

THEORETICAL ARTICLE

Shared mechanisms for cognitive impairment and physical frailty: A model for complex systems

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Abstract

Introduction: We describe findings from a large study that provide empirical support for the emerging construct of cognitive frailty and put forth a theoretical framework that may advance the future study of complex aging conditions. While cognitive impairment and physical frailty have long been studied as separate constructs, recent studies suggest they share common etiologies. We aimed to create a population predictive model to gain an understanding of the underlying biological mechanisms for the relationship between physical frailty and cognitive impairment.

Methods: Data were obtained from the longitudinal “*Invecchiare in Chianti*” (Aging in Chianti, InCHIANTI Study) with a representative sample ($n = 1453$) of older adults from two small towns in Tuscany, Italy. Our previous work informed the candidate 132 single nucleotide polymorphisms (SNPs) and 155 protein biomarkers we tested in association with clinical outcomes using a tree boosting, machine learning (ML) technique for supervised learning analysis.

Results: We developed two highly accurate predictive models, with a Model I area under the curve (AUC) of 0.88 (95% confidence interval [CI] 0.83-0.90) and a Model II AUC of 0.86 (95% CI 0.80-0.90). These models indicate cognitive frailty is driven by dysregulation across multiple cellular processes including genetic alterations, nutrient and lipid metabolism, and elevated levels of circulating pro-inflammatory proteins.

Discussion: While our results establish a foundation for understanding the underlying biological mechanisms for the relationship between cognitive decline and physical frailty, further examination of the molecular pathways associated with our predictive biomarkers is warranted. Our framework is in alignment with other proposed biological underpinnings of Alzheimer’s disease such as genetic alterations, immune system dysfunction, and neuroinflammation.

KEYWORDS

bioinformatics, cognitive frailty, cognitive impairment, frailty, machine learning

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1 | INTRODUCTION

1.1 | Objective

We present data from a large study that provide empirical support that there are shared clinical and biological mechanisms for cognitive impairment and physical frailty, termed “cognitive frailty.”¹ Our results suggest that a larger number of prognostic factors contribute to the heterogeneity seen in Alzheimer’s disease (AD) than is currently recognized. Based on these study findings, we propose an updated hypothesis of multi-system dysfunction that will help operationalize the emerging understanding of cognitive frailty and advance the future study of complex aging conditions.

1.2 | Historical evolution and rationale

Associating cognitive impairment and physical frailty began approximately 20 years ago in studies of individuals with mild cognitive impairment (MCI) and AD. Prior to that time, few older adults with cognitive impairment were included in frailty studies.² The term “cognitive frailty” was first used in 2001 in relation to the clock drawing task as a measure for identifying individuals at high risk for AD.³ Since 2001, definitions of cognitive frailty have evolved as shared features between physical frailty and cognitive impairment were identified and described. In 2013, the International Consensus Group from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) examined this connection based on epidemiologic evidence and common etiologies suggesting that cognitive frailty may represent a precursor to neurodegenerative disorders.¹ The recommendations from IANA “Cognitive Frailty: Rationale and Definition” now provide a foundation from which to study the complex heterogeneity seen in AD.¹ Evidence of a common pathophysiology between the two conditions is mounting, including a shared brain AD pathology found in individuals with physical frailty.^{4,6-8}

Physical frailty and cognitive impairment are considered complex aging syndromes with pathology that often involves more than one physiological system. In studying complex aging syndromes, scientists have often focused on a small number of variables in association with one type of pathology or phenotype. Yet, a growing number of seemingly unrelated factors are now associated with dementia risk including: impaired sleep, depression, inflammation, toxicity exposure (eg, pesticides, medications), and vascular and genetic risk factors.⁹⁻¹¹ These risk factors collectively can cause a “deficit accumulation.”⁹ Deficit accumulation occurs when the number of insults to the body surpasses the ability for the damage to be removed or repaired.¹² Therefore, research that accounts for multiple risk factors using system-based approaches has the potential to greatly facilitate our understanding of complex aging syndromes.⁸

Such considerations also inform our approach with the view that machine learning (ML) statistical approaches can model complex biological systems such as diseases of aging. One emerging analytical tool

RESEARCH IN CONTEXT

1. Systematic review: The study was informed by a previously published systematic review using traditional sources (e.g., PubMed) to investigate shared biological predictors for cognitive frailty. While there is shared pathophysiology, there have been few studies exploring the biological predictors for individuals presenting with cognitive frailty. These relevant citations are appropriately cited.
2. Interpretation: Our findings led to an updated hypothesis describing cognitive frailty as a result of multi-system dysfunction. This hypothesis closely aligns with the aging theory of cellular senescence; the concept of biological cellular damage and aberrant gene expression.
3. Future directions: We propose a theoretical framework and two statistical models that will allow for the generation of future hypotheses, and that can guide the design of additional studies of complex aging. Future exploration can include: (a) patterns of biomarker change, disease progression, and directions and rates of change over time; (b) the potential pathways associated with significant genes and protein biomarkers; (c) the relationship between high risk medications and associated gene variants for drug metabolism; and (d) the role of cellular senescence in cognitive frailty.

