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Biomarkers of cellular senescence predict risk of mild cognitive impairment: Results from the lifestyle interventions for elders (LIFE) study

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Abstract

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CRediT authorship contribution statement

All authors contributed to the study design and conceptualization, data collection, data analysis, interpretation of data, and drafting of the manuscript. All authors approved the final version.

Ethics approval and consent to participate

The LIFE study was approved by the Institutional Review Boards at all participating sites and monitored by a data safety monitoring board. Written informed consent was obtained from all participants.

Declaration of competing interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2025.100529.

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Objectives: Cellular senescence, characterized by a marked and multifactorial senescence-associated secretory phenotype (SASP), is a potential unifying mechanism of aging and chronic disease. Most studies of the SASP have focused on frailty and other functional outcomes. Senescent cells have been detected in the brains of patients with Alzheimer's disease, but few studies have examined associations between plasma SASP markers and cognition. The objective of this study was to examine the cross-sectional and longitudinal associations between plasma SASP markers and mild cognitive impairment among older adults at high risk of mobility disability.

Design: The Lifestyle Interventions for Elders (LIFE) study was a randomized controlled trial of a group-based physical activity program compared to a "successful aging" health education program to assess effects on major mobility disability that was conducted from February 2010 to December 2013.

Setting: Recruitment occurred at eight centers in the United States.

Participants: We included 1,373 participants enrolled in the study with baseline measures of 27 biomarkers of cellular senescence and adjudication of mild cognitive impairment (MCI) and dementia at baseline and 24-month follow-up. At baseline, participants were aged 70–80, sedentary, and at high risk of mobility disability.

Measurements: A neuropsychological assessment was administered at baseline and 24 months post-randomization. At both timepoints, a clinical adjudication committee determined whether individuals had a diagnosis of cognitively normal, MCI, or dementia; individuals with dementia at baseline were excluded. The concentrations of 26 of the 27 plasma proteins identified as components of the SASP were measured with commercially available Luminex xMAP multiplex magnetic bead-based immunoassays analyzed on the MAGPIX System while 1 protein (Activin A) was measured using an enzyme-linked immunosorbent assay.

Results: Logistic regression models were used to examine the associations of each senescence biomarker, in quartiles, with baseline or incident MCI. Models stratified by clinical site and adjusted for intervention assignment, age, gender, race, and education. Among 1,373 participants, 117 (8.5%) were diagnosed with MCI at baseline. Increasing quartiles of myeloperoxidase (MPO) was associated with higher odds of MCI compared to quartile 1 (Q2: OR = 1.34, 95% CI: 0.74–2.45; Q3: OR = 1.43, 95% CI: 0.80–2.59; Q4: OR = 1.79, 95% CI: 1.02–3.22). Additionally, matrix metalloproteinase 1 (MMP1) quartiles 2–4 had lower odds of MCI compared to quartile 1 (Q2: OR = 0.61, 95% CI:0.35–1.02; Q3: OR = 0.58, 95% CI: 0.33–0.98; Q4: OR = 0.64, 95% CI: 0.37–1.08). Of the 1,256 cognitively unimpaired participants at baseline, 141 (11.2%) were diagnosed with incident MCI or dementia at the 24-month follow-up. Compared to quartile 1, increasing baseline quartiles of MPO (Q2: OR = 1.10, 95% CI: 0.63–1.92; Q3: OR = 1.36, 95% CI: 0.80–2.33; Q4: OR = 1.92, 95% CI: 1.16–3.25) and matrix metalloproteinase 7 (MMP7, Q2: OR = 0.88, 95% CI: 0.47–1.62; Q3: OR = 1.46, 95% CI: 0.85–2.55; Q4: OR = 2.14, 95% CI: 1.28–3.65) were associated with increased odds of MCI or dementia at 24 months.

Conclusions: Among older adults at high risk of mobility disability, high plasma MPO was cross-sectionally and, along with MMP7, longitudinally associated with increased odds of MCI and dementia. In contrast, high MMP1 was cross-sectionally associated with reduced odds of MCI.

Keywords

Cognition; SASP; Mobility disability; Myeloperoxidase; Matrix metalloproteinase 7

1. Introduction

Aging is the strongest risk factor for mild cognitive impairment (MCI) and dementia. It causes dramatic changes in many systems that together lead to a multi-system loss of reserve and function. The identification of underlying biological processes that contribute to cognitive aging could substantially impact our understanding of the pathophysiological mechanisms that increase the risk of Alzheimer's disease and related dementias (ADRD).

Cellular senescence is a potential unifying mechanism of aging and chronic disease, and may contribute to risk of cognitive impairment and dementia [1–3]. With advancing age, senescent cells develop in many tissues in response to multiple forms of genotoxic, proteotoxic, metabolic, and inflammatory stress [4,5]. They are characterized by distinct changes in morphology, upregulation of cell cycle regulators and anti-apoptosis pathways, alterations in metabolism, and, notably, a marked and pluripotent senescence-associated secretory phenotype (SASP) [6]. The SASP typically includes cytokines, chemokines, matrix remodeling proteins, growth factors, and a host of other bioactive molecules. Senescent cells mediate age-related inflammatory responses, deterioration, and cellular remodeling, and, simultaneously, reduce regenerative capacity both locally and systemically [7].

