2017

Establishing Biological Plausibility for Cognitive Frailty

Lana Jean Sargent
Medical University of South Carolina

Establishing Biological Plausibility for Cognitive Frailty

by

Lana Jean Sargent

A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing.

July/2017

Dissertation Committee

Member (Committee Chair): Elaine J. Amella, PhD, RN

Signature: Elaine Amella Date: 07-13-17

Member (CON Faculty): Martina Mueller, PhD

Signature: Date: 07/17/17

Member (External Scholar): Patricia W. Slattum, PhD, PharmD

Signature: Patricia W. Slattum Date:7-13-17

Member (External Scholar): Andrew Singleton, PhD Signature:

Date:7-14-17 Member

(External Scholar): Mike Nalls, PhD

Signature: Date:7-14-17

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

In the past 5 years, I have had the good fortune to work with mentors who were genuinely concerned about my success and believed in my ideas. Each one of them is highly regarded in their own field and is doing their own work to improve and change the world around them. Pam Parsons, Ph.D. and Patty Slattum, Ph.D. were my first set of mentors. Their bold thinking, determination, and willingness to share their wisdom took me on an adventure that changed the way health care is delivered to low income underserved residents in the Greater Richmond Community.

I met my third mentor the first day of residency at the Medical University of South Carolina (MUSC). Elaine Amella, Ph.D. was the reason I came to MUSC. She understands the full scope of geriatric research and always believed that I could achieve any crazy idea we talked about. The open dialog, ease in which ideas were shared, and the mutual respect have been unparalleled. She provided direction and held high standards while providing space for me to find my own way. She had the vision to encourage me to find a way to connect my biomedical research background with my clinical knowledge by encouraging me to apply for the National Institute of Health (NIH) Graduate Partnership Program.

I was then lucky enough to meet my fourth and fifth mentors at NIH. When I walked into Andy Singleton's, Ph.D. lab, I knew he was the kind of mentor that had bold ideas, was curious and inquisitive beyond his scope of knowledge, and is a strong advocate for those who just wanted to do good science. Mike Nalls, Ph.D. is going to run his own empire someday. I am at a loss of words for how to thank him for his ability to teach me

volumes of knowledge in a five-word sentence. Those five word sentences usually took me two weeks to unpack until in the end I had achieved a completely new and totally awesome skill. I thank you both for believing in my ideas and me.

Martina Meuller, Ph.D. has been a steady support throughout the dissertation process, always available, and able to simplify complex concepts. Her ubiquitous support to doctoral students is unprecedented and appreciated. I am thankful to Deans Langston and Giddens at Virginia Commonwealth University for supporting me in returning to school and through my graduate position at NIH. They both had the vision and grace to know that empowering faculty to grow will only help develop a stronger profession of nurse educators and researchers.

I am eternally grateful to my husband Alex and sons James and Benjamin, who joined me on this journey. Alex, always my partner in this delightfully chaotic, beautiful mess we call life. James and Benjamin, I thank you for helping me keep life in perspective.

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Cognitive frailty is considered a potentially reversible age-related condition characterized by the simultaneous presence of both physical frailty and cognitive decline. The concept of cognitive frailty existing in older adults is indisputable, although the mechanisms and the directional relationship behind the dynamic association remain unexplained. Mechanisms have been suggested, often linking cognitive frailty to cognitive impairment or as a component of frailty but without an understanding of the biological bases for these associations we cannot not move forward with intervention trials.

This dissertation examines the biological mechanisms for cognitive frailty. The study is the first to use a large number of protein and genetic markers identified by a systematic review to define the underlying pathology for cognitive frailty. We use an innovative Boosted trees machine learning technique for developing a population based predictive model. Xgboost is based in boosted trees and provides more efficient and accurate predictive modeling with large datasets and a rapid / robust framework for feature selection. Statistical modeling is used to design, test, and validate an accurate method for and identifying and classifying the features that predict individuals with cognitive frailty. The tree boosting model is used for the evaluation of multiple variables simultaneously and provides a high predictive value with low bias.

The results presented within this dissertation create a foundation of understanding for a new aging condition and encourage translational research focused on the detection and prevention of cognitive frailty.

INTRODUCTION

"I forget what I was trying to say, one word or another gets in the way of the word I meant to use. Nothing stays. So I say something else, I compensate….are these the words I meant to say? But wait, are these the words I meant to say? These words migrate, they refuse to stay in place. This is my new life, my new way, I forget what I was trying to say." Sherman Alexie.

Caregivers of patients with cognitive decline and patients themselves will suggest that their symptoms for memory loss and changes in physical function came long before they received a diagnosis by their provider. A report on the economic implications of cognitive decline estimates in 2015 there are 5.1 million individuals(1,2). With the aging "baby boomer" generation the trajectory that individuals will exhibit cognitive decline will be 13.5 million by the year 2050 in the United States(1,2). Efforts to unravel the mechanisms for cognitive decline have led to the recognition of a unique cluster of individuals who present with the simultaneous presences of both physical frailty and cognitive impairment without dementia(3). Both cognitive decline and physical frailty independently lead to increased disability, falls, mortality, an increase in health service need, and high direct/indirect costs to healthcare, often long-term care and hospitalization(4,5). Individuals with physical frailty and cognitive impairment may have a higher risk for disability than individuals with isolated physical frailty or cognitive impairment. Yet, historically, most research groups have excluded older adults with cognitive impairment from frailty studies(4). The International Consensus Group organized by the International Academy on Nutrition and Aging (I.A.N.A) and the

International Association of Gerontology and Geriatrics (I.A.G.G) convened in 2013 to identify related domains of physical frailty and cognition and termed the phenomenon "cognitive frailty"(3).

Establishing a model to detect cognitive frailty

The Institute of Medicine Report on Cognitive Aging described a need to develop an operational definition of cognitive frailty for use in research, clinical detection, and public health surveillance(6). A model for detecting cognitive frailty could provide practitioners with the tools needed for early detection and secondary prevention. Currently, the instrumental assessments for cognitive frailty are time-consuming, expensive, and require extensive training, and the clinical translation properties are not clear(3). The translation of the cognitive frailty construct into the clinical setting is limited by the lack of consensus on an operational definition and considerable heterogeneity and complexity in the diagnostic criteria. The primary purpose of this research was to create a population predictive model to gain a more in-depth understanding of the underlying biological mechanisms for cognitive frailty as currently defined by the International Consensus Group in 2013. This dissertation focuses on defining the shared mechanisms for physical frailty and cognitive impairment and establishing a model for determining the presence of risk factors that may predict cognitive frailty in the clinical setting. The model will advance the development of an operational definition by determining whether the potential risk factors at present may predict cognitive frailty in the clinical setting.

Mechanisms behind cognitive frailty

The mechanisms and the directional relationship behind the dynamic association of physical frailty and cognitive impairment or cognitive frailty remain unexplained. Pathological events leading to cognitive frailty years before the onset of cognitive decline may be marked by epigenetic modifications that influence memory-associated gene transcription. However, to date, no investigators have simultaneously characterized the trajectory of cognitive decline and physical function, underlying cellular events that include physiological factors, and epigenetic modifications. The results presented here will further explicate the shared mechanisms, including putative biomarkers for physical frailty and cognitive impairment to enhance our understanding of the shared neuropathology in a secondary data analysis. Such an understanding will lead to intervention studies focused on preventing disability and mortality, decreasing health service use, and improving health outcomes for older adults.

OPERATIONAL DEFINTIONS

The extent to which we can predict cognitive frailty using biomarkers depends on the accuracy that our behavioral markers have on early identification. Screening for the detection of cognitive decline (i.e. neuropsychological) and frailty is determined by the identification tools for defining individuals with cognitive frailty. Individuals with cognitive frailty present with a unique neuropsychological profile, scoring worse on executive and attention tests with individuals having 3 or more of the frailty criteria being more impaired than individuals with only 1 of the frailty criteria(7). This dissertation focused on markers for early detection therefore, definitions used to

establish phenotype sub-groups in this study were structured to detect early cognitive decline including pre-frail individuals using neuropsychological testing focused on executive and attention memory domains. The definitions used are as follows:

Cognitive decline – mild neurocognitive disorders

Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) with a modest impairment in cognitive performance by standardized neuropsychological testing or clinical assessment in absence of a diagnosis of dementia(8,9).

Frailty

The operational definition for frailty is defined as a clinical syndrome condition including 3 out of the 5 criteria related a physical phenotype including: 1) weak muscle strength (grip strength), 2) slow gait speed, 3) unintentional weight loss, 4) exhaustion and low physical activity(4). Pre-frailty includes 1 or 2 of the criteria is present, identifying a sub-group of individuals potentially progressing to frailty(4).

Cognitive frailty

The International Consensus Group (I.A.N.A. /I.A.G.G.) report is an acknowledgment of the need to focus research efforts on a clinical condition characterized by the co-occurrence of physical frailty and cognitive impairment, in absence of overt dementia diagnosis or underlying neurological conditions(3). The cognitive frailty construct is considered a heterogeneous clinical syndrome in older adults with evidence of: 1)

physical frailty and cognitive impairment (Clinical Dementia Rating score of 0.5); and 2) exclusion of a clinical diagnosis of Alzheimer's Disease or other dementia(3).

Details on the cut-off scores used to define the phenotypes are explained in further detail in manuscripts 3 and 4.

INNOVATION

An important innovation in this study was the use of machine learning (ML) statistical modeling to build a predictive model for cognitive frailty while further defining the unique features for cognitive decline and frailty. We use Boosted trees, a machine learning technique for supervised learning, these are ensembles of regression trees, similar to decision trees and are used for prediction or classification. Xgboost is based in boosted trees and provides more efficient and accurate predictive modeling with large datasets and a rapid / robust framework for feature selection. Statistical modeling is used to design, test, and validate an accurate method for classifying patients into phenotypic outcomes. The tree boosting model for the evaluation of multiple variables simultaneously provides a high predictive value with low bias. The second innovation in this study is the defining of putative biomarkers related to cognitive frailty leading to a better understanding of the interrelated neuropathology between physical frailty and cognitive impairment. The study is the first to use a large number of protein and genetic markers (n=289) identified by a systematic review to define the underlying pathology for cognitive frailty.

Impact of Proposed Research

Developing and validating a model for the detection and classification of cognitive frailty will improve the ability to detect patients with a potentially reversible cognitive and physical decline. Identification of biomarkers and an understanding of the physiological and genetic factors for cognitive frailty will help distinguish between changes related to normal aging, irreversible pathological process, and specific neurological diseases that may be reversible(6). The findings will encourage new research and may lead to effective interventions for the prevention and treatment of cognitive and physical decline in an aging population.

THEORETICAL FRAMEWORK

This dissertation used Complex Systems Theory as a primary theoretical framework. Complex Systems Theory (CTS) is an approach to science that involves multiple factors that interact nonlinearly to form a dynamic set of relationships leading to physiological change(10). Based in the tradition of ontology, CTS can identify the grouping together of the mechanistic elements of biology and the heuristic elements of philosophy to model the linkages that create a complex concept such as cognitive frailty. Biological mechanisms, proteins or gene expression and their patterns of interaction are inherently complex systems about which numerous empirical data exist (in this case within population databases) that are “dynamic and transformational” vs. inductive assumptions (11,12). Computational methods developed in bioinformatics are uniquely designed to analyze and interpret large amounts of biological data. This dissertation

created a theoretical framework based on the modeling of complex systems using bioinformatics (figure 1).

SPECIFIC AIMS

This dissertation consists of four manuscripts; 1) an integrative review assessing the measurement properties for cognitive frailty, 2) a systematic review exploring the biological factors for cognitive frailty, 3) a population based modeling study establishing biological plausibility for cognitive frailty, and 4) additional analysis of a unique feature from the modeling study and potential epigenetic factor for cognitive frailty; anticholinergic burden's association with cognitive decline, physical frailty, and cognitive frailty.

Aim 1. To determine associations between putative biomarkers and cognitive frailty as currently defined by the International Consensus Group in 2013 using a focused secondary analysis of the InCHIANTI study dataset.

1a. Establish a predictive model using statistical methodologies using an integrative approach to precisely define and predict cognitive frailty based on overlapping risk factors for frailty and cognitive decline.

1b. Establish a relationship among measurable physiological, clinical factors, and the development of cognitive frailty.

1c. Establish associations between physical frailty and cognitive parameters (i.e., losses in specific types of memory and mental acuity).

Manuscript 1 includes a comprehensive review of the measurement tools for defining the phenotype cognitive frailty. Manuscript 2 includes a large systematic review

of the potential putative clinical, protein, and genetic biomarkers for cognitive frailty. The markers identified in this comprehensive review were used as predictors in the population modeling study. Manuscripts 3, is the population based predictive model analysis. Findings from the model study resulted in anticholinergic burden as a unique predictor of cognitive decline, frailty, and cognitive frailty. Considering anticholinergic medication burden could be a potentially reversible cause for cognitive frailty additional analyses was completed which resulted in manuscript 4.

Aim 2. *To determine associations between genetic biomarkers; single-nucleotide polymorphisms (SNPs) to explain the phenotypic variance for cognitive frailty using a focused secondary analysis of the InCHIANTI study dataset.*

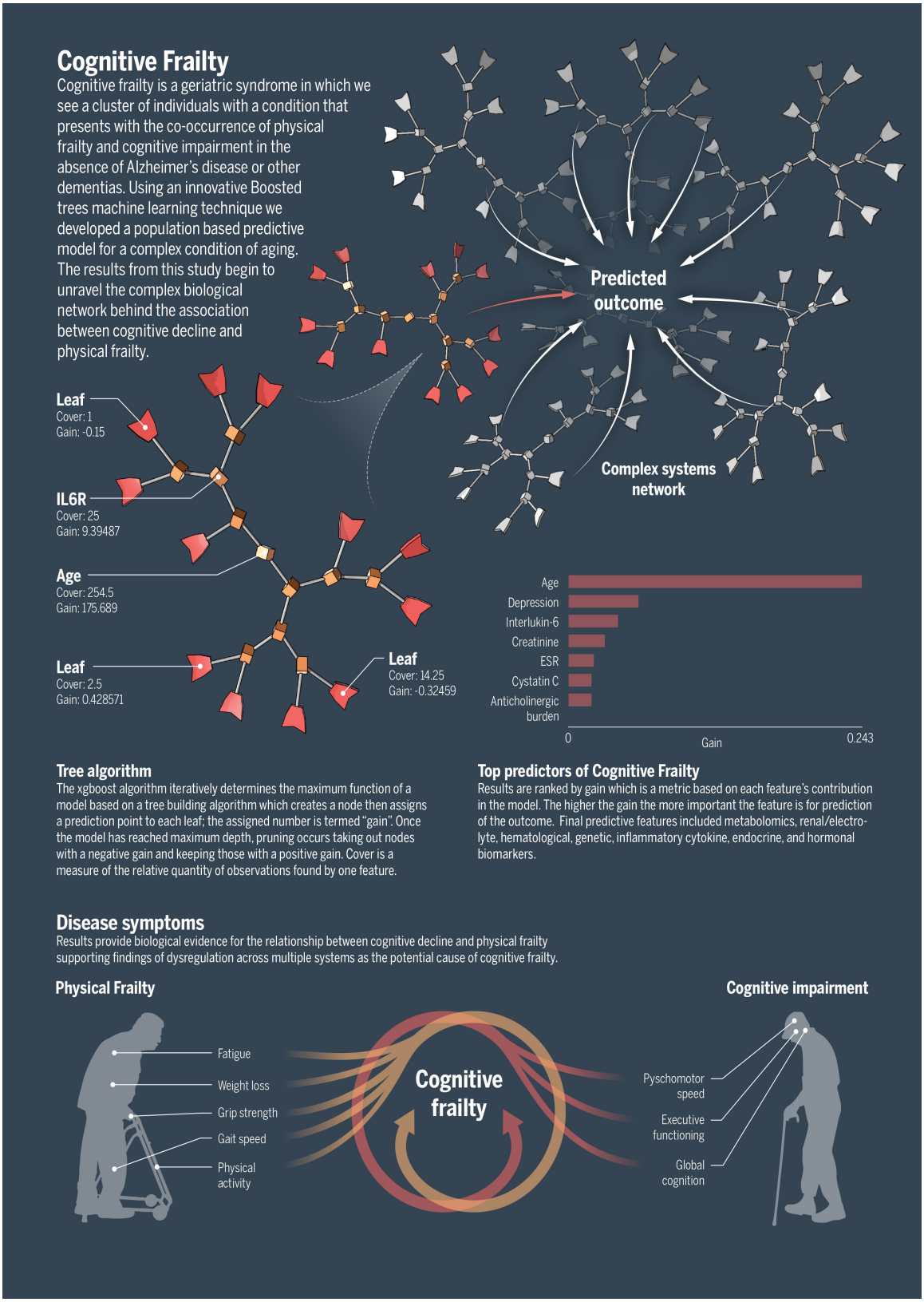
Manuscript 3 includes analyses of genetic biomarkers (SNPs) and highlights the variance seen for individuals with cognitive frailty compared to unique genetic predictors of cognitive decline and frailty alone.

Training Aim3. Acquire the necessary training, expertise, and knowledge to accomplish aims 1 and 2. Goal 1: Apply advanced statistical methods; Goal 2: Develop neuropsychiatric assessment skills.

Due to the innovative statistical modeling and bioinformatics utilized in this dissertation, additional training was needed beyond the standard Doctoral in Philosophy in Nursing Science curriculum to build knowledge and achieve stated aims. I completed the bioinformatics 101 seminar series which included training on: high-throughput technology, high-throughput sequencing data types and public data repositories, DNA and RNA-seq applications and analyses, ChIP-seq applications and analyses, and

pathway and functional enrichment analysis methods. The bioinformatics certificate is included in the supplemental documents. Additionally, I attended conference training on Health Measures, which included training on the NIH neurophysiological, and physical measures toolbox and Patient-Reported Outcomes Measurement Information Systems (PROMIS) measures.

Figure1. Complex systems theory for Cognitive Frailty



References

1. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement [Internet]. 2011 May [cited 2017 Jun 23];7(3):280–92. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1552526011000999
2. Association A. Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars [Internet]. [cited 2017 Jun 24]. Available from: http://www.alz.org/documents_custom/trajectory.pdf
3. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset P-J, Gillette-Guyonnet S, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging [Internet]. 2013 Sep [cited 2015 Jan 19];17(9):726–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24154642
4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci [Internet]. 2001 Mar [cited 2014 Aug 27];56(3):M146-56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11253156
5. NIH, WHO. Global health and aging [Internet]. 2011 [cited 2015 Feb 7]. p. 1–32. Available from: http://www.nia.nih.gov/sites/default/files/global_health_and_aging.pdf
6. Blazer D, Yaffee K, Liverman C. Cognitive Aging: Progress in Understanding and Opportunities for Action - PubMed - NCBI [Internet]. Institute of Medicine Of the National Academies. 2015 [cited 2015 Sep 13]. p. 1–331. Available from: http://www-ncbi-nlm-nih-gov.proxy.library.vcu.edu/pubmed?term=cognitive aging process in understanding opportunities for action&cmd=correctspelling
7. Delrieu J, Andrieu S, Cantet C, Cesari M, Ousset P.J., Voisin T, Fougere B, Gillette S, Carrie I and VB. Neuropsychological Profile of "Cognitive Frailty" Subjects in MAPT Study. 2016;116(8):1477–90.
8. Millward D, Paul S, Brown M, Porter D, Stilson M, Cohen R, et al. The diagnosis of asthma and exercise-induced bronchospasm in division I athletes. Clin J Sport Med [Internet]. 2009/11/10. 2009;19(6):482–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19898076
9. Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. J Neurol Neurosurg Psychiatry [Internet]. 2006 Jun 1 [cited 2015 Jan 27];77(6):714–8. Available from: /pmc/articles/PMC2077456/?report=abstract
10. Rocha L. Agent-based complex systems modeling [Internet]. Los Alamos National Laboratory. 1999 [cited 2017 Jul 22]. Available from: https://www.informatics.indiana.edu/rocha/projects/agent-based-modeling/index.php
11. Bryne, D. (1998). Complexity Theory and the Social Sciences: An Introduction. London; Routledge.
12. Popper, K. (1953). Science: Conjecture and refutations (pp. 38-47). In E. D. Klemke, R. Hollinger, & D. W. Rudge (Eds.) Introductory Readings in the Philosophy of Science. Amherst, NY: Promethethus Books.

MANUSCRIPT 1:

Assessing the Current State of Cognitive Frailty: Measurement Properties

This manuscript was accepted for publication in the international journal Nutritional Health and Aging (reprinted with permission). Sargent, L., & Brown, R. Assessing the Current State of Cognitive Frailty: Measurement Properties. *Journal of Nutrition Health and Aging.* January 2017, Vol 21, Issue 1.

J Nutr Health Aging

ASSESSING THE CURRENT STATE OF COGNITIVE FRAILTY: MEASUREMENT PROPERTIES

L. SARGENT[1], R. BROWN[2]

1. Ph.D. Candidate at Medical University of South Carolina, Faculty of Virginia Commonwealth University, School of Nursing, Richmond, VA, USA; 2. Assistant Professor Research & Education Librarian, Virginia Commonwealth University School of Nursing Affiliate Faculty, Tompkins-McCaw Library for the Health Sciences, Richmond, VA, USA. Corresponding author: L. Sargent, Candidate at Medical University of South Carolina, Faculty of Virginia Commonwealth University, School of Nursing, Richmond, VA, USA, lsargent@vcu.edu.

Abstract: *Background:* Currently, an estimated 25-30% of people ages 85 or older have dementia, with a projected 115 million people worldwide living with dementia by 2050. With this worldwide phenomenon fast approaching, early detection of at-risk older adults and development of interventions focused on preventing loss in quality of life are increasingly important. A new construct defined by the International Consensus Group (I.A.N.A/I.A.G.G) as «cognitive frailty» combines domains of physical frailty with cognitive impairment and provides a framework for research that may provide a means to identify individuals with cognitive impairment caused by nonneurodegenerative conditions. Using the integrative review method of Whittemore and Knafl., 2005 this study examines and appraises the optimal measures for detecting cognitive frailty in clinical populations of older adults. *Methods:* The integrative review was conducted using PubMed, CINAHL, Web of Science, PsycInfo, and ProQuest Dissertations & Theses. From the total 185 articles retrieved, review of titles and key words were conducted. Following the initial review, 168 articles did not meet the inclusion criteria for association of frailty and cognition. Of the 18 fulltext articles reviewed, 11 articles met the inclusion criteria; these articles were reviewed in-depth to determine validity and reliability of the cognitive frailty measures. *Results:* Predictive validity was established by the studies reviewed in four main areas: frailty and type of dementia MCI (OR 7.4, 95% CI 4.2-13.2), vascular dementia (OR 6.7, 95% CI 1.6-27.4) and Alzheimer's dementia (OR 3.2, 95% CI 1.7-6.2), frailty and vascular dementia (VaAD) is further supported by the rate of change in frailty x macroinfarcts ($r = 0.032$, $p < 0.001$); frailty and the individual domains of cognitive function established with the relationship of neurocognitive speed and change in cognition using regression coefficients; individual components of frailty and individual domains of cognitive function associations inculded slow gait and executive function (β -0.20, $p < 0.008$), attention (β -0.25 $p < 0.008$), processing speed (β -0.16, $p < 0.008$), word recall (β - 0.18, $p = 0.02$), and logical memory ($\beta = 0.04$, $p = 0.04$). Weak grip was predictive for changes in executive function (β - 0.16, $p = 0.008$). Physical activity was associated with changes in executive function (β = -0.18, p= 0.02) and word recall ($\beta = 0.17$, p= 0.02), individual components of frailty and global cognitive function were found in several studies which included grip strength ($r = - 0.51$, $p < 0.001$), gait speed ($r = - 0.067$, $p < 0.001$), and exhaustion (β - 0.18, $p < 0.008$). *Conclusions:* This paper presents the first-known review of the measurement properties for the cognitive frailty construct since the published results from the International Consensus Group (I.A.N.A/I.A.G.G). Evidence presented in this review continues to support the link between physical frailty and cognition with developing validity to support distinct relationships between components of physical frailty and cognitive decline. Results call attention to inconsistencies in reporting of reliability, validity, and heterogeneity in the measurements and operational definition for cognitive frailty. Further research is needed to establish an operational definition and develop psychometrically appropriate clinical measures to construct an understanding of the relationship between physical frailty and cognitive decline.

Key words: Cognitive decline, physical frailty, measurements, cognitive frailty

Introduction

With the number of individuals ages 80 and older on the rise, the burden of dementia is expected to be one of the most daunting and costly consequences of longer life expectancies. Early detection of at-risk older adults and the development of interventions focused on preventing loss in quality of life are increasingly more important. Diagnosing dementia, especially in the early stages of the disease is difficult; many cases go undiagnosed even in the intermediate or more advanced stages (1). This is partly because dementia is a complex condition that cannot be attributed to a single functional or cognitive domain and the need to better understand the underlying neuropathology contributing to non-aging related cognitive impairment (2–4).

The relationship between physical frailty and cognitive impairment has become increasingly more apparent with recent studies suggesting that the two are interrelated. Efforts focused on understanding the relationship may provide a means to identify individuals with cognitive impairment caused by non-neurodegenerative conditions which might be reversible (2, 3). Although, frailty and cognitive impairment have been shown to be related, both constructs have long been studied separately (3). To address this gap, the International Consensus Group organized by the International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) convened on April 16th, 2013 in an effort to identify domains of physical frailty and

Received September 28, 2015
Accepted for publication November 30, 2015

cognition. Additionally, the consensus group recommended formal assessments based on studies that supported findings of an association between progressive physical frailty and cognitive impairment in older adults. The new construct called cognitive frailty (3), extends the physical frailty construct with a formal cognitive assessment and a comprehensive assessment of depressive symptoms.

The construct cognitive frailty, will provide new opportunities for research, assist in further defining cognitive impairment related to physical causes, and promote interventions that lead to improved quality of life in older adults. Multiple studies have been conducted to develop clinical screening tools for the detection of cognitive and functional decline independently, with many clinical screening instruments available to clinicians. However, the optimal measures or combination of measures to accurately detect cognitive frailty in the clinical setting is unclear (3). As researchers attempt to deconstruct the relationship between physical frailty and cognitive impairment, the emphasis must be placed on evaluating the strength of the psychometric tests used to evaluate the new construct. The purpose of this integrative review was to examine the literature to determine progress in the establishment of validity and reliability for the measurement of cognitive frailty.

Operational and Theoretical Definitions

Establishing a comprehensive understanding of the new construct cognitive frailty requires a critical review of what is known about the consensus on operational definitions and tools used to study frailty and cognitive impairment individually.

Frailty

The first definition of frailty was proposed in 1988 (6), but since that time the international community has come to no consensus on a definition of the term or an assessment tool to measure the condition (7). The International (I.A.N.A.) Task Force on Frailty identified 17 cohort-based definitions, all using different frailty assessment tools. More recently, Rodríguez-Mañas et al, 2013 attempted to achieve consensus for an operational definition using a Delphi process, which resulted in consensus on the value of screening for physical frailty in the following six domains: physical performance, including gait speed and mobility, nutritional status, mental health, and cognition. Because there is still a need to identify a specific combination of clinical and laboratory biomarkers for a diagnosis, an operational definition was not recommended (8). Even though consensus has not been reached regarding an operational definition of frailty, the theoretical definition, which is generally agreed upon, describes frailty as a multidimensional geriatric syndrome with increased vulnerability to stressors as a result of reduced capacity of different physiological systems with adverse health outcomes that include falls, disability, hospitalizations, and mortality (7, 9, 10).

The criteria used to identify frailty often depend on the operational definition. The commonly-known criterion is the "phenotypic" definition developed by the work completed in the Cardiovascular Health Study (CHS) (5, 11). The CHS phenotype includes decline in lean body mass, strength, endurance, balance, walking performance, and low activity (5). It allows for a continuous scoring system versus a nominal system because it can capture the multidimentional nature of frailty. The components have concurrent and predictive validity with hazard ratios (HR) ranging from 1.82-4.46 ($p < 0.05$) for outcomes that include incident disease, hospitalization, falls, disability and mortality in community-dwelling older adults (5). Additionally, the CHS model has positive predictive validity (PPV) in detection of physical limitations. The Edmonton Frail Scale (EFS) includes evaluation of the social support domain and has been validated with non-specialists with no formal training in geriatric care (12). Construct validity for the EFS for detection of physical performance was statistically significant ($r = -0.58$, $p = 0.006$, $n=21$) along with inter-rater reliability ($k = 0.77$. $p = 0.0001$) and internal consistency (Cronbach $\alpha = 0.62$)12. However, the use of the EFS for the detection of cognitive impairment ($r = -0.005$, $p = 0.801$, $n=30$) was not statistically significant (12).

Other validated frailty instruments with unique operational definitions have been described in the literature: the Frailty Index (FI), Clinical Frailty Scale, Study of Osteoporotic Fractures (SOF), SPPB (gait speed, repeated chair stands, and tandem balance tests) validated in the Established Population for Epidemiologic Studies of the Elderly (EPESSE), and Tilburg Frailty Indicator (TFI) which includes three frailty domains (physical, psychological and social) (13–16). Several frailty assessment tools are time consuming, not practical except for research purposes, and have slightly different measurement properties. The literature reflects the lack of consensus and ongoing debate about how to operationalize a definition for frailty (17).

Cognitive Impairment

The theoretical and operational definition for the progressive loss of memory unrelated to the normal aging process has been controversial. Mild cognitive impairment (MCI) was first proposed by Petersen et al, 1999 then revised with the International Working Group on Mild Cognitive Impairment (19). MCI is the most commonly used term to describe a progressive measurable change in memory that differs from healthy aging adults. The recommended criteria for MCI is self and/or informant report of memory impairment and/or evidence of decline over time on objective tasks with preserved activities of daily living, and minimal impairment in complex instrumental functions with no diagnosis of dementia (19). Resulting from the research on MCI the Diagnostic Statistical Manual-5 (DSM-5) included a category of neurocognitive disorder and distinguishes between mild (mNCD) and major (mNCD) neurocognitive disorders to describe the heterogeneity

these articles were reviewed in-depth to determine validity and reliability of the cognitive frailty measures.

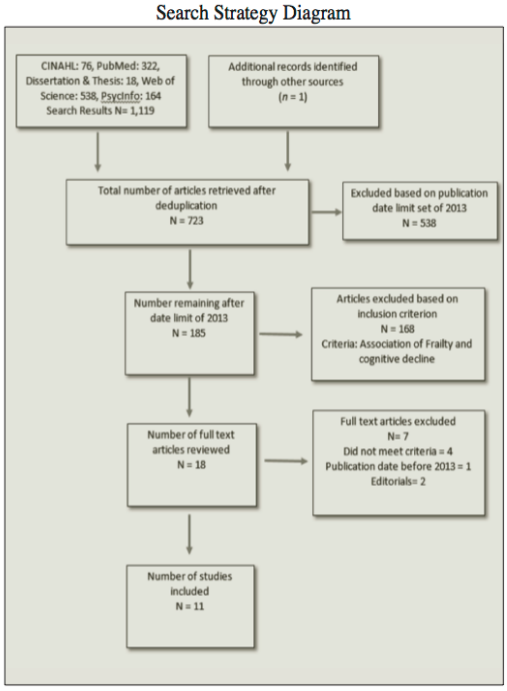
Data extraction, was used to identify the psychometric properties based on the measurements provided in the article or if the criteria could be found in the original longitudinal study as referenced by the author. The level of evidence was appraised for each study using the Center for Evidence Based Medicine Levels of Evidence (23). Studies were evaluated with a systematic approach and rated based on their strength of evidence. The operational definitions for both frailty and cognition were reported separately to highlight the combination of tools being used to study the relationship between physical frailty and cognition and report on measurement properties and significant findings. A framework, presented in Table 1, was developed to report the operational definition criteria being used for cognitive frailty based on impairment in the physiological domains defined by The Interventions on Frailty Working Group: mobility, balance, muscle strength, motor processing, nutrition (often operationalized as nutritional status or weight change/sarcopenia), cognition, endurance (including feelings of fatigue and exhaustion), and physical activity (24). Cognition was further defined in the framework based on the use of neuropsychiatric testing and/or a clinical cognitive assessment tool (i.e. MMSE or CDR) in the operational definition. To accompany these results, and to help with replication of the work, the search strategy and data extraction results have been made available online.

Results

The association between phsycial frailty and cognitive decline was established in cross-sectional and longitudinal studies before the International Consensus Group (I.A.N.A/I.A.G.G) proposed the definition of cognitive frailty in 2013 (25). Additionally, evidence presented in this review supports the link between physical frailty and cognitive decline with developing validity to support distinct relationships between components of physical frailty and cognition in community-dwelling older adults. Table 2 presents a comparison of the screening tools used by the ten studies included in this review and those proposed by the International Consensus Group (I.A.N.A/I.A.G.G) as a framework for evaluating the development and validation of an operational definition for cognitive frailty.

None of the researchers explicity described using a theoretical framework; however, all the studies discussed components of cognitive frailty in relation to the International Consensus Group's (I.A.N.A/I.A.G.G) proposed definition. All 11 studies examined the correlation of physical frailty and cognitive impairment. Additionally, six studies examined rate of change in frailty scores in associaton to rate of deterioration of cognitive scores. Participants were non-demented at baseline in all but two studies, including baseline amnestic Mild Cognitive Impairment (aMCI) and a probable/possible diagnosis of dementia (26, 27). Although several studies reported baseline cognitive status, scores were not always considered in the statistical model. This finding may be important because baseline cognition can decrease the association between frailty and all dementia outcomes; association between frailty and dementia was stronger with higher baseline scores (HR 1.78, 95% CI 1.14-2.78) than those with lower baseline cognitive scores (HR 0.79, 95% CI 0.50-1.26 p value for interaction = 0.02) (28).

Figure 1
Search Strategy Diagram



Cross-sectional studies

Six cross-sectional studies examined the association of frailty and cognitive decline using a modified CHS criterion (5). Functional status evaluations were added in several studies (26, 29, 30) and co-morbidies, age, gender, BMI, and depression were often considered in the covariate analysis (26, 27, 31). The cross-sectional studies relied on clinincal evaluations including MMSE, executive tests, gait speed, grip strength, weight loss, and psychological markers (Table 2). Few of the studies used biomarkers, and only one used imaging in the operational definition (30).

Cohort study

One cohort study examined the associations between frailty and cognitive decline over 12 months (32). The study used

Table 1
Operational Definitions of Cognitive Frailty

Reference	Mobility/ Gait Speed	Strength	Balance	Motor Processing	Nutrition/ Weight loss	Endurance/ Fatigue	Physical Activity	Neuropsychiatric Testing	Clinical Cognitive Assessment Tool¥
Shimada et al. 2013	X	X			X	X	X	X	X
Kulmala et al. 2014	X	X			X	X	X		X
Buchman et al. 2014	X	X			X	X		X	X
Rolfson et al. 2013*	X	X	X	X	X	X		X	X
Oosterveld et al. 2014	X	X			X	X	X	X	X
McGough et al. 2013	X	X			X		X	X	X
Alencar et al. 2013	X	X			X	X	X	X	X
Gray et al. 2013	X	X			X	X	X	X	X
Solfrizzi et al. 2013	X	X	X	X	X	X	X		X
Robertson et al. 2014	X	X			X	X	X	X	X
Han et al. 2014	X	X			X	X	X		X

*Rolfson et al. (2013) used 3 operational definitions: CHS, Edmonton Frail Scale, and Frailty Index; ¥ Clinical Cognitive Assessment Tool was defined as use of any of the following: MMSE, MoCA, CDR, ADAS-Cog or CASI

the CHS criterion (5) with the addition of a functional status evaluation and tested the MMSE and Clinical Dementia Rating Scale (CDR). The study did not control for chronic diseases or depression. Additionally total sample size (n=182) was small, affecting power for individual classifications of frailty (non-frail n=43, pre-frail n=104, frail n=35) (30).

Longitudinal studies

Results from four longitudinal studies were published after 2013. A modified CHS criterion (5) was used in three of the studies. One study used more than one frailty instrument to determine if the relationship between neurocogntive speed (NCS) and frailty was affected by how frailty was operationalized (33). The use of biomarkers, clinical markers, and imaging varied among studies. The use of biomarkers and imaging was more commonly used in the longitudinal studies than cohort and cross-sectional studies (Table 2). Functional status evaluation was added in one study (34) and co-morbidities were considered in the analysis for all of the studies.

Validity

For all the studies in this review, criterion validity was examined for performance of the operationalization of various cogntive frailty measurements. Predictive and discriminant validity was commonly reported as odds ratio (OR) or hazard ratio (HR); two studies used Pearson correlations and multiple linear regression models to establish associations between components of physical frailty and cognitive function. Predictive validity was established by investigating frailty and rate of change in cognition or correlation of frailty and cognitive decline. Discriminant validity was established by analyzing the relationship between measures of frailty (frail, pre-frail, and robust) and type of demenia (MCI, clinically diagnosed dementia, vascular dementia, and Alzheimer's) (26, 28, 30, 32). All of the studies evaluated community-dwelling older adults for which the CHS frailty measures are validated (5). Only one study compared more than one operational defintion of frailty: CHS, FI, and EFS (33). Heterogeneity was present in the objective measures, and the terminology-specific language for the components of the CHS frailty construct often varied from the validated CHS criteria (5).

Heterogeneity was present in the objective measures for cognitive assessment and neuropsychiatric testing. Two studies assessed global cognition with the MMSE (30, 34), four used the MMSE and domain specific neuropsychiatric testing (26, 29, 32, 33), three used only domain neuropsychiatric testing (27, 28, 35), and one assessed global cognition with both the MMSE and MoCA with domain specific neuropsychiatric testing (36). The Cognitive Dementia Rating scale (CDR) had no predictive validity with evidence of no difference between frailty and cognition (relative risk = 2.1; p = 0.393) (32). The National Center for Geriatrics and Gerontology-Functional Assessment tool (NCGG-FAT) had good test-retest reliability with moderate to high external validity (Person r= 0.496 to 0.842). The MMSE continues to be the most commonly used clinical cognitive assessment tool for operationalizing cognitive frailty (25); concurrent validity (Pearson r = 0.776; p < 0.001) and reliability test-retest (Person r = 0.827; p = 0.001) (37) with neuropsychiatric testing predictive and discriminate validity is established by the rate of change in MMSE and CHS frailty criterion (32).

Predictive validity was established in four main areas: 1) frailty and type of dementia: MCI (OR 2.0; p= <0.001) and (OR 7.4, 95% CI 4.2-13.2) (29, 30); vascular dementia (OR 6.7, 95% CI 1.6-27.4) and (HR 2.68, 95% CI 1.16-7.17) (30, 34); and Alzheimer's dementia (OR 3.2, 95% CI 1.7-6.2), (HR 1.08, 95% CI 0.74-1.57), and (HR 0.62, 95% CI 0.20-1.89) (28, 30, 34). The relationship between frailty and vascular dementia (VaAD) is further supported by the rate of change in frailty x macroinfarcts (r= 0.032, p < 0.001) (35). Evidence of convergent validity exists between dementia and non-dementia types with findings to support the associations between frailty and non-Alzheimer's dementia (OR 2.57, 95% CI 1.08-6.11).

2) Frailty and the individual domains of cognitive function was identified by evaluating the relationship of neurocognitive speed and change in cognition using regression coefficients (33) and evaluation of the MMSE subdomains. Individual domains of cognitive function were found to be gender specific (31). Predictive validity was dependent on the frailty operational definition; Frailty Index (FI) and NCS (OR 0.87, 95% CI 0.81-0.95) compaired to the modified CHS and EFS which found no correlation with neurocognitive speed (33).

3) Individual components of frailty and individual domains of cognitive function associations inculded slow gait and executive function (β -0.20), attention (β -0.25), processing speed (β -0.16) (36), word recall (β -.0.18, p = 0.02), and logical memory (β = 0.04, p =0.04) (27). Weak grip was predictive for changes in executive function (β – 0.16, p =0.008) (27). Physical activity was associated with changes in executive function (β = -0.18, p= 0.02) and word recall (β = 0.17, p= 0.02) (27).

4) Individual components of frailty and global cognitive function were found in several studies (27, 28, 34–36). Individual components included grip strength (r = - 0.51, p < 0.001), gait speed (r = -0,067, p < 0.001) (35), and exhaustion (β – 0.18) (36) were predictive for changes in global cognition.

Psychological markers were frequently used for the assessment of endurance, fatigue, or depression. However, variability existed in the type of assessment scale used and how the psychological marker was operationalized. Psychological markers were typically used to either assess endurance for fatigue in the CHS criteria (29, 35) or considered as a covariate in the statistical analysis (27, 28, 32, 34). Variability in the psychological markers can be seen in Table 2 and online material.

Reliability

Due to the heterogeneity in the objective measures for frailty, reliability was not consistently examined for cognitive frailty. The limited reliability and variability in the operational measurements used for the CHS frailty criteria add challenges to establishing an operational definition for cognitive frailty. Motor performance was the only measurement for which validity and reliability was established (34).

Feasability

Instrumental assessments for cognitive frailty are currently time-consuming, expensive, require extensive training, and the clinical translation properties are not clear. The addition of biomarkers and imaging potentiates the complexity of the feasability for measures and complicates the process for detection of cognitive frailty in the clinical setting.

Discussion

The findings from this review continue to support evidence for the association between physical frailty and cognitive decline. However, while cross-sectional studies have detected a relationship, further studies are needed to determine causal pathways (38). Studies continue to use different combinations of measurement instruments for cognitive frailty, but are measuring similar domains of physical frailty and cognition. Based on the findings in this review the CHF criteria with measures of mobility/gait speed, strength, nutrition/weight loss, endurance/fatigue, and physical activity, neuropsychiatric testing and a cognitive assessment tool was the most common operational definition (Table 1). Further testing of the cognitive frailty construct should attempt to provide validity and reliability for objective measures and scales which are based on self-report. Self-report scales must prove to be stable over time (test-retest reliability), and those administered by several individuals need to exhibit good inter-rater reliability. Additionally, inclusion of a theoretical framework will provide a structure for generating cumulative knowledge on which interventions can be based.

Studies are starting to deconstruct the relationship between the components of physical frailty and cognitive decline. Unravelling of the complex cognitive frailty construct will refine the operational definition and improve an

Table 2

Use of biological, clinical, and imaging markers for cognitive frailty: International Consensus Group (I.A.N.A/I.A.G.G)

	Shimada et al. 2013	Kulmala et al. 2014¥	Buchman et al. 2014	Rolfson et al. 2013	Oosterveld et al. 2014	McGough et al. 2013	Alencar et al. 2013	Gray et al. 2013	Solfrizzi et al. 2013	Robertson et al. 2014	Han et al. 2014
Biomarkers											
Inflammatory markers (e.g. CRP, IL-6)			X								
Beta-amyloid protein (aβ)			X					X			
aPOEε4 genotype									X		
Anemia											
Serum albumin									X		
Cholesterol									Xβ		
Vitamin D status											
Clinical markers											
MMSE	X	X		X	X	X	X		X	X	X
Executive tests	X		X		X	X		X		X	
ADAS-Cog						X					
CDR					X	X	X				
MoCA										X	
Gait speed	X	X	X	X	X	X	X	X	X	X	X
Hand grip strength	X	X	X	X	X	X	X	X	X	X	X
Weight loss	X	X	X	X	X	X	X	X	X	X	X
Psychological marker: GDS	X®		X£	X€		X§	Xф	XΩ	X ᵏ		X§
Actigraphy											
Imaging											
Dual energy											
X-ray absorptiometry scans (DEXA)											
Cerebral Computed tomography		X						X	X		
Cerebral Magnetic resonance imaging		X						X	X		
Functional MRI											
Diffusion tensor imaging (DTI)											
Tractography											
Electrophysiological methods											
Cognitive evoked potentials											

¥ CT scan, MRI, and laboratory tests (not specified) were used to make a diagnosis of vascular dementia, Alzheimer's disease, Lewy bodies, and dementia related to other medical causes;® Partial GDS scale; £ Psychological maker evaluated with two questions from the Center for Epidemiologic Studies; € Psychological maker evaluated with the Edmonton Frail Scale; § GDS-15 scale; Φ GDS-15 scale and Cornell Depression Scale; Ω Psychological maker evaluated with Center for Epidemiological Studies Depression; ᵏ GDS 30 scale; β Reported in original study.

understanding of the clinical distinction between cognitive impairment due to physical frailty and an isolated neurological condition. Disentangling the association between frailty and cognitive decline requires the use of convergent validity to determine if the cognitive frailty construct is able to distinguish among between different types of dementia (e.g., Vascular, Alzheimer's, Lewy Body, and Parkinson's dementia) (27). The association of cognitive decline and frailty may be responsible for part of the heterogeneity in the presentation of dementia. Movement toward evaluating specfic domains of cognitive impairment such as executive functioning and psychomotor speed versus a global assessment of dementia will facilitate an understanding of the implications for cogintive frailty. However, the current lack of validity and reliability of a cognitive frailty operational definition means that it is not possible to recommend translation of measures to detect the presence of risk factors that may predict cognitive frailty in the clinical settings.

A limitation of this review was the exclusion of studies that did not address the cognitive frailty construct. In the future, a review of the literature focused on individual physical function measures may identify other markers associated with cognitive impairment. Further research with epidemiological and population based studies that includes diverse ethnic and social economic groups will help establish a better understanding of the prevalence of cognitive frailty. The majority of studies in this review either did not report ethnicity or the sample included a high proportion of white (88%-99%) females (58%-80%). Only two studies provided a population-based estimate of cognitive frailty with samples of 5,104 Japanese (29) and 4,649 Irish community-dwelling older adults (36). Understanding how demographics effect the measurement of cognitive frailty are important since psychometric tools may be effected by populations which have higher rates frailty, comorbidity, cardiovascular disease, poorer health, decreased access to care, and low education and income (5). Inclusion of chronic diseases, such as depression and cardiovascular disease, as a part of the study design is an important part of describing other factors that may contribute to cognitive frailty over time. Additionally, adjustment for the presence of apolipoprotein (APOE) ε4 alleles and other biomarkers (e.g. inflammatory makers, beta-amyloid protein) could help describe the pathophysiological mechanisms.

The early detection of cognitive decline emphasizes a promising focus for the development of preventive and therapeutic interventions. Current studies suggest the importance in understanding both constructs separately as a way to deconstruct dissociable components, describe common pathologies, and develop a single operational definition which would allow for targeted interventions. Ensuring validity and reliability in the measures used is paramount if providers are to identify individuals at risk for pathological non-normal aging changes and develop interventions to improve the quality of life of older adults. Further research is needed to establish an operational definition for cognitive frailty, develop a better understanding of the directional relationship between physical frailty and cognitive impairment, gender differences, and identify biomarkers to assist with detection of diagnosis and disease progression.

Acknowledgments: We would like to thank Elaine Amella, Ph.D., RN, FAAN, Martina Mueller, Ph.D., and Mathew Gregoski, Ph.D., MS for their support.

Conflict of interest: The authors have no conflict of interests to report

Ethical Standards: To reduce bias in this rigorous review the authors adhered to the Whittemkore & Knafl., 2005 and PRISMA guidelines. This study did not use human subjects.

References

1. NIH, WHO. Global health and aging. 2011:1-32. http://www.nia.nih.gov/sites/default/files/global_health_and_aging.pdf. Accessed February 7, 2015.
2. Buchman AS, Bennett DA. Cognitive frailty. J Nutr Health Aging. 2013;17(9):738-739. doi:10.1007/s12603-013-0397-9.
3. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2.
4. Canevelli M, Kelaiditi E. The complex construct of mild cognitive impairment: Be aware of cognitive frailty. J Frailty Aging. 2014;3(2):87-88.
5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-M156. http://www.ncbi.nlm.nih.gov/pubmed/11253156. Accessed August 27, 2014.
6. Woodhouse, K. W., Wynne, H., Baillie, S., James, O. F. W., & Rawlins MD. Who are the frail elderly? Q J Med. 1988;68(1):505-506.
7. Van Kan GA, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A. task force on frailty assessment of older people in clinical practice. J Nutr Heal Aging. 2008;12(1):29-37. doi:10.1007/BF02982161.
8. Rodríguez-Mañas L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62-67. doi:10.1093/gerona/gls119.
9. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. Journals Gerontol Ser A Biol Sci Med Sci. 2004;59(3):M255-M263. doi:10.1093/gerona/59.3.M255.
10. Panza F, Solfrizzi V, Frisardi V, et al. Different models of frailty in predementia and dementia syndromes. J Nutr Health Aging. 2011;15(8):711-719. http://www.ncbi.nlm.nih.gov/pubmed/21968870. Accessed February 5, 2015.
11. Nguyen T, Cumming R, Hilmer S. A Review Of Frailty In Developing Countries. Ageing Res Rev. 2013;20C(9):741-743. doi:10.1007/s12603-013-0398-8.
12. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing. 2006;35(5):526-529. doi:10.1093/ageing/afl041.
13. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet. 1999;353(9148):205-206. doi:10.1016/S0140-6736(98)04402-X.
14. Gobbens RJJ, van Assen MALM, Schalk MJD. The prediction of disability by self-reported physical frailty components of the Tilburg Frailty Indicator (TFI). Arch Gerontol Geriatr. 2014;59(2):280-287. doi:10.1016/j.archger.2014.06.008.
15. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med. 2008;168(4):382-389. doi:10.1001/archinternmed.2007.113.
16. Studenski S, Perera S, Wallace D, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc. 2003;51(3):314-322. http://www.ncbi.nlm.nih.gov/pubmed/12588574. Accessed August 13, 2015.
17. Pel-Littel RE, Schuurmans MJ, Emmelot-Vonk MH, Verhaar HJJ. Frailty: defining and measuring of a concept. J Nutr Health Aging. 2009;13(4):390-394. http://www.ncbi.nlm.nih.gov/pubmed/19300888. Accessed March 1, 2015.
18. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303-308. http://www.ncbi.nlm.nih.gov/pubmed/10190820. Accessed January 14, 2015.
19. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256(3):240-246. doi:10.1111/j.1365-2796.2004.01380.x.
20. Sachs-Ericsson N, Blazer DG. The new DSM-5 diagnosis of mild neurocognitive disorder and its relation to research in mild cognitive impairment. Aging Ment Health. 2015;19(1):2-12. doi:10.1080/13607863.2014.920303.

21. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res. 2009;43(4):411-431. doi:10.1016/j.jpsychires.2008.04.014.
22. Larner AJ. Effect Size (Cohen's d) of Cognitive Screening Instruments Examined in Pragmatic Diagnostic Accuracy Studies. Dement Geriatr Cogn Dis Extra. 2014;4(2):236-241. doi:10.1159/000363735.
23. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Cent Evidence-Based Med. 2011. http://www.cebm.net/index.aspx?o=5653. Accessed February 7, 2015.
24. Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB, Walston JD. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. J Am Geriatr Soc. 2004;52(4):625-634. doi:10.1111/j.1532-5415.2004.52174.x.
25. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment--a review of the evidence and causal mechanisms. Ageing Res Rev. 2013;12(4):840-851. doi:10.1016/j.arr.2013.06.004.
26. Oosterveld SM, Kessels RPC, Hamel R, et al. The influence of co-morbidity and frailty on the clinical manifestation of patients with Alzheimer's disease. J Alzheimers Dis. 2014;42(2):501-509. doi:10.3233/JAD-140138.
27. McGough EL, Cochrane BB, Pike KC, Logsdon RG, McCurry SM, Teri L. Dimensions of physical frailty and cognitive function in older adults with amnestic mild cognitive impairment. Ann Phys Rehabil Med. 2013;56(5):329-341. doi:10.1016/j.rehab.2013.02.005.
28. Gray SL, Anderson ML, Hubbard RA, et al. Frailty and incident dementia. J Gerontol A Biol Sci Med Sci. 2013;68(9):1083-1090. doi:10.1093/gerona/glt013.
29. Shimada H, Makizako H, Doi T, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J Am Med Dir Assoc. 2013;14(7):518-524. doi:10.1016/j.jamda.2013.03.010.
30. Kulmala J, Nykänen I, Mänty M, Hartikainen S. Association between frailty and dementia: a population-based study. Gerontology. 2014;60(1):16-21. doi:10.1159/000353859.
31. Han ES, Lee Y, Kim J. Association of cognitive impairment with frailty in community-dwelling older adults. Int Psychogeriatr. 2014;26(1):155-163. doi:10.1017/S1041610213001841.
32. Alencar MA, Dias JMD, Figueiredo LC, Dias RC. Frailty and cognitive impairment among community-dwelling elderly. Arq Neuropsiquiatr. 2013;71(6):362-367. doi:10.1590/0004-282X20130039.
33. Rolfson DB, Wilcock G, Mitnitski A, et al. An assessment of neurocognitive speed in relation to frailty. Age Ageing. 2013;42(2):191-196. doi:10.1093/ageing/afs185.
34. Solfrizzi V, Scafato E, Frisardi V, et al. Frailty syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Aging. Alzheimers Dement. 2013;9(2):113-122. doi:10.1016/j.jalz.2011.09.223.
35. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. J Gerontol A Biol Sci Med Sci. 2014;69(12):1536-1544. doi:10.1093/gerona/glu117.
36. Robertson DA, Savva GM, Coen RF, Kenny R-A. Cognitive function in the prefrailty and frailty syndrome. J Am Geriatr Soc. 2014;62(11):2118-2124. doi:10.1111/jgs.13111.
37. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-198. http://www.ncbi.nlm.nih.gov/pubmed/1202204. Accessed July 9, 2014.

MANUSCRIPT 2:

Determining Biological Factors for Cognitive Frailty: A Systematic Review

Abstract: On April 16th, 2013 the International Consensus Group (I.A.N.A/I.A.G.G) formally defined the novel phenotype cognitive frailty; a condition characterized by the co-occurrence of physical frailty and cognitive impairment. We hypothesize that there are biological factors to describe the interconnection between physical frailty and cognitive impairment. This systematic review focuses on identifying the shared measurable biological and genomic mechanisms for physical frailty and cognitive decline. Two independent reviewers assessed the eligibility of each report based on predefined inclusion criteria to ensure interrater reliability; a third reviewer resolved conflicting assessments. The review was conducted using PubMed, Embase, Scopus, Web of Science, LILACS, Gene Indexer, and GWAS Central. Findings resulted in 1232 abstracts for full review, 327 articles were included in the final review. Data extraction identified a correlation between 16 distinct inflammatory and protein markers with biomarker-related gene expression for cognitive frailty. Meaningful findings were identified in the relationship between protein and genetic markers found for both cognitive decline and physical frailty. This systematic review presence the first known findings of the underlying biological characteristics for cognitive frailty providing evidence for converging pathophysiological pathways.

Introduction

In the past century, scientific research has been driven by molecular science with the common goal of identifying a single group of biological or genetic mechanisms as the

cause of disease. We now understand that the mechanisms underlying disease processes are multi-factorial and system based. A multi-system physiological disease requires a systems approach to precision research especially with older adults who have variable trajectories to the aging process with multiple co-morbidities. Efforts to unravel this complexity start with understanding the unique biological factors for a cluster of individuals presenting with similar symptoms and trajectories. Cognitive frailty can be considered a unique geriatric phenomenon in which we see a cluster of individuals with a condition which simultaneously presents with both physical frailty and cognitive impairment[1]. The International Consensus Group organized by the International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) convened in 2013 to identify related domains of physical frailty and cognition. The new construct called "cognitive frailty" is defined by the presence of physical frailty and cognitive impairment in the absence of Alzheimer's disease or other dementias[1]. The mechanisms and the directional relationship behind the dynamic association of these two constructs remains unexplained. There exists strong evidence for the association of frailty and cognitive decline with suggestion for pathophysiological mechanisms which are shared by both clinical manifestations[2]. Although, some research has been conducted on the association between physical function and cognitive decline there is still no comprehensive list or understanding of the underlying mechanisms for cognitive frailty. Therefore, to further develop an understanding of cognitive frailty, it is critical that the operational definition explore both clinical and biological markers for cognitive decline and physical frailty.

Identification of a measurable cellular, biochemical, or molecular markers for cognitive frailty has not been identified. Because both cognitive decline and physical frailty are large heterogeneous conditions it may not be possible to identify one biomarker to measure both cognitive decline and frailty. The use of one or more biomarkers specific to both constructs will improve our understanding of the association[3,4]. It is possible that the underlying biological mechanisms for cognitive frailty are at the intersect between cognitive decline and physical frailty or cognitive frailty may contain some of its own unique markers of disease.

Some evidence exists to support inflammatory biomarkers (neuroinflammatory cytokines) such as C-reactive protein (CRP) and Interleukin-6 (IL-6) as antecedent biomarkers since they are associated with frailty and cognitive decline[1,3]. The complicated use of inflammatory biomarkers, such as CRP, for detection of disease is that they can be detected in other co-morbid diseases found in older adults (i.e. cardiovascular disease, rheumatologic disease). Wilson, Finch, and Cohen (2002) completed a review exploring over 30 neuroinflammatory cytokines and their findings indicate the potential for detection of cognitive decline and evidence for associated improvement of cognition with targeted interventions to reduce the production of specific neuroinflammatory cytokine markers[5]. Finally, genetic factors associated with cognitive frailty have not been fully explored. There have been several genome-wide association studies (GWAS) and candidate gene studies for cognitive decline with only more recent studies exploring the genetic mechanisms for frailty.

Methods

Search strategy

In this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[6]. A systematic review of the literature was performed using the following online databases: PubMed, Embase, Scopus, Web of Science, LILACS, Gene Indexer, and GWAS Central. For reproducibility, we have provided the PubMed search strategy in the supplementary appendix (Figure I). Databases were searched from the start date of the database to 22 December, 2015. An update of the searches was performed prior to the data extraction phase on 26 May, 2016 to identify any new publications. In addition to database searching, articles were hand-pulled from references and identified through other sources.

Inclusion and exclusion criteria

Studies that included information on biomarkers or genetic markers for dementia, physical frailty, or cognitive frailty were included. Reviews, animal studies, imaging biomarkers, and case studies were excluded. Studies on a geriatric population, aged 65 and older, were included. Articles about other disease states such as cancer, Multiple Sclerosis, Down syndrome, Parkinson's disease, human immunodeficiency virus (HIV), and Huntingdon's disease were excluded. Articles published in English were included.

Study appraisals

A multi-step approach was used to evaluate relevant articles using Covidence, a web-based software platform selected by Cochrane Reviews that organizes and streamlines the systematic review process[7]. Figure I shows the stages (PRISMA) for retrieving the

studies for inclusion and extraction. We conducted a review of the titles and abstracts of all the papers identified through database searching and hand pulling from references lists. Three reviewers participated in this step and each article was reviewed by two reviewers (LS and AS) to ensure interrater reliability. A third reviewer (SH) resolved conflicting assessments. A fourth reviewer (EA) was available for additional arbitration however their services were not required. From 5942 articles identified, titles and/or abstracts reporting on information pertaining to biomarkers or genetic markers for cognitive decline, physical frailty, or cognitive frailty was included. 1232 potential relevant articles were chosen for closer review, two reviewers with appropriate subject expertise (LS and AS) assessed the full-text of the articles for relevancy. 327 full-text articles reporting on the relevant topic met inclusion/exclusion criteria and 899 articles were excluded. Reviewer disagreements were addressed in regular meetings and resolved. A final 327 articles were included in this systematic review.

Extraction

The analysis for this paper was generated using Qualtrics software, Version 9.2017 of Qualtric (Copyright © [2017] Qualtrics. Qualtrics and all other Qualtrics product or service names are registered trademarks or trademarks of Qualtrics, Provo, UT, USA. http://www.qualtrics.com.) The survey created in Qualtrix (Qualtrics, Provo, UT) ensured consistency in reporting of biological markers limiting open text boxes, consistent categorizing of biomarkers by clinical, genetic, and fluid markers in the following categories: inflammatory/immunity, protein, metabolomics, oxidative stress. The database assigned each biomarker unique numeric code (i.e. IL6-3, CRP-27). When

data entry was complete, the final data frame was exported from Qualtrix and an analysis was carried out using R V. 3.2.1. R is free, open-source software that provides many statistical and graphic techniques. R packages used included 'MASS' and 'ggplot2'[8,9].

We did not complete a formal method of assessment for the quality of the studies with a meta-analysis given that the goal of this review is to identify potential putative markers for a new phenotype "cognitive frailty". Level of evidence was appraised for longitudinal, observational (cohort, cross Sectional, case-control studies), and randomized clinical trials (RCTs) using the Center for Evidence Based Medicine Levels of Evidence[10]. Additionally, there are limited (RCTs) for frailty and none for cognitive frailty. We do provide a compressive list of the principle results, study design, and detail list of genetic findings correlated to one of the following phenotypes: cognitive decline, frailty, and cognitive frailty. The markers extracted for correlation to cognitive frailty were identified by the reviews to be studies that explored both frailty and cognitive decline in the same study.

Findings and discussion

A total of 327 articles were used to extract the clinical, genetic, and protein markers for three phenotypes: cognitive decline, physical frailty, and cognitive frailty. Date ranges for the studies are shown in Figure II. Studies were reviewed in the following categories 39 genetic studies: 9 GWAS and 30 candidate gene studies, 279 biological protein studies, 9 medication risk studies. Additional study designs included observational (Cohort, cross sectional, and case-control studies), longitudinal, RCT and In Vitro studies.

For the 13 studies that included both a longitudinal and observational (Cohort, cross sectional, and case-control studies) study design we extracted markers from both study designs. The studies were categorized by phenotype: cognitive decline (n= 243), frailty (n= 72), and cognitive frailty (n= 11). Phenotypes were further defined by the type of cognitive decline (i.e. Alzheimer's disease, mild cognitive impairment) and component of frailty (i.e. gait, sarcopenia, grip strength, physical activity) as stated in the study or a combination both was considered cognitive frailty. The supplementary appendix (table I) shows the clinical and biomarkers extracted from 288 articles. Tables I-III show the biomarkers extracted by phenotype in the following categories: clinical, inflammatory/immunity, laboratory, protein, metabolomics, and oxidative stress. Additionally, a summation or frequency in which the biomarker occurred out of the 288 articles is shown by phenotype.

Clinical markers

Although, clinical markers were not a part of the search strategy several of the studies reported clinical findings associated with cognitive decline, physical frailty, and cognitive frailty. Demographics such as increasing age were a factor for all phenotypes, lower education and income were factors for individuals with cognitive decline and frailty. Other clinical markers included: measures of cardiovascular disease, elevated blood pressure, multiple co-morbidities, changes in body mass index (BMI), and alcohol intake. One of the most interesting clinical findings was an association between medications and all phenotypes. These included hypertension, benzodiazepine, anticholinergic, and psychoactive medications. Two categories of hypertensive medications beta-blockers

(i.e. metoprolol and atenolol) and angiotensin-converting enzyme (ACE) inhibitors were found to have the most significant effect on cognitive decline[11,12]. Additionally, there was a significant interaction between ACE inhibitor use and carriers of *ApoE4 (odds ratio: 20.9, 95% CI 3.08-140.95, p= .002)*[12]. Anticholinergic burden was found to be associated with cognitive decline and physical frailty. An interaction was found between *ApoE4* carriers and anticholinergic medications with users having the lowest cognitive scores. Irrespective of *ApoE4* status, drugs with high anticholinergic properties were associated with cognitive and physical decline[11,13–16]. Methods for measuring medication burden varied significantly between studies making it difficult compare study results.

Inflammatory/Immunity markers

There were 16 neuroinflammatory cytokine markers associated with cognitive decline and frailty. These included: elevated levels of IL6, CRP, tumor necrosis factor (TNF-alpha), uric acid, IL1-beta, erythrocyte sedimentation rate (ESR), cortisol/dehydroepiandrosterone ratio, IL1RA, CD8, IL6R, TNF-a receptor I (TNFR1), cortisol, homocysteine, fibrinogen, and beta 2-microglobulin (B2M). Additionally, all the neuroinflammatory markers associated with cognitive frailty were associated with either cognitive decline or frailty. These neuroinflammatory cytokines were found to be associated with cognitive decline and frailty in cross-sectional and longitudinal studies suggesting that these markers could be both early and persistent markers. The presence of the hypothalamic-pituitary-adrenal (HPA) axis hormones such as dehydroepiandrosterone can interact with inflammatory markers to influence disease.

This relationship should be explored further with clinical markers such as gender and body mass index.

Laboratory markers

Twenty laboratory markers are associated with both phenotypes and include: Nutritional markers: low levels of vitamin D, total albumin, and selenium; Cardiovascular/endocrine markers: elevated total cholesterol, triglycerides, LDL, insulin like growth factor protein (IGF-1), glucose, insulin resistance, HbA1c; Hematology/renal markers: elevated creatinine, creatinine clearance, blood urea nitrogen (BUN), white blood cells (WBC); and decreased hemoglobin, hematocrit, cobalamin deficiency (B12), and increased methylmalonic acid (MMA), and hormonal marker: low levels of total testosterone associated with decreased lean muscle mass and cognitive decline. These markers combined with endocrine and immune markers suggest changes to the cellular immune system and HPA axis that are related to cognitive and physical decline. Additionally, several studies included these markers and the inflammatory/immune markers as a composite score and found an increased risk for developing cognitive decline, frailty, and mortality[17–22].

Protein markers

Several of the protein markers were measured by cerebrospinal fluid (CSF) and included known biomarkers associated with the neurofibrillary tangles involved in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease and frontotemporal dementia[23]. None of these markers (i.e. p-tau, Aβeta-42) have been studied in frailty. Three markers measured by serum/plasma were associated with both

cognitive decline and frailty, these included: sirtuin 1 and cystatin C. The down regulation of Sirtuin 1 has been reported to be involved in the pathway that controls the expression of Aβeta peptide through *ADAM10*[24]. Concentrations of sirtuin 1 decline with age but the decline was found to be more significant in individuals with cognitive decline and frailty compared to age matched healthy individuals[24,25]. Additionally, cystatin C has been thought to bind to soluble Aβeta preventing accumulation in the brain[26]. Decreased serum cystatin C has been associated with higher risk for cognitive decline and gait speed decline[27,28].

Metabolomics and oxidative stress markers

No metabolomics markers were found to be related to cognitive frailty. Two oxidative stress markers were associated, these included: malondialdehyde (MDA) and protein carbonyls. MDA and protein carbonyls are well established oxidative biomarkers and are considered to be a good measure of systemic oxidative stress[29]. Both are associated with frailty and cognitive decline but not predictive of the development or progression of disease[29,30].

