

**Body Mass and Cognitive Decline are  
Indirectly Associated via Inflammation among Aging Adults**

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### Abstract

Inflammatory models of neurodegeneration suggest that higher circulating levels of inflammation can lead to cognitive decline. Despite established independent associations between greater body mass, increased inflammation, and cognitive decline, no prior research has explored whether markers of systemic inflammation might mediate the association between body mass and changes in cognitive functioning. To test such a model, we used two longitudinal subsamples ( $n = 9066$ ;  $12,561$ ) of aging adults from the English Longitudinal Study of Ageing (ELSA) study, which included two cognitive measures components of memory and executive functioning, as well as measurements of body mass and systemic inflammation, assessed via C-reactive protein (CRP). Greater body mass was indirectly associated with declines in memory and executive functioning over 6 years via relatively higher levels of CRP. Our results suggest that systemic inflammation is one biologically plausible mechanism through which differences in body mass might influence changes in cognitive functioning among aging adults.

*Keywords:* Inflammation, C-reactive protein, body mass, cognition, executive functioning, memory

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## 1. Introduction

Preserved cognitive functioning is an important marker of quality of life among aging adults (Abrahamson et al., 2011; Nys et al., 2006). Although cognitive decline is linked with aging, the rate of this decline in aging is highly variable (Fillit et al. 2002; Park, O'Connell, & Thomson, 2003) and can depend on a variety of individual differences, including exaggerated inflammatory responses (Tegeler et al., 2016; Tuenissen et al., 2003; Yaffe et al., 2003) and elevated body mass (Memel, Bourassa, Woolverton, & Sbarra, 2016), as well as a host of psychosocial and health behavior variables (e.g., social engagement, physical health, physical activity, and depression (Bourassa, Memel, Woolverton, & Sbarra, 2015). With the rate of adults 65 years and older rising relative to the overall population in almost all developed countries (Restrepo & Rozentel, 1994), understanding what risk factors are associated with cognitive decline is essential for developing interventions to promote successful aging. To explore one potential pathway that might explain risk for cognitive decline among aging adults, we examined the associations among body mass, inflammation, and change in cognition over 6 years in a nationally representative sample of older adults.

### 1.2 Inflammation and cognitive decline

Inflammation is one biologically-mediated pathway that might explain individual differences in cognitive decline among aging adults. Higher systemic inflammation levels are associated with cognitive decline in normative aging populations (Tegeler et al., 2016; Tuenissen et al., 2003; Yaffe et al., 2003), as well as in clinical samples experiencing age-related neurological disorders (Perry, Cunningham, & Holmes, 2007). Inflammatory models of

neurodegeneration propose that systemic inflammation is negatively associated with cognition via increases in neuro-inflammation. Inflammatory cytokines – including Tumor Necrosis Factor(TNF) $\alpha$ , Interleukin(IL)-1 $\beta$ , and IL-6 – secreted by microglia in the brain likely establish and maintain neuro-inflammation (Glass, Saijo, Winner, Marchetto, & Gage, 2010), which can lead to neuronal apoptosis over the long-term (McCoy & Tansey, 2008; Simi, Tsakiri, Wang, & Rothwell, 2007), and inhibits neurogenesis in adults (Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003). Systemic inflammation in the periphery is tied to neuro-inflammation in neurodegenerative disorders (Perry, 2004), as well as in aging populations more generally (Perry, 2010). For example, IL-6 and C-reactive protein (CRP) assessed in the periphery are associated with changes in brain morphology and cognitive decline in midlife (Marsland et al., 2015). As a result, individual differences in systemic inflammation may explain a portion of the variability in cognitive decline among aging adults.

### **1.3 Body mass, inflammation, and cognition**

Body mass is broadly associated with both inflammation (Visser, Bouter, McQuillan, Werner, & Harris, 1999; Wisse, 2004) and cognition (Benito-León, Mitchell, Hernández-Gallego, & Bermejo-Pareja, 2013; Cournot et al., 2006; Memel et al., 2015). For example, people with higher body mass index scores perform worse than people with body mass in the healthy range across a variety of cognitive tasks (Gunstad et al., 2007). Despite the large literature exploring the association of body mass and cognition for aging adults, there is relatively less research examining the specific biologically-mediated pathways through which body mass might influence cognition. There are several pathways through which body mass might influence changes in cognitive functioning over time. For example, greater adipose tissue and body mass, for example, increases the production of proinflammatory cytokines tied to

metabolic syndrome (Wisse, 2004) and greater body mass predicts greater leptin and insulin resistance, insulin dysregulation, and inflammation, all of which are associated with cognitive decline (Consondine et al., 1996; Al Hazzouri, Stone, Haan, & Yaffe, 2013; Greenwood & Winocur, 2005; Visser et al, 1999; Wisse, 2004). One potential biologically-mediated pathway that could explain the association between higher body mass and cognitive decline is inflammation. Higher body mass is associated with specific markers of systemic inflammation, including IL-6 and CRP (Park, Park, & Yu, 2005), both of which are implicated in inflammatory models of neurodegeneration (Glass et al., 2010). Thus, inflammation is one biologically-mediated pathway that might help explain the link between body mass and subsequent cognitive decline.