Senescent cells have been detected in the brains of ADRD patients [8–10], and senolytic treatment has been shown to reduce the burden of amyloid-beta plaques, neurofibrillary tangles, degeneration of cortical and hippocampal neurons, and decline in memory and cognition in mouse models of ADRD [9,11]. In addition, a recent phase I clinical trial also reported that senolytic treatment increased CSF amyloid-beta 42 levels [12]. However, few studies have assessed whether blood levels of senescent markers differ between older adults with versus without MCI or predict risk of MCI and dementia. In this study we examined whether plasma biomarkers of cellular senescence would be associated with risk of MCI among older women and men with reduced mobility who participated in the Lifestyle Interventions for Elders (LIFE) study.

2. Methods

2.1. Design

The LIFE study was a randomized controlled trial of a group-based physical activity program (PA) compared to a "successful aging" health education program (SA) to assess effects on major mobility disability that was conducted from February 2010 to December 2013, enrolling 1,635 sedentary older adults [13]. Recruitment occurred at eight centers in the United States (University of Florida, Gainesville and Jacksonville, Florida; Northwestern University, Chicago, Illinois; Pennington Biomedical Research Center, Baton Rouge, Louisiana; University of Pittsburgh, Pittsburgh, Pennsylvania; Stanford University, Stanford,

California; Tufts University, Boston, Massachusetts; Wake Forest School of Medicine, Winston–Salem, North Carolina; and Yale University, New Haven, Connecticut). The LIFE study was approved by the Institutional Review Boards at all participating sites and monitored by a data safety monitoring board. Written informed consent was obtained from all participants.

To be included in the study, women and men aged 70–89 years had to meet the following inclusion criteria: (1) sedentary lifestyle (defined as reporting <20 min/day of regular physical activity and <125 min/week of moderate physical activity); (2) at high risk of disability based upon a score between 4 and 10 on the short physical performance battery (SPPB); (3) ability to complete the 400-meter (400 m) walk test without an assistive device within 15 min; (4) absence of dementia; and (5) willingness to consent to randomization. In addition, persons were also excluded if their Mini Mental State Examination (3MSE) [14] was so low as to be concerning for dementia. Education- and race/ethnicity-based cutoffs were employed. Participants with <9 years of education were excluded if their 3MSE score was <70 for African Americans and Spanish speakers or <76 for English-speaking, non-African Americans. Participants with ≥9 years of education were excluded if their 3MSE score was <76 for African Americans and <80 for Spanish speakers and English-speaking, non-African Americans [15].

Study exclusions were unstable chronic disease and factors that would likely affect adherence to the intervention or underlying conditions that might limit survival. Subjects were randomized (1:1) to either PA or SA using block randomization stratified by field center and participant gender.

2.2. Interventions

The PA intervention consisted of group-based walking, aerobic, resistance, flexibility, and balance training in a supervised setting (twice per week) with additional home-based physical activity goals [16]. Each physical activity session consisted primarily of walking; participants also completed a 10-minute lower extremity resistance training program with ankle weights, balance exercises, and lower extremity stretching.

The SA intervention was designed to deliver age-specific health information about “successful aging”. Health education consisted of workshops on topics relevant to older adults (e.g., negotiating the health care system, home safety, nutrition, etc.). Classes met weekly for the first 26 weeks, and from week 27 on the program was offered two times per month and participants were prompted to attend at least once per month.

2.3. Cognitive assessment

The neuropsychological assessment administered at baseline and 24 months post-randomization has previously been described [15]. Briefly, baseline tests included the 3MSE [14], Wechsler Adult Intelligence Scale-III Digit Symbol Coding (DSC) [17], the Hopkins Verbal Learning Test-Revised (HVLT-R) [18], and a modified version of the Rey-Osterrieth Complex Figure to assess visuospatial function (copy) and figural memory (immediate recall). At 24 months these measures were repeated along with the Boston Naming Test [19], Trail Making Test parts A and B [20], and Category Fluency for animals.

2.4. Clinical cognitive diagnosis

At baseline and 24 months post-randomization, all participants were assigned one of the following cognitive classifications: No Cognitive Impairment, MCI, or Dementia. Participants who scored ≤88 on the 3MSE were sent for central adjudication by a panel of eight clinical experts in the diagnosis of late life cognitive impairment, blinded to treatment assignment [15]. Each case was assigned to 2 independent adjudicators; disagreements were resolved by the full panel. Adjudicators reviewed data from the neuropsychological battery, medical history, medications, discharge diagnoses for hospitalizations during the trial, Center for Epidemiology Studies-Depression (CESD) scores [21], self-reported disability, and informant-reported functional status using the Functional Assessment Questionnaire (FAQ) [22]. The FAQ is a 10-item interviewer-administered questionnaire assessing degree of dependence in cognitively challenging activities of daily living such as preparing balanced meals, traveling outside the neighborhood, and managing finances. The FAQ was administered to the participant's proxy for all participants with a 3MSE score ≤88 at baseline and 24 months. MCI and dementia were adjudicated based on the 2011 National Institute on Aging/Alzheimer's Association criteria [23,24].