Genetic

The supplementary appendix table II shows a complete list of genetic markers identified by phenotype. Three genes were found to be associated with cognitive decline and frailty in candidate gene studies: *IL6* rs1800796, *TNF* rs1800629, and *COMT* with different SNPs, rs4680 for cognitive decline and rs4646316 for frailty. *IL6* and *TNF* have corresponding serum markers that are associated with both phenotypes (see inflammatory/immunity markers) [31–34].

There are 12 serum biomarker and gene correlations, these are shown in table IV. Further evaluation is need to determine if there is a direct correlation between gene expression and serum marker function.

Conclusions

It has previously been postulated that a dysregulation across multiple systems may be the potential cause for both cognitive and physical decline[18,19,21]. The results from this systematic review provide evidence for a biological association between cognitive decline and physical frailty. The potential in identifying a unique biomarker that is the key to a specific molecular or cellular event is enticing but considering the complexity and individual variability to aging we need to consider the possibility that these interactions are non-linear. Several studies presented here have taken various approaches to combining biomarkers using method such as allostatic load index, physiologic dysfunction scores, principle components analysis (PCA), and serum protein based algorithms (random forest methods) to yield a more accurate understanding in the relationship between biomarkers and detection of disease[18,19,21,22]. Future research should focus approaches that could include multiple markers of disease to build an accurate model for the detection of cognitive frailty. Finding should be reproducible and validated before translating into clinical practice. Integrating multiple biomarkers has potential to help us better understand the complex physiological interactions. Such validated models for disease detection will be invaluable in the prevention and early detection of diseases unique to aging.

Figure I. PRISMA flow diagram of study selection and citation analysis[6]

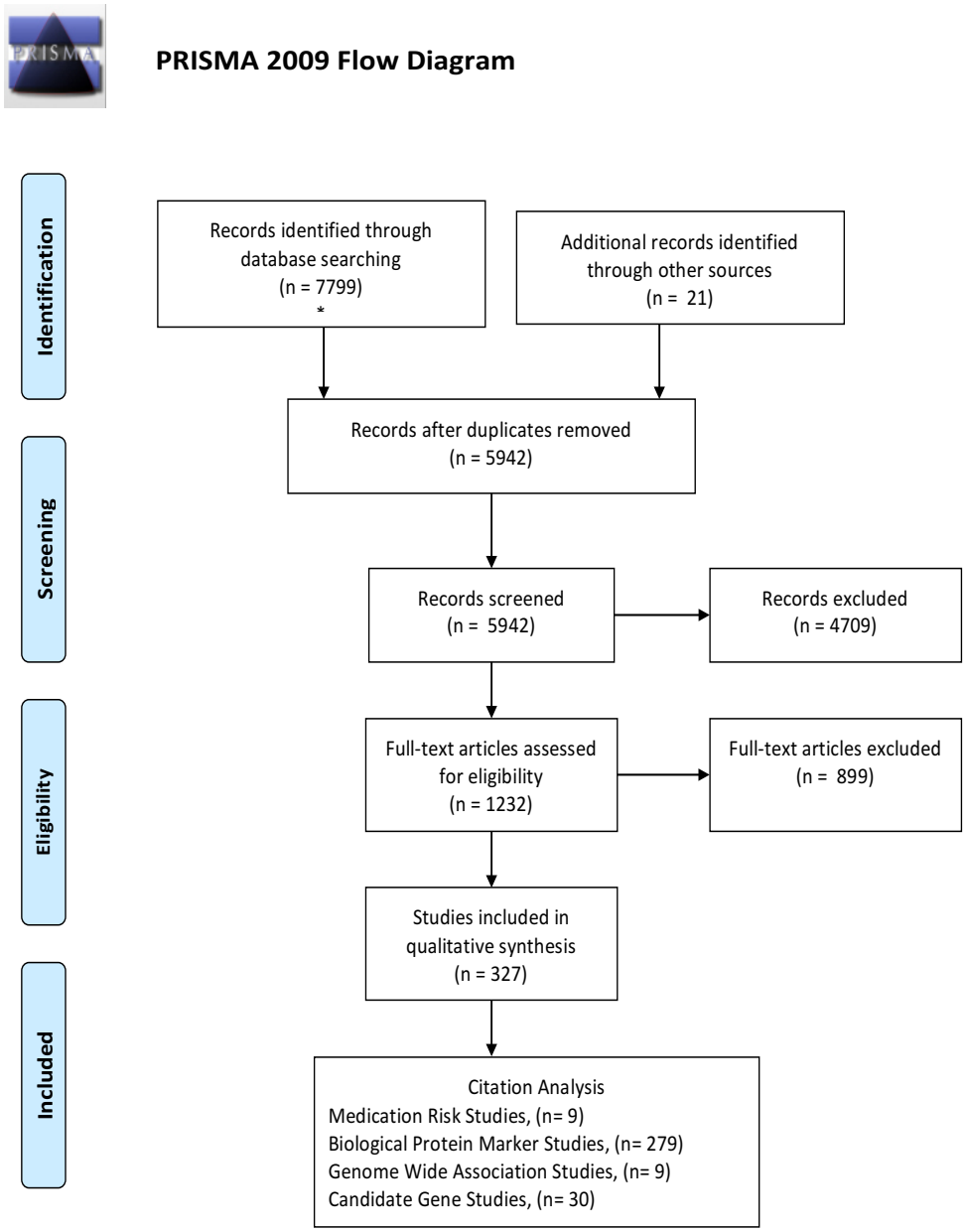


Figure II. Systematic review publication date range

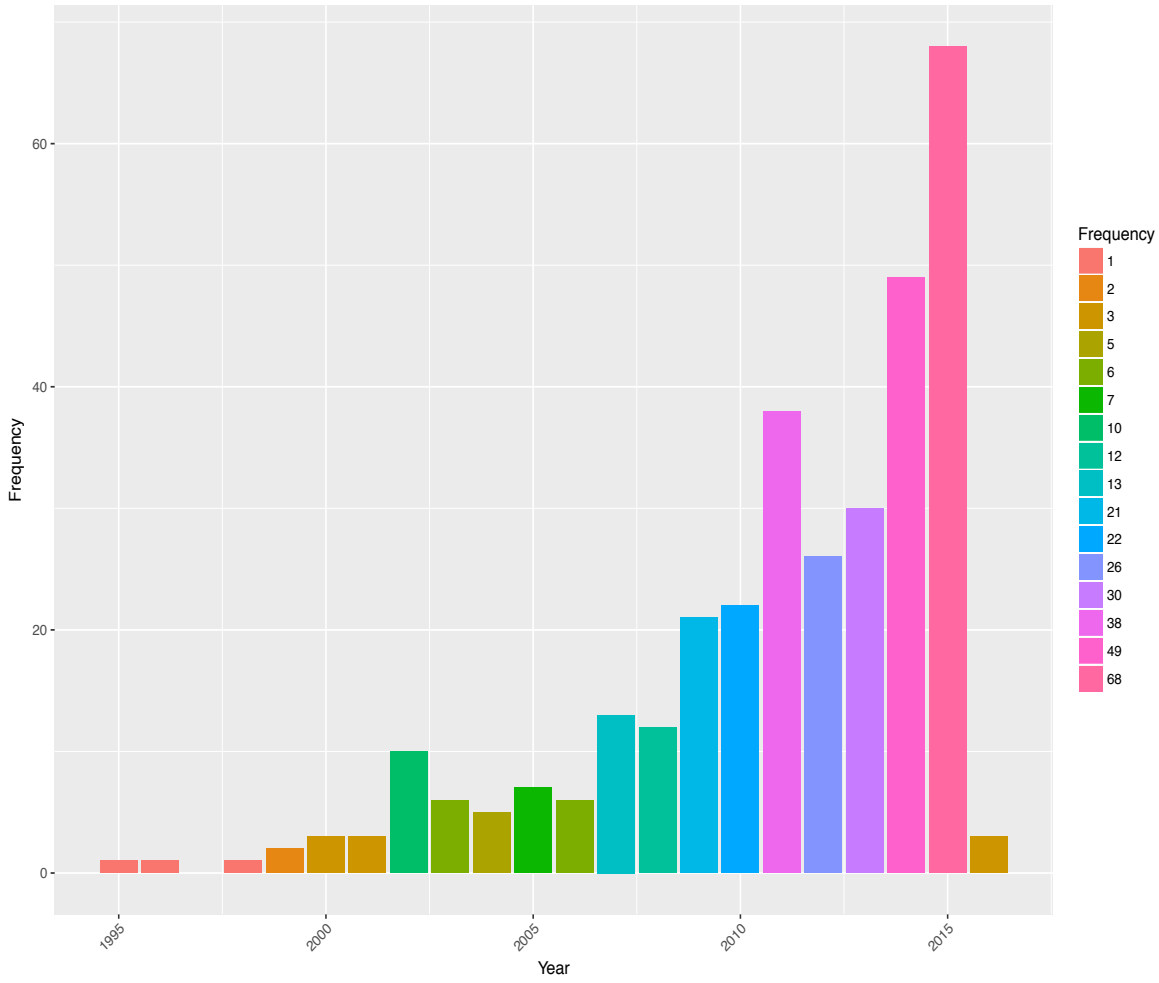


Table I. Cognitive decline biomarkers by category and frequency

1.Frequency	1.Inflammatory/Immunity Markers	2.Frequency	2.Laboratory Markers	3.Frequency	3.Protein Markers	4.Frequency	4.Metabolomic Markers	5.Frequency	5.Oxidative Stress Markers	6.Frequency	6.Clincal Markers
19	C-reactive protein	9	Composite Score (multiple markers)	37	Aβ 1-40/t-tau ratio	2	Docosahexaenoic acid (DHA)	6	F2-isoprostanes/isoprostanes	6	Elevated blood pressure
17	IL6	8	Albumin	32	Aβ42	1	Sphingolipid- SM(d18:1/18:0)	2	Choline plasmalogen(PlsCho)	5	Anticholinergic medications
9	Homocysteine	7	Olfactory marker	26	Aβ 1-42	1	sphingomyelin [SM(39:1)]	2	Glutathione peroxidase (GSH-Px)	5	Change in Body Mass Index
8	Tumor necrosis factor (TNF-alpha)	5	Ocular marker	19	PhosphoTau181 (P-tau181)	1	SM/ceramide ratio	2	Oxidative stress markers /Total antioxidant stat	2	Alcohol intake
5	YKL-40 (neuroinflammation or Chitinase-3 ChI3L3)	4	Folate	13	P-tau	1	SM/ceramide ratio	1	Peroxisomal b-oxidation levels	2	Elevated systolic pressure
5	Cortisol	3	Creatinine	8	Aβ1-42/ Aβ1-40 ratio	1	PC aa 36:1 Glycerophospholipids	1	Ethonalamin plasmalogen (PlsEtn)	2	Elevated diastolic pressure
4	IL8	3	Cobalamin deficiency (B12)	7	Aβ 1-40	1	PC aa 32:0 Glycerophospholipids	1	PLsCho + PlsEtn	2	Increase Waist Circ/Waist-to-hip
3	TNF-a receptor I (TNFR1)	3	Platelet distribution width (PDW)	7	P-tau231	1	PC 16:0/20:5 phosphatidylcholine	1	PLsCho/PlsEtn Ratio	1	Change in resting heart rate
3	Fibrinogen	2	Nutrient biomarker patterns (NBP)	5	Aβ40	1	PC 16:0/22:6 phosphatidylcholine	1	Plasmalogen	1	Cardiovascular disease
3	Uric Acid	2	Blood urea nitrogen (BUN)	5	P-tau181/Aβ42	1	PC 18:0/22:6 phosphatidylcholine	1	Protein carbonyls	1	Benzodiazepine medications
3	Monocyte chemotactic Protein-2 (MCP-2)	2	Methylmalonic acid (MMA)	5	Cystatin C	1	Ceramides C16:0	1	Malondialdehyde (MDA)	1	Hypertensive medications
3	Resistin	2	Glucose	4	t-tau/ Aβ42	1	Ceramides C20:0			1	Angiotension converting enzyme medications
2	IL10	2	Insulin resistance (IR-HOMA)	3	Aβ 1-42/t-tau ratio	1	Ceramides C22:0			2	Psychoactive medications
2	IL1beta	2	Lipids: Triglycerides	3	Apolipoprotein A-I (ApoA1)	1	Ceramides C24:0			1	Low level of education
2	IL17E	2	Lipids: LDL cholesterol	3	Brain derived neurotrophic factor (BDNF)	1	Ceramides C26:0			1	Instrumental activities of daily living (IADL)
2	Clusterin	2	Lipids: HDL cholesterol	3	Lysosomal-associated membrane protein 1 (LAM	1	Stearoyl			1	Activities of daily living (ADLs)
2	TNF-a receptor II (TNFR2)	2	Free Testosterone	2	sAβ/APP ratio	1	Eicosapentaenoic acid (EPA)				
2	Macrophage Migration Inhibitory Factor (MIF)	2	Insulin like growth factor protein (IGF-1)	2	Aβ42/ Aβ40						
2	Cortisol/Dehydroepiandrosterone ratio	2	Insulin like growth factor protein (IGF-2)	2	Neurofilament light chain (NFL)						
2	Vascular cell adhesion molecule 1 (VCAM1)	2	Insulin like growth factor protein Binding Protein (	2	Apolipoprotein A-I I (ApoA2)						
2	Soluble receptor for advanced glycation end products	2	Insulin like growth factor protein Binding Protein (	2	Complement factor H (CFH) protein 1						
2	Plasma Pentraxin 3 (PTX3)	2	Anemia	2	Chromogranin A (CgA)						
2	alpha 2-macroglobulin (A2M)	2	Hemoglobin	2	Visinin-like protein-1 (VILIP-1)						
2	Adiponectin	2	Polyunsaturated fatty acids (O3PUFAs)/ n-6/n-3 ra	2	β-secretase (BACE-1)						
1	IL1	2	alpha-1-antichymotrypsin (ACT)	2	Ubiquitin						
1	IL6R	2	Vascular endothelial growth factor (VEGF)	2	Heat shock protein 70						
1	IL13	1	Peroxidase	2	Epidermal growth factor (EGF)						
1	IL1RA	1	Creatinine Clearance	2	Pancreatic peptide (PP)						
1	IL7	1	*N*-acetylaspartate (NAA)/creatine (Cr)	1	Soluble amyloid β protein (sAβ)						
1	IL12p70	1	Methylcitric acid (MCA)	1	Amyloid β precursor protein (APP)						
1	D-dimer	1	Holotranscobalamin (holoTC)	1	Aβ 1-42/p-tau ratio						
1	Procalcitonin	1	Glycohemoglobin (HbA1c)	1	P-tau231/Aβ42/40 ratio						
1	Erythrocyte sedimentation rate (ESR)	1	Lipids: Total Cholesterol	1	T-tau/Aβ42/40 ratio						
1	GlycA	1	24S-hydroxycholesterol	1	Apolipoprotein C2						
1	Macrophage inflammatory protein 1-alpha (MIP 1α)	1	Aspartate transaminase (AST)	1	Apolipoprotein H						
1	Plasminogen activator inhibitor (PAI-1)	1	Gamma glutamyl transferase (GGT)	1	ApoB/ApoA1 ratio						
1	Serum Amyloid A	1	Total Testosterone	1	A1AcidG						
1	Fibrinogen gamma-chain	1	Total Bilirubin	1	Transthyretin (TTR)						
1	Neural cell adhesion molecule (NCAM)	1	Vitamin E	1	Ceruloplasmin						
1	Adhesion molecule soluble intercellular adhesion mole	1	Vitamin D	1	Cathepsin D						
1	Soluble receptor for advanced glycation end products	1	Vitamin C	1	Glycogen synthase kinase-3 (GSK3-α)						
1	Neutrophil/Lymphocyte ratio	1	Beta-Carotene	1	Neuronal Cell Adhesion Molecule (NrCAM)						
1	Monocyte chemotactic protein-1 (MCP-1)	1	Calcium	1	Axl receptor tyrosine kinase (AXL)						
1	CD40	1	Nitrate2+Nitrate3	1	VILIP-1/Abeta1-42						
1	IgG2	1	Selenium	1	Sirtuin/SIRT1						
1	IgA	1	Hematocrit	1	Aβ/β-actin						
1	P-selectin	1	Mean platelet volume (MPV)	1	α-secretase (ADAM10)						
1	Matrix Metalloproteinase-10 (MMP-10)	1	Transferrin	1	Rab3						
1	Chemokine receptor 2 (CCR2) (protein2 list)	1	Haptoglobin	1	Rab7						
1	Beta 2-microglobulin (B2M)	1	White blood cells (WBC)	1	Early Endosome Marker (EEA1)						
1	FAS ligand belongs to TNF family	1	Total Urinary polyphenols (TUPs)	1	Lysosomal-associated membrane protein 2 (LAMP-2)						
1	CD8	1	Alpha-1-antitrypsin (alpha1-AT)	1	Microtubule-associated protein 1A/1B-light chain 3 (LC3)						
		1	Lactoferrin (LTF)	1	Phospholipase A2 (PLA2)						
		1	N-terminal pro b-type natriuretic peptide (NT-proE	1	Carcinoembryonic antigen						
		1	Luteinizing hormone (LH)	1	Osteoprotegerin (OPG)						
				1	Neruogranin (NGRN)						
				1	Cellular prion protein (PrPc)						
				1	Kidney Injury Molecule (KIM-1)						
				1	Growth-regulated alpha protein (GRO-α)						
				1	Eotaxin-3						
				1	Unfolded p53						
				1	P-t181p/Ab1-42 ratio						

Table II. Frailty biomarkers by category and frequency

1.Frequency	1.Inflammatory/Immunity Markers	2.Frequency	2.Laboratory Markers	3.Frequency	3.Protein Markers	4.Frequency	4.Metabolomic Markers	5.Frequency	5.Oxidative Stress Markers	6.Frequency	6.Clincal Markers
33	IL6	10	Vitamin D	2	Propeptide of type I procollagen (PINP)	1	X12063	2	Serum 8-hydroxy-2-deoxyguanosine (8-OHdG)	4	Cardiovascular disease
24	C-reactive protein	6	Albumin	2	C-terminal telopeptide of type-1 collagen (Beta CTX)	1	Urate	1	Protein carbonyls	3	Increase Waist Circ/Waist-to-hip
6	Tumor necrosis factor (TNF-alpha)	5	Composite Score (multiple markers)	2	Extracellular heat shock protein (eHsp) 72	1	Mannose	1	thol level (TTL)	2	Calibrated Protein intake
6	Uric Acid	5	Lipids: Total Cholesterol	1	Cystatin C	1	Myostatin	1	Derivate of reactive oxygen metabolites (d-ROM)	1	Increased falls
5	Fibrinogen	5	Insulin like growth factor protein (IGF-1)	1	Cytomegalovirus			1	Malondialdehyde (MDA)	1	Alcohol intake
4	IL1beta	5	Parathyroid hormone (PTH)	1	C-terminal Agrin Fragment (CAF)					1	Change in Body Mass Index
3	Erythrocyte sedimentation rate (ESR)	5	White blood cells (WBC)	1	Sirtuin 1					1	More than 2 chronic diseases
3	Cortisol/Dehydroepiandrosterone ratio	4	Insulin resistance (IR-HOMA)	1	Sirtuin 2					1	Anticholinergic medications
2	IL1RA	3	Creatinine	1	Sirtuin 3						
2	Motif chemokine 10/ Interferon-gamma (CXCL-10/IFN-gama)	3	Glycohemoglobin (HbA1c)	1	Complement component protein (C1q)						
2	CD8	3	Hemoglobin	1	Klotho						
2	Dehydroepiandrosterone sulphate (DHEAS)	3	Lymphocytes	1	Lipopolysaccharide bining protein (LBP)						
1	IL2	2	Estimated glomerular filtration rate (eGFR)								
1	IL6R	2	Cobalamin deficiency (B12)								
1	IL18	2	Methylmalonic acid (MMA)								
1	TNF-a receptor I (TNFR1)	2	Carotenoids								
1	Cortisol	2	Lipids: Triglycerides								
1	Homocysteine	2	Neutrophils								
1	Beta 2-microglobulin (B2M)	2	Follistatin								
		2	Von Willebrand Factor VIIc								
		1	Creatinine Clearance								
		1	Glucose								
		1	Lipids: LDL cholesterol								
		1	Free thyroxine, fT4								
		1	Phytohemagglutinin								
		1	Pokeweed mitogen								
		1	Total Testosterone								
		1	Estrogen								
		1	Vitamin B6								
		1	Selenium								
		1	Blood urea nitrogen (BUN)								
		1	Thyroid stimulating hormone, TSH								
		1	Free thyroxine, fT3								
		1	Anemia								
		1	Hematocrit								
		1	Monocytes								
		1	Cystathionine								
		1	Ratio-Zinc/Copper								
		1	Total Urinary polyphenols (TUPs)								
		1	Total dietary polyphenols (TDPs)								
		1	alpha-tocopherol								
		1	alpha-1-antichymotrypsin (ACT)								
		1	Von Willebrand Factor VIIIc								

Table III. Cognitive frailty biomarkers by category and frequency

1.Frequency	1.Inflammatory/Immunity Markers	2.Frequency	2.Laboratory Markers	3.Frequency	3.Protein Markers	6.Frequency	6.Clincal Markers
6	C-reactive protein	2	Creatinine Clearance	1	Apolipoprotein A-I (ApoA1)	4	Change in Body Mass Index
4	IL6	2	Cobalamin deficiency (B12)	1	Prostaglandin F2-alpha	2	More than 2 chronic diseases
2	Dehydroepiandrosterone sulphate (DHEAS)	2	Insulin like growth factor protein (IGF-1)	1	Apolipoprotein B	1	Income
1	IL8	2	Vitamin D			1	Low level of education
1	IL1beta	2	White blood cells (WBC)			1	Alcohol intake
1	IL1alpha	1	Albumin			1	Elevated blood pressure
1	Fibrinogen	1	Creatinine			1	Elevated systolic pressure
1	CD8	1	Glucose			1	Cardiovascular disease
1	Homocysteine	1	Glycohemoglobin (HbA1c)			1	Psychoactive medications
1	Cortisol	1	Lipids: LDL cholesterol			1	Depression
		1	Alpha-linolenic acid			1	Instrumental activities of daily living (IADL)
		1	Anemia			1	Activities of daily living (ADL)
		1	Sodium				
		1	Phosphate				
		1	Polyunsaturated fatty acids (O3PUFAs)/ n-6/n-3 ratio				
		1	Hematocrit				
		1	Hemoglobin				
		1	Mean corpuscular volume (MCV)				
		1	Red blood cells (RBC)				
		1	White blood cells (WBC)				
		1	Lymphocytes				
		1	Monocytes				
		1	Neutrophils				
		1	Urate				
		1	Glucose				
		1	Total protein				
		1	Alanine aminotransferase (ALT)				
		1	Calcium				
		1	Lipids: Triglycerides				
		1	Lipids: Total Cholesterol				
		1	Free thyroxine, fT4				
		1	Ferritin,				
		1	Lipids: HDL cholesterol				
		1	Free thyroxine, fT3				
		1	N-terminal pro b-type natriuretic peptide (NT-proBNP)				

Table IV. Serum and genetic correlations by phenotype

Serum biomarker	Phenotype assocated with serum biomarker	Genetic biomarker	Phenotype assocated with genetic biomarker
Vitamin D (25(OH)D)	Frailty and cognitive decline	VDR (Vitamin D receptor)	Sarcopenia
Cystatin C	Frailty and cognitive decline	CST3 (cystatin)	Cognitive decline
Chemokine receptor 2 (CCR2)	Cognitive decline	CCL2	Cognitive decline
Myostatin	Frailty	MSTN (myostatin)	Sarcopenia
Klotho	Frailty	*KLOTHO*	Cognitive function
IL-6	Frailty and cognitive decline	IL-6	Sarcopenia and cognitive decline
TNF-alpha	Frailty and cognitive decline	TNF-alpha	Sarcopenia, frailty, and cognitive decline
IL-6R	Frailty and cognitive decline	IL-6R	Cognitive decline
CRP	Frailty and cognitive decline	AP2A2 (trait CRP), USP50 (trait CRP)	Cognitive decline
IL-1βeta	Frailty and cognitive decline	IL-1βeta	Cognitive decline
IL-18	Frailty	IL-18	Frailty
IL-12p70	Cognitive decline	IL-12A	Frailty
Brain derived neurotrophic factor (BDNF)	Cognitive decline	BDNFval66Met	Cognitive decline

References

1. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2.
2. Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. *Neurology*. 2013;80(22):2055-2061. doi:10.1212/WNL.0b013e318294b462.
3. Mayeux R. Biomarkers: potential uses and limitations. *NeuroRx*. 2004;1(2):182-188. doi:10.1602/neurorx.1.2.182.
4. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89-95. doi:10.1067/mcp.2001.113989.
5. Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc*. 2002;50(12):2041-2056. http://www.ncbi.nlm.nih.gov/pubmed/12473019. Accessed March 9, 2015.
6. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;349:g7647. http://www.ncbi.nlm.nih.gov/pubmed/25555855. Accessed June 6, 2017.
7. Covidence systematic review sotware, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org. Accessed May 1, 2016.
8. Ripley, Brian, Venables, Bill, Bates D, Hornik, Kurt, Gebhardt, Albrecht, Firth D. Package “MASS.” https://cran.r-project.org/web/packages/MASS/MASS.pdf. Accessed June 21, 2017.
9. Wickham, Hadley, Chang W. Package “ggplot2.” https://cran.r-project.org/web/packages/ggplot2/ggplot2.pdf. Accessed June 21, 2017.
10. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653. Published 2011. Accessed February 7, 2015.
11. Lanctôt KL, Ph D, Regan JO, et al. Original Research Reports Assessing Cognitive Effects of Anticholinergic Medications in Patients With Coronary Artery Disease. *Psychosomatics*. 2014;55(1):61-68. doi:10.1016/j.psym.2013.04.004.
12. Qiu WWQ, Lai A, Mon T, et al. Angiotensin Converting Enzyme Inhibitors and Alzheimer Disease in the Presence of the Apolipoprotein E4 Allele. *Am J Geriatr Psychiatry*. 2014;22(2):177-185. doi:10.1016/j.jagp.2012.08.017.
13. Jamsen KM, Bell JS, Hilmer SN, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. *J Am Geriatr Soc*. 2016;64(1):89-95. doi:10.1111/jgs.13877.
14. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-1483. doi:10.1111/j.1532-5415.2011.03491.x.

15. Retrospective A, Study C, Fortin M, et al. Effects of Anticholinergic Drugs on Verbal Episodic Memory Function in the Elderly. 2011;28(3):195-204.
16. Uusvaara J, Pitkala KH, Tienari PJ, Kautiainen H, Tilvis RS, Strandberg TE. Association between anticholinergic drugs and apolipoprotein E epsilon4 allele and poorer cognitive function in older cardiovascular patients: a cross-sectional study. *J Am Geriatr Soc*. 2009;57(3):427-431. doi:10.1111/j.1532-5415.2008.02129.x.
17. Baylis D, Bartlett DB, Syddall HE, et al. Immune-endocrine biomarkers as predictors of frailty and mortality: A 10-year longitudinal study in community-dwelling older people. *Age (Omaha)*. 2013;35(3):963-971. doi:10.1007/s11357-012-9396-8.
18. Cohen AA, Milot E, Li Q, et al. Detection of a novel, integrative aging process suggests complex physiological integration. *PLoS One*. 2015;10(3):1-26. doi:10.1371/journal.pone.0116489.
19. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic load and frailty in older adults. *J Am Geriatr Soc*. 2009;57(9):1525-1531. doi:10.1111/j.1532-5415.2009.02389.x.
20. Heringa SM, Van den Berg E, Reijmer YD, et al. Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. *Psychoneuroendocrinology*. 2014;40(1):108-118. doi:10.1016/j.psyneuen.2013.11.011.
21. Kobrosly RW, Seplaki CL, Jones CM, van Wijngaarden E. Physiologic Dysfunction Scores and Cognitive Function Test Performance in US Adults. *Psychosom Med*. 2012;74(1):81-88. doi:10.1097/PSY.0b013e3182385b1e.
22. O'Bryant SE, Xiao G, Barber R, et al. A serum protein-based algorithm for the detection of Alzheimer disease. *Arch Neurol*. 2010;67(9):1077-1081. doi:10.1001/archneurol.2010.215.
23. Mattsson N, Insel P, Nosheny R, et al. CSF protein biomarkers predicting longitudinal reduction of CSF β-amyloid42 in cognitively healthy elders. *Transl Psychiatry*. 2013;3(8):e293. doi:10.1038/tp.2013.69.
24. Kumar R, Chaterjee P, Sharma PK, et al. Sirtuin1: A Promising Serum Protein Marker for Early Detection of Alzheimer's Disease. *PLoS One*. 2013;8(4):4-9. doi:10.1371/journal.pone.0061560.
25. Kumar R, Mohan N, Upadhyay AD, et al. Identification of serum sirtuins as novel noninvasive protein markers for frailty. *Aging Cell*. 2014;13(6):975-980. doi:10.1111/acel.12260.
26. Sundelof J, Arnlov J, Ingelsson E, et al. Serum cystatin C and the risk of Alzheimer disease in elderly men. *Neurology*. 2008;71(14):1072-1079. doi:10.1212/01.wnl.0000326894.40353.93.
27. Liu CK, Lyass A, Massaro JM, D'Agostino RB, Fox CS, Murabito JM. Chronic kidney disease defined by cystatin C predicts mobility disability and changes in gait speed: The Framingham Offspring Study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2014;69 A(3):301-307. doi:10.1093/gerona/glt096.

28. Yaffe K, Lindquist K, Shlipak MG, et al. Cystatin C as a marker of cognitive function in elders: Findings from the Health ABC Study. *Ann Neurol*. 2008;63(6):798-802. doi:10.1002/ana.21383.
29. Inglés M, Gambini J, Carnicero JA, et al. Oxidative stress is related to frailty, not to age or sex, in a geriatric population: Lipid and protein oxidation as biomarkers of frailty. *J Am Geriatr Soc*. 2014;62(7):1324-1328. doi:10.1111/jgs.12876.
30. Baldeiras I, Santana I, Proença MT, et al. Oxidative damage and progression to Alzheimer's disease in patients with mild cognitive impairment. *J Alzheimer's Dis*. 2010;21(4):1165-1177. doi:10.3233/JAD-2010-091723.
31. Dixon RA, DeCarlo CA, MacDonald SWS, Vergote D, Jhamandas J, Westaway D. APOE and COMT polymorphisms are complementary biomarkers of status, stability, and transitions in normal aging and early mild cognitive impairment. *Front Aging Neurosci*. 2014;6(SEP):1-11. doi:10.3389/fnagi.2014.00236.
32. Mekli K, Nazroo JY, Marshall AD, Kumari M, Pendleton N. Proinflammatory genotype is associated with the frailty phenotype in the English Longitudinal Study of Ageing. *Aging Clin Exp Res*. 2016;28(3):413-421. doi:10.1007/s40520-015-0419-z.
33. Baune BT, Ponath G, Rothermundt M, Riess O, Funke H, Berger K. Association between genetic variants of IL-1beta, IL-6 and TNF-alpha cytokines and cognitive performance in the elderly general population of the MEMO-study. *Psychoneuroendocrinology*. 2008;33(1):68-76. doi:10.1016/j.psyneuen.2007.10.002.
34. Patel HP, Al-Shanti N, Davies LC, et al. Lean Mass, Muscle Strength and Gene Expression in Community Dwelling Older Men: Findings from the Hertfordshire Sarcopenia Study (HSS). *Calcif Tissue Int*. 2014;95(4):308-316. doi:10.1007/s00223-014-9894-z.

MANUSCRIPT 3:

Establishing Biological Plausibility for Cognitive Frailty: A Population Predictive Model

Abstract:

Background: This study aims to create a population predictive model to gain a more in-depth understanding of the underlying biological mechanisms for cognitive frailty as currently defined by the International Consensus Group in 2013. Methods: Data were from the InCHIANTI study, collected at baseline from 1998-2000. This group is a representative sample (n=1,453) of a population of white European origin from two small towns in Tuscany, Italy. To build our model, we used biomarkers with implications for clinical research and practice; a total of 132 putative SNPs and 155 protein biomarkers were identified from a systematic review (manuscript 2). We used a tree boosting model, Extreme Gradient Boosting (xgboost), a machine learning technique for supervised learning. Results: We developed two predictive models with high accuracy, AUCs for Model I is 0.877 (95% CI 0.825-0.903) and 0.864 (95% CI 0.804-0.899) for Model II. Results provide biological evidence for the relationship between cognitive decline and physical frailty supporting findings of dysregulation across multiple systems as the potential cause of cognitive frailty. One of the top predictors for cognitive frailty included anticholinergic burden with the presents of *SLCO1B1* rs4363657 (TMT-A β = .20 ,TMT-B β = .38). Conclusions: The results from this study establish a foundation for an understanding of the underlying biological mechanisms for the relationship between cognitive decline and physical frailty.

Introduction

The relationship between the phenotypes physical frailty and cognitive decline has been established in epidemiological studies. Both are associated with higher rates of disability, falls, mortality, an increase in health service need, and high direct/indirect costs to healthcare from long-term care and hospitalization[1–6]. Evidence exists to support a longitudinal bidirectional relationship between physical function and cognitive decline; finding that associations between physical functioning and consequent cognitive decline are similar to associations with individuals with cognitive decline and consequent physical functioning[7]. These findings support an a priori hypothesis for shared biological mechanisms that underlie the association of physical and cognitive decline.

Although physical and cognitive impairment have been shown to be related, both phenotypes have long been studied separately[4]. To address this gap, the International Consensus Group organized by the International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) convened in 2013 to identify related domains of physical frailty and cognition. The new construct called "cognitive frailty" is defined by the presence of physical frailty and cognitive impairment in the absence of Alzheimer's disease or other dementias[4]. The International Consensus Group (I.A.N.A. /I.A.G.G.) report is an acknowledgment of the need to focus research efforts on a clinical condition characterized by the occurrence of physical frailty and cognitive impairment, in the absence of overt dementia diagnosis or underlying neurological conditions[4]. The cognitive frailty construct is considered a

heterogeneous clinical syndrome in older adults with evidence of: 1) physical frailty and cognitive impairment; and 2) exclusion of a clinical diagnosis of Alzheimer's Disease or other dementia[4].

The introduction of this new phenotype demonstrates evidence for cognitive frailty as a subgroup of cognitive decline and physical frailty. Genetic risk factors and biological markers may be unique to individuals who present with cognitive frailty in contrast to those with isolated cognitive or physical decline. A model for detecting cognitive frailty could provide practitioners with the tools needed for early detection and secondary prevention for individuals with cognitive frailty. Currently, the instrumental assessments for cognitive frailty are time-consuming, expensive, require extensive training, and the clinical translation of these assessments is not clear[4]. Translating the cognitive frailty construct into the clinical setting is limited by the lack of consensus on an operational definition and considerable heterogeneity in the diagnostic criteria[8]. An understanding of the biomarkers that define cognitive frailty will help distinguish between changes related to normal aging, irreversible pathological process, and specific neurological diseases that may be reversible[9]. The strength in understanding the biological underpinnings of cognitive frailty is the ability to provide early detection and accurate diagnosis.

The primary purpose of this research was to create a population predictive model to gain a more in-depth understanding of the underlying biological mechanisms for cognitive frailty as currently defined by the International Consensus Group in 2013. This paper focuses on defining the shared mechanisms for physical frailty and cognitive

impairment and establishing a model for determining the presence of risk factors that may predict cognitive frailty in the clinical setting. An important innovation in this study was the use of machine learning (ML) statistical modeling to define the differences between the following groups: cognitive decline, physical frailty and cognitive frailty. The study builds an algorithmic classifier for cognitive frailty with candidate factors identified by a systematic review (results published elsewhere). Notably, the identification of unique biomarkers may also serve to group patients by underlying pathophysiologic processes and further refine the assignment to a clinical diagnostic category. Such precision in the determination of genetic and biological biomarkers related to cognitive frailty will lead to a better understanding of the interrelated pathology between physical frailty and cognitive impairment and, ultimately, to early detection and targeted interventions focused on the prevention of cognitive and functional disabilities.

Methods

Study Population

Figure 1 shows a summary of our workflow, further details on phenotypes and the list of biomarkers are available in the supplementary appendix. Clinical, protein, and genetic biomarker samples were from participants of the InCHIANTI study, collected at baseline from 1998-2000. This group is a representative sample (n=1,453) of the population of white European origin from two small towns in Tuscany, Italy. The primary aim of the InCHIANTI study to evaluate function and mobility in older community-dwelling individuals. A detailed description of the study design, data collection, and sampling

procedure are published elsewhere[10]. This secondary study was approved by the ethics committee at *Centre de recherché Clinique du CHUS*, project #547.

Predictive Measures

The International Consensus Group's (I.A.N.A. /I.A.G.G.) list of potential biomarkers is not meant to be complete, accurate, or exhaustive[4]. Since an exhaustive list of biomarkers is not present in the literature; we used a systematic review to identify factors associated with cognitive decline, physical frailty, and cognitive frailty based on the current operational definitions (Sargent et al., 2018). We searched the following online databases: PubMed, Embase, Scopus, Web of Science, LILACS, Gene Indexer, and GWAS Central. Databases were searched from the start date of the database to 22 December, 2015. An update of the searches was performed prior to the data extraction phase on 26 May, 2016 to identify any new publications. The systematic review resulted in 327 articles for the final synthesis, identifying 456 predictive protein and genetic biomarkers. A total of 289 variables identified from the systematic review were available in the InCHIANTI database. Variables were removed if there was > 12% missing data, resulting in 132 putative SNPs and 155 protein biomarkers. To build our model, we used protein markers with implications for clinical research and practice, and completed genetic risk score estimates (i.e. the cumulative genetic risk burden estimated from SNPs of interest, or GRS) before including the individual single nucleotide polymorphisms (SNPs) in the final models. Many of the protein markers included in our model are used clinically for detection of disease; therefore we organized the results by using the clinical designation identified by clinical pathology laboratories. The categories

include inflammation/immunity, nutrient, lipid metabolism, metabolomics, renal/electrolyte, hematology/liver, endocrine/hormones, and clinical features. Known predictive clinical features identified repeatedly in the systematic review were age, depression, gender, and level of education. Baseline diagnosis of dementia was included in the models for frailty and cognitive frailty. Additionally, systematic review identified a group of medications, specifically anticholinergic medications, as a risk for cognitive and physical decline[11,12]. Anticholinergic burden was calculated using the Anticholinergic Cognitive Burden Scale (ACB) and examined as a predictor for all phenotypes.

Outcome Measures

Neuropsychological tests include the Mini-Mental State Examination (MMSE) as a test of general cognition and the Trail Making Test, Part A and B (TMT). Psychomotor speed is assessed using the TMT-A, scoring based on time in seconds to completion with a score range of 0 to 300 seconds[13]. The executive functioning domain was assessed using the TMT-B (any individual scoring 300-600 seconds were included as 300)[13]. TMT, part A and B cut off scores are based off of established norms for mild neurocognitive disorders[14]. Normative data for time to complete the TMT tests in seconds was stratified by age and education[15]. Additionally, the neuropsychological profile for individuals with cognitive frailty is different from those with frailty or cognitive decline alone with recent findings of lower performance on TMT tests, scoring worse on executive and attention domains[16]. The CES-D self-report scale (0-60) is used to measure depressive symptoms. Reliability, validity, and factor structure have been similar across a diverse demographic

and the scale has been used extensively in epidemiologic studies for depression and physical function[17].

Frailty measures included the number of frailty symptoms for subjects ≥65 years of age. Frailty as defined by the cardiovascular health study (CHS), allows for a continuous scoring system versus a nominal system because it can capture the multidimensional nature of frailty[18]. The InCHIANTI criteria for frailty defined unintentional weight loss as losing weight not related to diet, classified the values of body mass index, strength, walking speed and height based on all subjects ≥65 years and used two questions of the CES-D for the definition of exhaustion.

In this study two models of cognitive frailty were developed, because conceptually the models need to cover variables of physical frailty and cognitive decline for populations seen in geriatric and primary care centers with implications for future clinical research and translation into practice. Primary care has a key role in early identification of cognitive and physical decline. The MMSE, despite known limitations for the diagnosis of dementia, has retained popularity in the primary care setting with increased use for screening and diagnosis and is recommended by the Alzheimer's Society[19]. *Model I* defines cognitive decline and cognitive frailty with the use of criteria from the MMSE while *Model II* defines these phenotypes with participants who have completed the MMSE with additional Trail Making Tests, Part A and B[20–22]. In this study frailty was characterized by individuals with one or more of the frailty criteria, including pre-frail and frail as one group[1]. Cognitive frailty is defined as individuals with cognitive decline and one or more of the frailty criteria[16].

Statistical Analysis

The supplementary appendix includes additional details of the statistical methods, beginning with detail about model development in the InCHIANTI dataset, which we used to train and test the initial model, internal validation, and calibration of the model. Evidence supports the use of tree boosting models using Extreme Gradient Boosting (xgboost) in R, statistical software, as an effective method for building a reproducible predictive model for the detection of a complex heterogeneous phenotype with large numbers of potential biomarkers[23,24]. Boosted trees, a machine learning technique for supervised learning, are ensembles of regression trees, similar to decision trees and are used for prediction or classification. Xgboost is based in boosted trees and provides more efficient and accurate predictive modeling with large datasets and a rapid / robust framework for feature selection. Statistical modeling is used to design, test, and validate an accurate method for classifying patients into phenotypic outcomes.

The tree boosting model for the evaluation of multiple variables simultaneously provides a high predictive value with low bias. Additionally, parameters are set to prevent over fitting for the models. The data were randomly divided, two thirds was assigned to the training cohort, and one third was assigned to the validation cohort. One of the features that is central to xgboost is its ability to combine multiple trees or "weak predictors" to reach maximum prediction performance while reducing bias. This approach uses large amounts of data from different aspects of clinical, genetic, and biomarker research, strengthening the models' generalizability and classification power. Xgboost iteratively re-weighs the variables, taking a weighted majority; the parameters

identified after pruning comprised the final predictive model[25]. None of the candidate features in the models are used in the diagnosis of cognitive decline, physical frailty, or cognitive frailty. This standard technique prevents circularity, overestimation, and over fitting for both the models generated. Parameters for the model include: max depth = "10", nthread = "12", nrounds = 5-200, objective = "binary:logistic", evaluation metric = "auc", silent ="1", gamma = default ="0" to control the number of trees, and eta default= "0.3" to prevent over fitting. We used the default setting for all other parameters which can be found in the xgboost 0.6 documentation[24].

To evaluate the models, we used the evaluation metric area under the receiver operating curve (AUC). AUC were calculated from each model and used to determine discrimination of participants with cognitive frailty (case), cognitive decline (case), and physical frailty (case) from healthy individuals (control) in the training cohort. An AUC of 0.5 was considered chance, > 0.8 informative, and > 0.9 clinically relevant.

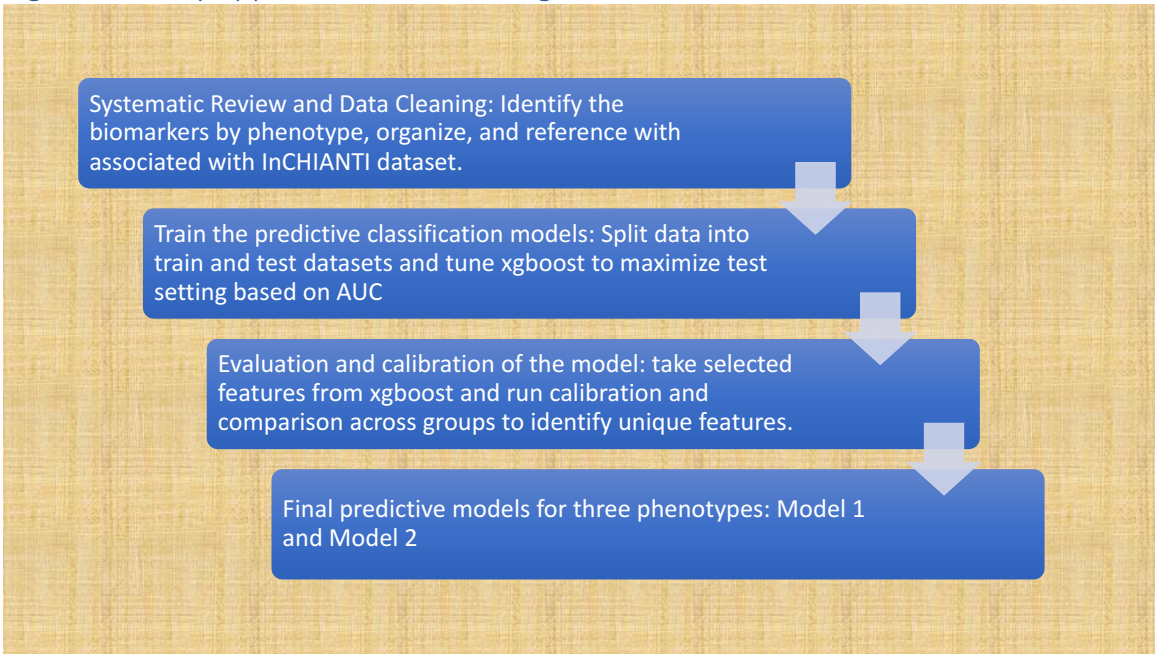
The xgboost algorithm iteratively determines the maximum function of a model based on a tree building algorithm (quadratic problem) which creates a node then assigns a prediction point to each leaf; the assigned number is termed "gain". Once the model has reached maximum depth, pruning occurs by taking out the nodes with a negative gain and keeping those with a positive gain. Results from the population predictive model are ranked by gain which is a metric based on each feature's contribution in the model. When comparing top features to other features in the model, the higher the gain the more important the feature is for prediction of the outcome. Cover is a measure of the relative quantity of observations found by one feature and frequency is the percentage

representing the relative number of time a feature is used in the trees of the model[24]. Gain is the most relevant metric to interpreting the rank and importance of each feature.

A case-control design is used to study genome wide variations between participants with cognitive frailty (case) and those with only cognitive decline (control), only physical frailty (control), and healthy individuals (control). Univariate analysis, *t*-tests for continuous and chi-squared tests for binomial traits, were used to determine the significance of the predictor. We used logistic regression for case-control analyses under additive allele dosage. To evaluate additive effects of SNPs, a positive regression coefficient means that each copy of the allele of interest increases the risk for the cognitive frailty phenotype[26,27]. The appendix includes further details and results about the generation of the genetic data and creation of the GRS from 132 genetic risk factors implicated in one or more studies from the systematic review. Our study used the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health (Bethesda, MD, USA) in the and genotypic data from the InCHIANTI study.

The final models identified features that were predictive of cognitive frailty with unique features for cognitive decline and physical frailty. Mechanisms that contribute to the development of cognitive frailty were determined by evaluation of fluid biomarkers and genome wide genetic variability as a predictor of the development and persistence of cognitive frailty.

Figure 1. Study approach workflow diagram



Note: Profile of model development and validation workflow. Blue boxes indicate steps of the workflow specific to the InCHIANTI data set.

Results

A total of 1,453 adults participated, 1,326 provided blood samples at baseline. Participants had a mean age of 69 years (S.D.=15.7), 56% were female and 44% were male, and completed a secondary level of education. All participants completed the MMSE, 369 participants scored ≤ 23 (*M*=25, S.D.=5.1), 525 scored ≥ 78 on the TMT-A (n=1,240), and 634 scored ≥ 106 on the TMT-B (n=1,057).

The supplementary appendix (tables IV-IX) contains the tables for final predictive model features ranked by gain. The results show predictive features for cognitive frailty when measured using the MMSE (Model 1) and TMT part A and B (Model II) with unique features for cognitive decline and physical frailty in both models. Bivariate results for clinical, genomic, and protein biomarkers are shown in the appendix (tables X - XVIII).

For discrimination of participants with cognitive frailty from healthy controls, the AUC of Model I is 0.877 (95% CI 0.825-0.903) and 0.864 (95% CI 0.804-0.899) for Model II. Parameter estimates for each predictive factor and associated descriptive statistics were evaluated to provide biological insight into the underpinnings of the classification algorithm. Next, we carried out calibration tests for all possible values between 5-200 groups and evaluated the distribution of the test statistics per subgrouping. We noted a normal distribution of AUCs across all iterations, with no statistically significant deviation from the expected values in any group, suggesting good model fit. Both models showed high accuracy with AUCs ranging from 0.808-0.877 for model I and 0.831-0.864 model II within the framework of the calibration tests.

Demographic features and anticholinergic burden results are shown in Table 5-6 and significant differences between healthy control and phenotype are shown in Table 10 of the supplementary appendix. Gender was a predictor for all three phenotypes in Model I but not a predictor in Model II. There were more females than males with cognitive decline for all three phenotypes in both models. Baseline diagnosis of dementia, while found to be a predictor in Model I for frailty and cognitive frailty was not a predictor in Model II. Anticholinergic burden (ACB) was a predictor for all three phenotypes in both models with larger ACB mean scores for those with cognitive decline, frailty, and cognitive frailty. In Model II, anticholinergic burden had a significant effect on both psychomotor speed (TMT-A) and executive functioning (TMT-B) for all three phenotypes. Anticholinergic burden was found to be one of the top predictors for all phenotypes in model I and II. Detailed analyses for anticholinergic burden are described

elsewhere and included in the results tables of this manuscript (Sargent et al., 2018 in manuscript 4).

Genomic results

Table 1 and 2 shows the comparison of genomic features by phenotype for Model I and Model II respectively.

Model I

Ten genes were predictive of cognitive frailty measured by the MMSE and CHS criteria; four genes are unique to cognitive frailty: (*BIN1*) rs7561528 allele A (β = -.04), *ACE* rs4968782 allele G (β = .10), and *WTAPP1* rs603050 allele G (β = -.14), *MTRR* rs1801394 allele G (β = .80) and six overlap with features associated with cognitive decline and frailty: *IL6* rs1800796 allele C (β = .25), (*ACOT11)* rs12752888 allele C (β = -.47), *DAB1* rs1539053 allele A (β = .51), (*MMP3*) rs948399 allele C (β = .41), *CD33* rs3865444 allele A (β = .62), and *UBR5* rs7840202 allele C (β = -.15). Of these markers five showed a significant difference between control and cognitive frailty: (*ACOT11*) rs12752888 (p = .001), *DAB1* rs1539053 (p = .01), (*MMP3)* rs948399 (p = .01), *CD33* rs3865444 (p = .03), and *MTRR* rs1801394 (p = .001).

Four SNPs were uniquely associated with frailty: *CNTN5* rs10501927 allele G (β = -.10), *WTAPP1* rs11225434 allele C (β = .10), *SORL1* rs4935774 allele C (β = .04), and *CREBBP* rs129968 allele A (β = .10) Eight SNPs are unique to cognitive decline *BTRC* rs10883631 allele G (β = .11), *TOMM40* rs2075650 allele G (β = .10), *IL6R* rs2228145 allele C (β = -.31), *USP50* rs3131609 allele C (β = .10), *COMT* rs4646316 allele T (β = -.62), *AP2A2* rs7396366 allele C (β = .10), *KLOTHO* rs9527025 allele C (β = .20).

Model II

Individual variants were predictive for psychomotor speed (TMT-A) and executive functioning domain (TMT-B). Significant differences between control and disease are shown in appendix (tables XVI - XVIII).

Twenty-one genes were predictive of cognitive frailty measured by TMT and CHS criteria in model II; eight are unique to cognitive frailty *ACE* rs4316 allele T (TMT-A β = -.07, TMT-B β = -.06), *ACE* rs1800764 allele C (TMT-A β = .06, TMT-B β = .06), *EPHA1* rs11771145 allele A (TMT-A β = -.10, TMT-B β = .13), *CREBBP* rs129968 allele A (TMT-A β = .05, TMT-B β = .03), *TNF* rs1800629 allele A (TMT-A β = .15, TMT-B β = .10), *IL18* rs360722 allele A (TMT-A β = .05, TMT-B β = -.02), WTAPP1 rs603050 allele T (TMT-A β = -.21, TMT-B β = -.10), and SELP rs6131 allele T (TMT-A β = -.07, TMT-B β = -.03).

Thirteen of the cognitive frailty genetic features overlap with variants from cognitive decline and frailty: (*MMP3*) rs948399 allele C (TMT-A β = .29, TMT-B β = 0.02), (*ACOT11*) rs12752888 allele C (TMT-A β = -.34, TMT-B β = -.37), *APOE* rs429358 allele C (TMT-A β = -.23,TMT-B β = -.59), *SLCO1B1* rs4363657 allele C (TMT-A β = .20 ,TMT-B β = .38), *TOMM40* rs8106922 allele G (TMT-A β = -.31, TMT-B β = .09), *CNTN5* rs10501927 allele G (TMT-A β = -.11, TMT-B β = -.06), *SORL1* rs1614735 allele G (TMT-A β = .02, TMT-B β = .07), *IL1-beta* rs16944 allele A (TMT-A β = -.01, TMT-B β = -.13), *ACE* rs4343 allele A (TMT-A β = -.02, TMT-B β = -.02), (*SSB*) rs11894266 allele C (TMT-A β = -.05, TMT-B β = -.06), *UBR5* rs7840202 allele C (TMT-A β = -.06, TMT-B β = -.05), *MAPT* rs3785880 allele G (TMT-A β = -.06, TMT-B β = -.05), *BTRC* rs10883631 allele G (TMT-A β = -.01, TMT-B β = .01).

Of these markers five showed a significant difference between control and cognitive frailty for psychomotor speed or executive functioning: (*ACOT11)* rs12752888 allele C (TMT-A, p = .01, TMT-B p = .02), *APOE* rs429358 allele C (TMT-B, p = .01), *SLCO1B1* rs4363657 allele C (TMT-B, p= .02), *TOMM40* rs8106922 allele G (TMT-A, p = .05), (*MMP3*) rs948399 allele C (TMT-A, p = .05).

Frailty has one unique SNP: *NECTIN2* rs6859 allele A (TMT-A β = -.02, TMT-B β = -0.07). and cognitive decline has eleven unique SNPs: *KCNU1* rs1157242 allele T (TMT-A β = .13, TMT-B β = .44), *SORL1* rs1133174 allele A (TMT-A β = .05, TMT-B β = .02), *KLOTHO* rs1207568 allele A (TMT-A β = -.05, TMT-B β = -.18), *GCKR* rs1260326 allele C (TMT-A β = .02, TMT-B β = .08), *COMT* rs4680 allele A (TMT-A β = -.02, TMT-B β = .06), *SORL1* rs4935774 allele C (TMT-A β = .11, TMT-B β = .05), *ATM* rs611646 allele T (TMT-A β = .08, TMT-B β = .04), *MS4A4E* rs676309 allele C (TMT-A β = -.07, TMT-B β = -.17), *SLC2A9* rs737267 allele T (TMT-A β = .10, TMT-B β = -.08), *TCN2* rs740234 allele G (TMT-A β = -.02, TMT-B β = -.10), (*BIN1)* rs744373 allele G (TMT-A β = .01, TMT-B β = -15). Cognitive decline and frailty have three shared SNPs that were not features for cognitive frailty *PRNP* rs1799990 allele G (TMT-A β = .45, TMT-B β = .30), *CR1* rs3818361 allele A (TMT-A β = .20, TMT-B β = .14), and *ABCA7* rs4147929 allele A (TMT-A β = .02, TMT-B β = .03).

Protein biomarker results

Tables III and IV shows a comparison of the protein markers by category and phenotype. Significant differences between control and cognitive frailty are shown in the supplementary appendix (Tables XI-XVIII). The results show a mean difference in the laboratory value between healthy controls and those with cognitive decline, physical

frailty, and cognitive frailty. In Model I and Model II, all phenotypes share features in all categories and each phenotype has unique features. Cognitive frailty in Model I has seven unique features transforming growth factor B1 and fatty acid 22:0 with a mean increase in cystatin C ($p < 0.0001$), decrease serum calcium ($p = .0004$), increase serum creatinine ($p = .02$), increase urine nitrites ($p = .02$), increase soluble transferrin receptor ($p = .01$) for individuals with cognitive frailty compared to healthy controls. Cognitive frailty (Model I) shared 70 of the 91 features with frailty and 53 of the 93 protein fluid biomarkers features with cognitive decline. Cognitive frailty in Model II had only two unique features; urine glucose and serum IGF binding protein; IGF binding protein is decreased in individuals with cognitive frailty for psychomotor speed ($p = .0001$) and executive functioning ($p = .0004$). Cognitive frailty (Model 2) shared 70 of the 90 features with frailty and 82 of the 125 protein fluid biomarkers features with cognitive decline.

Discussion

In this study, we developed two models using xgboost for the prediction of cognitive frailty and further defined the association between cognitive decline and frailty. Both models have a larger population of women with older age being associated with cognitive frailty. Anticholinergic burden was highly predictive of cognitive frailty and is found as a unique predictive feature of frailty and cognitive decline in both models.

Genomic results suggest that Model I and Model II are measuring different variants. Model I has unique genomic features *DAB1* rs1539053 allele A, *CD33* rs3865444 allele A, and *MTRR* rs1801394 allele G, as predictive of cognitive frailty. *CD33* has putative functions in the immune system involved in processes at the cell membrane with links

to greater cell surface expression of monocytes and is considered an Alzheimer's disease susceptibility loci[28]. *DAB1* is required for the organization of multiple neuronal types in the cerebral cortex and is important for normal cognitive function[29,30]. *MTRR* rs1801394 is a marker for vitamin B12 in a pathway with methylmalonic acid (MMA) levels[31]. Lower serum MMA leads to higher serum lipids and higher homocysteine levels potentially leading to reduced energy metabolism[31]. All three of these protein markers were found in the cognitive frailty model I. Additionally, *MTRR* has been linked to 2-4 times greater odd of being frail.

One of the interesting genomic findings was *SLCO1B1* rs4363657 allele C that is predictive of frailly and cognitive frailty in Model II. The *SLCO1B1* has been associated with X12063 which is a metabolite, both are associated as markers of lean muscle mass loss[32]. Additionally, *SLOCO1B1* has been linked to drug metabolism specifically, higher blood concentrations of statins[33]. *SLOCO1B1* is essential for the hepatic uptake and the C variant is associated with reduced *OATP1B1* activity. *OATP1B1* can facilitate drug uptake and at the blood-brain barrier may affect the distribution of drugs into the central nervous system[34]. The association with anticholinergic metabolism and *SLOCO1B1* has not been explored. Variants in model I and II included *MMP3* and (*ACOT11)*. *MMP3* rs948399 allele C is predictive of frailty and cognitive decline and (*ACOT11)*, rs12752888 allele C is a member of the acyl-CoA thioesterase family that catalyzes the conversion of activated fatty acids[35]. In this study (*ACOT11)* rs12752888 allele C was found to have a protective effect. (*ACOT11)* rs12752888 has not been studied in individuals with physical frailty or cognitive frailty previously.

Protein marker results show a relationship between neuroinflammatory cytokines and cognitive frailty. Neuroinflammatory cytokines (nonantibody proteins) have a role in the neuroimmunoendocrine processes and have been postulated to be related to cognition due to their ability to penetrate the blood-brain barrier and affect the central nervous system[1]. This study found elevated levels of neuroinflammatory cytokines with interleukins IL1, IL6, IL6R, and tumor necrosis factors (TNF) as predictive features for cognitive frailty in both models along with associated genetic markers: *IL6* rs1800796, *IL6R* rs2228145, *TNF* rs1800629, and *IL1-beta* rs16944. Additionally, participants with cognitive frailty had higher levels of resistin ($p < .0001$) compared to controls in both models; resistin regulates IL-6, TNF, and hs-CRP[2]. Both fibrinogen and advanced glycation end product (AGE) ($p < .0001$) were both found to be elevated showing a link to oxidative stress and high levels of alpha-2 globulin (A2M) ($p < .0001$). A2M is considered a protease inhibitor cytokine transporter linked to Alzheimer's disease was found in participants with cognitive frailty[3]. Several studies have shown a relationship between many of these neuroinflammatory markers and cognitive and physical decline[5,6]. In this study, we found many of these markers to be predictive for both cognitive decline and physical frailty. Additionally, these patterns of neuroinflammatory cytokines have been found in the InCHIANTI study to be associated with other complex chronic disease highlighting comorbidity as a cofounding factor[4].

Dehydroephiandrosterone sulfate (DHEA) was found to be low for those with cognitive frailty when compared to control ($p<0.001$). DHEA has been found to inhibit IL-6 providing a connection between endocrine and immune function. Another interesting

finding is the connection between nutrition and cognitive frailty with low fatty acid levels and high levels of c- terminal telopeptide of type-1 collagen l (PINP) and parathyroid hormone (PTH). Both PINP and PTH have been linked to low levels of vitamin D which was a finding in this study for participants with cognitive frailty[7]. Methlymalonic acid (MMA) is linked to vitamin B12 and high levels of homocysteine found in both models ($p<.0001$) in addition, *MTRR* rs1801394 is associated with the same pathway. Serum MMA has been link to both cognitive performance and increased risk for frailty[8,9].

Metabolomic (ceramides C16:0, C20:0, C20:5, C22:0, C24:0) markers were found in both models, some markers were found to be elevated and others low for participants with cognitive frailty. Since this study evaluated individuals with early cognitive decline at a single time point it is possible that serum ceramides varied according to the timing and onset of memory impairment and need to be explored further[10,11].

Cognitive frailty model I (n=101) and II n=110) feature comparison show a difference some biomarkers however, there were 66 shared biomarkers; 58 protein, 4 genomic, and 4 clinical markers. Some differences in the model features suggest lack of concordance between the clinical measures MMSE and TMT part A and B. These observations highlight the fact that pathways between clinical decision tools and precision science are not strictly linear in nature. When comparing models I and II for all phenotypes less variability with fewer unique features and more shared mechanisms.

There are several potential genomic and protein biomarker interactions, which are not fully explored in this manuscript. We did not attempt to complete a comprehensive

pathway analysis for the variables in the predictive models. The exploratory nature of this work will encourage new research into understanding these pathways. The study included a small homogenous sample with large numbers of biomarkers creating limitations for translation into clinical research. Additionally, the study was retrospective using existing data. Future research should be directed towards understanding the potentially reversible cause of cognitive frailty, validating the models in epidemiological data with more diverse demographic groups, and exploring the predictive features in prospective studies.

Conclusion

The results from this study support the use of an innovative Boosted trees machine learning technique in developing a population based predictive model for a complex condition of aging, cognitive frailty. Results provide biological evidence for the relationship between cognitive decline and physical frailty supporting findings of dysregulation across multiple systems as the potential cause of cognitive frailty. The results from this study begin to unravel the complex biological network behind the association between cognitive decline and physical frailty.

