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Shared biological pathways for frailty and cognitive impairment: A systematic review

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1. Introduction

1.1. Background

The rates of older adults with a functional disability related to frailty have been estimated to be about 30% in adults ages 80 and older (Fried et al., 2004). Frailty is a unique health condition characterized by a symptom cluster including fatigue, decreased physical activity, weight loss, grip strength, and slowed gait (Fried et al., 2001). Both cognitive impairment 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 (Fried et al., 2001; Global Health and Aging, 2015). A growing body of evidence suggests that factors such as mental health and cognition may influence the frailty status of an older adult (Brown et al., 2014; Gray et al., 2013; Han et al., 2014). Frail older adults with cognitive impairment who have a fivefold increase (HR, 5.12) in mortality risk, a twelvefold increase (OR, 12.2) in functional disability, and lower quality of life compared to individuals with isolated frailty or cognitive impairment (Feng et al., 2017). The relationship

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Appendix A. Supplementary data

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between physical frailty and cognitive impairment with evidence of an interrelated neuropathology (Buchman et al., 2014; Lista and Sorrentino, 2010) may provide a means to identify individuals with cognitive impairment caused by non-neurodegenerative conditions that might be reversible (Buchman and Bennett, 2013; Kelaiditi et al., 2013; Solfrizzi et al., 2017). Although frailty and cognitive impairment have been shown to be related, both constructs have long been studied separately (Kelaiditi et al., 2013).

1.2. Conceptual frameworks

Several researchers have suggested new conceptual frameworks such as motoric cognitive risk syndrome (MCR) and “cognitive frailty” to provide stimulus for new research into understanding the shared pathology (Kelaiditi et al., 2013; Verghese et al., 2013). MCR is described as both slow gait and the presence of subjective cognitive complaints and has been associated with an increased risk of developing dementia (Verghese et al., 2013, 2014). The loss of muscle mass involving decreased muscle fibers called sarcopenia can lead to changes in gait and physical performance in older adults. 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 International Consensus Group (I.A.A.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 (Kelaiditi et al., 2013). 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 (Kelaiditi et al., 2013). Cognitive frailty can be considered a geriatric syndrome in which we see a cluster of individuals with a condition which simultaneously presents with both physical frailty and mild cognitive impairment (MCI) (Kelaiditi et al., 2013; Panza et al., 2006). However, the mechanisms and the directional relationship behind the dynamic association of these two constructs remains unexplained. There exists evidence for the association of frailty and cognitive impairment suggesting shared pathophysiological mechanisms such as vascular disease that influence both clinical manifestations (Buchman and Bennett, 2013; Panza et al., 2006). Although, some research has been conducted on the association between physical function and cognitive impairment there is still no comprehensive list or understanding of the underlying mechanisms for cognitive frailty. Identification of emerging biomarkers from studies of sarcopenia, physical frailty, and cognitive impairment will help distinguish between changes related to normal aging, irreversible pathological process, and specific neurological diseases that may be reversible and establish a reliable research criteria for a novel clinical construct (Blazer et al., 2015; Solfrizzi et al., 2017).

1.3. Purpose

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. Therefore, efforts to unravel this complexity start with

understanding the unique biological factors that discriminate between conditions, as well as shared biological mechanisms in individuals presenting with similar symptoms and trajectories. Although, some research has been conducted on the association between physical function and cognitive impairment there is still no comprehensive list or understanding of the underlying mechanisms for this relationship. Because both cognitive impairment and frailty are large heterogeneous conditions it may not be possible to identify one biomarker to measure both. The use of one or more biomarkers specific to both constructs will improve our understanding of the association (Biomarkers Definitions Working Group, 2001; Mayeux, 2004). It is possible that the underlying biological mechanisms are at the intersect between cognitive impairment and frailty or cognitive frailty may contain some of its own unique markers of disease. The purpose of this review is to examine biological and genomic factors for cognitive impairment and frailty as a method for identifying shared mechanisms for these two important aging conditions.

