Family history of cardiovascular disease is associated with self-reported cognitive function: the Emory Healthy Aging Study

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Background: Family history of cardiovascular disease (FHxCVD) is a CVD risk indicator that captures the influence of genetic and shared familial factors and is readily available to individuals and clinicians. Though CVD risk factors associate with greater risk of cognitive impairment, less is known about the association between FHxCVD and self-reported cognitive function. Evaluating this association may further elucidate links between cardiovascular and cognitive health.

Methods: The Emory Healthy Aging Study is a community-based prospective cohort study aimed at identifying predictors of healthy aging and age-related diseases. Participants are primarily residents of the Atlanta area, at least 18 years old, who completed an online baseline health survey. Information about demographic (age, self-reported race, gender), socioeconomic (education, household income), lifestyle (physical activity, smoking) and CVD risk factors (diabetes, hyperlipidemia, BMI, hypertension) and family health history were collected at enrollment. Family history of CVD was defined as self-reported history of coronary artery disease, myocardial infarction, or stroke for any biological parent or sibling. Self-reported cognitive function was measured using the validated Cognitive Function Instrument (CFI) and categorized into quartiles. Associations between FHxCVD and CFI score quartile were assessed using multinomial logistic regression, adjusting for demographic, socioeconomic, lifestyle and the participant's own CVD risk factors, as well as family history of any diagnosed cognitive impairment.

Results: We studied 6,115 participants (75% female, 84% white, 11% black, and 5% other self-reported race), without existing CVD, recruited between October 2015 and 2017. Mean age was 59±13 years and 61% reported a family history of CVD. Comparing extreme quartiles of CFI score, adjusted for demographic, socioeconomic, and lifestyle factors, plus family history of any diagnosed cognitive impairment, FHxCVD was associated with poorer self-reported cognitive function (OR=1.43; 95% CI (1.21, 1.70)). The OR after additional adjustment for CVD risk factors was not meaningfully different (OR=1.47; 95% CI (1.23, 1.76)). In the same fully adjusted model, the estimated OR for family history of any cognitive impairment was slightly larger: 1.54 (1.30, 1.83).

Conclusion: In this cross-sectional community sample, family history of CVD was associated with poorer self-reported cognitive function, and this association was of a similar magnitude as having a family history of cognitive impairment. Although longitudinal studies are needed, these results underscore the link between cardiovascular and cognitive health. Twin studies are needed to estimate the contribution of genetic and shared familial factors.

Construct Validity of Montreal Cognitive Assessment Index Scores in Cognitively Normal Adults

EMORY Healthy Brain Study

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Introduction

- Increasing numbers of individuals are surviving into advanced ages, expanding the proportion of the population at risk for the development of Alzheimer's disease and other neurodegenerative disorders. Thus, there is great need for simple and effective tools for dementia screening.
- The Montreal Cognitive Assessment (MoCA) is a cognitive screen used to characterize global cognitive status. It has been shown to have high sensitivity for detecting individuals with Mild Cognitive Impairment (90%) and Alzheimer's Disease (100%)[1].
- Julayanont & colleagues have categorized the items of the MoCA into six domain-specific indices: Memory, Visuospatial, Executive, Attention, Language, and Orientation.[2]

Objective

- Current research has primarily focused on the MoCA Memory Index and its ability to act as a predictor of conversion from Mild Cognitive Impairment to Alzheimer's disease.[2]
- There is minimal research establishing the construct validity, reliability, and sensitivity of all six MoCA indices.
- We examined the relationship between performance on the MoCA indices and other established neuropsychological measures to determine the construct validity and clinical application of the MoCA indices.

Method

- Participants: 409 cognitively normal (M_{MoCA} = 26.51, SD_{MoCA} = 2.32) middle-aged and older adults (M_{age} = 62.59, SD_{age} = 7.00) completed comprehensive cognitive testing as part of their participation in the Emory Healthy Brain Study (EHBS).
- The EHBS is a prospective study of preclinical Alzheimer's disease and other chronic diseases of aging that aims to identify predictors of disease development through in-depth characterization of potential biomarkers within a cognitively normal sample of those at-risk for disease. The EHBS includes a comprehensive neuropsychological battery.
- We utilized correlation analyses to examine the construct validity of five of the six MoCA indices: memory, executive functioning, attention, language, and visuospatial.

Results

Table 1. EHBS Participant Characteristics

	M	*SD*	%
Demographic Variables (N = 409)			
Age (years)	62.59	7.00	
Gender (% female)			75.8
Race (%)			
Asian			1.2
Black or African American			11.5
White or Caucasian			84.4
Other			2.9
Ethnicity (% Non-Hispanic)			97.1
Education	16.48	2.21	
Handedness (% Right)			90.2
MoCA	26.51	2.32	

Table 2. Components of the MoCA Indices by Domain and Associated Neuropsychological Measures from the EHBS Battery

MoCA Index	MoCA Components	Study Battery
Memory (MIS)	Delayed recall; Category-cued recall; Multiple choice-cued recall	Rey-Osterrieth Immediate Rey-Osterrieth Delay Rey-Osterrieth Recognition
Executive (EF)	Digit Span; Mini-Trails; Clock drawing; Serial 7s; Letter A tapping; Abstraction; Letter fluency	Trail-Making Test B FAS Number Span Backward
Attention (ATTN)	Serial 7s; Letter A tapping; Sentence repetition; Digit Span; Immediate word recall	Trail-Making Test A Number Span Forward Number Span Backward
Language (LANG)	Animal picture naming; Sentence repetition; Letter fluency	Multilingual Naming Test Animal Fluency FAS
Visuospatial (VS)	Cube drawing; Clock drawing; Animal picture naming	Rey-Osterrieth Figure Copy Judgment of Line Orientation

Table 3. Participant Performance Scores on the EHBS Neuropsychological Battery

Test Name	*M*	*SD*	*Range*
Animal Fluency	21.53	4.89	4-42
JoLO	25.16	3.95	8-30
MINT	30.78	1.74	17-32
MoCA	26.51	2.32	19-31
RCFT Copy	31.68	3.79	10-36
RCFT Immed	17.49	6.46	0-35
RCFT Delay	16.55	6.11	0-34
RCFT Rec	20.35	1.90	13-24
NS Backward	7.19	2.24	0-14
NS Forward	8.73	2.52	0-14
TMT-A	34.58	12.50	0-108
TMT-B	74.07	33.61	20-300
FAS	43.12	11.53	3-79

