Cytokines are associated with longitudinal changes in cognitive performance among urban adults

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A R T I C L E I N F O

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A B S T R A C T

Background: Chronic systemic inflammation has been positively associated with structural and functional brain changes representing early markers of Alzheimer's Disease (AD) and cognitive decline. The current study examined associations between systemic inflammation and cognitive performance among African-Americans and Whites urban adults.

Methods: Participants were selected from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (2004–2013, baseline age: 30–64 y, mean ± SD follow-up time of 4.64 ± 0.93 y, N = 189–222, k = 1.5–1.7 observations/participant). Cytokines known to be positively linked to AD incidence among others were tested against cross-sectional and longitudinal cognitive function, stratifying by age group (≤50 y vs. > 50 y), sex and race. A series of mixed-effects regression models were conducted, adjusting for key confounders.

Results: Among key findings, IL1β was positively associated with a faster rate of decline on a test of executive functioning, among older adults (age > 50 y, γ_{11} = +2.49 ± 0.89, p = 0.005), while in the total population, IL-6 was linked to a faster decline on a test of verbal memory (γ_{11} = −0.011 ± 0.004, p = 0.009). Among younger participants, IL-18 was linked to a poorer performance on a test of attention at baseline (age ≤50 y, γ_{01} = −0.007 ± 0.0025, p = 0.004) though a slower rate of decline with higher IL-18 was detected for a test of psychomotor speed in older adults (age > 50 y, γ_{11} = +0.0010 ± 0.0004, p = 0.008). Finally, among Whites, unlike among African-Americans, IL-6 was associated with a better baseline performance on two tests of verbal and working memory.

Conclusions: Cytokines were shown to be associated with age-related cognitive decline among middle-aged and older urban adults in an age group and race-specific manner. Further longitudinal studies are needed to replicate our findings and mediation through relevant biological and psychosocial factors need to be studied as well.

1. Introduction

Chronic systemic inflammation has been positively associated with structural and functional brain changes representing early markers of Alzheimer's Disease (AD) and cognitive decline during normal aging (Arfanakis et al., 2013; Bettcher et al., 2012; Corlier et al., 2018; Gu

et al., 2018; Hoshi et al., 2010; Jefferson et al., 2007; Satizabal et al., 2012; Taki et al., 2013; Wada et al., 2011; Walker et al., 2017; Warren et al., 2018; Wersching et al., 2010). Recent meta-analyses have implicated inflammatory biomarkers in the onset and progression of neurodegenerative processes (Bradburn et al., 2017; Darweesh et al., 2018a; Gorelick, 2010; Lai et al., 2017). To date, studies examining the link between inflammation and cognitive health have focused primarily on C-reactive protein (CRP). This may be due, in part, to CRP's documented utility as a non-specific proxy for inflammatory processes (Black et al., 2004). However, the expression of CRP is largely determined by interleukin 6 (IL-6) and other proinflammatory cytokines (Black et al., 2004). Relatively few studies have examined the relationship between interleukins (IL) and cognitive health. Those that have were limited by their measures of cognitive health (Palta et al., 2015; Tegeler et al., 2016); they did not differentiate between proinflammatory and anti-inflammatory markers (Jordanova et al., 2007; Metti et al., 2014); and they had for the most part a cross-sectional design (Trollor et al., 2012; Trollor et al., 2010). Further, several studies have produced mixed results which may be due, in part, to differential sample selection and population heterogeneity (Jefferson et al., 2007; Satizabal et al., 2012). Thus, despite the promise of using the interleukins diagnostically as early markers of Alzheimer's Disease and related dementias (ADRD) (Hull et al., 1996), it remains unclear whether and to what extent these markers are associated with cognitive function and decline during normal aging, which domains of cognition are affected the most, and whether those relationships can vary by age group, sex and race. In fact, with possibly one exception, (Simpson et al., 2013) none of the studies previously showing an association between cytokines such as IL-6 and cognitive performance or change in specific domains of cognition have systematically stratified their sample by age group, race and/or sex (Elderkin-Thompson et al., 2012; Frydecka et al., 2015; Heringa et al., 2014; Marsland et al., 2006; Mooijaart et al., 2013; Simpson et al., 2013). Recent meta-analyses suggest that among the various cytokines which were available in our present study, IL-1β, IL-6 and IL-18 (and not IL-10 or IL-12) were shown to be adversely related to cognitive function, while increasing the risk of all-cause and AD dementia (Bradburn et al., 2017; Darweesh et al., 2018a; Gorelick, 2010; Lai et al., 2017). Whereas the vast majority of the primary studies included in these reviews did not compare findings across key socio-demographic groups, to our knowledge, only a handful of studies reported differential associations between cytokines and cognitive performance across sex, race and/or age (Canon and Crimmins, 2011; Goldstein et al., 2015; Simpson et al., 2013; Yaffe et al., 2003). Three of these studies were cross-sectional, (Canon and Crimmins, 2011; Goldstein et al., 2015; Simpson et al., 2013) while the only prospective cohort study among them utilized a single global measure (3MS) for cognitive assessment (Yaffe et al., 2003).

Furthermore, it is important to assess those stratum-specific associations given that various inflammatory markers have been shown to vary by age, sex and race groups (Allison et al., 2006; Aulock et al., 2006; Chapman et al., 2009; Ferrucci et al., 2005; Lu et al., 2017; McCarrey et al., 2016b; Mehta and Yeo, 2017; Miles et al., 2001; O'Connor et al., 2007; Ranjit et al., 2007; Slopen et al., 2010; Stepanikova et al., 2017; Weuve et al., 2018; Yaffe et al., 2013) Specifically, one study has shown that men had more elevated levels of IL-6 and IL-1β compared to women in response to an immune challenge, (Aulock et al., 2006), while IL-6 was generally shown to be higher among women in other studies(Chapman et al., 2009; O'Connor et al., 2007). Nevertheless, it was shown that cytokines including IL-6 and IL-18 tended to increase with age among both men and women (Ferrucci et al., 2005). Extant literature consistently demonstrates that African-Americans had higher levels of systemic inflammation compared to Whites, including a higher level of IL-6 (Allison et al., 2006; Ranjit et al., 2007; Slopen et al., 2010; Stepanikova et al., 2017). In addition, various cognitive aging measures, including prevalent and incident dementia, were shown to differ across those same socio-demographic

factors (McCarrey et al., 2016b; Mehta and Yeo, 2017; Miles et al., 2001; Weuve et al., 2018; Yaffe et al., 2013). For instance, men were shown to have accelerated decline on measures of mental status, perceptuomotor speed and integration, and visuospatial ability compared to women (McCarrey et al., 2016a). More consistently, it was shown that African-Americans had worse cognitive outcomes than Whites, which for the most part, could be accounted for by differences in socio-economic status (Mehta and Yeo, 2017; Miles et al., 2001; Weuve et al., 2018; Yaffe et al., 2013).

The current study examined associations between systemic inflammation and cognitive performance among African-Americans and Whites urban adults participating in the Health Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. Cytokines known to be positively linked to AD incidence among others (IL-1β, IL-6 and IL-18) were tested against cross-sectional and longitudinal cognitive function, stratifying by age group, sex and race.

2. Materials and methods

2.1. Database

HANDLS is a prospective cohort study that was initiated in 2004, with primary focus on cardiovascular disease and cognitive aging in the context of health disparities, by recruiting an ethnically and socio-economically diverse urban adult population. An area probability sampling strategy was adopted to recruit African American and White urban adults (baseline age: 30–64 y) both above and below poverty who resided within thirteen Baltimore city, MD neighborhoods (Evans et al., 2010). Our present study extracted data from baseline (visit 1, 2004–2009) and the first follow-up examination (visit 2; 2009–2013), with a follow-up period ranging between < 1 y and ~8 y, mean ± SD of 4.64 ± 0.93 y. Data collected included an extensive battery of cognitive tests measured both at visits 1 and 2 and markers of inflammation measured at visit 1. As part of the study protocol, written informed consent was obtained from all participants who were also provided with a booklet and a video explaining key study procedures. The National Institute on Environmental Health Sciences Institutional Review Board of the National Institutes of Health approved the study protocol.

2.2. Study sample

The original sample of HANDLS consisted of 3720 participants (Phase I, visit 1). At Phase II of visit 1 (or the Medical Research Vehicle (MRV) baseline visit), biochemical indices and cognitive performance data were obtained from a sub-set of the total Phase I sample. Specifically, sample sizes varied for the cognitive tests between 2044 and 2582 at baseline and between 1728 and 2139 for visit 2 follow-up MRV visits. However, the serum samples used for cytokine analysis were collected at the baseline MRV visit from HANDLS participants who were selected for studying DNA repair and age-related changes in microRNA. More details are provided elsewhere (Noren Hooten et al., 2012; Noren Hooten et al., 2013). This sample consisted of 244–249 participants with IL-1β, IL-6 or IL18 data available. Consequently, the final analytic sample was determined based on mutual exposure and covariate non-missingness at baseline and cognitive performance measure completeness at either visit (N = 189–222, k = 1.5–1.7) and is summarized in Fig. S1.

2.3. Cognitive assessment

Cognitive performance was assessed with 8 tests from which 11 test scores were computed, 7 distinctive domains were identified (Global, attention, learning/memory, executive function, visuo-spatial/visuo-construction ability, psychomotor speed, language/verbal). These domains stemmed from the following measures: Mini-Mental State

Examination (MMSE), the California Verbal Learning Test (CVLT) immediate (List A) and Delayed Free Recall (DFR), Digit Span Forward and Backwards tests (DS-F and DS-B), the Benton Visual Retention Test (BVRT), Animal Fluency test (AF), Brief Test of Attention (BTA), Trails A and B and the Clock Drawing Test (CDT) (Supplemental Method 1). Following a probe for understanding the protocol, HANDLS participants undergoing examination at the MRV were able to complete informed consent. Despite the lack of dementia diagnosis, all participants were screened using the MMSE as a global mental status test, which for the most part they completed successfully (total score ≥24). In cases where MMSE was low (~6.6% were < 24 at visit 1 and 1.9% at visit 2), the cause was judged to be poor literacy rather than dementia.

2.4. Cytokines

The IL cytokines were assayed by Aushon (https://www.aushon.com/). Aushon Ciraplex® ULTRA Ultrasensitive Assays combine the power of multiplexing and ultrasensitivity with femtogram/ml (fg/ml) levels of detection. The serum samples were collected from HANDLS participants for studies of DNA repair and age-related microRNA changes (Noren Hooten et al., 2012; Noren Hooten et al., 2013). As stated earlier, cytokines selected for this analysis included IL-1β, IL-6 and IL-18 (in pg/mL) (thus excluding IL-10 and IL-12), which were shown to be adversely related to cognitive function and increase risk of all-cause and AD dementia based on several recent meta-analyses (Bradburn et al., 2017; Darweesh et al., 2018a; Gorelick, 2010; Lai et al., 2017).

