Does inflammation predict cognitive decline in older adults?

Evidence from Taiwan

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Abstract

Numerous studies have identified a link between inflammation and clinical cognitive impairment, such as Alzheimer's disease and other dementias. Less is known, however, about the relationship between inflammation and subclinical cognitive decline.

In this study, I investigate whether baseline biomarkers of inflammation predict cognitive change among older Taiwanese adults. Data are from the Taiwan Longitudinal Study of Aging and the Social Environment and Biomarkers of Aging Study. I examine five biomarkers of inflammation: C-reactive protein, interleukin-6, soluble e-selectin, soluble intercellular adhesion molecule-1, and white blood cell count. Cognition is assessed via ten cognitive and memory tasks. I use growth curve models to examine the relationship between inflammation (measured in 2000 and 2006) and cognitive scores (measured in 2006, 2007, and 2011).

I find that higher levels of inflammation are generally associated with lower baseline cognitive scores. Inflammation is not associated, however, with the rate of change in cognitive score.

Background

Systemic inflammation is believed to play an important role in neurodegenerative diseases such as Alzheimer's disease and other dementias. Although the relationship between inflammation and cognitive impairment is not fully understood, neurologic, genetic, and epidemiologic evidence supports the link. Alzheimer's disease is characterized by chronic brain inflammation (Wilson, Finch, and Cohen 2002), and patients with Alzheimer's disease have been shown to have upregulated inflammatory responses in regions of the brain most related to Alzheimer's pathology (Giunta et al. 2008; Dziedzic 2006). Gene polymorphisms of inflammatory factors have been shown to influence Alzheimer's disease risk (Dziedzic 2006). Epidemiologic studies suggest that non-steroidal anti-inflammatory drugs may delay the progression of Alzheimer's disease (Dziedzic 2006).

Several population-based studies have found a link between clinical cognitive impairment and biomarkers of systemic inflammation. One study found that baseline C-reactive protein predicts the risk of developing dementia over 25 years (Schmidt et al. 2002). Another study found that high levels of α1-antichymotrypsin, interleukin-6 and C-reactive protein increased the risk of dementia over 7 years of follow-up; however, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 were not related to dementia (Engelhart et al. 2004).

This work on dementia and inflammation has led some researchers to speculate that inflammation might influence cognitive function among those who are not clinically impaired. While a link between inflammation and dementia has been found across numerous studies, evidence on inflammation and cognitive function among non-impaired individuals has been mixed. In some cross-sectional studies of non-demented populations, cognitive function has been found to be associated with interleukin-6 levels (Schram et al. 2007; Weaver et al. 2002) and C-reactive protein (Schram et al. 2007). Other studies, however, fail to find cross-sectional relationships between cognitive function and interleukin-6 (Baune et al. 2008; Alley et al. 2008) or C-reactive protein (Weuve et al. 2006; Alley et al. 2008). Longitudinal studies are similarly mixed. Baseline C-reactive protein has

been found to predict worse cognitive function at follow-up (Komulainen et al. 2007) and cognitive decline (Yaffe et al. 2003); baseline interleukin-6 has been shown to predict subsequent cognitive decline (Schram et al. 2007; Weaver et al. 2002; Yaffe et al. 2003; Jordanova et al. 2007). However, two other studies found that neither interleukin-6 nor C-reactive protein predicted cognitive decline among the non-clinically impaired (Dik et al. 2005; Teunissen et al. 2003).

I add to this literature by assessing whether inflammation predicts cognitive function among older Taiwanese adults using growth curve analysis. Data are from the Taiwan Longitudinal Study of Aging and the Social Environment and Biomarkers of Aging Study. My study's biggest advantage over the existing literature on inflammation and cognitive function is the richness of the inflammation biomarkers and the longitudinal nature of the data. While many studies use one or two measures of inflammation, I have five biomarkers of inflammation, providing a fuller picture of the relationship between inflammation and cognition. Studies often rely on biomarker measurement from a single point in time; I have biomarkers measured at two time points, six years apart, allowing the examination of average six-year measures of inflammation as well as six-year trajectories in inflammation. Rather than a single measure of cognitive function as the outcome, I have three measures of cognition spanning five years, so I can observe trajectories in cognitive ability using growth curve analysis. This is the first study of which I am aware that studies inflammation and subclinical cognitive decline in an Asian population.