is the use of bioinformatics; the process of analyzing complex biological data such as genetic codes with ML predictive analytic methods. ML methods for studying large amounts of available clinical and biological (“big-omics”) data can be hypothesis generating, expand our capacity to learn from data, and accelerate discovery and disease prediction with the potential to impact clinical care.¹³

In recent studies, our team has demonstrated ML methods to be effective in distinguishing patients with Parkinson’s disease from healthy patients and identifying individuals with prodromal or preclinical Parkinson’s disease.¹² We now seek to apply these methods to understanding the clinical and biological factors for individuals with cognitive frailty.

1.3 | Updated hypothesis

Our study design was informed by findings from a previously published systematic review. In this review we collated results from previous studies on physical frailty and cognitive impairment and examined the overlap between predictive variables in these two historically independent conditions.¹⁴ From a review of 342 studies, 456 protein and genetic single nucleotide polymorphisms (SNPs) were found to be predictive of both physical frailty and cognitive impairment. From this systematic review we identified overlapping cardiovascular risk

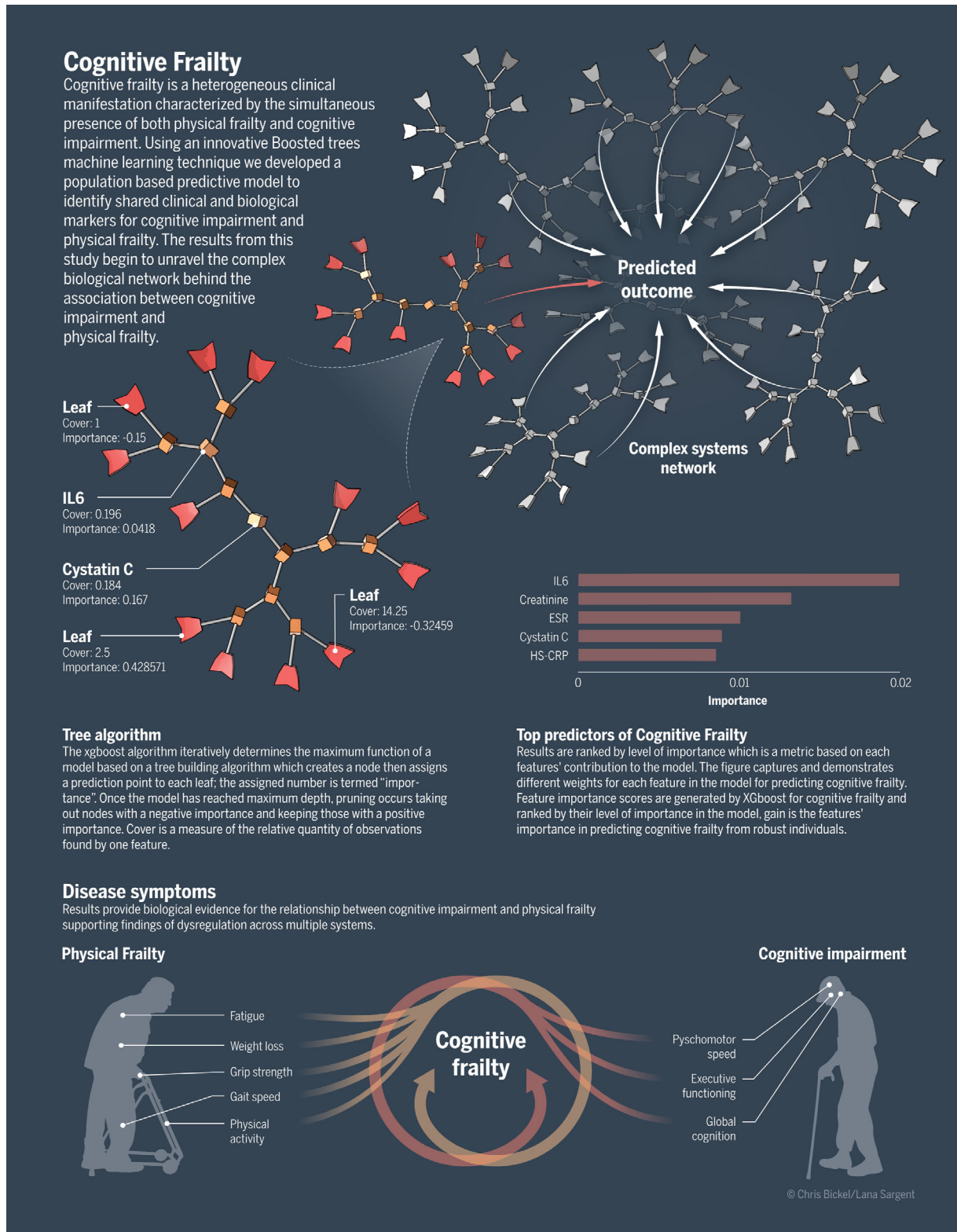


FIGURE 1 Theoretical framework for future study of cognitive frailty

factors (diabetes, dyslipidemia, hypertension); neuroinflammatory proteins (IL-6, tumor necrosis factor [TNF]-alpha, IL-18, and IL-1 beta) and their associated SNPs (IL6 rs1800796, TNF rs1800629, IL-18 rs360722, and IL1-beta rs16944); and multi-system physiological changes such as nutritional, hematologic, renal, and hormonal

biomarkers.¹⁴⁻¹⁷ These findings informed the current study goal to explore multi-system dysfunction as the underlying pathology for the association of physical frailty with cognitive impairment. Herein, we put forth a theoretical framework of complex systems for the future study of cognitive frailty (Figure 1).

2 | METHODS

2.1 | Study design

Participants were a part of the longitudinal study in aging *Invecchiare in Chianti*. All human subjects provided informed consent and all sample and data collection was approved by the ethics committee at Centre de recherche Clinique du CHUS. Two statistical predictive models were built to evaluate genetic variants (eg, SNPs), protein expression, and clinical markers as predictors of cognitive frailty. Model I tested prediction of genetic, protein, and clinical markers of cognitive frailty using criteria from the Mini-Mental State Examination (MMSE), while Model II tested prediction of genetic, protein, and clinical markers of cognitive frailty with additional neuropsychological testing using the Trail Making Tests (TMT, Part A and B).^{18,19} Three instruments were used to measure neuropsychological dimensions of cognitive frailty as determined by Delrieu et al.²⁰ The MMSE as a test of global mental status, the TMT-A as a test of executive function, and the TMT-B to assess attention.