Characterising the Clinical and Cognitive Features and Dementia Subtypes of Participants in the Oxford Project to Investigate Memory and Ageing (OPTIMA)

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ABSTRACT

The Oxford Project to Investigate Memory and Ageing (OPTIMA) was a longitudinal study that aimed to promote a better understanding of dementia causes, enable treatment development, and generate prevention strategies. A cohort of older adults, including healthy controls and individuals experiencing cognitive decline, was followed from 1988 until 2011. The comprehensive data collected from these participants included cognitive assessments, health history, imaging (SPECT, CT, and MRI), blood and cerebrospinal fluid, clinical and neuropathological diagnoses, and postmortem brains. Additionally, two later related studies, the Challenge and Longitudinal Early Alzheimer's Disease (LEAD) cohorts, collected similar data and had some overlap in participants, as some individuals joined multiple studies.

Despite the contributions these cohorts have already made to advancing our understanding of dementia, much of the existing research was done using subsets of participants, and a comprehensive summary of OPTIMA and its related cohorts was lacking. This MSc project aimed to address this gap by cleaning and assembling study data in order to describe the overall demographic, clinical, and neuropathological characteristics of the participants: first, for each cohort (OPTIMA, LEAD, Challenge) separately, and second, for the three cohorts combined (the "unified cohort" of individuals). Availability of cognitive, clinical, neuropathological, imaging, blood, and CSF data was evaluated, and serial cognitive assessments were used to calculate the rate of cognitive decline for each participant. Finally, an analysis comparing the last available clinical diagnosis with the neuropathology findings was completed, with the aim of determining the accuracy of clinical diagnosis in life.

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LIST OF ABBREVIATIONS

MCI	Mild Cognitive Impairment
AD	Alzheimer's Disease
VCI	Vascular Cognitive Impairment
VD	Vascular Dementia
Aβ	Amyloid-β
SVD	Small vessel disease
OPTIMA	Oxford Project to Investigate Memory and Ageing
MMSE	Mini Mental State Examination
FTD	Frontotemporal dementia
DLB	Dementia with Lewy Bodies
LBD	Lewy Body Disease
PD	Parkinson's Disease
ODS	Other dementia syndrome
CJD	Creutzfeldt-Jakob disease
PSP	Progressive supranuclear palsy
CBD	Corticobasal degeneration
HD	Huntington's disease
ALS	Amyotrophic lateral sclerosis
CTE	Chronic traumatic encephalopathy
MS	Multiple sclerosis
DALY	Disability adjusted life year
CFAS	Cognitive Function and Ageing Study
ELSA	English Longitudinal Study of Ageing
LMICs	Low- and middle-income countries
APOE	Apolipoprotein E
PSEN1	Presenilin 1
PSEN2	Presenilin 2
APP	Amyloid precursor protein
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
PM2.5	Particulate matter ≤2.5 μm
UK	United Kingdom
LDL	Low-density lipoprotein
TBI	Traumatic brain injury
MoCA	Montreal Cognitive Assessment
ACE	Addenbrooke's Cognitive Assessment
CT	Computed tomography
MRI	Magnetic resonance imaging
CSF	Cerebrospinal fluid
NHS	National Health Service

VICCCS	Vascular Impairment of Cognition Classification Consensus Study
VASCOG	International Society for Vascular Behavioural and Cognitive Disorders
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NINCDS-ADRA	National Institute of Neurological and Communicative Diseases and Alzheimer's Disease and Related Disorders Association
NIA-AA	National Institute of Aging and Alzheimer’s Association
CERAD	Consortium to Establish a Registry for Alzheimer’s disease
VCING	Vascular cognitive impairment neuropathology guidelines
NICE	National Institute for Health Care and Excellence
AChE	Acetylcholinesterase
NMDA	N-methyl-D-aspartate
SSRI	Selective serotonin reuptake inhibitors
LEAD	Longitudinal Early Alzheimer’s Disease cohort
BDR	Brains for Dementia Research
HIV	Human immunodeficiency virus
SPECT	Single-photon emission computed tomography
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CAMCOG	Cambridge Cognitive Examination
NART	National Adult Reading Test
CDR	Clinical Dementia Rating
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
HVLT	Hopkins Verbal Learning Test
CLOX	Executive clock drawing task
SDMT	Symbol Digital Modalities Test
NPI	Neuropsychiatric Inventory
BADLS+	Expanded Bristol Activities of Daily Living
PM	Postmortem
TR	Total Recall
DR	Delayed Recall
HVLT	Hopkins Verbal Learning Test
CANTAB PAL	Cambridge Neuropsychological Test Automated Battery Paired Associates Learning
ADLs	Activities of daily living
ECG	Electrocardiogram
EEG	Electroencephalogram
FTLD	Frontotemporal lobar degeneration
TDP-43	TAR DNA Binding Protein 34

CHAPTER 1: INTRODUCTION

1.1. Introduction to Dementia

Dementia consists of a significant impairment in cognition relative to an individual's baseline level that inhibits the person from completing daily activities, such as work, social engagement, and personal care tasks (1, 2). Rather than being a specific disease, dementia is a syndrome, meaning that it is characterized by certain symptoms, though its presentation can vary to a degree from person to person. Dementia can have devastating effects, both for the patient and for their loved ones (2). As the population worldwide grows older, investigating how to effectively prevent, diagnose, and treat dementia is a crucial research priority.

1.2. Overview of Cognitive Impairment and Dementia Subtypes

There are a variety of conditions that can give rise to cognitive impairments (which can be mild, moderate, or severe), including dementia. This section will provide a brief overview of cognitive impairments, as well as some of the most prominent subtypes of dementia (Figure 1.1).

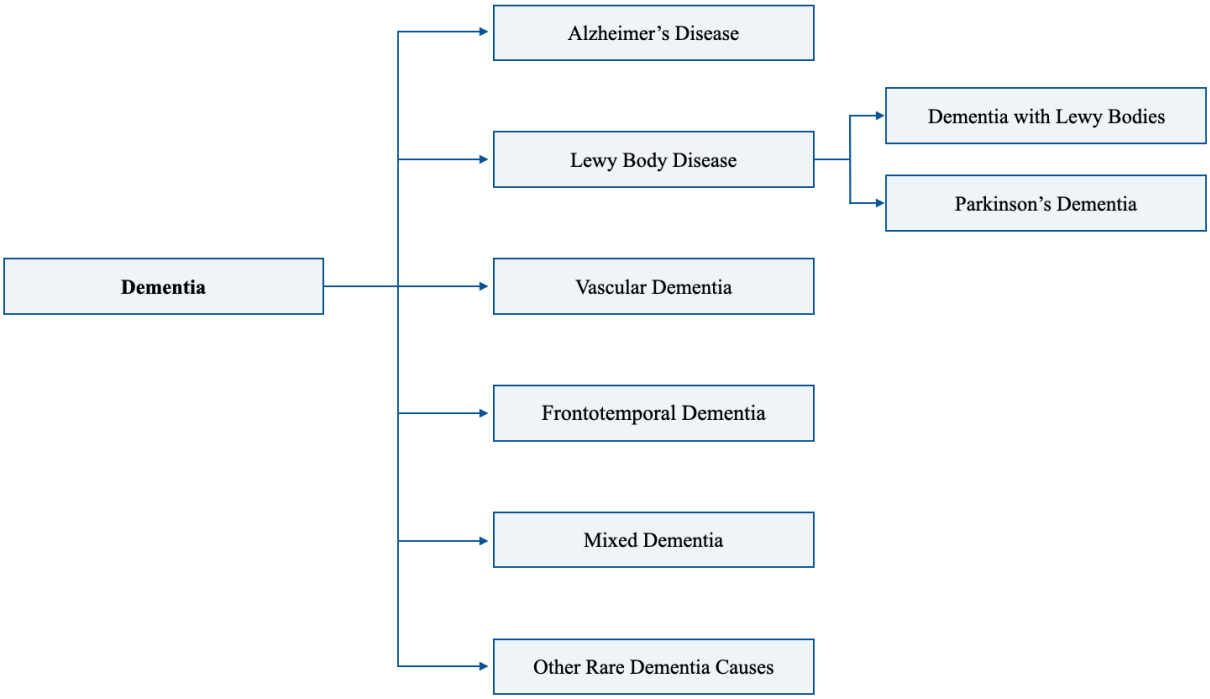


Figure 1.1. Overview of subtypes of dementia.

1.2.1. *Cognitive Impairment*

The term "cognitive impairment," also referred to as "cognitive deficit", encompasses a wide range of problems within any facet of cognition (3). This designation can be used to describe any severity of cognitive concern, and this may be permanent, progressive, or reversible depending on the cause (3). Some examples of causes of cognitive impairments include delirium, stroke, head injury, alcohol or drugs, psychiatric disorders, infections, and neurodegenerative conditions (4-9).

Mild cognitive impairment (MCI) denotes a decline in cognition that is worse than what would be expected with normal aging-related changes, but not severe enough impairment to warrant a dementia diagnosis (10). The two subtypes of MCI are amnestic (the more common subtype involving impaired memory and a high risk of developing into Alzheimer's Disease (AD)) and non-amnestic (characterized by worsening of other areas of cognition) (11, 12). As was described in the previous paragraph, MCI can have a range of causes, and not all patients with MCI will have further worsening of cognition and meet the threshold for dementia; some may even return to normal cognitive function over time (13).

Vascular cognitive impairment (VCI) is an impairment in cognitive function attributed to vascular causes, although there is not yet consensus on the criteria for diagnosis (14). Although some sources include vascular dementia (VD) cases within VCI (15), for this study, VCI was designated when an individual met criteria for MCI and had some evidence of a contributing vascular pathology, such as infarcts, lacunes, or small vessel disease (more detail on the diagnostic criteria can be found in Chapter 2). VCI has similar causes and presentation to VD but is less severe (15).

1.2.2. Alzheimer's Disease (AD)

AD is the most common disease underlying dementia, as this subtype causes an estimated 60% of all dementia cases (16). Late onset AD (age 65 and older) cases make up the majority of AD diagnoses, while early onset cases (starting as young as age 30) are less common, making up about one to six percent of AD (17).

Clinically, AD is characterized by memory loss, which typically begins with episodic memory problems, as well as impairments in additional cognitive domains, including attention, language, and mood (17-19). Neuropsychiatric symptoms, such as anxiety, depression, apathy, and problems with sleeping can also occur (20).

At the cellular level, AD arises from a "dual proteinopathy," consisting of aggregates of amyloid-β (Aβ) and tau proteins (16). Aβ proteins aggregate outside of cells in the brain, forming amyloid plaques, also referred to as neuritic plaques (16). Hyperphosphorylated tau proteins aggregate within neurons, forming neurofibrillary tangles, which can impede signalling between neurons (16).

1.2.3. Vascular Dementia (VD)

VD makes up at least one fifth of dementia cases, making it the second most common subtype after AD (15). VD is a heterogenous classification, as various pathologies can contribute this type of cognitive decline, including infarcts, small vessel disease (SVD), hypoperfusion, and haemorrhage (14, 21).

The clinical presentation of VD also varies, although there is often worsening attention and executive function (14). Additional symptoms of depression, emotional lability, and apathy are also common (14, 22). While difficulties with memory can occur, this symptom is not as predominant in VD as in AD (21). VD can often begin in the wake of a stroke or other vascular event, and there can be a stepwise decline in the individual's cognitive status over time (23).

1.2.4. Mixed Dementia

Mixed dementia, where one patient suffers from multiple pathologies, is another important classification. One noteworthy type of mixed dementia is a combination of AD and VD pathology (24). Various studies, including one published by Esiri et al. based on Oxford Project to Investigate Memory and Ageing (OPTIMA) data, have shown that those with Alzheimer's disease have worse cognition when cerebrovascular disease is also present (24, 25). Additionally, the Nun Study found that patients who had both AD pathology and infarcts had lower scores on the Mini Mental State Examination (MMSE) cognitive assessment and were more likely to develop dementia when compared to patients who had AD but no infarcts (24, 26). Having both AD and infarct pathology has been found to grow more common with age, as this is seen more frequently in older adults aged 90 or over when compared to those between 65 and 89 years old (27). In addition to mixed AD and VD, patients can also develop mixed dementia with any number of combinations of different dementia subtypes, such as with concurrent AD and Lewy Body Disease (LBD) or VD and LBD (28).

1.2.5. Frontotemporal Dementia (FTD)

Frontotemporal dementia (FTD) is the second most common subtype of dementia in younger age groups, with onset between ages 45 and 65 (29). FTD is a syndrome that is characterized by atrophy in the frontal and/or temporal lobes of the brain caused by abnormal protein clumping (30-32). FTD was initially called Pick's Disease, after the man who first described the condition in the late 19th century (30).

The majority of FTD cases (60%) have their onset between the ages of 45 and 64, and people typically live for six to 11 years after symptoms begin (30). There are three different types of FTD. The first is characterised by behavioural changes, with symptoms such as disinhibition, apathy, changes in food preferences, and executive impairments (30, 32). The other two variants are distinguished by speech-related symptoms: in the non-fluent primary progressive aphasia type there is difficult speaking, while the semantic type of FTD involves impaired ability to understand words (30, 32).

1.2.6. Dementia with Lewy Bodies (DLB)

Dementia with Lewy Bodies (DLB), which falls within the broader classification of LBD, is a dementia subtype characterised by the presence clumps of α-synuclein proteins known as Lewy Bodies (33).

Some clinical characteristics that can distinguish this type of dementia include visual hallucinations, problems with REM sleep, apathy and fluctuating cognitive abilities throughout the day (33, 34). Unlike Parkinson's Disease (PD), which will be discussed next, motor symptoms typically develop later than cognitive changes in patients with DLB (33). Memory tends not to be at the centre of DLB symptoms, with cognitive deficits instead appearing more prominently in executive and visual domains (34).

1.2.7. Parkinson's Disease (PD)

Dementia can develop in many patients with PD, with estimates ranging from 16% to 40% of those with PD (35, 36). Various pathologies can contribute to this neurodegenerative disease, ultimately causing insufficient dopamine production due to neuron death in the substantia nigra (37, 38). PD's most common clinical symptoms, aside from bradykinesia and rigidity, include motor tremors, constipation, and problems with REM sleep (38).

PD dementia is also characterized by the presence of Lewy Bodies, and it has been proposed that PD-associated dementia is on a spectrum with DLB, though the characterization of this connection is still being debated (35, 39). Symptoms associated with dementia caused by PD include problems with memory, hallucinations, attention, depression, fluctuating cognition, visuospatial impairment, among other signs (35, 38, 40).

1.2.8. Other Dementia Syndromes (ODS)

In addition to these more common causes of dementia, there are a range of other, more rare conditions. One such neurodegenerative disorder is Creutzfeldt-Jakob Disease (CJD), which is a condition caused by misfolded prion proteins (41-43). Dementia associated with CJD is typically sporadic, worsens rapidly, and the disease is ultimately fatal, typically within a year after CJD onset (41, 42).

Progressive supranuclear palsy (PSP), a condition caused by pathological tau protein aggregation, can also cause dementia (44). PSP can affect a range of areas in the central nervous system and, like CJD, PSP is typically sporadic (44).

Additionally, corticobasal degeneration (CBD), another tau protein-caused condition, can underlie dementia (45). Some of the symptoms that CBD patients may experience are motor-related, such as limb rigidity and apraxia, and with regards to cognitive changes, dementia is now recognized as a principal feature of the disorder (45).

Another rare cause of dementia is Huntington's disease (HD), a neurodegenerative condition that is inherited and typically begins to manifest between ages 30 and 50 (46). HD causes symptoms that include chorea, psychiatric symptoms, and cognitive decline (46).

An additional rare neurodegenerative disease associated with dementia is amyotrophic lateral sclerosis (ALS), which is characterized by progressive deterioration caused by the loss of motor neurons (47). Although not all patients with ALS will develop dementia, if they do it is typically of the frontotemporal variety (47).

There are a wide range of rare causes of dementia, and this section has highlighted just a subset. Table 1.1 below presents a more comprehensive list of rarer conditions that can cause dementia.

Other Causes of Dementia
Creutzfeldt-Jakob disease (CJD) and other prion diseases
Progressive supranuclear palsy (PSP)
Corticobasal degeneration (CBD)
Huntington's disease (HD)
Amyotrophic lateral sclerosis (ALS)
Normal pressure hydrocephalus
Binswanger's disease
Chronic traumatic encephalopathy (CTE)
Multiple Sclerosis (MS)
Vasculitis
Niemann-Pick disease type C
HIV-associated neurocognitive disorder
Vitamin deficiencies
Alcohol-related dementia
Wernicke-Korsakoff syndrome
Posterior cortical atrophy
Epilepsy
Autoimmune disorders
Toxin exposure (e.g., heavy metals like lead and mercury)
Cancer
Psychiatric disorders

Table 1.1. List of some additional causes of dementia (48-51).

1.3. Epidemiology of Dementia

Dementia exerts a significant impact on population health around the world. AD and other dementias are the seventh leading cause of death for all age groups globally, and for those over the age of 70, dementia is the fourth leading cause of death (52). In terms of disability adjusted life years (DALYs), which measures the sum of the years of life lived with disability and the years lost due to premature death, dementia is one of the top 10 contributors for the global population over the age of 60 (53, 54).

The prevalence of dementia in adults over age 50 is approximately 700 per 10,000, although the prevalence increases with age, with estimates between 422 to 970 per 10,000 for older adults between the ages of 85 and 89 (55, 56). The prevalence of AD is 324 per 10,000, while the prevalence of VD is 116 per 10,000 people (55). Population-based studies conducted around the world largely indicate that the prevalence and incidence of dementia have been either declining or stable (57). In the England, the Cognitive Function and Ageing Study (CFAS) demonstrated that the overall prevalence of dementia in adults age 65 and over decreased from 8.3% to 6.5% from CFAS I (from 1989 to 1994) to CFAS II (2008 to 2011), although the overall size of the population of older adults rose (58).

Given the range of costs associated with dementia, from medical treatment to caregiving, this condition has a large economic burden. The World Alzheimer Report from

2015 estimated that the annual global cost of dementia was $818 billion, with an expected rise to two trillion dollars by 2030 (54). Moreover, in 2019, it was estimated that the total cost of dementia was over $1.3 trillion dollars, which included medical care, formal caregiving, and informal caregiving (59).

The population worldwide is both growing and ageing, and thus, researchers predict that the burden of dementia will increase. One study based on the English Longitudinal Study of Ageing (ELSA) forecasts that, although there will be a decline in dementia incidence, the number of adults living with dementia in England and Wales would increase from 767,000 to approximately 1.2 million people between 2016 and 2040 (60). Another study using Chicago Health and Ageing Project data and United States Census projections predicts that the number of Americans living with AD will increase from approximately 6 million people in 2020 to 13.85 million people in 2060, with a disproportionate increase among women, Hispanic people, and non-Hispanic Black people (61). This study also estimates that between 2020 and 2060 the number of individuals with MCI in the United States will increase from 12.23 million to 21.55 million (61).

Worldwide, the Global Burden of Disease Study data predicts the dementia population will increase from 57.4 million people in 2019 to 152.8 million people in 2050, with varied increases in different regions (62). The greatest increases in people living with dementia are expected to take place in low- and middle-income countries (LMICs), where the older population as a whole will be rapidly growing (54). Although there is uncertainty as to how closely future dementia prevalence will match these extrapolations, the predicted burden of this condition which will necessitate significant medical and public health efforts to prepare for and effectively care for increased numbers of people living with dementia.

1.4. Risk Factors and Prevention

1.4.1. Genetic Risk Factors

Various genes that cause dementia or increase risk of dementia have been identified. One of the most well-known is the Apolipoprotein E (*APOE*) gene, which has certain alleles that increase or decrease one's risk of developing cerebral amyloid angiopathy and AD (63). One allele, ε2, is protective, while another, ε4, is linked to increased odds of AD occurrence, lower AD onset age, and more severe consequences of stroke and head trauma (17, 63). The ε4 allele is also linked to higher risk of developing LBD and dementia resulting from PD (64).

Additionally, genes that have been linked to autosomal dominant AD include Presenilin 1 (*PSEN1*), Presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP)* (17). These genes tend to cause early onset AD and are rare, accounting for only between 1-6% of AD cases.

The genes associated with VD are still being investigated, but some studies have identified that the APOE ε4 allele also increases VD risk, as does the *NOTCH3* gene underlying cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) that can cause VD (2, 14, 65, 66). Additional research has

linked VD to the *MTHFR C677T*, *TNF-α −850C/T, TGF-β1 +29C/T*, and *PON1 L55M* gene polymorphisms (66).

Genetic risk factors for other types of dementia have also been identified. FTD has been found to often have a genetic component, as between one-fifth to one half of patients are thought to have a family history of the condition (67, 68). The most common mutations associated with FTD occur in the following genes: *C9orf72*, *GRN*, and *MAPT* (67, 68).

Cognitive impairments and dementia are multifaceted conditions, and research has shown that genetics can play a role, and ongoing research continues to investigate the genetic component of dementia.

1.4.2. Modifiable Risk Factors and Prevention Strategies

While aging and certain genetics are risk factors for dementia and cognitive decline that are inevitable and unchangeable, there are various other modifiable risk factors. In 2020, the Lancet Commission report stated that if 12 modifiable risk factors could be addressed, then 40% of dementia cases around the world could theoretically be prevented or slowed (69). These factors are "less education, head injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, infrequent social contact, and air pollution" (70). The 2024 Lancet report adds two additional factors: vision loss and high cholesterol (70). In observational studies of risk factors, it should be noted that there can be confounding variables and potentially reverse causation, and factors may have a different impact across the life course.

There are various environmental exposures that have been found to increase the risk of developing dementia. With regards to air pollution, which people with low socioeconomic status are more exposed to, it has been shown that coming into contact with carbon monoxide, tobacco smoke, nitrogen oxides, nitrogen dioxide, and particulate matter ≤2.5 μm (PM2.5) can all increase dementia risk (71, 72). Exposures to some metals, including lead, aluminium, cadmium, or manganese, through drinking water and food can increase risk of cognitive decline (72, 73). While individuals may not have the ability to change the quality of environmental conditions directly, these factors can be improved at the population level through public policies (74).

In addition to environmental exposures, there are various lifestyle factors that can impact dementia risk. A retrospective cohort study using United Kingdom (UK) BioBank data found that leading a healthy lifestyle, with factors like physical activity, nutritious food, and not smoking, lowered dementia risk (75). This lowered risk occurred for both high and low genetic risk participants, indicating that genetic risk can be counteracted by implementing a healthy lifestyle (75). However, it should be noted that all of these protective factors are linked to affluence, so when deprivation is adjusted for these, the associations may not be as strong.

Physical inactivity is a well-established modifiable dementia risk factor. Not being physically active, particularly in older age, is associated with higher dementia risk, while exercising more increases the protective effect (70, 76). The benefits of physical activity may

counteract obesity, the development of cardiovascular problems, and diabetes, all of which are associated with dementia (69). High low-density lipoprotein (LDL) cholesterol, particularly in mid-life, has also been noted to increase dementia risk, as this is linked with increased Aβ and tau proteins and risk of stroke (70). Sleeping problems, such as insomnia, poor quality of sleep, and sleep apnoea, are also linked to increased risk of developing dementia, though the 2024 Lancet Commission notes that further research is needed (70, 77).

Smoking and alcohol are also potential modifiable risk factors for dementia. Research has found that smoking does increase dementia risk, but this risk can be reduced or eliminated when people stop smoking (70, 78). This emphasizes the importance of smoking cessation efforts to lessen dementia risk (70, 78). The effect of alcohol on dementia risk remains contentious, as some studies have reported that consuming small to moderate amounts of alcohol is linked to reduced risk of AD or VD onset, while others have reported that this is not the case (79, 80). However, it has been clearly demonstrated that consuming large amounts of alcohol and having an alcohol use disorder do increase dementia risk (80).

Social isolation and the feeling of loneliness can also increase the risk of cognitive decline and dementia (70, 81). Engaging with other people more often acts as a protective factor and is correlated with higher cognitive function in older adulthood (70). Programs that encourage social connection, such as Experience Corps®, where older adults go to elementary schools to tutor students for 15 hours each week, can improve the health of older adults and potentially lessen dementia risk (82). Further research about the potential effectiveness of interventions to increase socialization are needed (70).

In addition to these lifestyle-related variables, there are some additional factors related to the senses that can impact dementia risk. One of these is hearing loss, which is associated with higher dementia risk, and can be ameliorated through interventions including hearing aids (70). Vision loss, which could be due to conditions like cataracts or diabetic retinopathy, has also been deemed a risk factor for dementia (70). Treating visual impairments could be a straightforward and economical way to lower dementia risk, especially in countries with less resources where vision loss is frequently not addressed (70).

Being diagnosed with depression has also been associated with increase dementia risk, so it is important to ensure that people have access to care and treatment for this mental health condition (70, 83). Another potentially preventable factor that increases dementia risk is traumatic brain injury (TBI), particularly when the TBI is moderate to severe at younger ages or even when it is a mild TBI in older adulthood (69, 84). Interventions to prevent TBI can include measures like ensuring that protective head gear is worn in sports like American football and changing game rules to lessen the likelihood of head injury (70).

Additional health conditions that can increase dementia risk are infections. Serious infections requiring hospitalization were shown to increase long-term risk of dementia onset, with more frequent infections showing a dose-response with dementia risk (85). Given that this association was preserved regardless of the type of infection and location of infection, the researchers hypothesize that this increased risk of cognitive decline could be the result of inflammation throughout the body (85).

Delirium, referring to an acute worsening in a person's cognition relative to their baseline status, is also a syndrome that can increase dementia risk (4). Although they are discrete syndromes affecting cognition, there is a connection between dementia and delirium. Individuals with dementia are more likely to develop delirium, and if they do experience delirium, it has been shown to further hasten their cognitive decline (4).

Thus, there are a range of potentially modifiable or preventable factors that increase or decrease one's risk of developing dementia.

1.5. Current Clinical Approaches to Dementia

1.5.1. Diagnosis

Diagnosing dementia is typically a multifaceted process and generally involves clinical evaluation, cognitive assessments, neuropsychological testing, and potentially imaging or other tests. The clinician will take a comprehensive history, asking about topics such as how long the cognitive decline has been occurring, the patient's ability to complete their activities of daily living, and their family medical history (1). Cognitive assessments that are commonly used are the MMSE, the Montreal Cognitive Assessment (MoCA), and Addenbrooke's Cognitive Assessment (ACE) (1, 86). Neuropsychology tests can be useful to gain a better understanding of which domains are most affected, such as memory, visuospatial function, and language; these tests can also help distinguish between diagnoses in people with high levels of education or determine whether there are other psychological conditions that could be impacting cognition (87). Physical and neurological exams can also be helpful to identify additional signs, including the localized effects of a stroke (88).

Imaging and biomarkers contribute to the diagnostic process for dementia by helping with subtyping and excluding other conditions, such as cancer, subdural hematoma, or normal pressure hydrocephalus (89). Imaging with computed tomography (CT) or magnetic resonance imaging (MRI) scans can help reveal features such as focal atrophy, vascular changes, hydrocephalus, or other irregularities associated with dementia (89, 90). Cerebrospinal fluid (CSF) samples can also be used to measure levels of Aβ and tau tangles, although this is not consistently done in clinical settings because the invasive lumbar puncture procedure may not be appropriate for all older patients (89). Currently, the National Health Service (NHS) typically uses blood tests to exclude other potential causes of cognitive decline or to identify remediable factors (such as levels of vitamin B12 or folate), rather than to indicate whether a dementia diagnosis is appropriate (91). Blood tests can also be used for genetic testing, particularly for early onset dementia cases (1).

There are various guidelines for the diagnosis of different dementia subtypes which have been updated and modified as dementia research progresses. For example, the heterogeneous nature of VD can make it challenging to diagnose, but the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) produced improved guidelines in 2018, and the International Society for Vascular Behavioural and Cognitive Disorders (VASCOG) criteria can also be used to identify additional VD cases (2, 92, 93). Previously, and at the time of the OPTIMA study, criteria from the National Institute of

Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) were utilised (94).

There are different sets of criteria that are used for diagnosing AD. The AD diagnostic criteria used as the basis for diagnosis in the three cohorts described in this study were developed by the National Institute of Neurological and Communicative Diseases and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) in 1984 (95). The more recent National Institute of Aging and Alzheimer's Association (NIA-AA) guidelines are now utilised for research, as these were published in 2011, revised in 2018, and incorporate updated research to modify the original criteria (96, 97). Although these NIA-AA guidelines are intended for research purposes rather than for clinical care, this framework is useful for guiding AD-related research (97).

In addition to the criteria used to characterise VD and AD, there are additional guidelines for other dementia subtypes. Another example is for the diagnosis of DLB, which was first characterised by the International Consensus Diagnostic Criteria on Dementia with Lewy Bodies in 1996; these criteria were then refined at the DLB Consortiums in 2005 and 2017 (98-101). Despite guidelines like these, the clinical diagnosis of DLB remains difficult, and many patients with DLB are misdiagnosed (99).

Although various criteria and methods can be used to identify clinical characteristics that are associated with specific pathology, these clinical diagnoses have improved over time but are not perfect (16). Currently, definitive diagnosis of particular types of dementia requires neuropathology review following death (16). Neuropathologists can identify features such as the extent of amyloid plaques and neurofibrillary tangles, as well as Lewy bodies, infarcts, cerebrovascular disease, and more (102). There are various criteria for quantifying and classifying these findings, such as the Braak Lewy Body staging, the Braak Neurofibrillary Tangle staging, the Consortium to Establish a Registry for Alzheimer's disease (CERAD) score for amyloid plaque density, and the vascular cognitive impairment neuropathology guidelines (VCING) criteria (102).

As the accurate diagnosis of dementia subtype remains a challenge, this continues to be an area of active research. It is particularly challenging to diagnose preclinical and prodromal dementia, so this is a current research focus (103). Some researchers are working on using artificial intelligence to diagnose dementia using various sources of data, such as medical records, imaging, analysis of the patient's writing and speech, and genetics (104). Early diagnosis is needed to ensure prompt support, and refining clinical diagnoses of dementia subtype is a critical research priority to enable correct treatment when more pharmaceutical options become available in the future.

1.5.2. Management and Treatment

Important management approaches that apply broadly to all types of dementia include prompt diagnosis to enable the individual and their family to access resources, treatment of comorbid conditions, and appropriate education and support for the patient, their family, and their caregivers (14). In the UK, the National Institute for Health Care and Excellence (NICE)

guidelines provide evidence-based recommendations for managing and treating dementia, including both pharmacological and nonpharmacological interventions (105).

Nonpharmacological approaches to help manage behavioural symptoms can include maintaining a consistent routine, limiting alcohol use, and having the patient wear a bracelet with identifying information if they tend to wander (106). It is also important to prevent the individual with dementia from engaging in behaviours that could be dangerous to themselves and others, such as potentially driving (107). Other management strategies for FTD symptoms, which could apply to other dementia types as well, consist of encouraging the patient to engage in familiar hobbies, decreasing noise in the environment, and having the patient interact only with small groups to lessen overstimulation (31). Psychotherapy can also help with symptoms of depression and anxiety (107).

Although a cure for dementia has not yet been developed, there are some pharmacological options available, and many new pharmaceuticals are undergoing clinical trials. There are various approaches to manage symptoms, and some drugs were recently approved by the FDA to slow cognitive decline in early AD, including aducanumab and lecanemab (108).

In mild to moderate AD cases, acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, and rivastigmine) aim to improve cognition (105, 107, 109). They accomplish this by keeping the excitatory neurotransmitter acetylcholine in the synapse for longer, thereby counteracting the loss of cholinergic neurons that occurs in AD (107, 109). AChE inhibitors lose effectiveness with AD severity, but the drug memantine (an N-methyl-D-aspartate (NMDA) agonist) can be used alone and or in combination with AChE inhibitors for patients with moderate to severe AD (105, 109).

AChE inhibitors can also provide a slight improvement for VD patients, though these benefits may not be clinically significant and may not outweigh the drug's side effects (2, 110). There is evidence that memantine can be used to boost cognition for LBD and VD, and rivastigmine can be effective for cognitive symptoms and hallucinations in LBD patients (107, 111, 112). The NICE guidelines indicate that AChE inhibitors and memantine should only be used in VD patients if the clinician believes there is another dementia subtype that is comorbid, including AD, DLB, or PD (105). These guidelines also recommend "offer[ing] donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies," and only utilising galantamine if those two medications are not tolerated (105). The NICE guidelines also endorse considering donepezil or rivastigmine if DLB is severe, and they say to "consider memantine for people with [DLB] if AChE inhibitors are not tolerated or are contraindicated" (105). However, because of the limited effects of these treatment options, medical care for those with VD and LBD primarily focuses on addressing comorbidities and specific symptoms (2, 113, 114).

While no pharmaceuticals have been approved to address the progression of FTD, behavioural symptoms can be managed using selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics, and some studies with small cohorts have shown potential

benefits of stimulants to reduce risk-taking (30, 31). AChE inhibitors and Memantine have proven to be ineffective for FTD (30, 31).

1.6. The Oxford Project to Investigate Memory and Ageing (OPTIMA) and MSc Project Introduction

OPTIMA was a longitudinal study, from 1988 until 2011, that followed a cohort of older adults, including healthy controls and individuals experiencing cognitive decline. According to archived study materials, the cohort was designed to promote a better understanding of dementia causes, enable treatment development, and generate prevention strategies. The comprehensive data collected from these participants includes cognitive assessments, health history, imaging, blood and CSF, clinical and neuropathological diagnoses, and postmortem brains (115). Additionally, two related studies, the Challenge and Longitudinal Early Alzheimer's Disease (LEAD) cohorts, collected similar data and have some overlap in participants, as some individuals joined multiple studies (116).

The OPTIMA, Challenge, and LEAD cohorts have already contributed a tremendous amount to dementia research in a wide variety of areas, with over 250 publications. These findings range from exploring the relationship between small vessel disease and cognitive impairment, evaluating the stability of MCI and screening methods for this condition, analysing cognitive trajectories after surgery, assessing CSF biomarkers for AD, identifying a genetic risk factor for FTD, and more (116-120). The participants and researchers who contributed to these cohorts over many years have enabled significant steps forward in our understanding of aging and cognitive decline.

Despite the contributions that the OPTIMA, Challenge, and LEAD cohorts' data has already made to advancing our understanding of dementia, much of the existing research has been done using smaller subsets of participants, and a comprehensive overview of OPTIMA and its related cohorts is lacking. There has never been a paper describing the individuals in these cohorts, which is needed by researchers using this as a publicly available resource. This MSc project aims to address this gap by describing the overall demographic, clinical, and neuropathological characteristics, as well as the availability of cognitive, clinical, neuropathological, imaging, blood, and CSF data. Clarifying the nature of this extensive resource will add value to the Oxford Brain Bank and the biological sampling available, and researchers will be able to design additional research questions that can advance our understanding of dementia.

Moreover, this project includes an analysis of the alignment between the last clinical diagnosis made in life and neuropathology findings that were established postmortem. Given the importance of determining accurate clinical diagnoses of dementia subtype, particularly as new pharmaceuticals for various types of dementia undergo clinical trials and become more widely available, this evaluation could help refine clinical diagnosis going forward.

MSc Project Objectives:

1. Clean and assemble data from the OPTIMA, Challenge, and LEAD database on participants, including demographics, length of follow-up, cognitive testing results,

MCI and dementia diagnosis, and availability of brain imaging, CSF, and clinical bloods, and postmortem neuropathology.

2. Determine the degree of overlap between the OPTIMA, Challenge, and LEAD cohorts.
3. Look at the change in cognition over time by calculating a rate of cognitive decline for each individual (from first and final cognitive scores and time elapsed between scores).
4. Describe the characteristics of the combined cohorts of individuals (the "unified cohort" of individuals), without double counting individuals in multiple cohorts.
5. Compare the last available clinical diagnoses to the neuropathology findings to evaluate the alignment between them.

CHAPTER 2: Study Methods

2.1. OPTIMA, Challenge, and LEAD Overview

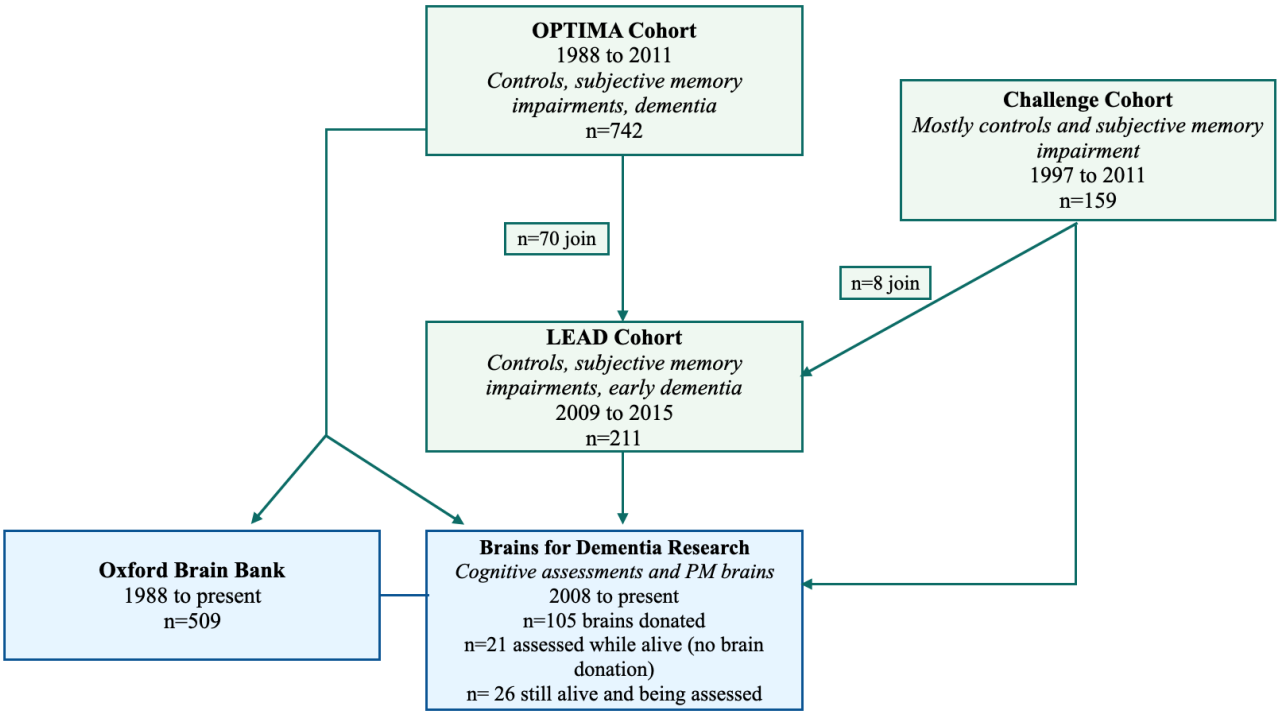


Figure 2.1. Schematic overview of connections between OPTIMA, Challenge, and LEAD cohorts (in green), as well as the Oxford Brain Bank and Brains for Dementia Research (in blue).

The Oxford Project to Investigate Memory and Ageing (OPTIMA) was a longitudinal study that was conducted from 1988 until 2011 (115). The OPTIMA study was founded by Margaret Esiri, Professor of Neuropathology, and A. David Smith, Professor of Pharmacology (115). While these two researchers were initially pursuing the specific goal of assessing whether acetylcholinesterase in CSF could be used as a biomarker of AD in living patients, OPTIMA's multimodal data collection has enabled the pursuit of a wide array of questions on aging and cognitive decline (115).

OPTIMA's broader aims were to provide insights into changes in the brain and body occurring because of dementia as compared to normal brain ageing (115). OPTIMA recruited 742 participants, who had yearly visits with a medical exam, laboratory samples, and imaging, in addition to cognitive assessments every six months. Information was also collected from each participant's study partner.

Several legacy cohorts related to OPTIMA were subsequently founded (Figure 2.1). The Challenge cohort, consisting of primarily healthy controls, began in 1997, with the goal of conducting a longitudinal study with a similar structure to OPTIMA, in order to better understand the predictors of cognitive decline and dementia (121). For this cohort, the study team recruited 159 older adults who had either MCI, a subjective memory complaint, or no cognitive symptoms, and lived in the Oxford community (121). Seventy participants from

OPTIMA and eight participants from Challenge (which concluded in 2011) also joined the Longitudinal Early AD (LEAD) cohort. LEAD ran from 2009 to 2015 and had a total of 211 participants. Although it will not be discussed further in this thesis, another legacy cohort related to OPTIMA is the VITACOG study, which consisted of a two-year-long randomised controlled clinical trial evaluating the effects of Vitamin B6, Vitamin B12, and folic acid on homocysteine levels and cognitive decline in 266 individuals with MCI (122). Fifteen OPTIMA participants were also included in VITACOG.

A key aspect of OPTIMA and the related studies that adds to their significant value for research is the number of participants who chose to donate their brains after death. From the inception of these cohorts, brains were donated to the Oxford Brain Bank, housed at the John Radcliffe Hospital and part of the larger UK Brain Banks Network (123, 124). In 2008, the Oxford Brain Bank became a member of the Brains for Dementia Research (BDR) Network, a separate research study (125, 126). After the OPTIMA, Challenge, and LEAD studies ended, some participants completed additional follow-up through the BDR while they were alive, which includes further cognitive assessments. Over the course of the study, the protocol was updated to reflect advances in neuropathology methods, as will be described in more detail in this chapter.

2.2. OPTIMA Study Methods

2.2.1. OPTIMA Referral Sources

Participants, including healthy controls and those with memory impairments, were recruited to participate in the OPTIMA cohort through a variety of methods (Figure 2.2). Participants with memory problems, as well as healthy controls, were recruited through the Oxfordshire Health Authority (previously the administrative body responsible for the NHS services in Oxfordshire) in England (127). Those who reported memory concerns were referred to the Memory Clinic in Oxford, and some recruitment for the study took place here.

Referral sources were recorded for 732 out of the 742 OPTIMA participants (Table 2.1). The largest proportion of the OPTIMA cohort (250 individuals) were recruited from outpatient settings in Oxfordshire. Of these participants recruited through outpatient settings, at baseline 162 had dementia, 24 were controls, 33 had MCI, 10 had VCI, and 21 had a psychiatric condition or were difficult to classify. GP referrals were also an important recruitment method, with 184 participants (approximately 25% of the cohort) joining through this route. A smaller subset of the cohort (15 participants with dementia at baseline and 7 people with psychiatric or difficult to classify condition) was recruited through psychiatric inpatient setting. Three participants were recruited through a geriatric outpatient clinical setting, and one individual with dementia was referred through a nursing home.

A further 242 OPTIMA participants were recruited through “Other” methods, and 30 individuals were referred through the community. One paper about a subset of the OPTIMA cohort describes how some healthy controls were recruited to the study through leaflets and talks that took place at "retirement association clubs,” so these methods could account for some of the referral sources listed as “Other” and “Community” (127). Some healthy control

participants were relatives of those with memory concerns participating in the study, so these participants could also be included in the "Other" categorization (127, 128).

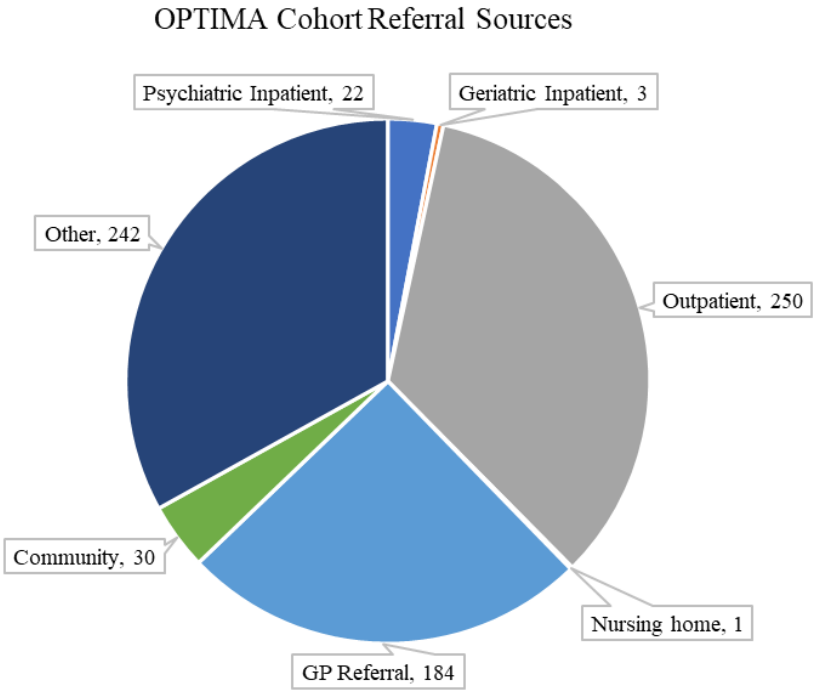


Figure 2.2. Pie chart of referral sources recorded for OPTIMA cohort participants (n=732).

Referral Source	**Total number of participants**	**Referral Source by Diagnosis at Baseline**				
		Control	**MCI**	**VCI**	**Dementia**	**Psychiatry or difficult to classify**
Psychiatric Inpatient, n	22	0	0	0	15	7
Geriatric Inpatient, n	3	0	0	0	2	1
Outpatient, n	250	24	33	10	162	21
Nursing home, n	1	0	0	0	1	0
GP Referral, n	184	53	28	10	80	13
Community, n	30	0	6	1	22	1
Other, n	242	153	18	5	62	4
Total, n	**732**	**230**	**85**	**26**	**344**	**47**

Table 2.1. OPTIMA cohort referral sources.

Insufficient information on referral sources for the Challenge and LEAD cohorts was recorded to provide participant-specific information. Archived study materials indicate that,

similarly to OPTIMA recruitment methods, LEAD participants were recruited through referrals from GPs, old age psychiatrists, gerontologists, and neurologists, as well as through other studies, self-referrals, leaflets, and advertisements in newspapers and newsletters. Previously published literature using Challenge cohort data mentioned that healthy controls living in the community in Oxfordshire were recruited via advertisements on the radio and lectures (129).

Hand-searching of some Challenge and LEAD files revealed that some participants were connected to the study team through their GP, some attempted to join the VITACOG clinical trial but were ineligible and joined one of these studies instead, others heard about the study by word of mouth from a friend who was already participating, among other reasons for joining.

2.2.2. OPTIMA Clinical Protocol (1988-2000)

The original protocol (implemented from 1988 until modifications were made in 2001) included a comprehensive annual visit, in addition to a cognitive assessment that was completed every six months (Figure 2.3). A research nurse conducted the clinical assessments, unless the diagnosis was ambiguous, or the participant had undergone significant medical changes. The study was approved by the local ethics committee in Oxford, and informed consent was acquired from all study participants (for participation during their lifetime and for postmortem brain donation) (127).

Clinical blood samples (collected annually) were tested for various haematology variables, which included the following: haemoglobin, platelets, haematocrit, white cell count, Vitamin B12, and folate. The biochemistry variables frequently measured included sodium, potassium, urea, creatinine, calcium, phosphate, glucose, and cholesterol. The virology tests in blood were for hepatitis, Human polyomavirus 2 (also known as JC virus), Human polyomavirus 2 (also known as BK virus), measles, and human immunodeficiency virus (HIV). Research blood samples of plasma, serum, and buffy coat were collected, along with a 40 ml sample of urine. Samples were stored in the Oxford Brain Bank at the John Radcliffe Hospital, in accordance with the Human Tissue Act 2004.

A one-time urine sample (40 millilitres) was also collected annually. Virology urine tests that could also be completed were for JC virus and BK virus. CSF collection via lumbar puncture was an optional additional procedure which was most often completed at the first study visit, although it could be done or repeated at later episodes as well. If CSF was collected, virology tests that could be done consisted of JC virus, BK virus, measles, and Epstein Barr virus.

The vital signs collected included pulse, height, weight, blood pressure lying down, and blood pressure after standing for 1 and 3 minutes. A clinician also collected information about the participant's medical history and completed a thorough examination (respiratory, cardiovascular, and neurological). Imaging, either a computed tomography (CT) or single-photon emission CT (SPECT) scan, was also completed.

For cognitive assessments, the participant completed the Cambridge Mental Disorders of the Elderly Examination (CAMDEX), a comprehensive procedure used to assess older adults (130). This includes a structured interview with the patient and with an informant who knows the participant well, in addition to cognitive tests (such as the Mini Mental State Examination (MMSE) and Cambridge Cognitive Examination (CAMCOG)). The CAMDEX was a key part of the protocol for all three cohorts, and the CAMDEX data contain detailed information about each participant's state over time. Participants also completed the National Adult Reading Test (NART).

The cognitive assessment every six months consisted of the CAMDEX. Some OPTIMA participants also had scores for the Clinical Dementia Rating (CDR), starting from 2000.

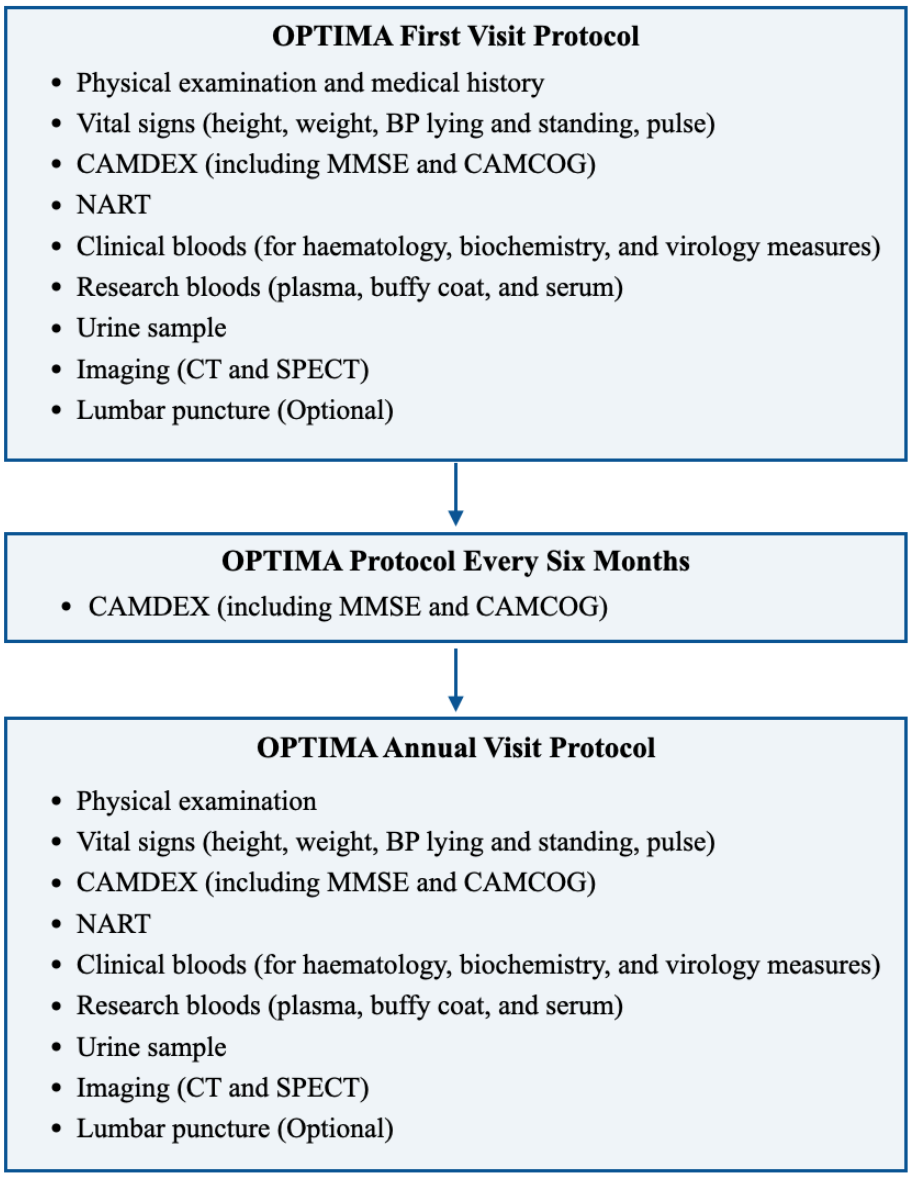


Figure 2.3. Overview of OPTIMA clinical protocol from 1988-2000 (based on archived study materials).

2.2.3. OPTIMA Clinical Protocol Updates (Starting 2001)

The updated protocol that was implemented in 2001 included more extensive neuropsychological assessments and newly added informant-rated scales (Figure 2.4). The frequency of some data collection was also modified.

New participants first had a home visit, during which they would learn about the research and consent to participate. The patient would complete the CAMDEX, and the informant would complete the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The researcher reviewed the expectations of research and communicated information about considering postmortem brain donation consent.

Participants had CT imaging done at the first hospital visit, and then again after two years, and then every 3 years. Clinical blood samples were collected at the baseline hospital visit, after one year, after 2 years, and then every three years; the bloodwork was unchanged from the original protocol. For the updated protocol, the urine sample (20 millilitres) was now only collected at the baseline session. Vital signs (the same as before with the addition of temperature) were then collected at baseline, after one year, and after two years. Information about the participant's medical history (respiratory, cardiovascular, and neurological) was now only collected at the baseline session.

The NART was now only assessed at the baseline visit. The neuropsychological test battery that was introduced included the Hopkins Verbal Learning Test (HVLT), Executive clock drawing task (CLOX), Pattern and Letter Speed Comparison, Graded Naming Test, Symbol Digital Modalities Test (SDMT), Placing Test, Digit Span, Dual Tasks, Category fluency, Doors, and Shapes B. The additional informant-rated scales consisted of the Neuropsychiatric Inventory (NPI), Expanded Bristol Activities of Daily Living (BADLS+), and the IQCODE. The Montreal Cognitive Assessment (MoCA) was introduced in 2009.

The CAMDEX was administered every six months over the course of years one and two, and then from year three onwards, information was collected from the informant via a telephone call at the six-month timepoint between annual visits. The annual assessments for the fourth year of study participation could be performed at the hospital or at the participant's home, and these included either the CAMDEX or neuropsychological assessments. If the participant was still coming into the hospital for an annual visit after six years, then a CT and blood samples were repeated. The CAMDEX, was then performed every other year, alternating with the newly added neuropsychological and informer-rated assessments.

While researchers aimed to follow the assessment schedules outlined in the protocol, various factors, such as cognitive change over the decades-long study period, mean that the extent of participation varied over the years. For example, if an individual was no longer able to participate in the extensive full assessment, they could still complete cognitive assessments and/or their informant could continue providing information via questionnaires.

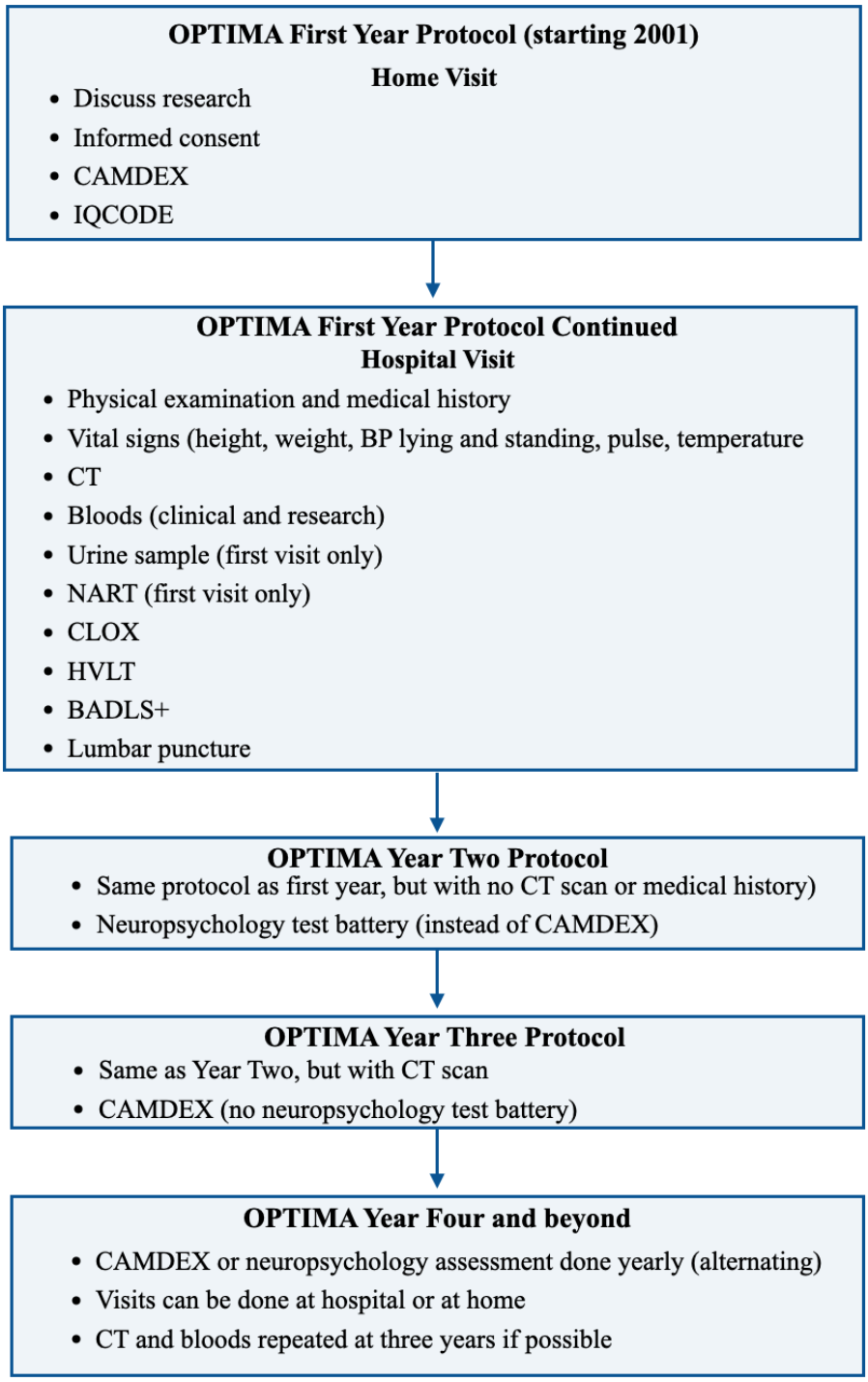


Figure 2.4. Overview of updated OPTIMA clinical protocol starting in 2001 (based on archived study materials).

2.2.4. Clinical Diagnosis

Clinicians working on the OPTIMA team had biweekly clinical meetings during which they would review a summary of the participants' assessment and come to a consensus about the appropriate diagnosis (listed in Table 2.2) using established criteria. Diagnostic coding was determined using criteria and guidance notes, and experienced research staff reviewed each episode before assigning a diagnosis.

Clinical Diagnosis Options
Control
Subjective memory complaint (SMC)
Mild Cognitive Impairment (MCI)
Vascular Cognitive Impairment
Vascular Dementia
Mixed Alzheimer's Disease (AD) and Vascular Dementia
Possible AD or amnestic disorder or mixed: AD with Other Dementia Syndrome (ODS)
Probable AD
Psychiatry or difficult to classify (i.e., drug or alcohol-related, severe psychiatric condition, or delirium)
Other Dementia Syndrome (ODS): Frontotemporal Dementia (FTD), Parkinson's Disease (PD), Creutzfeldt-Jakob Disease (CJD)
Lewy Body Disease (LBD) (LBD can be categorized with possible AD)
Parkinson's Disease (PD)

Table 2.2. List of possible clinical diagnoses for the OPTIMA, Challenge, and LEAD cohorts.

The diagnostic criteria used for guidance can be seen in Table 2.3.

Clinical Diagnosis	Diagnostic Criteria
MCI	Peterson Criteria for the Diagnosis of Mild Cognitive Impairment (131) And Criteria for identification of mild cognitive impairment (MCI), given by the MCI Working Group of the European Consortium on Alzheimer's disease (13)
AD	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria for the Diagnosis of Alzheimer's Disease (95)
VD	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) Criteria for Diagnosis of Vascular Dementia (132)
LBD	Criteria for the Diagnosis of Dementia with Lewy Bodies (98)
FTD	The clinical diagnostic features of FTD: Clinical profile (133)

Table 2.3. Diagnostic criteria for clinical diagnosis.

Below are the guidelines with additional detail provided to physicians determining these clinical diagnoses (Figure 2.5).

Guidance Used by Clinical Team for Diagnosis of Cognitive Impairment

Subjective Memory Complaint

Subjective memory complaint (SMC) is present if:

- There is a patient reported memory problem recorded in notes ***or***
- The patient answers 'yes' to 2 or more of questions 58 – 61 in Section A, Part I of the CAMDEX (even if they have not reported a memory complaint at any other point).
- The diagnosis of MCI is not fulfilled (i.e., they do not have cognitive impairment).

Cognitive Impairment

Cognitive impairment is present if the patient scores below normal in **two** or more cognitive tests, at least one of which should be in the domain of:

- Semantic memory
- Episodic memory
- Executive function
- Orientation

[The 'Total Recall' (TR) and 'Delayed Recall' (DR) sections of the Hopkins Verbal Learning Test (HVLT) are counted as two ***separate*** cognitive tests for this purpose.]
If the patient has cognitive impairment but there is no subjective or informant cognitive complaint and the patient does not meet the criteria for dementia they should be coded as 'control.'

