INVESTIGATING THE ROLE OF FRAILTY IN THE EXPRESSION OF DEMENTIA

by

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DEDICATION

This pursuit would not be possible without the support of my mentors, family, and friends. In many ways, it is a luxury to be a student for a living and I am truly grateful for the opportunity and support.

To my Dad, who has always nurtured my passion for learning, and spent every day of my childhood pursuing knowledge with me.

To my Mum, my confidante, best friend, and an incredible role model.

To my Sister, my kindred spirit who has provided endless support and comic relief.

To my Gramma, who was very pleased that I married a doctor, I know you would be proud no matter what I did, but especially that I worked to help others avoid the suffering you knew well (and that I got my own Dr. title to boot!).

And to my Husband, Tommy, who is my number one fan. Thank you for your unconditional love, support, encouragement, and unwavering belief in me. I love you.

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ABSTRACT

Background: Frailty is related to neuropathological features of Alzheimer's disease (AD) as well as cognitive decline and dementia.

Objectives: 1) determine whether frailty moderates the relationship between neuropathology and dementia status in Alzheimer's dementia; 2) examine the influence of frailty on the relationship between a neuropathological index and all-cause dementia; 3) examine the influence of frailty on the relationship between a neuropathological index and all-cause dementia in a population-representative dataset; 4) characterize longitudinal change in frailty and how this relates to dementia; and 5) validate a visual frailty tool in a memory clinic.

Methods: I used data from two clinical-pathological cohort studies to address objectives 1-4, and created a frailty index based on the deficit accumulation approach for each clinical evaluation. Cognitive status was ascertained at last evaluation or via clinical consensus post-mortem. Neuropathological assessment was completed post-mortem. I employed regression models to evaluate the relationship between neuropathology, frailty, and dementia status, and mixed-effects models to characterize longitudinal change in frailty. I collected data from patients at a memory clinic to address objective five.

Results: Frailty moderates the relationship between AD-pathology and Alzheimer's dementia such that as frailty increases, the relationship between AD-pathology and dementia becomes weaker. When I extended this analysis to include mild cognitive impairment and all-cause dementia and a broader conceptualization of neuropathology (10-item index), frailty and neuropathology were additive risk factors for cognitive impairment. I replicated these findings in a population-representative dataset and demonstrated that if severe frailty (FI>0.4) were prevented, 1/8 dementia cases could be avoided. People with more rapidly increasing frailty were more likely to develop dementia, even after controlling for neuropathology. I found the Pictorial Fit-Frail Scale to be feasible, reliable, and valid in a memory clinic setting among geriatricians, nurses, caregivers, and patients.

Conclusions: Frailty, as quantified by deficit accumulation, plays a key role in the clinical expression of dementia. Frailty intervention appears to be a promising avenue to mitigate the cognitive and functional consequences of neuropathology, and may suggest a resilience mechanism. Future research examining mechanisms of age-related disease should account for frailty to better understand risk and impact of treatment.

LIST OF ABBREVIATIONS USED

AB= Amyloid-beta

AD= Alzheimer's disease

AIC= Akaike Information Criteria

ANOVA= Analysis of Variance

APOE= Apolipoprotein E

AUC= Area Under the Curve

BIC= Bayesian Information Criteria

CAMDEX= Cambridge Mental Disorders of the Elderly Examination

CC75C= Cambridge City over 75's Cohort study

CDR= Clinical Dementia Rating Scale

CERAD= Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery

CES-D= Centre for Epidemiologic Studies Depression scale

CGA= Comprehensive Geriatric Assessment

CHF= Congestive Heart Failure

CI= Confidence Interval

CIND= Cognitive Impairment No Dementia

CSF= Cerebrospinal Fluid

DSM-IV= Diagnostic and Statistical Manual 4th Edition

FDG= Fluorodeoxyglucose

FI=Frailty Index

FRAIL scale= Fatigue, Resistance, Ambulation, Illness, and Loss of weight.

HAAS= Honolulu-Asia Aging Study

HR= Hazard Ratio

ICD= International Classification of Diseases

LATE-NC= Limbic-predominant Age-related TDP-43 Encephalopathy- Neuropathologic Changes

MAP= Memory and Aging Project

MCI= Mild Cognitive Impairment

MMSE= Multiple Mini State Examination

MRI= Magnetic Resonance Imaging

NINCDS-ADRDA= National Institute for Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association

NINCDS-AIREN= National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences

OR= Odds Ratio

PAF= Population Attributable Fraction

PAR= Population Attributable Risk

PET= Positron Emission Tomography

PFFS= Pictorial Fit-Frail Scale

PHF= Paired Helical Filaments

PiB= Pittsburgh B compound

PPT= Physical Performance Test

REB= Research Ethics Board

RNA= Ribonucleic acid

ROC= Receiver-Operating Characteristic curve

ROS= Religious Orders Study

SD= Standard Deviation

SHARE= Study of Health And Retirement in Europe

SPSS= Statistical Package for the Social Sciences

TDP= Transactive response DNA binding protein

UK= United Kingdom

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CHAPTER 1: Introduction

By 2031, 1.4 million Canadians will have cognitive impairment, many due to Alzheimer's Disease (AD)[1]. One of the reasons the burden of dementia is so high is that we do not have any disease-modifying treatments for AD, only interventions to treat symptoms. Therefore, there is significant motivation to better understand the mechanisms of AD development and expression in order to control the burden of disease. One of the most puzzling aspects of AD is that the neuropathological features (like amyloid-beta plaques and neurofibrillary tangles) do not correlate well with the clinical expression of dementia[2,3]. This suggests that some latent factor influences who is able to 'tolerate' higher levels of neuropathology without suffering from cognitive impairment. It cannot be ignored that people who get AD-type dementia are typically older and suffer from a number of other health problems; people with many health problems are often considered frail[4]. Frailty can be thought of as a state of increased vulnerability to adverse health outcomes –like hospitalization or death- compared to others of the same age[5]. Unfortunately, people who are frail are routinely excluded from clinical trials testing treatments that are aimed at helping them including trials targeting AD[6]. Previous research has shown that frailty is related to neuropathological features of AD as well as cognitive decline and dementia[7–9]. Frailty and AD-type dementia also share many risk factors and clinical features, including age, inflammation, functional impairment and atypical presentation of illness[8]. Given this background, I hypothesize that frailty may be a latent factor that modulates clinical dementia expression in relation to AD neuropathology. Specifically, the proposition that I seek to test is whether frailty reduces

a person's ability to tolerate AD neuropathology and more easily give rise to cognitive decline.

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CHAPTER 2: Background

2.1 Manuscript information

This section of the thesis includes excerpts from the following publications:

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Student contribution to manuscript: Lindsay Wallace designed and performed the literature review, wrote first draft, and revised all drafts.

2.2 Dementia in the context of population ageing

The global population is experiencing a demographic shift. While birth rates fall, life expectancy continues to rise[1]. Canada is one of the countries most affected by population ageing. By 2050, over 30% of our population will be over the age of 60[1] and the median age continues to increase[2].

Dementia is an age-related syndrome of cognitive and functional impairment. Importantly, as our population ages, the number of people with dementia in Canada and worldwide is increasing rapidly. By 2031, 1.4 million Canadians are projected to have cognitive impairment[3].

Dementia is understood to have several pathophysiologic causes. AD, historically characterized by tau and amyloid protein aggregates is the most common cause of dementia, making up ~70% of dementia cases[4], but other pathologies including Lewy bodies, vascular insults, and Parkinson's disease are recognized causes of the clinical syndrome of dementia. As one might expect, different pathologies can (but do not always) lead to different clinical presentations- i.e. dementia 'caused by' AD is

characterized by cognitive impairment including significant declines in episodic memory, which are enough to cause interference in social activities or activities of daily living. This information, along with medical history is used to diagnose dementia type in vivo, but the pathological diagnosis can only be ascertained upon autopsy.

It is important here to acknowledge the difference in terms: AD and dementia are frequently used interchangeably in colloquial language, but here I will refer to ***Alzheimer's dementia*** as the syndrome of cognitive and functional changes believed to be associated with ***AD pathology***, which refers to both plaques and tangles (protein aggregates to be elaborated on further the in the following section).

2.3 The relationship between neuropathology and dementia

One of the most intriguing challenges to understanding the mechanisms of AD development and expression is that the correlation between the so-called 'neuropathological hallmarks' of AD (i.e. accumulation of abnormal amyloid-beta and tau protein deposits) and cognitive decline is weak: people with no dementia (i.e. cognitively intact) or mild cognitive impairment can exhibit high burdens of neuropathology[5,6], and people with dementia may exhibit comparatively little neuropathology[7]. This discordance between pathology and cognition is particularly evident in community-based samples[8–13]. One study demonstrated that upwards of a third of adults 80+ without dementia exhibited pathology that met criteria for intermediate or high likelihood of AD[14]. Further, it has been suggested that people who survive into

advanced age may have different profiles of pathological indicators of disease[15].

Interestingly, many people with mild cognitive impairment who never went on to develop AD also exhibited AD pathology[14,16–20], suggesting that a) the disease state is actually a spectrum along which you can progress from mild cognitive impairment (MCI) to AD, and/or that b) the pathology represents the neural correlate of some types of memory impairment that are present in MCI and AD.

More recently, it has been suggested that Alzheimer's dementia is actually the result of mixed pathology, which is common in older adults[21]: one observational study demonstrated that almost half of participants with Alzheimer's dementia exhibited mixed pathology[22].

Understanding what influences the individual ability to tolerate neuropathological insults (i.e. why some people with high neuropathological burden do not experience dementia) motivates the inquiry here into the role of frailty in dementia expression.

2.4 Frailty

People of the same chronological age experience varying levels of health and risk of death; this variability in health status can be understood as frailty. Thus, frailty is associated with, but independent from, chronological age. Frailty represents physiologic vulnerability resulting from multiply-determined reduced capability to repair/respond to internal or external stressors or insults[23,24].

The decline in physiologic reserve that characterizes frailty produces conditions where even minor insults can give rise to catastrophic results such as falls, delirium, disability, hospitalization, institutionalization, and mortality. Measuring frailty can assist clinicians in clinical decision making to optimize patient care; for example, aggressive or invasive treatments may not be appropriate for a very frail person as they are less likely to be able to recover from the treatment itself, and thus unable to benefit from the intervention[25].

2.3.1 Frailty measurement

Frailty has been measured in a variety of ways; with dozens of tools and hundreds of modifications[26,27]. The most investigated and cited measurement tools are the frailty phenotype and the frailty index (FI), both introduced in 2001[28,29]. Others, including the Groningen Frailty Indicator[30], Tilburg Frailty Indicator[31], and Edmonton Frail Scale[32] have also been widely used. Frailty measurement must be considered carefully for the sample and purpose of the study as characteristics, such as prevalence, can change dramatically and significantly augment results[33]. Here, I will discuss the prevailing frailty theories: the phenotype and deficit accumulation approaches.

The frailty phenotype was developed by Linda Fried and colleagues at Johns Hopkins University using data from the Cardiovascular Health Study. They identified five key frailty symptoms, including weight loss, fatigue, low grip strength, slow walking speed, and physical inactivity. Based on this approach, frailty has been defined as deficits or impairment in at least three of the five domains, whereas pre-frailty is indicated by

impairment in one or two domains. Individuals are considered robust if they do not demonstrate any impairment. Advantages of this syndromic or phenotypic approach include its simplicity and that it has been the most commonly cited and examined among population studies. Disadvantages are the inclusion of performance-based measures (i.e. grip strength and walking speed) which are not part of routine care, difficult to implement, and typically excludes the frailest individuals. Further, the categorization of the phenotype does not readily enable gradation of the degree of frailty.

The FI is a health state measure (rather than a specific syndrome), designed to integrate multiple types of health information. It reflects the extent of illness and vulnerability to adverse outcomes and proximity to death[34] and it has been applied in large health databases from many countries, including Canada[35], United States of America[36,37], China[38,39], Sweden[40], and the European Union[41–43]. An FI can be created from routinely collected clinical or epidemiological information which are then recoded typically as binary (present/absent) health deficits using a standard set of criteria[44]. An FI score can be calculated by dividing the number of health deficits present in an individual by the number of health deficits measured. For example, a person with 20 of 40 deficits has an FI score of 20/40 = 0.5; for someone with 10 deficits, the FI is 10/40 = 0.25. Despite variability in the number and nature of deficits recorded in the various databases (e.g. from 30 self-report items to more than 100 items that range from self-report to laboratory and electrocardiographic data[45]) the FI has remarkably consistent characteristics: in population-based datasets, frailty increases exponentially with age and it is strongly associated with adverse health outcomes including hospitalization[46], institutionalization,

and mortality[45], as well as disease-specific outcomes such as coronary heart disease[46], chemotherapy toxicity[47], and cardiac surgery outcomes[25]. Additionally, at any age women have higher FI scores than men[48], and there is a demonstrated sub-maximal limit to the FI at ~0.7 beyond which it appears individuals cannot survive[49].

The FI approach has some key advantages. It can be used across many populations and datasets because the nature of the variables included does not matter so long as there are enough of them (~30) and they meet some basic criteria. Statistical weights are not imposed on specific variables - instead the index self-weights, increasing generalizability. If more serious health deficits are present (which are each given a value of 1 when present), many other related health deficits will also be present. For example, if congestive heart failure or chronic obstructive pulmonary disease is present, depending on severity, a person may also have dyspnea, functional impairments, or frequent infections. Further, by capturing information across multiple physiologic systems and transforming this into a continuous measure, the FI allows gradation of severity of frailty. The FI also greatly reduces the dimensionality; rather than including each health variable in a statistical model, we can combine them all in a single term. Some disadvantages include the amount of information required, as at least 30 variables should be included. It has been argued that this is arduous to collect from a clinical encounter, though typically these data are easily accessible from routine clinic assessments. For example, the Comprehensive Geriatric Assessment (CGA) is a fundamental tool in health care settings serving older adults[50] and can be easily operationalized into an FI as it typically includes 40-60 variables[34]. Also, more recently, it has been proposed that an FI can be comprised

of commonly used blood tests[51–53]. Another criticism of the FI approach is that different sets of variables are used in different constructions of the FI which is useful epidemiologically, but the clinical implications of variations between FIs in different clinical settings are potentially more unclear. In a geriatric medicine setting, a tool such as the CGA can be useful in both assessing frailty and targeting interventions[54].

Interestingly, all frailty tools can be analyzed as indices of deficit accumulation. That is, when existing frailty tools are recalculated as the proportion of criteria present of the number that were assessed, the similarities between scales are remarkable[55]. This lends support to the hypothesis that the number of deficits present may be more important than the nature of the deficits in the ageing individual. This observation may not be surprising when we consider the heterogeneity of health status in older adults, which nevertheless converge in common pathways characterized by failure of high order functions, such as mobility, balance, function, social engagement, and cognition. Frailty therefore manifests as progressive disintegration of multiple basic processes, which is the basis of the risk for loss of high order functions.

For the purposes of our inquiries here, we will be using the FI as it can be calculated in all databases used without excluding a significant proportion of participants, it is generalizable, and does not have ceiling or floor effects.

2.3.2 Mechanisms of deficit accumulation: Theory

As individuals age, they accumulate health deficits. Frailty can be conceptualized as this accumulation of health deficits over time. With age, our capacity to repair or remove cellular damage becomes impaired, leading to an exponential accumulation of deficits as further insults go unrepaired. Deficits can arise endogenously (e.g. oxidative stress, atherosclerosis) or exogenously (e.g. an accident leading to fracture)[56]. Acquiring a deficit (whether exogenous or endogenous) requires a response to either remove or repair the damage caused by the deficit. If we assume that individuals experience insults over the lifetime at a constant rate on average, and take into consideration the observation that unrepaired deficits accumulate exponentially over time, we can deduce that recovery time increases with age[57]. In younger people, in whom recovery time is faster, damage from deficits is quickly recovered, whereas older people, whose recovery time is slower, may suffer the same number of deficits in a given time period but have a much longer recovery time. As recovery time lengthens, more deficits accumulate[57]. The heterogeneity in frailty among people of the same age reflects individual differences in the rate/number of insults. This measure of frailty has also been referred to as biological ageing[57].

The mechanisms of deficit accumulation can be understood using a network model; it has been demonstrated that deficits arise as damage propagates through the network's nodes[58,59]. Each node can be either undamaged or damaged. Damage to a node is likely to cause damage to the nodes to which it is connected. Mortality arises when the most highly connected nodes in the network become damaged (Figure 2-1). Some items, such as single laboratory tests, have comparatively low connectively and therefore low

information value, whereas others such as mobility, balance, and cognition, and specific instrumental activities of daily living items have high connectivity and information value.

Overall, 'biological ageing' or increasing frailty, occurs as deficits are acquired and when redundant recovery systems are damaged[57]. Evidence is mounting to suggest that frailty arises over time from these endogenous and exogenous deficits at a subcellular level accumulating to produce cellular deficits, which 'scale up' to give rise to deficits at the tissue, organ, and eventually clinically detectable level[60].

2.2.4 Mechanisms of deficit accumulation: Evidence

Several mechanisms for the development and progression of frailty have been suggested. Some view frailty as integral to the ageing process, while others suggest frailty reflects a pathological condition. Here, I will briefly review some of these theories, with an emphasis on the former approach.

A 2013 paper on the "hallmarks of ageing" reviewed the literature on common factors of ageing across organisms[61]. The authors argue that altered cellular communication, genomic instability, telomere length, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion are common age-related factors that eventually give rise to clinical problems. This paper put forth a framework for understanding the context of these factors, suggesting that these hallmarks are either primary (those that cause damage), antagonistic (responses to damage, which may work initially but as they are exhausted

become deleterious), or integrative (the clinical manifestations of the previous two categories)[61]. This conceptualization endorses a systems perspective, where ageing occurs "due to the interaction between a variety of components"[60]. This review also proposed that the cause of organismal ageing can be essentially reduced to the accumulation of deficits. Further, it posits that the hallmarks are all so related and inter-dependent that alteration to one hallmark likely influences function of others.

Telomeres represent one well-established example of the redundancy in bodily systems as a protection mechanism. Telomeres are essentially caps of non-coding genetic material on the end of chromosomes. With each additional replication (i.e. age), the chromosome shortens, eating into the telomere bit by bit. The long telomere length seen at early ages appears to be a redundant mechanism in place to protect the important genetic material from the deterioration of constant damage with age[61]. Initial studies demonstrated that frailty indices constructed from self-reported data were not related to telomere length[62]. A later study reported that an FI constructed by combining blood tests with self-reported data was significantly associated with telomere length[63]. Given this evidence, it is possible that telomere length is an indicator of sub-cellular frailty that doesn't necessarily correspond to 'scaled-up' frailty (i.e. clinically visible frailty) because it needs to be accompanied by many other sub-cellular deficits.

Diseases of ageing (including neuropathological ones) have historically been studied using animal models that are selected to have few other deficits than the specific one of interest. Very little of the promising results of mouse work have translated to humans,

likely because they ignore the context in which these diseases arise: in ageing individuals with several complex and interacting health problems. Animal models of frailty are new[64]; a rodent FI has been developed based on 31 clinical health deficits including the integument, musculoskeletal, ocular, respiratory systems[65]. This FI was compared and validated against the human FI and the characteristics were remarkably similar: the FI values in mice were similar to their normalized age categories in humans; slopes of deficit accrual were similar; and the submaximal limit of 0.67 was almost identical[65]. These mouse models serve to advance the biological study of frailty and ageing and there is hope that the study of age-related conditions in ageing mice will provide translational benefit to these studies.

2.5 The relationship between frailty and dementia

Several studies have linked cognitive impairment or presence of dementia with frailty. A study by our group found that the frailer an individual was, the more likely they were to exhibit dementia[66]. Likewise, studies have been published from the Memory and Aging project (some of which are featured below) on the relationship between cognition and frailty; they have reported that baseline frailty level, as well annual change in frailty was associated with incident risk of AD[67], MCI[68], and rate of cognitive decline[69].

2.4.1 Associations

Frailty is a well-accepted exposure for cognitive decline and dementia, in both cross-sectional and longitudinal analyses[70–80]. Frailty has been associated with age-related cognitive decline[81] as well as development of mild cognitive impairment (MCI)[68] and

AD[82]. Among people with cognitive impairment, frailty has been shown to predict more rapid and severe decline[68], as well as conversion from MCI to AD[68,83]. Other reports have demonstrated that change in frailty and cognition were correlated[69,77,84]. These observations appear to hold across common confounders including sociodemographic status, sex, and vascular risk factors.

In 2016, a meta-analysis[85] of seven longitudinal studies concluded that frailty was a significant predictor of incident AD [four studies: pooled HR = 1.28 (1.00–1.63)], vascular dementia [(two studies: pooled HR = 2.70 (1.40–5.23)], and all dementia [(three studies: pooled HR = 1.33 (1.07–1.67)]. Another meta-analysis published in 2019[86], included six longitudinal studies and concluded that frailty was significantly associated with an increased risk of geriatric cognitive disorders [pooled OR = 1.80 (1.11-2.92)]. A more recent meta-analysis also published in 2019[87], focused on the co-occurrence of frailty and cognitive impairment no dementia (CIND). They identified five longitudinal studies that showed that in comparison to people without frailty and CIND, frailty [pooled HR = 1.47 (0.89-2.40)] and co-occurrence of frailty with CIND [pooled HR = 5.36 (3.26-8.81)] was associated with incident dementia.

In 2019, we completed a systematic review of the relationship between frailty and cognition. Our search strategy identified 11 longitudinal studies - most of these were included in the meta-analyses described above[67,88-97], though some were not. The sample size of these studies ranged from 252-8,722 with only two studies[67,92] including less than 1,000 people. The oldest study was published in 2007[82] and the follow up period ranged

from 3-10 years. Frailty was measured using the frailty phenotype (N=8) or the frailty index (N=3[91,94,95]). One study[96] used self-report to identify dementia whereas the rest used established diagnostic criteria: Diagnostic and Statistical Manual (DSM; versions 3R, 4, or 5), National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), National Institute for Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), Clinical Dementia Rating (CDR), and the International Classification of Disease manual (ICD; version 10). The participants of eight of the included studies had no cognitive impairment at baseline, whereas three studies [92,94,97] included people either with or without cognitive impairment. Among the included 11 studies, nine reported frailty as a significant predictor of dementia. The two studies that did not report a relationship between frailty and dementia used the Fried phenotype and the Physical Performance Test.

Most studies on cognition and frailty use the frailty phenotype, though some issues have arisen with this approach. The measurement and prevalence of frailty using the phenotype is extremely variable[27], and almost all of the individual factors in the frailty phenotype are individually associated with risk for cognitive impairment[28,83,98-101]. While this may demonstrate the truly inextricable link between cognition and frailty, it is possible that a frailty tool with few items is not able to wholly represent frailty in the ageing body and therefore overestimate the relationship. To help better understand this, our group created an FI of non-traditional dementia risk factors (i.e. variables that each were not individually associated with dementia). We found that this measurement of

frailty is significantly associated with dementia risk[66,91] and disease expression[102] after controlling for possible confounders. We have extended these analyses in varied cohorts including the Study of Health & Retirement in Europe[78,103] and the Honolulu-Asia Aging Study[76,77]. This suggests that the accumulation of health problems that are not known risk factors for dementia may combine to give rise to clinically relevant disease outcomes.

Another issue is the possible inclusion of cognitive variables in the measurement of frailty[104]. While we generally advocate for this, as the brain can be considered another bodily system and the aim of frailty is to capture vulnerability across systems, it will be important for our understanding of the mechanisms of this relationship to measure frailty without cognitive variables so as not to confound the overall relationship.

Multiple observational studies have reported that changes in frailty and cognition are correlated. Some reports were designed to show frailty as an exposure for cognitive decline[68,72,79,82,83,102], and others that cognitive decline precedes frailty change[77,78]. Given the common mechanisms, it is unlikely that one predictably causes the other, but rather that they each contribute to a cycle of decline.

Overall, this evidence suggests that general health impacts dementia risk and that frailty and cognitive decline may share pathophysiological mechanisms.

2.4.2 Possible mechanisms

Several mechanisms for the relationship between cognition and frailty have been proposed. Both cognitive decline and frailty are strongly associated with age and are thought to be multiply determined[78]. For this reason, many other age-related conditions show possibilities as mediators, but to date no experimental studies have demonstrated causal mechanisms. Based on the current literature, popular hypotheses for shared mechanisms include hormones, neuropathology, chronic inflammation, cardiovascular risk factors, nutrition and microbiome similarities, metabolic by-products, and mental health. I will briefly review some of these below, though note that other reports have reviewed them more in depth[105].

Interestingly, at any age women are more likely to have higher clinical FI scores than men and are more likely to develop dementia[48]. These observations suggest that sex differences including hormones may be a shared underlying mechanism. Estrogen has been linked with cognition. Peri- and post- menopausal women report declines in memory, and hormone replacement therapy ameliorates this decline in many cases, though this appears to be dependent on a critical window of initiation at menopause rather than later in life[106–110] and is not without controversy. Women are at higher risk for common age-related diseases, particularly after menopause, including osteoarthritis, stroke, and diabetes mellitus[48,111], suggesting that this age-related state may contribute to overall frailty as well.

Testosterone decreases with age and is associated with reduced muscle mass. In healthy adults, testosterone is thought to promote neuroplasticity, and to regulate the accumulation of amyloid-beta in the brain to some extent- though these functions appear

to work (and be associated with changes in) with a complex network of hormones. The majority of the evidence for the testosterone mechanism has been analyzed only in men[112], therefore further studies of the effect of sex hormones (including estrogen) should be undertaken with sex-stratified reporting to better understand their contribution.

AD pathology has been linked to both cognition and frailty[113]. Buchman and colleagues reported that a composite measure of AD pathology (specifically neuritic and diffuse plaques as well as neurofibrillary tangles) was associated with the frailty phenotype in both individuals with and without dementia[114]. In a later study, this group demonstrated that AD pathology was associated with baseline and change in cognition and in phenotypic frailty[69].

Chronic inflammation has been suggested as one of the main culprits for a shared mechanism between cognitive decline and frailty seen in older adults. In humans, acute injury initiates involvement of both local and systemic inflammatory markers that mount a response to repair the injury. If recovery/repair is prolonged, or the inflammation remains to respond to other subclinical issues, inflammation becomes chronic. What starts out as an appropriate response to damage becomes deleterious itself. This chronic inflammatory response (as measured by elevated levels of inflammatory markers such has C-reactive protein), has been associated with both frailty and cognitive decline; further, in women, inflammatory markers actually mediated the relationship between muscle strength and cognition[115].

This section summarizes evidence on the direct relationship between frailty and cognition, though frailty may also contribute to dementia expression indirectly, i.e. by modifying the effect of other key contributors, such as neuropathology.

2.6 The relationship between neuropathology and frailty

Given the strong relationship between frailty and cognition/dementia, it is possible that frailty may be related to the so-called 'causes' of dementia. This relationship has been little investigated, and the few articles published on this relate to AD. I undertook a scoping review with the objective of examining of the relationship between frailty and neuropathological features of AD in humans. Subsections here are taken from the paper 'Relationship between frailty and Alzheimer's disease biomarkers: A scoping review' published in *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring*[113].

2.5.1 Search Strategy

Pubmed, Embase, and PsycInfo were searched using 'frail elderly'; AND 'Alzheimer disease'; AND 'neuropathology' and synonyms (Figure 2-2). Selection was limited to original articles involving humans, published in English up to November 2015. All studies that measured frailty and any AD biomarker (amyloid-beta or tau, positron emission tomography [PET] imaging- Pittsburgh B [PiB] compound or Fluorodeoxyglucose [FDG], magnetic resonance imaging [MRI] atrophy) were included. Two reviewers independently completed a two-step screening process (title/abstract and full text). Disagreements were resolved by consensus. Our search identified 368

references; 285 articles were excluded during title and abstract screening, 75 more were excluded during full-text screening. This left eight articles for data extraction (Figure 2-3). Of these eight, four included participants with baseline cognitive impairment. Most were longitudinal (n=6) and measured frailty as a phenotype (n=5). Three studies examined post-mortem AD pathology, three other studies measured brain atrophy, and two assessed amyloid-beta and tau in vivo. All studies assessed the relationship between at least one AD biomarker and frailty (directly or indirectly); six reported positive relationships, i.e. increasing frailty was associated with increased levels of AD biomarkers- in some cases this was related to more rapid cognitive decline. Two studies reported no relationship.

Here, we found that few studies have examined the relationship between biomarkers of AD and frailty, and those that have done so show disparate results and varying conclusions (Figure 2-4). Our analysis suggests that, in general, the relationship between frailty and biomarker of AD strengthens as the disease courses progresses. That is, evidence for the relationship between early biomarkers (amyloid-beta) and frailty is inconclusive, whereas evidence for this relationship with mid-disease biomarkers (markers of neurodegeneration such as tau levels, and structural atrophy) is present but weak. Further, the relationship of frailty with post-mortem markers of AD is strong. This suggests that frailty may influence the relationship between biomarkers of AD and cognition; future research is needed to examine this empirically and elucidate mechanisms involved.

2.5.2 BIOMARKERS: IN VIVO PROTEIN PATHOLOGY FINDINGS

The two studies that examined biomarkers in vivo were inconsistent regarding the relationship between biomarkers of AD and frailty. The first study reported that only tau, but not amyloid-beta (AB) markers, were associated with frailty. The second found that frailty did not appear to influence the association between AB and mortality. Interestingly, the second study examined levels of AB in blood plasma, which some research has suggested is an early biomarker of AD[116]. It has been proposed that this biomarker is present earlier than abnormal AB levels in CSF, though there is conflicting evidence in support of this claim. An early study reported that baseline AB42 levels and AB42/40 ratio (but not AB40), were significantly elevated among older adults who went on to develop AD[116]. More recent reports have found that this difference may be attributable to age[117]. Evidence presented here, that AB42 is associated with mortality, does not necessarily clarify the link between AB and AD. Future research is needed to elucidate these mechanisms.

Several studies have suggested that AB actually functions as a protective mechanism[118,119], or at least that it is a non-specific neuropathology in the brain. Importantly, there is a weak correlation between AB pathology and cognitive impairment [120]; more than one study has demonstrated that people with plenty of AB plaque in the brain are cognitively intact[121] and some people with profound dementia are found to have next to no AB pathology upon autopsy [7]. In light of this, and the findings of this review, it is possible that AB is not an initiation factor of the AD pathogenesis, but rather a by-product or possibly one of many contributing features.

2.5.3 BIOMARKERS: IN VIVO ATROPHY FINDINGS

Evidence for the relationship between atrophy (global and regional) and frailty was present, but relatively weak. This is in part because one of the three studies[122] examined frailty as a moderator in the relationship between atrophy and cardiorespiratory fitness. Although authors had a sound rationale for the potential of this relationship, it is unlikely that the lack of moderation by frailty says much about its relationship to atrophy in the context of dementia.

Yamada et al.[123] demonstrated correlations between whole brain atrophy and frailty, but used the Physical Performance Test (PPT) to define frailty. As mobility assesses only one domain, and frailty is meant to capture multiple domains, it is likely that the relationship may change as a function of frailty measurement. Mobility has been used as a screen for frailty, as it is a higher order function that is vulnerable to deterioration as a result of any number of factors. Therefore, though the relationship may change slightly, it is possible that mobility (via the PPT) may act as an appropriate proxy for true frailty in this sample. Further, this analysis did not examine the PPT as a whole in relation to global brain atrophy, limiting the ability to understand the effect of overall mobility on brain atrophy. A major limitation of this article, for the purpose of our review, was small sample size and low variation of cognitive ability (all participants had MCI or early AD). This limits generalizability as the relationship seen here between frailty and atrophy may not be representative of those without clinically relevant cognitive impairment.

Tay et al.[124] reported medial temporal lobe atrophy was associated with baseline frailty but not frailty progression, which may suggest that biomarkers peak in their relevance early in the disease trajectory. This is consistent with Jack's model of biomarker pathophysiology[125,126]. This study modified the frailty phenotype to quantify frailty, which could affect results; we recently reported that modifications to the frailty phenotype resulted in broad differences in frailty prevalence[27].

Measures of brain atrophy likely reflect broad neurodegenerative processes, and are less specific than in vivo measures of AB, therefore, it is unsurprising that these measures are more closely related to frailty. Some limitations that future studies should address include better operationalization of frailty, as well as recruiting participants with a wider range of cognitive functioning to elucidate the relationship between frailty and MRI AD biomarkers.