2. Methods

2.1. Systematic review

The rationale for conducting a systematic review was to further develop an understanding of the shared pathology by determining the relevant biomarker data as defined by the National Institutes of Health Biomarkers Definitions Working Group (Biomarkers Definitions Working Group, 2001) for both cognitive impairment and frailty using the cognitive frailty framework (Kelaiditi et al., 2013).

2.2. Search strategy

In this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer et al., 2015). 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 (Table A). A systematic review of the literature was performed from studies published from the start date of the database till 29 December, 2017. In addition to database searching, articles were hand-pulled from references and identified through other sources.

2.3. Inclusion and exclusion criteria

Studies that included information on biomarkers or genetic markers for dementia, frailty, sarcopenia, 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 Huntington's disease were excluded. Only articles published in English were included. See Supplementary Appendix Table A.

2.4. 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 (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, 2016). Fig. 1 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 to ensure interrater reliability. A third reviewer resolved conflicting assessments. A fourth reviewer was available for additional arbitration however their services were not required.

2.5. Extraction

The analysis for this paper was generated using Qualtrics software, Version 9.2017 of Qualtrics (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, laboratory, protein, metabolomics, oxidative stress markers. The database assigned each biomarker a unique numeric code (i.e. IL6 = 3, CRP = 27). Biomarkers were extracted with a p-value .05 and genomic data extraction included: gene, single nucleotide polymorphisms (SNPs), chromosome, and effect/minor allele. When data entry was complete, the final data frame was exported from Qualtrix and analyses was carried out using R V. 3.2.1. R is a free, open-source software that provides many statistical and graphic techniques. R packages used included 'MASS' and 'ggplot2' (Ripley et al., 2017; Wickham and Chang, 2017).

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 makers 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 (OCEBM Levels of Evidence Working Group, 2011). 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 impairment, frailty, and cognitive frailty. The markers extracted for correlation to cognitive frailty were identified by the reviewers to be studies that explored both frailty and cognitive impairment in the same study.

3. Results

3.1. Study characteristics

From 6841 articles identified, titles and/or abstracts reporting on information pertaining to biomarkers or genetic markers for cognitive impairment, frailty, or cognitive frailty were included. 1316 potential relevant articles were chosen for closer review, two reviewers with appropriate subject expertise assessed the full-text of the articles for relevancy. 342 full-text articles reporting on the relevant topic met inclusion/exclusion criteria and 974 articles were excluded. Reviewer disagreements were addressed in regular meetings and resolved. A total

of 342 articles were used to extract the clinical, genetic, and protein markers for three phenotypes: cognitive impairment, frailty, and cognitive frailty. Studies were reviewed in the following categories 46 genetic studies: 13 genome wide association study (GWAS) and 33 candidate gene studies, 287 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 impairment (n = 248), frailty (n = 75), cognitive frailty (n = 15). Only one GWAS study included both cognitive and physical function measures however, the study did not use a standardized frailty tool (Thibeu et al., 2017). Phenotypes were further defined by the type of cognitive impairment (i.e. Alzheimer's disease, mild cognitive impairment), component of frailty (i.e. gait, sarcopenia, grip strength, physical activity) as stated in the study or a combination of both was considered cognitive frailty. Operational definitions for the frailty and cognitive frailty phenotypes differed among studies; the frailty phenotype (n = 32) using the Cardiovascular Heart Study measures (Fried et al., 2001) and Rockwood's Frailty Index (n = 2) where the most common frailty measures. The Supplementary appendix (Table B) shows the complete list of phenotypes, frailty measures, clinical, and protein biomarkers extracted. Tables 1–3 show the biomarkers extracted by phenotype in the following categories: clinical, inflammatory/immunity, laboratory, protein, metabolomics, and oxidative stress.