Cognitive Tests of Specific Domains

'Cut offs' for normal scores are given in brackets.

Semantic memory:

- Graded naming (<21)
- Category fluency (<16)

Episodic memory:

- CAMCOG learning memory score (<13)
- HVLT (TR < 19, DR < 6)
- Placing test (<13 total or objects only <7)
- Doors (<8/12)
- Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word list (<5/10 delayed recall)
- Cambridge Neuropsychological Test Automated Battery Paired Associates Learning (CANTAB PAL) (>12 errors)

Executive function:

- CLOX (>3 on CLOX2-1 or <11 on CLOX 1)

- SDMT (<29 for age 55 - 75 and <20 for age 76 and over)

Orientation:
- CAMCOG orientation section (<5/10)
- MMSE orientation section (<7/10)

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is present if the revised Petersen criteria (131) are fulfilled, i.e.:
- Cognitive complaints coming from the patients or their families
- The reporting of a decline in cognitive functioning relative to previous abilities during the past year by the patient or informant
- Cognitive impairment as evidenced by cognitive testing (as above)
- Absence of major repercussions on daily life (the patient may report difficulties concerning complex day-to-day activities, but scores on functioning should still be in the normal range, i.e., BADSL+ < 9)
- Absence of dementia

CAMCOG > 80
MMSE > 23

Amnestic MCI is present only if the patient scores below normal in a test of ***episodic*** memory.

Vascular Cognitive Impairment

Vascular cognitive impairment (VCI) is present if:
- The patient fulfils the criteria for MCI ***and***
- They have a history of TIA or stroke ***and*** evidence of infarcts, lacunes or at least moderate small vessel disease on neuroimaging

or

- They have vascular risk factors ***and*** evidence of infarcts, lacunes or at least moderate small vessel disease on neuroimaging

or

- They have a clinical course suggestive of a vascular aetiology (i.e., a sudden onset or stepwise decline) ***and*** evidence of infarcts, lacunes or at least moderate small vessel disease on neuroimaging

Dementia

Dementia is present (based on the NINCDS-ARDRA criteria) if:
- There is cognitive impairment in 2 or more **domains**, one of which must be memory
- The cognitive impairment is progressive over time (i.e., scores in cognitive tests decline from one assessment to the next)

- Activities of daily living (ADLs) are affected. (BADLS+ score > 9 due to cognitive or physical effects of dementia or evidence from CAMDEX Section H, Part I questions 247 – 267 of affected ADLs)
- There is no disturbance of consciousness

Probable Alzheimer's Disease

Features *required* for a diagnosis of probable AD:

- The criteria for dementia are met (as above) ***and***
- There is an absence of systemic disorders or other brain disease that could account for the cognitive deficits
- Onset is between ages 40 and 90

Features supportive of (but not required for) a diagnosis of probable AD:

- Progressive deterioration of language, motor skills, and perception
- Altered patterns of behaviour
- Family history of dementia

Features consistent with (but not required for) a diagnosis of probable AD:

- Plateau in the course of progression
- Associated symptoms such as: depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal emotional or physical outbursts, sexual disorders, weight loss, and other neurologic abnormalities (especially in advanced disease)
- CT normal for age

Features that make probable AD unlikely:

- Sudden onset
- Focal neurological findings
- Seizures or gait disturbance early in the course of the disease

Possible Alzheimer's disease

Features *required* for a diagnosis of possible AD:

- The criteria for dementia are met (as above) ***and***
- There is an absence of other neurologic, psychiatric or systemic disorders thought to be the *primary* cause of the dementia

Features permitted in possible AD (but not probable AD):

- Variation in the onset, presentation or clinical from that expected in probable AD
- The presence of a second systemic or brain disorder sufficient to cause dementia – as long it is not thought to be the *primary* cause of the dementia
- A single, gradually progressive severe cognitive deficit in the absence of other identifiable cause (research diagnoses only)

Vascular dementia is present if:

- The criteria for dementia are met as above except there should be cognitive impairment in at least three domains, one of which should be memory ***and***
- The other NINDS-AIREN for vascular criteria are met

Mixed AD/vascular dementia is present if:

- The criteria for 'Possible AD' are met (see above) ***and***
- The criteria for 'Probable' or 'Possible Vascular dementia are met (see above).

General Points

- If there are two possible diagnostic codes, e.g., Parkinson's disease and VCI, use the one most likely to be affecting cognition.
- Moderate to severe depression and anxiety, if current, should be entered as 'other illness affecting cognition.'
- When coding retrospectively, this should be done using the information available at the assessment in question, e.g., of a patient fits the criteria for MCI at an initial assessment and is subsequently found to have an organic cause for their cognitive deficits the coding for the initial assessment should remain MCI.

Figure 2.5. Guidance for clinical diagnosis used by the study team (from archived study materials).

Clinicians also made note of other diagnoses during the physical exam and medical history, including depression, anxiety, cancer, recent infections, hypertension, and more.

2.2.6. Postmortem Brain Donation

OPTIMA participants were able to donate their brains for research following their death. As of 2008, the postmortem (PM) brains that were donated through OPTIMA to the Oxford Brain Bank have formed part of the BDR, which is a component of the UK Brain Banks Network. After brains were removed, they were stored at the Thomas Willis Oxford Brain Collection, also known as the Oxford Brain Bank, at the John Radcliffe Hospital in Oxford, in accordance with both the Oxford Brain Bank and UK Human Tissue Authority regulations.

At the beginning of the study, the neuropathology protocol was formulated based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and Braak guidelines (134, 135). The protocol was periodically updated as new criteria for neurodegenerative disorders, in addition to novel antibodies for immunostaining, were introduced. Complete information about brain regions analysed and staining methods used over the course of the study period can be found in the Supplemental File for Chapter 2.

Postmortem information collected included date of death, cause of death, place of death, whether the patient had a terminal illness, if they had a behaviour change and if so for how long, and their last known National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnosis. Neuropathology information recorded based on postmortem brain

analysis included Braak neurofibrillary tangle stage, the maximum density of neocortical plaques, the maximum density of neocortical tangles (Braak neurofibrillary tangle staging), Braak Lewy Body disease staging, presence of atherosclerosis and arteriosclerosis, severity of small vessel disease, infarcts, microinfarcts, lacunar infarcts, haemorrhage, amyloid angiopathy, infarction, FTD, tumours, corticobasal degeneration, progressive supranuclear palsy (PSP), hippocampal sclerosis, Creutzfeldt-Jakob Disease (CJD), and Huntington's disease (HD). The protocol changed over time, and some participants have additional information from studies of subgroups within the cohorts, so the neuropathology information available for each participants varies.

The protocol also included a neuropathology-based PM diagnosis of AD for donated brains starting in 1989. This was based on the standardized criteria developed by the CERAD (134). Based on a histological analysis of the brain, a neuropathologist determined whether the participant had AD.

In addition to the tissue that the neuropathologists analysed, PM brain tissue was frozen and stored for research purposes. According to archived study materials, from the inception of OPTIMA until 2008, one half of each participant's brain was slow frozen (to -70 ˚C). This was typically completed with an unsliced brain half, although sometimes the brain half was sliced coronally prior to freezing. Small specimens that could potentially be used as cryostat sections to be analysed microscopically were occasionally frozen in Optimal Cutting Temperature compound.

Once OPTIMA became a part of BDR in 2008, the BDR frozen tissue sampling protocol was followed. This entailed collecting a total of 50 brain tissue samples (1 to 3 cm each) by first slicing the brain coronally in 1 to 1.5 cm pieces. These samples were then slow frozen (to -70 ˚C) and stored in separate small bags. From 2013 onward, slices of fresh brain have been quick frozen to improve tissue preservation and small sample removal.

2.2.7. Data Entry and Analysis

Study data entry was typically completed by the individual who was responsible for data collection, but sometimes a distinct individual would load the data into the database. Data entry was then checked by a different person, and audits were undergone periodically, according to archived study materials.

2.3. Challenge Study Methods

The Challenge cohort began in 1997 and consisted primarily of healthy controls. The goal was to better understand the predictors of cognitive decline and dementia (121). For this cohort, 159 older adults living in the Oxford community were recruited.

The exclusion criteria for the Challenge cohort were "scored ≤ 80 on the CAMCOG or ≤ 24 on the Mini-Mental State Examination (MMSE) at the initial screening visit, (2) reported significant progressive subjective memory complaints, (3) lived in institutional care, or (4) were unable to complete the CAMDEX examination" (121). The Challenge study was

approved by the Central Oxford Research Ethics Committee, and participants gave informed consent (121).

The Challenge study protocol closely resembled the OPTIMA protocol. MRI scanning was incorporated into the imaging methods. Each annual visit included the CAMDEX, the NART, the Geriatric Depression Scale (GDS), a thorough medical history, questions about substances and medications used, imaging, and non-fasting blood samples (121).

2.4. LEAD Study Methods

The LEAD cohort began in 2009, with the aims of increasing our understanding of AD by following participants with no memory problems, pre-dementia, or early AD. As of August 2012, no new LEAD participants were recruited, though study visits continued until 2015.

According to archived study materials, the inclusion criteria for LEAD participation consisted of being 60 years of age or older, living in Oxfordshire or within 30 miles, having a study partner willing to participate, being able to get to the hospital for study sessions, having an MMSE score over 20 points, and being able to give informed consent.

The protocol for a new LEAD participant took approximately four hours and involved the data collection listed in Figure 2.6 below. One year later, participants returned to complete the follow-up visit protocol, which took about two to three hours (Figure 2.6). Additional cognitive testing was also completed every six months for the first two years of participation, and the study partner also completed questionnaires by phone every six months. A lumbar puncture could also be completed at later visits.

After one more year (two years after the first visit), the participant returned to complete this same protocol, with the addition of a repeat medical examination and another CT or MRI scan. Another year later (three years after the first visit), the participant completed this same protocol again, with the medical examination, although this time a repeat scan was not done.

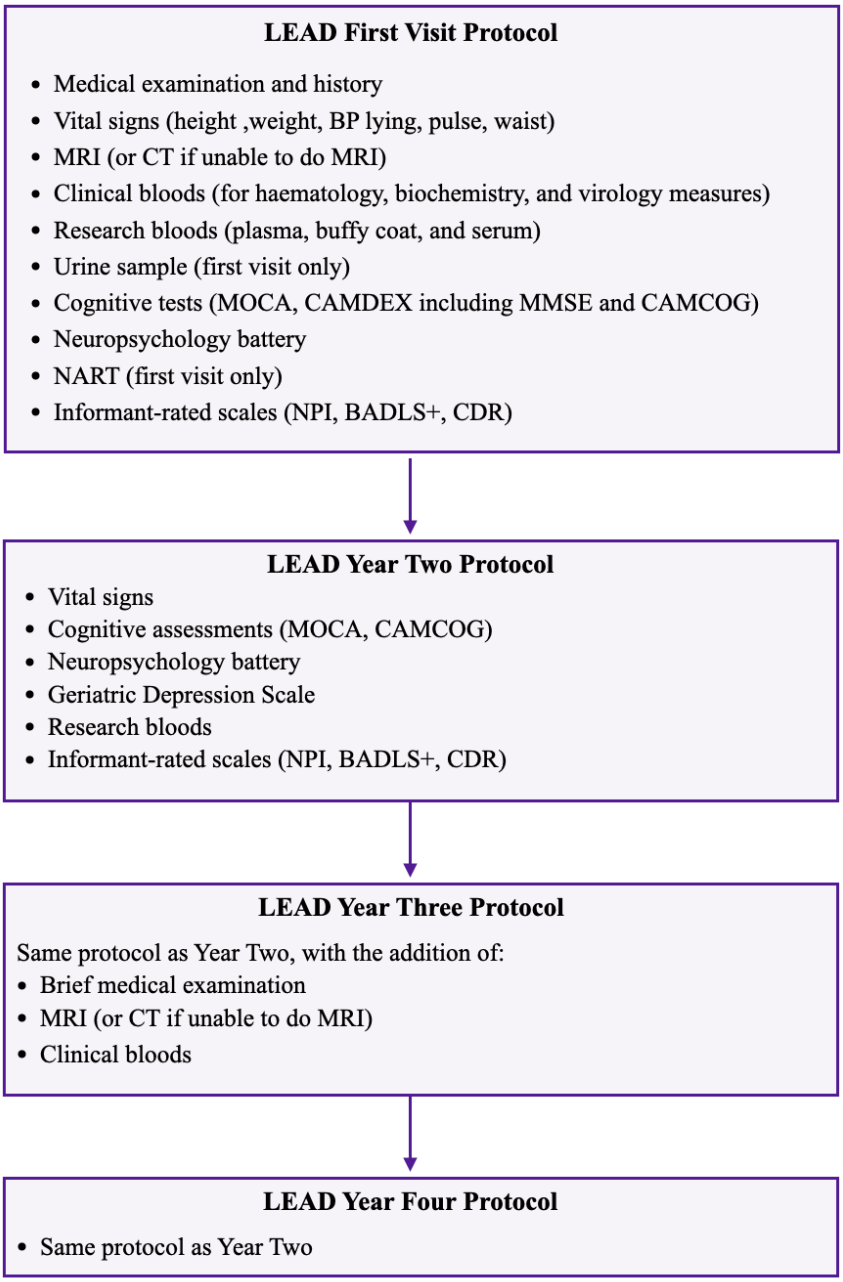


Figure 2.6. LEAD first and follow-up visit protocols.

2.5. Discussion

This chapter presented an overview of the study methods utilised by the OPTIMA, Challenge, and LEAD researchers. The information included here was determined and compiled using various archived study materials.

One important finding from this analysis of the study methods was that there was overlap between the study participants. Some participants who originally joined the OPTIMA and Challenge cohorts eventually joined the LEAD study and completed additional follow-up. Thus, these three cohorts are not discrete entities, but could potentially be characterised as one larger unified cohort, as will be explored in Chapter 5.

Upon reviewing the study methods, there are various similarities and differences between the methods followed by the three cohorts. One similarity is that all three cohorts collected longitudinal, multimodal data about the participants, including cognitive assessments, clinical assessments, biological samples, imaging, and neuropathology. However, these methods did change to some extent over the decades that these studies ran, as updated methods were added over time. For example, the OPTIMA study utilised the MMSE and CAMCOG cognitive assessments that are included in the CAMDEX evaluation, whereas the later LEAD study added the MOCA, a newer cognitive assessment tool. The updated OPTIMA study protocol also incorporated more neuropsychology testing, as well as additional newer tests like the CLOX test. Additionally, the OPTIMA study initially used the SPECT and CT imaging methods, and as MRI became more widely utilised and accessible, this imaging tool was incorporated into the study protocols for the Challenge and LEAD cohorts. The neuropathology methods used to assess the donated PM brains were also updated various times over the course of the study to reflect advancements in the field. While it is important that the study methods were periodically revised consistent with up-to-date research, this could also make it challenging to compare specific variables, such as neuropathology findings, over the course of the longitudinal study.

Reviewing the archived study materials also highlighted the different aims and target clinical populations of the three cohorts. The OPTIMA study followed a range of participants, from controls to those with dementia. This study recruited patients from outpatient and inpatient settings, GP clinics, and community settings. The Challenge study largely recruited healthy patients without cognitive impairments, while LEAD sought to focus more on healthy controls and those with early AD. Despite their unique features, all three cohorts sought to advance our understanding of aging and cognition.

CHAPTER 3: Follow-up and Description of Participant Protocol Completion by Cohort

3.1. Cohort Participation and Censor Reasons

3.1.1. OPTIMA Cohort Participation

There was a total of 742 participants in the Oxford Project to Investigate Memory and Ageing (OPTIMA) cohort (Figure 3.1). Of the original OPTIMA cohort, 420 (56.6%) died and donated their brains, 123 (16.6%) died without brain donation, 130 (17.5% were lost to follow-up), and 70 (9.4%) joined the Longitudinal Early Alzheimer's Disease cohort (LEAD) cohort. Of those who joined LEAD, 20 (2.7% of the original cohort) died with brain donation, five (0.7%) died without donating their brains, 30 (4.0%) were lost to follow-up, and 13 (1.8%) are still alive and being assessed in the Brains for Dementia Research (BDR) study. Participants did not donate their brains for various reasons, including participants not having consented, the study team not being notified of the death, or the coroner not being aware of the individual's participation in the study. Some of the participants lost to follow-up may have been unable to continue completing study visits or they joined the BDR study and subsequently withdrew.

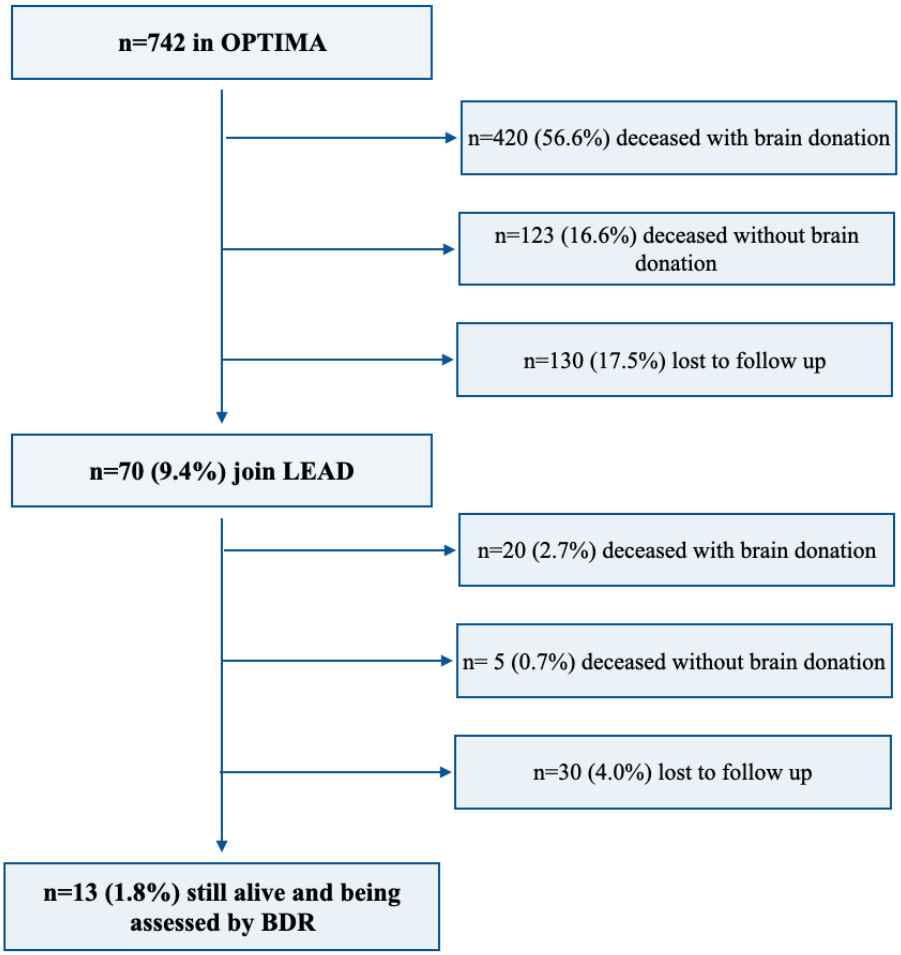


Figure 3.1. Flowchart of OPTIMA study participation and censor reasons.

3.1.2. Challenge Cohort Participation

From the outset, Challenge was a smaller cohort than OPTIMA, with a total of 159 participants (Figure 3.2). Of this original cohort, 49 people (30.8%) are known to have died and donated their brains, 20 individuals (12.6%) have passed away without brain donation, and 86 participants (54.1%) have been lost to follow-up.

Following the conclusion of the Challenge study in 2011, eight participants joined the LEAD cohort for further follow-up. Of these eight participants, four have died and donated their brains, and three have been lost to follow-up. One participant from the original Challenge cohort is still being followed by the BDR study.

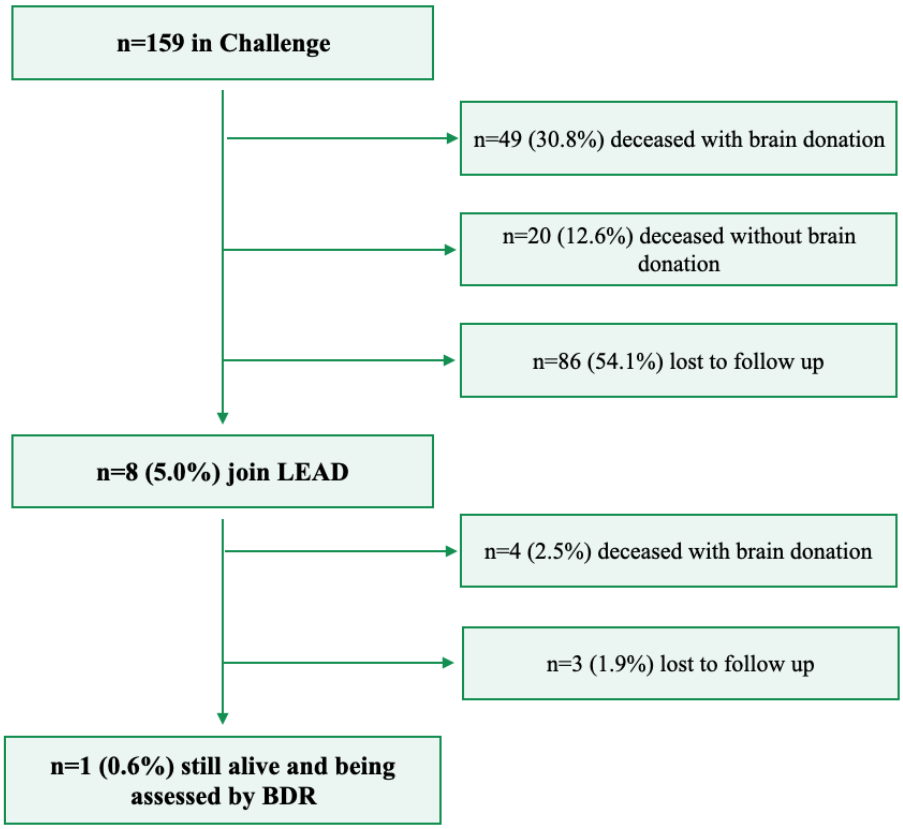


Figure 3.2. Flowchart of Challenge study participation and censor reasons.

3.1.3. LEAD Cohort Participation

The LEAD cohort consisted of 211 participants, 70 of whom had already been in OPTIMA and eight of whom were in the Challenge cohort. Of these 211 participants, 45 (21.3%) are known to be deceased and have donated their brains, 12 (5.7%) have passed away without brain donation, 131 (62.1%) have been lost to follow-up. Additionally, 23 LEAD participants (10.9% of the cohort) are still alive and completing annual follow-up with the BDR study team.

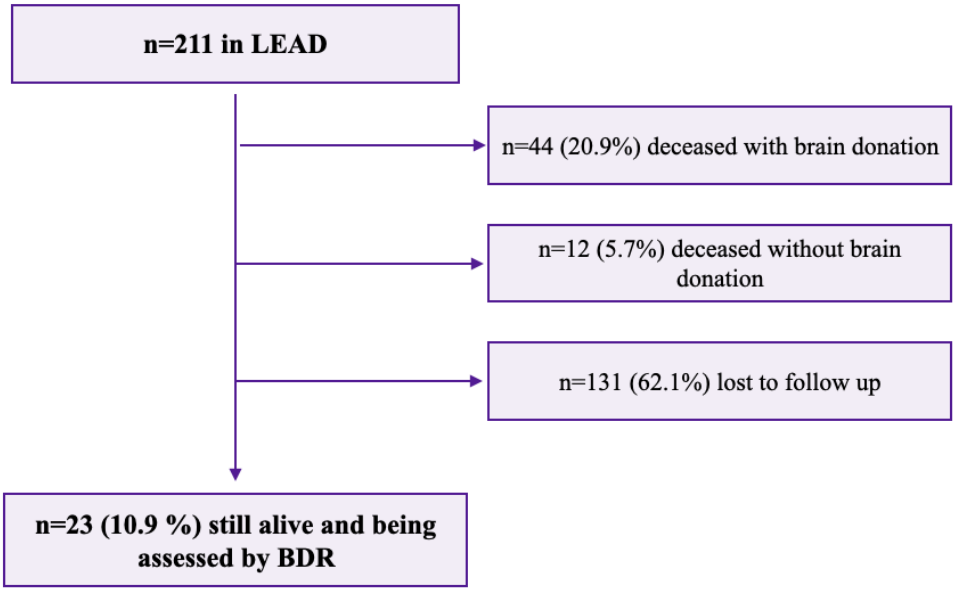


Figure 3.3. Flowchart of LEAD study participation and censor reasons.

Of all the participants lost to follow-up, a total of 33 of these OPTIMA, Challenge, and LEAD participants had joined the BDR but later withdrew from follow-up. For a flowchart of cohort participation and censors for all individual participants from the three cohorts combined, see Chapter 5.

3.2. Frequency and Length of Follow-Up

The distribution of follow-up times for participants in the OPTIMA, Challenge, and LEAD cohorts can be seen below in Figure 3.4. The length of follow-up was calculated as the number of years that had elapsed between the first visit to the last recorded visit for each person, while they were a member of a specific cohort, not including the date of death or brain donation.

For some participants, the true follow-up time was actually longer than is indicated by the figures below. This is because these figures quantify the amount of follow-up a participant underwent in one specific cohort (e.g., only as an OPTIMA participant), but there were various participants who continued to be followed for longer when they joined a subsequent cohort (either LEAD or BDR). Chapter 5 highlights the full length of follow-up for individual participants across the combined cohorts.

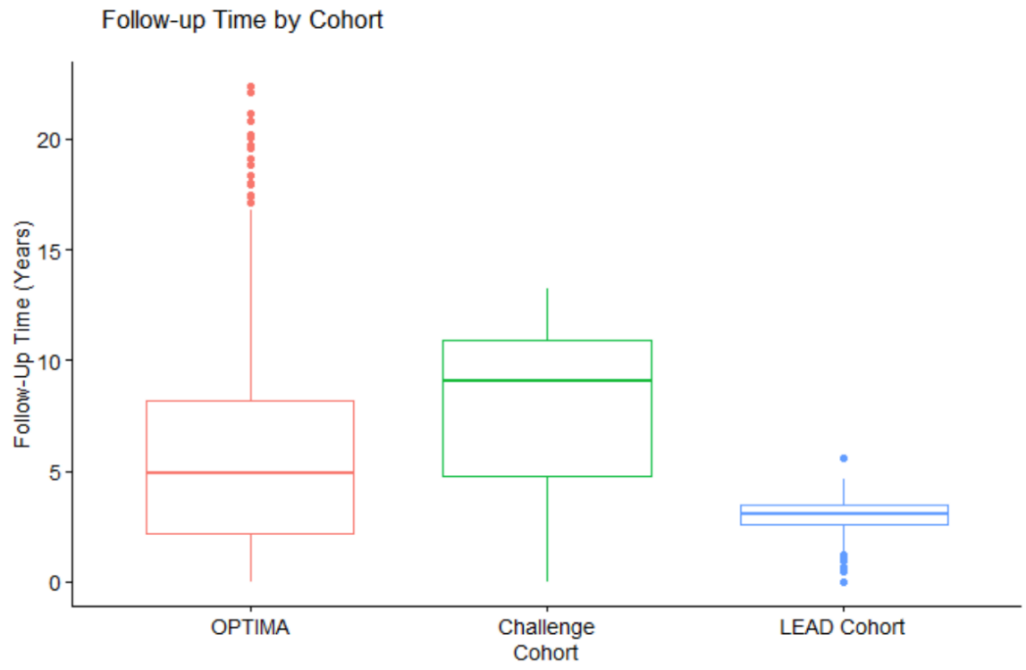


Figure 3.4. Box plot of follow-up time in years by cohort.

For the OPTIMA, Challenge, and LEAD cohorts, an episode (also referred to as a visit) was defined as any contact with the study team. An episode could include a comprehensive visit with cognitive assessments, imaging, bloods, CSF, and more, or an episode could consist of any combination of these methods. Figure 3.5 highlights the number of episodes completed per participant during each study.

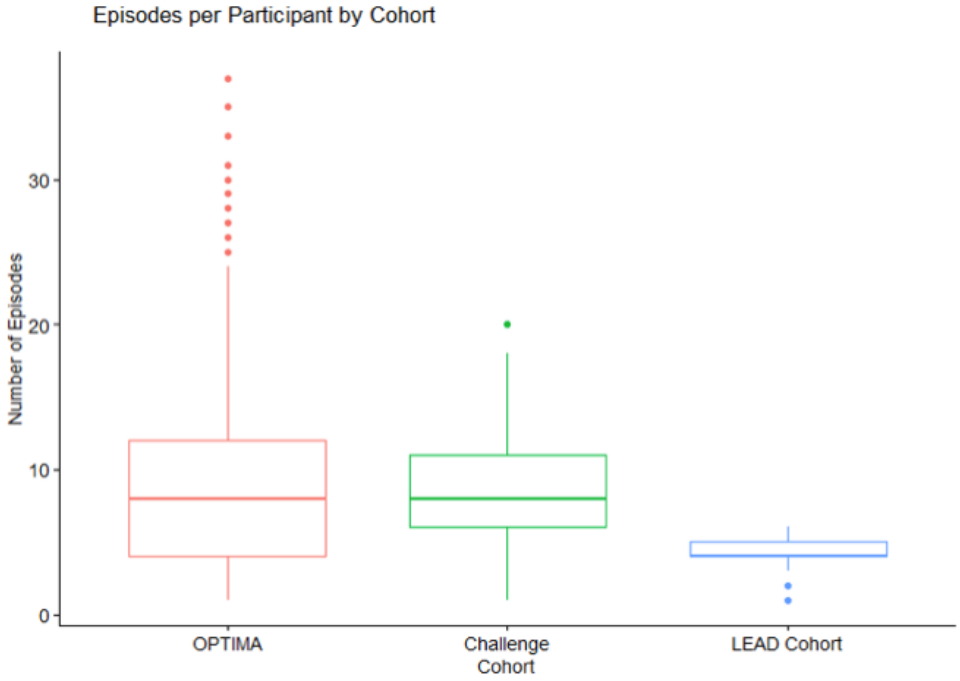


Figure 3.5. Box plot of episodes per participant by cohort.

3.2.1. OPTIMA Cohort Follow-up

For the OPTIMA cohort, the mean number of episodes per participant was 9.1 (SD=6.2), with a median of eight visits while alive (Figure 3.6). The number of episodes per person was wide, ranging from one to 37. The mean length of follow-up from the first to the last episode was 5.8 years (SD=4.7), with a median of 4.9 years (Figure 3.7). The longest follow-up time was 22.3 years, while the shortest was zero years for those who only participated in one episode. Of the 742 total OPTIMA participants, 701 had more than one visit, not including a postmortem episode.

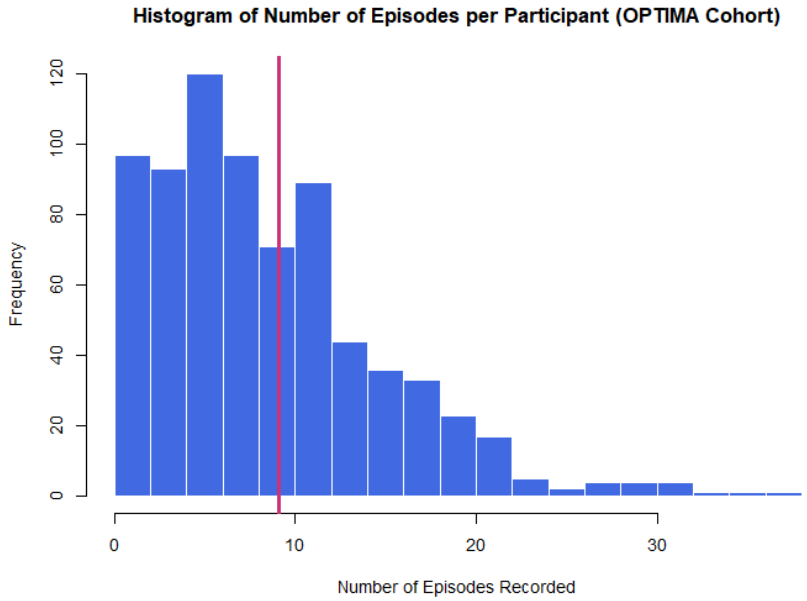


Figure 3.6. Histogram of number of episodes recorded per participant (OPTIMA cohort, n=742).

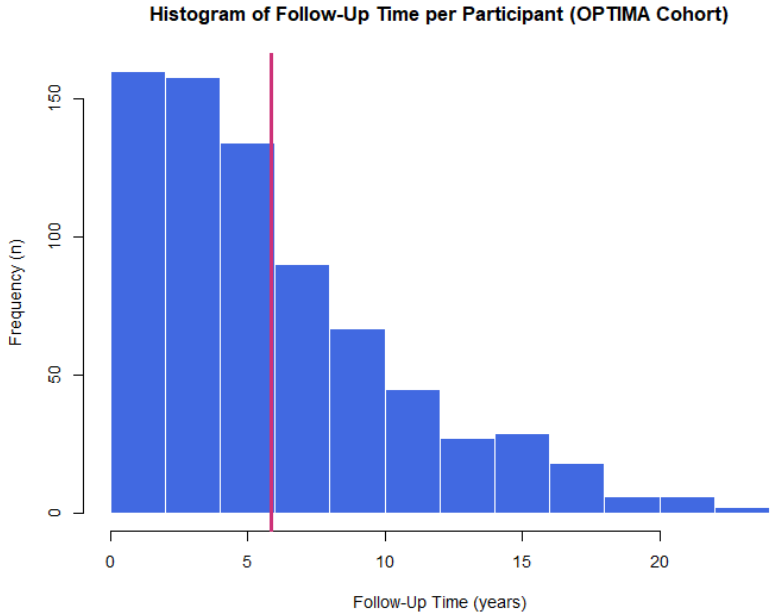


Figure 3.7. Histogram of the number of years of follow-up per participant (OPTIMA cohort, n=742).

3.2.2. Challenge Cohort Follow-up

With regards to the Challenge cohort, the mean number of visits completed was 8.4 (SD=3.8) (Figure 3.8). The median number of episodes was eight, although some individuals had up to 20 visits during their lives. 156 out the total of 159 participants had more than one visit recorded. The mean length of follow-up time while alive was 7.8 years (SD=3.8), with a median of 9.1 years of follow-up (Figure 3.9). The length of follow-up ranged from zero to 13.2 years.

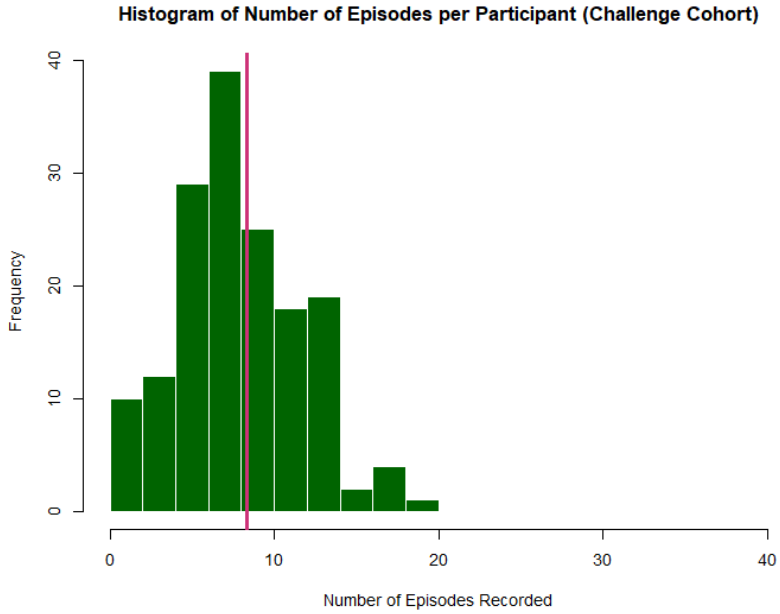


Figure 3.8. Histogram of number of episodes recorded per participant (Challenge cohort, n=159).

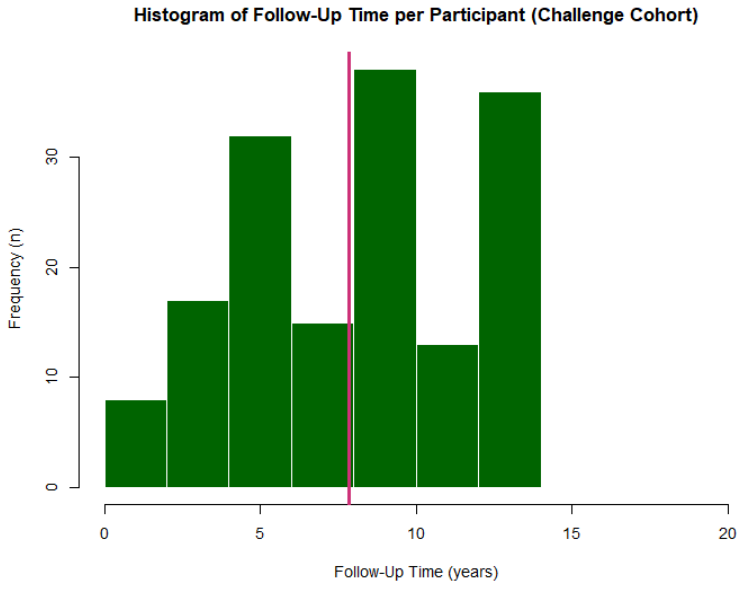


Figure 3.9. Histogram of the number of years of follow-up per participant (Challenge cohort, n=159).

3.2.3. LEAD Cohort Follow-up

For the LEAD cohort, the mean number of episodes per participant while alive was 4.2 (SD=1.3) (Figure 3.10). The median number of visits per person was four, and the range was from one to six episodes. In terms of length of follow-up for the LEAD cohort, the mean was 2.8 years (SD=1.0) (Figure 3.11). This cohort had a median of 3.1 years of follow-up with the study team, with a range from zero to 5.6 years.

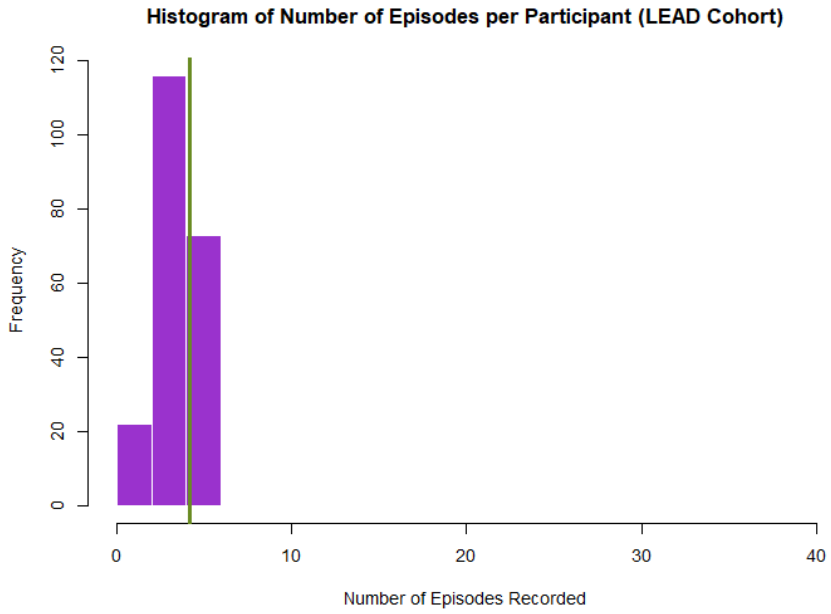


Figure 3.10. Histogram of number of episodes recorded per participant (LEAD cohort, n=211).

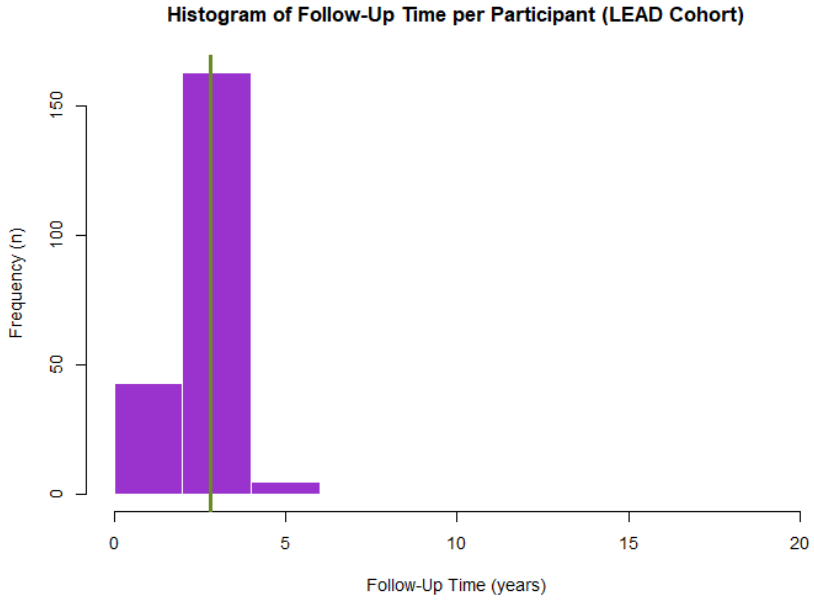


Figure 3.11. Histogram of the number of years of follow-up per participant (LEAD cohort, n=211).

3.3. Cognitive Assessment Completion

Out of the 742 of the OPTIMA participants, 738 (99.5%) completed at least one Cambridge Mental Disorders of the Elderly Examination (CAMDEX) visit, and 677 (91.2%) completed two or more. 468 (63.1%) had five or more CAMDEX listed, 224 (30.2%) had ten or more CAMDEX listed, and 30 (4.0%) had 20 or more done.

For the Challenge participants, 150 out of 159 (94.3%) completed at least two visits, but only 6 (3.8%) had done five or more CAMDEX visits.

LEAD participants had fewer CAMDEX visits, with 177 out of 211 (83.9%) completing at least one CAMDEX, but only 36 completing two or more of these visits. This lower CAMDEX completion can be explained by the protocol changes emphasizing specific cognitive assessments (such as the Montreal Cognitive Assessment (MoCA) and the Cambridge Cognitive Examination (CAMCOG)), rather than completing the full CAMDEX procedure.

	Episodes with a CAMDEX Listed					
Cohort	**1+**	**2+**	**5+**	**10+**	**15+**	**20+**
OPTIMA, n	738	677	468	224	78	30
Challenge, n	159	150	6	1	0	0
LEAD, n	177	36	0	0	0	0

Table 3.1. Number of participants with only one, more than one, more than five, or more than ten episodes with a CAMDEX listed.

3.4. Imaging Completion

Table 3.2 provides a summary of the imaging completed by participants in the three cohorts. Over 90% (n=677) of all OPTIMA participants had one or more computed tomography (CT) scans done, and about 78% (n=580) had at least one single-photon emission computed tomography (SPECT) scan done. Only 3.1% (n=23) had a magnetic resonance imaging (MRI) scan, as this was not included in the original protocol. In total, the OPTIMA participants had 1,962 CT scans, 1,684 SPECT scans, and 24 MRI scans listed in the database.

For the Challenge cohort, almost all of the participants (96.0%, n=151) completed at least one MRI scan, with a total of 392 MRI scans done. The majority (81.8%, n=130) also had one or more SPECT scans done. The least frequently completed scan type was the CT, with 42.8% (n=68) of Challenge participants having at least one.

For LEAD, the SPECT scan was no longer used. MRI was the frequently completed scan type, with about 79% of participants (n=167) having at least one. 43.1% (n=91) of the LEAD cohort had one or more CT scans done.

Imaging Type	OPTIMA n= 742		Challenge n= 159		LEAD n= 211	
	Participants with 1+ scan	Total number of scans done	Participants with 1+ scan	Total number of scans done	Participants with 1+ scan	Total number of scans done
CT, n (%)	677 (91.2)	1962	68 (42.8)	92	91 (43.1)	119
SPECT, n (%)	580 (78.2)	1684	130 (81.8)	204	0	0
MRI, n (%)	23 (3.1)	24	151 (96.0)	392	167 (79.1)	265

Table 3.2. Summary table of imaging completion for all three cohorts.

3.4.1. OPTIMA Cohort Imaging Completion

Table 3.3 contains more detailed information about the amount of imaging completed over the course of the OPTIMA cohort. This table highlights that some OPTIMA participants had repeated CT and SPECT scans, with some participants had up to 11 CT scans and 10 SPECT scans each. These repeated, longitudinal scans are valuable for assessing changes in the brain as people age and potentially undergo cognitive decline.

Also, it was noted that the first CT scan recorded in this cohort took place in 1980 (presumably through the participant's medical investigations unrelated to the study), although it was not read by the study team until a visit in 1995.

	OPTIMA Cohort Imaging			
Imaging type	**Number of participants completed at least once**	**Range of number of scans per person**	**Total number completed**	**Date of first scan in the database**
CT	677	0-11	1961	29-Oct-1980
SPECT	580	0-10	1684	16-May-1988
MRI	23	0-2	24	08-Sep-1997

Table 3.3. Imaging completion for the OPTIMA cohort (n=742).

3.4.2. Challenge Cohort Imaging Completion

Table 3.4 highlights the imaging completed by the Challenge cohort, starting in 1997. Participants in this study completed up to five CT, four SPECT, and three MRI scans each.

	Challenge Cohort Imaging			
Imaging type	**Number of participants completed at least once**	**Range of number of scans per person**	**Total number completed**	**Date of first scan included in the database**
CT	68	0-5	92	23-Nov-1997
SPECT	130	0-4	204	02-Nov-1998
MRI	151	0-3	392	11-Nov-1997

Table 3.4. Imaging completion for the Challenge cohort (n=159).

3.4.3. LEAD Cohort Imaging Completion

Detailed information about imaging completed by the LEAD cohort can be seen in Table 3.5 below. The first CT scan for this cohort took place in 2008, and participants completed up to two CT scans each. MRI scans began in 2010, and participants also had up to two MRI scans each. As was mentioned previously, SPECT scans were no longer used in the LEAD cohort protocol.

	LEAD Cohort Imaging			
Imaging type	**Number of participants completed at least once**	**Range of number of scans per person**	**Total number completed**	**Date of first scan included in the database**
CT	91	0-2	119	2-Sep-2008
SPECT	0	0	0	-
MRI	167	0-2	265	4-Mar-2010

Table 3.5. Imaging completion for the LEAD cohort (n=211).

3.4.4. OPTIMA Cohort Additional Investigations Completion

A subset of the OPTIMA cohort also had additional investigations done, in addition to the standard protocol imaging (Table 3.6). 42 out of 742 participants had a Chest X-Ray completed, 42 participants had an electrocardiogram (ECG) done, and 17 had an electroencephalogram (EEG) test done. These types of investigations were not often repeated, and the maximum number of each type completed per person was two.

	OPTIMA Cohort		
Investigation type	**Number of participants completed at least once**	**Range of number completed per person**	**Total number completed**
Chest X-Ray	42	0-2	45
ECG	42	0-2	43
EEG	17	0-2	18

Table 3.6 Additional investigations completed by some participants in the OPTIMA cohort (n=742).

3.5. Clinical Bloods and Cerebrospinal Fluid (CSF) Completion

In addition to the extensive imaging completed for the OPTIMA, Challenge, and LEAD participants, the availability of data from clinical blood and cerebrospinal fluid (CSF) samples contributes to the value of these cohorts. Tables 3.7 to 3.9 showcase the extent of clinical bloods and CSF completion for each cohort. Clinical bloods were classified as completed for a visit if the blood-based biochemistry, haematology, or virology variables were marked as done. CSF was considered as completed if any of the following CSF titres were marked as done: Epstein Barr, BK virus (Polyomavirus 1), JC virus (Polyomavirus 2), or Measles.

Although this project does not quantify the availability of blood or CSF samples that are currently available for research, the Oxford Brain Bank is currently working on establishing this information.

3.5.1. OPTIMA Cohort Clinical Bloods and CSF Completion

Table 3.7 shows that 98.7% of all OPTIMA participants had clinical blood samples analysed at least once throughout the study, with a range of up to 18 visits where bloods were taken. The average number of visits where clinical bloods were drawn was approximately four, and a total of 2,835 visits were recorded with clinical bloods included.

45.7% of the OPTIMA cohort had at least one visit with results from a CSF sample. Given the invasive nature of the lumbar puncture needed to collect CSF, it is notable that almost half of participants had at least one, and some participants had up to four visits with CSF collected. There was a total of 413 OPTIMA visits with CSF collection completed.

	OPTIMA Cohort (n=742)			
Investigation type	**Number of participants completed at least once**	**Mean number completed per person**	**Range of number completed per person**	**Total number completed**
Clinical Bloods	732	3.8	0-18	2835

CSF	339	0.4	0-4	413

Table 3.7. Clinical bloods and CSF completion for the OPTIMA cohort.

3.5.2. Challenge Cohort Clinical Bloods and CSF Completion

The Challenge participants' completion of clinical bloods and CSF can be seen in Table 3.8. All of the Challenge participants had their clinical bloods taken at least one time, with up to nine visits with bloods recorded per person. There were 799 total visits with clinical bloods completed. No CSF was collected for the Challenge cohort.

	Challenge Cohort (n=159)			
Investigation type	**Number of participants completed at least once**	**Mean number completed per person**	**Range of number completed per person**	**Total number completed**
Clinical Bloods	159	5.0	1-9	799
CSF	0	0	0	0

Table 3.8. Clinical bloods and CSF completion for the Challenge cohort.

3.5.3. LEAD Cohort Clinical Bloods and CSF Completion

Table 3.9 highlights the number of visits the LEAD participants completed where clinical bloods were completed. 98.1% of the cohort had their clinical bloods done at least once, with a range of up to three visits each. 242 visits with clinical bloods were done, and none of the LEAD participants underwent a lumbar puncture.

	LEAD Cohort (n=211)			
Investigation type	**Number of participants completed at least once**	**Mean number completed per person**	**Range of number completed per person**	**Total number completed**
Clinical Bloods	207	1.1	0-3	242
CSF	0	0	0	0

Table 3.9. Clinical bloods and CSF completion for the LEAD cohort.

3.6. Postmortem Brain Donation

Table 3.10 displays the number of participants who donated their brains for research, according to the UK Brain Bank Network online database, as of June, 2024. These brains were stored in the Oxford Brain Bank, and additional information about the neuropathology findings associated with the brain tissue can be found later on in Chapters 4 and 5.

Overall, 509 participants from the OPTIMA, Challenge, and LEAD cohorts have donated their brains for research (Table 3.10). A total of 420 participants who were only in the OPTIMA cohort donated their brains. Brain donation was also completed by 20 participants who were in OPTIMA and then subsequently joined the LEAD cohort. There

were 45 participants who were only in the Challenge study, and four individuals who were in both Challenge and LEAD who donated their brains as well. A total of 20 participants who were only in LEAD donated their brains for research.

Cohort	Number of participants with brains listed in the UK Brain Bank Network
Only in OPTIMA	420
Only in Challenge	45
Only in LEAD	20
In OPTIMA and LEAD	20
In Challenge and LEAD	4
Total	**509**

Table 3.10. Number of participants with a record of brain donation found in the UK Brain Bank Network as of June, 2024.

3.7. Cohorts Summary Table

Table 3.11 below summarizes the participation and follow-up of the OPTIMA, Challenge, and LEAD cohorts, which altogether spanned a period of 27 years. The number of follow-up visits here includes any study visit, regardless of whether the full CAMDEX was completed.

Cohort	N	When	Follow-up years Median (IQR)	Follow-up visits						Brains Donated	Shared Cohort Membership	
				1+	2+	3+	5+	10+	15+		Challenge	LEAD
OPTIMA	742	1988-2011	4.9 (6.0)	742	701	645	552	295	131	439	0	70
Challenge	159	1997-2011	9.1 (6.1)	159	156	149	137	55	7	49		8
LEAD	211	2008-2015	3.1 (0.8)	211	199	189	73	0	0	45		

Table 3.11. Summary table of OPTIMA, Challenge, and LEAD cohort size, follow-up completion, brain donation, and shared cohort membership.

3.8. Discussion

In summary, this chapter has provided insight into the extent of follow-up and protocol completion for participants in OPTIMA, Challenge, and LEAD. This analysis provides a new understanding of the information that was collected and can act as a resource for future researchers designing studies using these cohorts' data.

One notable aspect of this chapter was the assessment of cohort participation and follow-up. It was apparent that all three cohorts eventually lost participants to follow-up, though the proportion of those lost to follow-up was higher for the Challenge and LEAD cohorts. This could be due to the studies ending and not completing any more follow-up visits, or it is possible that some participants became too unwell to complete further study

visits. Hand-searching of the physical files would be needed to determine the reasons for participants being lost to follow-up, and further investigation could be completed to determine if these participants have passed away since the follow-up for these cohorts ended. Measures mentioned in the archived study materials to retain participants included having a study partner for each participant, conducting study visits in participants' homes, and having some assessments completed by phone; perhaps the OPTIMA cohort's lower percentage of participants lost to follow-up was because these measures were implemented more extensively than for the Challenge and LEAD participants.

Additionally, the length and frequency of follow-up analyses in this chapter indicated that the Challenge cohort had the longest mean length of follow-up (about eight years) per participant. Although the OPTIMA cohort ran for the longest number of years (from 1988 until 2011), the mean length of participant follow-up was shorter, at about six years. This difference is likely because the Challenge cohort (which ran from 1997 to 2011) predominantly consisted of healthy controls, who might have found it easier to continue attending study visits over a longer period than those with cognitive impairments. The OPTIMA cohort included many participants with dementia from the outset, and these participants might have had more difficulty continuing to complete study sessions or may have died after a shorter period than the healthy older adults in Challenge. The LEAD cohort had the shortest mean follow-up time of about three years, which is likely because the study ran for fewer years than the other two cohorts (from 2009 to 2015).

Another interesting finding was about the imaging completed by the three cohorts. The majority of participants in the OPTIMA cohort had at least one CT and SPECT scan completed, with very few MRIs done. Some participants even had as many as 10 CT scans and 11 SPECT scans listed. There was a shift towards MRI imaging and away from CT scans in the Challenge and LEAD cohorts. The mean number of CT scans per person was 2.9 in OPTIMA, 1. 4 in Challenge, and 1.3 in LEAD. This is likely because physicians and researchers learned about the risks inherent in repeated exposure to radiation during a CT during the time period of these cohorts, which raised questions about ethical research practices (136). The MRI machine, which utilises magnetic fields rather than radiation, was first introduced in the 1980s and became more accessible over time, likely leading to its incorporation into the protocols for these cohorts (137).

This analysis also highlighted the extent of biological samples collected over the course of the three cohorts. Clinical bloods were collected at least once in almost 99% of OPTIMA participants, all of the Challenge participants, and in 98% of those in LEAD, providing biochemistry and haematology information that will be described in Chapter 4. Additionally, it is remarkable that, despite the invasive nature of the collection process, 339 participants in the OPTIMA cohort had at least one lumbar puncture to collect CSF. Additionally, a total of 509 participants across the three cohorts donated their brains, which adds significant value to the research that can be completed using these cohorts. Further investigation remains to be done to assess how many biological samples remain in storage and are available for research use.

In conclusion, this chapter has deepened the understanding of these cohorts by presenting the length of follow-up and extent of completion of various parts of the protocol, including cognitive assessments, imaging, clinical bloods, CSF, and postmortem brain donation.

CHAPTER 4: Cohort Demographic, Clinical, and Neuropathological Characteristics

4.1. Demographic Characteristics

The table below summarizes the demographic characteristics of the participants in the Oxford Project to Investigate Memory and Ageing (OPTIMA), Challenge, and Longitudinal Early Alzheimer's Disease (LEAD) cohorts at their baseline Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Table 4.1). The baseline demographic information includes age, gender, family history of dementia, stroke, or heart attack, as well as personal history of smoking or drinking, and education. Some variables that were not recorded at every CAMDEX visit and were unlikely to change over time, such as age left school or family medical history, were used from the first recorded value if they were not completed at the first CAMDEX episode. Participants who either did not know or were not asked about these variables were excluded from the denominators. These variables will be discussed in more detail in the sections that follow. Statistical analyses comparing the three cohorts to one another were not completed because of the overlap between the cohort participants. Additionally, these volunteer populations had distinct inclusion criteria and characteristics that would not allow for meaningful conclusions to be drawn from comparisons between them.

Demographic Characteristic	OPTIMA, n=738	Challenge, n=159	LEAD, n=177
Age at assessment, mean (SD), range	71.7 (9.7), 26-99	73.6 (6.2), 60-90	75.4 (7.3), 55-94
Age ≥ 65 at baseline, n (%)	581/738 (78.7)	145/159 (91.2)	165/177 (93.2)
Age 55 to 64 at baseline, n (%)	126/738 (17.1)	14/159 (8.8)	12/177 (6.8)
Age < 55 at baseline, n (%)	31/738 (4.2)	0/159 (0)	0/177 (0)
Female, n (%)	383/738 (51.9)	77/159 (48.4)	80/177 (45.2)
Family history of dementia, n (%)	135/631 (21.4)	36/159 (22.6)	42/151 (27.8)
Family history of stroke, n (%)	164/623 (26.3)	41/158 (25.9)	44/145 (30.3)
Family history of heart attack, n (%)	208/622 (33.4)	58/157 (36.9)	66/150 (44.0)
History of heavy smoking, n (%)	158/650 (24.3)	53/158 (33.5)	23/143 (16.1)
History of regular drinking, n (%)	80/645 (12.4)	17/156 (10.9)	43/140 (30.7)
History of drug abuse, n (%)	61/664 (9.2)	27/159 (17.0)	2/157 (1.3)
Age left school, mean (SD)	16.0 (1.7) n=640	16.3 (1.6) n=158	16.3 (1.4) n=151

Years in further education, mean (SD)	1.7 (2.1) n=638	2.5 (2.7) n=159	2.6 (2.7) n=150
Number of participants known to be deceased, n (%)	567 (76.8)	69 (43.4)	57 (32.2)

Table 4.1. Summary table of demographic characteristics of the OPTIMA, LEAD, and Challenge cohorts for all participants with at least one CAMDEX listed.

4.2. Age

4.2.1. Age at First Visit and at Death

Figure 4.1A shows a box plot of the participants' ages at the first episode with a CAMDEX for the OPTIMA, Challenge, and LEAD cohorts. The mean age of the participants in the three cohorts were all in the 70s at the first visit, but the initial age ranges varied. The OPTIMA participants ranged from ages 26 to 99 at the first visit, the Challenge participants were between 60 and 90 years old at the baseline CAMDEX, and the LEAD cohort initial ages ranged from 55 and 94 years old. The reasons for some younger participants joining these aging and memory studies will be discussed further below (see Table 4.2).

The ages at death for each cohort are presented in Figure 4.1B. OPTIMA had the widest range of ages at death, from 52 to 102 years of age. The Challenge cohort ages at death ranged from age 71 to 102, and LEAD participants died between the ages of 73 and 102.

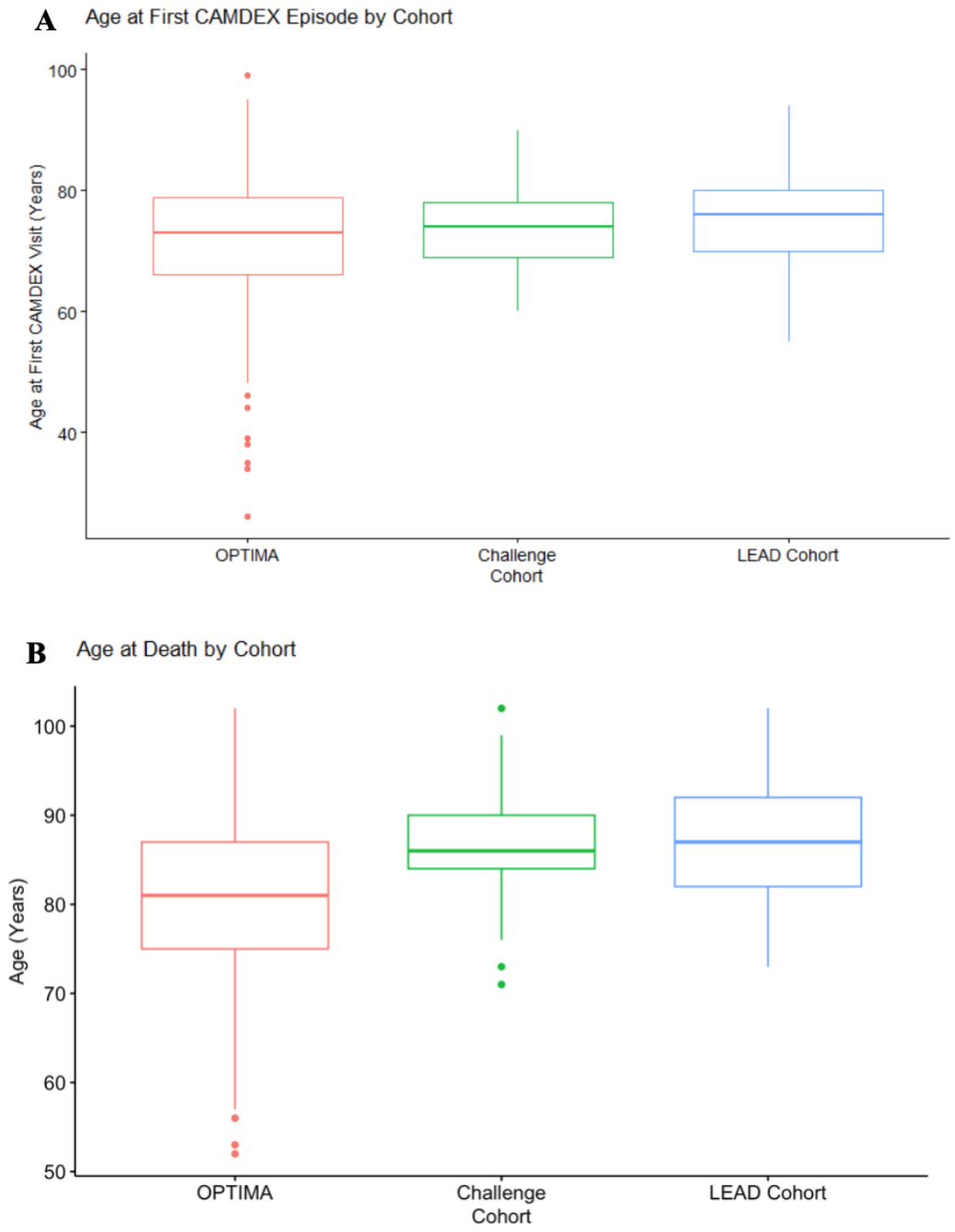


Figure 4.1. A) Box plot of age at first CAMDEX episode, separated by cohort (OPTIMA n=738, Challenge n=159, LEAD n=177). **B)** Box plot of age at death, separated by cohort (OPTIMA: n=567, Challenge: n=69, LEAD: n=56).