²¹ TMT, part A and B cutoff scores are based on established norms for mild neurocognitive disorders,¹⁹ and normative data for time to complete the TMT tests in seconds was stratified by age and education category.¹⁹ The criteria of cognitive impairment was based on an MMSE score ≤ 23 , a TMT-A ≥ 78 , and a score of ≥ 106 on the TMT-B.^{18,19} The InCHIANTI criteria for frailty is defined by Fried et al. as exhaustion, slowness, low physical activity, weakness, and weight loss.² Additional description of the InCHIANTI data collection and frailty classifications have been previously published.^{22,23} Individuals with evidence of both physical frailty and cognitive impairment without a baseline clinical diagnosis of AD or other dementia were defined as having the cognitive frailty phenotype.²⁰ (See the Appendix in supporting information for study population and measurement details.) Based on our previously published systematic review, which identified shared biological markers for physical frailty and cognitive impairment, we tested 132 SNPs and 155 protein biomarker (total of 287) variables that were available in the InCHIANTI database in association with frailty and cognitive impairment (see the Appendix in supporting information for biomarker details).¹⁴

2.2 | Statistical approach

In this cross-sectional study we used Extreme Gradient Boosting (*xgboost*) in R statistical software, to build a reproducible predictive model with large numbers of predictors. *xgboost* provides more efficient and accurate predictive modeling with large datasets and a rapid effective framework for feature selection.²⁴ The advantage of using a tree boosting approach model for the evaluation of multiple variables simultaneously is that it provides a high predictive value with low bias.²⁴ Boosted trees use individual decision trees that account for multi-collinearity between variables and that retain only the best features in the final model.²⁴ Additionally, parameters are set to prevent overfitting of the models. The statistical analysis was completed in three steps: (1) analysis of all available variables for feature selection

and data reduction; (2) model discovery followed by model validation; and (3) univariate analysis, *t*-tests for continuous, and chi-squared tests for binomial traits with a Bonferroni correction used to determine the significance of the variables between cognitive frailty and healthy older adults. To evaluate additive effects of the SNPs, a positive regression coefficient was used to indicate that each copy of the allele of interest increased the risk for cognitive frailty.²⁵

To evaluate the statistical models, we used the metric “area under the curve” (AUC). AUC was calculated from each model and used to determine discrimination of participants with cognitive frailty (cases) from healthy older adults (controls) in the training cohort. Covariates were selected to control for potential confounding effects, including sex, age, education, baseline diagnosis of dementia ($n = 82$), vascular dementia ($n = 41$), depression ($n = 412$), and Parkinson's disease ($n = 16$). (See the Appendix in supporting information for workflow and statistical analysis details.)