Data and Method

Data

Data are from the 2006, 2007, and 2011 waves of the Taiwan Longitudinal Study of Aging (TLSA) and the 2000 and 2006 waves of the Social Environment and Biomarkers of Aging Study (SEBAS). TLSA is a nationally representative longitudinal study of Taiwanese adults aged 50 and above (including the institutionalized population), which began in 1989; follow-up waves are ongoing. The 2000 wave of SEBAS is a random subsample of participants in the 1999 wave of TLSA. The 2006 wave includes survivors of the 2000 SEBAS wave, as well as a refresher sample drawn from the 2003 wave of TLSA. TLSA

provides information on demographic characteristics and cognitive ability; biomarker measures, including several markers of inflammation, are available for the SEBAS subsample.

639 participants completed the SEBAS examination in both 2000 and 2006. Of these, inflammation measures were not collected in at least one of the waves for 26 participants; an additional nine participants did not have a single valid cognition assessment in 2006, 2007, or 2011. The resulting analytic sample consists of 604 participants with inflammation measures in both 2000 and 2006, and at least one complete cognitive assessment in 2006, 2007, or 2011.

Variables

Inflammation

I use five biomarkers of inflammation, all measured in both 2000 and 2006: C-reactive protein, interleukin-6, soluble e-selectin, soluble intercellular adhesion molecule-1, and white blood cell count. C-reactive protein is an acute-phase protein, meaning it increases quickly and considerably as part of the inflammatory response to injury and illness (Gabay and Kushner 1999). It is considered a marker of systemic inflammation (Ridker et al. 2000). Interleukin-6 is a proinflammatory cytokine (signaling molecule) that is largely responsible for increases in C-reactive protein and other acute-phase proteins (Gabay and Kushner 1999). Soluble e-selectin and soluble intercellular adhesion molecule-1 (ICAM-1) facilitate the adhesion of white blood cells to endothelial cells as part of the inflammatory response (Albelda, Smith, and Ward 1994). White blood cells proliferate during inflammation, leading to an increase in the white blood cell count.

Each inflammatory biomarker is standardized. I consider each biomarker's relationship to cognition in separate models as well as combining all five markers into a single index (the sum of the five standardized variables) meant to capture overall inflammatory activity. My models include both the average of the inflammation measure from 2000 and 2006 as an indicator of the average level of inflammation, and the difference in the inflammation measure between 2006 and 2000 as an indicator of the trajectory of inflammation.

Cognition

In all TLSA waves, cognition is assessed via ten cognitive and memory tasks, shown in Table 1. These tasks are derived from the modified Short Portable Mental Status Questionnaire, the modified Rey Auditory Verbal Learning Test, a modified Digits Backward test, and the Mini-Mental State Examination (Chang et al. 2012). Following Herzog and Wallace (1997), I sum these ten tasks to create a cognition index score (range 0-24). If a respondent fails to answer a particular task (coded as either "don't know" or "refused"), the task is coded as incorrect (zero) for the purposes of creating the cognition index.

Method

I use growth curve analysis to examine the relationship between inflammation in 2000 and 2006; and cognitive assessment in 2006, 2007, and 2011. With this approach, I can model trajectories in cognitive score over time, allowing systematic and random differences between individuals in the intercept (baseline cognitive score) and slope (rate of cognitive change). An added advantage of growth curve analysis is that it incorporates all available data, so respondents with only one or two cognitive assessments are included.