For the OPTIMA cohort, the mean age at the first episode was 71.8 years (SD= 9.6), with a median age of 73 (Figure 4.2A). The mean age at death for the OPTIMA participants was 80.2 (SD= 8.9), with a median of 81 years (Figure 4.2B).

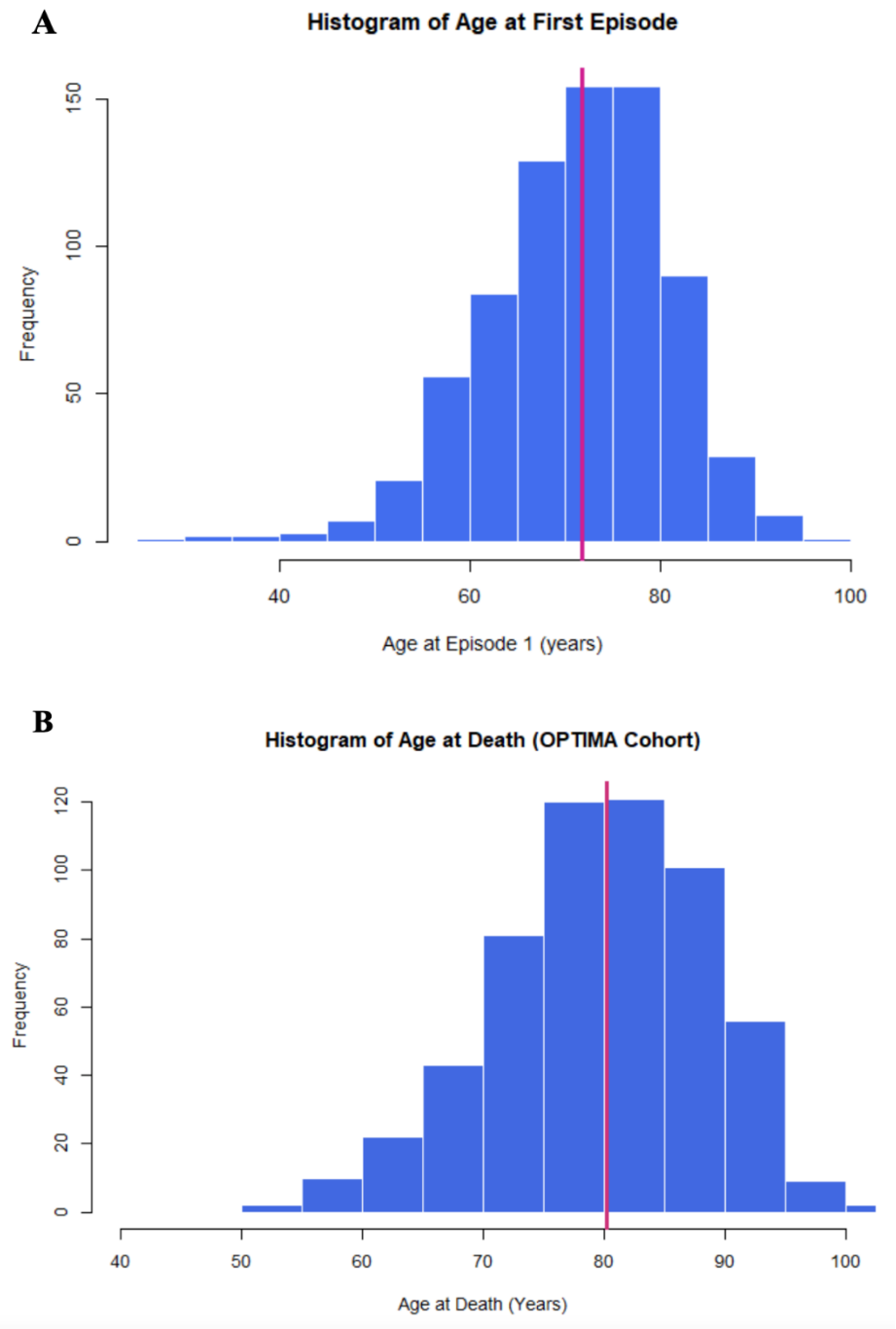


Figure 4.2. A) Histogram of OPTIMA cohort ages at first episode (n=742). **B)** Histogram of OPTIMA participant ages at death (n=568). Vertical red lines represent the mean age.

At baseline, the Challenge cohort had a mean age of 73.6 years (SD=6.2) and a median age of 74 years (Figure 4.3A). The mean age at death for the Challenge cohort was 86.6 years old (SD=5.8), with a median of 86 years of age (Figure 4.3B).

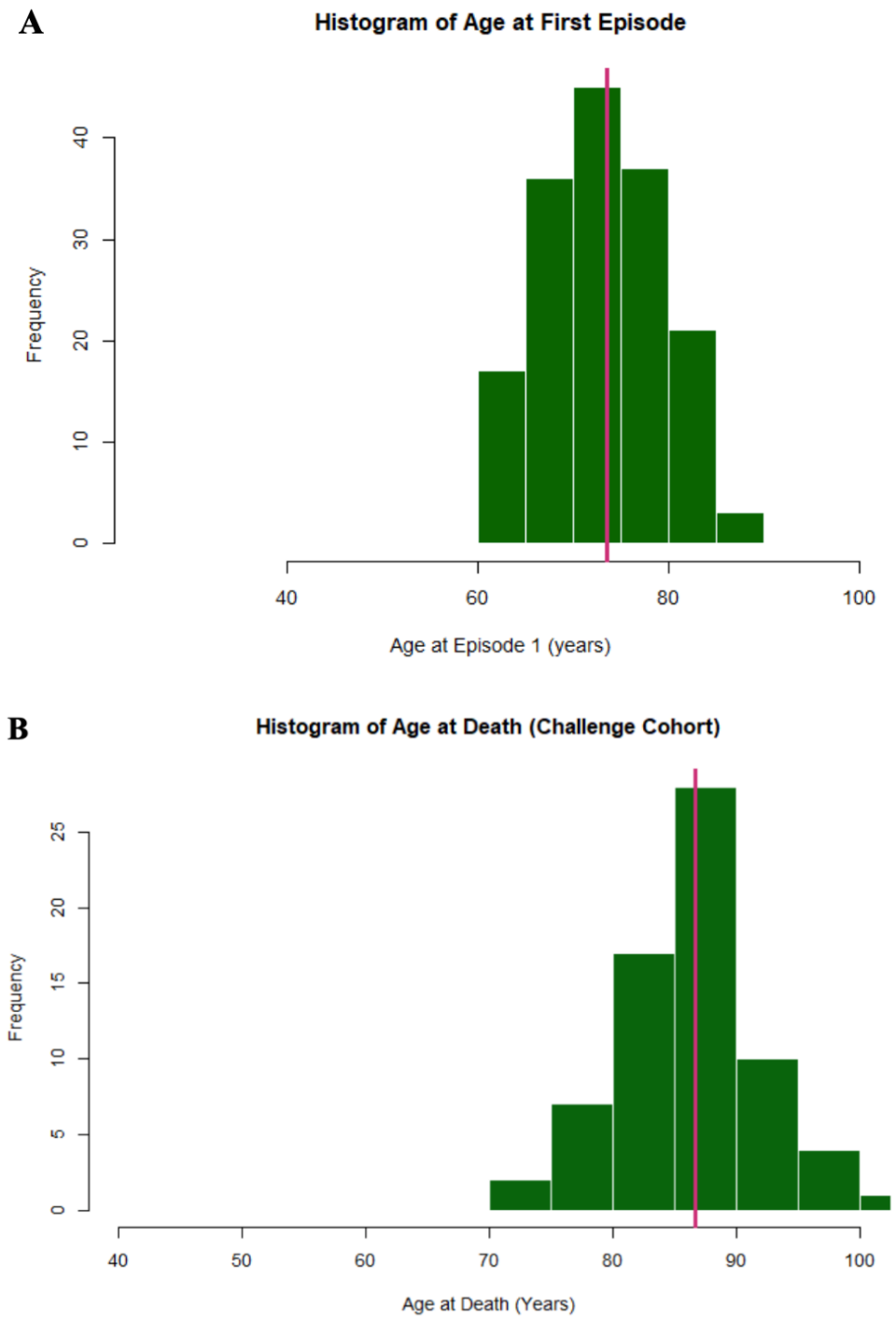


Figure 4.3. A) Histogram of Challenge cohort ages at first episode (n=159). **B)** Histogram of Challenge participant ages at death (n=69). Vertical red lines represent the mean age.

For the LEAD cohort, the mean age at the first episode was 75.4 years of age (SD=7.3), with a median of 76 years (Figure 4.4A). For age at death, the mean was 86.7 years old (SD=6.4), and the median was 87 years of age (Figure 4.4B).

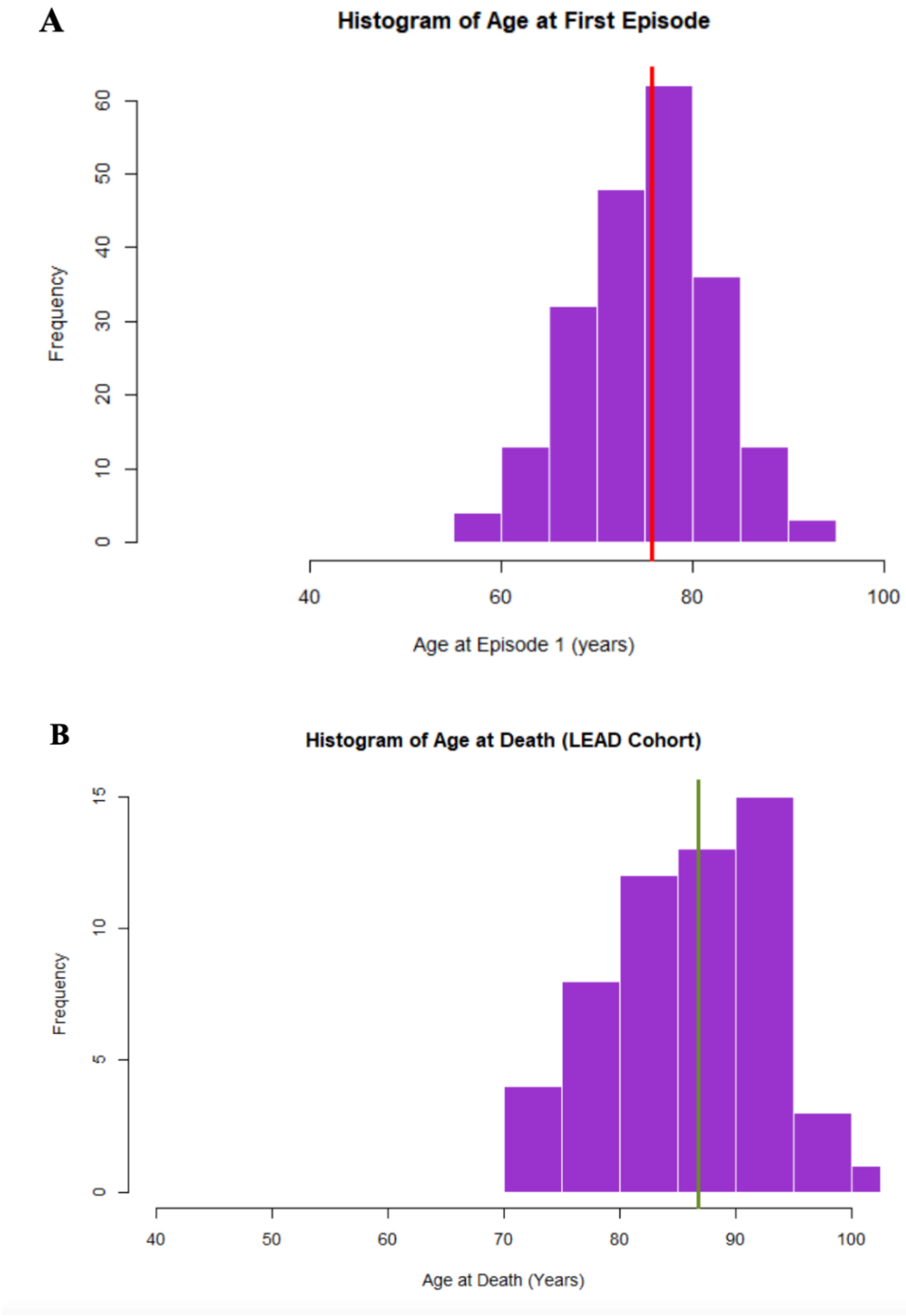


Figure 4.4. A) Histogram of LEAD cohort ages at first episode (n=211). **B)** Histogram of LEAD participant ages at death (n=56). Vertical red lines represent the mean age.

4.2.2. Young Participants

There were 157 participants in OPTIMA who were younger than 65, with ages ranging from 26 to 64, which may be unexpected given the cohort's focus on ageing (Table 4.2). There were also 14 participants in Challenge (ages 60 to 64), and 12 participants in LEAD (ages 55 to 64) who joined under the age of 65.

Upon examining the clinical notes and diagnoses for these younger participants, various apparent reasons for joining the study were noted. These reasons included acting as control subjects for the study, presenting with subjective memory concerns, having mild cognitive impairment (MCI) or vascular cognitive impairment (VCI), early onset Alzheimer's Disease (AD) or vascular dementia (VD), frontotemporal dementia (FTD), psychiatric conditions, and other rare conditions, including Huntington's disease (HD), Creutzfeldt-Jakob disease (CJD), multiple sclerosis (MS), and organic brain syndrome (Table 4.2).

Reasons Contributing to Joining Study at Age < 65	**OPTIMA** n (% of those under age 65 in the cohort)	**Challenge** n (% of those under age 65 in the cohort)	**LEAD** n (% of those under age 65 in the cohort)
Control or subjective memory concerns	62 (39.5)	14 (100.0)	6 (50.0)
Mild cognitive impairment or vascular cognitive impairment	17 (10.8)	0 (0)	3 (25.0)
Early onset dementia (Alzheimer's or Vascular)	47 (29.9)	0 (0)	3 (25.0)
Frontotemporal dementia	8 (5.1)	0 (0)	0 (0)
Other rare conditions (HD, CJD, MS, Organic brain syndrome, etc.)	13 (8.3)	0 (0)	0 (0)
Psychiatric conditions	28 (17.8)	0 (0)	2 (16.7)
Total number of participants under 65	**157**	**14**	**12**

Table 4.2. Table of reasons contributing to younger participants (ages 26-64) joining OPTIMA, Challenge, and LEAD. Some participants fit into multiple reasons for joining, so total count is greater than number of participants under 65.

4.3. Education

4.3.1. Age Left School

Education is another factor that has been shown to impact dementia risk, with more time spent in school correlating with a lower chance of developing dementia (138). Figure 4.5 highlights the age that participants in each cohort reported that they had left school. For the OPTIMA cohort, the mean was 16.0 years of age at the time of leaving school (SD=1.7). The

ages when participants reported leaving school ranged from nine to 20, along with one outlier of age 30 that is presumed to be an error and was excluded from the analysis. The Challenge cohort had an average age leaving school of 16.3 (SD=1.6 years), and a range of ages from 14 to 19. The mean age left school for the LEAD cohort was 16.3 (SD=1.4 years), with a range from 12 to 19 years old.

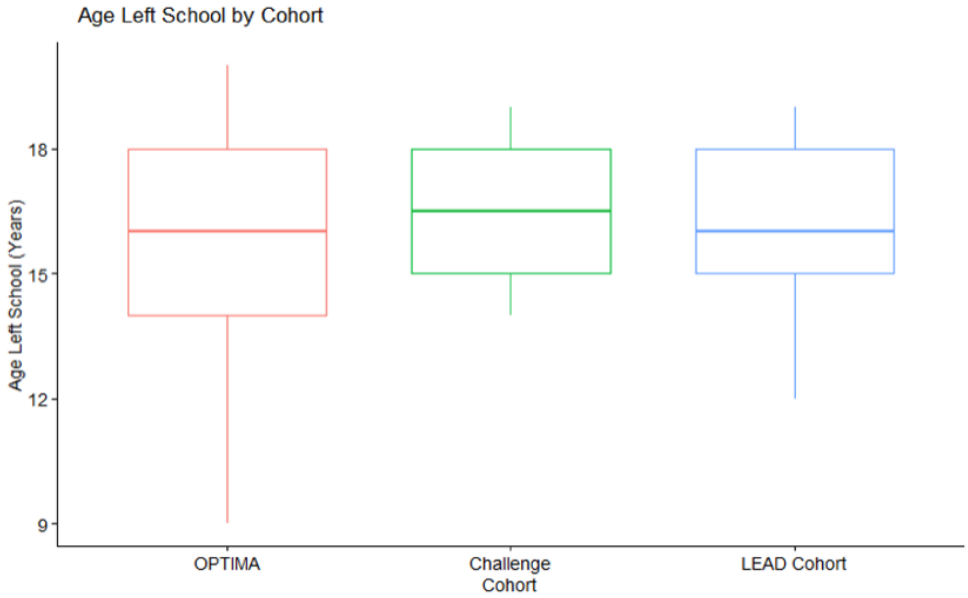


Figure 4.5. Box plot of the age participants reported leaving school, separated by cohort (OPTIMA n=640, Challenge n=158, LEAD n=151).

4.3.2. Years in Further Education

The CAMDEX also included a measure of the years spent in further education. By examining the free text associated with this variable, further education seemed to encompass time spent in university, graduate school, night school, nursing school, and other vocational training programs. Figure 4.6 highlights further education data for the OPTIMA, Challenge, and LEAD cohorts.

For the OPTIMA cohort, the mean was 1.7 years (SD=2.1 years), and participants had spent up to eight years in further education (Figure 4.7). The Challenge cohort participants spent an average of 2.5 years in further education (SD=2.7 years), with a range from zero to eighteen years (Figure 4.8). The LEAD cohort had a mean of 2.6 years in further education (SD=2.7), with an equivalent range from zero to eighteen years (Figure 4.9).

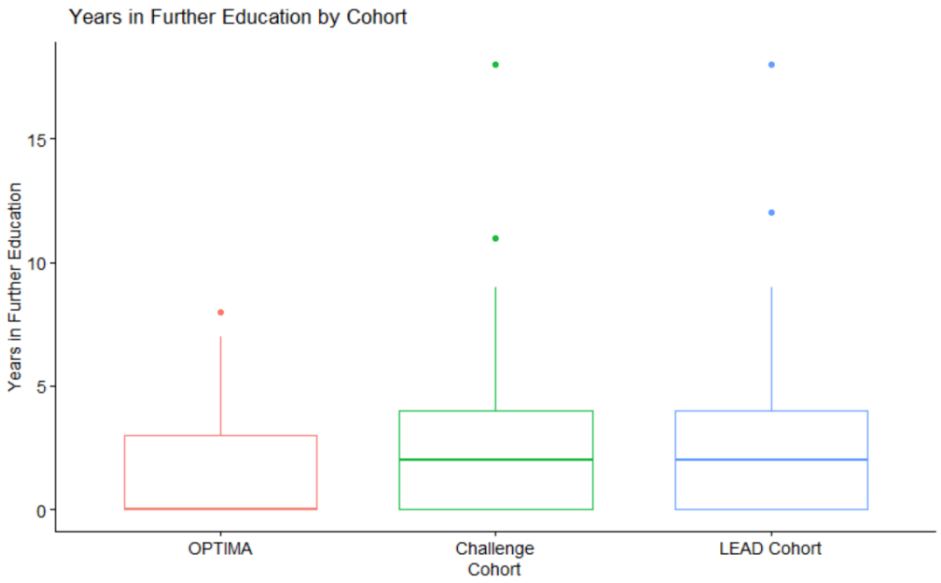


Figure 4.6. Box plot of the years each participant spent in further education, grouped by cohort (OPTIMA n=638, Challenge n=159, LEAD n=150).

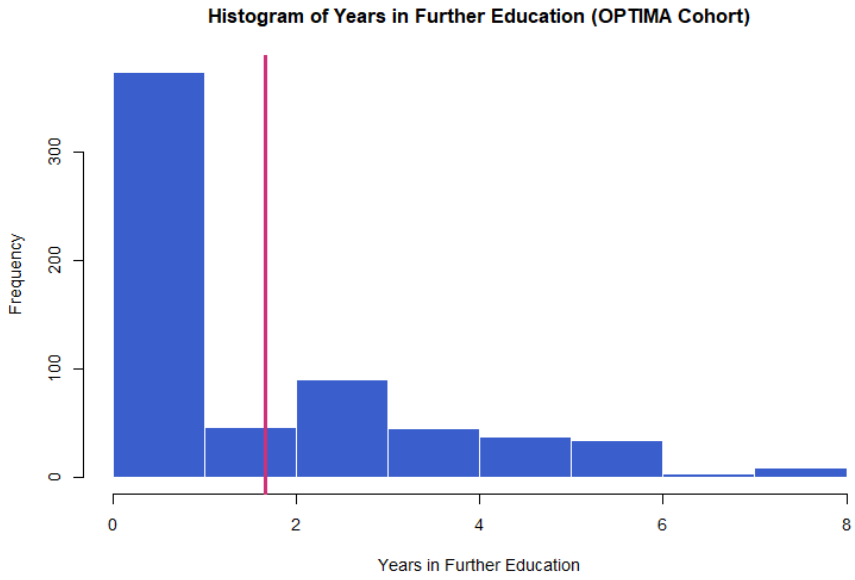


Figure 4.7. Histogram of years in further education (OPTIMA cohort, n=638).

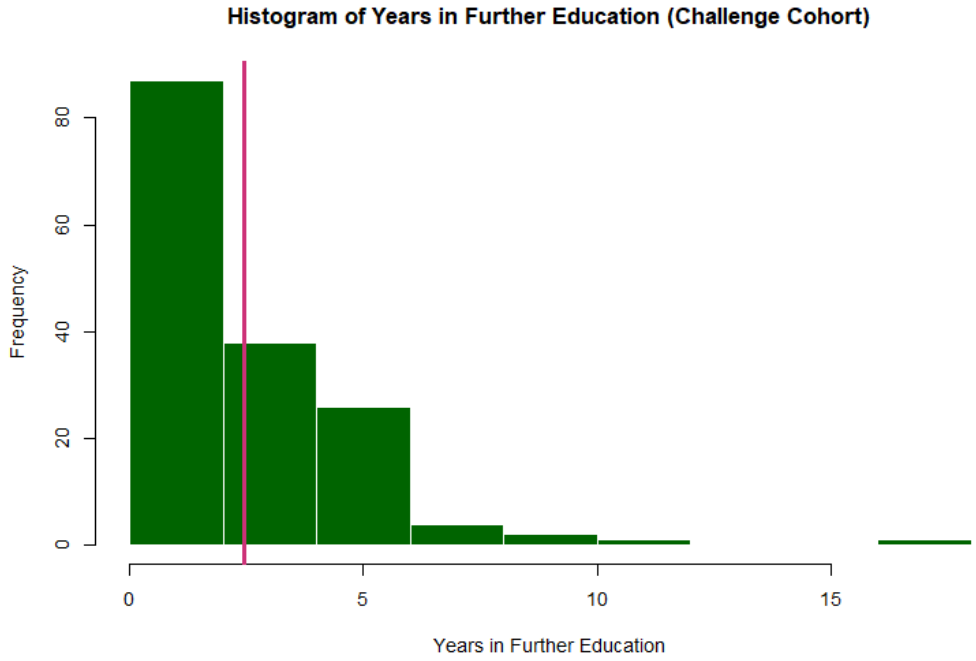


Figure 4.8. Histogram of years in further education (Challenge cohort, n=159).

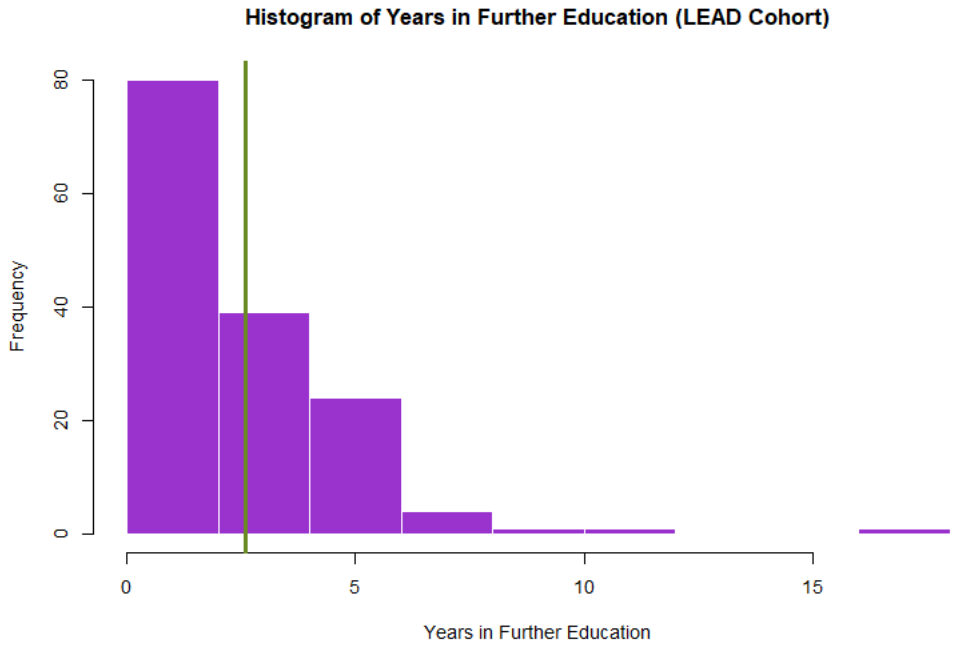


Figure 4.9. Histogram of years in further education (LEAD cohort, n=150).

4.4. Family Medical History

The CAMDEX also included questions about the participants' family medical history, including dementia, stroke, and heart attack, though the definition of family in the CAMDEX could not be ascertained. Some dementia cases are related to familial genetics and family history of dementia is an established risk factor (139). Additionally, family history of

cardiovascular events like stroke and heart attack can put an individual at greater risk of cardiovascular disease, which in turn elevate dementia risk (140, 141).

For the OPTIMA cohort, 135 out of 631 people reported a family history of dementia (21.4% of the cohort), 164 out of 623 participants (26.3%) had a family history of stroke, and 208 out of 622 people (33.4%) had a family history of heart attack.

For the Challenge cohort, 36 out of 159 people (22.6%) had a family history of dementia, 41 out 158 participants (25.9%) had a family history stroke, and 58 out of 157 people (36.9%) reported a family history heart attack.

In the LEAD cohort, 42 of 151 participants (27.8%) had a family history of dementia, 44 out of 145 (30.3%) reported a family history of stroke, and 66 out of 150 (44.0%) noted a family history of heart attack.

4.5. Substance Use History

4.5.1. Alcohol Use

The CAMDEX also collected information about the participants' history of alcohol use by asking about previous regular, heavy, or problem drinking (Figure 4.10, Supplemental Table 4.1). Heavy drinking was defined as having "ever drunk as much as 10 units (100 g) alcohol daily over a two-week period," and the CAMDEX definitions of regular and problem drinking could not be determined (142). The majority of participants in all three cohorts reported no history of regular, heavy, or problem drinking. Regular drinking was reported by 80 OPTIMA participants, 17 Challenge participants, and 43 LEAD participants. Heavy drinking was less common, with 42 OPTIMA, 11 Challenge, and 9 LEAD participants reporting this behaviour. Six OPTIMA participants and nine LEAD participants reported a history of problem drinking.

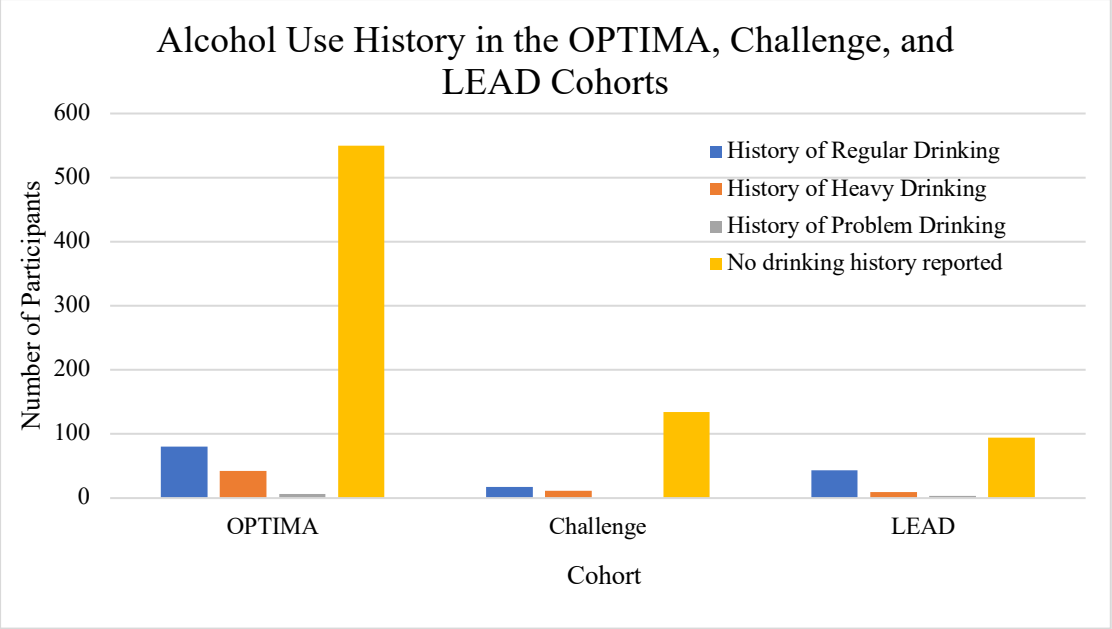


Figure 4.10. Graph of alcohol use history reported in the OPTIMA, Challenge, and LEAD cohorts.

The Challenge cohort also had additional baseline data about the frequency of alcohol consumption in the past twelve months. This additional questionnaire was completed by 157 out of 159 participants at the first CAMDEX visit (Figure 4.11, Supplemental Table 4.2). The largest proportion of the cohort (35.0%) reported drinking alcohol daily in the past year.

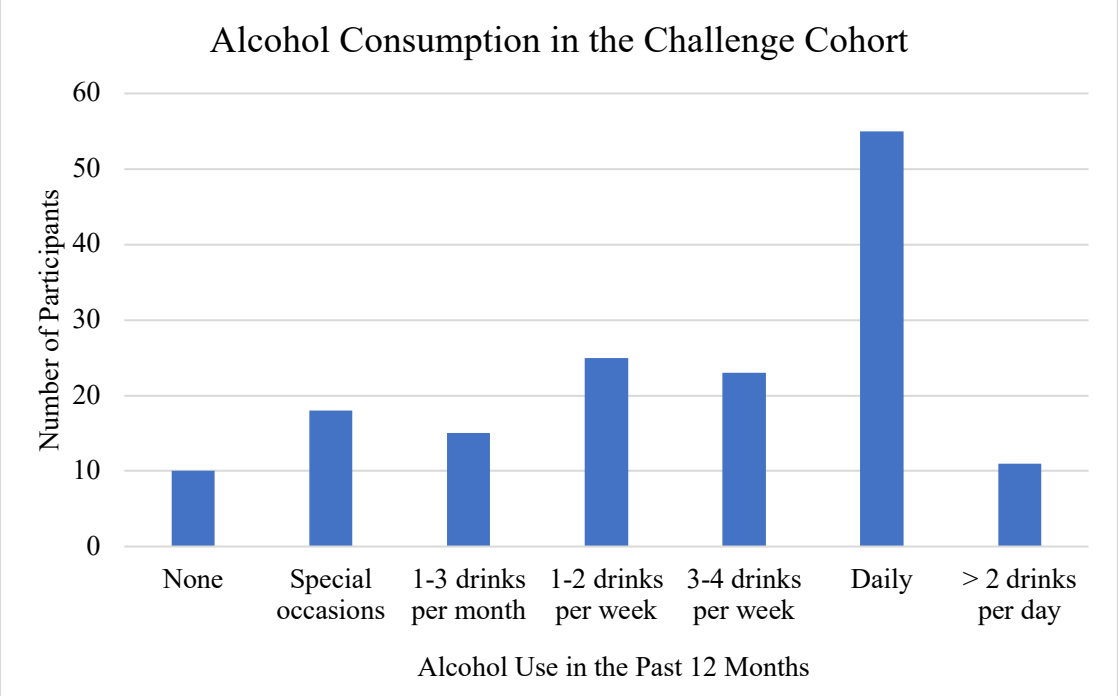


Figure 4.11. Reported alcohol use in the past 12 months in the Challenge cohort (n=157).

4.5.2. Smoking

The CAMDEX asked about the patient's history of heavy smoking, which was defined as "20 or more cigarettes per day for a year or more" (142). This level of smoking was reported by 158 OPTIMA participants (24.3%), 53 Challenge participants (33.5%), and 23 LEAD participants (16.1%) (Figure 4.12, Supplemental Table 4.3).

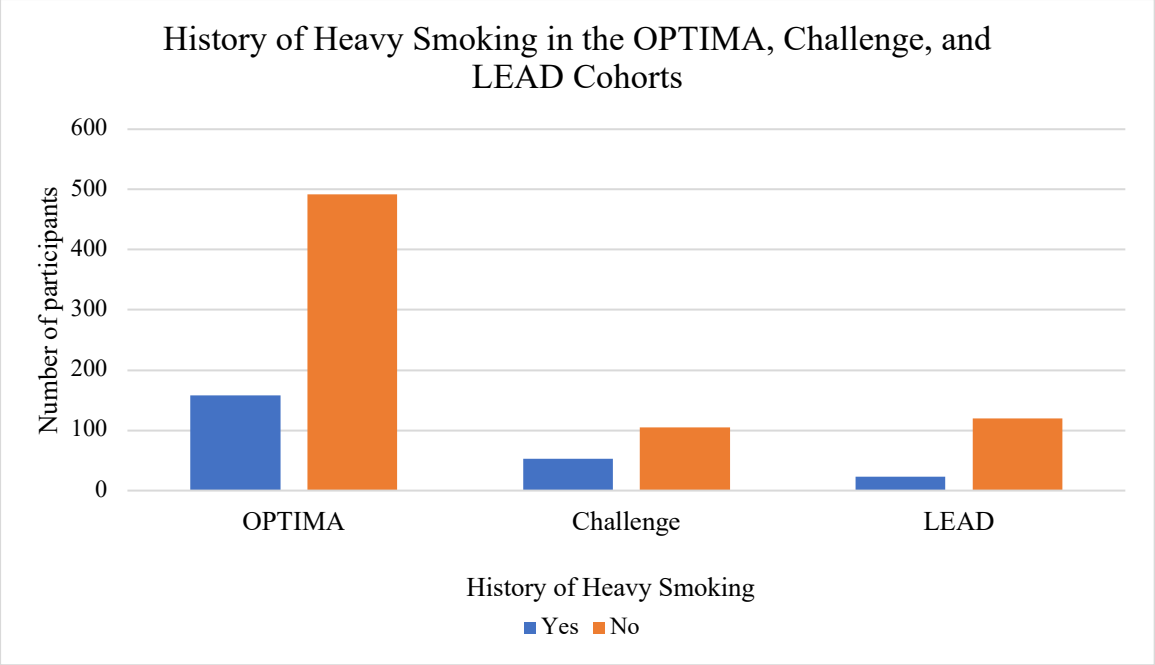


Figure 4.12. History of heavy smoking in the OPTIMA, Challenge, and LEAD cohorts.

The Challenge cohort had additional data with a general question about any current and past smoking collected at the baseline visit (Figure 4.13, Supplemental Table 4.4). 68 participants had never smoked (42.8%), nine participants reported being current smokers (5.7%), and 82 participants reported that they smoked in the past but stopped (51.6%).

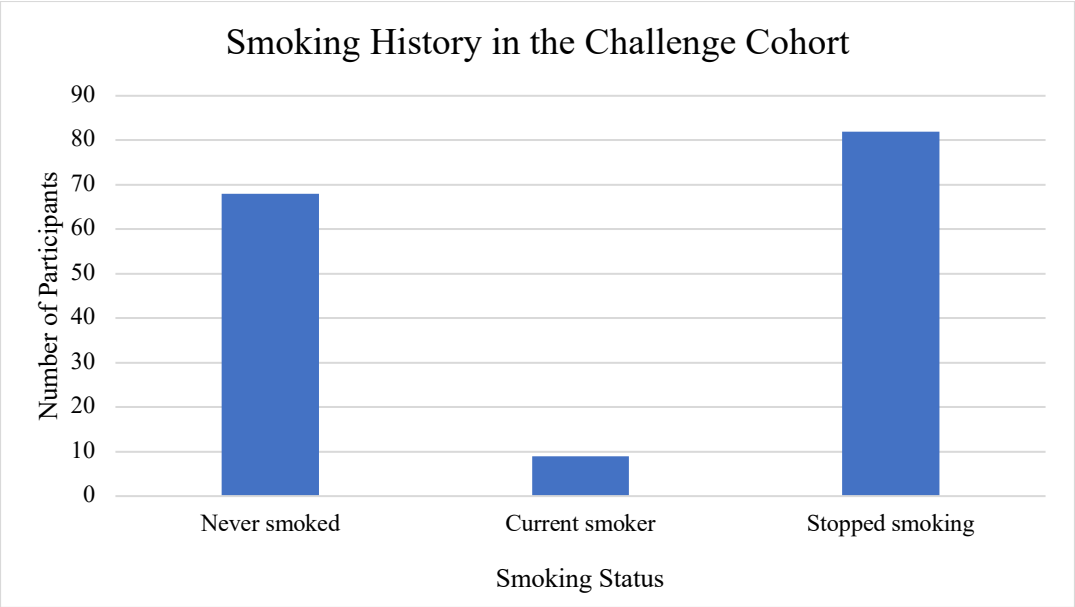


Figure 4.13. Smoking history and current status in the Challenge cohort.

4.5.3. Drug Abuse

History of drug abuse was also queried in the CAMDEX (Figure 4.14). The types of drug abuse considered were tranquilisers, hypnotics, barbiturates, stimulants, or others. Few participants reported history of drug abuse, although it is possible that participants may not have felt comfortable reporting illicit substance use.

664 out of the 742 OPTIMA participants reported whether or not they had a history of drug abuse, and 78 participants were missing data. Of those with complete data, just over 90% of participants (n=603) reported no history of drug abuse. Of those who did report a history of drug abuse (a total of n=61), 21 used tranquilisers, 13 used hypnotics, four used barbiturates, one used stimulants, and 22 used other types of drugs.

For the Challenge cohort, all 159 participants had complete drug abuse history data. 83% of the cohort (n=132) reported no past drug abuse. Of the participants who did report a drug abuse history, nine used tranquilisers, six used hypnotics, one used barbiturates, and 11 used another type of drug.

157 out of the 211 LEAD participants had complete data about their history of drug abuse, with 54 participants missing data. Of these participants with complete information, 98.7% (n=155) reported no drug abuse history. There was one person who had past tranquiliser drug use, and one participant reported a history of hypnotic drug abuse.

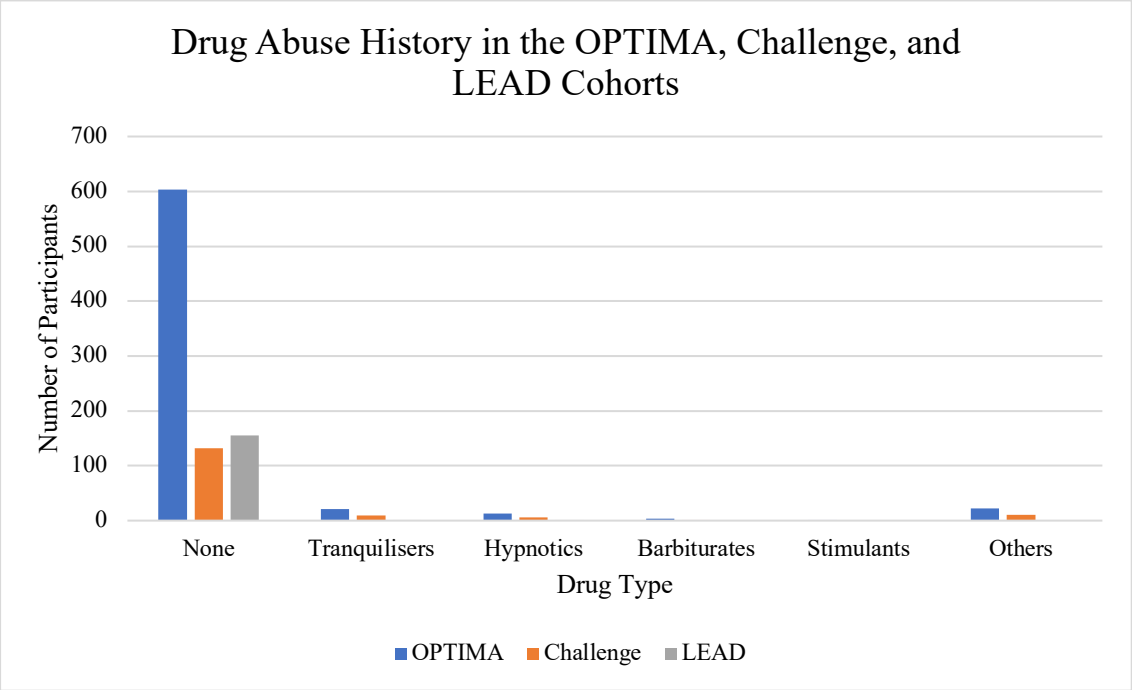


Figure 4.14. History of drug abuse reported by the OPTIMA, Challenge, and LEAD participants.

4.6. Living Arrangements

Another factor that the CAMDEX interview asked about was living arrangements, i.e. whether the participant was living in a long-term care facility, in a residential home, in sheltered accommodation, as a dependant at home, or independently with a spouse, relative, friend, or alone. Figure 4.15 and Supplemental Table 4.6 present the baseline information about the living arrangements for each OPTIMA, Challenge, and LEAD participant. There was not sufficient completion of this variable at later visits to allow for a comparison of living arrangements at the participants' early and late visits.

716 out of the 742 OPTIMA participants had at least one record of their living arrangements. Of those with complete data, over half lived independently with a spouse (n=414, 57.8%), about 20% (n=146) lived independently on their own, and 6% (n=43) lived independently with a relative or friend. About 5% (n=39) were dependent at home, almost 5% were in residential homes, and about 3% of participants were in sheltered accommodation and long-term hospitals, respectively.

For the Challenge cohort, the majority of participants were living independently with a spouse (n=102, 64.2%), with the second most common response being living independently and alone (n=50, 31.4%). There were also five individuals living independently with a relative or friend, as well as one participant dependant at home and one in sheltered accommodation. No participants were in residential homes or long-term hospitals, as expected given that the Challenge cohort recruited primarily cognitively normal older adults.

With regards to LEAD, 162 out of 211 participants had record of their living arrangements. Like the other cohorts, the majority lived independently with a spouse (n=107, 66.0%)), followed by independently alone (n=38, 23.5%). Seven participants lived as dependant at home or independently with a relative or friend, respectively. Additionally, two people resided in sheltered accommodation, and one was in a long-term hospital.

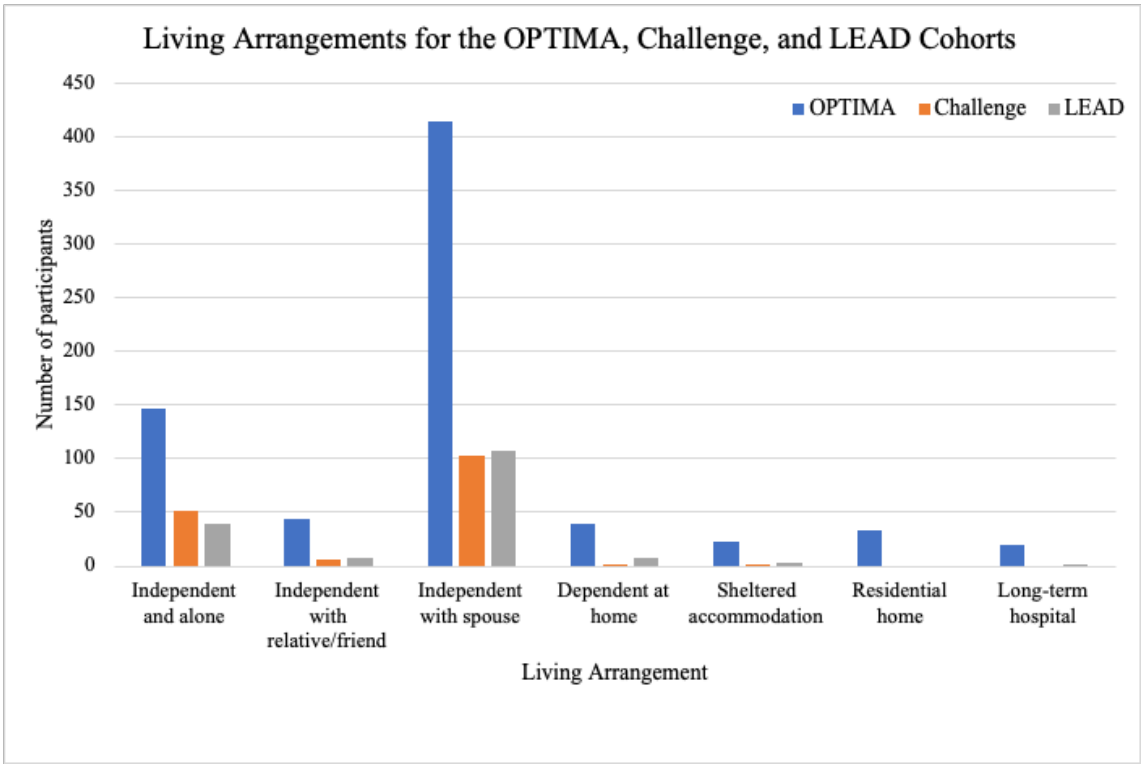


Figure 4.15. First reported living arrangement for the OPTIMA, Challenge, and LEAD cohort participants.

4.7. Biochemistry

Table 4.3 presents a summary of the baseline biochemistry values for the OPTIMA, Challenge, and LEAD cohorts. All mean values were within the normal ranges, except for cholesterol, which was higher than the normal range across all three cohorts.

Biochemistry Variables *Normal Range* *(Sources: (143, 144))*	**OPTIMA** Mean (SD) n=729	**Challenge** Mean (SD) n=159	**LEAD** Mean (SD) n=206
Sodium *133-146 mmol/L*	140.01 (3.34) n=719	140.63 (2.25)	139.04 (2.72) n=204
Potassium *3.5-5.3 mmol/L*	3.88 (0.37) n=719	3.88 (0.41)	3.95 (0.62) n=204
Urea *2.5-7.8 mmol/L*	6.15 (1.97) n=674	6.23 (1.53) n=154	6.20 (1.54) n=199
Creatinine *45-84 µmol/L (females)* *59-104 µmol/L (males)*	94.64 (19.73) n=718	104.69 (17.41)	82.59 (17.53) n=205
Calcium *2.2-2.6 mmol/L*	2.35 (0.12) n=718	2.43 (0.12)	2.51 (1.53) n=200
Phosphate *0.8-1.5 mmol/L*	0.97 (0.16) n=714	0.96 (0.15) n=158	1.03 (0.55) n=200
Blood glucose *3.0-6.0 mmol/L (fasting*)	5.51 (2.07) n=707	5.29 (1.79) n=155	5.94 (2.06) n= 199
Cholesterol *Below 5 mmol/L*	5.91 (1.28) n=153	6.31 (1.16) n=151	5.08 (1.19) n=194
HDL Cholesterol *>1.0mmol/L (men),* *>1.2mmol/L (women)*	1.45 (0.32) n=7	1.60 (0.49) n=143	1.52 (0.48) n=194

Table 4.3. Biochemical variable values at baseline for OPTIMA, Challenge, and LEAD cohorts.

4.8. Haematology

Table 4.4 highlights the baseline values for the following haematology variables: haemoglobin, platelets, haematocrit, white cell count, Vitamin B12, and serum folate. All mean values were within the normal range. One outlier serum folate value of 651.9 ng/mL was excluded from the LEAD cohort.

Haematology Variables *Normal Range* *(Sources: (145, 146))*	**OPTIMA** Mean (SD) n=728	**Challenge** Mean (SD) n=159	**LEAD** Mean (SD) n=205
Haemoglobin *12.1-15.1 g/dL (females)* *13.8-17.2 g/dL (males)*	13.8 (1.3) n=718	13.9 (1.2) n=157	13.6 (1.2) n=203
Platelets *140-400 x10^9/L*	255.9 (64.1) n=715	247.4 (64.9) n=157	233.0 (55.5) n=203
Haematocrit *0.37-0.47 (females)* *0.40-0.54 (males)*	0.4 (0.04) n=711	0.4 (0.03) n=157	0.42 (0.03) n=203
White cell count *3.6-11.0 x10^9/L*	6.5 (1.7) n=718	6.4 (1.7) n=157	6.7 (1.6) n=184
Vitamin B12 *180-1000 pg/mL*	374.0 (211.9) n=700	440.1 (262.4) n=158	434.2 (230.3) n=179
Serum Folate *>4.0 ng/mL*	10.6 (4.9) n=691	12.3 (3.5) n=158	13.0 (6.4) n=180

Table 4.4. Haematology variable values at baseline for OPTIMA, Challenge, and LEAD cohorts

4.9. Cognitive Assessments

4.9.1. Mini Mental State Examination (MMSE) Score

The Mini Mental State Examination (MMSE) is a brief cognitive assessment that tests a range of cognitive functions and has a maximum possible score of 30 points (147, 148). Although the appropriate cut-off score has continued to be a subject of debate, the longstanding cut-off MMSE score that indicates dementia is 23 or below (149). Upon examining the database, some participants with dementia appeared to stop undergoing the MMSE and other cognitive assessments when their symptoms presumably progressed to a level where these tests were no longer feasible.

At the first and last available MMSE, the OPTIMA participants had a much wider range than Challenge and LEAD, likely due to the greater number of participants with cognitive impairments from the outset (Figure 4.16A and B). For the 675 OPTIMA participants with at least two MMSE scores, the mean first score was 22.9 (SD=7.0), with a median of 25 (Figure 4.24A). The range of baseline MMSE scores was from zero to 30. At the last MMSE score, OPTIMA participants had a mean of 16.7 points (SD=10.6), with a median of 17 and a range from zero to 30 (Figure 4.24B).

For the 156 Challenge participants, the average first MMSE score was 28.6 (SD=1.4), with a median of 29 and a range from 24 to 30 (Figure 4.16A). All participants were above the cut-off for dementia. At the last MMSE, Challenge participants had a mean of 27.6 (SD=3.8), a median of 29, and a range from 9 to 30 (Figure 4.16B).

For the LEAD cohort, the 199 participants with two or more scores had a mean baseline MMSE score of 27.5 (SD=2.5) (Figure 4.16A). The median was 28 points, and the range of scores was from 20 to 30. At the final MMSE, LEAD participants had a mean of 25.6 (SD= 5.1), a median of 28 points, and a range from 6 to 30 (Figure 4.16B).

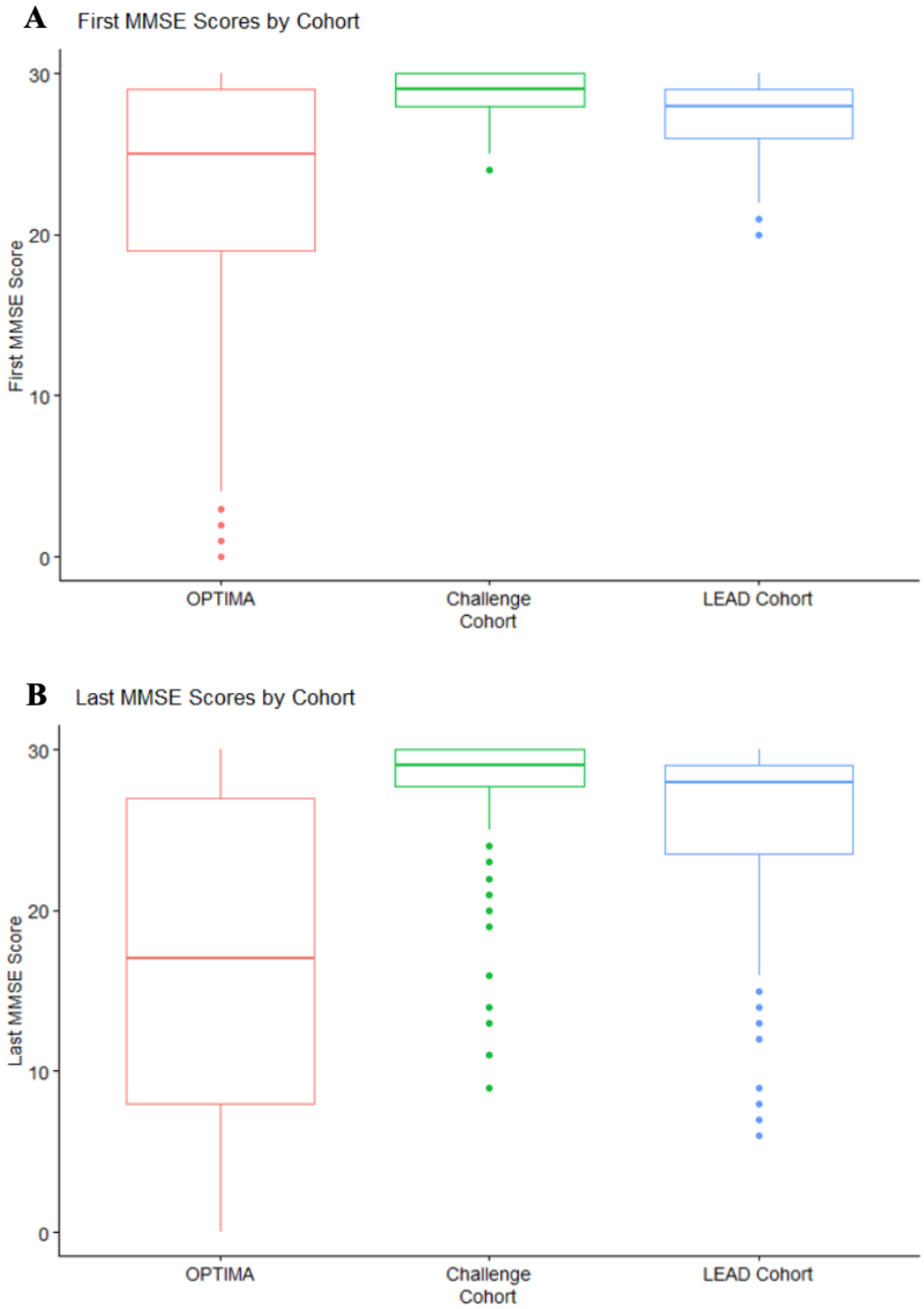


Figure 4.16. Box plot of the **A)** first and **B)** last MMSE scores for participants in the OPTIMA, Challenge, and LEAD cohorts (OPTIMA: n=675, Challenge: n=156, LEAD: n=199)

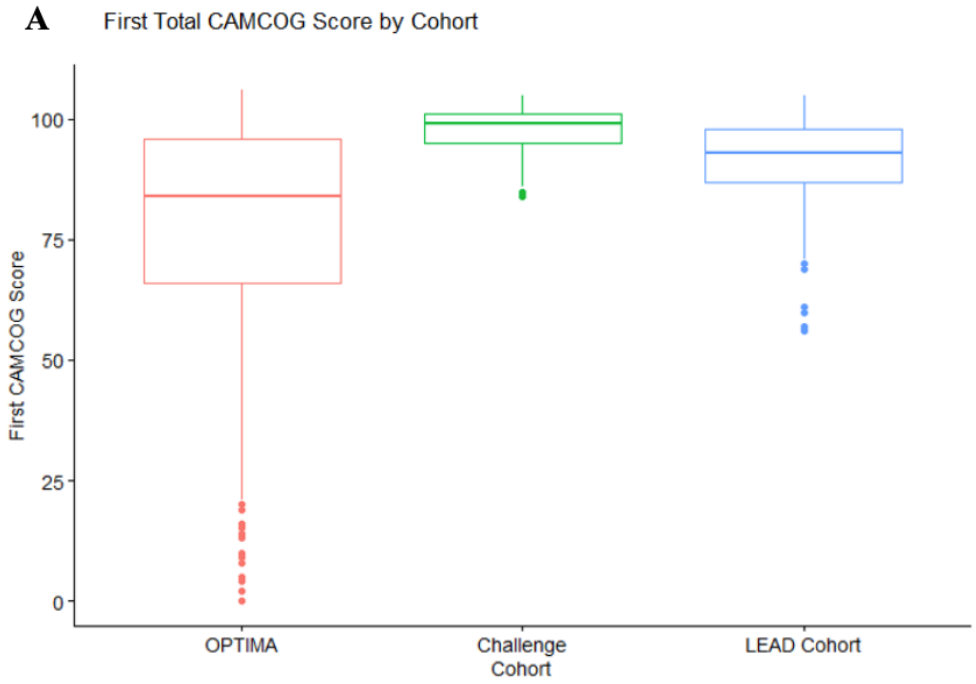
4.9.2. Cambridge Cognitive Examination (CAMCOG) Score

The total Cambridge Cognitive Examination (CAMCOG) score is a measure used to screen for dementia, with a maximum of 107 points (130, 150). The cut-off score is 80, and dementia is probable in individuals who score below this. Figures 4.25A and B highlight the first and last available total CAMCOG score for participants in the OPTIMA, Challenge, or LEAD cohorts, including only participants with two or more total CAMCOG scores.

The mean total CAMCOG score for OPTIMA participants (n=642) at baseline was 77.3 (SD=23.5) (Figure 4.17A). The median was 84 points, and the range of scores was from zero to 106. At the last CAMCOG, the mean score was 58.2 (SD=36.3), with a median of 63 and a range from zero to 107 (Figure 4.17B).

For the Challenge cohort (n=151), the mean initial total CAMCOG score was 98.0 points (SD=4.3), with a median score of 99 (Figure 4.17A). The range of scores was from 84 to 105. At the last assessment, the mean was 95.8 (SD=10.0), with a median of 98 and a range from 23 to 107 (Figure 4.17B).

For the LEAD cohort (n=199), the average first total CAMCOG score was 91.3 (SD=9.9), with a median of 93 points (Figure 4.17A). The baseline scores ranged from 56 to 105. For the last CAMCOG, the mean was 90.2 (SD=14.7), the median was 95.5 points, and the range was from 35 to 107 (Figure 4.17B).



