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## REVIEW

# Association between C-reactive protein and cognitive deficits in elderly men and women: a meta-analysis

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## ABSTRACT

**Background:** Certain risk factors for cognitive decline appear modifiable. A potentially modifiable marker of inflammation, C-reactive protein may be associated with cognitive deficits, although not all studies have found a relationship between C-reactive protein and cognitive ability. Further, few research papers have examined whether gender may affect any association between C-reactive protein and cognitive deficit.

**Methods:** To better understand the association between C-reactive protein, cognitive deficit, and gender in elderly people, we meta-analyzed cross-sectional studies that reported cognitive ability assessed by the Mini-Mental State Examination or an equivalent measure, C-reactive protein concentrations, and gender.

**Results:** While we identified no studies containing only male subjects, the two identified studies containing both female and male subjects ( $n = 2,525$ ) showed an effect size for cognition of  $-0.1809$  (95% confidence interval,  $-0.2652$  to  $-0.0967$ ,  $p = 0.00025$ ) between high and low C-reactive-protein groups. In contrast, the two identified studies containing only female subjects ( $n = 1,754$ ) showed an effect size for cognition of  $0.0345$  (95% confidence interval,  $-0.0594$  to  $0.1285$ , not significant).

**Conclusions:** In the context of a small number of source studies and lack of an all-male group, these results suggest that any association between C-reactive protein and cognitive deficits may be stronger in elderly men than in elderly women.

**Key words:** C-reactive protein, cognition, cognitive deficits, gender, Mini-Mental State Examination

## Introduction

Cognitive decline and dementia are important public health problems, but some risk factors for cognitive decline and dementia are potentially modifiable (Kukull, 2006). Adults tend to peak in cognitive ability at age 40 and then show a gradual decline in cognitive functioning thereafter (Anderson *et al.*, 2001). This decline involves a wide range of cognitive domains including executive functioning, processing speed, memory, and attention (Clark *et al.*, 2006). Years of education, genetics, general health, and socioeconomic status can affect cognitive decline (Compton *et al.*, 2003), as well as a variety of medical and neurological conditions. Furthermore, inflammation may be a factor in cognitive decline (Dziedzic, 2006).

C-reactive protein (CRP) is a biomarker for general inflammation, and high levels of CRP are associated with cardiovascular disease, stroke, cancer, and obesity (Ho and Lipman, 2009). In addition, elevated levels of CRP may be associated with cognitive deficits. Based on their review of six studies investigating the association between CRP and cognitive function, Kuo *et al.* (2005) concluded that elevated CRP is associated with cognitive decline and the progression of Alzheimer's disease. In a study of subjects with schizophrenia, Dickerson *et al.* (2007) found that while CRP was not associated with psychosis, patients with CRP levels higher than  $5.0 \text{ mg}/\mu\text{L}$  had significantly lower cognitive functioning than those with CRP levels less than  $5.0 \text{ mg}/\mu\text{L}$ . In a prospective study of cognitive function in older adults ( $n = 650$ ), Tilvis *et al.* (2004) reported that cognitive decline at 5 years was associated with elevated CRP. Similarly, Yaffe *et al.* (2003) determined that levels of interleukin-6 and CRP are associated with cognitive deficits but only in subjects having the highest levels of these proteins.

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In contrast to studies showing an association between CRP and cognitive deficits, Aiello *et al.* (2006) investigated whether CRP modified the association between cytomegalovirus, herpes simplex virus type-1, and cognitive function and found that although there was a relationship between high levels of cytomegalovirus and cognitive deficit, the latter was not modified by CRP. Dik *et al.* (2005) retrospectively examined cognitive functioning in a large cohort ( $n = 1284$ ) in relation to four inflammatory proteins and concluded that cognitive decline was associated with high levels of  $\alpha_1$ -antichymotrypsin but not CRP, interleukin-6, and albumin. Other research suggests that high inflammatory protein levels only have an effect on cognition in the presence of moderating variables. Alley *et al.* (2008) assessed levels of interleukin-6 and CRP in relation to baseline cognitive functioning and cognitive change over time. Initial results indicated that high levels of these inflammatory proteins were associated with lower baseline cognition. However, these effects were not present after control for confounding. Finally, Teunissen *et al.* (2003) reported that while CRP appears to have an effect on some aspects of cognitive performance, there was no overall strong relationship between CRP and cognitive decline.