3.2. Clinical markers

Several of the studies reported clinical findings associated with cognitive impairment, frailty, and cognitive frailty. Demographics such as increasing age was a factor for all phenotypes, lower education and income were factors for individuals with cognitive impairment 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 impairment (Lancôt et al., 2014; Qiu et al., 2014). Additionally, there was a significant interaction between ACE inhibitor use and carriers of *ApoE4* (odds ratio: 20.9, 95% CI 3.08–140.95, $p = .002$) (Qiu et al., 2014). Anticholinergic burden was found to be associated with cognitive impairment and frailty. Many of the medications used to control multiple chronic conditions in older adults (e.g., depression, hypertension, and heart failure) have unintended anticholinergic effects on the neurotransmitter acetylcholine in the central and peripheral nervous system (Nishtala et al., 2016; Salahudeen and Nishtala, 2016). The cumulative effects of these unintended anticholinergic properties are referred to as anticholinergic burden (ACB) (Fox et al., 2014; Jansen and Brouwers, 2012; Nishtala et al., 2016). For every ACB medication added, the Mini-Mental State Exam (MMSE) score decreases 0.33 points over 2 years, risk of cognitive decline is 46% over 6 years (Campbell et al., 2010; Fox et al., 2011a, b), and risk of transitioning from non-frail to frail is 73% (Jansen et al., 2016). Increased levels of

exposure to anticholinergic drugs are correlated with dementia ($p = .05$ to $< .001$) (Campbell et al., 2010; Fox et al., 2011a, b; Pfistermeister et al., 2017) and worsening Alzheimer's disease (AD) ($p < .001$) (Gray et al., 2015). 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 (Jansen et al., 2016; Kolanowski et al., 2015; Lanctot et al., 2014; Risacher et al., 2016; Uusvaara et al., 2009). Methods for measuring medication burden varied significantly between studies making it difficult compare study results. Thus, further research is need to understand ACB-associated cognitive impairment in frail older adults and how this issue might be managed (Salahudeen and Nishtala, 2016).

3.3. Inflammatory/Immunity markers

There were twenty neuroinflammatory markers are associated with both cognitive impairment and physical frailty. These included: elevated levels of IL6, C-reactive protein (CRP), tumor necrosis factor (TNF-alpha), uric acid, IL1-beta, IL1-alpha, erythrocyte sedimentation rate (ESR), cortisol/dehydroepiandrosterone ratio, IL1RA, CD4, CD8, IL6R, IL-18, TNF-a receptor I (TNFR1), cortisol, homocysteine, fibrinogen, Intercellular Adhesive Molecule-1 (ICAM-1), circulating osteogenic progenitor (COP) cells, and beta 2-microglobulin (B2M). Neuroinflammatory markers IL-6, TNF-alpha, and CRP were found to be elevated in older adults with sarcopenia. ICAM-1 was found to be elevated for both cognitive impairment and physical frailty (Lee et al., 2016; O'Bryant and Waring, 2010). Studies have shown ICAM-1 to be associated with enhanced production of IL-6, TNF-alpha suggesting that it activates a pro-inflammatory cascade (McCabe et al., 1993). ICAM-1 is associated with vascular inflammatory processes related to atherosclerosis, cerebral small vessel disease (Rouhl et al., 2012). The presence of the hypothalamic-pituitary-adrenal (HPA) axis hormones such as dehydroepiandrosterone can interact with inflammatory markers to influence disease. Additionally, all the neuroinflammatory markers associated with cognitive frailty were associated with either cognitive impairment or physical frailty. These neuroinflammatory cytokines were found to be associated with cognitive impairment and frailty in cross-sectional and longitudinal studies suggesting that these markers could be both early and persistent markers. This relationship should be explored further with clinical markers such as gender and body mass index (Gale et al., 2013).

3.4. 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 low levels of total testosterone associated with decreased lean muscle mass and cognitive impairment. 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 impairment, frailty, and mortality (Baylis et al., 2013; Cohen et al., 2015; Gruenewald et al., 2009; Heringa et al., 2014; Kobrosly et al., 2012; O'Bryant and Xiao, 2010).

3.5. 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 (Mattsson et al., 2013). None of these markers (i.e. p-tau, Apeta-42) have been studied in frailty. Two markers measured by serum/plasma were associated with both cognitive impairment 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 Apeta peptide through *ADAM10* (Kumar et al., 2013). Concentrations of sirtuin 1 decline with age but the decline was found to be more significant in individuals with cognitive impairment and frailty compared to age matched healthy individuals (Kumar et al., 2013, 2014). Additionally, cystatin C has been thought to bind to soluble Apeta preventing accumulation in the brain (Sundelof et al., 2008). Decreased serum cystatin C has been associated with higher risk for cognitive impairment and gait speed decline (Liu et al., 2014; Yaffe et al., 2008).