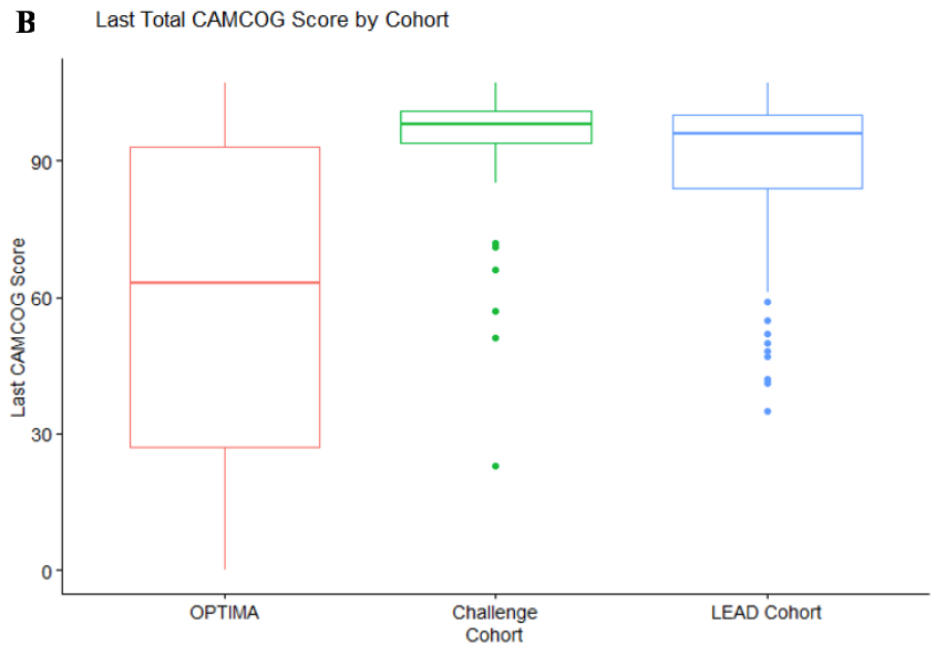


Figure 4.17. Box plot of the **A)** first and **B)** last total CAMCOG score for participants in the OPTIMA, Challenge, and LEAD cohorts (OPTIMA: n=642, Challenge: n=151, LEAD: n=199).

4.9.3. National Adult Reading Test (NART)

The NART is a tool meant to measure premorbid intelligence quotient (IQ). This measure is generated from a test where participants read 50 unusual words aloud, which is meant to evaluate intelligence that is maintained despite neurodegeneration (151). A comparison of the Predicted Full-Scale IQ from the NART for participants in each cohort can be seen in Figure 4.18.

For the OPTIMA cohort, the mean first recorded NART score was 110.9 (SD=14.1, n=612), and the median was 114. The scores ranged from 70 to 131 points. Reviewing the cases of individuals in OPTIMA with low IQs at baseline (less than or equal to 85) revealed that all but one of the 52 individuals had MCI, dementia, or Cushing's syndrome at the time they completed the NART. Additionally, it was noted that the predicted IQ score declined over time for some participants who had worsening dementia, which aligns with the critiques of NART for individuals experiencing cognitive decline.

The Challenge cohort had a mean baseline NART score of 117.7 (SD=9.5, n=159), with a median of 120. The range of baseline NART scores ranged from 73 to 131. Looking at the notes for the one individual with a NART score of 73, below the threshold score of 85, the reason was unclear, as this person was diagnosed as a control, and the NART test was not repeated at subsequent visits.

Similar to the Challenge results, for the LEAD cohort, the mean initial NART score was 117.4 (SD=9.4, n=200), and the median score was 120 points. The range of NART scores for the LEAD cohort was from 87 to 131 points.

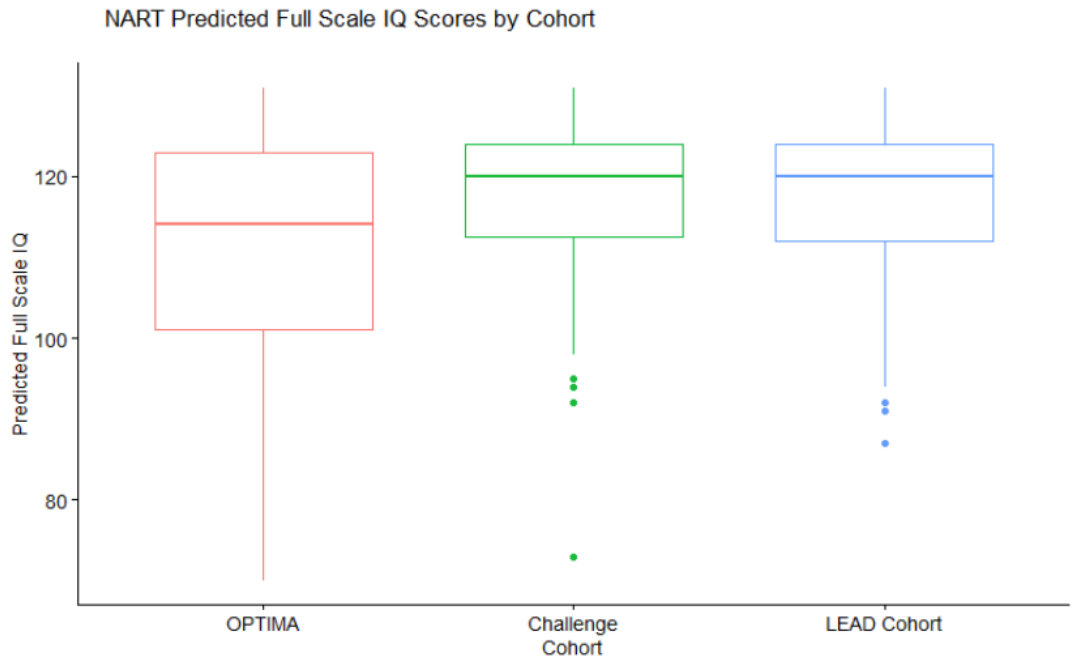


Figure 4.18. Box plot of the first NART Predicted Full Scale IQ score for participants in the OPTIMA, Challenge, and LEAD cohorts (OPTIMA: n=612, Challenge: n=159, LEAD: n=200).

4.10. Cognitive Decline Scores

Cognitive decline scores were calculated for individuals with at least one baseline and one follow-up CAMDEX administered. Two different cognitive decline scores were calculated based on two measures of cognitive function included in the CAMDEX: the MMSE score and the total CAMCOG score. The rate of cognitive decline for each participant was calculated using the following formulas:

$$MMSE\ Cognitive\ decline\ score = \frac{(Final\ MMSE\ score) - (Baseline\ MMSE\ score)}{Time\ elapsed\ between\ baseline\ and\ final\ CAMDEX\ (in\ years)}$$

$$Total\ CAMCOG\ Cognitive\ decline\ score = \frac{(final\ Total\ CAMCOG\ score) - (baseline\ Total\ CAMCOG\ score)}{Time\ elapsed\ between\ baseline\ and\ final\ CAMDEX\ (in\ years)}$$

Based on this formula, a negative cognitive decline score indicates worsening cognition over time, a score of zero indicates stable cognition, and a positive score indicates improvement in cognition over time.

Cognitive decline scores were calculated for participants who had at least two total CAMCOG or MMSE scores to be used in the calculation. Participants who had less than one year elapsed between their first and final CAMDEX administration were excluded from the analysis. One limitation of this method is that some participants no longer had cognitive assessments administered in their later episodes, presumably when their dementia was too severe, so the cognitive decline scores may not capture the true extent of the cognitive decline for these individuals who continued to be followed beyond the date of their last MMSE or total CAMCOG score.

4.10.1. MMSE-Based Cognitive Decline Scores

Figure 4.19 highlights the rate of cognitive decline for participants in the OPTIMA, Challenge, and LEAD cohorts, based on the change in their MMSE scores over time.

For the OPTIMA cohort (n=616), the mean MMSE-based cognitive decline score was -2.0 (SD=2.7), with a median of -1.2 (Figure 4.20). The cognitive decline scores ranged from -21.4 to 3.0. The average time elapsed between the first and last MMSE scores was 5.6 years (SD=4.3), with a range from to one to 22.3 years.

For the Challenge cohort participants with more than one MMSE result (n=154), the mean cognitive decline score was -0.2 (SD=0.8), with a median of zero (Figure 4.21). The range of MMSE cognitive decline scores was from -6.5 to 0.6. The mean time between first and last MMSE scores was 7.6 years (SD=3.7), with a range from 1.0 to 13.2 years.

For the LEAD cohort (n=190 with two or more MMSE scores), the mean cognitive decline score based on the first and last MMSE was -0.7 (SD=1.4), with a median of -0.3 (Figure 4.22). The MMSE-based cognitive decline scores ranged from -5.7 to 1.0. The average time elapsed between first and last MMSE scores was 3.0 years (SD=0.7), with a range from 1.0 to 5.6 years.

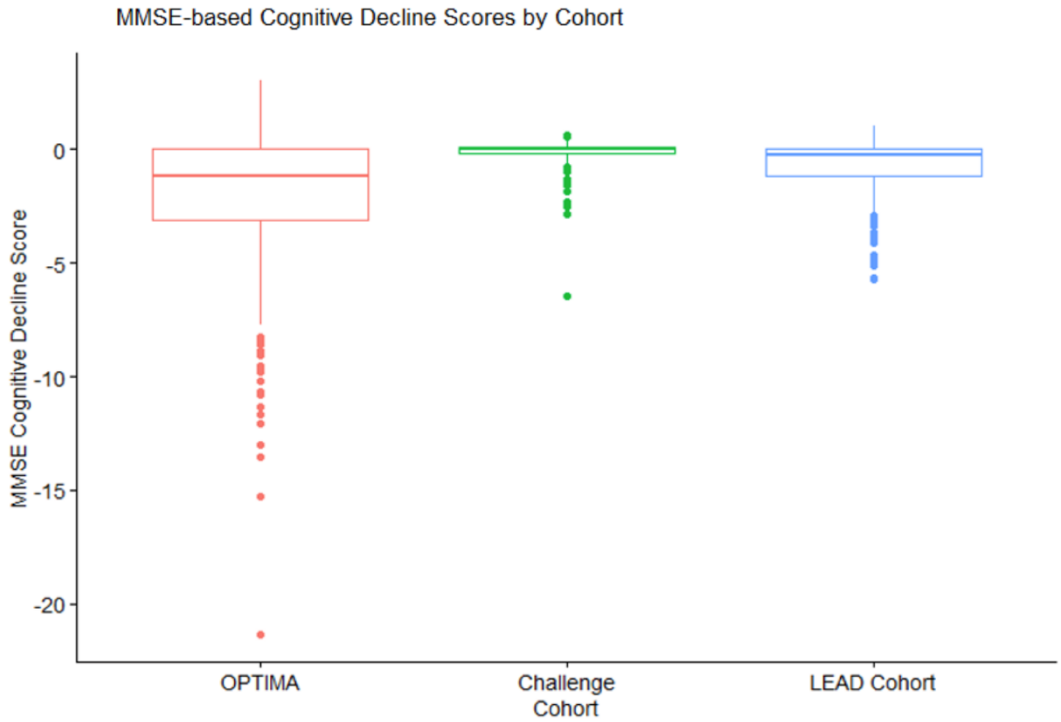


Figure 4.19. Box plot of MMSE-based cognitive decline scores during the OPTIMA, Challenge, and LEAD study follow-up (OPTIMA: n=616, Challenge: n=154, LEAD: n=190).

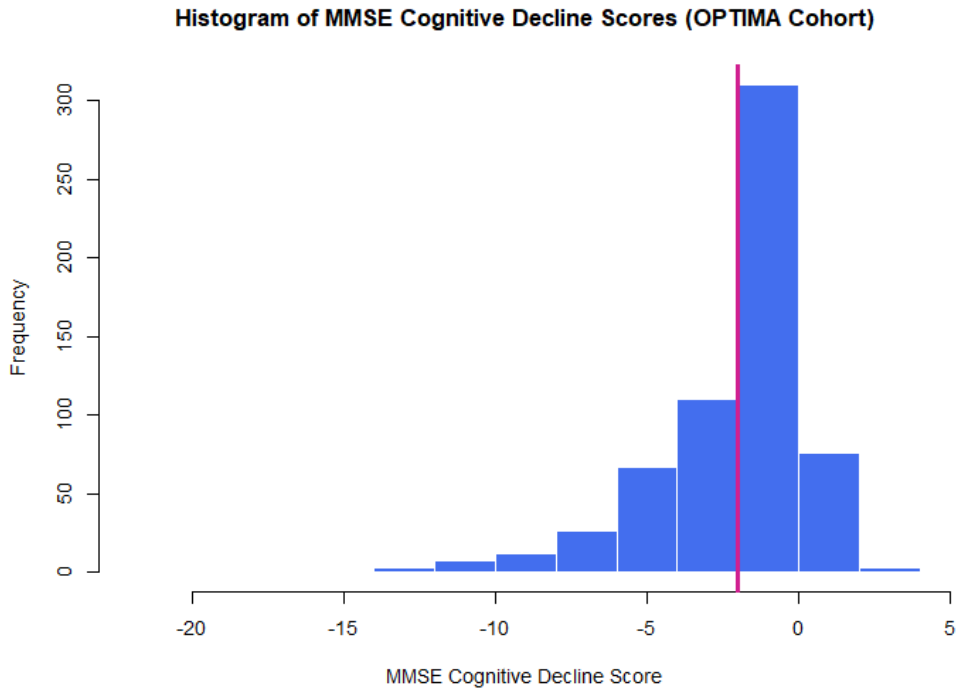


Figure 4.20. Histogram of cognitive decline scores based on first and last MMSE scores for OPTIMA participants (n=616).

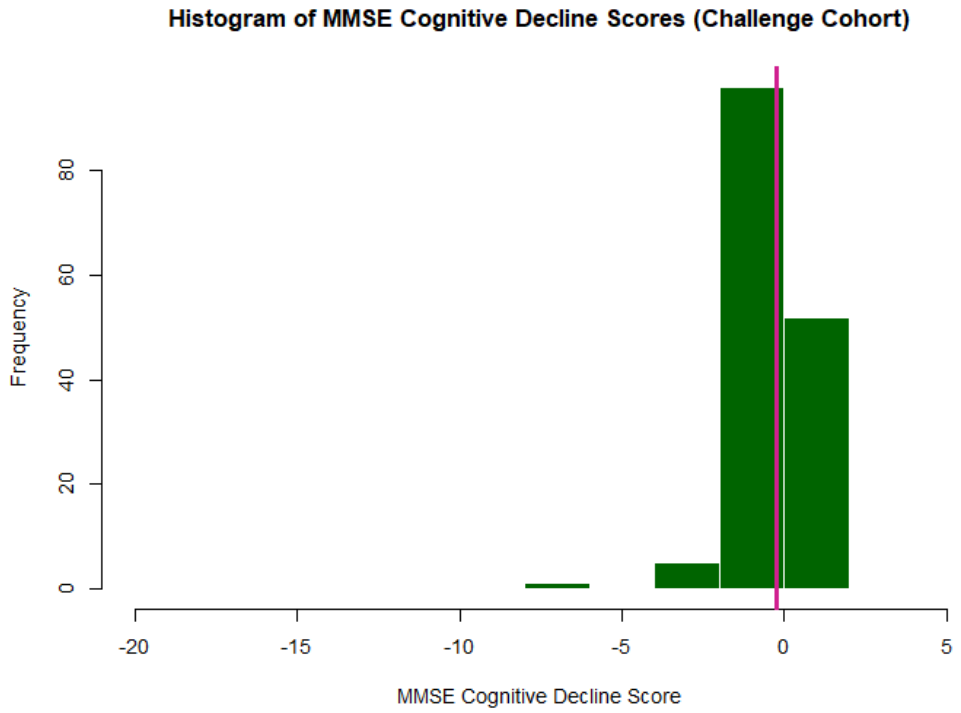


Figure 4.21. Histogram of cognitive decline scores based on first and last MMSE scores for Challenge participants (n=154).

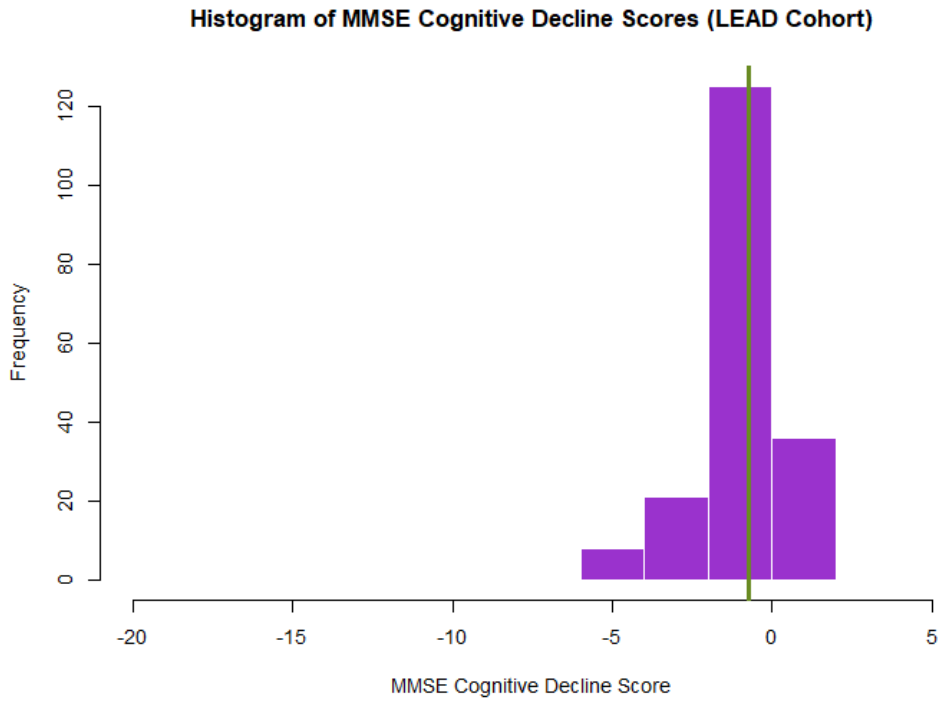


Figure 4.22. Histogram of cognitive decline scores based on first and last MMSE scores for LEAD participants (n=190).

4.10.2. CAMCOG-Based Cognitive Decline Scores

Figure 4.23 presents the cognitive decline of participants in the OPTIMA, Challenge, and LEAD cohorts, based on the change in their total CAMCOG scores over time.

For the OPTIMA cohort (n=573), the mean cognitive decline score based on first and last CAMCOG scores was -6.3 (SD=8.7) (Figure 4.24). The median decline score was -3.5, with a range from -78.6 to 18.6. The mean time elapsed between first and last total CAMCOG score was 5.32 years (SD=4.1). The median time between total CAMCOG scores was 5.3 years (SD=4.1), with a range from one to 22.3 years.

For the Challenge participants (n=151), the mean cognitive decline score based on Total CAMCOG was -0.4 (SD=2.0), and the median score was zero, indicating no change in most participants (Figure 4.25). The range of scores was from -13.4 to 4.8. The average time between first and last total CAMCOG score was 6.1 years (SD=4.6), with a range from 1.9 to 13.1 years.

For the LEAD participants (n=187), the mean cognitive decline score based on the total CAMCOG was -0.7 (SD=3.9) (Figure 4.26). The median was zero, and the range of decline scores was from -15.8 to 12.3. The mean time elapsed between first and last total CAMCOG score was 2.9 years (SD=0.8), with a range from one to 5.6 years.

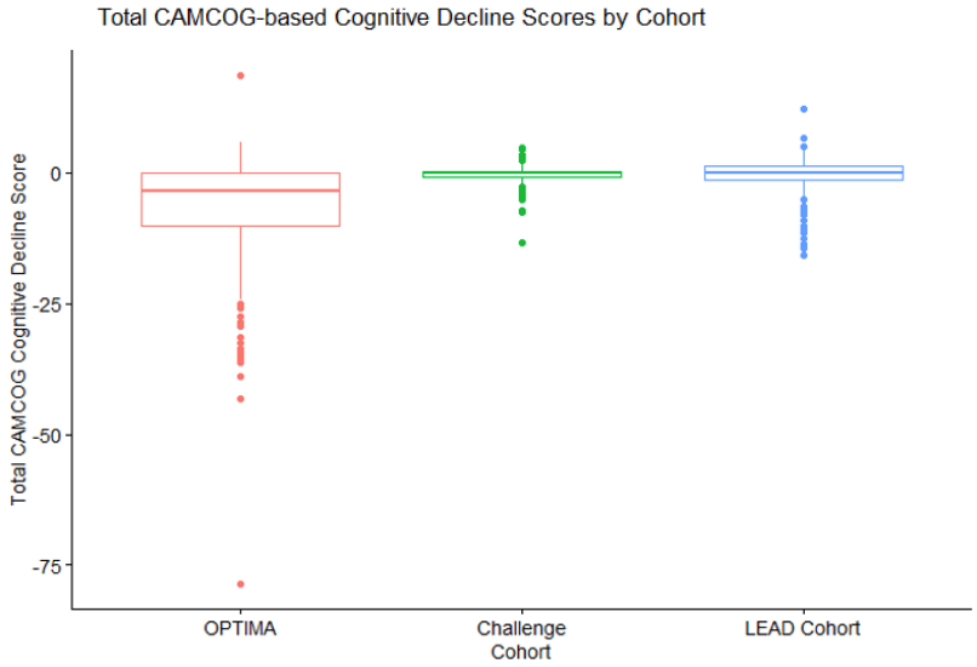


Figure 4.23. Box plot of total CAMCOG-based cognitive decline scores during the OPTIMA, Challenge, and LEAD study follow-up (OPTIMA: n=573, Challenge: n=151, LEAD: n=187).

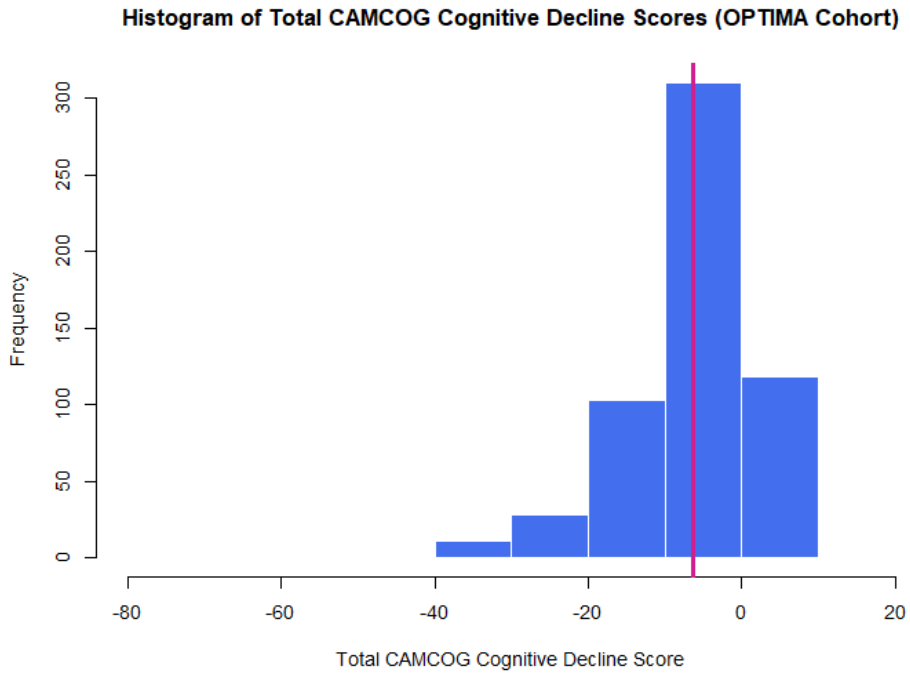


Figure 4.24. Histogram of cognitive decline scores based on first and last total CAMCOG scores for OPTIMA participants (n=573).

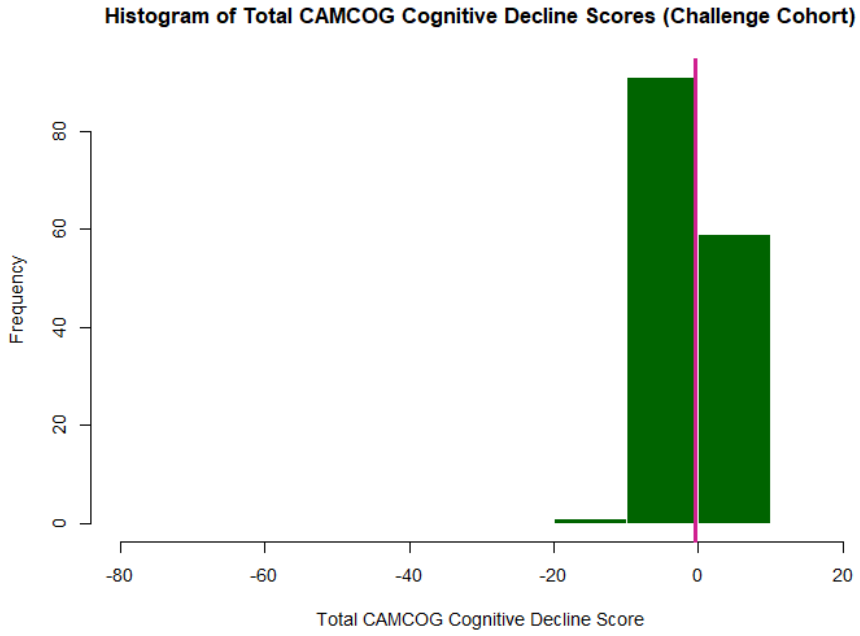


Figure 4.25. Histogram of cognitive decline scores based on first and last total CAMCOG scores for Challenge participants (n=151).

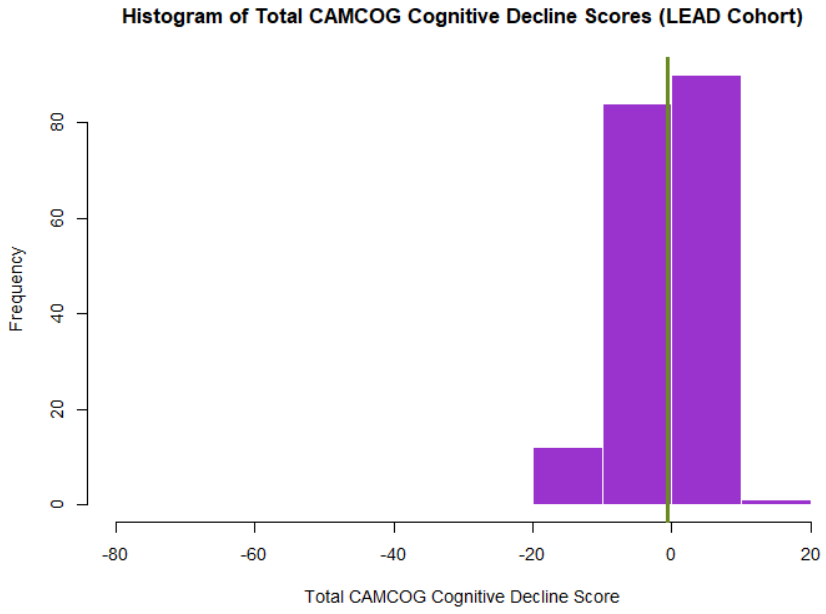


Figure 4.26. Histogram of cognitive decline scores based on first and last total CAMCOG scores for LEAD participants (n=187).

4.10.3. Correlation between MMSE- and CAMCOG-Based Cognitive Decline Scores

The correlation between the two sets of cognitive decline scores calculated based on the MMSE and total CAMCOG was computed for each cohort to assess the validity of these measures (Figures 4.27-4.29). In these scatterplots, each point represents one participant with both MMSE- and CAMCOG-based cognitive decline scores. Using, the non-parametric

Spearman's Rho, the MMSE- and CAMCOG-based scores had a strong positive correlation for the OPTIMA cohort (r(571)=0.9, p <0.001). Although the correlation coefficients were statistically significant for both the Challenge and LEAD cohorts, the strength of the correlations were moderate (Challenge: r(149)=0.4, p<0.001; LEAD: r(185)=0.5, p<0.001).

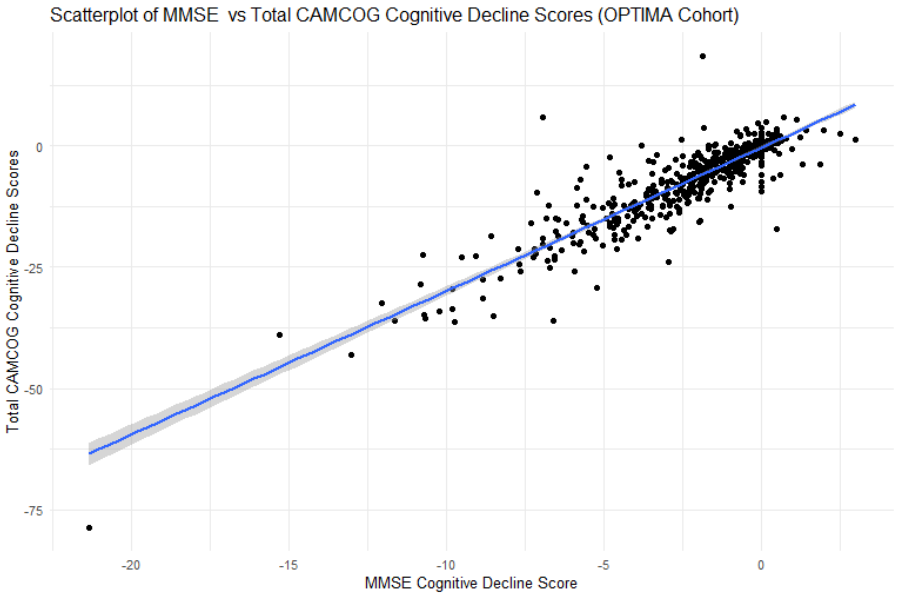


Figure 4.27. Scatterplot of cognitive decline scores based on MMSE and total CAMCOG scores for participants in the OPTIMA cohort (n=573).

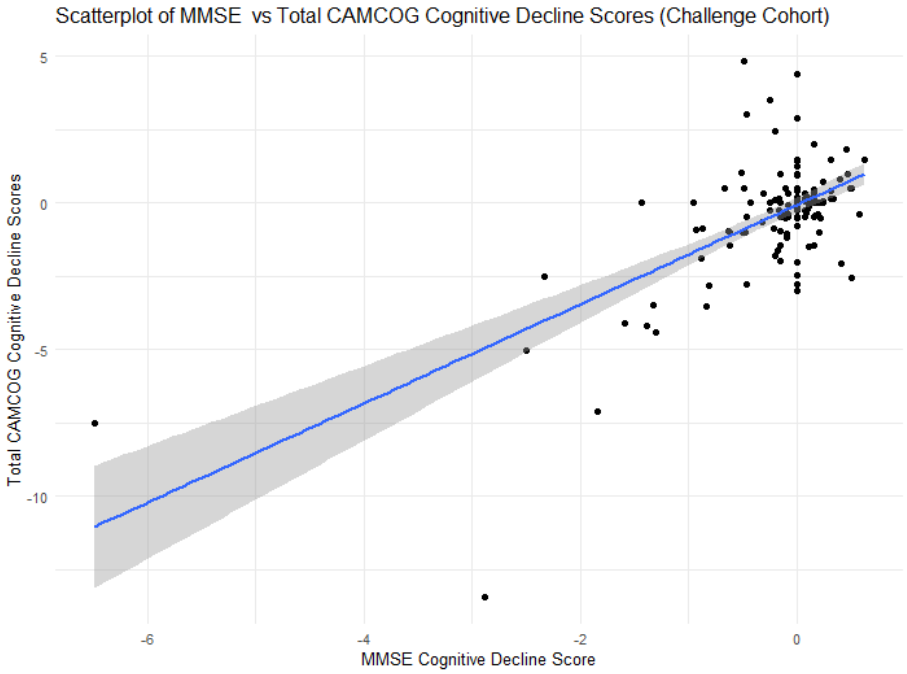


Figure 4.28. Scatterplot of cognitive decline scores based on MMSE and total CAMCOG scores for participants in the Challenge cohort (n=151).

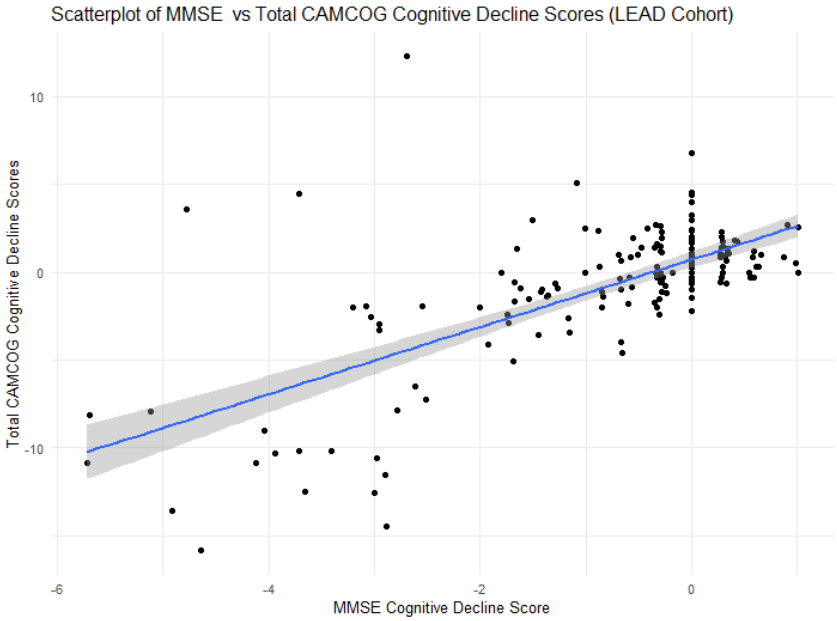


Figure 4.29. Scatterplot of cognitive decline scores based on MMSE and total CAMCOG scores for participants in the LEAD cohort (n=187).

4.11. Clinical Characteristics

4.11.1. Clinical Diagnosis

Clinical diagnoses were assigned retrospectively to each participant for each visit, using the criteria described previously in Chapter 2. The possible diagnoses were control, subjective memory complaint (with no evidence of cognitive impairment upon assessment), mild cognitive impairment (MCI), vascular cognitive impairment (VCI), vascular dementia (VD), possible Alzheimer's disease (AD) or amnestic disorder or mixed AD with Other Dementia Syndrome (ODS), probable AD, mixed AD and VD, Psychiatric or difficult to classify, and ODS (which includes additional dementia subtypes like Parkinson's Disease (PD), and Lewy Body Disease (LBD), Frontotemporal dementia (FTD)). Although there was a diagnostic code for LBD and for PD in the protocol, these were rarely used and these conditions were sometimes coded as ODS, so for this analysis, PD and LBD diagnoses were merged with ODS.

For participants with at least two clinical diagnoses assigned at different timepoints, Figures 4.30 through 4.32 highlight the number of participants with each diagnosis at their first and final study visit in a particular cohort. Figures 4.30A, 4.31A, and 4.32A are grouped by control (includes controls and subjective memory impairment), cognitive impairment (MCI and VCI), dementia (includes VD, possible or probable AD, mixed AD and VD, and ODS), and psychiatric or difficult to classify. A breakdown of the specific dementia subtypes can be seen in Figure 4.30B, Figure 4.31B, and Figure 4.32B. Supplemental Tables 4.7 and 4.8 also provide the exact numbers of participants with each clinical diagnosis.

There were 694 OPTIMA participants with diagnoses assigned at more than one study visit. At inception, 322 (46.4%) had dementia, 104 (15.0%) had cognitive impairment, and 227 (32.7%) were controls (Figure 4.30A). The OPTIMA cohort first and last diagnoses show

that the number of participants diagnosed as controls or with cognitive impairment decreased, while the number of participants with dementia increased (Figure 4.30A). The number of participants deemed to have a psychiatric or difficult to classify condition remained approximately stable (increasing from 41 to 44 participants from first to last diagnosis). The most notable increase in participants at the last diagnosis occurred in the Probable AD dementia subtype (Figure 4.30B).

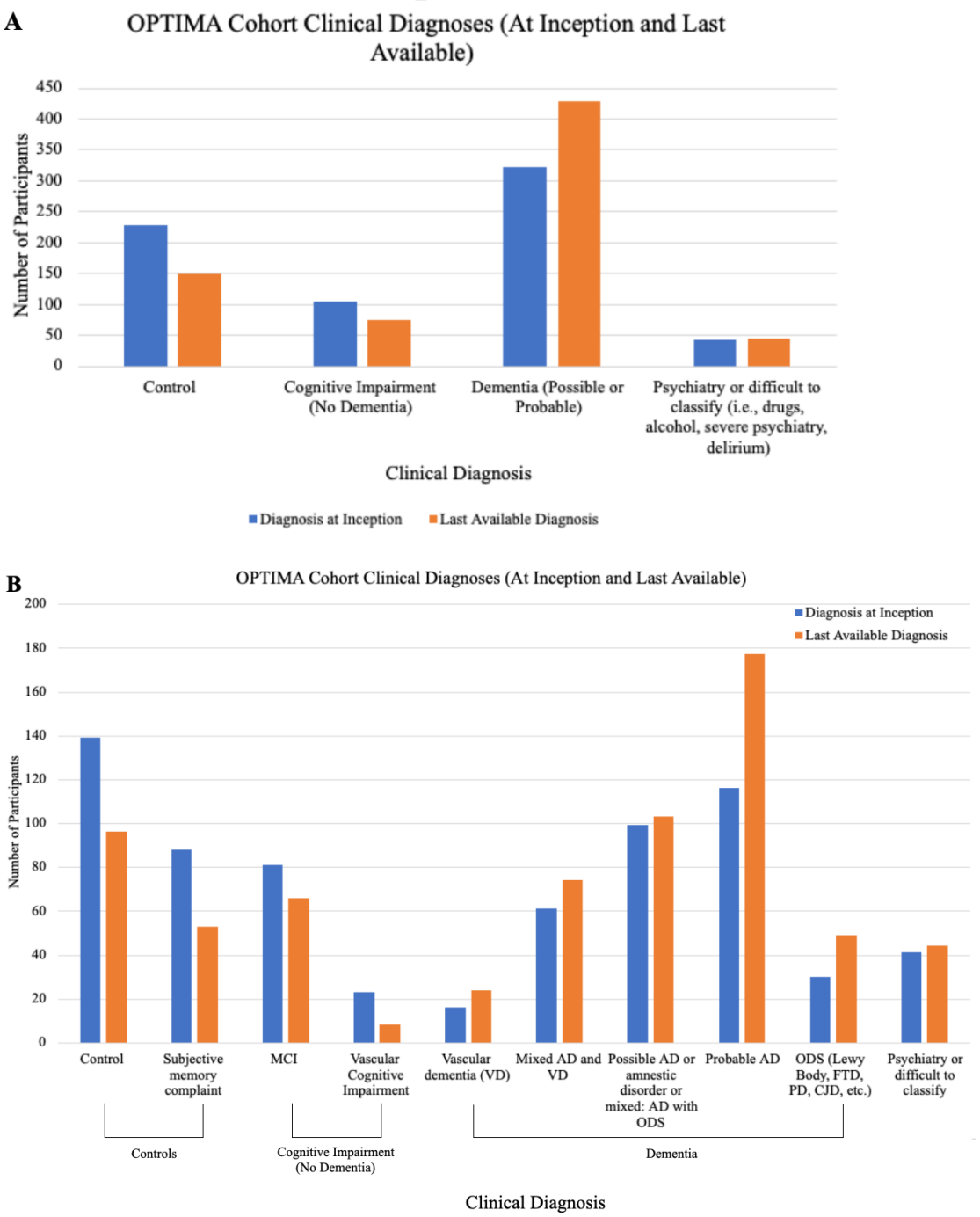


Figure 4.30. A) Bar graph of clinical diagnoses (at inception and last available) for the OPTIMA cohort, grouped into controls (control and subjective cognitive impairment), cognitive impairment (MCI or VCI, no dementia), dementia (all subtypes), and psychiatry or difficult to classify (n=694 only participants with more than one diagnosis). **B)** Bar graph of

clinical diagnoses (at inception and last available) for the OPTIMA, separated into detailed control, cognitive impairment, and dementia subtypes.

At the first clinical diagnosis, most of the Challenge cohort were classified as controls (146 out of 156 participants with diagnoses at multiple timepoints), with an additional ten participants with a cognitive impairment, and no participants with dementia or a psychiatric diagnosis (Figure 4.31A). At the final clinical diagnosis, there was a decrease in the number of controls (down to 107 participants), alongside an increase in the number with cognitive impairment (up to 39 participants) and an increase in the participants diagnosed with dementia (10 individuals). With regards to the subtype diagnoses, the largest increase was in MCI, with the dementia diagnoses spread across all subtypes at the final diagnosis (Figure 4.31B).

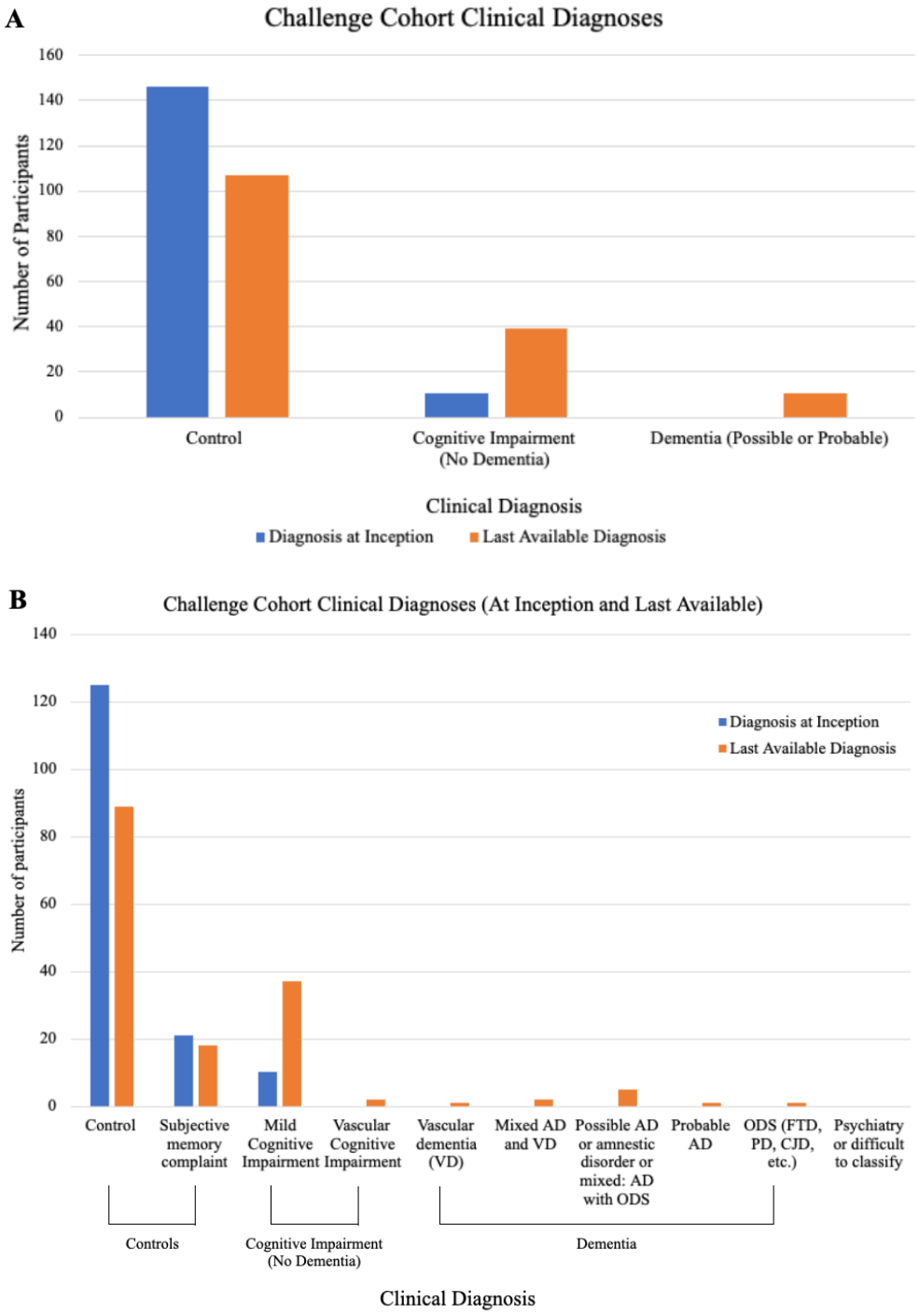


Figure 4.31. A) Bar graph of clinical diagnoses (at inception and last available) for the Challenge cohort, grouped into controls (control and subjective cognitive impairment), cognitive impairment (MCI or VCI, no dementia), dementia (all subtypes), and psychiatry or difficult to classify (n=156, only participants with more than one diagnosis). **B)** Bar graph of clinical diagnoses (at inception and last available) for the Challenge cohort, separated into detailed control, cognitive impairment, and dementia subtypes.

In the LEAD cohort, 199 participants had diagnoses at more than one timepoint (Figures 4.22A and B). At inception, 102 participants (51.3%) were controls, 53 (26.6%) had cognitive impairment (no dementia), 43 (21.6%) had dementia, and one (5.0%) had a

psychiatric or difficult to classify condition (Figure 4.32A). Like the OPTIMA cohort, in LEAD the number of controls decreased at the final diagnosis, while the number of individuals with dementia increased. The dementia subtype with the largest increase was mixed AD and VD (Figure 4.32B). With respect to cognitive impairment diagnoses, the total remained stable, although there was a small increase (n=3) in the number of participants with MCI and a small decrease (n=3) in the number of people with a VCI.

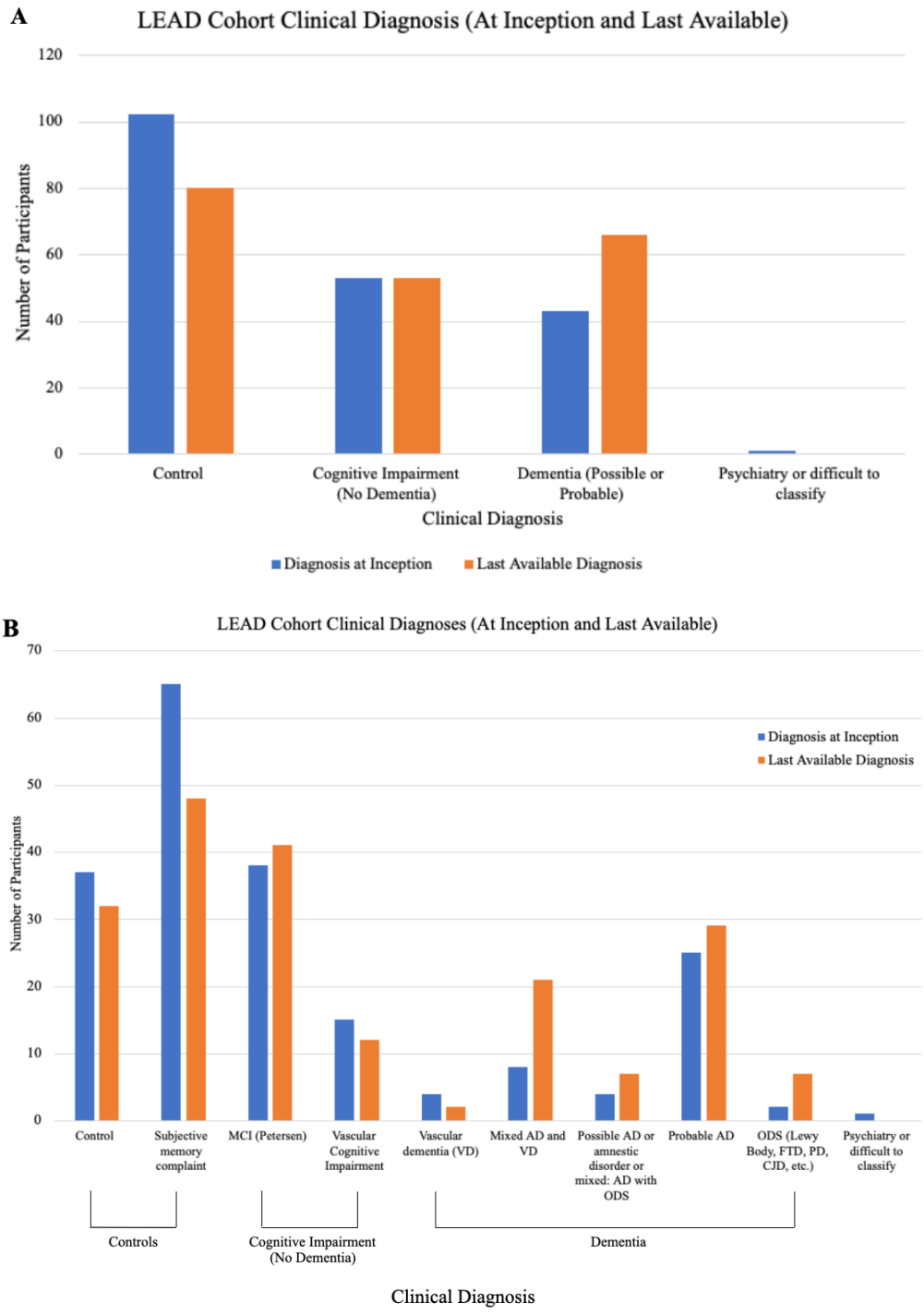


Figure 4.32. A) Bar graph of clinical diagnoses (at inception and last available) for the LEAD cohort, grouped into controls (control and subjective cognitive impairment), cognitive impairment (MCI or VCI, no dementia), dementia (all subtypes), and psychiatry or difficult

to classify (n=199, only participants with more than one diagnosis). **B)** Bar graph of clinical diagnoses (at inception and last available) for the LEAD cohort, separated into detailed control, cognitive impairment, and dementia subtypes.

4.11.2. Diagnostic Change Groups

Based on the first and last clinical diagnoses described above for each cohort, each participant with two or more diagnoses at different timepoints was assigned to a diagnostic change group based on how their clinical diagnosis remained stable or changed over the course of each study (Table 4.3). More detailed diagnostic change groups by dementia subtype, as well as the extent of data completion for each group, can be found in Chapter 5.

In the OPTIMA cohort, the largest group consisted of participants with dementia throughout (n=321), followed by those who were controls throughout (n=145). Of those who changed diagnosis over time, 27 participants went from control to dementia, 50 went from control to cognitive impairment, and 75 converted from cognitive impairment to dementia.

In the Challenge cohort, where most participants began as controls, 104 participants remained controls throughout the study, 34 converted from control to cognitive impairment, eight converted from control to dementia, and two converted from cognitive impairment to dementia.

For the LEAD cohort, whose participants began with a range of diagnoses, the largest group was of controls throughout (n=72), followed by people who had dementia throughout (n=43). Four control participants developed dementia, 26 controls developed cognitive impairment, and 19 people with a cognitive impairment progressed to dementia.

Diagnostic Change Group	**Cohort**		
	OPTIMA n=694	**Challenge** n=156	**LEAD** n=199
Controls throughout	145	104	72
Cognitive impairment throughout	22	5	27
Dementia throughout	321	0	43
Controls → Cognitive impairment	50	34	26
Controls → Dementia	27	8	4
Cognitive impairment → Dementia	75	2	19
Psychiatric or difficult to classify throughout	34	0	0
Psychiatric or difficult to classify → Cognitive impairment	1	0	0
Psychiatric or difficult to classify → Dementia	4	0	0
Other[1]	15	3	8

Table 4.3. Participants in the OPTIMA, Challenge, and LEAD cohorts in each diagnostic change group during that study.

[1]Other includes more unusual diagnostic changes over time (e.g., from psychiatric or difficult to classify to control or from cognitive impairment to control)

4.12. APOE Genetics

As was discussed in Chapter 1, certain alleles of the apolipoprotein E (*APOE)* gene can be protective (ε2) or increase dementia risk (ε4) (152). APOE genotype was identified for 730 OPTIMA participants (98.4% of the whole cohort), 159 Challenge participants (100%), and 203 LEAD participants (96.2%) (Figure 4.33 and Supplemental Table 4.9).

In OPTIMA, the most common genotype in the cohort was E3E3 (43.6%), followed by E3E4 (35.5%). Only two participants (0.3%) had the E2E2 genotype that confers the least dementia risk, while 58 participants (7.9%) had E4E4, which is linked to the greatest dementia risk.

The E3E3 genotype was also the most common in the Challenge cohort (65.4% of participants), followed by E2E3 (15.1%) and then E3E4 (14.5%). The E4E4 genotype was not common (1.3%), and no participants had E2E2.

For the LEAD cohort, E3E3 was the most frequent genotype (found in 42.4% of participants), followed closely by E3E4 (39.4%). Additionally, 8.9% of participants had E2E3, 3.9% had E2E4, 4.9% had E4E4, and only 0.5% had E2E2.

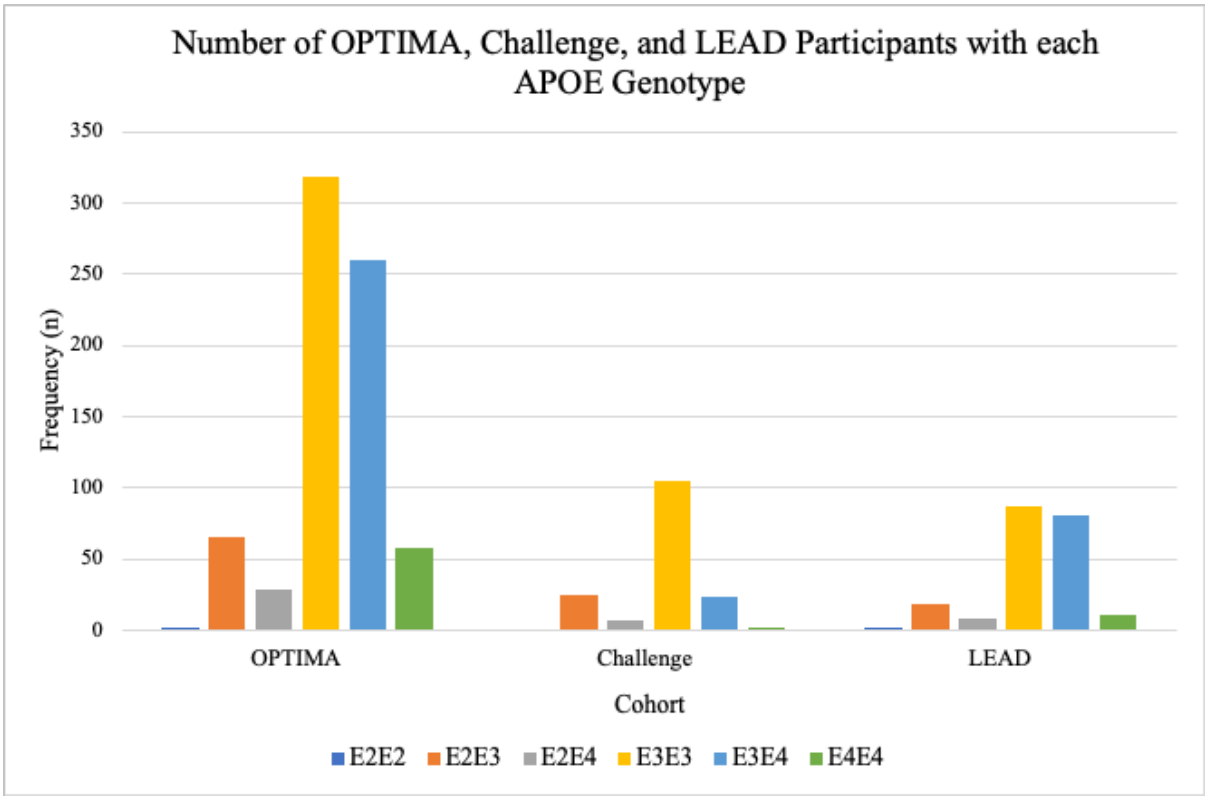


Figure 4.33. Bar graph showing the number of participants with each APOE genotype in the OPTIMA (n=730), Challenge (n=159), and LEAD (n=203) cohorts.

4.13. Neuropathological Characteristics

4.13.1. Neuropathology Summary Table

Brains were donated by some but not all participants. For the participants who donated their brain, neuropathology was completed to look at a range of pathologies that contribute to dementia and cognitive decline. Neuropathology findings assessed included AD, PD/LBD, frontotemporal lobar degeneration (FTLD, which includes FTLD with and without TAR DNA Binding Protein 34 (TDP-43) pathology and progressive supranuclear palsy (PSP) with FTLD), and infarcts (Table 4.6).

Neuropathology Present	**By Cohort**		
	OPTIMA n=440	**Challenge** n=49	**LEAD** n=44
Alzheimer's disease (low to high likelihood), n (%)	297 (67.5)	16 (32.7)	29 (65.9)
Alzheimer's disease (intermediate to high likelihood), n (%)	250 (56.8)	7 (14.3)	21 (47.7)
Any Parkinson's Disease or Lewy Body findings, n (%)	82 (18.6)	8 (16.3)	10 (22.7)
Frontotemporal lobar degeneration (FTLD), n (%)	25 (5.7)	0 (0)	0 (0)
Microinfarct/s, n (%)	106 (24.1)	22 (44.9)	9 (20.5)
Lacunar infarcts, n (%)	41 (9.3)	7 (14.3)	4 (9.1)
Infarct > 10 mm, (%)	57 (13.0)	9 (18.4)	5 (11.4)

Table 4.6. Summary table of neuropathology characteristics identified in postmortem brains donated, reported overall and by cohort.

4.13.2. Alzheimer's Disease Likelihood

The neuropathology notes and diagnostic codes were hand-searched to generate an estimate of the likelihood of AD for each participant. This estimate was based on the NIA-Reagan criteria that uses the Braak neurofibrillary tangle stage, along with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score for amyloid plaque density to evaluate AD likelihood (Figure 4.34 and Supplemental Table 4.10) (153). Approximately half of the OPTIMA cohort had tangle and plaque pathology indicating high likelihood of AD (n=210). The Challenge cohort had 16 participants with any likelihood of AD pathology, and the largest number (n=5) had low likelihood. The LEAD cohort had a total of 29 participants with low to high likelihood of AD based on pathology, in which most had high (n=11) and intermediate (n=10) likelihood.

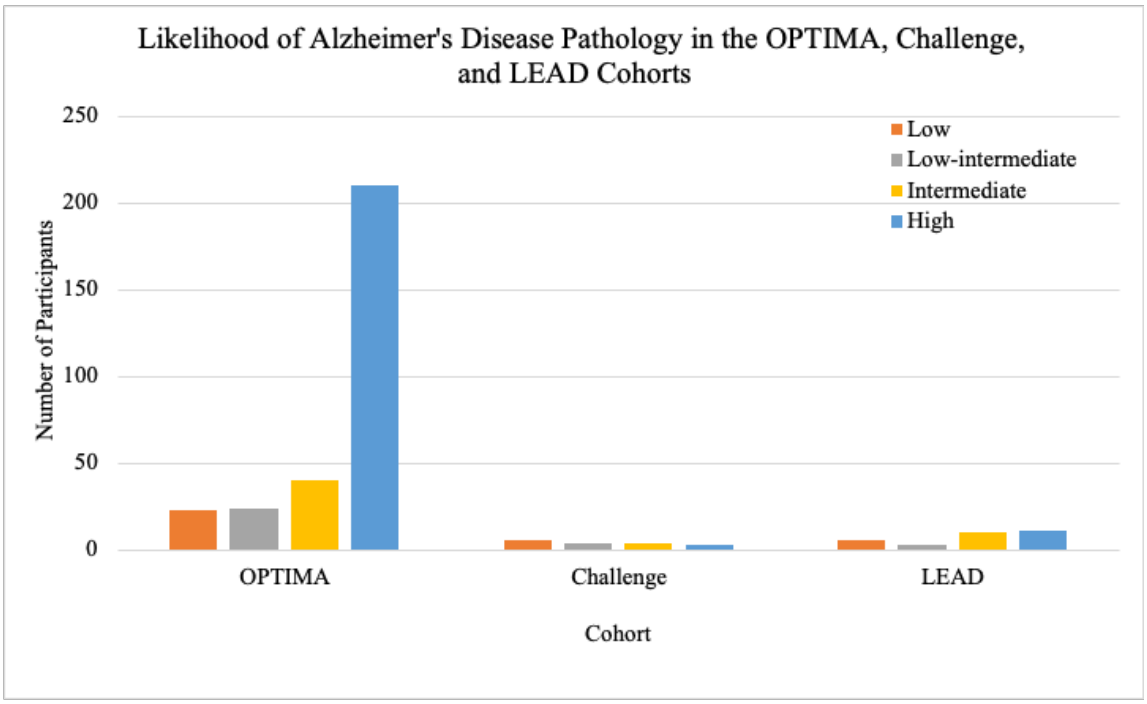


Figure 4.34. Likelihood of AD pathology in the OPTIMA, Challenge, and LEAD cohorts.

4.13.3. Braak Neurofibrillary Tangle Stage

Braak tangle staging characterizes the extent of neurofibrillary tangles in the brain (Figure 4.35, Supplemental Table 4.11) (135). The transentorhinal area is impacted in stages I-II, the limbic regions in stages III-IV, and the neocortex is affected in stages V-VI (154). The largest percentage of OPTIMA participants with a score available were in Braak tangle stage VI (n=178, 50.7%), which is the most severe. The Challenge cohort had the greatest percentage of participants in the Braak tangle stage I (n=16, 36.4%), followed by stages II and III (n=10, 22.7% in each), indicating that these participants had milder to moderate tangle progression. The largest proportion of LEAD participants were found to be Braak tangle stage III (n=12, 27.3%), followed by stage II (n=10, 22.7%).