3 | RESULTS

Of the 1453 adults participating, 1326 provided blood samples at study entry. (See Table 1 for sample characteristics of participants with cognitive frailty.) For discrimination of participants with cognitive frailty versus healthy older adults, the AUC of Model I was 0.88 (95% confidence interval [CI] 0.83–0.90) and 0.86 (95% CI 0.80–0.90) for Model II. We noted a normal distribution of AUCs across all iterations, with no statistically significant deviation from the expected values in any group, suggesting a good model fit. Both models showed high accuracy with AUCs ranging from 0.81–0.88 for Model I and 0.81–0.86 Model II.

The biomarkers identified as statistically significant between healthy older adults and individuals with cognitive frailty are discussed below. Biomarkers are ranked by level of importance based on its contribution to the model in Figures 2 and 3. (See Appendix Tables III–IV in supporting information for detail on significant biomarkers and association with specific cognitive domains.)

3.1 | Genomic predictors of cognitive frailty for Models I and II

Table 2 represents statistically significant gene polymorphisms (SNPs) for cognitive frailty. SNPs with significant differences between healthy older adults and cognitive frailty included: Model I (*ACOT11*) rs12752888 ($P = .001$), *DAB1* rs1539053 ($P = .01$), (*MMP3*) rs948399 ($P = .01$), *CD33* rs3865444 ($P = .03$), *MTRR* rs1801394 ($P = .001$), and Model II (*ACOT11*) rs12752888 allele C (TMT, $P = .01$), apolipoprotein E (*APOE*) rs429358 allele C ($P = .01$), *SLCO1B1* rs4363657 allele C ($P = .02$), *TOMM40* rs8106922 allele G ($P = .05$), and (*MMP3*) rs948399 allele C ($P = .05$). In this study, genetic factors for cognitive frailty support functional genes that have been associated with AD and physical frailty. These include genes such as *APOE* allele C that is associated with executive function, *TOMM40* associated with attention, rs12752888 allele C associated with all domains of

TABLE 1 Sample characteristics of participants with cognitive frailty for Model I and Model II

	Model I		P-value	Model II		P-value
Phenotype (n)						
Control	898			733		
Cognitive Frailty	257			412		
Sex, (n)	Male	Female		Male	Female	
Control	418	480		372	372	
Cognitive frailty	82	175		150	150	
Age, mean (SE)						
Control	73 (0.22)		<.0001	61 (.50)		<.0001
Cognitive frailty	82 (0.41)			76 (.67)		
Anticholinergic Burden, mean (SE)						
Control	2.2 (0.10)		<.0001	1.9 (.08)		<.0001
Cognitive frailty	3.0 (0.21)			3.0 (.21)		
Education, %	≥High school			≥High school		
Control	6%		<.0001	10%		<.0001
Cognitive frailty	0			2%		

Abbreviation: SE, standard error

cognitive decline, *DAB1* associated with global cognition, and *MTRR* polymorphisms linked to two to four times greater odds of having physical frailty.²⁶ The level of importance and contribution of each SNP in predicting cognitive frailty can be evaluated amongst other biological markers in the statistical model (see Figures 2 and 3).

3.2 | Medication genetic variants and risk

One of the interesting genomic findings was the *SLCO1B1* rs4363657 allele C ($P = .02$) in predictive Model II. *SLCO1B1* has been associated with the metabolite X12063, both of which are markers of lean muscle mass loss.²⁷ *SLCO1B1* has been linked to drug metabolism that results in higher blood concentrations of statins.²⁸ *SLCO1B1* is essential for drug hepatic uptake and the C variant is associated with reduced *OATP1B1* activity. *OATP1B1* can facilitate drug uptake at the blood-brain barrier and may lead to drug toxicity in the central nervous system.²⁹ Additionally, anticholinergic medications were significantly associated with both attention (TMT-A), executive functioning (TMT-B), and global cognition for individuals with cognitive frailty. Anticholinergic drug burden (ACB) was ranked as one of the top predictors of cognitive frailty in both models. A detailed description and analysis of the relationship between ACB and cognitive frailty is available in a separate publication.¹¹

3.3 | Neuroinflammatory cytokine markers

This study found elevated levels of neuroinflammatory cytokines, specifically interleukins IL1, IL6, IL6sR 1&2, TNF-alpha, ESR, and TNFR1&2 in association with cognitive frailty. Additionally, participants with cognitive frailty had higher levels of resistin ($P < .0001$) com-

pared to healthy adults in both models; notably, resistin regulates IL-6, TNF, and C-reactive protein (hs-CRP).³⁰ Both fibrinogen ($P < .0001$) and advanced glycation end product (AGE; $P < .0001$) were found to be elevated. Such increases in AGE have been linked to oxidative stress and high levels of alpha-2 globulin (A2M; $P < .0001$) and alpha-1 globulin (A1M; $P < .0001$). A2M and A1M are protease inhibitor cytokine transporters, whose aberrant expression has been linked to AD, and in this study, were also found in participants with cognitive frailty, but not in healthy older adults.³¹ TNF-related apoptosis-inducing ligand (TRAIL) was found to be lower ($P < .0001$) in individuals with cognitive frailty. Lower serum TRAIL levels are associated with a decrease in cellular apoptosis and an increased risk of stroke and cardiovascular disease.³² Taken together, these findings support the theory of chronic neuroinflammation as playing a role in neuro-immuno-endocrine dysfunction that may contribute to cognitive frailty.³³