2.5.4 Biomarkers: post-mortem pathological findings

The three studies that used the Religious Orders Study/Memory and Aging Project data were strong methodologically and demonstrated a consistent positive relationship between frailty and post-mortem neuropathological features of AD. Each subsequent study benefitted from increased sample size, increased variance, and built on previous findings to uncover novel relationships. Together, the studies found that post-mortem AD pathology (summarized in an index) was strongly associated with baseline frailty, 1-year frailty progression, and the rate of change in frailty (as well as the rate of change in cognition). Given results from other studies examining tau presented in this review, it is

possible that tau pathology is driving the relationship seen here. This should be addressed by future investigations.

A particular strength of these studies was that they included many types of pathology in their analysis. This enabled authors to examine whether relationships with frailty and cognition differed by pathology type, i.e. whether the relationship was specific to AD pathology. This is particularly relevant given that most people with Alzheimer's dementia actually have mixed pathology; one study reported as many as 39% of AD patients had mixed pathology[120]. In fact, Buchman[127] reports very few participants (even those who were cognitively intact) had no AD-related neuropathology at death.

Interestingly, other age-related pathologies were not associated with frailty[127] suggesting that AD pathology and frailty share some unique pathogenesis/etiology. Though it is also possible that the other pathologies are either rarer or more specific whereas (as has been a criticism of the amyloid cascade hypothesis before), neuropathologic markers of AD are notoriously non-specific and their mechanistic impact is still elusive.

AD pathology has also been found to predict cognitive function in individuals with and without cognitive impairment[20,128,129]; which may suggest that this neuropathology is more closely related to frailty than AD and that AD and frailty share a complex pathway where each can impact the other; i.e. increased frailty can lead to increased neuropathology, which together lead to cognitive decline, which in turn exacerbates frailty and neuropathological burden.

A few factors limited the generalization of these findings; the ROS/MAP studies were largely convenience volunteer samples that required agreeing to an autopsy, and may suffer from birth or cohort effects, therefore this group of participants is unlikely to be representative of the general population. Further, as will be discussed more in depth in the following sections, the frailty tool used (Fried phenotype) was incompletely measured, possibly introducing bias. This begs for more research to be undertaken that examines these questions in alternate databases with a more diverse group of participants.

2.5.5 Biomarker measurement

Biomarker studies reviewed here roughly reflected the recommendations report published in 2011[130,131]. This list includes biomarkers for AD that have the most evidence for links with the pathophysiological process, though articles are published regularly with new suggested biomarkers, including blood proteins associated with stress[132], abnormalities in microRNA expression [133], abnormal protein levels as identified using a mass spectrometer, and inflammatory cytokine markers[134,135]. When considering which biomarkers for AD may be plausible it is crucial to consider the criteria for a candidate biomarker. A true biomarker should be valid, and therefore reflect properties of measurement (whether the biomarker can be measured in a reliable and objective manner), i.e. internal validity (whether the biomarker accurately reflects the underlying clinical disease process, and external validity (whether the biomarker remains accurate in similar populations or studies)[136]. When considering the 'biomarkers' we currently have available for AD, it is useful to evaluate them in this context. Based on these criteria, it is unlikely that any of the proposed biomarkers actually constitute veritable biomarkers, and

attention should be drawn to the clinical utility of this biomarker search [137]. Given the complexity, heterogeneity, harms, and cost of measuring many of these biomarkers (lumbar puncture to get CSF, MRI, PET imaging), we in the field of dementia research should consider whether the pursuit of tools like this to detect risk for AD early is a valuable one. We have yet to truly make strides in connecting the presence and detection of these biomarkers to the veritable pathophysiologic process of AD in the brain and body; until we do, utilizing these tools may be less effective than clinical judgment and neuropsychological evaluation, cost more money, and present more harms to the patient.

2.5.6 Features of analysis

Many of the studies summarized here neglect the complex nature of the interaction between biomarkers of AD and frailty. Given the evidence, it is likely that their interactions are bi-directional and the nature of these interactions changes over time and are influenced by other internal and external factors[138].

Four of the eight articles included in this review used a cross-sectional design. Given the hypothesis that these interactions change with time, this limits the ability for the research to draw accurate conclusions on the total relationship. These are still very valuable endeavors and give a snapshot of the relationship at crucial time points. Putting this information together can give us useful information to inform future hypotheses and study designs across the life course.

2.5.7 Limitations and avenues of future research

One of the main purposes of this review was to identify gaps in knowledge to direct future research. All of the studies included in this review suffer from small sample size and it is possible that several are underpowered. However, it must be said that when drawing samples for biomarkers, whether it be MRI, CSF, blood plasma, or post-mortem brain autopsy, large numbers of participants are difficult to achieve and very costly. For this reason, data sharing will become an inevitable feature of continued quality research in this area. Further, half of the studies were cross-sectional, pointing to a need to invest in longitudinal observational studies of this nature. Poor measurement of frailty was common, demonstrated by frailty measures focusing only on one domain of function (i.e. mobility or cognition) or modifying previously established and validated tools (i.e. frailty phenotype). We have previously shown that modifications to the frailty phenotype greatly affect prevalence estimates and outcomes[27]. Other reports have shown the possible biologic heterogeneity of the frailty phenotype[139]. Few studies had a sample that included a broad range of cognitive function at baseline making it difficult to generalize reported relationships beyond their specific sample.

In the interpretation of the data presented here, we must draw attention to the fact that some over-arching studies produced more than one article included in this scoping review[69,114,127], potentially accounting for individuals more than one time. Each presents different outcomes and does not affect summary estimates as it would in a meta-analysis. Further, each subsequent paper presented additional novel results that build upon the previous paper(s).

We did not perform quality assessments on the articles included here as this was a scoping review and not a systematic review or meta-analysis. Due to the nature of the problem, no randomized controlled trials have been employed, so the next best line of evidence to draw from is longitudinal observational studies.

One limitation of our analysis here was that we only included publications that were written in English or French, this was due to lack of an appropriate translator, and the fact that common databases frequently exclude non-English journals. On this basis we excluded seven articles, five in German and two in Japanese. At least four of these articles would have been excluded under other criteria (i.e. article type), but it is possible that we have missed some important findings that could add to the discourse of AD development.

2.5.8 Conclusions

This scoping review of the frailty and biomarkers of AD is a starting point to summarize research in this area, generate hypotheses, and direct future research. Briefly, it has uncovered three critical points: 1) there is a dearth of evidence; 2) the few studies that have investigated this suffer from important challenges that limit generalizability; and 3) despite this, there does appear to be a close relationship between frailty and biomarkers of AD that differs slightly across biomarker type and disease stage, specifically it appears that later disease markers are more highly related to frailty. Further research in this area is needed to elucidate mechanisms and more specific relationships. The field of AD

research is ripe for a change in conceptualization of the process leading to dementia expression and examining the influence of frailty may be a useful way to achieve this.

2.7 Rationale

Given the relationships I have now reviewed between frailty with both neuropathology/biomarkers and cognition, it seems reasonable to think that frailty may influence the relationship between them and therefore, play an important role in dementia disease expression. Only one study to my knowledge has explored the relationship between these three constructs[69]. Briefly, it was demonstrated that change in frailty and cognition were highly correlated (ρ=-0.73, $p<0.001$), and neuropathologic burden was an independent predictor of change in both frailty and cognition. Here, I plan to extend these analyses by using a more sensitive frailty measure (the frailty index), directly examining the influence of frailty, and broadening the operationalization of neuropathology.

Against this background, there appears to be some possibility for a new conceptualization of risk for AD, such that frailty influences risk for cognitive impairment by interacting with the pathophysiological process. If this proves true, it may radically change our understanding of how risk for dementia arises, and possibilities for treatment and prevention. Understanding frailty may help us account for some of the discrepancy between neuropathology and dementia and create opportunities for novel therapeutics.

The overall aim of my thesis is to understand how frailty influences the relationship between pathology and clinical presentation of dementia in the hope that it can help explain or account for some of the discrepancy between neuropathology and dementia and create opportunities for novel therapeutics. This will be accomplished by the following objectives, which correspond to the chapters in this thesis and have all been submitted (and in some cases published) as manuscripts to scientific journals.

2.8 Objectives

1) Determine whether frailty moderates the relationship between neuropathology and dementia status in Alzheimer's disease dementia (Chapter 3).
2) Examine the influence of frailty on the relationship between a neuropathological index and all-cause dementia (Chapter 4).
3) Examine the influence of frailty on the relationship between a neuropathological index and all-cause dementia in a population-representative dataset (Chapter 5).
4) Characterize longitudinal change in frailty and how this relates to dementia (Chapter 6).
5) Explore frailty measurement among patients of a memory clinic and their caregivers (Chapter 7).

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Figure 2-1. Frailty network of an individual with moderate (left) and severe (right) levels of frailty.

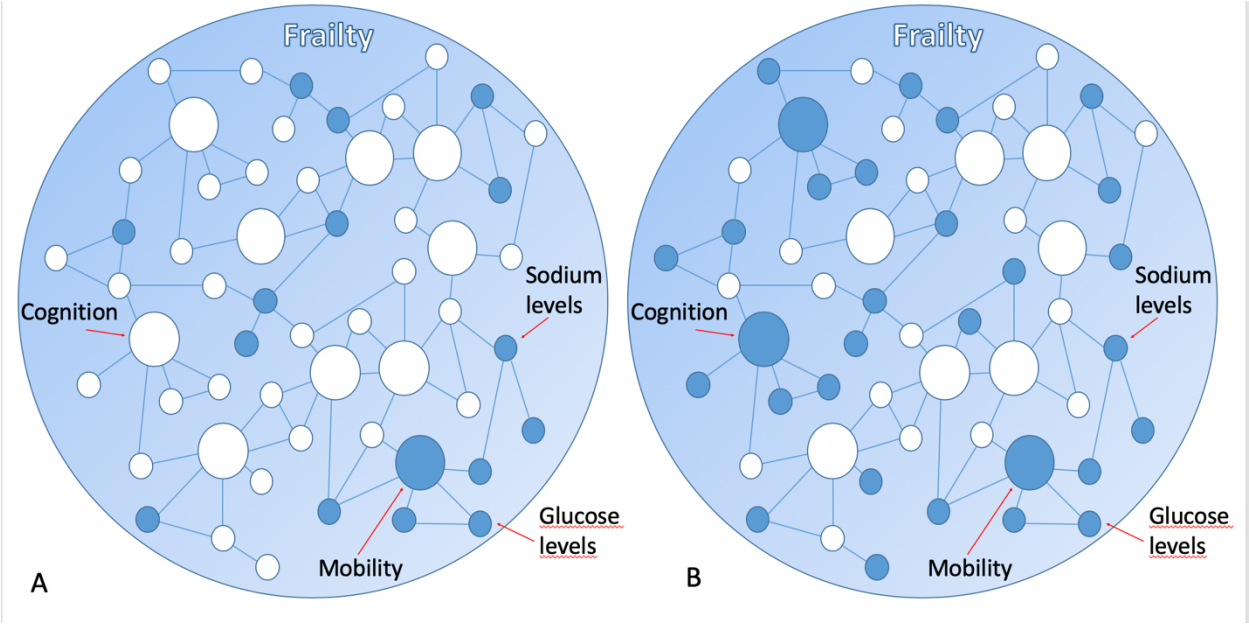

Figure caption. Frailty network of an individual with moderate (left) and severe (right) level of frailty. Each node represents health attributes; bigger nodes represent highly connected attributes (e.g. integrative measures such as mobility and cognition). Smaller nodes represent lower order more singular functions (e.g. sodium levels). When nodes become damaged (solid blue circles), they contribute to the overall frailty of the network; i.e. the human body. When nodes that are highly connected (the large circles) are damaged, they result in failure of higher order functions such as cognitive impairment, falls, or even death. Even though the node representing sodium levels itself as few connections, its nearest neighbors are highly connected. In this way, individual deficits can contribute to

the damage of the highly connected nodes. This is one way to represent how the impairment of high-order functions such as mobility integrate a lot of information about network damage. Panel A represents a network with a moderate degree of frailty; several lower order nodes have been damaged, and mobility has also become impaired. Panel B represents a network with a severe degree of frailty; many lower order nodes have been damaged, and both mobility and cognition have become impaired.

Figure 2-2. Search terms for scoping review.

PUBMED	EMBASE	PSYCINFO
"alzheimer disease"[MeSH] OR	alzheimer disease'/exp OR	DE "alzheimer disease" OR
"dementia"[MeSH] OR	dementia'/exp OR	DE "dementia" OR
"mild cognitive impairment"[MeSH] OR	mild cognitive impairment'/exp OR	-
"memory disorders"[MeSH] OR	memory disorders'/exp OR	DE "memory disorder" OR
alzheimer* [tiab] OR	alzheimer*:ab,ti OR	TI alzheimer* OR AB alzheimer* OR
"dementia"[tiab] OR	dementia':ab,ti OR	TI dementia OR AB dementia OR
"cognitive"[tiab] OR	cognitive':ab,ti OR	TI cognitive OR AB cognitive OR
"cognition"[tiab] OR	cognition':ab,ti OR	TI cognition OR AB cognition OR
"memory"[tiab] OR	memory':ab,ti OR	TI memory OR AB memory OR
senil*[tiab]	senil*:ab,ti	TI senil* OR AB senil*
AND		
"frail elderly" [MeSH] OR	frail elderly'/exp OR	-
frail* [tiab] OR	frail*':ab,ti OR	TI frail* OR AB frail* OR
"deficit accumulation" [tiab] OR	deficit accumulation':ab,ti OR	TI "deficit accumulation" OR AB "deficit accumulation" OR
prefrail* [tiab] OR	prefrail*:ab,ti OR	TI prefrail* OR AB prefrail* OR
pre-frail* [tiab] OR	pre-frail*:ab,ti OR	TI pre-frail* OR AB prefrail* OR
non-frail* [tiab] OR	non-frail*:ab,ti OR	TI non-frail* OR AB non-frail* OR
nonfrail* [tiab]	nonfrail*:ab,ti	TI nonfrail* OR AB nonfrail*
AND		
"amyloidosis"[MeSH Terms] OR	amyloidosis'/exp OR	-
"neurofibrillary tangles"[MeSH Terms] OR	neurofibrillary tangles'/exp OR	DE "neurofibrillary tangles" OR
"Amyloid beta- peptides" [MeSH] OR	amyloid beta- peptides'/exp OR	DE "amyloid precursor protein" OR
"amyloid plaque"[MeSH] OR	amyloid plaque'/exp OR	-
"positron emission tomography" [MeSH] OR	positron emission tomography'/exp OR	DE "positron emission tomography" OR
"tauopathies" [MeSH] OR	tauopathies'/exp OR	-
"tau Proteins" [MeSH] OR	tau proteins'/exp OR	-
"biological markers"[MeSH] OR	biological markers'/exp OR	DE "biological markers" OR
-	-	DE "neuropathology" OR
-	-	DE "neurodegeneration" OR
"magnetic resonance imaging"[MeSH] OR	magnetic resonance imaging'/exp OR	DE "magnetic resonance imaging" OR
neuropath*[tiab] OR	neuropath*:ab,ti OR	TI neuropath* OR AB neuropath* OR
amyloid[tiab] OR	amyloid':ab,ti OR	TI amyloid OR AB amyloid OR
tau[tiab] OR	tau':ab,ti OR	TI tau OR AB tau OR
"neurofibrillary tangle*"[tiab] OR	neurofibrillary tangle':ab,ti OR 'neurofibrillary tangles':ab,ti OR	TI neurofibrillary N0 tangle* OR AB neurofibrillary N0 tangle* OR
"amyloid plaque*" [tiab] OR	amyloid plaque':ab,ti OR 'amyloid plaques':ab,ti OR	TI amyloid N1 plaque* OR AB amyloid N1 plaque* OR
"neuritic plaque*" [tiab] OR	neuritic plaque':ab,ti OR 'neuritic plaques':ab,ti OR	TI neuritic N0 plaque* OR AB neuritic N0 plaque* OR
"magnetic resonance imaging"[tiab] OR	magnetic resonance imaging':ab,ti OR	TI magnetic N0 resonance N0 imag* OR AB magnetic N0 resonance N0 imag* OR
"MRI"[tiab] OR	MRI':ab,ti OR	TI "MRI" OR AB "MRI" OR
"biological marker*"[tiab] OR	biological marker':ab,ti OR 'biological markers':ab,ti OR	TI biological N0 marker* OR AB biological N0 marker* OR
biomarker*[tiab] OR	biomarker':ab,ti OR	TI biomarker* OR AB biomarker* OR
"positron emission tomography" [tiab] OR	positron emission tomography':ab,ti OR	TI "positron emission tomography" OR AB "positron emission tomography" OR
"PET" [tiab] OR	PET':ab,ti OR	TI "PET" OR AB "PET" OR
"neurodegeneration" [tiab]	neurodegeneration':ti,ab	TI neurodegeneration OR AB "neurodegeneration"

Figure 2-3. Flowchart illustrating inclusion process for scoping review.

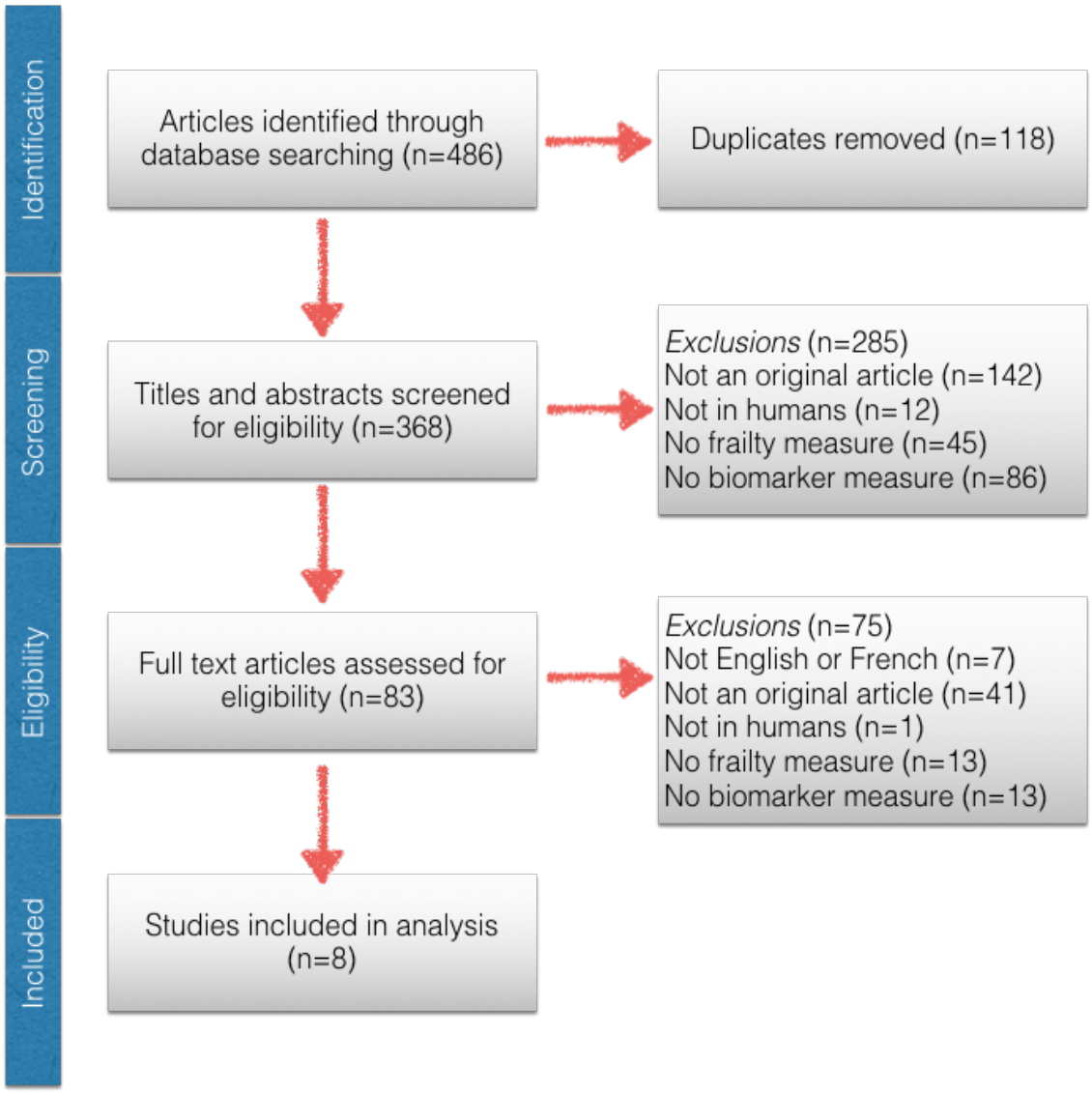

Figure 2-4. Characteristics of studies included in scoping review.

	Sample size (% female; % cognitively impaired at baseline)	Average age of participants at baseline	Study design; average length of follow-up (years)	Study/ database	Biomarker measured	Frailty measurement	Main finding
Koch et al., Neurolog Disorders 2013	72 (sex not reported; 100% mild-moderate AD)	69.9 ± 7.0	Cross-sectional	Tertiary Care Centre in Rome, Italy	**CSF: $A\beta_{42}$, p-tau, t-tau levels**	Rapid or slow progressing AD (based on MMSE)	AD progression significantly associated with t-tau, but not p-tau or $A\beta_{42}$ in one-way ANOVAs.
Gabelle et al., Alzheimers Dement 2014	1147 (60.0% female; 43% MCI)	73.0 ± 4.9	Nested case-cohort; 5.7	French 3-City study (Bordeaux, Dijon, Montpellier)	**Blood plasma: Aβ (40,42,40/42) levels**	Fried Phenotype	Frailty did not significantly influence the relationship between plasma Aβ and mortality in Cox regression models.
Burns et al., Neurology 2008	121 (54% female; 47% early AD)	73.5 ± 6.5	Cross-sectional	Brain Aging Project (Kansas, USA)	**Normalized whole brain volume**	Physical Performance Test	Frailty did not influence the relationship between whole brain atrophy and cardiorespiratory fitness (VO_2 peak) in linear regression models.
Yamada et al., Geriatr Gerontol Int 2013	31 (74% female; 35% MCI, 65% mild AD)	78.9 ± 7.3	Cross-sectional	Memory clinic data from Kyoto, Japan	**Global brain atrophy index (VBM)***	Physical Performance Test	Global brain atrophy was significantly correlated with frailty.
Tay et al., J Nutr Health Aging 2015	99 (35.4% female; 16% MCI, 69% mild AD, 15% moderate AD)	76.6 ± 6.7	Prospective cohort study, 1.0	Memory clinic data from Singapore	**Medial temporal atrophy (T1 MRI, consensus based 0-4 score)**	Modified Fried Phenotype	Baseline frailty and medial temporal atrophy were significantly related, but 1 year change in frailty was not associated with baseline atrophy in regression models.
Buchman et al., Neurology 2008	164 (56.4% female; 35.8% MCI or AD)	88.1 ± 5.7	Cross-sectional	Religious Orders Study/ Memory and Aging Project (USA)	**Post mortem index of AD pathology**	Modified Fried Phenotype	AD pathology was significantly associated with frailty status in adjusted linear regression models, no interaction with dementia diagnosis.
Buchman et al., Neurology 2013	791 (65.7% female; 0% AD)	81.5 ± 6.7	Longitudinal cohort; 6.0	Religious Orders Study/ Memory and Aging Project (USA)	**Post mortem index of AD pathology**	Modified Fried Phenotype	AD pathology was associated with frailty progression over 1 year in adjusted mixed effects models, no interaction with dementia diagnosis. AD pathology explained 8% of the variance in frailty progression.
Buchman et al., J Gerontol A Biol Sci Med Sci 2014	2167 (976 deceased; 72.5% female; 0% AD)	78.5 ± 7.7	Longitudinal cohort; 6.4	Religious Orders Study/ Memory and Aging Project (USA)	**Post mortem index of AD pathology**	Modified Fried Phenotype	Rate of frailty progression, and rate of cognitive decline were both significantly associated with AD pathology, and their change was correlated, suggesting a shared pathologic basis.

CHAPTER 3: Investigation Of Frailty As A Moderator Of The Relationship Between Neuropathology And Dementia In Alzheimer's Disease: Findings From The Rush Memory And Aging Project Cohort Study

3.1 Prologue

Based on the literature reviewed in the previous chapter, I was persuaded that frailty may influence risk for dementia. To this end, I aimed to examine the possible mediating and moderating effects of frailty on the relationship between neuropathology and dementia. As you will read in the section that follows, frailty was a moderator, but not a mediator of this relationship. In essence, this means that frailty is not the mechanism by which neuropathology exerts its effect on cognition (mediation), but rather the relationship between neuropathology and dementia changes over levels of frailty (moderation). In Alzheimer's disease this is particularly interesting because of the investment and subsequent failure of disease-modifying drug trials. I hope in this way that frailty provides a lens through which to better understand dementia expression in late-onset Alzheimer's disease.

3.2 Manuscript information

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Student contribution to manuscript: Lindsay Wallace, together with her supervisor, Kenneth Rockwood conceived the research hypothesis. Lindsay designed, completed and interpreted all analyses (with input from other authors), wrote the first draft and revised all drafts.

3.3 Manuscript

3.3.1 ABSTRACT

Background: The neuropathological features of Alzheimer's disease (AD) do not always correlate well with its clinical presentation; some people who show a high burden of AD pathology at autopsy demonstrate few characteristic clinical symptoms or signs, whereas others with very little AD pathology manifest Alzheimer's dementia. Given how strongly dementia is associated with age, it is possible that frailty, which is associated with both age and dementia, impacts how individuals tolerate AD pathology.

Objective: To examine whether frailty moderates the relationship between AD pathology and Alzheimer's dementia.

Methods: This was a cross-sectional analysis of data from the Rush Memory and Aging Project, a clinical-pathologic cohort study of older adults living in Illinois, USA. Participants underwent annual neuropsychological and clinical evaluations. We included

456 participants (mean age 89·7±6·1, 69·3% females) who died and had autopsy. AD pathology was quantified by a summary measure of neurofibrillary tangles, neuritic and diffuse plaques. Clinical diagnosis of Alzheimer's dementia was based on clinician consensus. Frailty was operationalized using the deficit accumulation approach (41-item frailty index). Logistic regression and moderation modeling assessed relationships between AD pathology, frailty and Alzheimer's dementia.

Findings: Frailty and AD pathology were independently associated with Alzheimer's dementia (OR=1·76, 95% CI 1·54-2·02, p<0·0001; OR=4·81, CI 3·31-7·01, p<0·0001, respectively), adjusting for age, sex, and education. When frailty was added to the model with AD pathology, model fit improved ($chi^2(1)=86$, p<0·001). Frailty interacted with AD pathology (OR=0·73, CI 0.57-0.94, p=0·015); people with higher frailty had a weaker relationship between AD pathology and Alzheimer's dementia.

Interpretation: The degree of age-related deficit accumulation improved the relationships between AD pathology and Alzheimer's dementia. That frailty is related to both odds of Alzheimer's dementia and disease expression has implications for clinical management. Further research should assess trajectories of change in frailty and cognition to better elucidate this complex relationship.

3.3.2 Research in Context

Evidence before this study

Using the terms 'neuropathology', 'frailty', 'dementia', 'Alzheimer's disease' and their synonyms we searched GoogleScholar and PubMed for relevant articles between Jan 2017 and Jul 2018 in English or French. The dementia literature raises several issues for

which no pathophysiologic mechanism has yet been able to account. 1) The weak relationship between AD pathology and dementia (i.e. AD pathology does not appear to be necessary or sufficient); 2) the high prevalence of mixed dementia; 3) the many, diverse risk factors; and 4) the failure of clinical trials.

Added value of this study

The moderation model presented here aims to respond to these challenges by explaining variance in the relationship between AD pathology and dementia, showing how AD pathology may be an interacting risk factor in a continuum of events that can eventually lead to the dementia syndrome, and opens the door for novel interventions that go beyond halting AD pathology progression.

Implications of all the available evidence

Dementia expression is proving to be multiply determined, and a single mechanism is unlikely to explain the diverse expressions we see in the people who most often develop dementia: those who are older and have multiple comorbidities. This characterizes an emerging conceptualization of dementia (and particularly AD) as a complex disease of ageing, rather than a single disease entity marked by genetic risk or particular protein abnormality. In a field with so many competing claims about individual risk factors, understanding how they work together to give rise to clinical dementia may offer a new way to understand dementia risk and target treatment.

3.3.3 Introduction

The neuropathological features of Alzheimer's disease (AD; including amyloid-based plaques and neurofibrillary tangles) do not always correlate well with the clinical expression of dementia (i.e. cognitive and functional decline)[1]. Many people with a high burden of AD pathology at autopsy had few characteristic clinical symptoms or signs, whereas others with little AD pathology suffered from Alzheimer's dementia. Together, these findings suggest that some latent factor influences who can 'tolerate' higher levels of AD pathology without suffering from dementia and who is more vulnerable to the pathology. While a minority of people who develop Alzheimer's dementia are young and otherwise healthy (typically with familial AD), the vast majority of people who develop Alzheimer's dementia are older with multiple other health problems. People with multiple, age-related health deficits are often considered frail[2]. Therefore, frailty may help explain the relationship between AD pathology and the clinical expression of dementia.

Frailty represents a state of decreased physiological reserve and increased vulnerability to adverse health outcomes (including hospitalization and death) compared to others of the same age[3]. Frailty has been most frequently operationalized using a deficit accumulation approach or a phenotypic/syndromic approach[4,5]. Unfortunately, people who are frail are routinely excluded from clinical trials testing treatments aimed at improving their condition[6].

Previous research has shown that frailty is related to neuropathological features of AD as well as cognitive decline and dementia[7–9]. Frailty and Alzheimer's dementia share many

risk factors and clinical features, including age, inflammation, functional impairment, and atypical illness presentation[8]. The link between frailty and Alzheimer's dementia has been demonstrated both in clinical and epidemiological settings, but less so using neuropathological studies. To date, such studies assessing AD pathology have been restricted to the syndromic/phenotypic definition of frailty and none have examined the moderating effect of frailty[9,10].

We hypothesized frailty to be a latent factor that moderates clinical dementia expression in relation to AD pathology. By reducing an individual's ability to tolerate AD pathology, frailty could precipitate dementia disease expression where it might have remained asymptomatic in a non-frail individual. Our objective was to examine the impact of frailty on the relationship between AD pathology and the expression of Alzheimer's dementia.

3.3.4 METHODS

Overview

Data come from the Rush Memory and Aging Project (MAP), which has been described elsewhere[11]. Briefly, MAP is a clinical-pathologic cohort study enrolling over 2100 older persons without dementia from about 40 residential facilities, senior and subsidized housing, church groups, and social service agencies in Northeastern Illinois, beginning in 1997. It aimed to identify factors associated with maintenance of cognitive health despite the accumulation of neuropathologic lesions. This cohort has been followed for 21 years with clinical evaluation data collected annually, via home visits. Participants provided

blood samples and underwent a detailed clinical evaluation, including cognitive assessments. All participants signed the Anatomical Gift Act and agreed to donate their brain, spinal cord, and other biospecimens at death (n=675). MAP was selected for our project as it is unique in combining comprehensive clinical and cognitive assessments, essential neuropathological characterization, and sufficient data to allow for the operationalization of a frailty index (FI).

Dependent variables- Dementia status

A clinical diagnosis of cognitive status was done at each annual assessment, comprising a three-step process: 1) computer scoring of a neuropsychological battery including 19 instruments (e.g. word list recall, category fluency, digit ordering, Stroop word reading)[12,13]; 2) clinical judgment by a neuropsychologist blinded to participant demographics; 3) diagnostic classification by a clinician (neurologist, geriatrician, geriatric nurse practitioner, or neuropsychologist) [14,15]. Clinical diagnoses of Alzheimer's dementia are based on criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA)[10]. For the analyses presented here, people diagnosed with mild cognitive impairment or other forms of dementia were excluded; our dementia status variable refers to only Alzheimer's dementia or no dementia.

Independent variables –Frailty Index (FI)

The FI is a health state measure designed to integrate multiple types of health information. The FI reflects the extent of illness and vulnerability to adverse outcomes and proximity to death[3]. It reliably predicts adverse outcomes in large health databases from many countries[3]. An FI can be created using different routinely collected clinical information such as symptoms, signs, disabilities and diseases that meet standard criteria[16]. The Frailty Index (FI) = (number of health deficits present) / (number of health deficits measured). For example, a person with 10 of 40 potential deficits measured has an FI score of 10/40 = 0·25. The FI takes advantage of the human organism's high redundancy, making it replicable across different databases, even when different items, and numbers of items, are used[3].