Table 4. Correlations Among Cognitive Measures and MoCA Indices

Test Name	Animal Fluency	JoLO	MINT	RCFT Copy	RCFT Immed	RCFT Delay	RCFT Rec	NS Back	NS Fwd	TMT-A	TMT-B	FAS
$MoCA_{MIS}$	.162**	.068	.063	.126*	.164**	.152**	.162*	.190**	.103*	-.195**	-.176**	.166**
$MoCA_{EF}$	.238**	.305**	.241**	.290**	.136**	.115*	.080	.226**	.176**	-.208**	-.302**	.388**
$MoCA_{Attn}$	.186**	.343**	.207**	.238**	.171**	.153**	.114*	.299**	.272**	-.180**	-.299**	.159**
$MoCA_{Lang}$	.276**	.202**	.215**	.101	.065	.057	.107*	.254**	.193**	-.149**	-.191**	.409**
$MoCA_{VS}$	.174**	.326**	.207**	.436**	.222**	.196**	.219**	.127*	.062	-.221**	-.299**	.125*

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Results & Conclusions

- Despite statistically significant correlations between the MoCA indices and other well-established measures of domain functioning, there is weak evidence of construct validity for the indices. Effect sizes are weak and reveal limitations in the MoCA's ability to accurately characterize domain functioning.
- The MoCA memory index was weakly correlated to the Rey Complex Figure Test immediate (r = .16), delayed (r = .15) (p_s < .01), and recognition (r = .16) trials (p < .05). The language index was moderately correlated to F-A-S letter fluency (r = .41), but only weakly correlated to Animal Fluency (r = .28) and the MINT (r = .22) (p_s < .01).
- The MoCA indices do not adequately relate to performance on full-length cognitive tests of the same domains, suggesting that evaluation of index scores cannot reliably predict performance across all domains of neuropsychological functioning.
- Current research examining the MoCA indices has shown moderate to strong correlations between MoCA indices and standardized domain scores within a cognitively impaired sample[3]. Additionally, Cecato *et al.* found that specific items from the MoCA could discriminate between healthy controls and Alzheimer's disease patients, as well as between those with Mild Cognitive Impairment and Alzheimer's disease[4].
- Our research supports the notion that comprehensive neuropsychological testing is needed to accurately assess the domains of cognitive functioning during the preclinical phase of disease in order to detect early and subtle signs of change.
- Future research on the MoCA indices should utilize cognitively heterogeneous samples of individuals to better understand the clinical usefulness of the indices to differentiate populations and predict future decline.

*** References available on handout.**

Mental Health and Demographic Characteristics, but Not Parental History, Influence Subjective Ratings of Cognitive Functioning

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Introduction

- As our population ages, more individuals are seeing their loved ones succumb to Alzheimer's disease (AD). Children of adults with AD are more likely to report subjective concerns[1]. The strongest predictors are factual knowledge of the disease and negative self-assessments of memory[2].
- There is an increased risk for the development of AD in African Americans[3], as well as decreased factual knowledge about the disorder[4]. However, previous research on subjective cognitive decline has focused primarily on Caucasian populations.
- Subjective memory complaints have also been linked to depression and overall mental health[5].

Objective

We examined predictors of subjective cognitive complaints in Caucasian and African American older adults. We hypothesized that parental history and psychological functioning would predict subjective ratings on the Cognitive Function Instrument (CFI).

Method

- Older adult (M_{age} = 64.37, SD_{age} = 7.99) participants completed an online health history questionnaire as part of a prospective study of preclinical MCI and AD.
- Participants provided basic demographic information and family medical history, and rated their current symptoms.
- Overall CFI score was regressed onto the following predictors in a standard multiple regression: scores from the Generalized Anxiety Disorder 7-item scale (GAD-7), Patient Health Questionnaire depression scale (PHQ-8), ratings of overall physical (0-4) and mental health (0-4), age, race, and parental history.
- Participant characteristics for the full sample are included in the table. Only those participants with a complete CFI (N = 3984) were included in the regression analysis.

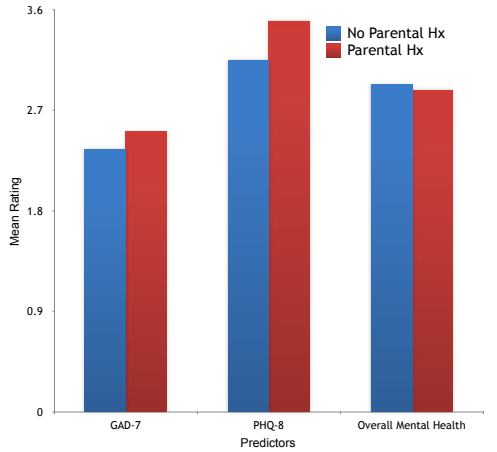
This data comes from the Emory Healthy Aging Study which is funded by the Goizueta Foundation.

Results

Participant Characteristics

Demographics	Participants		
	Range	(%)	M (*SD*)
Age	50 - 90		64.37 (7.99)
Female	-----	(76.0%)	-----
Male	-----	(23.7%)	-----
Education (≤15 Years)	0 - 22	(23.5%)	-----
Education (>15 Years)	0 - 22	(76.4%)	-----
Model Predictors			
GAD_total	0 - 21		2.15 (3.17)
PHQ_total	0 - 23		3.07 (3.70)
CFI_total	.0 – 14.0		1.96 (2.13)
Overall Physical Health	.00 – 4.00		2.77 (0.88)
Overall Mental Health	.00 – 4.00		2.98 (0.84)

Subjective Symptom and Health Ratings in Those With vs. Without a Parental History of AD



Note: ***Groups are significantly different, $p < .05$.

Mean ratings of self-reported symptoms using GAD-7, PHQ-8, and Overall Mental Health questions.

- The full regression model explained 36.5% of the variance in CFI score, $F(8,3975) = 285.37$, $p < .001$.
- The following were significant predictors: age, race, GAD-7, PHQ-8, and mental health rating.

Results (Cont.)

- 58.7% reported no parental history of AD or related memory problems, while 41.3% endorsed parental history for at least one parent.
- Neither parental history nor Overall Physical Health predicted CFI score.
- African Americans were more likely to report subjective cognitive complaints.

Table 2. Parameter Estimates of Predictors of CFI

Initial Visit Predictors	*B*	SE	Sig.
GAD-7	.092	.012	< .001
PHQ-8	.205	.011	< .001
Overall Mental Health	-.423	.041	< .001
Overall Physical Health	-.068	.037	.065
Age	.029	.002	< .001
Race	.495	.086	< .001
Parental History	.064	.059	.277

Conclusions

- Parental history did not predict perceptions of cognitive decline. Instead, minority race, older age, and greater psychological symptomatology were significant predictors.
- The finding of greater subjective cognitive complaints in African Americans differs from previous research[4], and may indicate success in more proactive self-monitoring. It has been hypothesized that subjective memory complaints could be a risk factor for developing AD[6].
- Those with psychological symptomatology are at a higher risk of perceived cognitive decline. These individuals should be monitored to determine if the subjective cognitive decline is a manifestation of the first signs of AD, or if it is more simply a side effect of a mental health disorder.

