Braak NFT stage			
III/IV vs 0/I/II	0.52 (0.37 - 0.86)*	0.49 (0.28 - 0.85)*	0.55 (0.32 - 0.95)*
V/VI vs 0/I/II	0.38 (0.26 - 0.55)	0.31 (0.19 - 0.51)	0.77 (0.44 - 1.31)
Diffuse Plaques			
Moderate /Frequent vs Sparse/Normal	0.53 (0.36 - 0.78)	0.47 (0.31 - 0.73)	0.71 (0.16 – 1.11)
Neuritic Plaques			
Moderate/Frequent vs. Sparse/None	0.52 (0.36 - 0.75)	0.50 (0.33 – 0.75)	0.82 (0.54 – 1.26)
Lewy bodies			
Present vs. Absent	0.74 (0.49 - 1.11)	0.74 (0.47 – 1.16)	0.86 (0.52 – 1.42)
TDP-43 inclusion bodies			
Present vs. Absent	0.79 (0.48 - 1.30)	0.80 (0.47 – 1.39)	0.71 (0.41 – 1.25)
Cerebral atrophy			
Moderate/Severe vs. None/Mild	0.76 (0.50 - 1.14)	0.65 (0.39 – 1.10)	1.12 (0.64 -1.96)
Hippocampal sclerosis			
Present vs. Absent	0.84 (0.50 - 1.42)	0.81 (0.43 – 1.52)	0.96 (0.51 – 1.78)
Cerebral amyloid angiopathy			
Moderate/severe vs None/Mild	0.58 (0.38 - 0.90)†	0.52 (0.30 - 0.91)†	0.82 (0.48 - 1.42)
Atherosclerosis			
≥ 50% Occluded vs. <50% Occluded	1.05 (0.73 - 1.50)	0.97 (0.65 – 1.45)	1.16 (0.73 - 1.70)
Arteriosclerosis			
Moderate/Severe vs. None/Mild	1.00 (0.66 - 1.54)	0.99 (0.55 – 1.77)	0.96 (0.57 - 1.62)
Brain Infarcts/Lacunes			
Present vs. Absent	0.78 (0.55 - 1.12)	0.86 (0.57 - 1.28)	0.57 (0.37- 0.87)
Argyrophilic grain disease			
Present vs. Absent	0.92 (0.54 - 1.56)	0.92 (0.50 -1.70)	0.73 (0.40 - 1.31)

* Weighted odds ratios for neuropathological features (Cancer history vs. No Cancer history
** Weighted odds ratios for neuropathological features (Incident Cancer history vs. No Cancer history
*** Weighted odds ratios for neuropathological features (Cancer history vs. No Cancer history) among participants who started as cognitively normal
†Not significant when multiple comparison p-value was applied.
Abbreviations: NFT, neurofibrillary tangle; CAA, Cerebral amyloid angiopathy; AGD, Argyrophilic grain disease; TDP-43, transactive response DNA-binding protein 43 kDa.