The growth curve model is given by:

$$cog_{it} = B_{0i} + B_{1i} age_{it} + e_{it}$$

where the intercept is:

$$B_{0i} = \beta_{00} + \beta_{01} infavg_i + \beta_{02} infdif_i + b_{0i} + \beta_{03} female_i$$

and the slope on age is:

$$B_{1i} = \beta_{10} + \beta_{11} infavg_i + \beta_{12} infdif_i + b_{1i}$$

where
cog = cognitive score
infavg = inflammation- average over 2000 and 2006
infdif = inflammation- difference between 2000 and 2006 (2006 – 2000)
e = error
for person *i* at time *t*

Uppercase *B*'s represent individual *i*'s intercept and slope on age
β's represent the fixed part of the model
Lowercase *b*'s represent the random part of the model

Results

Descriptive statistics

Table 2 shows descriptive statistics of my analytic sample. On average, measures of inflammation worsen (increase) between 2000 and 2006 for four of the five biomarkers: C-reactive protein, interleukin-6, soluble intercellular adhesion molecule-1, and white blood cell count. By contrast, soluble e-selectin decreases slightly.

Cognitive assessments were conducted in 2006, 2007, and 2011. Each respondent has cognitive assessments for between one and three of these years; on average, a respondent has 2.5 cognitive measures. Cognitive assessments in 2011 are sparser than assessments in 2006 and 2007. As shown in Figure 1, cognitive score is inversely associated with age. Selection obscures this pattern in Table 2, wherein cognitive scores decline from 2006 to 2007 then appear to *increase* in 2011. Respondents' average age across these years does not increase in step with chronological time, implying that older respondents (presumably with lower cognitive scores) were less likely to be assessed in later waves.

Figure 2 shows a heat map of pairwise correlation coefficients between the five biomarkers measured in 2000 and 2006. The top-left quadrant of the figure shows correlation between the five markers in 2000; the bottom-right quadrant shows correlation between the five markers in 2006. Within a given year, the five markers are weakly to moderately positively correlated; no pair has a negative correlation. The bottom-left quadrant of the figure shows the correlation between biomarkers across years; the diagonal in this quadrant indicates the correlation between a given marker in 2000 and 2006. Soluble e-selectin, soluble ICAM-1, and white blood cell count in 2000 and 2006 are moderately correlated across the two years, while C-reactive protein and interleukin-6 are weakly correlated across time. No matter the biomarker or the year, measures of inflammation are nearly universally positively correlated; a respondent with a high level of inflammation for one marker in one year is likely to have a high level of inflammation for other markers in other years. However, the correlations are weak to moderate, suggesting that multiple measures of

inflammation at multiple time points provides greater information on inflammation than would be obtained from one or two measures at a single point in time.

Growth curve models

Results from the growth curve models are shown in Table 3. All models show the relationship between the 2000 and 2006 average and difference of the inflammation marker noted, and cognitive score trajectory over 2006, 2007, and 2011. Models 1-5 separately consider the z-score of each of the five inflammation biomarkers, while Model 6 uses a five-item index created by summing the z-scores of the five markers.

All six models indicate significant variance between respondents in baseline cognitive score and change in cognitive score with age. The models agree that a 65-year-old man with average inflammation measures in 2000 and 2006 will start with a cognitive score of about 17.4 points (out of 24) in 2006; a comparable woman will have a slightly lower cognitive score of about 16. This baseline score varies significantly from person to person, with a standard deviation of about 2.3 points. These respondents with average inflammation scores will see their cognitive scores decrease by .17 points each year on average, though there is substantial variation in the annual decrease, with a standard deviation of .11 points per year. Baseline cognitive score is not significantly correlated with annual change in cognitive score; that is, respondents who start out with a low baseline cognitive score do not see annual changes in cognition that are significantly higher or lower than respondents who start out with a high baseline cognitive score.

In Models 1-5, higher recent levels of C-reactive protein, soluble e-selectin, and white blood cell count, are associated with lower baseline cognitive scores in independent models. A one standard deviation increase in average 2000/2006 C-reactive protein levels (Model 1) is associated with a 0.67-point lower baseline cognitive score, compared to average levels of C-reactive protein; this is equivalent to the difference in cognitive score that would be expected from nearly four additional years of age. A one standard deviation increase in soluble e-selectin (Model 3) and a one standard deviation increase in white blood cell count (Model 5) are each associated with a baseline cognitive score that is lower than average levels of the markers by an amount equivalent to just under three years of age. Interleukin-

6 and soluble ICAM-1 are not significantly associated with baseline cognitive score in independent models. When all five standardized inflammation markers are summed into one index (Model 6), an increase by one standard deviation of any one of the measures (or an increase in a combination of markers resulting in a one-point increase on the index) is associated with a baseline cognitive score that is lowered by slightly more than expected from an additional year of age.

