Interleukin 6 Plasma Concentration Associates with Cognitive Decline: The Northern Manhattan Study

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Abstract

Background—Interleukin 6 (IL-6) is an inflammatory cytokine that has been associated with vascular disease and cognitive impairment, but few studies have examined these relationships in population-based studies that include Hispanic white and black people who often have a greater prevalence of vascular risk factors and are at elevated risk of dementia. We examined relative elevations of plasma IL-6 concentrations in relation to cognitive decline in a stroke-free race/ethnically diverse community-based sample from Northern Manhattan.

Methods—We used mixed effects models to measure the effect of IL-6 on change in performance on the Telephone Interview for Cognitive Status (TICS-m) measured annually in our cohort, adjusting for sociodemographic and vascular risk factors.

Results—There were 1224 participants with IL-6 levels (median 1.5 pg/mL, interquartile range (IQR) 0.83 – 2.57 pg/mL) and TICS-m data available (mean=31.6 points, SD 6.5). The mean age was 71 (SD 9.3; 64% women, 59% Hispanic, 19% Black, 19% White) with 3,406 person- and a median 3.0 years of follow-up (IQR 1.1 – 4.0). Participants with IL-6 levels above the median showed greater cognitive decline on the TICS-m compared to those with levels below the median, adjusting for sociodemographic and vascular factors (β= −0.17 points per year, p=0.02). Decline on the TICS-m among participants with IL-6 above the median differed by age (P for interaction <0.001). There was no interaction by race-ethnicity, vascular risk factors, C-reactive protein (CRP), APOE4 allele status, or the metabolic syndrome among non-diabetics.

Conclusions—Interleukin 6 associated with cognitive decline among older participants in this race/ethnically diverse sample independent of other vascular risk factors and CRP.

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CONFLICTS OF INTEREST
The authors report no conflicts of interest regarding this manuscript.

INTRODUCTION

Interleukin 6 (IL-6) is an inflammatory cytokine linked to dementia, mild cognitive impairment (MCI), and Alzheimer Disease (AD) [1–4]. However, there are conflicting data on the effect of IL-6 on cognitive decline. Several studies have reported an association, but the Dutch Longitudinal Aging Study Amsterdam found IL-6 was not associated with cognitive decline, and the Whitehall II Study found raised levels of IL-6 had an inconsistent association with poor cognitive performance [5–9].

The role of traditional vascular risk factors in mediating an association between IL-6 and cognitive decline requires further clarification as well [10]. IL-6 combined with the constellation of risk factors making up the metabolic syndrome may increase the risk of cognitive decline. The Leiden 85-Plus Study found that the combination of cardiovascular disease and a pro-inflammatory cytokine response may be associated with cognitive impairment [11, 12]. On the other hand, the Edinburgh Artery Study found that IL-6 was associated with cognitive decline independent of cardiovascular disease (CVD) [13]. We have previously reported an inverse association between IL-6 and cognitive performance independent of carotid intima media thickness, a subclinical marker of CVD [14]. In addition, Il-6 stimulates CRP production, an established marker of cardiovascular risk, but there is conflicting data regarding the association of CRP with cognitive decline in combination with elevated IL-6 [6, 12]. In an African-Caribbean population, IL-6 was associated with cognitive decline, even when adjusted for vascular risk factors, however CRP was not found to exhibit such an association [15].

Prospective studies examining the relationship between IL-6 and cognitive function have found conflicting results, and it is unclear if vascular or neurodegenerative processes underlie the associations [5, 7, 9, 11, 13–15]. In addition, few studies on IL-6 and cognitive decline have included Hispanics and non-Hispanic Blacks who may be at greater risk of dementia than non-Hispanic whites [10, 16, 17]. We conducted a prospective study of the association between baseline plasma IL-6 levels and cognitive decline, and examined vascular risk factors, apolipoprotein epsilon 4 (APOE4) allele status, and inflammation in a stroke-free community-based multi-ethnic cohort.