2.5. Measurement of plasma senescence biomarkers

Plasma samples were collected after a minimum 8 h fast in EDTA tubes. The tubes were immediately placed on ice (4 ° C) for no more than 30 min, centrifuged, aliquoted, and then stored at −80 ° Celsius. For the current study, archived specimens were requested and shipped from the National Institute of Aging (NIA) Aging Research Biobank to Mayo Clinic for analysis.

The concentrations of protein biomarkers in plasma samples were determined with commercially available multiplex magnetic bead-based immunoassays (R&D Systems) on the Luminex xMAP multianalyte profiling platform and analyzed on MAGPIX System (Merck Millipore) according to the standard manufacturer's protocols (see Supplemental Table S1 for description of all proteins): ADAMTS13, eotaxin, Fas, GDF15, ICAM1, IL6, IL7, IL8, IL10, IL15, MCP1, MDC, MMP1, MMP7, MMP9, MPO, OPN, PAI1, PARC, RAGE, RANTES, SOST, TNFR1, TNFR2, TNFα, and VEGFA. Activin A concentration was measured using a Quantikine ELISA Kit (R&D Systems) according to the manufacturer's specifications.

The plasma concentrations of these 27 proteins were previously identified as components of the SASP that were elicited by several human senescent cell types and associated with chronological age and multi-morbidity; assay performance parameters have been reported previously [2,25]. In cases where a variable was below the limit of detection (LOD) in a sample, a value of half of the lowest measured value for that analyte was assigned, as previously described [2].

2.6. Data analysis

Continuous variables were summarized using mean (SD) and compared using the Wilcoxon rank sum or t-test as appropriate. Variables were compared pairwise using unadjusted and adjusted Spearman correlations. Biomarkers were evaluated for skewed distributions and

if appropriate were log transformed, then K-nearest neighbor imputation was applied to impute the small number of missing values. Senescence markers were examined in quartiles with the lowest quartile as reference. Logistic regression models were used to examine associations between the senescence markers and odds of MCI at baseline or incident MCI or dementia at 24 months adjusted for intervention assignment, age, gender, race, education and clinical site. In additional sensitivity analyses, we adjusted for physical activity and we also separately adjusted for health conditions (high blood pressure, diabetes, cancer, chronic lung disease, myocardial infarction, and stroke). As this was a hypothesis-generating analyses, we did not correct for multiple comparisons. All analyses were conducted using R version 4.3.2.

2.7. Data availability

LIFE Study datasets are available through the NIA Aging Research Biobank, https://agingresearchbiobank.nia.nih.gov/studies/life/. Biomarker data presented in the current study will be made available by the investigative team upon reasonable request.

3. Results

3.1. Demographic and clinical characteristics of participants

Subjects were screened for enrollment in the LIFE study between February 2010 and December 2011 (Fig. 1). The current analysis included 1,373 of the 1,635 LIFE Study participants at baseline who had available baseline blood samples and adjudicated cognitive outcome data for analysis. Similar to the overall cohort, baseline demographic and other characteristics were similar across randomized groups (Table 1).

The original publication examining the effects of PA on incident MCI, dementia, or both combined, did not find a significant difference between groups [26]. In the current analyses, we combined both interventions into one group to examine the association between senescence and odds of MCI at baseline or risk of MCI or dementia at 24 months for participants who were cognitively unimpaired at baseline.

3.2. Circulating senescence biomarkers and odds of mild cognitive impairment at baseline

At baseline, 117 (8.5%) participants were diagnosed with MCI. Compared to those without MCI, those with MCI were less likely to be White, less likely to have an education of college or more, had poorer performance for the SPPB total score and 400 meter walk test, and scored lower on the 3MSE (Table 2). The two groups did not differ with regards to health conditions or BMI.

We assessed whether each of the circulating baseline senescence biomarkers were associated with odds of MCI at baseline in models adjusting for age, gender, education, and race and stratified by clinical site (Table 3). Increasing quartiles (Q) of MPO, compared to Q1 were associated with increasing odds of MCI (Q2: odds ratio (OR) = 1.34, 95% confidence interval (CI): 0.74, 2.45); Q3: OR = 1.43, 95% CI:0.80, 2.59; Q4: OR = 1.79, 95% CI: 1.02, 3.22). In contrast, compared to Q1, Q2-Q4 of MMP1 were significantly, or trended

towards being, associated with a reduced odds of MCI to a similar effect (Q2: OR = 0.61, 95% CI:0.35, 1.02; Q3: OR = 0.58, 95% CI:0.33, 0.98; Q4: OR = 0.64, 95% CI: 0.37, 1.08). Only Q3 of MMP9 (Q3 vs. Q1: OR = 1.90, 95% CI:1.12, 3.26) and Q2 of RAGE (Q2 vs. Q1: OR = 1.75; 95% CI: 1.02, 3.04) was associated with increased odds of MCI; Q2 of SOST (Q2 vs. Q1: OR = 0.53; 95% CI: 0.29, 0.93) was associated with reduced odds of MCI. Additional sensitivity analyses adjusted for either physical activity or chronic health conditions, but the results remained similar.