We created an FI from health variables obtained at each clinical evaluation. Candidate variables included symptoms, signs, comorbidities, and function. Variables were screened for inclusion based on standard procedures[16]; variables strongly related to the outcome (i.e. cognitive variables) were excluded. Our 41-item FI can be found in Appendix B. Higher values of the FI indicate poorer health. For the purpose of interpretation, the FI value was multiplied by 10 so that the odds ratio would represent the proportion change for an increased increment of 0·1 of the FI (an additional 3-4 deficits).

Independent variables –neuropathological data

MAP includes data from post-mortem neuropathologic evaluation. Global AD pathology burden has been quantified and described elsewhere[9,13,17]. Briefly, it is a quantitative

summary of three AD pathologies (neuritic plaques, diffuse plaques, and neurofibrillary tangles), as determined by microscopic examination of silver-stained slides from five regions (midfrontal, midtemporal, inferior parietal, and entorhinal cortices, and the hippocampus). A summary score for each of the three pathologic findings is obtained by dividing the count for each region by the corresponding standard deviation and then averaging the five scaled regional measures to obtain a scaled mean. The three scaled means are then averaged and the square root is calculated to obtain the measure of AD pathology[18]. Higher values on the AD pathology measure indicate greater burden of pathology. For our sensitivity analyses, counts of the three individual pathological measures were also used, as were mean percent volume of amyloid (calculated over eight regions: hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal, angular gyrus, calcarine cortex, anterior cingulate, superior frontal cortex), and Braak staging (a score between 1 and 6 of tangle pathology burden and spread), where higher scores are worse[19].

Independent variables –confounding variables

Age, sex, and education, and *APOE* status were evaluated as confounders with respect to the outcome. Age and education were measured in years, whereas sex was a binary variable. Age was calculated from birth to date of cognitive assessment. Sex and education were self-reported. *APOE* status (i.e. presence of ≥1 e4 allele) was obtained via genotyping of brain tissue using high-throughput sequencing of codons 112 (position 3937) and 158 (4075) of exon 4 on the *APOE* gene on chromosome 19[20].

Statistical analysis

We investigated characteristics and validated the FI using a standard approach including descriptive statistics and appropriate statistical tests. For the purpose of describing our sample, we categorized participants into frailty groups using the median (FI=0·41) as the cut-point; this cut-point is very close the cut-point typically used to distinguish between moderately and severely frail people[21].

We used logistic regression to examine the relationship between neuropathological markers (exposure, continuous variable), FI (exposure, continuous variable), and dementia status (outcome, binary variable). We then assessed whether the FI improved model fit when added to an adjusted model including AD pathology, using Aikike Information Criterion (AIC), Bayesian Information Criterion (BIC), and deviance (-2 log likelihood).

We built moderated logistic regression models (Process syntax[22]) using 5000 bootstrapped samples and bias-corrected confidence intervals. We used this to report the relationship between AD pathology and Alzheimer's dementia at three different levels of frailty: the mean FI value ("intermediate frailty"), one standard deviation above ("high frailty"), and one standard deviation below ("low frailty").

All analyses were adjusted for age, sex, and education. Sensitivity analyses examining measures including a modified frailty phenotype, Braak stage, amyloid burden (calculated as percent volume), depression (as measured by the Centre for Epidemiologic

Studies 10-item Depression scale), and polypharmacy (as measured by the sum of prescription medications) were conducted. Details on these measures can be found elsewhere[17]. All analyses were conducted using SPSS 24.

Approval from the Dalhousie and Nova Scotia Health Authority Research Ethics Boards was sought before initiating any of the study procedures. MAP was approved by the Institutional Review Board of Rush University Medical Center. All participants signed an informed consent and Anatomical Gift Act for organ donation.

3.3.5 RESULTS

Since its inception 21 years ago, 3869 persons expressed interest, of those 2112 (54.9%) enrolled in MAP and 193 (9.1%) participants have discontinued study participation, reflecting an average loss to follow-up of ~1%. The dataset frozen January 2017 included 1843 of enrolled participants, of whom 831 had died, and 675 had complete autopsy data. Of those with autopsy records, 456 had either no dementia or Alzheimer's dementia, and had enough information to create a frailty index and were therefore included in this analysis (Appendix 3-A). Average time from last assessment to death was 0·89 years (median 0·61), average age at death was 89·7 years (standard deviation [SD] 6·1), and most were women (69·3%). Over half had a diagnosis of possible or probable Alzheimer's dementia at their last clinical assessment (53·1%; n=242). The mean FI for the whole sample was 0·42 (SD 0·18), with a median of 0·41 and range of 0·04-0·91. The 95th and 99th percentile was 0·71 and 0·81, respectively. The FI had a characteristic skewed distribution with a long right tail. People who had high FI scores (FI>0·41;

n=223) were older, had lower MMSE scores, more likely to have a dementia diagnosis, and higher Braak stage (Table 3-1).

Importantly, 35 people (7%) demonstrated a high burden of AD pathology without having been diagnosed with dementia and 50 people (10%) had Alzheimer's dementia, but demonstrated a low burden of AD pathology (Table 3-2). Therefore, for about one person in six the relationship between AD pathology and dementia was weak. The mean FI was significantly higher for people with Alzheimer's dementia compared to those without, however the mean FI was highest among people with Alzheimer's dementia with a low burden of AD pathology (Table 3-2). Among people with a low burden of AD pathology, the prevalence of Alzheimer's dementia was much higher in those who had high frailty than those with low frailty (69·0% vs. 5·3%; Table 3-3).

FI scores and AD pathology were independently associated with dementia status (Odds Ratio [OR] =1·76, 95% CI 1·54-2·02, p<0·0001; and OR=4·81, 95% CI 3·31-7·01, p<0·0001, respectively), after adjusting for age, sex, and education. When the FI was added to a model with AD pathology, the model fit improved according to the reduction in AIC (533·48 to 449·41), BIC (554·10 to 474·15), and deviance (523·48 to 437·41), which demonstrated a significant improvement (chi^2=86, p<0·001). Further, there was a significant interaction between the FI and AD pathology (OR=0·73, 95% CI 0.57-0.94, p=0·015).

Moderation analyses demonstrated that the relationship between AD pathology and dementia status changed over levels of frailty, as increasing frailty weakened the relationship (Figure 3-1).

Sensitivity analyses were undertaken to determine whether the relationship was being driven by the type of AD pathology. Only neuritic plaques demonstrated a significant interaction with the FI in predicting dementia status (OR=0·80, 95% CI 0.66-0.96, p=0·019). Moderation analyses suggested that with increasing frailty, the relationship between neuritic plaques and dementia status weakened (consistent with our original results). We also explored the effects of amyloid calculated as percent volume occupied (rather than plaque counts) and found that the relationship was consistent (i.e. significant interaction between amyloid and FI: OR=0·96, 95% CI 0.93-0.996, p=0·027). Braak staging also significantly interacted with the FI (OR=0·80, 95% CI 0·68-0·93, p=0·004) in relation to dementia status, and moderation analyses suggested that with increasing frailty the relationship between Braak stage and dementia status weakened (consistent with original results). We investigated whether including people with MCI in the reference group (i.e. no dementia) would alter the results and found that while the frailty index and AD pathology remained significant independent predictors of Alzheimer's dementia, their interaction was non-significant. To be sure that the results were not being driven by activities of daily living variables, we recreated the FI excluding these variables (those indicated with a star in Appendix B; n=14), and found similar results. We also controlled for the effects of possible risk factors, including self-reported history of stroke, hypertension, diabetes, congestive heart failure (CHF), and depression (as measured by

the CES-D) and found that while stroke and CHF were significantly associated with dementia status, the frailty*pathology interaction remained significant. When the frailty phenotype (z-score; as detailed elsewhere[9]) was used in place of the FI, it was found to significantly predict the outcome, but with no significant interaction with AD pathology.

3.3.6 Discussion

Three main conclusions can be drawn from our results. First, people with Alzheimer's dementia but with a low burden of AD pathology have the highest frailty levels, suggesting that frailty is implicated in dementia expression in this group. Its effect could arise by reducing the threshold of AD pathology needed to cause clinical disease, or as a marker of impaired repair processes that might allow for the AD pathology to be better tolerated[2]. Further, frailty levels were no higher than average in people with no Alzheimer's dementia but a high burden of AD pathology. Taken together, these results suggest that the frailer an individual is, the less likely that person is able to tolerate a given burden of AD pathology. Second, frailty improves the fit of a model relating AD pathology with dementia status. This is likely because frailty is able to account for several diverse causal pathways in older adults, in whom dementia is multiply determined[2,18,23,24]; Third, frailty is a significant moderator in the relationship between AD pathology and dementia status; increasing frailty weakens the relationship between AD pathology and dementia.

Together, these findings support the idea that frailty influences the clinical expression of dementia. While frailty may reduce the threshold for AD pathology to cause cognitive

decline, frailty is likely also contributing to other mechanisms in the body that give rise to dementia, weakening the direct link between cognition and dementia. This suggests that frailty should be considered in clinical care and management. It supports the view of late-life dementia as a multiply determined state, with many factors contributing to its development.

Our results are consistent with existing literature. Dementia is highly linked with ageing[25], yet the passage of time alone cannot cause mechanistic failures or account for the heterogeneity in health status among people of the same age. Therefore, failing mechanisms manifested by age-related signs, symptoms, and disease can be informative and the FI is able to package this information (i.e. reduce the dimensionality) into a single value that represents health status. Studies are beginning to suggest that 'age-related' disease are actually more frailty-related[26].

Frailty has also been linked with both cognition and dementia status, cross-sectionally and longitudinally, whether frailty is measured by the FI or phenotype[7,23,27]. While the construct of cognitive frailty remains debated, some researchers view it as a clinical entity with cognitive impairment related to physical causes and potentially a target for intervention in early or preclinical dementia[28]. A previous analysis of the dataset used here revealed that higher baseline frailty (as measured by a modified frailty phenotype) and change in frailty increased the risk for incident Alzheimer's dementia at 3-years. Higher baseline frailty was also associated with lower baseline cognition, and faster cognitive decline[12]. Change in frailty has been associated with change in cognition[13,29].

Here we build on work that has related frailty to AD pathology in two ways. First, we show that this relationship still holds with the broadly construed approach to frailty that is deficit accumulation. Second, we show that the degree of frailty helps explain the circumstances under which AD pathologic markers and dementia are less well correlated; people with a low degree of frailty were better able to tolerate AD pathology, whereas those with higher degrees of frailty were more likely both to have more AD pathology and for it to be expressed as dementia. This finding was robust; it held when controlled for vascular factors and when functional deficits were excluded from the FI.

In a recent scoping review, we synthesized evidence from existing studies that measured both AD biomarkers (such as in-vivo protein abnormalities, MRI abnormalities, or post-mortem plaque and tangle pathology) and frailty[24]. Ten studies were identified, of which eight reported direct relationships between biomarkers and frailty. All of these eight studies demonstrated a positive relationship between biomarkers and frailty (regardless of measurement) suggesting that frailty and AD pathology are somehow intrinsically related. Here, we confirm this relationship and suggest some mechanisms of shared etiology, and how these two factors interact to produce dementia.

When considering how dementia and frailty may be mechanistically related, it is clear that they have many commonalities. Their most potent risk factor is age. Risk factors and proposed mechanisms are numerous and diverse. This suggests that the accumulation of deficits resulting in cognitive impairment or frailty may be more dependent on how

insults are dealt with by the body (i.e. removal or repair of damage) rather than the specific nature of the deficit.

The dementia literature raises several issues for which no pathophysiologic mechanism has yet been able to account, including 1) the relatively weak relationship between AD-specific pathology and Alzheimer's dementia (i.e. Alzheimer's pathology does not appear to be necessary or sufficient), 2) the high prevalence of mixed dementia, and 3) many, diverse risk factors. Our current model responds to these challenges by explaining some of the heterogeneity between AD pathology and dementia, showing how AD pathology may be one factor in a continuum of events that can eventually lead to dementia, and opens the door for novel interventions that go beyond halting AD pathology progression.

Our data must be interpreted with caution. Secondary analyses are limited in that not all the relevant items necessarily have been collected. Here, however, the relevant measures (cognition and dementia status, AD pathology, and items to construct an FI) were generally available. Further, this was a cross-sectional analysis in which AD pathology was measured post-mortem. To overcome this, we used frailty measurement and dementia status from the last clinical interview before death (mean 0.89 years pre-mortem, median 0.61). As AD pathology begins to accumulate decades before clinical manifestations of the disease[30], and pathology at death is related to the rate of cognitive decline over many years prior[31], we can be relatively confident that this limitation would not significantly bias our results. Nevertheless, our results only confirm associations between frailty, Alzheimer's dementia, and AD pathology. Future studies should examine

longitudinal relationships between frailty, cognition, and biomarkers of Alzheimer's dementia in order to establish causation, and include more diverse pathological lesions to better understand the interplay between pathology and the dementia syndrome.

As frailty measurements were taken close to death, this raises the possibility that the recorded frailty state is reflective of terminal decline. If this were to be the case, the relationship between AD pathology and dementia status among people with high frailty may be overrepresented, though this would not explain cases where frailty was low and AD pathology was high in people with dementia.

Competing risks is also a consideration in interpretation; if participants died of causes other than those related to dementia without the chance to develop dementia, the results may be confounded. We did not have access to cause of death and could not control for this.

Our sampling was largely from retirement homes in Illinois. Though this may introduce bias, the utility of the data to represent varying cognitive and neuropathological profiles was overriding. Further, not only does the study enjoy extraordinarily high follow-up and autopsy rates (reducing bias and increasing internal validity), but clinical evaluations performed in MAP are identical to those in the population-based Chicago Health and Aging Project. All risk factor associations that have been examined in both cohorts have cross replicated. Nevertheless, future research should address this hypothesis using a population-based sample.

Our results suggest that dementia expression is multiply determined, and a single mechanism is unlikely to explain the diverse expressions we see in the people who most often develop dementia: those who are older and have multiple comorbidities. Individuals with even a low level of AD pathology may be at risk for dementia if they have high levels of frailty. This contributes to an emerging conceptualization of dementia (and particularly Alzheimer's) as a complex disease of ageing, rather than a single disease entity marked by genetic risk or particular protein abnormality[32]. This has the potential to improve our understanding of disease expression mechanisms, explain failures in pharmacological treatment, and aid in development of more appropriate therapeutic targets, approaches and measurements of success. These results may therefore contribute to more effective prevention and management of Alzheimer's dementia. This work is a novel contribution to the existing literature as it bridges epidemiological methodologies and clinical neuropathology in relation to deficit accumulation in Alzheimer's dementia and proposes a unique model of Alzheimer's dementia development.

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Table 3-1. Descriptive characteristics of the sample.

	All (n=456)	Frailty index <0·41 (n=233)	Frailty index ≥ 0·41 (n=223)
Age at baseline (mean±SD)	83·1±5·9	82·1±5·8	84·2±5·8*
Age at death (mean±SD)	89·7±6·1	88·3±6·2	91·2±5·6*
Sex (% female)	69·3	64·4	74·4
Years of education (mean±SD)	14·4±2·9	14·5±3·0	14·3±2·9
Frailty index (last assessment before death; mean±SD)	0·42±0·18	0·28±0·09	0·58±0·10*
AD-type dementia diagnosed before death (%)	53·1	33·9	73·1*
MMSE (last assessment before death; mean±SD)	19·8±9·8	23·4±8·2	16·1±10·0*
% meeting CERAD criteria (high or intermediate likelihood based on amyloid)	67·7	58·7	77·2*
Braak stage (mean±SD)	3·7±1·2	3·4±1·2	3·9±1·1*
APOE genotype (≥1 e4 alleles; %)	23·2	20·6	26·0

*p<0·05

SD=Standard deviation; AD=Alzheimer's Disease; MMSE=Mini Mental State Examination; CERAD=Consortium to Establish a Registry for Alzheimer's Disease

Table 3-2. Mean frailty index values (mean±standard deviation) by neuropathological burden and dementia status.

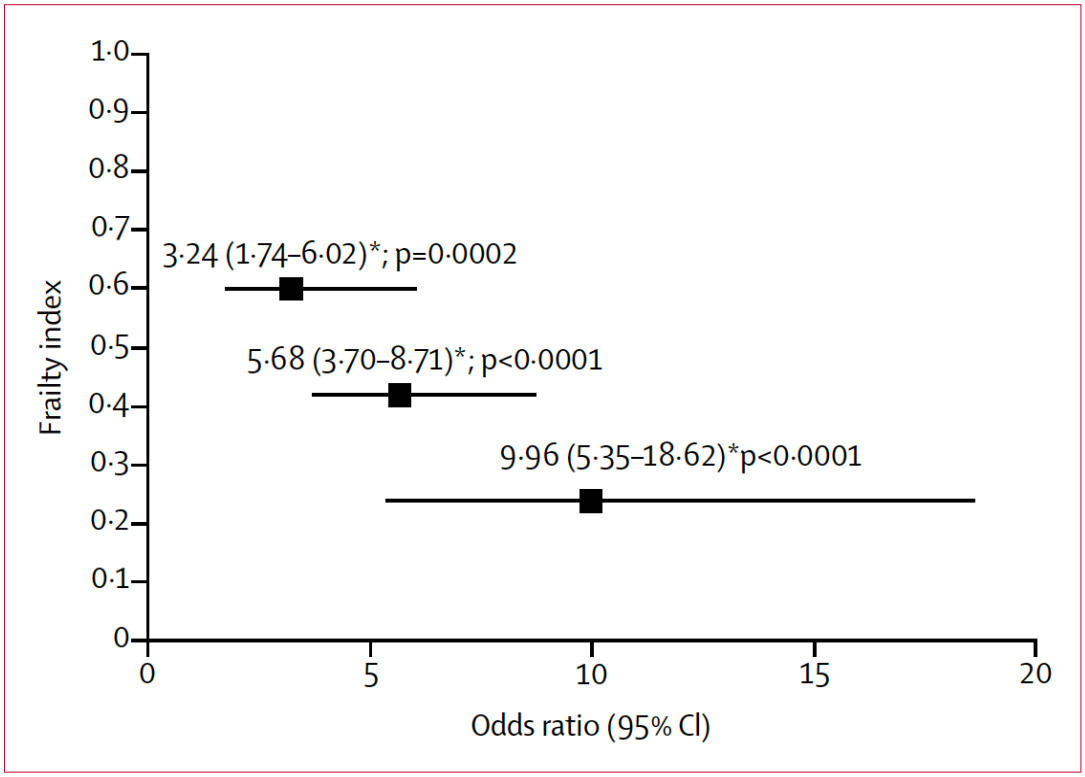
	Low burden of pathology	Intermediate burden of pathology	High burden of pathology	
No AD*	0·33±0·14 (n=102)	0·36±0·15 (n=77)	0·35±0·15 (n=35)	*F=1·01, p=0·37*
AD	0·55±0·15 (n=50)	0·50±0·18 (n=75)	0·46±0·18 (n=117)	*F=4·54, p=0·012*
	F=82·8, p<0·001	*F=27·17, p<0·001*	*F=10·88, p<0·001*	

*AD=Alzheimer's dementia

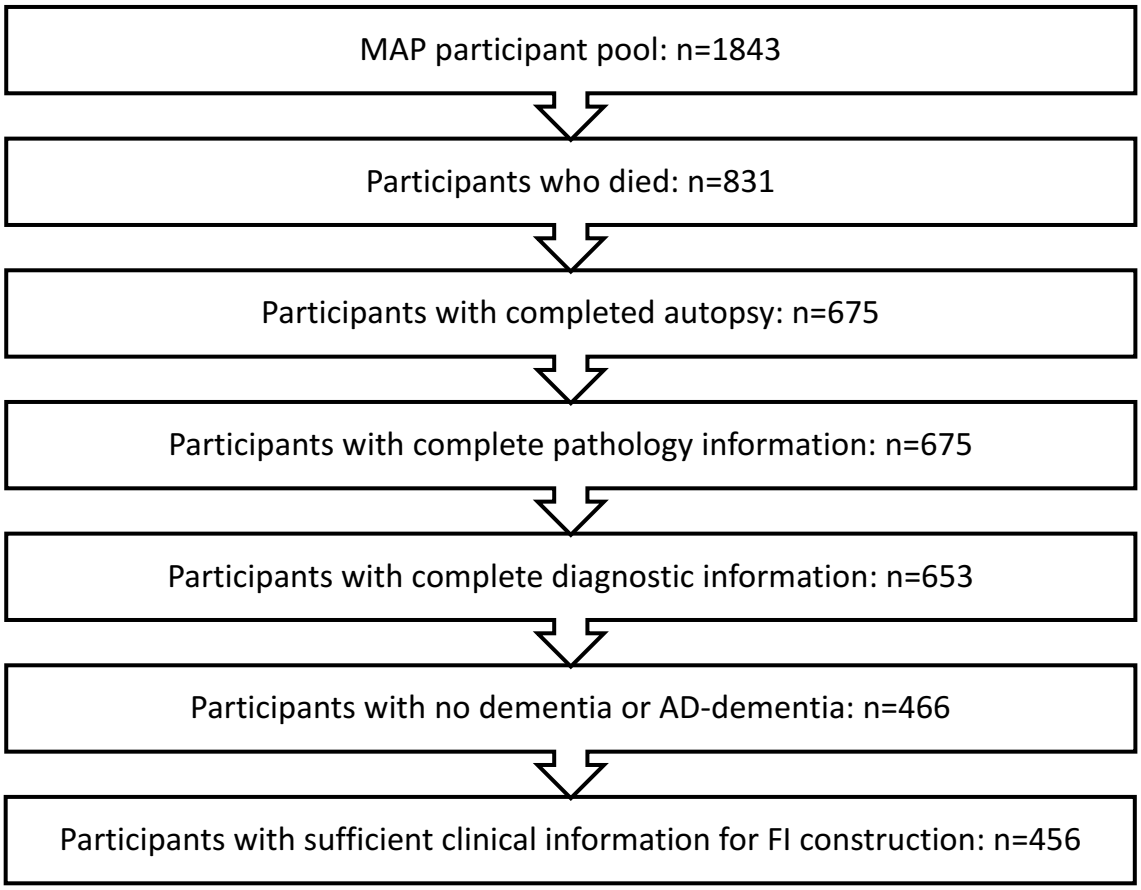
Table 3-3. Sample size and percent of sample with Alzheimer's disease by frailty index values and neuropathology burden.

		Frailty index			
		Low	Med	High	*Total*
Neuropathology burden	Low	n=56; 5·3%	n=54; 33·3%	n=42; 69·0%	*n=152; 32·9%*
	Med	n=54; 29·6%	n=48; 45·8%	n=50; 74·0%	*n=152; 49·3%*
	High	n=45; 66·6%	n=53;73·6%	n=54; 88·8%	*n=152; 77·0%*
	Total	*n=155; 31·6%*	*n=155; 51·0%*	*n=146; 78·1%*	*n=456; 53·1%*

Figure 3-1. Conditional effect of Alzheimer's disease pathology on Alzheimer's dementia status at values of the moderator (frailty), adjusted for age, sex, and education; n=456.



Appendix 3-A: Flowchart of participant inclusion.



Appendix 3-B: Items included in the Frailty Index (n=41).

• Walking speed • Physical activity (5 item sum) • Finger Tap • Leg stand • Purdue pegboard • Pinch strength • Hypertension • Cancer • Diabetes • Head injury • Congestive heart failure • Claudication • Diastolic blood pressure • Joint pain Number of joints with problems • Osteoporosis • Polypharmacy • Depression (CESD) • Stroke • Everything I did was an effort (fatigue) • I could not get going (fatigue)	• Shopping* • Using the telephone* • Handling finances* • Handing medications * • Meal preparation* • Light housekeeping* • Heavy housekeeping* • Travelling within community* • Eating* • Bathing* • Dressing • Toileting* • Walking* • Getting from bed to chair* • Take care of home • Walk half a mile • Walk up and down stairs • Body Mass Index • Grip strength • Heart problems

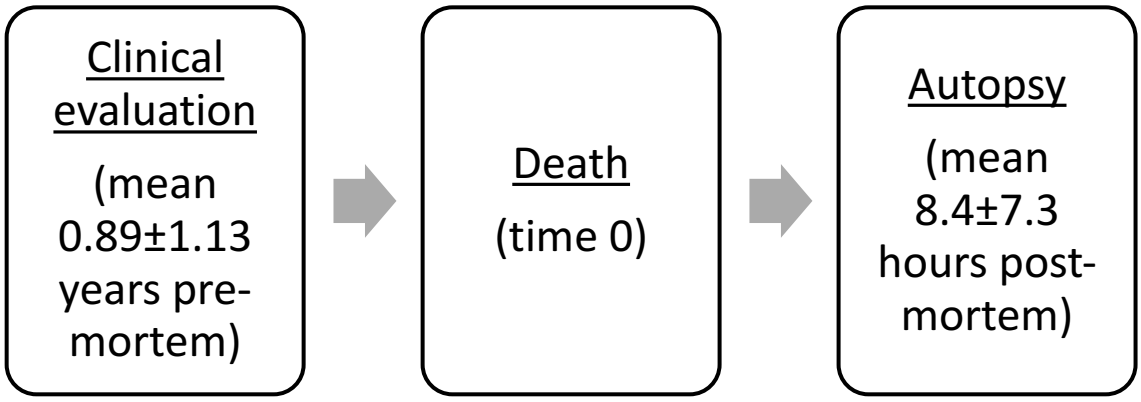
*Excluded in sensitivity analyses where a shorter Frailty Index excluding Activities of Daily Living was also created.

Appendix 3-C. Clinical dementia diagnosis descriptive analysis.

	Sample size	Percent
No cognitive impairment	215	32·9
Mild cognitive impairment*	178	27·3
Alzheimer's disease	251	38·4
Other primary cause of dementia	9	0·01
Total	653	100

*One cognitive domain impaired

Appendix 3-D. Measurement timeline.



CHAPTER 4: Neuropathological Burden And The Degree Of Frailty In Relation To Global Cognition And Dementia

4.1 Prologue

After exploring the influence of frailty on the relationship between neuropathology and Alzheimer's dementia and the literature surrounding it, it became clear that the culture of Alzheimer's research is shifting towards increasingly recognizing that Alzheimer's dementia is largely associated with mixed pathology, and the causal relationship between plaques/tangles and dementia is strained by evidence from community-based samples that show many people have neuropathological features of Alzheimer's disease but do not experience dementia. To this end, I wanted to extend my exploration of the influence of frailty on dementia expression to the whole spectrum of cognition so I broadened the analytic criteria to include participants with mild cognitive impairment and other dementias as well as Alzheimer's. Further, I expanded the definition of neuropathology to include mixed pathology. As such, I aimed to test whether my results from the previous chapter held and were generalizable to the whole cognitive spectrum.

4.2 Manuscript information

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Permission: N/A.

Student contribution to manuscript: Lindsay Wallace, with her supervisor, Kenneth Rockwood conceived the research hypothesis. Lindsay designed and undertook the analysis, interpreted results, wrote first draft of manuscript and revised all subsequent drafts.

4.3 Manuscript

4.3.1 ABSTRACT

Objective: To determine the relative contributions of neuropathological burden and the degree of frailty to global cognition and odds of dementia.

Methods: This was a secondary analysis of a prospective cohort study of older adults living in Illinois, USA. Participants underwent an annual neuropsychological and clinical evaluation. We included 625 participants (mean age 89.7±6.1 years; 67.5% female) who died and had autopsy. Neuropathology was quantified by an index measure of ten neuropathological features: β-amyloid deposition, hippocampal sclerosis, Lewy bodies, tangle density, TDP-43, cerebral amyloid angiopathy, arteriolosclerosis, atherosclerosis, gross and chronic cerebral infarcts. Dementia status was based on clinical consensus and coded as no cognitive impairment, mild cognitive impairment, or dementia. Global cognition was assessed using a battery of 19 tests spanning multiple domains. Frailty was operationalized using a 41-item, frailty index. Regression analyses quantified relationships between neuropathology, frailty, and dementia.

Results: Both frailty and a neuropathology index were independently associated with global cognition and dementia status. These results held after controlling for traditional

pathological measures in a sample of participants with Alzheimer's-type dementia. Frailty improved the fit of the model for dementia status ($X^2(2)=72.64$; $p<0.0001$), and explained an additional 8-12% of the variance in the outcomes.

Interpretation: Dementia is a multiply determined condition, to which both general health, as captured by frailty, and neuropathology significantly contribute. This integrative view of dementia and health has implications for prevention and therapy; specifically, future research should evaluate frailty as a means of dementia risk reduction.

4.3.1 Introduction

As populations age, the burden of dementia increases, lending force to the need for a contemporary understanding of dementing illnesses. By convention, Alzheimer's dementia is a clinical syndrome that is most commonly due to mixed Alzheimer's disease (AD), as well as other pathologies, i.e., mixed pathology[1–5].

Recently, we demonstrated that frailty moderated the relationship between the pathological features of AD and dementia status; specifically, higher frailty was associated with increased odds of dementia among people with low levels of plaques and tangles[6]. This work is in line with several other studies that suggest that frailty is associated with the burden of neuropathology[7], with the accumulation of AD-related biomarkers[8], and with cognition[9,10] and dementia status[11]. This emerging conceptualization of late-life Alzheimer's disease as a multiply determined age-related condition leads to questions of how diverse types of neuropathology contribute to

dementia (regardless of clinical diagnosis), and how frailty may influence this relationship across the cognitive spectrum.

Prior work has shown that a composite metric of physical frailty based on the categorical measure captured in the frailty phenotype and its individual components are associated with the level and rate of cognitive decline and predicts incident MCI and AD dementia[10,12–17]. Moreover, physical frailty together with other related motor constructs (i.e. bradykinesia, rigidity, parkinsonian gait and tremor) were more strongly associated with incident AD[18]. Physical frailty and its components including grip strength, gait speed, body mass index and physical activity are associated with incident Alzheimer's dementia and related disorders[4,9,19–21]. Modeling the trajectories of both cognition and physical frailty simultaneously showed that the rates of progression of physical frailty and cognitive decline in the same individuals were strongly correlated, and were correlated with AD neuropathology[9]. Given the strong relationship between frailty and cognitive decline, it is possible that they share a common pathologic basis.

Here, we extend this work by using broader definitions of both frailty and of neuropathology to better understand the mechanisms by which dementia arises. This approach, which considers age-related deficit accumulation both in general health and in brain pathology allows us to explicitly address the relationship between ageing and dementia. In particular, we can consider the extent to which general age-related deficit accumulation is related to the accumulation of neuropathology. Specifically, our objective was to determine the relative contributions of neuropathology and the degree of

frailty, both measured using a deficit accumulation approach, to global cognition and odds of dementia.

4.3.3 METHODS

Study design & participants

Data presented here were accessed from the Rush Memory and Aging Project (MAP), described elsewhere[22]. Briefly, MAP is a clinical-pathologic cohort study that, since 1997 has enrolled over 2100 older adults from residential facilities, senior and subsidized housing, church groups, and social service agencies in Northeastern Illinois. This cohort has been followed for over 20 years with annual clinical evaluations. Participants were eligible for enrollment if they were able and willing to sign both the informed consent and an Anatomical Gift Act for donation of their brain, spinal cord, nerve, muscle, and other biospecimens at death. Participants also signed a repository consent that allowed their data to be repurposed for other studies. The MAP study was approved by an Institutional Review Board of Rush University Medical Center, Chicago, IL, USA. Data access can be requested at www.radc.rush.edu.