#### **1.4 Present study**

Despite established associations among body mass, systemic inflammation, and cognitive decline, no prior research has examined the extent to which systemic inflammation might account for the association of individual differences in body mass and changes in cognitive decline among aging adults. The present study aimed to explore this possibility in two subsamples of aging adults ( $n_s = 9066; 12,561$ ) drawn from the longitudinal English Longitudinal Study of Ageing (ELSA). We hypothesized that body mass would be indirectly associated with change in two areas of cognitive functioning – memory and executive functioning – via systemic inflammation levels, as indexed by circulating CRP. More specifically, we predicted that higher body mass would positively predict change in CRP, which in turn would predict greater cognitive decline across the 6 years.

## **2. Method**

### **2.1 Participants**

The English Longitudinal Study of Aging (ELSA) currently has seven waves of data collected every two years from 1998-2013 (Marmot et al., 2015), which included cognitive measures in Waves 1-6. These waves were supplemented by home visits by a nurse every other wave (Waves 0, 2, 4) during which blood samples were collected and analyzed. ELSA was designed to collect information on a representative sample of people in England over the age of 50, and details regarding the selection, eligibility, and recruitment of participants, participant demographics, and study methodology are reported in more detail in the ELSA Technical Report and User Guide (Marmot et al., 2015).

For the present study, 29,808 unique participants had data across at least one of the waves. Figure 1 outlines the specific data collected at each of the waves used in the current study. Following standard practices, we excluded participants from the current study that had CRP scores above 10 mg/L, which likely reflects acute infection or an obvious source of inflammation (see Pearson et al., 2003). Participants were excluded from the sample in a stepwise fashion beginning with Wave 0, then Waves 2, and 4. This resulted in excluding 552, 428, and 348 participants from waves 0, 2, and 4, respectively. From the remaining 28,408 eligible participants, two subsamples were created by selecting and excluding participants who were assessed on the variables of interest during at least one of the relevant times points, as shown in Figure 2. For subsample 1 (assessing Waves 0-4), we included participants with assessments at Waves 0, 1, 2, and 4<sup>1</sup>, whereas for subsample 2 (assessing Waves 2-5) we

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<sup>1</sup> In subsample 1, we also then excluded participants without at least one valid CRP score, as this was necessary to reach valid covariance coverage due to high levels of missingness at Wave 0 compared to waves 1, 2 and 4.

included participants assessed at Waves 2, 4, and 5. This resulted in a final sample of 9,066 people for subsample 1 and 12,561 people for subsample 2 out of the original ELSA participants<sup>2</sup>. Of these participants, 6,354 people completed all the relevant waves of assessment used in the two subsamples (Waves 0-2, 4, and 5), and were included in both subsamples, as none of the measured variables overlapped between the two subsamples at a given wave of assessment. These two subsamples were selected to allow for analysis of change over time in both CRP and cognition—which required a six year time period due to the data collection timeline—and because it allowed us to test whether the effects seen in one subsample would replicate in a second subsample.

## 2.2 Measures

**2.2.1 Demographic covariates.** Demographic variables included self-reported age and gender.

**2.2.2 Cognition.** Cognition was assessed using three tasks—immediate word recall, delayed word recall, and verbal fluency—assessed by a trained interviewer using a standardized process in participants' home. These three measures were used to create two broad constructs for

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<sup>2</sup> We note that the specific waves that we selected from cognitive measures from were adjusted from subsample 1 to subsample 2. The cognitive measures of interest were not collected at Wave 0 and our measure of executive functioning was not collected at Wave 6. As a result, we included cognitive measures spanning Waves 1-4 for subsample 1 and waves 2-5 for subsample 2 to account for these differences and retain the same amount of time between measurements. As a result, the measurement of CRP was completed 2 years and 4 years after the measurement of body mass for subsample 1 and 2, respectively.

cognitive functioning, memory and executive functioning, similar to prior investigations using similar cognitive measures (Bourassa et al., 2015).

*2.2.2.1 Memory Function.* Memory function was assessed using immediate and delayed word recall task from the Ten-Word Delayed Recall Test. Ten words were presented and participants attempted to recall the words immediately, then again five minutes later, and the two scores were averaged. Similar assessments have been used extensively to measure immediate and delayed memory performance (Green, Montijo, & Brockhaus, 2011; Hoskins, Binder, Chaytor, Williamson, & Drane, 2010).

*2.2.2.2 Executive function.* Executive function was assessed using a category fluency task. Participants were asked to name as many animals correctly as possible during a one-minute period. The measure is sensitive to alterations in executive functions in patients with frontal lobe damage (Stuss et al., 1998) and has been used widely in neuropsychological batteries to differentiate between healthy age-related memory change and clinically significant impairments (Haugrud, Crossley, & Vrbancic, 2011).

**2.2.3 Body Mass.** Participants' weight and height were assessed by a trained nurse in participants' homes; height was measured using a portable stadiometer, whereas weight was recorded using a portable scale after removing bulky clothing. Body mass (BM) was calculated using as standard formula for the body mass index (BMI):  $(\text{weight in kilograms}/(\text{height in meters})^2)*10000$ .

**2.2.4 C-reactive protein (CRP).** Blood samples were collected during house visits by trained nurses. The blood samples were then analyzed by the Department of Clinical Biochemistry at the Royal Victoria Infirmary using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyzer, as described in more detail in Graig, Deverill, and Pickering

(2004), to assess C-reactive protein levels (mg/L). These values were then log-transformed to normalize the distribution of scores assesses participants' CRP level, as CRP levels are generally skewed (Kushner, Rzewnicki, & Samols, 2006). As noted above, participants with CRP levels > 10mg/L were excluded (see Pearson et al., 2003).