3.3. Associations between baseline senescence biomarkers and odds of MCI/dementia at 24 months

Of the 1,256 participants who were classified as cognitively unimpaired at baseline, 141 (11.2%) were diagnosed with incident MCI or dementia at the 24-month follow-up. Increasing baseline quartiles of MPO (Q2: OR = 1.10, 95% CI: 0.63, 1.92; Q3: OR = 1.36, 95% CI:0.80, 2.33; Q4: OR = 1.92, 95% CI: 1.16, 3.25) and MMP7 (Q2: OR = 0.88, 95% CI: 0.47, 1.62; Q3: OR = 1.46, 95% CI: 0.85, 2.55; Q4: OR = 2.14, 95% CI: 1.28, 3.65) were associated with increased odds of MCI at 24 months compared to the lowest quartile (Table 4). Additional sensitivity analyses adjusted for either physical activity or chronic health conditions, but the results did not appreciably change.

4. Discussion

Aging is the strongest risk factor for MCI and dementia. Cellular senescence is a potential unifying mechanism of aging and chronic disease, and may contribute to risk of cognitive impairment and dementia [1,2]. Senescent cells have been detected in the brains of ADRD patients [8–10]. However, few studies have assessed whether blood levels of candidate senescence markers differ between older adults with versus without MCI or predict risk of MCI or dementia. In this study, we found higher quartiles of MPO were cross-sectionally associated with higher odds of MCI at baseline whereas higher quartiles of MMP1 were associated with lower odds. In addition, higher quartiles of MPO and MMP7 were associated with increased odds of incident MCI or dementia at 24 months. These results suggest that specific biomarkers of cellular senescence may be either associated with an increased or decreased risk of cognitive impairment among older adults at high risk of mobility disability.

Myeloperoxidase (MPO), a prooxidant enzyme secreted by activated leukocytes, facilitates conversion of hydrogen peroxide to hypochlorous acid and generates reactive intermediates that promote lipid peroxidation [27]. MPO-immunoreactive cells have been shown to be increased in the brains of patients with neurodegenerative diseases including Alzheimer’s disease and Parkinson’s disease [28,29]. Some studies have also examined plasma MPO levels in ADRD cohorts, with mixed results. One study reported higher plasma MPO levels in AD patients compared to cognitively unimpaired participants [30], whereas another study did not find differences in MPO levels between cognitively impaired (MCI or AD) and unimpaired participants [31]. In the Framingham Heart Study (FHS) Offspring cohort, higher levels of MPO were associated with worse performance on a test of attention and executive function, but not with incident all-cause dementia over the next 10 years [32]. In

the present study, we found that MPO levels were higher among participants diagnosed with MCI, compared to those who were cognitively unimpaired, and were associated with incident MCI or dementia two years later. Compared to the FHS Offspring cohort, participants in the current study were older and at greater risk of disability, characteristics which could have enhanced the prognostic signal. Notably, we did not find associations between baseline MPO and incidence of major mobility disability or persistent mobility disability using this same cohort [33], but previous studies have shown associations of MPO levels with morality in frail community-living elderly individuals [34]. This suggests that MPO, which has also been implicated in senescence induction, might be a senescence marker more specifically associated with cognition.

Matrix metalloproteinases (MMPs) are a large family of structurally related zinc-dependent proteases and calcium-dependent endopeptidases that modulate a variety of biological processes including inflammation, immune response, tissue modeling, cell proliferation, and angiogenesis [35]. They are expressed in the brain by astrocytes and microglia, as well as neurons, and have been implicated in neurodegenerative diseases and amyloid and tau pathology [36–39]. Studies of blood MMPs and cognition have been largely inconsistent [40]. MMP-1 plasma concentrations have been found to be either unchanged [41,42], or decreased [43,44]. MMP-2 plasma levels were unchanged [35,42,45,46], or decreased in AD patients compared with cognitively unimpaired individuals [47]. MMP-9 levels were higher in neuronally-derived extracellular vesicles in plasma of AD patients compared to cognitively unimpaired controls [48] as well as in plasma in some studies [35,42,49], but not others [41,44,50–53]. One reason for the inconsistency may be that MMP-9 concentrations are affected by many comorbidities common in older adults with cognitive impairment [54–56]. In the present study of older adults at risk of mobility disability, we found higher quartiles of MMP-1 were cross-sectionally associated with lower odds of MCI. These findings are aligned with previous studies that reported lower MMP-1 levels in AD patients compared to controls [43,44]. We also found that increasing quartiles of MMP-7 at baseline were associated with increased odds of incident MCI or dementia at 24 months. Few studies have examined the association between MMP-7 and MCI or dementia so this finding needs to be replicated. Lastly, we did not find that baseline MMP-9 was associated with odds of baseline MCI or incident MCI or dementia 24-months later, except for a higher odds of baseline MCI for individuals in Q3 vs. Q1 of MMP-9. As mentioned, MMP-9 levels are affected by multiple diseases and the LIFE cohort includes participants with multiple comorbidities so that may be an explanation for the lack of association.