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Preliminary Assessment of a Flanker Smartphone App: Reliability, Feasibility, and Construct Validity

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EMORY Healthy Aging Study

EMORY UNIVERSITY SCHOOL OF MEDICINE

Introduction

- The widespread use of smartphones has led investigators to adopt this accessible technology for cognitive research (Defau et. al, 2011) through development of mobile applications that assess cognitive functioning (Dahmen, et. al., 2017; Ruggeri et. al., 2016).
- Remote cognitive assessment offers many benefits, including increased accessibility to large, heterogeneous samples and earlier detection of cognitive decline (Bauer et. al, 2012).
- We developed a smartphone app version of the computerized Flanker assessment to measure processing speed, visual attention, and inhibition.
- An ongoing pilot study assesses the reliability, construct validity, and feasibility of our mobile application ('Arrows').

Method

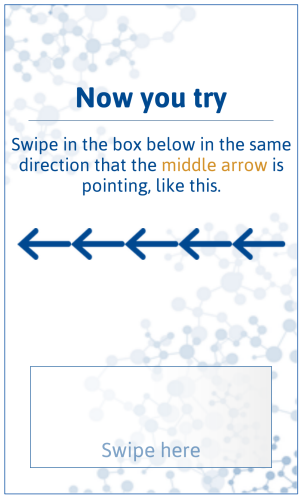
- Cognitively normal non-Hispanic Caucasian and African-American middle-aged and older adult smartphone users (N = 64) participated in a validation study of smartphone applications developed for remote cognitive assessment.
- Participants completed the original Flanker assessment and the novel Arrows application as well as other cognitive measures: Montreal Cognitive Assessment (MoCA), Wide Range Achievement Test-Word Reading subtest (WRAT), and Symbol-Digit Modalities Test (SDMT).
- Arrows reaction times were correlated to Flanker reaction times as well as other neuropsychological measures to assess reliability and construct validity. A paired samples t-test evaluated the difference between congruent and incongruent trial reaction times.
- Feasibility of the Arrows app was assessed through a self-report scale.

Participants

Table 1. Participant Characteristics

	Range	*M*	*SD*	%
Demographic Variables (N = 64)				
Age (years)	[45-75]	61.27	7.49	
Education (years)	[12-20]	16.52	2.32	
Gender (% female)				89.1
Race (% of sample)				
African American (N = 35)				54.7
Non-Hispanic Caucasian (N = 29)				45.3
Handedness (% Right)				85.9
Phone Model (% iPhone)				60.9

This project was supported by the Emory Healthy Aging Study, which is funded by the Goizueta Foundation, as well as through an NIH/NIA R03 grant (1R03AG055810).



Results

Table 2. Correlations Between Arrows and Neuropsychological Measures

Test Name	Flanker Mean RT	Flanker Congruent trials	Flanker Incongruent trials	MoCA Total	MoCA Attention	MoCA Visuospatial	MoCA Language	SDMT Total
Arrows Mean reaction time	.352**	--	--	-.295*	-.099	-.397**	-.149	-.221
Arrows Congruent trials	--	.362**	--	--	--	--	--	--
Arrows Incongruent trials	--	--	.316*	--	--	--	--	--

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).
Note: all reaction times are presented in milliseconds.

Table 3. Feasibility Ratings

Feasibility Assessment	Mean Rating (1-5)
I think that I would like to use this app frequently.	3.75 (1.07)
I found the app unnecessarily complex.	1.48 (.71)
I thought the app was easy to use.	4.36 (1.06)
I think that I would need tech support to use this app.	1.22 (.49)
Most people would learn to use this app quickly.	4.11 (.98)
I needed to learn a lot of things before using this app.	1.36 (.72)

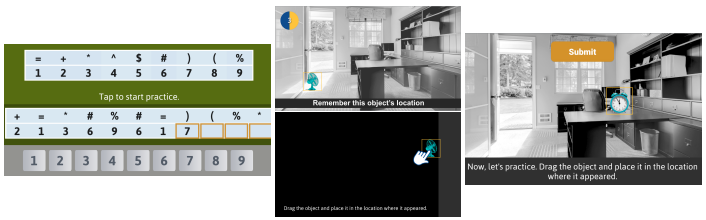
Note: Ratings were on a 1-5 scale, on which: 1= Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, and 5 = Strongly agree.

Results (cont.)

- The time difference between congruent (*M* = 1295.67 ms, *SD* = 466.65) and incongruent trials (*M* = 1283.22 ms, *SD* = 524.91) was not statistically significant, $t(62) = .29$, $p = .77$.
- There was significant agreement between overall, congruent, and incongruent trial reaction times on the Flanker and Arrows tasks.
- Mean reaction time on Arrows trials was significantly related to performance on the MoCA, and in particular, the visuospatial index of the MoCA. Mean reaction time on Arrows was not related to the SDMT total score, the MoCA attention index, or the MoCA language index.
- Participants rated the app as easy to understand and use.

Conclusions & Future Directions

- There is preliminary evidence for task reliability given the relationship between Arrows and Flanker reaction times. However, total performance scores between the two tasks cannot be evaluated since the majority of our sample obtained a perfect score on Arrows, suggesting that it differs in difficulty level from the Flanker.
- There is currently no difference in reaction time between congruent and incongruent trials on Arrows. This may be related to user response style (one-handed responding) that is specific to smartphone use.
- Arrows was significantly related to overall cognitive functioning and visuospatial skills. Arrows was not significantly related to cognitive tasks assessing language, attention, and executive functioning. These relationships provide initial evidence of convergent and discriminant construct validity.
- Future research will incorporate task modifications to increase the overall difficulty of Arrows to allow for greater performance variability and the detection of performance differences between diagnostic groups.
- Future research will also assess the reliability, feasibility, and construct validity of additional app-based measures of cognition (pictured below).



Journal of Affective Disorders 263 (2020) 310–317

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Purpose in life is a robust protective factor of reported cognitive decline among late middle-aged adults: The Emory Healthy Aging Study

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A B S T R A C T

Background: Cognitive abilities tend to decline in advanced age. A novel protective factor of cognitive decline in advanced age is purpose-in-life (PiL), a trait-like tendency to derive life meanings and purpose. However, whether PiL protects against cognitive decline in late-middle-age is unclear. Hence, we examined the association between PiL and perceived cognitive decline, one of the earliest detectable cognitive symptoms before the onset of cognitive impairment. Furthermore, we used a machine learning approach to investigate whether PiL is a robust predictor of cognitive decline when considered with the known protective and risk factors for cognition.

Methods: PiL was assessed with a 10-item questionnaire and perceived cognitive decline with the Cognitive Function Instrument among 5,441 Emory Healthy Aging Study participants, whose mean age was 63 and 51% were employed. Association between PiL and perceived cognitive decline was examined with linear regression adjusting for relevant confounding factors. Elastic Net was performed to identify the most robust predictors of cognitive decline.