**2.2.5 Depressive symptoms.** Self-reported depressive symptoms were collected using the sum of 8 binary yes-no items drawn from the CES-D (Radloff, 1977) adapted for use in the ELSA sample. The items captured whether participants has mood, motivation, affect, and somatic complaints much of the time over the past week. The scores ranged from 0-8, with higher scores representing more depressive symptoms.

**2.2.6 Self-reported physical health.** Physical health was assessed using participants' response to a five point scale read out to them asking "Would you say your health is..." with responses ranging from "excellent" to "very poor." Scores were coded such that higher scores denoted lower self-perceived physical health.

**2.2.7 Medical covariates.** Self-reported heart difficulties over the past two years and blood pressure medication use were assessed using binary items, "In the past two years, have you had a heart attack or myocardial infarction?" and "Are you taking any medication, tablets, or pills for high blood pressure?" respectively.

## **2.3 Data Analysis**

In the current study, we evaluated the associations of body mass (BM), change in inflammation – as indexed by C-reactive protein (CRP) levels – and change over time in two areas of cognition – memory and executive function (EF). In each subsample BM, CRP, and cognition were assessed across three time points, and these time points differed between the two subsamples. The waves used for each subsample represented by T1, T2, and T3 are illustrated in

Fig. 3. In addition, Memory and EF were assessed using a verbal memory task and semantic fluency task, respectively. CRP was log-transformed to account for skew (Kushner et al., 2006); no other variables were transformed. We used structural equation modeling (SEM) to construct our mediation models. First, we evaluated the association between BM and CRP at T2. We next examined whether T2 CRP predicted change in memory and EF at T3, including a test of the indirect effects of BM on memory and EF via the T2 mediator, CRP levels. We also included relevant demographic covariates (age and gender) to ensure these covariates did not account for the associations of interest. The final conceptual SEM is presented in Fig. 4. In our analyses, we used the root-mean-squared error of approximation (RMSEA) and comparative fit index (CFI) in addition to chi squared tests as common fit measures to use with maximum likelihood (ML) estimation for missing data (Hu and Bentler, 1999). Standardized values reported here were calculated using the formula  $\beta = b * SD(x)/SD(y)$  for continuous predictors, and  $\beta = b/SD(y)$  for dichotomous variables, described in further detail in Muthén and Muthén (2012). In all analyses, we used full likelihood maximum likelihood (FIML) estimation for missing data (Graham, 2009) and indirect effects were estimating using a bootstrapping approach (N = 1000) to derive bias corrected robust standard errors.

### 3. Results

Table 1 displays descriptive statistics and provides a correlation matrix of all variables included in the study estimated using FIML for study participants.

We first specified our path model for memory in each subsample. We included direct paths from T1 BM, age, and gender to T2 CRP, as well as a direct path from T1 CRP levels to account for participants' prior CRP levels. We then regressed T3 memory on T2 CRP, and included direct paths from T1 memory, age, and gender to T3 memory to account for prior

memory and individual differences in participants' demographics. The resulting model fit the data well in both the first,  $\chi^2(2, N = 9066) = 16.01, p = 0.001, CFI = 1.00, RMSEA = 0.022$ , and second subsample,  $\chi^2(2, N = 12,561) = 17.33, p = 0.001, CFI = 1.00, RMSEA = 0.019$ . The full results of the model, including confidence intervals around the unstandardized estimates, are presented in Table 2. T1 BM significantly predicted change in CRP in each subsample,  $\beta = 0.12$ , 95% Confidence Interval (CI) [0.09, 0.15],  $p < 0.001$ ,  $\beta = 0.11$  [0.07, 0.14],  $p < 0.001$ . T2 CRP levels also significantly predicted T3 memory when residualizing for T1 memory in the both subsamples,  $\beta = -0.05$  [-0.08, -0.03],  $p < 0.001$ ,  $\beta = -0.04$  [-0.06, -0.02],  $p = 0.001$ . We next explored the indirect effects of interest. There was a significant indirect effect from T1 BM to T3 memory via T2 CRP in both subsamples,  $\beta = -0.006$  [-0.009, -0.003],  $p = 0.001$ ,  $\beta = -0.004$  [-0.007, -0.001],  $p = 0.007$ .

We next specified our models for EF. Identical to our models with memory, we included direct paths from T1 BM, age, gender, to T2 CRP, as well as a direct path from T1 CRP levels to account for participants' prior CRP levels. We then regressed T3 EF on T2 CRP, and included direct paths from T1 EF, age, and gender to T3 memory to account for prior EF and individual differences in participants' demographics. The resulting model fit the data well in both the first,  $\chi^2(3, N = 9006) = 9.64, p = 0.022, CFI = 0.99, RMSEA = 0.016$ , and second subsample,  $\chi^2(3, N = 12,561) = 2.47, p = 0.481, CFI = 1.00, RMSEA = 0.000$ . The full results of that model, including confidence intervals around the unstandardized estimates, are presented in Table 3. T1 BM significantly predicted change in CRP in each subsample,  $\beta = 0.12$  [0.09, 0.15],  $p < 0.001$ ,  $\beta = 0.11$  [0.07, 0.14],  $p < 0.001$ . T2 CRP levels also significantly predicted T3 EF when residualizing for T1 EF in the both subsamples,  $\beta = -0.04$  [-0.06, -0.01],  $p = 0.003$ ,  $\beta = -0.04$  [-0.06, -0.02],  $p < 0.001$ . We next explored the indirect effects of interest. There was a

significant indirect effect from T1 BM to T3 EF via T2 CRP in both subsamples,  $\beta = -0.004$   $[-0.007, -0.001]$ ,  $p = 0.006$ ,  $\beta = -0.004$   $[-0.007, -0.002]$ ,  $p = 0.003$ . In addition, all substantive results of our models replicated when excluding age and gender from the models.