Table 4.8: Association of SNPs with Cancer History and Cognitive Status

Gene, (chromosome), SNP (effect allele)	Cancer vs No cancer		MCI/Dementia vs Normal	
	Covariates + weights	**Covariates + weights +PCs**	**Covariates + weights**	**Covariates + weights +PCs**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
CR1 (chr1) rs6656401 (A)	1.22 (0.76; 1.94)	1.22 (0.76; 1.95)	0.80 (0.48; 1.34)	0.79 (0.47; 1.32)
BIN1 (chr 2) rs6733839 (T)	1.08 (0.66; 1.74)	1.07 (0.66; 1.75)	1.05 (0.62; 1.80)	1.05 (0.61; 1.79)
INPP5D (chr2) rs35349669 (T)	1.18 (0.70; 2.01)	1.18 (0.69; 2.01)	0.91 (0.51; 1.64)	0.93 (0.52; 1.66)
MEF2C (chr 5) rs190982 (G)	1.03 (0.64; 1.68)	1.09 (0.67; 1.77)	0.99 (0.58; 1.69)	0.91 (0.53; 1.56)
HLA-DRB5-DBR1 (chr 6) rs9271192 (C)	1.13 (0.72; 1.78)	1.14 (0.71; 1.82)	0.61 (0.37; 1.02)	0.62 (0.36; 1.04)
CD2AP (chr 6) rs10948363 (G)	1.30 (0.82; 2.07)	1.32 (0.82; 2.12)	1.09 (0.65; 1.82)	1.08 (0.64; 1.81)
NME8 (chr 7) rs2718058 (G)	1.11 (0.70; 1.77)	1.15 (0.72; 1.84)	0.79 (0.47; 1.33)	0.76 (0.45; 1.28)
ZCWPW1 (chr7) rs1476679 (C)	0.57 (0.36; 0.91)	0.57 (0.35; 0.90)*	0.86 (0.52; 1.44)	0.86 (0.51; 1.44)
EPHA1 (chr7) rs11771145 (A)	1.35 (0.84; 2.16)	1.44 (0.89; 2.34)	0.84 (0.50; 1.44)	0.92 (0.55; 1.55)
PTK2B (chr8) rs28834970 (C)	0.83 (0.51; 1.35)	0.86 (0.54; 1.39)	1.12 (0.66; 1.90)	1.14 (0.67; 1.93)
CLU (chr8) rs11136000 (T)	1.79 (1.07; 3.00)**	1.70 (1.01; 2.86)***	0.46 (0.25; 0.85)+	0.42 (0.23; 0.77)++
CELF1 (chr11) rs10838725 (C)	1.07 (0.67; 1.71)	1.09 (0.68; 1.74)	0.67 (0.39; 1.13)	0.67 (0.40; 1.15)
MS4A (chr11) rs983392 (G)	1.35 (0.82; 2.21)	1.35 (0.82; 2.22)	0.62 (0.36; 1.09)	0.61 (0.35; 1.07)
PICALM (chr11) rs10792832 (A)	1.42 (0.87; 2.30)	1.50 (0.92; 2.45)	1.22 (0.73; 2.05)	1.12 (0.66; 1.89)
SORL1 (chr11) rs11218343 (C)	0.67 (0.28; 1.62)	0.56 (0.24; 1.39)	0.63 (0.28; 1.41)	0.67 (0.30; 1.50)
FERMT2 (chr14) rs17125944 (C)	1.19 (0.65; 2.19)	1.19 (0.62; 2.26)	0.55 (0.29; 1.02)	0.57 (0.30; 1.07)
SLC24A4-RIN3 (chr14) rs10498633 (T)	1.30 (0.80; 2.09)	1.36 (0.84; 2.20)	0.67 (0.40; 1.12)	0.69 (0.41; 1.16)
ABCA7 (chr19) rs4147929 (A)	0.98 (0.60; 1.59)	0.99 (0.61; 1.61)	1.31 (0.76; 2.27)	1.27 (0.73; 2.20)
CD33 (chr19) rs12459419 (T)	1.00 (0.63; 1.57)	1.01 (0.64; 1.60)	1.35 (0.81; 2.25)	1.29 (0.78; 2.17)
CASS4 (chr20) rs7274581 (C)	1.74 (0.95; 3.21)	1.76 (0.93; 3.34)	0.64 (0.32; 1.24)	0.70 (0.35; 1.38)

Odds ratios adjusted for sex, age at death, Pcs, Pcs=Principal components. *P = 0.0171, ** P= 0.0276, *** P=0.0457, +P= 0.0131, ++P=0.0049; SNPs=Single nucleotide polymorphisms for Alzheimer's Disease identified in the previous studies

CHAPTER FIVE

Conclusion

Summary

Despite an increase in research into the underlying pathology of neurodegenerative diseases over the last few decades, there remains a lacuna in understanding the complex nature of these diseases. There is an urgent need to find methods to enhance preventive and treatment measures. Neurodegenerative diseases such as AD, FTLD, Lewy body dementia, LATE, Parkinson's disease, amyotrophic lateral sclerosis, uncommon tauopathies result have aggregation of misfolded proteins or proteinopathies in common, which is considered as neuropathological hallmarks of the diseases.[6] The Tau, Aβ, α-synuclein, and TDP-43 are the most commonly aggregated proteins as pure proteinopathies or as mixed proteinopathies.