Among the studies that found a relationship between CRP and cognition, gender differences were unexplored. Gender, however, could be an important factor in the relationship between CRP and cognition in that previous research has consistently shown that there are gender differences in cognitive functioning among older individuals (Finkel *et al.*, 2006). Examining gender differences in cognition in 2,307 older adults, Aartsen *et al.* (2004) found that women had better memory function than men. In a group of 578 older adults, women performed better on verbal memory tasks than did men (van Hooren *et al.*, 2007). The apparent cognitive differences between elderly men and women indicate that gender may affect any association between CRP and cognition in the elderly.

To better understand the association between CRP and cognition in older women and men, we meta-analyzed cross-sectional studies comparing cognition assessed by the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) or an MMSE-based assessment and reporting CRP levels and gender.

## Methods

### Paper selection

Using the electronic databases PubMed and PsychInfo, we identified peer-reviewed studies that

examined the relationship between CRP and cognitive functioning with the following search terms: “C-reactive protein AND cognition”, Interleukin-6 AND cognition, inflammatory proteins AND cognition, cognition disorders AND C-reactive protein, and cognitive impairment AND C-reactive protein. Searches were repeated with neuropsychological function replacing cognition and inflammation replacing inflammatory. After identifying relevant papers, we reviewed the reference sections of these papers to identify additional relevant papers.

### Inclusion criteria

Identified papers were included in the study if they were written in English, contained MMSE scores or scores from an MMSE-based assessment, and their means and standard deviations or standard errors in high and low CRP groups (i.e. high tertile versus low tertile, high quintile versus low quintile, etc.), and the gender composition of the samples.

We included only studies that assessed cognitive function using the MMSE or an MMSE-based measure to minimize heterogeneity between cognitive assessments in the source studies. Because cognitive tests can differ in sensitivity and specificity, outcomes from different cognitive tests assessing similar constructs can produce different results. For example, assessing memory functioning in a sample of mild brain-injury patients, Guilmette and Rasile (1995) found that the use of cognitive tests of varying sensitivity and specificity led to a diagnostic accuracy ranging from 68% to 83%. Accordingly, we included only studies that used the MMSE (Folstein *et al.*, 1975) or an MMSE-based assessment of cognitive functioning because of its widespread use in clinical practice and research (Nieuwenhuis-Mark, 2010).

### Statistical analysis

We calculated standardized effect sizes for each identified study by subtracting the mean MMSE score for the low CRP group from the mean MMSE score for the high CRP group and dividing the difference by the pooled estimate of the standard deviation of the cognitive scores. To correct for bias from small sample sizes, we obtained an unbiased estimator of effect size by multiplying the standardized effect size by the J-correction factor to obtain the Hedges  $g$  statistic (Hedges and Olkin, 1985; Borenstein *et al.*, 2009). We then combined the individual effect sizes and associated variance according to the methods given by Whitehead (2002). We also calculated a  $U$  statistic (distributed as a  $\chi^2$ ) to test for the significance of the combined effect sizes from the individual studies and a  $Q$  statistic (also distributed as a  $\chi^2$ ), which evaluates

**Table 1.** Characteristics of the source studies

STUDY	N	AGE	DICHOTOMIZATION	COGNITIVE MEASURE
Komulainen <i>et al.</i> , 2007	64	63.77	high to low tertile	MMSE
Tilvis <i>et al.</i> , 2004	629	79.65	high half to low half	MMSE
Weuve <i>et al.</i> , 2006	1690 <sup>a</sup>	71.79	high to low quintile	Phone Interview <sup>b</sup>
Yaffe <i>et al.</i> , 2003	1896	73.63	high to low tertile	Revised MMSE

MMSE = Mini Mental State Examination.