Plasma growth-differentiation factor-15 (GDF-15) is a member of the TGFβ family that is secreted by numerous cells and increases with age [57]. Plasma GDF15 is elevated in the context of inflammation and chronic disease and has been associated with risk of incident mobility disability [58,59], including in the current study [33]. Fewer studies have examined GDF-15 as a risk factor for cognitive decline and dementia. Higher levels of GDF-15 in middle age have been associated with 25-year dementia risk [60]. In the present study we did not find an association between baseline GDF-15 and odds of MCI at baseline or with the development of MCI or dementia two years later. Given the strong association between GDF-15 and mobility disability, it is plausible that it overshadowed any association with

MCI or dementia. Similarly, this could also be a plausible explanation for other SASP proteins as there were few associations with MCI and dementia.

The present study has many strengths including the large, randomized sample of older adults with mobility limitations and multi-morbidity, rigorous assessment of cognitive function, and an evidence-based and validated platform to measure plasma levels of senescence-associated proteins. However, considerations of limitations are warranted. First, although there is a scientific foundation for senescent cells to be a plausible source of the measured circulating biomarkers, additional sources may contribute. We note that senescent cells also recruit, anchor, and amplify signals form immune cells, and thus, may indirectly contribute to circulating concentrations of the measured proteins. Second, there are some aspects of study enrollment that may limit generalizability. Participants were eligible if they were 70–80 years old, had a sedentary lifestyle, and were at high risk of disability. Thus, the results may not be as applicable to higher functioning older adults. Last, participants in the LIFE study were self-selected and/or referred for study enrollment and thus may represent a unique population of older adults.

In this study of older adults at high risk of mobility disability we found that high levels of MPO were both cross-sectionally associated with MCI and longitudinally associated with MCI or dementia. Elevated levels of MMP were also associated with increased odds of incident MCI or dementia. In contrast, higher levels of MMP1 were cross-sectionally associated with lower odds of MCI at baseline. These findings need to be replicated in additional studies of older adults who are, and are not, at high risk of mobility disability. In addition, it is unclear whether these SASP proteins are specifically associated with AD pathology or some other pathology or neurodegenerative mechanism that leads to cognitive impairment. It will be important to examine the association between the SASP markers and neuroimaging measures of AD and cerebrovascular pathologies, or blood-based ADRD biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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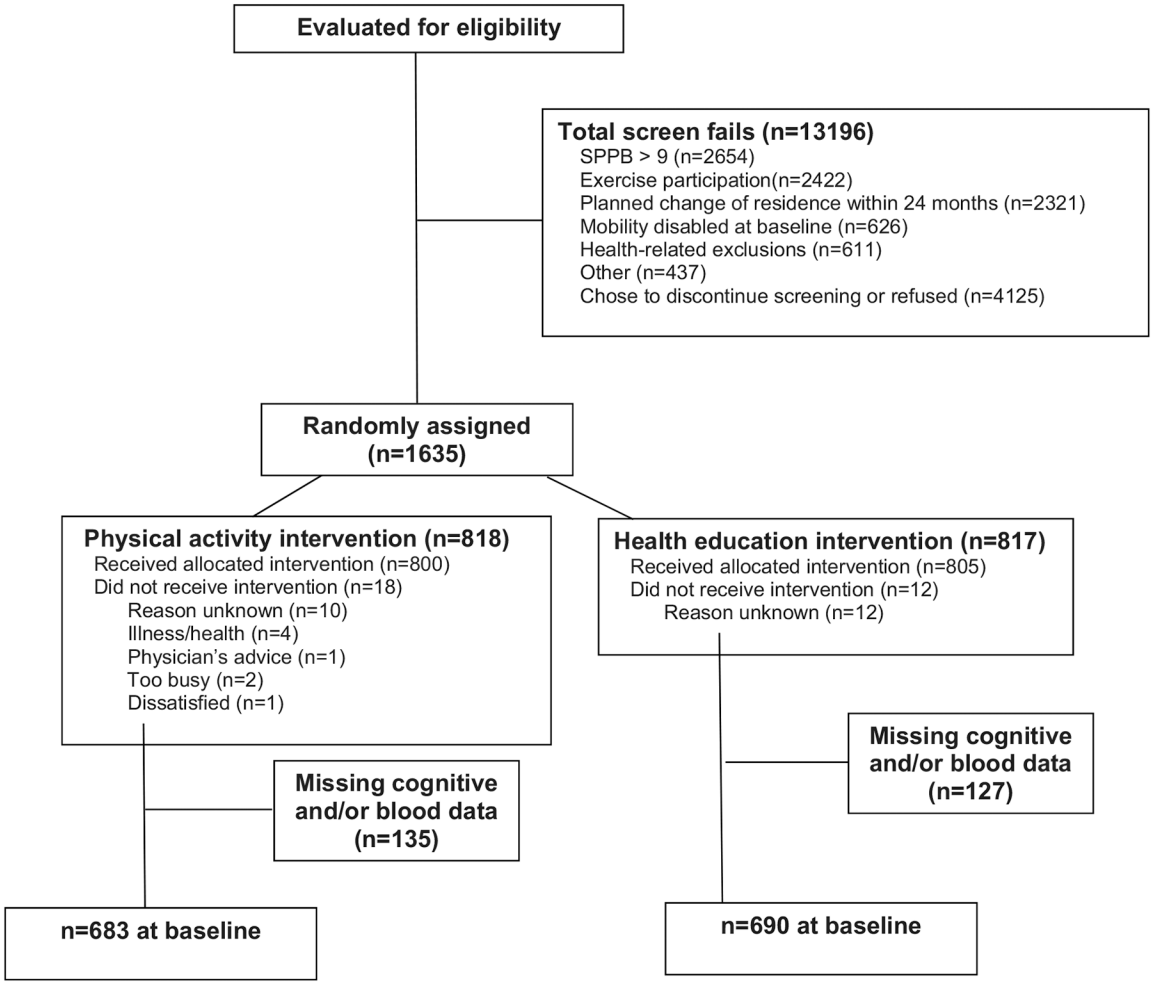

Fig. 1.