AD now known as a multifactorial disorder is characterized by progressive dementia. It is the 6th leading cause of death in the U.S.[28] The central pathology of AD classically is defined by the accumulation of Aβ and tau tangles, however, the occurrence of co-pathologies are now known to be common in older adults[2,3,24,26,46,52,54,79,84,166] and present as complex clinical presentations. Recent autopsy-based research studies have assessed the presence of mixed proteinopathies and their influence on cognition during life.[3,5,24,26,44]

The purpose of the study was to expand on the understanding of multiple proteinopathies, their role in cognitive decline, in a community-based cohort study of aging and dementia at the University of Kentucky Alzheimer's Disease Center. The three studies conducted: (1) "Prevalence and Clinical Phenotype of Quadruple Misfolded

Proteins in Older Adults." (2) "Four common late-life cognitive trajectories patterns associate with replicable underlying neuropathologies." (3) "Cancer history associates with a lower burden of dementia and Alzheimer's-type neuropathology in autopsied research volunteers." The major findings from these studies are summarized below:

Chapter Two described the frequency and associated characteristics of multiple proteinopathies, focusing on quadruple misfolded proteins (QMP: Tau, Amyloid β, α-Synuclein, TDP-43) among autopsied research volunteers. The proteinopathies were categorized into seven case groups, among participants with at least misfolded tau. The participants were included if they had data on all four proteins, which enabled us to carry out detailed neuropathologic analyses. Some of the important findings of the study revealed that mixed pathologies in our cohort were common rather than the exception. Two proteinopathies were detected in 43% of cases, 38% had three, and 12% had the QMP (i.e. presence of four proteinopathies) phenotype. The QMP pattern of co-pathologies was observed in 19.2% of demented subjects, equal to the prevalence of "pure" AD pathology. Among pathology-defined groups, QMP subjects had the highest dementia frequency (89.1%) and the lowest final mean (SD) MMSE scores (13.4 (9.8)). Longitudinal assessments revealed that persons with eventual autopsy-confirmed QMP traversed through MCI relatively quickly (1.7 years vs 2.9 years for pure AD). Further, the association of proteinopathies with age at death, sex, education, and *APOE* ε 4 was assessed. Adjusting for age at death and sex, the *APOE* ε4 was associated with higher odds of QMP proteinopathy (AOR= 2.55; 95%CI, 1.16, 5.62; P = .02). To evaluate the longitudinal association with global cognition, we used generalized estimating equations to estimate the predicted probability of having mental status scores within normal

(MMSE 27-30) or severely impaired (MMSE 0-13) ranges during the 12 years before death. The QMP group had both the lowest probability of having normal MMSE, even 12 years before death and the highest probability of having severe impairment on the MMSE. The presence of mixed pathologies (≥3) appears to play a major role in cognitive decline.

In Chapter Three, the study focused on the patterns of longitudinal cognitive status in older adults using the GBTM methods. The study was conducted using two independent datasets of autopsied, longitudinally followed Alzheimer's Disease Research Centers' participants (total N=1346). The GBTM models allow us to overcome challenges in longitudinal analysis, that there are subgroups within the population that follow distinctive trajectories over time.[85,87] An extension to the GBTM method is the GBMTM, using multiple variables in the same model, thereby there is 1:1 correspondence and the results are thus a cumulative group assignment across the variables used in the model. Here we use longitudinal cognitive test scores of the participants assessed longitudinally 10 years before death. The three test scores used here are part of the cognitive tests conducted approximately annually during the clinical visit. Cognitive test scores used were MMSE, Logical Memory Story A, and the Animal Naming, representing global cognition, episodic memory, and verbal fluency respectively. The GBMTM model identified four similar cognitive trajectories in both cohorts. The trajectories determined by shape were labeled as "*No Decline*", "*Mild Decline*", "*Moderate Decline*", and "*Accelerated Decline"*. Furthermore, the predictors and proteinopathies associated with the trajectories indicating cognitive status were examined. The results showed the four trajectories showed distinctive patterns of

cognitive function over a decade prior to death. In the Accelerated decline and Moderate decline, participants showed an increased rate of decline with lower baseline test scores and were more likely to be diagnosed with dementia before death. The Mild decline and the No decline trajectory groups had initially similar test scores, but the decline rate different in 4-5 years proximate to death. Analyzing the association of neuropathological variables with the identified trajectory subgroups, the Accelerated decline group were likely to die younger, were less likely to have higher education, have higher frequency Braak NFT stage V/VI, TDP-43, and HS among UK-ADRC participants. While among the NACC participants, the Accelerated decline group was additionally associated with α-synuclein and moderate to frequent arteriosclerosis. Other important findings of the study are the relationship between each trajectory group and cognitive performance correlated with both the number of proteinopathies and the burden of cerebrovascular pathology in the brain. Additionally, the RF analysis allowed us to determine the importance of all the variables of interest associated with trajectory groups. RF results suggested most important trajectory predictors were the Braak NFT stage, cerebral atrophy, death age, and brain weight.