Measures

Neuropathological Index: 10 neuropathologic features were quantified at post-mortem autopsy. 1) Overall level of β-amyloid was quantified as percent area of cortex occupied by β-amyloid as stained using immunohistochemistry over eight regions: hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal, angular gyrus, calcarine cortex, anterior cingulate cortex, superior frontal cortex[6]. As there are no appropriate clinical

cutpoints for this continuous measure, β-amyloid was recoded between 0 and 1 based on quartiles (0-0.67; 0.68-4.16; 4.17-8.17; 8.18-22.94). 2) Typical hippocampal sclerosis was evaluated as not present/possible or present but atypical (=0), and definitely present (=1) according to severe neuronal loss and gliosis in CA1 and/or subiculum[23]. 3) Lewy body pathology was determined by distribution of α-synuclein (as stained for α-synuclein immunostain) in midfrontal, midtemporal, inferior parietal, anterior cingulate, entorhinal and hippocampal cortices, basal ganglia, and midbrain). Severity was coded as not present (=0), nigral-predominant (=0.33), limbic-type (=0.67), and neocortical type (=1)[24]. 4) Cortical tangle density was quantified as the mean density (per mm^2) of eight regions: hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal, angular gyrus, calcarine cortex, anterior cingulate cortex, superior frontal cortex, as stained by immunochemistry. This measure of paired helical filaments (PHF) tau tangles was recoded for analysis into quartiles (0-1.69; 1.70-4.00; 4.01-8.78; 8.79-78.52)[6]. 5) TDP-43 pathology was staged using data from six regions (hippocampus-CA1 and dentate, amygdala, midfrontal, midtemporal, and entorhinal cortices), using immunohistochemistry. It was coded as no pathology (=0), stage 1-localized to amygdala only (=0.33), stage 2- extension to hippocampus/entorhinal cortex (=0.67), and stage 3-extension to neocortical (=1)[23]; this coding was also used for the limbic-predominant age-related TDP-43 encephalopathy neuropathological changes (LATE-NC) sensitivity analyses. 6) Arteriolosclerosis was evaluated using a semi-quantitative grading system of no occlusion (=0), mild occlusion (=0.33), moderate occlusion (=0.67), severe occlusion (=1). It is based on histological changes including intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening in the anterior basal ganglia[25]. 7) Cerebral

amyloid angiopathy was quantified as a summary score of amyloid deposition in meningeal and parenchymal vessels using immunostains in the midfrontal, midtemporal, angular, and calcarine cortices[26]. A four-level staging technique was applied where 0=no deposition, 0.33=mild deposition, 0.67=moderate deposition, and 1=severe deposition. 8) Cerebral large vessel atherosclerosis was evaluated using semi-quantitative four-level grading applied to vertebral, basilar, posterior cerebral, middle cerebral, and anterior cerebral arteries and their proximal branches. Coding of 0 indicates no significant atherosclerosis; 1 indicates mild atherosclerosis, with small amounts in several arteries but no significant occlusion; 2 indicates moderate atherosclerosis in up to half of visualized major arteries, with <50% occlusion of any single vessel; and 3 indicates severe atherosclerosis: present in more than half of all visualized vessels and/or more than 75% occlusion of one or more vessels[27]. 9) Acute gross cerebral infarcts, as determined by gross neuropathologic evaluation and confirmed by histopathology, was classified as no gross infarctions (=0), or one or more gross infarctions, regardless of age and location (=1)[28]. 10) Chronic gross cerebral infarcts, as determined by gross neuropathologic evaluation and confirmed by histopathology, was classified as no gross chronic infarctions (=0), or one or more gross chronic infarctions, regardless of age and location (=1)[28].

Traditional Alzheimer's disease staging measures: Traditional measures of AD pathology were also examined in relation to global cognition (e.g. test battery z-scores) and dementia status (e.g. no cognitive impairment, mild cognitive impairment (MCI), or dementia) in sensitivity analyses. Braak staging[29], a measure of the number and

distribution of tangle pathology, was scored between 1 and 6 (where higher scores indicate more pathology). Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score[30] is another measure of traditional AD pathology based on Braak score and neuritic plaque number and distribution. Both measures were semi-quantitatively scored by a technician and reviewed by a neuropathologist.

Frailty Index: The frailty index is a health state measure that reflects the extent of illness and vulnerability to adverse outcomes, including death[31]. The frailty index = (number of health deficits present) / (number of health deficits measured). For example, a person with 5 of 30 potential deficits measured has a frailty index score of 5/30 = 0·17. We used a 41-item frailty index from health variables obtained at each clinical evaluation, as detailed elsewhere[6]. Candidate variables included symptoms, signs, comorbidities, and function. Variables were screened for inclusion based on standard procedures[32]; those strongly related to the outcome (i.e. cognitive variables) were excluded. Higher frailty index values indicate poorer health. For ease of interpretation, frailty index values were multiplied by 10 so that the odds ratio would represent the proportion change for an increased increment of 0.1 of the frailty index (an additional 3-4 deficits).

Global cognition: Global cognition was assessed using a battery of 17 cognitive tests spanning multiple domains including episodic, semantic, and working memory, perceptual speed, and visuospatial ability[33]. Raw scores were converted to z-scores calculated on the basis of original baseline cohort data[34]. Negative scores indicate global cognition below average of the entire cohort from the baseline evaluation, while positive

scores indicate above average global cognition. Scores were taken at last study evaluation before death (0.9±1.2 years antemortem).

Dementia status: Dementia status was ascertained by clinical consensus at each annual assessment. A three-step process was employed: 1) computer scoring of the cognitive testing[33]; 2) clinical judgment by a neuropsychologist blinded to participant demographics; 3) diagnostic classification by a clinician (neurologist, geriatrician, geriatric nurse practitioner, or neuropsychologist[34] based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA). Classification was categorized as no cognitive impairment, mild cognitive impairment, or dementia (including possible and probable Alzheimer's and other dementias). For the purpose of some analyses (Receiver-Operating Characteristic curves), dummy variables were created for binary outcomes (no cognitive impairment vs. mild cognitive impairment, and mild cognitive impairment vs. dementia).

Confounders: Age, sex, and education were evaluated as confounders. Age was calculated from birth date to date of cognitive testing and used as years; self-reported education at the baseline evaluation was measured in years; sex was a self-report binary variable determined at baseline.

Statistical analysis

Descriptive analysis techniques were used to describe characteristics of the sample. ANOVA and chi square tests were used to compare means. Ordinal regression (logit function) was employed to evaluate the relationship between the neuropathological index, frailty index, and dementia status. Linear regression was used to evaluate the relationship of the neuropathological index and the frailty index with respect to global cognition. Logistic regression was employed in sensitivity analyses for binary outcomes. For ordinal regression models, beta coefficients were transformed into odds ratios for ease of interpretation. All analyses were adjusted for age, sex, and education. Model fit was evaluated by change in deviance (chi square of -2LogLikelihood values). Nagelkerke Pseudo R^2 were reported. Area under the receiver-operating characteristic curve (AUC-ROC) was employed to evaluate the sensitivity and specificity of the independent variables (neuropathological index and frailty index) in discriminating no cognitive impairment from mild cognitive impairment and mild cognitive impairment from dementia. SPSS version 25.0 was employed for all analyses.

4.3.4 Results

Demographics

At the time we froze the data set in Jan 2017 there were 645 autopsied participants with completed neuropathological assessment. We examined 625 participants with sufficient neuropathological, cognitive, and clinical data to create a frailty index (Figure 4-1 for inclusion flow chart). Participants were 89.7±6.1 years of age at time of death, and mostly female (67.5%) (Table 4-1 for full demographic information). Most participants (77.3%) were classified as having AD according to the CERAD pathological staging

measure, though only 37.2 % had a diagnosis of possible or probable AD. The frailty index and neuropathological index had near normal distributions that became more right skewed with increasing cognitive impairment. Prevalence of MCI and dementia increased as a function of both neuropathology and frailty (Figure 4-2), though it is most clear when dementia is compared to both no cognitive impairment and mild cognitive impairment grouped together- likely because of the increased sample size.

Outcome: dementia status

Ordinal regression models demonstrated that both the neuropathological index and frailty index were independently associated with dementia status (Table 4-2), after adjusting for age, sex, and education. The relationship between neuropathology and dementia was similar across levels of frailty (Figure 4-3). When the frailty index was added to the model with the neuropathological index, each remained statistically significant and model fit significantly improved (deviance change $X^2(2)=72.64$; $p<0.0001$). Pseudo R^2 increased from 0.27 to 0.35, suggesting that the frailty index increased the explained variance by 8%. AUC-ROC were used to evaluate the discrimination of outcome between the neuropathological index and frailty index. The first ROC used the outcome no cognitive impairment vs. mild cognitive impairment (n=384), where both the neuropathological index and frailty index statistically significantly classified the outcome: AUC=0.64 (95% Confidence Interval {CI} 0.58-0.69) and AUC=0.58 (95% CI 0.52-0.63), respectively. Similarly, when the outcome mild cognitive impairment vs. dementia (n=414) was used, both the neuropathological index and frailty index again were significant: AUC=0.70

(95% CI 0.65-0.75), and AUC=0.68, (95% CI 0.63-0.73), respectively. Analyses were repeated stratified by sex and results were did not differ between the sexes.

Outcome: global cognition

Linear regression models also demonstrated that higher neuropathological index and frailty index scores were independently associated with poorer cognition (Table 4-3). When the frailty index was added to the model with the neuropathological index, each remained statistically significant, and model fit improved: Pseudo R^2 increased from 0.27 to 0.39. Analyses were repeated stratified by sex and results were did not differ between the sexes.

Sensitivity analyses

We conducted a sensitivity analysis using logistic regression with an outcome of no cognitive impairment vs. Alzheimer's dementia (n=448) to test performance of the neuropathological index and frailty index after accounting for Braak and CERAD pathological AD staging measures. We found that the neuropathological index and frailty index remained significant after controlling for CERAD score and Braak stage. When the frailty index was added to the model, fit improved (deviance change $X^2(2)=56.19$; $p<0.0001$) and Pseudo R^2 increased from 0.46 to 0.56 (10%). ROC results also held in the AD sensitivity analysis. Further, the MCI group was collapsed into the non-dementia group, and subsequently into the dementia group, but neither demonstrated significant interactions between frailty and neuropathology (p=0.77 and p=0.90, respectively).

Ordinal regressions were used to evaluate the relationship between frailty and LATE-NC with dementia status. Frailty and LATE-NC were independent predictors of dementia status (unstandardized beta coefficients= 0.27 (95% CI 0.21-0.33, $p<0.001$) and 0.28 (95% CI 0.19-0.37, $p<0.001$), respectively, but did not interact. Frailty was significantly higher in those with dementia but did not differ according to LATE-NC staging. Analyses were repeated stratified by sex and results were did not differ between the sexes.

4.3.5 Discussion

In this analysis of 625 older adults, an index measure of frailty and of neuropathology were each significantly associated with dementia status and a measure of global cognitive functioning derived from neuropsychological tests. Sensitivity analyses demonstrated that even among clinical cases of AD, both the neuropathological index and frailty index independently contributed to odds of dementia over and above traditional pathological measures. Given the interest in the newly-defined LATE-NC[35], we also tested the relationship between frailty, LATE-NC, and dementia status, and found results consistent with our original analyses, suggesting that regardless of how we define neuropathology, frailty continues to play an important role in dementia risk.

Taken together these results suggest that dementia (including AD) is a multiply-determined condition. Importantly, frailty as measured using the deficit accumulation approach, improved the fit of the model for both dementia status and global cognition and explained 8-12% more of the variance in the outcomes (dementia status and cognition, respectively). This suggests that physical health, as quantified by the frailty index,

independently affects cognitive processes and frailty should be targeted for prevention and treatment of dementia.

The relationship between neuropathology and cognition has long been contentious in Alzheimer's disease research. Many reports, particularly from community-based samples, emphasize the discrepancy[2,24,36–38] For example, many people who were diagnosed clinically with Alzheimer's dementia show relatively low burden of plaques and tangles on autopsy. Conversely, other individuals who did not appear to have dementia during life have high levels of neuropathology on autopsy. The evidence of discordance suggests that Alzheimer's dementia may not be a homogeneous disease state that is marked by specific and discrete pathology, but rather a multiply-determined condition that arises from an imbalance between increasing pathologic mechanisms and decreasing resilience that comes with age as health deficits accumulate. In this analysis, frailty is associated with cognition and dementia independent of neuropathology, consistent with other reports of Alzheimer's disease risk factors[39,40], and evidence relating frailty to cognitive decline and dementia[17,41,42]. This suggests that frailty may be a measure of the latent resilience capacity continuum in the face of non-modifiable pathology. It also is a way to respond to the critique of Alzheimer disease being studied as though all that mattered about age was exposure duration, whereas "the problems of old age come as a package"[43].

These analyses extend prior work demonstrating that frailty moderates the relationship between AD pathology and dementia[6] by identifying a second mechanism through which

frailty independently may provide cognitive reserve. Further the present work confirms other reports that many neuropathologic lesions are associated with dementia status and global cognition, even among people with clinical Alzheimer's dementia[1]. We build on this by demonstrating that the number of neuropathological deficits, rather than their particular nature, is crucial in determining who develops dementia, and that this mechanism is in addition to frailty. This is consistent with our previous work on the deficit accumulation model of frailty[44,45]. In essence, frailty helps us quantify individual differences in resilience, or the ability to 'stave off' dementia, despite the accumulation of neuropathology.

Our results are consistent with other reports linking frailty and dementia. Frailty, operationalized both as an index and a phenotype, has been associated with cognitive decline and incident AD[6,10]. Further, both physical and psychiatric conditions work in tandem to influence dementia risk[46]. Previous work has also linked frailty to the neuropathological features of AD[20,47] as well as other dementia-related neuropathological features[1]. In acknowledging the complexity of dementia, and its context in ageing[48], we have added to the literature by demonstrating that frailty influences odds of cognitive impairment and dementia, even in the face of neuropathology, which suggests frailty interventions may be useful at any stage of neuropathological accumulation. Further, it supports the suggestion that discoveries in ageing research may also offer candidate therapeutics for age-related illnesses[49], of which late-life cognitive decline may be a leading example[5].

Our results should be interpreted with caution. Temporality could not be ascertained, and thus causality cannot be determined; neuropathological features were quantified at autopsy, while cognitive and frailty measures were taken at last study evaluation before death (an average of 11 months ante mortem). This raises the possibility that neuropathological burden could have changed significantly between the time of last assessment and autopsy, though there is consensus that most neuropathological features accumulate slowly[50]. It is also possible that the association reflects diverse phenotypes affected by the same pathology. Future work should address the longitudinal relationship between frailty, brain-based features of dementia, and clinical expression of the disease. Further, our study sample was not representative. All participants were recruited from retirement communities in a fixed geographic location. It is likely that this sample differs on levels of frailty, social vulnerability, and prevalence of dementia from the general population; therefore, population-based samples with analytics that can control for known risks such as social vulnerability and cardiovascular risk would be ideal to confirm the results presented here. Cause of death should also be controlled for in future investigations.

A neuropathological index of 10 features was associated with global cognition and dementia status, and the neuropathological index performed significantly better at discriminating AD-dementia status than traditional AD pathological staging measures. Adding frailty to a model with the neuropathological index significantly improved the fit of the model in discriminating the odds of dementia. Future research should focus on elucidating mechanisms linking frailty and dementia, evaluate frailty as a means of

dementia risk reduction, and employ longitudinal analysis to understand how dementia develops and progresses.

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Table 4-1. Descriptive characteristics of sample.

	Overall sample (n=625)	No cognitive impairment (n=211)	Mild cognitive impairment (n=173)	Dementia (n=241)
Age at death (years; mean±SD)	89.7±6.1	88.2±6.5	89.6±6.0	91.0±5.5*
Sex (n, % female)	422, 67.5%	151, 71.6%	109, 63.0%	162, 67.2%
Education (years; mean±SD)	14.5±2.9	14.4±2.9	14.8±2.8	14.4±3.0
MMSE	21.5±8.7	27.9±1.9	25.7±2.6	13.0±8.3*
Frailty index	0.41±0.18	0.34±0.15	0.39±0.16	0.50±0.17*
Neuropathological index	0.36±0.16	0.27±0.14	0.34±0.14	0.46±0.15*
Braak stage (mean±SD)	3.7±1.2	3.1±1.1	3.6±1.1	4.17±1.05*
CERAD score (n,%) Definite Probable Possible No AD	 208, 33.3% 213, 34.1% 62, 9.9% 142, 22.7%	 38, 18.0% 62, 29.4% 31, 14.7% 80, 37.9%	 51, 29.5% 65, 37.6% 22, 12.7% 35, 20.2%	* 119, 49.4% 86, 35.7% 9, 3.7% 27, 11.2%

	Overall sample (n=625)	No cognitive impairment (n=211)	Mild cognitive impairment (n=173)	Dementia (n=241)
Time from last clinical visit to death (years)	0.9±1.2	1.1±1.4	1.1±1.5	0.73±0.84*
Post-mortem interval (hours)	8.6±7.2	8.8±8.8	9.0±5.8	8.0±6.5

*Main effect $p<0.05$. SD=standard deviation; MMSE=Mini Mental State Examination; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; AD=Alzheimer's Disease

Table 4-2. Ordinal regression demonstrating relationship between the neuropathological index, frailty index, and dementia status.

		Odds ratio	β coefficient	95% CI Lower limit	95% CI Upper limit	*P* value
Model 1	Neuropathological index (per 0.1)	1.86	0.62	0.50	0.73	<0.0001
Model 2	Frailty index (per 0.1)	1.54	0.43	0.33	0.52	<0.0001
Model 3	Neuropathological index (per 0.1) Frailty index (per 0.1)	1.84 1.52	0.61 0.42	0.49 0.32	0.72 0.52	<0.0001 <0.0001

*β coefficients are unstandardized; CI=Confidence Interval, adjusted for age, sex, education

Table 4-3. Linear regression demonstrating relationship between the neuropathological index, frailty index, and global cognition.

		β coefficient	95% CI Lower limit	95% CI Upper limit	*P* value
Model 1	Neuropathological index (per 0.1)	-0.31	-0.36	-0.26	<0.0001
Model 2	Frailty index (per 0.1)	-0.26	-0.30	-0.21	<0.0001
Model 3	Neuropathological index (per 0.1) Frailty index (per 0.1)	-0.28 -0.22	-0.32 -0.26	-0.24 -0.18	<0.0001 <0.0001

*β coefficients are unstandardized; CI=Confidence Interval, adjusted for age, sex, education

Figure 4-1. Participant inclusion flow chart.

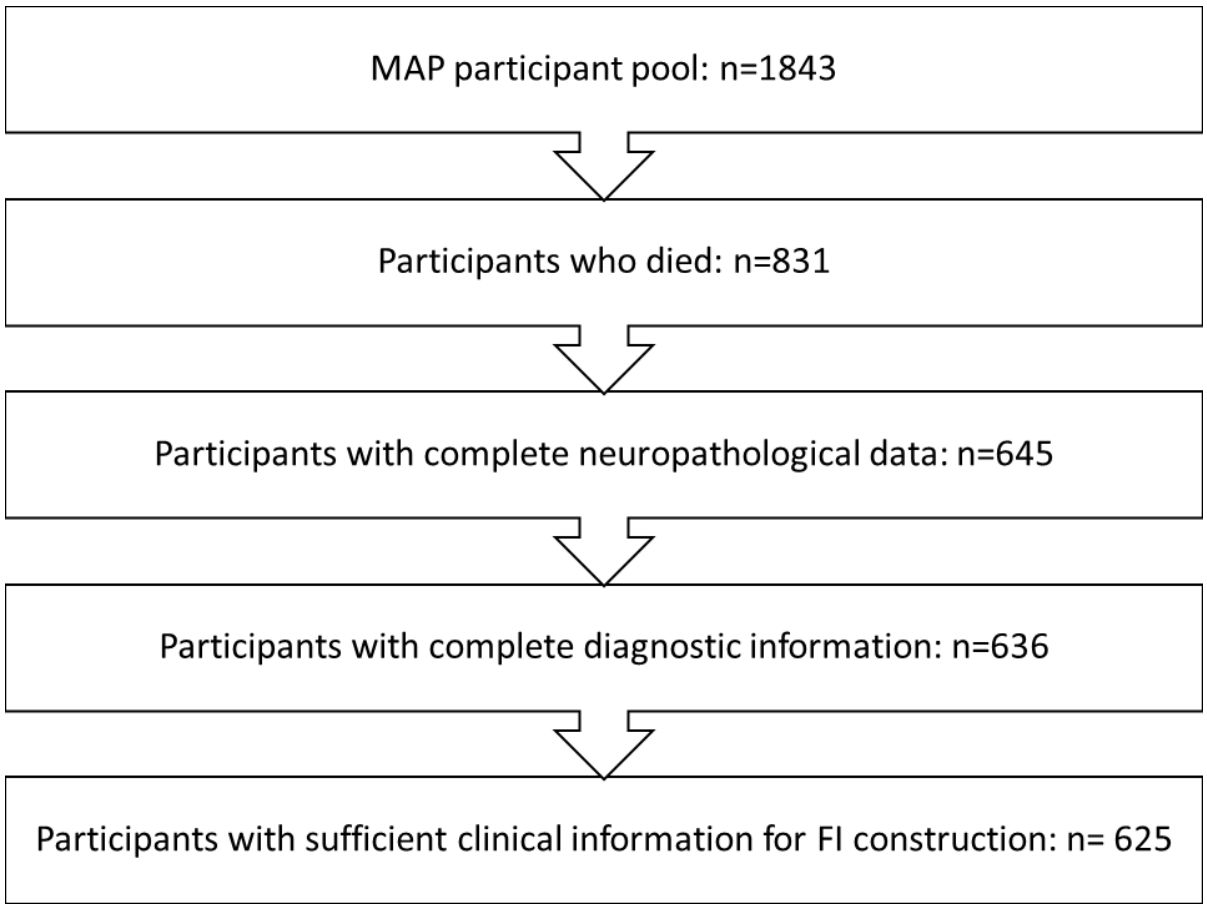
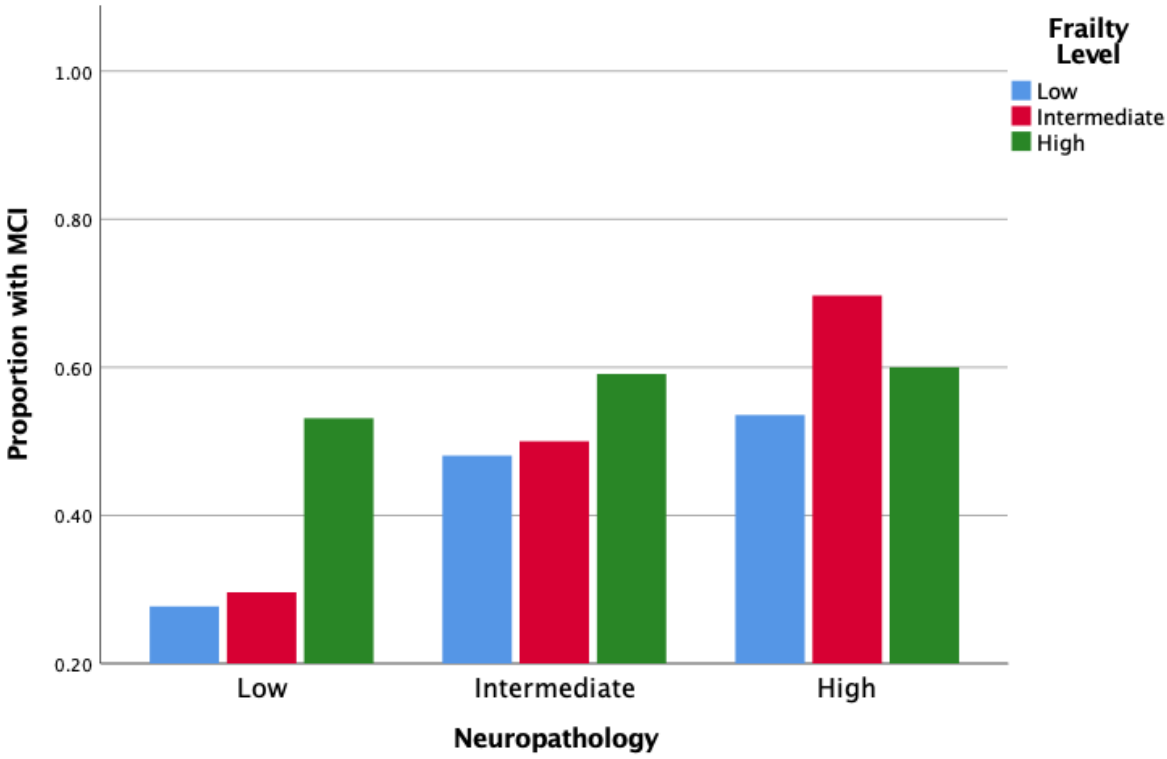


Figure 4-2. Panel A) Proportion of sample with mild cognitive impairment (MCI) by level of Alzheimer's pathology and frailty. Panel B) Proportion of sample with Alzheimer's dementia (compared to no cognitive impairment or mild cognitive impairment) by level of Alzheimer's pathology and frailty.

Panel A.



Panel B.

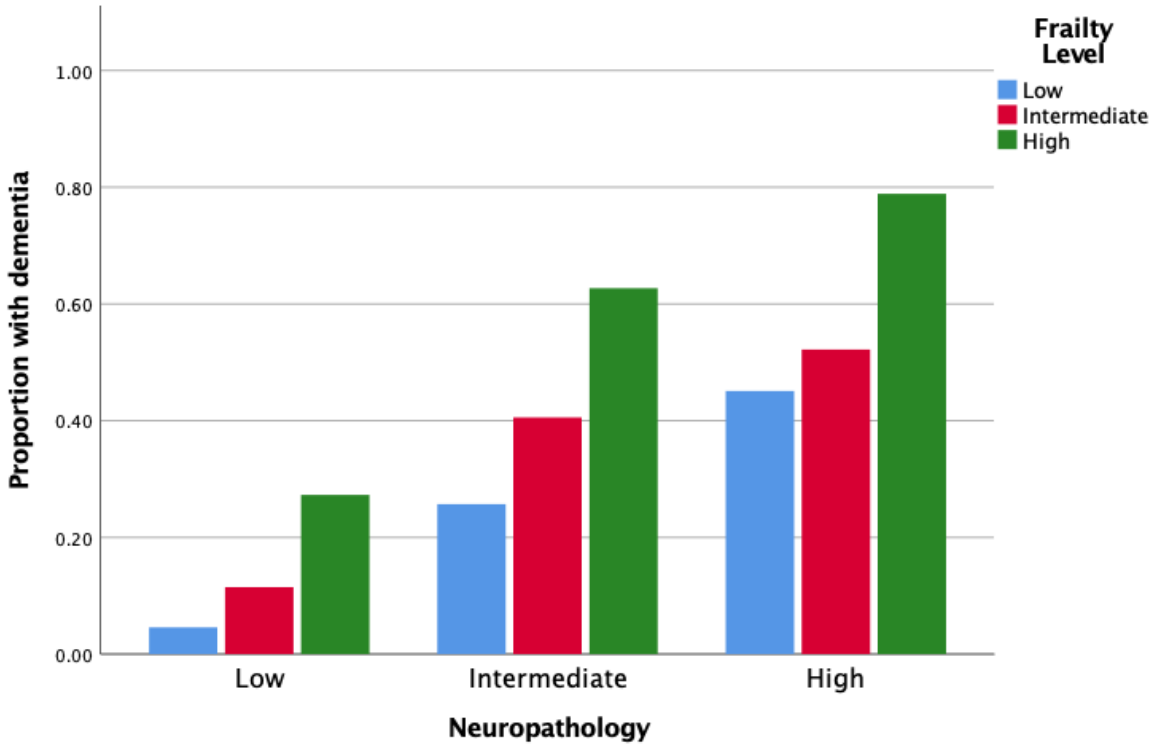
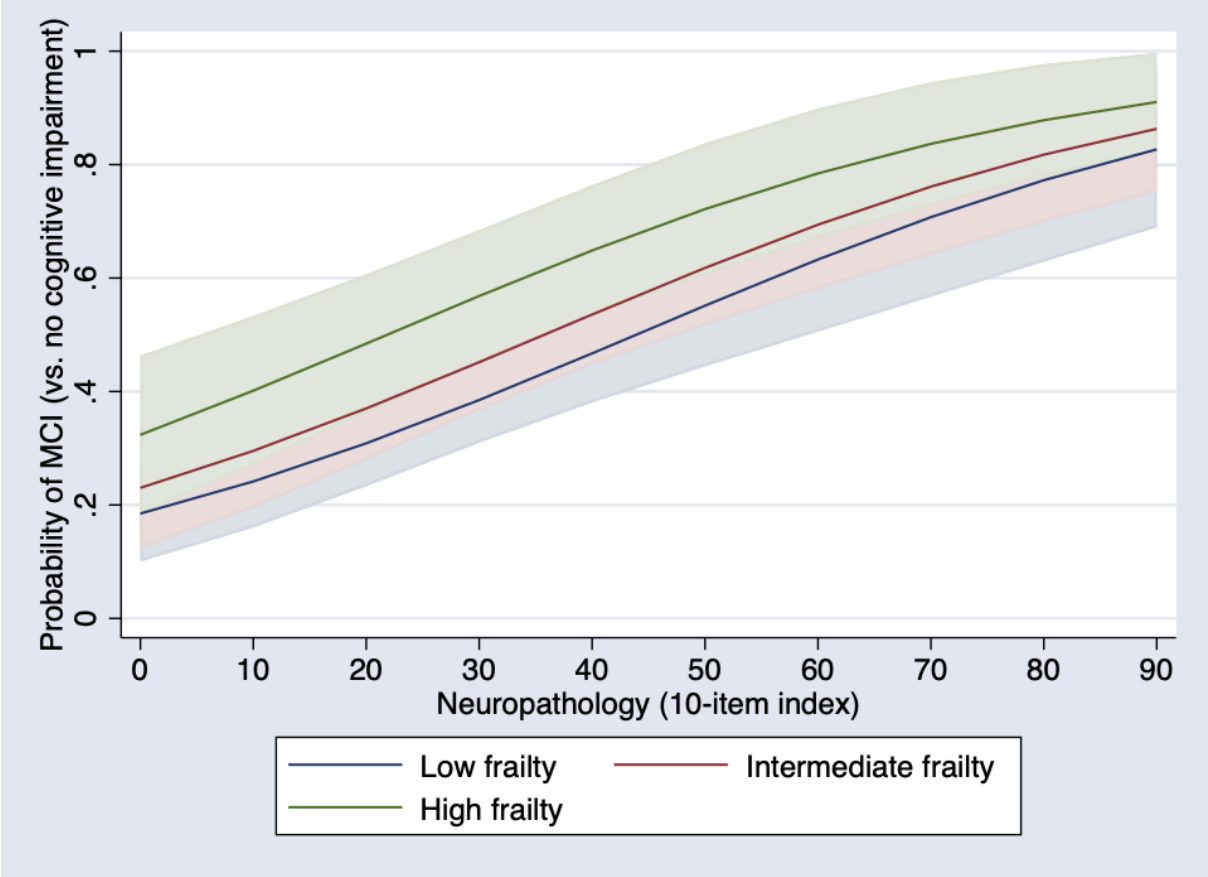
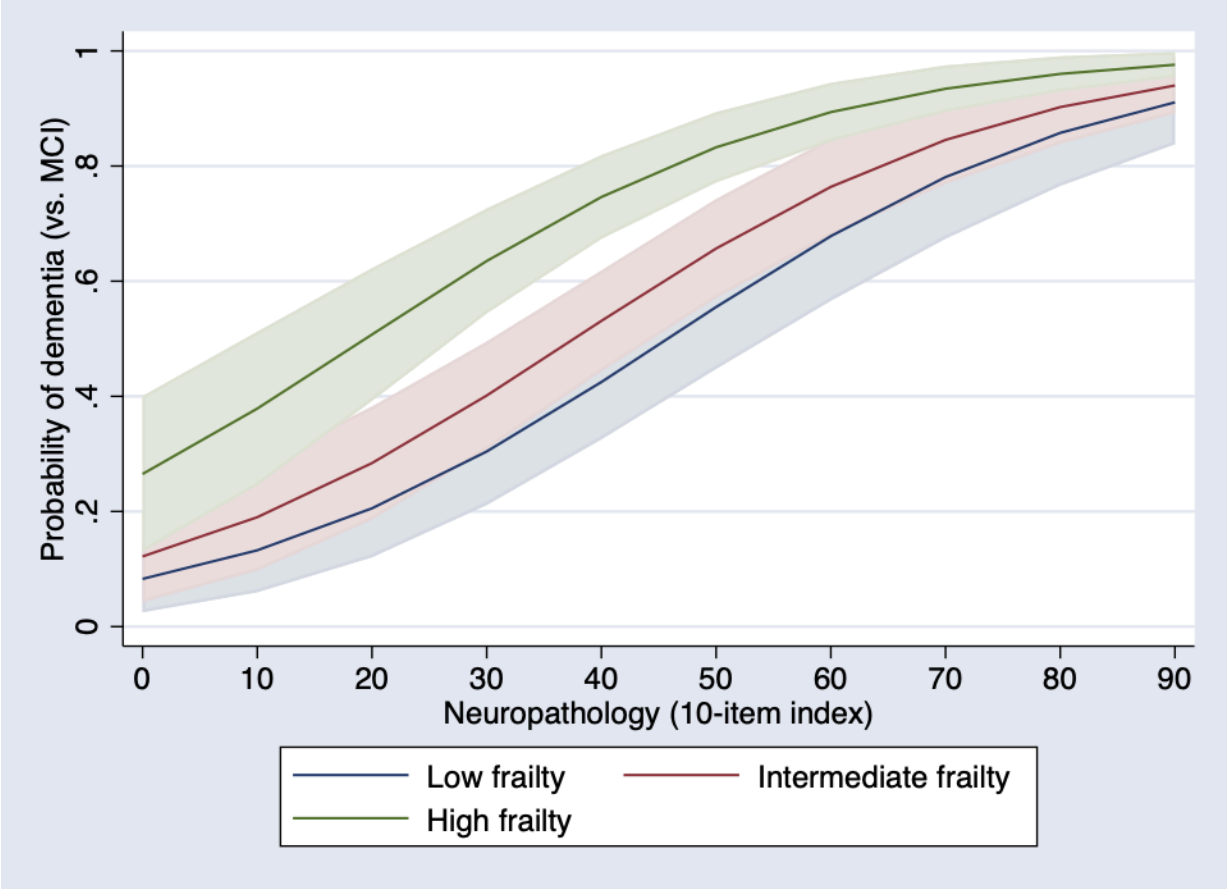

Frailty Level
Low
Intermediate
High
1.00
0.80
0.60
0.40
0.20
0.00
Proportion with dementia
Low
Intermediate
High
Neuropathology

Figure 4-3. Panel A) Probability of MCI (vs. no cognitive impairment) as a function of neuropathological burden, stratified by frailty level. Panel B) Probability of dementia (vs. MCI) as a function of neuropathological burden, stratified by frailty level. Panel C) Probability of dementia (vs. no cognitive impairment) as a function of neuropathological burden, stratified by frailty level.