Table I. Genomic features by phenotype model I

SNP	Associated Allele	Chromosome	Gene	Cognitive Decline	Frailty Genomic	Cognitive Frailty
rs10883631	G	10	BTRC	X		
rs12752888	C	1	**ACOT11/**LOC105378734	X		X
rs1539053	A	1	DAB1	X	X	X
rs1800796	C	7	IL6	X		X
rs2075650	G	19	TOMM40	X		
rs2228145	C	1	IL6R	X		
rs3131609	C	15	USP50	X		
rs4646316	T	22	COMT	X		
rs7396366	C	11	AP2A2	X		
rs948399	C	11	**MMP3**	X	X	X
rs9527025	C	13	Klotho	X		
rs10501927	G	11	CNTN5		X	
rs11225434	C	11	WTAPP1		X	
rs129968	A	16	CREBBP		X	
rs3865444	A	19	CD33		X	X
rs4935774	C	11	SORL1		X	
rs7840202	C	8	UBR5		X	X
rs1801394	G	5	MTRR			X
rs4968782	G	17	**ACE**			X
rs603050	T	11	WTAPP1			X
rs7561528	A	2	**BIN1**/LOC105373605			X

Note: bold text indicates the closes gene

Table II. Genomic features by phenotype model II

SNP	Associated Allele	Chromosome	Gene	Cognitive Decline	Frailty Genomic	Cognitive Frailty
rs10501927	G	11	CNTN5	X	X	X
rs1133174	A	11	SORL1	X		
rs1157242	T	8	**KCNU1**	X		
rs1207568	A	13	Klotho	X		
rs1260326	C	2	GCKR	X		
rs12752888	C	1	**ACOT11/**LOC105378734	X	X	X
rs1614735	G	11	SORL1	X		X
rs16944	A	2	IL-1beta	X		X
rs1799990	G	20	PRNP	X	X	
rs3818361	A	1	CR1	X	X	
rs4147929	A	19	ABCA7	X	X	
rs4343	A	1	ACE	X		X
rs4680	A	22	COMT	X		
rs4935774	C	11	SORL1	X		
rs611646	T	11	ATM	X		
rs676309	C	11	MS4A4E	X		
rs737267	T	4	SLC2A9	X		
rs740234	G	22	TCN2	X		
rs744373	G	2	**BIN1**	X		
rs948399	C	11	**MMP3**	X	X	X
rs429358	C	19	APOE		X	X
rs11894266	C	2	**SSB**		X	X
rs8106922	G	19	TOMM40		X	X
rs7840202	C	8	UBR5		X	X
rs3785880	G	17	MAPT		X	X
rs10883631	G	10	BTRC		X	X
rs4363657	C	12	SLCO1B1		X	X
rs6859	A	19	NECTIN2		X	
rs11771145	A	7	EPHA1			X
rs129968	A	16	CREBBP			X
rs1800629	A	6	TNF			X
rs1800764	C	17	ACE			X
rs360722	A	11	IL-18			X
rs4316	T	17	ACE			X
rs603050	T	11	WTAPP1			X
rs6131	T	1	SELP			X

Note: bold text indicates the closes gene

Table III. Protein and clinical features by phenotype model I

	Cogntive Decline	Frailty	Cogntive Frailty
Clinical Features			
Age	X	X	X
Anticolnergic Burden	X	X	X
Depression	X	X	X
Gender	X	X	X
Level of Education	X	X	X
Baseline Diagnosis of Dementia		X	X
Inflammatory/Immunity			
24-hour urinary cortisol (Âµg/24 hours)	X	X	X
Urinary cortisol (Âµg/mL)	X		X
Adiponectin via RIA (Âµg/mL)	X		X
Alpha-1 globulin (%)	X		X
Alpha-2 globulin (%)	X		X
Alpha-2-macroglobulin (mg/dL)	X		X
Cortisol:DHEAS ratio (based on nmols)	X	X	X
Dehydroepiandrosterone sulfate (Âµg/dL)	X	X	X
Fibrinogen (mg/dL)	X		X
Homocysteine via FPIA analysis (Âµmol/L)	X	X	X
Interleukin-10 via ELISA (pg/mL)	X		X
Interleukin-12 via Bio-Plex (pg/mL)	X	X	X
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	X		
Interleukin-6 via ELISA ultrasensitive (pg/mL)	X	X	
Resistin via EIA (ng/mL)	X	X	X
Serum cortisol (Âµg/dL)	X	X	X
Soluble IL-6 receptor via ELISA (ng/mL)	X	X	
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	X	X	X
TNF-related apoptosis-inducing ligand (pg/mL)	X	X	X
Uric acid (mg/dL)	X		X
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)		X	X
Beta globulins (%)		X	X
C-reactive protein - high sensitivity (Âµg/mL)		X	X
Endogenous secretory receptor for AGEs (ng/mL)		X	X
Erythrocyte sedimentation rate (ESR) (mm/hour)		X	X
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)		X	X
Interleukin-1B via ELISA (pg/mL)		X	X
Interleukin-8 via Bio-Plex (pg/mL)		X	
Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)		X	X
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)		X	X
Soluble CD14 via ELISA (ng/mL)		X	X
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)		X	X
Tumor necrosis factor-a via multiplex technology (pg/mL)		X	X
Cystatin C (mg/L)			X
Transforming growth factor-B1 (pg/mL)			X
Renal/Electrolyte			
24-hour urinary creatinine (mg/24 hours)	X	X	X
Blood urea nitrogen (mg/dL)	X	X	X
Creatine phosphokinase (U/L)	X	X	X
Creatinine clearance, 24-hr urine (mL/minute)	X	X	
Cystatin C (mg/L)	X	X	
Urinary Ca (mmol/L)	X	X	X
Urinary Na (mmol/L)	X	X	
24-hour urinary cortisol (Âµg/24 hours)		X	
Na+ (mEq/L)		X	
Urinary creatinine (mg/dL)		X	X
Urine proteins (mg/dL)		X	X
Ca++ (mg/dL)			X
Serum creatinine (mg/dL)			X
Urine nitrites			X
Nutrient Biomarker			
Albumin (%)	X	X	X
Beta-carotene via high performance liquid chromatography (Âµmol/L)	X	X	X
Lycopene via high performance liquid chromatography (Âµmol/L)	X	X	
Omega-3 plasma fatty acid weight (mg/L)	X	X	X
Omega-6 plasma fatty acid weight (mg/L)	X	X	X
Omega-6 fatty acids as % of total fatty acid area		X	X
Ratio of Omega-6:Omega-3 as % of total fatty acid area	X		
Ratio of Omega-6:Omega-3 as % of total fatty acid mols	X		
Total proteins (g/dL)	X		
Vitamin E alpha tocopherol, high performance liquid chromatography, (Âµmol/L)	X	X	X
Vitamin B6 via high performance liquid chromatography (ng/mL)		X	X
Vitamin E gamma tocopherol, high performance liquid chromatography, (Âµmol/L)		X	X

Hematology/Liver	Cogntive Decline	Frailty	Cogntive Frailty
Ferritin (ng/mL)	X	X	X
Folate via RIA (ng/mL)	X	X	
Gamma glutamyl transferase (U/L)	X	X	X
GPT (also known as ALT) (U/L)	X	X	
Lymphocytes (n, K/ÂµL)	X		
MCH concentration (MCHC) (g/dL)	X	X	X
Mean corpuscular hemoglobin (MCH) (pg)	X		
Mean corpuscular volume (MCV)	X		
Methylmalonic acid MMA (Âµmol/L)"	X		
Monocytes (%)	X	X	X
Red blood cells (RBC) (n, millions/ÂµL)	X		
Red cell distribution width (RDW) (%)	X	X	X
Vitamin B12 via RIA (pg/mL)	X	X	X
White blood cells (WBC) (n, K/ÂµL)	X	X	X
Hematocrit (%)		X	
Hemoglobin (g/dL)		X	X
Lymphocytes (%)		X	X
Mean corpuscular volume (MCV) (fL)		X	X
Mean platelet volume (MPV) (fL)		X	X
Methylmalonic acid, MMA (Âµmol/L)		X	
Monocytes (n, K/ÂµL)		X	
Neutrophils (%)		X	
Neutrophils (n, K/ÂµL)		X	
Retinol via high performance liquid chromatography (Âµmol/L)		X	X
Soluble transferrin receptor (nmol/L)			X
Lipid Metabolism			
Lipids: HDL cholesterol (mg/dL)	X	X	X
Lipids: total cholesterol (mg/dL)	X	X	
Lipids: triglycerides (mg/dL)	X		
Lipoprotein(a) (mg/dL)	X	X	
Lipids: LDL cholesterol (mg/dL)		X	X
Metabolomics(plasma lipids)			
Fatty acid C16:0 (palmitic) area	X		X
Fatty acid C16:0 as % of total fatty acid area	X	X	X
Fatty acid C16:0 as % of total fatty acid weight	X	X	X
Fatty acid C16:0 (Âµmol/L)		X	
Fatty acid C20:0 (arachidic) area	X		X
Fatty acid C20:0 as % of total fatty acid weight	X	X	
Fatty acid C20:0 weight (mg/L)	X	X	X
Fatty acid C20:0 as % of total fatty acid area		X	X
Fatty acid C20:5 n-3 as % of total fatty acid weight	X		X
Fatty acid C20:5 n-3 weight (mg/L)	X	X	
Fatty acid C20:5 n-3 as % of total fatty acid area		X	X
Fatty acid C22:0 (behenic) area	X		X
Fatty acid C22:0 weight (mg/L)	X	X	
Fatty acid C22:0 as % of total fatty acid area			X
Fatty acid C24:0 (lignoceric) area	X	X	
Fatty acid C24:0 as % of total fatty acid weight	X	X	X
Fatty acid C24:0 as % of total fatty acid area		X	X
Fatty acid C24:0 weight (mg/L)		X	
Endocrine/Hormones			
Blood glucose (mg/dL)	X	X	
C-terminal telopeptide of type-1 collagen (ng/mL)	X	X	X
Estradiol via radioimmunoassay (pg/mL)	X	X	
Free thyroxine, fT4 (ng/dL)	X	X	X
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***	X		X
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	X	X	X
Plasma insulin via RIA (mIU/L)	X	X	X
Thyroid stimulating hormone, TSH (mIU/L)	X	X	X
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)		X	X
Free testosterone (ng/dL), Vermeulen		X	
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)		X	X
Total testosterone (ng/mL)		X	X

Table IV. Protein and clinical marker features by phenotype model II

	Cogntive Decline	Frailty	Cogntive Frailty
Clinical Features			
Age	X	X	X
Anticholinergic Burden	X	X	X
Depression	X	X	X
Level of Education	X		X
Inflammatory/Immunity			
24-hour urinary cortisol (Âµg/24 hours)	X	X	X
Adiponectin via RIA (Âµg/mL)	X	X	X
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	X	X	X
Endogenous secretory receptor for AGEs (ng/mL)	X	X	X
Alpha-1 globulin (%)	X	X	X
Alpha-2 globulin (%)	X		
Alpha-2-macroglobulin (mg/dL)	X	X	X
Beta globulins (%)	X		
C-reactive protein - high sensitivity (Âµg/mL)	X	X	X
C-reactive protein - low sensitivity (Âµg/mL)	X		
Cortisol:DHEAS ratio (based on nmols)	X	X	
Dehydroepiandrosterone sulfate (Âµg/dL)	X	X	X
Erythrocyte sedimentation rate (ESR) (mm/hour)	X	X	X
Fibrinogen (mg/dL)	X		X
Homocysteine via FPIA analysis (Âµmol/L)	X	X	X
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	X	X	X
Interleukin-10 via ELISA (pg/mL)	X	X	
Interleukin-12 via Bio-Plex (pg/mL)	X		X
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	X	X	X
Interleukin-1B via ELISA (pg/mL)	X	X	X
Interleukin-6 via ELISA ultrasensitive (pg/mL)	X	X	X
Interleukin-8 via Bio-Plex (pg/mL)	X	X	X
Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)	X	X	
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	X	X	X
Resistin via EIA (ng/mL)	X	X	X
Retinol via high performance liquid chromatography (Âµmol/L)	X		
Serum cortisol (Âµg/dL)	X	X	X
Soluble CD14 via ELISA (ng/mL)	X	X	X
Soluble IL-6 receptor via ELISA (ng/mL)	X	X	
IL-6 high-sensitivity ELISA calculated from ELISA ultrasensitive (pg/mL)		X	
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	X	X	X
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	X	X	X
TNF-related apoptosis-inducing ligand (pg/mL)	X	X	X
Transforming growth factor-B1 (pg/mL)	X	X	
Tumor necrosis factor-a via multiplex technology (pg/mL)	X	X	X
Uric acid (mg/dL)	X	X	X
Urinary cortisol (Âµg/mL)	X	X	X
Renal/Electrolyte			
24-hour urinary creatinine (mg/24 hours)	X	X	X
Blood urea nitrogen (mg/dL)	X	X	X
Ca++ (mg/dL)	X		
Urinary Ca (mmol/L)	X	X	X
Creatine phosphokinase (U/L)	X	X	X
Creatinine clearance, 24-hr urine (mL/minute)	X	X	X
Cystatin C (mg/L)	X		X
Na+ (mEq/L)	X		
Serum creatinine (mg/dL)	X	X	X
Urinary creatinine (mg/dL)	X		X
Urinary Na (mmol/L)	X	X	X
Urine hemoglobin (mg/dL)	X	X	
Urine proteins (mg/dL)	X	X	X

Nutrient Biomarker	Cogntive Decline	Frailty	Cogntive Frailty
Albumin (%)	X		X
Beta-carotene via high performance liquid chromatography (Âµmol/L)	X	X	X
Lycopene via high performance liquid chromatography (Âµmol/L)	X		X
Omega-3 fatty acids as % of total fatty acid area	X	X	X
Omega-3 fatty acids as % of total fatty acid weight	X	X	
Omega-3 plasma fatty acid weight (mg/L)	X	X	
Omega-6 fatty acids as % of total fatty acid area	X	X	
Omega-6 fatty acids as % of total fatty acid mols	X		
Omega-6 fatty acids as % of total fatty acid weight	X		X
Omega-6 plasma fatty acid weight (mg/L)	X	X	X
Ratio of Omega-6:Omega-3 as % of total fatty acid area	X	X	X
Ratio of Omega-6:Omega-3 as % of total fatty acid mols	X		
Ratio of Omega-6:Omega-3 as % of total fatty acid weight	X	X	
Total proteins (g/dL)	X		
Vitamin B6 via high performance liquid chromatography (ng/mL)	X	X	X
Vitamin E alpha tocopherol, high performance liquid chromatography, (Âµmol/L)	X	X	X
Vitamin E gamma tocopherol, high performance liquid chromatography, (Âµmol/L)	X	X	X
Hematology/Liver			
AST (U/L)	X		
Ferritin (ng/mL)	X	X	
Gamma glutamyl transferase (U/L)	X	X	X
GPT (also known as ALT) (U/L)	X	X	
Hematocrit (%)	X		X
Hemoglobin (g/dL)	X		
Lymphocytes (%)	X	X	X
Lymphocytes (n, K/ÂµL)	X		X
MCH concentration (MCHC) (g/dL)	X	X	X
Mean corpuscular hemoglobin (MCH) (pg)	X		X
Mean corpuscular volume (MCV) (fL)	X	X	
Methylmalonic acid, MMA (Âµmol/L)	X	X	X
Monocytes (%)	X	X	X
Monocytes (n, K/ÂµL)	X	X	X
Neutrophils (%)	X		X
Neutrophils (n, K/ÂµL)	X	X	
Red blood cells (RBC) (n, millions/ÂµL)	X	X	
Red cell distribution width (RDW) (%)	X		
Soluble transferrin receptor (nmol/L)	X		
Vitamin B12 via RIA (pg/mL)	X	X	X
White blood cells (WBC) (n, K/ÂµL)	X	X	X
Folate via RIA (ng/mL)	X	X	X
Lipid Metabolism			
Lipids: HDL cholesterol (mg/dL)	X	X	X
Lipids: LDL cholesterol (mg/dL)	X	X	X
Lipids: total cholesterol (mg/dL)	X	X	X
Lipoprotein(a) (mg/dL)	X	X	X
Metabolomics(plasma lipids)			
Fatty acid C16:0 as % of total fatty acid area	X	X	X
Fatty acid C16:0 as % of total fatty acid weight	X	X	
Fatty acid C16:0 weight (mg/L)	X		X
Fatty acid C16:0 (palmitic) area		X	X
Fatty acid C20:0 (arachidic) area	X		
Fatty acid C20:0 as % of total fatty acid area	X	X	
Fatty acid C20:0 as % of total fatty acid mols	X		
Fatty acid C20:0 as % of total fatty acid weight	X		
Fatty acid C20:0 weight (mg/L)	X	X	
Fatty acid C20:5 n-3 as % of total fatty acid area	X	X	X
Fatty acid C20:5 n-3 as % of total fatty acid weight	X		
Fatty acid C20:5 n-3 cis (eicosapentaenoic, EPA) area	X	X	
Fatty acid C20:5 n-3 weight (mg/L)		X	X
Fatty acid C22:0 (behenic) area	X	X	X
Fatty acid C22:0 as % of total fatty acid area	X	X	
Fatty acid C22:0 as % of total fatty acid weight	X	X	
Fatty acid C22:0 weight (mg/L)	X		X
Fatty acid C24:0 (lignoceric) area	X		
Fatty acid C24:0 as % of total fatty acid weight	X	X	
Fatty acid C24:0 as % of total fatty acid area		X	
Fatty acid C24:0 weight (mg/L)		X	

Endocrine/Hormones	Cogntive Decline	Frailty	Cogntive Frailty
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	X	X	X
Blood glucose (mg/dL)	X	X	X
Urine glucose (mg/dL)			X
C-terminal telopeptide of type-1 collagen (ng/mL)	X	X	X
Estradiol via radioimmunoassay (pg/mL)	X	X	X
Free testosterone (ng/dL), Vermeulen	X	X	X
Total testosterone (ng/mL)	X	X	X
Free thyroxine, fT4 (ng/dL)	X	X	
IGF binding protein-3, serum, immunoradiometric assay (ng/mL)	X		
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***			X
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	X	X	X
Plasma insulin via RIA (mIU/L)	X	X	X
Thyroid stimulating hormone, TSH (mIU/L)	X		X
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	X	X	X

References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56. http://www.ncbi.nlm.nih.gov/pubmed/11253156. Accessed August 27, 2014.
2. NIH, WHO. Global health and aging. http://www.nia.nih.gov/sites/default/files/global_health_and_aging.pdf. Published 2011. Accessed February 7, 2015.
3. Canevelli M, Kelaiditi E. The complex construct of mild cognitive impairment: Be aware of cognitive frailty. *J Frailty Aging*. 2014;3(2):87-88.
4. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2.
5. Wilkins CH, Roe CM, Morris JC, Galvin JE. Mild Physical Impairment Predicts Future Diagnosis of Dementia of the Alzheimer's Type. *J Am Geriatr Soc*. 2013;61(7):1055-1059. doi:10.1111/jgs.12255.
6. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment--a review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12(4):840-851. doi:10.1016/j.arr.2013.06.004.
7. Krall JR, Carlson MC, Fried LP, Xue Q-L. Examining the dynamic, bidirectional associations between cognitive and physical functioning in older adults. *Am J Epidemiol*. 2014;180(8):838-846. doi:10.1093/aje/kwu198.
8. Sargent L, Brown R. Assessing the current state of cognitive frailty: Measurement properties. *J Nutr Health Aging*. 2017;21(2):152-160. doi:10.1007/s12603-016-0735-9.
9. Blazer D, Yaffee K, Liverman C. Cognitive Aging: Progress in Understanding and Opportunities for Action - PubMed - NCBI. Institute of Medicine Of the National Academies. http://www-ncbi-nlm-nih-gov.proxy.library.vcu.edu/pubmed?term=cognitive aging process in understanding opportunities for action&cmd=correctspelling. Published 2015.

Accessed September 13, 2015.

10. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc*. 2000;48(12):1618-1625. http://www.ncbi.nlm.nih.gov/pubmed/11129752. Accessed May 31, 2017.
11. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-1483. doi:10.1111/j.1532-5415.2011.03491.x.
12. Jamsen KM, Bell JS, Hilmer SN, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. *J Am Geriatr Soc*. 2016;64(1):89-95. doi:10.1111/jgs.13877.
13. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept Mot Skills*. 1958;8(3):271-276. doi:10.2466/pms.1958.8.3.271.
14. Ashendorf L, Jefferson AL, Connor MKO, et al. Trail Making Test Errors in Normal Aging, Mild Cognitive Impairment, and Dementia. 2009;23(2):129-137. doi:10.1016/j.acn.2007.11.005.Trail.
15. Ashendorf L, Jefferson AL, Connor MKO, et al. NIH Public Access. 2009;23(2):129-137. doi:10.1016/j.acn.2007.11.005.Trail.
16. Delrieu J, Andrieu S, Cantet C, Cesari M, Ousset P.J., Voisin T, Fougere B, Gillette S, Carrie I and VB. Neuropsychological Profile of "Cognitive Frailty" Subjects in MAPT Study. 2016;116(8):1477-1490. doi:10.14283/jpad.2016.94.
17. Radloff LS. A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas*. 1977;1(3):385-401. doi:10.1177/014662167700100306.
18. Sargent L, Brown R. Assessing the Current State of Cognitive Frailty: Measurement Properties. *J Nutr Health Aging*. 2017;21(2):152-160. doi:10.1007/s12603-016-0735-9.
19. Menon R, Larner AJ. Use of cognitive screening instruments in primary care: the

impact of national dementia directives (NICE/SCIE, National Dementia Strategy). *Fam Pract*. 2011;28:272-276. doi:10.1093/fampra/cmq100.

20. Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. *J Am Acad Nurse Pract*. 2006;18(8):351-360. doi:10.1111/j.1745-7599.2006.00137.x.
21. Folstein, Marshal F., Susan E. Folstein and PRM. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;2.3:189-198. doi:10.1016/j.pcad.2015.11.006.
22. Spering CC, Hobson V, Lucas JA, Menon C V., Hall JR, O'Bryant SE. Diagnostic accuracy of the MMSE in detecting probable and possible alzheimer's disease in ethnically diverse highly educated individuals: An analysis of the NACC database. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(8):890-896. doi:10.1093/gerona/gls006.
23. Nalls MA, McLean CY, Rick J, et al. Diagnosis of Parkinson's disease on the basis of clinical and genetic classification: a population-based modelling study. *Lancet Neurol*. 2015;14(10):1002-1009. doi:10.1016/S1474-4422(15)00178-7.
24. Chen, Tianqi, He, Tong, Benesty, Michael, Khotilovich, Vadim, Tang Y. "xgboost"-Extreme Gradient Boosting. 2017. doi:10.1145/2939672.2939785>.
25. Friedman J, Hastie T, Tibshirani R. Additive logistic regression: a statistical view of boosting (With discussion and a rejoinder by the authors). *Ann Stat*. 2000;28(2):337-407. http://projecteuclid.org/euclid.aos/1016218223. Accessed November 3, 2015.
26. Purcell S. PLINK V1.07. http://pngu.mgh.harvard.edu/purcell/plink/. Published 2009.
27. Purcell, S, Neale, B, Todd-Brown, K, Thomas, L, Ferreira, MAR, Bender, D, Maller, J, Sklar, P, de Bakker, PIW, Daly, MJ, Sham P. PLINK: a toolset for whole-genome association and population-based linkage analysis. *Am J Hum Genet*. 2007;81.
28. Hollingworth P, Harold D, Sims R, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's

disease. *Nat Genet*. 2011;43(5):429-435. doi:10.1038/ng.803.

29. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009;41(10):1088-1093. doi:10.1038/ng.440.
30. Cho S-K, Choi J-M, Kim J-M, et al. AKT-independent Reelin signaling requires interactions of heterotrimeric Go and Src. *Biochem Biophys Res Commun*. 2015;467(4):1063-1069. doi:10.1016/j.bbrc.2015.09.167.
31. Matteini AM, Walston JD, Fallin MD, et al. Transcobalamin-II variants, decreased vitamin B12 availablility and increased risk of frailty. *J Nutr Heal Aging*. 2008;12(5):303-308. doi:10.1007/BF02982659.
32. Korostishevsky M, Steves CJ, Malkin I, Spector T, Williams FM, Livshits G. Genomics and metabolomics of muscular mass in a community-based sample of UK females. *Eur J Hum Genet*. 2016;24(2):277-283. doi:10.1038/ejhg.2015.85.
33. Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters: Relevance to Precision Medicine. *Genomics, Proteomics Bioinforma*. 2016;14(5):298-313. doi:10.1016/j.gpb.2016.03.008.
34. Niemi M. Role of OATP transporters in the disposition of drugs. *Pharmacogenomics*. 2007;8(7):787-802. doi:10.2217/14622416.8.7.787.
35. Hu X, Pickering EH, Hall SK, et al. Genome-wide association study identifies multiple novel loci associated with disease progression in subjects with mild cognitive impairment. *Transl Psychiatry*. 2011;1:e54. doi:10.1038/tp.2011.50.

MANUSCRIPT 4:

Anticholinergic Burden is a Predictor of Cognitive Decline, Physical Frailty and Cognitive Frailty

Abstract:

OBJECTIVES: To investigate whether anticholinergic burden scores are associated with three phenotypes; cognitive decline, physical frailty and cognitive frailty.

DESIGN: Retrospective cohort study.

SETTING: InCHIANTI study, Chianti geographic area of Tuscany, Italy.

PARTICPANTS: Population of 1,453 adults aged 20-102 years.

MEASUREMENTS: Anticholinergic burden was calculated using the Anticholinergic Cognitive Burden Scale (ACB); neuropsychological tests included the Mini-Mental Status Examination and Trail Making Test A and B (TMT); frailty is defined by the Cardiovascular Heart Study, and cognitive frailty is defined by the International Consensus Group (I.A.N.A/ I.A.G.G). Anticholinergic burden was examined as a predictor for all phenotypes using logistic and ordinal regression models adjusting for covariates.

RESULTS: Anticholinergic burden is associated with cognitive decline, frailty, and cognitive frailty. The odds of having cognitive decline increased by 1.21 points (95% CI = 1.06-1.37, p< .001), the odds of being frail increased by 1.33 (95% CI = 1.18-1.50, p< .001), and the odds of cognitive frailty increased by 1.36 (95% CI = 1.21-1.54, p< .001). Population modeling results indicated the ACB score as one of the stronger predictors for cognitive decline, physical frailty and cognitive frailty with areas under the receiver operating curve of 0.88 and 0.86 respectively. Anticholinergic burden association with cognitive decline as measured by TMT adjusted for covariates was not significant; in

contrast the relationships of ACB with cognitive frailty measured by the TMT-A and TMT-B were statistically significant (both p< .001).

CONCLUSION: Our data support a relationship between anticholinergic burden and cognitive decline, further strengthen the association with physical frailty and provide new evidence for an association with cognitive frailty.

Key words: anticholinergic; burden; frailty; cognition; cognitive frailty, xgboost models

INTRODUCTION

The burden of multiple diseases perpetuates the increased consumption of medications. Older adults are especially susceptible to polypharmacy and medication adverse risks due to declines in physiological reserve, reduced liver and kidney function required to metabolize medications and increased central nervous system sensitivity to medications[1]. A decline in physiologic reserve coupled with the use of anticholinergic medicines increases the risk for impaired functional and cognitive performance[2–5]. Anticholinergic medications block the neurotransmitter acetylcholine in the central and peripheral nervous system, selectively blocking acetylcholine from binding to the muscarinic receptors in the brain[6,7]. Additionally, there is growing evidence that anticholinergic affect older adults in greater proportion due to the ability of these medications to permeate the blood-brain barrier [2,8]. Anticholinergic burden is considered to be the cumulative effect on an individual taking one or more medications with anticholinergic activity confounded by age-related pharmacokinetic and pharmacodynamic changes[1,5,6]. Higher anticholinergic burden can occur with specific medications known to have high anticholinergic activity or with an accumulation of

medications with low, medium, and high anticholinergic burden [9,10]. An increase in circulating anticholinergic activity causes inhibition of acetylcholine transmission to the central nervous system suggesting a cholinergic deficit that is hypothesized to be involved in causing impaired cognitive and motor function[11]. There are substantial differences in methods for measuring anticholinergic burden and no standard or consensus on how to quantify burden. Systematic reviews on the current anticholinergic burden scales have all shown an association between higher anticholinergic burden and adverse outcomes; cohort studies have mainly focused on cognitive and physical outcomes[5,9].

Less understood is the effect anticholinergic burden has on physical frailty[5]. Although there is evidence to support the relationship between physical function and higher anticholinergic burden, the methods for measuring physical functioning have focused on activities of daily living (ADLs) and instrumental activities of daily living (IADLs) without controlling for confounding health factors contributing to the outcome[5,9]. Changes in ADLs and IDLs can be affected by multiple psychosocial and physiological factors that are not a direct measure of disease. A recent study found a significant association of anticholinergic burden with gait and impaired balance measured by the timed-up and go(TUG), functional reach(FR), and grip strength(GS) assessments[12]. Frailty as defined by the Cardiovascular Heart Study (CHS) is a disease process and a non-normal process of aging[13]. The CHS frailty phenotype includes decline in lean body mass, strength, endurance, balance, walking performance, and low activity[13]. Additionally, there is growing evidence for a shared relationship between cognitive decline and physical

frailty[14–16]. The International Consensus Group organized by the International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) which convened in 2013 to identify related domains of physical frailty and cognition, termed this relationship as "cognitive frailty"[15].

Studies thus far have primarily used the Mini-Mental State Examination (MMSE) to measure cognitive decline which as a composite test does not capture distinct areas of cognitive function such as processing speed, attention, psychomotor speed, abstraction, flexibility, ability to execute and modify a plan of action[17]. The goal of this study was to use logistic and ordinal regression models to determine the relationship between anticholinergic burden and three phenotypes: cognitive decline defined by the MMSE and Trail Making Tests, part A and B, physical frailty, and cognitive frailty. Additionally, we included anticholinergic burden in a separate population based predictive model study to determine if anticholinergic burden is predictive of cognitive decline, frailty, and cognitive frailty. The population predictive model incorporates additional measures of disease such as protein and genomic biomarkers thereby evaluating ACB with confounding disease processes (Sargent et al., 2018 in preparation).

METHODS

Data

The subjects in the present study were participants in *Invecchiaare in Chianti* (Aging in Chianti, "InCHIANTI Study"). InCHIANTI was a prospective population based study of 1,453 adults aged 20-102 randomly selected from two towns in Tuscany, Italy using a multistage stratified sampling at baseline from 1998 to 2000[18]. All aspects of the

InCHIANTI research were approved by the ethics committees at the institutions responsible for data collection, and this secondary study was approved by the ethics committee at *Centre de recherché Clinique du CHUS*, project #547. During the initial InCHIANTI baseline 90-minute interview, information was collected on demographic and clinical characteristics for the three phenotypes and baseline medications taken regularly in the prior 15 days to determine anticholinergic burden. The name of the drug, preparation and dosage were collected from medication boxes or bottles including over the counter vitamins, food supplements, sleeping pills, or laxatives. Initial medication information was converted from the brand name to the active ingredient.

Measures

For the current study, a total of 2,883 baseline medications were used to analyze the anticholinergic burden effect on 1,155 individuals ≥65 years of age with cognitive decline, physical frailty, and cognitive frailty. Currently, there are 7 expert-based anticholinergic rating scales for which quantification of the tool is based on expert opinion, and published data, and includes both genders with a mean age of 65 years or older[4,9]. The Anticholinergic Cognitive Burden (ACB) scale is the most validated scale for evaluating adverse health outcomes including cognitive and physical function[4,10]. The anticholinergic properties of each medication were quantified using the ACB scale based on each drug's serum anticholinergic activity[19]. To determine ACB scores, each participants' medications were assigned points (0, 1, 2, 3) according to the published 2012 update and summed for a total anticholinergic burden score. Higher scores indicate higher anticholinergic properties. An example of medications with ACB scores

include: Amitriptyline = 3, Amantadine = 2, and Atenolol = 1. The ACB scale has identified medications with anticholinergic properties that have correlated with a 0.33-point decline in the MMSE score over 2 years [20]. The neuropsychological tests included the MMSE as a test of general cognition and Trail Making Test, part A and B (TMT). The TMT testing was included to further explore distinct areas of cognitive function. TMT-A is used to assess psychomotor speed; scoring is based on time in seconds to completion with a score range of 0 to 300 seconds[21]. TMT-B is used to assess the executive functioning domain (any individual time over the limit of 300-600 seconds was included as 300)[21]. Normative data for time to complete the TMT tests in seconds is stratified by age and education[22]. Additionally, the neuropsychological profile for individuals with cognitive frailty is considered to be different from those with frailty or cognitive decline alone with recent findings of lower performance on TMT tests[22,23]. The Center for Epidemiologic Studies Depression Scale (CES-D) self-report scale was used to measure depressive symptoms. The CES-D has been used extensively in epidemiologic studies for depression and physical function displaying similar reliability, validity, and factor structure across a diverse demographic[24].

Frailty measures included the number of frailty symptoms with performance test data. Frailty as defined by the cardiovascular health study (CHS), allows for a continuous scoring system versus a nominal system because it can capture the multidimensional nature of frailty[14]. The components have concurrent and predictive validity with hazard ratios (HR) ranging from 1.82-4.46 ($p < 0.05$) for outcomes that include incident disease, hospitalization, falls, disability and mortality in community-dwelling older adults[13]. The

InCHIANTI criteria for frailty defined unintentional weight loss as losing weight not related to diet, classified the values of body mass index, strength, walking speed and height based on all subjects ≥65 years and used two questions of the CES-D for the definition of exhaustion.

Phenotypic Classification

The MMSE score and the TMT part A and B was used to define two phenotypic classifications for cognitive decline and cognitive frailty. All participants completed the MMSE to define cognitive decline and cognitive frailty. Absence of cognitive decline is defined as a score of 24-30 on the education adjusted MMSE [25–27]. Frailty is characterized by individuals with one or more of the Frailty criteria[13]. Cognitive frailty is defined as individuals with cognitive decline and one or more of the frailty criteria[23].

- Robust with no physical frailty and absence of cognitive decline
- Robust with no physical frailty with cognitive decline (MMSE = ≤ 23)
- Frail (≥ 1 criterion) and absence of cognitive decline
- Frail (≥ 1 criterion) and cognitive decline (MMSE = ≤ 23)

Additional phenotypic classification included mild, moderate, or severe disease defined by the MMSE to characterize 24-30 as normal cognition, a score of 23-18 as moderate cognitive decline (combined mild and moderate degree of impairment), and a score ≤ 17 as cognitive impairment[25,26]. Frailty is characterized by the CHS criteria cut offs and cognitive frailty is defined as individuals with both criteria[13].

- Robust with no physical frailty and absence of cognitive decline
- Robust with no physical frailty with mild cognitive decline (MMSE = 18-23)
- Robust with no physical frailty with cognitive impairment (MMSE = ≤ 17)
- Pre-frail (1-2 criteria) and absence of cognitive decline
- Frail (≥ 3 criteria) and absence of cognitive decline

- Pre-frail (1-2 criteria) and with mild cognitive decline (MMSE = 18-23)
- Frail (≥ 3 criteria) and with mild cognitive decline (MMSE = 18-23)
- Pre-frail (1-2 criteria) and cognitive impairment (MMSE = ≤ 17)
- Frail (≥ 3 criteria) and cognitive impairment (MMSE = ≤ 17)

Additional neuropsychological testing (TMT-A and B) was used to define cognitive decline and as part of the definition of cognitive frailty[23]. TMT-A and B cut off scores for cognitive decline are based on cut off norms established by Ashendorf et al., 2008.

- Robust with no physical frailty and absence of cognitive decline
- Robust with no physical frailty with Cognitive Decline (both Trail A ≥ 78 and Trail B ≥ 106)
- Frail (≥ 1 criterion) and Cognitive Decline (both Trail A ≥ 78 and Trail B ≥ 106)
- Frail (≥ 1 criterion) and Cognitive Decline (both Trail A ≥ 78 and Trail B ≥ 106)

Numbers of participants were insufficient for statistical analysis to include cognitive decline or cognitive frailty categorized into levels of mild, moderate, and severe phenotype with the TMT.

Statistical Analyses

We used logistic and ordinal regression to investigate the relationship between anticholinergic burden and all three outcomes. Covariates were selected to control for potential confounding effects. Demographic covariates included gender, age, and level of education. Disease processes considered as confounders included baseline diagnosis of: baseline dementia (n=82), vascular dementia (n=41), depression (n=412), and Parkinson's disease (n=16) and were included in the models as binary covariates.

In addition to the logistic and ordinal regression, ACB score was included in separate population based predictive model analyses with 298 additional predictors; these

included protein, clinical, and genetic markers of disease. Modeling of the dynamic interactions between confounding disease processes determined the strength of the relationship and predictive value for anticholinergic burden and disease outcome. Predictive modeling via ensemble learning using xgboost allowed for better accuracy by building multiple models, each of which learns to improve upon the errors of a prior model producing a final model that reflects the complex interactions between biological processes (i.e., protein and genetic biomarkers) on cognitive decline and frailty. Parameters for the xgboost model included a stepsize eta of = "0.3", rounds = 5-200, max depth = "10", nthread = "12", objective = "binary:logistic", evaluation metric = "auc", gamma = default ="0" to control the number of trees and prevent overfitting[28]. Details on the population predictive model results and statistical methods beginning with model development in the InCHIANTI dataset used to train and test classifiers, complete internal validation, and calibration of the model are available in a separate publication (Sargent et al., 2018 in preparation). Bivariate analyses included non-parametric Kruskal-Wallis t-tests to assess differences between groups; medians and maximum quantiles are reported for healthy controls and three phenotypes. Next, Bonferroni correction was conducted to adjusted for multiple comparisons; adjusted p-values are reported. All statistical analyses were carried out using R V. 3.2.1.. R packages included 'glm2'-Fitting Generalized Linear Models, 'Ordinal'-Regression Models for Ordinal Data, and 'xgboost'-Extreme Gradient Boosting[28–30].

RESULTS

Medication data was complete for 1,155 participants; table 1 describes the characteristics of the participants by phenotype and the percent of individuals with a total daily ACB score, which ranged from 0-9. Distribution of anticholinergic burden score by phenotype and differences between health control and phenotype are shown in Table 2. Tables displaying results for the top predictive features from the xgboost predictive modeling study are published elsewhere (Sargent et al., 2018 in preparation)

There was a significant association between anticholinergic burden and cognitive decline ($p = 0.02$), frailty ($p < .001$) and cognitive frailty ($p < .001$). Additionally, the odds of having cognitive decline increased by 1.21 points (95% CI = 1.06-1.37, $p < .001$), the odds of being frail increased by 1.33 (95% CI = 1.18-1.50, $p < .001$), and odds of cognitive frailty increased by 1.36 (95% CI = 1.21-1.54, $p < .001$). Model fit for all three phenotypes using the Wald chi-square test statistic was associated with a p-value of $< .001$, indicating that the overall effect rank was significant. Logistic and ordinal regression results are presented in Table 3 and 4. Results from the population predictive model are ranked by gain, which is a metric based on each feature's contribution in the model. When comparing top features to other features in the model, the greater the gain the more important the feature is for prediction of the outcome. Anticholinergic burden was the top 4% predictor out of 105, 14% of 101, and 70% of 93 selected features during the classifier build, with AUCs ranging from 0.81-0.88 for the outcomes frailty, cognitive frailty, and cognitive decline respectively measured with the MMSE (Sargent et al., 2018 in preparation).

Similarly, there was a significant association found between ACB score and cognitive decline when measured with the TMT-A and TMT-B without adjusting for covariates. When including the covariates age, gender, and baseline dementia individually in the models with only ACB score for TMT-B or age and gender for TMT-A, anticholinergic burden was no longer significant. Additionally, this was true when covariate-by-ACB interaction terms were included; none of the interaction terms was statistically significant (all $p > 0.2$). There was a significant association found between ACB score and cognitive frailty, as measured with TMT-A ($p= 0.007$) and TMT-B ($p < .001$). Model fit for cognitive frailty TMT-A and TMT-B using the Wald chi-square test statistic was associated with a p-value of $< .001$. Logistic regression results for cognitive decline and cognitive frailty measured with TMT are shown in Table 3. In the population predictive modeling results, anticholinergic burden was the top 32% of 149 and 40% of 110 predictors, with AUCs ranging from 0.86-0.83 for the outcomes cognitive decline and cognitive frailty respectively measured with the TMT-A and B (Sargent et al., 2018 in preparation).

DISCUSSION

Participants for all phenotypes were older with a greater proportion of females; few completed a high school education. Participants with cognitive decline, frailty, and cognitive frailty took more medications than individuals without these phenotypes. There were smaller numbers of participants with an ACB score > 4 with most scores above zero clustered between 1-4; suggesting that an ACB score of 1-4 range is sufficient to show association.

Logistic and ordinal regression results found in this study continue to support a relationship between anticholinergic burden and cognitive decline, further strengthen the association with physical frailty, and provide new evidence for an association with cognitive frailty. The population predictive model results with xgboost, showed anticholinergic burden to be a significant predictor for all three phenotypes (Sargent et al., 2018 in preparation).

Although frailty and cognitive decline have been shown to be related, both diseases have long been studied separately. The findings from this study provide the first evidence for a relationship between anticholinergic burden and cognitive frailty, affecting both cognitive speed and executive functioning. The study results show a relationship between anticholinergic burden and cognitive decline when measured with the MMSE but no relationship was observed when cognitive decline was measured with the TMT-A and TMT-B unless cognitive frailty was present. Another study found lower executive function composite scores on the Wechsler Memory Scale-Revised, Logical Memory Immediate Recall, and TMT-B test in a small sample (n=402) of individuals taking anticholinergic medications over 1 year with additional findings of increased brain atrophy and clinical decline[31]. Additionally, previous studies have shown a relationship between anticholinergic burden and transitions between frailty states and increased mortality for individuals who were robust at baseline; with every unit increase in burden being associated with a 73% risk of transition from robust to pre-frail. Further these studies showed that anticholinergic burden is associated with poor mobility, functional decline, psychomotor slowing, and falls[5,12,32].

A limitation of the study is that this was a secondary analysis of existing data. As such, the medications are from an international database and represent a specific population of individuals and do not consider potential differences in prescribing patterns throughout the world. Additionally, confounding may be a factor; for which it becomes difficult to distinguish between the effects of the medications and the disease process. Therefore, further research with adequately powered randomized controlled trials or prospective cohort studies with follow up periods in the clinical setting are needed to distinguish medication effect from disease progression. These findings highlight the need for longitudinal studies focused on understanding which domains of memory are affected.

Future research should focus on methods for detecting high risk individuals in the clinical setting, the relationship between Apolipoprotein E ε4 and anticholinergic medications, and whether anticholinergic medications are a modifiable risk factor for the prevention of cognitive decline and physical frailty. Identification of reversible causes for cognitive and physical impairment is critical for the aging population.

Clinicians need to be aware of these findings and review cumulative anticholinergic burden in robust and vulnerable individuals and minimize the overall anticholinergic burden before symptoms of cognitive and physical decline are detectible. Until a better understanding of the implications that these findings have in the clinical setting, caution must be applied since medications with anticholinergic effects are used to treat many chronic diseases, such as congestive heart failure and hypertension. These findings

encourage new research and may lead to effective interventions for the prevention and treatment of cognitive and physical decline in an aging population.

CONCLUSION

Anticholinergic burden is associated with both cognitive decline and physical frailty. Efforts to better understand the epigenetic effects, sum dose effect, and identify individuals in clinical settings who may require anticholinergic medication discontinuation are important next steps to prevent anticholinergic burden induced outcomes.

Table 1. Characteristics of participants by phenotype

	Cognitive Decline (MMSE)	Frailty (CHS)	Cognitive Frailty (MMSE)	Cognitive Decline (TMT-A)	Cognitive Decline (TMT-B)	Cognitive Frailty (TMT-A)	Cognitive Frailty (TMT-B)
Phenotype (n)	(n=369)	(n=595)	(n=257)	(n=525)	(n=634)	(n=302)	(n=325)
Age,							
mean(SD)	80 (8.7)	78 (7.9)	82 (7.4)	76 (7.7)	72 (9.0)	78 (7.4)	76 (6.9)
Gender, %							
Male (n)	24.0 (120)	42.8 (214)	31.9 (82)	37.1 (195)	41.9 (266)	35.1 (106)	36.0 (117)
Female (n)	37.6 (249)	58.2 (381)	68.1 (175)	62.9 (330)	58.0 (368)	64.9 (196)	64.0 (208)
Education, %							
No Education	56.9 (210)	39.3 (234)	58.8 (151)	42.3 (222)	25.4 (161)	46.4 (140)	30.8 (100)
Elementary - Secondary	39.6 (146)	52.4 (312)	37.7 (97)	53.1 (279)	66.2 (420)	49.3 (149)	61.5 (200)
≧ High School	1.4 (5)	7.1 (42)	1.9 (5)	3.2 (17)	7.6 (48)	3.3 (10)	7.4 (24)
Medication use							
Number of drugs							
0 meds	73	83	34	107	141	35	51
1 to 4	228	305	169	334	408	201	208
5 to 7	56	100	45	70	73	53	56
≧8	12	23	9	14	12	13	10
mean(SD)							
Control	2.18 (2.01)	1.75 (1.76)	2.15 (2.02)	1.95 (1.87)	1.77 (1.73)	1.85 (1.82)	1.68 (1.66)
Phenotype	2.69 (2.19)	2.89 (2.21)	3.00 (2.16)	2.44 (2.12)	2.23 (2.02)	3.01 (2.20)	2.79 (2.19)
p-value*	<.001	<.001	<.001	<.001	<.006	<.001	<.001

Notes: SD = standard deviation, * two tailed t-Test with means and SD

Table 2. Distribution of anticholinergic burden score by phenotype and difference between health control and phenotype

% (n)	Cognitive Decline	Frailty	Cognitive Frailty	Cognitive Decline		Cognitive Frailty	
ACB	MMSE (n=296)	CHS (n=512)	MMSE (223)	Trail A (n=418)	Trail B (n=493)	Trail A (n=267)	Trail B (n=274)
0	47.0% (139)	51.0% (261)	42.2% (94)	57.9% (242)	62.9%(310)	50.2% (134)	55.5% (152)
1	23.6% (70)	22.9% (117)	25.1% (56)	20.6% (86)	20.1% (99)	22.5% (60)	21.2% (58)
2	14.5% (43)	11.9% (61)	16.1% (36)	10.8% (45)	7.9% (39)	13.1% (35)	9.9% (27)
3	10.1% (30)	8.8% (45)	11.2% (25)	6.7% (28)	5.5% (27)	8.2% (22)	7.7% (21)
4	2.7% (8)	3% (16)	3.1% (7)	2.4% (10)	2.4% (12)	3.4% (9)	3.6% (10)
5	1.0% (3)	1.4% (7)	.9% (2)	1.0% (4)	1.0% (5)	1.5% (4)	1.8% (5)
6	.7% (2)	.8% (4)	.9% (2)	.5% (2)	.2% (1)	.7% (2)	.4% (1)
9	.3% (1)	.2% (1)	.4% (1)	.2% (1)	(0)	.4% (1)	(0)
Control	0[6]	0[5]	0[6]	0[5]	0[4]	0[5]	0[4]
Phenotype	1[9]	0[9]	1[9]	0[9]	0[6]	0[9]	0[6]
p-value*	<.001	<.001	<.001	<.001	.042	<.001	<.001

Table 3. Generalized linear regression results: association between anticholinergic burden and phenotypes

Phenotype	(n)	Beta Coef	Std. Error	95%CI	p-value
Cognitive Decline (MMSE)	375	0.21	0.07	0.08-0.36	.004
Frailty (CHS)	595	0.31	0.07	0.17-45	<.001
Cognitive Frailty (MMSE)	257	0.26	0.08	0.11-0.41	<.001
Cognitive Decline (Trail A)	545	0.20	0.14	0.14-0.11	.14
Cognitive Decline (Trail B)	703	0.21	0.14	0.10-.47	.12
Cognitive Frailty (Trail A)	302	0.27	0.08	0.11-.43	<.001
Cognitive Frailty (Trail B)	325	0.38	0.09	0.19-0.57	<.001

Table 4. Ordinal regression results: association between anticholinergic burden and phenotype

Models	Phenotypes (MMSE & CHS)	n
1	**Cognition**	
	Cognitive Decline	501
	Cognitive Impairment	101
2	**Frailty**	
	Frail	88
	Pre-frail	507
3	**Cognitive Frailty**	
	Cognitive Decline & Frail	55
	Cognitive Decline & Pre-frail	217
	Cognitive Impaired & Frail	11
	Cognitive Impaired & Pre-frail	76

Models	Phenotype	Beta Coef	Std. Error	Odds Ratio	95%CI	p-value
1	Cognition	0.19	0.07	1.21	1.07-1.37	<.001
2	Frailty	0.29	0.06	1.33	1.87-1.50	<.001
3	Cognitive Frailty	0.31	0.06	1.36	1.21-1.54	<.001

References

1. Jansen P a. F, Brouwers JRBJ. Clinical Pharmacology in Old Persons. *Scientifica (Cairo)*. 2012;2012:1-17. doi:10.6064/2012/723678.
2. Salahudeen MS, Chyou T-Y, Nishtala PS. Serum Anticholinergic Activity and Cognitive and Functional Adverse Outcomes in Older People: A Systematic Review and Meta-Analysis of the Literature. *PLoS One*. 2016;11(3):e0151084. doi:10.1371/journal.pone.0151084.
3. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-1483. doi:10.1111/j.1532-5415.2011.03491.x.
4. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. 2015. doi:10.1186/s12877-015-0029-9.
5. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: A systematic review. *Age Ageing*. 2014;43(5):604-615. doi:10.1093/ageing/afu096.
6. Nishtala PS, Salahudeen MS, Hilmer SN. Anticholinergics: theoretical and clinical overview. *Expert Opin Drug Saf*. 2016;15(6):753-768. doi:10.1517/14740338.2016.1165664.
7. Salahudeen MS, Nishtala PS. Examination and Estimation of Anticholinergic Burden: Current Trends and Implications for Future Research. *Drugs and Aging*. 2016;33(5):305-313. doi:10.1007/s40266-016-0362-5.
8. Collamati A, Martone AM, Poscia A, et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. *Aging Clin Exp Res*. 2016;28(1):25-35. doi:10.1007/s40520-015-0359-7.
9. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. *J Am Geriatr Soc*. 2015;63(1):85-90. doi:10.1111/jgs.13206.
10. Campbell NL, Boustani M, Lane K, et al. Use of anticholinergics and the risk of cognitive impairment in an African-American population. *Neurology*. 2010;75:152-159. http://ovidsp.ovid.com/ovidweb.cgi?T=JS%7B&%7DPAGE=reference%7B&%7DD=emed11%7B&%7DNEWS=N%7B&%7DAN=70990267.
11. Staskin DR, Zoltan E. Anticholinergics and central nervous system effects: are we confused? *Rev Urol*. 2007;9(4):191-196. http://www.ncbi.nlm.nih.gov/pubmed/18231615%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2213887.
12. Zia A, Kamaruzzaman S, Myint PK, Tan MP. Anticholinergic burden is associated with recurrent and injurious falls in older individuals. *Maturitas*. 2016;84:32-37. doi:10.1016/j.maturitas.2015.10.009.
13. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56. http://www.ncbi.nlm.nih.gov/pubmed/11253156. Accessed August 27, 2014.
14. Sargent L, Brown R. Assessing the Current State of Cognitive Frailty: Measurement Properties. *J Nutr Health Aging*. 2017;21(2):152-160. doi:10.1007/s12603-016-0735-9.
15. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2.

16. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci*. 2014;69(12):1536-1544. doi:10.1093/gerona/glu117.
17. Salthouse TA. What cognitive abilities are involved in trail-making performance? *Intelligence*. 2011;39(4):222-232. doi:10.1016/j.intell.2011.03.001.
18. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems Contributing to the Decline in Ability to Walk: Bridging the Gap Between Epidemiology and Geriatric Practice in the InCHIANTI Study. *J Am Geriatr Soc*. 2000;48(12):1618-1625. doi:10.1111/j.1532-5415.2000.tb03873.x.
19. Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. *Alzheimer's Dement*. 2013;9(4):377-385. doi:10.1016/j.jalz.2012.02.005.
20. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-1483. doi:10.1111/j.1532-5415.2011.03491.x.
21. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept Mot Skills*. 1958;8(3):271-276. doi:10.2466/pms.1958.8.3.271.
22. Ashendorf L, Jefferson AL, Connor MKO, et al. Trail Making Test Errors in Normal Aging, Mild Cognitive Impairment, and Dementia. 2009;23(2):129-137. doi:10.1016/j.acn.2007.11.005.Trail.
23. Delrieu J, Andrieu S, Cantet C, Cesari M, Ousset P.J., Voisin T, Fougere B, Gillette S, Carrie I and VB. Neuropsychological Profile of "Cognitive Frailty" Subjects in MAPT Study. 2016;116(8):1477-1490. doi:10.14283/jpad.2016.94.
24. Radloff LS. A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas*. 1977;1(3):385-401. doi:10.1177/014662167700100306.
25. Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. *J Am Acad Nurse Pract*. 2006;18(8):351-360. doi:10.1111/j.1745-7599.2006.00137.x.
26. Folstein, Marshal F., Susan E. Folstein and PRM. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;2.3:189-198. doi:10.1016/j.pcad.2015.11.006.
27. Spering CC, Hobson V, Lucas JA, Menon C V., Hall JR, O'Bryant SE. Diagnostic accuracy of the MMSE in detecting probable and possible alzheimer's disease in ethnically diverse highly educated individuals: An analysis of the NACC database. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(8):890-896. doi:10.1093/gerona/gls006.
28. Chen, Tianqi, He, Tong, Benesty, Michael, Khotilovich, Vadim, Tang Y. "xgboost"-Extreme Gradient Boosting. 2017. doi:10.1145/2939672.2939785>.
29. Marschner I. "glm2"-Fitting GEneralized Linear Models. https://cran.r-project.org/web/packages/glm2/glm2.pdf. Accessed May 11, 2017.
30. Christensen R. "Ordinal"- Regression Models for Ordinal Data. https://cran.r-project.org/web/packages/ordinal/ordinal.pdf. Accessed May 11, 2017.
31. Risacher SL, McDonald BC, Tallman EF, et al. Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. *JAMA Neurol*. 2016;332(7539):455-459. doi:10.1001/jamaneurol.2016.0580.
32. Jamsen KM, Bell JS, Hilmer SN, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. *J Am Geriatr Soc*. 2016;64(1):89-95. doi:10.1111/jgs.13877.

33. Boccardi V, Baroni M, Paolacci L, et al. Anticholinergic burden and functional status in older people with cognitive impairment: Results from the ReGAl project. *J Nutr Health Aging*. 2017;21(4):389-396. doi:10.1007/s12603-016-0787-x.

SUMMARY

This dissertation consists of four manuscripts; 1) an integrative review of the measurements for cognitive frailty, 2) a systematic review of the clinical and biological markers for cognitive decline and physical frailty, 3) an innovative population predictive model analyses establishing biological plausibility for cognitive frailty, 4) and a new finding of anticholinergic burden as a predictor of frailty and cognitive frailty. The results from this study establish a foundation for an understanding of the underlying biological mechanisms for the relationship between cognitive decline and physical frailty and found anticholinergic burden as one of the top predictors for frailty and cognitive frailty. In seeking to explore the importance and applicability of these results it is critical that others continue to replicate the model results. To accompany manuscript 3, help with replication and extension of this work, the code has been made publically available for the population predictive model.

Implications

The results from this dissertation have several implications for future research and have a potential for translation into practice. Through the lens of Complex Systems Theory, this dissertation begins to unravel the complexity behind a geriatric syndrome providing biological plausibility to cognitive frailty. Geriatric syndromes such as cognitive frailty are highly multifactorial and variable across the aging spectrum lending themselves to new ways of investigation. As Bryne (1998) notes: Not only can the complex not always be derived, even in principle from the less complex,… we can often

only understand the simpler [cognitive frailty] in terms of its origins in the more complex (p. 16). By using the framework of complex systems theory and an innovative Boosted trees machine learning technique (xgboost) we determined key biological mechanism for a dysregulation across multiple systems as the potential cause for cognitive frailty. The future to understanding complex geriatric syndrome should include a systems approach by using highly accurate statistical modeling to identify measurable markers. There were multiple biological associations determined by the study results that should be investigated further. One of the interesting findings is anticholinergic burden in conjunction with the association of *SLCO1B1* as predictors for cognitive frailty. SLO1B1 is an important pharmacokinetic gene that is involved in the removal of drug compounds and transport of drug metabolites at the blood-brain barrier(1). It has been implicated as a marker of lean muscle mass loss and may affect the distribution of drugs into the central nervous system(1,2).

Limitations

The limitations of the dissertation research included the use of a small homogenous sample with large numbers of biomarkers creating limitations for translation into clinical research. Additionally, the study was retrospective using existing data. The analyses used a randomly assigned training subset to validate the model within a relatively homogenous InCHIANTI cohort. Additionally, no external validation of the model was completed. The model would be strengthened by external validation in a in a mixed ethnic and demographic age range. Through the process of completing this dissertation I have gained invaluable expertise in statically modeling of a large dataset and have

learned skills in the field of bioinformatics. The dissertation required me to learn bash and R coding, along with learning how to manipulate genetic data in PLINK.

Future research

There are several areas for future research based on this dissertation work. There is a need to test and validate the model in a second more ethnically diverse population before translation into clinical practice. Further investigate anticholinergic burden as an epigenetic cause of cognitive frailty by exploring the relationship between putative genetic markers discovered in the model analyses (i.e. *SLCO1B1* and *COMT*). Some of these findings can be translated into clinical studies. Research focusing on methods for detecting high-risk individuals in the clinical setting and descriptive studies to understand the scope and effect of cognitive frailty are needed. Intervention studies are essential to understanding the role of nutrition and/or physical activities have on neuroinflammatory cytokines and other system markers for cognitive frail individual's progression. Additionally, further work can be done on whether anticholinergic medications are a modifiable risk factor for the prevention of cognitive frailty. Identification of reversible causes for cognitive and physical impairment is critical for the aging population.

References

1. Oshiro C, Mangravite L, Klein T, Altman R. PharmGKB very important pharmacogene: SLCO1B1. Pharmacogenet Genomics [Internet]. 2010 Mar [cited 2017 Jun 24];20(3):211–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19952871
2. Niemi M. Role of OATP transporters in the disposition of drugs. Pharmacogenomics [Internet]. 2007 Jul [cited 2017 Jun 10];8(7):787–802. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18240907
3. Byrne, D. (1998). Complexity Theory and the Social Sciences: An Introduction. London: Routledge Press.

APPENDICES

MANUSCRIPT 1: Supplemental documents

Appendix A. Search Strategies – Conducted January 30, 2015

Database	Added Filters	Time Period	Terms	Results
PubMed	English, Human	1983-Present	(((((“Frailty”[TIAB] OR “Frail”[TIAB] OR “Physical Frailty”[TIAB] OR "Cognitive Frailty”[TIAB])))) OR "Frail Elderly"[Mesh])) AND ((Alzheimer*[TIAB] OR Presenile Dementia*[TIAB] OR Senile Dementia*[TIAB] OR Mild Cognitive Impairment*[TIAB] OR Mild Neurocognitive Disorder*[TIAB] OR Mild Neurocognitive Disorder*[TIAB] OR Early Dementia*[TIAB] OR Early Onset Dementia*[TIAB] OR Cognitive Decline[TIAB] OR Mild Cognitive Impairment*[TIAB]))	322
CINAHL	English, Human	1992-Present	(MH "Alzheimer's Disease") OR ("Alzheimer*" OR "Presenile Dementia*" OR "Senile Dementia*" OR "Mild Cognitive Impairment*" OR "Mild Neurocognitive Disorder* "OR "Mild Neurocognitive Disorder*" OR "Early Dementia*" OR "Early Onset Dementia*" OR "Cognitive Decline" OR "Mild Cognitive Impairment*") AND (MH "Frailty Syndrome") AND “Frailty” OR “Frail” OR “Physical Frailty” OR “Cognitive Frailty”	76
PsycInfo	None	2005-Present	(Title:("Frailty" OR "Frail" OR "Physical Frailty" OR "Cognitive Frailty") OR Abstract: ("Frailty" OR "Frail" OR "Physical Frailty" OR "Cognitive Frailty")) AND ((Index Terms: ("Cognitive Impairment")) OR Title: ("Alzheimer*" OR "Presenile Dementia*" OR "Senile Dementia*" OR "Mild Cognitive Impairment*" OR "Mild Neurocognitive Disorder* "OR "Mild Neurocognitive Disorder*" OR "Early Dementia*" OR "Early Onset Dementia*" OR "Cognitive Decline" OR "Mild Cognitive Impairment*") OR Abstract: ("Alzheimer*" OR "Presenile Dementia*" OR "Senile Dementia*" OR "Mild Cognitive Impairment*" OR "Mild Neurocognitive Disorder* "OR "Mild Neurocognitive Disorder*" OR "Early Dementia*" OR "Early Onset Dementia*" OR "Cognitive Decline" OR "Mild Cognitive Impairment*"))	164
Dissertation & Thesis	None	1984-Present	All ("Alzheimer*" OR "Presenile Dementia*" OR "Senile Dementia*" OR "Mild Cognitive Impairment*" OR "Mild Neurocognitive Disorder* " OR "Mild Neurocognitive Disorder*" OR "Early Dementia*" OR "Early Onset Dementia*" OR "Cognitive Decline" OR "Mild Cognitive Impairment*") AND all ("Frailty" OR "Frail" OR "Physical Frailty" OR "Cognitive Frailty")	18
Web of Science	English	1991-Present	(("Alzheimer*" OR "Presenile Dementia*" OR "Senile Dementia*" OR "Mild Cognitive Impairment*" OR "Mild Neurocognitive Disorder* "OR "Mild Neurocognitive Disorder*" OR "Early Dementia*" OR "Early Onset Dementia*" OR "Cognitive Decline" OR "Mild Cognitive Impairment*")) *AND* **TOPIC:** (Frailty OR Frail OR Physical Frailty OR Cognitive Frailty)	560

Table 3. Data Extraction and Measurement Properties

Author & Title	Theoretical Framework	Population Assessed	Frailty Assessment Instruments¥	Cognitive Assessment Instruments	Reliability	Validity	Feasibility	Principal Results	Level of Evidence*
Shimada et al. 2013 Combined Prevalence of Frailty and Mild Cognitive Impairment (MCI) in a Population of Elderly Japanese People	Indices of cognitive frailty were discussed	Country: Japan N= 5104 56 and older non-demented persons enrolled in Obu Study of Health Promotion for the Elderly (OSHPE)-community dwelling Exclusion criteria: history of Parkinson disease, stroke, or MMSE <18	CHS criteria: frailty phenotype defined by 3 or more of the 5 domains: Mobility: timed walk of 2.4 meter (3.2 feet) (cut off <1.0 m/s) Strength: Grip strength dynamometer (cut off male: <26 kg, female: <17kg) Physical activity: Self-report (no tool listed) Endurance: self-report & included questions from GDS® Nutrition: self-reported weight loss in previous 2 years	MCI criteria: Subjective memory complaint, cognitive impairment, no functional dependency and no clinical criteria for dementia MMSE (cut off <23 impaired) (Folstein, Folstein, and McHugh 1975) National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT)	§ NCGG-FAT – test-retest reliability (ICC = 0.764 to 0.942)	Frailty and MCI Odds Ratio (OR) (2.0, 95% CI 1.5-2.5 p <0.01) Reported values from original study: § NCGG-FAT – External validity (Pearson r = 0.496 to 0.842)	Time intensive to measure both domains MMSE- 11 questions; 5-10 minutes to perform NCGG-FAT-effective for assessing multidimensional cognitive screening; easily administered using tablet technology; instructions on display, training to use tool is limited; knowledge of neuropsychiatric measures not extensive, with a battery of neuropsychiatric test completed in 20-30 min	Frailty is strongly associated with cognitive impairment Additional Findings: Increasing age and Frailty p for trend <0.01, MCI p < 0.05 Education associated with frailty p <0.01, MCI p <0.01 Frailty higher in women than men p <0.05, MCI no differences for gender	1b Cross-sectional study

Kulmala et al. 2014 Association between Frailty and Dementia: A Population-Based Study	Indices of cognitive frailty were discussed	Country: Finland N=781 76-100 years, mean age 82 non-demented community dwelling Population based sample from the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS)	CHS criteria: frailty phenotype defined by 3 or more of the 5 domains: Slowness- timed maximal 10-meter (32.8 feet) walking test (no cut off mentioned) Weakness-grip strength dynamometer (highest of 2 measurements used) Low physical activity- Grimby scale Poor endurance and energy- self-report question Shrinking/sarcopenia- weight loss >5% over previous year	MMSE (cut off <25 impaired) (Folstein, Folstein, and McHugh 1975)	Not reported	Age & gender-adjust models support these findings Frail, pre-frail, & robust associated percentages with clinically diagnosed dementia: (52%, 19% and 11%, $p < 0.01$); vascular dementia (9%, 3%, and 1% $p = 0.001$); and Alzheimer's (30, 15, and 9%, $p < 0.001$) Frailty & cognitive impairment (OR 7.4, 95% CI 4.2-13.2) Frailty & clinically diagnosed dementia (OR 6.5%, 95% CI 3.6-11.8) Frailty & vascular dementia (OR 6.7, 95% CI 1.6-27.4) Frailty & Alzheimer's (OR 3.2, 95% CI 1.7-6.2)	Time intensive to measure both domains, clinical diagnosis, and imaging can be expensive Clinical translation properties for detection of cognitive frailty unclear	Frailty is associated with cognitive impairment Frail individuals were 7.4 times more likely to have cognitive impairment, 6.5 times more likely to have clinically diagnosed dementia; 6.7 times more likely to have vascular dementia, and over 3.2 times more likely to have Alzheimer's disease than those who were robust	1a Cross-sectional study

Buchman et al. 2014 Brain pathology contributes to simultaneous change in physical frailty and cognition in old age	Indices of cognitive frailty were discussed	Country: U.S. N=2167 Religious Order Study (ROS) and Memory and Aging Project	CHS criteria: Physical frailty Grip strength: dynamometer Gait: time to walk 8 feet Body composition was based on body mass index (BMI). Fatigue: two questions derived from a modified version of the Center for Epidemiologic Studies–Depression Scale	19 cognitive tests scored and reviewed by neuropsychologist (Wilson et al. 2002) Five cognitive domains: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability	Not reported	Slope measures for physical frailty and cognition (N = 1,794, 82.8%) Frailty and cognition controlling for number of chronic health conditions (r= -0.708, p<0.001); demographic variables/race (r= -0.68, p < 0.001) Gait and cognition (r= -0.67, p<0.001) Grip strength and cognition (r= - 0.51, p<0.001) BMI and cognition (r = -0.17 p=0.003) Association of brain pathologies with rates of change of frailty and cognition (r = -0.708, p <0.001)	Time and resource intensive Clinical translation of the cognitive frailty construct are unclear	Strong linear relationship between rates of change in frailty and cognition Relationship between frailty and cognition remained when controlling for demographic variables and race and number of chronic disease Strongest correlation between gait speed and cognition Presence of macroinfarcts, AD pathology, and nigral neuronal loss were each with rapid progression frailty and cognitive decline	1b Population-based, longitudinal study (10 years)

Rolfson et al. 2013 An assessment of neurocognitive speed in relation to frailty	Indices of cognitive frailty were discussed	Country: Canada N=164 Mean age 74 Baseline cohort of community based older adults; Non-demented population from the Oxford Project to Investigate Memory and Aging (OPTIMA)	Modified CHS criteria: Weight loss: "Have you lost a lot of weight in the last six months?" ("some change" or "considerable change") Subjective exhaustion: "Do you find you have recently lost energy and it is harder to get things done?" Physical activity: Immobility as defined by either (a) informant history (Does he or she have trouble getting about…? "some difficulty" or "great difficulty") or (b) physical examination suggesting the need for a mobility aid or another person. Slow walking speed: Physical Examination evidence of slow ambulation Weakness: Physical Examination evidence of suboptimal arm or leg power (Grade 4/5 or less) Frailty Index (FI): 70/83 items used Modified Edmonton Frail Scale (EFS): 5 items used in analysis (number of medications, depression, weight loss, urinary incontinence and clock drawing test	MMSE (cut off not mentioned) Neurocognitive speed (NCS) cut off <18 pattern Comparison test (PCT) <11 Letter comparison test (LCT) <7	Not reported	NCS (DV) and MMSE, FI, EFS (IVs): (OR 1.19, 95% CI 1.04-1.36, p = 0.012); OR 0.87, 95% CI 0.81-0.95, p=0.001), OR: 0.94, 95% CI 0.59-1.49, p=0.779) Modified EFS and NCS: (OR 0.94, 95% CI 0.59-1.49, p= 0.779)	Time and resource intensive Clinical translation properties unclear	Strong correlation between NCS and frailty. Association was evident with FI and NCS NCS was not associated with a modified CHS or modified EFS. Modified CHS was significant when the MMSE was taken out	1b Population-based, longitudinal study (3 years)

Oosterveld et al. 2014 The influence of co-morbidity and frailty on the clinical manifestation of patients with Alzheimer's disease	Indices of cognitive frailty were discussed	Country: Netherlands N=213 Clinical Course of Cognition and Comorbidity-Dementia Study (4C-Dementia study) 46-93 years old; mean 75 with probable (n=193) or possible (n=20) diagnosis of Alzheimer's Disease	Modified CHS: Scoring range from 0-5; 3 or higher = frail; 2 = pre-frail Measurement details were not listed; based on definition of Fried: Weight loss Activity level Emotion/energy level Grip strength Gait velocity: 15 feet walk test	Baseline measure: MMSE score ≥10, CDR[£] score 0.5-2 (0.5- very mild, 1-mild, 2-moderate) Study neuropsychological test domains: episodic memory, working memory, executive functioning, mental speed, perception, and verbal fluency	Not reported	Frailty association with poorer cognitive performance Able to distinguish between frail and non-frail patients with Alzheimer's Disease (AD) (β= -0.31, P < 0.001)	Time and resource intensive Clinical translation properties unclear	Higher frailty score was highly correlated with poorer cognitive performance and poorer clinical manifestations of Alzheimer's disease Association between co-morbidity, frailty, and clinical manifestation of Alzheimer's disease	1b Cross-sectional Population-based study