<sup>a</sup>approximate number.

<sup>b</sup>The correlation coefficient between the Phone Interview and the MMSE is 0.94.

**Table 2.** Scores on cognitive measure for high and low CRP groups

STUDY	HIGH CRP N	LOW CRP N	HIGH CRP GROUP MEAN (SD)	LOW CRP GROUP MEAN (SD)
Komulainen <i>et al.</i> , 2007	18	46	28.7 (1.7)	28.2 (2.0)
Tilvis <i>et al.</i> , 2004	549	80	22.6 (5.4)	23.7 (7.0)
Weuve <i>et al.</i> , 2006	844	846	34.2 (2.6)	34.1 (3.0)
Yaffe <i>et al.</i> , 2003	966	930	88.7 (9.3)	90.4 (9.1)

Notes: CRP = C-reactive protein; SD = standard deviation.

**Table 3.** Combined male and female subjects

	<i>n</i>	<i>M</i>	<i>SD</i>	<i>SEM</i>	<i>ES</i>	<i>VAR (ES)</i>	
Tilvis <i>et al.</i> , 2004	high CRP	80	22.6	5.37	0.60	-0.1606	0.0143
	low CRP	549	23.7	7.03	0.30		
Yaffe <i>et al.</i> , 2003	high CRP	966	88.7	9.32	0.30	-0.1839	0.0021
	low CRP	930	90.4	9.15	0.30		
	$\chi^2$	<i>df</i>	<i>p</i>				
	<i>U</i>	17.7285	1	0.000025			
	<i>Q</i>	0.0331	1	ns			
	pooled effect size	-0.1809					
	confidence interval	-0.2652	to	-0.0967			

Note: CRP = C-Reactive Protein; SD = standard deviation; SEM = standard error of the mean; ES = effect size; var (ES) = variance of the effect size; ns = not significant.

consistency among the individual effect sizes. A significant *Q* value warns of heterogeneity among the source studies (Borenstein *et al.*, 2009).

## Results

After screening abstracts and titles for potential studies, we retrieved and reviewed 46 full papers. From these, we identified four papers that met the inclusion criteria (Table 1). We excluded papers if they failed to measure cognitive status with the MMSE or an MMSE-based assessment, if they did not report cognitive function in high and low groups of CRP, if the sample was primarily composed of people with medical or neurological diseases that might affect cognitive functioning,

or if the participants were selected because of a cognitive disorder. In addition, we excluded papers that did not include the data needed to calculate effect sizes, such as mean MMSE scores and their standard deviations or standard errors or that used longitudinal rather than cross-sectional designs. Cognitive scores for the high and low CRP groups in each study are shown in Table 2.

Two of the identified studies used both male and female subjects (Yaffe *et al.*, 2003; Tilvis *et al.*, 2004), whereas the other two papers included only female subjects (Weuve *et al.*, 2006; Komulainen *et al.*, 2007). The combined analysis of the four identified studies produced a *U* value of 7.04 ( $p = 0.008$ ); however, the *Q* statistic (11.26) was significant ( $p = 0.010$ ), indicating significant heterogeneity among the four source studies and

**Table 4.** Female subjects only

		<i>n</i>	<i>M</i>	SD	SEM	ES	VAR (ES)
Komulainen <i>et al.</i> , 2007	high CRP	18	28.7	1.70	0.40	0.0000	0.0773
	low CRP	46	28.7	2.00	0.29		
Weuve <i>et al.</i> , 2006	high CRP	844	34.2	2.60	0.09	0.0356	0.0024
	low CRP	846	34.1	3.00	0.10		
		$\chi^2$	df	p			
		<i>U</i>	0.5196	1	ns		
		<i>Q</i>	0.0159	1	ns		
		pooled effect size	0.0345				
		confidence interval	−0.0594 to 0.1285				