Although we included age and gender as covariates in our models, it is possible that other variables may explain the associations among BM, CRP, and the cognitive measures used in the study. Therefore, we also tested a series of models that included a variety of alternative predictors of cognitive decline; these predictors included depressive symptoms, self-rated health, and presence of heart pain, as well as a reported myocardial infarction event or use of medication for high blood pressure over the past 2 years. All substantive results replicated when including these variables in both subsamples, with the exception of the model predicting EF in subsample 1, which was non-significant at the 0.05 level with the added covariates,  $\beta = -0.003$   $[-0.006, 0.000]$ ,  $p = 0.063$ . Both direct effects, however, remained significant in this model.

Having established indirect effects through CRP, the possibility remains that inflammation is the result of cognitive decline, rather than a precursor. In order to test the causal order of these variables, we specified an alternative model for both memory and EF where the cognitive functioning variables and CRP were reversed, such that BM at T1 predicted change in memory or EF at T2, which in turn predicted change in CRP at T3<sup>3</sup>. The results for both models in each subsample indicated that, although BM did predict a change in EF and memory, EF and memory did not predict change in CRP, nor was there a significant indirect effect of BM on CRP via EF or memory, except in one case. In subsample 2, Memory at T2 did predict CRP at T3,  $\beta =$

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<sup>3</sup> Due to the data collection pattern for CRP in ELSA, this required that the models use BM at Waves 0 and 2, change in EF and memory from Wave 1 to 3 and Wave 2 to Wave 4, and change in CRP from Wave 0 to 4 and Wave 2 to 6 for subsample 1 and 2 respectively.

$-0.05$  [ $-0.08, -0.02$ ],  $p = 0.003$ , and the indirect effect of BM on CRP via memory was significant,  $\beta = -0.003$  [ $-0.006, -0.000$ ],  $p = 0.011$ . These direct and indirect effect were non-significant and negligible in size in subsample 1, however, ( $\beta = -0.01$  [ $-0.05, 0.03$ ],  $p = 0.548$  and  $\beta = -0.000$  [ $-0.001, 0.001$ ],  $p = 0.579$ , respectively) which suggests this effect may be due to chance rather than a reliable effect. These analyses suggest the most appropriate models reflect BM predicting change in CRP, which in turn predicts cognitive decline.

#### 4. Discussion

We explored the association of body mass, inflammation, and cognition in two samples ( $n_s = 9066; 12,561$ ), drawn from a representative sample of English aging adults, to test the extent to which inflammation explained the association of body mass and cognitive decline over time. We found that greater body mass predicted an increase in systemic inflammation levels, as indexed by blood serum levels of CRP. Higher levels of inflammation in turn predicted greater decline in two verbal memory tasks and a semantic fluency task—indicators of memory and executive functioning, respectively. There was a significant indirect effect of body mass on cognition via inflammation. These substantive results replicated across our two subsamples with similar effect sizes for the associations of interest.

When using large samples, the statistical power to detect trivially small effects is high; therefore, it is important to establish the clinical importance of significant associations—that is, although the effects we observed are statistically significant, are they practically meaningful? To address this question, we used a benchmarking approach (Sechrest et al., 1996) to contextualize the magnitude and importance of the indirect effect relative to other effects observed in this analysis. The results indicated that a 1 SD change in age (10.39 years) predicted a 0.28 SD average change in cognition. On average, a 1 SD change in body mass – 4.34 points of BMI or

approximately 26 lbs. for someone who is at the average height of the sample (5' 5.4") – predicted a 0.12 *SD* change in CRP, or a change in 0.25 mg/L of CRP. This change in CRP in turn would predict a 0.05 *SD* change in cognition, on average, and result in an overall indirect effect size equaling 0.005 of a *SD*. A change in a participants' initial body mass of 1 *SD* would then be associated with approximately 2.22 months of cognitive decline based on chronological age, whereas a 1 *SD* change in CRP would be associated with 1.85 years of cognitive decline associated with chronological aging. Although these effects are small, they do appear to be comparable with the above lengths of chronological aging, suggesting they are clinically meaningful.

These results have implications for neurodegenerative models of inflammation. Higher body mass has been consistently linked with increased inflammation (Visser et al., 1999 and Wisse, 2004) as well as lower cognitive functioning (Benito-León et al., 2013, Cournot et al., 2006 and Memel et al., 2016), and higher levels of inflammation predicts cognitive decline (Perry et al., 2007, Tegeler et al., 2016, Teunissen et al., 2003 and Yaffe et al., 2003), but no previous studies have tested the associations body mass, inflammation, and cognitive decline in a single, integrated model. Once a robust link between a biometric risk factor, such as body mass, and an outcome of clinical interest is established, it essential to test the more proximal potential biological mechanisms that might help explain this association using mediation models that integrate the relevant biological intermediary into the pathways from risk factor to outcome (Miller et al., 2009). Our measure of circulating inflammation, CRP (a measure of systemic inflammation in the periphery), evidenced a significant indirect effect that accounted for the association between body mass and cognition; circulating levels of systemic inflammation are associated neuro-inflammation (Marsland et al., 2015, Perry, 2004 and Perry, 2010). Although