McGough et al. 2013 Dimensions of physical frailty and cognitive function in older adults with amnestic mild cognitive impairment	Indices of cognitive frailty were discussed	Country: U.S. N= 201 Analysis of baseline data from the Resources and Activities for Life-Long Independence (RALLI) Study 70 and older, sedentary, and classified as having amnestic-MCI	Modified CHS criteria: Physical slowness: gait speed calculating energy expenditure (MET levels) cut off: < 383 Kcals/week men & <270 Kcals/week women Physical activity: Self-report using the Physical Activity Scale for the Elderly (PASE) Strength: Grip strength – cut off points stratified by sex and BMI Gait speed: 8-foot timed walk (best of two) – cut off stratified by sex and height Weight loss – assessed as a covariate, BMI calculated using baseline height/weight	Baseline Neuropsychological testing: MMSE, Wechsler Memory Scale-Revised (WMS-R), Logical memory (LM) I & II, CDR[£] Study neuropsychological tests: severity measured with ADAS-Cog Attention and executive function: Trail Making A & B (TMT-A) Memory: WMS-R Logical Memory I (LM1), Word recall sub-item on ADAS-Cog *GDS: depression screening	Not reported	Reported on adjusted measures: Gait speed and cognitive function: ADAS-Cog (β= - 0.19, p <0.008) Executive function: TMT-A (β = -0.23, p= 0.001) TMT-B (β = -0.20, p=0.006), Word Recall (β = -0.18, p=0.02) and LM1(β=0.14, p =0.04) Grip strength and attention: TMT-A (β= -0.16, p=0.008) Physical activity and executive function (β = -0.18 p < 0.02) and word recall (β = 0.17, p =0.02)	Time and resource intensive Clinical translation properties unclear	Slower gait speed was associated with elevated severity of cognitive impairment Gait speed associated with individual cognitive domains: attention, executive function, word recall, & memory Physical activity associated with the individual cognitive domain of executive function Grip strength associated with the individual cognitive domain of attention Grip strength not associated with severity of cognitive impairment	1b Cross-sectional study Baseline data from RTC

Alencar, et al. 2013 Frailty and cognitive impairment among" community-dwelling elderly	Indices of cognitive frailty were discussed	Country: Brazil N= 182 Community-dwelling 65 years or older; with and without cognitive impairment Exclusion criteria: bed-ridden, restricted to wheelchair, terminal stage, hearing or vision impairment that would affect testing, stroke, severe stage Parkinson's disease, severe dementia (grade 3 on CDR[£])	CHS criterion: frailty phenotype defined by 3 or more of the 5 domains: Weight loss: Unintentional weight loss ≥ 4.5 kg Strength: Grip strength (adjusted gender & BMI) Fatigue: Two questions on the Center for Epidemiologic Studies Depression scale Slowness: time in seconds to walk 4.6 meters (14.8 feet-adjusted gender & BMI) Physical activity: Short version – Minnesota Leisure Time Activity Questionnaire Nutritional status: BMI with cut off: <22kg underweight; ≥22kg and ≤ 27kg ideal range; >27kg overweight Functional status: Katz scale: basic activities of daily living (BADL) instrumental activities of daily living (IADLs), Advanced activities of daily living	Cognitive function assessed in two-stage sequential testing: MMSE Cut off: 17/18 illiterate participants, 20/21 1-4 yrs of school, 23/24 5-8yrs of school, 25/26 9+ yrs of school (Nitrini and Caramelli 2007) When MMSE positive for cognitive changes then Brief Cognitive Screening Battery (BCSB) was completed [£]CDR used for classification for degree of dementia: score 0.5-2 (0.5- very mild, 1-mild, 2-moderate, 3-severe) *GDS-15 – depression symptoms in individuals without cognitive impairment and Cornell Depression Scale in Dementia for individuals with cognitive impairment	Not reported	Mean difference at baseline MMSE - 12 months MMSE for non-frail, pre-frail, frail: (1.31, 0.49, 0.77 p = 0.005) Change in CDR baseline - 12 months CDR for non-frail, pre-frail, frail: (4 n=43, 17 n=104, & 7 n=35 p=0.393) Relative risk (RR) with [£]CDR non-frail, pre-frail, frail: (RR = 1.0, 1.7 95% CI 0.63-0.49, 2.1 95% CI 0.68-6.7, p = 0.393) Relative risk with MMSE non-frail, pre-frail, frail: (RR = 1.0, 3.5 95% CI 1.51-8.4, 4.6 95% CI 1.9-11.2)	Time and resource intensive Clinical translation properties unclear	Risk of incidence and rates of progression for frailty and cognitive were significant when using the MMSE but not with the CDR	1b Prospective cohort study (12 months)

Gray et al. 2013 Frailty and incident dementia	Indices of cognitive frailty were discussed	Country: U.S. N=2619 From the Adult Changes in Thought (ACT) study 65 and older without dementia at baseline Exclusion criteria: History of stroke, Parkinson's disease, or any component of frailty missing	CHS criteria: ≥3 = frail, 1-2 = pre-frail, 0 not frail Weakness: grip strength-average of 3 attempts (cut off by sex and BMI) Slowness: walking speed-10 foot walk – 2 walks average time Physical activity: self-report based on type of activity and length of time Weight loss: loss of 7.5% of body weight since previous visit Exhaustion: 10-item Center for Epidemiological Studies Depression (CES-D)	Cognitive Abilities Screening Instrument (CASI; 13) 40 item, 100-point global cognitive functioning test (cut off 86) 1-hr neurocognitive battery: clock drawing, verbal fluency, Mattis Dementia Rating Scale, Boston naming, verbal paired associations and recall, logical memory and recall, Word List Memory, Constructional Praxis and recall, Trails A and B, and Information and Comprehension subtest items	Not reported	Frailty and all cause dementia Hazard Ratio (HR) (1.20, 95% CI 0.85-1.69) Frailty and Alzheimer's (HR 1.08, 95% CI 0.74-1.57) Frailty and non-Alzheimer's (HR 2.57, 95% CI 1.08-6.11) Gait speed and Alzheimer's disease (AD): (HR 2.13, 95% CI 1.09-4.16) CASI: Sensitivity 95.6%; specificity 92.0%	Time and resource intensive Clinical translation properties unclear	Frailty is associated with a 2.57 fold increase risk for non-AD dementia Individual frailty components were not significantly related to risk for dementia or AD. Slow gait speed was the only significantly related component to increased risk for non-AD dementia.	1b Population-based, longitudinal study (mean 6.5 years)

Solfrizzi et al. 2013 Frailty syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Aging	Indices of cognitive frailty were discussed	Country: Italy N=2581 From the Italian Longitudinal Study on Aging (ILSA) 65-84 years; no dementia at baseline Exclusion: severe sensorial deficit, bedridden, use of wheelchair, dizziness, severe osteoarthritis, Parkinson's disease, or stroke	Modified CHS criteria: Weight loss: Unintentional weight loss > 5kg in past year (additional question: "Do you think that your clothes are wide?" Exhaustion: ®GDS score ≥ 10 and negative answer to the question: "Do you feel full of energy?" Weakness: Negative chair stand test: Inability to stand from a chair unaided, or without using the arms (standardized by sex and body mass index) Slowness: Time ≥ 7 seconds spent to walk 5m (standardized by sex and height) Physical activity: structured questionnaire developed in the CHIANTI Study (Patel et al. 2006) Levels of physical activity in the past year. ADL and IADL tasks & ®GDS item "Do you practice physical activity?" Motor performance: six tests: 3 explored dynamic balance and coordination; 3 assessed static balance	MMSE score of > 15 were considered to make plausible ®GDS scores	Motor performance Intra-observer reliability: Dynamic balance: timed & counted tests 0.071 Tandem gain errors: 0.80 reaction time & .089-0.96 for chair stand, rapid step ups, standing on one leg, step length, and walking speed Intra-observer agreement; 0.63 gait – 0.82 abnormal turn ADL & IADL intra-observer agreement Cohen's Kappa=0.80 Inter-observer agreement; gait: 0.38 step asymmetry – 0.82 abnormal turn	Frailty association with overall dementia (HR 1.85, 95% CI 1.01-3.40) Frailty association with AD (HR 0.62, 95% CI 0.20-1.89) Frailty association with vascular dementia (HR 2.68, 95% CI 1.16-7.17)	Time and resource intensive Clinical translation properties unclear	Frailty syndrome at baseline was associated with a greater risk of developing overall dementia with strong associations with vascular dementia Relationship between grip strength and risk of AD	1b Population-based, longitudinal study (3.9 years)

Robertson et al. 2014 Cognitive function in the prefrailty and frailty syndrome	Indices of cognitive frailty were discussed	Country: Republic of Ireland N=4,649 Adults 50 and older Exclusion: stroke, Parkinson's disease, taking antidepressants, or severe cognitive impairment MMSE <18	CHS criteria: Poor grip strength: Two readings from dominant hand – mean strength Slow gait speed: GAITRite portable electronic walkway system (16-foot) walkway with extra 2.5 m at each end for acceleration/deceleration Low levels of physical activity: short form International Physical Activity Questionnaire Kcals per week Unintentional weight loss survey: "In the past year, have you lost 10lbs or more in weight when you were not trying to." Exhaustion: Used 2 items from the 20-item Center for Epidemiological Studies Depression (CES-D)	Global cognition MMSE & MoCA Executive function: visual reasoning, color trails Test B, & verbal fluency Memory: visual recall, visual recognition, immediate, delayed, & self-rated Attention: color trails Test A & sustained attention to response task Processing speed: Cognitive reaction time	Not reported	Components of frailty and domains of cognitive function: Exhaustion & global cognition (β- 0.18, p < 0.008) Slow gait & executive function (β- 0.20, p < 0.008), attention (β – 0.25, p < 0.008), and processing speed (β- -0.16, p < 0.008) Weak grip & global cognition (β- 0.26, p < 0.008) and executive function (β-0.14, p < 0.008)	Time and resource intensive Clinical translation properties unclear	Cognitive function is related to pre-frailty and frailty Gait speed and grip strength were associated with executive function, processing speed, and attention. These results were further validated with evidence that frail individuals had lower cognitive scores than pre-frail and robust.	1b Cross-sectional study

Han et al. 2014 Association of cognitive impairment with frailty in community-dwelling older adults	Indices of cognitive frailty were discussed	Country: South Korea N=10,388 Adults 65 and older, data from the 2008 Living Profiles of Older People Survey	CHS criteria: Weight loss: Unintentional weight loss of more than 5kg in past 6 months Exhaustion: Self-reported fatigue or depressive symptoms Low Physical Activity: Defined as energy expenditure due to physical activity in the lowest quintile in the last week Gait speed: Slowest quintile for the 2.5-m-walk speed (adjusted for height by gender) Grip strength: Lowest quintile (based on gender's body mass index)	Modified version of the Korean version of the MMSE (MMSE-KC) Cognitive impairment was defined as > 1.5 SD below age, gender, and education-specific mean scores	Not reported	MMSE-KC associated with higher odds of pre-frail (OR=1.27, 95% CI 1.04-1.55 in men; OR=1.25, 95% CI 1.02-1.53 in women) and frail (OR = 1.81, 95% CI 1.25-2.60 in men; OR = 1.69, 95% CI 1.25-2.30 in women) Higher cognitive function specific domains scores associated with lower likelihood of frailty by gender: Men: attention (OR =0.72, 95% CI 0.58-0.89), recall (OR = 0.89, 95% CI 0.80-0.98), judgement (OR = 0.80, 95% CI 0.64-0.99) Women: language repetition (OR = 0.83 95% CI 0.73-0.95) and visual construction (OR = 0.82 95% CI 0.70-0.96)	Time intensive to measure both domains Clinical translation properties unclear	Cognitive impairment is associated with pre-frail and frailty Higher scores in specific domains of cognitive function were identified as having a lower association with frailty; several were gender specific	1b Cross-sectional study

* OCEBM Levels of Evidence Working Group. "The Oxford Levels of Evidence 2". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/?s=levels+of+evidence.
§ Results reported from original study
¥ Operational definition terms were reported in the table as written in the original study
® Geriatric Depression Scale (GDS)
£ Clinical Dementia Rating (CDR)

THE JOURNAL OF NUTRITION
HEALTH & AGING

Editorial Office :
Carine Giry
International Department
SERDI Edition
43 Chemin del Prat
31320 Auzeville-Tolosane - France
Fax : 33 5 61 75 11 28

April 19, 2017

The JNHA gives permission to Lana Sargent to publish the article the dissertation compendium «**Assessing the Current State of Cognitive Frailty: Measurement Properties**»

SERDI EDITION
320 Rue Saint-Honoré, 75001 Paris - FRANCE. Fax: + 335 61 75 11 28
Email: serdi@serdi-publisher.com
www.serdi-publisher.com

MANUSCRIPT 2: Supplemental documents

Table I. Clinical and biomarkers results

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Abdullah et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	213	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-40								
(Aberg et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	80	Cognitive Decline Only	Alzheimer's disease, MCI		Insulin like growth factor protein (IGF-2)	Insulin like growth factor protein Binding Protein (IGFBP-2)							
(Adamis et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	142	Cognition Decline & Frailty	General cognitive decline	Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Insulin like growth factor protein (IGF-1)	IL-1 βeta	IL-1 Alpha						
(Adriaensen et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	415	Cognition Decline & Frailty	General cognitive decline	Physical Function	IL-6	CRP/hs-CRP	IL-8	Alcohol intake	Low level education				
(Aguilar et al., 2014)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	348	Cognitive Decline Only	Alzheimer's disease, MCI		ApoE-4 single allele								
	1b	Longitudinal Study	214	Cognitive Decline Only	MCI progression to AD		ApoE-4 single allele								
(Albrecht et al., 2015)	1a	Longitudinal Study	1112	Cognitive Decline Only	MCI progression to AD		ApoE-4 single allele								
(Alcolea et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	226	Cognitive Decline Only	MCI		Aβeta-42	t-tau	p-tau	YKL-40 (neuroinflammation or Chitinase-3 ChI3L3)					
(Al-Turki, Boston, McKirdy, & Barker, 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	470	Cognitive Decline Only	Alzheimer's disease		Body mass index	Alcohol intake							
(Alvarez-Ríos et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	592	Frailty (pre-frail & frail)		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Propeptide of type I procollagen (PINP)	C-terminal Cross-linked telopeptide of type I collagen (Beta CTX)	Parathyroid hormone (PTH)	Vitamin D (25(OH)D)	Propeptide of type I procollagen (PINP)				
(Andersson et al., 2008)	1b	Longitudinal Study	40	Cognitive Decline Only	MCI progression to AD		p-tau								
(Annweiler, Bataille, et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	43	Frailty only		Fatigue,Sarcopenia,Physical Activity	Beta 2-microglobulin (B2M)								
(Annweiler, Schott, et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1190	Cognition Decline & Frailty	General cognitive decline	Physical Function	Vitamin D (25(OH)D)	Chronic Disease 2 or more	Depression						
(Apostolova et al., 2015)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	400	Cognitive Decline Only	Alzheimer's disease		IL-6	Clusterin	ApoE-genotype	Brain derived neurotrophic factor (BDNF)	IL-13	TNF-alpha			
(S. Li, Okonkwo, Albert, & Wang, 2013)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	139	Cognitive Decline Only	MCI progression to AD		ApoE-4 two alleles	Aβeta 1-42	p-tau	P-tau181/Aβeta-42					
(Armstrong et al., 2014)		In Vitro	50	Cognitive Decline Only	Alzheimer's disease		Rab3	Rab7	EEA1	LAMP-1	LAMP-2	LC3			
(Aschenbrenner et al., 2015)	1b	Longitudinal Study	238	Cognitive Decline Only	MCI progression to AD		Aβeta-42	t-tau							
(Ashton et al., 2015)	1a	Longitudinal Study	78	Cognitive Decline Only	Alzheimer's disease		alpha 2-macroglobulin (A2M)	Fibrinogen gama-chain (FGG)	Complement factor H (CFH) protein 1						
(Atti et al., 2006)	1b	Longitudinal Study	1139	Cognitive Decline Only	General cognitive decline		Anemia								
(Auyeung et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1489	Frailty only		Gait,Sarcopenia,Grip Strength	Total Testosterone (TT)	Estradiol/Estrogen							
(Baldeiras et al., 2010)	1b	Longitudinal Study	70	Cognitive Decline Only	MCI progression to AD		Uric Acid	malondialdehyde (MDA)	Vitamin E	Oxidative stress markers /Total antioxidant status (TAS)	Protein carbonyls	NO2 + NO3			
(Bambo et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	56	Cognitive Decline Only	Alzheimer's disease		Ocular measures								
(Bambo et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	114	Cognitive Decline Only	Alzheimer's disease		Ocular measures								
(Bartali et al., 2006)	1b	Longitudinal Study	643	Frailty only		Physical Function	Vitamin B6	Cobalamin deficiency (B12)	Selenium						
(D. Baylis et al., 2013)	1b	Longitudinal Study	254	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	WBC	ESR	Neutrophils	Monocytes	Lymphocytes	Albumin	T4	DHEAS	Cortison/DHEAS ratio
(Daniel Baylis et al., 2014)	1b	Longitudinal Study	367	Frailty only		Sarcopenia,Grip Strength	IL-1beta	IL-6	Cortisol	DHEAS (dehydroepiandrosterone sulphate)	Cortisol/DHEAS ratio				
(Beasley et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	24417	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Calibrated protein intake - Food Frequency Questionnaire (FFQ)								
(Beasley et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	134961	Frailty only		Grip Strength,Physical Function	Calibrated protein intake - Food Frequency Questionnaire (FFQ)								
(Beauchet et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	934	Cognition Decline & Frailty	General cognitive decline	Gait,Grip Strength	Medication (Psychoactive drugs)	BMI		BMI					
(Berr, Balansard, Arnaud, Roussel, & Alpérovitch, 2000)	1b	Longitudinal Study	1166	Cognitive Decline Only	General cognitive decline		Oxidative stress markers /Total antioxidant status (TAS)	Selenium							
(Bertens, Knol, Scheltens, & Visser, 2015)	1b	Longitudinal Study	284	Cognitive Decline Only	MCI progression to AD		Aβeta 1-42	t-tau							
(Blain et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	220	Frailty only		Gait,Sarcopenia,Grip Strength,Physical Function	BMI	Creatinine	IL-6	CRP/hs-CRP	Insulin like growth factor protein (IGF-1)	Vit D	Total cholesterol	LDL	
(K Blennow et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	572	Cognitive Decline Only	Alzheimer's disease		Aβeta1-42/ Aβeta1-40 ratio	Aβeta 1-42	Aβeta 1-40						
(Kaj Blennow et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	53	Cognitive Decline Only	Alzheimer's disease		t-tau	Aβeta-42	phosphoTau181 (P-tau181)						
(Borroni et al., 2004)	1b	Longitudinal Study	48	Cognitive Decline Only	MCI progression to AD		Amyloid precursor protein (APPr)								
							Composite Score: Pyridoxal 5-phosphate (B6), Thiamin (B1), Riboflavin (B2), Folate (B9) Ascorbic acid (vitamin C), -Tocopherol (vitamin E), Cobalamin (B12), 25-Hydroxyvitamin D	Composite Score: trans linolelaidic acid (18:2w-6t), Trans-linolelaidic acid (18:2w6t)	Composite Score: Arachidonic acid (20:4-6), gama-Linolenic acid (18:3w6)						
(Bowman et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	104	Cognitive Decline Only	Alzheimer's disease										
(Bretsky et al., 1999)	1b	Longitudinal Study	195	Cognitive Decline Only	Alzheimer's disease		ApoE-4 two alleles	ApoE-4 single allele							
(Brys et al., 2009)	1b	Longitudinal Study	66	Cognitive Decline Only	MCI progression to AD		P-tau231	P-tau231/Aβeta-42/40 ratio	T-tau/Aβeta-42/40 ratio	t-tau	Aβeta-42/ Aβeta-40	Isoprostane (IP)			
(Breitling, Müller, Stegmaier, Kliegel, & Brenner, 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1322	Cognitive Decline Only	Alzheimer's disease		Cellular prion protein (PrPc)	BMI	Alcohol intake						

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
K Buerger et al., 2002)	1b	Longitudinal Study	162	Cognitive Decline Only	Alzheimer's disease, MCI		p-tau	P-tau231	ApoE-genotype						
(Katharina Buerger et al., 2002)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	192	Cognitive Decline Only	Alzheimer's,MCI,Frontal Temporal Dementia (FTD),Lewy Body Dementia (LBD),Vascular Dementia		P-tau231	P-tau231							
(Busch et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1245	Cognition Decline & Frailty	General cognitive decline	Gait,Grip Strength,Physical Activity	Education	IADL	ADL	Income	Chronic Disease 2 or more				
(Woodward et al., 2017)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	566	Cognitive Decline Only	Alzheimer's disease		Olfactory measures								
(Cankurtaran et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	2262	Cognitive Decline Only	Alzheimer's disease		Blood pressure	Nutrient biomarker patterns (NBPs)	Uric Acid	Homocysteine (tHcy)	Albumin (ALB)				
(Canon & Crimmins, 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	867	Cognition Decline & Frailty	General cognitive decline	Sarcopenia	CRP/hs-CRP								
(Cheung, Nguyen, Au, Tan, & Kung, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1145	Frailty only		Grip Strength	eGFR	TSH	Chronic Disease 2 or more	Anemia	History of falls in past 12 months				
(Chiu et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	60	Cognitive Decline Only	Alzheimer's disease, MCI		Aβeta 1-42	Aβeta1-42/ Aβeta1-40 ratio							
(Chin et al., 2008)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	466	Cognitive Decline Only	General cognitive decline		Homocysteine (tHcy)								
(Cho, Kivimäki, Bower, & Irwin, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	4847	Frailty only		Fatigue	CRP/hs-CRP	IL-6	Composite Score: CRP and IL-6						
(Roe et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	247	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42	t-tau	phosphoTau181 (P-tau181)	t-tau/ Aβeta-42	P-tau181/Aβeta-42				
	1b	Longitudinal Study	213	Cognitive Decline Only	Alzheimer's disease		Aβeta42	t-tau	phosphoTau181 (P-tau181)	t-tau/ Aβeta-42	P-tau181/Aβeta-42				
(Cohen et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	3694	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Composite Score: CRP, TG, IL-6, WBCs, Uric acid, HDL, GGT Glucose, Albumin, RBCs, Hematocrit, Alk. Phos, neutrophils, total protein, lymphocytes, chloride, hemoglobin, creatinine, ferritin, albumin								
(Cohen-Manheim et al., 2015)	1b	Longitudinal Study	507	Cognitive Decline Only	General cognitive decline		GlycA								
(Collerton et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	845	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity(CHS/Rockwood measures)	IL-6	TNF-alpha	CRP/hs-CRP	Neutrophils	Albumin (ALB)	memory/naive B cell ratio	CD8		
(Craig-Schapiro et al., 2011)	1b	Longitudinal Study	333	Cognitive Decline Only	MCI (top 15 predictors-listed)		A-beta42, MMP-10, Cystatin-C, MCP-2, NT-proBNP, MIF, IGFBP-2, TRAIL-R3, FAS, TNF, p-tau181, Cortisol, Resistin, Insulin, ApoA1, p-tau181, Fibrinogen								
	NA	In Vitro	333	Cognitive Decline Only	Alzheimer's disease		IL-17E	IL-7	ApoA1	Fibrinogen					
(Deschamps et al., 2002)	1b	Longitudinal Study	103	Cognitive Decline Only	General cognitive decline		BMI	IADL							
(Devanand et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	39	Cognitive Decline Only	MCI		Aβeta 1-42/ Aβeta 1-40 ratio	Aβeta-42							
(Doecke et al., 2012)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	247	Cognitive Decline Only	Alzheimer's disease		Insulin like growth factor protein (IGF-2)	Pancreatic peptide (PP)	Carcinoembryonic antigen	Cortisol	Homocysteine (tHcy)	Vascular cell adhesion molecule1	Albumin	Hemoglobin,Calcium,Interleukin 17 ,Beta2 microglobulin (B2M), CD40, Macrophage inflammatory protein 1 alpha, APOE e4, Epidermal growth factor receptor	
(Doets et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	2203	Cognitive Decline Only	General cognitive decline		Cobalamin deficiency (B12)	Folate							
(Dregan, Stewart, & Gulliford, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	8780	Cognitive Decline Only	General cognitive decline		BMI	Systolic pressure							
(Drey et al., 2013)	1b	Randomized control study	69	Frailty only		Sarcopenia	C-terminal Agrin Fragment (CAF)								
(Dumurgier et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	52	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42	p-tau181/tau ratio							
(Elosua et al., 2005)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1104	Frailty only		Physical Function	ESR	Uric Acid	Fibrinogen	IL-6	CRP/hs-CRP	IL-1βeta	IL-1 RA		
(Emanuele et al., 2005)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	152	Cognitive Decline Only	Alzheimer's disease		Soluble receptor for advanced glycation end products (sRAGE)								
(Stomrud et al., 2010)	1b	Longitudinal Study	37	Cognitive Decline Only	General cognitive decline		Aβeta 1-42	phosphoTau181 (P-tau181)	ApoE-4 single allele	t-tau					
(Feeney et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	4453	Cognitive Decline Only	General cognitive decline		Macular pigment (MP) is comprised of the carotenoids lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ) carotenoids are also present in the brain, and evidence suggests a close correlation between retinal and brain concentrations								
(Bouwman et al., 2007)	1b	Longitudinal Study	105	Cognitive Decline Only	Alzheimer's,MCI,Memory Complainers		Aβeta 1-42	phosphoTau181 (P-tau181)	t-tau						
(Fleisher et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	54	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42	t-tau	phosphoTau181 (P-tau181)						
(Anne M. Fagan et al., 2007)	1b	Longitudinal Study	139	Cognitive Decline Only	Alzheimer's disease, MCI		t-tau/ Aβeta-42	P-tau181/Aβeta-42							
(A. M. Fagan et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	492	Cognitive Decline Only	Late-Onset Alzheimer Disease (LOAD),Familial Alzheimer's Disease		Aβeta 1-42	Aβeta1-42/ Aβeta1-40 ratio	t-tau	phosphoTau181 (P-tau181)	Aβeta1-42/t-tau ratio				
(Forlenza et al., 2010)	1b	Longitudinal Study	258	Cognitive Decline Only	MCI progression to AD		Aβeta 1-42	p-tau	t-tau	ApoE-4 single allele					
(Noel G. Faux et al., 2011)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	1112	Cognitive Decline Only	Alzheimer's disease		Homocysteine (tHcy)	Folate							
(N G Faux et al., 2014)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	1439	Cognitive Decline Only	Alzheimer's disease, MCI		IL-6	ApoE-4 single allele	Anemia	Haptoglobin	Folate		Hemoglobin		
(Fei, Jianghua, Rujuan, Wei, & Qian, 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	565	Cognitive Decline Only	MCI progression to AD		Aβeta 1-42	Aβeta1-42/ Aβeta1-40 ratio	ApoE-4 single allele						
(Felicio et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	221	Frailty only		Gait,Sarcopenia,Grip Strength,Physical Activity	IL-6								
(Gale, Baylis, Cooper, & Sayer, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	2146	Cognition Decline & Frailty	General cognitive decline	Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	CRP/hs-CRP	Fibrinogen	BMI						
(Garcia et al., 2004)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	281	Cognitive Decline Only	General cognitive decline		Homocysteine (tHcy)	Methylcitric acid (MCA)							
(Berenguer et al., 2014)	1b	Longitudinal Study	39	Cognitive Decline Only	General cognitive decline		Aβeta 1-42/p-tau ratio	P-tau181/Ab1-42 ratio							

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Gattaz, Forlenza, Talib, Barbosa, & Bottino, 2004)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	49	Cognitive Decline Only	Alzheimer's disease, MCI		Phospholipase A2 (PLA2)								
(Ghidoni et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	185	Cognitive Decline Only	Alzheimer's disease, MCI										
	1b	Longitudinal Study	59	Cognitive Decline Only	MCI progression to AD		Cystatin C	ApoE-4 single allele							
(Ge Li et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	315	Cognitive Decline Only	Alzheimer's disease		F2-isoprostanes/isoprostanes	Aβeta 1-42							
	1b	Longitudinal Study	158	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42								
(Glodzik-Sobanska et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	78	Cognitive Decline Only	Alzheimer's disease		P-tau231	F2-isoprostanes/isoprostanes							
(Goetzl et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	84	Cognitive Decline Only	Alzheimer's, Frontal Temporal Dementia (FTD)		Cathepsin D	LAMP-1	Ubiquitin	HSP70					
	1b	Longitudinal Study	60	Cognitive Decline Only	Alzheimer's disease, MCI		LAMP-1	Ubiquitin	HSP70						
(Gomez-Marcos et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1284	Frailty only		Physical Activity	Fibrinogen	CRP/hs-CRP	Insulin resistance (IR-HOMA)	Creatinine	Uric Acid	Glycohemoglobin (HbA1c)	Triglyceride	Hemoglobin	
(Growdon et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	215	Cognitive Decline Only	Alzheimer's disease		Olfactory measures								
(Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009)	1b	Longitudinal Study	803	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Composite Score: Systolic BP, Diastolic BP, HDL, total/HDL ratio, glycosylated hemoglobin, waist-hip ratio, dehydroepiandrosterone sulfate, urinary cortisol, urinary norepinephrine, urinary epinephrine, fibrinogen, c-reactive protein, IL-6								
(Gupta et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1112	Cognitive Decline Only	Alzheimer's disease, MCI		ApoE-4 single allele								
(Heringa et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	363	Cognitive Decline Only	General cognitive decline		Composite Score: C-reactive protein (CRP) and serum amyloid A (SAA), cytokines such as tumor necrosis factor alpha (TNF-a), interkleukin-6 (IL-6), and interleukin-8 (IL-8), the enzyme myeloperoxidase (MPO), and the adhesion molecule soluble intercellular adhesion molecule-1 (sICAM-1) CRP, TNF-alpha, IL-6, IL-8, SAA, MPO, SICAM-1	Composite Score: von Willebrand factor (vWf), soluble vascular cell adhesion molecule 1 (sVCAM-1), soluble endothelial selectin (sE-selectin), soluble thrombomodulin (sTM), and sICAM-1							
(Hohman, Bell, & Jefferson, 2015)	1b	Longitudinal Study	279	Cognitive Decline Only	Alzheimer's disease		Vascular endothelial growth factor (VEGF)								
(Howard, Ferrucci, & Sun, 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	672	Cognition Decline & Frailty	General cognitive decline	Grip Strength	vascular endothelial growth factor (VEGF)	BMI							
(Hsu, Cumming, Naganathan, Blyth, & Handelsman, 2014)	1b	Longitudinal Study	955	Cognitive Decline Only	General cognitive decline		Total Testosterone (TT)	Free Testosterone (cFT)							
(Liaw et al., 2016)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	205	Frailty only		Gait	Follistatin								
(Hye et al., 2014)	1b	Longitudinal Study	1148	Cognitive Decline Only	Alzheimer's disease, MCI		CRP/hs-CRP	ApoE-4 single allele	Complement factor H (CFH) protein 1	Neural cell adhesion molecule (NCAM)	Aβeta-40				
(Hochstrasser, Ehrlich, Marksteiner, Sperner-Unterweger, & Humpel, 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	103	Cognitive Decline Only	Alzheimer's disease, MCI		Epidermal growth factor (EGF)	matrix metalloproteinases (MMP-2)							
(Hendrickson et al., 2015)	1b	Longitudinal Study	176	Cognitive Decline Only	Alzheimer's disease		t-tau	p-tau	Abeta-42						
(Hessen et al., 2015)	1b	Longitudinal Study	122	Cognitive Decline Only	MCI progression to AD		t-tau								
(Henrik Zetterberg et al., 2008)	1b	Longitudinal Study	87	Cognitive Decline Only	Alzheimer's,MCI progression to AD		βeta-secretase (BACE-1)								
(Inglés et al., 2014)	1b	Longitudinal Study	742	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	malondialdehyde (MDA)	Protein carbonyls							
(Jefferson et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1926	Cognitive Decline Only	General cognitive decline		IL-6	CRP/hs-CRP	Adhesion molecule soluble intercellular adhesion molecule-1 (sICAM-1)	Osteoprotegerin (OPG)	P-selectin	TNF-alpha			
(Jagielski et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	27971	Cognitive Decline Only	General cognitive decline		Glucose (FBG) or Insulin level (OGTT)								
(Hendrickson et al., 2015)	1b	Longitudinal Study	1677	Cognition Decline & Frailty	General cognitive decline	Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	CRP/hs-CRP	IL-6							
(Barnett et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	144	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42								
(Gomar et al., 2011)	1b	Longitudinal Study	116	Cognitive Decline Only	MCI progression to AD		t-tau	Aβeta 1-42	Aβeta1-42/t-tau ratio						
(Kanai, Matsubara, Isoe, & Utakami, 1998)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	60	Cognitive Decline Only	Alzheimer's disease, MCI		Insulin like growth factor protein (IGF-1)	Insulin like growth factor protein Binding Protein (IGFBP-3)							
(Kanai et al., 1998)	1b	Longitudinal Study	236	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42/ Aβeta 1-40 ratio	t-tau							
(Kantarci et al., 2007)	1b	Longitudinal Study	197	Cognitive Decline Only	Alzheimer's disease		N-acetylaspartate (NAA)/creatine (Cr)								
(Gruenewald et al., 2009)	1b	Longitudinal Study	756	Cognitive Decline Only	General cognitive decline		Cortisol								
(Kelly et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	226	Cognitive Decline Only	General cognitive decline		Ocular measures								
(Kester et al., 2015)	1b	Longitudinal Study	163	Cognitive Decline Only	MCI progression to AD		Neruogranin (NGRN)	Aβeta-42	t-tau	phosphoTau181 (P-tau181)					
(Kester et al., 2012)	1b	Longitudinal Study	154	Cognitive Decline Only	Alzheimer's,MCI,MCI progression to AD		F2-isoprostanes/isoprostanes								
(Kester et al., 2015)	1b	Longitudinal Study	163	Cognitive Decline Only	MCI progression to AD		YKL-40 (neuroinflammation or Chitinase-3 ChI3L3)	Visinin-like protein-1 (VILIP-1)	Aβeta42	t-tau	phosphoTau181 (P-tau181)				
(Simpson et al., 2016)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	59	Cognitive Decline Only	Alzheimer's disease, MCI		IL-8	IL-8	TNF-alpha						
(Kim et al., 2011)	1b	Longitudinal Study	70	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42	Aβeta 1-40	ApoE-Æ4 single allele	Fibrinogen	Platelet distribution width (PDW)				
(Kleinschmidt et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	94	Cognitive Decline Only	Alzheimer's,MCI,General cognitive decline		Aβeta 1-42/ Aβeta 1-40 ratio	Aβeta 1-42	IgG2	IL-6					
(Koal, Klavins, Seppi, Kemmler, & Humpel, 2015)	NA	In Vitro	100	Cognitive Decline Only	Alzheimer's disease		Aβeta 42	t-tau	phosphoTau181 (P-tau181)	Sphingolipid-SM(d18:1/18:0)	PC aa 36:1 Glycerophospholipids				

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Kobrosly, Seplaki, Jones, & van Wijngaarden, 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	4511	Cognitive Decline Only	General cognitive decline		Composite: systolic and diastolic blood pressure, waist-to-hip ratio, glycohemoglobin, albumin, creatinine clearance, total cholesterol, triglycerides, WBC, resting heart rate, CRP								
(Kravitz, Corrada, & Kawas, 2009)	1b	Longitudinal Study	305	Cognitive Decline Only	Alzheimer's disease		CRP/hs-CRP								
(Kumar et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	200	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Sirtuin 1	Sirtuin 2	Sirtuin 3						
(Kuyumcu et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	416	Cognitive Decline Only	Alzheimer's disease		Neutrophil/lymphocyte ratio	Blood pressure	BUN (blood urine nitrogen)	Creatinine	Albumin (ALB)				
(Lafaille-Magnan et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	73	Cognitive Decline Only	General cognitive decline		Olfactory measures								
(Laske et al., 2011)	1b	Longitudinal Study	40	Cognitive Decline Only	Alzheimer's, General cognitive decline		Brain derived neurotrophic factor (BDNF)								
(Licastro, Davis, Polazzi, Rossi, & Cucinotta, 1996)	1b	Longitudinal Study	40	Cognitive Decline Only	Alzheimer's disease		CRP/hs-CRP	Alpha-1-antitrypsin (alpha1-AT)	alpha 2-macroglobulin (A2M)	Ceruloplasmin	Acid glycoprotein	Alpha-1-antitrypsin (alpha1-AT)	Trasferrin		
(Licastro et al., 2001)	1b	Longitudinal Study	28	Cognitive Decline Only	Alzheimer's,Vascular Dementia		Lactoferrin (LTF)	alpha-1-antichymotrypsin (ACT)	Glutathione peroxidase (GSH-Px)						
(G Li et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	174	Cognitive Decline Only	Alzheimer's disease, MCI		t-tau/ Aβeta-42	ApoE-4 single allele							
(Lildballe et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	839	Cognitive Decline Only	General cognitive decline		Holotranscobalamin (holoTC)	Cobalamin deficiency (B12)	Methylmalonic acid (MMA)	Homocysteine (tHcy)					
(Zuliani et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	140	Cognitive Decline Only	Late-Onset Alzheimer Disease (LOAD),Vascular Dementia		IL-6	IL-6							
(Zubenko, Hughes III, & Stiffler, 2001)	1b	Longitudinal Study	325	Cognitive Decline Only	Alzheimer's disease		ApoE-4 two alleles								
(H Zetterberg et al., 2007)	1b	Longitudinal Study	100	Cognitive Decline Only	MCI progression to AD		t-tau	phosphoTau181 (P-tau181)	Aβeta 1-42						
(A. M. Zelisko, D. R. Kerwin, 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	89	Cognitive Decline Only	Alzheimer's disease		BMI	Waist Circumference/waist-to-hip ratio	Adiponectin						
(Zamroziewicz, Paul, Rubin, & Barbey, 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	40	Cognitive Decline Only	General cognitive decline		Polyunsaturated fatty acids (O3PUFAs)/ n-6/n-3 ratio								
(S. X. Leng et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	696	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Insulin like growth factor protein (IGF-1)	WBC							
(Sean X. Leng et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	133	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	IL-6R	IL-6							
(Liu et al., 2014)	1b	Longitudinal Study	230	Frailty only		Gait	eGFR	Cystatin C							
(Locascio et al., 2008)	1b	Longitudinal Study	122	Cognitive Decline Only	General cognitive decline		Aβeta-40	Aβeta-42	CRP/hs-CRP						
(Lopez et al., 2008)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	274	Cognitive Decline Only	MCI progression to AD		Aβeta 1-40	Abeta1-42	Cystatin C						
(Luchsinger et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	327	Cognitive Decline Only	Alzheimer's disease		Homocysteine (tHcy)	Aβeta-42							
(Luis et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	60	Cognitive Decline Only	Alzheimer's disease, MCI		Aβeta-40	Aβeta-42	Aβeta-42/ Aβeta-40						
(Ma, Li, Bao, Ruan, & Yu, 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	440	Cognitive Decline Only	Alzheimer's disease, MCI		Peroxidase (POD)	IL-6	HDL (low/increased)	ApoA1	ApoA2	ApoC2			
(Maeba, Nishimukai, Sakasegawa, Sugimori, & Hara, 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	201	Cognitive Decline Only	General cognitive decline		Choline plasmalogen(PlsCho)	Ethonalamin plasmalogen (PlsEtn)	PLsCho + PlsEtn	PLsCho/PlsEtn Ratio					
(Mancinella et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	198	Cognitive Decline Only	Alzheimer's disease		CRP/hs-CRP	CRP/hs-CRP	Fibrinogen						
(Marksteiner & Humpel, 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	138	Cognitive Decline Only	Alzheimer's disease, MCI		glycogen synthase kinase-3 (GSK3-alpha)								
(Martin-Ruiz et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	852	Cognition Decline & Frailty	General cognitive decline	Grip Strength,Physical Function	Blood pressure, hematocrit, hemoglobin, MCV, RBC,WBC, lymphocytes, monocytes, neutrophils, sodium, phosphate, urate, creatinine, glucose, total protein, ALT, Albumin, calcium, HbA1c, TG, HDL, LDL, TC, ApoA1, Cortisol, ApoB, Free T3, Free T4, hsCRP, NT-pro BNP, Ferritin, Homocysteine, Vit B12, Vit D, IL6, F2 alpha, CD8								
(Matteini et al., 2008)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	700	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Homocysteine (tHcy)	Cystathionine	Cobalamin deficiency (B12)	Methylmalonic acid (MMA)	Carotenoids				
(Niklas Mattsson et al., 2009)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	1583	Cognitive Decline Only	Alzheimer's,MCI,MCI progression to AD		Aβeta-42	p-tau	t-tau						
(Yin, Fan, Lin, Xu, & Zhang, 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	114	Cognitive Decline Only	MCI		Vitamin D (25(OH)D)	Folate	Eicosapentaenoic acid (EPA)	Docosahexaenoic acid (DHA)	Polyunsaturated fatty acids (O3PUFAs)/ n-6/n-3 ratio				
(Yavuz et al., 2008)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	290	Cognitive Decline Only	Alzheimer's disease		Systolic pressure	Diastolic pressure	Gamma glutamyltransferase (GGT)	AST	Triglyceride				
(Yano et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	210	Cognitive Decline Only	General cognitive decline		Plasma Pentraxin 3 (PTX3)	CRP/hs-CRP							
(Yarasheski, Bhasin, Sinha-Hikim, Pak-Loduca, & Gonzalez-Cadavid, 2002)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	95	Frailty only		Sarcopenia	Myostatin								
(Yang et al., 2011)	1b	Longitudinal Study	820	Cognitive Decline Only	Alzheimer's,MCI,MCI progression to AD		Aβeta-42	t-tau	p-tau						
(S. H. Wu et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1005	Frailty only		Physical Activity,Physical Function	IL-6	IL-1 alpha	TNF-alpha						
(I. C. Wu, Shiesh, Kuo, & Lin, 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	90	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Waist Circumference/waist-to-hip ratio	Albumin (ALB)	CRP/hs-CRP	Serum 8-hydroxy-2-deoxyguanosine (8-OHdG)					
(Wolfsgruber et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	245	Cognitive Decline Only	MCI		Aβeta 1-42								
(Wolfsgruber et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	245	Cognitive Decline Only	Alzheimer's disease		Aβeta-42								

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Windham et al., 2014)	1b	Longitudinal Study	1857	Cognitive Decline Only	General cognitive decline		Tumor necrosis factor receptor 2 (TNFR2)	Tumor necrosis factor receptor 1 (TNFR1)	CRP/hs-CRP	IL-6					
(Wildsmith, Schauer, Kaur, Mathews, & Honigberg, 2013)	1b	Longitudinal Study	66	Cognitive Decline Only	General cognitive decline		YKL-40 (neuroinflammation or Chitinase-3 ChI3L3)								
(Wikby et al., 2005)	1b	Longitudinal Study	240	Cognitive Decline Only	General cognitive decline		CD8	IL-2	IL-6	Persistent viral infection					
(Westin, Buchhave, Minthon, Janciauskiene, & Hansson, 2011)	1b	Longitudinal Study	149	Cognitive Decline Only	General cognitive decline		Chemokine receptor 2 (CCR2)								
(Weise et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	54	Cognitive Decline Only	Alzheimer's disease		Aβeta1-42	t-tau							
(Watanabe et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	131	Frailty only		Sarcopenia	C1q	TNF-alpha	IL-6						
(R. Wang, Jin, Li, & Liang, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	360	Cognitive Decline Only	Alzheimer's disease, MCI		Platelet distribution width (PDW)	Mean platelet volume (MPV)							
(L. Wang et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	207	Cognitive Decline Only	Alzheimer's disease		Aβeta-42	phosphoTau181 (P-tau181)							
(L. Wang et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	188	Cognitive Decline Only	Alzheimer's disease		Aβeta-42	t-tau							
(Madison, Shaw, Jack, & Weiner, 2010)	1b	Longitudinal Study	600	Cognitive Decline Only	MCI progression to AD		P-tau181/Aβeta-42	ApoE-4 single allele	Aβeta 1-42	phosphoTau181 (P-tau181) matrix	Aβeta 1-42/t-tau ratio				
(N Mattsson et al., 2013)	1b	Longitudinal Study	46	Cognitive Decline Only	Alzheimer's disease		Angiotensin converting enzyme (ACE)	Chromogranin A (CgA)	Axl receptor tyrosine kinase (AXL)	metalloproteinases (MMP-2)	Aβeta-42	t-tau	p-tau		
(Niklas Mattsson et al., 2015)	1b	Longitudinal Study	35	Cognitive Decline Only	Alzheimer's,MCI progression to AD		Aβeta-42	ApoE-2 single allele	ApoE-4 single allele						
(Meng et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1131	Frailty only		Gait,Sarcopenia,Grip Strength,Physical Activity,Physical Function	CRP/hs-CRP								
(Mielke, Bandaru, et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	100	Cognitive Decline Only	Alzheimer's disease		Ceramides C16:0	Ceramides C20:0	Stearoyl sphingomyelin [SM(39:1)]						
(Mielke et al., 2011)	1b	Longitudinal Study	120	Cognitive Decline Only	Alzheimer's disease		DHSM/DHCer ratio	SM/ceramide ratio	Ceramides C24:0						
(Mielke, Haughey, et al., 2010)	1b	Longitudinal Study	63	Cognitive Decline Only	Alzheimer's disease, MCI		Ceramides C22:0	Ceramides C26:0							
(De Leon et al., 2006)	1b	Longitudinal Study	16	Cognitive Decline Only	MCI progression to AD		F2-isoprostanes/isoprostanes	Aβeta-40	P-tau231						
(Mocchegiani et al., 2012)	1b	Longitudinal Study	346	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Ratio-Zinc /Copper (CZr)	IL-6	Albumin (ALB)	Blood urea nitrogen	Total Cholesterol	CRP			
(Hessen et al., 2015)	1b	Longitudinal Study	122	Cognitive Decline Only	MCI progression to AD		t-tau								
(Moore et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	24	Cognitive Decline Only	General cognitive decline		IL-6	CRP/hs-CRP							
(Moreno et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	120	Frailty only		Gait,Physical Activity	CRP/hs-CRP	Waist Circumference/waist-to-hip ratio							
(Thambisetty, Metter, et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	197	Cognitive Decline Only	Alzheimer's disease		Glucose (FBG) or Insulin level (OGTT)	Insulin resistance (IR-HOMA)							
(Muldoon et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	280	Cognitive Decline Only	General cognitive decline		Docosahexaenoic acid (DHA)								
(Muzembo et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	86	Frailty only		Grip Strength	Serum 8-hydroxy-2-deoxyguanosine (8-OHdG)								
(A. Ng, Jion, Zainal, & Kandiah, 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	64	Cognitive Decline Only	General cognitive decline		Creatinine								
(Noble et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1331	Cognitive Decline Only	General cognitive decline		CRP/hs-CRP	CRP/hs-CRP							
(T. P. Ng, Niti, Feng, Kua, & Yap, 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1654	Cognitive Decline Only	General cognitive decline		Albumin (ALB)	Albumin (ALB)							
	1b	Longitudinal Study	1654	Cognitive Decline Only	General cognitive decline		Albumin (ALB)								
(Nurk et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	2195	Cognitive Decline Only	General cognitive decline		Choline plasmalogen(PlsCho)	Cobalamin deficiency (B12)	Methylmalonic acid (MMA)						
(O'Bryant, Waring, et al., 2010)		Observational (Cohort, Cross Sectional, Case-Control Studies)	366	Cognitive Decline Only	General cognitive decline		CRP/hs-CRP								
(O'Bryant, Waring, et al., 2010)							Composite Score: 10 (macrophage inflammatory protein 1, eotaxin 1, tumor necrosis factor -alpha, fibrinogen, interleukin 5 [IL-5], IL-7, IL-10, C-reactive protein, monocyte chemoattractant protein 1, and von Willebrand factor								
(Ogawa et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	665	Frailty only		Gait,Sarcopenia,Grip Strength	IL-6	Extracellular heat shock protein (eHsp) 72	TNF-alpha						
(Olazaran et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	251	Cognitive Decline Only	Alzheimer's disease, MCI		Composite Score: metabolites: three amino acids (glutamic acid, alanine, and aspartic acid), one non-esterified fatty acid (22:6n-3, DHA), one bile acid (deoxycholic acid), one phosphatidylethanolamine [PE(36:4)], and one sphingomyelin [SM(39:1)]								
(Olazaran et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	57	Frailty only		Gait,Sarcopenia,Physical Function	IL-6								
(Forlenza et al., 2010)	1b	Longitudinal Study	258	Cognitive Decline Only	MCI progression to AD		Aβeta-42	t-tau	p-tau	ApoE-4 single allele					
(Öztürk et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	330	Cognitive Decline Only	Alzheimer's disease		Platelet distribution width (PDW)	ESR	CRP/hs-CRP	Albumin (ALB)	LDL				
(Pabst et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	940	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Vitamin D (25(OH)D)								
(Papassotiropoulos et al., 2000)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	53	Cognitive Decline Only	General cognitive decline		24S-hydroxycholesterol	ApoE-4 single allele							
(Buchhave et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	45	Cognitive Decline Only	MCI progression to AD		t-tau	Aβeta-42							
(Perna, Guido, Grassi, & Rondanelli, 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	290	Frailty only		Sarcopenia	Composite Score: adipo-metabolic profile (AMP) and albumin, triglycerides, homocysteine, folate, total cholesterol								

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Perrin et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	292	Cognitive Decline Only	General cognitive decline		YKL-40 (neuroinflammation or Chitinase-3 ChI3L3)	Transthyretin (TTR)	NrCAM	Chromogranin A (CgA)					
(Pirttilä et al., 1998)	1b	Longitudinal Study	25	Cognitive Decline Only	MCI progression to AD		ApoE-4 single allele	sAβeta/APP ratio	Soluble amyloid βeta protein (sAβeta)						
(P. et al., 2013)	1b	Longitudinal Study	396	Cognitive Decline Only	Alzheimer's disease		Aβeta-42	ApoE-4 single allele							
(Qiu et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	355	Cognitive Decline Only	Alzheimer's disease		Medication (ACE inhibitor)								
(Quinn et al., 2004)	1b	Longitudinal Study	40	Cognitive Decline Only	Alzheimer's disease		F2-isoprostanes/isoprostanes								
(Quintino-Santos et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1480	Cognitive Decline Only	General cognitive decline		ApoE-4 single allele								
(Rabassa et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	652	Cognitive Decline Only	General cognitive decline		Total Urinary polyphenols (TUPs)								
(Rasgon et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	50	Cognitive Decline Only	General cognitive decline		Insulin resistance (IR-HOMA)								
(Rembach et al., 2014)	1b	Longitudinal Study	1112	Cognitive Decline Only	MCI		Aβeta 1-42	Aβeta 1-40	Aβeta 1-40						
(Reuben, Judd-Hamilton, Harris, & Seeman, 2003)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	870	Frailty only		Physical Activity	IL-6	CRP/hs-CRP							
(Revel et al., 2015)	1b	Longitudinal Study	97	Cognitive Decline Only	General cognitive decline		Glutathione peroxidase (GSH-Px)								
(Riemenschneider et al., 2002)	1b	Longitudinal Study	28	Cognitive Decline Only	Alzheimer's disease, MCI		t-tau	Aβeta-42							
(Read & Grundy, 2014)	1b	Longitudinal Study	6132	Frailty only		Gait,Physical Function	Composite Score: Allostatic load= HDL/TC ratio, Triglycerides, A1c, fibrinogen, C-reactive protein, waist-to-hip ratio, systolic and diastolic blood pressure, and lung function (PEF). (all 9 belong to the highest 25% indicating health risk) composite allostatic load score. (inflammation, cardiovascular, metabolic, body fat, and respiratory)								
(Rgsler, Wichart, & Jellinger, 2001)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	170	Cognitive Decline Only	Alzheimer's disease		t-tau	Aβeta-42	IL-6	ApoE-4 single allele					
(Ruiz et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	140	Cognitive Decline Only	Alzheimer's disease, MCI		Diastolic pressure	Hematocrit	IgA	Creatinine	Homocysteine (tHcy)	Urea	Uric acid		
(Sämgård et al., 2010)	1b	Longitudinal Study	142	Cognitive Decline Only	Alzheimer's disease		t-tau		p-tau						
(Sanada et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1488	Frailty only		Sarcopenia,Grip Strength	Waist Circumference/waist-to-hip ratio	Glycohemoglobin (HbA1c)							
(Sanders et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	989	Cognition Decline & Frailty	General cognitive decline	Gait,Grip Strength	DHEAS (dehydroepiandrosterone sulphate)								
(Sato et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	401	Cognitive Decline Only	Alzheimer's disease		plasma desmosterol-to-cholesterol ratio (DES/CHO)								
(Saum et al., 2015)	1b	Longitudinal Study	55	Cognitive Decline Only	MCI progression to AD		plasma desmosterol-to-cholesterol ratio (DES/CHO)								
(Egli et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	2518	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Derivate of reactive oxygen metabolites (d-ROM)	CRP/hs-CRP	thol level (TTL)						
(Schaap, Pluijm, Deeg, & Visser, 2006)	1a	Longitudinal Study	36	Cognitive Decline Only	MCI progression to AD		Aβeta 1-42								
(Schofield, Ebrahimi, Jones, Bateman, & Murray, 2012)	1b	Longitudinal Study	986	Frailty only		Sarcopenia,Grip Strength	IL-6	CRP/hs-CRP	alpha-1-antichymotrypsin (ACT)						
(Von Arnim et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	56	Cognitive Decline Only	MCI progression to AD		Olfactory measures								
(Vieira et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	232	Cognitive Decline Only	General cognitive decline		Vitamin C	Beta-Carotene							
(S. Vestergaard et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	3150	Cognitive Decline Only	General cognitive decline		Tumor necrosis factor receptor 1 (TNFR1)	Blood pressure	HDL (low/increased)						
(P. F. Vestergaard et al., 2014	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1055	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity,Physical Function	IL-6	CRP/hs-CRP	fT3						
(Verghese et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	150	Frailty only		Sarcopenia,Grip Strength	Insulin like growth factor protein (IGF-1)								
(Velayudhan, Pritchard, Powell, Proitsi, & Lovestone, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	333	Frailty only		Gait	IL-6								
(L. Van Den Ingh, A. Ahmed, 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	57	Cognitive Decline Only	Alzheimer's disease		Olfactory measures								
(van den Boogaard et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	254	Cognitive Decline Only	General cognitive decline		Total bilirubin								
(Urpi-Sarda et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	100	Cognitive Decline Only	General cognitive decline		TNF-alpha	IL-6	IL-8	Macrophage Migration Inhibitory Factor (MIF)	IL-1RA				
(Umegaki et al., 2000)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	811	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Total dietary polyphenols (TDPs)	Total Urinary polyphenols (TUPs)	IL-6	CRP/hs-CRP	Total Cholesterol				
(Turana et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	66	Cognitive Decline Only	MCI		Cortisol								
(Trollor et al., 2011)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	109	Cognitive Decline Only	General cognitive decline		Ocular measures	Olfactory measures	Composite Score: Pupillary hypersensitivity response, olfactory nerve deficit, low BDNF plasma, APOE e4						
(Sundelof et al., 2008)	1b	Longitudinal Study	710	Cognitive Decline Only	MCI		Plasminogen activator inhibitor (PAI-1)	Serum amyloid A (SAA)	CRP/hs-CRP	TNF-alpha	IL-1 βeta				
			761	Cognitive Decline Only	MCI progression to AD		Cystatin C								

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Uchida et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	411	Cognitive Decline Only	Alzheimer's disease, MCI		ApoA1	Complement 3	Transthyretin (TTR)						
	1b	Longitudinal Study	35	Cognitive Decline Only	MCI progression to AD		Transthyretin (TTR)	ApoE-genotype							
(Sunderland et al., 2003)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	203	Cognitive Decline Only	Alzheimer's disease		Aβeta 1-42	t-tau							
(Toledo, Xie, Trojanowski, & Shaw, 2013)	1b	Longitudinal Study	142	Cognitive Decline Only	Alzheimer's disease, MCI		Aβeta 1-42	t-tau	phosphoTau181 (P-tau181)						
(Thuot et al., 2010)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	23	Cognitive Decline Only	Alzheimer's disease, MCI		Insulin resistance (IR-HOMA)								
(Satizabal, Zhu, Mazoyer, Dufouil, & Tzourio, 2012)	1b	Longitudinal Study	1841	Cognitive Decline Only	General cognitive decline		IL-6	CRP/hs-CRP							
(Schoonenboom et al., 2005)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	39	Cognitive Decline Only	General cognitive decline		Aβeta-42	t-tau							
(Schram et al., 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	4365	Cognitive Decline Only	General cognitive decline		CRP/hs-CRP	IL-6							
	1b	Longitudinal Study	4365	Cognitive Decline Only	General cognitive decline		IL-6	Composite Score: IL-6 and APOE e4							
(Semba et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	804	Frailty only		Sarcopenia,Grip Strength	Klotho								
(Seppälä et al., 2011)	1b	Longitudinal Study	131	Cognitive Decline Only	MCI progression to AD		Aβeta-42	t-tau	phosphoTau181 (P-tau181)						
		Observational (Cohort, Cross Sectional, Case-Control Studies)	131	Cognitive Decline Only	MCI		phosphoTau181 (P-tau181)	Aβeta-42							
(Shinkai et al., 1995)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	52	Frailty only		Physical Activity	Phytohemagglutinin	Pokeweed mitogen	IL-2	CXCL-10/ IFN-gama	IL-4				
(Shimada et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	827	Cognitive Decline Only	MCI		Brain derived neurotrophic factor (BDNF)								
(Singh-Manoux, 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	5217	Cognitive Decline Only	General cognitive decline		IL-6	CRP/hs-CRP							
	1b	Longitudinal Study	5217	Cognitive Decline Only	General cognitive decline		IL-6								
(Simpson et al., 2016)		In Vitro	107	Cognitive Decline Only	General cognitive decline		PC 16:0/20:5 phosphatidylcholine	PC 16:0/22:6 phosphatidylcholine	PC 18:0/22:6 phosphatidylcholine						
(Colbert et al., 2004)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	3075	Frailty only		Physical Activity	IL-6	CRP/hs-CRP							
(Snider et al., 2009)	1b	Longitudinal Study	49	Cognitive Decline Only	MCI progression to AD		Aβeta-42	t-tau	p-tau						
(Sohrabi et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	144	Cognitive Decline Only	General cognitive decline		Olfactory measures								
(F. Song et al., 2012)	1a	Longitudinal Study	664	Cognitive Decline Only	MCI progression to AD		ApoA1	ApoA2	ApoH	ApoB/ApoA1 ratio					
(I.-U. Song, Chung, Kim, & Maeng, 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	538	Cognitive Decline Only	Alzheimer's disease		CRP/hs-CRP								
(Spiegel et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	115	Cognitive Decline Only	Alzheimer's disease		phosphoTau181 (P-tau181)	P-tau231							
(Stricker et al., 2012)	1b	Longitudinal Study	342	Cognitive Decline Only	Alzheimer's disease, MCI		Aβeta-42	phosphoTau181 (P-tau181)							
(M. Soundarrajan et al., 2011)	1b	Randomized control study	100	Cognitive Decline Only	General cognitive decline		Neurofilament light chain (NFL)								
(Skillbäck, Zetterberg, Blennow, & Mattsson, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	5542	Cognitive Decline Only	Alzheimer's disease		Neurofilament light chain (NFL)								
(Teunissen et al., 2003)	1b	Longitudinal Study	144	Cognitive Decline Only	General cognitive decline		Homocysteine (tHcy)								
(Stomrud, Minthon, Zetterberg, Blennow, & Hansson, 2015)	1b	Longitudinal Study	44	Cognitive Decline Only	MCI progression to AD		Aβeta-42								
(Tapiola et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	123	Cognitive Decline Only	Alzheimer's disease		t-tau	Aβeta-42							
(Tang, Hynan, Baskin, & Rosenberg, 2006)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	41	Cognitive Decline Only	Alzheimer's disease		βeta-secretase (BACE-1)	alpha-secretase (ADAM10)	Ah/h-actin	APP ratio					
(Tajar et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1504	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Vitamin D (25(OH)D)	Parathyroid hormone (PTH)							
(Stehle et al., 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	59	Frailty only		Gait,Grip Strength,Physical Activity,Physical Function	Lipopolysaccharide bining protein (LBP)	CRP/hs-CRP	TNF-alpha	Tumor necrosis factor receptor 1 (TNFR1)					
(Sutphen et al., 2015)	1b	Longitudinal Study	169	Cognitive Decline Only	General cognitive decline		Aβeta-42	t-tau	phosphoTau181 (P-tau181)	Visinin-like protein-1 (VILIP-1)	YKL-40 (neuroinflammation or Chitinase-3 ChI3L3)				
(Stanga, Lanni, Sinforiani, Mazzini, & Racchi, 2012)	1b	Longitudinal Study	67	Cognitive Decline Only	MCI progression to AD		Unfolded p53								
(Tay et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	44	Frailty only		Sarcopenia	IL-6	WBC	Albumin (ALB)						
(Allard, Artero, & Ritchie, 2003)	1b	Longitudinal Study	372	Cognitive Decline Only	General cognitive decline		Medication (Psychoactive drugs)								
(Bernhard T. Baune et al., 2008	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	369	Cognitive Decline Only	General cognitive decline		IL-8	IL-1 βeta							
(Gray et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	3434	Cognitive Decline Only	Alzheimer's disease										
(Fox et al., 2011)	1a	Observational (Cohort, Cross Sectional, Case-Control Studies)	13004	Cognitive Decline Only	General cognitive decline		Medication (Anticholinergic)								

Citation	Level of Evidence	Type of study design	total (n)	Phenotype	Type of cognitive decline	Component of frailty	Biomarker - 1	Biomarker - 2	Biomarker - 3	Biomarker - 4	Biomarker - 5	Biomarker - 6	Biomarker - 7	Biomarker - 8	Biomarker - 9
(Ferrucci et al., 2002)	1b	Longitudinal Study	620	Frailty only		Gait,Sarcopenia,Grip Strength,Physical Function	IL-6								
(Boxer, Dauser, Walsh, Hager, & Kenny, 2008)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	60	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Vitamin D (25(OH)D)	Cortisol/DHEAS ratio	CRP/hs-CRP	IL-6	Parathyroid hormone (PTH)				
Butchart, Birch, Bassily, Wolfe, & Holmes, 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	94	Cognitive Decline Only	Alzheimer's disease		Free Testosterone (cFT)	LH	TNF-alpha						
(Beavers, Beavers, Serra, Bowden, & Wilson, 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	7544	Frailty only		Sarcopenia	Uric Acid								
(Barzilay, 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	3141	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Glucose (FBG) or Insulin level (OGTT)	WBC	CRP/hs-CRP	Fibrinogen	Von Willebrand Factor VIIc				
(Kizilarslanoglu et al., 2015)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	69	Cognitive Decline Only	Alzheimer's disease		Resistin								
(Schmaltz et al., 2005)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	724	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	IL-6	Cytomegalovirus (CMV)							
(Roubenoff et al., 2003)	1b	Longitudinal Study	403	Frailty only		Sarcopenia	TNF-alpha	IL-6	Insulin like growth factor protein (IGF-1)						
(Kumar et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	93	Cognitive Decline Only	Alzheimer's disease, MCI		Sirtuin/SIRT1								
(S. Leng, Chaves, Koenig, & Walston, 2002)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	30	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	IL-6	Hemoglobin	Hematocrit						
(S X Leng, Xue, Tian, Walston, & Fried, 2007)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	558	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	WBC	IL-6							
(Levine & Crimmins, 2012)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	2287	Frailty only		Sarcopenia,Physical Activity,Physical Function	CRP/hs-CRP	Insulin resistance (IR-HOMA)							
(Liaw et al., 2016)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	205	Frailty only		Gait,Grip Strength	Follistatin								
(Paterniti, Dufouil, & Alperovitch, 2002)	1b	Longitudinal Study	1389	Cognitive Decline Only	MCI		Medication (Benzodiazepine)								
(Puts, Visser, Twisk, Deeg, & Lips, 2005)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1271	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Vitamin D (25(OH)D)								
	1b	Longitudinal Study	885	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Vitamin D (25(OH)D)	CRP/hs-CRP							
(Paterniti et al., 2002)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	32	Frailty only		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	IL-6	CXCL-10/ IFN-gama							
(Uusvaara et al., 2009)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	295	Cognitive Decline Only	General cognitive decline		Medication (Anticholinergic)	Medication (Anticholinergic)							
(Visser et al., 2002)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	3075	Frailty only		Sarcopenia,Grip Strength	IL-6	IL-6							
(Wichmann et al., 2014)	1b	Longitudinal Study	1947	Cognitive Decline Only	General cognitive decline		IL-6	CRP/hs-CRP							
(Wilson, Cohen, & Pieper, 2003)	1b	Longitudinal Study	1752	Cognitive Decline Only	General cognitive decline		D-dimer	IL-6R		IL-10	Vascular cell adhesion molecule 1 (VCAM1)				
(Yaffe et al., 2008)	1b	Longitudinal Study	3030	Cognitive Decline Only	General cognitive decline		Cystatin C								
(Retrospective et al., 2011)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	134	Cognitive Decline Only	General cognitive decline		Medication (Anticholinergic)								
(Lanctôt et al., 2014)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	131	Cognitive Decline Only	General cognitive decline		Medication (Anticholinergic)	Medication (Hypertensive drug use)							
(Sharma et al., 2016)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1315	Cognitive Decline Only	General cognitive decline		Adiponectin	Plasma Pentraxin 3 (PTX3)							
(Mooijaart et al., 2013)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	5653	Cognitive Decline Only	General cognitive decline		IL-6								
(Herukka et al., 2011)	1b	Longitudinal Study	123	Cognitive Decline Only	Alzheimer's disease		p-tau	Aβeta-42							
(Jamsen et al., 2016)	2b	Observational (Cohort, Cross Sectional, Case-Control Studies)	1705	Frailty (pre-frail & frail)		Fatigue,Gait,Sarcopenia,Grip Strength,Physical Activity	Medication (Anticholinergic)								

* OCEBM Levels of Evidence Working Group. "The Oxford Levels of Evidence 2". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/?s=levels+of+evidence.