2.5. Covariates

Covariates were included based on prior evidence of their association with main outcome of interest, mainly cognitive decline (Barnes and Yaffe, 2011). Socio-demographic characteristics included baseline age, sex, race (White vs. African American), marital status (married vs. not), educational attainment (< High School (HS); HS, > HS) and poverty income ratio (PIR < 125% for "poor"), employment status (employed vs. not) and a continuous score reflecting literacy, the Wide Range Achievement Test (WRAT). Among lifestyle and health-related factors, analyses tested potential confounding effects of measured body mass index (BMI, kg/m^2), opiate, marijuana or cocaine use ("current" vs. "never or former"), smoking status ("current" vs. "never or former"). Depressive symptoms were measured using the 20-item Center for Epidemiological Studies-Depression scale (CES-D) and the total score was considered as a potential confounder as well. (See Supplemental Method 1) The overall quality of diet was operationalized using the total score on the Healthy Eating Index (HEI-2010), averaging two 24-hr recalls that were administered at the baseline visit (v1). The computation of the total HEI-2010 score and each of its 12 components are outline in: http://appliedresearch.cancer.gov/tools/hei/tools.html and http://handls.nih.gov/06Coll-dataDoc.html. Finally, other health-related baseline covariates that were considered as potential confounders included self-reported history of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease (stroke, congestive heart failure, nonfatal myocardial infarction or atrial fibrillation), inflammatory disease (multiple sclerosis, systemic lupus, gout, rheumatoid arthritis, psoriasis, thyroid disorder and Crohn's disease) and use of NSAIDs (prescription and over-the-counter) over the past two weeks, were considered as covariates, as was done in previous studies (Bettcher et al., 2012; Gimeno et al., 2009). Moreover, a sensitivity analysis was conducted by adding alcoholic beverage consumption as an additional covariate into the models. This covariate was centered and imputed at its mean when missing to obtain the same sample size for the full and the reduced models.

2.6. Statistical analysis

Analyses were conducted using Stata release 15.0 (STATA, 2017). Design complexity was accounted for by inclusion of sampling weights for estimating population means and proportions. Linear regression models (svy:reg) were used to contrast means across key stratifying variables (e.g. age/sex or race), while distributions of categorical variables across those socio-demographic groups were compared using svy:tab and design-based F-tests. A series of mixed-effects regression models with 11 continuous cognitive test score as outcomes were conducted and each of 3 cytokines as a separate exposure. Each model included the TIME variable, reflecting years elapsed between waves of data, which was entered as a fixed and random effect (along with the intercept), interacting it with key covariates including the main exposure variable, namely the 3 cytokines of interest. Assuming that the outcome was missing at random with repeated measures of ~1.5–1.7 visits/person, the models also took into account variability in follow-up time (See Supplemental Method 2) (Ibrahim and Molenberghs, 2009). All socio-demographic covariates were included in the models. Thus, rather than using scores already standardized by age and education, we have included age, education, literacy as well as other potentially confounding factors in the linear mixed model both to adjust the intercept (baseline performance) and the slope (annual rate of change), to be consistent with other similar analyses (Beydoun et al., 2018a; Beydoun et al., 2018c). Additional covariates were selected if they were found to be associated with each cytokine exposure at a type I error level of 0.05 based on a separate OLS regression model. Furthermore, selected significant findings from mixed-effects linear regression models were visualized using predictive margins of outcomes which were standardized as z-scores along with the exposures (i.e. cytokines) that were subsequently estimated and plotted across TIME (y), stratifying by cytokine levels (−1 = mean − 1 SD, 0 = mean, 1 = mean + 1 SD).

Moderating effects by sex, age group or race were tested by adding 2-way and 3-way interaction terms between exposure, the effect modifier and TIME. Models were also stratified by sex, age group and race separately (Supplemental Method 2), as various inflammatory markers have been shown to vary by age, sex and race groups (Lu et al., 2017).

Selection bias due to systematic differences on major characteristics between the selected sample and those excluded from the target population can occur. Accounting for this bias can be achieved in mixed-effect regression models through a 2-stage Heckman selection process. During the first sage, a binary outcome (selected = 1 vs. unselected = 0) is entered into a probit model and predicted by age, sex, race and poverty income ratio along with educational attainment. The predicted probability of being selected conditional on those characteristics is then used to compute an inverse mills ratio. At a second stage, this inverse mills ratio is entered into the final mixed-effects regression model as a covariate, as was done in prior studies (Beydoun et al., 2013).

Type I errors of 0.05 and 0.10 were chosen for main effects and interaction terms, respectively, (Selvin, 2004) prior to correcting for multiple testing. Correction for multiple testing was done using a familywise Bonferroni procedure by taking into account cognitive test multiplicity while assuming each exposure as a distinctive substantive hypothesis (Hochberg and Tamhane, 1987). Thus, a $p < 0.0045$ (0.05/11) was considered significant for main effects, while a critical p-value was reduced to (0.10/11 = 0.0090) for 2-way interaction terms. Finally, for 3-way interaction terms, critical p-value were reduced to 0.05, an overall approach similar to previous studies (Beydoun et al., 2016).

Table 1

Selected baseline (Visit 1) and time-dependent study participant characteristics by age group and sex for HANDLS participants with complete and reliable baseline MMSE scores and cytokine measures (N = 195).[a]

	All	Younger (≤50y)	Older (> 50y)	P_{Age}[b]	Women	Men	P_{sex}[b]	Whites	African-Americans	P_{race}[b]
% ± SE	(N = 195)	62.0 ± 5.0 (N = 97)	38.0 ± 5.0 (N = 98)		65.0 ± 5.0 (N = 127)	35.0 ± 5.0 (N = 68)		29.0 ± 5.0 (N = 63)	71.0 ± 4.0 (N = 132)	
Age at baseline, y	46.90 ± 1.00 (N = 195)	40.38 ± 0.82 (N = 97)	57.67 ± 0.64 (N = 98)	< 0.001	46.7 ± 1.31 (N = 127)	47.29 ± 1.49 (N = 68)	0.78	46.14 ± 1.81 (N = 63)	47.22 ± 1.21 (N = 132)	0.62
Sex, % male	35.0 ± 0.05 (N = 195)	35.0 ± 7.0 (N = 97)	33.0 ± 7.0 (N = 98)	0.84	– (N = 127)	– (N = 68)	0.40	40.8 ± 8.0 (N = 63)	32.1 ± 6.4 (N = 132)	0.39
Race, % African-American	70.9 ± 4.5 (N = 195)	72.6 ± 6.3 (N = 97)	68.1 ± 6.0 (N = 98)		73.6 ± 5.5 (N = 127)	65.7 ± 7.7 (N = 68)				
Married, %	30.1 ± 5.5 (N = 176)	27.8 ± 7.5 (N = 90)	34.4 ± 7.3 (N = 86)	0.52	31.8 ± 7.3 (N = 120)	26.4 ± 7.5 (N = 56)	0.60	38.0 ± 8.9 (N = 57)	26.9 ± 6.8 (N = 119)	0.31
Education, %										
< HS	3.8 ± 1.6	0.3 ± 0.2	9.7 ± 4.2	0.017	4.7 ± 2.4	2.2 ± 1.6	0.59	1.7 ± 1.5	4.7 ± 2.3	< 0.001
HS	52.7 ± 5.7	57.2 ± 8.1	45.2 ± 6.9		53.2 ± 7.5	51.6 ± 8.6		26.1 ± 6.7	63.6 ± 7.3	
> HS	43.0 ± 5.7	42.5 ± 8.2	43.9 ± 7.0		42.0 ± 7.5	44.9 ± 8.6		70.7 ± 6.9	31.7 ± 7.2	
Missing	0.4 ± 0.5 (N = 195)	0.0 (N = 97)	1.2 ± 1.2 (N = 98)		0.0 (N = 127)	1.3 ± 1.3 (N = 68)		1.5 ± 1.6 (N = 63)	0.0 (N = 132)	
Literacy (WRAT score)	44.1 ± 0.7 (N = 193)	44.4 ± 0.9 (N = 95)	43.7 ± 1.3 (N = 98)	0.65	43.6 ± 0.9 (N = 126)	45.0 ± 1.1 (N = 67)	0.31	49.26 ± 0.73 (N = 62)	41.99 ± 0.9 (N = 131)	< 0.001
PIR < 125%, %	23.7 ± 36.2 (N = 195)	21.5 ± 4.8 (N = 97)	27.2 ± 5.2 (N = 98)	0.42	22.0 ± 4.5 (N = 127)	26.8 ± 6.0 (N = 68)	0.53	8.3 ± 2.9 (N = 63)	30.0 ± 5.3 (N = 132)	< 0.001
Employment, %										
Yes	46.4 ± 5.7 (N = 195)	56.0 ± 8.1 (N = 97)	30.7 ± 6.0 (N = 98)	0.038	47.2 ± 7.5 (N = 127)	44.4 ± 8.8 (N = 68)	0.27	60.0 ± 7.6 (N = 63)	40.9 ± 7.3 (N = 132)	0.011
Missing	5.7 ± 2.1 (N = 195)	4.9 ± 2.2 (N = 97)	7.1 ± 4.0 (N = 98)		3.2 ± 1.2 (N = 127)	45.0 ± 8.4 (N = 68)		12.2 ± 4.6 (N = 63)	3.1 ± 2.1 (N = 132)	
Current smoking status, %										
Currently smoking	43.2 ± 5.7 (N = 195)	49.0 ± 8.2 (N = 97)	33.8 ± 6.6 (N = 98)	0.28	42.1 ± 4.2 (N = 127)	45.2 ± 8.7 (N = 68)	0.69	24.4 ± 6.3 (N = 63)	51.0 ± 7.3 (N = 132)	0.019
Missing	3.3 ± 1.6 (N = 195)	3.1 ± 2.2 (N = 97)	3.8 ± 2.0 (N = 98)		4.2 ± 2.3 (N = 127)	1.7 ± 1.3 (N = 68)		4.3 ± 2.5 (N = 63)	2.9 ± 1.9 (N = 132)	
Current use of illicit drugs, %										
Used any type	46.4 ± 5.7 (N = 195)	54.4 ± 8.2 (N = 97)	33.3 ± 6.3 (N = 98)	0.028	41.0 ± 7.3 (N = 127)	56.8 ± 8.4 (N = 68)	0.21	37.4 ± 8.5 (N = 63)	50.2 ± 7.3 (N = 132)	< 0.001
Missing	10.8 ± 2.7 (N = 195)	12.9 ± 3.9 (N = 97)	7.2 ± 3.1 (N = 98)		10.0 ± 3.3 (N = 127)	12.1 ± 4.5 (N = 68)		28.8 ± 7.0 (N = 63)	3.4 ± 2.0 (N = 132)	
Body mass index, $kg.m^{-2}$	30.8 ± 0.99 (N = 195)	29.25 ± 1.36 (N = 97)	33.29 ± 1.21 (N = 98)	0.027	31.79 ± 1.36 (N = 127)	28.86 ± 1.17 (N = 68)	0.10	28.7 ± 1.04 (N = 63)	31.63 ± 1.31 (N = 132)	0.081
HEI-2010 total score	44.36 ± 1.37 (N = 160)	43.84 ± 1.94 (N = 82)	45.26 ± 1.62 (N = 78)	0.60	43.91 ± 1.83 (N = 105)	45.24 ± 2.09 (N = 55)	0.58	48.24 ± 2.09 (N = 50)	42.97 ± 1.66 (N = 110)	0.049
Depressive symptoms										
CES-D score	15.08 ± 1.42 (N = 193)	14.8 ± 2.09 (N = 97)	15.55 ± 1.55 (N = 96)	0.77	15.12 ± 1.94 (N = 125)	15.01 ± 1.99 (N = 68)	0.97	12.38 ± 1.79 (N = 61)	16.15 ± 1.79 (N = 132)	0.16
Diabetes, %	20.0 ± 4.6 (N = 174)	6.6 ± 4.3 (N = 83)	41.4 ± 7.5 (N = 91)	< 0.001	22.7 ± 6.0 (N = 115)	15.4 ± 7.1 (N = 59)	0.46	13.9 ± 5.4 (N = 49)	22.2 ± 5.7 (N = 125)	0.31
Hypertension, %	54.9 ± 6.3 (N = 169)	43.3 ± 9.4 (N = 80)	72.2 ± 5.9 (N = 89)	0.010	59.0 ± 8.0 (N = 112)	46.9 ± 9.6 (N = 57)	0.33	35.1 ± 9.4 (N = 46)	60.0 ± 7.4 (N = 123)	0.043
Dyslipidemia, %	25.3 ± 5.0 (N = 169)	11.9 ± 5.5 (N = 80)	45.3 ± 7.5 (N = 89)	0.002	24.9 ± 6.2 (N = 112)	26.0 ± 8.5 (N = 57)	0.92	26.2 ± 8.9 (N = 46)	25.0 ± 5.9 (N = 123)	0.91
Cardiovascular disease[c], %	21.6 ± 4.6 (N = 174)	9.2 ± 4.7 (N = 83)	40.8 ± 7.4 (N = 91)	0.001	20.7 ± 5.6 (N = 115)	23.3 ± 7.9 (N = 59)	0.79	7.4 ± 3.7 (N = 49)	25.9 ± 5.9 (N = 125)	0.011
Inflammatory conditions[d], %	14.2 ± 4.6 (N = 174)	10.8 ± 6.5 (N = 83)	19.5 ± 6.2 (N = 91)	0.37	13.2 ± 6.0 (N = 115)	16.2 ± 7.0 (N = 59)	0.74	10.7 ± 4.2 (N = 49)	15.3 ± 5.8 (N = 125)	0.52
NSAIDs[e], %	32.5 ± 5.9 (N = 176)	30.0 ± 8.7 (N = 83)	36.3 ± 6.8 (N = 93)	0.58	35.0 ± 7.9 (N = 116)	27.8 ± 8.7 (N = 60)	0.52	27.8 ± 9.6 (N = 51)	34.0 ± 7.1 (N = 125)	0.61