Results: Greater PiL was associated with less perceived cognitive decline after adjusting for the relevant factors. Furthermore, Elastic Net modeling suggested that PiL is a robust predictor of cognitive decline when considered simultaneously with known protective (education, exercise, enrichment activities) and risk factors for cognition (depression, anxiety, diagnosed medical, mental health problems, smoking, alcohol use, family history of dementia, and others).

Limitation: This is a cross-sectional study.

Conclusions: PiL is a robust protective factor of perceived cognitive decline observed as early as middle age. Thus, interventions to enhance PiL merit further investigation.

Introduction

Cognitive abilities tend to decline in older age, and cognitive decline is a major concern for older adults (Deary et al., 2009; Wilson et al., 2002; Zaninotto et al., 2018). Cognitive decline may lead to overt impairment of cognition and thus a diagnosis of mild cognitive impairment (MCI) or, eventually, dementia (Rajan et al., 2015; Scheltens et al., 2016). Longitudinal studies have shown that subtle decline followed by a slow but more progressive decline of cognitive performance can precede the onset of MCI or dementia by up to 20 years, a period referred to as prodromal phase (Bilgel et al., 2018; Boyle et al., 2017; Li et al., 2017; Rajan et al., 2015).

Early detection of cognitive decline is essential to identify individuals at risk for MCI or dementia so that preventive treatments can be implemented to halt the progression from normal cognition to MCI or dementia (Scheltens et al., 2016). Interestingly, a growing literature suggests that the earliest detectable cognitive symptoms in the prodromal phase is a person's perception of his/her decline in cognitive abilities relative to previous level of performance, also known as perceived cognitive decline (Rabin et al., 2017; Scheef et al., 2012; Scheltens et al., 2016). Perceived cognitive decline can capture longitudinal change of cognitive abilities and predict objectively measured cognitive decline in longitudinal studies (Dufouil et al., 2005; Koppara et al., 2015; Rabin et al., 2017). Furthermore, the ability to detect cognitive impairment with neuropsychological tests is best at high levels of impairment, but decreases as people perform closer to the

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https://doi.org/10.1016/j.jad.2019.11.124
Received 6 June 2019; Received in revised form 19 October 2019; Accepted 29 November 2019
Available online 30 November 2019
0165-0327/ Published by Elsevier B.V.

normal ability range, whereas perceived cognitive decline is likely more sensitive (Rabin et al., 2017). Perceived cognitive decline in individuals clinically defined as cognitively normal has been found to be associated with Alzheimer's disease biomarkers and with higher rate of conversion from normal cognition to MCI or dementia in subsequent years (Jessen et al., 2010; Kaup et al., 2015; Rabin et al., 2017).

Purpose-in-life (PiL) is a recently recognized protective factor against cognitive decline (Boyle et al., 2010a, 2012; Kim et al., 2019). PiL here refers to a trait-like tendency to derive meaning from life experiences and to possess a sense of direction and purpose in life. Life purpose and meanings have been conceptualized as highly related. For instance, Reker and Wong defined life meaning as "the cognizance of order, coherence, purpose in one's existence, the pursuit and attainment of worthwhile goals, and an accompanying sense of fulfillment" (Zika and Chamberlain, 1992). Likewise in the more recent psychological literature, the greatest consensus in defining life meaning has centered on two dimensions – coherence (one's comprehension and sense made of life) and purpose (one's core aims and aspirations for life) (Martela and Steger, 2016). PiL is potentially modifiable and may be a target for treatment (Breitbart et al., 2012; Kissane et al., 2019; Park et al., 2019). Higher PiL has been associated with a slower decline in cognitive performance over time in advanced age in two longitudinal cohorts, the Rush Memory and Aging Project (MAP) and the Health and Retirement Study (Boyle et al., 2012; Kim et al., 2019). Additionally, higher baseline PiL was associated with lower incidence of MCI and of Alzheimer's dementia in the Rush MAP cohort (Boyle et al., 2010b). These findings point to an intriguing association between higher PiL and cognitive stability in advanced age. Participants in the prior studies tended to be older (mid-70 s) and retired (Boyle et al., 2010a, 2012; Kim et al., 2019). Hence, the relationship between PiL and cognitive decline is unclear among employed, younger adults in their 50 s and 60 s.

This present study examines whether PiL is associated with perceived cognitive decline, which may be among the earliest manifestations of cognitive symptoms before the expression of MCI or dementia, in primarily mid-life adults. Furthermore, we used a machine learning approach to investigate whether PiL is a robust predictor of perceived cognitive decline when considered with the known protective factors (i.e. education, exercise, enrichment activities) and risk factors (depression, anxiety, smoking, alcohol use, diagnosed medical and mental health problems, and family history of dementia) for cognition simultaneously (Becker et al., 2018; Bellou et al., 2016; Bhattarai et al., 2019; Milgram et al., 2006; Scheltens et al., 2016). We hypothesized that greater PiL is a robust predictor of less perceived cognitive decline among late-middle-aged individuals.

Methods

2.1. The Emory Healthy Aging Study (EHAS)

Participants in this study were from the EHAS, a longitudinal, online study launched in November of 2014 that aims to better understand factors that contribute to healthy aging and identify markers that can predict common age-related diseases such as Alzheimer's disease, cardiovascular disease, diabetes mellitus, and others. To date, the study has enrolled 20,523 consented community-based registrants from the greater Atlanta area and follows these individuals over time. EHAS participants complete surveys and health history questionnaires that include their family's medical history, age, sex, race, education, employment status, marital status, income, and many other factors as described below. All study procedures were approved by the Emory Institutional Review Board.

2.2. Psychological factors

Purpose-in-life (PiL) refers to a trait-like tendency to derive meaning from life experiences and to possess a sense of direction and purpose in life. It was assessed with a modified 10-item measure derived from Ryff's and Keyes's scale of psychological well-being, which has been evaluated psychometrically (Abbott et al., 2010, 2006; Ryff and Keyes, 1995). For this 10-item PiL scale, the Cronbach's coefficient alpha was 0.73 indicating a moderate level of internal consistency (Barnes et al., 2007). Some of these items are i) I feel good when I think of what I've done in the past and what I hope to do in the future; ii) I live life one day at a time and do not really think about the future; iii) I have a sense of direction and purpose in life. Participants rated their level of agreement with these items using a 5-point scale, 1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, and 5 = strongly agree. Ratings of items that were negatively worded were reverse-coded so that higher scores on all individual items indicate greater PiL. We took the average of the ratings for these 10 items to represent each participant's PiL, with higher scores indicating greater levels of meaning, purpose, and direction in life.

Current depressive symptoms were assessed with the eight-item Patient Health Questionnaire depression scale (PHQ-8) (Kroenke et al., 2009). The PHQ-8 is a valid measure of current depression in the general population (Kroenke et al., 2009). Response to each item ranges from 0 to 3, with higher score indicating more severity, and the total score on the PHQ-8 ranges from 0 – 24. A PHQ-8 score of 10 or more indicates clinically significant current depression (Kroenke et al., 2009). We excluded participants who did not respond to more than one question from the PHQ-8. In addition, to take into account potential missing response in one question on the PHQ-8, we took the average of the responses to these eight items to represent each participant's current depressive symptoms. Hence, our participants' PHQ-8 scores range from 0 to 3, with a score of 1.25 representing clinically significant current depression.