METHODS

Description of Cohort

The Northern Manhattan Study (NOMAS) includes a prospective cohort of 3,298 stroke-free participants recruited using random digit dialing in northern Manhattan between 1993 and 2001. The details of enrollment are described elsewhere [18]. Briefly, participants were eligible if they met the following conditions: 1) no history of stroke, 2) age greater than or equal to forty years, and 3) residence in a household with a telephone for at least three months in northern Manhattan. Written informed consent was obtained from all participants and the Columbia University Medical Center IRB approved the study.

Baseline Evaluation and Follow-Up

Trained bilingual research assistants and study physicians collected demographic, medical, and laboratory data at enrollment using standardized data collection techniques and risk factor questions. These standardized questions were adapted from the Behavioral Risk

Factor Surveillance System regarding the following conditions: hypertension, diabetes mellitus, and cigarette smoking [19, 20]. Depressive symptoms were quantified using the Hamilton Depression Scale (HAM-D) [21]. Subjects were contacted annually via telephone starting in 1998 to document information regarding illnesses, hospitalizations, vital status, and cardiovascular events.

Laboratory Measurements

Serum samples for IL-6 and high sensitivity C-reactive protein (hsCRP) were drawn into EDTA tubes at baseline, spun immediately at 3000 g at 4°C for 20 minutes, and then frozen at −70°C for later analysis. Inflammatory marker levels were then measured in batched samples by enzyme-linked immunosorbent assay using monoclonal antibodies to IL-6 with a lower limit of detection of 0.1 pg/mL (Biosource International, Camarillo, CA) and hs-CRP with a lower limit of detection of 0.1 mg/L(BioCheck Inc, Foster City, CA). ApoE ε2, ε3, and ε4 alleles were determined by two single-nucleotide polymorphisms (SNPs), i.e. *rs429358* and *rs7412*, according to Table x. The two SNPs were genotyped using TaqMan® allelic discrimination assays (Applied Biosystems, Foster City, CA) following manufacturer's instructions.

Cognitive Assessment

Cognitive status was estimated by trained research assistants using the modified Telephone Interview for Cognitive Status (TICS-m), and has been included in the annual follow-up since 2001. The original TICS was based on the Mini Mental State Examination and was designed to assess global cognition by testing the following domains: attention, language, calculation, and immediate recall of ten words. The modified TICS-m includes recall of the ten word list after a short delay, and has been validated in clinical and research settings [22, 23]. Details of the study cohort with both IL-6 and TICS-m measurements may be found in Figure 1 and the number of participants with N TICS-m evaluations is shown in Table 1.

Covariates—Established risk factors for cognitive impairment were selected as covariates for multivariable analysis. All variables were assessed at baseline. Race-ethnicity was based on self-identification. Educational status was dichotomized based on whether or not high school had been completed. Insurance status was dichotomized as Medicaid or no insurance versus Medicare or private insurance. A history of depression was defined as a Hamilton Depression Scale (HAM-D) score greater than 10 or current antidepressant use. Moderate physical activity was dichotomized as any recreational or physical activity in the prior two weeks versus none, according to our validated methods [24]. Diabetes was defined based on the subject's self-reported history, usage of hypoglycemic medications, or fasting blood sugar greater than 126 mg/dL [19,20]. Smoking status was categorized as never, current (within the last year), or former smoker. Reported alcohol consumption was categorized as moderate (1 drink/week to 2 drinks/day) versus light (<1 drink/week) or non-drinkers. The number of heavy drinkers (>2 drinks/day) was small and was included in the reference category. Metabolic syndrome was defined by ATP III criteria as three of the following: abdominal obesity, raised triglycerides, reduced HDL cholesterol, elevated blood pressure, and raised plasma glucose [25].