The difference between inflammation in 2000 and 2006 is significantly associated with baseline cognitive score only in the model of C-reactive protein (Model 1). On average, respondents saw an increase in C-reactive protein of 0.3 mg/L. An increase in C-reactive protein one standard deviation larger is associated with a 0.42-point lower baseline cognitive score—the equivalent of nearly three years of age. This indicates that a trajectory of increasing C-reactive protein between 2000 and 2006 is negatively associated with baseline cognition, even after controlling for the average level of C-reactive protein. Models 2-6 do not show a relationship between inflammation trajectory and baseline cognitive score, implying that, aside from C-reactive protein, baseline cognitive scores do not depend on whether inflammatory measures have been increasing or decreasing between 2000 and 2006; only the average level has an impact.

In each model, the inflammation measures are interacted with age to determine whether inflammation influences the rate of cognitive decline. This interaction is not significant for any of the inflammation measures, whether reflecting average inflammation levels or trajectories. This indicates that inflammation does not influence the rate of cognitive decline.

Sensitivity analyses

I test the sensitivity of my results to alternative specifications, none of which substantively changed my conclusions. These specifications are briefly outlined here; detailed results are available upon request. 1) Much of the literature on inflammation and health focuses on the risk of chronic low-grade inflammation for poor health (McDade, Burhop, and Dohnal 2004), sometimes excluding or trimming extremely high levels of inflammation that might indicate an acute infection (e.g., Das 2013). To reduce the influence of these outliers, I trim

the inflammation markers to be within two inter-quartile ranges of the 25th and 75th percentiles[1] (Chang et al. 2012). This trimming slightly changes the results of one growth curve model: after trimming, the coefficient on average levels of interleukin-6 in an independent model (i.e., parallel to Model 2) becomes slightly larger in magnitude and achieves statistical significance.

2) Many studies dichotomously define inflammatory markers as either high risk or not (e.g., Goldman et al. 2011). This approach allows a non-linear relationship between inflammation and health, and is robust to outliers. I construct an alternative five-item index (range: 0 to 5) that indicates the number of biomarkers for which a respondent falls into the high-risk category (defined either clinically or as the top quartile). Using this index leads to the same conclusion as the index created by summing the five standardized inflammation measures: having more biomarkers in the high-risk range is associated with lower baseline cognitive score, but is not associated with rate of cognitive change.

3) Several studies have found that the relationship between inflammation and health varies by sex (Baune et al. 2011; Bruunsgaard et al. 2003). To address this concern, I examine a five-item index model that is fully interacted with sex. I find that the relationship between average levels of inflammation and cognitive score does not significantly differ by sex. The relationship between the trajectory of inflammation and cognitive score does differ by sex; for men, a worsening trajectory of inflammation is associated with a slightly lower baseline cognitive score, while for women, a worsening trajectory is associated with a slightly higher baseline score.

Discussion

The aim of this study is to determine whether inflammation influences cognitive change among older Taiwanese adults. I find that higher levels of C-reactive protein, soluble e-selectin, and white blood cell count are associated with lower baseline cognitive score; I do not find a relationship with baseline cognitive score for interleukin-6 or soluble ICAM-1. None of the inflammation measures is associated with the rate of cognitive change.

[1] I.e., values smaller than P25-2*IQR are recoded to P25-2*IQR; values larger than P75+2*IQR are recoded to P75+2*IQR.

Past studies of inflammation and cognitive function have been mixed. One reason for the conflicting findings may be the considerable methodological differences between studies (Trollor et al. 2012). Inflammation is evaluated using various biomarkers, measured using different laboratory assay protocols, and assessments of cognition vary significantly from study to study. Table 4 shows the variation in inflammation and cognitive measures from a handful of studies examining inflammation and cognition.