Current anxiety symptoms were evaluated with the GAD-7 scale (Spitzer et al., 2006), a well-validated tool for assessing symptoms of generalized anxiety disorder. The GAD-7 has been validated both in the general population (Lowe et al., 2008) and primary care setting (Spitzer et al., 2006), showing excellent internal consistency (Cronbach $\alpha = 0.92$) and very good test-retest reliability (intraclass correlation = 0.83). Scores from the GAD-7 range from 0 to 21, with higher scores reflecting more anxiety symptoms. Participants who did not respond to more than one item on the GAD-7 were excluded from our analysis. To take into consideration potential non-response to one item on the GAD-7, we took the average of the responses for the seven items to represent current anxiety score for each participant; hence, our participants' GAD-7 scores range from 0 to 3, with a score cutoff of 0.7, 1.4, and 2.1 representing mild, moderate, and severe anxiety, respectively (Spitzer et al., 2006).

2.3. Behavioral health

The following self-reported behavioral health variables were used: ever smoked cigarettes, current alcohol use, current strenuous exercise, current non-strenuous exercise, current walking, and enrichment activities. Smoking was treated as a binary variable of yes or no in our analyses. Alcohol use in the last 12 months was assessed with respect to frequency and amount. Frequency of moderate to strenuous exercise (aka exercise frequency here), frequency of exercise through hobbies such as slow dancing, bowling, or golfing (aka exercise through hobby here), and frequency of walking were assessed. Enrichment activities such as reading newspapers, magazines, books, writing letters or e-mails, and playing board games were assessed and treated as a semi-quantitative variable with higher value indicating more enrichment activities that a participant performed.

2.4. Medical health

The following self-reported medical health conditions were

collected and used in our analyses: high blood pressure, stroke or transient ischemic attack, heart attack, coronary heart disease, congestive heart failure, atrial fibrillation, high cholesterol, pulmonary embolism, deep vein thrombosis, blood clots, other circulatory or vascular system problem, migraine, mild cognitive impairment or memory loss, Alzheimer's disease, other dementia, concussion, traumatic brain injury, spinal cord injury, seizures, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, other nervous system problems, tuberculosis, hepatitis B or C, HIV or AIDS, kidney disease, chronic lung disease, sleep apnea, thyroid problems, diabetes, organ transplant, pulmonary fibrosis, and other disease. For our analyses, the sum of all positive responses was used to indicate the burden of medical problems for each participant.

2.5. Mental health

Participants were asked if a doctor has ever diagnosed them with any of the following conditions: Post-traumatic stress disorder, bipolar disorder, depression, schizophrenia, other mental health disorder. For analysis, the sum of all positive responses was used to indicate the burden of mental health problems for each participant.

2.6. Family history

Maternal and paternal history of dementia was collected and used in our analyses. Family history of dementia for each parent was assessed in a systematic fashion. Participants were asked if their biological father was ever diagnosed with MCI or AD, memory loss, confusion or other dementia. If a participant answered "yes" to any of these questions, paternal history of dementia was coded as yes; otherwise, it was coded as no. Likewise, participants were asked if their biological mother was ever diagnosed with MCI or AD, memory loss, confusion or other dementia. If a participant answered "yes" to any of these questions, then maternal history of dementia was coded as yes; otherwise, it was coded as no.

2.7. Perceived cognitive decline

We used the Cognitive Function Instrument (CFI) to assess perceived memory decline and cognitive decline that interferes with daily functioning. The CFI has been shown to be a sensitive and reliable instrument in tracking early decline in cognitive function in older adults who do not have cognitive impairment at baseline in longitudinal studies (Amariglio et al., 2015; Li et al., 2017). Specifically, perceived memory decline was assessed using six questions from the CFI. Some of these items are: Please think about your current experiences *compared to one year ago*: (1) Do you feel that your memory has declined substantially? (2) Do others tell you that you tend to repeat questions over and over? (3) Have you been misplacing things more often? Response to each question was based on a 3-point scale, with 0 = no, 1 = maybe, 2 = yes. For each participant, the average score from these six questions was used to represent his/her perceived memory decline, with higher scores reflecting more perceived memory decline.

Cognitive decline that interferes with daily activities was assessed with eight questions from the CFI. Some of them are: Please think about your current experiences *compared to one year ago*: (1) Do you have more trouble driving (drive more slowly, tend to get lost, have accidents)? (2) Do you have more difficulty managing money? (3) Are you less involved in social activities? Response to each question was based on a 3-point scale, with 0 = no, 1 = maybe, 2 = yes. The average score from these eight questions was used to represent each participant's perceived cognitive decline, with higher scores reflecting worse cognitive decline that interfere with daily functioning.

2.8. Statistical analysis

Linear regression was used to assess for association between PiL and perceived memory decline, adjusting for age, sex, education, employment status, current depressive symptoms, current anxiety symptoms, the number of diagnosed medical problems, and the number of diagnosed mental health problems. A second linear regression model was performed to assess for association between PiL and cognitive decline that interferes with daily functioning, adjusting for the same covariates listed above.

Next, Elastic Net was used to select independent predictors and estimate their effects for perceived cognitive decline. Elastic Net is a machine learning algorithm for regularization of regression models combining Ridge and Lasso, which balances the model selection so that it is not overly complex (i.e. overfitted) or too simple (i.e. underfit) (Friedman et al., 2010). In other words, Elastic Net fits a model with all the provided variables (sometimes called features) but constrains the coefficients by shrinking the uninformative ones to zero. Data from the EHAS was divided into a training dataset and a test dataset using random sampling with a ratio of 2:1. Then we performed cross validation of the training dataset to obtain different models with different coefficient α values, ranging from 0 to1 (interval = 0.1). For each α value, we applied the corresponding model on our test dataset to predict the outcome. Then we calculated mean square error (MSE) or misclassification rate for each model. We declared the best model to be the one with the lowest MSE. In the best model, the coefficient estimates for particular variables indicate that these variables are robust predictors for the outcome. Variables without a coefficient estimate are not considered robust predictors of the outcome. Our primary analyses were to determine which variables best predicted i) perceived memory decline, and ii) cognitive decline interfering with daily activities, respectively. The predictors we included in the Elastic Net models were PiL, age, sex, education, employment status, marital status, income, current depressive symptoms, current anxiety symptoms, walk frequency, exercise frequency, frequency of exercising via hobbies, enrichment activities, smoking status, average sleep duration a night, frequency of alcohol use, typical amount of alcohol use, the number of diagnosed medical problems, the number of diagnosed mental health problems, the number of medications currently taking, maternal history of dementia, and paternal history of dementia. Due to different rates of missingness, sample sizes varied when including different variables in the model. We standardized the scales of all the predictors to provide standardized coefficients from the Elastic Net models. Of note, all the standardized coefficients for the robust predictors from Elastic Net models may be biased upward due to the nature of regularization (Friedman et al., 2010). All Elastic Net analyses were performed with the R 'glmnet' package version 3.5.1 (Friedman et al., 2010).