we were unable to include measures of neuro-inflammation in our current study, our results match well with neurodegenerative models of cognitive decline and suggest that inflammation is one biologically plausible mechanism through which body mass might affect cognition. Furthermore, this pathway is observable in large, non-clinical samples of aging adults, rather than only in clinical populations, such as people with dementia, Alzheimer's disease, or traumatic brain injury. It is important to note that although CRP evidenced a significant indirect effect, there are likely multiple biological intermediaries that explain the association between either body mass and CRP or CRP and cognitive decline. This study may provide evidence supporting inflammation as one potential link between linking body mass and increased risk for cognitive decline, but further research should refine the causal pathway(s) from body mass to cognition.

These results have clinical implications for primary care physicians treating aging adults. First, higher levels of body mass could be used as one possible indicator of both increasing circulating inflammation levels and relatively greater cognitive decline over time. Although inflammatory markers, such as CRP, may be more proximal measures of potential risk for cognitive decline in our models, body mass is a relatively simple biometric risk factor to assess, and in this respect may allow for better screening for at-risk individuals in settings where blood tests for inflammation are unlikely to be used. Second, this work adds another potential target for intervention to improve long-term cognition among aging adults. Inflammation and cognitive decline are associated with poorer outcomes individually, such as decreases in physical performance measures and muscle strength (Cesari et al., 2003), and all-cause mortality (Shiple, Der, Taylor, Deary, 2006) and are important clinical targets independently, but these results suggest that *both* lowering people's body mass or decreasing their inflammation levels might

decrease aging related cognitive decline. For example, a records review of patients admitted for Alzheimer's disease found that patients who were taking anti-inflammatories had lower levels of cognitive decline over the next year (Rich et al., 1995). It is unclear if these result could improve cognition in other non-clinical populations, such as those dealing with mild cognitive impairment (Jelic, Kivipelto, & Winblad, 2006), though anti-inflammatory drugs reduce age-related decreases in cognition and brain volume in healthy aging populations (Walther et al., 2011). An important question is whether anti-inflammatory medications would reduce the neuro-inflammation associated with both systemic inflammation and cognitive decline, improving cognitive functioning over time.

The results of this study should be considered in light of its limitations. First, the two samples in the study were not fully independent, as 6,354 participants had enough data to contribute to both subsamples. We included these participants in both subsamples in an effort to use all available data, as none of the two subsamples' measured variables overlapped, but fully independent subsamples would provide stronger evidence that our results replicate and protect against issues associated with statistical non-independence. Second, the size of the indirect effect observed in the current study was small, but stable across the two samples. Small effects *can* be meaningful, but it is incumbent upon any research team to demonstrate that a small effect in a given study *is* meaningful. Although we benchmarked the size of our effect to another established predictor of cognitive decline, chronological age, caution is still warranted in cases in which associations are small. Third, though our cognitive measures have been previously validated (Green et al., 2011; Haugrud et al., 2011; Hoskins et al., 2010), they are only single indicators of the broad constructs of EF and memory. It would be useful in future studies to assess multiple domains of EF and memory, among other cognitive domains. Fourth, we tested

our models using data from a publically-available dataset which included CRP as a measure of systemic inflammation, but not other biomarkers, such as TNF $\alpha$  or IL-6. It is possible these various indices of inflammation may evidence different results. Similarly, other measures that might influence the association of inflammation and cognition, such as red blood cell anti-oxidants or variables that affect the pathogenesis of inflammation, such as plasma lipid peroxides or nitric oxide levels, were not collected (Calabrese et al., 2007; Leonard & Maes, 2012; Panza et al., 2010). These variables might inform our hypothesized pathway from body mass to cognitive decline, and they should be included in future work exploring inflammation and cognitive decline. Finally, our subsamples were drawn from a representative, longitudinal study of aging adults from England. It is possible the associations of interest in the current study would not replicate in people from other countries, or in younger cohorts.

#### **4.1 Conclusion**

Using two large subsamples drawn from a representative, longitudinal study of English aging adults, we found that greater body mass directly predicted increased systemic inflammation, as measured by CRP, which was associated with declines in participants' memory and executive functioning in turn. There was an indirect association of body mass and cognitive decline via increases in inflammation, but the size of this effect was small. The results suggest that inflammation is one biologically plausible mechanism through which body mass can influence cognitive decline and provides additional support for neurodegenerative models of cognitive decline.

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Table 1  
*Correlations and Descriptive Statistics for Main Study Variables*

	1	2	3	4	5	6	7	8	9
T1 BM (1)	1.00								
T1 Memory (2)	0.01	1.00							
T1 EF (3)	0.01	0.48	1.00						
T1 CRP (4)	0.33	-0.08	-0.10	1.00					
T2 CRP (5)	0.28	-0.07	-0.07	0.56	1.00				
T3 Memory (6)	-0.02	0.58	0.43	-0.10	-0.08	1.00			
T3 EF (7)	0.00	0.45	0.61	-0.09	-0.09	0.54	1.00		
T1 Age (8)	-0.10	-0.43	-0.33	0.09	0.08	-0.50	-0.40	1.00	
T1 Gender (9)	0.00	0.09	-0.06	0.04	0.06	0.08	-0.04	-0.01	1.00
Mean	4.54	5.08	20.16	2.47	2.47	5.03	20.21	65.10	1.56
<i>SD</i>	1.21	1.81	4.79	2.12	2.13	1.93	7.14	10.71	-

All means and SDs were calculated using full information maximum likelihood estimation from the second subsample. Gender was dummy coded 1 = men, 2 = women.