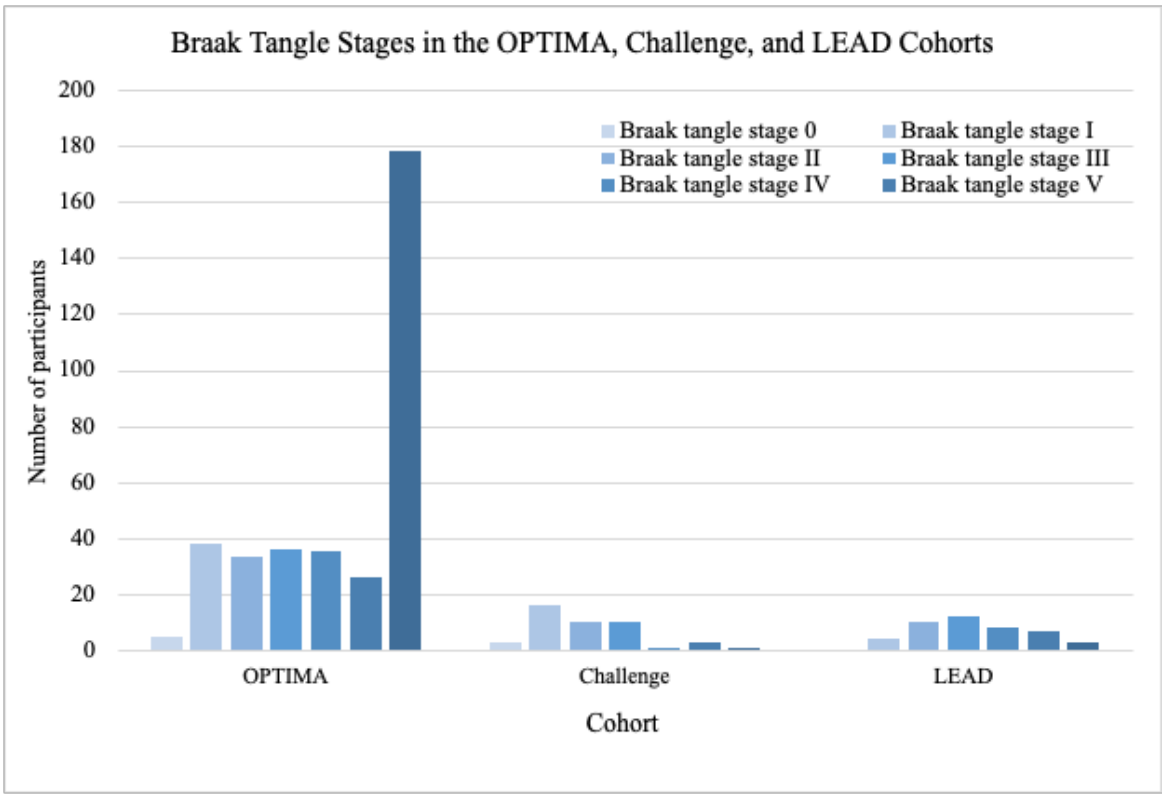


Figure 4.35. Bar graph of the number of OPTIMA (n=351), Challenge (n=44), and LEAD (n=44) participants in each Braak tangle stage.

4.13.4. CERAD Scores

The CERAD established a neuropathology protocol that is used to assess neuritic plaque (also known as amyloid plaque) density and determine if a person had possible, probable, or definite AD (134). A CERAD score of zero indicates no plaques, one indicates sparse plaques, two indicates moderate density, and three indicates a high density of plaques (Figure 4.36 and Supplemental Table 4.12).

Of the 182 OPTIMA participants with a CERAD score, 43 (13.6%) had no plaques, 35 (19.2%) had sparse neuritic plaques, 17 (9.3%) had a moderate density of plaques, and 87 (47.8%) had a high density of neuritic plaques. For the 38 Challenge cohort participants with a CERAD score, 20 (52.6%) had a score of zero, 12 (31.6%) had a score of one, three (7.9%) had a score of two, and three (7.9%) had a score of three. With regards to the 42 LEAD participants with a CERAD score, 19 (45.2%) had no plaques, eight (19.0%) had a score of one, seven (16.7%) had a score of two, and eight (19.0%) had a score of three.

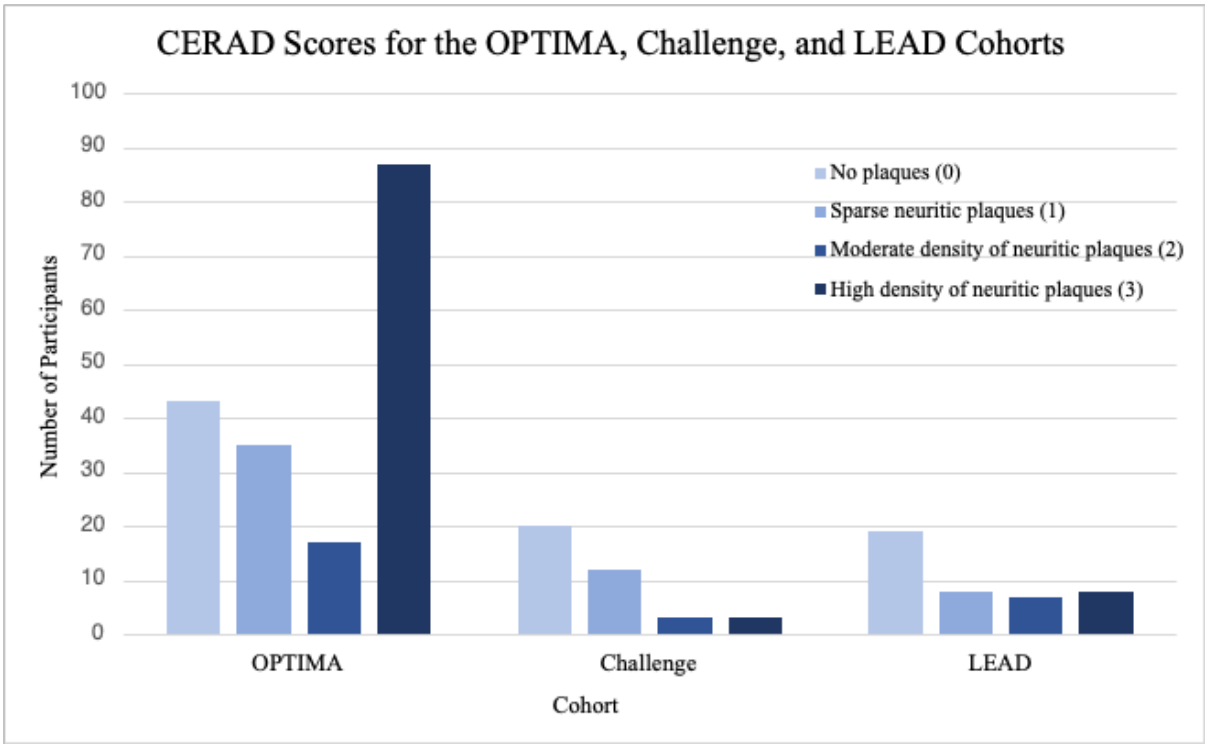


Figure 4.36. CERAD scores for the OPTIMA, Challenge, and LEAD cohorts.

4.13.5. Lewy Body Pathology

Lewy Body (LB) pathology was examined in the neocortex, limbic regions, and brain stem (Table 4.7). Some participants with LB pathology did not have the brain region specified in the diagnostic coding.

Braak LB staging, which characterizes the progression of the pathology, was also completed for a smaller subset of each cohort (Figure 4.37 and Supplemental Table 4.13). In Stages 1 and 2, LB are found in the medulla and pons, while in Stages 3 and 4, there is pathology in the mesencephalon, and in Stages 5 and 6, the neocortex is affected (155). The majority of each cohort with the Braak LB staging complete were in Stage 0, with no LB detected, although many participants were missing data for this metric.

Parkinson's Disease (PD)/Lewy Body Disease (LBD) Pathology	**By Cohort**		
	OPTIMA n=440	**Challenge** n=49	**LEAD** n=44
Neocortical LBD, n (%)	16 (3.6)	2 (4.1)	3 (6.8)
Limbic LBD, n (%)	12 (2.7)	1 (2.0)	2 (4.5)
Amygdala-only LBD, n (%)	4 (0.9)	0 (0)	1 (2.3)
Brain stem LBD, n (%)	7 (1.6)	3 (6.1)	1 (2.3)
Total with any PD/LBD findings, n (%)	**82 (18.6)**	**8 (16.3)**	**10 (22.7)**
No PD/LBD detected, n (%)	**358 (81.4)**	**41 (83.7)**	**34 (77.3)**

Table 4.7. Lewy body pathology data, by cohort (OPTIMA: n=74, Challenge: n=12, LEAD): n=39).

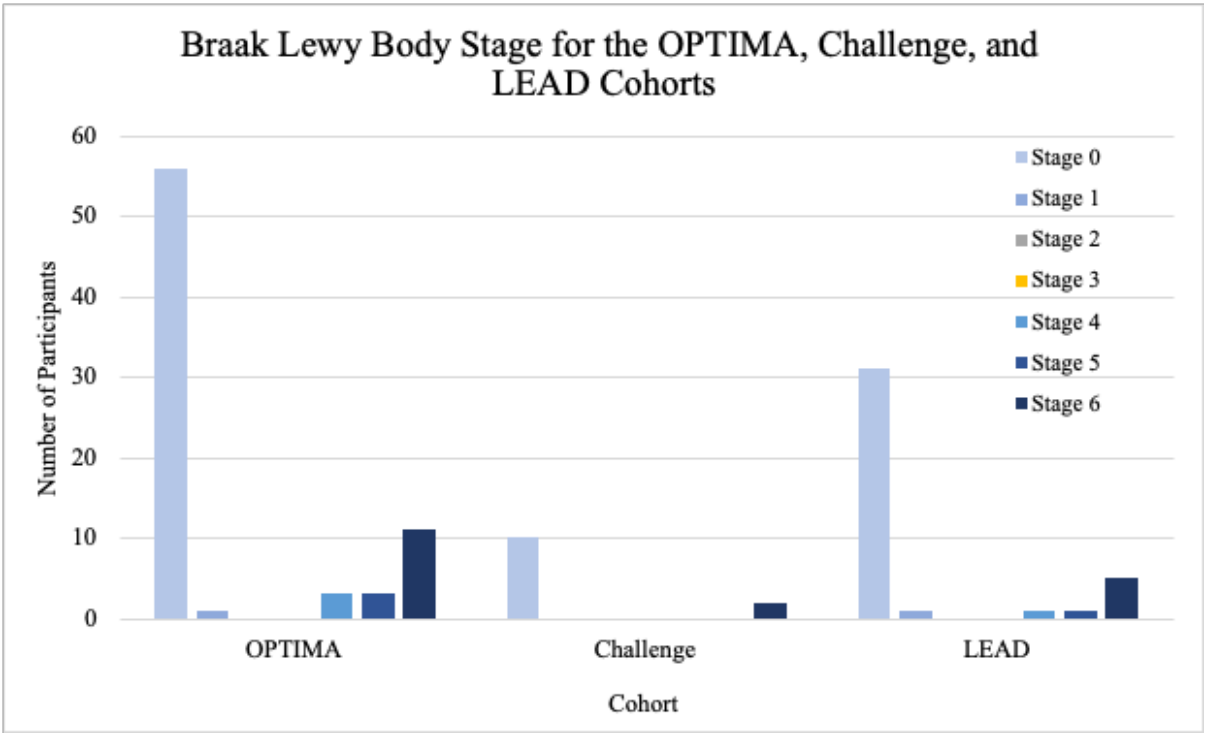


Figure 4.37. Braak Lewy Body staging by cohort.

4.13.6. Vascular Conditions

Microinfarcts are common, microscopic lesions that are associated with dementia; microinfarcts were identified in all three cohorts (Table 4.8) (156). The most common microinfarct location in OPTIMA and Challenge was the cerebral cortex, followed by the basal ganglia/thalamus and cerebral white matter. Some participants had microinfarcts in multiple locations, and others did not have the microinfarct location specified (e.g., all nine LEAD cohort participants with microinfarcts).

Microinfarct/s location	**By Cohort**		
	OPTIMA n=440	**Challenge** n=49	**LEAD** n=44
Cerebral white matter, n (%)	14 (3.2)	3 (6.1)	0 (0)
Cerebral cortex, n (%)	21 (4.8)	8 (16.3)	0 (0)
Basal ganglia/thalamus, n (%)	20 (4.5)	3 (6.1)	0 (0)
Cerebellum, n (%)	6 (1.4)	1 (2.0)	0 (0)
Brain stem, n (%)	4 (0.9)	0 (0)	0 (0)
Total with microinfarct/s in any location	**106 (24.1)**	**22 (44.9)**	**9 (20.5)**

Table 4.8. Microinfarct neuropathology data, by cohort.

Lacunar infarcts, which occur due to an artery in the brain being blocked, were also identified in participants from all three cohorts (Table 4.9). Some participants with a lacunar infarct identified did not have the location specified.

Lacunar infarct/s location	By Cohort		
	OPTIMA n=440	**Challenge** n=49	**LEAD** n=44
Cerebral white matter, n (%)	6 (1.4)	1 (2.0)	0 (0)
Cerebral cortex, n (%)	3 (0.7)	0 (0)	0 (0)
Basal ganglia/thalamus, n (%)	12 (2.7)	2 (4.1)	1 (2.3)
Cerebellum, n (%)	3 (0.7)	2 (4.1)	0 (0)
Total with lacunar infarct/s in any location, n (%)	**41 (9.3)**	**7 (14.3)**	**4 (9.1)**

Table 4.9. Lacunar infarct neuropathology data, by cohort.

Other vascular conditions that can contribute to cognitive decline include amyloid angiopathy, small vessel disease (SVD), atherosclerosis, and arteriosclerosis. The number of participants in each cohort with moderate to severe conditions are presented in Table 4.10.

Vascular Condition Present	By Cohort		
	OPTIMA n=440	**Challenge** n=49	**LEAD** n=44
Moderate to severe amyloid angiopathy, n (%)	87 (19.8)	6 (12.2)	13 (29.5)
Moderate to severe non-amyloid small vessel disease (SVD), n (%)	101 (23.0)	21 (42.9)	8 (18.2)
Moderate to severe atherosclerosis, n (%)	68 (15.5)	12 (24.5)	9 (20.5)
Moderate to severe arteriosclerosis, n (%)	103 (23.4)	17 (34.7)	23 (52.3)

Table 4.10. Vascular conditions neuropathology data, by cohort.

4.13.6. Other Neurological Conditions

The neuropathology information also includes findings about other rare neurological disorders that can contribute to dementia, including Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), Creutzfeldt-Jakob disease (CJD), PSP, and corticobasal degeneration (CBD), among others (Table 4.11). For PSP, there were pathology diagnoses with and without frontotemporal lobar degeneration, and both are counted as PSP here.

Neurological Disorder Present	By Cohort		
	OPTIMA n=440	**Challenge** n=49	**LEAD** n=44
Neurofibrillary tangle-only dementia, n (%)	5 (1.1)	0 (0)	0 (0)
Progressive supranuclear palsy (PSP), n (%)	5 (1.1)	2 (4.1)	0 (0)
Corticobasal degeneration, n (%)	4 (0.9)	0 (0)	0 (0)
Amyotrophic lateral sclerosis (ALS), n (%)	3 (0.7)	0 (0)	1 (2.3)
Sporadic Creutzfeldt-Jakob disease (sCJD), n (%)	1 (0.2)	0 (0)	0 (0)
Huntington's disease, n (%)	1 (0.2)	0 (0)	0 (0)

Table 4.11. Occurrence of rare neurological conditions (other than dementia) identified in neuropathology data.

4.14. Discussion

The analyses in this chapter provided context for the OPTIMA, Challenge, and LEAD cohorts. Some cohorts had more complete data for the baseline variables than others. For example, the LEAD cohort had more missing data for variables like the living arrangements and years in further education. This could be due to changes in the methods for data capture at the baseline visit or perhaps the study team did not find it necessary to complete another comprehensive baseline visit for participants who joined LEAD after participating in OPTIMA or Challenge. Nevertheless, the available data for the three cohorts is helpful in deepening the understanding of their general characteristics.

One noteworthy outcome was the finding that almost half of the OPTIMA participants already had dementia when they joined the study, which was not previously known. This may have been a driver for establishing the LEAD and Challenge cohorts. Although an explicit statement could not be found to explain why these cohorts were founded while the OPTIMA study was still ongoing, we can infer that these cohorts were intended to focus more on aging in people with normal cognition, cognitive impairment, or early dementia at baseline.

The data presented in this chapter have helped generate a better understanding of participants in each cohort. As was mentioned, the OPTIMA cohort had a large proportion of participants with a cognitive impairment or dementia at baseline. While the average age of participants at their first CAMDEX was about 72, the range of ages starting at 26 was surprising for a cohort focused on aging. The younger participants were found to have joined for a range of reasons, including acting as controls or having early onset dementia, a psychiatric condition, or another rare neurological condition. The Challenge and LEAD cohorts had older age ranges at baseline, more in line with the expectations for an aging cohort. LEAD participants had the oldest average age at baseline, which could be because

some participants in this cohort joined the study after having participated in OPTIMA or Challenge.

Additionally, this analysis highlighted that participants in all three cohorts left school at an average age of about 16. The legal age at which UK students could leave school used to be lower than current mandates, which may explain why some participants left school at younger ages than we might expect today. School attendance was required until age 14 from 1918 until 1939, when the minimum age to leave school was raised to 15 (157). In 1972, the age requirement to leave school was raised again to 16, and currently education or vocational training is required until age 18 (157).

Another noteworthy finding was the high proportion of participants in the Challenge cohort who reported a history of drug abuse (17%), which was greater than the approximately 10% in OPTIMA and the 1.3% of LEAD participants. Though the original criteria used to define "drug abuse" could not be ascertained, manually searching the free text related to this variable for the Challenge cohort indicated that the criteria were not very well-defined, as a wide range of substances were counted, including pharmaceuticals like antidepressants that were likely prescribed for a psychiatric condition. Other examples of drugs listed were Lorazepam, diazepam, alcohol, nitrazepam, Valium, chlordiazepoxide, and diet pills. Sometimes other medications, such as those for diabetes and thyroid problems, were also listed. Thus, the breadth of drugs that were included in this variable makes these findings related to drug abuse in the cohorts difficult to interpret and may indicate that this variable is not a valid measure. The higher rates of drug abuse could be due to changes in how drug abuse was characterised in the protocol for this cohort, but this cannot be confirmed as the original detailed protocols were not accessible.

Additionally, the MMSE and CAMCOG-based cognitive decline scores highlighted the range of cognitive trajectories represented within these cohorts, as some participants remained stable throughout their evaluations, and others exhibited steep decline, while some showed slight improvement over time. The OPTIMA cohort's strong correlation between the two scores based on the MMSE and CAMCOG also indicated that both cognitive assessments were capturing similar degrees of cognitive decline in the same individual over time, which aligned with previous research comparing the two instruments (158). Though the Challenge and LEAD cohorts' correlations were not as strong, this could be due to the smaller sample sizes and the predominance of higher cognitive scores in these two cohorts. Moreover, the steeper rate of cognitive decline seen in the OPTIMA cohort relative to Challenge and LEAD reflected the greater proportion of OPTIMA participants with a cognitive impairment or dementia at inception. Nevertheless, it is important to recognize that some of the changes in MMSE or CAMCOG scores over time reflected in the cognitive decline scores could be the result of test-retest error.

Another cognitive assessment of interest discussed in this chapter was the NART. The mean predicted full scale IQ scores were approximately 110 for OPTIMA and 117 for both Challenge and LEAD, all of which are above the population average IQ score of 100. These high mean IQs indicate that these cohorts of volunteer participants in the Oxford area may not reflect the general population.

Additionally, while the NART is intended to reflect premorbid intelligence, regardless of the patient's current condition, some studies have critiqued this test's ability to measure this in patients with dementia (151, 159, 160). In this analysis, the OPTIMA cohort had lower NART scores relative to the Challenge and LEAD cohorts, which could be explained by the large proportion of OPTIMA participants with dementia at baseline. Hand-searching of the database also indicated that some participants with repeated assessments had NART scores that decreased over time, as their dementia worsened, calling into question to the reliability and validity of the NART. Future research could analyse the NART data from these three cohorts to continue evaluating the effectiveness of this test.

The neuropathology data available thanks to the participants in all three cohorts who donated their brains is also valuable. The OPTIMA cohort results reflected the clinical findings that many participants in this cohort had dementia, as the neuropathology indicated that over half had intermediate to high likelihood of AD, about 19% had PD or LBD findings, half of participants with a Braak tangle neurofibrillary stage had severe spread, and almost half of those with a CERAD score had dense neuritic plaques. The OPTIMA cohort also had participants with rarer neurological conditions, including ALS, PSP, CJD, and HD. The Challenge cohort appeared to have less dementia-related neuropathology findings, as expected given that the cohort was predominantly composed of controls at both baseline and final clinical diagnosis. LEAD's mix of both controls and participants with clinically diagnosed dementia was also reflected in the neuropathology. Vascular conditions, such as SVD and atherosclerosis were seen across the three cohorts to different extents. Some findings, such as the higher proportion of Challenge participants with microinfarcts compared to OPTIMA or LEAD, could perhaps have been due to changes in neuropathology methods over time. Although the heterogenous neuropathology methods that were utilised over the years make comparison between the cohorts more difficult, the neuropathology findings did generally reflect the clinical characteristics of the cohorts and illustrate the breadth of information available thanks to PM brain donation.

4.15. Conclusion

Chapter Four presented comprehensive demographic, clinical, and neuropathological characterisations of the OPTIMA, Challenge, and LEAD cohorts. Through extensive data cleaning, hand searching of the extract, and presenting a range of variables to characterise these participants, this analysis serves to deepen our understanding of these cohorts and highlight the types of data that researchers can leverage to investigate memory and ageing.

Although these cohorts were analysed and presented as separated cohorts in this chapter, given the overlap in participants between OPTIMA and Challenge with the LEAD cohort, as well as the extended follow-up by the BDR, they may be characterised as one larger unified cohort, which will be presented in Chapter Five.

CHAPTER 5: Unified Cohort Characteristics by Diagnosis at Baseline

5.1. Introduction

Given the substantial overlap in the methods and timelines of the Oxford Project to Investigate Memory and Ageing (OPTIMA), Challenge, and Longitudinal Early Alzheimer's Disease (LEAD) cohorts, and that many individuals were included in more than one cohort, it made sense to combine them to increase statistical power and allow a more complete picture of individual cognitive trajectories over the course of follow-up. This chapter will therefore present the data from OPTIMA, Challenge, and LEAD cohorts as one combined entity of individual participants (the "unified cohort") and to describe the cohort characteristics by baseline and final clinical diagnosis.

Altogether, there were 1,034 unique participants with some data included in the unified cohort. 1,029 of these individuals have at least one clinical diagnosis, and 1,027 have at least one Cambridge Mental Disorders of the Elderly Examination (CAMDEX) episode. This chapter includes only episodes where a clinical diagnosis is listed for the participant.

Of the 1,034 total participants in the unified OPTIMA, Challenge, and LEAD cohorts, 509 individuals (49.2% of the cohort) have passed away and donated their brains to the Oxford Brain Bank (Figure 5.1). 155 individuals are now deceased but did not donate their brains. Additionally, 311 participants (29.8%) were lost to follow-up, and 33 people (3.2%) joined BDR, but subsequently withdrew. There were 26 study participants (2.5%) still alive and completing periodic assessment by the Brains for Dementia Research (BDR) study team.

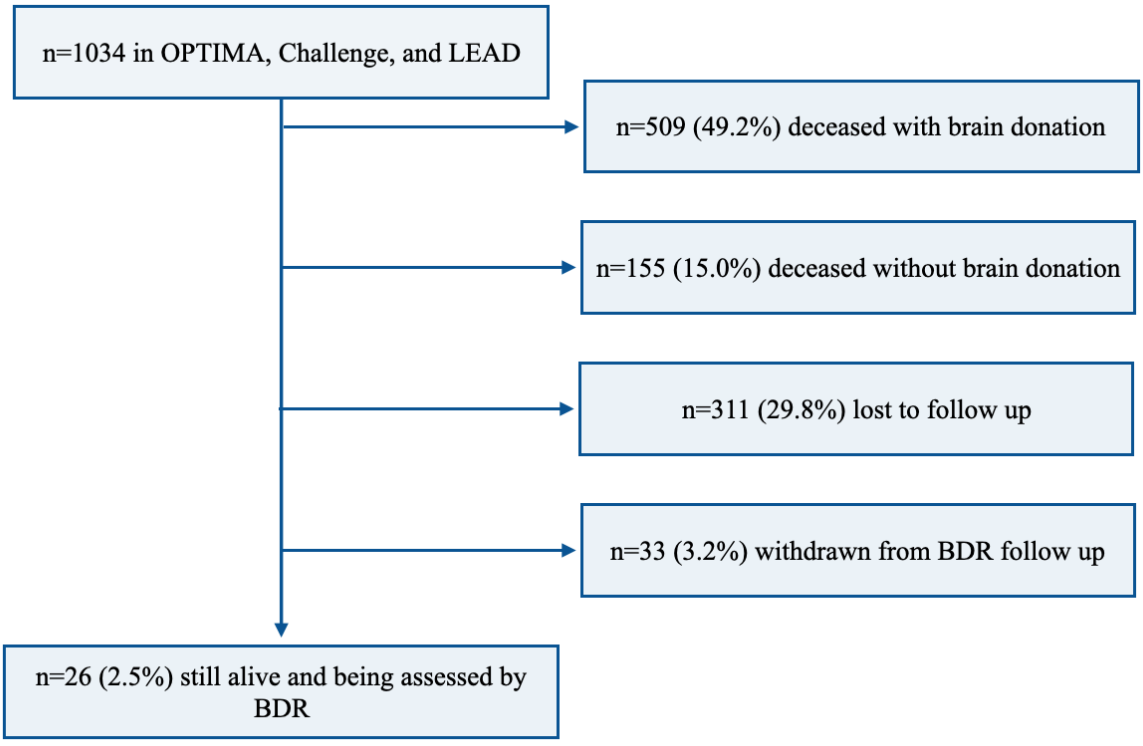


Figure 5.1. Flowchart of study participation for unique individual participants in the unified OPTIMA, Challenge, and LEAD cohorts.

5.2. Clinical Diagnoses for the Unified Cohort

Table 5.1. highlights the number of participants with a baseline and final clinical diagnosis of control, cognitive impairment, dementia, and psychiatric or difficult to classify for the unified OPTIMA, Challenge, and LEAD participants. Control includes both controls and those with subjective memory impairments (with no evidence of memory problems upon assessment), and the Cognitive Impairment category includes both MCI and VCI. The Dementia categorization includes all subtypes of dementia (AD, VD, mixed, and ODS). Figure 5.2 illustrates the number of participants in each baseline and clinical diagnosis category but only includes the 975 participants who have two or more clinical diagnoses.

At baseline, 43.1% of participants were diagnosed as controls, 15.1% had a cognitive impairment, 37.0% were diagnosed with dementia, and 4.8% had a psychiatric or difficult to diagnose condition. At the last available clinical diagnosis, 29.8% were classified as controls, 15.0% were diagnosed with cognitive impairment, 50.7% of the participants had dementia, and 4.5% had a psychiatric or difficult to classify condition.

The proportion of controls decreased from baseline to final clinical diagnosis, while the percentage of participants with cognitive impairment or a psychiatric condition remained stable. The percentage of people with dementia increased from baseline to the last diagnosis, indicating that people converted from either a control or cognitive impairment diagnosis to dementia over time.

Clinical Diagnosis	**Baseline Clinical Diagnosis** n (%)	**Final Clinical Diagnosis** n (%)
Control	444 (43.1)	291 (29.8)
Cognitive Impairment	155 (15.1)	146 (15.0)
Dementia	381 (37.0)	494 (50.7)
Psychiatric or difficult to classify	49 (4.8)	44 (4.5)
Total	**1029 (100.0)**	**975 (100.0)**

Table 5.1. Baseline and final clinical diagnoses for all participants, summarized into the categories of control, cognitive impairment, dementia, or psychiatric or difficult to classify.

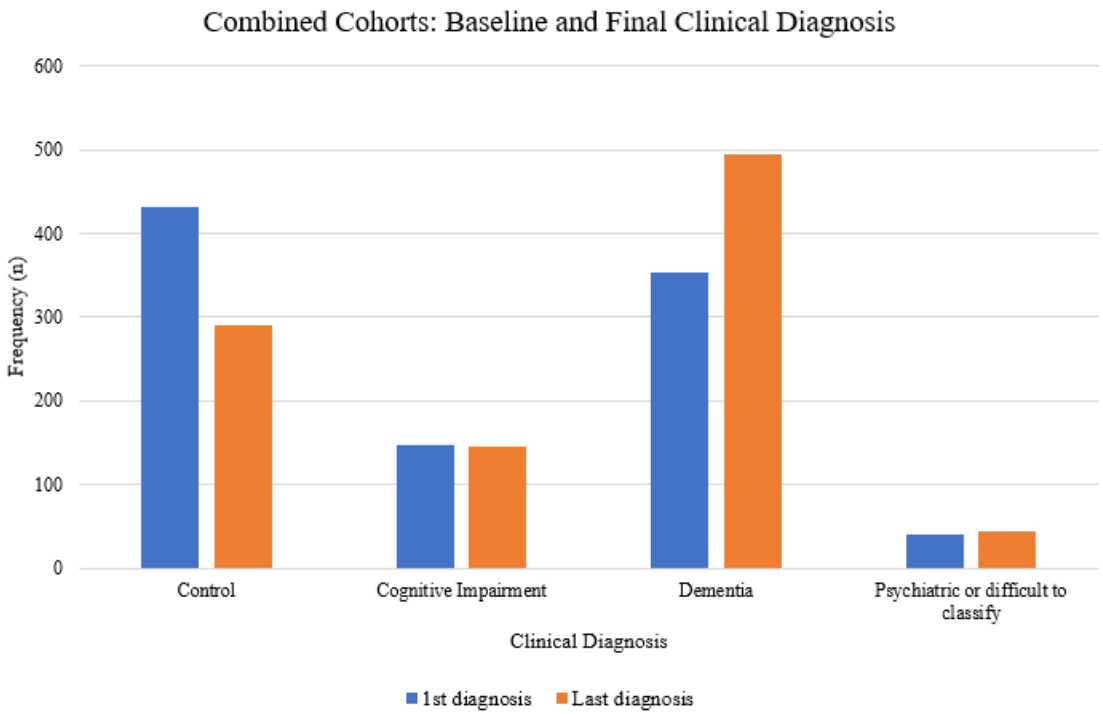


Figure 5.2. Bar graph of first and last clinical diagnoses for all participants, grouped into controls (control and subjective cognitive impairment), cognitive impairment (MCI or VCI, no dementia), dementia (all subtypes), and psychiatric or difficult to classify (n=975, only participants with more than one diagnosis).

Table 5.2 and Figure 5.3 also showcase the baseline and final clinical diagnoses, with the specific types of cognitive impairment and dementia included. At baseline, 27.0% of participants were controls and 16.1% had a subjective memory impairment. At the last diagnosis, these percentages decreased, with 19.2% classified as controls and 10.7% determined to have a subjective memory complaint.

At baseline, 11.8% of participants had MCI and 3.3% had VCI, and at final diagnosis, there were 12.8% with MCI and 2.2% with VCI. With regards to dementia subtypes, at baseline 1.9% had VD, 6.8% had mixed AD and VD, 10.9% had possible AD, 14.3% had probable AD, and 3.2% had another dementia syndrome. At the final clinical diagnosis, 2.7% had VD, 9.7% had mixed AD and VD, 11.8% had possible AD, 20.7% had probable AD, and 5.7% had another dementia type.

Clinical Diagnosis	Baseline Diagnosis n (%)	Final Diagnosis n (%)
Control	278 (27.0)	187 (19.2)
Subjective memory complaint	166 (16.1)	104 (10.7)
MCI	121 (11.8)	125 (12.8)
VCI	34 (3.3)	21 (2.2)
Vascular dementia (VD)	19 (1.9)	26 (2.7)
Mixed AD and VD	70 (6.8)	95 (9.7)
Possible AD or amnestic disorder or mixed: AD with other dementia syndrome (ODS)	112 (10.9)	115 (11.8)
Probable AD	147 (14.3)	202 (20.7)
ODS (PD, LBD, FTD, CJD, etc.)	33 (3.2)	56 (5.7)
Psychiatry or difficult to classify (i.e., drugs, alcohol, severe psychiatry, delirium)	49 (4.8)	44 (4.5)
Total	**1029 (100.0)**	**975 (100.0)**

Table 5.2. Baseline and final clinical diagnoses for all participants, by type of cognitive impairment or dementia.

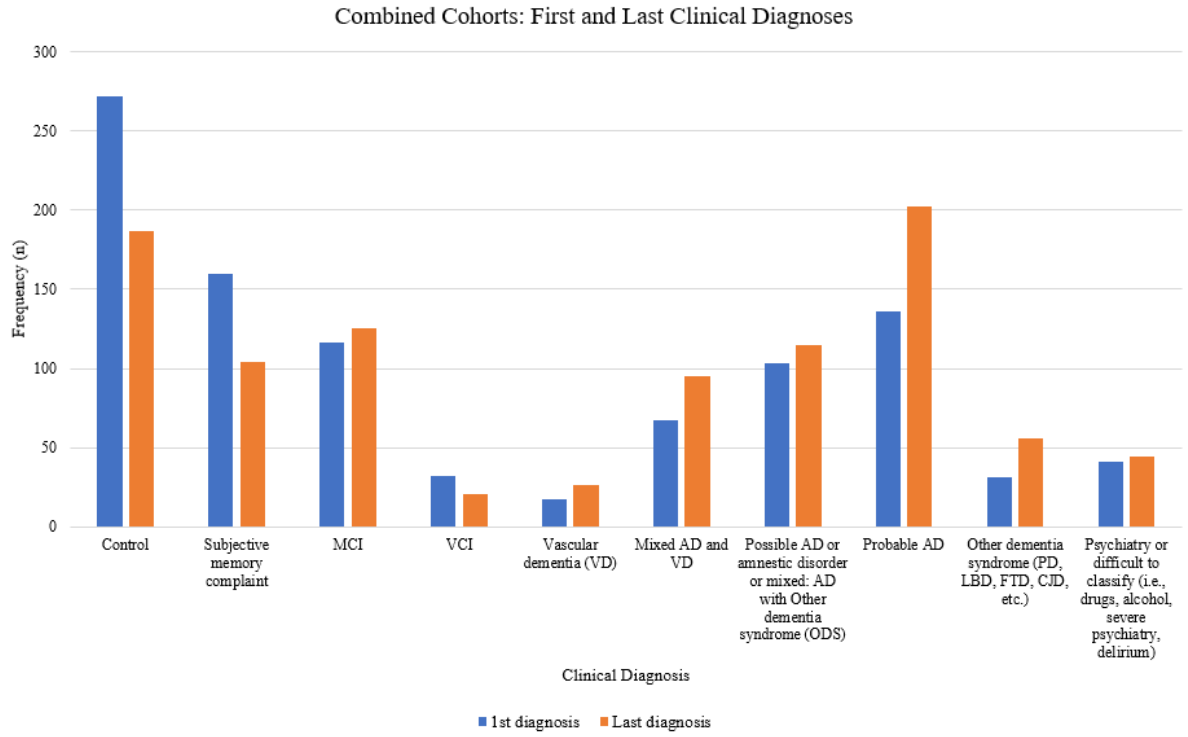


Figure 5.3. Bar graph of first and last clinical diagnoses, separated into detailed control, cognitive impairment, and dementia subtypes (n=975, only participants with more than one diagnosis).

5.3. Follow-up and Completion of Cognitive Assessments, Imaging, Clinical Bloods, and Cerebrospinal Fluid (CSF)

5.3.1. Overall Length of Follow-up for the Unified Cohort

The overall length of follow-up was determined, from first study visit to the individual censor date (either the date of death or the last visit in OPTIMA, Challenge, or LEAD before the participant was lost to follow-up). Those who are still alive and being assessed by the BDR were not included. In the future, length of follow-up will be updated to incorporate the last BDR examination date.

For the 1,005 participants with a clinical diagnosis and a censor date, the overall length of follow-up was an average of 6.9 years (SD=5.3, range from zero to 30.0), excluding additional BDR follow-up or postmortem dates (Figure 5.4). The median follow-up length was 5.6 years.

The length of follow-up was significantly different when grouped by baseline diagnosis (Kruskal-Wallis chi-squared=134.5, $p<0.001$). The controls had a mean follow-up of 9.1 years (SD=5.8, range from zero to 30 years), and those who began with a cognitive impairment (no dementia) were followed for a mean of 6.6 years (SD=4.3, range from zero to 19.1 years). Participants who joined the study with a clinical dementia diagnosis had follow-up for an average of 4.8 years (SD=3.6, range from zero to 17.5 years). Those with a psychiatric or difficult to classify condition at baseline had a mean of 6.7 years of follow-up (SD=6.3, range from zero to 29.3 years).

Of the participants who donated their brains to the Oxford Brain Bank/Brains for Dementia Research (BDR), 185 people had additional follow-up through the BDR while they were alive. As was mentioned previously, of the combined OPTIMA, Challenge, and LEAD participants who joined BDR, 26 participants are still alive and completing BDR follow-up, and 33 individuals have withdrawn from BDR follow-up.

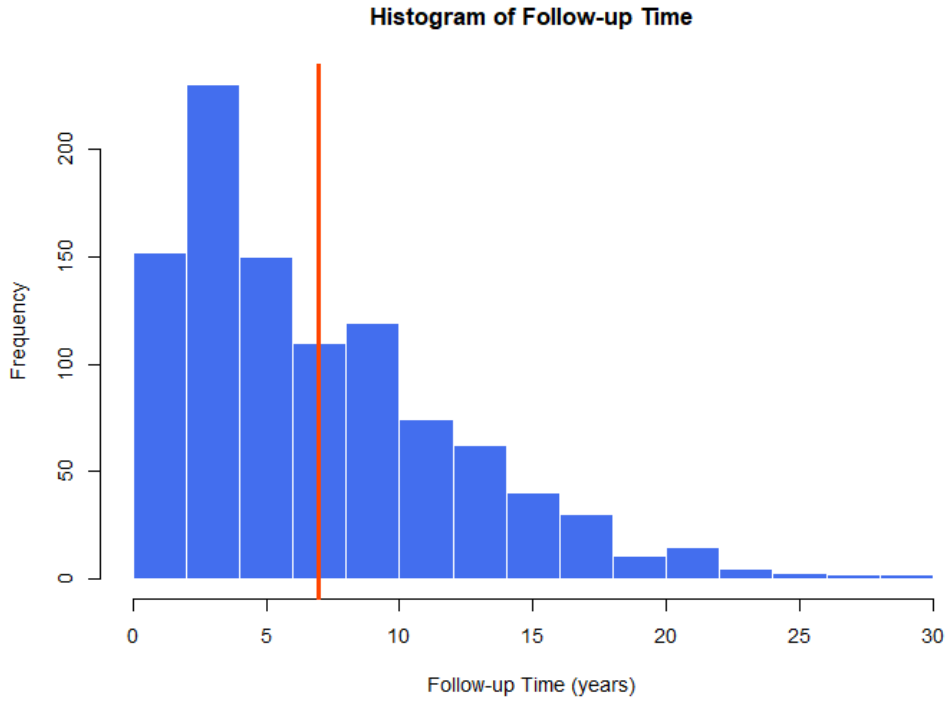


Figure 5.4. Histogram of follow-up time for individuals in the unified OPTIMA, Challenge, and LEAD cohorts (n=1005).

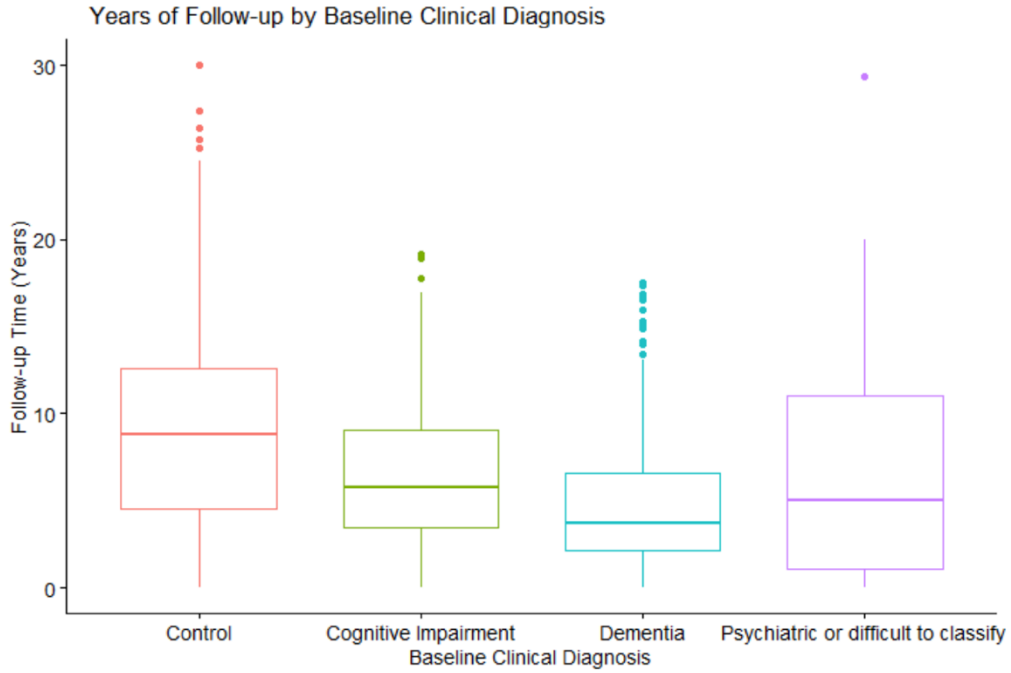


Figure 5.5. Box-plot of years of follow-up for each participant in the unified cohort, grouped by baseline clinical diagnosis (n=1005).

5.3.2. Cognitive Assessment Completion

Table 5.3 presents the number of CAMDEX visits completed by participants, grouped by baseline clinical diagnosis. While some participants completed only one CAMDEX, others completed over 20 examinations.

Baseline Clinical Diagnosis	**Episodes with a CAMDEX Listed**					
	1+	**2+**	**5+**	**10+**	**15+**	**20+**
Control, n	444	356	136	52	9	1
Cognitive impairment, n	155	122	85	52	17	6
Dementia, n	381	327	223	99	43	17
Psychiatric or difficult to classify, n	48	41	29	22	8	5

Table 5.3. Number of participants with only one, more than one, more than five, or more than ten episodes with a CAMDEX listed.

5.3.3. Imaging Completion Data

Participants in the OPTIMA, LEAD, and Challenge cohorts underwent various SPECT, CT, and MRI methods over the course of the study (Table 5.4). Overall, 793 participants got at least one CT scan, and a total of 2,122 CT scans are listed as completed. Additionally, 704 participants had at least one SPECT scan, and 1,871 scans were completed. There were 335 participants who had at least one MRI, with a total of 678 MRI scans done.

	Baseline Clinical Diagnosis							
Imaging Type	**Control** n=444		**Cognitive impairment** n=155		**Dementia** n=381		**Psychiatric or difficult to classify** n=49	
	Participants with 1+ scan	**Total of scans done**	**Participants with 1+ scan**	**Total of scans done**	**Participants with 1+ scan**	**Total of scans done**	**Participants with 1+ scan**	**Total of scans done**
CT, n	303	1009	126	323	324	674	41	117
SPECT, n	304	943	96	247	263	562	42	120
MRI, n	249	544	49	82	34	49	3	3

Table 5.4. Summary table of imaging completion for all three cohorts.

5.3.4. Clinical Bloods and CSF Completion

The number of participants who had clinical blood samples analysed for biochemistry, haematology, and/or virology can be seen in Table 5.5, both for the complete unified cohort and by baseline diagnosis. 99.1% of all participants had clinical bloods done at least once, with high proportions completing these samples across all baseline diagnoses. Participants had up to 18 visits with clinical bloods completed, and there was a total of 3,852 visits with clinical bloods.

Clinical Bloods Completion	**All participants** n=1029	**Baseline Clinical Diagnosis**			
		Control n=444	**Cognitive Impairment** n=155	**Dementia** n=381	**Psychiatric or difficult to classify** n=49
Participants completed at least once, n (%)	1020 (99.1)	443 (99.8)	154 (99.4)	376 (98.7)	47 (95.9)
Mean number completed per person	3.7	5.0	3.5	2.5	3.3
Range of number completed per person	0-18	0-18	0-10	0-10	0-11
Total completed	3852	2204	541	944	163

Table 5.5. Clinical bloods completion by baseline diagnosis.

Table 5.6 highlights the extent of CSF sampling for all participants, and by baseline clinical diagnosis. Of all the participants, 32.9% had their CSF analysed at least once, and there was a total of 413 visits with CSF done. The participants with a baseline diagnosis of cognitive impairment, dementia, and psychiatric or difficult to classify all had a range from zero to three visits with CSF completion per person. The control participants had a slightly larger range of up to four visits with CSF done. The baseline control and cognitive impairment participants had smaller proportions of participants completing CSF at least once (24.1% and 25.2% respectively), while a greater proportion of participants with a baseline diagnosis of dementia or a psychiatric condition had CSF done (43.6% and 55.1% respectively).

CSF Completion	Baseline Clinical Diagnosis			
	Control n=444	**Cognitive Impairment** n=155	**Dementia** n=381	**Psychiatric or difficult to classify** n=49
Completed at least once, n (%)	107 (24.1)	39 (25.2)	166 (43.6)	27 (55.1)
Mean number completed per person	0.3	0.3	0.5	0.7
Range of number completed per person	0-4	0-3	0-3	0-3
Total completed	122	52	204	35

Table 5.6. Cerebrospinal fluid (CSF) completion by baseline diagnosis.

5.4. Diagnostic Change Groups

Participants with multiple time points at which a diagnosis was assigned (n=975) were grouped by the way in which their clinical diagnoses changed from the beginning to the end of their study participation. Table 5.7 presents the number of participants in the main diagnostic change groups of interest, with their follow-up length and the number of participants with imaging, clinical bloods, CSF, and neuropathology completed. There were 16 participants in other more unusual diagnostic change groups (e.g., cognitive impairment to control). Supplemental tables 5.1-5.6 contain information about diagnostic change groups based on the dementia subtype diagnoses.

Diagnostic Change Group	Number of participants	Median follow-up length (years)	Participants completed at least once			
			Imaging	Clinical Bloods	CSF	Neuro-pathology
Controls throughout	280	7.7	276	280	53	82
Cognitive impairment throughout	42	3.7	42	42	4	13
Dementia throughout	353	4.0	340	351	159	256
Psychiatric or difficult to classify throughout	34	6.3	33	34	22	21
Controls → Cognitive impairment	102	9.5	102	102	31	36
Controls → Dementia	45	11.1	43	45	16	27
Control → Psychiatric or difficult to classify	5	6.5	5	5	4	3
Cognitive impairment → Dementia	92	7.2	92	92	32	56
Cognitive impairment → Psychiatric or difficult to classify	5	8.2	5	5	2	4
Psychiatric or difficult to classify → Cognitive impairment	1	7.0	1	1	0	1

Table 5.7. Summary table of diagnostic change groups, classified by clinical diagnosis of control, cognitive impairment, or dementia, along with median follow-up time and completion of imaging, bloods, CSF, and neuropathology.

5.5. Demographic Characteristics

Table 5.8 presents an overview of the demographic characteristics of the individuals from the unified OPTIMA, Challenge, and LEAD cohorts with at least one clinical diagnosis and CAMDEX completed.

Demographic Characteristic	All participants n=1027	Clinical Diagnosis at Baseline				P-values
		Control n=444	Cognitive Impairment n=155	Dementia n=381	Psychiatric or difficult to classify n=48	
Age at assessment, mean (SD), range	72.6 (8.9) 26 to 99	72.0 (8.6) 35 to 99	73.9 (7.8) 55 to 93	73.6 (8.8) 44 to 94	65.7 (12.7) 26 to 85	p<0.001[a]
Age ≥ 65 at baseline, n (%)	848 (82.6)	362 (81.7)	134 (86.5)	321 (84.3)	31 (64.6)	-
Age 55 to 64 at baseline, n (%)	148 (14.4)	67 (15.1)	21 (13.5)	51 (13.4)	9 (18.8)	-
Age < 55 at baseline, n (%)	31 (3.0)	14 (3.2)	0 (0)	9 (2.4)	8 (16.7)	-
Female, n (%)	518 (50.4)	233 (52.6)	63 (40.6)	201 (52.8)	21 (43.8)	p=0.036[b]
Family history of dementia, n (%)	204/916 (22.3)	107/438 (24.4)	37/151 (24.5)	57/284 (20.1)	3/43 (7.0)	p=0.042[b]
Family history of stroke, n (%)	242/900 (26.9)	144/437 (33.0)	36/148 (24.3)	55/272 (20.2)	7/43 (16.3)	p<0.001[b]
Family history of heart attack, n (%)	322/905 (35.6)	180/438 (41.1)	55/148 (37.2)	75/277 (27.1)	12/42 (28.6)	p=0.0014[b]
History of heavy smoking, n (%)	232/938 (24.7)	113/442 (25.6)	37/155 (23.9)	73/301 (24.3)	9/40 (22.5)	p=0.95[b]
History of regular drinking, n (%)	139/929 (15.0)	82/438 (18.7)	24/153 (15.7)	29/299 (9.7)	4/39 (10.3)	p=0.0070[b]
History of drug abuse, n (%)	88/953 (9.2)	54/440 (12.3)	11/155 (7.1)	14/315 (4.4)	9/43 (20.9)	p<0.001[c]
Age left school, mean (SD)	16.1 (1.7) n=924	16.5 (1.5) n=440	16.1 (1.6) n=153	15.5 (1.7) n=290	15.6 (1.8) n=41	p<0.001[a]
Years in further education, mean (SD)	2.0 (2.4) n=923	2.4 (2.5) n=436	2.3 (2.6) n=152	1.2 (2.0) n=291	1.3 (1.8) n=44	p<0.001[a]

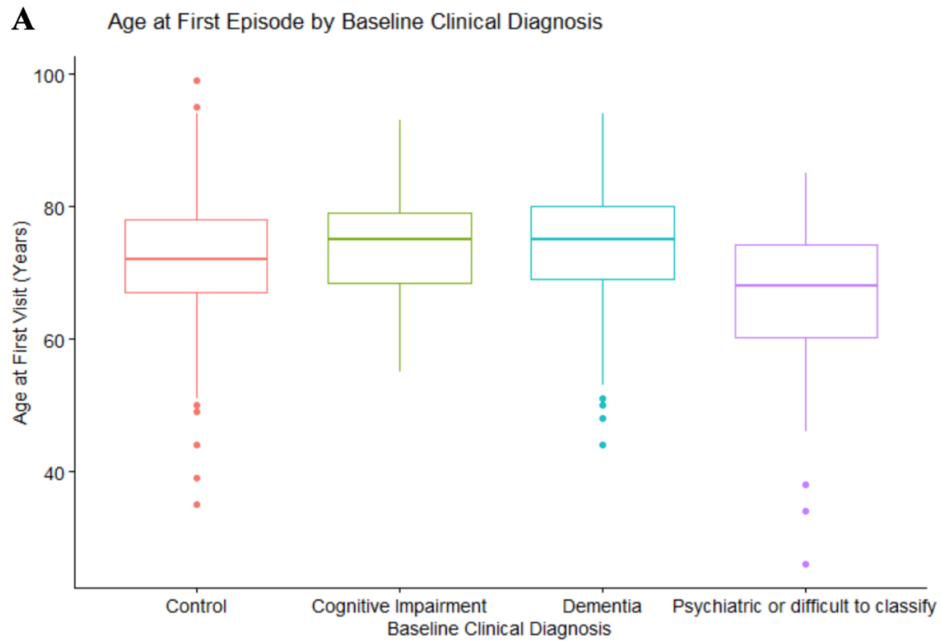
Table 5.8. Summary table of demographic characteristics of the unified OPTIMA, LEAD, and Challenge cohort participants, grouped by diagnosis at baseline.

([a] Kruskal-Wallis Test; [b] Chi-square test of independence, [c] Fisher's exact test)

5.6. Age at First Visit and at Death

The participants' ages at the first episode with a CAMDEX, as well as their ages at death, grouped by their baseline clinical diagnosis, can be seen in Figure 5.6. The mean age at first CAMDEX was in the 70s for the control, cognitive impairment, and dementia baseline diagnosis groups, and the mean age for the psychiatric or difficult to classify was about 65.7 years (Figure 5.6A). The non-parametric Kruskal-Wallis rank sum test showed a significant difference in the distributions of age at inception across the baseline diagnosis groups (Kruskal-Wallis chi-squared=26.0, $p<0.001$).

Ages at death ranged from 61 to 102 years (with a mean of 85.3 years) for baseline controls, 61 to 98 years (with a mean of 81.9 years) for those with a cognitive impairment at baseline, 53 to 100 years (78.7 years) with for those with dementia the first diagnosis, and 52 to 89 years (with a mean of 75.1 years) for participants with a psychiatric or difficult to classify condition at inception (Figure 5.6B). There was a significant difference between the ages at death grouped by baseline diagnosis (Kruskal-Wallis chi-squared=87.6, $p<0.001$).



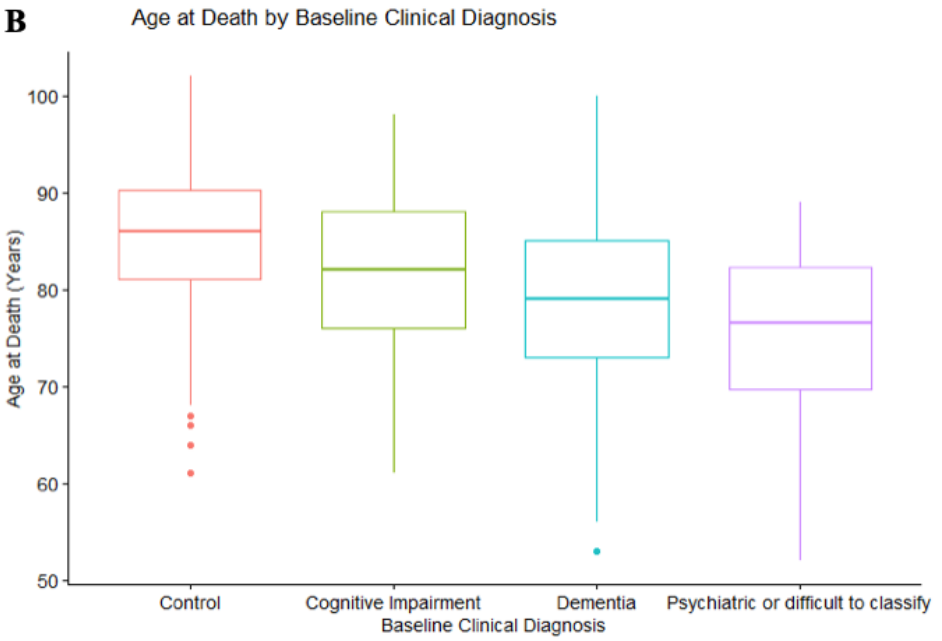


Figure 5.6. A) Box plot of age at first CAMDEX episode, separated by baseline diagnosis (Control: n=443, Cognitive impairment: n=155, Dementia: n=381, Psychiatric or difficult to classify: n=58). **B)** Box plot of age at death, separated by baseline diagnosis (Control: n=208, Cognitive impairment: n=97, Dementia: n=320, Psychiatric or difficult to classify: n=36).

5.7. Education

5.7.1. Age Left School

As was described in Chapter 4, the participants were asked about the age they left school during the CAMDEX examination (Figure 5.7). Overall, the range of ages the

participants left school was from nine to 20 (one person was excluded whose listed age left school was 30, as this was deemed likely to be due to a mistake in data entry or misunderstanding of the question). The ages left school ranged from 12 to 19 for the controls and those with a cognitive impairment, nine to 20 for those with dementia at baseline, and 12 to 20 for participants with a psychiatric or difficult to classify condition. The distributions of the age left school differed between the clinical diagnosis groups (Kruskal Wallis chi-squared=62.6, p<0.001).

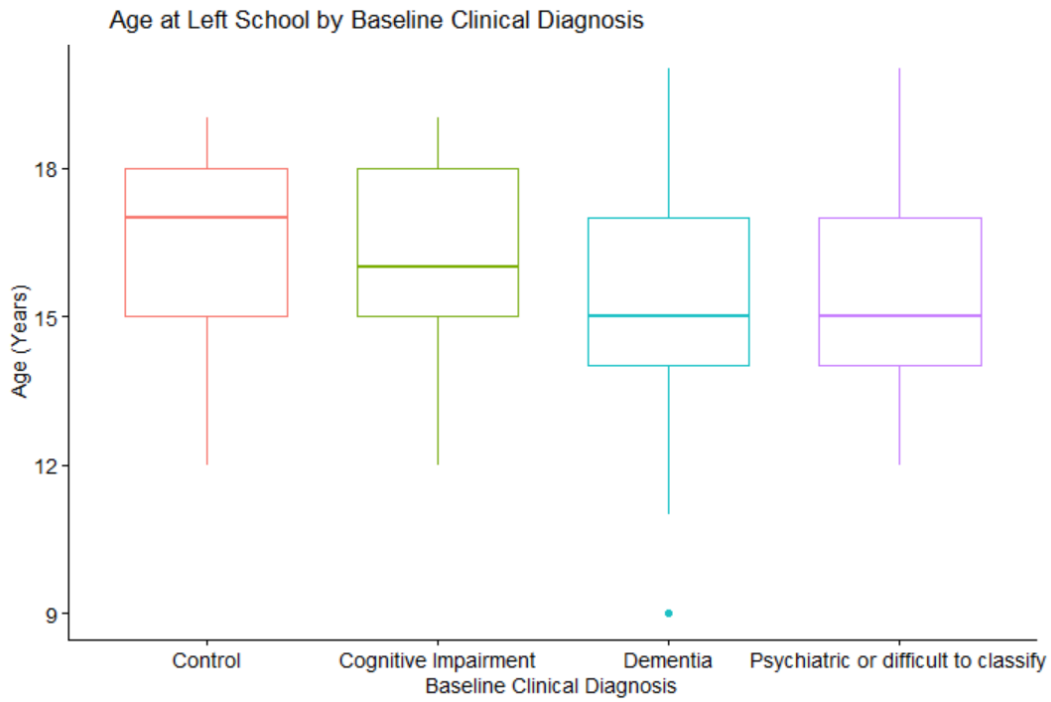


Figure 5.7. Box plot of the age participants reported leaving school, grouped by baseline clinical diagnosis.

5.7.2. Years in Further Education

Participants were also asked about how many years they spent in further education during the CAMDEX (Figure 5.8). There was a range from zero to 18 years in further education for those with a baseline control or cognitive impairment diagnosis, while the range was from zero to 12 years for those with dementia and zero to seven for those with a psychiatric or difficult to classify diagnosis. There was a significant difference in the years spent in further education between the baseline clinical diagnoses (Kruskal-Wallis chi-squared=64.5, p<0.001).

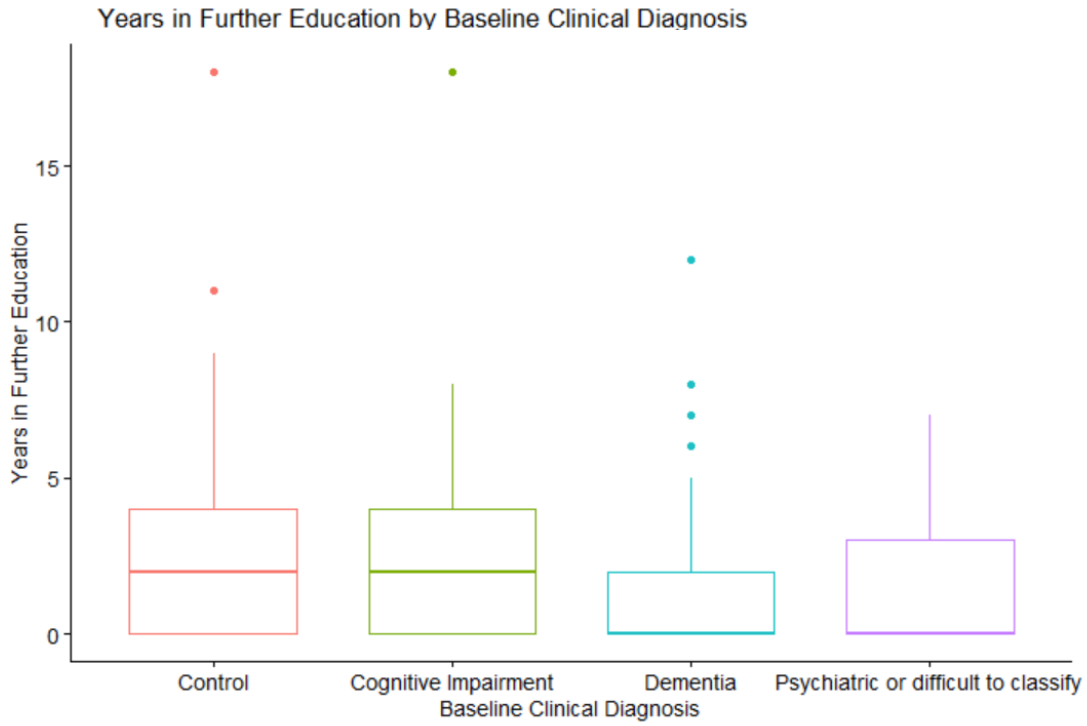


Figure 5.8. Box plot of the years each participant spent in further education, grouped by baseline clinical diagnosis.