Consort Diagram. SPPB = short physical performance battery.

Table 1

Baseline Demographic and health characteristics by randomized group.

Participant characteristics	Physical Activity (N = 683)	Successful Aging (N = 690)	p value
Age (yrs)	78.6 (5.2)	79.1 (5.3)	0.125[1]
Women	449 (65.7%)	460 (66.7%)	0.716[2]
Race			0.092[2]
White	517 (75.7%)	545 (79.0%)	
Black	126 (18.4%)	98 (14.2%)	
Other	40 (5.9%)	47 (6.8%)	
Education			0.411[2]
High School or less	233/681 (34.2%)	221/688 (32.1%)	
College or more	448/681 (65.8%)	467/688 (67.9%)	
Body Mass Index, kg/m^2	30.2 (5.8)	30.3 (6.1)	0.757[1]
Health Conditions, n(%)			
High blood pressure	482/681 (70.8%)	490/689 (71.1%)	0.824[2]
Diabetes	170/681 (25.0%)	176/689 (25.5%)	0.793[2]
Cancer	147/680 (21.6%)	160/689 (23.2%)	0.477[2]
Chronic Lung Disease	109/681 (16.0%)	95/689 (13.8%)	0.258[2]
Myocardial Infarction	49/681 (7.2%)	56/689 (8.1%)	0.512[2]
Stroke	52/681 (7.6%)	44/689 (6.4%)	0.361[2]
Physical function			
SPPB Total Score (corrected)	7.4 (1.6)	7.3 (1.6)	0.167[3]
400 m Walk, seconds	503.1 (110.9)	507.3 (111.4)	0.479[1]
Cognitive Function			
3MSE z-score	0.0 (1.0)	0.0 (1.0)	0.556[1]
MCI	57 (8.3%)	60 (8.7%)	0.816[2]

[1]Two-sample t-test.

[2]Chi-squared test.

[3]Wilcoxon rank sum test.

Table 2

Demographic and health characteristics by baseline adjudicated diagnosis of mild cognitive impairment (MCI).

	No MCI (N = 1256) Mean (SD)/N(%)	MCI (N = 117) Mean (SD)/N(%)	P value
Age (yrs)	78.8 (5.2)	79.3 (5.5)	0.347[1]
Women	832 (66.2%)	77 (65.8%)	0.925[2]
Race			<0.001[2]
White	997 (79.4%)	65 (55.6%)	
Black	186 (14.8%)	38 (32.5%)	
Other	73 (5.8%)	14 (12.0%)	
Education			<0.001[2]
High School or less	399/1252 (31.9%)	55 (47.0%)	
College or more	853/1252 (68.1%)	62 (53.0%)	
Body Mass Index, kg/m^2	30.2 (6.0)	30.1 (5.4)	0.901[1]
Health Conditions			
High blood pressure	882/1253 (70.4%)	90 (76.9%)	0.164[2]
Diabetes	312/1253 (24.9%)	34 (29.1%)	0.329[2]
Cancer	286/1256 (22.8%)	21 (17.9%)	0.225[2]
Chronic Lung Disease	186/1252 (14.8%)	18 (15.4%)	0.886[2]
Myocardial Infarction	98/1253 (7.8%)	7 (6.0%)	0.471[2]
Stroke	86/1253 (6.9%)	10 (8.5%)	0.500[2]
Physical Function			
SPPB Total Score (corrected)	7.4 (1.6)	7.0 (1.9)	0.019[3]
400 m Walk, seconds	502.9 (110.4)	529.6 (115.7)	0.013[1]
Cognitive Function			
Baseline: 3MSE z-score	0.2 (0.9)	−1.4 (0.5)	<0.001[1]

[1]Two-sample t-test.

[2]Chi-squared test.

[3]Wilcoxon rank sum test.

Table 3

Associations of senescence biomarkers and odds of mild cognitive impairment at baseline.