3.4 | Nutrient and lipid metabolism

We found distinct nutrient and lipid biomarkers were predictive of cognitive frailty. Specifically, the following nutrient pattern associated with cognitive frailty included lower levels of vitamin E alpha tocopherol ($P < .0001$), albumin ($P < .0001$), omega-6 and 3 ($P < .0001$) were found in cognitively frail older adults with global cognitive decline and lower vitamin B6 ($P < .0001$); albumin ($P < .0001$), omega-6 and 3 ($P < .001$) with poor attention and executive functioning. Low vitamin E alpha tocopherol was associated with global cognitive decline ($P < .0001$) and poor attention ($P = .037$) but not executive functioning. Interestingly, a second association pattern was characterized by low trans fats measured by low- and high-density lipoprotein (LDL and HDL). Frail older adults with poor global cognitive decline had lower levels of LDL ($P < .0001$) and HDL ($P < .047$) than healthy

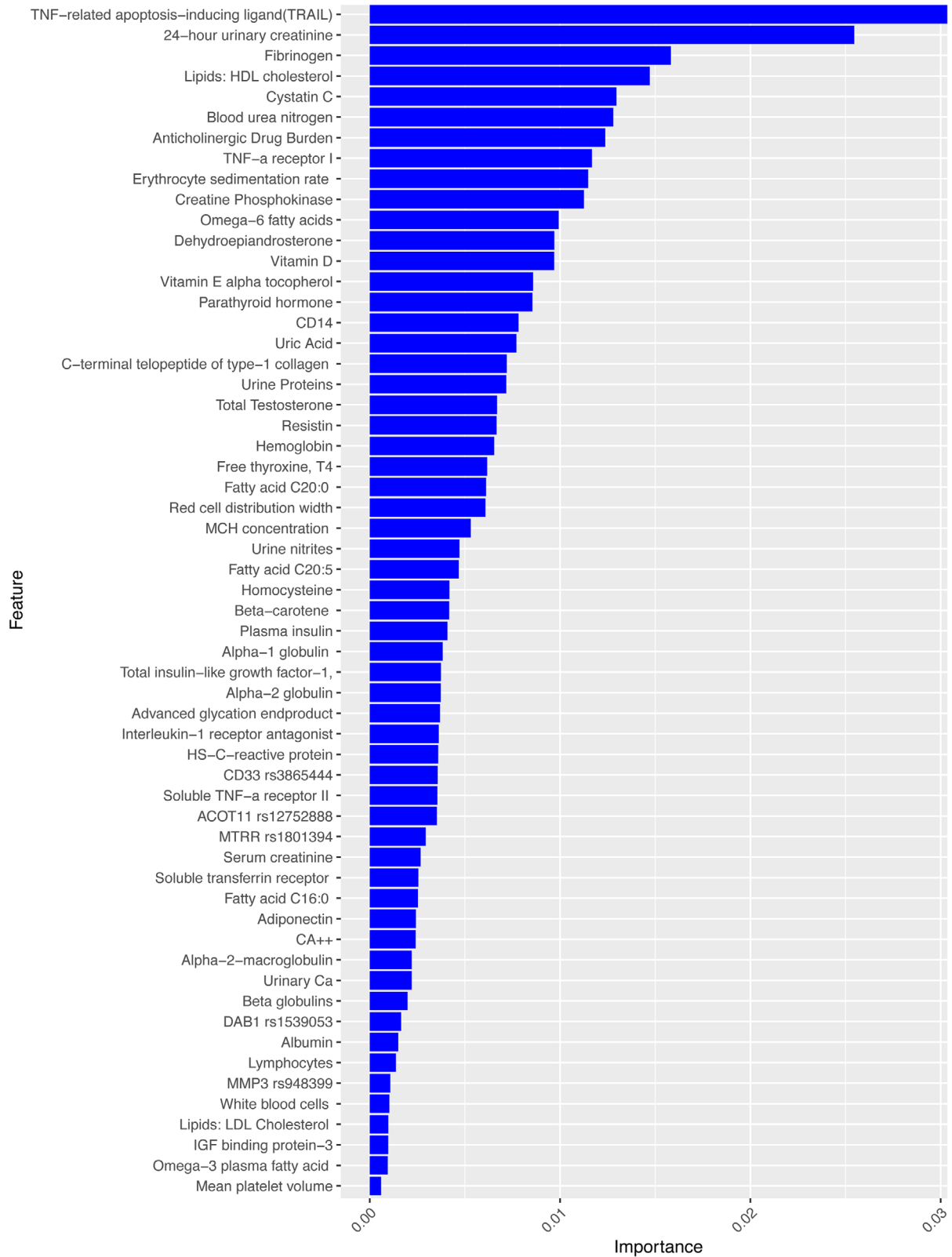


FIGURE 2 Feature importance scores for cognitive frailty in Model I. Note: Feature importance scores are generated by *xgboost* for cognitive frailty and ranked by their level of importance in the model. The figure demonstrates different weights for each feature's importance in predicting cognitive frailty from healthy individuals

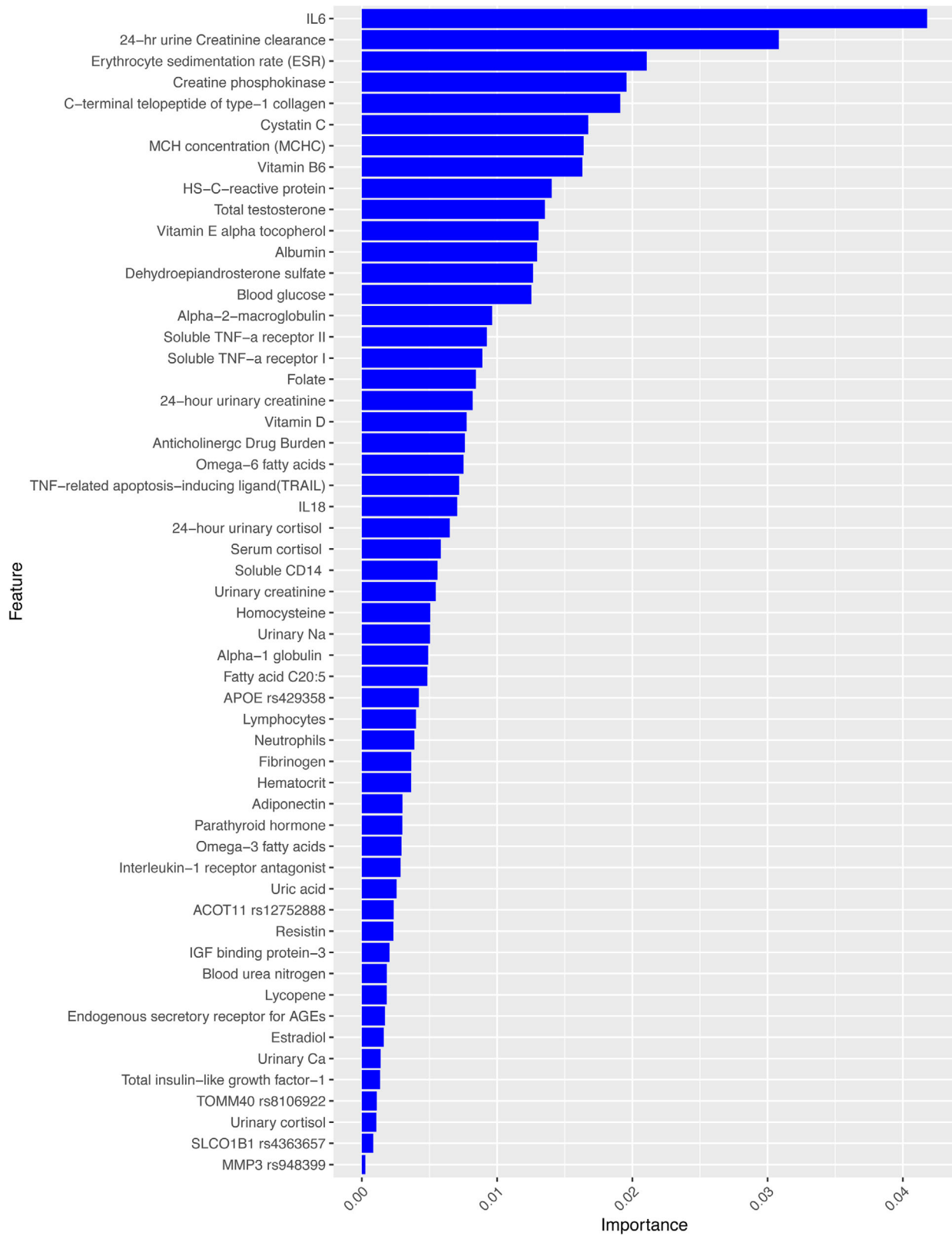


FIGURE 3 Feature importance scores for cognitive frailty in Model II. Note: Feature importance scores are generated by *xgboost* for cognitive frailty and ranked by their level of importance in the model. The figure demonstrates different weights for each feature's importance in predicting cognitive frailty from healthy individuals