My finding that inflammation does not predict cognitive decline could be interpreted in different ways. Alley et al. (2008) would argue that my study is consistent with their view that inflammation is related to cognitive impairment, but not cognitive change among the non-impaired. Most studies that find an association between cognitive decline and inflammation, they point out, typically examine the risk of cognitive decline above some threshold; by definition, a larger decline is more likely indicative of clinical impairment, and may obscure the relationship between inflammation and subclinical cognitive decline (Alley et al. 2008). Baune et al. (2008), on the other hand, would argue that by using a global measure of cognitive function, I am relying on a measure designed to screen for dementia, which may not be able to detect milder impairment. Ultimately, my study cannot distinguish between these two options: I may have correctly identified the absence of a relationship between inflammation and non-clinical cognitive decline, or I may have been unable to detect an existing relationship due to coarse measurement.

Despite these limitations, my results indicate that inflammation is moderately associated with a baseline global measure of cognitive function, but does not appear to play a large role in the rate of cognitive decline among the clinically unimpaired.

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Tables and Figures

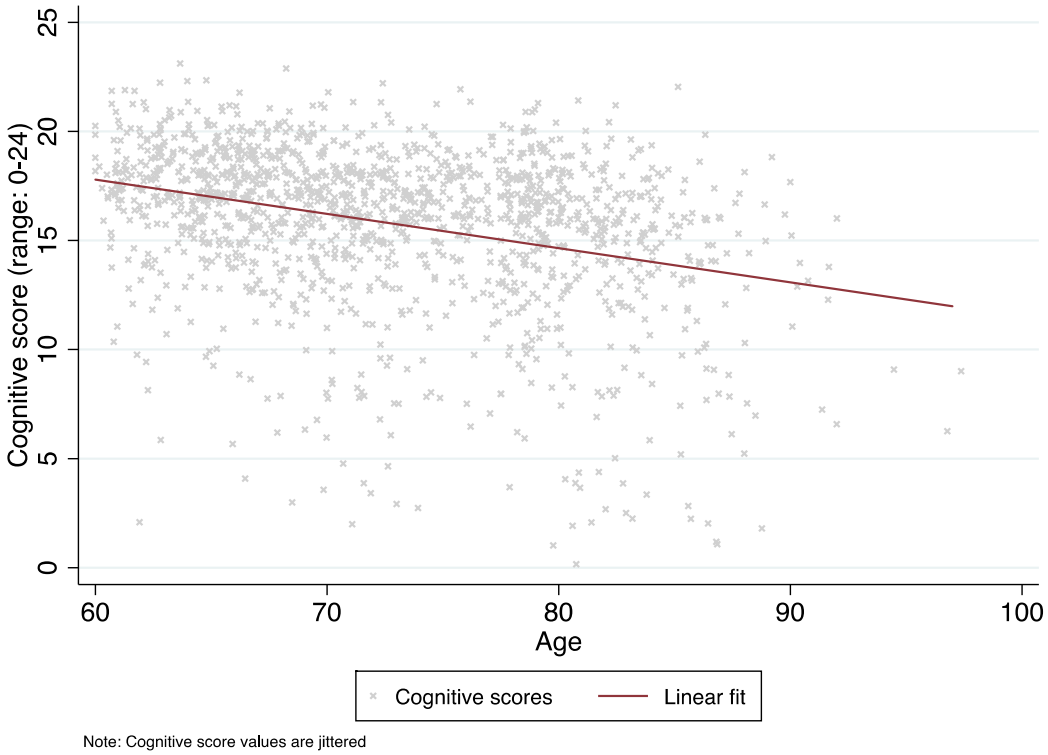
Table 1: Cognitive tasks included in the cognitive assessment

Item	Max score
Tell me your address	1
What is today's date? (Year, month and day)	3
What day of the week is it?	1
How old are you this year?	1
What is your mother's maiden name?	1
Who is the current president?	1
Who was the president before him?	1
Serial 3s subtraction task (4 times, starting at 20)	4
10-item recall task	10
5 numbers repeated in reverse order task	1