3.6. 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 (Inglés et al., 2014). Both are associated with frailty and cognitive impairment however, do not predict the development or progression of disease (Baldeiras et al., 2010; Inglés et al., 2014).

3.7. Genomic markers

The Supplementary Appendix Table C shows a complete list of genetic markers identified by phenotype. Six genes were found to be associated with cognitive impairment, physical frailty, and sarcopenia in candidate gene studies: *IL6* rs1800796, *TNF* rs1800629, *IL-18* rs360722, *IL1-beta* rs16944, and *COMT* with different SNPs, rs4680 for cognitive decline and rs4646316 for frailty. *IL6* and *TNF*, *IL-18*, *IL1-beta* have corresponding serum markers that are associated with both phenotypes (see inflammatory/immunity markers) (Baune et al., 2008; Dixon et al., 2014; Mekli et al., 2016; Patel et al., 2014). There are 13 serum biomarker and gene correlations, these are shown in Table 4. Further evaluation is needed to determine clinical relevance and if there is a direct correlation between gene expression and serum marker function.

4. Discussion

It has previously been postulated that a dysregulation across multiple systems may be the potential cause for both cognitive impairment and frailty (Cohen et al., 2015; Gruenewald et al., 2009; Kobrosly et al., 2012). The results from this systematic review provide biological

plausibility for the novel cognitive frailty construct. 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 methods 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 (Cohen et al., 2015; Gruenewald et al., 2009; Kobrosly et al., 2012; O'Bryant and Xiao, 2010). Of important note, are the findings of shared pro-inflammatory cytokines (*e.g.*, *IL-6*, *TNF-alpha*, *IL-18*, and *IL-1-beta*) and associated genetic variants that influenced the production of circulating proteins for both physical frailty and cognitive decline. Specifically, *IL6* rs1800796, *TNFR* rs1800629, *IL-18* rs360722, and *IL1-beta* rs16944 suggesting that they are clinically relevant SNPs. Chronic inflammation provides a basic mechanism for a shared pathogenesis of cognitive impairment and physical frailty. The concept of “inflammaging” (Franceschi et al., 2018) may provide a clinical and research framework to explore low-grade chronic inflammatory markers associated with vascular inflammatory processes related to atherosclerosis and cerebral small vessel disease leading cognitive frailty. Co-founding psychosocial and behavioral findings include depression and low health knowledge/ self-efficacy which decrease physiological reserves causing a decline in the ability to maintain allostasis leading to increased vulnerability to cognitive frailty.

Further defining the putative biomarkers related to cognitive frailty will lead to a better understanding of the interrelated neuropathology between physical frailty and cognitive impairment and, ultimately, to the development of targeted interventions focused on the prevention of cognitive and functional disabilities. Future research should focus on using systems biology approaches such as allostatic load index or boosted trees models which can include multiple markers of disease to build an accurate prediction model for the detection of cognitive impairment, frailty, and cognitive frailty. Integrating multiple biomarkers has the potential to help us better understand the complex physiological interactions of aging diseases. Such validated models for disease detection would be invaluable in the early detection and prevention of diseases unique to aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
PRISMA flow diagram of study selection and citation analysis.

Table 1

Cognitive decline biomarkers by category.