Table 2

*Model Fit, and Regression Coefficients Predicting Memory Function*

Subsample 1				Subsample 2		
Fit Statistics						
H1 log-likelihood	-100322.28			H1 log-likelihood	-116130.55	
No. of parameters	32			No. of parameters	32	
$\chi^2$	16.10			$\chi^2$	17.33	
RMSEA	0.022			RMSEA	0.019	
CFI	1.00			CFI	1.00	
Predicting T2 CRP	$\beta$	95% CI	<i>B</i>	$\beta$	95% CI	<i>B</i>
T1 BMI	0.12**	[0.08, 0.14]	0.06**	0.11**	[0.07, 0.14]	0.05**
T1 CRP	0.50**	[0.45, 0.54]	0.49**	0.53**	[0.49, 0.57]	0.53**
T1 Age	0.03*	[0.01, 0.06]	0.01*	0.04*	[0.01, 0.07]	0.01*
Gender	0.01	[-0.02, 0.03]	0.02	0.03	[0.01, 0.06]	0.14*
Predicting T3 Memory	$\beta$	95% CI	<i>B</i>	<i>B</i>	95% CI	<i>B</i>
T2 CRP	-0.05**	[-0.08, -0.03]	-0.05**	-0.04**	[-0.06, -0.02]	-0.03**
T1 Memory	0.44**	[0.41, 0.46]	0.48**	0.44**	[0.41, 0.46]	0.46**
T1 Age	-0.32**	[-0.35, -0.30]	-0.06**	-0.30**	[-0.33, -0.28]	-0.05**
Gender	0.06**	[0.04, 0.08]	0.23**	0.04**	[0.02, 0.06]	0.14**

Note: \*  $p < .05$ ; \*\*  $p < .01$ .

Table 3

*Model Fit, and Regression Coefficients Predicting Executive Function*

Subsample 1				Subsample 2		
Fit Statistics						
H1 log-likelihood	-115693.90			H1 log-likelihood	-139494.62	
No. of parameters	32			No. of parameters	32	
$\chi^2$	9.64			$\chi^2$	1.86	
RMSEA	0.016			RMSEA	0.000	
CFI	1.00			CFI	1.00	
Predicting T2 CRP	$\beta$	95% CI	<i>B</i>	$\beta$	95% CI	<i>B</i>
T1 BMI	0.12**	[0.09, 0.15]	0.06**	0.11**	[0.07, 0.14]	0.05**
T1 CRP	0.50**	[0.45, 0.54]	0.49**	0.53**	[0.49, 0.57]	0.53**
T1 Age	0.03*	[0.01, 0.06]	0.01*	0.04*	[0.01, 0.07]	0.01*
Gender	0.01	[-0.02, 0.03]	0.02	0.03	[0.01, 0.06]	0.14*
Predicting T3 EF	$\beta$	95% CI	<i>B</i>	$\beta$	95% CI	<i>B</i>
T2 CRP	-0.04**	[-0.06, -0.01]	-0.12**	-0.04**	[-0.06, -0.02]	-0.14**
T1 Memory	0.49**	[0.46, 0.51]	0.54**	0.52**	[0.50, 0.54]	0.55**
T1 Age	-0.25**	[-0.27, -0.22]	-0.17**	-0.22**	[-0.25, -0.20]	-0.15**
Gender	-0.01	[-0.03, 0.01]	-0.14	-0.01	[-0.03, 0.01]	-0.16

Note: \*  $p < .05$ ; \*\*  $p < .01$ .