3. Results

3.1. Characteristics of the Emory Healthy Aging Study (EHAS) participants

A total of 5441 EHAS participants had data on PiL, perceived memory decline, and cognitive decline interfering with daily functioning available for analysis. Their mean age was 63, 71% were female, 84% were Caucasian, 70% were married, mean education was 17 years, 51% were employed, and incomes ranged from $40,000 or less to $150,000 or more per year (Table 1 and Supplementary Table 1). With regard to age range, 4% of the participants were younger than 40, 46% were between 40 and 65, and 49% were older than 65.

Among these participants, 25% reported exercising once to twice a week, 27% reported exercising 3 to 4 days a week, and 11% more than five days a week. Participants reported engaging in a mean of 3 enrichment activities a week. With regard to tobacco and alcohol use, 33% of the participants reported having smoked cigarettes in the past, and 37% reported drinking alcohol three or more times a week (Table 1

Table 1
Characteristics of the Emory Healthy Aging Study participants (N = 5441). Please make sure the numbers in column 2 line up correctly with the variables in column 1. Based on what I saw, they are not.

Variable	Mean (SD), Median, Range
Age	63.5 (11.3), 65, [20–96]
Education level (years)	16.9 (2.8), 16, [8–22]
Female sex (N, %)	3837 (70.6%)
Ethnicity (N, %)	
White	1883 (83.7%)
African Americans	206 (9.1%)
Others	161 (7.2%)
Employment (N, % employed)	2747 (50.5%)
Marital status (N, %)	
Married	3779 (69.6%)
Separated	1167 (21.5%)
Never married	484 (8.9%)
Income (N, %)	
$39,999 or less	473 (9.1%)
$40,000 to $59,999	632 (12.2%)
$60,000 to $99,999	1360 (26.3%)
$100,000 to $149,999	1264 (24.4%)
$150,000 or more	1453 (28.0%)
Exercise frequency (N, %)	
None	2008 (36.9%)
1–2 days/week	1374 (25.2%)
3–4 days/week	1464 (26.9%)
5 or more days/week	590 (10.9%)
Exercise through hobby (N, %)	
None	3023 (56.9%)
1–2 days/week	1580 (29.7%)
3–4 days/week	493 (9.3%)
5 or more days/week	219 (4.1%)
Walk frequency (N, %)	
Rarely/never	503 (9.3%)
1–4 times a month	1010 (18.7%)
2 to 6 times a week	2749 (50.9%)
7 or more time a week	1136 (21.0%)
Sleep duration (N, %)	
6 or fewer hours a night	1614 (29.7%)
7 to 8 h a night	3410 (62.7%)
9 or more hours a night	413 (7.6%)
Enrichment activity	2.8 (0.7), 2.8, [0–4]
Purpose in life	4.0 (0.6), 4.1, [1.2–5.0]
Depressive symptoms	0.3 (0.4), 0.2, [0–3]
Anxiety symptoms	0.3 (0.4), 0.1, [0–3]
Ever smoke (yes, N, %)	1814 (33.4%)
Alcohol use frequency (N, %)	
No drinks in past year	654 (12.5%)
1 to 11 times in past year	883 (17.1%)
1 to 3 times a month	844 (16.3%)
1 to 2 times a week	914 (17.7%)
3 to 4 times a week	681 (13.2%)
5 to 7 times a week	1208 (23.4%)
Number of diagnosed medical problems	2.4 (2.1), 2, [0–34]
Number of diagnosed mental health problems	0.4 (0.7), 0, [0–5]
Number of medications taken for medical or mental health problems	1.4 (1.3), 1, [0–21]
Memory compared to 10 years ago (N, %)	
Same, better	2496 (48.2%)
Worse or much worse	2685 (51.8%)
Perceived memory decline	0.4 (0.4), 0.3, [0–2]
Cognitive decline affecting functioning	0.1 (0.3), 0, [0–2]

and Supplementary Table 1). Participants reported a mean of 2.4 diagnosed medical problems, a mean of 0.4 diagnosed mental health problem, and taking a mean of 1.4 medications for these problems (Table 1). Most participants did not have clinically significant current depressive or anxiety symptoms based on the score ranges for these measures (Table 1).

PiL among the EHAS participants ranged from 1.2 to 5, with a mean of 4, and median of 4.1, which is slightly higher than the mean PiL score of the Rush Memory and Aging cohort (mean PiL of 3.7; mean age at enrollment of 80) (Boyle et al., 2010a, 2012) and consistent with prior studies showing that PiL declines slightly with advancing age.

Among these participants, 52% reported that their memory was worse compared to ten years before (Table 1). However, their median score for perceived memory decline was 0.3, reflecting minimal perceived memory decline (Table 1). Likewise, their median score for cognitive decline that interferes with functioning was 0 indicating that at least 50% of the participants did not have cognitive decline that affected their daily functioning (Table 1). Indeed, 62% of the participants reported no cognitive decline that interfered with daily functioning (i.e. having a score of 0), consistent with a younger age range and still-employed status in these participants.

To investigate whether PiL is a robust predictor of perceived cognitive decline as early as middle age, we performed Elastic Net on a subset of participants aged 40 to 65, whose characteristics are presented in Supplementary Table 2. In this subset of middle-aged participants, mean age was 57, median age 58, and age ranged between 40 and 65.

3.2. Pairwise correlation between purpose in life and other sociodemographic characteristics

From pairwise correlations we found that higher PiL was associated with younger age, more years of education, being married, being employed, higher income, more enrichment activities, more frequent walk, more frequent exercise, longer sleep duration a night, less depressive symptoms, less anxiety symptoms, never smoked, and drinking alcohol 3 to 4 times a week (Table 2 and Supplementary Table 1). Likewise, higher PiL was associated with having fewer diagnosed medical problems, fewer diagnosed mental health problems, less perceived memory decline, less cognitive decline that interferes with daily functioning, and less memory decline compared to 10 years ago (Table 2 and Supplementary Table 1). Notably, PiL was not associated with sex or race (Table 2 and Supplementary Table 1).

Among participants aged 40 to 65, the pairwise associations between PiL and education, marital status, employment, income, enrichment activities, exercise, current depressive and anxiety symptoms, number of diagnosed medical and mental health problems, number of medications currently taking, perceived memory decline, perceived cognitive decline interfering with daily functioning are similar to those seen in all the participants (Supplementary Table 3).