Statistical Analyses

We compared sample characteristics across levels of IL-6 using Chi Square and Student *t* tests as appropriate. We used used mixed effects models with random intercepts to examine the association between IL-6 levels and cognitive decline measured with the TICS-m. There was no graded dose effect across quartiles, but the effect differed at the median-split. We

therefore created a categorical variable for IL-6 levels above and below the median. To estimate the effect of IL-6 and other covariates on change in TICS-m score over time, we examined the interaction between IL-6 and time between baseline and subsequent TICS-m measurement. The resulting coefficient provides the slope of change of TICS-m scores over time and is a standard approach [26]. In addition to IL-6, we examined the effect of hs-CRP on change in TICS-m scores over time as a continuous variable, using quartiles of hs-CRP, and using the established cutoffs of >3 mg/dL, 1–3 mg/dL and <1 mg/dL. To relate the rate of cognitive decline associated with these biomarkers to age-related change in TICS-m scores in our sample, we also examined age as a predictor of cognitive decline. We looked for effect modification by examining interactions between IL-6, time, and other covariates of interest such as age and CRP. Finally, we carried out two subanalyses, one to examine an interaction with metabolic syndrome among participants without diabetes and the other to examine the effect of APOE4 allele status. To allow us to estimate the effect of IL-6 on cognitive decline in a stroke-free population, for the primary analysis participants with stroke prior to the baseline TICS-m were excluded and we censored TICS-m scores acquired after a stroke event.

RESULTS

There were 1,224 NOMAS participants with both IL-6 (median 1.5 pg/mL, interquartile range (IQR) 0.83 – 2.57 pg/mL) and TICS-m measurements (overall mean=31.6 points, SD=6.5). Baseline characteristics of the sample are shown in Table 2. The IQR of scores for the first TICS-m done on participants was 26 – 35. Compared to NOMAS participants without these measurements, the current sample included a greater proportion of Hispanics (59% v. 48%), more participants with a high school education (47% v. 45%) and fewer people with diabetes (14% v. 27%). Twenty-two participants were excluded due to stroke prior to baseline TICS-m assessment, and 13 observations were censored after stroke.

Compared to those with IL-6 levels below the median, participants with IL-6 levels above the median were older, more likely to have hypertension, the metabolic syndrome, to be women, to have less than a high school education, Medicaid or no insurance, to be current smokers, and to report moderate alcohol consumption (Table 1). Over 3,406 person-years of follow-up (median 3.0 years, IQR 1.1 – 4.0; see table 1 for number of participants with N TICS-m measurements), we found that participants with IL6 levels above the median had greater decline on the TICS-m over time than those with levels below the median (Table 3). This effect was slightly attenuated after adjusting for age, race-ethnicity, education, sex, and insurance status but remained significant. The strength of the association between IL-6 and cognitive decline remained unchanged after adjusting for diabetes mellitus, hypertension, physical activity, depression, alcohol consumption, and smoking status (Table 3).

We found a significant interaction between IL-6, decline on TICS-m over time, and age (B= −0.40 points/per year for each additional year of age above the sample mean in those with IL-6 levels above the median compared to below, P for 3-way interaction <0.0001). Further stratifying by age, participants older than 71 with IL-6 levels above the median declined by 0.4 points more per year than those with IL-6 levels below the median (p<0.0001), while in younger participants IL-6 levels were not significantly associated with the rate of cognitive decline. We found no interaction by race-ethnicity or by modifiable vascular risk factors. Our findings were confirmed among a subsample limited to non-diabetics (N=1054): Those with IL6 levels above the median still showed a greater rate of decline on the TICS-m than below the median ($\beta = -0.17$ points/year, p=0.02), and there was no interaction with metabolic syndrome (data not shown). We did not examine the association between IL-6 and change in TICS-m scores among diabetics due to the small sample size (N=167).