TABLE 2 Genomic features for cognitive frailty Model I and Model II

Model I	Gene	SNP-associated allele	Chromosome	xgboost rank importance	β	SE	P-value
	<i>CD33</i>	rs3865444_A	19	0.0036	0.62	0.28	.03
	<i>ACOT11</i> / LOC105378734	rs12752888_C	1	0.0035	-0.47	0.18	<.01
	<i>MTRR</i>	rs1801394_G	5	0.0029	0.80	0.23	<.01
	<i>DAB1</i>	rs1539053_A	1	0.0017	0.50	0.20	.01
	<i>MMP3</i>	rs948399_C	11	0.0011	0.41	0.17	.01
Model II							
	<i>APOE</i>	rs429358_C	19	0.0042	-0.59	0.23	.01
	<i>ACOT11</i> / LOC105378734	rs12752888_C	1	0.0024	-0.37	0.15	.01
	<i>TOMM40</i>	rs8106922_G	19	0.0011	-0.31	0.16	.05
	<i>SLCO1B1</i>	rs4363657_C	12	0.0008	0.38	0.16	.02
	<i>MMP3</i>	rs948399_C	11	0.0003	0.29	0.15	.05

Notes: Statistically significant genes are shown in association with cognitive frailty compared to healthy adults Models I and II use Mini-Mental State Examination (MMSE) and Trail Making Tests (TMT) parameters, respectively, to define cognitive frailty. Bold text indicates the closest gene to an intergenic single nucleotide polymorphism (SNP). The *xgboost* rank importance: *xgboost* ranks each SNP by level of importance based on its contribution to the model. Beta coefficients, standard error (SE), and P-values for each SNP were derived from subsequent logistic regression analysis after *xgboost* ranking.

older adults. Overall, significantly lower levels of these lipids were present for older adults with cognitive frailty compared to healthy older adults.

3.5 | Metabolites

Metabolomic ceramides C16:0, C20:0, C20:5, C24:0, and C:22:0 markers were predictive of cognitive frailty in both analytic models; with significant differences in C20:0 ($P = .041$), C20:5 ($P < .0001$) and C16:0 fatty acid weight ($P = .008$) fatty acid area ($P = .013$) between cognitively frail and healthy older adults. Ceramides C16:0 and C20:0 have been associated with greater risk of impairment in attention as measured with the TMT-A,³⁴ and in this study, we found C20:5 to be lower in older adults with cognitive frailty and predictive for attention deficits as measured by TMT-A ($P = .028$) but not executive function. Additionally, serum ceramides varied with some high and others low supporting the finding that timing and onset of memory impairment may be a factor affecting levels.³⁴

3.6 | Renal function

Poor renal function was predictive of cognitive frailty; with lower 24-hour urinary creatinine ($P < .0001$), higher blood urea nitrogen (BUN; $P < .0001$), higher urine proteins ($P = .03$) and nitrates ($P < .0002$), higher serum creatinine ($P = .022$), lower serum and urinary calcium ($P < .001$), higher uric acid ($P < .01$), and higher cystatin C ($P < .0001$) than healthy older adults. Taken together, markers of poor renal function have been linked to changes in mobility disability³⁵ with higher cystatin C associated with increased likelihood of converting from MCI to AD.³⁶

3.7 | Hematologic/immune function

Iron deficient anemia was associated with individuals with cognitive frailty as noted by low hemoglobin ($P < .0001$), high red cell distribution width (RDW; $P < .0001$), low mean corpuscular hemoglobin (MCH) concentration ($P < .0001$), high soluble transferrin receptor ($P = 0.01$), and low mean platelet volume (MPV; $P = .08$). Furthermore, immune dysfunction was indicated by high white blood cell count (WBC; $P = .007$), low lymphocytes ($P < .0001$), high neutrophils ($P < .0001$), and low CD14 ($P < .0001$). Collectively, these findings support a theory of immune system dysfunction seen in both predictive models suggesting individuals with cognitive frailty have a decreased humoral immune response.³⁷