3.3. Association between purpose in life and perceived cognitive decline

We found that higher PiL was associated with less perceived memory decline after adjusting for age, sex, education, current depressive symptoms, current anxiety symptoms, number of diagnosed medical problems, number of diagnosed mental health problems, and employment status ($\beta = -0.03$; $p = 0.018$, $N = 4536$). Likewise, higher PiL was associated with less cognitive decline that interferes with daily functioning after adjusting for the same above-mentioned covariates ($\beta = -0.05$; $p = 8.2E\text{-}14$, $N = 4534$). While employment status was not predictive of perceived memory decline ($\beta = -0.02$; $p = 0.15$), it predicted cognitive decline that interfere with daily functioning ($\beta = -0.03$; $p = 2.3E\text{-}06$). These findings suggest that higher PiL is associated with less perceived memory decline regardless of the employment status. However, for more severe cognitive decline such as cognitive decline that interferes with functioning, being employed was associated with less cognitive decline.

3.4. Identifying robust predictors of perceived cognitive decline using elastic net

Since PiL was associated with the known protective factors of cognition, such as education, exercise, enrichment activities, and inversely

Table 2
Pairwise correlations between purpose-in-life and other characteristics among EHAS participants. Please make sure there's enough room for column 2 (p-value)

Characteristics	p-value*	Direction of association
Age	0.002	Higher PiL ~ lower age
Sex	0.133	N/A
Race	0.632	N/A
Education (years)	< 2.2e-16	Higher PiL ~ more years of education
Marital status	< 2.2e-16	Higher PiL ~ being married
Employment	< 2.2e-16	Higher PiL ~ being employed
Income	< 2.2e-16	Higher PiL ~ higher income level
Enrichment activities	3.2e-10	Higher PiL ~ more enrichment activities
Walk frequency	< 2.2e-16	Higher PiL ~ higher walk frequency
Exercise frequency	< 2.2e-16	Higher PiL ~ higher exercise frequency
Exercise through hobby	6.7e-09	Higher PiL ~ more frequent exercise
Sleep duration (hours)	2.5e-07	Higher PiL ~ longer sleep duration
Depressive symptoms	< 2.2e-16	Higher PiL ~ lower depressive symptoms
Anxiety symptoms	< 2.2e-16	Higher PiL ~ fewer anxiety symptoms
Ever smoke	1.1e-10	Higher PiL ~ never smoked
Alcohol use	1.5e-06	Higher PiL ~ drink alcohol a few times a week
Number of diagnosed medical problems	< 2.2e-16	Higher PiL ~ fewer diagnosed medical problems
Number of diagnosed mental health problems	< 2.2e-16	Higher PiL ~ fewer diagnosed mental health problems
Number of medications currently taking	7.9e-06	Higher PiL ~ fewer medications
Perceived memory decline	< 2.2e-16	Higher PiL ~ less perceived memory decline
Cognitive decline interfering with functioning	< 2.2e-16	Higher PiL ~ less cognitive decline that interferes with functioning
Memory worse compared to 10 years ago	< 2.2e-16	Higher PiL ~ less perceived memory decline compared to 10 years ago

*For continuous variables, Spearman correlation test was used. For categorical variables, ANOVA was used. See Supplementary Table for correlation coefficients.

associated with known risk factors of cognition including current depressive and anxiety symptoms, diagnosed medical and mental health problems, and alcohol and smoking habit, we sought to address whether PiL is a proxy for these protective factors or is an independent robust protective factor for cognitive stability. Thus, we used Elastic Net, a machine learning approach, to select the most robust risk and protective factors for the outcomes of (i) perceived memory decline and (ii) cognitive decline that interferes with functioning. We tested the following variables as potential predictors: PiL, age, sex, education, employment status, marital status, income, current depressive symptoms, current anxiety symptoms, walk frequency, exercise frequency, frequency of exercising via hobbies, enrichment activities, smoking status, average sleep duration a night, frequency of alcohol use, typical amount of alcohol use, the number of diagnosed medical problems, the number of diagnosed mental health problems, the number of medications taking currently, maternal history of dementia, and paternal history of dementia.

Table 3
Robust predictors of perceived memory decline from Elastic Net (N = 2737, α = 0.3). Variables with corresponding coefficients are considered important predictors of perceived memory decline.

Variable	Standardized coefficient
Purpose-in-life	−0.014
Age	–
Sex	–
Education (years)	–
Employment status	−0.003
Current depressive symptoms	0.102
Current anxiety symptoms	0.035
Frequency of walking	–
Frequency of exercise	−0.004
Number of enrichment activities	−0.017
Smoking status	–
Sleep duration a night	–
Marital status	–
Income	–
Frequency of exercising through hobbies	–
Frequency of alcohol use	–
Typical alcohol drink count per day	–
Number of diagnosed medical problems	0.013
Number of medications currently taking	0.013
Number of diagnosed mental health problems	0.004
Maternal history of dementia	–
Paternal history of dementia	–

"-" denotes coefficient approaching 0 or non-significant predictor.

Table 4
Robust predictors of perceived cognitive decline that interferes with daily functioning from Elastic Net (N = 2736, α = 1.0). Variables with corresponding coefficients are considered important predictors of cognitive decline that interferes with daily functioning.

Variable	Standardized coefficient
Purpose-in-life	−0.019
Age	–
Sex	–
Education (years)	–
Employment status	−0.009
Current depressive symptoms	0.110
Current anxiety symptoms	0.004
Frequency of walking	−0.001
Frequency of exercise	0.0009
Number of enrichment activities	−0.006
Smoking status	–
Sleep duration a night	–
Marital status	–
Income	–
Frequency of exercising through hobbies	–
Frequency of alcohol use	–
Typical alcohol drink count per day	–
Number of diagnosed medical problems	0.013
Number of medications currently taking	–
Number of diagnosed mental health problems	0.003
Maternal history of dementia	–
Paternal history of dementia	–

"-" denotes coefficient approaching 0 or non-significant predictor.

Elastic Net modeling suggests that PiL is a robust predictor of perceived memory decline and of cognitive decline that interferes with daily functioning (Tables 3 and 4). Particularly, we found the following important predictors for perceived memory decline in the order of higher to lower magnitude of effect - current depressive symptoms, current anxiety symptoms, number of enrichment activities, PiL, number of diagnosed medical problems, number of medications taking currently, number of diagnosed mental health problems, exercise frequency, and employment status (Table 3). For cognitive decline that interferes with daily functioning, we found the following robust

predictors in the order of higher to lower effect size - current depressive symptoms, PiL, number of diagnosed medical problems, employment status, number of enrichment activities, current anxiety symptoms, number of diagnosed mental health problems, frequency of walking, and frequency of exercise (Table 4).