In Chapter Four, we shifted our focus to the association of cancer and neuropathology. Interestingly several prior studies have shown history that history of cancer has an inverse association with clinical AD phenotype. In the current study, we linked the autopsy data drawn from the UK-ADRC to the Kentucky Cancer Registry. The goal of the study was to expand on the understanding of the causal association of history of cancer and clinical diagnosis of dementia, AD-type pathology and to evaluate the association of known single nucleotide polymorphisms associated with AD with cancer

history and cognitive status. The statistical analyses involved the use of inverse probability of treatment weights to account for confounding i.e., shared causes of cancer and neuropathology. The results of the study confirm the inverse association of history of cancer with MCI/Dementia diagnosis. The odds of having MCI/Dementia was lower by 55% among the participants with cancer history. Participants with cancer history had lower odds of Braak NFT stages III/IV, V/VI, Aβ plaques, and CAA.

Strengths and limitations

The dissertation primarily used UK-ADRC participant data, which is a community-based longitudinal cohort with lengthy (mean of 8.8 ±5.6 years) follow-up. The lengthy follow-up allowed us to examine the longitudinal cognitive performance of the participants using different statistical methods. Another major strength is the availability of well-characterized clinical diagnosis, multiple neuropathology measures, and genetic data. Furthermore, subgroup analyses were conducted among participants who were cognitively normal at baseline.

A limitation noteworthy is that UK-ADRC participants are not representative of the general population of older adults in the U.S. Majority of participants were white, well-educated, and thus generalizability of the results may be limited. Another limitation is the limited sample size, a larger sample would be beneficial to examine intergroup comparisons e.g. in chapter Four study we were unable to evaluate the cancer type, staging, and treatment potentially relevant to aggregation of proteinopathies in the brain as well as to the cognitive decline during life. The sample size also limited the examination of effect modifications. The medical comorbidities in the UK-ADRC data were self-reported and measured at baseline and hence could not be evaluated as time-

varying variables. Furthermore, because of exclusion criteria used, as well as the rarity, the burden of proteinopathies in rare dementia syndromes was not examined.

Future research

Several future research can be undertaken from the results of the dissertation. First, we can extend the study to a more diverse and larger population to examine the burden of proteinopathies. Some studies have reported that CVD pathology is more prevalent in black[79,80] and Hispanic[80] individuals and are more likely to have mixed AD pathology compared to white individuals. This is important as we are moving towards a precision medicine approach, factors that can vary with ethnoracial groups may become important in the management of neurodegenerative diseases. Furthermore, a larger sample of cognitively normal at baseline may lead to a better understanding of the cognitive performance of multiple proteinopathies.

Second, the GBMTM statistical analyses can be extended to other datasets using cognitive test scores involving varied cognitive domains, which will give a better discriminatory power to identify subgroups. Furthermore, the association of subgroups with extended clinical classification subtypes can be examined, e.g. type of dementia (AD dementia, vascular dementia, rare dementia syndromes, etc.). Third, genetic analysis of proteinopathy groups would be useful in determining the lifetime risk of an individual. It would be important to assess the genetic risks of individuals with multiple proteinopathies vs those having fewer proteinopathies. The risk assessment may broaden the understanding of multiple proteinopathies. Fourth, expand the association of cancer data to examine the effect of cancer therapies on neuropathology accounting for time-varying medical comorbidities. An important issue is to understand the pathways of the

inverse association of cancer history and AD pathology that may lead to finding adequate treatment modalities for AD.

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VITA

EDUCATION

Certificate in Advanced Training in Clinical Research — 2015 - 2016
Department of Epidemiology and Biostatistics,
University of California, San Francisco, USA

Post-Graduate Diploma in Clinical Research — 2013 - 2014
Institute of Clinical Research, India

Master of Dental Surgery (MDS) — 1996 - 1998
Department of Oral Medicine, Diagnosis & Radiology,
Manipal Academy of Higher Education, Manipal, India

Bachelor of Dental Surgery Practice — 1992 - 1995
SDM Dental College & Hospital, Dharwad, India

RESEARCH INTERESTS

Dementia; neurodegenerative diseases of aging; modifiable risk factors for dementia (e.g., metabolic syndrome, diabetes, cancer, oral health); causal inference methods (e.g. Mendelian randomization); cognitive trajectories in late life

PROFESSIONAL EXPERIENCE

Graduate Research Assistant — Jan 2019-April 2021
Sanders-Brown Center on Aging, Lexington, KY

Graduate Research Assistant — May 2018-Aug 2018
Department of Epidemiology, College of Public Health,
Lexington, KY

Graduate Research Assistant — Aug 2018-Dec 2018
Kentucky Injury Prevention and Research Center,
Lexington, KY

Teaching Assistant — Aug 2017-May 2018
Department of Epidemiology,
College of Public Health, University of Kentucky.