Protein (all vs. Q1)	OR (95% CI)	p-value	3-df	Protein	OR (95% CI)	p-value	3-df
TNF-α: Q2	0.71 (0.40, 1.23)	0.225	0.391	TNFR2: Q2	0.67 (0.38, 1.16)	0.158	0.579
Q3	1.06 (0.64, 1.77)	0.818		Q3	0.81 (0.47, 1.39)	0.450	
Q4	0.77 (0.43, 1.33)	0.346		Q4	0.86 (0.51, 1.45)	0.576	
IL6: Q2	0.82 (0.46, 1.43)	0.477	0.495	SOST: Q2	0.53 (0.29, 0.93)	0.028	0.171
Q3	0.80 (0.45, 1.41)	0.441		Q3	0.82 (0.49, 1.37)	0.453	
Q4	1.16 (0.69, 1.95)	0.580		Q4	0.76 (0.44, 1.30)	0.324	
IL7: Q2	0.90 (0.52, 1.54)	0.689	0.968	ADAMTS13: Q2	1.05 (0.59, 1.87)	0.865	0.421
Q3	1.02 (0.60, 1.75)	0.937		Q3	1.50 (0.88, 2.59)	0.138	
Q4	0.95 (0.55, 1.63)	0.844		Q4	1.07 (0.60, 1.92)	0.810	
IL15: Q2	1.00 (0.58, 1.75)	0.988	0.998	osteopontin: Q2	0.93 (0.53, 1.64)	0.804	
Q3	1.05 (0.60, 1.83)	0.867		Q3	0.81 (0.44, 1.45)	0.478	
Q4	1.04 (0.60, 1.80)	0.891		Q4	1.58 (0.94, 2.69)	0.089	
eotaxin: Q2	1.08 (0.63, 1.88)	0.779	0.487	ICAM1: Q2	0.96 (0.55, 1.68)	0.896	0.989
Q3	1.17 (0.69, 2.02)	0.563		Q3	1.06 (0.61, 1.83)	0.833	
Q4	0.77 (0.43, 1.37)	0.373		Q4	1.02 (0.59, 1.77)	0.934	
MCP1: Q2	1.29 (0.74, 2.25)	0.372	0.678	GDF15: Q2	0.89 (0.50, 1.56)	0.683	0.847
Q3	1.15 (0.65, 2.05)	0.638		Q3	1.05 (0.61, 1.81)	0.869	
Q4	1.35 (0.78, 2.36)	0.292		Q4	0.83 (0.46, 1.48)	0.520	
IL8: Q2	0.89 (0.50, 1.56)	0.682		TNFR1: Q2	0.54 (0.28, 1.00)	0.057	0.047
Q3	0.87 (0.50, 1.52)	0.619		Q3	1.21 (0.72, 2.04)	0.464	
Q4	0.97 (0.57, 1.67)	0.916		Q4	1.10 (0.64, 1.89)	0.736	
VEGF: Q2	1.29 (0.74, 2.25)	0.372	0.807	Fas: Q2	1.05 (0.60, 1.82)	0.868	0.937
Q3	1.20 (0.68, 2.12)	0.531		Q3	1.04 (0.60, 1.81)	0.883	
Q4	1.20 (0.68, 2.11)	0.528		Q4	1.18 (0.68, 2.06)	0.556	
Activin A: Q2	1.63 (0.92, 2.92)	0.097		MMP9: Q2	1.12 (0.63, 1.98)	0.697	0.054
Q3	1.73 (0.97, 3.12)	0.065		Q3	1.90 (1.12, 3.26)	0.018	
Q4	1.24 (0.67, 2.31)	0.494		Q4	1.01 (0.56, 1.82)	0.975	
MMP1: Q2	0.61 (0.35, 1.02)	0.063	0.155	MMP2: Q2	1.42 (0.81, 2.49)	0.223	0.530
Q3	0.58 (0.33, 0.98)	0.046		Q3	1.39 (0.80, 2.45)	0.240	

Protein (all vs. Q1)	OR (95% CI)	p-value	3-df	Protein	OR (95% CI)	p-value	3-df
Q4	0.64 (0.37, 1.08)	0.096		Q4	1.15 (0.65, 2.05)	0.635	
MMP7: Q2	0.94 (0.55, 1.63)	0.835		PARC: Q2	1.23 (0.73, 2.12)	0.439	0.621
Q3	0.82 (0.47, 1.44)	0.495		Q3	1.04 (0.60, 1.82)	0.891	
Q4	0.73 (0.42, 1.27)	0.270		Q4	0.86 (0.48, 1.52)	0.597	
MDC: Q2	0.79 (0.45, 1.35)	0.389	0.676	RANTES: Q2	0.73 (0.42, 1.25)	0.247	0.375
Q3	0.71 (0.41, 1.23)	0.220		Q3	0.69 (0.39, 1.21)	0.200	
Q4	0.82 (0.48, 1.41)	0.478		Q4	1.03 (0.61, 1.72)	0.916	
RAGE: Q2	1.75 (1.02, 3.04)	0.045	0.229	PAI: Q2	0.90 (0.53, 1.51)	0.680	
Q3	1.25 (0.68, 2.29)	0.474		Q3	0.72 (0.40, 1.26)	0.255	
Q4	1.35 (0.73, 2.52)	0.337		Q4	0.96 (0.55, 1.66)	0.890	
				MPO: Q2	1.34 (0.74, 2.45)	0.336	
				Q3	1.43 (0.80, 2.59)	0.236	
				Q4	1.79 (1.02, 3.22)	0.047	

Table 4

Associations of senescence biomarkers and odds of mild cognitive impairment or dementia at 24 months.