(continued on next page)

Table 1 (continued)

	All	Younger (≤50y)	Older (> 50y)	P_{Age}[b]	Women	Men	P_{sex}[b]	Whites	African-Americans	P_{race}[b]
IL-1β	3.4 ± 1.24 (N = 195)	3.96 ± 1.96 (N = 97)	2.48 ± 0.58 (N = 98)	0.47	4.4 ± 1.88 (N = 127)	1.52 ± 0.58 (N = 68)	0.13	1.55 ± 0.31 (N = 63)	4.16 ± 1.74 (N = 132)	0.14
IL-6	12.21 ± 1.37 (N = 195)	10.96 ± 1.49 (N = 97)	14.27 ± 2.68 (N = 98)	0.28	10.37 ± 0.97 (N = 127)	15.68 ± 3.27 (N = 68)	0.12	8.76 ± 1.03 (N = 63)	13.62 ± 1.85 (N = 132)	0.023
IL-18	157.43 ± 11.86 (N = 195)	145.78 ± 15.79 (N = 97)	176.63 ± 17.01 (N = 98)	0.18	141.87 ± 12.11 (N = 127)	186.74 ± 22.39 (N = 68)	0.078	149.9 ± 12.1 (N = 63)	160.51 ± 16.0 (N = 132)	0.59

Key: CES-D = Center for Epidemiologic Studies-Depression; MMSE = Mini-Mental State Examination; PIR = poverty income ratio; WRAT = Wide Range Achievement Test.

[a] Values are weighted mean ± SEM or percent ± SEP. Largest sample size is N = 195.
[b] P-value was based on linear regression models when row variable is continuous (svy:reg) with sex/age group/race and design-based F-test when row variable is categorical (svy:tab).
[c] Cardiovascular disease include self-reported stroke, congestive heart failure, non-fatal myocardial infarction or atrial fibrillation.
[d] Inflammatory conditions include multiple sclerosis, systemic lupus, gout, rheumatoid arthritis, psoriasis, thyroid disorder and Crohn's disease.
[e] Non-steroidal anti-inflammatory drugs (NSAIDS) include over the counter and prescription drugs in that category.

2.7. Data availability

Data are available upon request to researchers with valid proposals who agree to the confidentiality agreement as required by our Institutional Review Board. We publicize our policies on our website https://handls.nih.gov. Requests for data access may be sent to the PIs or the study manager, Jennifer Norbeck at norbeckje@mail.nih.gov. These data are owned by the National Institute on Aging at the National Institutes of Health. The Principal Investigators, have restricted public access to these data because (1) the study collects medical, psychological, cognitive, and psychosocial information on racial and poverty differences that could be misconstrued or willfully manipulated to promote racial discrimination; and (2) although the sample is fairly large, there are sufficient identifiers that the PIs cannot guarantee absolute confidentiality for every participant as we have stated in acquiring our confidentiality certificate.

3. Results

Table 1 summarizes selected baseline study characteristics, stratified by age group, sex and race. Lower education attainment was observed among older participants compared to their younger counterparts, a difference also noted for African-Americans when compared to Whites. Other important differentials by race include lower literacy (WRAT total score), income and employment rates among African-Americans, a higher likelihood of current smoking and drug use among younger participants and African-Americans, a higher mean BMI in the older group, and a higher mean HEI-2010 reflecting better overall dietary quality among Whites. Older participants were also more likely than their younger counterparts to have co-morbid conditions such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease. Furthermore, compared to Whites, African-Americans had a higher prevalence of hypertension and cardiovascular disease and a more elevated mean IL-6.

Table 2 displays results for age, sex and race differentials in cognitive performance within each wave of data, as well as between wave differentials. Most notably, marked racial disparities were observed in cognitive performance, which persisted across waves of data, reflecting poorer performance among African-Americans, for most tests. Out of the 11 selected cognitive test scores, marked decline was detected only in two within the overall population (CVLT-List A and DFR) within a marginally significant decline observed for BVRT (P = 0.05), mostly detected in women and among African-Americans.

To test our key hypotheses, a series of mixed-effects linear regression models (Tables 3–5) were conducted. Adjusting for multiple testing for 11 test scores, IL1β was positively associated with a faster rate of decline on a test of executive functioning, Trails B only among older participants aged > 50 y [γ_{11} = +2.49 ± 0.89, p = 0.005, Fig. 1A (standardized effect size (ES))]. Moreover, in the total population, IL-6 was linked to a faster decline on a test of verbal memory, the CVLT-DFR [γ_{11} = −0.011 ± 0.004, p = 0.009, Fig. 1B (ES)]. Finally, among younger participants, IL-18 was linked to a poorer performance on a test of attention (BTA) at baseline (γ_{01} = −0.007 ± 0.0025, p = 0.004), but slower rate of decline on a test of psychomotor speed (Digits Span, Forward), among older individuals [γ_{11} = +0.0010 ± 0.0004, p = 0.008, Fig. 1C (ES)]. Additionally, among Whites, unlike among African-Americans, IL-6 was associated with a better baseline performance on CVLT-DFR and DS-B tests, reflecting verbal and working memory, respectively. Further in-depth analysis of the findings indicated that Whites had lower levels of IL-6 than AA at baseline, with a smaller variability (SD = 12.6 vs. 18.7), coupled with better performance on the CVLT-List A and the DS-B tests that had a larger variability than among AA (SD = 3.4 vs. 2.8 for CVLT-List A, SD = 2.3 vs. 1.99). Thus, a positive association between IL-6 and cognitive performance on CVLT-List A and DS-B should be interpreted as an association between moderate level of this cytokine with

Table 2
Cognitive performance test scores at baseline (Visit 1), follow-up (Visit 2), and change between visits, by age group, sex and race, for HANDLS participants with complete and reliable baseline and/or follow-up cognitive scores and complete data on cytokines.[a]