Table 2: Descriptive statistics

	Mean or percent	Standard deviation	Median	N
Demographic characteristics				
Female	43%	--	--	606
Age, 2000	66.3	7.6	65.0	606
Age, 2006	72.3	7.6	72.0	606
Age, 2011	76.0	7.3	75.0	505
Cognitive function score (range: 0-24)				
2006	15.7	3.8	16.5	598
2007	15.5	3.9	16.0	576
2011	16.4	2.6	17.0	324
Inflammation, 2000				
C-reactive protein (mg/L)	2.7	6.4	0.8	604
Interleukin-6 (pg/L)	3.1	4.3	2.1	606
Soluble e-selectin (ng/mL)	46.6	23.8	40.6	606
Soluble intercellular adhesion molecule-1 (ng/mL)	246.0	96.8	233.8	606
White blood cell count (x 10^3/µL)	6.0	1.5	5.8	606
Inflammation, 2006				
C-reactive protein (mg/L)	3.1	7.6	1.1	606
Interleukin-6 (pg/L)	4.5	9.3	2.8	606
Soluble e-selectin (ng/mL)	42.3	28.8	35.2	606
Soluble intercellular adhesion molecule-1 (ng/mL)	281.5	101.3	267.8	606
White blood cell count (x 10^3/µL)	6.1	1.8	5.9	606
Inflammation, average of 2000 and 2006				
C-reactive protein (mg/L)	2.9	5.2	1.2	604
Interleukin-6 (pg/L)	3.8	5.7	2.7	606
Soluble e-selectin (ng/mL)	44.4	23.5	38.8	606
Soluble intercellular adhesion molecule-1 (ng/mL)	263.8	89.7	252.2	606
White blood cell count (x 10^3/µL)	6.0	1.4	5.9	606
Inflammation, difference between 2000 and 2006				
C-reactive protein (mg/L)	0.3	9.3	0.3	604
Interleukin-6 (pg/L)	1.4	9.1	0.5	606
Soluble e-selectin (ng/mL)	-4.3	23.9	-7.0	606
Soluble intercellular adhesion molecule-1 (ng/mL)	35.5	84.3	30.0	606
White blood cell count (x 10^3/µL)	0.1	1.5	0.0	606

Figure 1: Cognitive score by age



Note: Observations from all participants are combined; i.e., individual fixed effects are not considered.

Figure 2: Pairwise correlation coefficients between all biomarkers of inflammation in 2000 and 2006

	2000					2006				
	CRP	IL-6	sE-selectin	sICAM-1	WBC	CRP	IL-6	sE-selectin	sICAM-1	WBC
2000										
CRP	1.00									
IL-6	0.31	1.00								
sE-selectin	0.21	0.14	1.00							
sICAM-1	0.15	0.10	0.47	1.00						
WBC	0.22	0.15	0.29	0.08	1.00					
2006										
CRP	0.12	0.07	0.03	-0.02	0.03	1.00				
IL-6	0.04	0.28	0.03	0.04	-0.01	0.58	1.00			
sE-selectin	0.07	0.07	0.60	0.39	0.17	0.11	0.07	1.00		
sICAM-1	0.07	0.06	0.31	0.64	0.02	0.18	0.18	0.44	1.00	
WBC	0.11	0.05	0.25	0.07	0.59	0.22	0.13	0.20	0.06	1.00