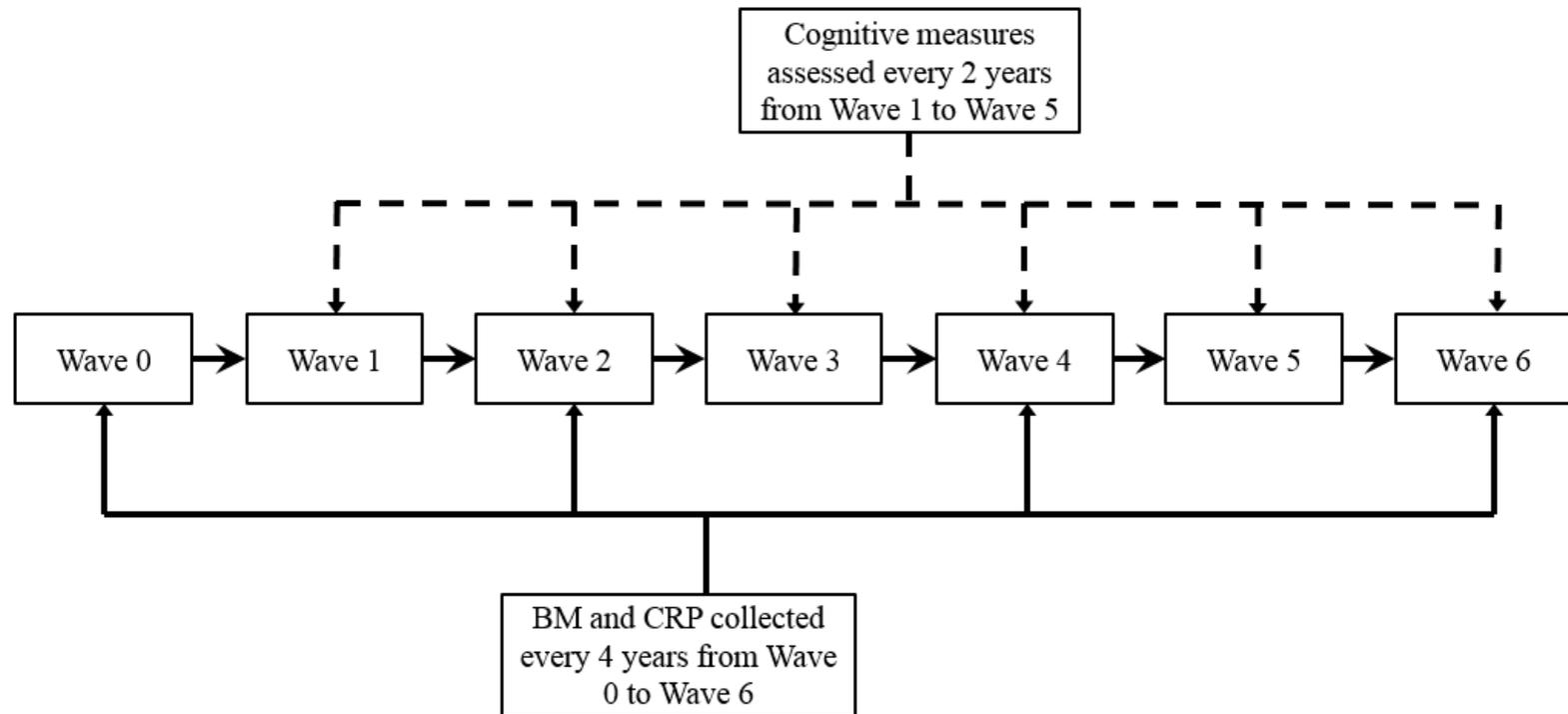


Figure 1. Outline of the data collection timeline over the course of the ELSA study. Data collection occurred every two years, resulting in 12 total years across the current waves.