	All	Younger (≤ 50y)	Older (> 50y)	Women	Men	Whites	African-Americans
Mini-Mental State Exam, total score							
Visit 1	27.733 ± 0.221 (N = 195)	27.898 ± 0.259 (N = 97)	27.461 ± 0.398 (N = 98)	27.713 ± 0.307 (N = 127)	27.771 ± 0.269 (N = 68)	28.681 ± 0.196 [d] (N = 63)	27.344 ± 0.294 (N = 132)
Visit 2	28.104 ± 0.23 (N = 138)	27.967 ± 0.316 (N = 76)	28.392 ± 0.233 (N = 62)	27.958 ± 0.323 (N = 93)	28.381 ± 0.221 (N = 45)	29.06 ± 0.17[d] (N = 44)	27.677 ± 0.303 (N = 94)
P (Visit2-Visit1)	0.25	0.87	0.045	0.58	0.081	0.15	0.43
California Verbal Learning Test (CVLT), List A							
Visit 1	25.248 ± 0.758 (N = 167)	26.208 ± 1.107 (N = 84)	23.664 ± 0.785 (N = 83)	26.088 ± 1.023 (N = 104)	23.919 ± 0.957 (N = 63)	29.377 ± 1.429[d] (N = 46)	23.85 ± 0.798 (N = 121)
Visit 2	20.422 ± 0.754 (N = 140)	21.291 ± 1.036 (N = 73)	18.869 ± 1.006 (N = 67)	20.232 ± 1.03 (N = 95)	20.772 ± 1.005 (N = 45)	24.015 ± 1.126[d] (N = 46)	18.709 ± 0.907 (N = 94)
P (Visit2-Visit1)	< 0.001	0.001	< 0.001	< 0.001	0.025	0.004	< 0.001
CVLT, free delayed recall							
Visit 1	7.282 ± 0.339 (N = 164)	7.87 ± 0.456[b] (N = 82)	6.317 ± 0.444 (N = 82)	7.443 ± 0.456 (N = 103)	7.018 ± 0.471 (N = 61)	9.114 ± 0.597[d] (N = 46)	6.654 ± 0.388 (N = 118)
Visit 2	5.706 ± 0.38 (N = 131)	6.104 ± 0.568 (N = 66)	5.053 ± 0.415 (N = 65)	5.8 ± 0.45 (N = 91)	5.507 ± 0.701 (N = 40)	7.536 ± 0.611[d] (N = 41)	4.953 ± 0.422 (N = 90)
P (Visit2-Visit1)	0.002	0.016	0.039	0.011	0.075	0.067	0.003
Benton Visual Retention Test							
Visit 1	5.837 ± 0.618 (N = 192)	5.828 ± 0.897 (N = 95)	5.852 ± 0.71 (N = 97)	6.065 ± 0.907 (N = 122)	5.439 ± 0.605 (N = 70)	4.727 ± 0.599 (N = 63)	6.316 ± 0.833 (N = 129)
Visit 2	7.651 ± 0.689 (N = 148)	7.075 ± 0.933 (N = 80)	8.742 ± 0.933 (N = 68)	8.75 ± 0.969 (N = 100)	5.606 ± 0.6 (N = 48)	4.744 ± 0.715611[d] (N = 47)	8.927 ± 0.889 (N = 101)
P (Visit2-Visit1)	0.05	0.34	0.14	0.044	0.84	0.99	0.033
Brief Test of Attention							
Visit 1	6.781 ± 0.256 (N = 186)	7.021 ± 0.337 (N = 90)	6.398 ± 0.371 (N = 96)	6.962 ± 0.347 (N = 120)	6.411 ± 0.296 (N = 66)	7.436 ± 0.301[d] (N = 61)	6.484 ± 0.346 (N = 125)
Visit 2	6.816 ± 0.25 (N = 135)	6.894 ± 0.363 (N = 70)	6.679 ± 0.28 (N = 65)	6.615 ± 0.351[c] (N = 90)	7.144 ± 0.328 (N = 45)	7.15 ± 0.337 (N = 45)	6.647 ± 0.339 (N = 90)
P (Visit2-Visit1)	0.92	0.79	0.55	0.48	0.099	0.525	0.737
Animal Fluency							
Visit 1	18.557 ± 0.634 (N = 195)	19.333 ± 0.954 (N = 93)	17.339 ± 0.635 (N = 102)	17.945 ± 0.909 (N = 125)	19.645 ± 0.661 (N = 70)	23.173 ± 1.057[d] (N = 63)	16.641 ± 0.63 (N = 132)
Visit 2	18.837 ± 0.62 (N = 151)	19.409 ± 0.834 (N = 80)	17.812 ± 0.883 (N = 71)	18.288 ± 0.706 (N = 101)	19.835 ± 1.222 (N = 50)	22.669 ± 0.997[d] (N = 47)	17.13 ± 0.684 (N = 104)
P (Visit2-Visit1)	0.75	0.95	0.66	0.77	0.89	0.73	0.59
Digits Span, Forward							
Visit 1	7.767 ± 0.283 (N = 194)	7.94 ± 0.408 (N = 96)	7.48 ± 0.332 (N = 98)	7.68 ± 0.401 (N = 122)	7.914 ± 0.339 (N = 72)	8.842 ± 0.363[d] (N = 64)	7.293 ± 0.365 (N = 130)
Visit 2	7.376 ± 0.203 (N = 147)	7.245 ± 0.25 (N = 77)	7.602 ± 0.335 (N = 70)	7.211 ± 0.266 (N = 99)	7.658 ± 0.3 (N = 48)	8.551 ± 0.289[d] (N = 48)	6.787 ± 0.235 (N = 99)
P (Visit2-Visit1)	0.26	0.15	0.79	0.33	0.57	0.53	0.24
Digits Span, Backward							
Visit 1	6.035 ± 0.244 (N = 193)	6.099 ± 0.315 (N = 95)	5.934 ± 0.384 (N = 98)	6.227 ± 0.35 (N = 121)	5.726 ± 0.276 (N = 72)	6.936 ± 0.375[d] (N = 65)	5.613 ± 0.31 (N = 128)
Visit 2	5.574 ± 0.215 (N = 147)	5.66 ± 0.271 (N = 77)	5.425 ± 0.358 (N = 70)	5.424 ± 0.305 (N = 99)	5.83 ± 0.253 (N = 48)	6.548 ± 0.311[d] (N = 48)	5.086 ± 0.277 (N = 99)
P (Visit2-Visit1)	0.16	0.29	0.33	0.084	0.78	0.43	0.20
Clock, command							
Visit 1	8.811 ± 0.14 (N = 194)	8.975 ± 0.167 (N = 95)	8.538 ± 0.241 (N = 99)	8.638 ± 0.194[c] (N = 126)	9.135 ± 0.152 (N = 68)	9.208 ± 0.162[d] (N = 65)	8.639 ± 0.188 (N = 129)
Visit 2	8.88 ± 0.165 (N = 148)	9.03 ± 0.161 (N = 80)	8.596 ± 0.355 (N = 68)	8.853 ± 0.236 (N = 100)	8.929 ± 0.184 (N = 48)	9.367 ± 0.119[d] (N = 48)	8.658 ± 0.233 (N = 100)
P (Visit2-Visit1)	0.75	0.81	0.89	0.48	0.39	0.43	0.95
Trailmaking test, Part A							
Visit 1	35.935 ± 2.035 (N = 185)	32.493 ± 2.007[b] (N = 92)	42.02 ± 4.198 (N = 93)	37.382 ± 2.958 (N = 120)	33.256 ± 1.666 (N = 65)	27.881 ± 1.724[d] (N = 61)	39.422 ± 2.725 (N = 124)
Visit 2	47.296 ± 10.695 (N = 142)	35.881 ± 5.925 (N = 77)	69.62 ± 28.291 (N = 65)	50.433 ± 15.294 (N = 96)	41.44 ± 11.156 (N = 46)	27.904 ± 1.669 (N = 48)	56.394 ± 15.705 (N = 94)
P (Visit2-Visit1)	0.29	0.59	0.33	0.4	0.47	0.99	0.29
Trailmaking test, Part B							
Visit 1	144.572 ± 19.57 (N = 185)	135.24 ± 27.558 (N = 92)	161.073 ± 24.538 (N = 93)	134.035 ± 16.447 (N = 120)	164.079 ± 45.361 (N = 65)	67.823 ± 5.893[d] (N = 61)	177.801 ± 26.704 (N = 124)

Table 2 (*continued*)

	All	Younger (≤50y)	Older (> 50y)	Women	Men	Whites	African-Americans
Visit 2	149.918 ± 24.57 (N = 138)	139.106 ± 33.301 (N = 76)	171.669 ± 33.268 (N = 62)	145.891 ± 19.754 (N = 91)	157.105 ± 58.258 (N = 47)	73.436 ± 8.229[d] (N = 46)	186.16 ± 34.571 (N = 92)
P (Visit2-Visit1)	0.87	0.93	0.79	0.64	0.93	0.58	0.85

Key: CES-D = Center for Epidemiologic Studies-Depression; MMSE = Mini-Mental State Examination; PIR = poverty income ratio; WRAT = Wide Range Achievement Test.

[a] Most cognitive test scores were in the direction of higher score = better performance, except for BVRT (total errors), and Trailmaking Test both parts (expressed in seconds).

[b] $p < 0.05$ for null hypothesis of no difference in means of cognitive test scores by Age group (referent category: Younger) within each visit. Wald test from svy:reg command.

[c] $p < 0.05$ for null hypothesis of no difference in means of cognitive test scores by sex (referent category: Women) within each visit. Wald test from svy:reg command.

[d] $p < 0.05$ for null hypothesis of no difference in means of cognitive test scores by race within each visit (referent category: Whites). Wald test from svy:reg command.

variations in verbal and working memory, rather than the highly elevated level found among AAs. None of the sex-specific mixed-effects linear regression models suggested a significant association between the cytokines of interest and cognitive performance or change over time after adjustment for multiple testing. In addition, when formally testing heterogeneity by age group, sex and race (using 2-way and 3-way interaction terms), none of the key associations were shown to differ significantly by those socio-demographic factors at a type I error level of 0.05. Additional control for alcoholic beverage consumption in a sensitivity analysis did not alter the key findings for all 3 cytokines.

4. Discussion

The association between various cytokines with longitudinal trajectories of cognitive performance have been explored in our present study using a sample of bi-racial middle-aged and older urban adults, while stratifying by age, sex and race. Among key findings, IL1β was positively associated with a faster rate of decline on a test of executive functioning, among older adults (age > 50 y), while in the total population, IL-6 was linked to a faster decline on a test of verbal memory. Among younger participants, IL-18 was linked to a poorer performance on a test of attention (BTA) at baseline though a slower rate of decline with higher IL-18 was detected for a test of psychomotor speed in older adults. Finally, among Whites, unlike among African-Americans, IL-6 was associated with a better baseline performance on two tests of verbal and working memory.

Interleukins have been linked cross-sectionally and prospectively with various cognitive outcomes. With respect to IL-6, two recent studies—one using data from the US-based Framingham Offspring Study (Jefferson et al., 2007) and the other from the France based Three City-Dijon cohort—found evidence linking the concentration of IL-6 to markers of brain atrophy (Jefferson et al., 2007; Satizabal et al., 2012). In the Framingham Offspring Study, Jefferson and colleagues (Jefferson et al., 2007) extracted data from a sample of nearly 2000 non-demented participants (Mean = 60 y, SD = 9 y) free of stroke and transient ischemic attacks. They found elevated IL-6 to be significantly inversely associated with total cerebral brain volume (TCBV) but not white matter hyperintensities (WMH) attained via magnetic resonance imaging (MRI). In their study, cardiovascular disease (CVD) was also associated with increased inflammatory markers which they found to be positively linked to brain atrophy. Satizabal and colleagues (Satizabal et al., 2012) used data on 1841 men and women (Mean = 72.5 y, SD = 4.1) from the Three City-Dijon cohort and found elevated levels of IL-6 to be cross-sectionally associated with reduced WMH integrity, gray matter, and hippocampal volume. However, these findings were not replicated using the baseline inflammatory markers and new MRI results at four years of follow-up. Based on a recent meta-analysis of 7 independent studies, adults with high circulating IL-6 were on average 1.42 times more likely to experience global cognitive decline (based on change in MMSE and other similar tests) at follow-up, over a 2–7 y period, compared to those with low IL-6 (OR = 1.42, 95% CI: 1.18–1.70; $P < 0.001$) (Bradburn et al., 2017). Similarly, based on 4 studies mostly conducted among White Europeans, another meta-analysis concluded that higher IL-6 (top quantile vs. lowest) was linked to a HR for all-cause dementia of 1.40, with a 95% CI: 1.13–1.73, $P < 0.05$ (Darweesh et al., 2018b). Finally, a recent meta-analysis comparing AD with health controls, found that the standardized mean difference (SMD) in the 3 cytokines of interest were: IL-1β [25 studies, SMD = 0.727 (95% CI: 0.335 to 1.120) $P < 0.001$], IL-6 [40 studies, SMD = 0.522 (95% CI: 0.240 to 0.804) $P < 0.001$] and IL-18 [9 studies, SMD = 0.945 (95% CI: 0.143 to 1.748) $P = 0.021$] (Lai et al., 2017).