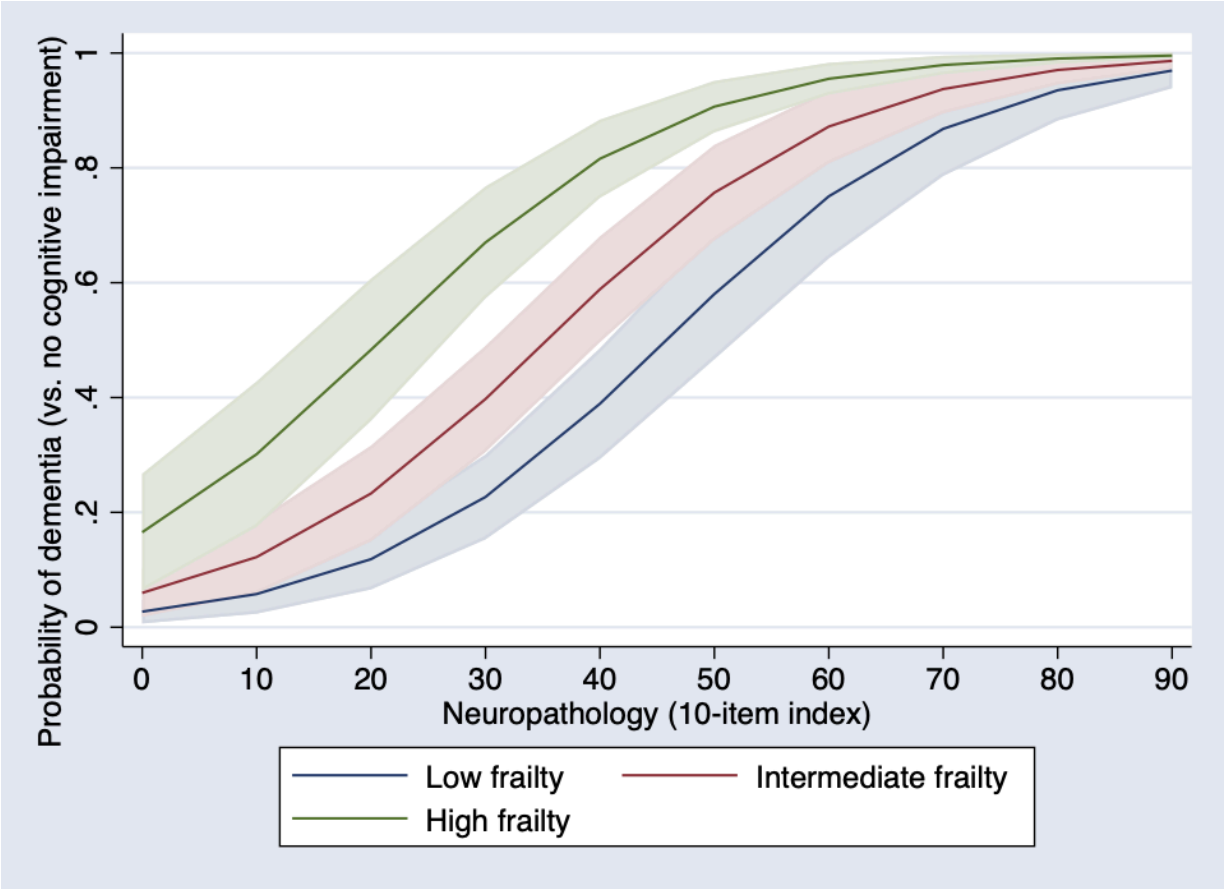
Panel A.



Panel B.


Probability of dementia (vs. MCI)
0
.2
.4
.6
.8
1
0
10
20
30
40
50
60
70
80
90
Neuropathology (10-item index)
Low frailty
Intermediate frailty
High frailty

Panel C.


Probability of dementia (vs. no cognitive impairment)
0
.2
.4
.6
.8
1
0
10
20
30
40
50
60
70
80
90
Neuropathology (10-item index)
Low frailty
Intermediate frailty
High frailty

CHAPTER 5: Frailty and neuropathology in relation to dementia status: The Cambridge City over-75s Cohort study

5.1 Prologue

My findings in the previous chapter suggest that frailty and neuropathological burden are additive risk factors for mild cognitive impairment and dementia expression. Given that the sample for that analysis had been recruited from retirement homes, subsidized housing and social service agencies in the greater Chicago area, the sample was not population-representative, and it is possible that the participants differed in social vulnerability, and other important risk factors, from the general population. For this reason, I wanted to test whether my results held in a population-representative dataset, and having this data also enabled me to investigate how much of an impact frailty makes as a risk factor in terms of population attributable risk.

5.2 Manuscript information

Status: Under review.

Citation: Wallace LMK, Hunter S, Theou O, Fleming J, Rockwood K, Brayne C. Frailty and neuropathology in relation to dementia status: The Cambridge City over-75s Cohort study. *International Psychogeriatrics (Revisions requested and submitted Aug, 2020).*

Permission: N/A.

Student contribution to manuscript: Lindsay Wallace, together with her supervisor Kenneth Rockwood conceived idea with input from Carol Brayne. Lindsay Wallace designed and undertook analyses, interpreted the data, wrote first draft and revised all

subsequent drafts. Jane Fleming advised on methodological design and analysis. Olga Theou aided in interpretation and analysis, and revised all drafts. Carol Brayne is the custodian of the data, and contributed to design, analyses, interpretation, and revised all drafts.

5.2 Manuscript

5.2.1 Abstract

Objective: To examine the relative contributions of frailty and neuropathology to dementia expression in a population-based cohort study.

Design: Cross-sectional analysis of observational data.

Setting: Population-representative clinicopathological cohort study.

Participants: Adults aged 75+ recruited from general practice registries in Cambridge, UK in 1985 (n=511).

Measurements: A 39-item frailty index and 15-item neuropathological index were used to define frailty and neuropathology, respectively. Dementia status was ascertained by clinical consensus at time of death. Relationships were evaluated using logistic regression models in participants with autopsy records (n=183). Model fit was assessed using change in deviance. Population attributable risk for frailty was evaluated in relation to dementia incidence in a representative sample of the survey participants (n=511).

Results: Participants with autopsy were 92.3±4.6 years at time of death, and mostly women (70%). Average frailty index value at last survey before death was 0.34±0.16. People with dementia (63% of the sample) were frailer, had lower MMSE scores, and a higher burden of neuropathology. Frailty and neuropathological burden were significantly

and independently associated with dementia status, without interaction; frailty explained an additional 3% of the variance in the model. Assuming a causal relationship and based on these population attributable risk analyses, preventing severe frailty (Frailty Index ≥0.40) could have avoided 12.6% of dementia cases in this population-based cohort. **Conclusions:** In the very old, frailty contributes to the risk for dementia beyond its relationship with the burden of traditional dementia neuropathologies. Reducing frailty could have important implications for controlling the burden of dementia. Future research on frailty interventions should include dementia risk as a key outcome, public health interventions and policy decisions should consider frailty as a key risk factor for dementia, and biomedical research should focus on elucidating shared mechanisms of frailty and dementia development.

5.2.2 Introduction

As treatments for clinically diagnosed Alzheimer's disease continue to fail in clinical trials, evidence is accumulating to suggest that diverse risk factors and mechanistic pathways are important, especially in late-life dementia[1]. Many studies have now shown that single-protein abnormalities (i.e. plaques and tangles) are not highly correlated with the clinical expression of dementia, especially in the oldest old[2–4]. The research paradigm for tackling dementia has assumed that Alzheimer's disease is responsible for the majority of clinical expression of dementia in all populations. Trials are increasingly targeted at earlier ages in individuals willing to be investigated for the imaging markers of protein aggregation[5]. However, the 'pure' dementias tend to be rare and typically in the youngest age groups. Researchers focused on 'usual' populations of people with

dementia have repeatedly noted that age is the most important risk for dementia in the population and it is important to create deep knowledge on this section of our populations[6]. Age-related diseases, such as heart disease and osteoarthritis, not only accumulate with age, but appear to be the result of small-scale (i.e. molecular) deficits which scale up to affect whole bodily systems in the form of frailty[7–9]. Internal or external insults are usually repaired easily by redundant repair mechanisms before becoming deficits, but as the system (i.e. body) ages, the repair mechanisms fail and lead to the accumulation of deficits[10–12].

Frailty is recognized as contributing to the dementia syndrome[13,14], brain atrophy[15], mild cognitive impairment[16], cognitive decline[17], and predicts dementia incidence[18]. This evidence suggests that it is possible that the expression of dementia, even in the face of neuropathology, may be modified by deficit accumulation, also known as frailty[19]. Therefore, the objective of the current study was to examine the relative contributions of frailty and neuropathology to dementia expression in a population-based representative cohort study and to build on earlier work where frailty and neuropathology contributed independently to dementia risk[3].

5.2.3 Methods

Sample/participants

The Cambridge City over-75s Cohort study was initiated in 1985 as a population representative sample (95% response rate) of people aged 75 or over on general practice registers in Cambridge, UK, including those living in care[20]. It aimed to study cognition

and function in older adults and enrolled 2610 participants of whom 2166 (all excluding one practice) were followed-up until their death (10 surveys over 28 years; see Appendix 5-1 for study design). Each survey included questions on demographics, activities of daily living, and health problems. In cases where participants were unable to respond, proxy informants were sought. Early surveys were supplemented with additional CAMDEX (Cambridge Mental Disorders of the Elderly Examination) psychiatric assessments which included mental state examination, psychiatric history, performance-based cognitive testing and a proxy informant interview. A brain donation programme was initiated in survey two (year 2), and donation was agreed to and fulfilled by 242 participants, with known representation from the base population.

For the purpose of this cross-sectional study, we used the survey three (seven years after the first survey) as our baseline as this sample had the largest number of relevant variables to create a frailty index which could be used consistently across the remaining surveys.

At survey three, 714 participants were interviewed, of whom 242 were brain donors and were eligible for inclusion (Appendix 5-2). Exclusions were due to incomplete neuropathological data, missing dementia diagnosis and missing data for the frailty index.

Measures

Dementia status: All clinical study records for brain donors were reviewed post-mortem and dementia status was ascertained by consensus by at least two clinicians using the

Diagnostic and Statistical Manual 4th Edition (DSM-IV) criteria and blinded to neuropathological data[20,21].

Frailty Index: The frailty index is a health state measure that reflects vulnerability to adverse health outcomes[22]. The frailty index = (number of health deficits present) / (number of health deficits measured). For example, a person with 5 of 30 potential deficits measured has a frailty index score of 5/30 = 0·17. Candidate variables from respondent interviews were indicative of poor health and included symptoms, signs, functional impairments, and comorbidities. These variables were screened against four criteria: 1) Relationship with age; 2) Prevalence of at least 1%; 3) Less than 5% missing data across participants at any survey; 4) No more than 80% prevalence (saturation). A total of 39 items met all criteria and were included in the index. The index demonstrated properties consistent with frailty indices from similar samples (i.e. normal distribution with right skewed tail, higher frailty index in women than men, increase with age). As the goal of the regression analyses was to examine the cross-sectional relationship between frailty, neuropathology, and dementia, but neuropathology could only be obtained post-mortem via autopsy, we used a frailty index and dementia measurements obtained from participants' last survey prior to death. Baseline frailty index (survey 3) was used to predict population attributable risk. Refer to Appendix 5-3 for list of variables included in the frailty index. The frailty index was categorized into tertiles for the descriptive analyses, using cut-points of 0.27, 0.43, and a cut-point of 0.40 (corresponding to severely frail[23]) was used for the population attributable risk analyses.

Neuropathological Index: Neuropathological data were obtained at autopsy by semi-quantitative scoring by trained neuropathologists according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol[24,25]. Fifteen neuropathological variables were included in the index including: 1) atrophy, 2) pallor of substantia nigra and/or locus coerulus, 3) significant obstruction of large cerebral vessels, 4) gross parenchymal vascular lesions, 5) small vessel disease, 6) microinfarcts, 7) white matter pallor, 8) neuritic plaques, 9) amyloid deposits, 10) neurofibrillary tangles, 11) vascular amyloid, 12) granulovacuolar degeneration, 13) severe neuronal loss, 14) severe gliosis, 15) Lewy bodies. Other neuropathologies available in this cohort relating to Pick's disease, leukoencephalopathy, lobar atrophy, Creutzfeldt-Jakob Disease, spongiform encephalopathy, neoplasms/tumors, Hirano bodies, ubiquitin, and Huntington's disease were not included in the index because they were absent in all cases. TDP-43 was excluded as there were too many missing cases. Full information on regional inclusions and coding are detailed in Appendix 5-4. Included neuropathological variables were summed and divided by the number of valid variables (according to the deficit accumulation approach detailed above). The neuropathological index was then categorized into tertiles for the descriptive analyses, using cut-points of 0.30, 0.42. Details of autopsy and neuropathological assessment can be found at cc75c.group.cam.ac.uk, and [21].

Confounders: Age, sex, education, post-mortem interval, and time from frailty evaluation to death were evaluated as confounders. Education (in years) was the only covariate

found to be a significant independent predictor of the outcome, so all others were dropped from the final model.

Statistical analysis

Descriptive analysis techniques (analysis of variance and chi square tests) were used to describe the characteristics of the sample and assess distributions of frailty, neuropathology, and dementia in the sample.

Logistic regression models were used to explore the effect of frailty (frailty index) and neuropathology (neuropathological index) on dementia status independently and in the same model. Their interaction was also evaluated. Model fit was evaluated by change in deviance (chi square of -2LogLikelihood values). Nagelkerke Pseudo R^2 were reported to show goodness of fit.

Complete-case analysis was employed, though 48 participants were excluded as they were missing more than 20% of the variables needed to calculate a frailty index.

Population attributable risk (or attributable fraction) estimates the proportion of cases that hypothetically could be avoided if the exposure were eliminated or reduced. Here, we used this to determine the fraction of dementia cases that could be avoided if severe frailty (frailty index $\geq$0.40) was 'eliminated' or avoided. Population attributable risk is calculated using the following formula:

*Population attributable risk = {[A/(A+B)] – [C/C+D]} *100*

where A= n with dementia and severe frailty (i.e. exposure and outcome are positive), B= n with severe frailty but no dementia, C= n without severe frailty but with dementia, and D= n without severe frailty or dementia. For this calculation the sample was extended to whole population data those with autopsy records in order to achieve representativeness and increase our sample to n=511 using incident dementia at survey 3. A sensitivity analysis was performed using prevalent dementia at survey 3 as well (to increase sample size to 692) and no significant differences were observed. Statistical analyses were performed in SPSS version 25.0 and R version 3.5.2.

5.3.4 Results

Participants were aged 92.3 (SD 4.6; normally distributed) years on average at time of death, and mostly women (69.4%). Average frailty index at last survey before death was 0.34 (SD 0.16; normally distributed). People with dementia were frailer, had lower Mini-Mental State Examination (MMSE) scores, and a higher burden of neuropathology (Table 5-1).

Very few participants demonstrated little to no neuropathology at death (n=7; 4%). Among people with no dementia, 7.1% had a high burden of neuropathology. Among people with dementia, 16.3% demonstrated a low burden of neuropathology (Figure 5-1). Within each level of neuropathological burden, those with dementia had higher frailty

(trend only for low and high burden, significant difference for intermediate burden; Figure 5-1).

The proportion of people with dementia was highest among people with a high frailty index and high burden of neuropathology, low among those with low frailty index and low burden of neuropathology, and in between for intermediate or either high frailty index or high neuropathology, suggesting these risk factors may be additive (Figure 5-2).

Logistic regression models demonstrated that both frailty (at last survey before death) and neuropathological burden (at death) were significantly and independently associated with dementia status at last survey (Table 5-2), although they did not interact (p=0.85). Addition of the frailty index to the model with the neuropathological index significantly improved model fit $X^2(1)$ 4.59, p=0.01). Pseudo R^2 increased from 0.083 to 0.115 suggesting that the addition of frailty to the model increased the explained variance by 3.2%.

Population attributable risk analyses demonstrated that preventing severe frailty (frailty index $\geq$0.40) would avoid 12.6% of dementia cases in this cohort (based on 2x2 table in Appendix 5-5). When we did a sensitivity analysis using prevalent dementia rather than incident dementia to include more cases (n=692; assessed at survey 3), results did not change significantly (population attributable risk of 11.4%).

5.3.5 Discussion

Almost a quarter of the sample (23.4%) demonstrated a mismatch between neuropathological burden and clinical dementia (that is, either dementia with low neuropathology, or no dementia with high neuropathology), similar to previous reports[21,26]. Frailty explained additional variance and significantly predicted dementia status, even after controlling for the neuropathological index, but did not interact with the neuropathological index. Taken together, these results suggest that frailty and neuropathology may be additive risk factors that independently are neither necessary nor sufficient but are largely responsible for creating the conditions in which the clinical syndrome of dementia is experienced. Given the independent risk conferred by frailty, we investigated what the scale of reduction of incidence of dementia would be assuming a causal relationship. If this is the case preventing severe frailty could reduce dementia risk by 12.6%. This indicates that frailty treatment and management is a worthwhile area to focus on not only in its own right but for its consequences as part of societal attempts to reduce the impact of dementia in populations.

Although the sample was drawn from a population-representative cohort, those who participated in the autopsy subset (i.e. brain donors) were slightly older and more cognitively impaired than those who did not and the analyses are not fully weighted back to the original population. Nevertheless, this subset has been used as a population-based cohort in other analyses showing very few differences[21,27]. The expected impact on our results here is minor, and likely reflects that frailty management would be slightly more important to control dementia in this group due to their other intersecting risks.

Another limitation was the sample size. While the sample size for the overall cohort study is quite large, missingness is to be expected as individuals become frail[28–31]. In an effort to determine the impact of the missing data on our results, we used an extreme sensitivity analysis in which imputed cases missing frailty index data were allocated the highest level of frailty. However, this sensitivity analysis did not change our results. Further, we attempted multiple imputation (chained equations algorithm) for frailty index values as a sensitivity analysis to ensure our results were not skewed by these exclusions. The only predictors of missing frailty index data were related to pathological measures that would be used in an interaction with the frailty index and would produce nonsensical results. Therefore, we did not use multiple imputation in these analyses. Interestingly, this suggests that frailty is highly associated with informative dropout in this sample. Future work will investigate this relationship.

The goal of the cross-sectional regression analyses was to examine the relationship between pathology, frailty, and dementia as close to death as possible, therefore data on frailty and dementia were obtained from the last survey prior to death. This was done to minimize the effect of the autopsy results reflecting worse pathology than was present at the time of the survey from which frailty and dementia measurements were obtained. Even so, the median time from last survey to autopsy was about two years and it is likely we were not able to capture terminal decline that would influence frailty.

Assessment of neuropathology was not stereological, being based on only one tissue section from each brain area for each staining method. This may lead to under- or over-

estimates of pathology in a few cases. However, given the sample size, we assume that the effects of any discrepancies will be minor and cancel out.

Our results are consistent with other reports which show that the vast majority community-dwelling people are not free of neuropathology at time of death[21,32], and neuropathologies typically occur together. In other words, not only are pathological substrates of dementia rarely singular or 'pure' in nature but a 'clean' or 'unburdened' brain from a pathological perspective is almost unseen in the oldest old[33]. A few groups have also examined the combined effect of pathology on disease and demonstrated generally, that the more pathology is considered, the better the prediction of dementia[32]. While this may not be surprising it is a fact that has been ignored by those seeking a specific treatment for a specific pathology. It is important to consider the combined small effects of all such pathologies as an indicator of the overall health of the system, rather than focus on which one is the most predictive as has been done with the amyloid hypothesis, and now Limbic-predominant Age-related TDP-43 Encephalopathy Neuropathologic Changes (LATE-NC)[34].

Previous work by our groups has shown not only that frailty is associated with biomarkers of Alzheimer's disease[35], but that the relationship between Alzheimer's-specific neuropathology and dementia changes over levels of frailty and age[3,26]. While our results were similar in that we see a significant mismatch in neuropathology and dementia status, we did not find an interaction between neuropathology and frailty in relation to dementia status. There are a few differences to take into account when

considering the implications of such findings. Perhaps the most influential is the type of pathology measured. The original analysis[3] included very specific 'hallmark' features of AD (i.e. plaques and tangles) and examined AD-specific dementia as the outcome, whereas, the analyses presented here combine several forms of neuropathology in an index with respect to all-cause dementia as an outcome. The mixed neuropathological index may represent a brain-specific frailty index, and may act as an indicator of overall deficit accumulation in the brain, and thus would not interact with the original frailty index (indicating bodily health) because it would be a reflection of it (with some expected variation).

As our population ages, a growing number of people will live long enough to accumulate several neuropathologies, but many of these people will reach older ages without necessarily experiencing dementia before their deaths. The implications of the current strategies for early detection of specific pathologies is that to 'prevent' dementia may actually create more harm than good, in that younger and fitter people will be screened and 'disease' will be detected in people who would not have necessarily gone on to develop symptoms. In this way, our work can inform a more public health oriented, preventative approach, by targeting frailty as a means of effective behavioural intervention for dementia risk. We hope this work will inform research and clinical approaches in considering dementia as a multi-determined disease that occurs in the ageing body, which in essence suggests that the interaction of many mechanisms leading to many diverse pathways that give rise to dementia are likely. Single-mechanism treatments are therefore unlikely to be widely successful, and broad pharmaceutical and

non-pharmaceutical therapies such as anti-ageing compounds[36] and exercise[37] should be explored more deeply for use in this population.

The analyses presented here suggest that frailty in its own right contributes to risk for dementia in the oldest old and reduction of frailty can contribute meaningfully to dementia risk. This suggests that future research on frailty interventions should include dementia risk as a key outcome, public health interventions and policy decisions should consider frailty as a key risk factor for dementia[38], and biomedical research should focus on elucidating shared mechanisms of frailty and dementia development.

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Table 5-1. Descriptive characteristics of sample.

	Whole sample (n=183)	No dementia (n=67)	Dementia (n=116)
Age at baseline (median; mean±SD)	85.2; 86.1±3.9	85.4; 86.3±4.3	85.0; 85.9±3.6
Age at death (median; mean±SD)	92.1; 92.3±4.6§	92.0; 92.3±4.8	92.1; 92.4±4.4§
Sex (n, % female)	127 (69.4%)	44 (65.7%)	84 (71.8%)
Years of education (median; mean±SD)	14.0; 15.3±2.4	15.0; 15.8±2.6	14.0; 15.0±2.2*
Years from last survey to death (median; mean±SD)	1.8; 2.2±1.8	1.8; 1.9±1.2	2.0; 2.4±2.0
MMSE at last survey before death (median; mean±SD)	24.0; 21.4±6.6	26.0; 25.7±3.1	19.0; 18.7±6.8*
Frailty index (mean±SD)	0.34±0.16§	0.30±0.13§	0.36±0.17*§
Neuropathological index (mean±SD)	0.37±0.13§	0.34±0.14§	0.39±0.13*§

§normally distributed

Table 5-2. Logistic regression models for dementia status (n=183; all models adjusted for education) demonstrating that the frailty index and neuropathological index are independently associated with dementia status, even when included in the same model. Model fit is significantly improved when both frailty index and neuropathological index are included in a model for dementia status.

Model 1	Frailty Index (per 0.1)	OR=1.29 (95% CI 1.05-1.58), p=0.014	Deviance=228.277 Nagelkerke R^2=0.082
Model 2	Neuropathological index (per 0.1)	OR=1.37 (95% CI 1.07-1.76), p<0.014	Deviance=228.108 Nagelkerke R^2=0.083
Model 3	Frailty Index (per 0.1) Neuropathological index (per 0.1)	OR=1.25 (95% CI 1.02-1.54), p=0.035 OR=1.32 (95% CI 1.02-1.70) p<0.034	Deviance=223.518 Nagelkerke R^2=0.115

OR=Odds Ratio.

Figure 5-1. Frailty index values by neuropathological burden (Neuropathological index) and dementia status; *p<0.05. Note: Frailty and dementia status were assessed at last survey before death (median 1.9 years pre-mortem), neuropathological burden was assessed at time of death.

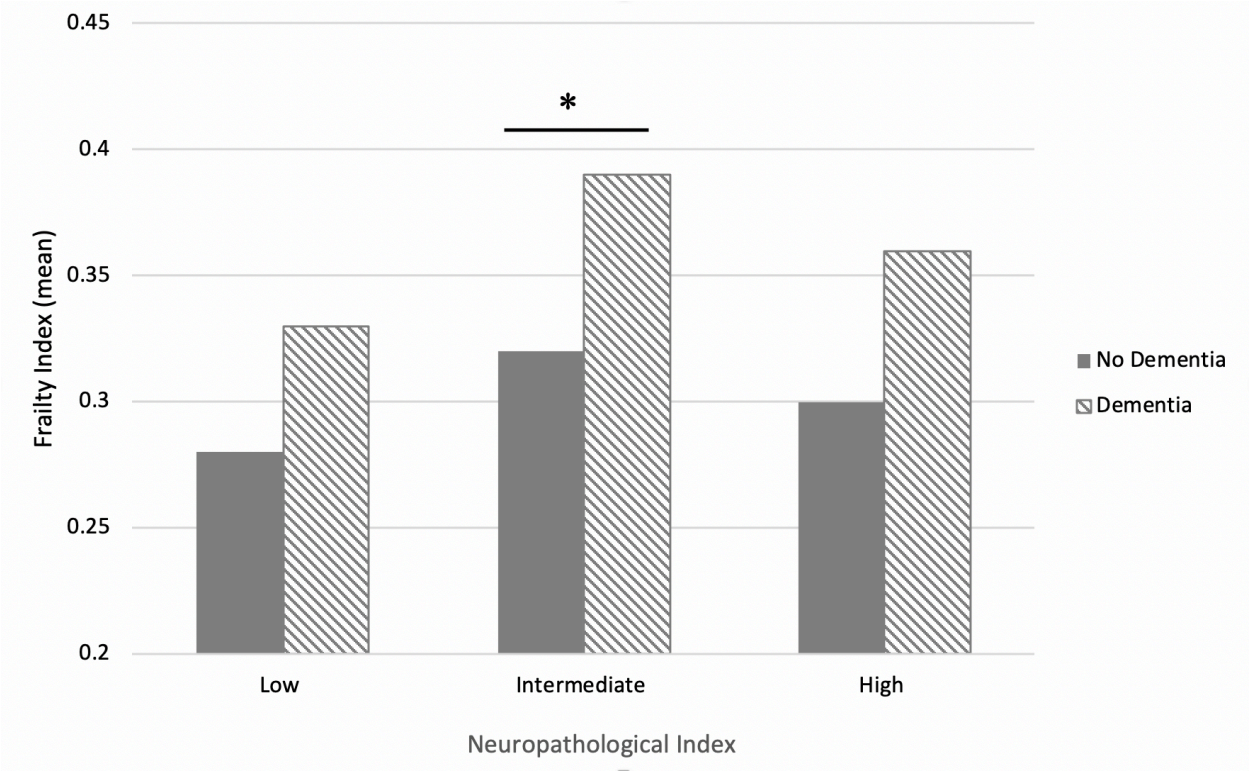
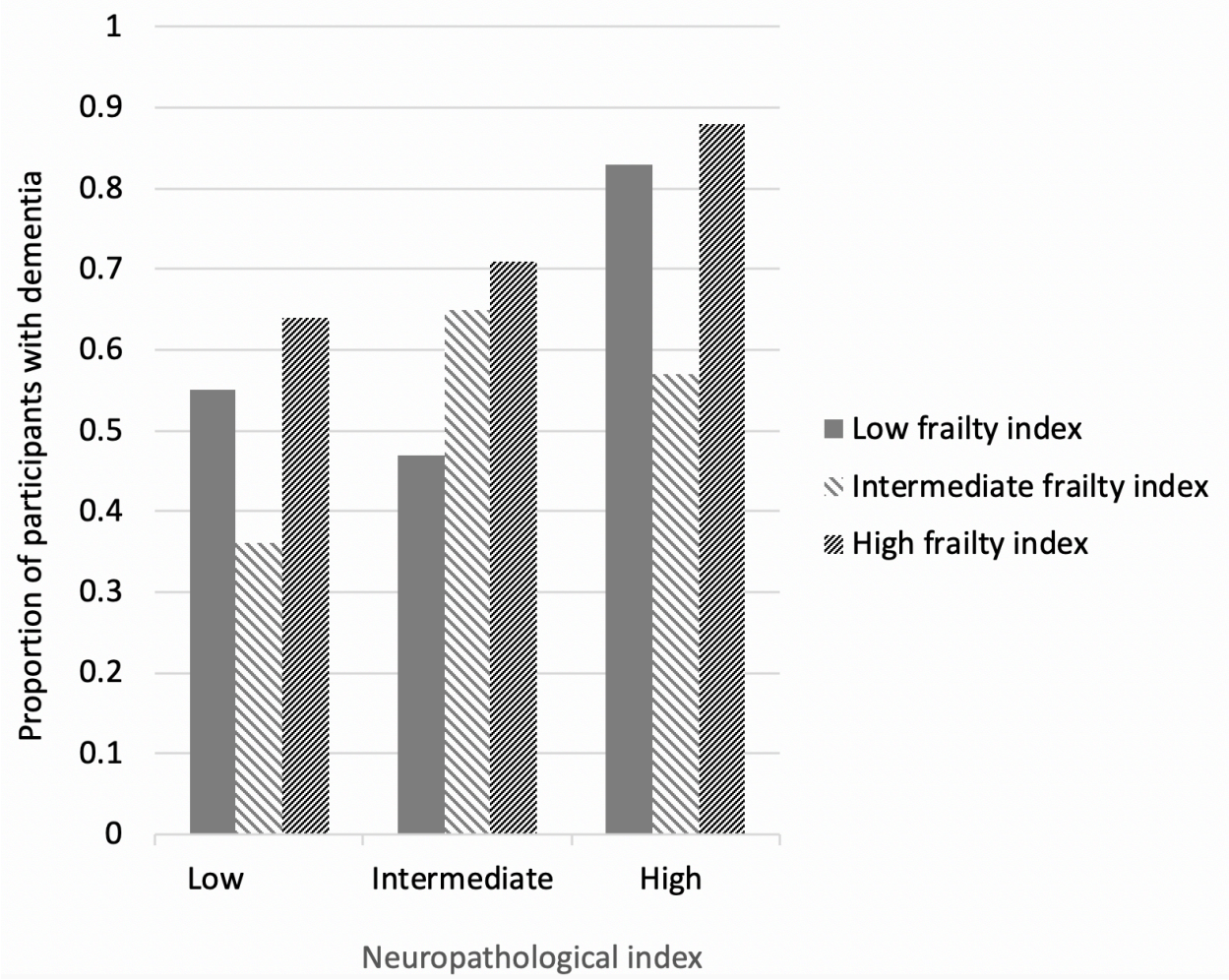
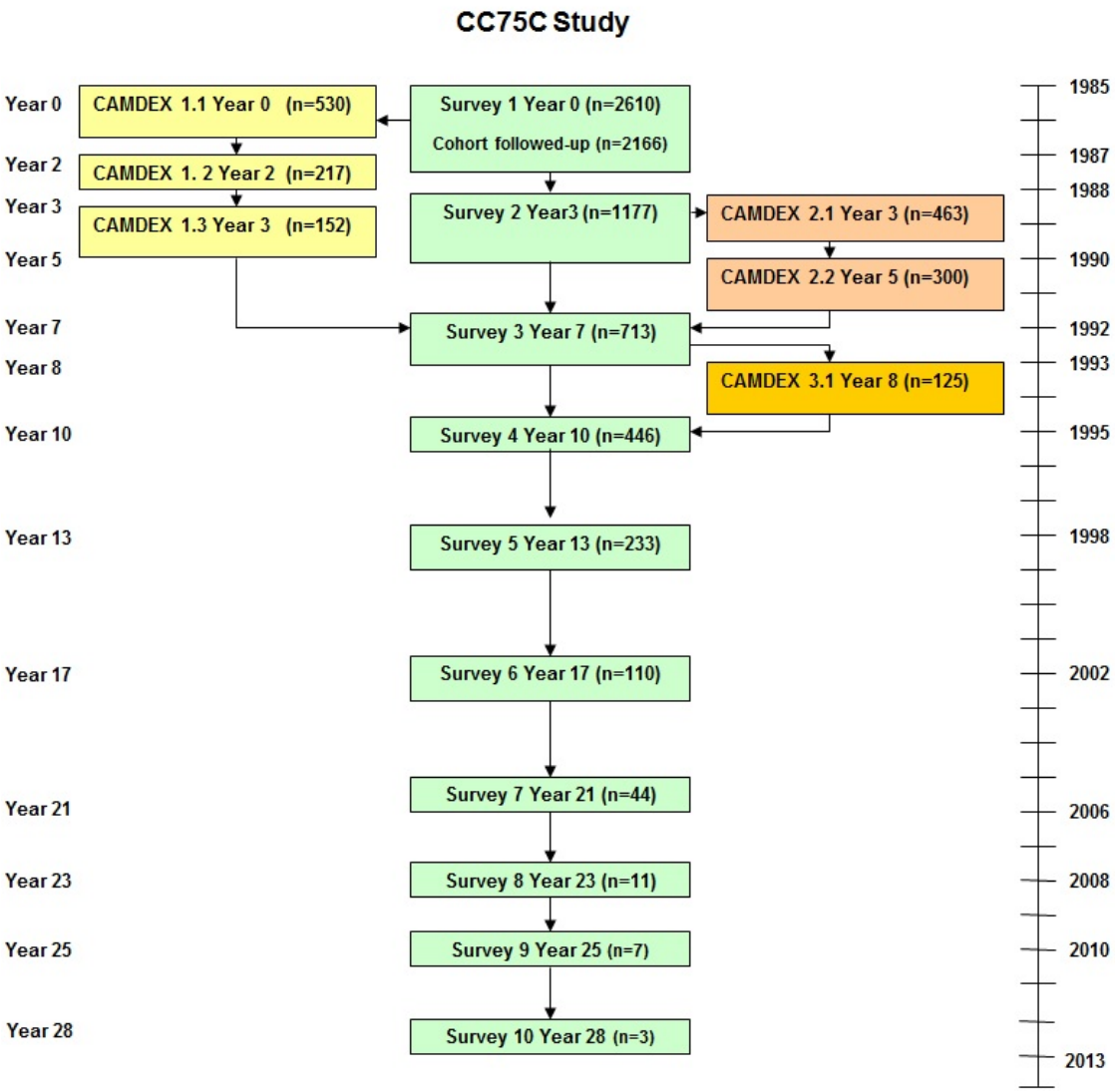