High sensitivity CRP (median 2.5 mg/L, interquartile range 1.0 – 5.7 mg/L) was not associated with cognitive decline on the TICS-m. In addition, change in TICS-m scores did not differ significantly for those with hs-CRP levels in any of the upper three quartiles compared to those with hs-CRP levels in the lowest quartile (Q4 β=−0.01 points/year; Q3 β=−0.001; Q2 β=0.05 each compared to Q1, p>0.1 for all comparisons) or for those with hs-CRP levels >3 mg/L (β = −0.05, P=0.50), or hs-CRP levels between 1 and 3 mg/L (β = 0.02, P=0.83), compared to those below 1 mg/L. There was also no interaction between IL-6 and hs-CRP in relation to cognitive decline (data not shown).

Examining APOE4 allele carrier status as a possible moderator of the association between IL-6 and TICS-m performance over time among a sub group for whom allele status was available (N=817), we included APOE4 as a covariate in our fully adjusted model and the association between IL-6 and cognitive decline diminished and was no longer significant (β=−0.13, P=0.1). There was no significant interaction, however, and thus the greater decline in TICS-m scores seen for those with IL-6 levels above the median did not differ by APOE4 status (data not shown).

Finally, to put our findings regarding IL-6 and cognitive decline into perspective we examined the effect of age on change in TICS-m scores over time. Participant age was associated with a decline of 0.02 points per year (p<0.001).

DISCUSSION

Participants with baseline serum IL-6 values above the median had greater cognitive decline than those below the median in this prospective stroke-free race/ethnically diverse urban U.S. population. The magnitude of decline in TICS-m scores among those with IL-6 levels above the median compared to below the median was equivalent to the average amount of cognitive aging occurring in this sample over about eight years. Based on a stratified analysis, the effect of IL-6 on cognitive decline was significant only among those older than the mean age of 71, independent of other sociodemographic and vascular risk factors.

The role of IL-6 in cognitive decline is poorly understood, but an association between relative elevations of IL-6 and cardiovascular disease (CVD), as well as CVD risk factors, has been found in prior studies. For example, serum IL-6 levels have been associated with a greater risk of recurrent stroke, as well as greater stroke severity, than lower levels of the marker, but causality in either case has not be determined [27]. The Health, Aging, and Body Composition (Health ABC) study showed that those with the metabolic syndrome were at greater risk of cognitive decline than those without the metabolic syndrome only if they had both C-reactive protein and IL-6 levels above the median [11]. In the current study, the association between IL-6 and cognitive decline did not depend on having metabolic syndrome even when restricted to non-diabetics. In addition, hs-CRP was not a predictor of cognitive decline in this sample and there was no interaction between relative elevations of IL-6 and hs-CRP and cognitive decline.

We also found that other vascular risk factors did not alter the strength of the association between IL-6 and cognitive decline. The populations in NOMAS and Health ABC are distinct, and we were unable to find studies of the association between IL-6 and cognitive decline that have included large samples of Hispanic people, while the Health ABC study included well-functioning white and African-American elders. In NOMAS the risk of cognitive decline for those with IL-6 levels above the median did not differ by race-ethnic group. While hypertension is very common among all three race/ethnic groups in NOMAS, as in Health ABC, there are some differences as well. For example, high triglycerides and low HDL cholesterol were common among Hispanics but less so for both whites and blacks

in our sample. Some of these differences may explain disparate findings between these studies regarding the role of IL6 and cognitive decline. High sensitivity CRP is an established inflammatory marker for future vascular disease, however data on hsCRP in the Hispanic population is scarce. The NOMAS population, of which approximately 52% are Hispanic, had higher hsCRP levels than whites [28].