5.8. Family Medical History

The CAMDEX also asked participants about their family history of various conditions, including dementia, stroke, and heart attack (Figure 5.9). Of those who were controls at baseline, 24.4% (n=107) reported a family history of dementia, 33.0% (n=144) had a family history of stroke, and 41.1% (n=180) had a family history of heart attack. Of those with a baseline clinical diagnosis of cognitive impairment, about 24% reported a family history of dementia and stroke (n=37 and n=36 respectively), and 37.2% had a family history of heart attack. For the participants with a baseline diagnosis of dementia, approximately 20% had a family history of dementia and stroke (n=57 and n=55 respectively), and 27.1% (n=75) reported a family history of heart attack. Those with a psychiatric or difficult to classify diagnosis at baseline had the lowest proportion of participants with a family history of dementia (n=3, 7.0%) and stroke (n=7, 16.3%). In this clinical diagnosis group, 28.6% (n=12) had a family history of heart attack.

There was a significant relationship between family medical history of dementia and baseline clinical diagnosis (Chi-square test of independence: χ^2=8.22, df=3, p=0.042). There were also significant differences with regards to initial clinical diagnosis and both family history of stroke (χ^2=17.28, df=3, p<0.001) and family history of heart attack (χ^2=15.62, df=3, p=0.0014).

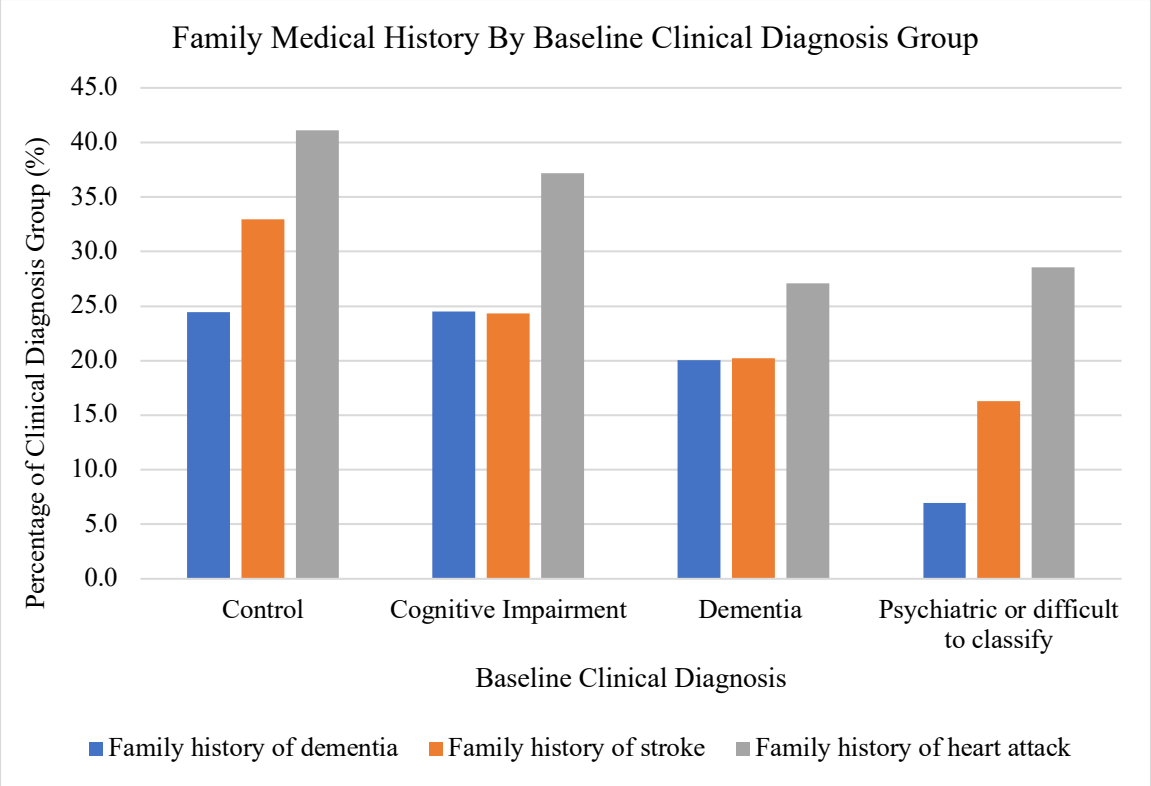


Figure 5.9. Participants' family history of dementia, stroke, and heart attack, grouped by baseline clinical diagnosis.

5.9. Vascular Risk Factors

5.9.1. Smoking History

The CAMDEX also asked the participant whether they had a history of heavy smoking, which was defined as "20 or more cigarettes per day for a year or more" (142). While the proportion of participants who had past heavy smoking did not differ significantly by baseline clinical diagnosis (Chi-square test of independence: χ^2=0.37, df=3, p=0.95), the control group had the largest proportion of participants reporting heavy smoking (n=113, 25.6%), followed by the dementia group (n=73, 24.3%) and the cognitive impairment group (n=37, 23.9%) (Figure 5.10). The psychiatric or difficult to classify clinical diagnosis group had a slightly lower proportion reporting past heavy smoking (n=9, 22.5%).

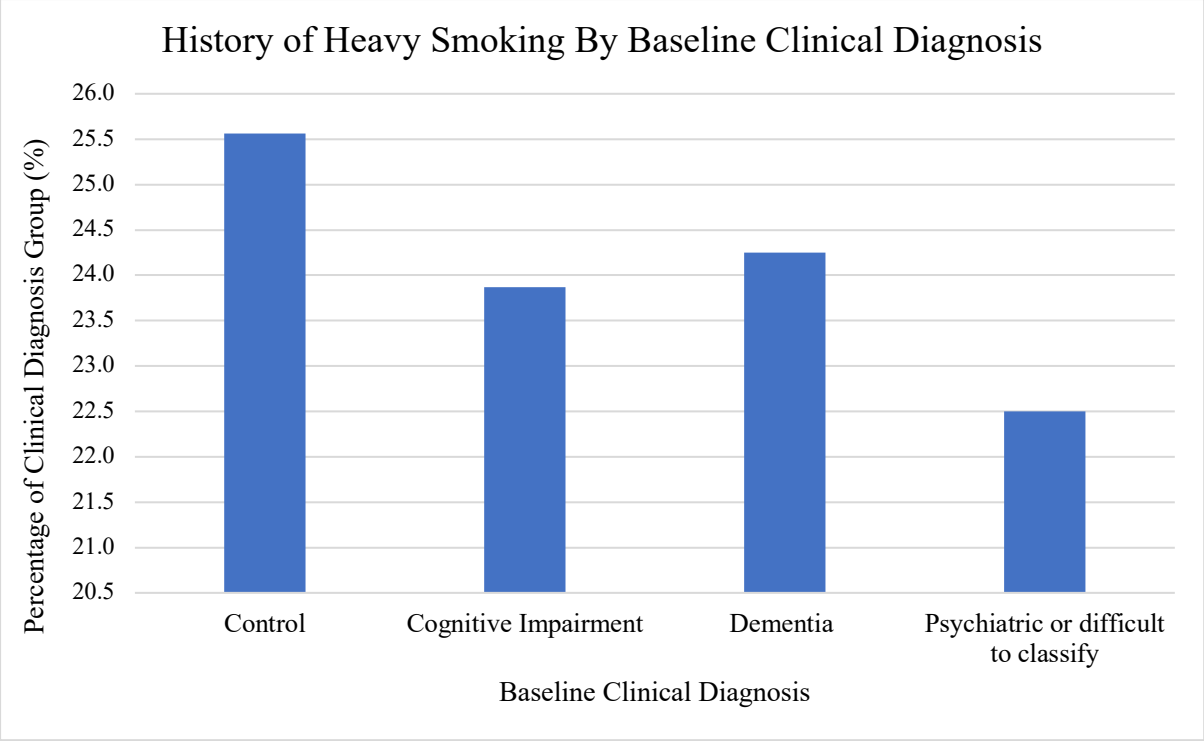


Figure 5.10. History of heavy smoking reported in participants with clinical diagnosis of control, cognitive impairment (no dementia), dementia, and psychiatric or difficult to classify.

5.9.2. Alcohol Use

The first available data about each participant's alcohol use history, recorded during the CAMDEX, can be seen in Figure 5.11. The majority of participants in all baseline clinical diagnosis groups reported no history of regular, heavy, or problem drinking (Supplemental Table 5.7). Heavy drinking was defined by the CAMDEX as having "ever drunk as much as 10 units (100 g) alcohol daily over a two-week period," and the definitions for regular and problem drinking could not be ascertained (142). The largest percentage with a regular drinking history was found in the control group (n=82, 18.8%), and the smallest proportion was found in the dementia baseline diagnosis group (n=29, 9.7%). There was a significant relationship between baseline clinical diagnosis and reported history of regular drinking (Chi-square test of independence: χ^2=12.12, df=3, p=0.0070). Less than 8% of the control, cognitive impairment, and dementia baseline groups reported a history of heavy drinking, while 20.5% of participants with a baseline psychiatric or difficult to classify diagnosis (n=8) had a heavy drinking history. The proportion of participants with a history of problem drinking was highest in the psychiatric or difficult to classify group (n=2, 5.0%).

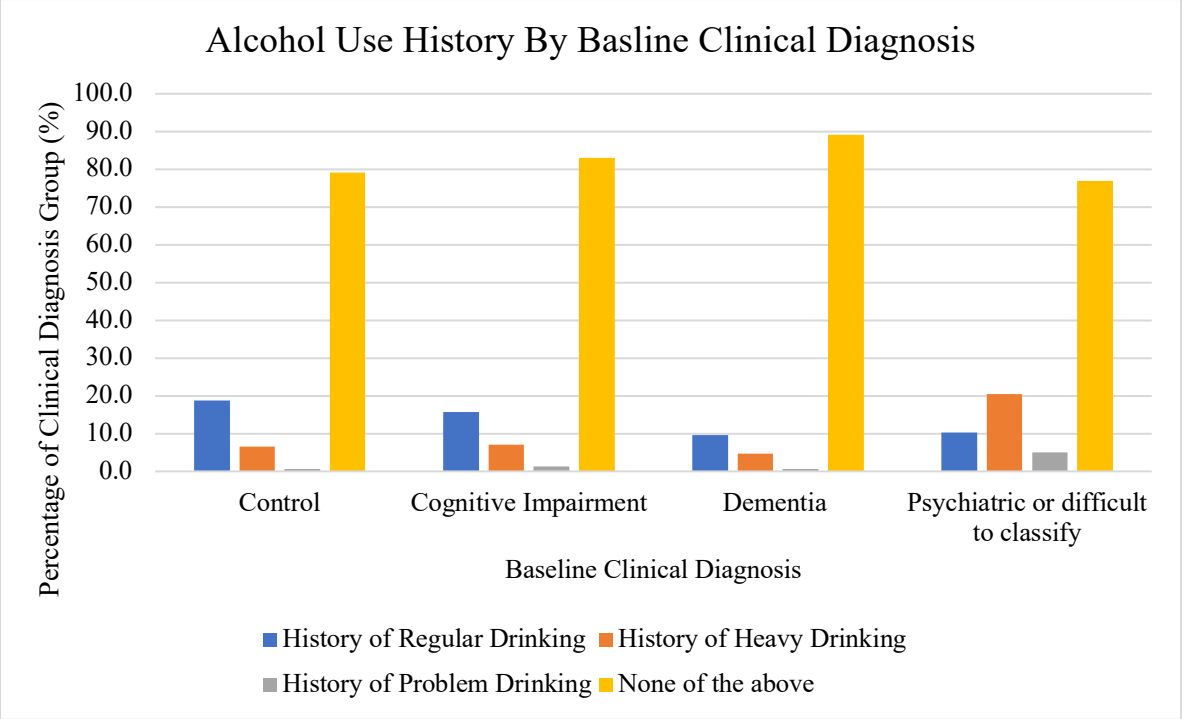


Figure 5.11. Alcohol use reported by participants, grouped by baseline clinical diagnosis.

5.9.3. Blood Pressure

Blood pressure (BP) can also be a vascular risk factor for dementia (161). The physical examination in the CAMDEX protocol included taking measurements of systolic and diastolic BP. The first available BP measurements for each participant, grouped by baseline clinical diagnosis, can be seen in Figures 5.12A and B and Table 5.9. Overall, there was a mean systolic BP of 149.9 mmHg (SD=22.9) and a mean diastolic BP of 84.8 mmHg (SD=11.8). The control group had the highest mean systolic BP of 151.5 mmHg (SD=22.6), and those with dementia had the highest mean diastolic BP of 86.0 mmHg (SD=12.1). The baseline diagnosis groups differed significantly with regards to systolic BP (Kruskal-Wallis chi-squared=12.92, $p<0.001$), but there was no significant difference in diastolic BP (Kruskal-Wallis chi-squared=6.08, $p=0.11$).

	All participants n=975	**Clinical Diagnosis at Baseline**			
		Control n=345	**Cognitive Impairment** n=107	**Dementia** n=297	**Psychiatric or difficult to classify** n=46
Systolic BP (mmHg), mean (SD), range	149.5 (22.9) 90-240	151.5 (22.6) 102-240	151.0 (11.3) 90-210	148.4 (23.5) 90-240	139.3 (20.9) 50-140
Diastolic BP (mmHg), mean (SD), range	84.8 (11.8) 50-140	83.6 (11.0) 54-140	85.2 (12.8) 60-140	86.0 (12.1) 50-130	84.6 (12.9) 60-110

Table 5.9. Baseline systolic and diastolic blood pressure (BP), grouped by baseline clinical diagnosis.

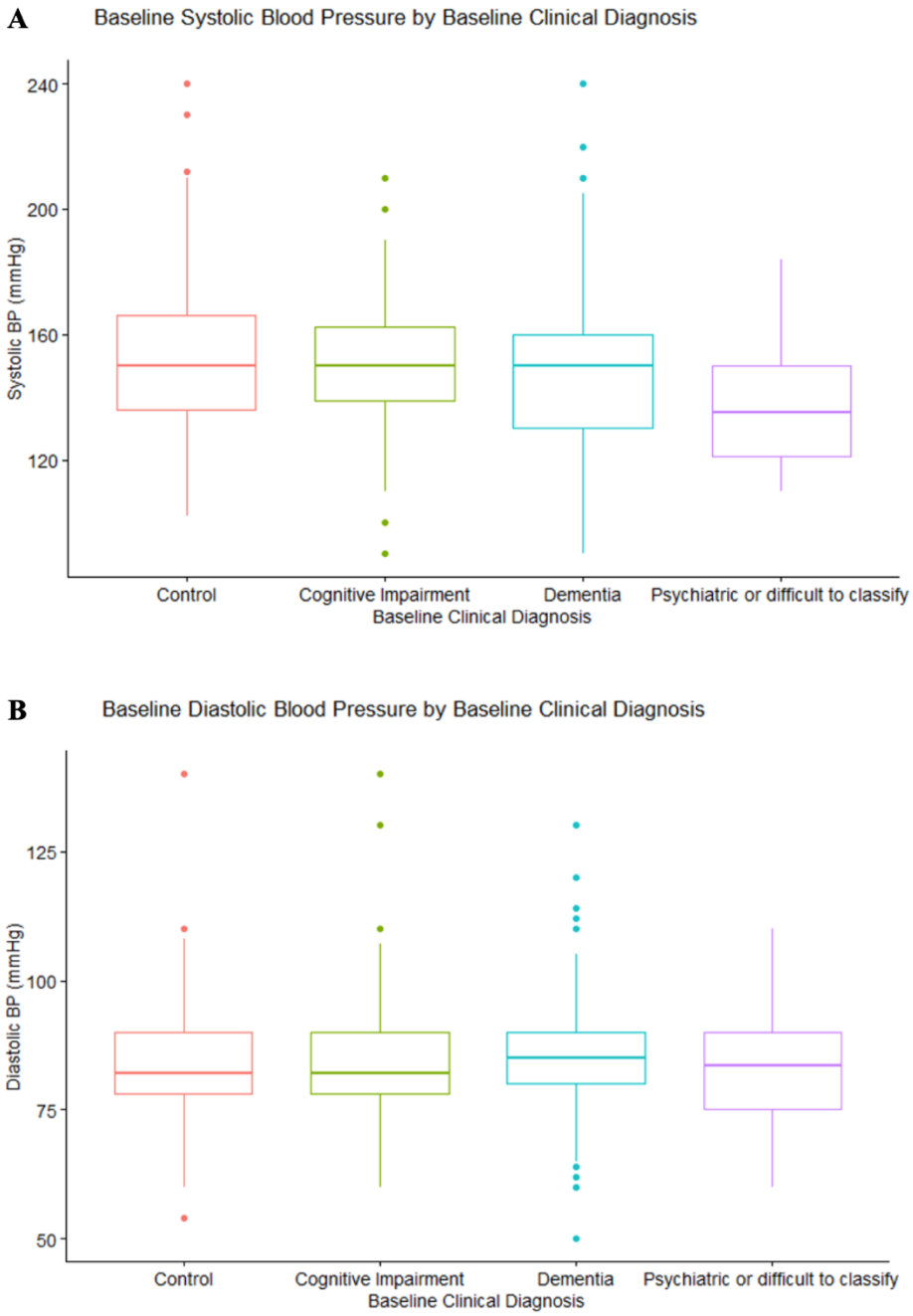


Figure 5.12. Baseline **A)** systolic BP and **B)** diastolic BP, grouped by baseline clinical diagnosis.

5.9.4. Cholesterol

Cholesterol has also been shown to be a risk factor for vascular health, although the link between cholesterol levels throughout life and dementia risk requires further research (162, 163). There were 598 participants with at least one measurement of their cholesterol, and the first available measures can be seen in Figure 5.13, grouped by baseline clinical diagnosis. The mean cholesterol level was 5.7 mmol/L (SD=1.3), which is higher than the normal range of less than 5 mmol/L. The range for all participants was from 2.4 to 10 mmol/L.

The cholesterol levels in the baseline clinical diagnosis groups were significantly different (Kruskal-Wallis chi-squared=21.93, p<0.001) and all above the normal level (Table 5.10).

	All participants n=598	**Clinical Diagnosis at Baseline**			
		Control n=357	**Cognitive Impairment** n=109	**Dementia** n=123	**Psychiatric or difficult to classify** n=9
First available cholesterol measurement, mean (SD), range	5.7 (1.3), 2.4-10	5.9 (1.2), 2.4-10	5.4 (1.3), 2.9-9.2	5.5 (1.3), 2.7-9.4	5.9 (1.6), 3.3-8.0

Table 5.10. First available cholesterol measurement, grouped by baseline clinical diagnosis.

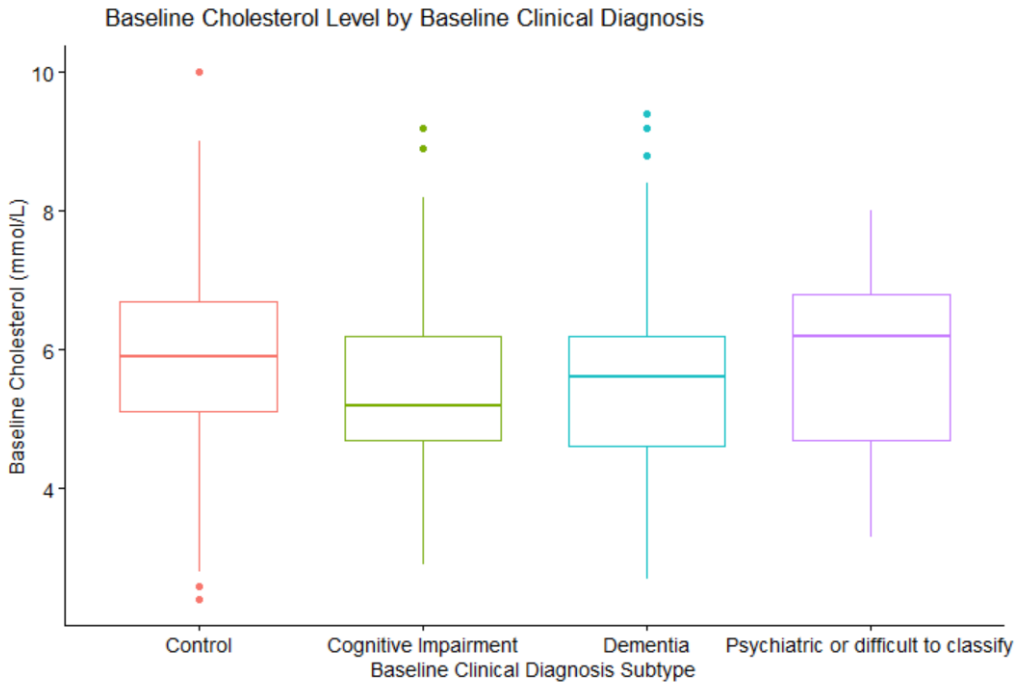


Figure 5.13. First cholesterol measurement for each participant, grouped by baseline clinical diagnosis.

5.10. Cognitive Assessments

5.10.1. Mini Mental State Examination (MMSE)

Figures 5.14 and 5.15 highlight the first and last MMSE scores for individuals in the unified OPTIMA, Challenge, and LEAD cohorts, by clinical diagnosis and subtype. These figures encompass MMSE scores from throughout each individual's participation (e.g., if a participant joined OPTIMA and then LEAD, their first score taken while in the OPTIMA cohort and the last score while in LEAD was utilised). Additional MMSE scores recorded during BDR study participation were added for 70 participants who were either still alive and being followed up or died and were listed in the UK Brain Bank Network. Future work will

incorporate additional MMSE scores for participants who withdrew or died without brain donation.

Overall, there were 956 people had two or more MMSE scores. The first MMSE scores for the baseline clinical diagnosis groups differed significantly (Figure 5.14A, Supplemental Table 5.8; Kruskal-Wallis chi-squared=596.6, $p<0.001$). The controls had the highest median score of 29, followed by those with a cognitive impairment (27), those with a psychiatric or difficult to classify condition (22), and those with dementia (20). There were some outliers, such as those with a control diagnosis but a first MMSE score below the cut-off of 23 points, which may be due to errors in data entry or perhaps to initial misdiagnosis.

At the last available MMSE, there was still a significant difference between the scores between the baseline diagnosis groups (Figure 5.14B; Kruskal-Wallis chi-squared=546.5, $p<0.001$). The median for the controls was still the highest at 28 points, while the median score dropped to 21 for those with a cognitive impairment at baseline, to 19 for those with a psychiatric or difficult to classify condition, and to nine for those with dementia.

When looking by diagnosis subtype, at the first MMSE, the highest median (29) was seen in the control and subjective memory impairment groups (Figure 5.15A). The lowest median at first MMSE is seen in the probable AD group (18). At the last MMSE, the highest median score is still seen in the baseline control subtype (still 29) (Figure 5.15B). The lowest last MMSE medians are seen in the probable AD (8), possible AD (10), mixed AD and VD (9), and ODS (9) baseline groups. There were significant differences between the diagnosis subtype groups at both first and last MMSE (Kruskal-Wallis chi-squared=604.0 and 556.4 respectively, $p<0.001$ for both).

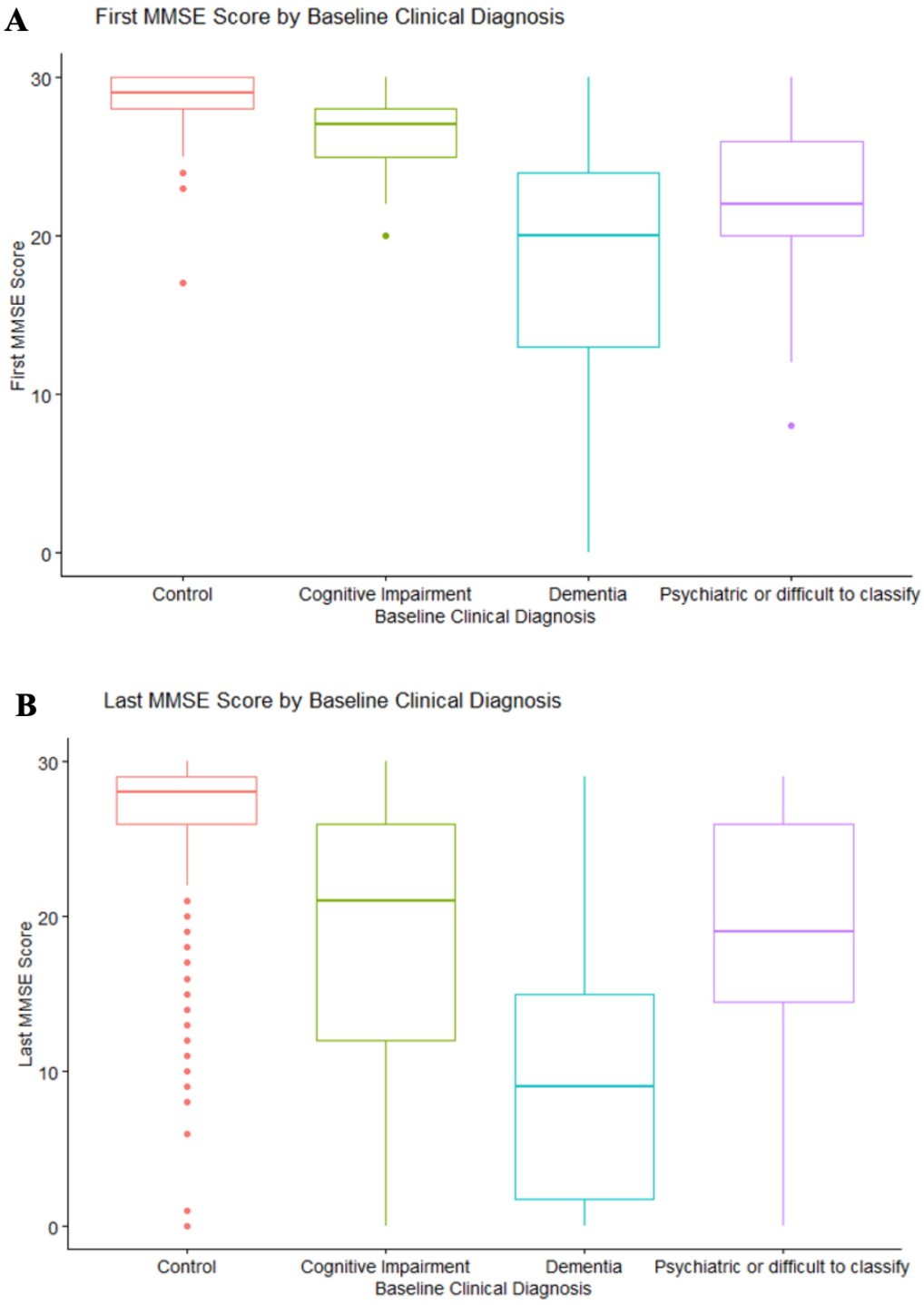


Figure 5.14. A) First MMSE score and **B)** Last MMSE score, grouped by baseline clinical diagnosis (n=956).

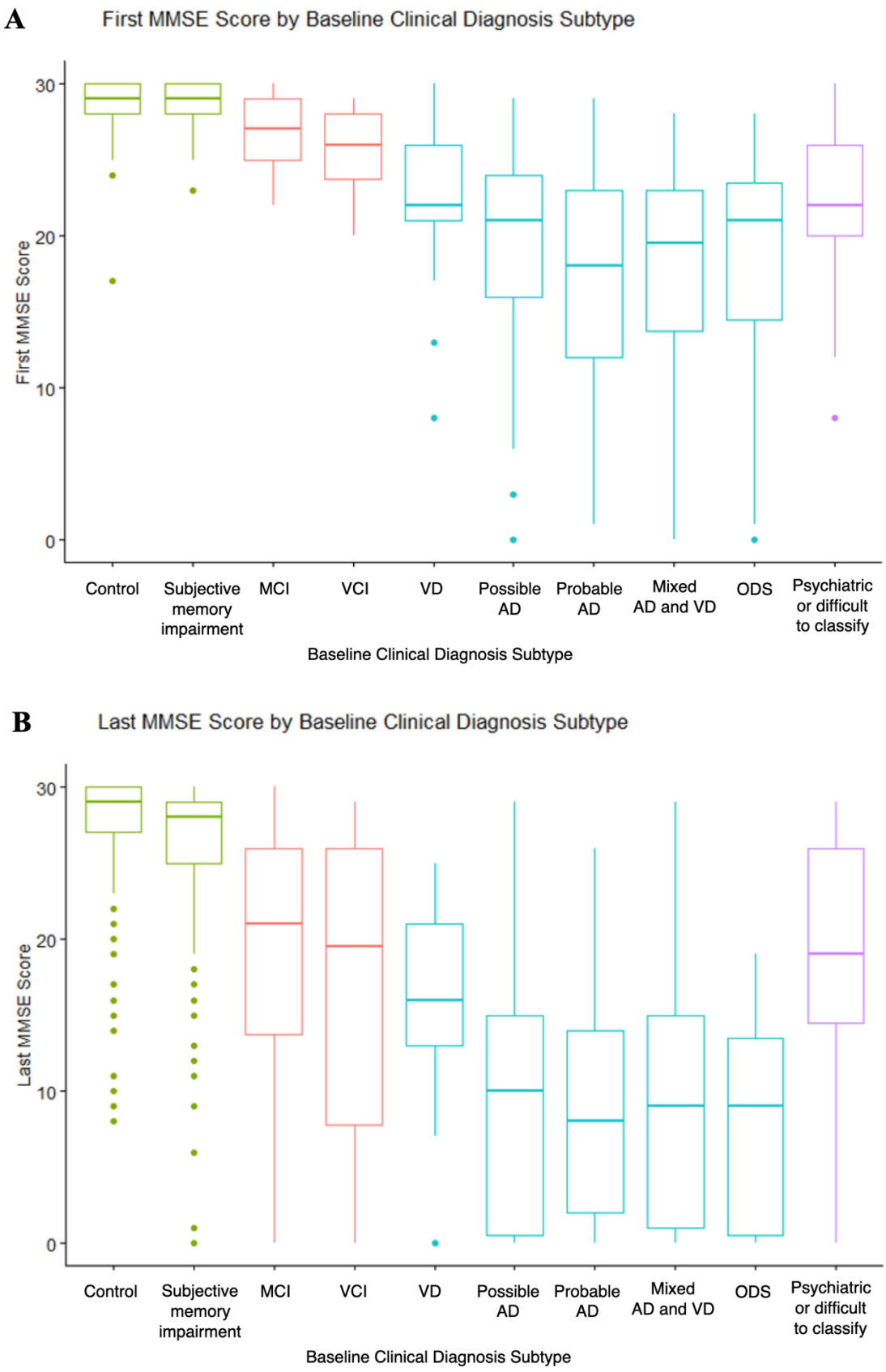


Figure 5.15. A) First MMSE score and **B)** last MMSE score, grouped by baseline clinical diagnosis subtype.

5.10.2. Cambridge Cognitive Examination (CAMCOG)

The Cambridge Cognitive Examination (CAMCOG) is another assessment included in the CAMDEX. Figures 5.16 and 5.17 highlight the first and last CAMCOG score for each individual over the course of their study participation, grouped by clinical diagnosis and subtype. There were 925 people with two or more CAMCOG scores.

The clinical diagnosis groups differed significantly at both the first and last total CAMCOG score (Figure 5.16 and Supplemental Table 5.9; First CAMCOG: Kruskal-Wallis chi-squared=680.0, $p<0.001$; Last CAMCOG: Kruskal-Wallis chi-squared=579.9, $p<0.001$). At first CAMCOG, the controls had the highest median score of 98, although there were two outliers with scores of 51 or 61 which may be errors in data entry or diagnosis. The cognitive impairment group had a median score of 88 at baseline, while those with a psychiatric or difficult to classify condition had a median score of 81. Those with a dementia diagnosis at inception had the lowest median score of 69 at first visit.

At the last available CAMCOG, the baseline controls continued to have the highest median score of 98 points, although the range of scores widened to span the lowest score of zero to the highest possible score of 107 (Figure 5.16B). The median last CAMCOG score was 75 points for both those with a cognitive impairment or a psychiatric or difficult to classify condition at baseline. The median also decreased for those with dementia at baseline, and the last CAMCOG score median was 37 points.

When considering baseline CAMCOG scores by subtype diagnosis, the highest median score of 99 is seen in the baseline control group, while the lowest median score of 64 is seen in the Probable AD and the mixed AD and VD subtype groups (Figure 5.17A). At the final CAMCOG score, the highest medians continue to be seen in the control and subjective memory impairment baseline groups, while the lowest medians are seen in the probable AD (score of 30) and ODS (27 points) baseline groups (Figure 5.17B). The baseline clinical diagnosis subtype groups' first and last CAMCOG scores differed significantly (First CAMCOG: Kruskal-Wallis chi-squared=686.9, $p<0.001$; Last CAMCOG: Kruskal-Wallis chi-squared=588.6, $p<0.001$).

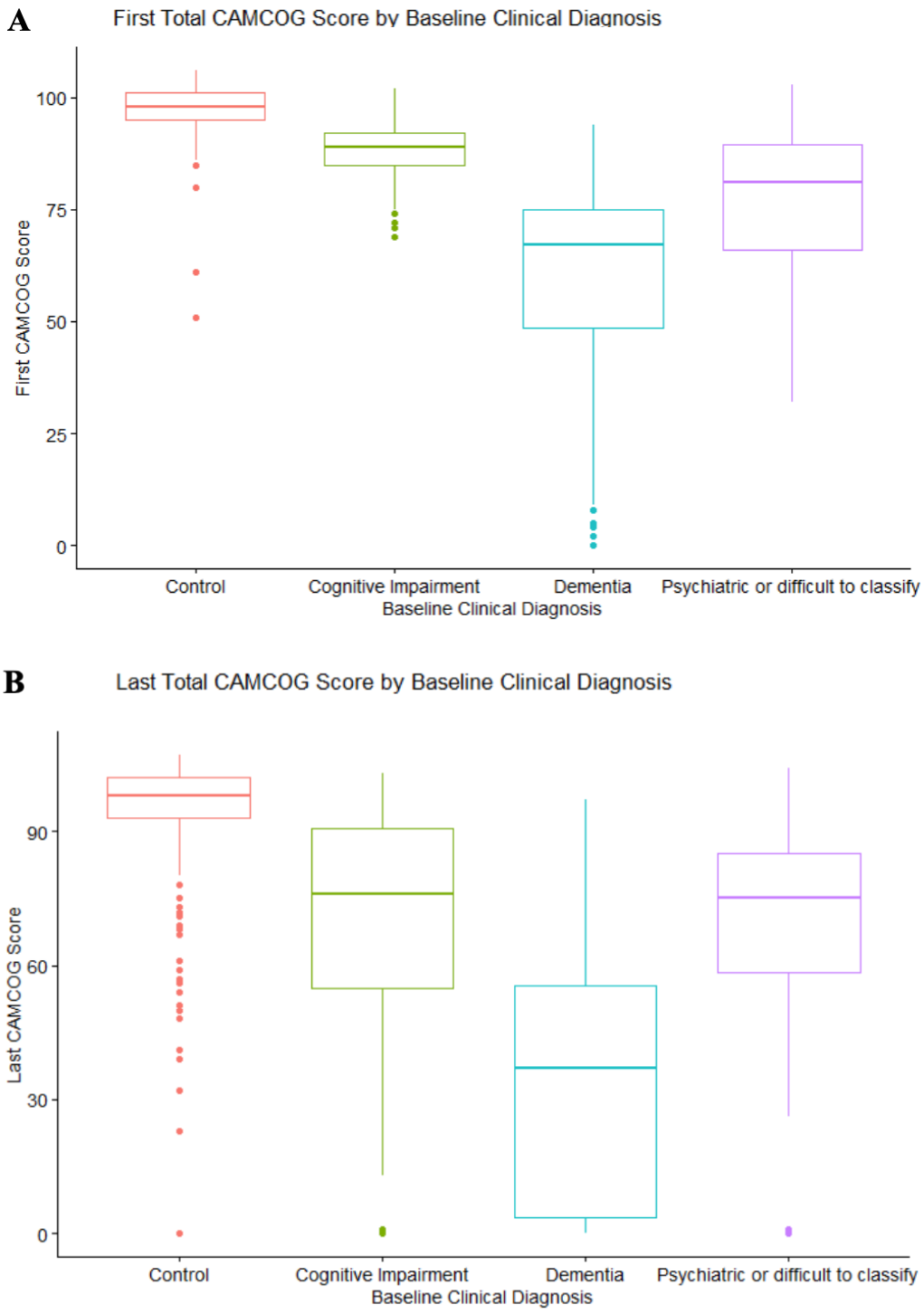


Figure 5.16. A) First and **B)** Last available total CAMCOG score, grouped by baseline clinical diagnosis.

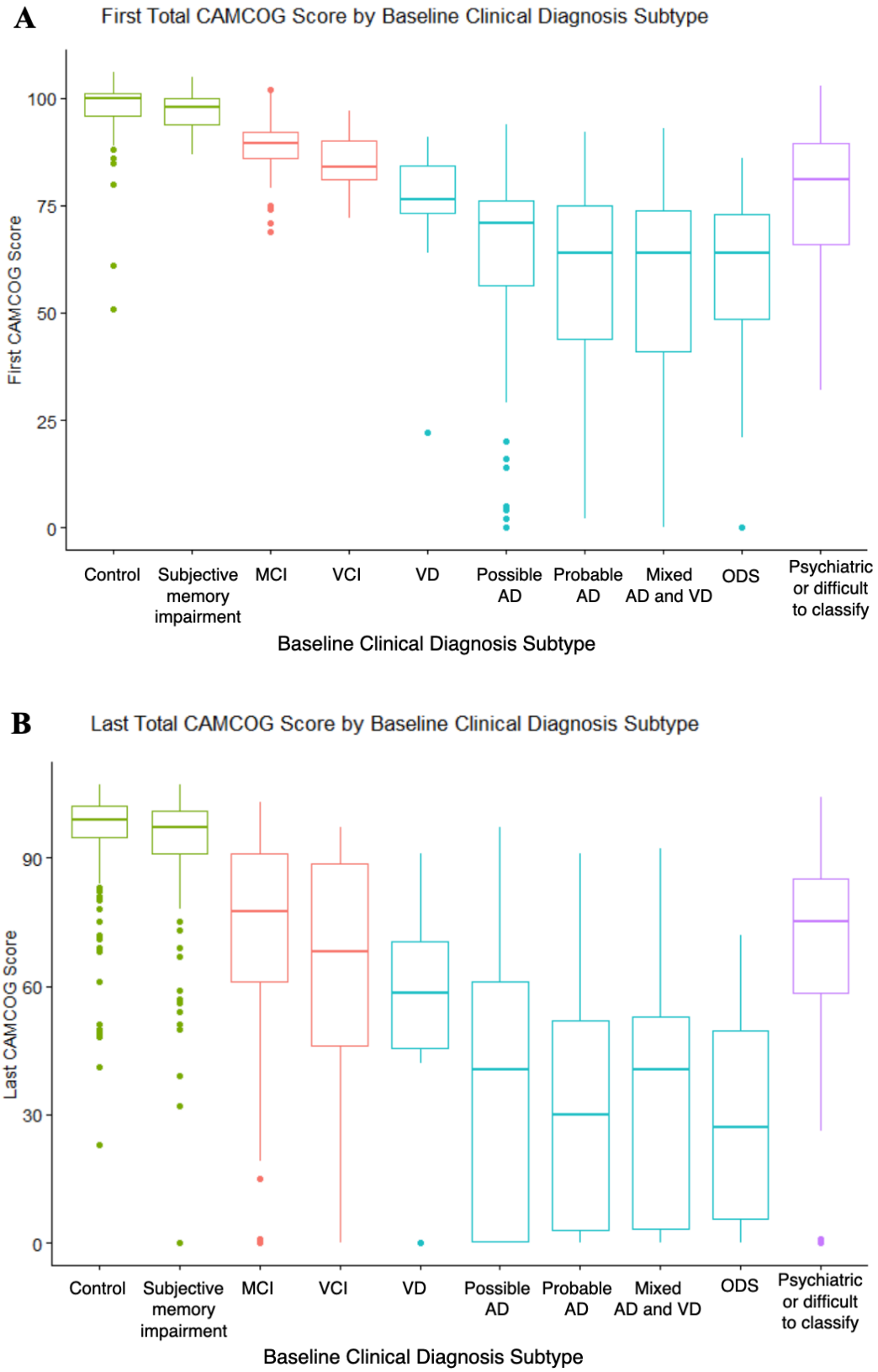


Figure 5.17. A) First total CAMCOG score and **B)** last total CAMCOG score, grouped by baseline clinical diagnosis subtype.

5.11. Cognitive Decline Scores

Cognitive decline scores were computed by taking the difference between the first and last cognitive assessment score for each participant (either MMSE or CAMCOG) and dividing by the time elapsed, to get a sense of their change in cognition over time. For this chapter, for individuals who were assessed in more than one study (e.g., OPTIMA and LEAD), cognitive assessment scores from their entire length of follow-up are included. Additional MMSE scores collected through BDR follow-up have also been incorporated for participants in the UK Brain Bank Network, and follow-up for additional participants will be incorporated in the future.

5.11.1. MMSE-Based Cognitive Decline Scores

Figure 5.18 highlights the cognitive decline of participants in the unified OPTIMA, Challenge, and LEAD cohorts, based on the change in their MMSE scores over time. There were 892 individuals with at least two MMSE scores and more than one year elapsed between them.

The MMSE-based cognitive decline scores differed significantly between the baseline clinical diagnosis groups (Kruskal-Wallis chi-squared=342.3, $p<0.001$) and when comparing scores between diagnosis subtypes (Kruskal-Wallis chi-squared=352.0, $p<0.001$).

Those with a control diagnosis at baseline had the least decline in MMSE scores on average, with a mean score of -0.3 (SD=0.9), though the scores ranged from -21.4 to 3.0 (Figure 5.18A, Supplemental Table 5.10). Those with a cognitive impairment had a mean decline score of -1.9 (SD=2.7), while those with dementia had the most decline, with a mean score of -3.3. (SD=2.8). Participants with a psychiatric or difficult to classify condition at baseline had a mean decline in MMSE score of -1.1 points per year (SD=2.1).

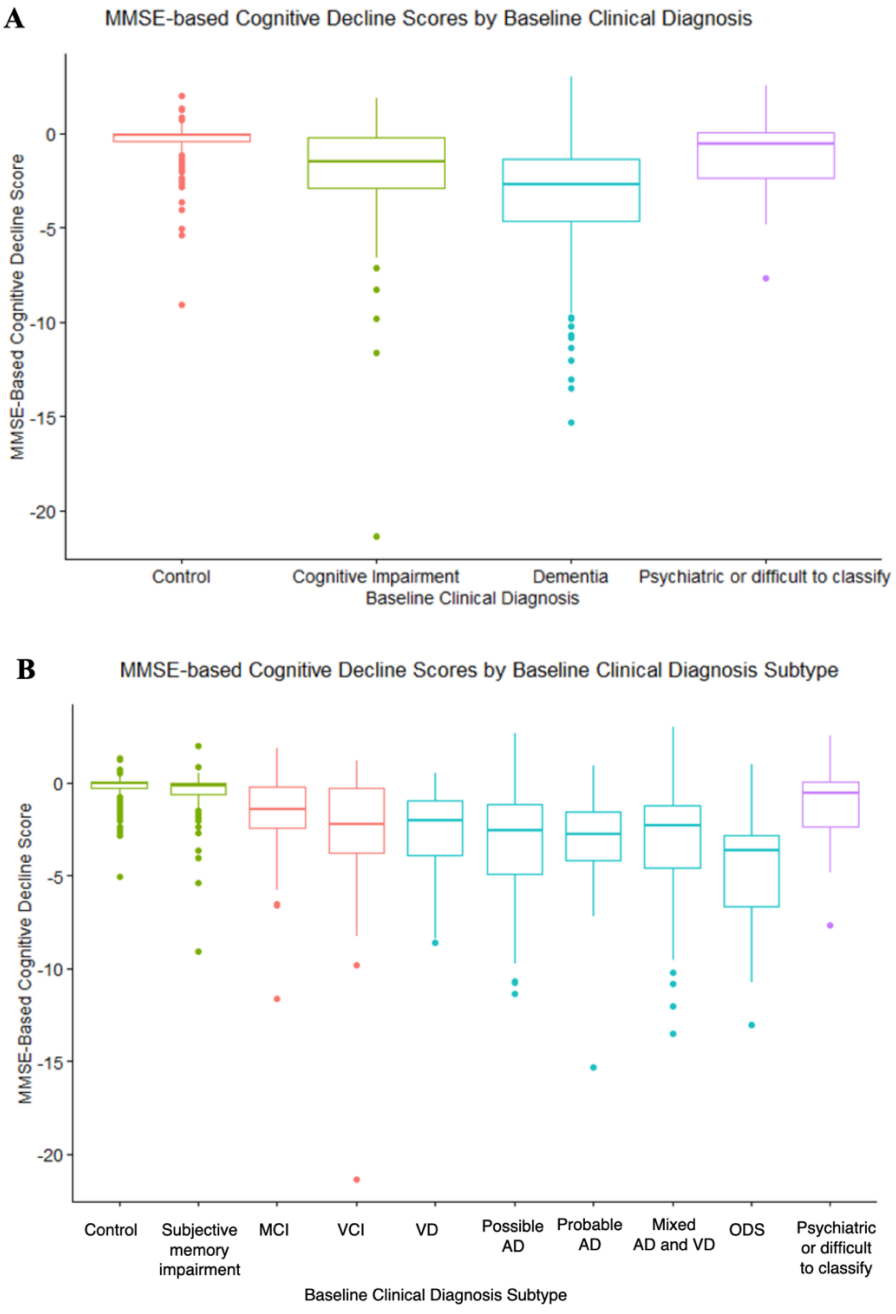


Figure 5.18. Box plot of MMSE-based cognitive decline scores, grouped by **A)** baseline clinical diagnosis and **B)** baseline clinical diagnosis subtype.

5.11.2. CAMCOG-Based Cognitive Decline Scores

Overall, there were 850 individuals with more than one CAMCOG score and at least one year between them, and the CAMCOG-based cognitive decline scores can be seen in Figures 5.19A and B. Their decline scores differed significantly by baseline clinical diagnosis and subtype diagnosis (Kruskal-Wallis chi-squared=331.4, $p<0.001$; Kruskal-Wallis chi-squared=336.1, $p<0.001$).

Those with a dementia diagnosis at baseline had the most cognitive decline, with a mean CAMCOG-based cognitive decline score of -10.1 points per year (SD=8.8) (Supplemental Table 5.10). Those with a control diagnosis at baseline had the least decline in CAMCOG scores over time, with a mean of -0.5 (SD=2.7), although there was a wide range of decline scores, from -22.7 to 18.6 (Figure 5.19A). The distribution of CAMCOG-based cognitive decline scores by subtype diagnosis resembles that of MMSE-based cognitive decline scores above (Figure 5.19B).

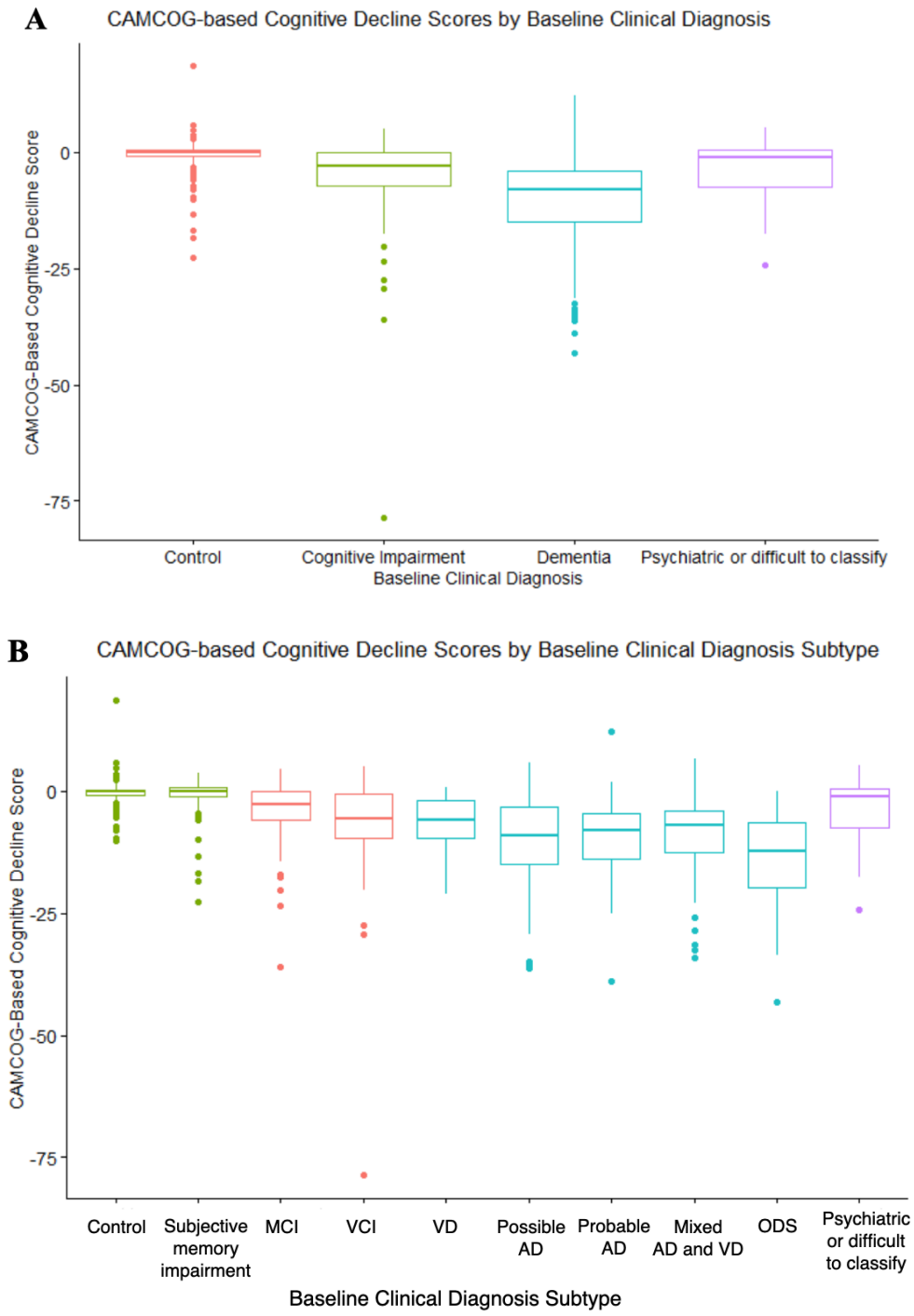


Figure 5.19. Box plot of CAMCOG-based cognitive decline scores, grouped by **A)** baseline clinical diagnosis and **B)** baseline clinical diagnosis subtype.

5.12. APOE Genotype

Figures 5.20 and 5.21 present the percentage of participants with each APOE genotype, grouped by final clinical diagnosis and dementia subtype (Supplemental Tables 5.11 and 5.12). E3E3, which is the most common genotype in the general population, made up the largest percentage of all clinical diagnosis groups, aside from those with dementia (Figure 5.18). The largest proportion of those with dementia at final clinical diagnosis had the E3E4 genotype (n=218, 42.7%); the E4 allele is associated with increased dementia risk. Those with baseline dementia had a larger percentage with the E4E4 genotype (n=57, 9.9%) than any of the other clinical diagnosis groups. E3E4 was especially predominant in those with probable AD (n=103, 48.8%), and this subtype also had the largest percentage with E4E4 (n=38, 18.0%) (Figure 5.19).

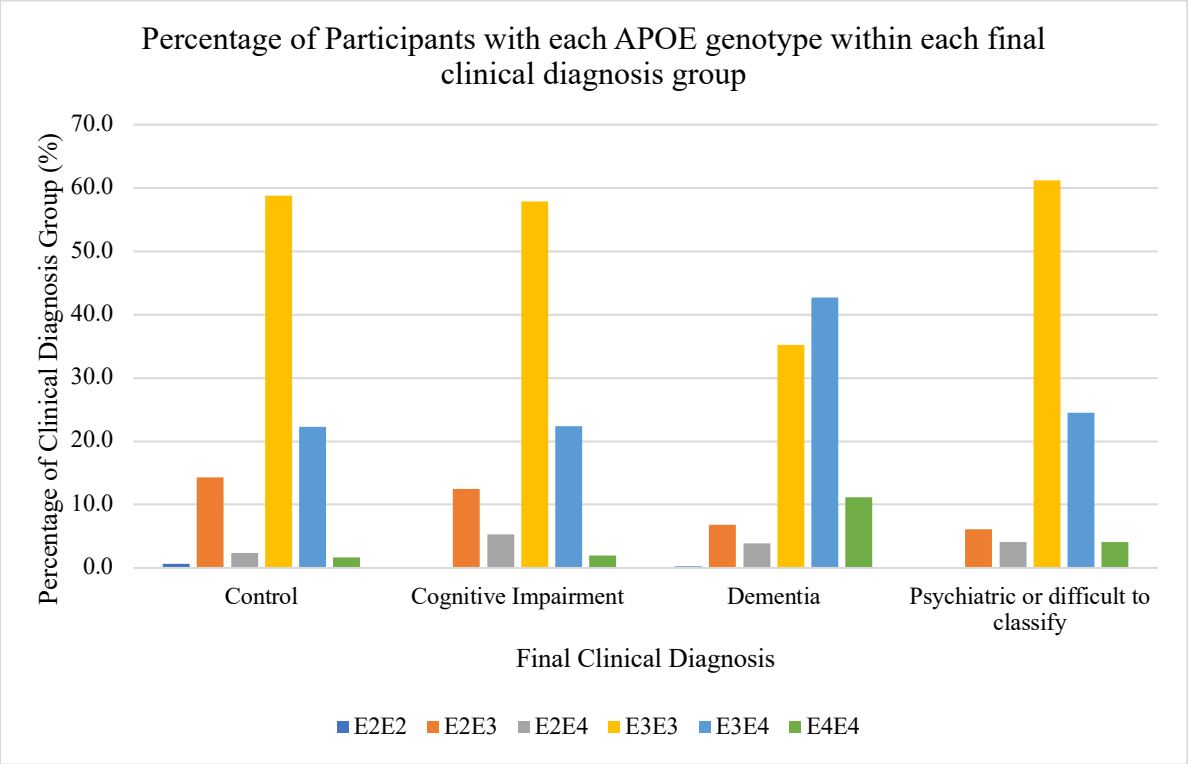


Figure 5.20. Percentage of participants in each final clinical diagnosis group with different APOE genotypes.

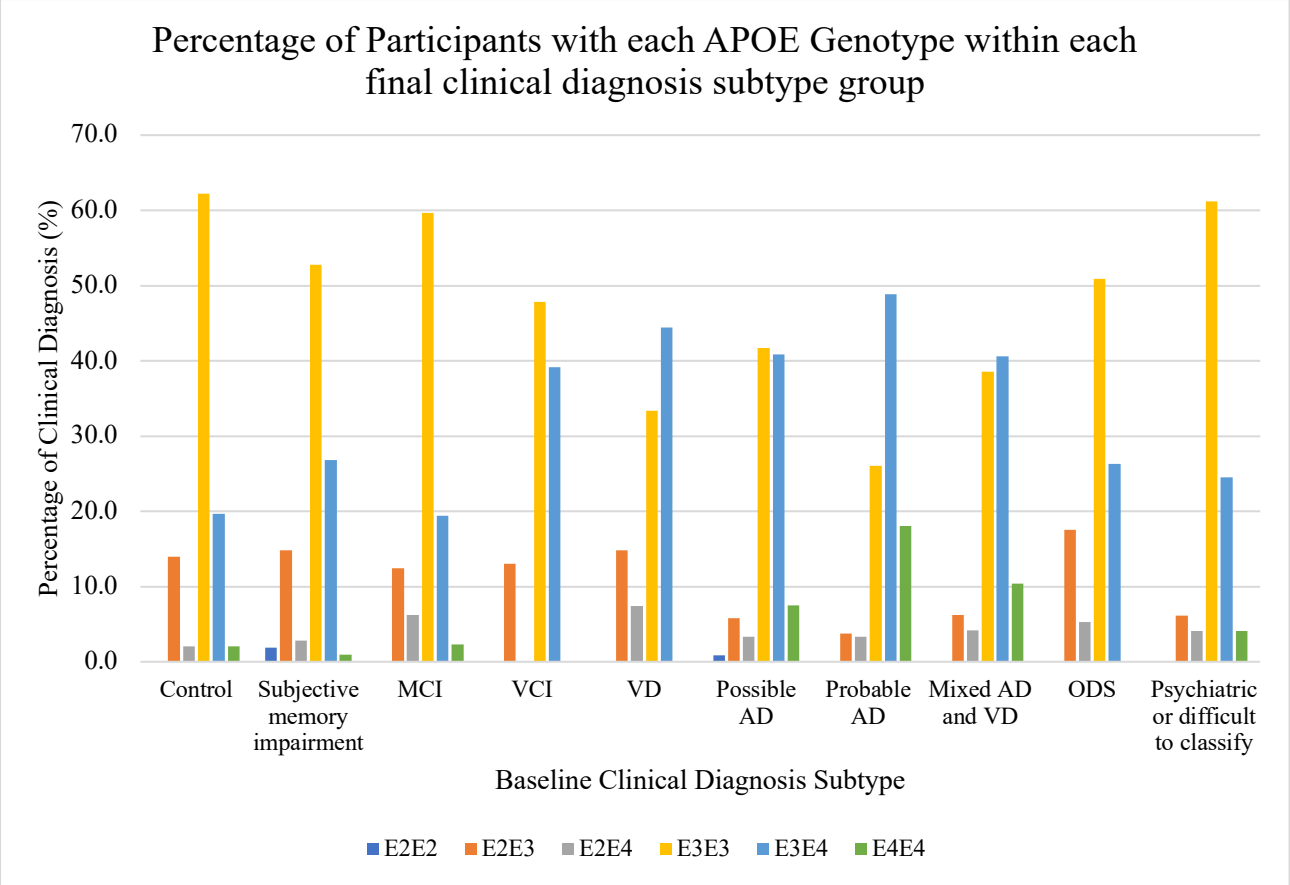


Figure 5.21. Percentage of participants in each final clinical diagnosis subtype group with different APOE genotypes.

5.13. Discussion

Notably, the baseline clinical diagnosis groups of the unified OPTIMA, LEAD and Challenge cohorts differed significantly across a range of variables, including age at baseline, age at death, age left school, years in further education, cognitive assessments, and cognitive decline over time.

Compared to the controls, participants who had dementia at baseline tended to leave school at a younger age, spend less years in further education, and die at a younger age. Those who had a psychiatric or difficult to classify condition tended to join the cohort and die at younger ages, which may be due to more unusual psychiatric and neurological disorders. These findings about education support previous research establishing shorter education length as a risk factor for dementia (138). With regards to age at death, these findings align with studies showing that dementia is associated with decreased life expectancy and increased risk of mortality (164).

Additionally, this analysis highlighted that participants across all clinical diagnosis baseline groups had vascular risk factors. Heavy smoking was common at baseline, with about one quarter of participants in all clinical diagnosis groups reporting this behaviour. This is much greater than the 13% of the UK population that smokes currently, and this difference may reflect the culture at the time of the study, when smoking was more prevalent and still

legal indoors until 2007 (165, 166). All baseline clinical diagnosis groups had mean systolic and diastolic BP readings that were above the normal range for older adults, which is "a systolic pressure of less than 120 and a diastolic pressure of less than 80" (167). High cholesterol (>5 mmol/L) was also seen across all clinical diagnosis groups. This could be because lowering cholesterol may not have been as much of a priority at the time the study began in the 1988, and statins only began to be used to lower cholesterol in the late 1980s in the UK (168).

It was also noteworthy that the percentage of the clinical diagnosis group with a history of regular drinking and heavy smoking was higher in the controls than those with a cognitive impairment. It is important to note that both alcohol and smoking have been shown to have deleterious health effects, and this finding should not be interpreted as confirming a protective effect of these behaviours, as there could be various explanations for the data. Some control patients who smoked heavily or drank regularly might have either not yet developed a dementia syndrome or they could have passed away from other smoking or alcohol-related conditions before dementia symptoms could develop. Other scientists have also suggested that when fewer moderate drinkers are found to have dementia, this may actually be due to other protective factors associated with moderate drinking, such as affluence, more frequent physical activity, and more education (80). It is also possible that participants with a cognitive impairment or dementia could have stopped smoking or consuming alcohol once they were diagnosed, leading them not to report substance use. Additionally, some participants with dementia may not have been able to travel to the store to buy alcohol or cigarettes due to their cognitive impairment. The CAMDEX also relies on self-reported data related smoking and drinking history, so it is possible that participants with dementia or a cognitive impairment and their study partners may not be correctly remembering or reporting their substance use history.