Protein (all vs. Q1)	OR (95% CI)	p-value	3-df	Protein	OR (95% CI)	p-value	3-df
TNF-α: Q2	1.24 (0.75, 2.07)	0.398	0.584	TNFR2: Q2	1.26 (0.77, 2.07)	0.356	0.293
Q3	1.18 (0.71, 1.97)	0.526		Q3	0.93 (0.55, 1.57)	0.792	
Q4	0.90 (0.53, 1.54)	0.705		Q4	0.77 (0.45, 1.1)	0.339	
IL6: Q2	0.82 (0.49, 1.35)	0.430	0.644	SOST: Q2	1.00 (0.59, 1.70)	0.991	0.453
Q3	0.72 (0.43, 1.21)	0.218		Q3	1.42 (0.86, 2.38)	0.173	
Q4	0.90 (0.55, 1.47)	0.672		Q4	1.18 (0.69, 2.01)	0.547	
IL7: Q2	0.90 (0.54, 1.48)	0.668	0.963	ADAMTS13: Q2	0.94 (0.56, 1.56)	0.800	0.930
Q3	0.90 (0.54, 1.50)	0.683		Q3	1.11 (0.67, 1.83)	0.683	
Q4	0.89 (0.53, 1.48)	0.648		Q4	1.02 (0.61, 1.70)	0.943	
IL.15: Q2	1.01 (0.60, 1.69)	0.970	0.698	osteopontin: Q2	0.82 (0.49, 1.38)	0.463	0.775
Q3	0.87 (0.51, 1.47)	0.600		Q3	0.97 (0.58, 1.62)	0.921	
Q4	1.18 (0.71, 1.96)	0.519		Q4	1.08 (0.65, 1.78)	0.774	
eotaxin: Q2	1.07 (0.62, 1.86)	0.802	0.324	ICAM1: Q2	1.27 (0.77, 2.12)	0.345	0.133
Q3	1.23 (0.72, 2.11)	0.446		Q3	0.79 (0.45, 1.37)	0.400	
Q4	1.55 (0.93, 2.62)	0.093		Q4	1.41 (0.86, 2.33)	0.177	
MCP1: Q2	1.07 (0.64, 1.81)	0.796	0.562	GDF15: Q2	0.90 (0.51, 1.60)	0.720	
Q3	1.36 (0.82, 2.27)	0.239		Q3	1.46 (0.86, 2.51)	0.170	
Q4	0.98 (0.58, 1.67)	0.942		Q4	1.56 (0.92, 2.71)	0.105	
IL8: Q2	1.31 (0.79, 2.18)	0.292		TNFR1: Q2	0.91 (0.54, 1.51)	0.709	
Q3	0.93 (0.55, 1.58)	0.784		Q3	0.99 (0.60, 1.65)	0.982	
Q4	0.96 (0.57, 1.62)	0.865		Q4	0.74 (0.43, 1.27)	0.274	
VEGF: Q2	1.33 (0.78, 2.28)	0.294	0.602	Fas: Q2	1.37 (0.81, 2.35)	0.246	0.505
Q3	1.22 (0.69, 1.86)	0.477		Q3	1.45 (0.86, 2.47)	0.169	
Q4	1.41 (0.51, 1.44)	0.201		Q4	1.39 (0.81, 2.40)	0.230	
Activan A: Q2	0.66 (0.38, 1.13)	0.149	0.211	MMP9: Q2	1.06 (0.63, 1.78)	0.839	0.510
Q3	1.13 (0.97, 3.12)	0.634		Q3	1.44 (0.86, 2.40)	0.163	
Q4	0.85 (0.67, 2.31)	0.187		Q4	1.20 (0.72, 2.01)	0.481	
MMP1: Q2	0.89 (0.54, 1.49)	0.662	0.911	MMP2: Q2	1.22 (0.73, 2.03)	0.443	0.708
Q3	0.96 (0.58, 1.59)	0.862		Q3	0.91 (0.53, 1.56)	0.742	

Protein (all vs. Q1)	OR (95% CI)	p-value	3-df	Protein	OR (95% CI)	p-value	3-df
Q4	0.84 (0.50, 1.41)	0.500		Q4	1.12 (0.67, 1.86)	0.668	
MMP7: Q2	0.88 (0.47, 1.62)	0.680	0.002	PARC: Q2	1.33 (0.79, 2.26)	0.280	0.412
Q3	1.46 (0.85, 2.55)	0.175		Q3	1.47 (0.88, 2.48)	0.140	
Q4	2.14 (1.28, 3.65)	0.004		Q4	1.08 (0.63, 1.86)	0.767	
MDC: Q2	1.10 (0.65, 1.87)	0.732		RANTES: Q2	0.90 (0.55, 1.47)	0.673	0.618
Q3	0.85 (0.49, 1.48)	0.567		Q3	0.78 (0.46, 1.30)	0.340	
Q4	1.51 (0.91, 2.52)	0.112		Q4	0.72 (0.4, 1.22)	0.224	
RAGE: Q2	1.31 (0.77, 2.22)	0.317	0.787	PAI: Q2	0.87 (0.53, 1.51)	0.560	0.602
Q3	1.22 (0.70, 2.14)	0.474		Q3	0.72 (0.43, 1.26)	0.210	
Q4	1.18 (0.67, 2.07)	0.574		Q4	0.76 (0.45, 1.66)	0.304	
				MPO: Q2	1.10 (0.63, 1.92)	0.743	0.050
				Q3	1.36 (0.80, 2.33)	0.263	
				Q4	1.92 (1.16, 3.25)	0.013	