Table II. Genetic studies for cognitive decline and frailty

Citation	Study country	Type of Study	Total (n)	Pimary focus of study	Gene	SNP	Chromosome	Effect/Minor allele
(A.A. et al., 2014)	Australia	Candidate Gene Study	292	Cognitive Decline	SORL1	rs2298813	11	G
				Cognitive Decline	SORL1	rs4935774	11	T
				Cognitive Decline	SORL1	rs1133174	11	G
(Chibnik et al., 2011)	US	Candidate Gene Study	1666	Cognitive Decline	CR1	rs6656401	1	A
				Cognitive Decline	PICALM	rs7110631	11	G
(Choi et al., 2003)	Korea	Candidate Gene Study	13667	Cognitive Decline	ApoE-genotype	rs429358_rs7412	19	e4
(Dixon et al., 2014)	Canada	Candidate Gene Study	237	Cognitive Decline	ApoE-genotype	rs429358_rs7412	19	e4
				Cognitive Decline	COMT	rs4680	22	G
(Erten-Lyons, Jacobson, Kramer, Grupe, & Kaye,	US	Candidate Gene Study	243	Cognitive Decline	FAS	RS1468063	10	T
(Fiocco et al., 2010)	US	Candidate Gene Study	2840	Cognitive Decline	COMT	rs4680	22	G
(Goh et al., 2015)	Singapore	Candidate Gene Study	27	Cognitive Decline	TOMM40	rs10524523	19	T
(Green et al., 2014)	US	Candidate Gene Study	160	Cognitive Decline	ApoE-genotype	rs429358 or rs7412	19	e4
				Cognitive Decline	CLU	rs11136000	8	C
(Lillenes et al., 2011)	Norway	Candidate Gene Study	1066	Cognitive Decline	OGG1	rs1052133	3	G
				Cognitive Decline	OGG1	rs1052133	3	G
				Cognitive Decline	APEX1	rs1048945	14	C
				Cognitive Decline	MUTYH	rs3219484	1	C
(Wang et al., 2015)	Australia	Candidate Gene Study	619	Cognitive Decline	EPHA1	rs11771145	7	A
(Schmidt, Wolff, Von Ahsen, & Zerr, 2012)	Germany	Candidate Gene Study	40	Cognitive Decline	CST3	rs1064039	20	T
				Cognitive Decline	EXOC3L2 or XTP7	rs597668	19	C
				Cognitive Decline	ApoE-e4 two alleles	rs429358_rs7412	19	e4/4
				Cognitive Decline	BIN1	rs744373	2	G
(Thambisetty et al.,	US	Candidate Gene Study	57	Cognitive Decline	CR1	rs3818361	1	A
(Hohman, Koran, & Thornton-Wells, 2014)	Australia	Genome Wide Association Studies (GWAS)	374	Cognitive Decline	POT1	rs4728019	7	A
(Hollingworth et al.,	ADGC-Multi-center study	Genome Wide Association Studies (GWAS)	30172	Cognitive Decline	ABCA7	rs3764650	19	G
				Cognitive Decline	MS4A6A	rs610932	11	T
				Cognitive Decline	MS4A4E	rs670139	11	T
				Cognitive Decline	CD2AP	rs9349407	6	C
				Cognitive Decline	CD33	rs3865444	19	A
				Cognitive Decline	EPHA1	rs11767557	7	C
(Kauwe et al., 2014)	US	Genome Wide Association Studies (GWAS)	840	Cognitive Decline	IL-6R	rs4845622	1	C
				Cognitive Decline	IL-6R	rs61812598	1	G
				Cognitive Decline	IL-6R	rs4129267	1	T
				Cognitive Decline	IL-6R	rs2228145	1	C
				Cognitive Decline	IL-6R	rs2229238	1	T
				Cognitive Decline	TDRD10	rs3811448	1	G
				Cognitive Decline	CCL2	rs2228467	3	C
				Cognitive Decline	CCL4	rs6808835	3	G
				Cognitive Decline	CCL4	rs6762266	3	C
				Cognitive Decline	CCL4/LOC102724297	rs11575821	3	G
				Cognitive Decline	CCL4/LOC102724297	rs113263161	3	G
				Cognitive Decline	CCL4	rs11574428	3	T
				Cognitive Decline	CCL4	rs3092960	3	G
				Cognitive Decline	CCL4	rs6441977	3	G
				Cognitive Decline	MMP3	rs573521	11	A
				Cognitive Decline	MMP3	rs645419	11	A
				Cognitive Decline	MMP3	rs679620	11	T
				Cognitive Decline	WTAPP1	rs7926920	11	A
				Cognitive Decline	WTAPP1	rs11225434	11	C
				Cognitive Decline	MMP3	rs948399	11	T
				Cognitive Decline	WTAPP1	rs495366	11	A
				Cognitive Decline	MMP3	rs650108	11	A
				Cognitive Decline	WTAPP1	rs603050	11	T
				Cognitive Decline	ACE	rs4968782	17	G
				Cognitive Decline	ACE	rs4459609	17	C
				Cognitive Decline	ACE	rs4316	17	C
				Cognitive Decline	ACE	rs4343	17	G
(Hu et al., 2011)	US	Genome Wide Association Studies (GWAS)	1605	Cognitive Decline	UBR5	rs7840202	8	C
				Cognitive Decline	PARP6	rs11637611	15	C
				Cognitive Decline	ACOT11/LOC105378734	rs12752888	1	C
				Cognitive Decline	MYO9A	rs3784313	15	G
				Cognitive Decline	MYO9A	rs2957734	15	A
				Cognitive Decline	MYO9A	rs4777466	15	T
				Cognitive Decline	MYO9A	rs7175373	15	C
				Cognitive Decline	MYO9A	rs1481862	15	C
				Cognitive Decline	MYO9A	rs7497104	15	T
				Cognitive Decline	MYO9A	rs2929525	15	C
				Cognitive Decline	MYO9A	rs2306489	15	T
(Desikan et al., 2016)	IGAP-Multi-center study	Candidate Gene Study	143878	Cognitive Decline	AP2A2	rs7396366	11	C
				Cognitive Decline	USP50	rs3131609	15	C
				Cognitive Decline	TSPOAP1	rs2526378	17	G
				Cognitive Decline	HS3ST1/LOC107986178	rs13113697	4	T
				Cognitive Decline	ECHDC3	rs7920721	10	A
(Feulner et al., 2010)	Germany	Genome Wide Association Studies (GWAS)	970	Cognitive Decline	MAPT	rs1467967	17	A
				Cognitive Decline	MAPT	rs3785880	17	G
				Cognitive Decline	KANSL1	rs6503454	17	G
				Cognitive Decline	MAPT-AS1	rs1158660	17	A
				Cognitive Decline	PCK1	rs17411904	20	C
				Cognitive Decline	LMNA	rs9919256	1	A
				Cognitive Decline	LMNA	rs11578696	1	G
				Cognitive Decline	LMNA	rs915179	1	A
				Cognitive Decline	LMNA	rs12128066	1	C
				Cognitive Decline	SEMA4A	rs12401573	1	C
				Cognitive Decline	LIPA	rs12780342	10	T
				Cognitive Decline	PGBD1	rs9461448	6	G
				Cognitive Decline	ZSCAN31	rs7772827	6	C
				Cognitive Decline	PGBD1	rs1320879	8	A
				Cognitive Decline	CH25H	rs17117126	10	A
				Cognitive Decline	ApoE-genotype	rs405509	19	T
				Cognitive Decline	TOMM40	rs8106922	19	G
				Cognitive Decline	TOMM40	rs2075650	19	G
				Cognitive Decline	TOMM40	rs157580	19	G
				Cognitive Decline	APOC1	rs439401	19	T
				Cognitive Decline	APOC2	rs5167	19	G
				Cognitive Decline	SORL1	rs4935774	11	T
				Cognitive Decline	SORL1	rs1614735	11	T
				Cognitive Decline	SORL1	rs12576704	11	G
				Cognitive Decline	SORL1	rs10502262	11	T
				Cognitive Decline	SORL1	rs3781835	11	G
				Cognitive Decline	TDRD10	rs3811448	1	A
				Cognitive Decline	TDRD10	rs7556449	1	G
				Cognitive Decline	UBE2Q1	rs7543174	1	C
				Cognitive Decline	ADAR	rs9427097	1	G
(Del-Aguila et al., 2015)	US	Candidate Gene Study	3476	Cognitive Decline	ABCA7	rs4147929	19	A
(Corneveaux et al.,	US, UK	Candidate Gene Study	1600	Cognitive Decline	CR1	rs6656401	1	A
				Cognitive Decline	LOC651924	rs6907175	6	A
				Cognitive Decline	CLU	rs11136000	8	T
				Cognitive Decline	PICALM	rs541458	11	C
				Cognitive Decline	GAB2	rs10793294	11	C
				Cognitive Decline	ACE	rs1800764	17	C
				Cognitive Decline	CST3	rs1064039	20	T

Citation	Study country	Type of Study	Total (n)	Pimary focus of study	Gene	SNP	Chromosome	Effect/Minor allele
(Baune et al., 2008)	Australia	Candidate Gene Study	369	Cognitive Decline	IL-1beta	rs16944	2	G
				Cognitive Decline	IL-6	rs1800796	7	G
				Cognitive Decline	TNF	rs1800629	6	A
(Lambert et al., 2009)	France	Candidate Gene Study	7275	Cognitive Decline	CR1	rs6656401	1	A
				Cognitive Decline	CLU	rs11136000	8	T
(Lim et al., 2015)	Australia	Candidate Gene Study	333	Cognitive Decline	BDNF	rs6265	11	T
(Reitz et al., 2013)	ADGC-Multi-center study	Genome Wide Association Studies (GWAS)	5896	Cognitive Decline	BIN1	rs55636820	2	G
				Cognitive Decline	ABCA7	rs115550680	19	G
				Cognitive Decline	EPHA1	rs6973770	7	G
				Cognitive Decline	CR1	rs9429784	1	G
				Cognitive Decline	CD33(rsq)	rs114282264	19	G
(Mooijaart et al., 2013)	US	Candidate Gene Study	5804	Cognitive Decline	IL-6	rs1729941	2	C
(Forlenza et al., 2010)	Brazil	Candidate Gene Study	258	Cognitive Decline	ApoE-e4 single allele	rs429358_rs7412	19	e4
(Vounou et al., 2012)	Australia	Genome Wide Association Studies (GWAS)	475	Cognitive Decline	ApoE-genotype	rs429358_rs7412	19	e4
				Cognitive Decline	TOMM40	rs2075650	19	e4
				Cognitive Decline	BZW1	rs3815501	2	G
				Cognitive Decline		rs11132507	4	T
				Cognitive Decline		rs11132508	4	C
				Cognitive Decline	MIR924HG	rs1681052	18	T
				Cognitive Decline		rs7761213	6	T
				Cognitive Decline		rs17345545	1	C
				Cognitive Decline	PDZD2	rs13340334	5	C
				Cognitive Decline		rs17103124	14	T
				Cognitive Decline	FAM171B	rs8025706	15	T
				Cognitive Decline	YES1	rs12185469	18	A
				Cognitive Decline	YES1	rs12185470	18	T
				Cognitive Decline	TEAD1	rs10766003	11	G
				Cognitive Decline		rs1503659	4	C
				Cognitive Decline	KDM4C	rs913587	9	A
				Cognitive Decline		rs17380902	2	C
				Cognitive Decline	LINC01019	rs17686103	5	C
				Cognitive Decline	C2orf88	rs785232	2	T
				Cognitive Decline		rs4771473	13	T
				Cognitive Decline		rs11740943	5	T
				Cognitive Decline		rs7536709	1	T
				Cognitive Decline	YES1	rs17516202	18	G
				Cognitive Decline	TOMM40	rs157580	19	G
				Cognitive Decline	MEF2D	rs1750304	1	A
				Cognitive Decline	MEF2D	rs1171560	1	G
				Cognitive Decline		rs9263844	6	T
				Cognitive Decline		rs9263846	6	G
				Cognitive Decline	MTRF1	rs7999394	13	G
				Cognitive Decline	MTRF1	rs3794328	13	C
				Cognitive Decline		rs11590365	1	A
				Cognitive Decline		rs11204949	1	C
				Cognitive Decline		rs11204971	1	G
				Cognitive Decline	FLG	rs12405278	1	A
				Cognitive Decline		rs215340	12	A
				Cognitive Decline		rs7603289	2	C
				Cognitive Decline	OSTF1	rs11144246	9	A
				Cognitive Decline	MICA	rs6910087	6	T
				Cognitive Decline		rs4685279	3	C
(Vounou et al., 2012)	Australia	Genome Wide Association Studies (GWAS)	475	Cognitive Decline	ARHGEF10	rs3824139	8	A
				Cognitive Decline		rs6932730	6	C
				Cognitive Decline	MEF2D	rs1750304	1	A
				Cognitive Decline	MEF2D	rs1171560	1	A
				Cognitive Decline		rs9263969	6	T
				Cognitive Decline		rs6700106	1	A
				Cognitive Decline		rs795342	12	A
				Cognitive Decline		rs10026499	4	A
				Cognitive Decline		rs7979925	12	C
				Cognitive Decline		rs2325	10	T
				Cognitive Decline		rs7944761	11	C
				Cognitive Decline		rs9501132	6	T
				Cognitive Decline		rs215347	12	G
				Cognitive Decline	USP13	rs2268939	3	A
				Cognitive Decline	KAZ	rs6429696	1	C
				Cognitive Decline		rs11215380	11	A
				Cognitive Decline	ADCY2	rs727432	5	T
				Cognitive Decline		rs11783329	8	A
				Cognitive Decline	MAML2	rs7114756	11	T
				Cognitive Decline		rs17309585	8	T
				Cognitive Decline		rs10491327	5	T
				Cognitive Decline	PDE1C	rs12534148	7	A
				Cognitive Decline	MYO3B	rs2883782	2	T
				Cognitive Decline		rs2798062	9	A
				Cognitive Decline		rs10934170	3	T
				Cognitive Decline		rs17826780	4	T
				Cognitive Decline		rs7843577	8	T
				Cognitive Decline	TOMM40	rs2075650	19	G
				Cognitive Decline		rs1405443	7	A
				Cognitive Decline	RBFOX1	rs758491	16	C
				Cognitive Decline		rs914166	21	T
				Cognitive Decline		rs11150643	16	C
				Cognitive Decline	COX7A2L	rs1981664	2	A
				Cognitive Decline	COX7A2L	rs10206058	2	G
				Cognitive Decline	PAPPA	rs717963	9	A
				Cognitive Decline		rs10509839	10	A
				Cognitive Decline	RGS6	rs763732	14	T
				Cognitive Decline		rs6884345	5	C
				Cognitive Decline		rs11242336	5	C
				Cognitive Decline	ANK3	rs10994250	10	A
				Cognitive Decline	ANK3	rs10821707	10	G
				Cognitive Decline		rs3912887	4	A
				Cognitive Decline		rs419867	21	A
				Cognitive Decline		rs2837900	21	C
				Cognitive Decline		rs2837902	21	A
				Cognitive Decline	SORBS2	rs13132552	4	T
				Cognitive Decline		rs12633719	3	C
				Cognitive Decline		rs9522088	13	T
				Cognitive Decline		rs885339	13	A
				Cognitive Decline		rs2381958	5	A
				Cognitive Decline		rs10041184	5	A
				Cognitive Decline		rs4265409	1	C
				Cognitive Decline	ANTXR1	rs7584948	2	G

Citation	Study country	Type of Study	Total (n)	Pimary focus of study	Gene	SNP	Chromosome	Effect/Minor allele
(Vounou et al., 2012)	Australia	Genome Wide Association Studies (GWAS)	475	Cognitive Decline	TENM4	rs501435	11	C
				Cognitive Decline		rs1001684	5	A
				Cognitive Decline		rs1257687	14	A
				Cognitive Decline		rs7336788	13	G
				Cognitive Decline	RPL37	rs10065570	5	T
				Cognitive Decline		rs6783007	3	T
				Cognitive Decline		rs10070362	5	C
				Cognitive Decline		rs9522086	13	T
				Cognitive Decline		rs11946115	4	T
				Cognitive Decline		rs7734346	5	T
				Cognitive Decline		rs10155062	4	A
				Cognitive Decline		rs1289501	11	C
				Cognitive Decline	PLEKHG4B	rs11949577	5	A
				Cognitive Decline	PLEKHG4B	rs13436090	5	A
				Cognitive Decline		rs17370295	3	A
				Cognitive Decline	TLE2	rs3760961	19	G
				Cognitive Decline		rs2965069	7	T
				Cognitive Decline	ODZ4_TENM4	rs478090	11	C
				Cognitive Decline	ZNF677	rs2965245	19	A
				Cognitive Decline		rs962492	5	C
				Cognitive Decline	C12orf63_CFAP54	rs7963861	12	T
				Cognitive Decline	PRSS12	rs705837	4	T
				Cognitive Decline	MAP2K5	rs11856999	15	T
				Cognitive Decline	MGLL	rs7653663	3	A
				Cognitive Decline		rs12597064	16	G
				Cognitive Decline	NDST3	rs633398	4	C
				Cognitive Decline	NDST3	rs631271	4	A
				Cognitive Decline	LVRN	rs1529442	5	C
				Cognitive Decline	LVRN	rs6864491	5	A
				Cognitive Decline	NRXN1	rs10445932	2	C
				Cognitive Decline	LVRN	rs885120	5	G
				Cognitive Decline		rs12236788	9	A
(Harold et al., 2009)	Multi-center study	Genome Wide Association Studies (GWAS)	16000	Cognitive Decline	TOMM40	rs2075650	19	G
				Cognitive Decline	CLU	rs11136000	8	G
				Cognitive Decline	PICALM	rs3851179	11	T
				Cognitive Decline	TOMM40	rs157580	19	T
				Cognitive Decline	NECTIN2	rs6859	19	G
				Cognitive Decline	TOMM40	rs8106922	19	A
				Cognitive Decline	SSB	rs11894266	2	G
				Cognitive Decline	MS4A6A	rs610932	11	T
				Cognitive Decline	CNTN5	rs10501927	11	T
				Cognitive Decline	C6orf155	rs9446432	6	G
				Cognitive Decline	BIN1	rs7561528	2	C
				Cognitive Decline	BIN1	rs744373	2	A
				Cognitive Decline	MS4A6A	rs662196	11	G
				Cognitive Decline	MS4A6A	rs583791	11	C
				Cognitive Decline	MS4A4E	rs676309	11	C
				Cognitive Decline	KCNU1	rs1157242	8	C
				Cognitive Decline	DAB1	rs1539053	1	T
				Cognitive Decline	EMSY-AMC11orf30	rs11827375	11	G
				Cognitive Decline	CR1	rs1408077	1	A
				Cognitive Decline	MIR1202/LOC101928923	rs9384428	6	A
				Cognitive Decline	CR1	rs6701713	1	C
				Cognitive Decline	CR1	rs3818361	1	A
(Mengel-from et al.,	Denmark	Candidate Gene Study	1480	Cognitive Decline	Klotho	rs562020	13	G
				Cognitive Decline	Klotho	rs398655	13	G
				Cognitive Decline	Klotho-Haplotype	rs398655/rs562020		C
				Cognitive Decline	Klotho	rs2283368	13	AG
				Cognitive Decline	Klotho	rs9526984	13	C
				Cognitive Decline	Klotho	rs9536314	13	G
				Cognitive Decline	Klotho	rs9527024	13	G
				Cognitive Decline	Klotho	rs648202	13	A
(Yokoyama et al., 2015)	US	Candidate Gene Study	422	Cognitive Decline	Klotho	rs9536314	13	T
				Cognitive Decline	Klotho	rs9527025	13	C
(Hao, Ding, Gao, Yang,	China	Candidate Gene Study	706	Cognitive Decline	Klotho	rs1207568	13	A
(Kachiwala et al., 2005)	UK	Candidate Gene Study	417	Cognitive Decline	PRNP	rs1799990	20	G
(Korostishevsky et al.,	UK	Genome Wide Association Studies (GWAS)	3953	Lean body mass	CYP3A5	rs4646450	7	A
				Lean body mass	SLCO1B1	rs4363657	12	T
				Lean body mass	SLC2A9	rs737267	4	T
				Lean body mass	GCKR	rs1260326	2	T
(Mekli, Nazroo, Marshall, Kumari, &	UK	Candidate Gene Study	3160	Frailty phenotype	TNF	rs1800629	6	A
				Frailty phenotype	PPRJ	rs1566729	11	T
				Frailty phenotype	PPRJ	rs2047812	11	A
				Frailty phenotype	PPRJ	rs1566728	11	C
				Frailty phenotype	ATM	rs611646	11	T
				Frailty phenotype	COMT	rs4646316	22	A
(Patel et al., 2014)	UK	Candidate Gene Study	88	Sarcopenia	VDR	rs731236	12	G
				Sarcopenia	IFNG	rs121913168	12	T
				Sarcopenia	MSTN	rs397515373	2	ClinVar
				Sarcopenia	IL-6	rs1800796	7	G
				Sarcopenia	TNF	rs361525	6	A
				Sarcopenia	IL1R1	rs28362304	2	T
				Sarcopenia	IL1R1	rs949963	2	T
(Matteini et al., 2008)	US	Candidate Gene Study	326	Frailty phenotype	TCN2	rs1544468	22	G
				Frailty phenotype	TCN2-pro259arg	rs2267163	22	T
				Frailty phenotype	FASTKD3/MTRR	rs1801394	5	G
(Frayling et al., 2007)	Italy	Candidate Gene Study	1671	Physcial Function	IL18	rs5744256	11	C
				Physcial Function	IL18	rs543810	11	C
				Physcial Function	IL18	rs1293344	11	G
(Mekli, Marshall, Nazroo, Vanhoutte, &	UK	Candidate Gene Study	3160	Frailty phenotype	IL-18	rs360722	11	A
				Frailty phenotype	IL-12A	rs4679868	3	A
				Frailty phenotype	IL-12A	rs9852519	3	A
				Frailty phenotype	LRP1	rs1799986	12	T
				Frailty phenotype	SELP	rs6131	1	T
(Ho et al., 2011)	US	Candidate Gene Study	349	Frailty phenotype	MTR	rs1770449	1	A
				Frailty phenotype	MTR	rs10925235	1	G
				Frailty phenotype	MTR	rs2297967	1	A
				Frailty phenotype	MTR	rs10802569	1	A
				Frailty phenotype	MTR	rs4659725	1	G
				Frailty phenotype	MTR	rs1050993	1	C
				Frailty phenotype	FN1	rs7567647	2	A
				Frailty phenotype	CREBBP	rs129968	16	A
				Frailty phenotype	CASP8	rs3769827	2	A
				Frailty phenotype	CASP8	rs6747918	2	G
				Frailty phenotype	CASP8	rs2037815	2	G
				Frailty phenotype	CASP8	rs6745051	2	G
				Frailty phenotype	GSTZ1	rs2287396	14	C
				Frailty phenotype	KAT2B	rs2929408	3	T
				Frailty phenotype	TIAM1	rs2833383	21	A
				Frailty phenotype	STAT1	rs1400657	2	T
				Frailty phenotype	TCN2	rs740234	22	C
				Frailty phenotype	BTRC	rs10883642	10	G
				Frailty phenotype	BTRC	rs10883631	10	A
				Frailty phenotype	VTN	rs2227729	17	A

Figure I. PubMed search strategy

((“Frailty”[TIAB] OR “Frail”[TIAB] OR “Physical Frailty”[TIAB] OR "Frail Elderly"[Mesh] OR “Sarcopenia”[Mesh] OR "Muscle Weakness"[Mesh] OR “hand strength”[Mesh] OR “motor activity”[Mesh] OR “weight loss”[Mesh] OR “fatigue”[Mesh] OR “lassitude”[tiab] OR “motor activity”[tiab] OR “motor activities”[tiab] OR “physical activities”[tiab] OR “locomotor activity”[tiab] OR “locomotor activities”[tiab] OR “hand strength”[tiab] OR “grip”[tiab] OR “grips”[tiab] OR “grasp”[tiab] OR “grasps”[tiab] OR “gait speed”[tiab] OR “grip strength”[tiab] OR “physical activity”[tiab] OR “weight loss”[tiab] OR “fatigue”[tiab] OR “sarcopenia”[tiab] OR “tiredness”[tiab] OR “muscular weakness”[tiab])

OR

(“Alzheimer Disease”[Mesh] OR “Dementia”[Mesh] OR “Mild Cognitive Impairment”[Mesh] OR “Cognition Disorders”[Mesh] OR “Alzheimer”[tiab] OR “Alzheimers”[tiab] OR “Alzheimer’s”[tiab] OR “presenile dementia”[tiab] OR “senile dementia”[tiab] OR “cognitive impairment”[tiab] OR “cognitive impairments”[tiab] OR “neurocognitive disorder”[tiab] OR “neurocognitive disorders”[tiab] OR “dementia”[tiab] OR “dementias”[tiab] OR “cognitive decline”[tiab] OR “cognitive declines”[tiab] OR “cognition disorder”[tiab] OR “cognition disorders”[tiab])

OR

(“cognitive frailty”[tiab])

AND

(("Biomarkers "[Mesh] OR "biological markers”[tiab] OR "biological marker”[tiab] OR “biologic markers”[tiab] OR “biologic marker”[tiab] OR "biomarkers”[tiab] OR "biomarker”[tiab] OR "clinical markers”[tiab] OR "clinical marker”[tiab] OR “Immunologic markers”[tiab] OR “immunologic marker”[tiab] OR “immune marker”[tiab] OR “immune markers”[tiab] OR “viral markers”[tiab] OR “viral marker”[tiab] OR “serum markers”[tiab] OR “serum marker”[tiab] OR “surrogate endpoints”[tiab] OR “surrogate endpoints”[tiab] OR “surrogate end points”[tiab] OR “surrogate end point”[tiab] OR “surrogate markers”[tiab] OR “surrogate marker”[tiab] OR “biochemical markers”[tiab] OR “biochemical marker”[tiab] OR “laboratory markers”[tiab] OR “laboratory marker”[tiab] OR “disease marker”[tiab] OR “disease markers”[tiab])

OR

(“Genetic markers”[Mesh] OR “genetic markers”[tiab] OR “genetic marker”[tiab] OR “DNA markers”[tiab] OR “DNA marker”[tiab] OR “Chromosome marker”[tiab] OR “Chromosome markers”)

OR

("Genome-Wide Association Study"[Mesh] OR “genome wide association”[tiab] OR “whole genome association”[tiab] OR “GWAS”[tiab] OR “candidate gene study”[tiab] OR “candidate gene studies”[tiab]))

AND

("Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Longitudinal Studies"[Mesh] OR "Random Allocation"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR “randomized controlled”[tiab] OR “randomised controlled”[tiab] “random allocation”[tiab] OR “cross sectional study”[tiab] OR “cross sectional studies”[tiab] OR “cross sectional analysis”[tiab] OR “cross sectional analyses”[tiab] OR “longitudinal study”[tiab] OR “longitudinal studies”[tiab] OR “cross sectional survey”[tiab] OR “cross sectional surveys”[tiab] OR “prevalence study”[tiab] OR “prevalence studies”[tiab] OR “randomization”[tiab] OR “randomisation”[tiab] OR “cross-sectional research”[tiab] OR “cross-sectional design”[tiab] OR "Genome-Wide Association Study"[Mesh] OR “genome wide association”[tiab] OR “whole genome association”[tiab] OR “GWAS”[tiab] OR “candidate gene study”[tiab] OR “candidate gene studies”[tiab])

References

1. Abdullah L, Paris D, Luis C, et al. The influence of diagnosis, intra- and inter-person variability on serum and plasma Aβ levels. *Neurosci Lett*. 2007;428(2-3):53-58. doi:10.1016/j.neulet.2007.09.058.
2. Aberg D, Johansson P, Isgaard J, et al. Increased Cerebrospinal Fluid Level of Insulin-like Growth Factor-II in Male Patients with Alzheimer's Disease. *J Alzheimer's Dis*. 2015;48(3):637-646. doi:10.3233/JAD-150351.
3. Adamis D, Meagher D, Treloar A, et al. Phenomenological and biological correlates of improved cognitive function in hospitalized elderly medical inpatients. *Arch Gerontol Geriatr*. 2014;59(3):593-598. doi:10.1016/j.archger.2014.08.007.
4. Adriaensen W, Matheï C, Van Pottelbergh G, et al. Significance of serum immune markers in identification of global functional impairment in the oldest old: Cross-sectional results from the BELFRAIL study. *Age (Omaha)*. 2014;36(1):457-467. doi:10.1007/s11357-013-9558-3.
5. Aguilar C, Muehlboeck JS, Mecocci P, et al. Application of a MRI based index to longitudinal atrophy change in Alzheimer disease, mild cognitive impairment and healthy older individuals in the AddNeuroMed cohort. *Front Aging Neurosci*. 2014;6(JUL):1-12. doi:10.3389/fnagi.2014.00145.
6. Albrecht MA, Szoeke C, Maruff P, et al. Longitudinal cognitive decline in the AIBL cohort: The role of APOE ε4 status. *Neuropsychologia*. 2015;75:411-419. doi:10.1016/j.neuropsychologia.2015.06.008.
7. Alcolea D, Martínez-Lage P, Sánchez-Juan P, et al. Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. *Neurology*. 2015;85(7):626-633. doi:10.1212/WNL.0000000000001859.
8. Al-Turki MA, Boston P, McKirdy S, Barker ME. Vitamin B12 and folate status in patients with confirmed Alzheimer's disease. *Proc Nutr Soc*. 2011;70(6):E395. doi:10.1017/S0029665111004800.
9. Alvarez-Ríos AI, Guerrero JM, García-García FJ, et al. Associations between frailty and serum N-terminal propeptide of type I procollagen and 25-hydroxyvitamin D in older Spanish women: The Toledo Study for Healthy Aging. *Exp Gerontol*. 2015;69:79-84. doi:10.1016/j.exger.2015.05.011.
10. Andersson C, Blennow K, Almkvist O, et al. Increasing CSF phospho-tau levels during cognitive decline and progression to dementia. *Neurobiol Aging*. 2008;29(10):1466-1473. doi:10.1016/j.neurobiolaging.2007.03.027.
11. Annweiler C, Bataille R, Ferrire N, Douillet D, Fantino B, Beauchet O. Plasma beta-2 microglobulin as a marker of frailty in older adults: A pilot study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2011;66 A(10):1077-1079. doi:10.1093/gerona/glr104.
12. Annweiler C, Schott AM, Abellan Van Kan G, et al. The Five-Times-Sit-to-stand test, a marker of global cognitive functioning among community-dwelling older women. *J Nutr Heal Aging*. 2011;15(4):271-276. doi:10.1007/s12603-011-0037-1.
13. Apostolova LG, Hwang KS, Avila D, et al. Brain amyloidosis ascertainment from cognitive, imaging, and peripheral blood protein measures. *Neurology*. 2015;84(7):729-737. doi:10.1212/WNL.0000000000001231.
14. Li S, Okonkwo O, Albert M, Wang M-C. Variation in Variables that Predict Progression

from MCI to AD Dementia over Duration of Follow-up. *Am J Alzheimer's Dis (Columbia, Mo)*. 2013;2(1):12-28. doi:10.7726/ajad.2013.1002.
15. Armstrong A, Mattsson N, Appelqvist H, et al. Lysosomal network proteins as potential novel CSF biomarkers for Alzheimer's disease. *NeuroMolecular Med*. 2014;16(1):150-160. doi:10.1007/s12017-013-8269-3.
16. Aschenbrenner AJ, Balota DA, Fagan AM, Duchek JM, Benzinger TLS, Morris JC. Alzheimer Disease Cerebrospinal Fluid Biomarkers Moderate Baseline Differences and Predict Longitudinal Change in Attentional Control and Episodic Memory Composites in the Adult Children Study. *J Int Neuropsychol Soc*. 2015;21(8):573-583. doi:10.1017/S1355617715000776.
17. Ashton NJ, Kiddle SJ, Graf J, et al. Blood protein predictors of brain amyloid for enrichment in clinical trials? *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2015;1(1):48-60. doi:10.1016/j.dadm.2014.11.005.
18. Atti AR, Palmer K, Volpato S, Zuliani G, Winblad B, Fratiglioni L. Anaemia increases the risk of dementia in cognitively intact elderly. *Neurobiol Aging*. 2006;27(2):278-284. doi:10.1016/j.neurobiolaging.2005.02.007.
19. Auyeung TW, Lee JSW, Kwok T, et al. Testosterone but not estradiol level is positively related to muscle strength and physical performance independent of muscle mass: A cross-sectional study in 1489 older men. *Eur J Endocrinol*. 2011;164(5):811-817. doi:10.1530/EJE-10-0952.
20. Baldeiras I, Santana I, Proença MT, et al. Oxidative damage and progression to Alzheimer's disease in patients with mild cognitive impairment. *J Alzheimer's Dis*. 2010;21(4):1165-1177. doi:10.3233/JAD-2010-091723.
21. Bambo MP, Garcia-Martin E, Gutierrez-Ruiz F, et al. Analysis of optic disk color changes in Alzheimer's disease: A potential new biomarker. *Clin Neurol Neurosurg*. 2015;132:68-73. doi:10.1016/j.clineuro.2015.02.016.
22. Bambo MP, Garcia-Martin E, Pinilla J, et al. Detection of retinal nerve fiber layer degeneration in patients with Alzheimer's disease using optical coherence tomography: searching new biomarkers. *Acta Ophthalmol*. 2014;92(7):e581-e582. doi:10.1111/aos.12374.
23. Bartali B, Semba RD, Frongillo EA, et al. Low micronutrient levels as a predictor of incident disability in older women. *Arch Intern Med*. 2006;166(21):2335-2340. doi:10.1001/archinte.166.21.2335.
24. Baylis D, Bartlett DB, Syddall HE, et al. Immune-endocrine biomarkers as predictors of frailty and mortality: A 10-year longitudinal study in community-dwelling older people. *Age (Omaha)*. 2013;35(3):963-971. doi:10.1007/s11357-012-9396-8.
25. Baylis D, Ntani G, Edwards MH, et al. Inflammation, telomere length, and grip strength: A 10-year longitudinal study. *Calcif Tissue Int*. 2014;95(1):54-63. doi:10.1007/s00223-014-9862-7.
26. Beasley JM, Lacroix AZ, Neuhouser ML, et al. Protein intake and incident frailty in the women's health initiative observational study. *J Am Geriatr Soc*. 2010;58(6):1063-1071. doi:10.1111/j.1532-5415.2010.02866.x.
27. Beasley JM, Wertheim BC, Lacroix AZ, et al. Biomarker-calibrated protein intake and physical function in the women's health initiative. *J Am Geriatr Soc*. 2013;61(11):1863-

1871. doi:10.1111/jgs.12503.
28. Beauchet O, Allali G, Montero-Odasso M, Sejdić E, Fantino B, Annweiler C. Motor phenotype of decline in cognitive performance among community-dwellers without dementia: Population-based study and meta-analysis. *PLoS One*. 2014;9(6). doi:10.1371/journal.pone.0099318.
29. Berr C, Balansard B, Arnaud J, Roussel AM, Alpérovitch A. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Artériel. *J Am Geriatr Soc*. 2000;48(10):1285-1291. doi:10.1111/j.1532-5415.2000.tb02603.x.
30. Bertens D, Knol DL, Scheltens P, Visser PJ. Temporal evolution of biomarkers and cognitive markers in the asymptomatic, MCI, and dementia stage of Alzheimer's disease. *Alzheimer's Dement*. 2015;11(5):511-522. doi:10.1016/j.jalz.2014.05.1754.
31. Blain H, Jaussent A, Béziat S, et al. Low serum IL-6 is associated with high 6-minute walking performance in asymptomatic women aged 20 to 70years. *Exp Gerontol*. 2012;47(2):143-148. doi:10.1016/j.exger.2011.11.008.
32. Blennow K, De Meyer G, Hansson O, et al. Evolution of Abeta42 and Abeta40 levels and Abeta42/Abeta40 ratio in plasma during progression of Alzheimer's disease: a multicenter assessment. *J Nutr Health Aging*. 2009;13(3):205-208.
33. Blennow K, Zetterberg H, Minthon L, et al. Longitudinal stability of CSF biomarkers in Alzheimer's disease. *Neurosci Lett*. 2007;419(1):18-22. doi:10.1016/j.neulet.2007.03.064.
34. Borroni B, Colciaghi F, Archetti S, et al. Predicting Cognitive Decline in Alzheimer Disease: Role of Platelet Amyloid Precursor Protein. 2004;18(1):32-34. doi:10.1097/00002093-200401000-00006.
35. Bowman GL, Silbert LC, Howieson D, et al. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. *Neurology*. 2012;78(4):241-249. doi:10.1212/WNL.0b013e3182436598.
36. Bretsky PM, Buckwalter JG, Seeman TE, et al. Evidence for an interaction between apolipoprotein E genotype, gender, and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1999;13(4):216-221. http://www.ncbi.nlm.nih.gov/pubmed/10609670.
37. Brys M, Pirraglia E, Rich K, et al. Prediction and longitudinal study of CSF biomarkers in mild cognitive impairment. *Neurobiol Aging*. 2009;30(5):682-690. doi:10.1016/j.neurobiolaging.2007.08.010.
38. Breitling LP, Müller H, Stegmaier C, Kliegel M, Brenner H. Association of prion protein with cognitive functioning in humans. *Exp Gerontol*. 2012;47(12):919-924. doi:10.1016/j.exger.2012.08.001.
39. Buerger K, Teipel SJ, Zinkowski R, et al. CSF tau protein phosphorylated at threonine-231 correlates with cognitive decline in MCI subjects. *Neurology*. 2002;59:627-629.
40. Buerger K, Zinkowski R, Teipel SJ, et al. Differential diagnosis of Alzheimer disease with cerebrospinal fluid levels of tau protein phosphorylated at threonine 231. *Arch Neurol*. 2002;59(8):1267-1272. doi:10.1001/archneur.59.8.1267.
41. Busch T de A, Duarte YA, Pires Nunes D, et al. Factors associated with lower gait speed among the elderly living in a developing country: a cross-sectional population-based study. *BMC Geriatr*. 2015;15(1):35. doi:10.1186/s12877-015-0031-2.
42. Woodward MR, Amrutkar C V, Shah HC, et al. Validation of olfactory deficit as a biomarker of Alzheimer disease. *Neurol Clin Pract*. 2017;7(1):5-14.

doi:10.1212/CPJ.0000000000000293.
43. Cankurtaran M, Yesil Y, Kuyumcu ME, et al. Altered levels of homocysteine and serum natural antioxidants links oxidative damage to Alzheimer's disease. *J Alzheimer's Dis*. 2013;33(4):1051-1058. doi:10.3233/JAD-2012-121630.
44. Canon ME, Crimmins EM. Sex DifferenceS in the ASSociAtion between MuScle QuAlity , inflAMMAtory MArkerS , AnD cognitive Decline. 2011;15(8):695-698.
45. Cheung CL, Nguyen USDT, Au E, Tan KCB, Kung AWC. Association of handgrip strength with chronic diseases and multimorbidity: A cross-sectional study. *Age (Omaha)*. 2013;35(3):929-941. doi:10.1007/s11357-012-9385-y.
46. Chiu MJ, Yang SY, Chen TF, et al. New assay for old markers-plasma beta amyloid of mild cognitive impairment and Alzheimer's disease. *Curr Alzheimer Res*. 2012;9(10):1142-1148. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L368517719%5Cnhttp://dx.doi.org/10.2174/156720512804142967%5Cnhttp://nihlibrarysfx.nih.gov:9003/sfx_local?sid=EMBASE&issn=15672050&id=doi:10.2174/156720512804142967&atitle=New+assay+.
47. Chin AV, Robinson DJ, O'Connell H, et al. Vascular biomarkers of cognitive performance in a community-based elderly population: The Dublin Healthy Ageing study. *Age Ageing*. 2008;37(5):559-564. doi:10.1093/ageing/afn144.
48. Cho HJ, Kivimäki M, Bower JE, Irwin MR. Association of C-reactive protein and interleukin-6 with new-onset fatigue in the Whitehall II prospective cohort study. *Psychol Med*. 2013;43(8):1773-1783. doi:10.1017/S0033291712002437.
49. Roe CM, Fagan AM, Williams MM, et al. Improving CSF biomarker accuracy in predicting prevalent and incident Alzheimer disease. *Neurology*. 2011;76(6):501-510. doi:10.1212/WNL.0b013e31820af900.
50. Cohen AA, Milot E, Li Q, et al. Detection of a novel, integrative aging process suggests complex physiological integration. *PLoS One*. 2015;10(3):1-26. doi:10.1371/journal.pone.0116489.
51. Cohen-Manheim I, Doniger GM, Sinnreich R, et al. Increase in the inflammatory marker GlycA over 13 years in young adults is associated with poorer cognitive function in midlife. *PLoS One*. 2015;10(9):12-16. doi:10.1371/journal.pone.0138036.
52. Collerton J, Martin-Ruiz C, Davies K, et al. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: Cross-sectional findings from the Newcastle 85+ Study. *Mech Ageing Dev*. 2012;133(6):456-466. doi:10.1016/j.mad.2012.05.005.
53. Craig-Schapiro R, Kuhn M, Xiong C, et al. Multiplexed immunoassay panel identifies novel CSF biomarkers for alzheimer's disease diagnosis and prognosis. *PLoS One*. 2011;6(4). doi:10.1371/journal.pone.0018850.
54. Deschamps V, Astier X, Ferry M, Rainfray M, Emeriau J, Barberger-Gateau P. Nutritional status of healthy elderly persons living in Dordogne, France, and relation with mortality and cognitive or functional decline. *Eur J Clin Nutr*. 2002;56(4):305-312. doi:10.1038/sj.ejcn.1601311.
55. Devanand DP, Schupf N, Stern Y, et al. Plasma A β and PET PiB binding are inversely related in mild cognitive impairment. *Neurology*. 2011;77(2):125-131.

doi:10.1212/WNL.0b013e318224afb7.
56. Doecke JD, Laws SM, Faux NG, et al. Blood-Based Protein Biomarkers for Diagnosis of Alzheimer Disease. *Arch Neurol*. 2012;69(10):1318. doi:10.1001/archneurol.2012.1282.
57. Doets EL, Ueland PM, Tell GS, et al. Interactions between plasma concentrations of folate and markers of vitamin B12 status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. *Br J Nutr*. 2014;111(6):1085-1095. doi:10.1017/S000711451300336X.
58. Dregan A, Stewart R, Gulliford MC. Cardiovascular risk factors and cognitive decline in adults aged 50 and over: A population-based cohort study. *Age Ageing*. 2013;42(3):338-345. doi:10.1093/ageing/afs166.
59. Drey M, Sieber CC, Bauer JM, et al. C-terminal Agrin Fragment as a potential marker for sarcopenia caused by degeneration of the neuromuscular junction. *Exp Gerontol*. 2013;48(1):76-80. doi:10.1016/j.exger.2012.05.021.
60. Dumurgier J, Mouton-Liger F, Lapalus P, et al. Cerebrospinal Fluid PKR Level Predicts Cognitive Decline in Alzheimer's Disease. *PLoS One*. 2013;8(1):1-5. doi:10.1371/journal.pone.0053587.
61. Elosua R, Bartali B, Ordovas JM, Corsi AM, Lauretani F, Ferrucci L. Association between physical activity, physical performance, and inflammatory biomarkers in an elderly population: The InCHIANTI study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2005;60(6):760-767. http://www.scopus.com/inward/record.url?eid=2-s2.0-21144432015&partnerID=40&md5=a2b8d1fc8c7a4a3d8a1f2ef88a69f2aa.
62. Emanuele E, D'Angelo A, Tomaino C, et al. Circulating Levels of Soluble Receptor for Advanced Glycation End Products in Alzheimer Disease and Vascular Dementia. *Arch Neurol*. 2005;62(11):1734. doi:10.1001/archneur.62.11.1734.
63. Stomrud E, Hansson O, Zetterberg H, Blennow K, Minthon L, Londos E. Correlation of Longitudinal Cerebrospinal Fluid Biomarkers With Cognitive Decline in Healthy Older Adults. *Arch Neurol*. 2010;67(2):217-223. doi:10.1001/archneurol.2009.316.
64. Feeney J, Finucane C, Savva GM, et al. Low macular pigment optical density is associated with lower cognitive performance in a large, population-based sample of older adults. *Neurobiol Aging*. 2013;34(11):2449-2456. doi:10.1016/j.neurobiolaging.2013.05.007.
65. Bouwman FH, van der Flier WM, Schoonenboom NS, et al. Longitudinal changes of CSF biomarkers in memory clinic patients. *Neurology*. 2007;69(10):1006-1011. doi:10.1212/01.wnl.0000271375.37131.04.
66. Fleisher AS, Chen K, Quiroz YT, et al. Associations Between Biomarkers and Age in the Presenilin 1 E280A Autosomal Dominant Alzheimer Disease Kindred. *JAMA Neurol*. 2015;72(3):316. doi:10.1001/jamaneurol.2014.3314.
67. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal Fluid tau/β-Amyloid42 Ratio as a Prediction of Cognitive Decline in Nondemented Older Adults. *Arch Neurol*. 2007;64(3):343. doi:10.1001/archneur.64.3.noc60123.
68. Fagan AM, Xiong C, Jasielec MS, et al. Longitudinal Change in CSF Biomarkers in Autosomal-Dominant Alzheimer's Disease. *Sci Transl Med*. 2014;6(226):226ra30-226ra30. doi:10.1126/scitranslmed.3007901.
69. Forlenza O V, Diniz BS, Talib LL, et al. Clinical and biological predictors of Alzheimer's disease in patients with amnestic mild cognitive impairment TT -

Preditores clínicos e biológicos da evolução para doença de Alzheimer em pacientes com comprometimento cognitivo leve amnéstico. *Rev Bras Psiquiatr*. 2010;32(3):216-222. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1516-44462010000300004&lang=pt%0Ahttp://www.scielo.br/pdf/rbp/v32n3/aop0210.pdf.

70. Faux NG, Ellis KA, Porter L, et al. Homocysteine, vitamin B12, and folic acid levels in Alzheimer's disease, mild cognitive impairment, and healthy elderly: Baseline characteristics in subjects of the australian imaging biomarker lifestyle study. *J Alzheimer's Dis*. 2011;27(4):909-922. doi:10.3233/JAD-2011-110752.
71. Faux NG, Rembach A, Wiley J, et al. An anemia of Alzheimer's disease. *Mol Psychiatry*. 2014;19(11):1227-1234. doi:10.1038/mp.2013.178.
72. Fei M, Jianghua W, Rujuan M, Wei Z, Qian W. The relationship of plasma A?? levels to dementia in aging individuals with mild cognitive impairment. *J Neurol Sci*. 2011;305(1-2):92-96. doi:10.1016/j.jns.2011.03.005.
73. Felicio DC, Pereira DS, Assumpção AM, et al. Inflammatory mediators, muscle and functional performance of community-dwelling elderly women. *Arch Gerontol Geriatr*. 2014;59(3):549-553. doi:10.1016/j.archger.2014.08.004.
74. Gale CR, Baylis D, Cooper C, Sayer AA. Inflammatory markers and incident frailty in men and women: The english longitudinal study of ageing. *Age (Omaha)*. 2013;35(6):2493-2501. doi:10.1007/s11357-013-9528-9.
75. Garcia AA, Haron Y, Evans LR, Smith MG, Freedman M, Roman GC. Metabolic markers of cobalamin deficiency and cognitive function in normal older adults. *J Am Geriatr Soc*. 2004;52(1):66-71. http://sfx.scholarsportal.info/waterloo?sid=OVID:medline%7B&%7Did=pmid:14687317%7B&%7Did=doi:%7B&%7Dissn=0002-8614%7B&%7Disbn=%7B&%7Dvolume=52%7B&%7Dissue=1%7B&%7Dspage=66%7B&%7Dpages=66-71%7B&%7Ddate=2004%7B&%7Dtitle=Journal+of+the+American+Geriatrics+So.
76. Berenguer RG, Monge Argilés JA, Ruiz CM, Payá JS, Blanco Cantó MA, Santana CL. Alzheimer disease cerebrospinal fluid biomarkers predict cognitive decline in healthy elderly over 2 years. *Alzheimer Dis Assoc Disord*. 2014;28(3):234-238. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L53054907%5Cnhttp://dx.doi.org/10.1097/WAD.0000000000000025.
77. Gattaz WF, Forlenza O V., Talib LL, Barbosa NR, Bottino CMC. Platelet phospholipase A2 activity in Alzheimer's disease and mild cognitive impairment. *J Neural Transm*. 2004;111(5):591-601. doi:10.1007/s00702-004-0142-y.
78. Ghidoni R, Benussi L, Glionna M, et al. Plasma cystatin C and risk of developing Alzheimer's disease in subjects with mild cognitive impairment. *J Alzheimer's Dis JAD*. 2010;22(3):985-991. doi:10.3233/JAD-2010-101095.
79. Li G, Millard SP, Peskind ER, et al. Cross-Sectional and Longitudinal Relationships Between Cerebrospinal Fluid Biomarkers and Cognitive Function in People Without Cognitive Impairment From Across the Adult Life Span. *JAMA Neurol*. 2014;71(6):742. doi:10.1001/jamaneurol.2014.445.
80. Glodzik-Sobanska L, Pirraglia E, Brys M, et al. The effects of normal aging and ApoE genotype on the levels of CSF biomarkers for Alzheimer's disease. *Neurobiol Aging*.

2009;30(5):672-681. doi:10.1016/j.neurobiolaging.2007.08.019.
81. Goetzl EJ, Boxer A, Schwartz JB, et al. Altered lysosomal proteins in neural-derived plasma exosomes in preclinical Alzheimer disease. *Neurology*. 2015;85(1):40-47. doi:10.1212/WNL.0000000000001702.
82. Gomez-Marcos MA, Recio-Rodríguez JI, Patino-Alonso MC, et al. Relationship between Physical Activity and Plasma Fibrinogen Concentrations in Adults without Chronic Diseases. *PLoS One*. 2014;9(2):e87954. doi:10.1371/journal.pone.0087954.
83. Growdon ME, Schultz AP, Dagley AS, et al. Odor identification and Alzheimer disease biomarkers in clinically normal elderly. *Neurology*. 2015;84(21):2153-2160. doi:10.1212/WNL.0000000000001614 [doi].
84. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic load and frailty in older adults. *J Am Geriatr Soc*. 2009;57(9):1525-1531. doi:10.1111/j.1532-5415.2009.02389.x.
85. Gupta VB, Wilson AC, Burnham S, et al. Follow-up plasma apolipoprotein E levels in the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) cohort. *Alzheimers Res Ther*. 2015;7(1):16. doi:10.1186/s13195-015-0105-6.
86. Heringa SM, Van den Berg E, Reijmer YD, et al. Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. *Psychoneuroendocrinology*. 2014;40(1):108-118. doi:10.1016/j.psyneuen.2013.11.011.
87. Hohman TJ, Bell SP, Jefferson AL. The Role of Vascular Endothelial Growth Factor in Neurodegeneration and Cognitive Decline. *JAMA Neurol*. 2015;72(5):520. doi:10.1001/jamaneurol.2014.4761.
88. Howard C, Ferrucci L, Sun K. Oxidative protein damage is associated with poor grip strength among older women living in the community. *J Appl Physiol*. 2007;21205:17-20. doi:10.1152/japplphysiol.00133.2007.
89. Hsu B, Cumming R, Naganathan V, Blyth F, Handelsman D. Reproductive Hormones and Cognitive Impairment Among Community-Dwelling Older Men: the Concord Health and Ageing in Men Project. *Alzheimer's Dement*. 2014;10(4):P587. doi:10.1016/j.jalz.2014.05.977.
90. Liaw F-Y, Kao T-W, Fang W-H, Han D-S, Chi Y-C, Yang W-S. Increased follistatin associated with decreased gait speed among old adults. *Eur J Clin Invest*. 2016;46(4):321-327. doi:10.1111/eci.12595.
91. Hye A, Riddoch-Contreras J, Baird AL, et al. Plasma proteins predict conversion to dementia from prodromal disease. *Alzheimer's Dement*. 2014;10(6):799-807. doi:10.1016/j.jalz.2014.05.1749.
92. Hochstrasser T, Ehrlich D, Marksteiner J, Sperner-Unterweger B, Humpel C. Matrix metalloproteinase-2 and epidermal growth factor are decreased in platelets of Alzheimer patients. *Curr Alzheimer Res*. 2012;9(8):982-989. doi:10.2174/156720512803251156.
93. Hendrickson RC, Lee AYH, Song Q, et al. High resolution discovery proteomics reveals candidate disease progression markers of Alzheimer's disease in human cerebrospinal fluid. *PLoS One*. 2015;10(8):1-20. doi:10.1371/journal.pone.0135365.
94. Hessen E, Nordlund A, Stalhammar J, et al. T-Tau is Associated with Objective Memory Decline over Two Years in Persons Seeking Help for Subjective Cognitive Decline: A

Report from the Gothenburg-Oslo MCI Study. *J Alzheimer's Dis*. 2015;47(3):619-628. doi:10.3233/JAD-150109.
95. Zetterberg H, Andreasson U, Hansson O, et al. Elevated cerebrospinal fluid BACE1 activity in incipient Alzheimer disease. *Arch Neurol*. 2008;65(8):1102-1107. doi:10.1001/archneur.65.8.1102.
96. Inglés M, Gambini J, Carnicero JA, et al. Oxidative stress is related to frailty, not to age or sex, in a geriatric population: Lipid and protein oxidation as biomarkers of frailty. *J Am Geriatr Soc*. 2014;62(7):1324-1328. doi:10.1111/jgs.12876.
97. Jefferson AL, Massaro JM, Wolf PA, et al. Inflammatory biomarkers are associated with total brain volume The Framingham Heart Study. *Neurology*. 2007;68:1032-1038. doi:10.1212/01.wnl.0000257815.20548.df.Inflammatory.
98. Jagielski AC, Jiang CQ, Xu L, et al. Glycaemia is associated with cognitive impairment in older adults: the Guangzhou Biobank Cohort Study. *Age Ageing*. 2015;44(1):65-71. doi:10.1093/ageing/afu088.
99. Barnett JH, Damian M, Verhey FRJ, et al. Cognitive and CSF biomarkers in older adults, MCI, and dementia. *Alzheimer's Dement*. 2011;7(4):S129-S130. doi:10.1016/j.jalz.2011.05.340.
100. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE, Alzheimer's Disease Neuroimaging Initiative. Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to Alzheimer disease in patients in the Alzheimer's disease neuroimaging initiative. *Arch Gen Psychiatry*. 2011;68(9):961-969. doi:10.1001/archgenpsychiatry.2011.96.
101. Kanai M, Matsubara E, Isoe K, Utakami K. Longitudinal Study of Cerebrospinal Fluid Alzheimer ' s Disease : A Study in Japan. *Ann Neurol*. 1998;42(43).
102. Kantarci K, Weigand SD, Petersen RC, et al. Longitudinal 1H MRS changes in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2007;28(9):1330-1339. doi:10.1016/j.neurobiolaging.2006.06.018.
103. Kelly D, Coen RF, Akuffo KO, et al. Cognitive function and its relationship with macular pigment optical density and serum concentrations of its constituent carotenoids. *J Alzheimer's Dis*. 2015;48(1):261-277. doi:10.3233/JAD-150199.
104. Kester MI, Teunissen CE, Sutphen C, et al. Cerebrospinal fluid VILIP-1 and YKL-40, candidate biomarkers to diagnose, predict and monitor Alzheimer's disease in a memory clinic cohort. *Alzheimers Res Ther*. 2015;7(1):59. doi:10.1186/s13195-015-0142-1.
105. Kester MI, Scheffer PG, Koel-Simmelink MJ, et al. Serial CSF sampling in Alzheimer's disease: Specific versus non-specific markers. *Neurobiol Aging*. 2012;33(8):1591-1598. doi:10.1016/j.neurobiolaging.2011.05.013.
106. Simpson BN, Kim M, Chuang Y-F, et al. Blood metabolite markers of cognitive performance and brain function in aging. *J Cereb Blood Flow Metab*. 2016;36(7):1212-1223. doi:10.1177/0271678X15611678.
107. Kim S-M, Song J, Kim S, et al. Identification of peripheral inflammatory markers between normal control and Alzheimer's disease. *BMC Neurol*. 2011;11(1):51. doi:10.1186/1471-2377-11-51.
108. Kleinschmidt M, Schoenfeld R, G'ottlich C, et al. Characterizing Aging, Mild Cognitive Impairment, and Dementia with Blood-Based Biomarkers and Neuropsychology. *J*

Alzheimer's Dis. 2015;50(1):111-126. doi:10.3233/JAD-143189.
109. Koal T, Klavins K, Seppi D, Kemmler G, Humpel C. Sphingomyelin SM(d18:1/18:0) is significantly enhanced in cerebrospinal fluid samples dichotomized by pathological amyloid-β42, tau, and phospho-tau-181 levels. *J Alzheimers Dis*. 2015;44(4):1193-1201. doi:10.3233/JAD-142319.
110. Kobrosly RW, Seplaki CL, Jones CM, van Wijngaarden E. Physiologic Dysfunction Scores and Cognitive Function Test Performance in US Adults. *Psychosom Med*. 2012;74(1):81-88. doi:10.1097/PSY.0b013e3182385b1e.
111. Kravitz BA, Corrada MM, Kawas CH. Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. *Alzheimer's Dement*. 2009;5(4):318-323. doi:10.1016/j.jalz.2009.04.1230.
112. Kumar R, Mohan N, Upadhyay AD, et al. Identification of serum sirtuins as novel noninvasive protein markers for frailty. *Aging Cell*. 2014;13(6):975-980. doi:10.1111/acel.12260.
113. Kuyumcu ME, Yesil Y, Oztürk ZA, et al. The evaluation of neutrophil-lymphocyte ratio in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2012;34(2):69-74. doi:10.1159/000341583.
114. Lafaille-Magnan M-E, Breitner J, Etienne P, et al. Olfactory identification as a potential marker of presymptomatic Alzheimer's disease. *Alzheimer's Dement*. 2013;9(4):P208. doi:http://dx.doi.org/10.1016/j.jalz.2013.05.383.
115. Laske C, Stellos K, Hoffmann N, et al. Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. *Int J Neuropsychopharmacol*. 2011;14(3):399-404. doi:10.1017/S1461145710001008.
116. Licastro F, Davis LJ, Polazzi E, Rossi S, Cucinotta D. Serological alpha 1-antichymotrypsin in patients with probable senile dementia of Alzheimer type: a short-term longitudinal study. *Alzheimer Dis Assoc Disord*. 1996;10(4):192-196.
117. Licastro F, Pedrini S, Davis LJ, et al. α-1-Antichymotrypsin and oxidative stress in the peripheral blood from patients with probable Alzheimer disease: A short-term longitudinal study. *Alzheimer Dis Assoc Disord*. 2001;15(1):51-55. doi:10.1097/00002093-200101000-00007.
118. Li G, Sokal I, Quinn JF, et al. CSF tau/Abeta42 ratio for increased risk of mild cognitive impairment: a follow-up study. *Neurology*. 2007;69(7):631-639. doi:10.1212/01.wnl.0000267428.62582.aa.
119. Lildballe DL, Fedosov S, Sherliker P, Hin H, Clarke R, Nexo E. Association of cognitive impairment with combinations of vitamin B \n 12-related parameters. *Clin Chem*. 2011;57(10):1436-1443. doi:10.1373/clinchem.2011.165944.
120. Zuliani G, Guerra G, Ranzini M, et al. High interleukin-6 plasma levels are associated with functional impairment in older patients with vascular dementia. *Int J Geriatr Psychiatry*. 2007;22(4):305-311. doi:10.1002/gps.1674.
121. Zubenko GS, Hughes III HB, Stiffler JS. D10S1423 identifies a susceptibility locus for Alzheimer's disease in a prospective, longitudinal, double-blind study of asymptomatic individuals. *Mol Psychiatry*. 2001;6(4):413-419. doi:10.1038/sj.mp.4000900.
122. Zetterberg H, Pedersen M, Lind K, et al. Intra-individual stability of CSF biomarkers for Alzheimer's disease over two years. *J Alzheimer's Dis*. 2007;12(3):255-260.

http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L350179256%5Cnhttp://nihlibrarysfx.nih.gov:9003/sfx_local?sid=EMBASE&issn=13872877&id=doi:&atitle=Intra-individual+stability+of+CSF+biomarkers+for+Alzheimer's+disease+over+two+years&.

123. A. M. Zelisko, D. R. Kerwin JMK. The relationship between body mass index, adipocytokines, estrone and cognitive function in postmenopausal women of the Women's Health Initiative Study of Cognitive Aging(WHISCA). 2010:176-177.
124. Zamroziewicz MK, Paul EJ, Rubin RD, Barbey AK. Anterior cingulate cortex mediates the relationship between O3PUFAs and executive functions in APOE e4 carriers. *Front Aging Neurosci*. 2015;7(MAY):1-7. doi:10.3389/fnagi.2015.00087.
125. Leng SX, Hung W, Cappola AR, Yu Q, Xue Q-L, Fried LP. White Blood Cell Counts, Insulinlike Growth Factor-1 Levels, and Frailty in Community-Dwelling Older Women. *Journals Gerontol Ser A Biol Sci Med Sci*. 2009;64A(4):499-502. doi:10.1093/gerona/gln047.
126. Leng SX, Tian X, Matteini A, et al. Il-6-independent association of elevated serum neopterin levels with prevalent frailty in community-dwelling older adults. *Age Ageing*. 2011;40(4):475-481. doi:10.1093/ageing/afr047.
127. Liu CK, Lyass A, Massaro JM, D'Agostino RB, Fox CS, Murabito JM. Chronic kidney disease defined by cystatin C predicts mobility disability and changes in gait speed: The Framingham Offspring Study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2014;69 A(3):301-307. doi:10.1093/gerona/glt096.
128. Locascio JJ, Fukumoto H, Yap L, et al. Plasma Amyloid β-Protein and C-reactive Protein in Relation to the Rate of Progression of Alzheimer Disease. *Arch Neurol*. 2008;65(6):776-785. doi:10.1001/archneur.65.6.776.
129. Lopez OL, Kuller LH, Mehta PD, et al. Plasma amyloid levels and the risk of AD in normal subjects in the Cardiovascular Health Study. *Neurology*. 2008;70(19 PART 1):1664-1671. doi:10.1212/01.wnl.0000306696.82017.66.
130. Luchsinger JA, Tang MX, Miller J, Green R, Mehta PD, Mayeux R. Relation of plasma homocysteine to plasma amyloid beta levels. *Neurochem Res*. 2007;32(4-5):775-781. doi:10.1007/s11064-006-9207-7.
131. Luis C, Abdullah L, Ait-Ghezala G, et al. A novel screening approach for MCI/AD. *Alzheimer's Dement*. 2011;7(4):S254-S255. doi:http://dx.doi.org/10.1016/j.jalz.2011.05.722.
132. Ma C, Li J, Bao Z, Ruan Q, Yu Z. Serum Levels of ApoA1 and ApoA2 Are Associated with Cognitive Status in Older Men. *Biomed Res Int*. 2015;2015. doi:10.1155/2015/481621.
133. Maeba R, Nishimukai M, Sakasegawa S, Sugimori D, Hara H. *Plasma/Serum Plasmalogens: Methods of Analysis and Clinical Significance*. Vol 70. 1st ed. Elsevier Inc.; 2015. doi:10.1016/bs.acc.2015.03.005.
134. Mancinella A, Mancinella M, Carpinteri G, et al. Is there a relationship between high C-reactive protein (CRP) levels and dementia? *Arch Gerontol Geriatr*. 2009;49 Suppl 1:185-194. doi:10.1016/j.archger.2009.09.028.
135. Marksteiner J, Humpel C. Glycogen-synthase kinase-3β is decreased in peripheral blood mononuclear cells of patients with mild cognitive impairment. *Exp Gerontol*. 2009;44(6-7):370-371. doi:10.1016/j.exger.2009.02.007.

136. Martin-Ruiz C, Jagger C, Kingston A, et al. Assessment of a large panel of candidate biomarkers of ageing in the Newcastle 85+ study. *Mech Ageing Dev*. 2011;132(10):496-502. doi:10.1016/j.mad.2011.08.001.
137. Matteini AM, Walston JD, Fallin MD, et al. Markers of B-Vitamin Deficiency and Frailty in Older Women. *J Nutr Heal Aging*. 2008;12(5):303-308. doi:10.1007/BF02982659.
138. Mattsson N, Ewers M, Rich K, Kaiser E, Mulugeta E, Rose E. CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment. *JAMA*. 2009;302(4):385-393.
139. Yin Y, Fan Y, Lin F, Xu Y, Zhang J. Nutrient biomarkers and vascular risk factors in subtypes of mild cognitive impairment: A cross-sectional study. *J Nutr Heal Aging*. 2014;19(1):39-47. doi:10.1007/s12603-014-0510-8.
140. Yavuz, Burcu Balam, Yavuz,Bunyamin, Halil, Meltem, Cankurtaran, Mustafa, Ulger, Zeheriya, Cankurtaran, Eylem S., Aytemir, Kudret, Ariogul S. Serum elevated gamma glutamyltransferase levels may be a marker for oxidative stress in Alzheimer's disease. 2008.
141. Yano Y, Matsuda S, Hatakeyama K, et al. Plasma pentraxin 3, but not high-sensitivity c-reactive protein, is a useful inflammatory biomarker for predicting cognitive impairment in elderly hypertensive patients. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2010;65 A(5):547-552. doi:10.1093/gerona/glq030.
142. Yarasheski KE, Bhasin S, Sinha-Hikim I, Pak-Loduca J, Gonzalez-Cadavid NF. Serum myostatin-immunoreactive protein is increased in 60-92 year old women and men with muscle wasting. *J Nutr Health Aging*. 2002;6(5):343-348.
143. Yang E, Farnum M, Lobanov V, et al. Quantifying the pathophysiological timeline of Alzheimer's disease. *J Alzheimer's Dis*. 2011;26(4):745-753. doi:10.3233/JAD-2011-110551.
144. Wu SH, Shu XO, Chow W-H, et al. Nonexercise Physical Activity and Inflammatory and Oxidative Stress Markers in Women. *J Women's Heal*. 2014;23(2):159-167. doi:10.1089/jwh.2013.4456.
145. Wu IC, Shiesh SC, Kuo PH, Lin XZ. High oxidative stress is correlated with frailty in elderly Chinese. *J Am Geriatr Soc*. 2009;57(9):1666-1671. doi:10.1111/j.1532-5415.2009.02392.x.
146. Wolfsgruber S, Jessen F, Koppara A, et al. Subjective cognitive decline is related to CSF biomarkers of AD in patients with MCI. *Neurology*. 2015;84(12):1261-1268. doi:10.1212/WNL.0000000000001399.
147. Windham BG, Simpson BN, Lirette S, et al. Associations between inflammation and cognitive function in African Americans and European Americans. *J Am Geriatr Soc*. 2014;62(12):2303-2310. doi:10.1111/jgs.13165.
148. Wildsmith K, Schauer S, Kaur S, Mathews W, Honigberg L. Multiplexed MRM assay verifies candidate Alzheimer's disease biomarkers in CSF. *Alzheimer's Dement*. 2013;9(4):P210. doi:10.1016/j.jalz.2013.05.391.
149. Wikby A, Ferguson F, Forsey R, et al. An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. *J Gerontol A Biol Sci Med Sci*. 2005;60(5):556-565. doi:60/5/556 [pii].