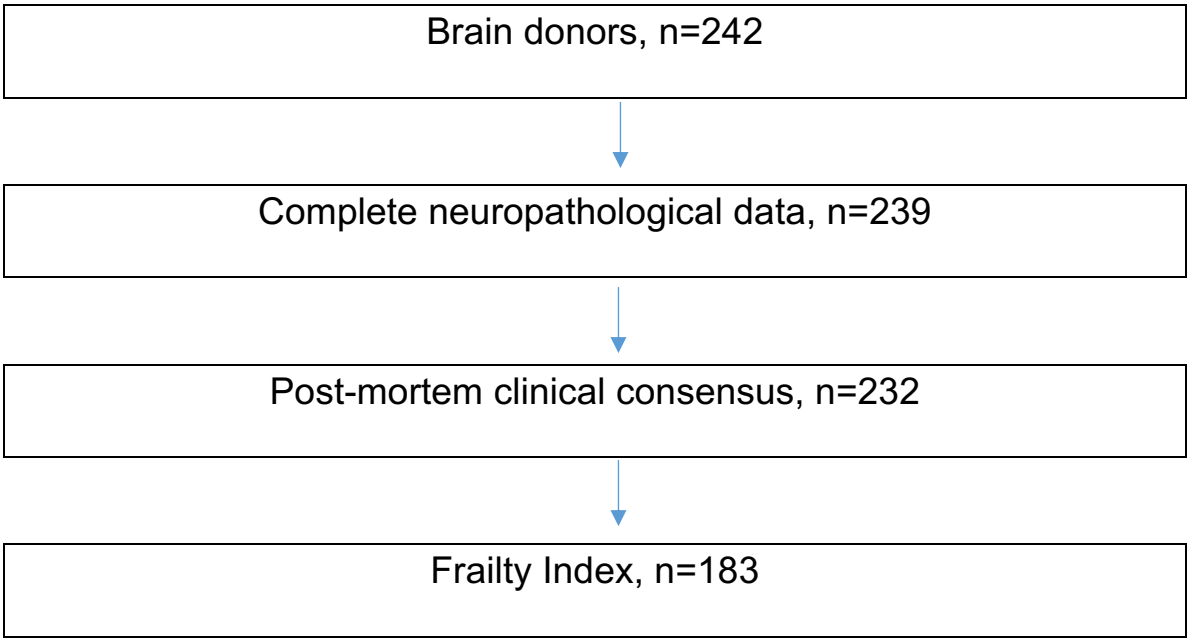
Figure 5-2. Proportion of participants with dementia according to neuropathological index groups by frailty level. Note: Frailty and dementia status were assessed at last survey before death (median 1.9 years pre-mortem), neuropathological burden was assessed at time of death.



Appendix 5-1. CC75C study design[20].



Appendix 5-2. Sample flow chart.



Appendix 5-3. Frailty index variables.

1. Vision problems
2. Hearing problems
3. Arthritis/rheumatism
4. Back pain
5. Chest pain
6. Shortness of breath
7. Weakness in arm or leg
8. Unsteady on feet
9. Falls
10. How do you manage with using a telephone
11. How do you manage with shopping
12. How do you manage with preparing meals?
13. How do you manage with housework?
14. How do you manage with laundry?
15. How do you manage with walking?
16. Do you use a walking stick or other aid?
17. How do you manage with bathing or showering?
18. How do you manage with reaching up to comb your hair (or shave) or down to cut your toenails?
19. How do you manage with dressing and undressing?
20. How do you manage with getting to the toilet on time?

21. How do you manage taking medicines?
22. How do you manage with finance?
23. How do you manage with transportation?
24. How do you manage with feeding?/eating
25. Angina
26. Heart attack
27. Problems with circulation in your legs
28. High blood pressure
29. Chronic bronchitis
30. Stroke
31. Stroke symptoms
32. Thyroid problems
33. Migraine/headaches
34. Trouble with nerves
35. Have you had to go into hospital to stay because of any of these difficulties in the last 6 months?
36. How many times have you been in hospital in the last 6 months/year?
37. Keep fit (reverse coded)
38. Walking (reverse coded)
39. Gardening (reverse coded)

Appendix 5-4. Neuropathological index.

	Variable	Original CERAD coding	Neuropathological index coding
1	Gross evidence of brain atrophy	No=0, Yes=1	No=0, Yes=1
2	Pallor of substantia nigra and/or locus coeruleus	No=0, Yes=1	Neither=0, 1=0.5, 2=1
3	Significant obstruction of large or cerebral vessels	No=0, Yes=1	No=0, Yes=1
4	Gross parenchymal vascular lesions	No=0, Yes=1	No=0, Yes=1
5	Small vessel disease *(atherosclerosis, arteriolosclerosis, V-R space expansion, perivascular gliosis)*	No=0, Yes=1	No=0, Yes=1; then averaged over each type
6	Microinfarcts	No=0, Yes=1	No=0, Yes=1
7	White matter pallor	No=0, Yes=1	No=0, Yes=1

	Variable	Original CERAD coding	Neuropathological index coding
8	Neuritic plaques*	None=0, Sparse=1, Moderate=3, Frequent/Severe=5	None=0, Sparse=0.334, Moderate=0.667, Frequent/Severe=1; then averaged over regions
9	Amyloid deposits*	None=0, Sparse=1, Moderate=3, Frequent/Severe=5	None=0, Sparse=0.334, Moderate=0.667, Frequent/Severe=1; then averaged over regions
10	Neurofibrillary tangles*	None=0, Sparse=1, Moderate=3, Frequent/Severe=5	None=0, Sparse=0.334, Moderate=0.667, Frequent/Severe=1; then averaged over regions
11	Vascular amyloid *(parenchymal,*	None=0, Sparse=1,	None=0, Sparse=0.334,

	*meningeal, and/or associated haemorrhages)**	Moderate=3, Frequent/Severe=5	Moderate=0.667, Frequent/Severe=1; then averaged over regions and type
	Variable	Original CERAD coding	Neuropathological index coding
13	Severe neuronal loss*	No=0, Yes=1	No=0, Yes=1; then averaged over regions
14	Severe gliosis*	No=0, Yes=1	No=0, Yes=1; then averaged over regions
15	Lewy bodies*	Absent=0, 1-2 neurons with inclusions=1, 3-5 neurons with inclusions=3, >5 neurons with inclusions=5	Absent=0, 1-2 neurons with inclusions=0.334, 3-5 neurons with inclusions=0.667, >5 neurons with inclusions=1; then averaged over regions

*Evaluated in hippocampus, entorhinal, frontal, temporal, parietal, and occipital cortices

**Evaluated in hippocampus and entorhinal cortex only

Appendix 5-5. Population attributable risk (n=511) calculated for incident dementia after survey three.

	Dementia	No dementia
Severe frailty (frailty index ≥ 0.40)	n=45	n=113
No severe frailty (frailty index < 0.40)	n=56	n=297

CHAPTER 6: Frailty Trajectory Predicts Alzheimer's Dementia After Considering Neuropathological Burden

6.1 Prologue

The previous chapters have demonstrated that frailty influences the relationship between neuropathology and dementia, as well as contributing to risk for cognitive impairment on its own. All of the previous analyses were cross-sectional and here, I aimed to extend these observations by understanding how frailty changes over a period of many years relate to dementia incidence. Although I do not have dementia diagnoses or neuropathological data until time of death, I was able to improve my understanding of the relationship between frailty and dementia expression by observing the development and progression of risk over time.

6.2 Manuscript information

Status: Not yet submitted.

Citation: Wallace LMK, Theou O, Godin J, Ward DD, Andrew M, Bennett DA, Rockwood K. Frailty trajectory predicts Alzheimer's dementia after considering neuropathological burden. *Not yet submitted.*

Permission: N/A.

Student contribution to manuscript: Lindsay Wallace, with her supervisor, Kenneth Rockwood conceived the research hypothesis. Lindsay designed and undertook the analysis, interpreted results, wrote first draft of manuscript and revised all subsequent drafts.

6.3 Manuscript

6.3.1 Abstract

Background: Frailty is an established risk factor for cognitive decline and Alzheimer's disease. Few studies have examined the longitudinal relationship between frailty and cognition.

Objective: 1) examine longitudinal change in the degree of frailty and how it is related to sex, neuropathology, and clinical diagnosis of mild cognitive impairment (MCI) and dementia; 2) determine whether frailty trajectories are associated with MCI and/or dementia.

Methods: Older adult participants of the Rush Memory and Aging project (n=625, 67.5% female, 83.2±5.9 years of age at baseline) underwent annual clinical evaluations (average follow-up 5.6±3.7 years) followed by neuropathologic assessment after death. A frailty index was calculated from 41 health variables at each annual study evaluation. Clinical diagnosis of MCI and/or dementia was ascertained by review of clinical data (blinded to neuropathological data) after death. Age, sex, education, and neuropathological burden (10-item index) were evaluated as covariates. Frailty trajectories were calculated using a mixed effects model.

Results: At baseline the mean frailty index=0.24±0.12, and increased at an average rate of 0.026 units or ~1 deficit per year. At time of death, 27.7% of the sample had MCI, and 38.6% had dementia. Higher baseline frailty was associated with being female (p<0.0001), but not with neuropathological burden (p=0.26) or dementia status at death (p=0.10). Frailty trajectories were significantly steeper among those individuals who

were ultimately diagnosed as clinically impaired prior to death, even after controlling for age, sex, education and neuropathological index.

Discussion: Findings suggest a strong link between health status as measured by a frailty index and cognitive status, even after considering neuropathology. Frailty trajectories in older adults predicted risk for MCI and dementia, underscoring the potential importance of frailty intervention to manage dementia risk.

6.3.2 Introduction

As our population ages, the burden of age-related disease, including dementia, is growing. Many risk factors for dementia have been identified both in midlife and later life[1], but it remains unclear how they interact to produce dementia in late life.

Frailty is a measure of physiologic vulnerability and can be characterized by the accumulation of health deficits over time[2]. Frailty is an established risk factor for cognitive decline and dementia[3–5]. Longitudinal changes in frailty have been associated with adverse health outcomes including mortality[6], health service use[7], disease-specific morbidity[8], institutionalization and disability[9]. Few studies have examined the longitudinal relationship between frailty and cognition[10,11]. Those that have demonstrate that changes in frailty and cognition are correlated, and a shared pathologic basis is suspected[10,11]. In a previous report, we have shown that frailty influences the relationship between neuropathology and clinical presentation of dementia in Alzheimer's disease[12]. Here, we use data from the Rush Memory and Aging Project, a longitudinal clinical-pathologic cohort study to extend this work by: 1) describing longitudinal change in

frailty; and 2) examining how frailty trajectories are associated with sex, neuropathology, and clinical diagnosis of mild cognitive impairment (MCI) and dementia.

6.3.3 METHODS

Study design & participants

Data presented here were from the Rush Memory and Aging Project (MAP), which has been described in depth elsewhere[13]. Briefly, MAP is a clinical-pathologic cohort study that, since its inception in 1997, has enrolled over 2100 older adults with annual clinical evaluations. This study recruited from residential facilities, senior and subsidized housing, church groups, and social service agencies in Northeastern Illinois. Participants were eligible for enrolment if they were able and willing to sign an informed consent and an Anatomical Gift Act and agreed to donate their brain, spinal cord, and other biospecimens at death. Participants also signed a repository consent that allowed their data to be repurposed for other studies. MAP was approved by an Institutional Review Board of Rush University Medical Center, Chicago, IL, USA. Data access can be requested at www.radc.rush.edu.

Measures

Frailty Index (FI): The FI is a measure of health status that reflects the extent of age-related deficit accumulation and vulnerability to adverse health outcomes[2]. A frailty index was constructed from 41 items (Appendix 6-A) according to standard criteria[14]. Candidate variables included symptoms, signs, comorbidities, and function; variables

strongly related to the outcome (i.e. cognitive variables) were excluded. The FI was calculated as:

FI = (number of health deficits present) / (number of health deficits measured)

For example, a person with 5 of the 41 potential deficits measured has an FI score of 5/41 = 0.12. Higher FI scores indicate poorer health and theoretically, the FI ranges from 0-1, with linear regression models using units of the FI of 0.01. The frailty index was calculated based on clinical data for each participant at each annual evaluation (mean follow-up=5.6±3.7 years, range 0-17 years) and trajectories were plotted over time.

Clinical diagnoses: At the time of death, an experienced neurologist reviewed select clinical data and rendered a summary diagnosis; this was done blinded to all post-mortem data. This process is based on the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA)[15]. Participants were classified as having: no cognitive impairment (NCI; coded as 0), mild cognitive impairment (MCI; coded as 1), or dementia (including possible and probable Alzheimer's and other dementias). For our purposes, possible or probable dementia were coded as 2 and other dementias were excluded (n=9) as they were undetermined or diverse in origin.

Neuropathological index: burden of neuropathology was quantified at autopsy using an index composed of ten unique neuropathological features (amyloid load, neurofibrillary

tangle density, TDP-43, hippocampal sclerosis, cerebral amyloid angiopathy, gross infarcts, gross chronic infarcts, atherosclerosis, arteriolosclerosis, and presence of Lewy bodies). This index and the details of neuropathological assessment have been detailed elsewhere (Chapter Four).

Confounders: Age, sex, and education were evaluated as confounders; all were treated as time-invariant covariates. Age was measured in years and calculated from birth to date of last cognitive assessment before death. Education was self-reported in years. Sex was a self-report binary variable, with female as the referent.

Statistical analyses

Descriptive statistics (t-tests, chi-square, and analyses of variance [ANOVA]) were used to describe the characteristics of the sample. Frailty was plotted against time (unadjusted). ANOVAs were used to evaluate unadjusted differences in baseline frailty by sex, neuropathological index groups, and clinical diagnosis.

Multilevel (also known as mixed effects) models were used to model linear within-person change in frailty over time, as well as between-person differences in frailty. Models were built from an empty means, fixed intercept, base model, and terms were added sequentially. Terms were conserved if they demonstrated a significant change in deviance from the previous model.

First, we modelled frailty change over time (*FI ~ random intercept + time*). A sensitivity analysis to determine whether frailty change over time was quadratic rather than linear was undertaken by adding a quadratic term for time. Then, we evaluated whether frailty trajectory differed as a function of key covariates including sex, neuropathological index (tertiles), and clinical diagnosis, by modelling the interaction between each covariate and time in the prediction of frailty (in separate models). Finally, we tested whether frailty trajectory differed over levels of clinical diagnosis after controlling for all other covariates, including the neuropathological index. This final mixed linear model was as follows:

$$FI \sim random\ intercept + time + sex + education + clinical\ diagnosis + neuropathological\ index + clinical\ diagnosis*time$$

All analyses were completed using R version 3.5.2. Figures were truncated at 11 years, as less than 10% of the sample remained and estimates became unstable.

6.3.4 Results

Most (67.5%) of the 625 autopsied participants were female, and the mean age at baseline was 83.2±5.9 years. Participants were followed for 5.6±3.7 years from baseline (range 0-17 years), by which time 33.8% remained cognitively normal, 27.7% had MCI, and 38.6% had dementia (Table 6-1). Higher baseline frailty was associated with being female ($p<0.0001$), but not with neuropathological burden ($p=0.26$) or cognitive status at death ($p=0.10$).

Frailty changed significantly over time (Estimate=0.026 per 0.01 FI unit, 95% confidence interval [CI] 0.025-0.027, $p<0.0001$); this means the FI increased at a rate of about one deficit per year on average (0.026*41 deficits in FI; Figure 6-1).

Prior to adjusting for covariates, frailty trajectory differed as a function of neuropathological index (time*neuropathological index interaction estimate=0.020, 95% CI 0.013-0.026, $p<0.0001$) and clinical diagnosis (time*MCI interaction estimate=0.005, 95% CI 0.003-0.008, $p<0.0001$; time*dementia interaction estimate=0.021; 95% CI 0.018-0.023, $p<0.0001$), see Figure 6-2. Specifically, higher neuropathological burden and worse clinical diagnosis were associated with accumulating deficits at a significantly faster rate (i.e. increasing frailty index score). Frailty trajectory did not differ by sex (sex*time interaction estimate= -0.0002, 95% CI -0.003-0.002, $p=0.84$).

Frailty trajectories remained significantly different over levels of clinical diagnosis after controlling for relevant covariates (age, sex, education, neuropathological index); indicating that frailty increased over time at a faster rate in those with worsening clinical diagnosis; Table 6-2. Specifically, people with no cognitive impairment at death show an average increase of 0.018 FI units/year (corresponding to 0.74 additional deficits/year), people with mild cognitive impairment at death show an average increase of 0.023 FI units/year (corresponding to 0.94 additional deficits/year), and people with dementia at death show an average increase of 0.038 FI units/year (corresponding to 1.56 additional deficits/year). Age at death and the neuropathological index were found not to contribute

significantly to the model; age at death was dropped from the final model, but the neuropathological index was conserved for conceptual reasons.

A sensitivity analysis examined whether a quadratic model improved fit, but it did not lead to a significant change in deviance from the linear model, and the quadratic term for time was not significant. We also tested the relationships with a binary outcome variable of no cognitive impairment vs. Alzheimer's dementia and results did not change significantly.

6.3.5 Discussion

In this study of how changes in the degree of frailty affected the probability of a diagnosis of Alzheimer's dementia, we highlight two key findings: 1) frailty increased at a rate of approximately one deficit per year in a sample of older adults from retirement communities in the USA; and 2) people who ultimately developed MCI or Alzheimer's dementia became frailer more quickly than those who did not, regardless of their neuropathological burden.

Our results are consistent with other longitudinal reports linking frailty and cognition[10,11,16]. The only other study that to our knowledge has examined change in frailty with cognition and neuropathology found that baseline frailty predicted both future frailty and cognitive decline[10]. That study was from the same cohort but used a different measure of frailty. Here, we find that baseline frailty did not differ by clinical diagnosis, but frailty worsened more quickly in those who eventually developed MCI than in those

with no cognitive impairment, and quicker still in those who developed dementia. That study[10] also demonstrated a correlation between change in cognition and physical frailty, not just on average, but within individuals. Moreover, the association remained after controlling for five common brain pathologies (macroinfarcts, microinfarcts, Lewy bodies, AD pathology, and nigral neuronal loss). Pathologies were examined individually and AD pathology, macroinfarcts, and nigral neuronal loss demonstrated additive risk for both frailty and cognitive decline. This is consistent with our results showing that level of pathology increased the slope of frailty change.

An important difference between this study and ours is the measurement of frailty: the prior report operationalized frailty using a modified frailty phenotype- a composite measure of four impairments including grip strength, timed walk, body composition, and fatigue. By contrast, we operationalized frailty as deficit accumulation using the frailty index- an index of 41 health variables that reflect overall health state. We chose to use the frailty index to overcome some challenges of employing the frailty phenotype in observational data: the grading is crude, there are frequently floor effects in healthy samples and ceiling effects or much missing data due to performance-based measures in impaired ageing samples, and the modifications can limit generalizability[17].

Interestingly, our analysis demonstrated that longitudinal changes in frailty were not significantly associated with neuropathology after controlling for possible confounders. Other reports have linked common dementia-related pathologies with frailty[18,19], and hypothesized that these common pathologies are a shared mechanism between cognitive

decline and frailty[10], though our data do not support this conclusion. It is possible that frailty influences the expression of dementia by reducing the threshold of pathology necessary to give rise to cognitive impairment[12]. Whether this reflects a single mechanism in all patients with cognitive impairment, differing single mechanisms in individual patients, or an accumulation of age-related decrements - the combinations of which vary between patients - is not clear. Other reports using the Rush data that indicate multiple pathologies are common in late-life dementia, and that dementia itself may represent a form of pre-terminal decline, would seem to make single uniting mechanisms less likely. In this regard, variability in responses to treatment may prove to be informative[20].

Our results should be interpreted with caution. Our sample was not population-representative and due to the recruitment strategies may over-represent frailty and dementia. Further, it would be ideal to be able to measure changes in neuropathological burden over time, but since pathological confirmation can only be completed after death, this limits our ability to make causal inferences. We excluded other dementias from analysis as there were few (n=9) and of diverse origin. Future work with larger sample sizes should investigate whether these relationships hold across dementia types. Despite these limitations, this study has several strengths. The quality of the data and long follow-up period makes this data unique as a clinical-pathologic cohort. Mixed effects analyses allowed us to model person-specific intercepts improving the validity of the model. Alzheimer's disease research has been criticized for the over-emphasis on

amyloid and tau pathology. Here, we were able to model mixed pathology, which is common in dementia[21–23].

Overall, results of this study suggest a strong link between frailty and Alzheimer's dementia, even after considering degree of neuropathology. Frailty trajectories over an average period of six years in older adults predicted dementia risk, underscoring the importance of frailty intervention and management in later life. Frailty and cognition are known to be highly related and may even share a pathologic basis, and the bidirectional mechanisms that explain how they influence each other motivate future inquiries.

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Table 6-1. Sample demographics (n=625).

Age (years at baseline; mean±SD)*	83.1±5.9
Age (years at death; mean±SD)*	89.7±6.1
Sex (n, % female)	422, 67.5
Education (years at baseline, mean±SD)*	14.5±2.9
Cognitive status at time of death (n,%) Cognitively normal Mild cognitive impairment Dementia	 211, 33.8 173, 27.7 241, 38.6
MMSE at baseline (mean±SD, median)	26.7±4.0, 28.0
MMSE at last evaluation before death (mean±SD)*	21.5±8.7
Neuropathological index at time of death (mean±SD)*	0.36±0.17
Frailty Index at baseline (mean±SD, median)	0.24±0.12, 0.22
Frailty Index at time of death (mean±SD)*	0.41±0.18
Time in study (years baseline to last evaluation before death; mean±SD, median)	5.6±3.7, 5.0

*normally distributed

Table 6-2. Mixed effects model for outcome of frailty.

Covariates	Estimate	95% Confidence interval – lower limit	95% Confidence interval – upper limit	P value
Time (years since baseline)	0.017	0.016	0.019	<0.0001
Sex (female)	-0.038	-0.061	-0.015	0.001
Education (years)	-0.003	-0.007	0.0003	0.07
Clinical diagnosis				
MCI† vs. NCI††	0.020	-0.008	0.049	0.16
Dementia vs. NCI	0.025	-0.004	0.054	0.09
Neuropathological Index (per 0.01)	-0.008	-0.081	0.064	0.82
Time*Clinical diagnosis				
Time*MCI	0.005	0.003	0.008	<0.0001
Time*Dementia	0.020	0.018	0.023	<0.0001

†Mild Cognitive Impairment; ††No Cognitive Impairment.

Figure 6-1. Longitudinal change in frailty as measured by the frailty index (unadjusted).

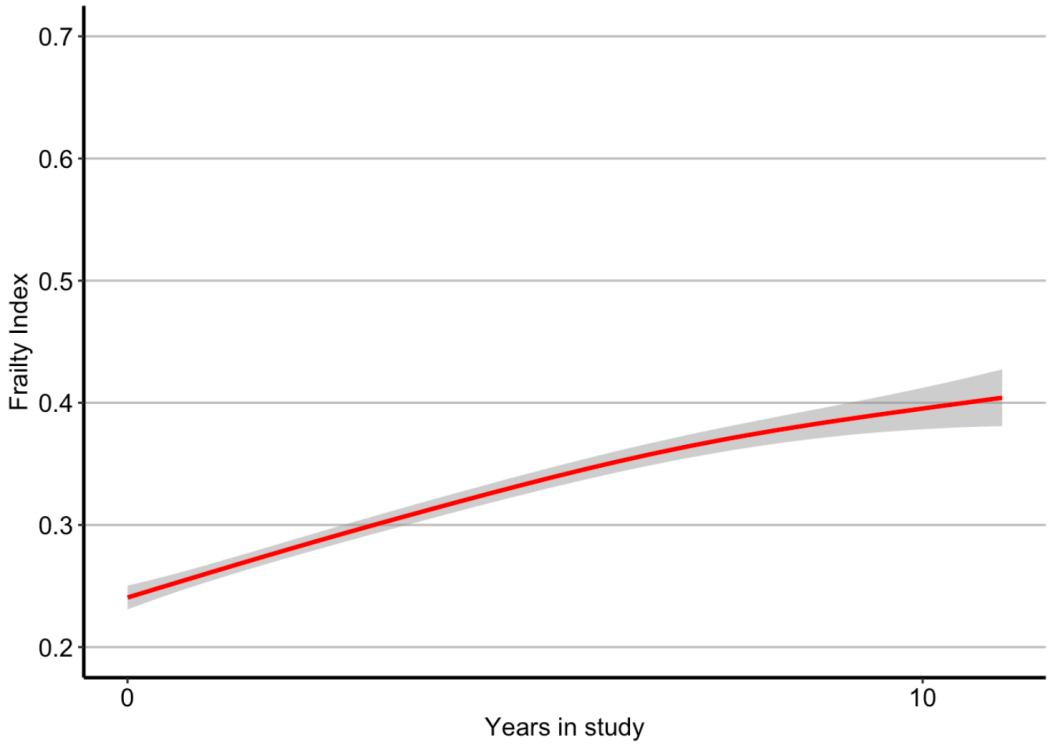
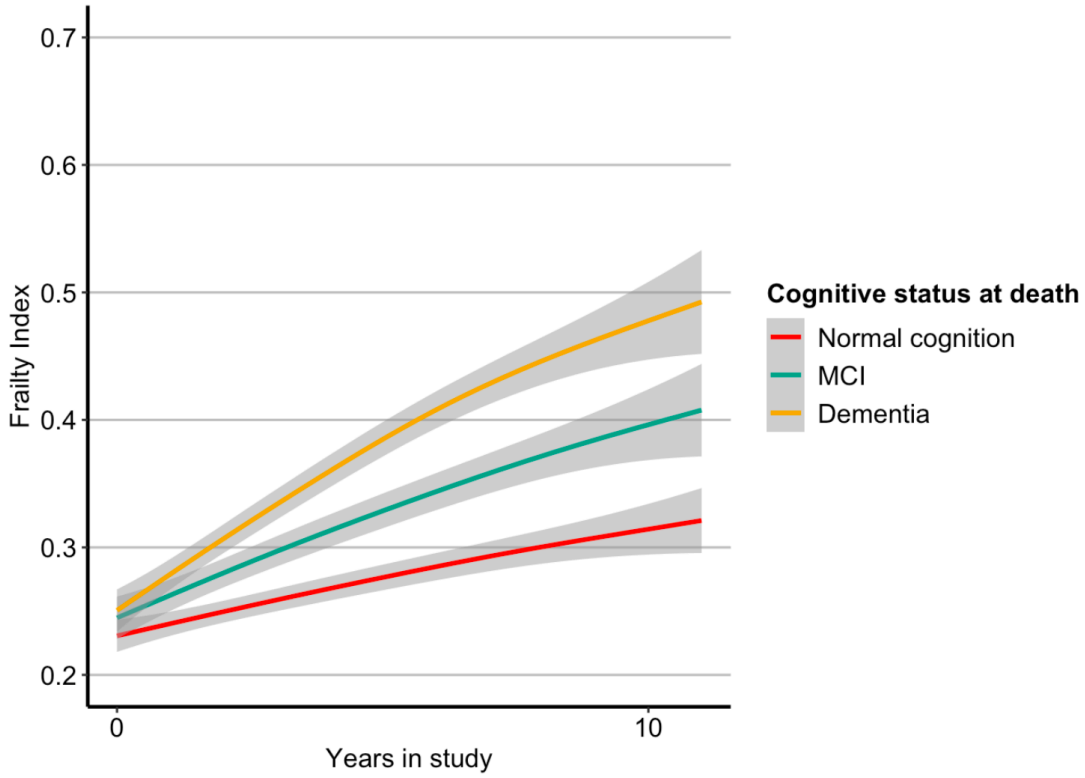


Figure 6-2. Frailty over time (years) stratified by cognitive status (unadjusted).



CHAPTER 7: Validation Of The Pictorial Fit-Frail Scale In A Memory Clinic Setting

7.1 Prologue

Frailty measurement in older adults with cognitive impairment has been little studied. In the context of understanding how frailty contributes to cognitive decline and dementia, tools that are appropriate for patients with cognitive impairment, and empower them to participate in their own health care are crucial. After developing the PFFS over the last several years in response to these barriers, it was my priority to test the feasibility, reliability, and validity of the tool in people with cognitive complaints at risk for impairment. In this way, I hope to make frailty assessment more accessible and useful in care settings that deal with older adults in order to improve their care management and treatment.

7.2 Manuscript information

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Permission: see Thesis Appendix 2.

Student contribution to manuscript: All authors were involved in the development of the PFFS. Lindsay Wallace designed the current study, collected and analyzed the data, and wrote the first draft. Olga Theou supervised Lindsay Wallace and contributed to the analysis of the data and interpretation of the results.

7.3 Manuscript

7.3.1 Abstract

Objective: To assess the feasibility, reliability, and validity of the Pictorial Fit-Frail Scale (PFFS) among patients, caregivers, nurses, and geriatricians in an outpatient memory clinic.

Design: Observational study.

Setting: A Canadian referral-based outpatient memory clinic.

Participants: Fifty-one consecutive patients and/or their caregivers, as well as attending nurse and geriatricians.