3.8 | Endocrine/hormone function

Dehydroepiandrosterone sulfate (DHEA), testosterone, and urinary cortisol were found to be low for those with cognitive frailty compared to healthy adults ($P < .001$). DHEA has been found to inhibit IL-6, thus providing a connection between endocrine and immune function.³⁸⁻⁴⁰ Another interesting finding was the connection between biomarkers of nutrition, low fatty acid levels, and high levels of c-terminal telopeptide of type-1 collagen I (PINP; $P < .0001$) and parathyroid hormone (PTH; $P < .0001$) in association with cognitive frailty. Both PINP and PTH have been linked to low levels of vitamin D ($P < .0001$), which we also found in our participants with cognitive frailty.⁴¹ Total insulin-like growth factor, plasma insulin ($P = .04$), and free thyroxine fT4 were low in individuals with cognitive frailty ($P < .0001$). Methylmalonic acid (MMA) is linked to high levels of vitamin B12 and high levels of homocysteine ($P < .0001$) together with the *MTRR* SNP rs1801394, all of which share the same pathway and are predictive of cognitive

frailty. This pathway interaction has been linked to both cognitive performance and increased risk for physical frailty.^{26,42}

Figures 2 and 3 summarize the top SNPs and protein biomarkers ranked by the level of importance in predicting cognitive frailty. These feature importance scores were generated during statistical analysis in *xgboost*.

4 | DISCUSSION

When the results are interpreted by individual biological pathways, several proposed theories on AD are supported including (1) immunological system dysfunction, (2) environmental exposures and toxicities (ie, ACB), (3) genetic factors, and (4) chronic neuroinflammation.³⁷ In contrast, when the results are summarized using the updated hypothesis of multi-system dysfunction, the findings closely align with the aging theory of cellular senescence.^{12,43,44} Cellular senescence theory is based on the concept of biological cellular damage and aberrant gene expression leading to loss of cell function and age-related disease.^{7,9,43} For example, participants with cognitive frailty had higher levels of inflammatory protein markers including; hs-CRP, resistin, and A2M compared to healthy older adults. Resistin regulates IL-6, TNF, IL-1, and A2M which are protease inhibitor cytokine transporters linked to AD.^{30,31} These findings highlight specific pathway interactions for neuroinflammatory cytokines coupled with gene SNPs associated with cellular senescence; eg, *MMP3* rs948399 and *CD33* rs3865444. Functional studies in AD have shown when *CD33* is over-expressed, microglia-mediated neuroinflammation pathways are activated and amyloid beta ($A\beta$) phagocytosis is inhibited.^{45,46} Additional markers of cellular senescence in this study include metabolomic ceramides C16:0, C20:0, and C20:5. Ceramides regulate cellular proliferation and apoptosis and have been positively correlated with the number of $A\beta$ plaques on *post mortem* biopsy.³⁴ At low levels, ceramides regulate cellular proliferation and apoptosis; at high levels they inhibit cell division and are intermediates of inflammatory cytokines and sub-clinical atherosclerosis.⁴⁷ Together, these biological markers define the senescence-associated secretor phenotype (SASP).⁴⁴ While cellular senescence in peripheral tissues has been linked to aging and age-related diseases, its involvement in neurodegenerative diseases and AD is still being explored.^{44,48}

The findings from the proposed models herein allows hypothesis testing for additional study including (1) examining specific pathway associations with significant SNPs and protein biomarkers to determine whether the identified genes are clinically relevant; (2) exploring gene variant risk of medication metabolism, thereby expanding upon findings in this study to better understand the relationship between a group of high-risk medications (ACB) and specific gene variants associated with drug metabolism;^{11,49} and (3) understanding the role of cellular senescence in cognitive frailty.

Nevertheless, challenges still exist in generating hypothesis testing based on our models. Generalizability may be limited due to the cross-sectional analysis of existing data with a primarily homogeneous European population. Additionally, the systems model proposed in this

study accounts for known human genetic, clinical, and laboratory data; yet, systems models must also be able to suggest causal roles for the findings and ultimately offer interventions.^{48,50} At this time, our results should be replicated in other large studies with similar biomarker measures such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). Although ML methods are promising for reducing complex biological systems and characterizing key contributing variables, the results presented in this study do not provide insight into the dynamic relationship of multisystem dysfunction and AD over time. Future systems models should include longitudinal observational studies to better understand patterns of biomarker change associated with AD, elucidate disease progression, and examine the direction and rate of change over time. One way to accomplish this goal is to use ML statistical analysis to model changes in protein, genetic, and neuroimaging markers in existing population-based studies. Innovative data sharing and collaborations such as the Integrative Analysis of Longitudinal Studies on Aging (IALSA) will be important for generalizability and modeling of complex biological interactions in future dementia studies. Considering the progressive course of AD, studies that use ML predictive analytic methods to model biomarker changes longitudinally will be essential. This effort will require specialized training for research teams, collaborative efforts between computer science and basic science disciplines, and epidemiological studies with consistent biomarker measures over the participants' lifetime. Our results support the theoretical framework of cognitive frailty as a complex system when modeled with a ML statistical approach (Figure 1). Fortunately, analytical tools are now available to explore complex aging syndromes that may be pivotal in shedding light on the multiple dimensions of cognitive frailty.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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