It is not clear if IL-6 is playing a role in cognitive dysfunction through vascular damage. A genetic propensity to a heightened inflammatory response predisposing to cognitive impairment has been proposed, however, and some of these studies support a vascular mechanism [11]. We have previously reported that individuals homozygous for the GG genotype at position 174 of the IL-6 gene had greater carotid artery wall thickness, and the Atherosclerosis Risk in Communities Study showed an association between cognitive dysfunction and increased carotid intima media thickness (IMT) [29, 30]. However, adjusting for baseline vascular risk factors did not alter the association between IL-6 and cognitive decline in our study, suggesting that a non-vascular mechanism may be operative. Another plausible mechanism by which IL-6 could influence the rate of cognitive decline is through a neurodegenerative process, and one study in a community sample of middle-aged adults has found that elevated plasma IL-6 levels were associated with lower hippocampal gray matter volumes independent of body fat and hypertension [31]. In the current study, adjusting for APOE4 allele status in a subsample attenuated the effect of IL-6 on cognitive decline and it was no longer significant, suggesting possible mediation. However, there was no significant interaction between IL-6, change in TICS-m scores over time, and APOE4 status. It is likely that our power to detect both the main effect of IL-6 on cognitive decline and the interaction between IL-6 and APOE4 status was limited by the smaller sample size. Larger studies are needed to clarify this finding. Interestingly, the Rotterdam study, contrary to what was hypothesized, found that the risk for dementia with increased levels of IL-6 was independent of atherosclerosis, and the authors proposed a peripheral inflammatory mechanism related to beta amyloid deposition [32].

An important limitation of this study is that serum there are limited data showing that IL-6 crosses the blood-brain barrier, and that serum IL-6 may accurately reflect cerebrospinal fluid levels [33]. Another concern is that serum IL-6 levels were measured only at baseline in NOMAS, and thus it is possible that levels changed later. However, studies examining the validity of IL-6 levels show that intra-individual concentrations do not vary much over time, though the time periods examined have been short, and therefore remain an indicator of chronic inflammatory states that both precede and follow the actual measurement [34, 35, 36]. Another concern is that the TICS-m is a global test of cognition and lacks sensitivity for specific domains, such as verbal memory or executive function. However, this would tend to decrease our ability to detect an association between IL-6 and cognition. Further data examining more sensitive neuropsychological tests are warranted. Despite the relatively large sample size the median follow-up per individual was three years and studies with longer follow-up are needed to confirm our findings. In addition, the study sample lacked enough people with diabetes to assess IL-6 levels and cognitive decline in this group. Despite the limitations, this study also has important strengths, including the large sample size, the population-based multi-ethnic cohort, and the longitudinal design.

CONCLUSION

In summary, we found that participants in a population-based urban U.S. sample with IL-6 levels above the median had a greater rate of cognitive decline than those with levels below the median. This association was independent of traditional vascular risk factors, and was more pronounced with advancing age. We did not find race-ethnic differences in the effect

of IL-6 on cognitive decline and these results are applicable to a race/ethnically diverse population.

Acknowledgments

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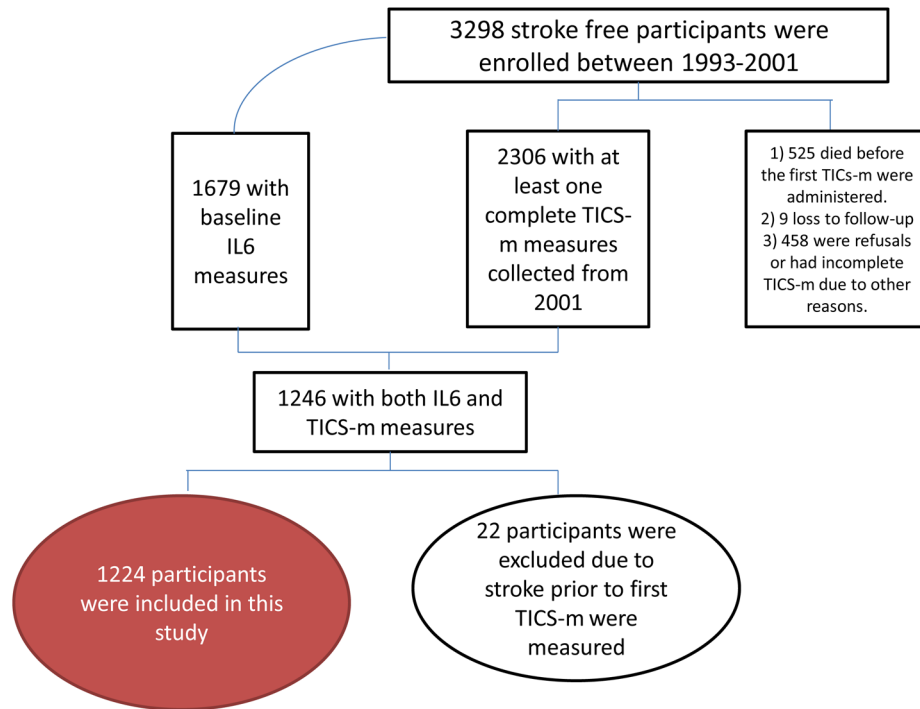
Figure 1. Study Enrollment
Flow Diagram of Participant Inclusion
N/A