150. Westin K, Buchhave P, Minthon L, Janciauskiene S, Hansson O. The CSF levels of CCL-2 (MCP-1) are associated with a faster cognitive decline in prodromal Alzheimer's disease. *Neurodegener Dis*. 2011;8:5477. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70486033%5Cnhttp://dx.doi.org/10.1159/000327701%5Cnhttp://nihlibrarysfx.nih.gov:9003/sfx_local?sid=EMBASE&issn=16602854&id=doi:10.1159/000327701&atitle=The+CSF+levels+of+CCL-2+(MCP-.
151. Weise D, Tiepolt S, Awissus C, et al. Critical Comparison of Different Biomarkers for Alzheimer's Disease in a Clinical Setting. *J Alzheimer's Dis*. 2015;48(2):425-432. doi:10.3233/JAD-150229.
152. Watanabe S, Sato K, Hasegawa N, et al. Serum C1q as a novel biomarker of sarcopenia in older adults. *FASEB J*. 2015;29(3):1003-1010. doi:10.1096/fj.14-262154.
153. Wang R, Jin D, Li Y, Liang Q. Decreased mean platelet volume and platelet distribution width are associated with mild cognitive impairment and Alzheimer's disease. *J Psychiatr Res*. 2013;47(5):644-649. doi:10.1016/j.jpsychires.2013.01.014.
154. Wang L, Brier MR, Snyder AZ, et al. Cerebrospinal Fluid Aβ42, Phosphorylated Tau $_{181}$, and Resting-State Functional Connectivity. *JAMA Neurol*. 2013. doi:10.1001/jamaneurol.2013.3253.
155. Wang L, Benzinger TL, Hassenstab J, et al. Spatially distinct atrophy is linked to ??-amyloid and tau in preclinical Alzheimer disease. *Neurology*. 2015;84(12):1254-1260. doi:10.1212/WNL.0000000000001401.
156. Madison CM, Shaw LM, Jack CR, Weiner MW. Comparing predictors of conversion and decline in mild cognitive impairment. 2010;(July). doi:10.1212/WNL.0b013e3181e8e8b8.
157. Mattsson N, Insel P, Nosheny R, et al. CSF protein biomarkers predicting longitudinal reduction of CSF β-amyloid42 in cognitively healthy elders. *Transl Psychiatry*. 2013;3(8):e293. doi:10.1038/tp.2013.69.
158. Mattsson N, Insel PS, Donohue M, et al. Predicting Reduction of Cerebrospinal Fluid β-Amyloid 42 in Cognitively Healthy Controls. *JAMA Neurol*. 2015;72(5):554. doi:10.1001/jamaneurol.2014.4530.
159. Meng Y, Wu H, Yang Y, et al. Relationship of anabolic and catabolic biomarkers with muscle strength and physical performance in older adults: a population-based cross-sectional study. *BMC Musculoskelet Disord*. 2015;16(1):202. doi:10.1186/s12891-015-0654-7.
160. Mielke MM, Bandaru VVR, Haughey NJ, Rabins P V., Lyketsos CG, Carlson MC. Serum sphingomyelins and ceramides are early predictors of memory impairment. *Neurobiol Aging*. 2010;31(1):17-24. doi:10.1016/j.neurobiolaging.2008.03.011.
161. Mielke MM, Haughey NJ, Bandaru VVR, et al. Plasma sphingomyelins are associated with cognitive progression in alzheimer's disease. *J Alzheimer's Dis*. 2011;27(2):259-269. doi:10.3233/JAD-2011-110405.
162. Mielke MM, Haughey NJ, Ratnam Bandaru VV, et al. Plasma ceramides are altered in mild cognitive impairment and predict cognitive decline and hippocampal volume loss. *Alzheimer's Dement*. 2010;6(5):378-385. doi:10.1016/j.jalz.2010.03.014.
163. De Leon MJ, DeSanti S, Zinkowski R, et al. Longitudinal CSF and MRI biomarkers improve the diagnosis of mild cognitive impairment. *Neurobiol Aging*. 2006;27(3):394-401.

doi:10.1016/j.neurobiolaging.2005.07.003.
164. Mocchegiani E, Malavolta M, Lattanzio F, et al. Cu to Zn ratio, physical function, disability, and mortality risk in older elderly (ilSIRENTE study). *Age (Omaha)*. 2012;34(3):539-552. doi:10.1007/s11357-011-9252-2.
165. Moore R, Jones SR, Dev SI, et al. Association between peripheral immune markers and functional neuroimaging findings among healthy older adults. *Am J Geriatr Psychiatry*. 2015;23(3):S134-S135. doi:10.1016/j.jagp.2014.12.136.
166. Moreno G, Mangione CM, Wang PC, et al. Physical activity, physical performance, and biological markers of health among sedentary older Latinos. *Curr Gerontol Geriatr Res*. 2014;2014:16-18. doi:10.1155/2014/535071.
167. Thambisetty M, Metter EJ, Yang A, et al. Glucose Intolerance, Insulin Resistance, and Pathological Features of Alzheimer Disease in the Baltimore Longitudinal Study of Aging. *JAMA Neurol*. 2013;70(9):1167. doi:10.1001/jamaneurol.2013.284.
168. Muldoon MF, Ryan CM, Sheu L, Yao JK, Conklin SM, Manuck SB. Serum Phospholipid Docosahexaenonic Acid Is Associated with Cognitive Functioning during Middle Adulthood 1 , 2. *Online*. 2010:848-853. doi:10.3945/jn.109.119578.Fish.
169. Muzembo BA, Nagano Y, Eitoku M, et al. A cross-sectional assessment of oxidative DNA damage and muscle strength among elderly people living in the community. *Environ Health Prev Med*. 2014;19(1):21-29. doi:10.1007/s12199-013-0350-x.
170. Ng A, Jion YI, Zainal H, Kandiah N. Renal Dysfunction Contributes To Episodic Memory Deficits and Medial Temporal Atrophy in Early Dementia: Pilot Study. *Alzheimer's Dement*. 2014;10(4):P668. doi:10.1016/j.jalz.2014.05.1198.
171. Noble JM, Manly JJ, Schupf N, Tang MX, Mayeux R, Luchsinger JA. Association of C-reactive protein with cognitive impairment. *Arch Neurol*. 2010;67(1):87-92. doi:10.1001/archneurol.2009.308.
172. Ng TP, Niti M, Feng L, Kua EH, Yap KB. Albumin, Apolipoprotein e-??4 and cognitive decline in community-dwelling chinese older adults. *J Am Geriatr Soc*. 2009;57(1):101-106. doi:10.1111/j.1532-5415.2008.02086.x.
173. Nurk E, Refsum H, Bjelland I, et al. Plasma free choline, betaine and cognitive performance: the Hordaland Health Study. *Br J Nutr*. 2013;109(3):511-519. doi:10.1017/S0007114512001249.
174. O'Bryant SE, Waring SC, Hobson V, et al. Decreased C-Reactive Protein Levels in Alzheimer Disease. *J Geriatr Psychiatry Neurol*. 2010;23(1):49-53. doi:10.1177/0891988709351832.
175. Ogawa K, Kim HK, Shimizu T, Abe S, Shiga Y, Calderwood SK. Plasma heat shock protein 72 as a biomarker of sarcopenia in elderly people. *Cell Stress Chaperones*. 2012;17(3):349-359. doi:10.1007/s12192-011-0310-6.
176. Olazaran J, Gil-De-Gomez L, Rodriguez-Martin A, et al. A blood-based, 7-metabolite signature for the early diagnosis of Alzheimer's disease. *J Alzheimer's Dis*. 2015;45(4):1157-1173. doi:10.3233/JAD-142925.
177. Öztürk ZA, Ünal A, Yiğiter R, et al. Is increased red cell distribution width (RDW) indicating the inflammation in Alzheimer's disease (AD)? *Arch Gerontol Geriatr*. 2013;56(1):50-54. doi:10.1016/j.archger.2012.10.002.
178. Pabst G, Zimmermann AK, Huth C, et al. Association of low 25-hydroxyvitamin D levels

with the frailty syndrome in an aged population: Results from the KORA-Age Augsburg study. *J Nutr Heal Aging*. 2015;19(3):258-264. doi:10.1007/s12603-014-0546-9.
179. Papassotiropoulos A, Lutjohann D, Bagli M, et al. Plasma 24S-hydroxycholesterol: a peripheral indicator of neuronal degeneration and potential state marker for Alzheimer's disease. *Neuroreport*. 2000;11(9):1959-1962. doi:10.1016/S0197-4580(00)82775-X.
180. Buchhave P, Blennow K, Zetterberg H, et al. Longitudinal study of CSF biomarkers in patients with Alzheimer's disease. *PLoS One*. 2009;4(7):2-6. doi:10.1371/journal.pone.0006294.
181. Perna S, Guido D, Grassi M, Rondanelli M. Association between muscle mass and adipo-metabolic profile: A cross-sectional study in older subjects. *Clin Interv Aging*. 2015;10:499-504. doi:10.2147/CIA.S67872.
182. Perrin RJ, Craig-Schapiro R, Malone JP, et al. Identification and Validation of Novel Cerebrospinal Fluid Biomarkers for Staging Early Alzheimer's Disease. *PLoS One*. 2011;6(1):e16032. doi:10.1371/journal.pone.0016032.
183. Pirttilä T, Koivisto K, Mehta PD, et al. Longitudinal study of cerebrospinal fluid amyloid proteins and apolipoprotein E in patients with probable Alzheimer's disease. *Neurosci Lett*. 1998;249(1):21-24. doi:10.1016/S0304-3940(98)00381-4.
184. P. M-L, A. I, M. E-T, et al. Prevalence of preclinical Alzheimer's disease among young adults: The gipuzkoa alzheimer project study. *Alzheimer's Dement*. 2013;9(4 SUPPL. 1):P731. doi:10.1016/j.jalz.2013.05.1462.
185. Qiu WWQ, Lai A, Mon T, et al. Angiotensin Converting Enzyme Inhibitors and Alzheimer Disease in the Presence of the Apolipoprotein E4 Allele. *Am J Geriatr Psychiatry*. 2014;22(2):177-185. doi:10.1016/j.jagp.2012.08.017.
186. Quinn JF, Montine KS, Moore M, Morrow JD, Kaye JA, Montine TJ. Suppression of longitudinal increase in CSF F2-isoprostanes in Alzkeimer's disease. *J Alzheimer's Dis*. 2004;6(1):93-97. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L38418561%5Cnhttp://nihlibrarysfx.nih.gov:9003/sfx_local?sid=EMBASE&issn=13872877&id=doi:&atitle=Suppression+of+longitudinal+increase+in+CSF+F2-isoprostanes+in+Alzkeimer's+disease&st.
187. Quintino-Santos S, Diniz BS, Firmo JOA, Moriguchi EH, Lima-Costa MF, Castro-Costa E. APOE ε4 allele is associated with worse performance in memory dimensions of the mini-mental state examination: The Bambuí Cohort Study of Aging. *Int J Geriatr Psychiatry*. 2015;30(6):573-579. doi:10.1002/gps.4186.
188. Rabassa M, Cherubini A, Zamora-Ros R, et al. Low levels of a urinary biomarker of dietary polyphenol are associated with substantial cognitive decline over a 3-year period in older adults: The invecchiare in chianti study. *J Am Geriatr Soc*. 2015;63(5):938-946. doi:10.1111/jgs.13379.
189. Rasgon NL, Kenna HA, Wroolie TE, et al. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. *Neurobiol Aging*. 2011;32(11):1942-1948. doi:10.1016/j.neurobiolaging.2009.12.005.
190. Rembach A, Faux NG, Watt AD, et al. Changes in plasma amyloid beta in a longitudinal study of aging and Alzheimer's disease. *Alzheimer's Dement*. 2014;10(1):53-61. doi:10.1016/j.jalz.2012.12.006.

191. Reuben DB, Judd-Hamilton L, Harris TB, Seeman TE. The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur studies of successful aging. *J Am Geriatr Soc*. 2003;51(8):1125-1130. doi:10.1046/j.1532-5415.2003.51380.x.
192. Revel F, Gilbert T, Roche S, et al. Influence of oxidative stress biomarkers on cognitive decline. *J Alzheimers Dis*. 2015;45(2):553-560. doi:10.3233/JAD-141797.
193. Riemenschneider M, Lautenschlager N, Wagenpfeil S, Diehl J, Drzezga A, Kurz A. Cerebrospinal fluid tau and β-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. *Arch Neurol*. 2002;59(11):1729-1734. doi:10.1001/archneur.59.11.1729.
194. Read S, Grundy E. Allostatic Load and Health in the Older Population of England: A Crossed-Lagged Analysis. *Psychosom Med*. 2014;76(7):490-496. doi:10.1097/PSY.0000000000000083.
195. Rgsler N, Wichart I, Jellinger KA. Neural Transmission Clinical significance of neurobiochemical profiles in the lumbar cerebrospinal fluid of Alzheimer ' s disease patients. 2001:231-246.
196. Ruiz A, Pesini P, Espinosa A, et al. Blood amyloid beta levels in healthy, mild cognitive impairment and Alzheimer's disease individuals: Replication of diastolic blood pressure correlations and analysis of critical covariates. *PLoS One*. 2013;8(11):1-9. doi:10.1371/journal.pone.0081334.
197. Sämgård K, Zetterberg H, Blennow K, Hansson O, Minthon L, Londos E. Cerebrospinal fluid total tau as a marker of Alzheimer's disease intensity. *Int J Geriatr Psychiatry*. 2010;25(4):403-410. doi:10.1002/gps.2353.
198. Sanada K, Miyachi M, Tanimoto M, et al. A cross-sectional study of sarcopenia in Japanese men and women: Reference values and association with cardiovascular risk factors. *Eur J Appl Physiol*. 2010;110(1):57-65. doi:10.1007/s00421-010-1473-z.
199. Sanders JL, Cappola AR, Arnold AM, et al. Concurrent change in dehydroepiandrosterone sulfate and functional performance in the oldest old: Results from the Cardiovascular Health study all Stars study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2010;65 A(9):976-981. doi:10.1093/gerona/glq072.
200. Sato Y, Bernier F, Yamanaka Y, et al. Reduced plasma desmosterol-to-cholesterol ratio and longitudinal cognitive decline in Alzheimer's disease. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2015;1(1):67-74. doi:10.1016/j.dadm.2014.11.009.
201. Saum KU, Dieffenbach AK, Jansen EHJM, et al. Association between Oxidative Stress and Frailty in an Elderly German Population: Results from the ESTHER Cohort Study. *Gerontology*. 2015;61(5):407-415. doi:10.1159/000380881.
202. Egli SC, Hirni DI, Taylor KI, et al. Varying strength of cognitive markers and biomarkers to predict conversion and cognitive decline in an early-stage-enriched mild cognitive impairment sample. *J Alzheimer's Dis*. 2015;44(2):625-633. doi:10.3233/JAD-141716.
203. Schaap LA, Pluijm SMF, Deeg DJH, Visser M. Inflammatory Markers and Loss of Muscle Mass (Sarcopenia) and Strength. *Am J Med*. 2006;119(6). doi:10.1016/j.amjmed.2005.10.049.
204. Schofield PW, Ebrahimi H, Jones AL, Bateman GA, Murray SR. An olfactory "stress test" may detect preclinical Alzheimer's disease. *BMC Neurol*. 2012;12(1):24.

doi:10.1186/1471-2377-12-24.
205. Von Arnim CAF, Herbolsheimer F, Nikolaus T, et al. Dietary antioxidants and dementia in a population-based case-control study among older people in South Germany. *J Alzheimer's Dis*. 2012;31(4):717-724. doi:10.3233/JAD-2012-120634.
206. Vieira JR, Elkind MS V, Moon YP, et al. The metabolic syndrome and cognitive performance: The Northern Manhattan Study. *Neuroepidemiology*. 2011;37(3-4):153-159. doi:10.1159/000332208.
207. Vestergaard S, Nayfield SG, Patel K V., et al. Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2009;64(1):76-82. doi:10.1093/gerona/gln017.
208. Vestergaard PF, Hansen M, Frystyk J, et al. Serum levels of bioactive IGF1 and physiological markers of ageing in healthy adults. *Eur J Endocrinol*. 2014;170(2):229-236. doi:10.1530/EJE-13-0661.
209. Verghese J, Holtzer R, Oh-Park M, Derby CA, Lipton RB, Wang C. Inflammatory Markers and Gait Speed Decline in Older Adults. *Journals Gerontol Ser A Biol Sci Med Sci*. 2011;66A(10):1083-1089. doi:10.1093/gerona/glr099.
210. Velayudhan L, Pritchard M, Powell JF, Proitsi P, Lovestone S. Smell identification function as a severity and progression marker in Alzheimer's disease. *Int psychogeriatrics*. 2013;25(7):1157-1166. doi:10.1017/S1041610213000446.
211. L. Van Den Ingh, A. Ahmed MOR. The role of bilirubin in the plasma as biomarker in the detection of Alzheimer's disease. *Eur Geriatr Med*. 2011;2:S147. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70705703%0Ahttp://dx.doi.org/10.1016/j.eurger.2011.06.002%0Ahttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=18787649&id=doi:10.1016/j.eurger.2011.06.002&atitle=Detecting+delirium,+.
212. van den Boogaard M, Kox M, Quinn KL, et al. Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Crit Care*. 2011;15(6):R297. doi:10.1186/cc10598.
213. Urpi-Sarda M, Andres-Lacueva C, Rabassa M, et al. The relationship between urinary total polyphenols and the frailty phenotype in a community-dwelling older population: The InCHIANTI Study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2015;70(9):1141-1147. doi:10.1093/gerona/glv026.
214. Umegaki H, Ikari H, Nakahata H, et al. Plasma cortisol levels in elderly female subjects with Alzheimer's disease: a cross-sectional longitudinal study. *Brain Res*. 2000;881(March):241-243.
215. Turana Y, Ranakusuma TAS, Purba JS, et al. Enhancing diagnostic accuracy of aMCI in the elderly: Combination of olfactory test, pupillary response test, BDNF plasma level, and APOE genotype. *Int J Alzheimers Dis*. 2014;2014. doi:10.1155/2014/912586.
216. Trollor JN, Smith E, Baune BT, et al. Systemic inflammation is associated with MCI and its subtypes: The Sydney memory and aging study. *Dement Geriatr Cogn Disord*. 2011;30(6):569-578. doi:10.1159/000322092.
217. Sundelof J, Arnlov J, Ingelsson E, et al. Serum cystatin C and the risk of Alzheimer disease

in elderly men. *Neurology*. 2008;71(14):1072-1079. doi:10.1212/01.wnl.0000326894.40353.93.
218. Uchida K, Shan L, Suzuki H, et al. Amyloid-Beta sequester proteins as blood-based biomarkers of cognitivedecline. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2015;1(2):270-280. doi:10.1016/j.dadm.2015.04.003.
219. Sunderland T, Putnam KT, Friedman DL, et al. Tau Levels in Cerebrospinal Fluid of Patients With Alzheimer Disease. *JAMA Neurol*. 2003;289(16):2094-2103. doi:10.1001/jama.289.16.2094.
220. Toledo JB, Xie SX, Trojanowski JQ, Shaw LM. Longitudinal change in CSF Tau and ABeta biomarkers for up to 48 months in ADNI. *Acta Neuropathol*. 2013;126(5):659-670. doi:10.1007/s00401-013-1151-4.
221. Thuot E, Subramanian R, Desautels R, Rajah N, Ditomasso M, Hospital D. Insulin Resistance and Alzheimer ' s Disease : A Pilot Study. 2010:74-75.
222. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: The 3C-Dijon Study. *Neurology*. 2012;78(10):720-727. doi:10.1212/WNL.0b013e318248e50f.
223. Schoonenboom SNM, Visser PJ, Mulder C, et al. Biomarker profiles and their relation to clinical variables in mild cognitive impairment. *Neurocase*. 2005;11(1):8-13. doi:10.1080/13554790490896785.
224. Schram MT, Euser SM, De Craen AJM, et al. Systemic markers of inflammation and cognitive decline in old age. *J Am Geriatr Soc*. 2007;55(5):708-716. doi:10.1111/j.1532-5415.2007.01159.x.
225. Semba RD, Cappola AR, Sun K, et al. Relationship of low plasma klotho with poor grip strength in older community-dwelling adults: the InCHIANTI study. *Eur J Appl Physiol*. 2012;112(4):1215-1220. doi:10.1007/s00421-011-2072-3.
226. Seppälä TT, Koivisto AM, Hartikainen P, Helisalmi S, Soininen H, Herukka SK. Longitudinal changes of CSF biomarkers in alzheimer's disease. *J Alzheimer's Dis*. 2011;25(4):583-594. doi:10.3233/JAD-2011-101911.
227. Shinkai S, Kohno H, Kimura K, et al. Physical activity and immune senescence in men. *Med Sci Sports Exerc*. 1995;27(11):1516-1526. http://www.ncbi.nlm.nih.gov/pubmed/8587488. Accessed June 23, 2017.
228. Shimada H, Makizako H, Doi T, et al. A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly. *Front Aging Neurosci*. 2014;6(APR):1-9. doi:10.3389/fnagi.2014.00069.
229. Singh-Manoux A et al. Interleukin-6 and C-reactive protein as prdictors o cognitive decline in late midlife. *Neurology*. 2014;83:486-493. http://discovery.ucl.ac.uk/1434277/1/Neurology-2014-Singh-Manoux-486-93.pdf.
230. Colbert LH, Visser ÃM, Simonsick EM, et al. Physical Activity, Exercise, and Inflammatory Markers in Older Adults: Findings from The Health, Aging and Body Composition Study. 2004:1098-1104.
231. Snider BJ, Fagan AM, Roe C, et al. Cerebrospinal Fluid Biomarkers and Rate of Cognitive Decline in Very Mild Dementia of the Alzheimer Type. *Arch Neurol*. 2009;66(5):638-645. doi:10.1001/archneurol.2009.55.
232. Sohrabi HR, Bates KA, Rodrigues M, et al. Olfactory dysfunction is associated with

subjective memory complaints in community-dwelling elderly individuals. *J Alzheimer's Dis*. 2009;17(1):135-142. doi:10.3233/JAD-2009-1020.
233. Song F, Poljak A, Crawford J, et al. Plasma apolipoprotein levels are associated with cognitive status and decline in a community cohort of older individuals. *PLoS One*. 2012;7(6). doi:10.1371/journal.pone.0034078.
234. Song I-U, Chung S-W, Kim Y-D, Maeng L-S. Relationship between the hs-CRP as non-specific biomarker and Alzheimer's disease according to aging process. *Int J Med Sci*. 2015;12(8):613-617. doi:10.7150/ijms.12742.
235. Spiegel J, Pirraglia E, Osorio RS, et al. Greater Specificity for Cerebrospinal Fluid P-tau231 over P-tau181 in the Differentiation of Healthy Controls from Alzheimer's Disease. *J Alzheimer's Dis*. 2015;49(1):93-100. doi:10.3233/JAD-150167.
236. Stricker NH, Dodge HH, Dowling NM, Han SD, Erosheva EA, Jagust WJ. CSF biomarker associations with change in hippocampal volume and precuneus thickness: Implications for the Alzheimer's pathological cascade. *Brain Imaging Behav*. 2012;6(4):599-609. doi:10.1007/s11682-012-9171-6.
237. M. Soundarrajan, M. Ali, H. M. Blazel HZ, K. Blennow, S. C. Johnson, C. E. Gleason BPH, N. M. Dowling, L. Puglielli, C. S. Atwood MAS, S. Asthana CMC. Simvastatin's Effect on CSF Neurofilament Light Chain in Adults at Risk for Alzheimer's Disease. 2011:2011.
238. Skillbäck T, Zetterberg H, Blennow K, Mattsson N. Cerebrospinal fluid biomarkers for Alzheimer disease and subcortical axonal damage in 5,542 clinical samples. *Alzheimers Res Ther*. 2013;5(5):47. doi:10.1186/alzrt212.
239. Teunissen CE, Blom AHJ, Van Boxtel MPJ, et al. Homocysteine: a marker for cognitive performance? A longitudinal follow-up study. *J Nutr Health Aging*. 2003;7(3):153-159. http://www.ncbi.nlm.nih.gov/pubmed/12766792. Accessed June 23, 2017.
240. Stomrud E, Minthon L, Zetterberg H, Blennow K, Hansson O. Longitudinal cerebrospinal fluid biomarker measurements in preclinical sporadic Alzheimer's disease: A prospective 9-year study. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2015;1(4):403-411. doi:10.1016/j.dadm.2015.09.002.
241. Tapiola T, Alafuzoff I, Herukka S-K, et al. Cerebrospinal Fluid β-Amyloid 42 and Tau Proteins as Biomarkers of Alzheimer-Type Pathologic Changes in the Brain. *Arch Neurol*. 2009;66(3):382-389. doi:10.1001/archneurol.2008.596.
242. Tang K, Hynan LS, Baskin F, Rosenberg RN. Platelet amyloid precursor protein processing: A bio-marker for Alzheimer's disease. *J Neurol Sci*. 2006;240(1-2):53-58. doi:10.1016/j.jns.2005.09.002.
243. Tajar A, Lee DM, Pye SR, et al. The association of frailty with serum 25-hydroxyvitamin d and parathyroid hormone levels in older european men. *Age Ageing*. 2013;42(3):352-359. doi:10.1093/ageing/afs162.
244. Stehle JR, Leng X, Kitzman DW, Nicklas BJ, Kritchevsky SB, High KP. Lipopolysaccharide-Binding Protein, a Surrogate Marker of Microbial Translocation, Is Associated With Physical Function in Healthy Older Adults. *Journals Gerontol Ser A Biol Sci Med Sci*. 2012;67(11):1212-1218. doi:10.1093/gerona/gls178.
245. Sutphen CL, Jasielec MS, Shah AR, et al. Longitudinal Cerebrospinal Fluid Biomarker Changes in Preclinical Alzheimer Disease During Middle Age. *JAMA Neurol*. 2015;72(9):1029. doi:10.1001/jamaneurol.2015.1285.

246. Stanga S, Lanni C, Sinforiani E, Mazzini G, Racchi M. Searching for predictive blood biomarkers: misfolded p53 in mild cognitive impairment. *Curr Alzheimer Res*. 2012;9(10):1191-1197. doi:10.2174/156720512804142886.
247. Tay, L.; Hafizah, N.; Tan, C. H.; Yeo, A.; Yew, S.; Fong, Y. L.; Yang, J.; Chong MS. Inflammation and the interaction between anabolic-catabolic pathways in sarcopenia. 2014.
248. Allard J, Artero S, Ritchie K. Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance. *Int J Geriatr Psychiatry*. 2003;18(10):874-878. doi:10.1002/gps.891.
249. Baune BT, Ponath G, Golledge J, et al. Association between IL-8 cytokine and cognitive performance in an elderly general population-The MEMO-Study. *Neurobiol Aging*. 2008;29(6):937-944. doi:10.1016/j.neurobiolaging.2006.12.003.
250. Gray SL, Anderson ML, Dublin S, et al. Cumulative Use of Strong Anticholinergics and Incident Dementia. *JAMA Intern Med*. 2015;175(3):401. doi:10.1001/jamainternmed.2014.7663.
251. Fox C, Richardson K, Maidment ID, et al. Anticholinergic medication use and cognitive impairment in the older population: The medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-1483. doi:10.1111/j.1532-5415.2011.03491.x.
252. Ferrucci L, Penninx BWJH, Volpato S, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc*. 2002;50(12):1947-1954. doi:10.1046/j.1532-5415.2002.50605.x.
253. Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. *J Am Geriatr Soc*. 2008;56(3):454-461. doi:10.1111/j.1532-5415.2007.01601.x.
254. Butchart J, Birch B, Bassily R, Wolfe L, Holmes C. Male sex hormones and systemic inflammation in Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2013;27(2):153-156. doi:10.1097/WAD.0b013e318258cd63.
255. Beavers KM, Beavers DP, Serra MC, Bowden RG, Wilson RL. Low relative skeletal muscle mass indicative of sarcopenia is associated with elevations in serum uric acid levels: findings from NHANES III. *J Nutr Heal Aging*. 2009;13(3):177-182.
256. Barzilay JI. Insulin Resistance and Inflammation as Precursors of Frailty. *Arch Intern Med*. 2007;167(7):635. doi:10.1001/archinte.167.7.635.
257. Kizilarslanoglu MC, Kara O, Yesil Y, et al. Alzheimer disease, inflammation, and novel inflammatory marker: Resistin. *Turkish J Med Sci*. 2015;45(5):1040-1046. doi:10.3906/sag-1403-55.
258. Schmaltz HN, Fried LP, Xue QL, Walston J, Leng SX, Semba RD. Chronic cytomegalovirus infection and inflammation are associated with prevalent frailty in community-dwelling older women. *J Am Geriatr Soc*. 2005;53(5):747-754. doi:10.1111/j.1532.5415.2005.53250.x.
259. Roubenoff R, Parise H, Payette HA, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: The Framingham Heart Study. *Am J Med*. 2003;115(6):429-435. doi:10.1016/j.amjmed.2003.05.001.

260. Kumar R, Chaterjee P, Sharma PK, et al. Sirtuin1: A Promising Serum Protein Marker for Early Detection of Alzheimer's Disease. *PLoS One*. 2013;8(4):4-9. doi:10.1371/journal.pone.0061560.
261. Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: A pilot study. *J Am Geriatr Soc*. 2002;50(7):1268-1271. doi:10.1046/j.1532-5415.2002.50315.x.
262. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *J Am Geriatr Soc*. 2007;55(6):864-871. doi:10.1111/j.1532-5415.2007.01186.x.
263. Levine ME, Crimmins EM. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. *Obes (Silver Spring)*. 2012;20(10):2101-2106. doi:10.1038/oby.2012.20.
264. Paterniti S, Dufouil C, Alperovitch A. Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. *J Clin Psychopharmacol*. 2002;22(3):285-293. http://ovidsp.tx.ovid.com/ovftpdfs/FPDDNCGCIFCOML00/fs012/ovft/live/gv011/00004714/00004714-200206000-00009.pdf.
265. Puts MTE, Visser M, Twisk JWR, Deeg DJH, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol (Oxf)*. 2005;63(4):403-411. doi:10.1111/j.1365-2265.2005.02355.x.
266. Uusvaara J, Pitkala KH, Tienari PJ, Kautiainen H, Tilvis RS, Strandberg TE. Association between anticholinergic drugs and apolipoprotein E epsilon4 allele and poorer cognitive function in older cardiovascular patients: a cross-sectional study. *J Am Geriatr Soc*. 2009;57(3):427-431. doi:10.1111/j.1532-5415.2008.02129.x.
267. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol Med Sci*. 2002;57A(5):M326-M332. doi:10.1093/gerona/57.5.M326.
268. Wichmann MA, Cruickshanks KJ, Carlsson CM, et al. Long-term systemic inflammation and cognitive impairment in a population-based cohort. *J Am Geriatr Soc*. 2014;62(9):1683-1691. doi:10.1111/jgs.12994.
269. Wilson CJ, Cohen HJ, Pieper CF. Cross-linked fibrin degradation products (D-dimer), plasma cytokines, and cognitive decline in community-dwelling elderly persons. *J Am Geriatr Soc*. 2003;51(10):1374-1381. http://onlinelibrary.wiley.com/store/10.1046/j.1532-5415.2003.51454.x/asset/j.1532-5415.2003.51454.x.pdf?v=1&t=iooo3ev6&s=976c6f3afcce978243b88cbfbe29828507e1a936.
270. Yaffe K, Lindquist K, Shlipak MG, et al. Cystatin C as a marker of cognitive function in elders: Findings from the Health ABC Study. *Ann Neurol*. 2008;63(6):798-802. doi:10.1002/ana.21383.
271. Retrospective A, Study C, Fortin M, et al. Effects of Anticholinergic Drugs on Verbal Episodic Memory Function in the Elderly. 2011;28(3):195-204.
272. Lanctôt KL, Ph D, Regan JO, et al. Original Research Reports Assessing Cognitive Effects of Anticholinergic Medications in Patients With Coronary Artery Disease. *Psychosomatics*. 2014;55(1):61-68. doi:10.1016/j.psym.2013.04.004.

273. Sharma M, Fitzpatrick AL, Arnold AM, et al. Inflammatory Biomarkers and Cognitive Decline : The Ginkgo Evaluation of Memory Study. 2016:1171-1177. doi:10.1111/jgs.14140.
274. Mooijaart SP, Sattar N, Trompet S, et al. Circulating interleukin-6 concentration and cognitive decline in old age: the PROSPER study. *J Intern Med*. 2013;274(1):77-85. doi:10.1111/joim.12052.
275. Herukka SK, Seppala TT, Hartikainen P, Helisalmi S, Soininen H, Koivisto A. Longitudinal changes in CSF biomarkers. *Alzheimer's Dement*. 2011;7(4):S103. doi:10.1016/j.jalz.2011.05.255.
276. Jamsen KM, Bell JS, Hilmer SN, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. *J Am Geriatr Soc*. 2016;64(1):89-95. doi:10.1111/jgs.13877.
277. A.A. A, O. P, T.C. L, et al. Association of SORL1 gene variants with hippocampal and cerebral atrophy and Alzheimer's disease. *Curr Alzheimer Res*. 2014;11(6):558-563. doi:10.2174/1567205011666140618101408.
278. Chibnik LB, Shulman JM, Leurgans SE, et al. CR1 is associated with amyloid plaque burden and age-related cognitive decline. *Ann Neurol*. 2011;69(3):560-569. doi:10.1002/ana.22277.
279. Choi Y-H, Kim J-H, Kim DK, et al. Distributions of ACE and APOE polymorphisms and their relations with dementia status in Korean centenarians. *journals Gerontol Med Sci*. 2003;58A(3):227-231. doi:10.1093/gerona/58.3.M227.
280. Dixon RA, DeCarlo CA, MacDonald SWS, Vergote D, Jhamandas J, Westaway D. APOE and COMT polymorphisms are complementary biomarkers of status, stability, and transitions in normal aging and early mild cognitive impairment. *Front Aging Neurosci*. 2014;6(SEP):1-11. doi:10.3389/fnagi.2014.00236.
281. Erten-Lyons D, Jacobson A, Kramer P, Grupe A, Kaye J. The FAS gene, brain volume, and disease progression in Alzheimer's disease. *Alzheimer's Dement*. 2010;6(2):118-124. doi:10.1016/j.jalz.2009.05.663.
282. Fiocco AJ, Lindquist K, Ferrell R, et al. COMT genotype and cognitive function: An 8-year longitudinal study in white and black elders. *Neurology*. 2010;74(16):1296-1302. doi:10.1212/WNL.0b013e3181d9edba.
283. Goh LK, Lim WS, Teo S, et al. TOMM40 alterations in Alzheimer's disease over a 2-year follow-up period. *J Alzheimer's Dis*. 2015;44(1):57-61. doi:10.3233/JAD-141590.
284. Green AE, Gray JR, DeYoung CG, et al. A combined effect of two Alzheimer's risk genes on medial temporal activity during executive attention in young adults. *Neuropsychologia*. 2014;56(1):1-8. doi:10.1016/j.neuropsychologia.2013.12.020.
285. Lillenes MS, Espeseth T, St??en M, et al. DNA base excision repair gene polymorphisms modulate human cognitive performance and decline during normal life span. *Mech Ageing Dev*. 2011;132(8-9):449-458. doi:10.1016/j.mad.2011.08.002.
286. Wang HF, Tan L, Hao XK, et al. Effect of EPHA1 genetic variation on cerebrospinal fluid and neuroimaging biomarkers in healthy, mild cognitive impairment and Alzheimer's disease cohorts. *J Alzheimer's Dis*. 2015;44(1):115-123. doi:10.3233/JAD-141488.
287. Schmidt C, Wolff M, Von Ahsen N, Zerr I. Alzheimer's disease: Genetic polymorphisms

and rate of decline. *Dement Geriatr Cogn Disord*. 2012;33(2-3):84-89. doi:10.1159/000336790.
288. Thambisetty M, An Y, Nalls M, et al. Effect of complement CR1 on brain amyloid burden during aging and its modification by APOE genotype. *Biol Psychiatry*. 2013;73(5):422-428. doi:10.1016/j.biopsych.2012.08.015.
289. Hohman TJ, Koran MEI, Thornton-Wells TA. Genetic modification of the relationship between phosphorylated tau and neurodegeneration. *Alzheimer's Dement*. 2014;10(6):637-645. doi:10.1016/j.jalz.2013.12.022.
290. Hollingworth P, Harold D, Sims R, et al. Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet*. 2011;43(5):429-435. doi:10.1038/ng.803.
291. Kauwe JS, Bailey MH, Ridge PG, et al. Genome-wide association study of CSF levels of 59 alzheimer's disease candidate proteins: significant associations with proteins involved in amyloid processing and inflammation. *PLoS Genet*. 2014;10(10):e1004758. doi:10.1371/journal.pgen.1004758.
292. Hu X, Pickering EH, Hall SK, et al. Genome-wide association study identifies multiple novel loci associated with disease progression in subjects with mild cognitive impairment. *Transl Psychiatry*. 2011;1:e54. doi:10.1038/tp.2011.50.
293. Desikan RS, Schork AJ, Wang Y, et al. Polygenic overlap between C-reactive protein, plasma lipids, and alzheimer disease. 2016. doi:10.1161/CIRCULATIONAHA.115.015489.
294. Feulner TM, Laws SM, Friedrich P, et al. Examination of the current top candidate genes for AD in a genome-wide association study. *Mol Psychiatry*. 2010;15(7):756-766. doi:10.1038/mp.2008.141.
295. Del-Aguila JL, Fernández MV, Jimenez J, et al. Role of ABCA7 loss-of-function variant in Alzheimer's disease: a replication study in European-Americans. *Alzheimers Res Ther*. 2015;7(1):73. doi:10.1186/s13195-015-0154-x.
296. Corneveaux JJ, Myers AJ, Allen AN, et al. Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals. *Hum Mol Genet*. 2010;19(16):3295-3301. doi:10.1093/hmg/ddq221.
297. Baune BT, Ponath G, Rothermundt M, Riess O, Funke H, Berger K. Association between genetic variants of IL-1beta, IL-6 and TNF-alpha cytokines and cognitive performance in the elderly general population of the MEMO-study. *Psychoneuroendocrinology*. 2008;33(1):68-76. doi:10.1016/j.psyneuen.2007.10.002.
298. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009;41(10):1094-1099. doi:10.1038/ng.439.
299. Lim YY, Villemagne VL, Laws SM, et al. APOE and BDNF polymorphisms moderate amyloid β-related cognitive decline in preclinical Alzheimer's disease. *Mol Psychiatry*. 2015;20(11):1322-1328. doi:10.1038/mp.2014.123.
300. Reitz C, Wang L, Lin C, et al. Variants in the ATP-Binding Cassette Transporter (ABCA7), Apolipoprotein E and the Risk of Late-Onset Alzheimer Disease in African Americans. *JAMA*. 2013;309(14):1483-1492. http://archopht.jamanetwork.com/article.aspx?articleid=1677372.
301. Vounou M, Janousova E, Wolz R, et al. Sparse reduced-rank regression detects genetic

associations with voxel-wise longitudinal phenotypes in Alzheimer's disease. *Neuroimage*. 2012;60(1):700-716. doi:10.1016/j.neuroimage.2011.12.029.
302. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009;41(10):1088-1093. doi:10.1038/ng.440.
303. Mengel-from J, Soerensen M, Nygaard M, Mcgue M, Christensen K, Christiansen L. Genetic Variants in KLOTHO Associate With Cognitive Function in the Oldest Old Group. 2016;71(9):1151-1159. doi:10.1093/gerona/glv163.
304. Yokoyama JS, Sturm VE, Bonham LW, et al. Variation in longevity gene KLOTHO is associated with greater cortical volumes. 2015:215-230. doi:10.1002/acn3.161.
305. Hao Q, Ding X, Gao L, Yang M, Dong B. G-395A polymorphism in the promoter region of the KLOTHO gene associates with reduced cognitive impairment among the oldest old. *Age (Dordr)*. 2016;38(1):7. doi:10.1007/s11357-015-9869-7.
306. Kachiwala SJ, Harris SE, Wright AF, et al. Genetic influences on oxidative stress and their association with normal cognitive ageing. 2005;386:116-120. doi:10.1016/j.neulet.2005.05.067.
307. Korostishevsky M, Steves CJ, Malkin I, Spector T, Williams FM, Livshits G. Genomics and metabolomics of muscular mass in a community-based sample of UK females. *Eur J Hum Genet*. 2016;24(2):277-283. doi:10.1038/ejhg.2015.85.
308. Mekli K, Nazroo JY, Marshall AD, Kumari M, Pendleton N. Proinflammatory genotype is associated with the frailty phenotype in the English Longitudinal Study of Ageing. *Aging Clin Exp Res*. 2016;28(3):413-421. doi:10.1007/s40520-015-0419-z.
309. Patel HP, Al-Shanti N, Davies LC, et al. Lean Mass, Muscle Strength and Gene Expression in Community Dwelling Older Men: Findings from the Hertfordshire Sarcopenia Study (HSS). *Calcif Tissue Int*. 2014;95(4):308-316. doi:10.1007/s00223-014-9894-z.
310. Frayling TM, Rafiq S, Murray A, et al. An interleukin-18 polymorphism is associated with reduced serum concentrations and better physical functioning in older people. *Journals Gerontol Ser a-Biological Sci Med Sci*. 2007;62(1):73-78.
311. Mekli K, Marshall A, Nazroo J, Vanhoutte B, Pendleton N. Genetic variant of Interleukin-18 gene is associated with the Frailty Index in the English Longitudinal Study of Ageing. *Age Ageing*. 2015;44(6):938-942. doi:10.1093/ageing/afv122.
312. Ho YY, Matteini AM, Beamer B, et al. Exploring biologically relevant pathways in frailty. *J Gerontol A Biol Sci Med Sci*. 2011;66(9):975-979. doi:10.1093/gerona/glr061.

Reproducibility

In seeking to explore the importance and applicability of these results it is critical that others continue to replicate model results before they can be used in the clinical setting. To accompany this report, help with replication and extension of our work, the code has been made publically available for model I and model II online.

Database

The subjects in the present study were participants in *Invecchiaare in Chianti* (Aging in Chianti, "InCHIANTI Study"). InCHIANTI is a prospective population based study of 1,453 adults aged 20-102 randomly selected from two towns in Tuscany, Italy using a multistage stratified sampling at baseline from 1998 to 2000[1]. All aspects of the InCHIANTI research were approved by the ethics committees at the institutions responsible for data collection.

Definitions used to establish phenotype sub-groups in this study

Cognitive decline – mild neurocognitive disorders

Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) with a modest impairment in cognitive performance by standardized neuropsychological testing or clinical assessment in absence of a diagnosis of dementia[2,34].

Frailty

The operational definition for frailty is defined as a clinical syndrome condition including 3 out of the 5 criteria related a physical phenotype including: 1) weak muscle strength (grip strength), 2) slow gait speed, 3) unintentional weight loss, 4) exhaustion and low physical activity[5]. Pre-frailty includes 1 or 2 of the criteria is present, identifying a sub-group of individuals potentially progressing to frailty[5].

Cognitive Frailty

A syndrome in older adults with evidence of both physical frailty and cognitive impairment without a clinical diagnosis of Alzheimer's Disease or other dementia[6].

Phenotypic classification for this study

Model I

Participants with an MMSE normal cognition 24-30 and cognitive decline ≤ 23[7–9]. In this study frailty is characterized by individuals with one or more of the frailty criterion[5]. Cognitive frailty is defined as individuals with cognitive decline and one or more of frailty criterion[10].

- Robust with no physical frailty and absence of cognitive decline
- Robust with no physical frailty with cognitive (MMSE = ≤ 23)
- Frail (≥ 1 criteria) and absence of cognitive decline
- Frail (≥ 1 criteria) and cognitive decline (MMSE = ≤ 23)

Model II

Participants that completed the MMSE with additional neuropsychiatric testing Trail Making Test, Part A and B (TMT) to define cognitive decline and cognitive frailty[10,11]. TMT cut off scores for cognitive decline are based on cut off norms established by Ashendorf et al., 2008.

- Robust with no physical frailty and absence of cognitive decline
- Robust with no physical frailty with cognitive decline (Trail A ≥ 78, Trail B ≥ 106)
- Frail (≥ 1 criteria) and cognitive decline (Trail A ≥ 78, Trail B ≥ 106)
- Frail (≥ 1 criteria) and cognitive decline (Trail A ≥ 78, Trail B ≥ 106)

Laboratory assay methods

At the baseline survey, most of the participants performed 24-hour urine collection early in the morning mid-stream sample urine for the routine examination. Total urinary polyphenols were measured at the Department of Food Science and Technology, School of Pharmacy, University of Barcelona, Spain. Prior to blood collection all participants consumed a diet free of meat and fish. Participants donated fasting blood samples for routine blood examinations. Blood collection was performed with the standard procedure method to prevent red cell hemolysis. The blood collection included two sets of collection tubes: one for routine tests and second for collecting specimens including serum, plasma, DNA for the biological bank. All routine blood tests, performed in the Laboratory of Clinical Chemistry and Microbiological Assays, Annunziata Hospital in Florence, Italy. Plasma fatty acids (FAs) were measured by the Section of Gerontology and Geriatrics, Department of Clinical and Experimental Medicine, Perugia, Italy.

The technique used was gas chromatography with a fused silica capillary column to achieve the optimum separation of the different fatty acids.

Software for analyses

All statistical analyses were carried out using R V. 3.2.1. R is free, open-source software that provides many statistical and graphic techniques. R packages used included 'glm2'-Fitting Generalized Linear Models, 'Ordinal'-Regression Models for Ordinal Data, and 'xgboost'-Extreme Gradient Boosting[12–14]. The software package PLINK, an analysis toolset was used for the management of genotype data and basic associating testing[15,16].

Model generation

The predictive genetic and laboratory biomarkers were identified in a comprehensive systematic review and analyzed using an Extreme Gradient Boosting (xgboost) in R[14]. While boosting was initially developed for machine learning, 'xgboost' in R is based in boosted trees. Xgboost is an open source tool and a variant of the gradient boosting machine and uses a tree based model. Xgboost is used in this study for a supervised learning problem where the variables identified from the systematic review are used to predict three phenotypes cognitive decline, physical frailty, and cognitive frailty.

Evaluation of the model

With the use of any predictive model in machine learning there is a chance for inflated risk of capitalizing on chance features (over fitting) in the data. Over fitting of the integrative model was mitigated in two ways: 1) having a distinct training and validation process for the model and 2) using xgb in R which has a built-in parameter settings for selection to reduce poor predictive performance. *Internal validation:* A randomly assigned training subset was used to validate the model within the InCHIANTI cohort *in silico* (via simulation).

Calibration of the model

Parameter estimates for each predictive factor and associated descriptive statistics was evaluated to provide biological insight into the underpinnings of the classification algorithm. We first evaluated the calibration by partitioning the data into 5, 10, 20, 30, 40, 50, 75, 100 and 200 groups and then ran the calibration test. Next, we repeated tests for all possible values between 5-200 groups and evaluated the distribution of the test statistic. The best prediction

thresholds were determined using AUC, 87.7% for Model I and 86.4% for Model II. Population predictive features by phenotype ranked by gain for Model I are presented in Tables 4-6 and Model II Tables 7-9.

Genetic Data

Genotypic data was generated at the National Institute on Aging's Laboratory of Neurogenics. Samples of genomic DNA extracted from leukocytes[17]. Genotypic data used for the model were extracted out of the binary Plink files from the InCHIANTI database. SNPs which could not be identified in the binary files were extracted from genotype imputed files, genotype imputation was completed with Minimac (V2). The SNPs included meet the following standard: per variant and per sample missingness < 5%, European ancestry, MAF < 0.001 and a rsq < 0.3. Additionally, Samples were filtered for 95% or greater genotyping call rate, no ancestry outliers, and no sex discrepancies.

Supplementary Data Table I: Laboratory values as they appear in the InCHIANTI Datasets by Clinical Category

Inflammatory/Immunity	Nutrient Biomarker	Lipid Metabolism
BL Uric acid (mg/dL)	BL Omega-3 fatty acids as % of total fatty acid area	BL Lipids: total cholesterol (mg/dL)
BL Urinary cortisol (µg/mL)	BL Omega-3 plasma fatty acid weight (mg/L)	BL Lipids: HDL cholesterol (mg/dL)
BL 24-hour urinary cortisol (µg/24 hours)	BL Omega-3 fatty acids as % of total fatty acid weight	BL Lipids: triglycerides (mg/dL)
BL C-reactive protein - low sensitivity (µg/mL)	BL Omega-3 fatty acids as % of total fatty acid mols	BL Lipids: LDL cholesterol (mg/dL)
BL C-reactive protein - high sensitivity (µg/mL)	BL Omega-6 fatty acids as % of total fatty acid area	BL Lipoprotein(a) (mg/dL)
BL Interleukin-6 via ELISA ultrasensitive (pg/mL)	BL Omega-6 plasma fatty acid weight (mg/L)	
BL IL-6 high-sensitivity ELISA calculated from ELISA ultrasensitive (pg/mL)	BL Omega-6 fatty acids as % of total fatty acid weight	**Metabolomics(plasma lipids)**
BL Soluble IL-6 receptor via ELISA (ng/mL)	BL Omega-6 fatty acids as % of total fatty acid mols	BL Fatty acid C16:0 (palmitiA91:A116c) area
BL Interleukin-10 via ELISA (pg/mL)	BL Ratio of Omega-6:Omega-3 as % of total fatty acid area	BL Fatty acid C16:0 (palmitic) area
BL Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	BL Ratio of Omega-6:Omega-3 as % of total fatty acid weight	BL Fatty acid C16:0 as % of total fatty acid area
BL Interleukin-1B via ELISA (pg/mL)	BL Ratio of Omega-6:Omega-3 as % of total fatty acid mols	BL Fatty acid C16:0 weight (mg/L)

BL Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	BL Vitamin B6 via high performance liquid chromatography (ng/mL)	BL Fatty acid C16:0 as % of total fatty acid weight
BL Transforming growth factor-B1 (pg/mL)	BL Vitamin B6 via high performance liquid chromatography (nmol/L)	BL Fatty acid C16:0 (µmol/L)
BL Tumor necrosis factor-a via multiplex technology (pg/mL)	BL Vitamin E gamma tocopherol, high performance liquid chromatography (µmol/L)	BL Fatty acid C16:0 as % of total fatty acid mols
BL Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	BL Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)	BL Fatty acid C20:0 (arachidic) area
BL Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	BL Vitamin E gamma tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	BL Fatty acid C20:0 as % of total fatty acid area
BL TNF-related apoptosis-inducing ligand (pg/mL)	BL Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	BL Fatty acid C20:0 weight (mg/L)
BL Interleukin-8 via Bio-Plex (pg/mL)	BL Beta-carotene via high performance liquid chromatography (µmol/L)	BL Fatty acid C20:0 as % of total fatty acid weight
BL Interleukin-12 via Bio-Plex (pg/mL)	BL Lycopene via high performance liquid chromatography (µmol/L)	BL Fatty acid C20:0 (µmol/L)
BL Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	BL Total proteins (g/dL)	BL Fatty acid C20:0 as % of total fatty acid mols
BL Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)	BL Albumin (%)	BL Fatty acid C20:5 n-3 cis (eicosapentaenoic, EPA) area
BL Serum cortisol (µg/dL)		BL Fatty acid C20:5 n-3 as % of total fatty acid area
BL Serum cortisol (nmol/L)		BL Fatty acid C20:5 n-3 weight (mg/L)
BL Dehydroepiandrosterone sulfate (µg/dL)		BL Fatty acid C20:5 n-3 as % of total fatty acid weight
BL Dehydroepiandrosterone sulfate (nmol/L)		BL Fatty acid C20:5 n-3 (µmol/L)
BL Cortisol:DHEAS ratio (based on nmols)		BL Fatty acid C20:5 n-3 as % of total fatty acid mols
BL Soluble CD14 via ELISA (ng/mL)		BL Fatty acid C22:0 (behenic) area
BL Fibrinogen (mg/dL)		BL Fatty acid C22:0 as % of total fatty acid area
BL Erythrocyte sedimentation rate (ESR) (mm/hour)		BL Fatty acid C22:0 weight (mg/L)

BL Homocysteine via FPIA analysis (µmol/L)		BL Fatty acid C22:0 as % of total fatty acid weight
BL Resistin via EIA (ng/mL)-		BL Fatty acid C22:0 (µmol/L)
BL Adiponectin via RIA (µg/mL)- (metabolic function)		BL Fatty acid C22:0 as % of total fatty acid mols
BL Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)		BL Fatty acid C24:0 (lignoceric) area
BL Alpha-1 globulin (%)		BL Fatty acid C24:0 as % of total fatty acid area
BL Alpha-2 globulin (%)		BL Fatty acid C24:0 weight (mg/L)
BL Alpha-2-macroglobulin (mg/dL)		BL Fatty acid C24:0 as % of total fatty acid weight
BL Beta globulins (%)		BL Fatty acid C24:0 (µmol/L)
BL Endogenous secretory receptor for AGEs (ng/mL)		BL Fatty acid C24:0 as % of total fatty acid mols
Renal/Electrolyte	**Hematology/Liver**	**Endocrine/Hormones**
BL Na+ (mEq/L)	BL White blood cells (WBC) (n, K/µL)	BL Blood glucose (mg/dL)
BL Ca++ (mg/dL)	BL Neutrophils (n, K/µL)	BL 25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)
BL Urinary creatinine (mg/dL)	BL Lymphocytes (n, K/µL)	BL Parathyroid hormone, two-site immunoradiometric assay (pg/mL)
BL 24-hour urinary creatinine (mg/24 hours)	BL Monocytes (n, K/µL)	BL Thyroid stimulating hormone, TSH (mIU/L)
BL Creatinine clearance, 24-hr urine (mL/minute)	BL Neutrophils (%)	BL Free thyroxine, fT4 (ng/dL)
BL Urinary Ca (mmol/L)	BL Lymphocytes (%)	BL Plasma insulin via RIA (mIU/L)
BL Urinary Na (mmol/L)	BL Monocytes (%)	BL Total testosterone (ng/mL)
BL Urine glucose (mg/dL)	BL Red blood cells (RBC) (n, millions/µL)	BL Total testosterone (nmol/L)
BL Urine proteins (mg/dL)	BL Hemoglobin (g/dL)	BL Free testosterone (ng/dL), Vermeulen
BL Urine hemoglobin (mg/dL)	BL Hematocrit (%)	BL Free testosterone (nmol/L), Vermeulen
BL Urine ketones (mg/dL)	BL Mean corpuscular volume (MCV) (fL)	BL Estradiol via radioimmunoassay (pg/mL)
BL Urine bilirubin (mg/dL)	BL Mean corpuscular hemoglobin (MCH) (pg)	BL Estradiol via radioimmunoassay (nmol/L)
BL Urine urobilinogen (mg/dL)	BL MCH concentration (MCHC) (g/dL)	BL C-terminal telopeptide of type-1 collagen (ng/mL)

BL Urine nitrites	BL Red cell distribution width (RDW) (%)	BL Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)-(IGFBP1)
BL Serum creatinine (mg/dL)	BL Mean platelet volume (MPV) (fL)	BL IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***
BL Blood urea nitrogen (mg/dL)	BL Ferritin (ng/mL)	BL IGF binding protein-3, serum, immunoradiometric assay (nmol/L)
BL Creatine phosphokinase (U/L)	BL Folate via RIA (ng/mL)	
BL Cystatin C (mg/L)	BL Folate via RIA (nmol/L)	
	BL Vitamin B12 via RIA (pg/mL)	
	BL Vitamin B12 via RIA (pmol/L)	
	BL Methylmalonic acid(methylmalonic aciduria), MMA (µmol/L)	
	BL Soluble transferrin receptor (nmol/L)	
	BL Soluble transferrin receptor (mg/L)	
	BL GOT (also known as AST) (U/L)	
	BL GPT (also known as ALT) (U/L)	
	BL Gamma glutamyl transferase (U/L)	
	BL Retinol via high performance liquid chromatography (µmol/L)	

Supplementary Data Table II: Variants included in the Genomic Risk Score GRS calculations and individual effect estimates of single variants for predictive modeling. Phenotype association is based on the findings from the systematic review and the relationship found between variant and disease outcome.

Variant Name-Allele	Allele Frequency (%)	Gene/Closest RefSeq Gene	Variant Detail-dbSNP	Phenotype Association
rs1048945_C	1.3	APEX1	rs1048945 C/G Ancestral: G Minor: C	Cognition
rs1052133_G	20.6	OGG1	rs1052133 C/G Ancestral: C Minor: G	Cognition
rs1064039_T	19.0	CST3	rs1064039 A/G Ancestral: G Minor: T	Cognition
rs10793294_C	21.7	GAB2	rs10793294 A/C Ancestral: G Minor: C	Cognition
rs10883631_G	48.4	BTRC	rs10883631 A/G Ancestral: G Minor: A	Frail
rs10883642_G	48.4	BTRC	rs10883642 A/G Ancestral: A Minor: A	Frail
rs11225434_C	47.9	WTAPP1	rs11225434 C/T Ancestral: T Minor: C	Cognition
rs113263161_A	10.4	**CCRL2**/LOC102724297	rs113263161 A/G Ancestral: G Minor: A	Cognition
rs1133174_A	41.0	SORL1	rs1133174 A/G Ancestral: G Minor: A	Cognition
rs11574428_A	10.2	CCRL2	rs11574428 A/T Ancestral: T Minor: A	Cognition
rs11575821_A	11.4	**CCRL2**/LOC102724297	rs11575821 A/G Ancestral: G Minor: A	Cognition
rs1207568_A	19.4	KLOTHO	rs1207568 C/T Ancestral: C Minor: A	Cognition
rs13113697_T	27.2	**HS3ST1**/LOC107986178	rs13113697 G/T Ancestral: G Minor: T	Cognition
rs1468063_T	12.4	FAS	rs1468063 A/G Ancestral: G Minor: T	Cognition
rs1566728_C	14.1	PTPRJ	rs1566728 A/G Ancestral: G Minor: C	Frail
rs16944_A	33.4	IL1B	rs16944 A/G Ancestral: A Minor: A	Cognition
rs1799990_G	30.9	PRNP	rs1799990 A/G Ancestral: A Minor: G	Cognition
rs1800629_A	12.3	TNF	rs1800629 A/G Ancestral: G Minor: A	Cog/Frail
rs1800764_C	47.6	ACE	rs1800764 C/T Ancestral: C Minor: T	Cognition
rs1800796_C	5.0	IL6	rs1800796 C/G Ancestral: G Minor: C	Cog/Frail
rs1801394_G	43.9	MTRR	rs1801394 A/G Ancestral: A Minor: G	Frail
rs2047812_A	14.8	PTPRJ	rs2047812 C/T Ancestral: C Minor: A	Frail
rs2227729_G	7.5	VTN	rs2227729 C/T Ancestral: C Minor: G	Frail
rs2228145_C	38.0	IL6-R	rs2228145 A/C/T Ancestral: A Minor: C	Cognition
rs2228467_C	8.2	CCL4	rs2228467 C/T Ancestral: T Minor: C	Cognition
rs2229238_T	16.9	IL6-R	rs2229238 C/T Ancestral: C Minor: T	Cognition
rs2267163_T	36.5	TCN2	rs2267163 C/T Ancestral: C Minor: T	Frail
rs2283368_C	12.3	KLOTHO	rs2283368 C/T Ancestral: T Minor: C	Cognition
rs2465481_A	47.0	GNAI1	rs2465481 C/T Ancestral: C Minor: A	Cognition
rs2714465_G	45.0	GNAI1	rs2714465 A/G Ancestral: A Minor: G	Cognition
rs3092960_A	10.7	CCR2	rs3092960 A/G Ancestral: G Minor: A	Cognition
rs3131609_C	32.8	USP50	rs3131609 A/G Ancestral: A Minor: C	Cognition
rs360722_A	16.9	IL18	rs360722 C/T Ancestral: T Minor: A	Frail
rs3865444_A	27.1	CD33	rs3865444 G/T Ancestral: G Minor: A	Cognition
rs4147929_A	19.3	ABCA7	rs4147929 A/G Ancestral: G Minor: A	Cognition
rs429358_C	6.9	APOE	rs429358 C/T Ancestral: C Minor: C	Cognition
rs4316_T	38.1	ACE	rs4316 C/T Ancestral: C Minor: T	Cognition
rs4845622_C	38.6	IL6R	rs4845622 A/C Ancestral: A Minor: C	Cognition
rs4968782_G	41.0	**ACE**	rs4968782 A/G Ancestral: G Minor: G	Cognition
rs55636820_A	6.0	BIN1	rs55636820 A/G Ancestral: G Minor: A	Cognition
rs562020_A	34.6	KLOTHO	rs562020 C/T Ancestral: T Minor: A	Cognition
rs573521_A	47.2	MMP3	rs573521 C/T Ancestral: C Minor: A	Cognition
rs5744256_G	18.3	IL18	rs5744256 C/T Ancestral: T Minor: G	Frail
rs603050_T	31.3	WTAPP1	rs603050 A/G Ancestral: G Minor: T	Cognition
rs611646_T	48.6	ATM	rs611646 A/T Ancestral: A Minor: A	Frail

rs61812598_A	37.9	IL6-R	rs61812598 A/G Ancestral: G Minor: A	Cognition
rs6441977_A	10.2	CCRL2	rs6441977 A/G Ancestral: G Minor: A	Cognition
rs650108_A	30.1	MMP3	rs650108 A/G Ancestral: G Minor: A	Cognition
rs6762266_C	10.4	**CCRL2**	rs6762266 C/T Ancestral: T Minor: C	Cognition
rs679620_T	46.7	MMP3	rs679620 A/G Ancestral: G Minor: T	Cognition
rs6808835_T	10.5	CCRL2	rs6808835 G/T Ancestral: T Minor: T	Cognition
rs7110631_C	31.2	**PICALM**	rs7110631 C/G Ancestral: G Minor: C	Cognition
rs7396366_C	36.0	AP2A2	rs7396366 G/T Ancestral: T Minor: C	Cognition
rs7412_T	6.6	APOE	rs7412 C/T Ancestral: C Minor: T	Cognition
rs7497104_T	28.6	MYO9A	rs7497104 C/T Ancestral: T Minor: T	Cognition
rs7926920_A	46.9	WTAPP1	rs7926920 A/G Ancestral: G Minor: A	Cognition
rs9267487_C	6.5	DDX39B	rs9267487 C/T Ancestral: T Minor: C	Frail
rs9349407_C	24.5	CD2AP	rs9349407 C/G Ancestral: G Minor: C	Cognition
rs948399_C	26.9	MMP3	rs948399 C/T Ancestral: T Minor: C	Cognition
rs9527025_C	14.8	KLOTHO	rs9527025 C/G Ancestral: C Minor: C	Cognition
rs3219484_T	3.8	MUTYH	rs3219484_ A/G Ancestral: G Minor: T	Cognition
rs12752888_C	26.8	**ACOT11**/LOC105378734	rs12752888 C/T Ancestral: T Minor: C	Cognition
rs1539053_A	45.6	DAB1	rs1539053 C/T Ancestral: T Minor: G	Cognition
rs3811448_A	19.3	TDRD10	rs3811448 A/G Ancestral: A Minor: A	Cognition
rs4129267_T	37.9	IL6-R	rs4129267 C/T Ancestral: C Minor: T	Cognition
rs915179_G	36.0	LMNA	rs915179 A/G Ancestral: G Minor: A	Cognition
rs9919256_A	13.7	LMNA	rs9919256 A/G Ancestral: A Minor: A	Cognition
rs6131_T	19.4	SELP	rs6131 A/G Ancestral: A Minor: T	Frail
rs3818361_A	19.5	CR1	rs3818361 C/T Ancestral: C Minor: A	Cognition
rs1260326_C	46.3	GCKR	rs1260326 C/T Ancestral: C Minor: T	Frail
rs744373_G	28.2	**BIN1**	rs744373 C/T Ancestral: T Minor: G	Cognition
rs7561528_A	31.2	**BIN1**/LOC105373605	rs7561528 A/G Ancestral: A Minor: A	Cognition
rs11894266_C	43.5	**SSB**	rs11894266 C/T Ancestral: C Minor: T	Cognition
rs6747918_A	49.2	CASP8	rs6747918 A/G Ancestral: A Minor: A	Frail
rs2929408_A	22.4	KAT2B	rs2929408 G/T Ancestral: G Minor: A	Frail
rs737267_T	25.6	SLC2A9	rs737267 A/G/T Ancestral: G Minor: T	Frail
rs9461448_G	4.7	PGBD1	rs9461448 G/T Ancestral: T Minor: G	Cognition
rs9446432_C	8.2	**C6orf155**	rs9446432 C/T Ancestral: T Minor: C	Cognition
rs9384428_C	32.5	**MIR1202**/LOC101928923	rs9384428 C/T Ancestral: T Minor: C	Cognition
rs4646450_A	16.4	CYP3A5	rs4646450 C/T Ancestral: T Minor: A	Frail
rs11767557_C	16.8	EPHA1-AS1	rs11767557 C/T Ancestral: T Minor: C	Cognition
rs11771145_A	32.9	EPHA1-AS1	rs11771145 A/G Ancestral: A Minor: A	Cognition
rs11136000_T	39.0	CLU	rs11136000 C/T Ancestral: T Minor: T	Cognition
rs1157242_T	16.2	**KCNU1**	rs1157242 A/G Ancestral: G Minor: T	Cognition
rs7840202_C	29.9	UBR5	rs7840202 A/C Ancestral: C Minor: C	Cognition
rs7920721_G	39.4	ECHDC3	rs7920721 A/G Ancestral: A Minor: G	Cognition
rs7905675_A	34.9	**TFAM**	rs7905675 A/G Ancestral: A Minor: G	Cognition
rs17117126_G	9.5	**CH25H**	rs17117126 A/G Ancestral: G Minor: G	Cognition
rs6265_T	21.6	BDNF	rs6265 A/G Ancestral: G Minor: T	Cognition
rs1566729_T	14.1	PTPRJ	rs1566729 A/G Ancestral: G Minor: T	Frail
rs583791_C	49.5	MS4A6A	rs583791 A/G Ancestral: G Minor: C	Cognition
rs610932_T	48.5	MS4A6A	rs610932 A/C Ancestral: A Minor: T	Cognition
rs662196_C	49.6	MS4A6A	rs662196 A/G Ancestral: G Minor: C	Cognition
rs670139_T	31.2	MS4A4E	rs670139 A/C/T Ancestral: C Minor: T	Cognition
rs676309_C	31.1	MS4A4E	rs676309 A/G Ancestral: A Minor: C	Cognition

rs11827375_A	10.5	**C11orf30**	rs11827375 A/G Ancestral: G Minor: A	Cognition
rs3851179_T	36.0	**PICALM**	rs3851179 A/G Ancestral: G Minor: T	Cognition
rs541458_C	31.6	**PICALM**	rs541458 C/T Ancestral: T Minor: C	Cognition
rs10501927_G	23.6	CNTN5	rs10501927 G/T Ancestral: T Minor: G	Cognition
rs495366_A	30.1	WTAPP1	rs495366 A/G Ancestral: G Minor: A	Cognition
rs645419_A	46.7	MMP3	rs645419 A/G Ancestral: G Minor: A	Cognition
rs10502262_T	27.7	SORL1	rs10502262 A/G Ancestral: G Minor: T	Cognition
rs1614735_G	47.6	SORL1	rs1614735 G/T Ancestral: T Minor: G	Cognition
rs2298813_A	4.0	SORL1	rs2298813 A/G Ancestral: G Minor: A	Cognition
rs3781835_A	2.3	SORL1	rs3781835 A/G Ancestral: G Minor: A	Cognition
rs4935774_C	20.5	SORL1	rs4935774 C/T Ancestral: C Minor: C	Cognition
rs4363657_C	15.2	SLCO1B1	rs4363657 C/T Ancestral: T Minor: C	Frail
rs1799986_T	17.4	LRP1	rs1799986 A/C/T Ancestral: C Minor: T	Frail
rs398655_C	45.0	KLOTHO	rs398655 G/T Ancestral: G Minor: A	Cognition
rs648202_T	13.7	KLOTHO	rs648202 C/T Ancestral: C Minor: T	Cognition
rs9526984_G	7.4	KLOTHO	rs9526984 A/G Ancestral: A Minor: G	Cognition
rs9527024_A	14.8	KLOTHO	rs9527024 A/G Ancestral: A Minor: A	Cognition
rs9536314_G	14.7	KLOTHO	rs9536314 A/G/T Ancestral: T Minor: G	Cognition
rs2287396_T	17.7	GSTZ1	rs2287396 C/T Ancestral: C Minor: T	Frail
rs7175373_C	29.1	**MYO9A**	rs7175373 A/C/G Ancestral: C Minor: C	Cognition
rs129968_A	39.8	CREBBP	rs129968 A/G Ancestral: A Minor: G	Frail
rs3785880_G	39.8	MAPT	rs3785880 G/T Ancestral: T Minor: G	Cognition
rs2526378_G	46.8	TSPOAP1	rs2526378 C/T Ancestral: C Minor: A	Cognition
rs4343_A	40.1	ACE	rs4343 A/G Ancestral: A Minor: G	Cognition
rs4459609_C	40.9	**ACE**	rs4459609 A/C Ancestral: A Minor: C	Cognition
rs3764650_G	11.8	ABCA7	rs3764650 G/T Ancestral: T Minor: G	Cognition
rs157580_G	39.1	TOMM40	rs157580 A/G Ancestral: G Minor: G	Cognition
rs2075650_G	7.5	TOMM40	rs2075650 A/G Ancestral: G Minor: G	Cognition
rs405509_T	42.8	APOE	rs405509 A/C Ancestral: C Minor: T	Cognition
rs597668_C	12.0	**EXOC3L2**	rs597668 C/T Ancestral: C Minor: C	Cognition
rs6859_A	38.8	NECTIN2	rs6859 A/G Ancestral: G Minor: A	Cognition
rs8106922_G	44.8	TOMM40	rs8106922 A/G Ancestral: A Minor: G	Cognition
rs17411904_C	7.7	**PCK1**	rs17411904 C/T Ancestral: T Minor: C	Cognition
rs2833383_T	27.9	TIAM1	rs2833383 C/T Ancestral: C Minor: T	Frail
rs4646316_T	27.7	COMT	rs4646316 C/T Ancestral: C Minor: T	Frail
rs4680_A	46.4	COMT	rs4680 C/T Ancestral: G Minor: A	Cognition
rs740234_G	24.2	TCN2	rs740234 C/T Ancestral: T Minor: G	Frail

Notes: *Proxy SNP, Cog/Frail – variant was found for both phenotypes in the systematic review, bold text indicates the closest gene

Genetic risk scores

One hundred and thirty-one variants where catalogued from a large systematic review and used to construct genetic risk scores for three models. All variants were used to create an all risk score (n=132), variants related to the phenotypes cognitive decline and physical frailty constructed cognitive risk scores (n=105) and frailty risk scores (n=27). Risk scores were calculated by summation of the number of risk alleles across all the variants divided by the number of SNPs in the score to obtain an average number of risk alleles per locus. After the scaled risk allele counts were summed and divided by the number of loci, they were transformed into Z scores. Z score transformation assists in communicating the effect estimates with the Z corresponding to a single standard deviation from the control mean genetic risk for the phenotypes. All risk scores were calculated using PLINK. R V. 3.2.1 was used to fit multinomial and logistic regression models using standard covariates and risk scores as predictors of cognitive decline, physical frailty, and cognitive frailty as the outcome variable. Stepwise backward and forward selection using AIC and p values facilitated the best fit models.