Several studies also indicate that interleukins, especially IL-6, are associated with a range of cognitive domains, including processing speed and attention (Heringa et al., 2014), executive function (Mooijaart et al., 2013), immediate and delayed recall (Elderkin-Thompson et al., 2012), visuospatial skills (Frydecka et al., 2015), and working memory in midlife (Marsland et al., 2006) and older ages (Simpson et al., 2013). Our study found that IL-6 was linked to faster decline on a test of verbal memory in the total population, though at baseline it was associated with a better performance on that test. Thus, our findings partially replicate findings by Elderkin-Thompson et al. (2012). In contrast, among Whites, IL-6 was found to be protective against impairment in verbal and working memory at baseline, thus contradicting findings by Elderkin-Thompson et al. (2012) and Marsland et al. (2006) for that group. This finding should be interpreted with caution given that IL-6 cytokine levels were on average higher among AA compared to Whites, as was shown in numerous other reports (Allison et al., 2006; Ranjit et al., 2007; Slopen et al., 2010; Stepanikova et al., 2017). Thus, a protective effect among Whites is that of a moderate increase in IL-6 rather than the larger increments found among AAs. More studies are needed comparing racial groups in terms of the association between cytokines such as IL-6 and memory-related performance, both cross-sectionally and longitudinally. We did not detect any association between cytokines IL-1β, IL-6 or IL-18 and MMSE, possibly due to the younger age of our cohort compared to previous studies [e.g. (Bradburn et al., 2017)]. In addition, IL-1β was the only cytokine to have a single finding that is consistent with previous studies, showing that higher levels had an adverse effect in older adults (> 50 y) on cognitive change in the domain of executive function. This is in line with the findings from the meta-analysis previously described (Lai et al., 2017). In addition, both IL-6 and IL-1β gene polymorphisms were shown to linked with increased risk for AD (Ravaglia et al., 2006). Specifically, IL-1β polymorphism was shown to

Table 3

Cognitive performance test scores by IL-1β, stratified by age group, sex and race, for HANDLS participants with complete and reliable baseline and/or follow-up cognitive scores: mixed-effects regression models.[a]

	All	Younger (≤50y)	Older (> 50y)	Women	Men	Whites	African-Americans
Mini-Mental State Exam, total score							
IL-1β	−0.004 ± 0.014	−0.019 ± 0.016	+0.012 ± 0.037	−0.011 ± 0.016	+0.080 ± 0.073	+0.039 ± 0.036	−0.015 ± 0.019
IL-1β × TIME	+0.005 ± 0.003	+0.006 ± 0.004	+0.003 ± 0.008	+0.004 ± 0.004	−0.004 ± 0.022	−0.013 ± 0.009	+0.009 ± 0.004[b]
	(N = 216; k = 1.6)	(N = 103; k = 1.7)	(N = 113; k = 1.6)	(N = 143; k = 1.7)	(N = 73; k = 1.6)	(N = 70; k = 1.7)	(N = 146; k = 1.6)
California Verbal Learning Test (CVLT), List A							
IL-1β	+0.060 ± 0.050	+0.111 ± 0.063	+0.130 ± 0.100	+0.091 ± 0.053	+0.182 ± 0.231	+0.086 ± 0.289	+0.135 ± 0.057[b]
IL-1β × TIME	−0.007 ± 0.010	−0.017 ± 0.012	−0.003 ± 0.023	−0.005 ± 0.010	−0.126 ± 0.098	−0.051 ± 0.069	−0.012 ± 0.011
	(N = 207; k = 1.6)	(N = 100; k = 1.6)	(N = 107; k = 1.5)	(N = 135; k = 1.6)	(N = 72; k = 1.5)	(N = 68; k = 1.5)	(N = 139; k = 1.6)
CVLT, Free Delayed Recall							
IL-1β	+0.044 ± 0.023	+0.055 ± 0.030	+0.044 ± 0.045	+0.046 ± 0.024	+0.142 ± 0.099	+0.111 ± 0.120	+0.063 ± 0.027[b]
IL-1β × TIME	−0.009 ± 0.005	−0.012 ± 0.006	−0.020 ± 0.011	−0.008 ± 0.005	−0.07 ± 0.043	−0.045 ± 0.028	−0.009 ± 0.006
	(N = 206; k = 1.5)	(N = 100; k = 1.5)	(N = 106; k = 1.5)	(N = 136; k = 1.6)	(N = 70; k = 1.5)	(N = 66; k = 1.5)	(N = 140; k = 1.6)
Benton Visual Retention Test							
IL-1β	+0.036 ± 0.038	+0.022 ± 0.042	+0.028 ± 0.090	+0.030 ± 0.042	−0.15 ± 0.182	+0.221 ± 0.208	−0.055 ± 0.155
IL-1β × TIME	−0.001 ± 0.009	−0.001 ± 0.008	+0.044 ± 0.033	+0.001 ± 0.010	+0.011 ± 0.059	−0.236 ± 0.149	+0.053 ± 0.050
	(N = 217; k = 1.7)	(N = 103; k = 1.8)	(N = 114; k = 1.6)	(N = 141; k = 1.7)	(N = 76; k = 1.6)	(N = 44; k = 1.7)	(N = 111; k = 1.7)
Brief Test of Attention							
IL-1β	−0.011 ± 0.018	−0.034 ± 0.022	+0.086 ± 0.061	−0.019 ± 0.020	+0.112 ± 0.076	+0.111 ± 0.088	−0.039 ± 0.024
IL-1β × TIME	+0.003 ± 0.004	+0.009 ± 0.005	−0.026 ± 0.017	+0.005 ± 0.004	−0.040 ± 0.039	−0.028 ± 0.021	+0.008 ± 0.005
	(N = 212; k = 1.6)	(N = 101; k = 1.7)	(N = 111; k = 1.6)	(N = 141; k = 1.6)	(N = 71; k = 1.6)	(N = 71; k = 1.7)	(N = 141; k = 1.6)
Animal Fluency							
IL-1β	−0.032 ± 0.036	+0.02 ± 0.046	+0.003 ± 0.080	−0.023 ± 0.037	+0.184 ± 0.183	+0.037 ± 0.108	+0.020 ± 0.043
IL-1β × TIME	+0.004 ± 0.008	+0.001 ± 0.01	+0.006 ± 0.017	+0.003 ± 0.007	+0.059 ± 0.071	−0.043 ± 0.030	+0.002 ± 0.009
	(N = 222; k = 1.7)	(N = 104; k = 1.7)	(N = 118; k = 1.6)	(N = 145; k = 1.7)	(N = 77; k = 1.6)	(N = 72; k = 1.7)	(N = 150; k = 1.6)
Digits Span, Forward							
IL-1β	+0.015 ± 0.016	+0.025 ± 0.020	−0.106 ± 0.057	+0.020 ± 0.017	−0.115 ± 0.078	−0.046 ± 0.046	+0.020 ± 0.021
IL-1β × TIME	+0.000 ± 0.003	−0.003 ± 0.004	+0.031 ± 0.016	−0.001 ± 0.004	−0.038 ± 0.028	+0.025 ± 0.010[b]	−0.003 ± 0.004
	(N = 219; k = 1.7)	(N = 103; k = 1.7)	(N = 116; k = 1.6)	(N = 144; k = 1.7)	(N = 75; k = 1.6)	(N = 72; k = 1.7)	(N = 147; k = 1.6)
Digits Span,Backward							
IL-1β	+0.008 ± 0.015	−0.003 ± 0.017	+0.071 ± 0.057	+0.011 ± 0.016	−0.068 ± 0.064	+0.034 ± 0.044	−0.011 ± 0.018
IL-1β × TIME	−0.003 ± 0.003	+0.000 ± 0.003	−0.029 ± 0.016	−0.004 ± 0.004	+0.011 ± 0.026	+0.007 ± 0.011	−0.001 ± 0.004
	(N = 219; k = 1.7)	(N = 103; k = 1.7)	(N = 116; k = 1.6)	(N = 144; k = 1.7)	(N = 75; k = 1.6)	(N = 72; k = 1.7)	(N = 147; k = 1.6)
Clock, Command							
IL-1β	+0.009 ± 0.010	−0.001 ± 0.013	−0.024 ± 0.036	+0.008 ± 0.011	+0.016 ± 0.045	+0.000 ± 0.025	−0.008 ± 0.014
IL-1β × TIME	−0.002 ± 0.002	+0.001 ± 0.003	+0.009 ± 0.010	−0.002 ± 0.002	+0.031 ± 0.018	+0.003 ± 0.007	+0.001 ± 0.003
	(N = 219; k = 1.7)	(N = 104; k = 1.8)	(N = 115; k = 1.6)	(N = 145; k = 1.7)	(N = 74; k = 1.6)	(N = 73; k = 1.7)	(N = 146; k = 1.7)
Trailmaking Test, Part A							
IL-1β	−0.174 ± 0.367	−0.116 ± 0.538	−0.176 ± 0.822	−0.067 ± 0.335	−1.061 ± 2.629	−0.278 ± 0.251	−0.254 ± 0.530
IL-1β × TIME	+0.043 ± 0.111	+0.010 ± 0.151	+0.105 ± 0.313	+0.016 ± 0.100	−0.866 ± 1.251	−0.001 ± 0.084	+0.045 ± 0.163
	(N' = 352)	(N' = 177)	(N' = 175)	(N' = 236)	(N' = 116)	(N' = 122)	(N' = 230)
Trailmaking Test, Part B							
IL-1β	−1.099 ± 1.147	+0.220 ± 1.276	−1.214 ± 2.788	−0.295 ± 1.354	−2.333 ± 6.138	−1.221 ± 1.265	−0.769 ± 1.657
IL-1β × TIME	+0.387 ± 0.243	+0.026 ± 0.201	+2.492 ± 0.893[c]	+0.387 ± 0.404	+0.604 ± 2.877	−0.159 ± 0.257	+0.709 ± 0.375
	(N = 207; k = 1.7)	(N = 99; k = 1.8)	(N = 108; k = 1.6)	(N = 230)	(N = 117)	(N = 69; k = 1.7)	(N = 138; k = 1.6)

Key: CES-D = Center for Epidemiologic Studies-Depression; IL = Interleukin; k = number of observations/participant; MMSE = Mini-Mental State Examination; NSAIDs = Non-steroidal anti-inflammatory drugs; PIR = poverty income ratio; N = number of participants; N' = Number of observations (when ordinary least square linear regression is used instead of mixed-effects regression models); WRAT = Wide Range Achievement Test.

[a] Most cognitive test scores were in the direction of higher score = better performance, except for BVRT (total errors), and Trailmaking Test both parts (expressed in seconds). Models were controlled for socio-demographic factors, namely age (centered at 50y), sex, race, poverty status, education, marital status, literacy, and employment status and the inverse mills ratio. Additional covariates were considered for inclusion namely current smoking status, current drug use, body mass index (BMI, centered at 30), CES-D total score (centered at 15), HEI-2010 (centered at 40), self-reported diabetes, hypertension, high cholesterol, cardiovascular disease, inflammatory conditions, NSAIDs. Only those that were associated with IL-1β in a separate bivariate OLS regression model were included (current smoking). All covariates were interacted with TIME. All inverse mills ratios were centered at zero.

[b] P < 0.05 for null hypothesis that γ = 0.

[c] P < 0.009 for null hypothesis that γ = 0 for interaction between IL and 1β and TIME.

be associated with higher total homocysteine (tHcy) in that report (Ravaglia et al., 2006). tHcy has been linked with poor cognitive outcomes in numerous cohort studies (Beydoun et al., 2014).

In contrast, our findings with IL-18 were largely inconsistent, suggesting that higher IL-18 was linked to a poorer performance on a test of attention at baseline (age ≤50 y, $\gamma_{01} = -0.007 \pm 0.0025$, p = 0.004) though a slower rate of decline with higher IL-18 was

detected for a test of psychomotor speed in older adults (age > 50 y, $\gamma_{11} = +0.0010 \pm 0.0004$, p = 0.008). While the first finding is in line with the previous meta-analysis (Lai et al., 2017) for the younger group in its acute effect on attention, this was not the case among the older group in terms of rate of change in psychomotor speed. As is the case for IL-6, more studies are needed to examine the association between IL-1β, IL-18 and cognitive performance or change in cognition over time.