Another noteworthy aspect of this chapter is the APOE genotype findings. The E3 allele, which does not impact dementia risk, is known to be the most common form in the general population (152). The E3E3 genotype was predominant in the control, cognitive impairment, and psychiatric or difficult to classify clinical diagnosis groups. Given that the E4 allele is associated with higher dementia risk, it makes sense that the proportion of participants with the E3E4 and E4E4 genotypes were highest in the dementia clinical diagnosis group, and particularly in the AD and mixed AD and VD subtypes.

5.14. Conclusion

In conclusion, Chapter 5 explored the characteristics of the individual participants in the combined OPTIMA, Challenge, and LEAD cohorts, grouped by clinical diagnosis. This information included the number of study visits completed, demographic characteristics, cognitive assessments, and APOE genetics. Additionally, calculations were completed across all OPTIMA, LEAD, and Challenge follow-ups to provide data on the overall length of follow-up from the first study visit to the censor date, and extent of cognitive decline including BDR follow-up where available.

To summarise, this characterisation of individual participants, some of whom joined multiple cohorts, presents a new way of viewing OPTIMA, Challenge, and LEAD as a unified cohort. This chapter highlights the breadth and depth of information available on individual participants including inception and final diagnosis, transitions in cognitive status over time, and availability of imaging and samples, to help guide future research including biomarker studies using this unique resource.

CHAPTER 6: Comparison of Clinical and Neuropathology Diagnoses

6.1. Background

Despite the development of guidelines, assessments, and criteria to guide physicians, the clinical diagnosis of cognitive impairment and dementia subtypes remains imperfect. A definitive diagnosis can only be established by neuropathology analysis once the patient is deceased (16). Distinguishing between neurodegenerative conditions, such as Alzheimer's disease (AD) and vascular dementia (VD), can be challenging due to overlapping symptoms, variety in the clinical presentations within one type of dementia, and a lack of definitive blood biomarkers (16). Even one type of dementia alone, such as AD, can have a range of clinical presentations, with variation in factors such as age of onset, domain of cognition most affected, or APOE genotype (169). The clinical diagnosis of dementia subtype is a challenging and important undertaking, particularly as new treatments for specific subtypes become available.

With growing efforts to discover drugs to treat neurodegenerative conditions, it is of the utmost importance to improve clinical diagnosis to ensure that these drugs are being properly targeted at patients with the intended subtype of dementia (170). The United States' National Institute of Aging (NIA) alone is now funding clinical trials for over sixty pharmaceuticals that aim to address symptoms, slow disease progression, or stop the development of different types of dementia (171). In order to maximize the effectiveness of trials like these, scientists need to accurately identify patients with the type of dementia they are intending to target. Moreover, once effective treatments are approved and available, precise clinical diagnosis will be essential for patients to access the appropriate medical care.

Previous studies have evaluated the concordance of clinical and pathology-based diagnoses of dementia (57, 170, 172-177). A study of the Rush Memory and Aging Project cohort comparing the clinical and pathological diagnoses of 141 community-dwelling older adults found that the majority of the cohort had neuropathology findings that could cause dementia or cognitive decline (172). This study also found that, of the 50 participants clinically diagnosed with dementia, over half had more than one pathology underlying their dementia. Additionally, just over 70% of participants who were clinically diagnosed as controls had significant brain pathology. Other studies have also found more mixed pathology than was expected based on the clinical diagnosis (27, 176, 177).

Another study evaluated the alignment of clinical and neuropathology diagnoses using data from 180 patients in the London and Cardiff cohorts of the Brains for Dementia Research (BDR) study (170). This study by Selvackadunco et al. found that 36% of the participants had a clinical diagnosis that did not match the neuropathology findings. Their findings also indicated that clinical diagnoses often missed combined additional vascular and Lewy body pathologies that co-occurred with AD. Thus, this study, along with others with similar designs previously mentioned, indicate that there is room for improvement in the accurate clinical diagnosis of dementia subtypes, particularly with regards to mixed dementia.

The analysis presented in this chapter focuses on the large sample of patients from the Oxford Project to Investigate Memory and Ageing (OPTIMA), Challenge, and Longitudinal

Early Alzheimer's Disease (LEAD) cohorts who donated their brains to the Oxford Brain Bank. This investigation will evaluate whether the neuropathology findings support the last available clinical diagnosis from the OPTIMA, Challenge, and LEAD cohorts. This analysis can help further our understanding of the accuracy of clinical diagnoses of dementia subtypes.

6.2. Methods

6.2.1. Inclusion Criteria

Participants from the OPTIMA, Challenge, and LEAD cohorts were selected for inclusion in this analysis (Figure 6.1). In order to be included, participants needed to have at least one clinical diagnosis while alive and to have record of their brain donation in the Oxford Brain Bank.

To focus on clinical and neuropathology findings in older adults, this analysis was restricted to patients who were over the age of 60 at the time of their final clinical diagnosis. The participants also had to have donated their brain and have neuropathology information recorded in the UK Brain Bank Network downloadable data. The provision of data used in this study was supported by the UK Brain Banks Network with funding from Brains for Dementia Research (BDR) (123).

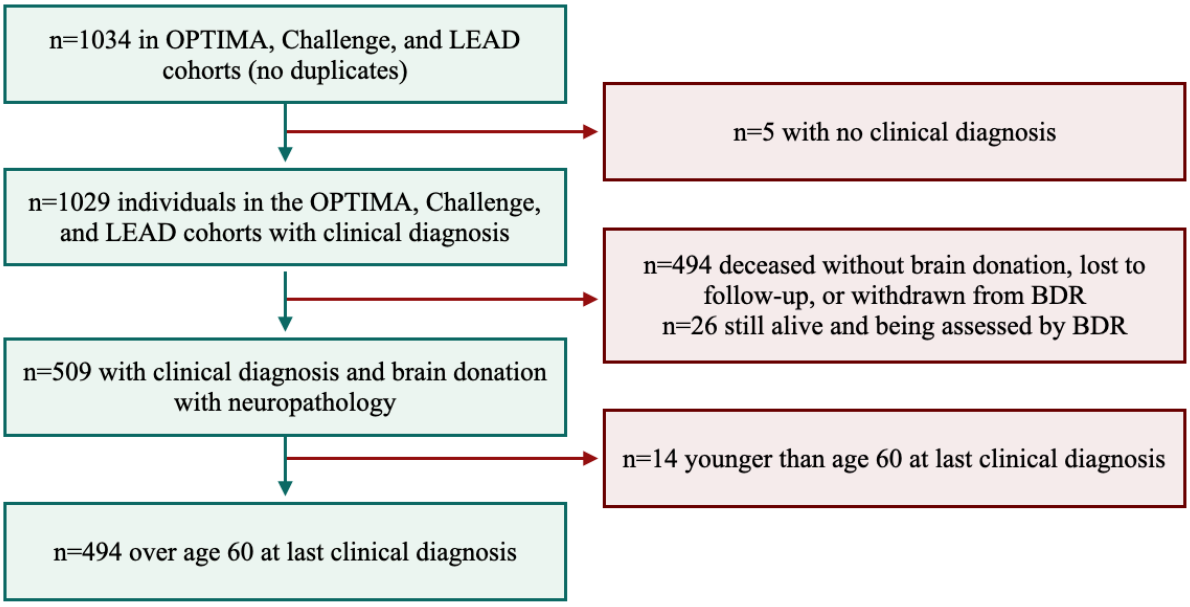


Figure 6.1. Flowchart of participants included in comparison of clinical and neuropathology diagnoses.

6.2.2. Comparison of Last Clinical Diagnosis with Neuropathology Findings

An overview of the criteria used for the clinical diagnosis of control, probable AD, VD, or mixed AD and VD can be seen below (Table 6.1). Each participant was given a clinical diagnosis which was determined by a consensus decision by the research team using all available information, including study interview, cognitive test scores, and informant

reports (see Chapter 2 for additional detail). Only the last available clinical diagnosis for each participant was considered in this analysis.

Diagnostic Group	**Clinical Criteria**
Control or subjective memory concerns	No criteria for cognitive impairment were met
Mild cognitive impairment (MCI)	Peterson Criteria for the Diagnosis of Mild Cognitive Impairment (131) and the Criteria for identification of mild cognitive impairment (MCI), given by the MCI Working Group of the European Consortium on Alzheimer's disease (10)
Vascular cognitive impairment (VCI)	Fulfils MCI criteria and has history of stroke, evidence of infarcts, lacunes, or moderate small vessel disease (SVD) (see Chapter 2 for more detail)
Possible or probable Alzheimer's Disease (AD)	NINCDS-ARDRA Criteria for the Diagnosis of Alzheimer's Disease (95)
Vascular dementia (VD)	NINDS-AIREN Criteria for Diagnosis of Vascular Dementia (132)
Mixed AD and VD	AD and VD criteria above met
Psychiatric or difficult to classify	Unspecified criteria
Other dementia syndrome (FTD, PD/LBD, etc.)	Criteria for the Diagnosis of Dementia with Lewy Bodies (103) The clinical diagnostic features of FTD: Clinical profile (104)

Table 6.1. Description of clinical diagnostic criteria

Pathology diagnostic codes and notes recorded in the UK Brain Bank Network (which were presumably uploaded from the Oxford Brain Bank) were manually searched to ascertain the neuropathology findings, including likelihood of AD, Braak Tangle staging, CERAD scores, Braak Lewy Body (LB) staging, and the presence of infarcts, Parkinson's Disease/Lewy body disease (LBD), moderate to severe vascular conditions, and other conditions that can contribute to cognitive decline.

The criteria used to determine whether the neuropathology findings supported the last clinical diagnosis can be seen in Table 6.2. A clinical diagnosis was considered to be partially supported if the final clinical diagnosis was correct but additional pathology was found (e.g., if the final clinical diagnosis was probable AD and the neuropathology showed both AD and PD/LBD pathology). The clinical diagnosis was also classified as partially supported if it was partially correct, but there was one less pathology than was clinically diagnosed (e.g., when the clinical diagnosis was mixed AD and VD but only infarcts were found with no significant AD pathology).

Clinical Diagnosis	Neuropathology Support
No significant pathology	• Low to low-intermediate AD pathology (NIA-Reagan criteri) Or • CERAD Score 0 (No neuritic plaques) • Braak Tangle Stage 0
Vascular Cognitive Impairment (VCI)	• Infarct(s)
Possible AD or amnestic disorder or mixed: AD with Other Dementia Syndrome (ODS) (Abbreviated as "Possible AD" in results section)	• Intermediate to high AD pathology (NIA-Reagan Criteria) with or without ODS pathology (see below)
Probable Alzheimer's Disease (AD)	• Intermediate to high AD pathology (NIA-Reagan Criteria)
Vascular Dementia (VD)	• Infarcts (microinfarcts, lacunar infarcts, and/or infarcts > 10 mm, any location)
Lewy Body Disease (LBD)	Lewy Body findings: • Parkinson's/Lewy body findings • Neocortical LBD • Limbic LBD • Brainstem LBD • LBD in other brain region
Other neurodegenerative or neurological condition	Other neurodegenerative or neurological condition listed, including: • Frontotemporal dementia (FTD) • Huntington's disease (HD) • Progressive supranuclear palsy (PSP) • Amyotrophic lateral sclerosis (ALS) • Corticobasal degeneration (CBD) • Hippocampal sclerosis • Past traumatic brain injury (TBI) (not acute head trauma leading to death) • Brain tumours (meningioma, glioblastoma, metastases, etc.) • Motor neuron disease • Argyrophilic grain disease • Normal pressure hydrocephalus • Central pontine myelinosis

Table 6.2. Description of neuropathology-based diagnostic criteria used postmortem.

Although a range of vascular conditions can contribute to dementia, there were no definitive criteria for the neuropathological diagnosis of VD (14). For the purposes of this study, only infarcts, which indicate end-stage organ disease, were considered as neuropathology support for the clinical diagnoses of VCI and VD, following the approach modelled by Schneider et al (172). This approach was taken because it is not always possible to distinguish between small but impactful infarcts versus silent infarcts that may not have noticeable symptoms (156, 172, 178). The presence of microinfarcts, lacunar infarcts, and infarcts > 10 mm in size was determined through the diagnostic codes and notes written by the neuropathologist. Additionally, this analysis is focused on neurodegeneration, so neuropathology findings related to head trauma near the time of death were not considered.

In order to the determine whether the extent of AD pathology, including neurofibrillary tangles and amyloid plaques, was sufficient to support a clinical diagnosis of AD, the NIA-Reagan criteria were used (Table 6.3, reproduced from (153)). Only intermediate to high AD likelihood based on the neuropathology was considered to support the clinical diagnosis of AD. Some participants did not have a CERAD score, but they did have notes indicating whether AD was possible, probable, or definite based on the CERAD criteria, so in these cases the CERAD criteria and NIA-Reagan criteria were used to estimate AD likelihood. If these notes indicated CERAD definite and Braak tangle stage V/VI, the AD likelihood was recorded as high. If there was CERAD definite with Braak tangle stage III/IV, then the AD likelihood was deemed to be intermediate. If there was a note that CERAD criteria indicated probable AD and the Braak tangle stage was I/II, the AD likelihood was recorded as low-intermediate.

Given that there is not a clear neuropathological correlate for the clinical diagnosis of MCI, these cases were excluded from the analysis of neuropathology support. Because there was also not a clear set of neuropathological findings that would support or disprove the clinical diagnosis of "Psychiatric or difficult to classify," participants with this clinical diagnosis were also excluded from the analysis of supported, partially supported, and unsupported diagnoses.

Likelihood of AD NIA-Reagan Criteria			
	CERAD Neuritic Plaque Score		
Braak Tangle Stage	Sparse	Moderate	Frequent
I-II	Low	Low-intermediate	High
III-IV	Low-intermediate	Intermediate	High
V-VI	Intermediate	High	High

Table 6.3. NIA-Reagan Criteria for AD pathology severity (Table reproduced from (153))

6.3. Results

6.3.1. Overview of Clinical and Neuropathology Characteristics

The 494 participants were 43.4% female (Table 6.4). The mean age at the last clinical diagnosis was 80.4 years (SD=8.0), with a range from 61 to 100 years. The mean age at death was 81.7 years (SD=8.2), with a range from 61 to 102 years. At the final clinical diagnosis,

86 (17.4%) were controls, 50 (10.1%) had a cognitive impairment, 334 (67.6%) had dementia, and 24 (4.9%) had a psychiatric or difficult to classify condition.

Clinical Characteristics	Values
Age at last clinical diagnosis, mean (SD)	80.4 (8.0)
Age at death, mean (SD)	81.8 (8.2)
Female, n (%)	234 (43.4%)
Final clinical diagnosis of control, n (%)	86 (17.4)
Final clinical diagnosis of cognitive impairment (no dementia), n (%)	50 (10.1)
Final clinical diagnosis of dementia, n (%)	334 (67.6)
Final clinical diagnosis of psychiatric or difficult to classify, n (%)	24 (4.9)

Table 6.4. Cohort clinical characteristics.

With regards to their clinical diagnosis subtype, there were 40 participants with MCI (8.1%), 10 (2.0%) with VCI, 18 (3.6%) with VD, 80 (16.2%) with possible AD, 143 (28.9%) with probable AD, 59 (11.9%) with mixed AD and VD, and 34 (6.9%) with ODS (including LBD, FTD, and other causes of dementia) (Figure 6.2).

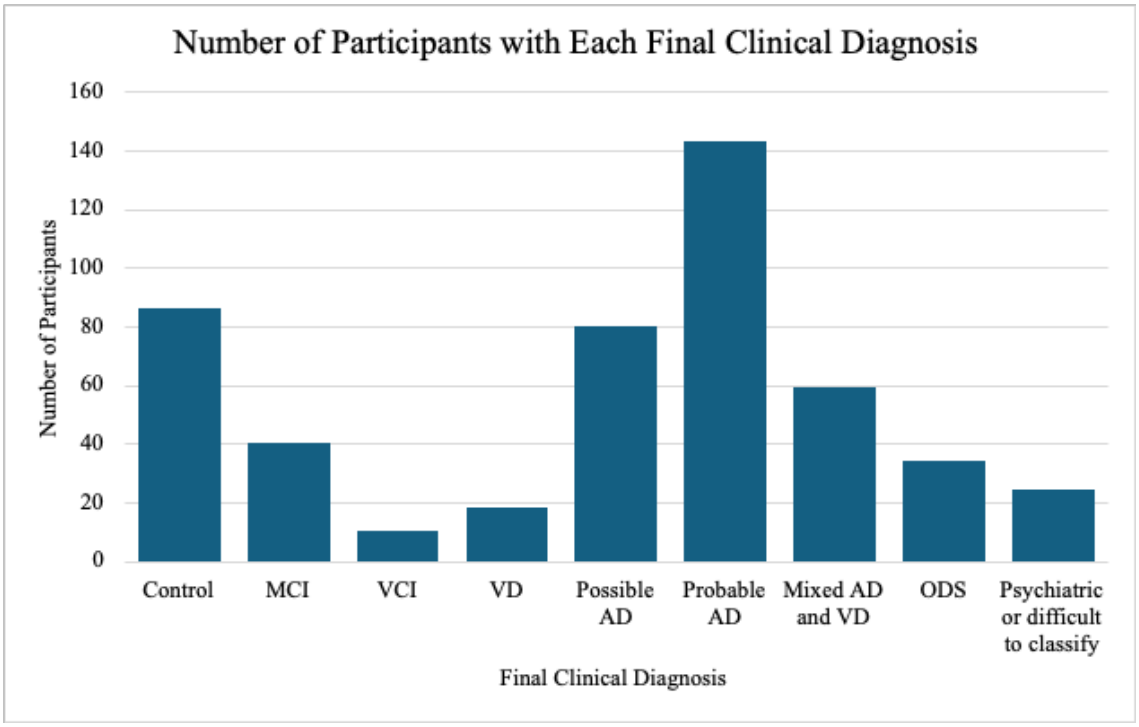


Figure 6.2. Final clinical diagnoses with cognitive impairment and dementia subtypes.

Out of the 494 participants, 56 (11.3%) had no significant neuropathology findings (Table 6.5, Figure 6.3). There were 278 participants (56.3%) with one neuropathology finding, and of these, 130 participants had AD only, 74 had infarct only, 21 had LBD only, 53 had another condition that could contribute to cognitive impairment.

Mixed pathology was also identified (Table 6.5, Figure 6.3). There were 125 participants (25.3%) with two neuropathology findings. These mixed findings included AD and infarct (n=54), AD and LBD (n=30), AD and Other (n=14), infarct and LBD (n=8),

infarct and Other (n=16), and LBD and Other (n=3). Additionally, there were 33 people (6.7%) with three neuropathology findings. These combinations of three types of pathology included AD, infarct, and LBD (n=18), AD, LBD, and Other (n=8), and AD, infarct, and Other (n=7). There were also two participants with four types of neuropathology findings: AD, infarcts, LBD, and another condition (which was hippocampal sclerosis in both cases).

The "Other" category included a range of neuropathology findings that could contribute to cognitive decline. Pathology findings included hippocampal sclerosis (n=37), FTD (n=16), PSP (n=7), argyrophilic grain disease (n=6), ALS, (n=4), neurofibrillary tangle only dementia (n=4), damage from past TBI (n=3), HD (n=2), CBD (n=2), MS (n=2), central pontine myelinosis (n=1), and gangliosidosis (n=1). Additionally, there were twelve participants with brain tumours, which included glioblastoma (n=5), meningioma (n=4), and metastatic tumours from cancer elsewhere in the body (n=3).

Neuropathology Findings	Participants n (%)
No significant pathology	**56 (11.3)**
One neuropathology finding	**278 (56.3)**
AD only	130 (26.3)
Infarct only	74 (15.0)
LBD only	21 (4.3)
Other	53 (10.7)
Two neuropathology findings	**125 (25.3)**
AD + infarct	54 (10.9)
AD + LBD	30 (6.1)
AD + Other	14 (2.8)
Infarct + LBD	8 (1.6)
Infarct + Other	16 (3.2)
LBD + Other	3 (0.6)
Three neuropathology findings	**33 (6.7)**
AD + infarct + LBD	18 (3.6)
AD + LBD + Other	8 (1.6)
AD + infarct + Other	7 (1.4)
Four neuropathology findings	**2 (0.4)**
AD + infarct + LBD + Other	2 (0.4)

Table 6.5. Neuropathology characteristics of all participants (n=494).

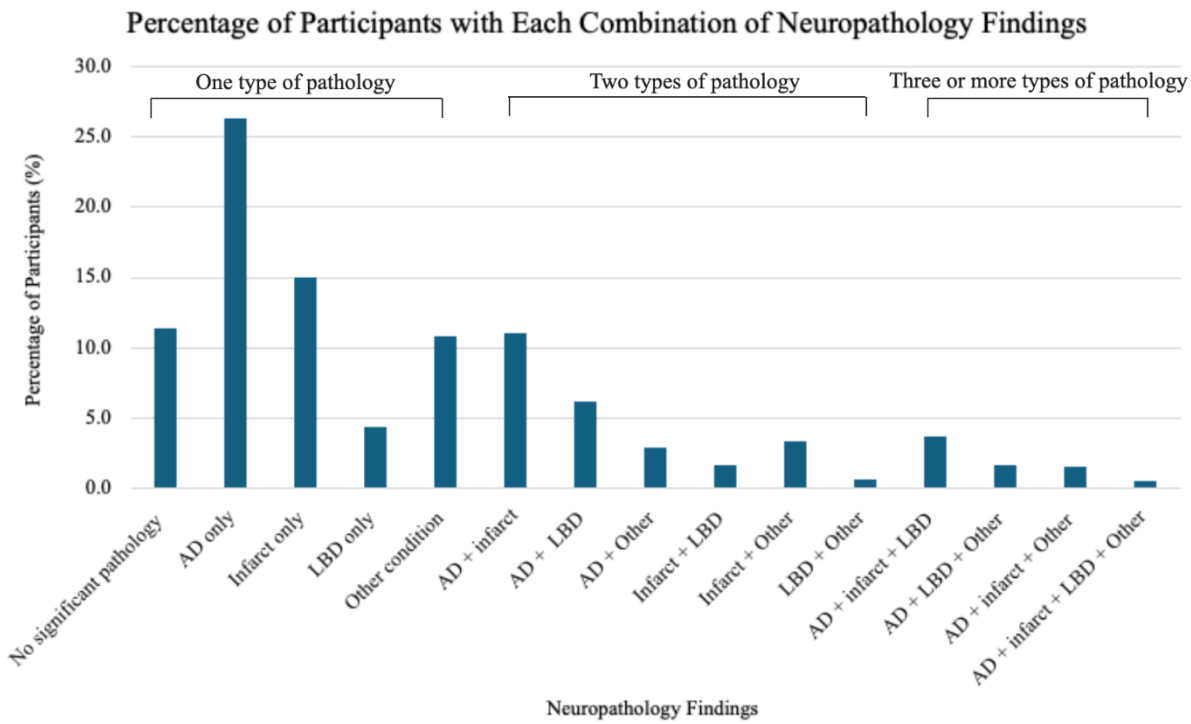


Figure 6.3. Percentage of participants with each combination of neuropathology findings (n=494).

Based on NIA-Reagan criteria, the likelihood of AD (with or without additional pathology) was low for 30 participants (6.1%), low-intermediate for 30 participants (6.1%), intermediate for 49 participants (9.9%), and high for 214 participants (43.3%) (Figure 6.4, Supplemental Table 6.1).

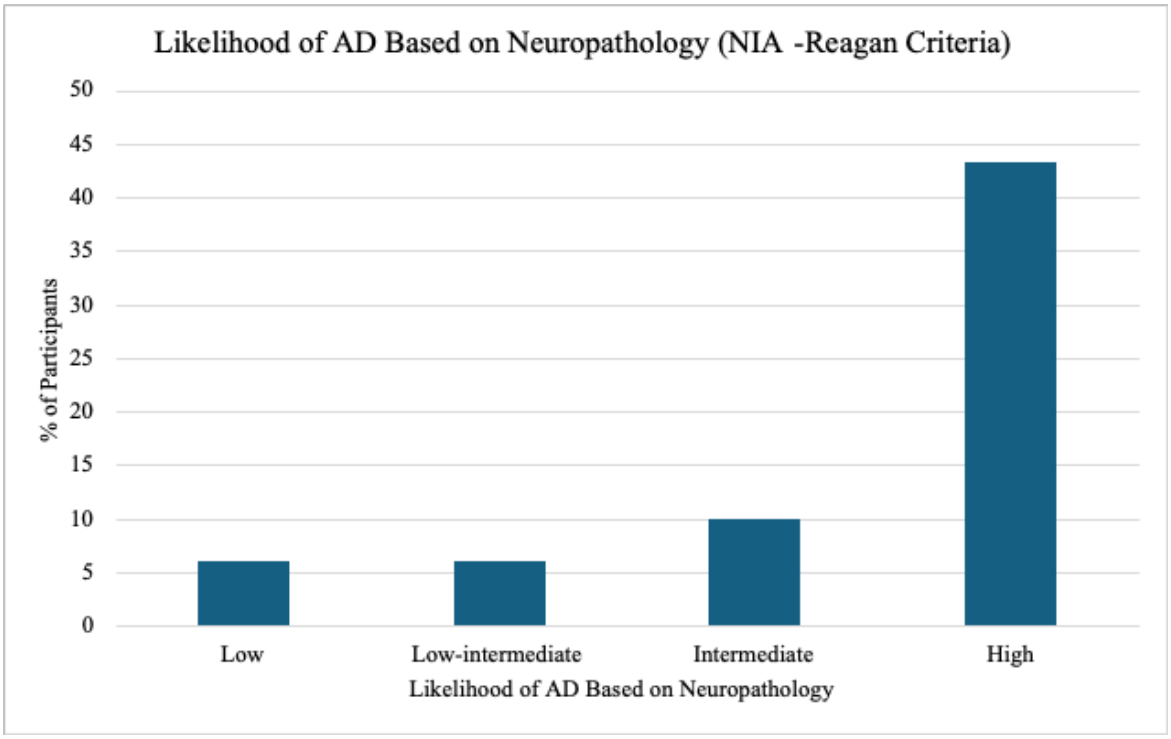


Figure 6.4. Percentage of participants with low, low-intermediate, intermediate, or high likelihood of AD based on neuropathology.

6.3.2. Comparison of Clinical Diagnoses and Neuropathology Findings

Overall, the last available clinical diagnosis was found to be supported by the neuropathology findings for 219 out of 430 cases (50.9%) (Table 6.6, Figure 6.5). Additionally, 110 clinical diagnoses (25.6%) were partially supported by the neuropathology findings, meaning that part of the clinical diagnosis was correct, but there was either additional pathology identified, or one part of the clinical diagnosis of mixed AD and VD was not supported by the neuropathology. The clinical diagnosis was unsupported in 101 cases (23.5%).

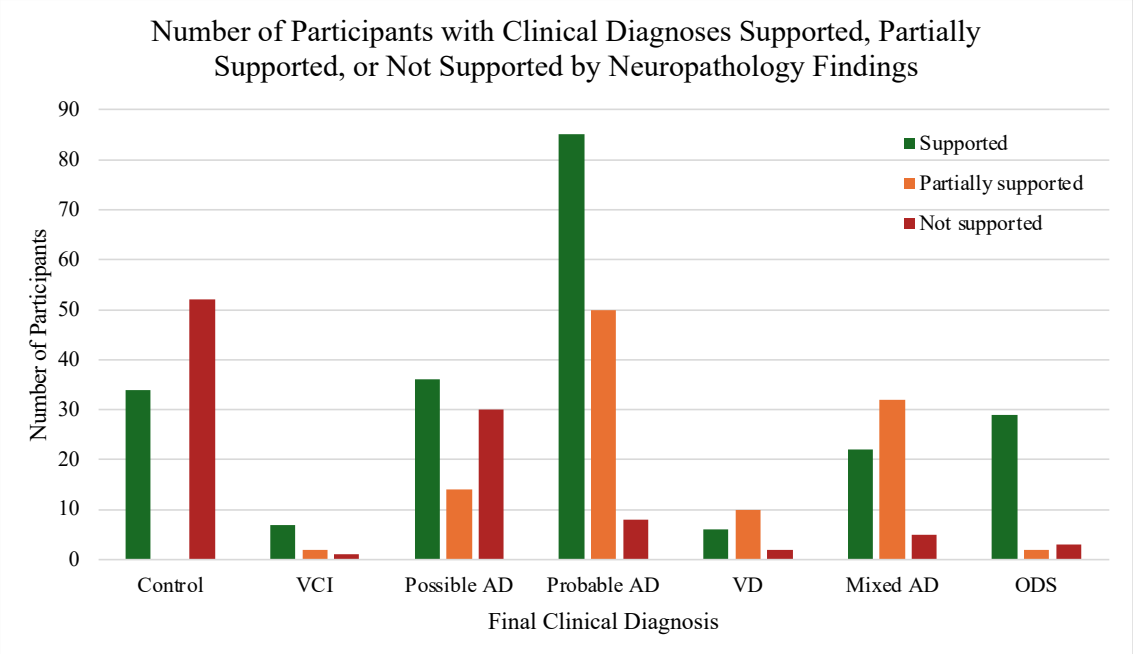


Figure 6.5. Number of participants with clinical diagnoses that are supported, partially supported, or not supported by neuropathology findings.

	Clinical Diagnosis Support from Neuropathology Findings			
Clinical Diagnosis (Subtypes)	Supported	Partially supported	Not supported	**Total**
Control, n (%)	34 (39.5)	0 (0)	52 (60.5)	**86 (20.0)**
VCI, n (%)	7 (70.0)	2 (20.0)	1 (10.0)	**10 (2.3)**
Possible AD, n (%)	36 (45.0)	14 (17.5)	30 (37.5)	**80 (18.6)**
Probable AD, n (%)	85 (59.4)	50 (35.0)	8 (5.6)	**143 (33.3)**
VD, n (%)	6 (33.3)	10 (55.6)	2 (11.1)	**18 (4.2)**
Mixed AD and VD, n (%)	22 (37.3)	32 (54.2)	5 (8.5)	**59 (13.7)**
ODS (FTD, PD/LBD, etc.), n (%)	29 (85.3)	2 (5.9)	3 (8.8)	**34 (7.9)**
Total, n (%)	**219 (50.9)**	**110 (25.6)**	**101 (23.5)**	**430 (100.0)**

Table 6.6. Clinical-neuropathological diagnostic relationships, with cognitive impairment and dementia subtypes.

The number of participants with each combination of clinical diagnosis and neuropathology findings can be seen in Table 6.7, with clinical diagnoses supported by neuropathology findings highlighted in darker grey and partially supported clinical diagnoses highlighted in light grey.

In the control group, 34 diagnoses were supported (no significant neuropathology was identified), and 52 diagnoses were not supported by neuropathology (Figure 6.5). For the participants who had clinical diagnoses of control but had neuropathology findings, three participants had pure AD pathology, 31 had infarcts only, 7 had other pathology (Table 6.7). Clinically diagnosed controls also had mixed neuropathology, as there were three participants with AD and infarcts, two with infarcts and LBD, one with infarcts and other pathology, one with AD, infarcts, and LBD, and one with AD, infarcts, and other pathology.

For the 40 participants clinically diagnosed with MCI, the neuropathology findings indicated that 12 participants had no significant pathology, four had AD only, 11 had infarcts only, three had LBD only, and three had another pathology only. Additionally, there were seven participants with mixed pathology. Given that the clinical diagnosis of MCI does not implicate a specific neuropathology finding, support from neuropathology was not assessed.

For those clinically diagnosed with VCI, the majority (n=7) had infarcts only on neuropathology examination, indicating that their cognitive impairment was driven by vascular pathology. One participant had AD and infarct findings, one had infarcts and other pathology, and one had no significant pathology.

For participants with the clinical diagnosis “possible AD or amnestic disorder or mixed AD with ODS” (which includes LBD), 45.0% had their clinical diagnosis supported by neuropathology. AD pathology only was seen in 21 participants, AD and LBD pathology was found in eleven people, four participants had AD and other pathology. For those with a partially supported clinical diagnosis (17.5%), nine people had mixed AD and infarct pathology, four had AD, infarct, and LBD pathology, and one person had AD, infarcts, LBD, and another condition. There were also 30 participants with unsupported clinical diagnoses, and their neuropathology findings included infarcts only (n=8), LBD only (n=3), other neurological conditions (n=16), infarcts and LBD (n=1), and no significant pathology (n=2).

The clinical diagnosis of probable AD made up the largest proportion of the total cohort, and 85 out of 143 participants had AD only neuropathology, supporting this clinical diagnosis. Mixed pathologies, with AD and additional pathology, was also found in 35.0% of this clinical diagnosis group. The additional pathologies found along with AD included infarcts (n=19), LBD (n=16), other conditions (n=6), infarcts and LBD (n=4), LBD and another condition (n=5). There was also one participant with AD, infarcts, LBD, and another condition. 5.6% of the probable AD clinical diagnoses were not supported by neuropathology, and these participants were found to have no significant pathology (n=2, with low to low-intermediate likelihood of AD), infarcts with another condition (n=1), or another neurological condition (n=5).

For those with a clinical diagnosis of VD, one third (n=6) had neuropathology findings of infarcts only that supported their clinical diagnosis. Ten participants had partially

supported diagnoses, with findings of infarcts and AD (n=2), infarcts and LBD (n=2), infarcts and other conditions (n=4), or infarcts, AD, and another contributing condition (n=2). Two participants who were clinically diagnosed with VD were found to have AD only on neuropathology examination.

For the mixed AD and VD clinical diagnosis group, 37.3% (n=22) had their clinical diagnosis supported by neuropathology findings of AD and infarcts. An additional 54.2% had their clinical diagnosis partially supported, as 14 participants had AD only, seven had infarcts only, two had AD and LBD findings (without infarcts), and eight had AD, infarcts, and LBD. There were also five individuals with unsupported clinical diagnoses, as they were found to have no significant pathology (n=1), LBD only (n=1), another neurological condition (n=2), and LBD and another condition (n=1).

For the 24 participants with a clinical diagnosis of “Psychiatric or difficult to classify,” the neuropathology findings included no significant pathology (n=3), AD only (n=1), infarcts only (n=4), LBD only (n=1), another neurological condition (n=7), AD and infarcts (n=1), AD and another neurological condition (n=2), infarcts with another condition (n=3), and AD, LBD and another condition (n=2).

Thirty-four participants were clinically diagnosed with “Other Dementia Syndrome (ODS),” which encompassed PD/LBD, FTD, other more rare causes of dementia, and mixed dementia subtypes not encompassed by other diagnoses (e.g., infarcts with LBD, infarcts with another condition, or LBD with another condition). 85.3% had neuropathology support for this broad clinical diagnosis. LBD pathology was found alone (n=10), with infarcts (n=2), and with other conditions (n=2). The ODS clinical diagnosis was also supported by findings of other conditions (n=13) and infarcts with other conditions (n=2). Given that AD with ODS (such as LBD) was meant to be clinically diagnosed with "possible AD or amnestic disorder or mixed AD with ODS,” the two participants with clinical diagnoses of ODS and neuropathology findings of AD with another contributing condition were considered partially supported due to the presence of LBD. There were also 3 unsupported ODS clinical diagnoses, as these participants were found to have AD pathology only (n=1), infarcts only (n=1), and no significant pathology (n=1).

	Neuropathology Findings															
Clinical Diagnosis Subtypes	No significant pathology	AD only	Infarct only	LBD only	Other	AD + infarct	AD + LBD	AD + Other	Infarct + LBD	Infarct + Other	LBD + Other	AD + Infarct + LBD	AD + LBD + Other	AD + infarct + Other	AD + infarct + LBD + Other	**Total**
Control	34	3	31	3	7	3	-	-	2	1	-	1	-	1	-	**86**
MCI	12	4	11	3	3	-	-	1	1	2	-	1	1	1	-	**40**
VCI	1	-	7	-	-	1	-	-	-	1	-	-	-	-		**10**
Possible AD	2	21	8	3	16	9	11	4	1	-	-	4	-	-	1	**80**
Probable AD	2	85	-	-	5	16	15	6	-	1	-	4	5	3	1	**143**
VD	-	2	6	-	-	2	-	-	2	4	-	-	-	2	-	**18**
Mixed AD and VD	**1**	**13**	**6**	**1**	**2**	**22**	**2**	**1**	-	**2**	**1**	**8**	-	-	-	**59**
Psychiatric or difficult to classify	3	1	4	1	7	1	-	2	-	3	-	-	2	-	-	**24**
ODS	1	1	1	10	13	-	2	-	2	2	2	-	-	-	-	**34**
Total	**56**	**130**	**74**	**21**	**53**	**54**	**30**	**14**	**8**	**16**	**3**	**18**	**8**	7	**2**	**494**

Table 6.7. Clinical-neuropathological diagnostic relationships, with cognitive impairment and dementia subtypes (clinical diagnoses supported by neuropathology findings are highlighted in dark grey, and partially supported clinical diagnoses are highlighted in light grey).

6.3.3. Neuropathology Characteristics by Final Clinical Diagnosis

6.3.3.1. Likelihood of AD Based on Neuropathology

The likelihood of AD based on the severity of neuropathology was determined using the NIA-Reagan criteria, and are presented by clinical diagnosis of control, cognitive impairment, dementia, or psychiatric or difficult to classify (Figure 6.6), and by dementia subtype (Table 6.8, Figure 6.7). Overall, 30 participants (6.1%) had a low likelihood of AD, 30 (6.1%) had low-intermediate likelihood, 49 (9.9%) had intermediate likelihood, and 214 (43.3%) had a high likelihood.

In the control clinical diagnosis group, nine participants (10.5%) had a low likelihood, seven (8.1%) had an intermediate likelihood, and one person (1.2%) had a high likelihood of AD based on the neuropathology (Figure 6.6). In the cognitive impairment group, five (10.0%) people had a low likelihood, seven (14.0%) had a low-intermediate chance, five (10.0%) had an intermediate likelihood, and four people (8.0%) had a high chance of having AD. Based on the neuropathology, AD was highly likely in 207 of the 334 (62.0%) participants with a clinical diagnosis of dementia (any subtype). Additionally, there was an intermediate likelihood of AD in 33 participants (9.9%) with a dementia diagnosis.

With regards to AD likelihood in different cognitive impairment subtypes, 10% of participants with a clinical diagnosis of MCI had a high likelihood of AD, and 10% had an intermediate likelihood (Figure 6.7). One person with a VCI diagnosis had an intermediate likelihood of AD, and none had a high likelihood. For those with a clinical diagnosis of AD, a high likelihood of AD was found in 34 (42.5%) of those with a possible AD diagnosis, 126 (88.1%) participants with a probable AD diagnosis, and 41 (69.5%) of those with a clinical diagnosis of mixed AD and VD.

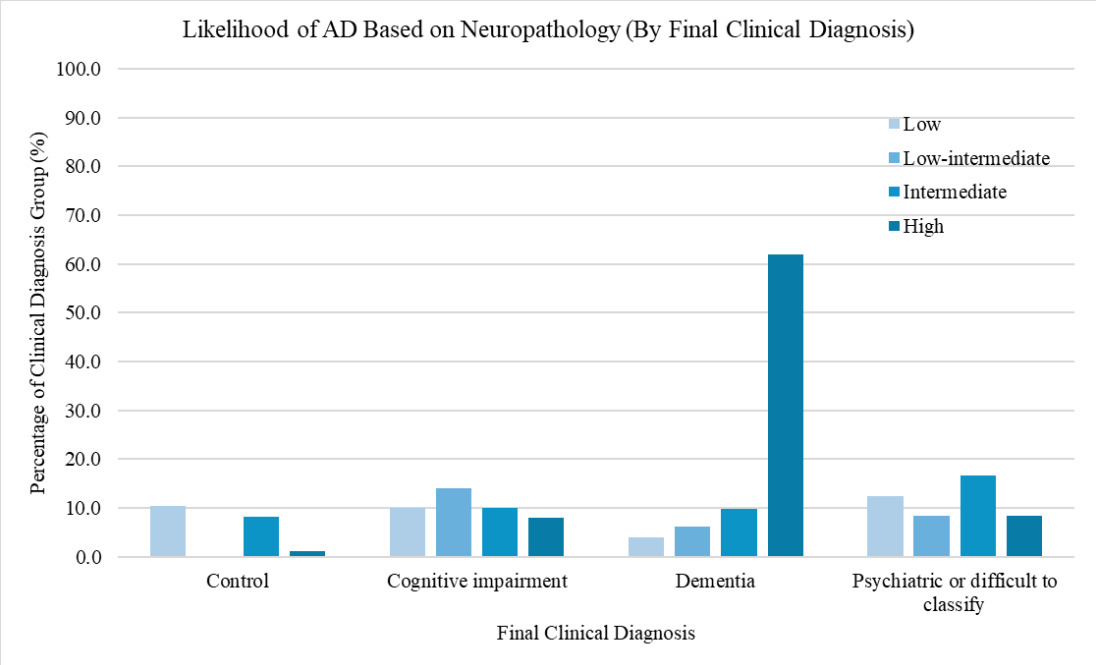


Figure 6.6. Percentage of participants in each clinical diagnosis group with low, low-intermediate, intermediate, or high likelihood of AD based on neuropathology.

Final Clinical Diagnosis (with Subtypes)	Likelihood of AD Based on Neuropathology (with or without additional pathology) n (% of clinical diagnosis group)			
	Low	**Low-intermediate**	**Intermediate**	**High**
Control (n=86)	9 (10.5)	0 (0)	7 (8.1)	1 (1.2)
MCI (n=40)	5 (12.5)	4 (10.0)	4 (10.0)	4 (10.0)
VCI (n=10)	0 (0)	3 (30.0)	1 (10.0)	0 (0)
VD (n=18)	3 (16.7)	0 (0)	3 (16.7)	3 (16.7)
Possible AD (n=80)	3 (3.8)	10 (12.5)	16 (20.0)	34 (42.5)
Probable AD (n=143)	2 (1.4)	3 (2.1)	9 (6.3)	126 (88.1)
Mixed AD and VD (n=59)	2 (3.4)	4 (6.8)	5 (8.5)	41 (69.5)
ODS (n=34)	3 (12.5)	4 (16.7)	0 (0)	3 (12.5)
Psychiatric or difficult to classify (n=24)	3 (8.8)	2 (5.9)	4 (11.8)	2 (5.9)
Total with AD likelihood n (% of total cohort)	**30 (6.1)**	**30 (6.1)**	**49 (9.9)**	**214 (43.3)**

Table 6.8. Likelihood of AD based on neuropathology findings (NIA-Reagan Criteria).

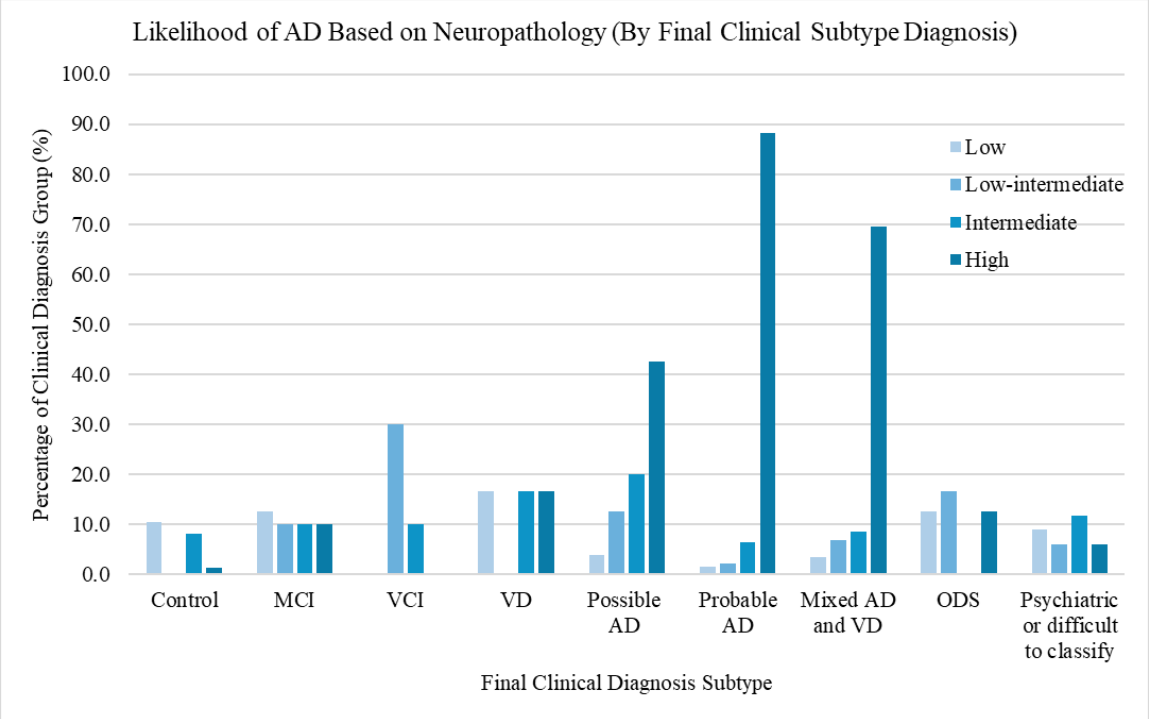


Figure 6.7. Percentage of participants in each clinical diagnosis subtype group with low, low-intermediate, intermediate, or high likelihood of AD based on neuropathology.

6.3.3.2. Braak Neurofibrillary Tangle Stage

The distribution of Braak tangle stages in each clinical diagnosis group was also determined (Figure 6.8, Supplemental Table 6.2). The largest proportion of controls were in Stage I (n=25, 43.1%), followed by Stage II (n=15, 25.9%). For those with a cognitive impairment diagnosis, the most predominant tangle stages were I (n=15, 32.6%) and III (n=13, 28.3%). Participants with clinically diagnoseed dementia predominantly had Stage VI pathology (n=175, 60.1%), which is the most severe. Those with a psychiatric or difficult to diagnose clinical diagnosis most often had Stage II tangles (n=4, 33.3%), but participants had a range of stages.

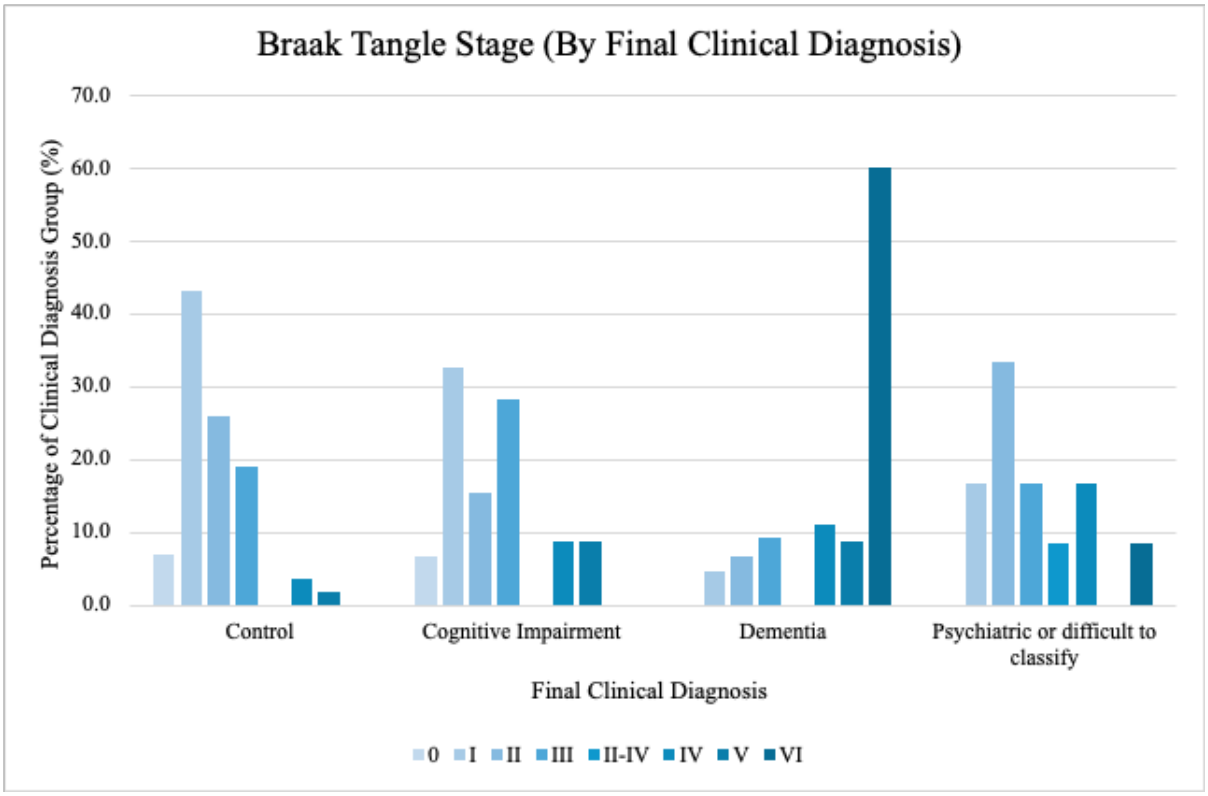


Figure 6.8. Percentage of participants in each clinical diagnosis group in each Braak tangle stage.

When looking at the Braak Tangle stages grouped by clinical diagnosis subtype, Stage VI pathology was most common in those with possible AD, probable AD, and mixed AD and VD (Figure 6.9, Supplemental Table 6.3). However, some neurofibrillary tangle pathology was seen across all control, cognitive impairment, and dementia subtypes.

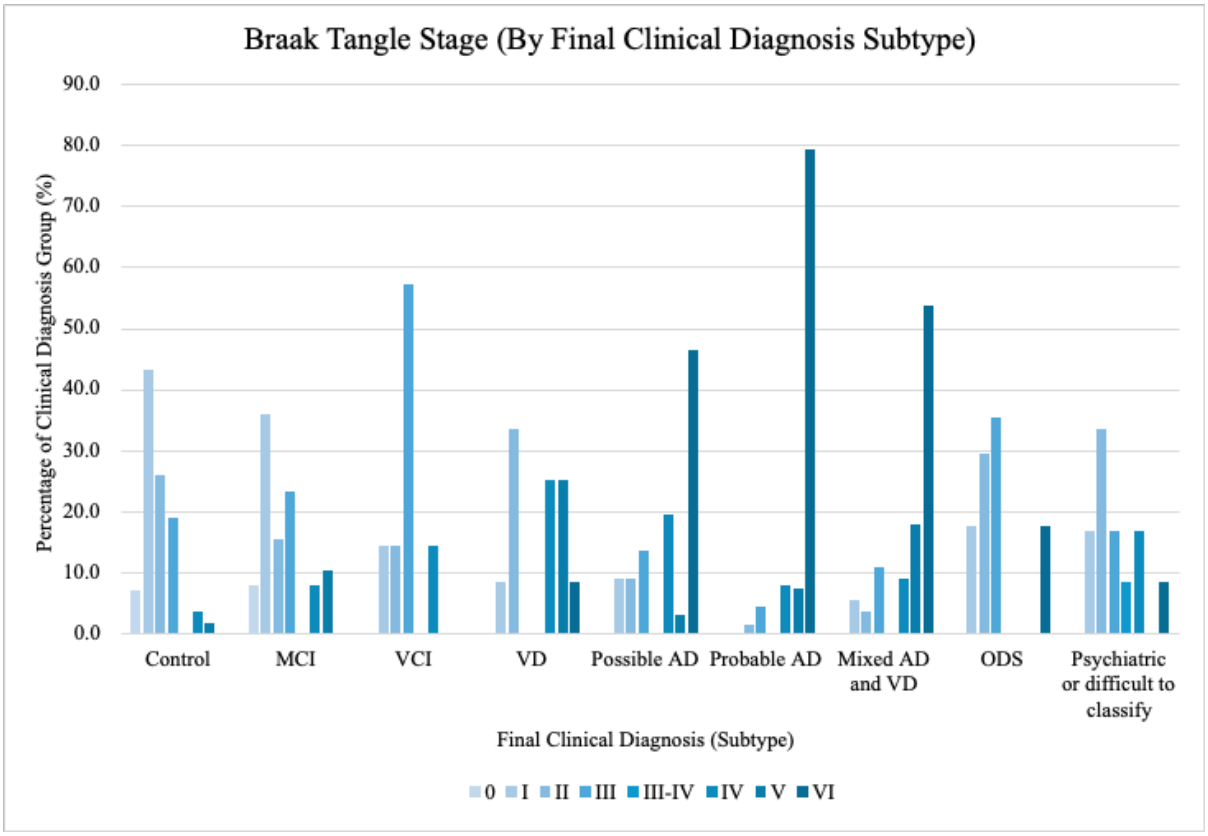


Figure 6.9. Percentage of participants in each clinical diagnosis subtype group in each Braak tangle stage.

6.3.3.3. CERAD Scores

Out of the total of 233 participants (47.2% of total cohort) who had a CERAD score recorded in their pathology diagnoses, 68 had no plaques (CERAD score of 0), 49 had sparse neuritic plaques (CERAD score of 1), 24 had a moderate density of neuritic plaques (CERAD score of 2), and 92 had a high density of neuritic plaques (CERAD score of 3) (Figure 6.10, Supplemental Table 6.4).

When looking at the CERAD scores grouped by final clinical diagnosis, the majority of the controls had no plaques (n=29, 61.7%), and there were 13 participants with sparse plaques, as well as five with a moderate density (Figure 6.10). Most of the cognitive impairment clinical diagnosis group had no plaques (n=15, 45.5%) or sparse plaques (n=13, 39.4%), while two people had a moderate density and had a high density. In the dementia group, 60.5% (n=89) had a high density of neuritic plaques. The psychiatric or difficult to classify participants had no neuritic plaques (n=4, 66.7%) or sparse plaques (n=2, 33.3%). Because relatively few participants had a CERAD score available, the distribution of scores was not assessed by dementia subtype.

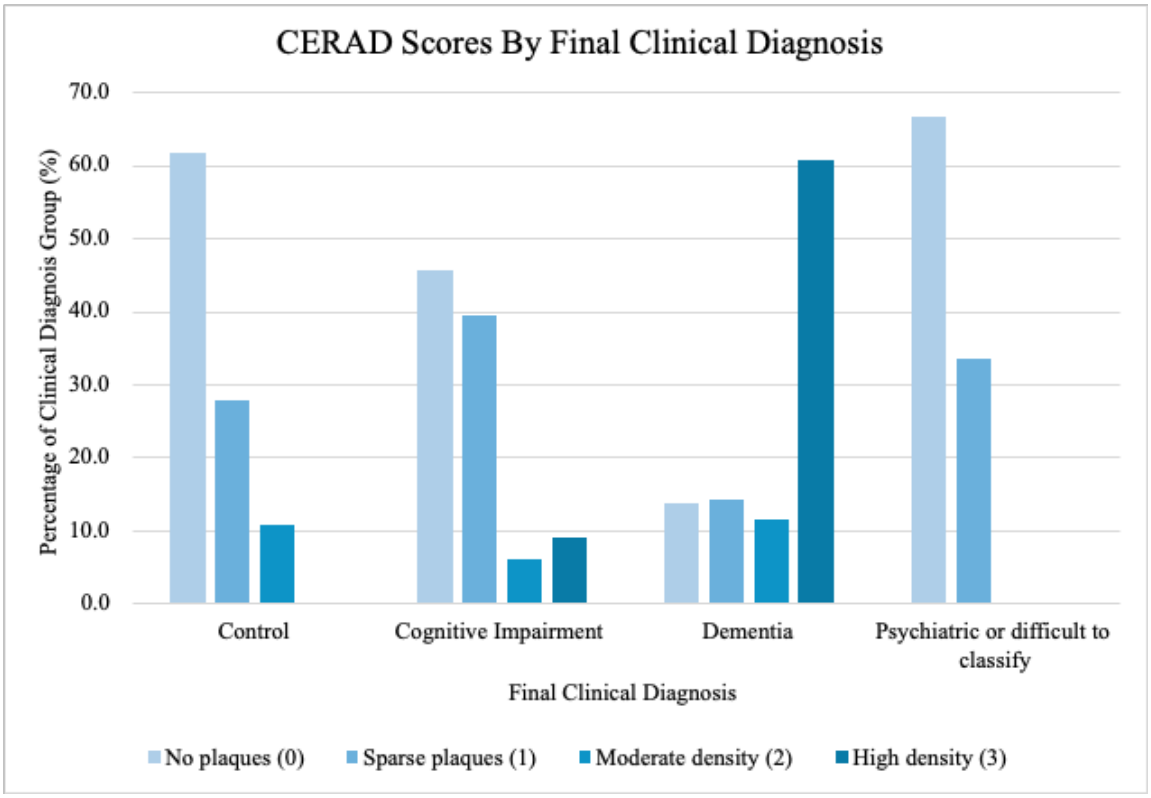


Figure 6.10. Bar chart showing the number of participants with each Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score, grouped by final clinical diagnosis.

6.3.3.4. Lewy Body Pathology

In total, 18.6% of all participants (n=92) had LBD neuropathology findings. Clinically, these participants were diagnosed as controls (n=6), with cognitive impairment, (n=6), with dementia (n=77), and with a psychiatric or difficult to classify condition (n=2) (Supplemental Table 6.5). Although the brain region where the LBD was localized was not specified for all participants, the most common location was the neocortex (LBD was found here in 14 participants with dementia and three with cognitive impairment), followed by the limbic system (LBD was found here for 12 participants with dementia and one control) (Supplemental Table 6.6).

Lewy Body pathology was found in participants with all clinical diagnoses, except for VCI (Figure 6.11). The clinical diagnosis subtype with largest percentage of participants with LBD was ODS, which includes the diagnosis of PD/LBD. 47.1% of participants with ODS (n=16) had LBD. This was followed by the "Possible AD or amnestic disorder or mixed AD with ODS" group (which includes AD with PD/LBD clinical diagnoses), which had LBD findings in 26.3% of participants (n=21). About 20% of the probable AD (n=26) and mixed AD and VD (n=12) clinical diagnosis groups also had LBD findings.

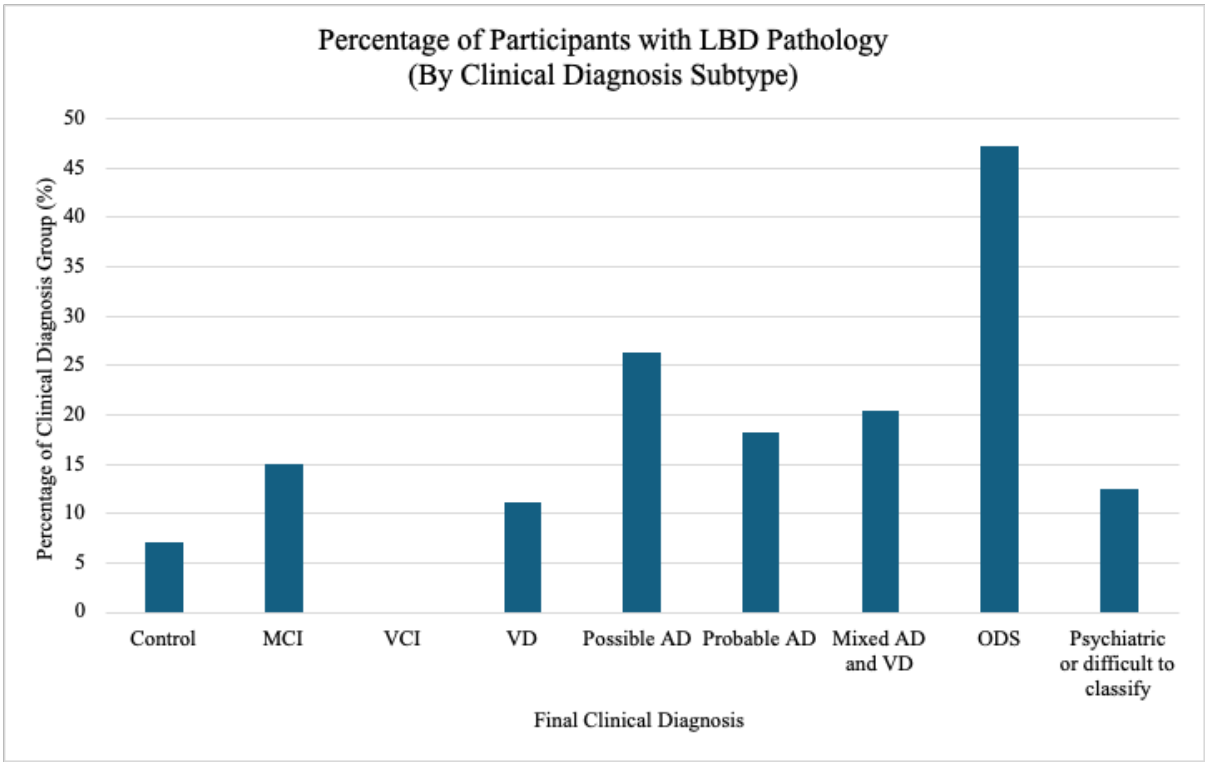


Figure 6.11. Percentage of participants with each final clinical diagnosis with PD/LBD neuropathology.