Likewise, in the subset of participants aged 40 to 65, PiL is a robust predictor of perceived memory decline (Supplementary Table 4) and perceived cognitive decline interfering with daily activities (Supplementary Table 5). Interestingly, for perceived memory decline in middle age, all the predictors we provided were considered important based on Elastic Net, and PiL was ranked fourth in its effect size among the 22 predictors (Supplementary Table 4). The magnitude of effect of PiL on perceived memory decline was less than those of current depressive symptoms, marital status, and current anxiety symptoms based on the standardized coefficients from Elastic Net (Supplementary Table 4). For perceived cognitive decline that interferes with daily functioning in middle age, PiL was ranked third among the 12 robust predictors (Supplementary Table 5). The salient predictors of perceived cognitive decline that interferes with functioning in the order of higher to lower magnitude of effect were current depressive symptoms, employment status, PiL, current anxiety symptoms, number of enrichment activities, number of diagnosed mental health problems, number of diagnosed medical problems, frequency of exercise, income, frequency of walking, typical alcohol drink counts per day, and education (Supplementary Table 5).

4. Discussion

PiL has been suggested to be a novel protective factor for cognitive decline in advanced age in two longitudinal community-based cohorts of older (baseline mean age of 79 and 73, respectively), retired individuals (Boyle et al., 2012; Kim et al., 2019). Here, we investigated whether PiL is also a mitigating factor for cognitive decline among community-based participants with a younger age range (mean age of 63) and 50.5% were employed. The age range of fifties and sixties tends to coincide with the prodromal phase before the onset of MCI or dementia, when some subtle cognitive changes may emerge. During this time period, mild cognitive difficulties may be difficult to distinguish from normal ability using neuropsychological testing due to issues related to test sensitivity and the adequacy of normative data (Rabin et al., 2017). Hence, we evaluated perceived cognitive decline because it has been suggested to be one of the earliest detectable cognitive symptoms during the prodromal phase. We found that higher PiL was indeed associated with less perceived memory decline and less reported cognitive decline that interferes with daily functioning after adjusting for potential confounding factors.

Next, we used a machine learning approach, Elastic Net, to examine whether PiL is simply a proxy for the known protective factors of cognition (i.e. education, exercise, enrichment activities) or an independent protective factor of cognitive decline. We found that higher PiL was an independent, robust predictor of less perceived memory decline and less reported cognitive decline that interferes with daily functioning when considered alongside the known protective factors (education, exercise, enrichment activities) and known risk factors for cognition (depression, anxiety, diagnosed medical problems, mental health problems, smoking, alcohol use, and family history of dementia). These findings hold true in the subset of middle-age participants aged 40 to 65. Together, our findings suggest that PiL is an important protective factor for cognitive decline among employed as well as retired persons as early as middle age.

Beyond being a robust protective factor of cognitive resilience against the effects of aging, PiL has been conceptualized as an important building block for psychological resilience and psychological well-being (Chen et al., 2019; Rutten et al., 2013; Ryff and Keyes, 1995). PiL is not simply the absence of depression; it has been shown to decrease the risk of depression (Wood and Joseph, 2010), post-traumatic stress disorder (Shrira et al., 2015), suicide ideation (Harlow et al., 1986; Kachadourian et al., 2019), alcohol and substance use (Martin et al., 2011; Roos et al., 2015), as well as risk of stroke (Kim et al., 2013b; Yu et al., 2015) and cardiovascular disease (Boehm et al., 2016; Kim et al., 2013a). PiL is a multidimensional construct influenced by both genetic and environmental factors (Keyes et al., 2010). Additionally, PiL is potentially modifiable and may be a target for treatment (Breitbart et al., 2012; Kissane et al., 2019; Park et al., 2019). For instance, a meta-analysis of randomized controlled trials evaluating effects of psychosocial interventions on meaning/purpose in adults with cancer found significant improvements in meaning/purpose with small to medium effect sizes (Park et al., 2019). Our study highlights the potential benefit of enhancing one's tendency for deriving purpose and meaning in life as a means of protecting against cognitive decline.

Our findings also shed light on the other important predictors of perceived memory decline and cognitive decline that interferes with daily functioning. For perceived memory decline, the important predictors in the order of higher to lower magnitude of effect include current depressive symptoms, current anxiety symptoms, number of enrichment activities, PiL, number of diagnosed medical problems, number of medications taking currently, number of diagnosed mental health problems, frequency of exercise, and employment status. The predominant predictors for perceived cognitive decline that interferes with daily activities in the order of higher to lower effect size include current depressive symptoms, PiL, number of diagnosed medical problems, employment status, number of enrichment activities, current anxiety symptoms, number of diagnosed mental health problems, frequency of walking, and frequency of exercise.

Our findings are consistent with observations that higher PiL was associated with better performance in episodic memory, executive function, and overall cognition in a cross-sectional study of 3489 middle-aged adults (mean age of 56) recruited by the Midlife in the US study (Lewis et al., 2017). While the Midlife in the US study shows an association between higher PiL and better objectively tested cognitive performance in mid-life, our findings suggest that higher PiL is an important predictor of less perceived memory decline as early as in middle age. Taken together, both studies suggest that PiL may be a robust protective factor for cognition as early as late middle age.

Interpretation of our findings should take into consideration the study's limitations. First, perceived memory decline was not based on cognitive testing but on self-perception. Therefore, perceived memory or cognitive decline can be influenced by mood state such as current depressive or anxiety symptoms. This concern is tempered by our adjustment for current depressive and anxiety symptoms in our regression models and Elastic Net models. Second, this is a cross-sectional study and thus we cannot establish a causal relationship between higher PiL and less perceived memory decline. There is a possibility that decline in cognition could reduce one's sense of purpose-in-life. Third, the generalizability of the study may be limited given that the majority of the participants were women, Caucasian, and highly educated.

Our study has some notable strengths. For instance, to our knowledge, this is the first study to examine the relationship between PiL and perceived cognitive decline, which constitutes one of the earliest detectable cognitive symptoms in the prodromal phase before the onset of MCI or dementia. In addition, we leveraged a machine learning approach to identify robust predictors of perceived cognitive decline. Furthermore, we performed the analyses in a subset of participants aged 40 to 65, of whom 73% were employed to provide insights into the important effects of PiL on perceived cognitive decline in an earlier life window, i.e. middle age, and among employed persons.

In conclusion, our findings together with the extant literature suggest that PiL is an important and novel protective factor against cognitive decline among middle-aged and advanced aged individuals regardless of their employment status. Future studies are needed to investigate the underlying mechanisms for this protective effect.

CRediT authorship contribution statement

Aliza P. Wingo: Formal analysis, Writing - original draft, Data curation. **Thomas S. Wingo:** Formal analysis, Data curation. **Wen Fan:** Formal analysis. **Sharon Bergquist:** Data curation. **Alvaro Alonso:** . **Michele Marcus:** Data curation. **Allan I. Levey:** Data curation. **James J. Lah:** Data curation.

Declaration of Competing Interest

None

Acknowledgements

We express our gratitude to the Emory Healthy Aging Study (EHAS) participants for their time and participation. We gratefully acknowledge the effort and support of the EHAS staff and Investigators.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.11.124.

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