Supplementary Table III:
Model I Genetic risk scores – Population predictive model features by phenotype

Phenotype (n)		All Risk Scores	Cognition Risk Scores	Frail Risk Scores
Cognitive Decline MMSE (369)	p	.1286	.0659	.8768
	β	.12	.15	-.01
	SE	.08	.08	.08
Frail CHS (595)	p	.0488	.0401	.6509
	β	0.14	.14	.03
	SE	0.07	.07	.07
Cognitive frailty MMSE (257)	p	.0455	.0479	.7775
	β	0.19	.19	-0.03
	SE	0.10	.10	.09

Model II Genetic risk scores – Population predictive model features by phenotype

Phenotype (n)		All Risk Scores	Cognition Risk Scores	Frail Risk Scores
Cognitive Decline Trail B (634)	p	.6097	.5959	.4440
	β	.05	.05	-.07
	SE	.09	.09	.09
Cognitive Decline Trail A (525)	p	.0351	.0370	.3274
	β	.16	.16	.07
	SE	.08	.07	.07
Cognitive Frailty Trail B (325)	p	.2082	.1992	.7394
	β	.11	.11	.03
	SE	.08	.09	.08
Cognitive Frailty Trail A (302)	p	.6298	.4242	.2734
	β	.04	.06	-.08
	SE	.08	.08	.08

Table IV: Cognitive Decline Features Model I

Cogntive Decline Features	Gain	Cover	Frequency	Importance
Age	0.247016911	0.117594993	0.048543689	0.247016911
Level of Education	0.160608946	0.187763494	0.097087379	0.160608946
TNF-related apoptosis-inducing ligand	0.025564877	0.029595722	0.029126214	0.025564877
24-hour urinary creatinine	0.02142342	0.016832239	0.014563107	0.02142342
Fatty acid C16:0 as % of total fatty acid area	0.018881415	0.036076992	0.024271845	0.018881415
Dx Depression	0.018852494	0.021616819	0.019417476	0.018852494
Cystatin C	0.017786637	0.035118001	0.024271845	0.017786637
Dehydroepiandrosterone sulfate	0.01624112	0.0178982	0.014563107	0.01624112
Adiponectin via RIA	0.0154553	0.018357822	0.019417476	0.0154553
Beta-carotene via high performance liquid chromatography (µmol/L)	0.015327296	0.014660641	0.019417476	0.015327296
Mean corpuscular volume (MCV)	0.013822196	0.015698515	0.024271845	0.013822196
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***	0.012997192	0.007511319	0.019417476	0.012997192
Free thyroxine fT4 (ng/dL)	0.012865081	0.006865344	0.014563107	0.012865081
Fibrinogen (mg/dL)	0.010709775	0.023801966	0.014563107	0.010709775
Lymphocytes	0.010046812	0.008887038	0.014563107	0.010046812
Red cell distribution width (RDW) (%)	0.008983628	0.003876676	0.009708738	0.008983628
Interleukin-12	0.008595815	0.002439156	0.009708738	0.008595815
Fatty acid C16:0 (palmitic) area	0.008348097	0.00299276	0.009708738	0.008348097
Fatty acid C20:0 (arachidic) area	0.00819782	0.01193878	0.014563107	0.00819782
Lipids: HDL cholesterol	0.007781061	0.013694142	0.019417476	0.007781061
Fatty acid C20:5 n-3 as % of total fatty acid weight	0.007714811	0.016204393	0.009708738	0.007714811
Ferritin	0.007209597	0.010436238	0.009708738	0.007209597
Gender	0.007151353	0.00641112	0.009708738	0.007151353
Fatty acid C24:0 as % of total fatty acid weight	0.007083429	0.010963022	0.014563107	0.007083429
24-hour urinary cortisol (µg/24 hours)	0.006833969	0.003491305	0.009708738	0.006833969
Creatinine clearance 24-hr urine	0.006443681	0.007022278	0.009708738	0.006443681
Fatty acid C20:0 weight (mg/L)	0.006025751	0.005788322	0.009708738	0.006025751
Vitamin E gamma tocopherol high performance liquid chromatography	0.005902007	0.00573116	0.009708738	0.005902007
Soluble IL-6 receptor via ELISA	0.005647251	0.002059633	0.004854369	0.005647251
Cortisol:DHEAS ratio	0.005261354	0.019818409	0.014563107	0.005261354
Methylmalonic acid MMA (µmol/L)"	0.005213763	0.001448349	0.009708738	0.005213763
Resistin via EIA	0.00521251	0.006015127	0.009708738	0.00521251
Plasma insulin via RIA	0.005080217	0.003755668	0.009708738	0.005080217
Creatine phosphokinase	0.004950723	0.001190354	0.004854369	0.004950723
Homocysteine via FPIA analysis	0.004917852	0.007184674	0.004854369	0.004917852
Interleukin-10 via ELISA	0.004745208	0.00376727	0.004854369	0.004745208
Fatty acid C24:0 (lignoceric) area	0.004584681	0.00330742	0.004854369	0.004584681
Red blood cells	0.004528429	0.011768391	0.009708738	0.004528429
Fatty acid C20:5 n-3 weight (mg/L)	0.004501496	0.001118337	0.004854369	0.004501496
Estradiol via radioimmunoassay (pg/mL)	0.00425931	0.000629884	0.004854369	0.00425931
Vitamin B12 via RIA	0.004252471	0.018127967	0.009708738	0.004252471
BL Omega-3 plasma fatty acid weight (mg/L)	0.004221882	0.002369331	0.004854369	0.004221882
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	0.004149518	0.014263272	0.009708738	0.004149518
Fatty acid C24:0 as % of total fatty acid area	0.004102069	0.005203763	0.004854369	0.004102069
Ratio of Omega-6:Omega-3 as % of total fatty acid area	0.004049393	0.008024251	0.009708738	0.004049393

Urinary Na	0.003793497	0.000890377	0.009708738	0.003793497
Alpha-2-macroglobulin	0.003641408	0.01779343	0.009708738	0.003641408
Lipids: triglycerides (mg/dL)	0.003635412	0.000947582	0.009708738	0.003635412
rs3131609_C	0.003539956	0.002923127	0.004854369	0.003539956
rs1800796_C	0.003487553	0.001642754	0.004854369	0.003487553
Lycopene via high performance liquid chromatography	0.003366475	0.001272687	0.004854369	0.003366475
Soluble TNF-a receptor I via quantitative sandwich EIA	0.003259691	0.001869279	0.004854369	0.003259691
Albumin (%)	0.003252256	0.000885554	0.004854369	0.003252256
MCH concentration (MCHC) (g/dL)	0.003207126	0.001501542	0.004854369	0.003207126
C-terminal telopeptide of type-1 collagen	0.003132828	0.001238391	0.004854369	0.003132828
Alpha-1 globulin	0.003093762	0.001077661	0.004854369	0.003093762
Alpha-2 globulin (%)	0.002957393	0.001951717	0.004854369	0.002957393
Urinary cortisol	0.002954808	0.005640344	0.004854369	0.002954808
Lipoprotein(a)	0.002822909	0.004583778	0.004854369	0.002822909
BL Blood glucose (mg/dL)	0.002796243	0.005340663	0.009708738	0.002796243
Anticolnergic Burden	0.002789313	0.009621728	0.004854369	0.002789313
rs2228145_C	0.002741554	0.001278252	0.004854369	0.002741554
BL Ratio of Omega-6:Omega-3 as % of total fatty acid mols	0.002656076	0.004937615	0.004854369	0.002656076
Blood urea nitrogen	0.002558617	0.00897141	0.004854369	0.002558617
Parathyroid hormone two-site immunoradiometric assay "	0.002550438	0.000968729	0.004854369	0.002550438
Serum cortisol	0.00249517	0.002893942	0.004854369	0.00249517
Lipids: total cholesterol	0.002460557	0.001170389	0.004854369	0.002460557
Fatty acid C22:0 (behenic) area	0.002339895	0.00187473	0.004854369	0.002339895
Vitamin E alpha tocopherol high performance liquid chromatography	0.002198081	0.005823143	0.004854369	0.002198081
Urinary Ca	0.002164721	0.000730392	0.004854369	0.002164721
Folate via RIA	0.002113781	0.00106923	0.004854369	0.002113781
Monocytes (%)	0.00199266	0.000547857	0.004854369	0.00199266
Total proteins (g/dL)	0.001944932	0.007589282	0.004854369	0.001944932
rs948399_C	0.001742443	0.001020202	0.004854369	0.001742443
Omega-6 plasma fatty acid weight (mg/L)	0.001653381	0.001473014	0.004854369	0.001653381
rs10883631_G	0.001571027	0.000810486	0.004854369	0.001571027
White blood cells (WBC)	0.001509285	0.000889183	0.004854369	0.001509285
ALT	0.001401955	0.000216533	0.004854369	0.001401955
Fatty acid C20:0 as % of total fatty acid weight	0.001362604	0.007402723	0.004854369	0.001362604
Interleukin-18 via ELISA ultrasensitive using plasma	0.001317785	0.000289673	0.004854369	0.001317785
rs7396366_C	0.001163588	0.000555404	0.004854369	0.001163588
Gamma glutamyl transferase	0.000800672	0.002452777	0.004854369	0.000800672
Fatty acid C22:0	0.000561923	0.000672233	0.004854369	0.000561923
Fatty acid C16:0 as % of total fatty acid weight	0.000554415	0.000510348	0.004854369	0.000554415
Uric acid	0.000537078	0.000186889	0.004854369	0.000537078
rs2075650_G	0.000487925	0.000597468	0.004854369	0.000487925
Thyroid stimulating hormone	0.000404183	0.000235127	0.004854369	0.000404183
rs4646316_T	0.000302482	0.00026136	0.004854369	0.000302482
Mean corpuscular hemoglobin	0.000184601	0.002295018	0.004854369	0.000184601
Interleukin-6 via ELISA ultrasensitive	6.12E-05	0.000353843	0.004854369	6.12E-05

Table V: Frailty Features Model I

Frailty Features	Gain	Cover	Frequency	Importance
Depression	0.098775745	0.084652562	0.027559055	0.098775745
Creatinine clearance, 24-hr urine (mL/minute)	0.052445936	0.033303749	0.011811024	0.052445936
Age	0.049474709	0.022604179	0.019685039	0.049474709
Anticholinergic Burden	0.030906413	0.030358874	0.023622047	0.030906413
Homocysteine via FPIA analysis (µmol/L)	0.024715965	0.023600409	0.007874016	0.024715965
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	0.023717251	0.022258754	0.015748031	0.023717251
Vitamin B6 via high performance liquid chromatography (ng/mL)	0.022823838	0.024226924	0.015748031	0.022823838
Interleukin-6 via ELISA ultrasensitive (pg/mL)	0.021999328	0.031654032	0.015748031	0.021999328
Dehydroepiandrosterone sulfate (µg/dL)	0.021750399	0.00821273	0.019685039	0.021750399
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	0.021744382	0.029219322	0.019685039	0.021744382
Erythrocyte sedimentation rate (ESR) (mm/hour)	0.019839941	0.028859155	0.019685039	0.019839941
Endogenous secretory receptor for AGEs (ng/mL)	0.018672872	0.019026448	0.023622047	0.018672872
24-hour urinary creatinine (mg/24 hours)	0.017065385	0.008624125	0.019685039	0.017065385
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	0.016999208	0.005822401	0.011811024	0.016999208
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	0.01625036	0.019029454	0.015748031	0.01625036
Lipoprotein(a) (mg/dL)	0.015535882	0.02537913	0.019685039	0.015535882
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.015019838	0.023585828	0.015748031	0.015019838
Vitamin B12 via RIA (pg/mL)	0.014433258	0.012129297	0.019685039	0.014433258
Vitamin E gamma tocopherol, high performance liquid chromatography (µmol/L)	0.014300271	0.007085453	0.011811024	0.014300271
Folate via RIA (ng/mL)	0.014001884	0.011108339	0.011811024	0.014001884
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	0.013772642	0.017304651	0.015748031	0.013772642
Interleukin-1B via ELISA (pg/mL)	0.013205983	0.030090209	0.015748031	0.013205983
Beta-carotene via high performance liquid chromatography (µmol/L)	0.013116604	0.008019449	0.011811024	0.013116604
Creatine phosphokinase (U/L)	0.012919658	0.015168335	0.007874016	0.012919658
Plasma insulin via RIA (mIU/L)	0.011798838	0.011456837	0.011811024	0.011798838
Retinol via high performance liquid chromatography (µmol/L)	0.011423155	0.00461384	0.011811024	0.011423155
Methylmalonic acid, MMA (µmol/L)	0.011339303	0.008264588	0.015748031	0.011339303
Omega-6 fatty acids as % of total fatty acid area	0.011008005	0.004272542	0.019685039	0.011008005
Monocytes (n, K/µL)	0.010487533	0.018913621	0.011811024	0.010487533
Lipids: LDL cholesterol (mg/dL)	0.009591423	0.003739115	0.011811024	0.009591423
Tumor necrosis factor-a via multiplex technology (pg/mL)	0.009463133	0.006942978	0.011811024	0.009463133
Urinary Na (mmol/L)	0.009315233	0.004721585	0.011811024	0.009315233
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	0.009129694	0.013434801	0.015748031	0.009129694
Urinary Ca (mmol/L)	0.009022724	0.012591808	0.015748031	0.009022724
C-terminal telopeptide of type-1 collagen (ng/mL)	0.008609358	0.007960146	0.007874016	0.008609358
Interleukin-8 via Bio-Plex (pg/mL)	0.008566678	0.00594986	0.003937008	0.008566678
Fatty acid C24:0 as % of total fatty acid area	0.008095749	0.012731259	0.011811024	0.008095749
TNF-related apoptosis-inducing ligand (pg/mL)	0.007711265	0.003574424	0.011811024	0.007711265
Free testosterone (ng/dL), Vermeulen	0.007578292	0.011968667	0.015748031	0.007578292
Cystatin C (mg/L)	0.006550153	0.000712653	0.003937008	0.006550153
Na+ (mEq/L)	0.006516226	0.007030191	0.003937008	0.006516226
Monocytes (%)	0.00639573	0.01284515	0.011811024	0.00639573
Hematocrit (%)	0.00623512	0.006186332	0.003937008	0.00623512
24-hour urinary cortisol (µg/24 hours)	0.006090747	0.010514246	0.007874016	0.006090747
Interleukin-12 via Bio-Plex (pg/mL)	0.006015217	0.004092294	0.007874016	0.006015217
Blood glucose (mg/dL)	0.005694126	0.001798266	0.007874016	0.005694126
Soluble CD14 via ELISA (ng/mL)	0.0055483	0.001419796	0.003937008	0.0055483
Soluble IL-6 receptor via ELISA (ng/mL)	0.005477014	0.003230929	0.007874016	0.005477014
Fatty acid C24:0 as % of total fatty acid weight	0.005404971	0.002740247	0.003937008	0.005404971
Total testosterone (ng/mL)	0.005367844	0.01031343	0.003937008	0.005367844
rs948399_C	0.005345514	0.002189977	0.003937008	0.005345514

Urine proteins (mg/dL)	0.005280709	0.01350518	0.007874016	0.005280709
Neutrophils (n, K/µL)	0.005181902	0.000457207	0.003937008	0.005181902
Fatty acid C20:0 as % of total fatty acid weight	0.005052286	0.000994181	0.003937008	0.005052286
Serum cortisol (µg/dL)	0.005017158	0.027936629	0.011811024	0.005017158
Level of Education	0.00493252	0.005284448	0.003937008	0.00493252
Red cell distribution width (RDW) (%)	0.004763014	0.005996977	0.003937008	0.004763014
Vitamin E gamma tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.004502593	0.002631694	0.003937008	0.004502593
Blood urea nitrogen (mg/dL)	0.004480007	0.006420977	0.011811024	0.004480007
Thyroid stimulating hormone, TSH (mIU/L)	0.004433716	0.00184381	0.007874016	0.004433716
rs10501927_G	0.004414743	0.009323168	0.007874016	0.004414743
Lipids: HDL cholesterol (mg/dL)	0.004247467	0.002294261	0.003937008	0.004247467
rs129968_A	0.004192118	0.003263095	0.007874016	0.004192118
Resistin via EIA (ng/mL)	0.0041092	0.006075858	0.003937008	0.0041092
Gamma glutamyl transferase (U/L)	0.004070941	0.011275891	0.007874016	0.004070941
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	0.004052691	0.001761794	0.003937008	0.004052691
Baseline diagnosis of Dementia	0.003942136	0.019120532	0.007874016	0.003942136
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	0.003824567	0.000791652	0.007874016	0.003824567
Urinary creatinine (mg/dL)	0.003755628	0.000396059	0.007874016	0.003755628
Ferritin (ng/mL)	0.003742311	0.008416166	0.007874016	0.003742311
C-reactive protein - high sensitivity (µg/mL)	0.003565832	0.002077369	0.003937008	0.003565832
Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)	0.003520041	0.002588955	0.003937008	0.003520041
Lymphocytes (%)	0.003478691	0.000977976	0.003937008	0.003478691
Fatty acid C16:0 as % of total fatty acid weight	0.003475484	0.004796531	0.003937008	0.003475484
rs11225434_C	0.003330988	0.004787995	0.003937008	0.003330988
Fatty acid C16:0 (palmitic) area	0.003293404	0.000936887	0.003937008	0.003293404
Neutrophils (%)	0.003128871	0.00067737	0.003937008	0.003128871
Fatty acid C20:5 n-3 weight (mg/L)	0.003123782	0.001971299	0.003937008	0.003123782
Fatty acid C20:0 as % of total fatty acid area	0.003010934	0.002094985	0.003937008	0.003010934
GPT (also known as ALT) (U/L)	0.002937445	0.00592063	0.003937008	0.002937445
Albumin (%)	0.002854574	0.002198538	0.003937008	0.002854574
Mean platelet volume (MPV) (fL)	0.002770872	0.000419397	0.003937008	0.002770872
rs1539053_A	0.002756129	0.012007864	0.003937008	0.002756129
Cortisol:DHEAS ratio (based on nmols)	0.002566654	0.000898211	0.003937008	0.002566654
MCH concentration (MCHC) (g/dL)	0.002565159	0.010052336	0.003937008	0.002565159
Free thyroxine, fT4 (ng/dL)	0.002443825	0.007244682	0.007874016	0.002443825
Beta globulins (%)	0.002269127	0.000431623	0.003937008	0.002269127
Lipids: total cholesterol (mg/dL)	0.002175655	0.002408026	0.003937008	0.002175655
Fatty acid C20:0 weight (mg/L)	0.002119043	0.001718137	0.003937008	0.002119043
Estradiol via radioimmunoassay (pg/mL)	0.002044564	0.000316794	0.003937008	0.002044564
Fatty acid C22:0 weight (mg/L)	0.001960255	0.000352188	0.003937008	0.001960255
Lycopene via high performance liquid chromatography (µmol/L)	0.001838456	0.002966245	0.003937008	0.001838456
Fatty acid C16:0 as % of total fatty acid area	0.001816434	0.010717187	0.003937008	0.001816434
Omega-6 plasma fatty acid weight (mg/L)	0.001762988	0.001987793	0.003937008	0.001762988
rs7840202_C	0.001405255	0.001059102	0.003937008	0.001405255
Hemoglobin (g/dL)	0.001237461	0.000333737	0.003937008	0.001237461
Gender	0.001217717	0.001564023	0.003937008	0.001217717
Omega-3 plasma fatty acid weight (mg/L)	0.001079396	0.000479765	0.007874016	0.001079396
Fatty acid C20:5 n-3 as % of total fatty acid area	0.001022163	0.000592968	0.003937008	0.001022163
White blood cells (WBC) (n, K/µL)	0.001016876	0.000724366	0.003937008	0.001016876
Fatty acid C24:0 (lignoceric) area	0.000965197	0.000281381	0.003937008	0.000965197
Fatty acid C24:0 weight (mg/L)	0.000951989	0.000337432	0.003937008	0.000951989
rs3865444_A	0.00059402	0.000268936	0.003937008	0.00059402
rs4935774_C	0.000287175	0.000250477	0.003937008	0.000287175
Mean corpuscular volume (MCV) (fL)	0.000204245	0.00046439	0.003937008	0.000204245

Table VI: Cognitive Frailty Features Model I

Cognitive Frailty Features	Gain	Cover	Frequency	Importance
Age	0.226782261	0.171557774	0.059322034	0.226782261
Baseline Diagnosis of Dementia	0.099398955	0.098462848	0.029661017	0.099398955
Level of Education	0.044233154	0.075160958	0.029661017	0.044233154
Depression	0.034553704	0.038157217	0.029661017	0.034553704
TNF-related apoptosis-inducing ligand (pg/mL)	0.03034655	0.028129602	0.033898305	0.03034655
24-hour urinary creatinine (mg/24 hours)	0.025460108	0.014329518	0.008474576	0.025460108
Fatty acid C24:0 as % of total fatty acid area	0.023009514	0.008399373	0.012711864	0.023009514
Fibrinogen (mg/dL)	0.015823506	0.009692466	0.021186441	0.015823506
24-hour urinary cortisol (µg/24 hours)	0.015266068	0.037498193	0.021186441	0.015266068
Lipids: HDL cholesterol (mg/dL)	0.014715469	0.011976521	0.016949153	0.014715469
Transforming growth factor-B1 (pg/mL)	0.014096962	0.022255665	0.016949153	0.014096962
Urinary cortisol (µg/mL)	0.014020579	0.027768583	0.021186441	0.014020579
Cystatin C (mg/L)	0.012966575	0.012313314	0.012711864	0.012966575
Blood urea nitrogen (mg/dL)	0.012798018	0.015478663	0.016949153	0.012798018
Anticholinergic Burden	0.012377409	0.015077936	0.029661017	0.012377409
Gender	0.011802004	0.013718017	0.021186441	0.011802004
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	0.011677247	0.005056691	0.016949153	0.011677247
Erythrocyte sedimentation rate (ESR) (mm/hour)	0.011479619	0.027685275	0.016949153	0.011479619
Creatine phosphokinase (U/L)	0.011252254	0.009828549	0.008474576	0.011252254
Serum cortisol (µg/dL)	0.009997371	0.006957488	0.012711864	0.009997371
Omega-6 fatty acids as % of total fatty acid area	0.009927552	0.003755798	0.004237288	0.009927552
Dehydroepiandrosterone sulfate (µg/dL)	0.009699038	0.004094407	0.008474576	0.009699038
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	0.009690317	0.011910741	0.008474576	0.009690317
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.008586559	0.00937805	0.016949153	0.008586559
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	0.008545621	0.011291322	0.016949153	0.008545621
Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)	0.007953886	0.004648823	0.012711864	0.007953886
Vitamin B6 via high performance liquid chromatography (ng/mL)	0.007871375	0.004486658	0.012711864	0.007871375
Soluble CD14 via ELISA (ng/mL)	0.00781868	0.006603146	0.008474576	0.00781868
Uric acid (mg/dL)	0.007707399	0.004887846	0.012711864	0.007707399
Fatty acid C20:0 as % of total fatty acid area	0.007346802	0.001933709	0.008474576	0.007346802
Thyroid stimulating hormone, TSH (mIU/L)	0.007266114	0.005429717	0.012711864	0.007266114
C-terminal telopeptide of type-1 collagen (ng/mL)	0.007200276	0.009389035	0.004237288	0.007200276
Urine proteins (mg/dL)	0.007174622	0.011835413	0.008474576	0.007174622
Total testosterone (ng/mL)	0.006692034	0.004245555	0.008474576	0.006692034
Resistin via EIA (ng/mL)	0.006665635	0.003066128	0.012711864	0.006665635
Hemoglobin (g/dL)	0.006538294	0.001687461	0.004237288	0.006538294
Gamma glutamyl transferase (U/L)	0.006461435	0.002914706	0.004237288	0.006461435
Fatty acid C24:0 as % of total fatty acid weight	0.006316549	0.006171081	0.008474576	0.006316549
Free thyroxine, fT4 (ng/dL)	0.006171355	0.00694256	0.008474576	0.006171355
Fatty acid C20:0 weight (mg/L)	0.006114046	0.003017798	0.008474576	0.006114046
Red cell distribution width (RDW) (%)	0.006079822	0.00257699	0.008474576	0.006079822
Cortisol:DHEAS ratio (based on nmols)	0.005840558	0.010952017	0.012711864	0.005840558
Vitamin E gamma tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.005830235	0.004808919	0.012711864	0.005830235
Monocytes (%)	0.005572667	0.003896981	0.008474576	0.005572667
rs1800796_C	0.005375181	0.001349969	0.004237288	0.005375181
MCH concentration (MCHC) (g/dL)	0.005308074	0.00983547	0.004237288	0.005308074
Fatty acid C22:0 (behenic) area	0.004956023	0.0045059	0.012711864	0.004956023
Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)	0.004726676	0.010909678	0.008474576	0.004726676
Urine nitrites	0.004714047	0.002983739	0.004237288	0.004714047
Fatty acid C20:5 n-3 as % of total fatty acid weight	0.004676963	0.00545449	0.008474576	0.004676963

Interleukin-10 via ELISA (pg/mL)	0.004582369	0.003833224	0.008474576	0.004582369
rs7561528_A	0.004441844	0.002401485	0.004237288	0.004441844
Fatty acid C22:0 as % of total fatty acid area	0.004203919	0.001526901	0.004237288	0.004203919
Homocysteine via FPIA analysis (µmol/L)	0.004184592	0.001820163	0.004237288	0.004184592
Beta-carotene via high performance liquid chromatography (µmol/L)	0.004176619	0.001453662	0.008474576	0.004176619
Ferritin (ng/mL)	0.0041346	0.005952456	0.008474576	0.0041346
Plasma insulin via RIA (mIU/L)	0.004084085	0.005935122	0.012711864	0.004084085
Vitamin B12 via RIA (pg/mL)	0.00402366	0.00333813	0.004237288	0.00402366
Alpha-1 globulin (%)	0.003832509	0.014051952	0.004237288	0.003832509
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	0.003743268	0.00657122	0.008474576	0.003743268
Alpha-2 globulin (%)	0.00373557	0.004502258	0.004237288	0.00373557
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	0.003691119	0.002535915	0.008474576	0.003691119
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	0.003628467	0.007143239	0.004237288	0.003628467
C-reactive protein - high sensitivity (µg/mL)	0.003595036	0.004072452	0.004237288	0.003595036
rs3865444_A	0.003568828	0.006992619	0.004237288	0.003568828
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	0.003553408	0.003953066	0.008474576	0.003553408
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	0.003538457	0.00071027	0.008474576	0.003538457
rs12752888_C	0.003529126	0.003210877	0.004237288	0.003529126
rs1801394_G	0.002941323	0.009906123	0.004237288	0.002941323
Serum creatinine (mg/dL)	0.002671886	0.001135792	0.004237288	0.002671886
rs7840202_C	0.002603431	0.000660589	0.004237288	0.002603431
Endogenous secretory receptor for AGEs (ng/mL)	0.002571665	0.003716514	0.004237288	0.002571665
Soluble transferrin receptor (nmol/L)	0.002553661	0.003976923	0.004237288	0.002553661
Fatty acid C16:0 as % of total fatty acid weight	0.002533683	0.003256162	0.004237288	0.002533683
Retinol via high performance liquid chromatography (µmol/L)	0.002487013	0.004645502	0.004237288	0.002487013
Adiponectin via RIA (µg/mL)	0.002423759	0.003373917	0.004237288	0.002423759
Ca++ (mg/dL)	0.002412787	0.009697184	0.004237288	0.002412787
Alpha-2-macroglobulin (mg/dL)	0.002206422	0.003378556	0.004237288	0.002206422
Urinary Ca (mmol/L)	0.002203996	0.001244438	0.004237288	0.002203996
Interleukin-1B via ELISA (pg/mL)	0.002202815	0.001684749	0.004237288	0.002202815
Omega-6 fatty acids as % of total fatty acid mols	0.002083401	0.005710026	0.004237288	0.002083401
Beta globulins (%)	0.00198861	0.002508954	0.004237288	0.00198861
Fatty acid C20:5 n-3 as % of total fatty acid area	0.001750099	0.001527257	0.004237288	0.001750099
rs1539053_A	0.001651772	0.002032121	0.004237288	0.001651772
rs603050_T	0.001603176	0.000828142	0.004237288	0.001603176
Albumin (%)	0.001497865	0.00144821	0.004237288	0.001497865
Fatty acid C20:0 (arachidic) area	0.00142038	0.000965866	0.004237288	0.00142038
Lymphocytes (%)	0.001375674	0.000826441	0.008474576	0.001375674
Tumor necrosis factor-a via multiplex technology (pg/mL)	0.001189543	0.000626886	0.004237288	0.001189543
Mean corpuscular volume (MCV) (fL)	0.001108848	0.002522049	0.004237288	0.001108848
Fatty acid C16:0 (palmitic) area	0.001087023	0.000250191	0.004237288	0.001087023
rs948399_C	0.001081045	0.006526954	0.004237288	0.001081045
Fatty acid C16:0 as % of total fatty acid area	0.001062891	0.00384092	0.004237288	0.001062891
White blood cells (WBC) (n, K/µL)	0.001029476	0.000265338	0.004237288	0.001029476
Urinary creatinine (mg/dL)	0.001010878	0.001412657	0.004237288	0.001010878
Lipids: LDL cholesterol (mg/dL)	0.000972468	0.004258281	0.004237288	0.000972468
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***	0.000969549	0.002657776	0.008474576	0.000969549
Omega-3 plasma fatty acid weight (mg/L)	0.000945649	0.000533488	0.004237288	0.000945649
Interleukin-12 via Bio-Plex (pg/mL)	0.000902174	0.000602753	0.004237288	0.000902174
Mean platelet volume (MPV) (fL)	0.00059614	0.000315899	0.004237288	0.00059614
rs4968782_G	0.00026173	0.000367413	0.004237288	0.00026173

Table VII: Cognitive Decline Features Model II

Cognitive Decline Features	Gain	Cover	Frequency	Importance
Age	0.337620007	0.169876149	0.04730832	0.337620007
Level of Education	0.101396229	0.107996945	0.042414356	0.101396229
Soluble IL-6 receptor via ELISA (ng/mL)	0.036437613	0.034064328	0.019575856	0.036437613
Retinol via high performance liquid chromatography (µmol/L)	0.02218011	0.02573877	0.020391517	0.02218011
Hemoglobin (g/dL)	0.014452739	0.007164163	0.005709625	0.014452739
Alpha-2 globulin (%)	0.012001659	0.007818561	0.008972268	0.012001659
Albumin (%)	0.0113596	0.015724044	0.01141925	0.0113596
Fatty acid C22:0 as % of total fatty acid area	0.011304629	0.009233553	0.008972268	0.011304629
Soluble CD14 via ELISA (ng/mL)	0.010711498	0.009622826	0.010603589	0.010711498
White blood cells (WBC) (n, K/µL)	0.010337767	0.006623209	0.009787928	0.010337767
Free thyroxine, fT4 (ng/dL)	0.010186247	0.012097542	0.018760196	0.010186247
Alpha-2-macroglobulin (mg/dL)	0.010031357	0.006651148	0.006525285	0.010031357
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	0.009701129	0.010461974	0.01223491	0.009701129
Soluble transferrin receptor (nmol/L)	0.008957121	0.005636462	0.004893964	0.008957121
Tumor necrosis factor-a via multiplex technology (pg/mL)	0.008815898	0.004477882	0.009787928	0.008815898
IGF binding protein-3, serum, immunoradiometric assay (ng/mL)	0.008096051	0.007201284	0.01141925	0.008096051
Neutrophils (n, K/µL)	0.007846614	0.013026383	0.003262643	0.007846614
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	0.007495273	0.010668779	0.013050571	0.007495273
Monocytes (n, K/µL)	0.007009487	0.008960452	0.008156607	0.007009487
Total testosterone (ng/mL)	0.006935307	0.004804623	0.005709625	0.006935307
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	0.006418083	0.010770744	0.015497553	0.006418083
Lycopene via high performance liquid chromatography (µmol/L)	0.006368592	0.013556497	0.010603589	0.006368592
Red cell distribution width (RDW) (%)	0.00632215	0.007376994	0.004078303	0.00632215
Urinary Na (mmol/L)	0.006308561	0.004860064	0.010603589	0.006308561
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	0.006234605	0.015158455	0.01223491	0.006234605
Estradiol via radioimmunoassay (pg/mL)	0.006087853	0.010731789	0.010603589	0.006087853
Interleukin-8 via Bio-Plex (pg/mL)	0.005942379	0.010463931	0.004078303	0.005942379
Urinary Ca (mmol/L)	0.005933618	0.013130706	0.013866232	0.005933618
Mean corpuscular volume (MCV) (fL)	0.005816721	0.005494248	0.007340946	0.005816721
MCH concentration (MCHC) (g/dL)	0.005676189	0.016226196	0.009787928	0.005676189
Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)	0.005299693	0.002967166	0.004893964	0.005299693
Neutrophils (%)	0.005259012	0.011038932	0.007340946	0.005259012
Omega-6 fatty acids as % of total fatty acid area	0.005235156	0.008265979	0.009787928	0.005235156
Fatty acid C22:0 (behenic) area	0.005221169	0.002244553	0.005709625	0.005221169
Fibrinogen (mg/dL)	0.005135355	0.013681843	0.015497553	0.005135355
Resistin via EIA (ng/mL)	0.00507799	0.004782631	0.01141925	0.00507799
Endogenous secretory receptor for AGEs (ng/mL)	0.005063804	0.005090446	0.01223491	0.005063804
Na+ (mEq/L)	0.005060928	0.003545462	0.003262643	0.005060928
Lipids: total cholesterol (mg/dL)	0.00494213	0.004189768	0.003262643	0.00494213
C-reactive protein - high sensitivity (µg/mL)	0.004882981	0.007480991	0.003262643	0.004882981
Vitamin E alpha tocopherol	0.004726757	0.003329939	0.006525285	0.004726757
Cystatin C (mg/L)	0.004380661	0.009384469	0.008972268	0.004380661
Parathyroid hormone	0.004375232	0.011901958	0.015497553	0.004375232
Adiponectin via RIA (µg/mL)	0.004335486	0.008986282	0.016313214	0.004335486
Urinary cortisol (µg/mL)	0.004259415	0.004101516	0.004893964	0.004259415
Plasma insulin via RIA (mIU/L)	0.004230209	0.004566037	0.008972268	0.004230209
Blood glucose (mg/dL)	0.004019193	0.00527928	0.007340946	0.004019193
Fatty acid C24:0 (lignoceric) area	0.003943775	0.003301283	0.003262643	0.003943775
C-terminal telopeptide of type-1 collagen (ng/mL)	0.003927989	0.006010915	0.013050571	0.003927989
24-hour urinary cortisol (µg/24 hours)	0.003839175	0.00320971	0.004078303	0.003839175
Lymphocytes (%)	0.003810109	0.005980394	0.008156607	0.003810109
Homocysteine via FPIA analysis (µmol/L)	0.003723506	0.008958335	0.005709625	0.003723506
Folate via RIA (ng/mL)	0.003721675	0.007480933	0.01223491	0.003721675
Ratio of Omega-6:Omega-3 as % of total fatty acid weight	0.003719853	0.00421514	0.004893964	0.003719853
Ca++ (mg/dL)	0.003651681	0.000474762	0.001631321	0.003651681
GPT (also known as ALT) (U/L)	0.003632801	0.004977336	0.007340946	0.003632801
24-hour urinary creatinine (mg/24 hours)	0.003451352	0.00780884	0.007340946	0.003451352
Anticholinergic Burden Scale Sum Score	0.00332339	0.002536376	0.002446982	0.00332339
Interleukin-10 via ELISA (pg/mL)	0.003322959	0.001514995	0.003262643	0.003322959
Beta globulins (%)	0.003321289	0.001896441	0.002446982	0.003321289
Creatinine clearance, 24-hr urine (mL/minute)	0.003264735	0.006994998	0.004893964	0.003264735
Interleukin-12 via Bio-Plex (pg/mL)	0.003192173	0.002789774	0.005709625	0.003192173
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	0.003185556	0.002444962	0.004893964	0.003185556
Vitamin B12 via RIA (pg/mL)	0.003166109	0.006439686	0.008156607	0.003166109
Urinary creatinine (mg/dL)	0.003122104	0.004013699	0.004893964	0.003122104
Transforming growth factor-B1 (pg/mL)	0.003012441	0.005744855	0.006525285	0.003012441
Fatty acid C24:0 as % of total fatty acid weight	0.002794238	0.005796356	0.003262643	0.002794238
Thyroid stimulating hormone, TSH (mIU/L)	0.002728823	0.008640367	0.01223491	0.002728823
Dehydroepiandrosterone sulfate (µg/dL)	0.002672337	0.003760759	0.004078303	0.002672337
Blood urea nitrogen (mg/dL)	0.002618936	0.003559652	0.01223491	0.002618936

Lipoprotein(a) (mg/dL)	0.002613825	0.004184359	0.006525285	0.002613825
Gamma glutamyl transferase (U/L)	0.002507317	0.001113761	0.001631321	0.002507317
Omega-3 fatty acids as % of total fatty acid weight	0.002446855	0.002262325	0.004078303	0.002446855
Serum creatinine (mg/dL)	0.002434934	0.003678538	0.004893964	0.002434934
Monocytes (%)	0.002412472	0.001491166	0.002446982	0.002412472
Serum cortisol (µg/dL)	0.002348164	0.00222644	0.004893964	0.002348164
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	0.002246116	0.00345916	0.008156607	0.002246116
Fatty acid C16:0 weight (mg/L)	0.002240052	0.002564482	0.004078303	0.002240052
Fatty acid C16:0 as % of total fatty acid weight	0.00223029	0.003813884	0.008156607	0.00223029
Fatty acid C20:5 n-3 as % of total fatty acid area	0.002230142	0.001064622	0.001631321	0.002230142
Methylmalonic acid, MMA (µmol/L)	0.002226268	0.002950204	0.002446982	0.002226268
Omega-3 plasma fatty acid weight (mg/L)	0.002058344	0.001317004	0.002446982	0.002058344
Ferritin (ng/mL)	0.00196076	0.005336786	0.008972268	0.00196076
Fatty acid C22:0 weight (mg/L)	0.001816603	0.00405515	0.005709625	0.001816603
Vitamin E gamma tocopherol	0.001806414	0.002203634	0.004893964	0.001806414
Lymphocytes (n, K/µL)	0.001690487	0.001349849	0.002446982	0.001690487
Lipids: LDL cholesterol (mg/dL)	0.00168208	0.005742559	0.004078303	0.00168208
Omega-6 plasma fatty acid weight (mg/L)	0.001668354	0.001010453	0.003262643	0.001668354
Interleukin-6 via ELISA ultrasensitive (pg/mL)	0.001545979	0.003147402	0.007340946	0.001545979
Creatine phosphokinase (U/L)	0.00148699	0.003371184	0.006525285	0.00148699
AST (U/L)	0.00148228	0.001280547	0.003262643	0.00148228
Red blood cells (RBC) (n, millions/µL)	0.001465528	0.003944097	0.002446982	0.001465528
Interleukin-1B via ELISA (pg/mL)	0.001462355	0.004043732	0.003262643	0.001462355
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	0.001341605	0.000218363	0.000815661	0.001341605
Fatty acid C20:5 n-3 as % of total fatty acid weight	0.001325055	0.003336324	0.006525285	0.001325055
Fatty acid C22:0 as % of total fatty acid weight	0.001245406	0.004586598	0.004893964	0.001245406
Vitamin B6 via high performance liquid chromatography (ng/mL)	0.001214394	0.002876213	0.003262643	0.001214394
Lipids: HDL cholesterol (mg/dL)	0.001198349	0.002421287	0.001631321	0.001198349
Urine hemoglobin (mg/dL)	0.001125041	0.002413289	0.000815661	0.001125041
Urine proteins (mg/dL)	0.001117313	0.001020134	0.000815661	0.001117313
Vitamin E gamma tocopherol	0.001085563	0.004068181	0.004893964	0.001085563
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	0.001080915	0.002484724	0.002446982	0.001080915
Total proteins (g/dL)	0.001012553	0.001464147	0.001631321	0.001012553
Free testosterone (ng/dL), Vermeulen	0.000911295	0.003313265	0.004893964	0.000911295
Hematocrit (%)	0.0008604	0.001047362	0.002446982	0.0008604
Uric acid (mg/dL)	0.000829065	0.000289542	0.000815661	0.000829065
Fatty acid C20:0 as % of total fatty acid area	0.000757176	0.000224922	0.000815661	0.000757176
Fatty acid C20:5 n-3 cis (eicosapentaenoic, EPA) area	0.000723203	0.00149168	0.003262643	0.000723203
C-reactive protein - low sensitivity (µg/mL)	0.000710255	0.001478066	0.002446982	0.000710255
TNF-related apoptosis-inducing ligand (pg/mL)	0.000646151	0.00201871	0.006525285	0.000646151
Omega-3 fatty acids as % of total fatty acid area	0.000637288	0.001485081	0.002446982	0.000637288
Fatty acid C20:0 weight (mg/L)	0.000636213	0.000729121	0.002446982	0.000636213
Fatty acid C20:0 (arachidic) area	0.00062639	0.002906608	0.000815661	0.00062639
Erythrocyte sedimentation rate (ESR) (mm/hour)	0.000622845	0.001423501	0.003262643	0.000622845
Omega-6 fatty acids as % of total fatty acid weight	0.000620856	0.00168309	0.005709625	0.000620856
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	0.000596805	0.001070486	0.003262643	0.000596805
Depression	0.000535185	0.001586769	0.001631321	0.000535185
Cortisol:DHEAS ratio (based on nmols)	0.000500719	0.001411308	0.004078303	0.000500719
Fatty acid C16:0 as % of total fatty acid weight	0.000453894	0.000722058	0.001631321	0.000453894
Beta-carotene via high performance liquid chromatography (µmol/L)	0.000433366	0.001824619	0.004078303	0.000433366
Mean corpuscular hemoglobin (MCH) (pg)	0.000407813	0.001502518	0.002446982	0.000407813
Vitamin E alpha tocopherol	0.000407016	0.00132765	0.004078303	0.000407016
Alpha-1 globulin (%)	0.00028578	0.001049279	0.002446982	0.00028578
Ratio of Omega-6:Omega-3 as % of total fatty acid mols	0.000218333	0.001446424	0.004893964	0.000218333
Fatty acid C20:0 as % of total fatty acid mols	0.000178967	0.001169142	0.003262643	0.000178967
Fatty acid C16:0 as % of total fatty acid area	0.000166057	0.000634616	0.002446982	0.000166057
Fatty acid C20:0 as % of total fatty acid weight	6.18E-05	0.000575459	0.002446982	6.18E-05
Omega-6 fatty acids as % of total fatty acid mols	5.70E-05	0.001159185	0.002446982	5.70E-05
Ratio of Omega-6:Omega-3 as % of total fatty acid area	1.80E-05	0.000249955	0.000815661	1.80E-05

Table VIII: Frailty Features Model II

Frailty Features	Gain	Cover	Frequency	Importance
Depression	0.087477094	0.037432424	0.023728814	0.087477094
Age	0.050692047	0.012070795	0.010169492	0.050692047
Creatinine clearance, 24-hr urine (mL/minute)	0.037570335	0.008241562	0.006779661	0.037570335
Anticholinergic Burden Scale Sum Score	0.031644308	0.019787206	0.013559322	0.031644308
Homocysteine via FPIA analysis (µmol/L)	0.030538058	0.023689405	0.016949153	0.030538058
Vitamin B6 via high performance liquid chromatography (ng/mL)	0.024418035	0.013747038	0.016949153	0.024418035
Interleukin-6 via ELISA ultrasensitive (pg/mL)	0.023153468	0.019395502	0.016949153	0.023153468
Erythrocyte sedimentation rate (ESR) (mm/hour)	0.021774327	0.012878682	0.010169492	0.021774327
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	0.020875442	0.028967385	0.027118644	0.020875442
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	0.020207291	0.029445221	0.020338983	0.020207291
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	0.019045838	0.026328877	0.023728814	0.019045838
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	0.017850277	0.010389129	0.013559322	0.017850277
Interleukin-8 via Bio-Plex (pg/mL)	0.016988136	0.00439415	0.006779661	0.016988136
24-hour urinary cortisol (µg/24 hours)	0.016449453	0.033101985	0.023728814	0.016449453
24-hour urinary creatinine (mg/24 hours)	0.014868273	0.007683043	0.010169492	0.014868273
Cortisol:DHEAS ratio (based on nmols)	0.014535409	0.009961332	0.013559322	0.014535409
Interleukin-1B via ELISA (pg/mL)	0.014350009	0.023361053	0.016949153	0.014350009
Creatine phosphokinase (U/L)	0.013873065	0.004025311	0.006779661	0.013873065
Plasma insulin via RIA (mIU/L)	0.013636196	0.00598363	0.013559322	0.013636196
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.013177049	0.013905765	0.013559322	0.013177049
Vitamin E gamma tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.012842565	0.022567257	0.016949153	0.012842565
Methylmalonic acid, MMA (µmol/L)	0.012496487	0.017167754	0.013559322	0.012496487
C-terminal telopeptide of type-1 collagen (ng/mL)	0.012409377	0.007676331	0.010169492	0.012409377
Fatty acid C20:5 n-3 weight (mg/L)	0.011973673	0.009092363	0.013559322	0.011973673
Blood urea nitrogen (mg/dL)	0.0116946	0.010837487	0.016949153	0.0116946
Dehydroepiandrosterone sulfate (µg/dL)	0.011520092	0.002702369	0.010169492	0.011520092
Serum cortisol (µg/dL)	0.011018876	0.022298275	0.020338983	0.011018876
Ratio of Omega-6:Omega-3 as % of total fatty acid weight	0.010754702	0.001495996	0.010169492	0.010754702
Endogenous secretory receptor for AGEs (ng/mL)	0.010218501	0.01710008	0.016949153	0.010218501
Vitamin E gamma tocopherol, high performance liquid chromatography (µmol/L)	0.010084578	0.010687575	0.010169492	0.010084578
Free testosterone (ng/dL), Vermeulen	0.009711035	0.018664758	0.016949153	0.009711035
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	0.009156656	0.00691564	0.006779661	0.009156656
Monocytes (%)	0.008981439	0.021490956	0.016949153	0.008981439
C-reactive protein - high sensitivity (µg/mL)	0.008807614	0.009176731	0.010169492	0.008807614
Urine proteins (mg/dL)	0.008690624	0.009293653	0.006779661	0.008690624
Lipoprotein(a) (mg/dL)	0.008365481	0.014865471	0.010169492	0.008365481
Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)	0.0083467	0.001745162	0.003389831	0.0083467
Lipids: LDL cholesterol (mg/dL)	0.008345016	0.014511828	0.013559322	0.008345016
Tumor necrosis factor-a via multiplex technology (pg/mL)	0.008263742	0.006171901	0.013559322	0.008263742
rs429358_C	0.008207264	0.009874568	0.006779661	0.008207264
Mean corpuscular volume (MCV) (fL)	0.007813068	0.002890419	0.003389831	0.007813068
White blood cells (WBC) (n, K/µL)	0.007684036	0.010274828	0.010169492	0.007684036
Lymphocytes (%)	0.007590389	0.000963582	0.006779661	0.007590389
rs10501927_G	0.007400781	0.00947889	0.010169492	0.007400781
Fatty acid C22:0 as % of total fatty acid area	0.007284487	0.008147218	0.006779661	0.007284487
Ferritin (ng/mL)	0.007123548	0.00835951	0.013559322	0.007123548
Urinary Na (mmol/L)	0.007073396	0.019248543	0.013559322	0.007073396
Folate via RIA (ng/mL)	0.007011844	0.015035268	0.010169492	0.007011844
Red blood cells (RBC) (n, millions/µL)	0.006799328	0.006376907	0.003389831	0.006799328
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	0.006789192	0.001887906	0.006779661	0.006789192
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	0.006415482	0.012690498	0.010169492	0.006415482
Fatty acid C20:0 as % of total fatty acid area	0.006179054	0.001341804	0.003389831	0.006179054
Transforming growth factor-B1 (pg/mL)	0.00593631	0.010002974	0.010169492	0.00593631
Beta-carotene via high performance liquid chromatography (µmol/L)	0.005883288	0.004352394	0.010169492	0.005883288
Free thyroxine, fT4 (ng/dL)	0.005714929	0.010081288	0.010169492	0.005714929

Monocytes (n, K/µL)	0.005607768	0.017694614	0.013559322	0.005607768
rs12752888_C	0.005524297	0.001255391	0.003389831	0.005524297
Fatty acid C16:0 (palmitic) area	0.005491614	0.009704169	0.010169492	0.005491614
IL-6 high-sensitivity ELISA calculated from ELISA ultrasensitive (pg/mL)	0.005425693	0.006151266	0.003389831	0.005425693
TNF-related apoptosis-inducing ligand (pg/mL)	0.005359504	0.00793391	0.006779661	0.005359504
Fatty acid C22:0 (behenic) area	0.004905328	0.003961571	0.006779661	0.004905328
Serum creatinine (mg/dL)	0.004786974	0.000934218	0.006779661	0.004786974
Macrophage inflammatory protein-1b via Bio-Plex (pg/mL)	0.004784017	0.012336797	0.010169492	0.004784017
Fatty acid C16:0 as % of total fatty acid area	0.004516237	0.004702992	0.003389831	0.004516237
Vitamin B12 via RIA (pg/mL)	0.004424143	0.000391277	0.003389831	0.004424143
Fatty acid C16:0 as % of total fatty acid weight	0.004402626	0.00403443	0.006779661	0.004402626
Estradiol via radioimmunoassay (pg/mL)	0.004344044	0.000553	0.003389831	0.004344044
rs1799990_G	0.004294903	0.000615221	0.003389831	0.004294903
Interleukin-10 via ELISA (pg/mL)	0.004255737	0.000180399	0.003389831	0.004255737
Urinary Ca (mmol/L)	0.004248745	0.010166493	0.006779661	0.004248745
Omega-3 plasma fatty acid weight (mg/L)	0.004240931	0.010351219	0.006779661	0.004240931
Alpha-2-macroglobulin (mg/dL)	0.004052975	0.005200807	0.006779661	0.004052975
Alpha-1 globulin (%)	0.003887647	0.010139885	0.006779661	0.003887647
Soluble CD14 via ELISA (ng/mL)	0.003845678	0.005222931	0.003389831	0.003845678
Fatty acid C20:5 n-3 as % of total fatty acid area	0.003796235	0.008663351	0.010169492	0.003796235
MCH concentration (MCHC) (g/dL)	0.003719857	0.005707609	0.006779661	0.003719857
rs11894266_C	0.003698922	0.00444944	0.006779661	0.003698922
rs8106922_G	0.003649847	0.000344203	0.003389831	0.003649847
Total testosterone (ng/mL)	0.003388364	0.006891703	0.006779661	0.003388364
rs7840202_C	0.003264864	0.003877332	0.003389831	0.003264864
Ratio of Omega-6:Omega-3 as % of total fatty acid area	0.003164728	0.009068617	0.006779661	0.003164728
Gamma glutamyl transferase (U/L)	0.003062083	0.012510653	0.010169492	0.003062083
Lipids: HDL cholesterol (mg/dL)	0.003057754	0.008728878	0.006779661	0.003057754
Resistin via EIA (ng/mL)	0.003006318	0.004709943	0.006779661	0.003006318
Urine hemoglobin (mg/dL)	0.002983008	0.004156007	0.003389831	0.002983008
Lipids: total cholesterol (mg/dL)	0.002916458	0.009319371	0.006779661	0.002916458
Adiponectin via RIA (µg/mL)	0.00276724	0.008715665	0.006779661	0.00276724
Uric acid (mg/dL)	0.002622806	0.001158878	0.003389831	0.002622806
Fatty acid C22:0 as % of total fatty acid weight	0.002467219	0.000332762	0.003389831	0.002467219
rs3785880_G	0.002427357	0.000734247	0.003389831	0.002427357
rs10883631_G	0.002364875	0.000173967	0.006779661	0.002364875
Omega-3 fatty acids as % of total fatty acid area	0.002326994	0.0085397	0.006779661	0.002326994
Omega-6 plasma fatty acid weight (mg/L)	0.00219113	0.00264264	0.003389831	0.00219113
Fatty acid C24:0 weight (mg/L)	0.002189504	0.001294336	0.003389831	0.002189504
Soluble IL-6 receptor via ELISA (ng/mL)	0.002001984	0.003757795	0.003389831	0.002001984
Omega-6 fatty acids as % of total fatty acid area	0.001960985	0.00316459	0.003389831	0.001960985
rs4363657_C	0.001848912	0.005068245	0.003389831	0.001848912
ALT (U/L)	0.001744514	0.003480211	0.003389831	0.001744514
rs6859_A	0.001731615	0.000162633	0.003389831	0.001731615
Omega-3 fatty acids as % of total fatty acid weight	0.001710078	0.004212545	0.003389831	0.001710078
Urinary cortisol (µg/mL)	0.001597598	0.000305797	0.003389831	0.001597598
Fatty acid C20:0 weight (mg/L)	0.001571151	0.000274045	0.003389831	0.001571151
rs948399_C	0.001532092	0.004343178	0.003389831	0.001532092
Blood glucose (mg/dL)	0.001363833	0.004740806	0.003389831	0.001363833
Fatty acid C24:0 as % of total fatty acid weight	0.001273097	0.003990736	0.003389831	0.001273097
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	0.000967469	0.003538632	0.003389831	0.000967469
rs4147929_A	0.000892763	0.004034426	0.003389831	0.000892763
Fatty acid C24:0 as % of total fatty acid area	0.000868838	0.004156007	0.003389831	0.000868838
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	0.000847489	0.004086658	0.003389831	0.000847489
Fatty acid C20:5 n-3 cis (eicosapentaenoic, EPA) area	0.000807547	0.003996284	0.003389831	0.000807547
Neutrophils (n, K/µL)	0.000572539	0.000112781	0.003389831	0.000572539

Table IX: Cognitive Frailty Features Model II

Cognitive Frailty Features	Gain	Cover	Frequency	Importance
Age	0.243224429	0.110510017	0.056140351	0.243224429
Depression	0.058485822	0.040044719	0.028070175	0.058485822
Interleukin-6 via ELISA ultrasensitive (pg/mL)	0.041790268	0.019616729	0.014035088	0.041790268
Creatinine clearance, 24-hr urine (mL/minute)	0.030831483	0.018261243	0.014035088	0.030831483
Erythrocyte sedimentation rate (ESR) (mm/hour)	0.02106198	0.017790494	0.014035088	0.02106198
Creatine phosphokinase (U/L)	0.019570487	0.025241618	0.021052632	0.019570487
C-terminal telopeptide of type-1 collagen (ng/mL)	0.019104806	0.01358605	0.014035088	0.019104806
Level of Education	0.018254792	0.013650884	0.010526316	0.018254792
Cystatin C (mg/L)	0.016738529	0.018435368	0.028070175	0.016738529
MCH concentration (MCHC) (g/dL)	0.016397158	0.008585323	0.010526316	0.016397158
Vitamin B6 via high performance liquid chromatography (ng/mL)	0.016303861	0.020917254	0.01754386	0.016303861
Plasma insulin via RIA (mIU/L)	0.01479562	0.015709937	0.01754386	0.01479562
Tumor necrosis factor-a via multiplex technology (pg/mL)	0.014217085	0.018035692	0.01754386	0.014217085
C-reactive protein - high sensitivity (µg/mL)	0.014035509	0.015325407	0.01754386	0.014035509
Total testosterone (ng/mL)	0.013534893	0.018254719	0.010526316	0.013534893
Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)	0.013064167	0.012399389	0.010526316	0.013064167
Vitamin E gamma tocopherol, high performance liquid chromatography (µmol/L)	0.013060202	0.01874998	0.021052632	0.013060202
Albumin (%)	0.012957738	0.006378732	0.010526316	0.012957738
rs4343_A	0.012850391	0.014645507	0.010526316	0.012850391
Dehydroepiandrosterone sulfate (µg/dL)	0.012658594	0.011407339	0.007017544	0.012658594
Blood glucose (mg/dL)	0.012532317	0.010288275	0.014035088	0.012532317
Vitamin E gamma tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.011033869	0.022001512	0.021052632	0.011033869
Serum creatinine (mg/dL)	0.010983672	0.023256757	0.01754386	0.010983672
Monocytes (n, K/µL)	0.010578729	0.02257873	0.01754386	0.010578729
Vitamin B12 via RIA (pg/mL)	0.010033777	0.01388142	0.01754386	0.010033777
Alpha-2-macroglobulin (mg/dL)	0.009632353	0.015012622	0.010526316	0.009632353
Monocytes (%)	0.009258662	0.020772466	0.014035088	0.009258662
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	0.009249448	0.006819346	0.010526316	0.009249448
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	0.008910896	0.011338502	0.007017544	0.008910896
Fatty acid C16:0 (palmitic) area	0.008774872	0.012353205	0.01754386	0.008774872
Folate via RIA (ng/mL)	0.008433119	0.009100673	0.01754386	0.008433119
Fatty acid C20:5 n-3 weight (mg/L)	0.008258345	0.012186001	0.010526316	0.008258345
24-hour urinary creatinine (mg/24 hours)	0.008193473	0.007541586	0.014035088	0.008193473
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	0.007746372	0.010792335	0.014035088	0.007746372
Anticholinergic Burden Scale Sum Score	0.007620497	0.004940168	0.003508772	0.007620497
Interleukin-1B via ELISA (pg/mL)	0.007547503	0.007646187	0.014035088	0.007547503
Omega-6 fatty acids as % of total fatty acid weight	0.007517237	0.005039685	0.007017544	0.007517237
Ratio of Omega-6:Omega-3 as % of total fatty acid area	0.007500432	0.00741643	0.010526316	0.007500432
TNF-related apoptosis-inducing ligand (pg/mL)	0.00719579	0.004106597	0.014035088	0.00719579
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	0.007054061	0.014543542	0.010526316	0.007054061
White blood cells (WBC) (n, K/µL)	0.006973812	0.008888854	0.01754386	0.006973812
24-hour urinary cortisol (µg/24 hours)	0.00650171	0.007939441	0.010526316	0.00650171
Serum cortisol (µg/dL)	0.00583663	0.007164907	0.014035088	0.00583663
Soluble CD14 via ELISA (ng/mL)	0.005597229	0.008704836	0.010526316	0.005597229
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	0.005576786	0.006297576	0.007017544	0.005576786
Urinary creatinine (mg/dL)	0.005467574	0.004446002	0.003508772	0.005467574
Mean corpuscular hemoglobin (MCH) (pg)	0.005181663	0.013591552	0.010526316	0.005181663
Homocysteine via FPIA analysis (µmol/L)	0.005058175	0.01368253	0.014035088	0.005058175
Urinary Na (mmol/L)	0.005040676	0.00568806	0.003508772	0.005040676
Alpha-1 globulin (%)	0.004905499	0.00071443	0.003508772	0.004905499
Fatty acid C20:5 n-3 as % of total fatty acid area	0.004842838	0.004365281	0.007017544	0.004842838
rs11894266_C	0.004815596	0.001626576	0.003508772	0.004815596
rs429358_C	0.004217372	0.009503585	0.007017544	0.004217372
Lymphocytes (%)	0.00400406	0.005602415	0.003508772	0.00400406