6.3.3.5. Vascular Conditions

Information on microinfarcts, lacunar infarcts, and larger infarcts was also extracted from the neuropathology records (Table 6.9, Figure 6.12, Supplemental Tables 6.7 to 6.8). Overall, 26.7% of the cohort had microinfarcts, 9.9% had lacunar infarcts, and 13.6% had infarcts > 10 mm in size (Table 6.9, Figure 6.12). All three infarct types were found throughout all of the clinical diagnosis groups. The clinical groups with greatest proportions of participants with microinfarcts were VD (n=12, 66.7%), mixed AD and VD (n=30, 50.8%), and VCI (n=5, 50.0%). Microinfarcts were also found in around 35% of participants with clinical diagnoses of control, MCI, and psychiatric or difficult to classify, as well as 21.3% of participants with possible AD and 10.5% of those with probable AD.

Lacunar infarcts were less common overall but were found in 27.8% of those clinically diagnosed with VD and 20.0% of VCI participants (Table 6.9, Figure 6.12). Additionally, lacunar infarcts were found in between 10 to 15% of participants with a clinical diagnosis of control, MCI, possible AD, mixed AD and VD, and psychiatric or difficult to classify.

Larger infarcts (> 10 mm) were found in one third of participants with a VD diagnosis (n=6), half of participants with VCI (n=5), and 27.1% of participants with mixed AD and VD (n=16) (Table 6.9, Figure 6.12). These infarcts were also found in participants without vascular clinical diagnoses, including 19.8% of controls (n=17), 8.8% of those with probable AD (n=7), and 4.9% of with probable AD (n=7).

Final Clinical Diagnosis	Infarct Neuropathology Findings		
	Microinfarcts	Lacunar infarcts	Infarcts > 10 mm
Control (n=86)	28 (32.6)	9 (10.5)	17 (19.8)
MCI (n=40)	14 (35.0)	6 (15.0)	4 (10.0)
VCI (n=10)	5 (50.0)	2 (20.0)	5 (50.0)
VD (n=18)	12 (66.7)	5 (27.8)	6 (33.3)
Possible AD (n=80)	17 (21.3)	9 (11.3)	7 (8.8)
Probable AD (n=143)	15 (10.5)	4 (2.8)	7 (4.9)
Mixed AD and VD (n=59)	30 (50.8)	8 (13.6)	16 (27.1)
ODS (n=34)	3 (8.8)	3 (8.8)	2 (5.9)
Psychiatric or difficult to classify (n=24)	8 (33.3)	3 (12.5)	3 (12.5)
Total (n=494)	**132 (26.7)**	**49 (9.9)**	**67 (13.6)**

Table 6.9. Microinfarct, lacunar infarct, and infarct > 10 mm neuropathology findings by final clinical diagnosis.

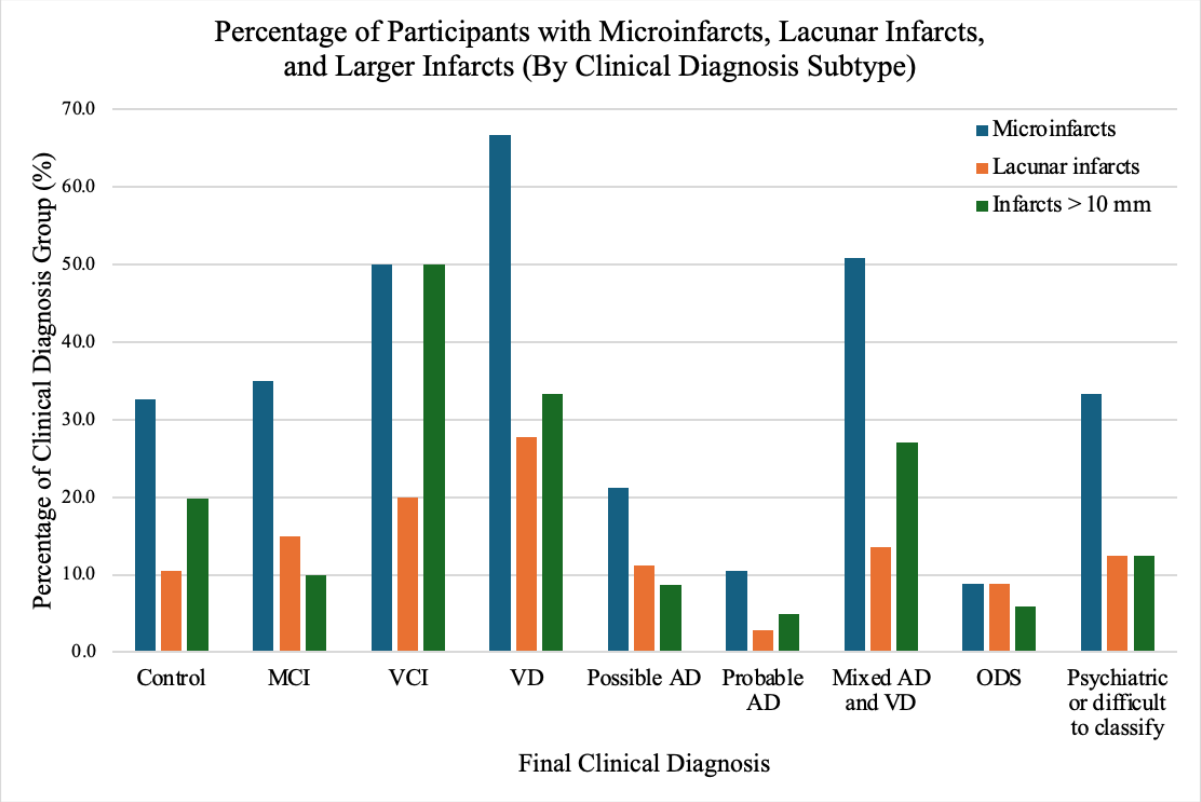


Figure 6.12. Percentage of participants in each clinical diagnosis group with microinfarcts, lacunar infarcts, and infarcts >10 mm.

Although only infarcts were considered in the comparison of clinical diagnoses and neuropathology support, the neuropathology records were also searched for the following vascular conditions that can contribute to cognitive decline: moderate to severe cerebral amyloid angiopathy, non-amyloid small vessel disease (SVD), atherosclerosis, and arteriosclerosis (Table 6.10, Figure 6.13, Supplemental Table 6.9). Overall, 98 participants (19.8%) had moderate to severe amyloid angiopathy, 123 (24.9%) had moderate to severe SVD, 84 (17.0%) had moderate to severe atherosclerosis, and 133 (26.9%) had moderate to severe arteriosclerosis (Table 6.10).

Looking by clinical diagnosis subtype, amyloid angiopathy was found in the largest proportion of participants with a mixed AD and VD diagnosis, (n=25, 42.4%), followed by those with a VD diagnosis (n=10, 55.6%), participants with a probable AD diagnosis (n=37, 25.9%), and participants with MCI (n=9, 22.5%). Moderate to severe non-amyloid SVD was most common in participants with a clinical diagnosis of VD (n=10, 55.6%), as was arteriosclerosis (n=12, 66.7%). Atherosclerosis was found in the largest proportion of those with a VCI (n=5, 50.0%), VD (n=7, 38.9%), and mixed AD and VD diagnosis (n=20, 33.9%).

Final Clinical Diagnosis	**Vascular Condition Neuropathology Findings** n (% of clinical diagnosis group)			
	Moderate to severe cerebral amyloid angiopathy	**Moderate to severe non-amyloid SVD**	**Moderate to severe atherosclerosis**	**Moderate to severe arteriosclerosis**
Control (n=86)	2 (2.3)	21 (24.4)	13 (15.1)	22 (25.6)
MCI (n=40)	9 (22.5)	16 (40.0)	10 (25.0)	12 (30.0)
VCI (n=10)	2 (20.0)	4 (40.0)	5 (50.0)	4 (40.0)
VD (n=18)	5 (27.8)	10 (55.6)	7 (38.9)	12 (66.7)
Possible AD (n=80)	13 (16.3)	18 (22.5)	7 (8.8)	20 (25.0)
Probable AD (n=143)	37 (25.9)	27 (18.9)	17 (11.9)	30 (21.0)
Mixed AD and VD (n=59)	25 (42.4)	22 (37.3)	20 (33.9)	22 (37.3)
ODS (n=34)	3 (8.8)	3 (8.8)	3 (8.8)	6 (17.6)
Psychiatric or difficult to classify (n=24)	2 (8.3)	2 (8.3)	2 (8.3)	5 (20.8)
Total (n=494)	**98 (19.8)**	**123 (24.9)**	**84 (17.0)**	**133 (26.9)**

Table 6.10. Moderate to severe vascular condition neuropathology findings by final clinical diagnosis.

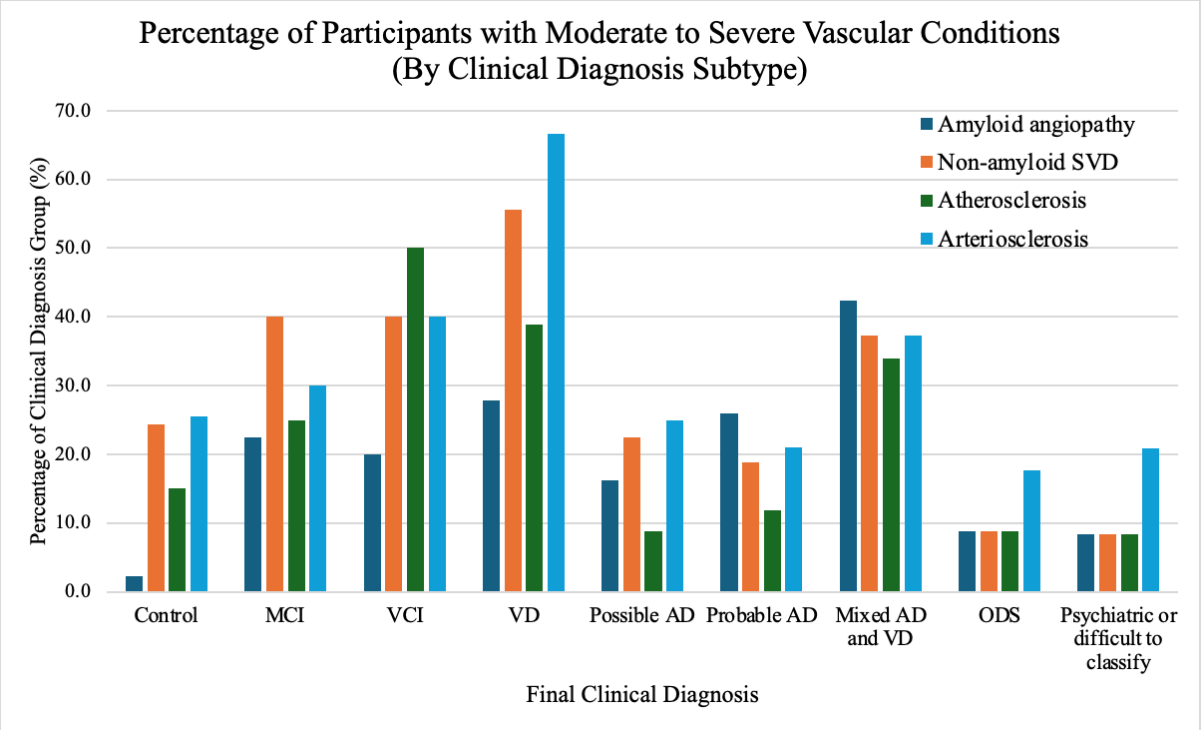


Figure 6.13. Percentage of participants in each clinical diagnosis group with moderate to severe amyloid angiopathy, non-amyloid SVD, atherosclerosis, and arteriosclerosis.

6.4. Discussion

This study compared the clinical diagnoses and neuropathology findings from 494 participants from the OPTIMA, Challenge, and LEAD cohorts. One of the main findings was that mixed dementia pathology is common and not always captured by the clinical diagnosis, supporting findings from previous clinicopathologic studies (176, 177). While 56.3% had one significant pathology finding, about one quarter had two pathology findings, and about 10% of the cohort had three or more pathology findings. The most common mixed pathology was AD with infarcts, followed by AD with LBD and the combination of AD, infarcts, and LBD. Overall, however, there was good face validity, as the neuropathology was generally in keeping with the main clinical diagnosis.

Looking at the Braak tangle stages and the CERAD amyloid plaque scores (two hallmark pathologies of AD) by clinical diagnosis subtype, it is evident that clinical diagnoses of possible and probable AD are capturing those with more severe pathology. However, these clinical diagnoses of AD can miss additional pathology, similarly to the findings of a previous clinicopathologic study (179). 11% of those clinically diagnosed with probable AD had AD findings along with infarcts, and another 10% had AD and LBD pathology. These findings support previous studies showing that many patients with AD also have infarcts or Lewy Bodies (176, 179, 180).

Additionally, although the sample sizes for the vascular dementia subtypes were smaller than those for AD, the clinical diagnoses did seem to capture vascular pathologies, as these groups had the largest proportions of infarcts, SVD, atherosclerosis, and arteriosclerosis. However, these vascular pathology findings across all subtypes also

highlights the extent of mixed pathologies, as they were also found in controls, those with MCI, and throughout the non-vascular dementia subtype clinical diagnoses.

Importantly, there were a total of 101 cases where the clinical diagnosis was not supported by the neuropathology findings, and there are various explanations as to why this could be the case. For those with a clinical diagnosis of a specific dementia subtype who had a different neuropathology than expected, this could be due to overlap between the symptoms of different dementia subtypes, because the clinical assessments used did not pick up on subtle differences between subtypes, or perhaps because the clinical presentation was milder or difficult to categorize (170).

There were also 52 participants who were clinically diagnosed as controls were found to have pathology postmortem. While about 40% of controls had no significant neuropathology findings, as their clinical diagnosis would predict, the remaining 60% were found to have infarcts, intermediate to high likelihood of AD, LBD, other conditions, and various combinations of these pathologies. Potential explanations of the pathology seen in those presumed to have normal cognitive function could be that a significant period of time had elapsed between the last clinical diagnosis and their death, during which they developed dementia. These participants could also have had preclinical dementia when these were seen for their last study visit, at which point there would not be sufficient deficits to warrant a diagnosis. It is also possible that no cognitive deficits were detected because they had high cognitive reserve that was compensating for the pathology, as might be suggested by the high NART scores previously described in Chapter 4 (181). The analysis of time elapsed between last diagnosis and death, as well as investigations into other possible explanations for unsupported clinical diagnoses, could be investigated in the future.

Although comparisons of clinical and pathological diagnoses of dementia have been done before, one of the strengths of this study is the large sample size of participants who had both extensive clinical assessments while they were alive and neuropathology examination of their brains after death. Another strength of this analysis was the identification of a wide range of clinical and pathological findings. These included the more common AD, infarct, and LBD pathologies, in addition to less common conditions like FTD, hippocampal sclerosis, and corticobasal degeneration. As previous research has indicated that a range of rarer pathologies are associated with dementia, this heterogeneous cohort could be used to assess the impact of different combinations of common and rare pathology in the future (182).

One limitation of this study arises from the heterogeneous neuropathology methods used over the course of the study, as was described in Chapter 2 (see Supplemental Table 2.1). To address this problem in the future it would be beneficial to re-ascertain the neuropathology findings for brains currently in the Oxford Brain Bank. Standardised neuropathology criteria for vascular dementia, such as those delineated by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network in 2006 (183). Re-examining the brain pathology using a consistently applied method would ensure that the pathology is investigated in the same way across participants, which would enable more confidence in the reliability of the clinicopathologic comparison.

Another limitation of this analysis is that the cohort may not be representative of the broader population, as the OPTIMA, Challenge, and LEAD cohorts were not random samples, but rather a group of volunteer participants assembled through a range of recruitment methods (see Chapter 2). This is also a limitation in clinicopathologic studies in general, as there could be a selection bias in those who end up having an autopsy and donating their brains (184).

In the future, further exploration could be done to elucidate differences between those who were correctly and incorrectly diagnosed with different dementia subtypes during life. This could be accomplished using the extensive longitudinal data collected in the OPTIMA and related cohorts, including cognitive assessments, medical examinations, imaging, and postmortem brain tissue for additional pathology analysis. This research would build on previous work looking for differences in patients with distinct dementia subtypes diagnoses that have been verified postmortem (185).

Given the prevalence of a range of mixed pathologies, it would be interesting to investigate how different combinations of dementia subtypes influence the patients' clinical presentations and rate of progression. Future studies could also investigate the relationship between APOE genotype, which is a known risk factor for dementia, and the neuropathology findings in this cohort. It could also be worthwhile to investigate brain resilience and cognitive reserve by identifying differences between those who had significant pathology but were diagnosed as controls near their time of death and those with a similar level of pathology who were diagnosed with a cognitive impairment or dementia. Additionally, this data could be used to build on previous studies investigating how much of the clinical presentation of participants with a cognitive impairment or dementia at death is explained by the observed pathology and whether previously uncaptured pathology or processes are important (186). The range of clinical diagnoses in the OPTIMA, Challenge, and LEAD cohorts could enable comparison of more dementia subtypes than previous studies. Determining distinguishing factors between these patients could help refine clinical diagnostic guidance for dementia subtypes in the future.

CHAPTER 7: Conclusions and Future Directions

7.1. Conclusion

In summary, this project accomplished the objectives of assembling and cleaning the large Oxford Project to Investigate Memory and Ageing (OPTIMA), Challenge, and Longitudinal Early Alzheimer's Disease cohort (LEAD) datasets, and integrating additional data from the Brains for Dementia Research (BDR) study and the UK Brain Bank Network. A range of discrepancies in the data and missing data were resolved, and hand-searching of study records was done to extract further information. The overlap between the three cohorts was established and the total number of individuals across all cohorts was determined, as this was not understood previously. Then, the cleaned data was analysed to determine the demographic characteristics, length of follow-up, availability of imaging and biological sampling, and neuropathology findings. Using serial cognitive assessment scores, as well as some additional scores from further BDR follow-up, the rate of cognitive decline was established for each participant. Finally, an analysis of the alignment between the clinical and neuropathology diagnoses was completed, highlighting the extent of mixed pathology in the cohorts.

7.2. Strengths

There are a range of strengths of the OPTIMA, Challenge and LEAD cohorts highlighted by this project. One clear strong suit of these studies is their longitudinal nature. Many participants returned for years with their study partners to complete cognitive assessments, imaging, blood and CSF sampling, and more at their comprehensive visits. With some participants completing cognitive assessments for over twenty years, the data provides a long and detailed picture of their experience of aging. Additionally, some participants had even more extensive follow-up by joining an additional cohort, the BDR, enabling an even more complete picture of their trajectories as they aged.

An additional strength of OPTIMA, Challenge, and LEAD is that, due to the similarity of the methods for the three cohorts, as well as some overlap between the participants, they can be treated as one unified cohort, as was done in Chapters 5 and 6 of this thesis. This melding of the cohorts allows for a larger sample size, enabling more statistical power, and more comprehensive follow-up for those who began in OPTIMA and Challenge and subsequently joined LEAD and/or the BDR.

Another advantage is the large collection of postmortem brains and neuropathology information. The combination of comprehensive cognitive and clinical assessment during life with the neuropathological evaluation of over 500 participants' brains provides a unique resource by which researchers will be able to answer challenging questions about the prevention, diagnosis, and treatment of dementia.

The OPTIMA study was initiated with the intention of promoting the understanding of the causes, treatment, and prevention of dementia. While progress has been made in the investigation of dementia, these aims remain current priorities in the field, as researchers continue to search for ways to treat, cure, and prevent dementia (187). This work to fully

describe the OPTIMA, Challenge, and LEAD cohorts, and the unified cohort of the individuals contained across the three cohorts, will facilitate more efficient use of this important resource to deepen our understanding of this devastating syndrome that impacts so many patients and families.

7.3. Limitations

Despite the strengths of the OPTIMA, Challenge, and LEAD cohorts, various limitations exist. Because recruitment for the study seems to have occurred in a fairly ad hoc manner in the 1980s, without strict inclusion and exclusion criteria, there is heterogeneity within the participants. For example, the young participants who were recruited (under the age of 50-60), particularly those who were controls and did not have early onset cognitive decline, will likely need to be excluded from future studies looking at dementia in older adults. Moreover, due to the small numbers of patients with rare neurological diseases, such as Creutzfeldt-Jakob disease (CJD) or Huntington's disease (HD), there is likely not sufficient power to study these conditions in-depth.

Another limitation of OPTIMA and its related cohorts is the number of patients lost to follow-up and missing data for unknown reasons. Because many of the participants had debilitating dementia, it is likely that some were unable to continue completing cognitive assessments or attending study sessions due to the severity of their condition. Although home visits were used to try to avoid missing follow-up, some participants were still lost. If those with more severe cognitive impairments were lost to follow-up, the cohorts' data could be biased towards those with milder to moderate dementia severity.

Additionally, because the participants were recruited from the Oxford area, this may be a largely homogenous cohort with regards to socioeconomic status, given that Oxford is a predominantly affluent area. Another limitation is that no data regarding race and ethnicity was collected for the OPTIMA, Challenge, and LEAD cohorts. However, for those who joined the BDR cohort subsequently and had their ethnicity recorded, the majority identified as "British White." This limited data suggested that the cohorts were not very diverse with regards to race and ethnicity, though this cannot be determined conclusively due to the lack of data for most participants.

An additional limitation that became apparent through this analysis is that a large portion of the OPTIMA cohort already had a cognitive impairment at their first visit. For these participants, their cognitive assessments and imaging data, as well as their blood and CSF samples, cannot be used for studies aiming to identify signs that could predict dementia before onset. Only the smaller subsets of patients who converted from control to a dementia diagnosis, or from a mild or vascular cognitive impairment to a dementia diagnosis, during the study period could be used to investigate this type of research question related to dementia progression.

Another potential limitation of the OPTIMA cohort is that, because the study began in the 1980s and continued for multiple decades, there were various changes in study protocol over time as new guidelines, cognitive assessments, and standard practices were released over the course of the study. Therefore, the types of data available for the participants varies

depending on when they joined the study or how long they continued to do follow-up. While some approaches remained constant, such as the use of the Mini Mental State Examination (MMSE) cognitive assessment, some metrics were added later and therefore were completed by fewer participants and not as repeatedly. Moreover, the neuropathology information currently available, such as that used in Chapter 6, was impacted by the changing methods over time.

7.4. Future Directions

Due to the longitudinal and comprehensive data collections available for the OPTIMA, Challenge, and LEAD cohorts, there are many potential future directions that researchers can take to use this resource and further our understanding of aging and dementia.

Given the extensive nature of the follow-up for participants who joined OPTIMA and its related cohorts, as well as the multimodal nature of the data, a future study could look at the difference between patients whose dementia progressed slowly versus quickly. For example, within the group of participants with a clinical diagnosis of Alzheimer's disease, it would be worthwhile to evaluate whether there were specific factors that predicted rapid or gradual cognitive decline.

The blood, cerebrospinal fluid (CSF), and postmortem brain samples from OPTIMA participants could also be used to help discover novel biomarkers for dementia subtypes. The data from participants in these cohorts who began as controls or with a cognitive impairment and subsequently developed dementia are especially valuable, as their early data could be used to search for early biomarkers that could predict future dementia onset. Particularly if blood or CSF markers could be identified, this would help improve diagnostic accuracy in life. Moreover, once more treatments for specific dementia subtypes are developed and become available, better dementia biomarkers will enable patients to receive appropriate treatment for their condition as soon as possible and enable physicians to monitor patients' responses to treatment (103).

Given the large number of participants who donated their brains, these cohorts have significant potential to continue making an impact in neuropathology-related dementia research. There have been many advances in methods in the field of neuropathology since the OPTIMA cohort began in the 1980s. Thus, further research can be done to characterise the neuropathology of these participants, particularly those who passed away early in the study when neuropathology methods were less advanced.

The OPTIMA, Challenge, and LEAD cohorts' extensive cognitive, clinical, imaging, neuropsychology, and neuropathology information has already expanded our understanding of dementia risk, diagnosis, and assessment. However, there are many unanswered questions that remain to be explored and answered for the benefit of our aging population.

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Chapter 2 Supplemental Files: Neuropathology Methods																		
	Stain																	
Brain region	**H&E**						**AT8**						**4G8**					
	1995 - 1996	1997	1998 - 2008	Mid-2008 - 2009	2010	2011-2013	1995 - 1996	1997	1998 - 2008	Mid-2008 - 2009	2010	2011 - 2013	1995 - 1996	1997	1998 - 2008	Mid-2008 - 2009	2010	2011 - 2013
Sup and mid temporal	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	-	-	-	-	✓	✓
Middle frontal	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	-	-	-	-	✓	✓
Inf parietal	✓	✓	✓	-	✓	-	-	-	✓	-	-	-	-	-	-	-	-	-
Parietal area 7	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sup parietal	-	-	-	✓	✓	✓	-	-	-	✓	✓	✓	-	-	-	-	✓	✓
Occipital area 19	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant cingulate	✓	✓	✓	✓	✓	✓	-	-	-	-	✓	✓	-	-	-	-	✓	✓
Ant caud/put	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Frontal periventricular white matter	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal periventricular white matter	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital periventricular white matter	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Amygdala/entorhinal cortex	✓	✓	✓	✓	✓	✓	-	-	-	-	✓	✓	-	-	-	-	✓	✓
Ant hippo	✓	✓	✓	✓	✓	✓	-	-	-	✓	✓	✓	-	-	-	-	✓	✓
Post hippo at LGN	✓	✓	✓	✓	✓	✓	-	-	✓	✓	✓	✓	-	-	-	-	✓	✓

Thalamus	✓	✓	✓	✓	✓	✓	-	-	-	-	-	✓	-	-	-	-	✓	✓
Midbrain	✓	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	✓	✓
Pons	✓	✓	✓	✓	✓	✓	-	-	-	-	✓	✓	-	-	-	-	-	✓
Medulla	✓	✓	✓	✓	✓	✓	-	-	-	-	✓	✓	-	-	-	-	-	✓
Cerebellum	✓	✓	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-	✓	✓
Ant basal forebrain	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Post basal forebrain	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insula	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Motor cortex	-	✓	✓	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-
Occipital calcarine cortex	-	-	-	✓	✓	✓	-	-	-	-	-	✓	-	-	-	-	✓	✓
Basal ganglia	-	-	-	✓	✓	✓	-	-	-	-	-	✓	-	-	-	-	✓	✓
Deep frontal white matter	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-
Deep occipital white matter	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-

	Stain																	
Brain region	**α-synuclein** *done on select cases starting in 2003						**LFB/PAS**						**LFB/CV**					
	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013
Sup and mid temporal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Middle frontal	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-
Inf parietal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal area 7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sup parietal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital area 19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant cingulate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant caud/put	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Frontal periventricular white matter	-	-	-	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-
Parietal periventricular white matter	-	-	-	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-
Occipital periventricular white matter	-	-	-	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-
Amygdala/entorhinal cortex	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant hippo	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Post hippo at LGN	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thalamus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Midbrain	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Pons	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medulla	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Cerebellum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant basal forebrain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Post basal forebrain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insula	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Motor cortex	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital calcarine cortex	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Basal ganglia	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Deep frontal white matter	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	✓	✓
Deep occipital white matter	-	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	✓	✓

	Stain																	
Brain region	**Cross silver stain (Cross)**						**Methenamine Silver (MS)**						**Congo Red (CR)**					
	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013
Sup and mid temporal	✓	-	-	-	-	-	✓	✓	✓	✓	-	-	✓	✓	✓	✓	✓	-
Middle frontal	✓	-	-	-	-	-	✓	✓	✓	✓	-	-	✓	✓	✓	✓	✓	-
Inf parietal	✓	-	-	-	-	-	✓	✓	✓	-	-	-	✓	✓	✓	-	-	-
Parietal area 7	✓	-	-	-	-	-	✓	-	-	-	-	-	✓	-	-	-	-	-
Sup parietal	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	✓	✓	-
Occipital area 19	✓	-	-	-	-	-	✓	✓	✓		-	-	✓	✓	✓	-	-	-
Ant cingulate	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Ant caud/put	-	-	-	-	-	-	✓	✓	✓		-	-	-	-	-	-	-	-
Frontal periventricular white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal periventricular white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital periventricular white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
amygdala/entorhinal cortex	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Amygdala/entorhinal cortex	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Ant hippo	✓	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-

Post hippo at LGN	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Thalamus	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Midbrain	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Pons	-	-	-	-	-	-	✓	✓	✓	✓	-	-	-	-	-	-	-	-
Medulla	-	-	-	-	-	-	✓	✓	✓	✓	-	-	✓	✓	✓	✓	✓	-
Ant basal forebrain	-	-	-	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-
Post basal forebrain	-	-	-	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-
Insula	-	-	-	-	-	-	✓	✓	✓	-	-	-	-	-	-	-	-	-
Motor cortex	-	-	-	-	-	-	-	✓	✓	-	-	-	-	✓	✓	-	-	-
Occipital calcarine cortex	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	✓	✓	-
Basal ganglia	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-
Deep frontal white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Deep occipital white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

	Stain																	
Brain region	**Bielschowsky silver (Biel)**						**p62**						**TDP-43** *added to select cases starting in 2007					
	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013	1995-1996	1997	1998-2008	Mid-2008-2009	2010	2011-2013
Sup and mid temporal	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Middle frontal	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Inf parietal	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal area 7	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sup parietal	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital area 19	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant cingulate	✓	✓	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant caud/put	✓	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Frontal periventricular white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal periventricular white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital periventricular white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Amygdala/entorhinal cortex	✓	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant hippo	✓	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-

Post hippo at LGN	✓	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	✓
Thalamus	✓	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Midbrain	✓	✓	-	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pons	✓	✓	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Medulla	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Cerebellum	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Ant basal forebrain	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Post basal forebrain	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Insula	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Motor cortex	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Occipital calcarine cortex	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Basal ganglia	-	-	-	✓	✓	-	-	-	-	-	-	-	-	-	-	-	-	-
Deep frontal white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Deep occipital white matter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Neuropathology methods from 2014 to present	
Brain region	**Method**
M1/S1 leg area	H&E, p62
M1/S1 hand knob	H&E, p62
Dorsolateral pre-frontal-middle frontal lobe (BA9/46), level of amygdala	H&E, AT8, 4G8, p62
Superior and middle temporal cortex (BA22/21), level of amygdala	H&E, AT8, 4G8, p62
Parietal - supramarginal gyrus (BA40)	H&E, AT8, 4G8, p62
primary visual cortex (occipital BA17), peri-striate cortex (BA18/19)	H&E, AT8, 4G8
Deep frontal white matter	H&E, LFB/CV
Deep occipital white matter	H&E, LFB/CV
Amygdala	H&E, AT8, 4G8, α-syn, TDP-43
Anterior hippocampus	H&E, AT8, 4G8
Hippocampus at LGN	H&E, AT8, 4G8, p62, α-syn, TDP-43
Midbrain at Cranial nerve III	H&E, 4G8, α-syn
Pons at locus coeruleus	H&E
Mid-lower medulla	H&E, p62, α-syn
Putamen/globus pallidus	H&E, AT8, 4G8, α-syn, TDP-43
Thalamus and STN	H&E
Dentate and cerebellar cortex	H&E, 4G8, p62
Composite spinal cord	H&E, p62, LFB/CV
Upper medulla	Embed only
Upper cervical spinal cord	

Mid-cervical spinal cord	Embed only
Upper thoracic spinal cord	
Mid-thoracic spinal cord	
Lower thoracic spinal cord	
Lumbar cord	
Lumbo-sacral	
Olfactory bulb and tract	
Optic nerve	
Internal carotid artery	
Middle cerebral artery	
Basilar artery	
M1/S1 hand knob	
M1/S1 lateral	
Orbitofrontal cortex	
Dorsolateral pre-frontal-middle frontal lobe (BA9/46), level of amygdala	
Superior and middle temporal cortex (BA22/21), level of amygdala	
Genu of corpus callosum	
Body of corpus callosum	
Splenium of corpus callosum	
Hippocampus at LGN	
Anterior caudate/putamen	
Hypothalamus/3rd ventricle	
Pulvinar	
Composite hippocampus, cerebellum, basal ganglia, frontal	

Choroid plexus, lateral ventricle	Embed only
Choroid plexus, 4th ventricle	
Sup vermis	
Dentate and cerebellar cortex	
Upper midbrain	

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History of Alcohol Use	Cohort		
	OPTIMA n=742	**Challenge** n=159	**LEAD** n=211
History of Regular Drinking, n (%)	80/645 (12.4)	17/156 (10.9)	43/140 (30.7)
History of Heavy Drinking, n (%)	42/651 (6.5)	11/158 (7.0)	9/143 (6.3)
History of Problem Drinking, n (%)	6/653 (0.9)	0/159 (0)	3/142 (2.1)
None of the above, n (%)	550/642 (85.7)	134/156 (85.9)	94/139 (67.6)

Supplemental Table 4.1. History of alcohol use reported in the OPTIMA, Challenge, and LEAD cohorts.

Alcohol Use in the Past 12 Months	Challenge Cohort n=157
None, n (%)	10 (6.4)
Special occasions, n (%)	18 (11.5)
1-3 drinks per month, n (%)	15 (9.6)
1-2 drinks per week, n (%)	25 (15.9)
3-4 drinks per week, n (%)	23 (14.6)
Daily, n (%)	55 (35.0)
> 2 drinks per day, n (%)	11 (7.0)

Supplemental Table 4.2. Reported alcohol use in the past 12 months in the Challenge cohort.

History of Heavy Smoking	Cohort		
	OPTIMA	**Challenge**	**LEAD**
History of Heavy Smoking, n (%)	158/650 (24.3)	53/158 (33.5)	23/143 (16.1)

Supplemental Table 4.3. History of heavy smoking in the OPTIMA, Challenge, and LEAD cohorts.

Smoking History	Challenge Cohort n=159
Never smoked, n (%)	68 (42.8)
Current smoker, n (%)	9 (5.7)
Stopped smoking, n (%)	82 (51.6)

Supplemental Table 4.4. Smoking history and current smoking status in the Challenge cohort.

Type of Drug Abuse History	Cohort		
	OPTIMA n=664	**Challenge** n=159	**LEAD** n=157
None, n (%)	603 (90.8)	132 (83.0)	155 (98.7)
Tranquilisers, n (%)	21 (3.2)	9 (5.7)	1 (0.6)
Hypnotics, n (%)	13 (2.0)	6 (3.8)	1 (0.6)
Barbiturates, n (%)	4 (0.6)	1 (0.6)	0 (0)
Stimulants, n (%)	1 (0.2)	0 (0)	0 (0)
Others, n (%)	22 (3.3)	11 (6.9)	0 (0)
Total with history of drug abuse	**61 (9.2)**	**27 (17.0)**	**2 (1.3)**

Supplemental Table 4.5. History of drug abuse reported by the OPTIMA, Challenge, and LEAD participants.

Living Arrangements	Cohort		
	OPTIMA n=716	**Challenge** n=159	**LEAD** n=162
Independent and alone, n (%)	146 (20.4)	50 (31.4)	38 (23.5)
Independent with relative/friend, n (%)	43 (6.0)	5 (3.1)	7 (4.3)
Independent with spouse, n (%)	414 (57.8)	102 (64.2)	107 (66.0)
Dependant at home, n (%)	39 (5.4)	1 (0.6)	7 (4.3)
Sheltered accommodation, n (%)	22 (3.1)	1 (0.6)	2 (1.2)
Residential home, n (%)	33 (4.6)	0 (0)	0 (0)
Long-term hospital, n (%)	19 (2.7)	0 (0)	1 (0.6)

Supplemental Table 4.6. First reported living arrangements for the OPTIMA, Challenge, and LEAD cohorts.

Clinical Diagnosis	Cohort					
	OPTIMA n=694		**Challenge** n=156		**LEAD** n=199	
	First	**Last**	**First**	**Last**	**First**	**Last**
Control, n (%)	227 (32.7)	149 (21.5)	146 (93.6)	107 (68.6)	102 (51.3)	80 (40.2)
Cognitive Impairment, n (%)	104 (15.0)	74 (10.7)	10 (6.4)	39 (25.0)	53 (26.6)	53 (26.6)
Dementia, n (%)	322 (46.4)	427 (61.5)	0 (0)	10 (6.4)	43 (21.6)	66 (33.2)
Psychiatric or difficult to classify, n (%)	41 (5.9)	44 (6.3)	0 (0)	0 (0)	1 (0.5)	0 (0)

Supplemental Table 4.7. First and last clinical diagnoses of control, cognitive impairment, dementia, or psychiatric or difficult to classify condition for OPTIMA, Challenge, and LEAD participants with more than one diagnosis.

Clinical Diagnosis	Cohort					
	OPTIMA n=694		**Challenge** n=156		**LEAD** n=199	
	First	**Last**	**First**	**Last**	**First**	**Last**
Control, n (%)	139 (20.0)	96 (13.8)	125 (80.1)	89 (57.1)	37 (18.6)	32 (16.1)
Subjective memory complaint	88 (12.7)	53 (7.6)	21 (13.5)	18 (11.5)	65 (32.7)	48 (24.1)
MCI, n (%)	81 (11.7)	66 (9.5)	10 (6.4)	37 (23.7)	38 (19.1)	41 (20.6)
VCI, n (%)	23 (3.3)	8 (1.2)	0 (0)	2 (1.3)	15 (7.5)	12 (6.0)
VD, n (%)	16 (2.3)	24 (3.5)	0 (0)	1 (0.6)	4 (2.0)	2 (1.0)
Mixed AD and VD, n (%)	61 (8.8)	74 (10.7)	0 (0)	2 (1.3)	8 (4.0)	21 (10.6)
Possible AD, n (%)	99 (14.3)	103 (14.8)	0 (0)	5 (3.2)	4 (2.0)	7 (3.5)
Probable AD, n (%)	116 (16.7)	177 (25.5)	0 (0)	1 (0.6)	25 (12.6)	29 (14.6)
ODS (LBD, PD, CJD, etc.) , n (%)	30 (4.3)	49 (7.1)	0 (0)	1 (0.6)	2 (1.0)	7 (3.5)
Psychiatric or difficult to classify, n (%)	41 (5.9)	44 (6.3)	0 (0)	0 (0)	1 (0.5)	0 (0)

Supplemental Table 4.8. First and last clinical diagnoses of control, cognitive impairment, or dementia subtype for OPTIMA, Challenge, and LEAD participants with more than one diagnosis.

APOE Genotype	Cohort		
	OPTIMA n=730	**Challenge** n=159	**LEAD** n=203
E2E2, n (%)	2 (0.3)	0 (0)	1 (0.5)
E2E3, n (%)	65 (8.9)	24 (15.1)	18 (8.9)
E2E4, n (%)	28 (3.8)	6 (3.8)	8 (3.9)
E3E3, n (%)	318 (43.6)	104 (65.4)	86 (42.4)
E3E4, n (%)	259 (35.5)	23 (14.5)	80 (39.4)
E4E4, n (%)	58 (7.9)	2 (1.3)	10 (4.9)

Supplemental Table 4.9. Participants with each APOE genotype, separated by cohort.

	By Cohort

Alzheimer's Disease Pathology Severity	**OPTIMA** n=439	**Challenge** n=49	**LEAD** n=44
Low, n (%)	23 (5.2)	5 (10.2)	5 (11.4)
Low-intermediate, n (%)	24 (5.5)	4 (8.2)	3 (6.8)
Intermediate, n (%)	40 (9.1)	4 (8.2)	10 (22.7)
High, n (%)	210 (47.7)	3 (6.1)	11 (25.0)
Total with any AD likelihood, n (%)	**297 (67.5)**	**16 (32.7)**	**29 (65.9)**

Supplemental Table 4.10. Alzheimer's disease pathology severity, by cohort.

Braak Tangle Stage	**By Cohort**		
	OPTIMA n=351	**Challenge** n=44	**LEAD** n=44
Stage 0, n (%)	5 (1.4)	3 (6.8)	0 (0)
Stage I, n (%)	38 (10.8)	16 (36.4)	4 (9.1)
Stage II, n (%)	33 (9.4)	10 (22.7)	10 (22.7)
Stage III, n (%)	36 (10.3)	10 (22.7)	12 (27.3)
Stage IV, n (%)	35 (10.0)	1 (2.3)	8 (18.2)
Stage V, n (%)	26 (7.4)	3 (6.8)	7 (15.9)
Stage VI, n (%)	178 (50.7)	1 (2.3)	3 (6.8)

Supplemental Table 4.11. Braak tangle staging neuropathology data, by cohort.

CERAD Score	**By Cohort**		
	OPTIMA n=181	**Challenge** n=38	**LEAD** n=42
No plaques (0), n (%)	43 (23.6)	20 (52.6)	19 (45.2)
Sparse neuritic plaques (1), n (%)	35 (19.2)	12 (31.6)	8 (19.0)
Moderate density of neuritic plaques (2), n (%)	17 (9.3)	3 (7.9)	7 (16.7)
High density of neuritic plaques (3), n (%)	87 (47.8)	3 (7.9)	8 (19.0)

Supplemental Table 4.12. CERAD scores for the OPTIMA, Challenge, and LEAD cohorts.

Braak Lewy Body Stage	By Cohort		
	OPTIMA n=74	**Challenge** n=12	**LEAD** n=39
Stage 0, n (%)	56 (75.7)	10 (83.3)	31 (79.5)
Stage 1, n (%)	1 (1.4)	0 (0)	1 (2.6)
Stage 2, n (%)	0 (0)	0 (0)	0 (0)
Stage 3, n (%)	0 (0)	0 (0)	0 (0)
Stage 4, n (%)	3 (4.1)	0 (0)	1 (2.6)
Stage 5, n (%)	3 (4.1)	0 (0)	1 (2.6)
Stage 6, n (%)	11 (14.9)	2 (16.7)	5 (12.8)

Supplemental Table 4.13. Braak Lewy Body staging, by cohort.

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Diagnostic Change Group	Number of participants	Median follow up length (years)	Participants completed at least once			
			Imaging	Clinical Bloods	CSF	Neuro-pathology
Psychiatric or difficult to classify throughout	34	6.3	33	34	22	21
Control → Psychiatric or difficult to classify	5	6.5	5	5	4	3
Cognitive impairment → Psychiatric or difficult to classify	5	8.2	5	5	2	4
Dementia → Psychiatric or difficult to classify	0	-	-	-	-	-
Psychiatric or difficult to classify → Control	2	16.7	2	2	1	2
Psychiatric or difficult to classify → Cognitive impairment	1	7.0	1	1	0	1
Psychiatric or difficult to classify → Dementia	4	7.6	4	4	1	4

Supplemental Table 5.1. Summary table of diagnostic change groups and data completion for participants who had a stable or converting diagnosis of "Psychiatric or difficult to classify."

Diagnostic Change Group	Number of participants	Median follow up length	Participants completed at least once			
			Imaging	Clinical Bloods	CSF	Neuro-pathology
Control → MCI	93	9.4	93	93	28	31
Control → VCI	9	12.5	9	9	3	5
Control → VD	3	13.3	3	3	0	2
Control → Mixed AD and VD	9	10.6	9	9	1	6
Control → Possible AD or amnestic disorder or mixed: AD with ODS	11	9.5	11	11	4	5
Control → Probable AD	12	14.1	11	12	5	8
Control → ODS	10	9.4	9	10	6	6

Supplemental Table 5.2. Table of clinical diagnosis over time and data completion for participants who began as controls and developed a cognitive impairment or dementia.

Diagnostic Change Group	Number of participants	Median follow up length (years)	Participants completed at least once			
			Imaging	Clinical Bloods	CSF	Neuro-pathology
MCI → VCI	3	8.5	3	3	0	1
MCI → VD	0	-	-	-	-	-
MCI → Mixed AD and VD	5	6.9	5	5	0	3
MCI → Possible AD or amnestic disorder or mixed: AD with ODS	25	8.0	25	25	9	13
MCI → Probable AD	33	8.6	33	33	13	20
MCI → ODS	7	5.1	7	7	3	4

Supplemental Table 5.3. Table of clinical diagnosis over time and data completion for participants who began with MCI and changed diagnosis.

		Median	Participants completed at least once

Diagnostic Change Group	Number of participants	follow up length (years)	Imaging	Clinical Bloods	CSF	Neuro-pathology
VCI throughout	9	3.6	9	9	1	4
VCI → MCI	0	-	-	-	-	-
VCI → VD	10	4.7	10	10	4	7
VCI → Mixed AD and VD	7	4.6	7	7	1	5
VCI → Possible AD or amnestic disorder or mixed: AD with ODS	1	4.0	1	1	1	1
VCI → Probable AD	2	4.3	2	2	1	2
VCI → ODS	2	3.1	2	2	0	1

Supplemental Table 5.4. Table of clinical diagnosis over time and data completion for participants who began with VCI changed diagnosis.

Diagnostic Group	Number of participants	Median follow up length (years)	Participants completed at least once			
			Imaging	Clinical Bloods	CSF	Neuro-pathology
VD throughout	11	3.2	9	11	3	8
Mixed AD and VD throughout	64	3.9	63	64	30	40
Possible AD or amnestic disorder or mixed: AD with ODS throughout	72	3.3	68	72	31	58
Probable AD throughout	128	4.0	125	126	65	101
ODS (FTD, LBD, PD, CJD, etc.) throughout	30	3.9	29	30	18	25

Supplemental Table 5.5. Table of clinical diagnosis over time and data completion for participants who maintained the same type of dementia diagnosis throughout the study.

Diagnostic Change Group	Number of participants	Median follow up length	Participants completed at least once			
			Imaging	Clinical Bloods	CSF	Neuro-pathology

		(years)				
VD→ Mixed AD and VD	4	4.8	4	4	0	2
Possible AD/amnestic/mixed with ODS→ Probable AD	24	6.6	22	24	7	13
Possible AD/amnestic/mixed with ODS → Mixed AD and VD	2	5.1	2	2	0	0
Possible AD → VD	1	9.3	1	1	0	1

Supplemental Table 5.6. Table of clinical diagnosis over time and data completion for participants who changed from one type of dementia diagnosis to another over the course of the study.

History of Alcohol Use	**Baseline Clinical Diagnosis**			
	Control n=443	**Cognitive Impairment** n=155	**Dementia** n=381	**Psychiatric or difficult to classify** n=48
History of Regular Drinking, n (%)	82/437 (18.8)	24/153 (15.7)	29/299 (9.7)	4/39 (10.3)
History of Heavy Drinking, n (%)	29/441 (6.6)	11/155 (7.1)	14/303 (4.6)	8/39 (20.5)
History of Problem Drinking, n (%)	3/440 (0.7)	2/155 (1.3)	2/305 (0.7)	2/40 (5.0)
None of the above, n (%)	345/436 (79.1)	127/153 (83.0)	264/296 (89.2)	30/39 (76.9)

Supplemental Table 5.7. History of alcohol use reported in participants with clinical diagnosis of control, cognitive impairment (no dementia), dementia, and psychiatric or difficult to classify.

	Clinical Diagnosis at Baseline			
	Control n=432	**Cognitive Impairment** n=148	**Dementia** n=336	**Psychiatric or difficult to classify** n=40
First MMSE score, mean (SD), range	28.6 (1.6) 17-30	26.5 (2.2) 20-30	18.3 (6.9) 0-30	22.5 (4.7) 8-30
Last MMSE score, mean (SD), range	26.7 (4.8) 0-30	18.3 (8.9) 0-30	9.7 (7.9) 0-29	18.5 (8.1) 0-29

Supplemental Table 5.8. First and last MMSE scores, grouped by clinical diagnosis at baseline.

	Clinical Diagnosis at Baseline			
	Control n=419	**Cognitive Impairment** n=147	**Dementia** n=319	**Psychiatric or difficult to classify** n=39
First total CAMCOG score, mean (SD), range	97.7 (5.2) 51-106	88.0 (6.4) 69-102	62.3 (21.0) 0-94	76.6 (16.0) 32-103
Last total CAMCOG score, mean (SD), range	94.3 (13.7) 0-107	67.5 (28.2) 0-103	34.0 (28.4) 0-97	67.0 (27.2) 0-104

Supplemental Table 5.9. First and last total CAMCOG scores, grouped by clinical diagnosis at baseline.

	Overall	Clinical Diagnosis at Baseline			
		Control	Cognitive Impairment	Dementia	Psychiatric or difficult to classify
MMSE-based cognitive decline score, mean (SD), range	-1.6 (2.4) -21.4-3.0 n=892	-0.3 (0.9) -9.1-2.0 n=423	-1.9 (2.7) -21.4-1.9 n=142	-3.3 (2.8) -15.3-3.0 n=292	-1.1 (2.1) -7.7-2.5 n=35
CAMCOG-based cognitive decline score, mean (SD), range	-4.4 (7.8) -78.6-18.6 n=850	-0.5 (2.7) -22.7-18.6 n=410	-5.2 (9.3) -78.6-5.1 n=137	-10.1 (8.8) -43.1-12.3 n= 270	-3.8 (7.0) -24.3-5.3 n=33

Supplemental Table 5.10. MMSE- and CAMCOG-based cogntive decline scores, grouped by clinical diagnosis at baseline.

APOE Genotype	All participants n=1013	By Final Clinical Diagnosis			
		Control n=301	Cognitive Impairment n=152	Dementia n=511	Psychiatric or difficult to classify n=49
E2E2, n (%)	3 (0.3)	2 (0.7)	0 (0)	1 (0.2)	0 (0)
E2E3, n (%)	100 (9.9)	43 (14.3)	19 (12.5)	35 (6.8)	3 (6.1)
E2E4, n (%)	37 (3.7)	7 (2.3)	8 (5.3)	20 (3.9)	2 (4.1)
E3E3, n (%)	475 (46.9)	177 (58.8)	88 (57.9)	180 (35.2)	30 (61.2)
E3E4, n (%)	331 (32.7)	67 (22.3)	34 (22.4)	218 (42.7)	12 (24.5)
E4E4, n (%)	67 (6.6)	5 (1.3)	3 (2.0)	57 (11.2)	2 (4.1)

Supplemental Table 5.11. Participants with each APOE genotype, separated by last available clinical diagnosis.

Final Clinical Diagnosis (with Subtypes)	APOE Genotype n (% of clinical diagnosis group)					
	E2E2	**E2E3**	**E2E4**	**E3E3**	**E3E4**	**E4E4**
Control (n=193)	0 (0)	27 (14.0)	4 (2.1)	120 (62.2)	38 (19.7)	4 (2.1)
Subjective memory impairment (n=108)	2 (1.9)	16 (14.8)	3 (2.8)	57 (52.8)	29 (26.9(	1 (0.9)
MCI (n=129)	0 (0)	16 (12.4)	8 (6.2)	77 (59.7)	25 (19.4)	3 (2.3)
VCI (n=23)	0 (0)	3 (13.0)	0 (0)	11 (47.8)	9 (39.1)	0 (0)
VD (n=27)	0 (0)	4 (14.8)	2 (7.4)	9 (33.3)	12 (44.4)	0 (0)
Possible AD (n=120)	1 (0.8)	7 (5.8)	4 (3.3)	50 (41.7)	49 (40.8)	9 (7.5)
Probable AD (n=211)	0 (0)	8 (3.8)	7 (3.3)	55 (26.1)	103 (48.8)	38 (18.0)
Mixed AD and VD (n=96)	0 (0)	6 (6.3)	4 (4.2)	37 (38.5)	39 (40.6)	10 (10.4)
ODS (n=57)	0 (0)	10 (17.5)	3 (5.3)	29 (50.9)	15 (26.3)	0 (0)
Psychiatric or difficult to classify (n=49)	0 (0)	3 (6.1)	2 (4.1)	30 (61.2)	12 (24.5)	2 (4.1)

Supplemental Table 5.12. Participants with each APOE genotype, separated by last available clinical diagnosis subtype.

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Final Clinical Diagnosis	**Likelihood of AD Based on Neuropathology (with or without additional pathology)** n (% of clinical diagnosis group)			
	Low	**Low-intermediate**	**Intermediate**	**High**
Control (n=86)	9 (10.5)	0 (0)	7 (8.1)	1 (1.2)
Cognitive impairment (n=50)	5 (10.0)	7 (14.0)	5 (10.0)	4 (8.0)
Dementia (n=334)	13 (3.9)	21 (6.3)	33 (9.9)	207 (62.0)
Psychiatric or difficult to classify (n=24)	3 (12.5)	2 (8.3)	4 (16.7)	2 (8.3)

Supplemental Table 6.1. Alzheimer's disease likelihood, by final clinical diagnosis.

Braak Tangle Stage	**Final Clinical Diagnosis**			
	Control n=58	**Cognitive impairment (no dementia)** n=46	**Dementia** n=291	**Psychiatric or difficult to classify** n=12
Stage 0, n (%)	4 (6.9)	3 (6.5)	0 (0)	0 (0)
Stage I, n (%)	25 (43.1)	15 (32.6)	13 (4.5)	2 (16.7)
Stage II, n (%)	15 (25.9)	7 (15.2)	19 (6.5)	4 (33.3)
Stage III, n (%)	11 (19.0)	13 (28.3)	27 (9.3)	2 (16.7)
Stage III-IV	0 (0)	0 (0)	0 (0)	1 (8.3)
Stage IV, n (%)	2 (3.4)	4 (8.7)	32 (11.0)	2 (16.7)
Stage V, n (%)	1 (1.7)	4 (8.7)	25 (8.6)	0 (0)
Stage VI, n (%)	0 (0)	0 (0)	175 (60.1)	1 (8.3)

Supplemental Table 6.2. Braak tangle staging neuropathology data, grouped by last available clinical diagnosis.

Final Clinical Diagnosis (with Subtypes)	**Braak Tangle Stage** n (% of clinical diagnosis group)							
	0	**I**	**II**	**III**	**III-IV**	**IV**	**V**	**VI**
Control (n=58)	4 (6.9)	25 (43.1)	15 (25.9)	11 (19.0)	0 (0)	2 (3.4)	1 (1.7)	0 (0)
MCI (n=39)	3 (7.7)	14 (35.9)	6 (15.4)	9 (23.1)	0 (0)	3 (7.7)	4 (10.3)	0 (0)
VCI (n=7)	0 (0)	1 (14.3)	1 (14.3)	4 (57.1)	0 (0)	1 (14.3)	0 (0)	0 (0)
VD (n=12)	0 (0)	1 (8.3)	4 (33.3)	0 (0)	0 (0)	3 (25.0)	3 (25.0)	1 (8.3)
Possible AD (n=67)	0 (0)	6 (9.0)	6 (9.0)	9 (13.4)	0 (0)	13 (19.4)	2 (3.0)	31 (46.3)
Probable AD (n=139)	0 (0)	0 (0)	2 (1.4)	6 (4.3)	0 (0)	11 (7.9)	10 (7.2)	110 (79.1)
Mixed AD and VD (n=56)	0 (0)	3 (5.4)	2 (3.6)	6 (10.7)	0 (0)	5 (8.9)	10 (17.9)	30 (53.6)
ODS (n=17)	0 (0)	3 (17.6)	5 (29.4)	6 (35.3)	0 (0)	0 (0)	0 (0)	3 (17.6)
Psychiatric or difficult to classify (n=12)	0 (0)	2 (16.7)	4 (33.3)	2 (16.7)	1 (8.3)	2 (16.7)	0 (0)	1 (8.3)
Total with AD likelihood n (% of total cohort)	**7 (1.7)**	**55 (13.5)**	**45 (11.1)**	**53 (13.0)**	**1 (0.2)**	**40 (9.8)**	**30 (7.4)**	**176 (43.2)**

Supplemental Table 6.3. Braak tangle staging neuropathology data, grouped by last available clinical diagnosis subtype.

CERAD Score	Final Clinical Diagnosis				
	Control n=47	**Cognitive impairment (no dementia)** n=33	**Dementia** n=147	**Psychiatric or difficult to classify** n=6	**Total** n=233
No plaques (0), n (%)	29 (61.7)	15 (45.5)	20 (13.6)	4 (66.7)	**68 (29.2)**
Sparse neuritic plaques (1), n (%)	13 (27.7)	13 (39.4)	21 (14.3)	2 (33.3)	**49 (21.0)**
Moderate density of neuritic plaques (2), n (%)	5 (10.6)	2 (6.1)	17 (11.6)	0 (0)	**24 (10.3)**
High density of neuritic plaques (3), n (%)	0 (0)	3 (9.1)	89 (60.5)	0 (0)	**92 (39.5)**

Supplemental Table 6.4. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score neuropathology data, by last available clinical diagnosis.

Final Clinical Diagnosis	Participants with LBD Neuropathology Findings n (% of clinical diagnosis group)
Control (n=86)	6 (7.0)
MCI (n=40)	6 (15.0)
VCI (n=10)	0 (0.0)
VD (n=18)	2 (11.1)
Possible AD (n=80)	21 (26.3)
Probable AD (n=143)	26 (18.2)
Mixed AD and VD (n=59)	12 (20.3)
ODS (n=34)	16 (47.1)
Psychiatric or difficult to classify (n=24)	3 (12.5)
Total number of participants with LBD pathology	**92/494 (18.6)**

Supplemental Table 6.5. Participants with PD/LBD neuropathology findings, grouped by last clinical diagnosis.

Parkinson's Disease (PD)/Lewy Body Disease (LBD) Pathology	Final Clinical Diagnosis			
	Control n=86	**Cognitive impairment (no dementia)** n=50	**Dementia** n=334	**Psychiatric or difficult to classify** n=24
Neocortical LBD, n (%)	0 (0)	3 (6.0)	14 (4.2)	0 (0)
Limbic LBD, n (%)	1 (1.2)	0 (0)	12 (3.6)	0 (0)
Amygdala-only LBD, n (%)	0 (0)	0 (0)	4 (1.2)	0 (0)
Brain stem LBD, n (%)	3 (3.5)	1 (2.0)	6 (1.8)	0 (0)
***Total with any PD/LBD findings, n (%)**	**6 (7.0)**	**6 (12.0)**	**77 (23.1)**	**3 (12.5)**

Supplemental Table 6.6. Lewy body pathology data, by final clinical diagnosis.

*Brain region was not specified for all participants with LBD, so the total does not necessarily match the sum of the specified regions

Microinfarct/s location	Final Clinical Diagnosis			
	Control n=86	**Cognitive impairment (no dementia)** n=50	**Dementia** n=334	**Psychiatric or difficult to classify** n=24
Cerebral white matter, n (%)	3 (3.5)	1 (2.0)	12 (3.6)	1 (4.2)
Cerebral cortex, n (%)	4 (4.7)	5 (10.0)	19 (5.7)	1 (4.2)
Basal ganglia/thalamus, n (%)	3 (3.5)	4 (8.0)	14 (4.2)	2 (8.3)
Cerebellum, n (%)	1 (1.2)	1 (2.0)	3 (0.9)	2 (8.3)
Brain stem, n (%)	1 (1.2)	2 (4.0)	1 (0.3)	0 (0)
***Total with microinfarct/s in any location**, n (%)	**28 (32.6)**	**19 (38.0)**	**77 (23.1)**	**8 (33.3)**

Supplemental Table 6.7. Microinfarct neuropathology data, by last available clinical diagnosis.

*Brain region was not specified for all participants with microinfarcts, so the total does not necessarily match the sum of the specified regions

Lacunar infarct/s location	Final Clinical Diagnosis			
	Control n=86	**Cognitive impairment (no dementia)** n=50	**Dementia** n=334	**Psychiatric or difficult to classify** n=24
Cerebral white matter, n (% of clinical diagnosis group)	2 (2.3)	1 (2.0)	4 (1.2)	0 (0)
Cerebral cortex, n (% of clinical diagnosis group)	1 (1.2)	1 (2.0)	1 (0.3)	0 (0)
Basal ganglia/thalamus, n (% of clinical diagnosis group)	3 (3.5)	3 (6.0)	8 (2.4)	0 (0)
Cerebellum, n (% of clinical diagnosis group)	1 (1.2)	2 (4.0)	1 (0.3)	1 (4.2)
***Total with lacunar infarct/s in any location**, n (%)	**9 (10.5)**	**8 (16.0)**	**29 (8.7)**	**3 (12.5)**

Supplemental Table 6.8. Lacunar infarct neuropathology data, overall and by last available clinical diagnosis.

*Brain region was not specified for all participants with lacunar infarcts, so the total does not necessarily match the sum of the specified regions

Vascular Condition Present	Final Clinical Diagnosis			
	Control n=86	**Cognitive impairment (no dementia)** n=50	**Dementia** n=334	**Psychiatric or difficult to classify** n=24
Moderate to severe amyloid angiopathy, n (% of clinical diagnosis group)	2 (2.3)	11 (22.0)	83 (24.9)	2 (8.3)
Moderate to severe non-amyloid small vessel disease (SVD), n (% of clinical diagnosis group)	21 (24.4)	20 (40.0)	80 (24.0)	2 (8.3)
Moderate to severe atherosclerosis, n (% of clinical diagnosis group)	13 (15.1)	15 (30.0)	54 (16.2)	2 (8.3)
Moderate to severe arteriosclerosis, n (% of clinical diagnosis group)	22 (25.6)	16 (32.0)	90 (26.9)	5 (20.8)

Supplemental Table 6.9. Vascular conditions neuropathology data, overall and by last available clinical diagnosis.