Table 4

Cognitive performance test scores by IL-6, stratified by age group, sex and race, for HANDLS participants with complete and reliable baseline and/or follow-up cognitive scores: mixed-effects regression models.[a]

	All	Younger (≤ 50y)	Older (> 50y)	Women	Men	Whites	African-Americans
Mini-Mental State Exam, total score							
IL-6	−0.001 ± 0.009	−0.015 ± 0.013	+0.003 ± 0.012	+0.012 ± 0.012	−0.011 ± 0.012	+0.038 ± 0.013[b]	−0.012 ± 0.011
IL-6 × TIME	+0.000 ± 0.003	−0.002 ± 0.005	+0.004 ± 0.004	−0.001 ± 0.004	−0.004 ± 0.006	−0.005 ± 0.005	+0.001 ± 0.004
	(N = 204; k = 1.6)	(N = 88; k = 1.7)	(N = 116; k = 1.6)	(N = 137; k = 1.7)	(N = 67; k = 1.6)	(N = 59; k = 1.7)	(N = 145; k = 1.6)
California Verbal Learning Test (CVLT), List A							
IL-6	+0.053 ± 0.028	+0.092 ± 0.045[b]	+0.03 ± 0.034	+0.079 ± 0.038[b]	+0.075 ± 0.039	+0.098 ± 0.059	+0.040 ± 0.032
IL-6 × TIME	−0.018 ± 0.009[b]	−0.024 ± 0.015	−0.008 ± 0.011	−0.019 ± 0.009[b]	−0.037 ± 0.022	+0.004 ± 0.016	−0.014 ± 0.011
	(N = 195; k = 1.6)	(N = 86; k = 1.6)	(N = 109; k = 1.5)	(N = 129; k = 1.6)	(N = 66; k = 1.5)	(N = 57; k = 1.5)	(N = 138; k = 1.6)
CVLT, Free Delayed Recall							
IL-6	+0.035 ± 0.012[c]	+0.048 ± 0.018[b]	+0.033 ± 0.016[b]	+0.041 ± 0.017[b]	+0.033 ± 0.015[b]	+0.069 ± 0.023[c]	+0.028 ± 0.014
IL-6 × TIME	−0.011 ± 0.004[d]	−0.013 ± 0.007	−0.008 ± 0.005	−0.01 ± 0.005[b]	−0.02 ± 0.009[b]	−0.007 ± 0.006	−0.011 ± 0.006[b]
	(N = 194; k = 1.5)	(N = 86; k = 1.5)	(N = 108; k = 1.5)	(N = 130; k = 1.6)	(N = 64; k = 1.4)	(N = 55; k = 1.5)	(N = 139; k = 1.5)
Benton Visual Retention Test							
IL-6	+0.039 ± 0.023	+0.012 ± 0.033	+0.070 ± 0.030[b]	+0.060 ± 0.033	−0.009 ± 0.031	−0.025 ± 0.031	+0.078 ± 0.0315[b]
IL-6 × TIME	−0.006 ± 0.008	+0.000 ± 0.009	−0.011 ± 0.014	−0.011 ± 0.011	+0.021 ± 0.012	−0.007 ± 0.014	−0.014 ± 0.012
	(N = 205; k = 1.7)	(N = 88; k = 1.8)	(N = 117; k = 1.6)	(N = 135; k = 1.7)	(N = 70; k = 1.6)	(N = 45; k = 1.7)	(N = 120; k = 1.7)
Brief Test of Attention							
IL-6	−0.010 ± 0.011	−0.019 ± 0.015	+0.000 ± 0.016	−0.036 ± 0.015[b]	+0.03 ± 0.014[b]	−0.016 ± 0.019	−0.006 ± 0.014
IL-6 × TIME	−0.003 ± 0.004	−0.005 ± 0.005	−0.004 ± 0.005	+0.002 ± 0.004	−0.016 ± 0.009	−0.004 ± 0.005	−0.006 ± 0.005
	(N = 200; k = 1.6)	(N = 87; k = 1.7)	(N = 113; k = 1.6)	(N = 136; k = 1.6)	(N = 64; k = 1.6)	(N = 60; k = 1.7)	(N = 140; k = 1.6)
Animal Fluency							
IL-6	+0.003 ± 0.022	+0.006 ± 0.034	−0.007 ± 0.026	+0.027 ± 0.028	−0.016 ± 0.031	+0.092 ± 0.043[b]	−0.022 ± 0.024
IL-6 × TIME	−0.001 ± 0.007	−0.020 ± 0.012	+0.012 ± 0.008	−0.007 ± 0.007	+0.008 ± 0.017	+0.011 ± 0.013	−0.010 ± 0.008
	(N = 209; k = 1.7)	(N = 89; k = 1.7)	(N = 120; k = 1.6)	(N = 139; k = 1.7)	(N = 70; k = 1.6)	(N = 61; k = 1.7)	(N = 148; k = 1.6)
Digits Span, Forward							
IL-6	−0.007 ± 0.010	+0.027 ± 0.016	−0.031 ± 0.012[b]	−0.009 ± 0.014	+0.002 ± 0.013	−0.008 ± 0.020	−0.002 ± 0.012
IL-6 × TIME	+0.000 ± 0.003	−0.008 ± 0.005	+0.007 ± 0.004	+0.001 ± 0.004	−0.001 ± 0.007	+0.001 ± 0.004	+0.000 ± 0.004
	(N = 206; k = 1.6)	(N = 87; k = 1.7)	(N = 119; k = 1.6)	(N = 137; k = 1.7)	(N = 69; k = 1.6)	(N = 60; k = 1.7)	(N = 146; k = 1.6)
Digits Span, Backward							
IL-6	+0.005 ± 0.009	+0.008 ± 0.012	+0.000 ± 0.012	+0.029 ± 0.012[b]	−0.013 ± 0.010	+0.053 ± 0.017[c]	−0.008 ± 0.010
IL-6 × TIME	+0.004 ± 0.003	+0.003 ± 0.004	+0.006 ± 0.005	−0.001 ± 0.004	+0.012 ± 0.006	−0.005 ± 0.006	+0.006 ± 0.004
	(N = 206; k = 1.6)	(N = 87; k = 1.7)	(N = 119; k = 1.6)	(N = 137; k = 1.7)	(N = 69; k = 1.6)	(N = 60; k = 1.7)	(N = 146; k = 1.6)
Clock, Command							
IL-6	+0.009 ± 0.006	+0.008 ± 0.009	+0.008 ± 0.009	+0.011 ± 0.009	+0.001 ± 0.008	+0.012 ± 0.009	+0.007 ± 0.008
IL-6 × TIME	−0.002 ± 0.002	−0.007 ± 0.003[b]	+0.000 ± 0.003	−0.002 ± 0.003	+0.004 ± 0.004	−0.002 ± 0.003	−0.002 ± 0.003
	(N = 206; k = 1.7)	(N = 89; k = 1.7)	(N = 117; k = 1.6)	(N = 139; k = 1.7)	(N = 67; k = 1.6)	(N = 62; k = 1.7)	(N = 144; k = 1.7)
Trailmaking Test, PartA							
IL-6	−0.002 ± 0.251	+0.057 ± 0.467	−0.086 ± 0.322	+0.007 ± 0.263	−0.022 ± 0.602	−0.091 ± 0.109	+0.035 ± 0.367
IL-6 × TIME	−0.047 ± 0.102	−0.076 ± 0.182	+0.011 ± 0.134	−0.063 ± 0.100	+0.079 ± 0.318	+0.034 ± 0.047	−0.117 ± 0.147
	(N = 331)	(N = 152)	(N = 179)	(N = 227)	(N = 104)	(N = 103)	(N = 228)
Trailmaking Test, Part B							
IL-6	+0.763 ± 0.766	+1.400 ± 1.009	−0.235 ± 1.132	−0.664 ± 1.065	+3.499 ± 1.209[b]	−1.464 ± 0.625[b]	+1.589 ± 1.094
IL-6 × TIME	+0.485 ± 0.232[b]	−0.008 ± 0.270	+1.138 ± 0.392[b]	+0.738 ± 0.407	−0.050 ± 0.638	+0.282 ± 0.276	+0.572 ± 0.445
	(N = 197; k = 1.7)	(N = 86; k = 1.8)	(N = 111; k = 1.6)	(N = 221)	(N = 105)	(N = 101)	(N = 225)

Key: CES-D = Center for Epidemiologic Studies-Depression; IL = Interleukin; k = number of observations/participant; MMSE = Mini-Mental State Examination; NSAIDs = Non-steroidal anti-inflammatory drugs; PIR = poverty income ratio; N = number of participants; N′ = Number of observations (when ordinary least square linear regression is used instead of mixed-effects regression models); WRAT = Wide Range Achievement Test.

[a] Most cognitive test scores were in the direction of higher score = better performance, except for BVRT (total errors), and Trailmaking Test both parts (expressed in seconds). Models were controlled for socio-demographic factors, namely age (centered at 50y), sex, race, poverty status, education, marital status, literacy, and employment status and the inverse mills ratio. Additional covariates were considered for inclusion namely current smoking status, current drug use, body mass index (BMI, centered at 30), CES-D total score (centered at 15), HEI-2010 (centered at 40), self-reported diabetes, hypertension, high cholesterol, cardiovascular disease, inflammatory conditions, NSAIDs. Only those that were associated with IL-6 in a separate bivariate OLS regression model were included (current smoking, cardiovascular disease). All covariates were interacted with TIME. All inverse mills ratios were centered at zero.

[b] $P < 0.05$ for null hypothesis that $\gamma = 0$.

[c] $P < 0.004$ for null hypothesis that $\gamma = 0$ for main effect IL-6.

[d] $P < 0.009$ for null hypothesis that $\gamma = 0$ for interaction between IL-6 and TIME.

Despite a growing body of work linking cytokines and other inflammatory markers to cognitive health and deterioration, the biological pathways remain unclear (Meyer, 2011). Some studies suggest that the deposition of beta-amyloid in the brain sets off a cascade of effects including the secretion of IL-1β from microglia ultimately resulting in neuroinflammation, neuronal dysfunction, and accelerated neurogenerative processes (Teixeira et al., 2008). There is also evidence that IL-1β induces the expression of VCAM-1, a cell adhesion molecule involved in the regulation of microvasculature permeability, which in turn plays a role in the transmission of leukocytes along with other signaling cascades which have been found in AD patients (Guerriero et al., 2017). A recent review (McAfoose and Baune, 2009) provides

Table 5

Cognitive performance test scores by IL-18, stratified by age group, sex and race, for HANDLS participants with complete and reliable baseline and/or follow-up cognitive scores: mixed-effects regression models.[a]