Visiting Scholar — Oct 2016-Apr 2017
Center for Oral Health Research,
College of Dentistry, University of Kentucky

Adjunct Professor — Jul 2013 - Aug 2014
Department of Oral Medicine and Radiology
Treethankar Mahaveer Dental College, Moradabad, India

Assistant Professor — Oct 2009 - Oct 2011
Department of Oral Medicine, Benghazi University, Benghazi, Libya

Associate Professor — July 2007 - Oct 2009
Department of Oral Medicine and Radiology,
M.Ms.N.G.H. Institute of Dental Sciences and Research Center.
Belgaum, India

Lecturer — Nov 1998 - May 2006
Department of Oral Medicine and Radiology
Goa Dental College and Hospital, Goa, India

General DentistryPractice
2003 - 2009 and 2011 - 2015
"Smile 'N' Braces, Dental & Orthodontic Clinic" at Goa, India

PEER-REVIEWED PUBLICATIONS

Karanth S, Schmitt FA, Nelson PT, Katsumata Y, Kryscio RJ, Harp J, Fardo DW, Abner EL. Four common late-life cognitive trajectories patterns associate with replicable underlying neuropathologies. (Accepted, 2021)

Karanth S, Nelson PT, Katsumata Y, Kryscio RJ, Schmitt FA, Fardo DW, Cykowski MD, Jicha GA, Van Eldik LJ, Abner EL. Prevalence and Clinical Phenotype of Quadruple Misfolded Proteins in Older Adults. *JAMA Neurol* 2020;77 (10):1299–1307.

Katsumata Y, Abner EL, Karanth S, Teylan MA, Mock C, Cykowski MD, Lee EB, Boehme KL, Mukherjee S, Kauwe JSK, Kryscio RJ, Schmitt FA, Fardo DW, Nelson PT. Distinct clinicopathologic clusters of persons with TDP-43 proteinopathy. *Acta Neuropathol* 2020;140, 659–674.

Bardach SH, Jicha GA, Karanth S, Zhang X, Abner EL. Genetic Sample Provision Among National Alzheimer's Coordinating Center Participants. *J Alzheimers Dis.* 2019; 69(1): 123–133.

Karanth S, Fowler ME, Mao X, Wilson LE, Huang B, Pisu M, Potosky A, Tucker T, Akinyemiju T. Race, Socioeconomic Status, and Health-Care Access Disparities in Ovarian Cancer Treatment and Mortality: Systematic Review and Meta-Analysis. JNCI Cancer Spectrum. 2019;3(4).

Volvoikar P, Patil S, Dinkar A. Tooth exfoliation, osteonecrosis and neuralgia following herpes zoster of trigeminal nerve. *Indian Journal of Dental Research: Official Publication of Indian Society for Dental Research* 2002 Jan-Mar; 13(1):11-14.

Patil S, Suvarna P, Dayal PK. Central mucoepidermoid carcinoma--a case report. *Indian Journal of Cancer* 2000 Jun-Sep; 37(2-3):123-126.

Patil S, Dayal, P.K., Srinivasan, S. Mandibulo-facial dysostosis (Treacher collins Syndrome*). Karnataka State Dental Journal*, 1997;17:11-14.

Patil S, Dayal, P.K., Srinivasan, S.. Maxillary Metastasis of Osteosarcoma- A Case Report. *The Indian Journal of Dental Research,*1997;8:86-89.

Srinivasan, S. Dayal, P.K., Patil, S. Metastatic Malignant Melanoma of the maxillary gingiva. *The Indian Journal of Dental Research*, 1997;8:119-122.

Divakar H.S., Patil S., Shetty, S.,. Genetic Considerations in Orthodontics. *Indian Journal of Orofacial Genetics,* 1998;1:6-12.

Divakar, H.S., Patil S, Jayade, V.P. Interpretation of Hand and Wrist Radiographs in estimating skeletal maturational status. *Journal of Indian Dental Assosciation*, 2000;71:122-125.