Measurements: Participants (patients, caregivers, nurses, and geriatricians) were asked to complete the PFFS based on the patient's current level of functioning. Time-to-complete and level of assistance required was recorded. Participants also completed a demographic survey and patients' medical history (including the Mini-Mental State Examination [MMSE], and Comprehensive Geriatric Assessment [CGA]) was obtained via chart review.

Results: Patients had a mean age of 77.3±10.1 years, and average MMSE of 22.0±7.0, and 53% were female. Participants were able to complete the PFFS with minimal assistance and their average times to completion were 4:38±2:09, 3:11±1:16, 1:05±0:19, and 0:57±0:30 (mins:sec) for patients, caregivers, nurses, and geriatricians, respectively. Mean PFFS scores as rated by patients, caregivers, nurses, and geriatricians were 9.0±5.7, 13.1±6.6, 11.2±4.5, 11.9±5.9, respectively. Patients with low MMSE scores (0-24) took significantly longer to complete the scale and had higher PFFS scores. Inter-rater

reliability between nurses and geriatricians was 0.74, but lower when assessments were done for patients with low MMSE scores (0.47, $p<0.05$). The correlation between PFFS and a Frailty Index based on the CGA was moderately high and statistically significant for caregivers, nurses, and geriatricians ($r=0.66$, $r=0.59$, $r=0.64$, respectively), but not patients.

Conclusions: The PFFS is feasible, even among people with some slight cognitive impairment, though it may be less useful when patients with severe dementia administer it to themselves. Further, the PFFS may help inform clinicians about areas of concern as identified by patients, enabling them to contribute more to diagnostic and treatment decisions, or aid in health tracking and care planning.

7.3.2 Introduction

As our population ages, the proportion of people who experience frailty is increasing. In Canada, almost a quarter of individuals over the age of 65 are frail[1], and this number is expected to increase. Frailty can be understood as a state of increased vulnerability to adverse health outcomes among people of the same chronological age[2], and is characterized by multiple, interacting, medical and social problems which compromises the ability to respond to physiological and psychological stressors (internal or external). Therefore, frailty affects functional capacity and quality of life and is associated with hospitalization, institutionalization and mortality[2].

Frail patients often have complex and atypical presentations of common medical problems[3]. This makes frailty measurement a crucial step in understanding how to diagnose, treat, and manage health problems in older adults. In hospital, frailty

measurement has been used in personalization of interventions and modification of standard protocols[4], considering harms vs. benefits of invasive procedures[5], and tracking symptoms and decline or improvement[6]. Frailty mitigation has been demonstrated[7], and trials are ongoing to determine the best frailty intervention [8].

Although research on the development of frailty tools has been prolific - over 65 unique frailty tools have been identified[9], with 10 screening tools in primary care alone[10] - few have been developed which do not require clinical judgment, are suitable for patients with communication issues, and do not depend on performance-based tests. For example, the Frailty Index requires at least 30 items to be considered, which has made clinicians skeptical about its practicality when it is employed with other than routinely collected data, as in the electronic FI in England and Wales[11,12]. The Clinical Frailty Scale[13], which is now expanded to include nine levels (from very fit to terminally ill), has good predictive validity and combines items such as co-morbidity, cognitive impairment, and disability; however, it requires clinical judgment. Some other scales (e.g. frailty phenotype[14], Edmonton Frail Scale[15]) measure physical performance, such as timed walks or grip strength, in ways that are impractical for people who are severely frail. Others (e.g. frailty phenotype, FRAIL scale[16]) identify only a small number of symptoms, leaving out important information from patients and caregivers. Some scales ask patients to verbally report their problems and limitations, which is not feasible for people with communication issues, including dementia, or people facing language barriers (e.g. Tilburg[17] and Groningen Frailty[18] Indicators).

The goal of the PFFS was to create a frailty screening tool that would be simpler, easier to administer, more sensitive to cultural differences, and a more practical approach for identifying frailty compared with previous frailty scales. In addition, it is meant to provide direction about the type of assessment that is needed for people who screen positive. To achieve this, we used visual prompts to assess a person's ability in 14 health domains to determine their level of fitness or frailty (Appendix 7-1).

The objective of the current study was to assess the feasibility, reliability, and validity of the PFFS among patients, caregivers, nurses, and geriatricians in a tertiary care (outpatient memory clinic) setting and compare these psychometric properties between cognitively intact and impaired participants.

7.3.3 Methods

Design & setting

This was a single-site study which took place in the Geriatric Ambulatory Care and Memory Clinic (for the purpose of this paper referred to as memory clinic) of the Centre for Health Care of the Elderly at the Nova Scotia Health Authority in Halifax, Canada. The memory clinic is an outpatient clinic that provides integrative services by a multi-disciplinary team including geriatricians, nursing staff, and social workers, with the goal of assessment and management of complex problems in older adults. Patients are generally referred by their family doctor for cognitive complaints or decompensation. Caregivers frequently accompany patients to the memory clinic visits or are contacted to give collateral information.

Participants

Consecutive patients from selected days of the memory clinic and their caregivers were invited to participate. They were eligible if they did not have significant visual impairments and were able either to consent or to assent and have their substitute decision maker consent on their behalf. A memory clinic nurse was also invited to participate, as were the geriatricians rotating on the clinic service. Written informed consent was obtained from all participating patients, caregivers, nurses, and geriatricians prior to initiating any study procedures. Neither of the geriatrician co-authors (MKA, KR) were assessors for this study, so data were not collected when they were attending.

Procedure

The memory clinic nurse assessed patients for eligibility at their initial visit. If patients were eligible and wanted to learn more about the study, the nurse introduced them to our researcher. The researcher explained the study, invited them and their caregivers to participate, and went through the process of informed consent. Those who provided informed consent were then asked to read the instructions of the PFFS and complete the scale independently, based on the patient's current functioning. The time (minutes and seconds) to complete the initial PFFS was recorded by the researcher. Next, patients and caregivers were asked to independently complete a survey that included demographic questions and questions regarding their understanding of the scale (Appendix B). The nurse and geriatrician who assessed the patient were asked to record the PFFS, based on their assessments, and to note the time it took to complete the scale.

Measures

Data on demographics were obtained via survey (Appendix 7-B). Data on health and medical history (including MMSE, and CGA) were obtained via chart review, with participant consent.

Mini-Mental State Examination (MMSE[19]*);* The widely employed, 30-item MMSE is routinely administered by nursing staff at memory clinic admission as a dementia screening tool. Its cognitive screening domains including attention, recall, language, and orientation. MMSE scores were accessed via chart review and a cut-off score of 24 was used to group participants into high and low MMSE groups (>24, 0-24, respectively) to stratify our analyses. This facilitated our examination of whether cognitive function affects the ability of the patients to complete the PFFS.

Frailty Index based on a Comprehensive Geriatric Assessment (CGA[20]*);* Geriatricians in the memory clinic routinely use the CGA to assess the overall health state of the patients by evaluating a wide range of health domains such as medical history, activities of daily living, and mobility. The CGA can be used to calculate a Frailty Index score (FI-CGA) following a standard procedure as the proportion of potential deficits present in a given individual[20].

PFFS: The PFFS is made up of 14 domains, such as cognition, mobility, daytime tiredness, etc. (Appendix 7-A). Each domain refers to a different aspect of functioning. Levels within each domain are presented from best (optimal functioning; left) to worse (extremely poor functioning or impairment; right). Participants are asked to mark the box beneath the level that best corresponds to their current level of function.

No additional instructions were initially given to participants. If they were not completing the scale independently or asked for help, aid was given by the researcher in the following manner and recorded as follows: 0=no help; 1=orientation to first domain, verbal prompts "which level is closest to your usual state?"; 2=Verbally describe each level of the first domain, e.g. "The first picture shows someone who feels happy, would you say that you typically feel happy?" If no, describe each of the adjacent levels.

For each domain the first level was scored as 0, the second level as 1, the third level as 2 etc. Two domains include 7 levels (score 0-6), 6 domains included 5 levels (score 0-4), and 6 domains includes 3 levels (score 0-2). The scores for all domains are then summed and the total score for the scale ranges from 0 to 43. A lower score indicates better health (higher fitness, lower frailty) and a higher score indicated worse health (lower fitness, higher frailty). For the purpose of comparison to the FI-CGA, the PFFS was transformed to an index ($PFFS_{trans}$) by dividing the PFFS sum score by the total number of levels with a response.

Statistical analysis

Descriptive statistics (numbers, proportions for categorical variables; means, standard deviations, and ranges for continuous variables) were used to report patient demographics and baseline characteristics.

We calculated average time to complete the scale for all participants and compared completion time and average PFFS score between raters (i.e. patients, caregivers, nurses, geriatricians) using linear mixed models.

Intraclass correlation coefficients were calculated to determine agreement between the PFFS score for nurses and geriatricians. We also stratified the analysis by cognitive level of the patients.

Parametric (Pearson's r) and non-parametric (Spearman's Rho) correlations were employed to examine the relationship between the patient, caregiver, nurse, and geriatrician PFFS scores and FI-CGA scores from the geriatrician. Analyses were stratified by age, sex, and cognitive level of the patients.

This research protocol has been approved by the Dalhousie University and Nova Scotia Health Authority Research Ethics Boards (approval # 1021824). All participants signed an informed consent form prior to initiation of any study procedures.

7.3.4 RESULTS

Descriptive analysis

A total of 92 patients were eligible to participate. Fifty-one patients provided informed consent and agreed to participate themselves and/or have their caregiver participate. See Figure 7-1 for patient inclusion flow chart.

The 51 enrolled patients had a mean age of 77.3 (SD 10.1). Slightly more than half (53%) were female. The average MMSE of participants was 22.0 (SD 7.0). Forty-four caregivers agreed to participate, of whom 43 completed the PFFS. Caregivers had a mean age of 60.2 (SD 13.1), and 84% were female. Caregivers were most often a spouse or child of the patient (41.9% and 46.5%, respectively). Health care professionals (one nurse and four geriatricians) had a mean of 12.2 years in practice, most were male (60%, n=3), and all identified as white (Table 7-1).

Average PFFS scores for all raters can be found in Figure 7-2. The only significant difference in PFFS scores between groups of raters was that caregivers rated patients higher than patients rated themselves (p=0.024). Patients with low MMSE scores had significantly higher PFFS scores from all raters.

Feasibility

The mean length of time for patients to fill out the PFFS scale was 4:38 (min:sec; SD 2:10), with a range of 1:27 to 10:47. Caregivers took 3:11 on average (SD 1:16) and

nurses and geriatricians took 1:05 (SD 0:19) and 0:57 (SD 0:30), respectively. PFFS completion times significantly differed between all raters ($p<0.01$) except for nurses and geriatricians. The majority of caregivers did not need any assistance to complete the scale (n=39, 91%), four caregivers needed level one assistance (9%). Patients needed more assistance to complete the scale than their caregivers: 11 received level one assistance (31%), and 11 received level two assistance (31%).

When the analysis was divided by MMSE score (high=MMSE>24, low=MMSE≤24), patients with low MMSE scores took significantly longer to complete the scale than those who were cognitively intact ($p=0.001$). Nine patients were missing an MMSE score and were excluded from these sub-analyses. Among patients who had low MMSE scores, four received no assistance, four received level one prompts, and eight received level two prompts when completing the PFFS.

Patients and caregivers who were older also took significantly longer to fill out the PFFS ($p=0.003$ and $p=0.001$, respectively). There were no differences in times between sexes for patients or caregivers ($p=0.75$ and $p=0.69$, respectively).

In eight cases, one of the raters accidentally skipped one domain on the scale. In these cases, we manually adjusted the PFFS score subtracting the missing score from the denominator. Patients and caregivers noted very few issues with the scale. The only domains that were flagged by more than one participant were aggression (three participants- all caregivers- noted confusion with this domain, particularly that it did not

capture important aspects such as agitation and withdrawal), and two participants each commented on the clarity of the function and daytime tiredness domains.

Reliability

Inter-rater reliability between nurses and geriatricians was 0.74 for the overall sample, 0.67 for the high MMSE group, and 0.47 for the low MMSE group; Table 7-2.

Validity

Bivariate correlation was used to test construct validity by evaluating the relationship between the $PFFS_{trans}$ score and the FI-CGA, both as rated by a geriatrician. This correlation was moderately high and statistically significant ($r=0.64$, $p<0.001$; Table 7-3). Distributions of the FI-CGA and PFFS were similar and characteristic of the FI with a right-skewed tail.

The correlation between the FI-CGA as rated by geriatricians and the $PFFS_{trans}$ as rated by caregivers and nurses was statistically significant ($r=0.66$, $p<0.001$; $r=0.59$, $p<0.001$, respectively), but not for patients (Table 7-3).

Among patients with high MMSE scores, all raters (patients, caregivers, nurses, and doctors) had high and statistically significant correlations between the PFFS and FI-CGA score (Table 7-3).

7.3.5 Discussion

This study of older patients of a memory clinic demonstrated good feasibility, reliability, and validity of the PFFS tool especially among patients with MMSE greater than 24. Patients and caregivers were able to fill out the scale relatively quickly and without help in the time they were waiting for their appointment. Health care professionals were also able to quickly and accurately complete the scale. There was moderate agreement among scores between health care professionals (nurses and geriatricians), although this agreement decreased when the patient scored low on the MMSE, an indicator of cognitive impairment. The PFFS was correlated with the routine frailty assessment used in clinic: the Comprehensive Geriatric Assessment.

An important finding from the current study was that the PFFS was feasible among patients and their caregivers. Although two participants with MMSE's below 12 were not able to participate, all others who wanted to participate were able to complete the scale independently or with some assistance and the correlation with the standard frailty measure (FI-CGA) was reasonable. An important consideration here is that in this way the PFFS may be useful in screening for frailty, targeting domain-specific interventions, and monitoring change. Further research will be needed to examine the impact of personalized interventions and responsiveness to change.

Reliability was found to be moderate among health care professionals (nurse and geriatricians), though this was decreased when the patient being assessed had a low MMSE score; geriatricians scored patients with low MMSE scores slightly worse (i.e. higher PFFS scores) than the nurse. This suggests that patients experiencing cognitive

impairment or decline may need closer management and careful communication between health care professionals to optimize health care delivery. We debated whether to include a measure of 'reliability' between patients and caregivers, as there is ample evidence demonstrating discrepancies in health perception of the patient[21]. Rather than examine this as a property of the scale, we were curious to see whether patients and caregivers had high agreement and found that interestingly, there was higher agreement in the low MMSE group than the cognitively intact group. While the confidence intervals suggest this may be an artifact, it is possible that caregivers are more attuned to the health of the patient when they are more impaired.

We used convergent construct validation as our main validation measure[22]: i.e. testing the relationship between a standard measure of frailty (FI-CGA) and the PFFS. The CGA has been widely used as a frailty assessment and is the reference standard in the field[10,20]. It is typically used to target care and create a management plan. It has been demonstrated that this practice improves function[23], cognition[24], and reduces medical costs and service use[25,26]. Although the use of a CGA is key in specialized geriatric practice, it is not commonly used in other settings. This reflects that it is time consuming to complete, requires clinical judgement, and health state scoring (e.g. FI score calculation) is not necessarily easily accessible. Although our PFFS is based on the premise of the FI-CGA, we have adapted the method to include important geriatric domains in a manageable visual format that can be filled out by patients and caregivers while in the waiting room. It is easy for physicians to glance at to get an impression of the overall level of frailty, as well as to easily see domains where interventions should be targeted.

Although there was generally a high correlation between PFFS scores and FI-CGA score, several caveats remain. First, while the correlation is generally high for the sample, it may not be high enough to apply to individuals. When patients with low MMSE scores were assessed, only the nurse's PFFS scores were significantly correlated to the FI-CGA score. Since the FI-CGA was completed by the geriatrician, this suggests some key information was being missed on the PFFS. Based on these findings, it is possible that the PFFS is not as useful for patients with cognitive impairment. Future research is needed to test this in a larger sample as it is possible that the sample was too small to detect a signal.

Some frailty measures have shown the propensity for floor or ceiling effects. The distributions of the PFFS suggest floor and ceiling effects are not a problem of this measure. Future research needs to evaluate responsiveness, and test interpretability using evaluation.

Over 20 frailty tools have been identified (and reviewed elsewhere[6,10,27]), though few have been rigorously validated and all have encountered several barriers to large-scale and routine implementation[4]. The majority of these frailty tools are based on the same premise- measuring multisystem physiologic vulnerability- though they are operationalized quite differently. These tools include anywhere from one to hundreds of items, and rely on data of all types, including self-report, lab tests, and performance-based tests. Typically, they conform to one of two prevailing frailty theories[9,28]: the

deficit accumulation model[29] or the syndromic phenotype model[14]. The frailty index is the operationalization of the deficit accumulation model, and other tools have followed this general premise while making some modifications to the number and specificity of included items, these such scales include the Edmonton Frail Scale[15], Clinical Global Impression of Change in Physical Frailty[30], and Groningen Frailty Indicator[18]. Others are modifications of the phenotype, which proposes five specific criteria: weight loss, poor grip strength, exhaustion, slow walking time, and low physical activity[31]. Such modified scales include: Rothman[32] and FRAIL scale[16]. Others still are so-called screening tools that aim to boil frailty down to a one-item indicator, such as grip strength[33]. Importantly, the latter two groups of tools omit complex functional, social, and cognitive tasks which are dementia defining and thereby key indicators of decline in people living with cognitive impairment.

In a systematic review analyzing outcome instruments to measure frailty, authors suggested that ideal frailty measures should include eight essential factors: nutritional status, mobility, physical activity, strength, energy, cognition, mood, and social support[6]. The only frailty tool that measured each of these factors was the frailty index (with a social vulnerability index more broadly accounting for social factors). With the PFFS we aim to build on the premise of the frailty index but adapt the design for a measure that is simpler, easier to administer, and culturally and linguistically universal. The PFFS also includes each of the eight essential domains lending to its construct validity.

Our results are consistent with other studies of frailty in older adults. PFFS scores were higher among women (although this was a trend and not statistically significant) and among those who were cognitively impaired. PFFS scores were more closely related to FI-CGA scores than age. The range of the FI-CGA and $PFFS_{trans}$ were similar to other reports with a demonstrated sub-maximal limit ~0.7. The FI-CGA had a higher mean than the $PFFS_{trans}$, likely due to the inclusion of comorbidities.

Frailty and dementia appear to be inextricably linked. People with cognitive impairment are frequently frail[34] even when these frailty measures do not include any traditional cognitive risk factors[35]. The literature on assessment of frailty among people experiencing cognitive decline is sparse, though it can be imagined that this presents a challenge that will only grow greater as the prevalence of dementia rises[36].

Previous reports suggest that frailty assessment can be useful in a variety of ways. It has the potential to 1) identify frailty among at-risk individuals; 2) be used in clinical-decision making; 3) target personalize interventions and inform management; 4) be used to track changes[9,37,38]. There is some debate as to whether certain tools are more suitable for screening purposes while others may be more appropriate as outcome measures[39]. Different clinimetric standards would be applied accordingly (e.g. screening tools would not need to be as responsive to change as outcome measures; content validity is prioritized and includes considerations of relevance and non-arbitrariness, in an effort to identify clinical meaningfulness and not just statistical significance). Here, we suggest that the PFFS is useful in the context that the CGA is used, which is to be used to screen

for frailty, but also to inform care planning. Further, it responds to challenges of complex and lengthy examinations[40].

Our findings should be interpreted with caution. An important limitation of the current study is the small sample size. If anything, this would bias results towards the null. Given that our results are largely consistent with previous findings using the FI, we have confidence in the validity and accuracy of our findings.

In the memory clinic setting, follow-up appointments are not always necessary, and when they do occur, the length of time until the next appointment varies by case. For this reason, it was not feasible or practical to measure test-retest reliability. This is an important consideration because patients with cognitive impairment are known to have 'good days and bad days'[41]; performance as indicated by their self-reported account of the scale, and their ease of completing it may be dependent on this, though we cannot be sure as there was no retest. It is also possible that results may differ for different types of dementia, though sample size here was prohibitively small in testing this.

Another limitation is that the health care professionals included in the study were all trained in geriatric medicine. Therefore, this study cannot determine whether this scale would be useful in a primary care setting. This setting was chosen to 1) ensure variation in cognitive profiles, and 2) ensure that an appropriate convergent construct validity measure (i.e. the Comprehensive Geriatric Assessment) would be available to compare the PFFS against. Future research should examine this in other settings that frequently

serve geriatric patients. Further, in the studied memory clinic, the nurse typically assessed patients, while geriatricians obtain collateral information from the family, followed by a meeting all together, so that knowledge of patient vs. family concerns might therefore systematically affect ratings by health care professionals.

Other properties of the PFFS were not reported here, including predictive validity and responsiveness to change. These are key determinants of the utility of the scale but were not feasible to examine at this time. Future work is needed to evaluate these characteristics of the scale in various settings.

Our work in the development of the PFFS was to create a tool to measure frailty that would be simple, easily understood, that could empower patients to participate in their own care and go beyond cultural/language barriers. For this reason, its use among people who may have cognitive impairment is an important area of study. Here, we demonstrated that the PFFS is feasible, even among people with slight cognitive impairment, though it may be less accurate among people with severe dementia. Further, it may be able to inform clinicians about areas of concern as indicated by the patient, and therefore direct diagnostic and treatment decisions, or aid in health tracking and care planning.

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Table 7-1. Descriptive characteristics of the sample.

	Total sample (n=51)	High MMSE (>24) (n=20)	Low MMSE (0-24) (n=22)
Patient age (mean±SD)	77.3±10.1	76.8±8.4	79.0±8.5
Patient sex (%female)	52.9%	60.0%	45.5%
Patient education	Grade 8- 12.5% Grade 12- 39.6% Certificate- 14.6% Bachelors- 25.0% Post-graduate- 8.3%	Grade 8- 15.8% Grade 12- 21.1% Certificate- 15.8% Bachelors- 36.8% Post-graduate- 10.5%	Grade 8- 14.3% Grade 12- 57.1% Certificate- 9.5% Bachelors- 14.3% Post-graduate- 4.8%
Patient self-rated health	Excellent- 8.3% Very good- 33.3% Good- 38.9% Fair- 13.9% Poor- 5.6%	Excellent- 11.8% Very good- 23.5% Good- 47.1% Fair- 11.8% Poor- 5.9%	Excellent- 6.7% Very good- 40.0% Good- 26.7% Fair- 20.0% Poor- 6.7%
Caregiver age (mean±SD)	60.2±13.1	58.9±11.4	62.4±14.8
Caregiver sex (female)	84.1%	81.3%	80.0%

	Total sample (n=51)	High MMSE (>24) (n=20)	Low MMSE (0-24) (n=22)
Caregiver relationship	Spouse- 41.9% Child- 46.5% Other- 11.6%	Spouse- 43.8% Child- 43.8% Other- 12.6%	Spouse- 45.0% Child- 45.0% Other- 10.0%
MMSE (mean±SD; range)	22.0±7.0; 1.0-30.0	27.5±1.9; 25.0-30.0	17.0±6.2; 1.0-24.0*
Frailty Index based on the Comprehensive Geriatric Assessment (mean±SD; range)	0.35±0.18; 0.05-0.72	0.28±0.19; 0.05-0.65	0.41±0.16; 0.21-0.72

SD=standard deviation; MMSE=Mini-Mental State Examination; *p<0.001

Table 7-2. Inter-rater reliability (intraclass correlation).

	Nurse	Geriatrician
Total sample (n=48)	0.74 (0.58-0.85)**	
High MMSE (n=19)	0.67 (0.33-0.86)**	
Low MMSE (n=21)	0.47 (0.05-0.76)*	

*p<0.05
**p<0.001

Table 7-3. Parametric (Pearson's) correlation between PFFS and FI-CGA.

	Patient	Caregiver	Nurse	Geriatrician
Total sample (n=27)	0.38	0.66**	0.59**	0.64**
High MMSE (n=12)	0.83**	0.85**	0.61**	0.87**
Low MMSE (n=13)	-0.41	0.47	0.60*	0.36

*$p<0.05$
**$p<0.001$

Figure 7-1. Participant inclusion flow chart.

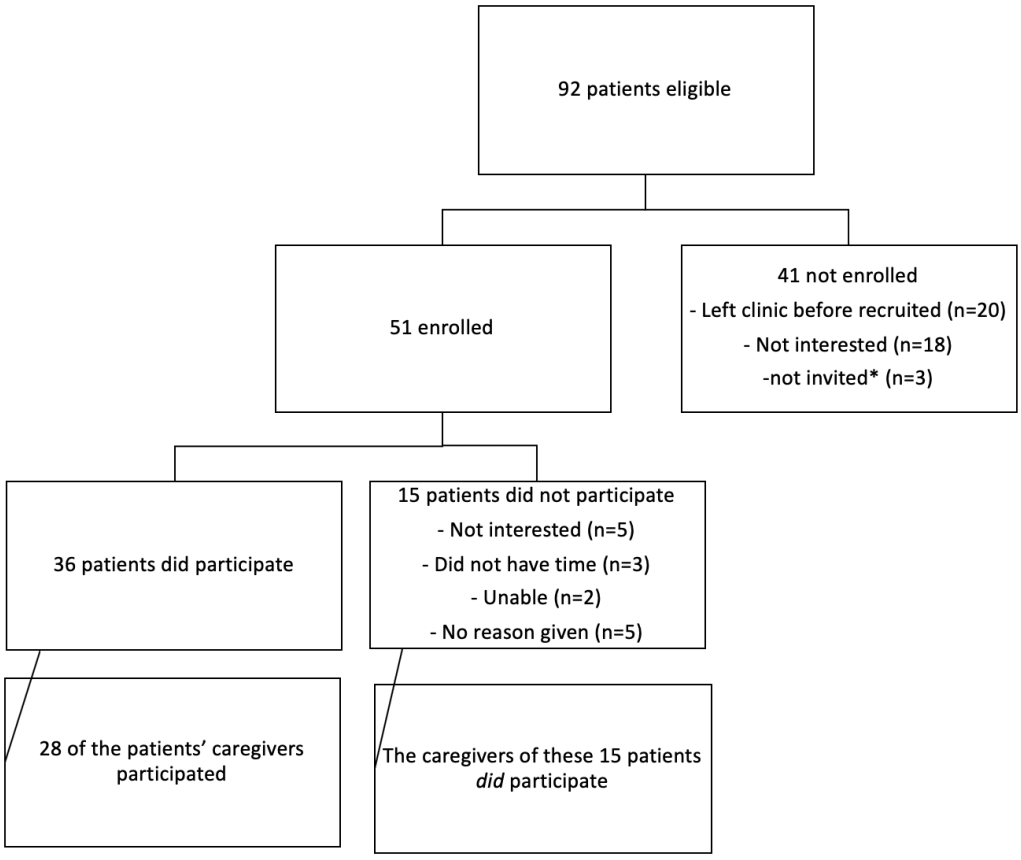
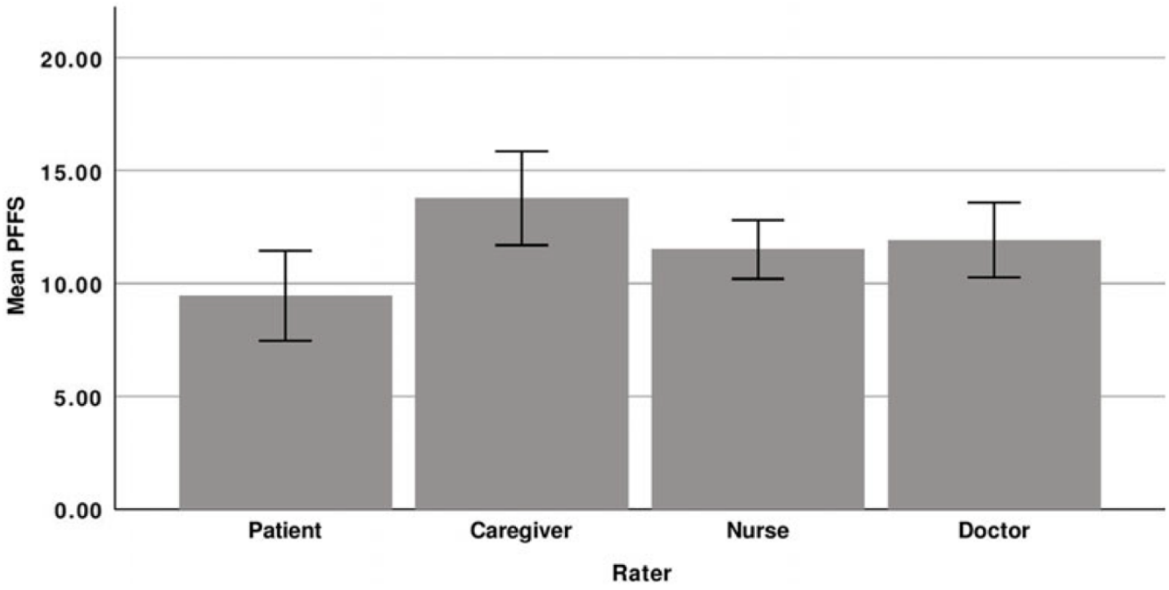


Figure 7-2. Pictorial Fit-Frail Scale scores by rater type.



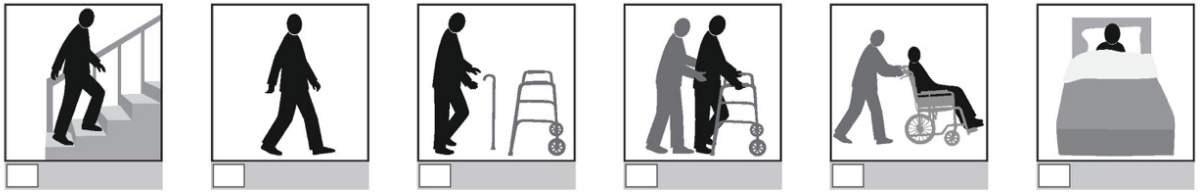
Appendix 7-A. The Pictorial Fit-Frail Scale (Theou et al., The Pictorial Fit-Frail Scale: Developing a visual scale to assess frailty. *Canadian Geriatrics Journal*, 2019) Permission in Thesis Appendix 3.

PFFS

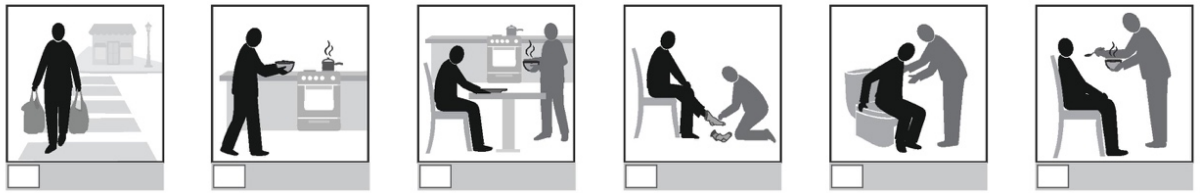
For each category, mark **ONE BOX** that is the closest to your **USUAL STATE**.

BEST ◀ ▶ **WORST**

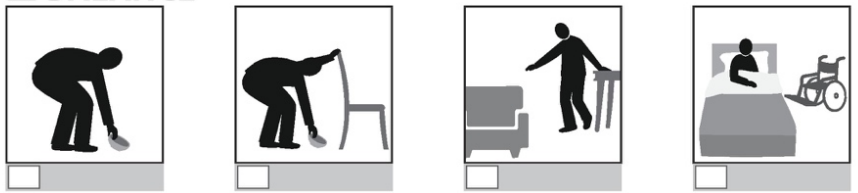
3 MOBILITY



4 FUNCTION



5 BALANCE



PFFS

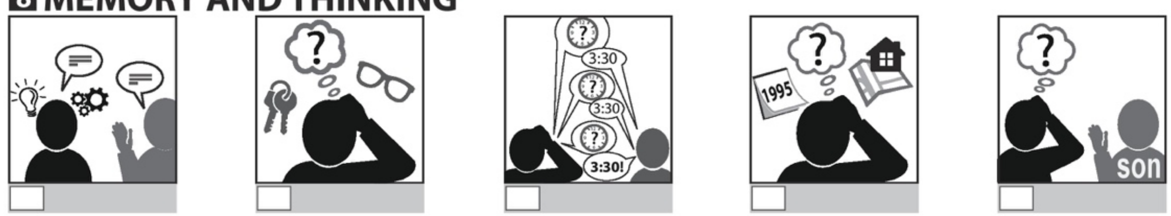
For each category, mark **ONE BOX** that is the closest to your **USUAL STATE**.