	All	Younger (≤50y)	Older (>50y)	Women	Men	Whites	African-Americans
Mini-Mental State Exam, total score							
IL-18	−0.0009 ± 0.0008	+0.0009 ± 0.0020	−0.0007 ± 0.0010	−0.0013 ± 0.0010	+0.0006 ± 0.0017	−0.0008 ± 0.0024	−0.0008 ± 0.0010
IL-18 × TIME	+0.0002 ± 0.0003	+0.0001 ± 0.0006	+0.0002 ± 0.0004	+0.0003 ± 0.0005	−0.0003 ± 0.0003	+0.0015 ± 0.0010[b]	+0.0000 ± 0.0004
	(N = 198; k = 1.6)	(N = 86; k = 1.7)	(N = 112; k = 1.6)	(N = 132; k = 27)	(N = 66; k = 1.6)	(N = 57; k = 1.6)	(N = 141; k = 1.6)
California Verbal Learning Test (CVLT), List A							
IL-18	−0.0026 ± 0.0028	+0.0094 ± 0.0071	−0.0035 ± 0.0028	−0.0019 ± 0.0033	+0.0007 ± 0.0051	+0.0075 ± 0.0116	−0.0036 ± 0.0028
IL-18 × TIME	+0.0010 ± 0.0010	−0.0012 ± 0.0019	+0.0017 ± 0.0011	+0.0015 ± 0.0014	+0.0014 ± 0.0015	+0.0050 ± 0.0020[b]	+0.0014 ± 0.0010
	(N = 190; k = 1.6)	(N = 84; k = 1.6)	(N = 106; k = 1.5)	(N = 125; k = 1.6)	(N = 65; k = 1.5)	(N = 55; k = 1.5)	(N = 135; k = 1.6)
CVLT, Free Delayed Recall							
IL-18	+0.0001 ± 0.0012	+0.0038 ± 0.0032	+0.0002 ± 0.0012	−0.0001 ± 0.0015	+0.0011 ± 0.0021	−0.0008 ± 0.0049	+0.0001 ± 0.0013
IL-18 × TIME	+0.0006 ± 0.0005	−0.0004 ± 0.0009	+0.0011 ± 0.0005[b]	+0.0005 ± 0.0007	+0.0001 ± 0.0005[b]	+0.0014 ± 0.0010	+0.0007 ± 0.0005
	(N = 189; k = 1.5)	(N = 84; k = 1.5)	(N = 105; k = 1.5)	(N = 126; k = 1.6)	(N = 63; k = 1.4)	(N = 53; k = 1.5)	(N = 136; k = 1.6)
Benton Visual Retention Test							
IL-18	−0.0046 ± 0.0023[b]	+0.001 ± 0.0054	−0.0054 ± 0.0025[b]	−0.0036 ± 0.0028	−0.0062 ± 0.0041	+0.0141 ± 0.0056[b]	−0.0048 ± 0.0026
IL-18 × TIME	+0.001 ± 0.0009	−0.001 ± 0.0011	+0.0014 ± 0.0013	+0.0004 ± 0.0013	+0.0002 ± 0.0009[b]	+0.0006 ± 0.0026	−0.0001 ± 0.0013
	(N = 199; k = 1.7)	(N = 86; k = 1.8)	(N = 113; k = 1.6)	(N = 130; k = 1.7)	(N = 69; k = 1.6)	(N = 45; k = 1.7)	(N = 120; k = 1.7)
Brief Test of Attention							
IL-18	−0.0015 ± 0.0011	−0.007 ± 0.0025[c]	−0.0010 ± 0.0011	−0.0019 ± 0.0012	−0.0013 ± 0.0019	−0.0042 ± 0.0031	−0.0008 ± 0.0011
IL-18 × TIME	−0.0001 ± 0.0005	+0.001 ± 0.0007	−0.0001 ± 0.0004	+0.0005 ± 0.0005	−0.0002 ± 0.0007	+0.0003 ± 0.0008	+0.000 ± 0.0004
	(N = 195; k = 1.7)	(N = 86; k = 1.7)	(N = 109; k = 1.6)	(N = 131; k = 1.6)	(N = 64; k = 1.6)	(N = 57; k = 1.7)	(N = 138; k = 1.6)
Animal Fluency							
IL-18	−0.0021 ± 0.0021	+0.0031 ± 0.0055	−0.0029 ± 0.0021	−0.0022 ± 0.0024	−0.0013 ± 0.0039	+0.0030 ± 0.0069	−0.0031 ± 0.0022
IL-18 × TIME	+0.0001 ± 0.0008	−0.0009 ± 0.0014	+0.0012 ± 0.0008	+0.0000 ± 0.0011	+0.0000 ± 0.0011	+0.0027 ± 0.0019	−0.0003 ± 0.0008
	(N = 201; k = 1.7)	(N = 87; k = 1.7)	(N = 114; k = 1.6)	(N = 132; k = 1.7)	(N = 69; k = 1.6)	(N = 58; k = 1.7)	(N = 143; k = 1.7)
Digits Span, Forward							
IL-18	+0.0005 ± 0.0009	+0.0023 ± 0.0026	+0.0003 ± 0.0010	+0.0006 ± 0.0011	−0.0005 ± 0.0018	−0.0028 ± 0.0033	+0.0008 ± 0.0010
IL-18 × TIME	+0.0004 ± 0.0003	−0.0007 ± 0.0006	+0.0010 ± 0.0004[d]	+0.0004 ± 0.0004	+0.0006 ± 0.0005	+0.0007 ± 0.0007	+0.0004 ± 0.0004
	(N = 201; k = 1.7)	(N = 86; k = 1.7)	(N = 115; k = 1.6)	(N = 132; k = 1.7)	(N = 69; k = 1.6)	(N = 58; k = 1.7)	(N = 143; k = 1.6)
Digits Span, Backward							
IL-18	−0.0005 ± 0.0008	−0.0001 ± 0.0020	−0.0005 ± 0.0009	−0.0008 ± 0.0010	+0.0009 ± 0.0014	−0.0015 ± 0.0030	−0.0002 ± 0.0008
IL-18 × TIME	+0.0004 ± 0.0003	+0.0002 ± 0.0005	+0.0006 ± 0.0004	+0.0012 ± 0.0005	−0.0002 ± 0.0004	+0.0011 ± 0.0009	+0.0003 ± 0.0004
	(N = 201; k = 1.6)	(N = 86; k = 1.7)	(N = 115; k = 1.6)	(N = 132; k = 1.7)	(N = 69; k = 1.6)	(N = 58; k = 1.7)	(N = 143; k = 1.6)
Clock, Command							
IL-18	−0.0004 ± 0.0006	−0.0009 ± 0.0015	−0.0005 ± 0.0006	−0.0002 ± 0.0007	−0.0023 ± 0.0010	−0.0033 ± 0.0014	−0.0002 ± 0.0006
IL-18 × TIME	−0.0003 ± 0.0002	−0.0005 ± 0.0004	+0.0000 ± 0.0002	+0.0000 ± 0.0003	−0.0002 ± 0.0003	+0.0011 ± 0.0004	−0.0004 ± 0.0002
	(N = 198; k = 1.7)	(N = 87; k = 1.7)	(N = 111; k = 1.7)	(N = 132; k = 1.7)	(N = 66; k = 1.6)	(N = 59; k = 1.7)	(N = 139; k = 1.7)
Trailmaking Test, Part A							
IL-18	−0.0076 ± 0.0238	−0.0258 ± 0.0775	−0.0108 ± 0.0239	−0.0019 ± 0.0234	−0.0187 ± 0.0741	−0.0281 ± 0.0178	−0.0066 ± 0.0302
IL-18 × TIME	+0.0094 ± 0.0105	−0.0072 ± 0.0240	+0.0286 ± 0.0122	+0.0272 ± 0.0120	−0.0149 ± 0.0248	+0.0061 ± 0.0067	+0.0103 ± 0.0138
	(N' = 324)	(N' = 150)	(N' = 174)	(N' = 220)	(N' = 104)	(N' = 98)	(N' = 226)
Trailmaking Test, Part B							

Table 5 (*continued*)

	All	Younger (≤50y)	Older (> 50y)	Women	Men	Whites	African-Americans
IL-18	−0.0807 ± 0.0718	+0.0789 ± 0.1719	−0.1324 ± 0.0833	−0.1443 ± 0.0838	+0.0156 ± 0.1444	+0.0386 ± 0.1143	−0.1043 ± 0.0828
IL-18 × TIME	+0.0477 ± 0.0249	+0.0185 ± 0.0287	+0.0621 ± 0.037	+0.0756 ± 0.0421	−0.0189 ± 0.0082	+0.0081 ± 0.0434	+0.0481 ± 0.0314
	(N = 193; k = 1.7)	(N = 85; k = 1.8)	(N = 108; k = 1.6)	(N = 129; k = 1.7)	(N = 64; k = 1.6)	(N' = 96)	(N' = 223)

Key: CES-D = Center for Epidemiologic Studies-Depression; IL = Interleukin; k = number of observations/participant; MMSE = Mini-Mental State Examination; NSAIDs = Non-steroidal anti-inflammatory drugs; PIR = poverty income ratio; N = number of participants; N' = Number of observations (when ordinary least square linear regression is used instead of mixed-effects regression models); WRAT = Wide Range Achievement Test.

[a] Most cognitive test scores were in the direction of higher score = better performance, except for BVRT (total errors), and Trailmaking Test both parts (expressed in seconds). Models were controlled for socio-demographic factors, namely age (centered at 50y), sex, race, poverty status, education, marital status, literacy, and employment status and the inverse mills ratio. Additional covariates were considered for inclusion namely current smoking status, current drug use, body mass index (BMI, centered at 30), CES-D total score (centered at 15), HEI-2010 (centered at 40), self-reported diabetes, hypertension, high cholesterol, cardio-vascular disease, inflammatory conditions, NSAIDs. Only those that were associated with IL-18 in a separate bivariate OLS regression model were included (current smoking, inflammatory conditions).

[b] P < 0.05 for null hypothesis that γ = 0.

[c] P < 0.004 for null hypothesis that γ = 0 for main effect IL-18.

[d] P < 0.009 for null hypothesis that γ = 0 for interaction between IL-18 and TIME.

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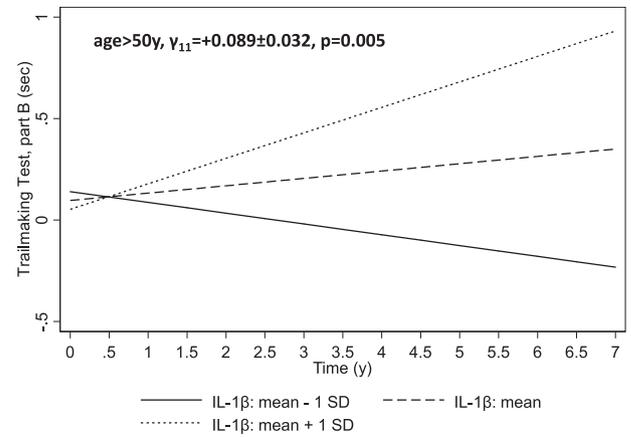
Fig. 1A. Predictive margins for Trailmaking test, part B (standardized z-score) by IL-1β (mean-1SD, mean, mean + 1 SD): mixed-effects regression models: older adults (> 50 y of age at baseline). *KEY*: TRAILS B = Trailmaking test, part B; IL-1β = Interleukin-1β. *Note*: Among subgroup > 50 y with complete and reliable Trailmaking Test, part B: mean ± SD IL-1β: 2.19 ± 5.45; mean ± SD Trailmaking Test, part B total score (sec.): 155.8 ± 151.9.
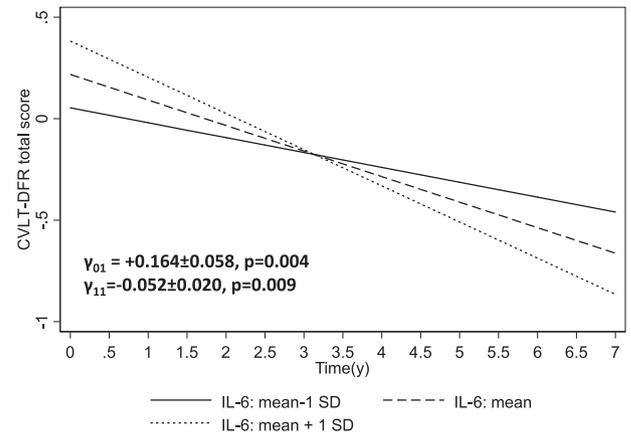
Fig. 1B. Predictive margins for CVLT-DFR (standardized z-score) by IL-6 (mean-1SD, mean, mean + 1 SD): mixed-effects regression models: total population. *KEY*: CVLT-DFR = California Verbal Learning Test, Delayed Free Recall (List A); IL-6 = Interleukin-6. *Note*: Among total population with reliable CVLT-DFR: mean ± SD IL-6: 12.52 ± 15.04; mean ± SD CVLT-DFR: 6.35 ± 3.24.
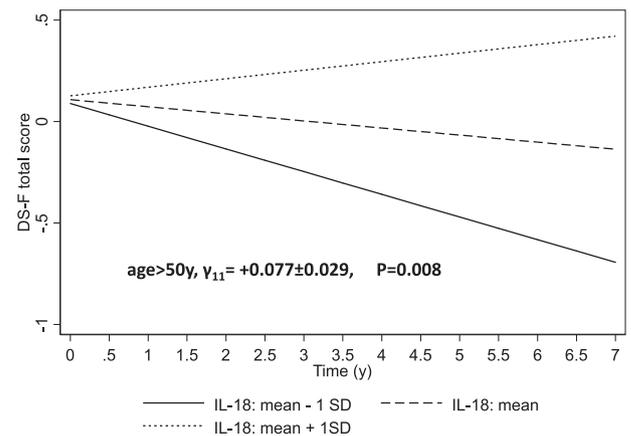
Fig. 1C. Predictive margins for Digits Span-Forward (standardized z-score) by IL-18 (mean-1SD, mean, mean + 1 SD): mixed-effects regression models: older adults (> 50 y of age at baseline). *KEY*: DS-F = Digits Span-Forward; IL-18 = Interleukin-18. *Note*: Among subgroup > 50 y with complete and reliable DS-F: mean ± SD IL-18: 168.3 ± 160.1; mean ± SD DS-F: 7.02 ± 2.13.