Inflammatory/Immunity Markers	Laboratory Markers	Protein Markers	Metabolomics Markers	Oxidative Stress Markers	Clinical Markers
C-reactive protein	Albumin	Aβ 1–40/t-tau ratio	Docosahexaenoic acid (DHA)	F2-isoprostanes/ isoprostanes	Elevated blood pressure
IL6	Olfactory marker	Aβ42	Sphingolipid-SM(d18:1/18:0)	Choline plasmalogen(PlsCho)	Anticholinergic Medications
Homocysteine	Ocular marker Aβ 1–42	Aβ 1–42	sphingomyelin [SM(39:1)]	Glutathione peroxidase (GSH-Px)	Body Mass Index
Tumor necrosis factor (TNF-alpha)	Folate	PhosphoTau181 (P-tau 181)	SM/ceramide ratio	Total antioxidant status (TAS)	Alcohol Intake
YKL-40 (neuroinflammation or Chitinase-3 Ch3L3)	Creatinine	P-tau	SM/ceramide ratio	Peroxisomal b-oxidation levels	Elevated Systolic pressure
Cortisol	Cobalamin deficiency (B12)	Aβ1-42/ Aβ1-40 ratio	PC aa 36:1 Glycerophospholipids	Ethanolamin plasmalogen (PlsEin)	Elevated diastolic pressure
IL8	Platelet distribution width (PDW)	Aβ 1–40	PC aa 32:0 Glycerophospholipids	PLsCho + PlsEin	Increase waist circ/waist-to-hip
TNF-a receptor 1 (TNFR1)	Nutrient biomarker patterns (NBP)	P-tau231	PC 16:0/20:5 phosphatidylcholine	PLsCho/PlsEin Ratio	Change in resting hear rate
Fibrinogen	Blood urea nitrogen (BUN)	Aβ40	PC 16:0/22:6 phosphatidylcholine	Plasmalogen	Cardiovascular disease
Uric Acid	Methylmalonic acid (MMA)	P-tau181/Aβ42	PC 18:0/22:6 phosphatidylcholine	Protein carbonyls	Benzodiazepine medications
Monocyte chemotactic Protein-2 (MCP-2)	Glucose	Cystatin C	Ceramides C16:0	Malondialdehyde (MDA)	Angiotensin converting enzyme medications
Resistin	Insulin resistance (IR-HOMA)	t-tau/ Aβ42	Ceramides C20:0	Ceramides C20:0	Psychoactive medications
IL10	Lipids: Triglycerides	Aβ 1–42/t-tau ratio	Ceramides C22:0	Ceramides C22:0	Low level of education
IL1beta	Lipids: LDL cholesterol	Apolipoprotein A-I (ApoAI)	Ceramides C24:0	Ceramides C24:0	Instrumental activities of daily living (IADL)
IL17E	Lipids: HDL cholesterol	Brain derived neurotrophic factor (BDNF)	Ceramides C26:0	Ceramides C26:0	Activities of daily living (ADLs)
Clusterin	Free Testosterone	Lysosomal-associated membrane	Stearoyl		
protein 1 (LAMP-1)					
TNF-a receptor II (TNFR2)	Insulin like growth factor protein (IGF-1)	sAβ/APP ratio	Eicosapentaenoic acid (EPA)		
Macrophage Migration Inhibitory Factor (MIF)	Insulin like growth factor protein (IGF-2)	Aβ42/ Aβ40			
Cortisol/Dehydroepiandrosterone ratio	Insulin like growth factor protein Binding Protein (IGFBP-2)	Neurofilament light chain (NFL)			
	Insulin like growth factor protein Binding Protein (IGFBP-3)	Apolipoprotein A-II (ApoA2)			
Vascular cell adhesion molecule 1 (VCAM1)	Anemia	Complement factor H (CFH) protein 1			
Soluble receptor for advanced glycation end products (sRAGE)	Hemoglobin	Chromogranin A (CgA)			
Plasma Pentraxin 3 (PTX3)	Polyunsaturated fatty acids (O3PUFAs)/	Visinin-like protein-1 (VILIP-1)			
alpha 2-macroglobulin (A2M)					