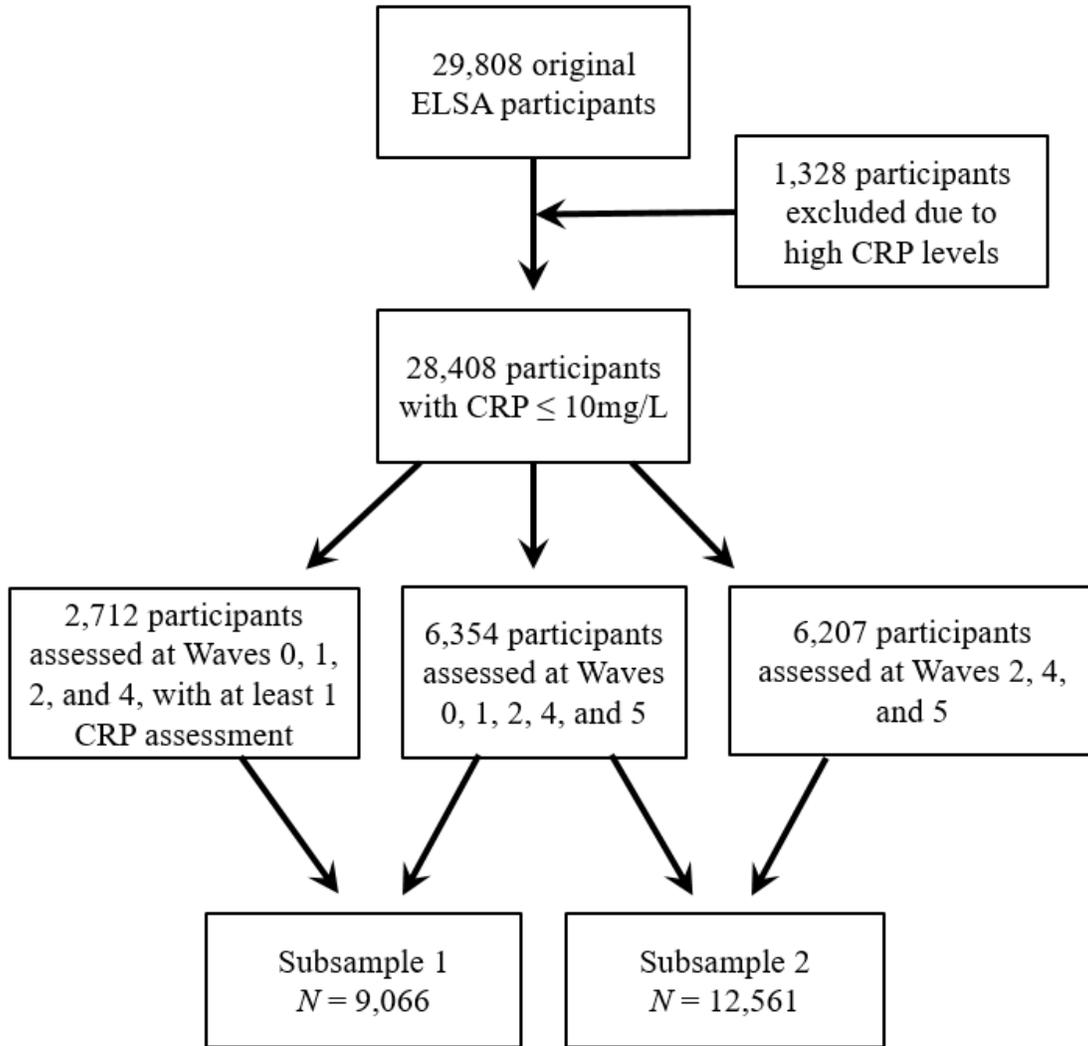
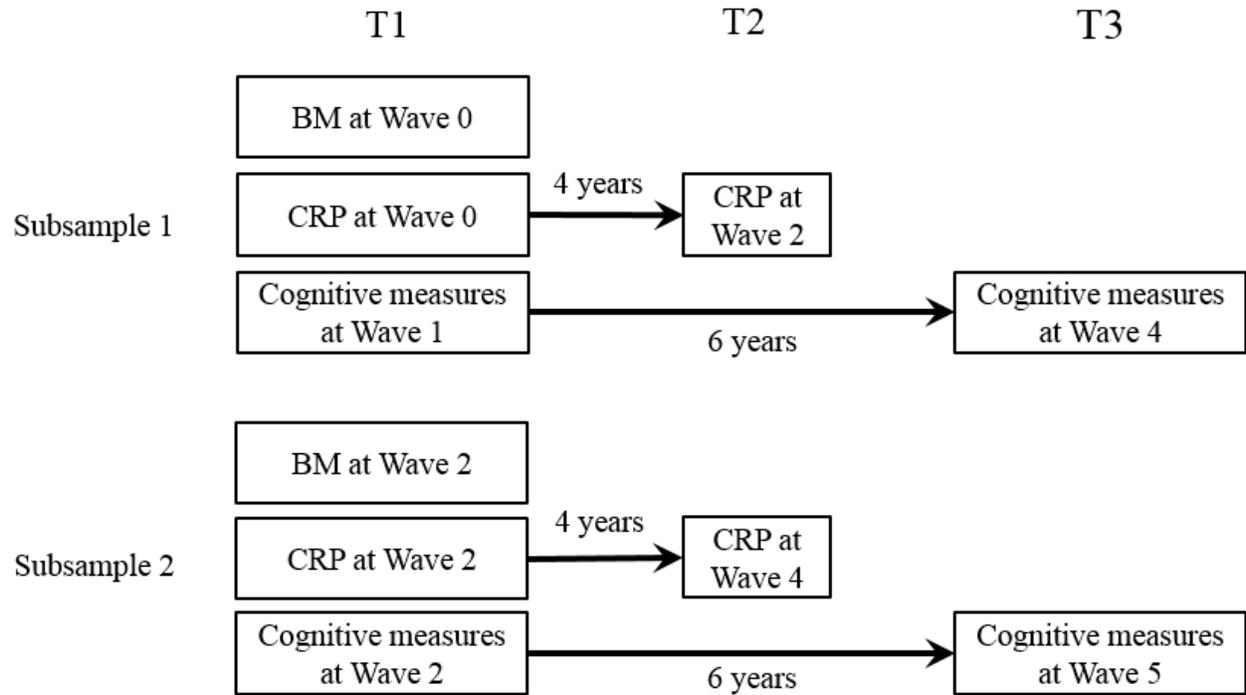
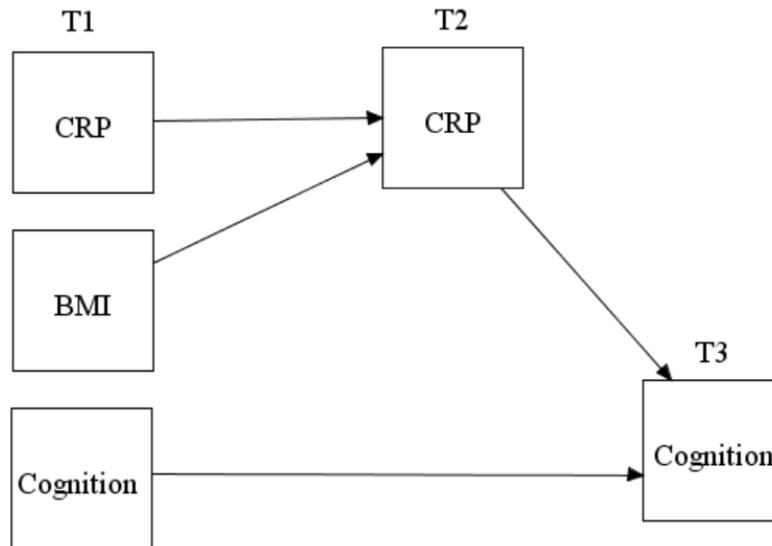


Figure 2. Flowchart outlining the selection of the participants making up the two subsamples.



*Figure 2.* Outline of the waves each of the variables of interest were sampled from by subsample.

In subsample 1, cognitive measures were drawn from Wave 1 rather than Wave 0 because the relevant cognitive tasks were not available at Wave 0.



*Figure 4.* The conceptual structural equation model testing the direct and indirect associations between body mass (BMI), C-reactive protein (CRP) and cognition. An earlier measure of CRP and cognition are used to create a residualized regression to assess change in CRP and cognition over time. The full model also includes age and gender predicting T2 CRP and the T3 cognitive outcomes. This model was used to assess the effects of interest in memory and executive functioning independently.