evidence that IL-1β and IL-6 may operate at the molecular level via synaptic plasticity, neurogenesis, or neuromodulation as well as at the cellular level affecting learning, memory, and cognitive functioning. In addition to their association with beta-amyloid accumulation, IL-1β and IL-6 have been associated with neurofibrillary tangles in AD patients (Da Mesquita et al., 2016). Elevated IL-6 has also been linked with reduced hippocampal volume in dementia-free patients suggesting that IL-6 may be useful in early AD detection and with staging the severity of the disease (Satizabal et al., 2012). Despite IL-6 being the most frequently studied interleukin, others such as IL-18 and IL-10 play important roles in regulating inflammatory processes. For example, IL-18 plays a key role in signaling during an inflammatory response via the recruitment of leukocytes, lymphocytes, and macrophages (Dinarello et al., 2013). There is further evidence suggesting that the anti-inflammatory IL-10 operates through deactivation of macrophage proinflammatory cytokine synthesis processes (Iyer and Cheng, 2012).

Several strengths are notable in our study, including the use of a comprehensive cognitive test battery and the adequate statistical power allowing for stratification by key socio-demographic factors. With up to two waves of cognitive data, it was possible to ascertain temporal relationships using longitudinal design and analyses. Furthermore, the cognitive battery available consistently between the two waves was extensive allowing to assess change in various cognitive domains in relation to cytokine levels. Additionally, advanced techniques were used to adjust for potential confounding and sample selectivity, while providing population estimates using sampling weights for baseline covariates for the descriptive part of the analyses.

Despite those strengths, several limitations are also worth noting. First, residual confounding cannot be ruled out given the observational nature of the study, though key covariates were adjusted for, particularly socio-demographic factors and selected covariates that were shown to be related to each of the cytokines. A second limitation is the availability of only up to 2 time points of cognitive data, limited individual-level decline with time due to a younger baseline age range (30–64 y), the restricted ability to create reliable cognitive domains due to poor factorial invariance across age groups, sex, race and poverty status among others. These are among several limitations detailed in previous studies (e.g. (Beydoun et al., 2018b)). Moreover, though statistical power was adequate in our current analysis, studying non-linear relationships using tertiles or clinical cut-points of cytokines was not readily possible, nor was it possible to stratify by imbalanced factors such as chronic conditions. Furthermore, since our sample population was limited to the African-American and White urban adults who were relatively young and healthy, the results may have insufficient power to generalize to older populations. Finally, the opportunity to control for important confounding and to study other related phenotypes (e.g. MRI data) was limited. In fact, MRI data on HANDLS participants was limited to ~10% of MRV participants which would have reduced our sample substantially. Additionally, since genotype data was only available on a sub-sample of African-American participants, adjustment for or stratification by ApoE4 status was precluded (Watanabe et al., 2016).

In sum, there were substantial longitudinal and cross-sectional associations between cytokine levels (IL-1β, IL-6 and IL-18) with cognitive performance, generally indicative of poorer performance and faster decline with higher systemic inflammation. Those associations were found for domains of executive function in older adults (IL-1β), verbal memory in the total population (IL-6), attention for younger adults (IL-18, at baseline). Nevertheless, IL-18 had an inconsistent relationship with a measure of psychomotor speed and was found to be potentially protective over time among older individuals. Finally, among Whites, unlike among African-Americans, IL-6 was associated with a better baseline performance on two tests of verbal and working memory. Further longitudinal studies are needed to replicate our findings and mediation through relevant biological and psychosocial factors need to be studied as well.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.04.027.

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Supplemental method 1: Description of cognitive tests, literacy and the CES-D

Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) is a brief mental status test and global cognitive functioning measuring orientation, concentration, immediate and delayed memory, language and constructional praxis. Scores range from 0 to 30, with higher scores indicating better cognitive performance.

California Verbal Learning Test (CVLT)

The CVLT (Delis et al., 1988) is a 16-item shopping list measuring verbal learning and memory. A modified version of the CVLT was used with three, rather than five, list A learning trials. Cued recall was not administered. Variables of interest in this study were total correct for List A sum across trials 1-3 and List A long-delay free recall. Scores ranged from 0 to 48 for List A sum and 0 to 16 for List A long-delay free recall. Higher scores indicate better verbal memory. The CVLT is described in detail elsewhere (Delis et al., 1988).

Benton Visual Retention Test (BVRT)

The BVRT (Benton, 1974) is a test of short-term figural memory and visuo-constructional abilities. Administration A, Form D was used. Two trained examiners independently scored the BVRT using a modified error scoring system, based on the BVRT Manual scoring. A consensus was achieved for discrepancies in scoring. If a consensus between the two examiners could not be reached, MKT, a research psychologist assigned the score. Scores were total errors, such that higher values indicate poorer visual memory.

Digit Span Forward and Backward (DS-F and DS-B)

The Wechsler Adult Intelligence Scale, Revised(Wechsler, 1981) Digit Span Forward and Backward are tests of attention and executive functioning, specifically working memory. They were administered according to standard instructions, and the total score was the total number correct for each test.

Animal Fluency

Animal fluency, (Morris et al., 1989; Morris et al., 1988) a measure of semantic verbal fluency, requires participants to generate as many animals as possible for 60 seconds. Higher scores indicate better verbal fluency, with the total number of words, minus intrusions and perseverations analyzed.

Brief Test of Attention (BTA)

The BTA (Schretlen et al., 1996) is a measure of divided auditory attention. An examiner administered 10 trials where increasing longer lists of letters and numbers (containing 4-18 items) were read. Participants were instructed to keep track of how many numbers were read during each trial, disregarding the number of letters, and were told to keep their hands in fists to discourage counting on their fingers. Only the numbers portion of the test was administered. The total score was the total number of trials correct out of 10.

Trail Making Tests A and B (Trails A and Trails B)

Trailmaking test A and B(Reitan, 1992) are tests of attention and executive functioning, respectively, specifically cognitive control and visuo-motor scanning/processing speed. Participants were instructed to draw lines between consecutive numbers (Trails A) or alternate between numbers and letter (Trails B) as fast as they could while a stop watch recorded time. When errors were committed the participant corrected the error by returning to his/her last correct response and continued from there. The stop-watch ran while corrections were made. Scores reflected time to completion (in seconds) separately for Trails A and B. Higher scores indicate poorer performance.

Clock Drawing Test – Clock to Command (CDT)

The Clock Drawing Test (Rouleau et al., 1992) is a test of visuo-spatial and visuo-constructional abilities. Participants are asked to draw a clock, put in all of the numbers and set the hands for 10 after 11. Scores are assessed for the clock face (0-2), numbers (0-4) and hands (0-4), with a range from 0 to 10, with higher scores indicating more accurate clock drawing. Participants who did not score a 10 on the command version of the test were asked to copy a clock with the time set to 10 after 11.

Wide Range Achievement Test – 3rd Edition: Word and Letter Reading Subtest (WRAT)

The WRAT Word and Letter Reading Subtest (Wilkinson, 1993) is a test of verbal knowledge, frequently used as a proxy for literacy and educational quality. Participants were asked to pronounce a list of 50 words that increased in difficulty. If a criterion of the first five words correctly pronounced was not

reached, letter reading was administered. The tan form was administered according to standard instruction and the score was the total number of words correctly pronounced.

Online Supporting Material

Center for Epidemiological Studies Depression Scale (CES-D)

The CES-D (Nguyen et al., 2004) is a 20-item measure of depressive symptoms. Participants are asked to rate the frequency and severity of symptoms over the past week. Scores range from 0 to 60, with scores of 16 and higher indicating significant depressive symptoms, and scores of 20 and higher indicating significant clinically depressive symptoms.

Supplemental Method 2: Description of mixed-effects regression models

The main multiple mixed-effects regression models can be summarized as follows:

Multi-level models vs. **Composite models**

Eq.

1.1-1.4

$$\pi_{0i} = \gamma_{00} + \gamma_{0a}X_{aij} + \sum_{k=1}^{l}\gamma_{0k}Z_{ik} + \zeta_{0i} \qquad Y_{ij} = \gamma_{00} + \gamma_{0a}X_{aij} + \sum_{k=1}^{l}\gamma_{0k}Z_{ik}$$

$$Y_{ij} = \pi_{0i} + \pi_{1i}Time_{ij} + \varepsilon_{ij} \qquad\qquad + \gamma_{10}Time_{ij} + \gamma_{1a}X_{aij}Time_{ij}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{1a}X_{aij} + \sum_{m=1}^{n}\gamma_{1m}Z_{im} + \zeta_{1i} \qquad + \sum_{m=1}^{n}\gamma_{1m}Z_{im}Time_{ij}$$

$$+ (\zeta_{0i} + \zeta_{1i}Time_{ij} + \varepsilon_{ij})$$

Where Y_{ij} is the outcome (cognitive test scores) for each individual "i" and visit "j"; π_{0i} is the level-1

intercept for individual i; π_{1i} is the level-1 slope for individual i; γ_{00} is the level-2 intercept of the random

intercept π_{0i}; γ_{10} is the level-2 intercept of the slope π_{1i}; Z_{ik} is a vector of fixed covariates for each

individual *i* that are used to predict level-1 intercepts and slopes and included baseline age (Age$_{base}$) among

other covariates. $X_{ija,}$ represents the main predictor variables (one of the cytokine exposures); ζ_{0i} and ζ_{1i}

are level-2 disturbances; ε_{ij} is the within-person level-1 disturbance. Of primary interest are the main

effects of each exposure X_a (γ_{0a}) and their interaction with *TIME* (γ_{1a}), as described in a previous methodolgical paper.(Blackwell et al., 2006)

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Figure S1. Participant flowchart