Inflammatory/Immunity Markers	Laboratory Markers	Protein Markers	Metabolomics Markers	Oxidative Stress Markers	Clinical Markers
Adiponectin	n-6/n-3 ratio				
IL1	alpha-1-antichymotrypsin (ACT)	β-secretase (BACE-1)			
IL6R	Vascular endothelial growth factor (VEGF)	Ubiquitin			
IL13	Peroxidase	Heat shock protein 70			
IL1RA	Creatinine Clearance	Epidermal growth factor (EGF)			
IL7	N-acetylaspartate (NAA)/creatinine (Cr)	Pancreatic peptide (PP)			
IL12p70	Methyletric acid (MCA)	Soluble amyloid β protein (sAβ)			
D-dimer	Holotranscobalamin (holoTC)	Amyloid β precursor protein (APP)			
Procalcitonin	Glycohemoglobin (HbA1c)	Aβ 1-42/p-tau ratio			
Erythrocyte sedimentation rate (ESR)	Lipids: Total Cholesterol	P-tau231/Aβ42/40 ratio			
GlycA	24S-hydroxycholesterol	T-tau/Aβ42/40 ratio			
Macrophage inflammatory protein 1-alpha (MIP 1α)	Aspartate transaminase (AST)	Apolipoprotein C2			
Plasminogen activator inhibitor (PAI-1)	Macrophage inflammatory protein 1-alpha (MIP 1α)	Apolipoprotein H			
Serum Amyloid A	Total Testosterone	ApoB/ApoA1 ratio			
Fibrinogen gamma-chain	Total Bilirubin	A1AcidG			
Neural cell adhesion molecule (NCAM)	Vitamin E	Transthyretin (TTR)			
Adhesion molecule soluble intercellular adhesion molecule-1 (sICAM-1)	Vitamin D	Ceruloplasmin			
Soluble receptor for advanced glycation end products (sRAGE)	Vitamin C	Cathepsin D			
Neutrophil/Lymphocyte ratio	Beta-Carotene	Glycogen synthase kinase-3 (GSK3-α)			
Monocyte chemotactic protein-1 (MCP-1)	Calcium	Neuronal Cell Adhesion Molecule (NfCAM)			
CD40	Nitrate2+Nitrate3	Ax1 receptor tyrosine kinase (AXL)			
IgG2	Selenium	VILIP-1/Abeta 1-42			
IgA	Hematocrit	Sirtuin/SIRT1			
P-selectin	Mean platelet volume (MPV)	Aβ/β-actin			
Matrix Metalloproteinase-10 (MMP-10)	Transferrin	α-secretase (ADAM10)			
Chemokine receptor 2 (CCR2) (protein2 list)	Haptoglobin	Rab3			
Beta 2-microglobulin (B2M)	White blood cells (WBC)	Rab7			
FAS ligand belongs to TNF family	Total Urinary polyphenols (TUPs)	Early Endosome Marker (EEA1)			
	Alpha-1-antitrypsin (alpha 1-AT)	Lysosomal-associated membrane			

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Inflammatory/Immunity Markers	Laboratory Markers	Protein Markers	Metabolomics Markers	Oxidative Stress Markers	Clinical Markers
CD8	Lactoferrin (LTF)	protein 2 (LAMP-2)			
		Microtubule-associated protein 1A/1B-light chain 3 (LC3)			
	N-terminal pro b-type natriuretic peptide (NT-proBNP)	Phospholipase A2 (PLA2)			
		Carcinoembryonic antigen Osteoprotegerin (OPG) Nervegrainin (NGRN) Cellular prion protein (PrPc) Kidney Injury Molecule (KIM-1) Growth-regulated alpha protein (GRO-α) Unfolded p53 P-t181p/Abl-42 ratio			
	Luteinizing hormone (LH)				

