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Blood-Based Biomarkers

# Repeated systemic inflammation was associated with cognitive deficits in older Britons

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**Abstract**

**Introduction:** The relationship of C-reactive protein (CRP) to cognition in the older old group (≥75 years) has recently been found positive on both sides of the Atlantic. We hypothesized that higher levels of CRP and fibrinogen are related to worse episodic memory throughout later life (≥50 years).

**Methods:** Data are drawn from older Britons free of dementias in the English Longitudinal Study of Aging 2004–2013. We applied growth trajectory models to repeated observations of episodic memory, CRP, and fibrinogen levels (and sociodemographic confounders). We accounted for practice effects in repeated tests of cognition.

**Results:** Higher levels of both inflammatory markers were associated with worse episodic memory, where a fibrinogen effect is evident throughout later life (coefficient −0.154; 95% confidence interval [CI] −0.254 to −0.054). Most importantly, the CRP effect is strongly negative among the older old group (coefficient −0.179; CI −0.320 to −0.038).

**Discussion:** Higher levels of fibrinogen are detrimental to older people's cognition, and among the older old, raised CRP levels are comparably deleterious. Repeated measures of inflammation can be considered in clinical practice as part of a response to the challenge of dementias.



*Keywords:* C-reactive protein; Fibrinogen; Episodic memory; England

## 1. Introduction

Dementias have a long period of preclinical development [1,2]. With increase in life expectancy of the aging population, it is all the more important to understand early changes in cognitive function that presage cognitive impairment. Systemic inflammatory markers have been investigated for this purpose in middle aged and older people and have been found to be associated with many cognitive abilities including episodic memory, executive function, and global cognition [3–12].

Two biomarkers are often used in studies of cognition and inflammation: fibrinogen and C-reactive protein (CRP). Epidemiologic, genetic, or pharmacologic studies on the relationship of fibrinogen to cognition suggest that higher levels of fibrinogen in the peripheral system are related to worse cognition [13–16]. In the Aspirin for Asymptomatic Atherosclerosis Trial of older people in Scotland (aged 50–80 years), higher levels of baseline fibrinogen and CRP were associated with worse cognition during follow-up in cross-sectional design [9]. Also in Scotland, the Edinburgh Artery Study (aged 55–74 years) found that higher levels of fibrinogen at baseline predicted cognition deficits 14 years later in cross-sectional design [8]. The baseline levels were also associated with cognitive decline in change-scores longitudinal design, where only cognition is repeatedly measured.

Epidemiologic studies of the link between CRP and cognition have found results that cover the negative to positive spectrum of associations. In the Rotterdam Study (aged 55–106 years), higher levels of CRP at baseline were associated with worse cognition in cross-sectional

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design, but the baseline CRP levels were not associated with decline in cognitive function in change-scores longitudinal design [11]. Across the Atlantic, the Health, Aging, and Body Composition study found that being in the highest tertile of CRP levels at baseline had the same odds as being in the lower tertiles when predicting 4 years cognitive decline in change-scores longitudinal design [4]. Weak evidence is also found in the British Whitehall II study (mean age 48, standard deviation [SD] 6 years) where levels of CRP at baseline were associated with worse reasoning and vocabulary functions in cross-sectional design but were not associated with cognitive decline in change-scores longitudinal design [6]. Remarkably in the older old (age ≥75 years), raised CRP is associated with better cognition [10,17], suggesting some genetic factors are responsible; see also [2]. An active inflammatory system may be found protective, delaying cognitive decline among the older old.

From a clinical perspective, this literature on peripheral inflammation has yet to bear fruit. Some are equivocal about the possibility [16], but others are less sanguine about the use of blood-based biomarkers in practice [11]. Such a view may be hasty given the weaknesses in the literature. First, it is unclear whether the positive relationship between inflammation and cognition applies to the younger old (50–75 years), a group of some importance given the well-known long duration of development of severe cognitive impairment. Second, many of these studies used one baseline measure of inflammation against repeated measures of cognition, effectively explaining change scores or decline as the dependent variable (change-scores longitudinal design). This poses two problems, one of which applies to any outcome (dilution bias), whereas the another applies specifically to cognition (practice effect). As is widely acknowledged in longitudinal studies, such change-scores design is susceptible to regression dilution bias [2–8,11,18]. It is possible that prospectively collected repeated measures of both cognition and biomarkers will modify the results mentioned.

In addition, a well-known threat to inference in longitudinal studies of cognition arises from practice effects [19–22]. Apparent change in the test scores at two time points is partly down to the fact that participants have completed the same tests before. In the pages of this journal, it has been suggested that practice effects are "large, pervasive and under-appreciated" [22]. So in change-scores longitudinal design, if dilution bias can compromise analysis of any health outcomes, including physical and cognitive functions, practice effects can additionally compromise cognitive outcomes. Together, they render many biomarkers studies of cognitive decline doubly unsafe and unsatisfactory.

Finally, cognition in older people is maintained through mechanisms involving various biological and social factors. Careful accounting of cognitive deficits in later life requires social factors to be considered as well.

To address these weaknesses, this study used the English Longitudinal Study of Aging (ELSA) 2004–2013, a nationally representative prospective longitudinal study of older people (≥50 years) with repeated measures of the exposures, the outcomes and other demographic, economic, chronic conditions, and health behaviors as well as social factors. This study aimed to test two hypotheses. First, levels of high sensitivity CRP are related to worse episodic memory in younger old (<75 years) and in older old (≥75 years) Britons. Second, analogously, levels of circulating fibrinogen are independently related to worse episodic memory.

This measure of cognition is an important and popular measure in research on cognitive aging since it is easy to collect, easy to understand, and at the same time has been shown to be instrumental in life changing decisions such as pension decisions [23,24,25]. So not only does it enable research replication or cross-country comparison, it is also immediately relevant.

## 2. Materials and methods

### 2.1. English Longitudinal Study of Aging

The ELSA is the primary resource for a nationally representative aging study of the English older population; it was started in 2002 and subsequent waves follow biennially. In every even-numbered wave, a nurse assessment is given to collect biomedical information. The repeated biomarkers and episodic memory variables are, therefore, available from 2004 to 2005, 2008 to 2009, and 2012 to 2013 waves. The data are freely available from the UK Data Archive (www.data-archive.ac.uk) as study number 5050. More details of the study are given elsewhere [26–31].

### 2.2. Ethics

Ethical approval for all the ELSA waves was granted from the National Research and Ethics Committee of the UK National Health Service www.nres.nhs.uk. The University of Manchester's institutional review board has exempted this study because it used publicly available anonymized secondary data.

### 2.3. Dependent variable

The dependent variable is episodic memory, the sum of delayed and immediate recall, available in all waves [23]. It is notable that this variable is also available in its sister study, the US Health and Retirement Study [32].

### 2.4. Independent variables

Information from respondents aged 50 to 89 years was used because age is capped at 90 years in ELSA. Demographic covariates include sex, age and squared-age to capture possible curvilinear trajectories [20,21,33]. To capture practice effects, an indicator variable is constructed, coding 1 if a respondent