Table 1

Number of participants with N TICS-m assessments

Number of TICS-m	N (%)
1	201 (16)
2	213 (17)
3	273 (22)
4	256 (21)
5+	281 (24)

Table 2

Baseline Characteristics of Sample (N = 1224) with Interleukin 6 and TICS-m Measurements

Characteristic		IL6			
		< median	>median	Total	P-value
Sex, N (%)	Men	237 (54)	204 (46)	441	0.0496
	Women	375 (48)	408 (52)	783	
Race/ethnicity	White	125 (53)	109 (47)	234	Ref.
	Black	116 (50)	115 (50)	231	0.216
	Other	18 (51)	17 (49)	35	NA
	Hispanic	353 (49)	371 (51)	724	0.49
Education	<HS	305 (47)	342 (53)	647	0.035
	>HS	307 (53)	270 (47)	577	
Medical Insurance	Medicare or private Insurance	344 (53)	306 (47)	650	0.025
	Medicaid or no insurance	266 (46)	306 (54)	572	
Current Smoker	No	537 (52)	492 (48)	1029	0.0005
	Yes	75 (38)	120 (62)	195	
Diabetes[a]	No	530 (50)	524 (50)	1054	0.669
	Yes	81 (49)	86 (51)	167	
Moderate Alcohol consumption[b]	No	365 (48)	398 (52)	763	0.047
	Yes	246 (54)	212 (46)	458	
Hypertension	No	198 (57) 56.57	152 (43) 43.43	350	0.0037
	Yes	414 (47)	460 (53)	874	

		IL6			
Characteristic		< median	>median	Total	P-value
Any Physical Activity	No	262 (49)	268 (51)	530	0.729
	Yes	350 (50)	344 (50)	694	
Depression[c]	No	558 (51)	541 (49)	1099	0.1045
	Yes	52 (43)	69 (57)	121	
Metabolic Syndrome	No	409 (57)	308 (43)	717	<0.0001
	Yes	203 (40)	304 (60)	507	

[a]Diabetes was defined as a fasting blood glucose of >126 mg/dL or a history of insulin or hypoglycemic use.

[b]Moderate alcohol consumption was defined as taking more than one alcoholic beverage per month up to two per day.

[c]Depression was defined as a Hamilton Depression Scale score >10 or current antidepressant use.

Table 3

Multivariable Analysis of Interleukin-6 as a predictor of Change in Modified Telephone Interview for Cognitive Status Score

	Parameter estimate (95% CI)[a]	P
Dichotomized IL-6		
Unadjusted		
IL-6 above mean	−0.19 (−0.32, −0.06)	0.006
IL-6 below mean	Reference	
Model 1 [b]		
IL-6 above mean	−0.17 (−0.30, −0.36)	0.013
IL-6 below mean	Reference	
Model 2 [c]		
IL-6 above mean	−0.17 (−0.30, −0.03)	0.015
IL-6 below mean	Reference	

[a] Parameter estimate represents average point decline per year in modified Telephone Interview for Cognitive Status score.

[b] Model 1: adjusted for age, race-ethnicity, education, gender, and insurance status, depression, physical activity.

[c] Model 2: adjusted for covariates in model 1 plus diabetes mellitus, alcohol consumption, and smoking status.