Table 3: Growth curve models of inflammation and cognitive score

	C-reactive protein		Interleukin-6		E-selectin		ICAM-1		White blood cell count		Five-item index	
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	95% CI
Constant	17.39	(17.01, 17.77)	17.40	(17.01, 17.78)	17.41	(17.03, 17.79)	17.40	(17.01, 17.78)	17.46	(17.08, 17.84)	17.42	(17.04, 17.80)
Female	-1.37	(-1.86, -0.87)	-1.34	(-1.84, -0.84)	-1.32	(-1.81, -0.82)	-1.29	(-1.79, -0.79)	-1.38	(-1.88, -0.89)	-1.37	(-1.86, -0.87)
Inflammation (z-scores)												
C-reactive protein z-score, average	-0.67	(-1.13, -0.21)										
C-reactive protein z-score, difference	-0.42	(-0.67, -0.18)										
Interleukin-6 z-score, average			-0.47	(-1.03, 0.08)								
Interleukin-6 z-score, difference			-0.03	(-0.37, 0.30)								
e-Selectin z-score, average					-0.45	(-0.77, -0.14)						
e-Selectin z-score, difference					0.42	(0.09, 0.74)						
ICAM-1 z-score, average							-0.24	(-0.59, 0.12)				
ICAM-1 z-score, difference							0.08	(-0.27, 0.44)				
WBC z-score, average									-0.47	(-0.82, -0.12)		
WBC z-score, difference									0.16	(-0.19, 0.51)		
Five-item index z-score, average											-0.20	(-0.32, -0.08)
Five-item index z-score, difference											-0.03	(-0.13, 0.08)
Age (centered at 65)	-0.17	(-0.20, -0.13)	-0.17	(-0.20, -0.14)	-0.17	(-0.20, -0.14)	-0.17	(-0.20, -0.14)	-0.17	(-0.20, -0.14)	-0.17	(-0.20, -0.14)
Inflammation * age												
Age * C-reactive protein z-score, average	0.03	(-0.02, 0.08)										
Age * C-reactive protein z-score, difference	0.04	(0.01, 0.07)										
Age * interleukin-6 z-score, average			0.02	(-0.03, 0.07)								
Age * interleukin-6 z-score, difference			0.00	(-0.03, 0.03)								
Age * e-Selectin z-score, average					0.00	(-0.03, 0.04)						
Age * e-Selectin z-score, difference					-0.03	(-0.07, 0.01)						
Age * ICAM-1 z-score, average							0.02	(-0.02, 0.05)				
Age * ICAM-1 z-score, difference							-0.01	(-0.04, 0.03)				
Age * WBC z-score, average									-0.01	(-0.05, 0.02)		
Age * WBC z-score, difference									-0.02	(-0.05, 0.02)		
Age * five-item index z-score, average											0.00	(-0.01, 0.01)
Age * five-item index z-score, difference											0.00	(-0.01, 0.01)
SD(constant)	2.38	(2.11, 2.68)	2.41	(2.14, 2.71)	2.36	(2.10, 2.66)	2.41	(2.14, 2.71)	2.39	(2.12, 2.69)	2.39	(2.12, 2.70)
SD(coeff on age)	0.11	(0.05, 0.25)	0.11	(0.05, 0.24)	0.11	(0.05, 0.24)	0.11	(0.05, 0.24)	0.11	(0.05, 0.24)	0.13	(0.07, 0.23)
Corr(constant, coeff on age)	0.34	(-0.55, 0.87)	0.29	(-0.49, 0.82)	0.34	(-0.51, 0.85)	0.31	(-0.50, 0.83)	0.29	(-0.50, 0.82)	0.17	(-0.42, 0.66)
Number of observations	1,494		1,498		1,498		1,498		1,498		1,494	
Number of respondents	604		606		606		606		606		604	
Average observations per respondent	2.5		2.5		2.5		2.5		2.5		2.5	

Table 4: Measures and findings from selected studies of Inflammation and cognition