BEST **WORST**

6 SOCIAL CONNECTIONS

7 DAYTIME TIREDNESS

8 MEMORY AND THINKING

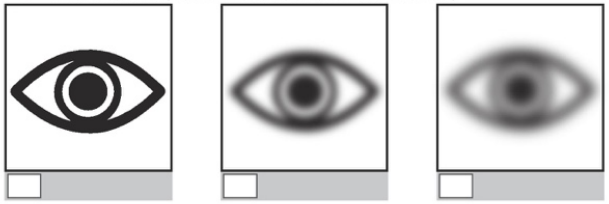


PFFS

For each category, mark **ONE BOX** that is the closest to your **USUAL STATE**.

BEST WORST

9 VISION (WITH GLASSES IF NEEDED)



10 HEARING (WITH HEARING AID IF NEEDED)

11 PAIN

BEST WORST

12 UNINTENTIONAL WEIGHT-LOSS

13 AGGRESSION

14 BLADDER CONTROL

Appendix 7-B. Participant survey.

Pictorial Fit-Frail Scale- Patient form

Please circle the appropriate response.

1. Date of birth: Day____/Month_____/Year_____

2. Sex:
    a. Male
    b. Female
    c. Other:_____

3. Race/ethnic group:
    a. White
    b. Black
    c. Hispanic
    d. Asian
    e. Multiple
    f. Other:_____

4. Marital status:
    a. Married/registered partnership
    b. Never married
    c. Divorced
    d. Widowed

5. Highest level of education completed:
    a. Primary/elementary school (up to grade 8)
    b. Secondary school/GED (up to grade 12 or equivalent)
    c. Post-secondary certificate or diploma
    d. University bachelors degree
    e. University degree above bachelors degree

6. Employment status:
    a. Retired
    b. Homemaker
    c. Employed full-time
    d. Employed part-time
    e. Looking for work
    f. Unable to work due to health or other reasons

g. Volunteer full-time
h. Volunteer part-time

7. How would you rate your overall health?
    a. Excellent
    b. Very good
    c. Good
    d. Fair
    e. Poor

8. How would you assess your health compared to others of the same age?
    a. Much better
    b. Slightly better
    c. Neither better or worse
    d. Slightly worse
    e. Much worse

CHAPTER 8: Discussion

In this final chapter of the thesis, I will summarize the findings of each study, consider their limitations, and discuss the potential implications of the results as well as identify areas of future inquiry. Though each chapter has its own discussion section, the aim here is to synthesize our findings and interpret their meaning in the context of all the evidence. To this end, I have also created new figures presented in this section based on the data from each chapter, as well as included figures from previous chapters, in order to best represent similarities and differences in the relationship between frailty, neuropathology, and dementia in each analytic sample.

8.1 Summary of findings

In the analysis described in Chapter Three, I found that the relationship between AD-pathology (i.e. diffuse and neuritic plaques, and neurofibrillary tangles) and Alzheimer's dementia is dependent on the level of frailty: as frailty increases the relationship between AD-pathology and Alzheimer's dementia becomes *weaker* (Figure 8-1). This is evidence of statistical moderation. Importantly, frailty was also evaluated as a mediator between neuropathology and Alzheimer's dementia and was not significant. In essence, this suggests that frailty is *not* necessarily the mechanism by which plaques and tangles exert their effect, but rather frailty influences one's ability to 'tolerate' the neuropathology. Further, it points to the likelihood that dementia arises in frail older people as a result of diverse mechanisms, and not only by plaques and tangles. Interestingly, although frailty and neuropathology both independently increase the risk for dementia, there appears to

be a level of neuropathology for which dementia is essentially inevitable (Figure 8-1). This suggests that AD pathology can be sufficient, but not essential to produce Alzheimer's dementia, and the risk of dementia is much higher if frailty is also present. The fact that dementia can occur in people with high levels of frailty but low levels of neuropathology (Figure 8-2) indicates that frailty is also sufficient, but not essential. Taken together, this evidence suggests that Alzheimer's dementia can be the result of diverse mechanisms, including frailty. This calls into question the validity of the strong case for the amyloid hypothesis considering other mechanisms are at play routinely in older people with dementia – who on a population basis, numerically make up the majority of those affected[1].

In Chapter Four, I extended the work of the project described in Chapter Three by broadening my criteria for neuropathology to a neuropathological index (a novel construct composed of ten features), and my outcome criteria to include MCI and all-cause dementia (not only Alzheimer's-type) in order to investigate whether this relationship was specific to Alzheimer's disease. I demonstrated that frailty and a neuropathological index each contribute independently to all-cause dementia status. In this case, frailty and the neuropathology index did not interact, meaning that the impact of frailty on dementia is the same regardless of neuropathological burden; frailty and neuropathology are additive risk factors for dementia (Figure 4-2, Panel B). This is consistent with other work that has shown a dose-response relationship between risk for dementia and number of risk factors or health deficits present[2].

This finding from the Chapter Four study seemed to conflict with the results of the Chapter Three study, in that I did not see an interaction between frailty and neuropathology. There are two key differences in design to consider in explaining these apparently contradictory results. First, I expanded my measure of neuropathology from AD-specific plaques and tangles to ten different neuropathological features. In so doing, created something of an organ-specific frailty index, as evidenced by a weak but significant correlation between the neuropathological index and FI in this sample (*Pearson's r*=0.20, p<0.0001). In this way, it is possible that the neuropathological index reflects more the overall frailty than it does the AD-specific pathology (correlation with FI: *Pearson's r*=0.11, *p*=0.024).

Second, I broadened my outcome from Alzheimer's dementia to MCI or all-cause dementia. One assumption of the ordinal regression is that levels of the variable (i.e. no cognitive impairment, MCI, all-cause dementia) are stops along a continuum, which remains equivocal. Although many people with MCI eventually transition to dementia, some do not, and it remains unclear whether they would have (had they lived long enough), or if this represents a unique pathological entity[3–5]. When outcomes were plotted as dummy-coded binary variables (no cognitive impairment vs. MCI, MCI vs. dementia, and no cognitive impairment vs. dementia) the MCI group appears to be behaving more similarly to the no cognitive impairment group than the dementia group (Figure 4-3). In essence, frailty is not as good at distinguishing between no cognitive impairment and MCI than it is distinguishing either from frank dementia. This remains true when functional items are removed from the frailty index. Again, we see in the no

cognitive impairment vs. dementia outcome that there is a level of pathology for which dementia is almost universal, and there appears to be an interaction between frailty and neuropathology approaching significance in this subgroup (Figure 4-3), though it is also possible that it is due to the increased sample size in this group.

Findings in Chapter Four may depict a phenomenon that is specific to Alzheimer's disease, but it is more likely that the relationship between structure (pathology) and function (cognition) improves when I broadened the criteria for neuropathology (which may also be a reflection of frailty) and dementia. This may also speak to the 'misnomer' of Alzheimer's disease dementia as a disease entity rather than a reflection of a collection of pathologies and deficits in a complex system close to failure.

In Chapter Five, I successfully replicated my results from Chapter Four in a population-representative dataset, despite a different sample, a different frailty index, and a different neuropathological index. Again, I saw that frailty and neuropathological burden were additive risks for dementia (Figure 8-3). Further, there was quite an overlap in frailty levels that can likely be explained by the small sample size (Figure 8-4). Future research should aim to design longitudinal population cohort studies with autopsy and biomarker data collection a priority. I then extended my replication to examine the potential impact of frailty reduction on dementia risk. The population attributable risk (PAR) of frailty for dementia suggests that were severe frailty (FI>0.4) to be prevented, as many as one in eight dementia cases could be avoided. This analysis is somewhat difficult to interpret because it is based on FI at the time of the third survey (when people were 85 years on

average), and incident dementia at death (i.e. average time from survey three to death was 6.2±4.6 years, 0-21 year range). So what it means to 'prevent' dementia at this stage is a bit unclear since I expect people to get frailer as they approach end of life, and can't account for this 'compression of morbidity', control (due to PAR method) or stratify (due to small sample size) for neuropathology. Even after considering these limitations, the results are consistent in suggesting that frailty intervention at any stage may be useful in delaying or preventing cognitive impairment.

One way to examine the potency of risk for dementia conferred by frailty or neuropathology is to examine the 'zero state'; in other words, what is the prevalence of dementia when frailty or neuropathology are close to zero? In the MAP data, I found only 6 participants (<1%) had an FI value below 0.1, two were cognitively normal at time of death, three had MCI, and one had dementia, their neuropathological index scores ranged from 0.10-0.47. Three percent of the sample had a neuropathological index score <0.1 (n=20), of whom 15 were cognitively normal, four had MCI, and one had dementia at time of death, their frailty scores at last assessment before death ranged from 0.08-0.61. Similarly, in the CC75C data we also found that few people have very little pathology (no participants with NPI<0.1), and few are completely robust (i.e. not frail; only 14 participants had an FI<0.1) at time of death. I was also curious to investigate the prevalence of dementia at the *highest* state of frailty or neuropathological burden. When I selected the highest 10% of frailty scores (FI>0.65 in MAP and FI>0.53 in CC75C), cognitive impairment was almost universal: 57/63 (90%) people in MAP and 18/19 (95%) people in CC75C. When the highest 10% of neuropathological (NP) index scores

were selected (NP>0.56 in MAP and NP>0.52 in CC75C), 68/75 (91%) in MAP and 17/22 (77%) in CC75C were cognitively impaired. I did this second comparison based on the distribution of the sample as there is a submaximal limit to both the neuropathological index and frailty index, but no clear clinical cut-points. Taken together, this evidence suggests both frailty and neuropathology can be sufficient risk factors, but in community-dwelling samples many people have frailty and neuropathology by the time they die but do not have clinical dementia.

Based on my findings from Chapter Five that preventing severe frailty impacts dementia risk, I was motivated to test the longitudinal relationship between frailty and dementia status. In the project described in Chapter Six, I found that people with more rapid increases in frailty are more likely to develop dementia; essentially deficit accumulation predicts dementia status. Interestingly, this was the case even after controlling for neuropathological burden, which did not interact or even contribute independently to dementia risk after frailty trajectories were modeled. This is an important piece of evidence suggesting that frailty interventions, particularly preventing severe frailty in mid to late life, may prevent dementia, even in the face of non-modifiable neuropathology. This work highlights an area where future investigation is needed, particularly as neuropathological burden and dementia were only ascertained at time of death.

Given my findings that frailty is a modifiable risk factor for dementia, it follows that frailty should be assessed in people with, or at-risk of, dementia. To this end, I wanted to develop and test a tool for frailty assessment in settings dealing with older adults,

particularly those with memory complaints in order to improve clinical practice. In Chapter Seven, we demonstrated the feasibility of the Pictorial Fit-Frail Scale (PFFS) in a memory clinic setting among geriatricians, nurses, caregivers, and patients (even those experiencing significant cognitive impairment). Further, I found this tool to be valid when compared with a comprehensive and validated frailty tool: Frailty Index based on a Comprehensive Geriatric Assessment. Other studies have since validated the PFFS in other health care settings[6]. While other frailty tools may be prohibitively complex for self-assessment in persons with memory impairment, we were able to create and validate a tool that can be inclusive for patients who may need frailty assessment most: those who are older with complex medical issues, particularly dementia.

The sum of this evidence suggests a strong link between frailty and dementia and provides some novel insight into *how* they may be related. Specifically, that frailty and mixed neuropathology likely impart independent risk, and that deficit accumulation makes up a key risk for dementia creating opportunity for public health interventions on frailty to reduce population dementia risk.

8.2 Limitations

All data collected and analyzed as part of this thesis were observational. This use of observational data comes with limitations. Most notably, I am unable to make firm statements about specific mechanisms, though I can demonstrate relationships and interpret results with associative inferences.

Secondary analysis of data from the Rush MAP cohort study and CC75C study formed the majority of the studies as part of this thesis. As with any analysis of previously collected data, some barriers to analytic design are expected. In this case, I was unable to ascertain some variables which were non-essential but may provide additional information on the nature of the relationship between neuropathology, frailty, and dementia, such as type of dementia and TDP-43 pathology for the CC75C data. Future research should investigate these nuanced features in a population-representative dataset.

While the MAP and CC75C samples were uniquely well-suited to my pursuits given that they had several clinical evaluations, autopsy data, and clinical diagnostic data, my work could always benefit from an increased sample size, something I hope to ascertain by adding cases through the Religious Orders Study from Rush in the future. As many of my variables were generated as a combination of several other items (i.e. the frailty index and neuropathological index), my analytic samples had some missing data. While I had a large enough sample size to detect expected effect sizes, in some instances I was unable to stratify the sample into subgroups of interest as the cell samples became too small, and in cases where I could stratify, increased sample size would likely narrow confidence intervals and the interaction between neuropathology and frailty would likely reach significance.

I was not able to directly test the hypothesized shared mechanisms between frailty and dementia mentioned in the introduction, such as inflammatory markers, immunosenescence, and hormones (though I did complete sex-stratified analyses). It is

likely that these contribute more to frailty than to the accumulation of neuropathology to create an effect on dementia risk. The fundamental shared risk between frailty and dementia is ageing, and frailty is an attempt at quantifying biologic ageing in a clinically meaningful way.

8.3 Implications and future research

The findings detailed in this thesis present opportunities for impact in a wide range of settings, with potential significance to clinical practice, policy, and industry. They also suggest potential avenues of future research to improve our understanding of the complex relationship between ageing and dementia.

Frailty is a multifactorial construct representing physiologic vulnerability. One of the advantages of operationalizing frailty as deficit accumulation is that it is able to capture multiple mechanisms at play in age-related disease, including subclinical deficits, that give rise to clinical impairments and increase the risk of death[7]. This approach embraces the complexity of ageing and the interdependence of risk factors for dementia[8]. Previous work has demonstrated that frailty is a key risk for age-related (i.e. non-communicable) disease of all kinds[8–10], not only dementia[11]. It appears that in the context of age-related disease, ageing represents a collection of mechanisms that are giving rise to impairment, rather than specific pathological mechanisms of disease that we observe in younger fit people. The crucial aspect of this conceptualization of frailty is that it aims to represent overall health, and my findings here suggest that this is a key consideration in the expression of dementia. This has major implications in clinical practice where the focus

is on specific pathological mechanisms, rather than ageing mechanisms. Given this knowledge, multifactorial interventions (e.g. exercise) will likely be most promising in mitigating the effects of frailty on dementia risk.

My findings also have implications for the conceptualizations of "*resistance*", "*resilience*", and "*reserve*", which is an active area of the dementia literature[12–15]. *Resistance* can be understood as the capability to prevent development of (or remove/repair) neuropathology, thus (theoretically) avoiding onset of dementia[16,17]. *Resilience* and *reserve* have frequently been used interchangeably, and represent the ability to tolerate accumulating neuropathology without developing clinical symptoms, whether this be through using alternate brain networks (i.e. cognitive reserve), or increased structural capacity (i.e. brain reserve)[12,17,18]. The discordance between neuropathology and cognition has been referred to as *resilience* by some[19] and reserve by others[13]. In the frailty literature, it has been debated whether resilience/reserve reflects the absence of frailty or is a separate but related construct. A recent review by Whitson and colleagues stated that "if the spectrum of robustness to frailty reflects the amount of physiological potential one has to react to stressors, physical resilience refers to the actualization of this potential"[20]. An example of this would be the risk for surgical complications (reflected by an individual's degree of frailty) vs. the actual recovery time (an individual's resilience); that while frailty and resilience are closely related, and theoretically may overlap to some extent, empirically resilience can explain the heterogeneity in risk of adverse outcomes for people of the same frailty level, the way that frailty explains the heterogeneity of risk in people of the same age.

Another way that risk for age-related adverse health outcomes has been conceptualized is using intrinsic capacity– defined as the composite of all the physical and mental capacities of an individual, and emphasizing the positive attributes and protective resources of an individual[21]. Although frailty and intrinsic capacity overlap, frailty likely represents only a part of intrinsic capacity[22].

In the studies presented in this thesis, people who are less frail have a significantly lower burden of neuropathology, potentially reflecting increased resistance. Importantly, frailty appears to closely reflect resilience/reserve: the ability to tolerate accumulating neuropathology without developing clinical symptoms differs by level of frailty in Alzheimer's disease.

This suggests two potential ways to avoid dementia: 1) to increase resistance, i.e. strengthen mechanisms that prevent development of or remove/repair neuropathology; or 2) to increase reserve/resilience, i.e. improve the ability to tolerate neuropathology and adapt without threatening cognitive function. Based on my findings, I would argue that pharmaceutical therapies may be best at improving resistance (i.e. clearing specific pathologies) while frailty prevention can bolster reserve and potentially improve resistance by creating multifactorial interventions. This conceptualization accounts for the failure of clinical trials to date – since they may only be targeting resistance and thus missing an important piece of the puzzle to improve outcomes (i.e. reserve/resilience) –

and allows for these treatment options to work in complement to reduce overall dementia risk.

Frailty can provide a useful framework for understanding risk and targeting improvement in vulnerability to cognitive decline. Many have suggested that management of frailty should start in primary care[23]. There, frailty measurement allows simple risk stratification for older adults[24,25]. This has been operationalized by using a comprehensive geriatric assessment (CGA; from which an FI can be easily calculated)[26], and the development and validation of the PFFS in a memory clinic setting[27] aims to improve the uptake of this strategy. While there is some evidence that frailty measurement in primary care contributes to proper care management and improves patient outcomes[28,29] including reversing frailty levels[30], more randomized controlled trials are necessary to evaluate this important question[31].

Frailty interventions are still an active area of study, though initial studies have taken a multi-modal approach- targeting improvement in physical activity (via exercise), sleep quality, nutrition, social engagement, and chronic disease management. Others have primarily focused on exercise interventions, which are multifactorial in their effects; importantly, it has been shown that physical activity can modify prognosis at any level of frailty[30]. These interventions have been well-regarded as they are cost-effective, easy, and can target many aspects of frailty with just one mode of intervention. Several studies have demonstrated reductions in frailty with multimodal interventions[32–35], though this remains equivocal[36]. The majority of these studies evaluated frailty using a three to five

item phenotype or performance-based measures, though it has been noted that the frailty index may be better suited to evaluating these intervention approaches as they target the multiple biologic hallmarks of ageing[37].

The only multidomain (i.e. frailty) intervention to my knowledge that evaluated cognitive-related outcomes reported significant improvement on global cognition, as well as specific domains including executive function and processing speed, but not memory[38]. The intervention involved extensive nutritional advice, an individualized physical activity programme, group cognitive training/education sessions, and lifestyle/chronic disease management through physician check-ups. Importantly, this two-year intervention included only young older adults (ages 60-77 at baseline) at risk of dementia with slight cognitive impairment (MMSE <26).

Importantly, a key component to almost all of the frailty interventions is exercise. There is evidence that exercise can improve or maintain cognition in people with[39–41] and without[42,43] dementia as well as mitigate atrophy[44], though evidence for specific types of exercise (e.g. aerobic) is more scarce[45]. In healthy older adults, exercise has been shown to attenuate age-related declines in gray matter volume[46], hippocampal volume, serum levels of Brain Derived Neurotrophic Factor (BDNF) which mediates neurogenesis, and consequently, spatial memory[47]. It is possible that frailty may be a mediator in the relationship between exercise and these brain changes. Interestingly, there is also some suggestion that the effects of exercise on cognition may be more pronounced in women than men[48].

While the majority of my findings in this thesis focused on dementia status as an outcome, the relationship between neuropathology, frailty, and cognition, remains largely unexplored. It is possible that frailty is highly related to the disability aspect of dementia, and the relationship between frailty, neuropathology, and cognition could uncover new insights regarding mechanisms. Further analyses should also explore the effects of sex and gender on this relationship. Gendered activities in older cohorts may make functional decline more detectable in women than men adding another layer to investigate in future studies.

Evidence that frailty influences dementia expression presents a key opportunity for improving discovery techniques and evaluation metrics for dementia drug development. For example, it is possible that drugs effective in reducing the burden of amyloid or tau may be effective for halting the progression of Alzheimer's disease in a subset of people who are not frail, but more frail people (i.e. the majority of people with dementia) will require a different treatment approach. Given the attributable risk of frailty to dementia, public health interventions targeting frailty may prove more fruitful on a population level than costly drug trials that fail to embrace the complexity of ageing.

Dementia research should embrace the complex interaction between ageing and dementia by including more frail older adults in samples of study, rather than focusing on younger and fitter individuals[49–51]. Further, studies examining potential mechanisms of disease

should account for frailty and potentially stratify results this way to better understand differential risk and impact of treatment.

8.4 Conclusions

The evidence produced in this thesis demonstrates that frailty, as conceptualized by the deficit accumulation approach, influences the relationship between neuropathology and dementia. Frailty intervention appears to be a promising avenue to mitigate the cognitive and functional consequences of neuropathology, and to some extent suggests a resilience mechanism. Given the failure to date of clinical trials for dementia, particularly Alzheimer's dementia, exploiting this resilience factor by employing frailty interventions may be very useful from a public health and epidemiological perspective.

8.5 References

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Figure 8-1. Probability of Alzheimer's dementia as a function of Alzheimer's pathology, stratified by frailty level. Coloured bands around lines indicated 95% confidence intervals. Rush Memory and Aging Project Data; n=456.

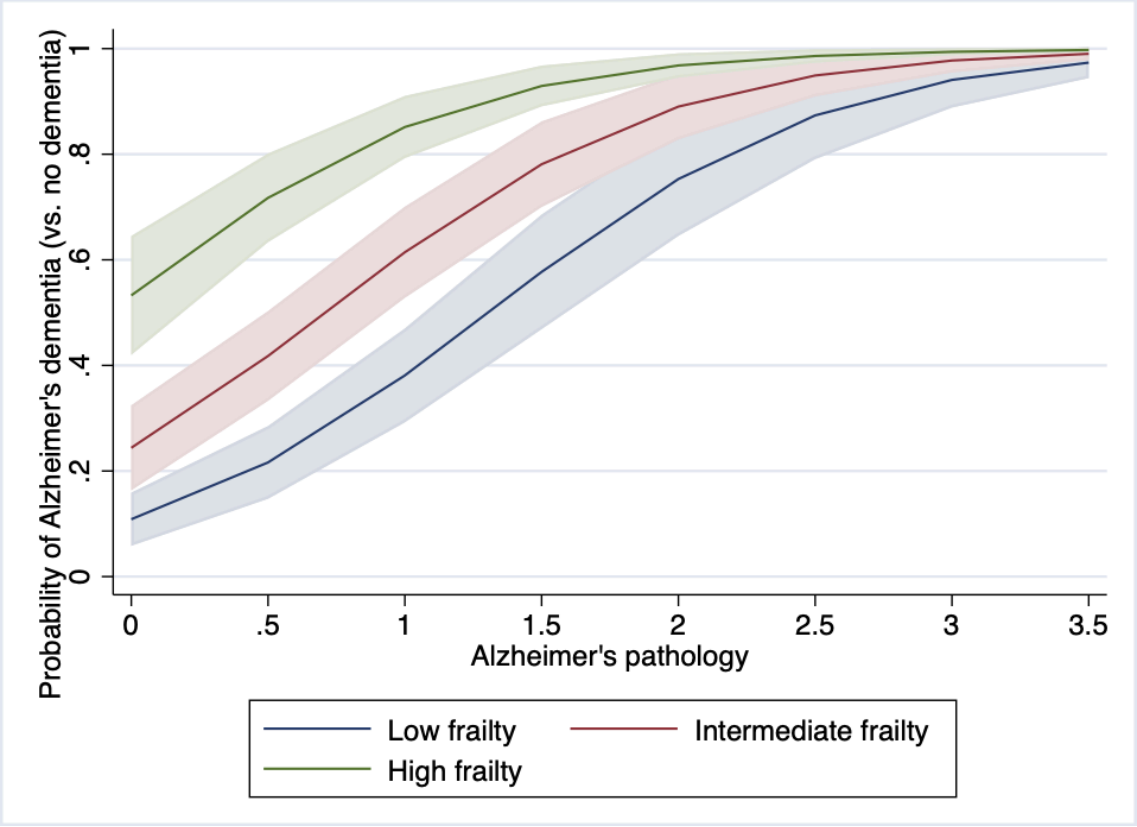


Figure 8-2. Proportion of sample with Alzheimer's dementia by level of Alzheimer's pathology and frailty. Rush Memory and Aging Project Data; n=456.

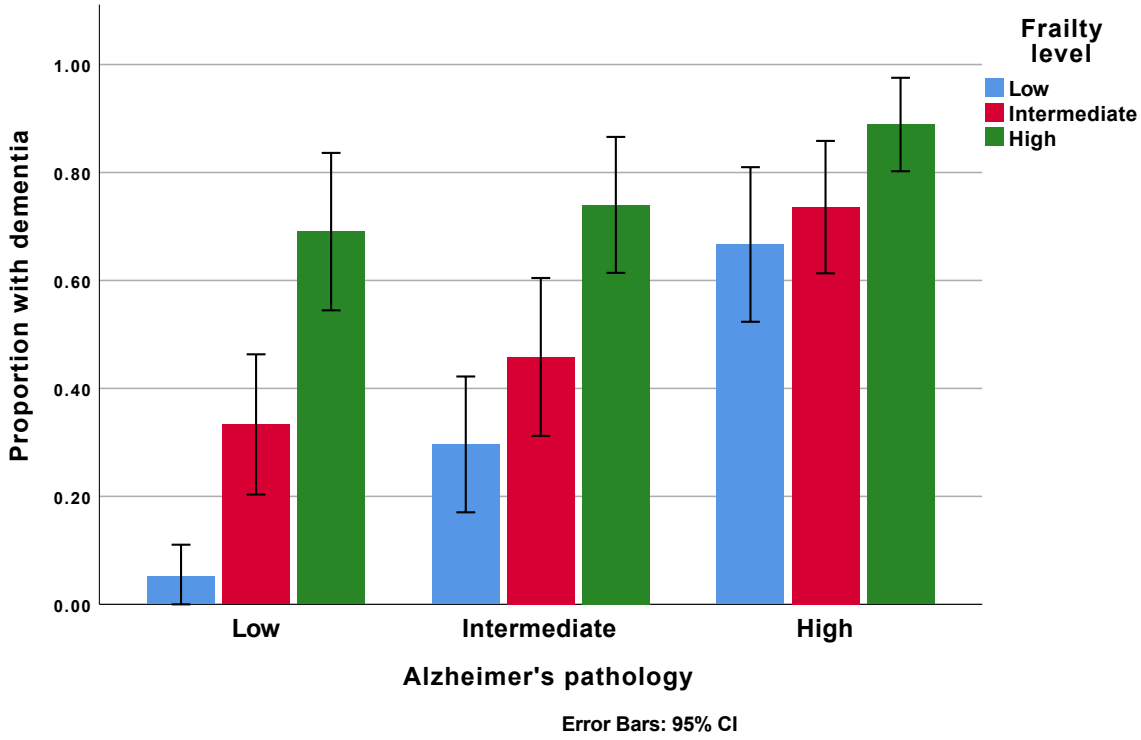


Figure 8-3. Proportion of sample with dementia by level of neuropathological burden and frailty. Cambridge City Over 75s Cohort study; n=183.

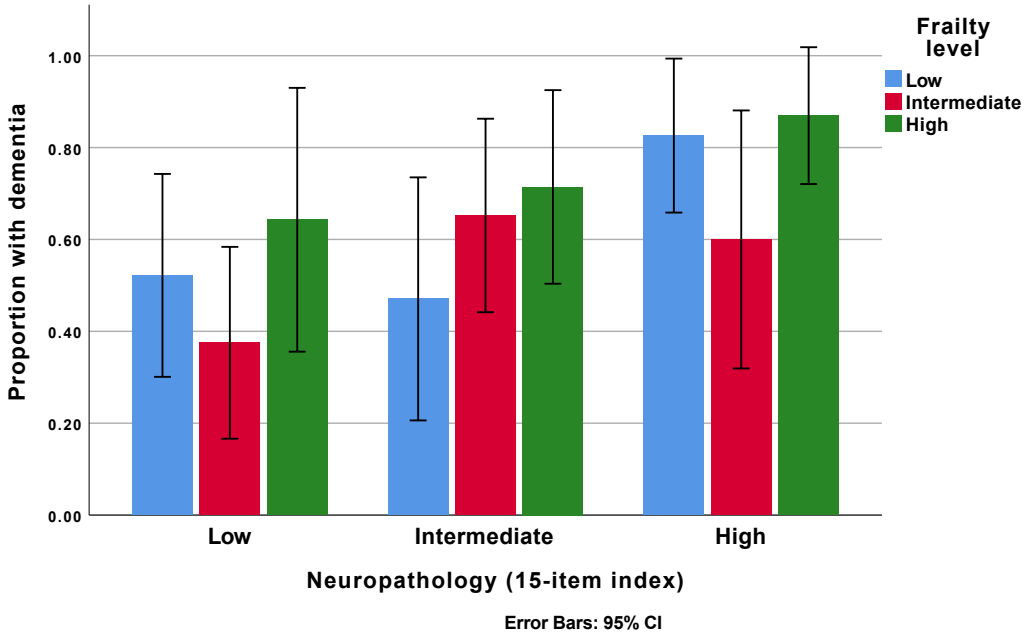
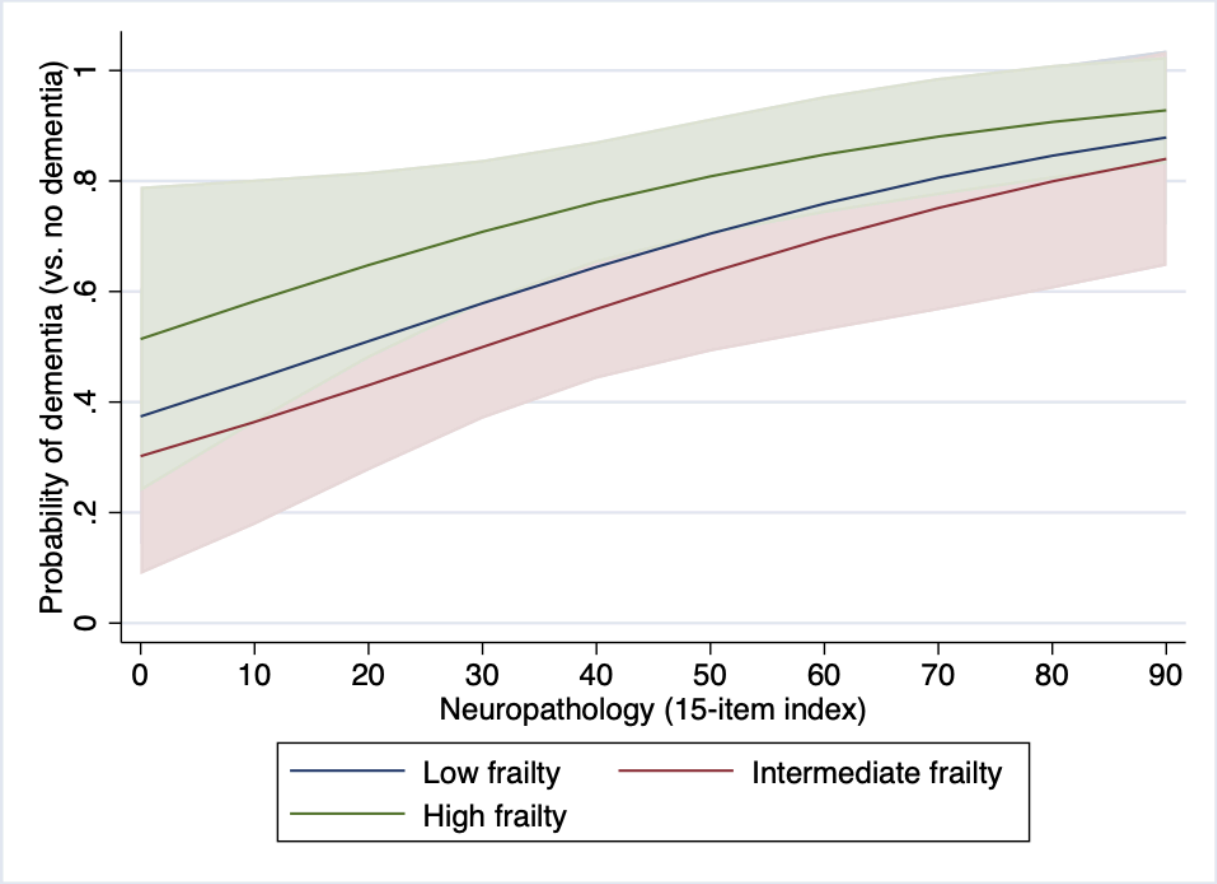


Figure 8-4. Probability of dementia as a function of neuropathologic burden, stratified by frailty level. Coloured bands around lines indicated 95% confidence intervals. Cambridge City Over 75s Cohort study; n=183.



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