Note: CRP = C-Reactive Protein; SD = standard deviation; SEM = standard error of the mean; ES = effect size; var (ES) = variance of the effect size; ns = not significant.

suggesting that combining them into a summary statistic was inappropriate. The *U* statistic for the male–female combined group (with a total number of subjects of 2,525) was significant ( $U = 17.73$ ,  $p = 0.000025$ ) with a pooled effect size of  $-0.1809$  (95% confidence interval,  $-0.2652$  to  $-0.0967$ ,  $p = 0.000025$ , Table 3), indicating that the cognitive performance of the low CRP subjects was higher than the cognitive performance of the high CRP subjects. Further, the *Q* statistic (0.033) was not significant, indicating that it was appropriate to combine the individual effects sizes into a summary measure. In contrast, the *U* statistic for the all-female studies (with a total of 1,754 subjects, although 96.4% of the subjects came from just one of the two studies) was not significant ( $U = 0.520$ ) with a pooled effect size of 0.0345 (95% confidence interval,  $-0.0594$  to 0.1285, Table 4). The *Q* statistic (0.016) also was not significant, indicating that it was appropriate to combine effects. The difference in effect size between the two groups (combined male–female groups versus the all-female group) suggests that CRP may be associated with lower cognitive scores in the combined group than in the female-only group).

## Discussion

The primary aim of this study was to determine whether gender affects the association between CRP concentrations and cognitive ability in elderly people. Indeed, even though there was a significant difference in cognitive ability between high and low CRP groups overall ( $p = 0.008$ ), the associated *Q* statistic indicated significant heterogeneity between studies. When female-only source studies and male–female combined source studies were analyzed separately, the associated *Q* statistics became non-significant, indicating that it was appropriate to pool those particular source studies into one effect size.

Upon doing this, the effect size between the high and low CRP groups in the female-only sample was not significant, but the difference between high and low CRP groups in the combined male–female sample was significant ( $p = 0.000025$ ). As such, the main finding is that CRP is significantly associated with deficits in general cognitive ability determined by the MMSE or MMSE-related methods in samples composed of both women and men but not in the women-only samples. This finding suggests that the association between CRP and cognitive deficits may be stronger in men than in women. That is, cognitive ability in elderly men may be more susceptible to elevated concentrations of CRP than in elderly women. If so, findings on the association between CRP and cognition may tend toward inconsistency unless gender is taken into account.

Broadly consistent with the observation that cognition in elderly men may be more susceptible to elevated levels of CRP than it is in elderly women are findings that men aged 70–89 years have a higher prevalence of mild cognitive impairment than do women (Petersen *et al.*, 2010). Further, older men appear to have more cognitive deficits than do older women (Aartsen *et al.*, 2004; Finkel *et al.*, 2006; van Hooren *et al.*, 2007). Men may generally be more susceptible to the deleterious effects of inflammation than are women as suggested by the finding that CRP was associated with a 12% reduction in survival time and a one-year reduction in expected lifespan in men but not in women (Wassel *et al.*, 2010). While factors in addition to inflammation may well contribute to differences in cognitive ability between elderly men and women, part of the difference in cognitive deficits between older women and men could be due to differential susceptibility to CRP.

The cross-sectional design of this meta-analysis precludes an assessment of the causal relationship between CRP and cognitive deficits wherein cognitive deficits could lead to elevated



CRP concentrations instead of elevated CRP concentrations resulting in cognitive deficits. Similarly, we did not investigate other potentially confounding variables such as smoking history and socioeconomic status that may alter the association between CRP concentrations and cognitive deficits.

Several additional factors temper the interpretation of the findings reported herein. Only four studies met our inclusion criteria. Two of these reported data on only female subjects, two reported data on combined female–male sample, and none reported data on male-only subjects. We therefore based the analysis on the percentage of male or female subjects and not solely on male samples versus female samples. If anything though, this design would tend to underestimate the differences between women and men. If there is a difference between women and men, an all-male sample compared to an all-female sample would show a greater difference between groups than would the available mixed male–female sample we used compared to an all-female sample. Although the number of source studies in the meta-analysis was small, the results are based on a fairly large number of individual subjects. An additional limitation, however, is that in the female-only studies, one study contributed 96.4% of the subjects; in the mixed-sex samples, one study contributed 75.1% of the subjects.