Inflammation measure	Findings
Alley et al. 2008. Study population: MacArthur Study of Successful Aging. Outcome: measures of abstraction, language, spatial ability, verbal recall, spatial recognition, and global cognitive function.	
C-reactive protein	Higher level cross-sectionally associated with lower cognitive score, but not decline. Cross-sectional relationship disappears with controls.
Interleukin-6	Higher level cross-sectionally associated with lower cognitive score, but not decline. Cross-sectional relationship disappears with controls.
Baune et al. 2008. Study population: Memory and Morbidity in Augsburg Elderly Study. Outcome: measures of memory, word fluency, perceptual/cognitive speed, attention and executive functioning, and motor speed	
Interleukin-1beta	No relationship with cross-sectional cognitive score after Bonferroni correction.
Soluble interleukin-4R	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-6	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-8	Higher level cross-sectionally associated with lower cognitive score.
Interleukin-10	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-12	No relationship with cross-sectional cognitive score after Bonferroni correction.
Tumor necrosis factor-alpha	No relationship with cross-sectional cognitive score after Bonferroni correction.
Dik et al. 2005. Study population: Longitudinal Aging Study Amsterdam. Outcome: measurse of general cognition, memory, fluid intelligence, and information-processing speed.	
Alpha 1-antichymotrypsin	Higher level associated with 3-year cognitive decline.
C-reactive protein	No relationship with 3-year cognitive decline.
Interleukin-6	No relationship with 3-year cognitive decline.
Jordanova et al. 2007. Study population: from Primary Care registration lists in south London. Outcome: measures of orientation, immediate word list recall, delayed word list recall, delayed word list recognition, and visual attention/motor speed.	
C-reactive protein	No relationship with 3-year cognitive decline.
Interleukin-6	Higher level associated with 3-year cognitive decline.
Serum amyloid A	No relationship with 3-year cognitive decline.
Komulainen et al. 2007. Study population: subsample of a large risk factor survey in Finland. Outcome: measures of global cognitive function, memory, and cognitive speed.	
C-reactive protein	Higher level associated with 12-year cognitive decline.
Schram et al. 2007. Study population: the Rotterdam Study and the Leiden 85-plus Study. Outcome: global cognition, executive function, and memory.	
C-reactive protein	RS: Higher level cross-sectionally associated with lower cognitive score. L85: No relationship with cross-sectional cognitive score.
Interleukin-6	RS: Higher level cross-sectionally associated with lower cognitive score. L85: No relationship with cross-sectional cognitive score. Higher level associated with steeper decline.
Alpha 1-antichymotrypsin	No relationship with cognitive score.
Teunnissen et al. 2003. Study population: Maastricht Aging Study. Ourcome: measures of cognitive speed, attention and information processing, and memory.	
Interleukin-6	No relationship with cognitive score.
Clara cell protein 16	No relationship with cognitive score.
C-reactive protein	Higher level associated with lower baseline cognitive score and 6-year cognitive decline.
Albumin	No relationship with cognitive score.
Protein fractions	No relationship with cognitive score.
Haptoglobin	Higher level associated with lower baseline cognitive score and 6-year cognitive decline.
Haptoglobin phenotype	No relationship with cognitive score.
Troller et al. 2012. Study population: Sydney Memory and Ageing Study. Outcome: measures of processing speed, fine motor, memory, language, spatial, executive.	
C-reactive protein	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-1beta	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-6	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-8	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-10	No relationship with cross-sectional cognitive score after Bonferroni correction.
Interleukin-12	Higher level cross-sectionally associated with lower cognitive score.
Plasmingoen activator inhibitor	No relationship with cross-sectional cognitive score after Bonferroni correction.
Serum amyloid A	No relationship with cross-sectional cognitive score after Bonferroni correction.
Tumor necrosis factor-alpha	No relationship with cross-sectional cognitive score after Bonferroni correction.
Vascular adhesion molecule-1	No relationship with cross-sectional cognitive score after Bonferroni correction.
Weaver et al. 2002. Study population: MacArthur Study of Successful Aging. Outcome: measures of naming, verbal memory, spatial recognition, abstraction, and spatial ability.	
Interleukin-6	Higher level associated with lower cross-sectional cognitive score and steeper decline.
Weuve et al. 2006. Srudy population: The Women's Health Study. Outcome: measures of general cognition, verbal memory, and category fluency.	
C-reactive protein	No relationship with cognitive score.
Yaffe et al. 2003. Study population: Health, Aging, and Body Composition Study. Outcome: global cognition.	
Interleukin-6	Higher level associated with lower baseline cognitive score and 2-year cognitive decline.
C-reactive protein	Higher level associated with lower baseline cognitive score and 2-year cognitive decline.
Tumor necrosis factor-alpha	No relationship with cognitive score.