Patil S, Dayal, P.K. Association of oral lichen planus with systemic disorders. *Journal of Dental Research*, 1998;7:827.(Abstract)

MANUSCRIPTS IN PREPARATION

Cancer history associates lower burden of dementia and Alzheimer's-type neuropathology in autopsied research volunteers

Role of Type 2 diabetes in cognitive decline and neurodegeneration in late life: A causal inference approach

Meta-Analysis of the Association between Reproductive Risk Factors and Breast Cancer Hormone Receptor Subtype

ORAL PRESENTATIONS

Karanth S, Abner EL. Cancer history associates with lower burden of dementia and Alzheimer's-type neuropathology in autopsied research volunteers 2020
5th Annual Kentucky Neuroscience Institute Clinical Translational Research symposium, Lexington, Kentucky

Karanth S, Katsumata Y, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Abner EL. Association of metabolic syndrome and cognitive function in a population-based cross-sectional study of adults aged 60 years or older. 2020
Society for Epidemiologic Research Annual Meeting,

Karanth S, Katsumata Y, Kryscio RJ, Nelson PT, Fardo DW, Abner EL. Association of multiple proteinopathies, cognitive decline, and dementia in a community- based autopsy cohort. 2019
4th Annual Kentucky Neuroscience Institute Clinical Translational Research symposium

POSTER PRESENTATIONS

Karanth S, Katsumata Y, Nelson PT, Kryscio RJ, Schmitt FA, Slade E, Vsevolozhskaya O, Fardo DW, Abner EL. Association of metabolic syndrome and cognitive function in a population-based cross-sectional study of adults aged 60 years or older. 2020
Alzheimer's Association International Conference, Virtual

Katsumata Y, Karanth S, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Abner EL. Type 2 diabetes and cognitive status: A causal inference approach to estimate effects 2020
Poster Presentation, Alzheimer's Association International Conference, Virtual

Karanth S, Schmitt FA, Katsumata Y, Nelson PT, Kryscio RJ, Fardo DW, Abner EL. Latent Cognitive Trajectories in Late Life: Results from Alzheimer's Disease Research Centers. 2020
Alzheimer's Association International Conference Neuroscience Next, Virtual

Karanth S, Katsumata Y, Nelson PT, Kryscio RJ, Fardo DW, Abner EL. Association of multiple proteinopathies, cognitive decline, and dementia in a community-based autopsy cohort. 2019
Society for Epidemiologic Research Annual Meeting, Minneapolis, MN

Karanth S, Katsumata Y, Nelson PT, Kryscio RJ, Fardo DW, Abner EL. Association of multiple proteinopathies, cognitive decline, and dementia in a community-based autopsy cohort. 2019
15th Annual Spring Conference, CCTS, Lexington, KY

AWARDS

Graduate Student Congress Conference Travel Award University of Kentucky	2020
Women and Philanthropy Travel Scholarship Sanders-Brown Center on Aging, University of Kentucky	2020
Book Award, Epidemiology/Biostatistics PhD program Highest Score in Comprehensive Examination College of Public Health, Departments of Epidemiology and Biostatistics	2019
Student Conference Travel Scholarship College of Public Health, University of Kentucky.	2019
Medical Center Provost Scholarship College of Public Health, University of Kentucky	2018

MEDIA COVERAGE

"It's not just Alzheimer's disease: Sanders-Brown research highlights form of severe dementia." June 26, 2020. https://sciencenewsnet.in/it-s-not-just-alzheimer-s-disease-sanders-brown-research-highlights-form-of-severe-dementia/,

"Brains of Older Adults Often Harbor Four Common Proteinopathies." July 03, 2020. https://www.medscape.com/viewarticle/933248?src=rss

"Distinct Clinicopathologic Clusters Of Persons With TDP-43 Proteinopathy." Aug 14, 2020. https://myneuronews.com/blog/2020/08/14/distinct-clinicopathologic-clusters-of-persons-with-tdp-43-proteinopathy/

"Ovarian Cancer Studies Aim to Reduce Racial Disparities, Improve Outcomes." July 16, 2020. https://www.cancer.gov/news-events/cancer-currents-blog/2020/ovarian-cancer-racial-disparities-studies

PROFESSIONAL AFFILIATIONS

Society of Epidemiologic Research	2019-to date
Indian Academy of Oral Medicine & Radiology	Life Member
Indian Academy of Aesthetic & Cosmetic Dentistry	Life member
Indian Dental Association	Life Member