Neutrophils (%)	0.00388351	0.007716045	0.010526316	0.00388351
Lymphocytes (n, K/µL)	0.003737902	0.004870851	0.007017544	0.003737902
Fibrinogen (mg/dL)	0.003655515	0.008378834	0.010526316	0.003655515
Omega-6 plasma fatty acid weight (mg/L)	0.00365299	0.002054096	0.003508772	0.00365299
Hematocrit (%)	0.003643905	0.003572639	0.003508772	0.003643905
rs129968_A	0.003602199	0.006056578	0.003508772	0.003602199
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	0.003578744	0.00854427	0.010526316	0.003578744
Lipids: LDL cholesterol (mg/dL)	0.003552118	0.005060933	0.003508772	0.003552118
rs129968_A	0.003366369	0.001166338	0.003508772	0.003366369
rs129968_A	0.003136504	0.008586573	0.007017544	0.003136504
Interleukin-8 via Bio-Plex (pg/mL)	0.003044247	0.001130557	0.007017544	0.003044247
Adiponectin via RIA (µg/mL)	0.003007961	0.003092498	0.003508772	0.003007961
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	0.002996903	0.008428031	0.007017544	0.002996903
Omega-3 fatty acids as % of total fatty acid area	0.002933676	0.009319042	0.007017544	0.002933676
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	0.002864988	0.008290595	0.007017544	0.002864988
rs3785880_G	0.002812	0.002084713	0.003508772	0.002812
Fatty acid C16:0 weight (mg/L)	0.002756752	0.008702471	0.007017544	0.002756752
rs3785880_G	0.002755476	0.00205785	0.003508772	0.002755476
Urine proteins (mg/dL)	0.00272263	0.005708104	0.003508772	0.00272263
Uric acid (mg/dL)	0.002571323	0.005440035	0.003508772	0.002571323
Monocyte chemoattractant protein-1 via Bio-Plex (pg/mL)	0.002567023	0.00851028	0.007017544	0.002567023
rs1800629_A	0.002566224	0.000827461	0.003508772	0.002566224
rs7840202_C	0.002544047	0.000872785	0.003508772	0.002544047
Beta-carotene via high performance liquid chromatography (µmol/L)	0.002486527	0.002014956	0.003508772	0.002486527
rs360722_A	0.002412795	0.002982585	0.003508772	0.002412795
rs12752888_C	0.002354584	0.003431046	0.003508772	0.002354584
Resistin via EIA (ng/mL)	0.00233496	0.005168944	0.007017544	0.00233496
Lipoprotein(a) (mg/dL)	0.002292647	0.003466989	0.003508772	0.002292647
Fatty acid C16:0 as % of total fatty acid area	0.002120433	0.000759578	0.003508772	0.002120433
Urine glucose (mg/dL)	0.002063151	0.00532065	0.003508772	0.002063151
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***	0.00204864	0.002395909	0.003508772	0.00204864
Fatty acid C22:0 weight (mg/L)	0.001854603	0.003613198	0.003508772	0.001854603
Blood urea nitrogen (mg/dL)	0.001848406	0.00356917	0.007017544	0.001848406
Lycopene via high performance liquid chromatography (µmol/L)	0.001844727	0.004465825	0.003508772	0.001844727
Interleukin-12 via Bio-Plex (pg/mL)	0.001789151	0.000398635	0.003508772	0.001789151
Endogenous secretory receptor for AGEs (ng/mL)	0.001712395	0.000343816	0.003508772	0.001712395
Gamma glutamyl transferase (U/L)	0.001699071	0.000303829	0.003508772	0.001699071
Lipids: HDL cholesterol (mg/dL)	0.001657368	0.003377608	0.007017544	0.001657368
Estradiol via radioimmunoassay (pg/mL)	0.001620834	0.002680514	0.003508772	0.001620834
Lipids: total cholesterol (mg/dL)	0.001591306	0.003105553	0.003508772	0.001591306
Thyroid stimulating hormone, TSH (mIU/L)	0.001578132	0.00108992	0.003508772	0.001578132
Urinary Ca (mmol/L)	0.001387468	0.004556416	0.003508772	0.001387468
Methylmalonic acid, MMA (µmol/L)	0.00137796	0.001595891	0.003508772	0.00137796
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	0.001353188	0.004284569	0.007017544	0.001353188
rs16944_A	0.001347871	0.006524396	0.007017544	0.001347871
rs1614735_G	0.001347489	0.004511853	0.003508772	0.001347489
Fatty acid C22:0 (behenic) area	0.0011975	0.000379567	0.003508772	0.0011975
rs6131_T	0.001162675	0.004222359	0.003508772	0.001162675
rs8106922_G	0.001103625	0.003949645	0.003508772	0.001103625
Urinary cortisol (µg/mL)	0.001072581	0.004113434	0.003508772	0.001072581
rs10501927_G	0.001051906	0.004078632	0.003508772	0.001051906
rs4363657_C	0.000844935	0.003497748	0.003508772	0.000844935
Free testosterone (ng/dL), Vermeulen	0.00078235	0.003440932	0.003508772	0.00078235
rs10883631_G	0.000627947	0.003206086	0.003508772	0.000627947
rs11771145_A	0.000341898	0.000144683	0.003508772	0.000341898
rs948399_C	0.00025933	0.000123066	0.003508772	0.00025933

Table X. Clinical features by healthy control and phenotype

Model 1	Cognitive Decline		Frailty		Cognitive Frailty					
	mean(SD)	p-value	mean(SD)	p-value	mean(SD)	p-value				
Age										
Control	65(15.7)		72(6.2)		73(6.4)					
Phenotype	80(8.7)	<0.0001	78(7.9)	<0.0001	82(7.4)	<0.0001				
Anicholinergic Burden										
Control	2.18 (2.01)		1.75 (1.76)		2.15 (2.02)					
Phenotype	2.69 (2.19)	<0.0001	2.89 (2.21)	<0.0001	3.00 (2.16)	<0.0001				
Gender	(n)		(n)		(n)					
Healthy Control(M/F)	521/557		286/274		418/480					
Phenotype(M/F)	121/254	<0.0001	214/381	<0.0001	82/175	<0.0001				
Depression										
Control	272		91		250					
Phenotype	140	<0.0001	269	<0.0001	110	<0.0001				
Baseline Dementia										
Control			12		12					
Phenotype			70	<0.0001	70	<0.0001				
Model 2	**Cognitive Decline**				**Frailty**		**Cognitive Frailty**			
	TrailA		TrailB				TrailA		TrailB	
Age	mean(SD)	p-value	mean(SD)	p-value	mean(SD)	p-value	mean(SD)	p-value	mean(SD)	p-value
Control	61(16.4)		52(17.4)		72(6.2)		64(15.6)		61(16.2)	
Phenotype	76(7.7)	<0.0001	72(9.0)	<0.0001	78(7.9)	<0.0001	78(7.4)	<0.0001	76(6.9)	<0.0001
Anicholinergic Burden										
Control	1.95 (1.87)		1.77 (1.73)		1.75 (1.76)		1.85 (1.82)		1.68 (1.66)	
Phenotype	2.44 (2.12)	<0.0011	2.23 (2.02)	0.042	2.89 (2.21)	<0.0001	3.01 (2.20)	<0.0001	2.79 (2.19)	<0.0001
Depression	(n)		(n)		(n)		(n)		(n)	
Control	135		52		91		188		120	
Phenotype	339	<0.0001	220	<0.0001	269	<0.0001	151	<0.0001	152	<0.0001

Table XI. Genomic univariate results Model I

Gene/Phenotype	Chromosome	SNP-allele	Allele Count	Estimate	Std. Error	z value	Pr(>|z|)
Cognitive Decline							
ACOT11	1	rs12752888_C	1	-0.48	0.15	-3.30	0.001
DAB1	1	rs1539053_A	1	0.33	0.16	1.99	0.05
DAB1	1	rs1539053_A	2	0.45	0.19	2.29	0.02
COMT	22	rs4646316_T	2	-0.62	0.29	-2.11	0.04
IL6R	1	rs2228145_C	1	-0.31	0.15	-2.13	0.03
Frailty							
MMP3	11	rs948399_C	2	0.60	0.30	2.01	0.05
Cognitive Frailty							
ACOT11	1	rs12752888_C	1	-0.47	0.18	-2.67	0.01
DAB1	1	rs1539053_A	1	0.51	0.20	2.58	0.01
MMP3	11	rs948399_C	1	0.41	0.17	2.46	0.01
MTRR	5	rs1801394_G	2	0.80	0.23	3.48	0.001
CD33	19	rs3865444_A	2	0.62	0.28	2.24	0.03

Note: bold text indicates the closes gene

Table XII. Genomic univariate results Model II

Gene/Phenotype	Neurocognitive Test	Chromosome	SNP-allele	Allele Count	Estimate	Std. Error	z value	Pr(>|z|)
Cognitive Decline								
ACOT11	Trail B	1	rs12752888_C	2	-0.58	0.27	-2.12	0.03
ACOT11	Trail A	1	rs12752888_C	1	-0.25	0.13	-1.96	0.05
KCNU1	Trail B	8	rs1157242_T	1	0.47	0.16	2.90	0.004
PRNP	Trail B	20	rs1799990_G	1	0.30	0.15	2.10	0.04
PRNP	Trail A	20	rs1799990_G	2	0.45	0.22	2.06	0.04
BIN1	Trail B	2	rs744373_G	1	-0.31	0.14	-2.16	0.03
Frailty								
NECTIN2		19	rs6859_A	1	0.33	0.14	2.34	0.02
ABCA7		19	rs4147929_A	2	-0.27	0.14	-1.96	0.05
APOE		19	rs429358_C	1	-0.45	0.19	-2.27	0.02
SLCO1B1		12	rs4363657_C	1	0.38	0.14	2.57	0.01
MMP3		11	rs948399_C	2	0.60	0.29	2.01	0.04
Cognitive Frailty								
ACOT11	Trail B	1	rs12752888_C	1	-0.37	0.15	-2.46	0.01
ACOT11	Trail A	1	rs12752888_C	1	-0.34	0.15	-2.28	0.02
APOE	Trail B	19	rs429358_C	1	-0.59	0.23	-2.54	0.01
SLCO1B1	Trail B	12	rs4363657_C	1	0.38	0.16	2.39	0.02
MMP3	Trail A	11	rs948399_C	1	0.29	0.15	2.00	0.05
TOMM40	Trail A	19	rs8106922_G	1	-0.31	0.16	-1.92	0.05

Note: bold text indicates the closes gene

Table XIII. Difference between health control and cognitive decline results Model I

Cognitive Decline Model1	Control Mean	SD	Cognitive Mean	SD	|t|-test	Corrected p-value
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	56.26	36.69	39.66	29.96	<0.0001	<0.0001
Adiponectin via RIA (µg/mL)	12.50	8.79	17.15	12.21	<0.0001	<0.0001
Albumin (%)	59.58	3.40	57.43	3.86	<0.0001	<0.0001
Alpha-2-macroglobulin (mg/dL)	203.26	66.61	222.27	66.26	<0.0001	<0.0001
Alpha-1 globulin (%)	2.54	0.39	2.79	0.48	<0.0001	<0.0001
Alpha-2 globulin (%)	11.06	1.28	11.59	1.46	<0.0001	<0.0001
Blood urea nitrogen (mg/dL)	32.98	9.09	39.03	17.24	<0.0001	<0.0001
Fatty acid C20:5 n-3 weight (mg/L)	20.16	8.93	17.85	6.99	<0.0001	<0.0001
Fatty acid C20:5 n-3 as % of total fatty acid weight	0.63	0.22	0.56	0.18	<0.0001	<0.0001
Creatinine clearance, 24-hr urine (mL/minute)	86.84	30.09	66.91	25.91	<0.0001	<0.0001
MCH concentration (MCHC) (g/dL)	33.95	0.98	33.47	1.15	<0.0001	<0.0001
Creatine phosphokinase (U/L)	108.00	89.65	85.68	58.45	<0.0001	<0.0001
C-terminal telopeptide of type-1 collagen (ng/mL)	0.46	0.23	0.62	0.39	<0.0001	<0.0001
Cystatin C (mg/L)	0.93	0.26	1.16	0.46	<0.0001	<0.0001
Dehydroepiandrosterone sulfate (µg/dL)	115.68	96.75	72.89	64.01	<0.0001	<0.0001
Estradiol via radioimmunoassay (pg/mL)	13.46	17.95	8.90	6.13	<0.0001	<0.0001
Fibrinogen (mg/dL)	341.17	73.84	378.87	76.32	<0.0001	<0.0001
Free thyroxine, fT4 (ng/dL)	1.42	0.31	1.53	0.45	<0.0001	<0.0001
ALT (U/L)	21.19	14.29	17.22	9.37	<0.0001	<0.0001
Red blood cells (RBC) (n, millions/µL)	4.56	0.41	4.35	0.48	<0.0001	<0.0001
Homocysteine via FPIA analysis (µmol/L)	14.59	6.43	17.62	7.69	<0.0001	<0.0001
Red cell distribution width (RDW) (%)	13.54	0.95	14.01	1.23	<0.0001	<0.0001
Methylmalonic acid, MMA (µmol/L)	0.10	0.03	0.11	0.03	<0.0001	<0.0001
Omega-3 plasma fatty acid weight (mg/L)	110.63	41.96	98.98	37.76	<0.0001	<0.0001
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	23.69	17.54	31.58	24.54	<0.0001	<0.0001
Resistin via EIA (ng/mL)	3.78	1.84	4.62	2.57	<0.0001	<0.0001
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	1310.62	578.43	1842.17	1068.12	<0.0001	<0.0001
Urinary Ca (mmol/L)	2.43	1.65	1.97	1.55	<0.0001	<0.0001
24-hour urinary creatinine (mg/24 hours)	1058.67	372.66	825.55	326.16	<0.0001	<0.0001
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)	388.48	148.94	429.37	175.28	0.0002	0.0003
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***	4397.72	1104.44	4122.44	1097.82	0.0002	0.0003
Omega-6 plasma fatty acid weight (mg/L)	1060.54	234.87	998.91	256.10	0.0003	0.0004
Lymphocytes (n, K/µL)	1.94	0.65	1.79	0.63	0.0005	0.0007
TNF-related apoptosis-inducing ligand (pg/mL)	75.80	40.87	69.69	23.55	0.001	0.002
Interleukin-6 via ELISA ultrasensitive (pg/mL)	1.76	2.07	3.04	7.1	0.002	0.002
Cortisol:DHEAS ratio (nmols)	0.28	0.71	0.53	1.81	0.002	0.002
Ratio of Omega-6:Omega-3 as % of total fatty acid area	16.38	5.05	17.51	6.06	0.005	0.005
Beta-carotene via high performance liquid chromatography (µmol/L)	0.43	0.28	0.38	0.23	0.009	0.011
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	33.68	7.32	32.33	8.31	0.011	0.012
Ratio of Omega-6:Omega-3 as % of total fatty acid mols	11.52	3.34	12.17	4.11	0.016	0.018
Uric acid (mg/dL)	5.03	1.35	5.27	1.65	0.019	0.021
Mean corpuscular volume (MCV) (fL)	90.04	4.65	90.76	5.22	0.03	0.031
Serum cortisol (µg/dL)	13.62	5.00	13.02	4.32	0.039	0.039

Table XIV. Difference between healthy control and frailty results Model I

Frailty Model 1	Control Mean	SD	Frailty Mean	SD	|t|-test	Corrected p-value
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	54.93	34.51	43.53	35.76	<0.0001	<0.0001
Albumin (%)	59.18	3.38	57.96	3.73	<0.0001	<0.0001
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	34.44	7.65	32.65	7.39	<0.0001	<0.0001
Blood urea nitrogen (mg/dL)	33.79	7.44	37.5	15.92	<0.0001	<0.0001
Creatinine clearance, 24-hr urine (mL/minute)	81.09	24.06	70.00	26.43	<0.0001	<0.0001
MCH concentration (MCHC) (g/dL)	33.90	1.02	33.56	1.05	<0.0001	<0.0001
Creatine phosphokinase (U/L)	104.22	61.69	86.84	55.12	<0.0001	<0.0001
C-terminal telopeptide of type-1 collagen (ng/mL)	0.47	0.23	0.58	0.35	<0.0001	<0.0001
Cystatin C (mg/L)	0.97	0.19	1.13	0.42	<0.0001	<0.0001
Homocysteine via FPIA analysis (µmol/L)	14.97	5.70	17.31	8.12	<0.0001	<0.0001
Red cell distribution width (RDW) (%)	13.62	0.93	13.89	1.16	<0.0001	<0.0001
Interleukin-6 via ELISA ultrasensitive (pg/mL)	1.66	1.75	2.92	5.74	<0.0001	<0.0001
Omega-6 plasma fatty acid weight (mg/L)	1069.54	249.81	1005.32	234.97	<0.0001	<0.0001
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	24.06	19.79	30.54	22.59	<0.0001	<0.0001
Resistin via EIA (ng/mL)	3.72	1.67	4.36	2.48	<0.0001	<0.0001
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	1343.02	429.61	1780.92	979.8	<0.0001	<0.0001
24-hour urinary creatinine (mg/24 hours)	1020.45	334.7	860.38	323.47	<0.0001	<0.0001
C-reactive protein - high sensitivity (µg/mL)	4.06	5.99	6.79	11.93	<0.0001	<0.0001
Free testosterone (ng/dL), Vermeulen	2.41	2.22	1.72	1.9	<0.0001	<0.0001
Hemoglobin (g/dL)	13.99	1.25	13.43	1.51	<0.0001	<0.0001
Hematocrit (%)	41.25	3.23	39.96	3.95	<0.0001	<0.0001
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	142.73	85.5	177.97	159.09	<0.0001	<0.0001
Neutrophils (n, K/µL)	3.59	1.18	3.90	1.31	<0.0001	<0.0001
Lymphocytes (%)	31.42	7.87	29.5	8.23	<0.0001	<0.0001
Total testosterone (ng/mL)	2.58	2.09	1.91	1.89	<0.0001	<0.0001
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	2625.69	612.55	3053.98	958.87	<0.0001	<0.0001
Erythrocyte sedimentation rate (ESR) (mm/hour)	17.72	14.75	25.45	21.55	<0.0001	<0.0001
Dehydroepiandrosterone sulfate (µg/dL)	91.21	69.26	75.51	63.29	0.0002	0.0003
Folate via RIA (ng/mL)	3.50	2.12	3.03	1.88	0.0002	0.0003
Free thyroxine, fT4 (ng/dL)	1.43	0.29	1.51	0.41	0.0002	0.0003
Neutrophils (%)	59.52	8.49	61.48	8.52	0.0002	0.0003
Soluble CD14 via ELISA (ng/mL)	1724.25	315.92	1810.47	383.4	0.0002	0.0003
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	122.04	54.74	109.52	53.64	0.0002	0.0003
TNF-related apoptosis-inducing ligand (pg/mL)	79.52	54.09	70.44	20.08	0.0005	0.0008
Endogenous secretory receptor for AGEs (ng/mL)	0.43	0.19	0.48	0.27	0.0005	0.0008
Omega-6 fatty acids as % of total fatty acid area	30.16	4.16	29.17	4.57	0.0005	0.0008
Lipids: LDL cholesterol (mg/dL)	139.09	35.77	132.56	32.7	0.0022	0.0032
Urinary creatinine (mg/dL)	73.94	35.12	67.37	31.9	0.0023	0.0033
Omega-3 plasma fatty acid weight (mg/L)	110.92	44.27	102.85	37.76	0.003	0.004
Lipids: total cholesterol (mg/dL)	220.84	40.73	213.53	38.74	0.0031	0.0042
Urinary Ca (mmol/L)	2.35	1.65	2.04	1.58	0.0036	0.0047
White blood cells (WBC) (n, K/µL)	6.01	1.56	6.29	1.63	0.0037	0.0048
Vitamin B6 via high performance liquid chromatography (ng/mL)	7.47	6.61	6.09	9.08	0.0057	0.0072
ALT (U/L)	20.47	11.99	18.43	12.05	0.0062	0.0076
Lycopene via high performance liquid chromatography (µmol/L)	0.71	0.34	0.65	0.34	0.0081	0.0097
Fatty acid C20:5 n-3 weight (mg/L)	20.46	9.87	18.95	7.51	0.0088	0.0103
Retinol via high performance liquid chromatography (µmol/L)	1.97	0.50	1.88	0.54	0.0103	0.0118
Urinary Na (mmol/L)	96.75	46.4	89.89	39.48	0.0153	0.0172
24-hour urinary cortisol (µg/24 hours)	105.33	52.21	95.94	73.57	0.0231	0.0255
Urine proteins (mg/dL)	0.73	7.61	1.92	8.98	0.0292	0.0315
Fatty acid C24:0 weight (mg/L)	4.66	4.51	4.05	4.11	0.0316	0.0331
Fatty acid C16:0 as % of total fatty acid weight	22.38	2.36	22.72	2.48	0.0319	0.0331
Fatty acid C16:0 as % of total fatty acid area	24.66	2.36	24.99	2.47	0.0408	0.0416
Fatty acid C20:5 n-3 as % of total fatty acid area	0.47	0.21	0.44	0.19	0.0471	0.0471

Table XV. Difference between healthy control and cognitive frailty Model I

Cogntive Frailty Model 1	Control Mean	SD	Cognitive Frialty Mean	SD	|t|-test	Corrected p-value
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	52.59	36.24	35.7	29.34	<0.0001	<0.0001
Adiponectin via RIA (µg/mL)	13.24	9.5	17.84	12.39	<0.0001	<0.0001
Albumin (%)	58.98	0.38	56.96	4.01	<0.0001	<0.0001
Alpha-1 globulin (%)	2.59	0.39	2.86	0.51	<0.0001	<0.0001
Alpha-2 globulin (%)	11.21	1.25	11.71	1.55	<0.0001	<0.0001
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	34.18	7.33	31.05	7.93	<0.0001	<0.0001
Blood urea nitrogen (mg/dL)	37.14	9.44	41.67	19.73	<0.0001	<0.0001
Fatty acid C20:5 n-3 as % of total fatty acid weight	0.63	0.23	0.55	0.17	<0.0001	<0.0001
MCH concentration (MCHC) (g/dL)	33.84	1	33.3	1.11	<0.0001	<0.0001
Creatine phosphokinase (U/L)	99.49	59.53	79.37	54.47	<0.0001	<0.0001
C-terminal telopeptide of type-1 collagen (ng/mL)	0.49	0.25	0.68	0.41	<0.0001	<0.0001
Cystatin C (mg/L)	0.99	0.26	1.26	0.51	<0.0001	<0.0001
Dehydroepiandrosterone sulfate (µg/dL)	87.58	67.99	66.59	58.9	<0.0001	<0.0001
Fibrinogen (mg/dL)	351.8	72.83	388.15	80.03	<0.0001	<0.0001
Homocysteine via FPIA analysis (µmol/L)	15.46	6.66	18.84	8.18	<0.0001	<0.0001
Red cell distribution width (RDW) (%)	13.66	0.94	14.15	1.31	<0.0001	<0.0001
Omega-3 plasma fatty acid weight (mg/L)	109.63	42.53	96.43	34.25	<0.0001	<0.0001
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	25.32	18.84	35.26	28.42	<0.0001	<0.0001
Resistin via EIA (ng/mL)	3.81	1.86	4.94	2.82	<0.0001	<0.0001
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	1430.03	579.89	2091.58	82.89	<0.0001	<0.0001
TNF-related apoptosis-inducing ligand (pg/mL)	77.35	44.29	65.53	19.93	<0.0001	<0.0001
24-hour urinary creatinine (mg/24 hours)	979.14	333.91	767.17	306.4	<0.0001	<0.0001
Fatty acid C20:5 n-3 as % of total fatty acid area	0.47	0.21	0.4	0.16	<0.0001	<0.0001
Lipids: LDL cholesterol (mg/dL)	138	33.95	127.04	34.78	<0.0001	<0.0001
Hemoglobin (g/dL)	13.9	1.29	12.95	1.6	<0.0001	<0.0001
Omega-6 fatty acids as % of total fatty acid area	29.98	4.23	28.41	4.77	<0.0001	<0.0001
Soluble CD14 via ELISA (ng/mL)	1741.7	334.78	1870.97	406.93	<0.0001	<0.0001
Total testosterone (ng/mL)	2.37	2.06	1.74	1.75	<0.0001	<0.0001
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	119.35	54.96	101.45	50.44	<0.0001	<0.0001
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	2709.69	709.84	3362.15	1054.91	<0.0001	<0.0001
Erythrocyte sedimentation rate (ESR) (mm/hour)	19.3	16.32	30.9	24.75	<0.0001	<0.0001
Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)	30.7	8.31	27.17	8.37	<0.0001	<0.0001
Omega-6 fatty acids as % of total fatty acid mols	31.76	4.32	30.18	4.85	<0.0001	<0.0001
Lymphocytes (%)	30.92	8.02	28.56	8.17	0.0002	0.0003
Urine nitrites	0.1	0.42	0.32	0.71	0.0002	0.0003
Urinary Ca (mmol/L)	2.28	1.64	1.83	1.47	0.0004	0.0006
Ca++ (mg/dL)	9.46	0.45	9.32	0.5	0.0004	0.0006
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	151.95	111.77	194.04	178.49	0.0011	0.0016
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***	4279.38	1121.16	4009.81	1077.64	0.0018	0.0025
C-reactive protein - high sensitivity (µg/mL)	4.81	8.05	7.91	13.73	0.0018	0.0025
Free thyroxine, fT4 (ng/dL)	1.45	0.31	1.56	0.5	0.002	0.003
Beta-carotene via high performance liquid chromatography (µmol/L)	0.43	0.27	0.37	0.24	0.0039	0.0052
Beta globulins (%)	11.94	1.18	12.25	1.55	0.0065	0.0085
White blood cells (WBC) (n, K/µL)	6.08	1.55	6.44	1.76	0.007	0.0089
Mean platelet volume (MPV) (fL)	11.14	0.97	10.94	1	0.0079	0.0097
Fatty acid C16:0 as % of total fatty acid weight	22.44	2.36	22.98	2.62	0.008	0.0097
Uric acid (mg/dL)	5.13	1.37	5.47	1.76	0.009	0.0107
Soluble transferrin receptor (nmol/L)	16.66	5.65	18.3	8.56	0.0097	0.0113
Advanced glycation endproduct (AGE): Carboxymethyl-lysine (ng/mL)	361.53	105.78	390.73	152.77	0.0107	0.0122
Fatty acid C16:0 as % of total fatty acid area	24.42	2.36	25.24	2.61	0.0112	0.0125
Alpha-2-macroglobulin (mg/dL)	210.52	68.3	223.74	68.06	0.0122	0.0134
Serum creatinine (mg/dL)	0.92	0.19	0.98	38	0.0217	0.0234
Urine proteins (mg/dL)	0.98	7.78	2.8	10.35	0.0333	0.0352
Fatty acid C20:0 weight (mg/L)	2.87	2.84	2.52	1.94	0.0412	0.0427
Plasma insulin via RIA (mIU/L)	11.47	6.05	10.5	6.27	0.0429	0.0437
Lipids: HDL cholesterol (mg/dL)	56.27	14.72	53.8	16.43	0.0466	0.0466

Table XVI. Difference between healthy control and cognitive decline Model II

Cognitive Decline Model II	TrailA	Control Mean	SD	Cognitive Mean	SD	|t|-test	Corrected p-value	TrailB	Control Mean	SD	Cognitive Mean	SD	|t|-test	Corrected p-value
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)		60.15	35.34	45.59	35.96	<0.0001	<0.0001		65.04	35.67	50.09	35.12	<0.0001	<0.0001
Adiponectin via RIA (µg/mL)		12.02	8.69	15.3	11.07	<0.0001	<0.0001		11.26	8.43	14.02	10.52	<0.0001	<0.0001
Albumin (%)		60.08	3.24	58.34	3.47	<0.0001	<0.0001		60.9	31.4	58.86	3.32	<0.0001	<0.0001
Alpha-2-macroglobulin (mg/dL)		198.81	63.42	216.06	70.31	<0.0001	<0.0001		192.94	59.16	211.62	69.68	<0.0001	<0.0001
Alpha-1 globulin (%)		2.5	0.38	2.67	0.41	<0.0001	<0.0001		2.46	0.39	2.6	0.39	<0.0001	<0.0001
Alpha-2 globulin (%)		10.94	1.24	11.35	1.31	<0.0001	<0.0001		10.66	1.25	11.24	1.25	<0.0001	<0.0001
Beta globulins (%)		11.66	1.24	12.04	1.31	<0.0001	<0.0001		11.43	1.28	11.97	1.27	<0.0001	<0.0001
Blood urea nitrogen (mg/dL)		32.23	7.68	35.75	12.41	<0.0001	<0.0001		30.77	7.1	34.43	10.32	<0.0001	<0.0001
Fatty acid C16:0 weight (mg/L)		NA	NA	NA	NA	NA	NA		704.19	201.01	733.25	183.76	0.0341	0.0366
Fatty acid C20:5 n-3 as % of total fatty acid area		0.49	0.21	0.45	0.18	0.0011	0.0015		NA	NA	NA	NA	NA	NA
Fatty acid C20:5 n-3 weight (mg/L)		20.55	9.62	19.22	7.22	0.0097	0.0112		NA	NA	NA	NA	NA	NA
Fatty acid C20:5 n-3 as % of total fatty acid weight		0.64	0.24	0.59	0.19	0.0011	0.0015		NA	NA	NA	NA	NA	NA
Fatty acid C24:0 as % of total fatty acid weight		0.15	0.13	0.13	0.14	0.016	0.0176		0.16	0.14	0.14	0.13	0.0071	0.0085
Ca++ (mg/dL)		9.49	0.44	9.42	0.45	0.0093	0.0109		NA	NA	NA	NA	NA	NA
Creatinine clearance, 24-hr urine (mL/minute)		92.61	30.4	72.83	25.51	<0.0001	<0.0001		99.97	31.39	79.81	26.95	<0.0001	<0.0001
MCH concentration (MCHC) (g/dL)		34.09	0.94	33.64	1.02	<0.0001	<0.0001		34.26	0.93	33.8	0.99	<0.0001	<0.0001
Mean corpuscular hemoglobin (MCH) (pg)		30.67	1.74	30.45	1.96	0.0368	0.0385		NA	NA	NA	NA	NA	NA
Cortisol:DHEAS ratio (nmols)		0.25	0.58	0.43	1.54	0.0118	0.0133		0.23	0.61	0.45	1.25	0.0437	0.046
Creatine phosphokinase (U/L)		113.55	100.7	95.32	58.92	<0.0001	<0.0001		125.29	128.15	99.28	58.23	0.0004	0.0006
C-reactive protein - high sensitivity (µg/mL)		3.89	5.78	5.87	11.73	0.0004	0.0006		3.18	5.17	5	8.07	<0.0001	<0.0001
C-terminal telopeptide of type-1 collagen (ng/mL)		0.43	0.2	0.54	0.3	<0.0001	<0.0001		0.41	0.19	0.48	0.26	<0.0001	<0.0001
Cystatin C (mg/L)		0.89	0.2	1.06	0.35	<0.0001	<0.0001		0.84	0.19	0.99	0.28	<0.0001	<0.0001
Dehydroepiandrosterone sulfate (µg/dL)		124.75	101.28	85.52	70.91	<0.0001	<0.0001		153.71	115.09	91.51	72.62	<0.0001	<0.0001
Endogenous secretory receptor for AGEs (ng/mL)		0.43	0.21	0.46	0.22	0.0382	0.0393		NA	NA	NA	NA	NA	NA
Estradiol via radioimmunoassay (pg/mL)		14.79	17.95	9.25	6.72	<0.0001	<0.0001		18.56	21.94	9.89	0.34	<0.0001	<0.0001
Fibrinogen (mg/dL)		334.82	71.84	361.82	75.38	<0.0001	<0.0001		320.51	70.23	353.39	73.21	<0.0001	<0.0001
Free testosterone (ng/dL), Vermeulen		3.04	2.98	1.73	1.91	<0.0001	<0.0001		3.5	3.3	2.13	2.27	<0.0001	<0.0001
Free thyroxine, fT4 (ng/dL)		1.39	0.29	1.48	0.37	<0.0001	<0.0001		1.39	0.27	1.44	0.33	0.0081	0.0096
Blood glucose (mg/dL)		91.66	23.24	97.13	28.81	0.0004	0.0006		87.99	18.83	96.84	28.52	<0.0001	<0.0001
ALT (U/L)		21.76	13.91	18.88	11.88	0.0001	0.0001		NA	NA	NA	NA	NA	NA
Red blood cells (RBC) (n, millions/µL)		4.58	0.39	4.47	0.43	<0.0001	<0.0001		NA	NA	NA	NA	NA	NA
BL Hemoglobin (g/dL)		14.03	1.28	13.58	1.31	<0.0001	<0.0001		14.05	1.32	13.82	1.27	0.0056	0.007
BL Hematocrit (%)		41.13	3.28	40.36	3.5	<0.0001	<0.0001		NA	NA	NA	NA	NA	NA
Homocysteine via FPIA analysis (µmol/L)		13.91	5.44	16.26	7.09	<0.0001	<0.0001		13.39	5.22	15.17	6.22	<0.0001	<0.0001
Red cell distribution width (RDW) (%)		13.44	0.89	13.81	1	<0.0001	<0.0001		13.33	0.87	13.68	0.97	<0.0001	<0.0001
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)		NA	NA	NA	NA	NA	NA		365.8	143.93	399.41	151.46	0.0005	0.0007
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)		146.07	101.47	164.11	128.81	0.0078	0.0093		135.45	82.99	161.09	130.16	0.0001	<0.0001
Interleukin-6 via ELISA ultrasensitive (pg/mL)		1.55	1.82	2.47	5.54	0.0002	0.0003		1.31	1.84	1.97	2.18	<0.0001	<0.0001
Plasma insulin via RIA (mIU/L)		10.57	6.24	22.45	6.24	0.0161	0.0176		9.93	6.45	11.27	6.19	0.0016	0.0021
Lipoprotein(a) (mg/dL)		NA	NA	NA	NA	NA	NA		19.14	22.85	22.22	25.42	0.0495	0.0495
Methylmalonic acid, MMA (µmol/L)		0.1	0.03	0.11	0.03	0.0012	0.0016		0.1	0.03	0.11	0.03	0.0002	0.0003
Lymphocytes (n, K/µL)		1.96	0.65	1.85	0.65	0.0007	0.001		2.04	0.65	1.9	0.67	0.0012	0.0016
Na+ (mEq/L)		141.6	2.35	142.045	2.63	0.0019	0.0024		141.51	2.28	141.93	2.52	0.0064	0.0079

Cognitive Decline Model II	TrailA	Control Mean	SD	Cognitive Mean	SD	|t|-test	Corrected p-value	TrailB	Control Mean	SD	Cognitive Mean	SD	|t|-test	Corrected p-value
Omega-3 fatty acids as % of total fatty acid area		2.09	0.62	1.88	0.57	<0.0001	<0.0001		2.16	0.67	1.97	0.59	<0.0001	<0.0001
Omega-3 plasma fatty acid weight (mg/L)		113.81	43.61	104.23	37.54	<0.0001	<0.0001		NA	NA	NA	NA	NA	NA
Ratio of Omega-6:Omega-3 as % of total fatty acid weight		3.53	0.98	3.21	0.93	<0.0001	<0.0001		3.64	1.04	3.34	0.94	<0.0001	<0.0001
Ratio of Omega-6:Omega-3 as % of total fatty acid weight		10.34	2.95	10.7	3.19	0.0479	0.0486		NA	NA	NA	NA	NA	NA
Omega-6 fatty acids as % of total fatty acid area		31.41	4.39	29.3	4.38	<0.0001	<0.0001		32.26	4.3	30.02	4.35	<0.0001	<0.0001
Omega-6 fatty acids as % of total fatty acid mols		33.15	4.43	331.08	4.46	<0.0001	<0.0001		33.99	0.25	31.8	4.42	<0.0001	<0.0001
Omega-6 plasma fatty acid weight (mg/L)		1082.37	243.69	1028.01	223.72	0.0001	0.0001		NA	NA	NA	NA	NA	NA
Omega-6 fatty acids as % of total fatty acid weight		34.05	4.43	31.98	4.47	<0.0001	<0.0001		34.89	4.31	32.7	4.43	<0.0001	<0.0001
Lymphocytes (%)		31.98	8.19	30.58	8.03	0.0028	0.0034		32.9	8.42	31.03	8.09	0.0007	0.001
Neutrophils (%)		59.12	8.81	60.47	8.4	0.0067	0.0081		58.2	9.19	60.03	8.52	0.002	0.0026
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)		22.24	17.65	27.87	19.24	<0.0001	<0.0001		22.33	22.59	25.03	14.54	0.0466	0.0474
Resistin via EIA (ng/mL)		3.71	1.72	4.13	2.23	0.0007	0.001		3.59	1.65	3.89	1.95	0.0126	0.0143
Retinol via high performance liquid chromatography (µmol/L)		1.97	0.48	1.88	0.49	0.0005	0.0007		1.99	0.47	1.91	0.49	0.0105	0.0121
Soluble CD14 via ELISA (ng/mL)		1651.2	339.4	1781.38	335.52	<0.0001	<0.0001		1595.57	318.07	1733.72	340.59	<0.0001	<0.0001
Soluble transferrin receptor (nmol/L)		15.98	5.49	16.99	5.48	0.0016	0.002		NA	NA	NA	NA	NA	NA
Total testosterone (ng/mL)		2.76	2.2	1.94	1.92	<0.0001	<0.0001		2.97	2.29	2.17	1.99	<0.0001	<0.0001
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)		147.92	72.25	109.88	51.83	<0.0001	<0.0001		164.2	78.49	121.24	57.78	<0.0001	<0.0001
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)		1200.34	443.28	1594.19	785.34	<0.0001	<0.0001		1101.48	441.51	1418.13	603.9	<0.0001	<0.0001
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)		2416.55	657.28	2869.39	827.95	<0.0001	<0.0001		2267.59	638.78	2695.09	747.26	<0.0001	<0.0001
Thyroid stimulating hormone, TSH (mIU/L)		1.66	2.24	2.36	7	0.0357	0.0379		NA	NA	NA	NA	NA	NA
Urinary Ca (mmol/L)		2.57	1.74	2.09	1.47	<0.0001	<0.0001		2.62	1.56	2.31	1.66	0.0054	0.0069
24-hour urinary cortisol (µg/24 hours)		108.88	55.55	100.63	68.22	0.0273	0.0294		111.52	50.52	102.66	58.56	0.0145	0.0161
Urinary cortisol (µg/mL)		NA	NA	NA	NA	NA	NA		0.08	0.06	0.07	0.05	0.0201	0.022
24-hour urinary creatinine (mg/24 hours)		1132.16	384.36	884.66	304.86	<0.0001	<0.0001		1211	383.23	977.63	348.15	<0.0001	<0.0001
Urinary creatinine (mg/dL)		81.52	39.44	67.67	32.17	<0.0001	<0.0001		88.75	42.01	71.27	34.64	<0.0001	<0.0001
Urinary Na (mmol/L)		101.12	45.54	92.5	41.92	0.0011	0.0015		106.71	46.11	93.3	41.77	<0.0001	<0.0001
Erythrocyte sedimentation rate (ESR) (mm/hour)		16.98	15.83	22.82	19.49	<0.0001	<0.0001		15.18	14.53	20.48	18.15	<0.0001	<0.0001
Mean corpuscular volume (MCV) (fL)		89.96	4.47	90.49	4.86	0.0492	0.0492		89.6	4.55	90.21	4.74	0.0458	0.0474
Vitamin B6 via high performance liquid chromatography (ng/mL)		8.32	5.57	6.56	6.64	<0.0001	<0.0001		9.34	5.91	6.93	6.24	<0.0001	<0.0001
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***		4497.55	1077.25	4229.28	1103.01	<0.0001	<0.0001		4595.71	993.38	4347.15	1145.3	0.0005	0.0007

Table XVII. Difference between healthy control and frailty Model II

Frailty Model II	Control Mean	SD	Frailty Mean	SD	|t|-test	Corrected p-value
Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)	30.99	8.29	29.00	8.46	<0.0001	<0.0001
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)	34.44	7.65	32.65	7.39	<0.0001	<0.0001
Lymphocytes (%)	31.42	7.88	29.50	8.23	<0.0001	<0.0001
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)	54.93	34.5	43.52	35.77	<0.0001	<0.0001
Alpha-1 globulin (%)	2.57	0.36	2.72	0.47	<0.0001	<0.0001
Blood urea nitrogen (mg/dL)	33.79	7.44	37.5	15.92	<0.0001	<0.0001
Creatinine clearance, 24-hr urine (mL/minute)	81.09	24.06	70.00	26.43	<0.0001	<0.0001
MCH concentration (MCHC) (g/dL)	33.9	1.02	33.56	1.05	<0.0001	<0.0001
Creatine phosphokinase (U/L)	104.23	61.69	86.84	55.12	<0.0001	<0.0001
C-reactive protein - high sensitivity (µg/mL)	4.06	5.99	6.79	11.93	<0.0001	<0.0001
C-terminal telopeptide of type-1 collagen (ng/mL)	0.47	0.23	0.58	0.35	<0.0001	<0.0001
Free testosterone (ng/dL), Vermeulen	2.41	2.22	1.72	1.9	<0.0001	<0.0001
Red blood cells (RBC) (n, millions/µL)	4.57	0.38	4.42	0.48	<0.0001	<0.0001
Homocysteine via FPIA analysis (µmol/L)	14.97	5.70	17.32	8.12	<0.0001	<0.0001
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)	142.73	85.50	177.97	159.09	<0.0001	<0.0001
Interleukin-6 via ELISA ultrasensitive (pg/mL)	1.67	1.75	2.92	5.74	<0.0001	<0.0001
Neutrophils (n, K/µL)	3.60	1.18	3.90	1.31	<0.0001	<0.0001
Omega-6 plasma fatty acid weight (mg/L)	1069.54	249.81	1005.32	234.97	<0.0001	<0.0001
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)	24.06	19.79	30.55	22.59	<0.0001	<0.0001
Resistin via EIA (ng/mL)	3.72	1.67	4.36	2.48	<0.0001	<0.0001
Total testosterone (ng/mL)	2.58	2.09	1.91	1.89	<0.0001	<0.0001
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)	1343.02	429.62	1780.92	979.8	<0.0001	<0.0001
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)	2625.69	612.55	3053.98	958.87	<0.0001	<0.0001
24-hour urinary creatinine (mg/24 hours)	1020.45	334.70	860.38	323.47	<0.0001	<0.0001
Erythrocyte sedimentation rate (ESR) (mm/hour)	17.72	14.75	25.45	21.55	<0.0001	<0.0001
IL-6 high-sensitivity ELISA calculated from ELISA ultrasensitive (pg/mL)	3.11	2.00	4.23	2.82	<0.0001	<0.0001
Alpha-2-macroglobulin (mg/dL)	205.18	66.26	221.01	69.64	0.0002	0.0003
Dehydroepiandrosterone sulfate (µg/dL)	91.21	69.26	75.51	63.3	0.0002	0.0003
Folate via RIA (ng/mL)	3.50	2.12	3.03	1.88	0.0002	0.0003
Free thyroxine, fT4 (ng/dL)	1.43	0.30	1.51	0.41	0.0002	0.0003
Soluble CD14 via ELISA (ng/mL)	1724.25	315.92	1810.47	383.4	0.0002	0.0003
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)	122.04	54.74	109.52	53.63	0.0002	0.0003
Endogenous secretory receptor for AGEs (ng/mL)	0.43	0.19	0.48	0.27	0.0005	0.0008
Omega-6 fatty acids as % of total fatty acid area	30.16	4.16	29.17	4.57	0.0005	0.0008
TNF-related apoptosis-inducing ligand (pg/mL)	79.52	54.09	70.44	20.08	0.0005	0.0008
Lipids: LDL cholesterol (mg/dL)	139.01	35.77	132.56	32.70	0.0022	0.0034
Omega-3 plasma fatty acid weight (mg/L)	110.92	44.27	102.85	37.76	0.0029	0.0043
Lipids: total cholesterol (mg/dL)	220.84	40.73	213.53	38.74	0.0031	0.0045
Urinary Ca (mmol/L)	2.35	1.65	2.04	1.58	0.0036	0.0051
White blood cells (WBC) (n, K/µL)	6.01	1.56	6.3	1.63	0.0037	0.0051
Vitamin B6 via high performance liquid chromatography (ng/mL)	7.47	6.61	6.09	9.08	0.0057	0.0076
ALT (U/L)	20.48	11.99	18.44	12.05	0.0062	0.0081
Fatty acid C20:5 n-3 weight (mg/L)	20.46	9.87	18.95	7.51	0.0088	0.0113
Adiponectin via RIA (µg/mL)	13.31	9.72	15.05	10.83	0.0094	0.0118
Omega-3 fatty acids as % of total fatty acid area	1.99	0.62	1.89	0.59	0.0141	0.0172
Urinary Na (mmol/L)	96.75	46.40	89.89	39.48	0.0153	0.0183
Uric acid (mg/dL)	5.09	1.29	5.30	1.60	0.0175	0.0205
24-hour urinary cortisol (µg/24 hours)	105.33	52.21	95.94	73.57	0.0231	0.0265
Fatty acid C20:5 n-3 cis (eicosapentaenoic, EPA) area	79.94	51.57	73.05	43.36	0.0275	0.0309
Urine proteins (mg/dL)	0.73	7.61	1.93	8.98	0.0292	0.0321
Fatty acid C24:0 weight (mg/L)	4.65	4.51	4.05	4.11	0.0316	0.0337
Fatty acid C16:0 as % of total fatty acid weight	22.38	2.36	22.72	2.48	0.0319	0.0337
Fatty acid C16:0 as % of total fatty acid area	24.66	2.36	24.98	2.46	0.0408	0.0423
Omega-3 fatty acids as % of total fatty acid weight	3.35	0.97	3.23	0.95	0.0457	0.0465
Fatty acid C20:5 n-3 as % of total fatty acid area	0.47	0.22	0.44	0.19	0.0471	0.0471

Table XVIII. Difference between healthy control and cognitive frailty Model II

Cognitive Frailty Model II	TrailA	Control Mean	SD	Cognitive Frailty Mean	SD	|t|-test	Corrected p-value	TrailB	Control Mean	SD	Cognitive Frailty Mean	SD	|t|-test	Corrected p-value
25(OH)-D (25-hydroxyvitamin D) via RIA (nmol/L)		57.82	36.01	40.97	34.34	<0.0001	<0.0001		58.33	33.73	47.92	40.02	<0.0001	<0.0001
Adiponectin via RIA (µg/mL)		12.66	9.11	15.85	11.71	<0.0001	<0.0001		12.41	9.13	14.66	11.45	0.0028	0.0034
Albumin (%)		59.71	3.34	58.09	3.51	<0.0001	<0.0001		59.99	3.27	58.52	3.45	<0.0001	<0.0001
Alpha-2-macroglobulin (mg/dL)		201.68	64.3	221.07	73.22	<0.0001	<0.0001		197.37	61.88	223.54	74.06	<0.0001	<0.0001
Alpha-1 globulin (%)		2.53	0.38	2.69	0.43	<0.0001	<0.0001		2.51	0.39	2.64	0.43	<0.0001	<0.0001
Vitamin E alpha tocopherol, high performance liquid chromatography (µmol/L)		30.47	8.24	29.01	8.39	0.0092	0.01		NA	NA	NA	NA	NA	NA
Vitamin E alpha tocopherol, high performance liquid chromatography, assay #2 (µmol/L)		33.91	7.54	32.86	7.43	0.0367	0.0367		NA	NA	NA	NA	NA	NA
Blood urea nitrogen (mg/dL)		32.61	7.77	37.42	14.90	<0.0001	<0.0001		32.12	7.20	0.27	13.06	<0.0001	<0.0001
Fatty acid C20:5 n-3 as % of total fatty acid area		0.48	0.20	0.19	0.19	0.027	0.0275		NA	NA	NA	NA	NA	NA
Creatinine clearance, 24-hr urine (mL/minute)		88.69	29.71	68.68	25.64	<0.0001	<0.0001		9.48	30.34	74.67	25.66	<0.0001	<0.0001
MCH concentration (MCHC) (g/dL)		34.01	1.00	33.54	0.96	<0.0001	<0.0001		34.07	1.00	33.67	0.96	<0.0001	<0.0001
Serum cortisol (µg/dL)		NA	NA	NA	NA	NA	NA		13.67	5.06	12.73	4.37	0.0026	0.0033
Creatine phosphokinase (U/L)		110.89	92.60	88.84	53.96	<0.0001	<0.0001		115.10	99.11	91.46	54.64	<0.0001	<0.0001
C-reactive protein - high sensitivity (µg/mL)		4.01	6.14	7.11	14.37	0.0004	0.0005		3.77	6.02	5.83	9.44	0.0004	0.0006
C-terminal telopeptide of type-1 collagen (ng/mL)		0.44	0.21	0.59	0.35	<0.0001	<0.0001		0.43	0.20	0.53	0.31	<0.0001	<0.0001
Cystatin C (mg/L)		0.91	0.21	1.13	0.42	<0.0001	<0.0001		0.88	0.19	1.07	0.35	<0.0001	<0.0001
Dehydroepiandrosterone sulfate (µg/dL)		116.98	95.79	77.99	67.71	<0.0001	<0.0001		125.8	100.15	80.97	67.13	<0.0001	<0.0001
Endogenous secretory receptor for AGEs (ng/mL)		0.43	0.2	0.48	0.25	0.0077	0.0083		0.43	0.18	0.48	0.27	0.0086	0.0094
Estradiol via radioimmunoassay (pg/mL)		13.29	15.99	9.52	7.18	<0.0001	<0.0001		14.30	17.34	9.35	6.52	<0.0001	<0.0001
Fibrinogen (mg/dL)		339.88	72.16	367.95	78.12	<0.0001	<0.0001		334.56	73.08	360.54	72.38	<0.0001	<0.0001
Folate via RIA (ng/mL)		3.41	2.14	3.02	1.70	0.0013	0.0017		3.43	2.14	3.07	1.91	0.0078	0.0087
Free testosterone (ng/dL), Vermeulen		2.72	2.80	1.67	1.92	<0.0001	<0.0001		2.95	2.96	1.74	1.89	<0.0001	<0.0001
Blood glucose (mg/dL)		NA	NA	NA	NA	NA	NA		92.18	24.40	97.77	29.05	0.0028	0.0034
Hematocrit (%)		41.02	3.28	40.06	3.64	<0.0001	<0.0001		41.07	3.23	40.51	3.48	0.0147	0.0153
Homocysteine via FPIA analysis (µmol/L)		14.16	5.57	17.39	7.78	<0.0001	<0.0001		13.88	5.59	16.17	6.47	<0.0001	<0.0001
Interleukin-18 via ELISA ultrasensitive using plasma (pg/mL)		386.20	149.66	411.61	156.28	0.0146	0.0154		382.19	150.56	402.02	147.03	0.0478	0.0478
Interleukin-1 receptor antagonist via ELISA ultrasensitive (pg/mL)		146.60	97.39	177.16	154.61	0.0015	0.0019		142.80	95.94	174.54	153.13	0.0007	0.001
Interleukin-6 via ELISA ultrasensitive (pg/mL)		1.57	1.81	3.14	7.22	0.0003	0.0004		1.46	1.77	2.42	2.57	<0.0001	<0.0001
Lycopene via high performance liquid chromatography (µmol/L)		0.71	0.34	0.65	0.31	0.0042	0.005		NA	NA	NA	NA	NA	NA
Lymphocytes (n, K/µL)		1.95	0.64	1.83	0.67	0.0073	0.0085		1.98	0.65	1.87	0.69	0.0184	0.0188
Omega-3 fatty acids as % of total fatty acid area		2.04	0.62	1.88	0.56	0.0002	0.0003		2.07	0.63	1.96	0.60	0.0049	0.0056
Omega-6 plasma fatty acid weight (mg/L)		1069.85	241.60	1022.35	216.50	0.0024	0.0029		1086.09	239.82	1034.56	223.86	0.0016	0.0021
Omega-6 fatty acids as % of total fatty acid weight		33.57	4.45	31.76	4.64	<0.0001	<0.0001		33.93	4.42	32.32	4.52	<0.0001	<0.0001
Lymphocytes (%)		31.96	8.07	29.53	8.13	<0.0001	<0.0001		32.45	8.16	29.87	8.16	<0.0001	<0.0001
Neutrophils (%)		59.15	8.64	61.46	8.47	<0.0001	<0.0001		58.64	8.83	61.19	8.42	<0.0001	<0.0001
Parathyroid hormone, two-site immunoradiometric assay (pg/mL)		22.68	16.32	31.12	23.23	<0.0001	<0.0001		22.36	17.44	28.13	17.47	<0.0001	<0.0001
Resistin via EIA (ng/mL)		3.75	1.87	4.33	2.19	<0.0001	<0.0001		3.67	1.66	4.05	2.23	0.0094	0.01
Soluble CD14 via ELISA (ng/mL)		1670.14	331.90	1824.72	386.26	<0.0001	<0.0001		1653.78	323.41	1760.93	361.97	<0.0001	<0.0001
Total testosterone (ng/mL)		2.57	2.17	1.85	1.87	<0.0001	<0.0001		2.68	2.20	1.87	1.84	<0.0001	<0.0001
Total insulin-like growth factor-1, serum, immunoradiometric assay (ng/mL)		139.07	69.69	106.54	49.24	<0.0001	<0.0001		145.42	71.16	113.21	55.61	<0.0001	<0.0001
Soluble TNF-a receptor I via quantitative sandwich EIA (pg/mL)		1248.81	471.88	1763.25	914.92	<0.0001	<0.0001		1191.01	432.04	1592.49	741.76	<0.0001	<0.0001
Soluble TNF-a receptor II via quantitative sandwich EIA (pg/mL)		2473.75	654.70	3059.1	924.41	<0.0001	<0.0001		2399.93	623.03	2903.60	862.17	<0.0001	<0.0001
TNF-related apoptosis-inducing ligand (pg/mL)		76.51	42.76	71.47	19.74	0.0064	0.0074		NA	NA	NA	NA	NA	NA
Urinary Ca (mmol/L)		2.50	1.74	1.90	1.18	<0.0001	<0.0001		2.52	1.63	2.15	1.64	0.0001	0.0001
24-hour urinary cortisol (µg/24 hours)		108.98	32.17	93.34	57.87	0.0001	0.0001		109.66	50.09	96.01	67.41	0.0018	0.0023
Urinary cortisol (µg/mL)		1082.84	374.84	833.83	294.48	<0.0001	<0.0001		1119.54	381.66	902.09	314.87	<0.0001	<0.0001
24-hour urinary creatinine (mg/24 hours)		1082.84	374.84	833.83	294.48	<0.0001	<0.0001		1119.54	381.66	902.09	314.87	<0.0001	<0.0001
Urinary creatinine (mg/dL)		78.09	38.10	66.78	32.12	<0.0001	<0.0001		80.74	39.52	68.38	33.02	<0.0001	<0.0001
Urinary Na (mmol/L)		99.50	45.59	90.34	38.51	0.0014	0.0018		101.58	44.78	88.47	39.39	<0.0001	<0.0001
Uric acid (mg/dL)		4.98	1.28	5.22	1.56	0.0148	0.0154		4.93	1.29	5.19	1.36	0.0036	0.0042
Erythrocyte sedimentation rate (ESR) (mm/hour)		17.59	15.96	25.67	21.42	<0.0001	<0.0001		16.67	14.84	23.32	20.66	<0.0001	<0.0001
Vitamin B6 via high performance liquid chromatography (ng/mL)		8.12	6.21	5.75	5.47	<0.0001	<0.0001		8.48	6.28	6.08	5.79	<0.0001	<0.0001
IGF binding protein-3, serum, immunoradiometric assay (ng/mL) ***corrected***		4452.55	1077.41	4158.20	1124.84	0.0001	0.0001		4517.72	1060.85	4238.12	1166.19	0.0004	0.0006

References

1. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems Contributing to the Decline in Ability to Walk: Bridging the Gap Between Epidemiology and Geriatric Practice in the InCHIANTI Study. *J Am Geriatr Soc*. 2000;48(12):1618-1625. doi:10.1111/j.1532-5415.2000.tb03873.x.
2. Millward D, Paul S, Brown M, et al. The diagnosis of asthma and exercise-induced bronchospasm in division I athletes. *Clin J Sport Med*. 2009;19(6):482-486. doi:10.1097/JSM.0b013e3181bcde2c00042752-200911000-00008 [pii].
3. Portet F, Ousset PJ, Visser PJ, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease. *J Neurol Neurosurg Psychiatry*. 2006;77(6):714-718. doi:10.1136/jnnp.2005.085332.
4. Simpson JR. DSM-5 and Neurocognitive Disorders. *J Am Acad Psychiatry Law Online*. 2014;42(2). http://jaapl.org/content/42/2/159. Accessed May 30, 2017.
5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56. http://www.ncbi.nlm.nih.gov/pubmed/11253156. Accessed August 27, 2014.
6. Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging*. 2013;17(9):726-734. doi:10.1007/s12603-013-0367-2.
7. Harvan JR, Cotter V. An evaluation of dementia screening in the primary care setting. *J Am Acad Nurse Pract*. 2006;18(8):351-360. doi:10.1111/j.1745-7599.2006.00137.x.
8. Folstein, Marshal F., Susan E. Folstein and PRM. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;2.3:189-198. doi:10.1016/j.pcad.2015.11.006.
9. Spering CC, Hobson V, Lucas JA, Menon C V., Hall JR, O'Bryant SE. Diagnostic accuracy of the MMSE in detecting probable and possible alzheimer's disease in ethnically diverse highly educated individuals: An analysis of the NACC database. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(8):890-896. doi:10.1093/gerona/gls006.
10. Delrieu J, Andrieu S, Cantet C, Cesari M, Ousset P.J., Voisin T, Fougere B, Gillette S, Carrie I and VB. Neuropsychological Profile of "Cognitive Frailty" Subjects in MAPT Study. 2016;116(8):1477-1490. doi:10.14283/jpad.2016.94.
11. Ashendorf L, Jefferson AL, Connor MKO, et al. Trail Making Test Errors in Normal Aging, Mild Cognitive Impairment, and Dementia. 2009;23(2):129-137. doi:10.1016/j.acn.2007.11.005.Trail.
12. Marschner I. "glm2"-Fitting GEneralized Linear Models. https://cran.r-project.org/web/packages/glm2/glm2.pdf. Accessed May 11, 2017.
13. Christensen R. "Ordinal"- Regression Models for Ordinal Data. https://cran.r-project.org/web/packages/ordinal/ordinal.pdf. Accessed May 11, 2017.
14. Chen, Tianqi, He, Tong, Benesty, Michael, Khotilovich, Vadim, Tang Y. "xgboost"-Extreme Gradient Boosting. 2017. doi:10.1145/2939672.2939785>.
15. Purcell, S, Neale, B, Todd-Brown, K, Thomas, L, Ferreira, MAR, Bender, D, Maller, J, Sklar, P, de Bakker, PIW, Daly, MJ, Sham P. PLINK: a toolset for whole-genome association and

population-based linkage analysis. *Am J Hum Genet*. 2007;81.
16. Purcell S. PLINK V1.07. http://pngu.mgh.harvard.edu/purcell/plink/. Published 2009.
17. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc*. 2000;48(12):1618-1625. http://www.ncbi.nlm.nih.gov/pubmed/11129752. Accessed May 31, 2017.

Drugs with ACB Score of 1

Generic Name	Brand Name
Alimemazine	Theralen™
Alverine	Spasmonal™
Alprazolam	Xanax™
Aripiprazole	Abilify™
Asenapine	Saphris™
Atenolol	Tenormin™
Bupropion	Wellbutrin™, Zyban™
Captopril	Capoten™
Cetirizine	Zyrtec™
Chlorthalidone	Diuril™, Hygroton™
Cimetidine	Tagamet™
Clidinium	Librax™
Clorazepate	Tranxene™
Codeine	Contin™
Colchicine	Colcrys™
Desloratadine	Clarinex™
Diazepam	Valium™
Digoxin	Lanoxin™
Dipyridamole	Persantine™
Disopyramide	Norpace™
Fentanyl	Duragesic™, Actiq™
Furosemide	Lasix™
Fluvoxamine	Luvox™
Haloperidol	Haldol™
Hydralazine	Apresoline™
Hydrocortisone	Cortef™, Cortaid™
Iloperidone	Fanapt™
Isosorbide	Isordil™, Ismo™
Levocetirizine	Xyzal™
Loperamide	Immodium™, others
Loratadine	Claritin™
Metoprolol	Lopressor™, Toprol™
Morphine	MS Contin™, Avinza™
Nifedipine	Procardia™, Adalat™
Paliperidone	Invega™
Prednisone	Deltasone™, Sterapred™
Quinidine	Quinaglute™
Ranitidine	Zantac™
Risperidone	Risperdal™
Theophylline	Theodur™, Uniphyl™
Trazodone	Desyrel™
Triamterene	Dyrenium™
Venlafaxine	Effexor™
Warfarin	Coumadin™

Drugs with ACB Score of 2

Generic Name	Brand Name
Amantadine	Symmetrel™
Belladonna	Multiple
Carbamazepine	Tegretol™
Cyclobenzaprine	Flexeril™
Cyproheptadine	Periactin™
Loxapine	Loxitane™
Meperidine	Demerol™
Methotrimeprazine	Levoprome™
Molindone	Moban™
Nefopam	Nefogesic™
Oxcarbazepine	Trileptal™
Pimozide	Orap™

Categorical Scoring:

- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

Numerical Scoring:

- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

Notes:

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. [3]
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. [4]
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. [4]

Aging Brain Care

www.agingbraincare.org

Drugs with ACB Score of 3

Generic Name	Brand Name
Amitriptyline	Elavil™
Amoxapine	Asendin™
Atropine	Sal-Tropine™
Benztropine	Cogentin™
Brompheniramine	Dimetapp™
Carbinoxamine	Histex™, Carbihist™
Chlorpheniramine	Chlor-Trimeton™
Chlorpromazine	Thorazine™
Clemastine	Tavist™
Clomipramine	Anafranil™
Clozapine	Clozaril™
Darifenacin	Enablex™
Desipramine	Norpramin™
Dicyclomine	Bentyl™
Dimenhydrinate	Dramamine™, others
Diphenhydramine	Benadryl™, others
Doxepin	Sinequan™
Doxylamine	Unisom™, others
Fesoterodine	Toviaz™
Flavoxate	Urispas™
Hydroxyzine	Atarax™, Vistaril™
Hyoscyamine	Anaspaz™, Levsin™
Imipramine	Tofranil™
Meclizine	Antivert™
Methocarbamol	Robaxin™
Nortriptyline	Pamelor™
Olanzapine	Zyprexa™
Orphenadrine	Norflex™
Oxybutynin	Ditropan™
Paroxetine	Paxil™
Perphenazine	Trilafon™
Promethazine	Phenergan™
Propantheline	Pro-Banthine™
Propiverine	Detrunorm™
Quetiapine	Seroquel™
Scopolamine	Transderm Scop™
Solifenacin	Vesicare™
Thioridazine	Mellaril™
Tolterodine	Detrol™
Trifluoperazine	Stelazine™
Trihexyphenidyl	Artane™
Trimipramine	Surmontil™
Trospium	Sanctura™

Medications Reviewed in 2012 Update

Medications Added with Score of 1:
Aripiprazole (Abilify™)
Asenapine (Saphris™)
Cetirizine (Zyrtec™)
Clidinium (Librax™)
Desloratadine (Clarinex™)
Iloperidone (Fanapt™)
Levocetirizine (Xyzal™)
Loratadine (Claritin™)
Paliperidone (Invega™)
Venlafaxine (Effexor™)

Medications Added with Score of 2:
Nefopam (Nefogesic™)

Medications Added with Score of 3:
Doxylamine (Unisom™, others)
Fesoterodine (Toviaz™)
Propiverine (Detrunorm™)
Solifenacin (Vesicare™)
Trospium (Sanctura™)

Medications Reviewed But NOT Added:
Fexofenadine (Allegra™)
Gabapentin (Neurontin™)
Topiramate (Topamax™)
Levetiracetam (Keppra™)
Tamoxifen (Nolvadex™)
Nizatidine (Axid™)
Duloxetine (Cymbalta™)

Criteria for Categorization:
Score of 1: Evidence from in vitro data that chemical entity has antagonist activity at muscarinic receptor.

Score of 2: Evidence from literature, prescriber's information, or expert opinion of clinical anticholinergic effect.

Score of 3: Evidence from literature, expert opinion, or prescribers information that medication may cause delirium.

Complete References:

1. Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and practical application. Aging Heatlh. 2008;4(3):311-320.

2. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. Clinical Interventions in Aging. 2009;4(1):225-233.

3. Campbell N, Boustani M, Lane K, etal. Use of anticholinergics and the risk of cognitive impairment in an African-American population. Neurology. 2010;75:152-159.

4. Fox C, Richardson K, Maidment I, et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing Study. Journal of the American Geriatric Society. 2011; 59(8): 1477-1483.

5. Cai X, Campbell N, Khan B, Callahan C, Boustani M. Long-term anticholinergic use and the aging brain. Alzheimers Dementia. 2012; epub ahead of print.

Aging Brain Care

ANTICHOLINERGIC COGNITIVE BURDEN SCALE

2012 Update

Developed by the Aging Brain Program of the Indiana University Center for Aging Research

Regenstrief Institute

IDND FROM DISCOVERY TO DELIVERY

THE NEW WISHARD ESKENAZI HEALTH

Anticholinergic Burden Scale script with instructions for research assistant and/or participant permission to use instrument from author

Anticholinergic Burden Scale Permission

We do not have a formal letter. You can use the following email:

You have permission to use the Anticholinergic Cognitive Burden Scale for your dissertation related work including both research and educational purposes.

Malaz

Malaz Boustani, MD, MPH

Office of Research and Innovation
Office of Research Subjects Protection
BioTechnology Research Park
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, Virginia 23298-0568

(804) 828-0868
Fax: (804) 827-1448

TO: Patricia Slattum

CC: Lana Sargent

FROM: VCU IRB Panel B

RE: Patricia Slattum ; IRB HM20006652 Predicting cognitive frailty: a population modeling study

On 2/3/2016 the referenced research study ***qualified for exemption*** according to 45 CFR 46.101(b), category 4.

The information found in the electronic version of this study's smart form and uploaded documents now represents the currently approved study, documents, and HIPAA pathway (if applicable). You may access this information by clicking the Study Number above.

If you have any questions, please contact the Office of Research Subjects Protection (ORSP) or the IRB reviewer(s) assigned to this study.

- The reviewer(s) assigned to your study will be listed in the History tab and on the study workspace. Click on their name to see their contact information.

Attachment – Conditions of Exempt Approval
Conditions of Exempt Approval:

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (as applicable):

1. Conduct the research as described in and required by the Protocol.
2. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant's first language. The Panel must approve the translation.
3. The following changes to the protocol **must be** submitted to the IRB panel for review and approval before the changes are instituted. Changes that do not meet these criteria do not have to be submitted to the IRB. If there is a question about whether a change must be sent to the IRB please call the ORSP for clarification.

   THESE CHANGES MUST BE SUBMITTED:
   - Change in principal investigator
   - Any change that increases the risk to the participant