Table 2

Frailty biomarkers by category

Inflammatory/Immunity Markers	Laboratory Markers	Protein Markers	Metabolomics Markers	Oxidative Stress Markers	Clinical Markers
IL6	Vitamin D	Propeptide of type I procollagen (PINP)	X12063	Serum 8-hydroxy-2-deoxyguanosine (8-OHdG)	Cardiovascular disease
C-reactive protein	Albumin	C-terminal telopeptide of type-I collagen(Beta CTX)	Urate	Protein carbonyls	Increase Waist Circ/Waist-to-hip
Tumor necrosis factor (TNF-alpha)	Composite Score (multiple markers)	Extracellular heat shock protein (eHsp) 72	Mannose	thol level (TTL)	Calibrated Protein intake
Uric Acid	Lipids: Total Cholesterol	Cystatin C	Myostatin	Derivate of reactive oxygen metabolites (d-ROM)	Increased falls
Fibrinogen	Insulin like growth factor protein (IGF-1)	Cytomegalovirus		Malondialdehyde (MDA)	Alcohol intake
IL1beta	Parathyroid hormone (PTH)	C-terminal Agrin Fragment (CAF)			Body Mass Index
Erythrocyte sedimentation rate (ESR)	White blood cells (WBC)	Sirtuin 1			> 2 chronic diseases
Cortisol/Dehydroepiandrosterone ratio	Insulin resistance (IR-HOMA)	Sirtuin 2			Anticholinergic medications
IL1RA	Creatinine	Sirtuin 3			
Motif chemokine 10/ Interferon-gamma (CXCL-10/IFN-gama)	Glycohemoglobin (HbA1c)	Complement component protein (Clq)			
CD8	Hemoglobin	Klotho			
Dehydroepiandrosterone sulphate (DHEAS)	Lymphocytes	Lipopolysaccharide binding protein (LBP)			
IL2	Estimated glomerular filtration rate (eGFR)				
IL18	Methylmalonic acid (MMA)				
TNF-a receptor 1 (TNFR1)	Carotenoids				
IL6R	Cobalamin deficiency (B12)				
Cortisol	Lipids: Triglycerides				
Homocysteine	Neutrophils				
Beta 2-microglobulin (B2M)	Follistatin				
	Urine albumin-creatinine ratio				
	Vitamin A				
	Vitamin B1				
	Vitamin B6				
	Phosphorus				

Table 3

Cognitive frailty biomarkers by category.

Inflammatory/Immunity Markers	Laboratory Markers	Protein Markers	Clinical Markers
C-reactive protein	Creatinine Clearance	Apolipoprotein A-I (ApoA1)	Body Mass Index
IL6	Cobalamin deficiency (B12)	Prostaglandin F2-alpha	> 2 chronic diseases
Dehydroepiandrosterone sulphate (DHEAS)	Insulin like growth factor protein (IGF-1)	Apolipoprotein B	Income
IL8	Vitamin D		Low level of education
IL1beta	White blood cells (WBC)		Alcohol intake
IL1alpha	Albumin		Elevated blood pressure
Fibrinogen	Creatinine		Elevated systolic pressure
CD8	Glucose		Cardiovascular disease
Homocysteine	Glycohemoglobin (HbA1c)		Psychoactive medications
Cortisol	Lipids: LDL cholesterol		Depression
CD4	Alpha-linolenic acid		Activities of daily living (ADL)
Circulating Osteogenic Progenitor (COP) cells	Sodium		Instrumental activities of daily living (IADL)
Intercellular Adhesive Molecule-1	Monocytes		
	Neutrophils		
	Urate		
	Glucose		
	Total protein		
	Alanine aminotransferase (ALT)		
	Calcium		
	Lipids: Triglycerides		
	Lipids: Total Cholesterol		
	Free thyroxine, fT4		
	Ferritin,		
	Lipids: HDL cholesterol		
	Free thyroxine, fT3		
	Red blood cells (RBC)		
	White blood cells (WBC)		
	Lymphocytes		

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Inflammatory/Immunity Markers	Laboratory Markers	Protein Markers	Clinical Markers
	Hemoglobin		
	Phosphate		
	Polyunsaturated fatty acids (O3PUFAs)/ n-6/n-3 ratio		
	Hematocrit		

Serum and gene correlations by phenotype Genetic.

Table 4

Serum biomarker	Phenotype associated with serum biomarker	Genetic biomarker	Phenotype associated with genetic biomarker
Vitamin D (25(OH)D)	Frailty and cognitive decline	<i>VDR</i> (Vitamin D receptor)	Sarcopenia
Cystatin C	Frailty and cognitive decline	<i>CST3</i> (cystatin)	Cognitive decline
Chemokine receptor 2 (CCR2)	Cognitive decline	<i>CCL2</i>	Cognitive decline
Myostatin	Frailty	<i>MSTN</i> (myostatin)	Sarcopenia
Klotho	Frailty	<i>KLOTHO</i>	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-1beta	Frailty and cognitive decline	IL-1beta	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

Note: see Supplementary Appendix Table C for full list of genes and references.