In summary, the association between CRP and cognitive deficits appeared stronger in elderly men than in elderly women in this small meta-analysis, although limitations based primarily on the small numbers of source studies and factors common to all cross-sectional designs limit this conclusion and make the results susceptible to new studies. Within the context of these limitations, the results suggest that gender may be an important variable to consider when studying the association between inflammation and cognition.

### Conflict of interest

None.

### Description of authors' roles

Dawson Hedges and Thomas Farrer were involved in study design and analysis, data entry, and writing of the paper. Bruce Brown conducted data analysis and was involved in writing the paper.

### References

Aartsen, M. J., Martin, M., Zimprich, D. and the Longitudinal Aging Study Amsterdam (2004). Gender differences in level and change in cognitive functioning:

results from the Longitudinal Aging Study Amsterdam. *Gerontology*, 50, 35–38.

- Aiello, A. E., Haan, M., Blythe, L., Moore, K., Gonzalez, J. M. and Jagust, W. (2006). The influence of latent viral infection on rate of cognitive decline over 4 years. *Journal of the American Geriatrics Society*, 54, 1046–1054.
- Alley, D. E., Crimmins, E. M., Karlamangla, A., Hu, P. and Seeman, T. E. (2008). Inflammation and rate of cognitive change in high-functioning older adults. *Journal of Gerontology Series A: Biological Sciences and Medical Sciences*, 63, 50–55.
- Anderson, V. A., Anderson, P., Northam, E., Jacobs, R. and Catroppa, C. (2001). Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology*, 20, 385–406.
- Borenstein, M., Hedges, L. V., Higgins, J. P. T. and Rothstein, H. R. (2009). *Introduction to Meta-Analysis*. Chichester: John Wiley & Sons, Ltd.
- Clark, C. R. et al. (2006). Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. *Archives of Clinical Neuropsychology*, 21, 449–467.
- Compton, D. M., Avet-Compton, T., Bachman, L. D. and Brand, D. (2003). Working memory and perceptual speed mediation of age-associated changes in cognition within a sample of highly-educated adults. *North American Journal of Psychology*, 5, 451–477.
- Dickerson, F., Stallings, C., Origoni, A., Boronow, J. and Yolken, R. (2007). C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. *Schizophrenia Research*, 93, 261–265.
- Dik, M. G., Jonker, C., Hack, C. E., Smit, J. H., Comijs, H. C. and Eikelenboom, P. (2005). Serum inflammatory proteins and cognitive decline in older persons. *Neurology*, 64, 1371–1377.
- Dziedzic, T. (2006). Systemic inflammatory markers and risk of dementia. *American Journal of Alzheimer's Disease and Other Dementias*, 21, 258–262.
- Finkel, D., Reynolds, C. A., Berg, S. and Pedersen, N. L. (2006). Surprising lack of sex differences in normal cognitive aging in twins. *International Journal of Aging & Human Development*, 62, 335–357.
- Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Mini-mental state:" a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.
- Guilmette, T. J. and Rasile, D. (1995). Sensitivity, specificity, and diagnostic accuracy of three verbal memory measures in the assessment of mild brain injury. *Neuropsychology*, 9, 338–344.
- Hedges, L. V. and Olkin, I. (1985). *Statistical Methods for Meta-Analysis*. Orlando, FL: Academic Press.
- Ho, K. M. and Lipman, J. (2009). An update on C-reactive protein for intensivists. *Anaesthesia and Intensive Care*, 37, 234–241.
- Komulainen, P. et al. (2007). Serum high sensitivity C-reactive protein and cognitive function in elderly women. *Age and Ageing*, 36, 443–448.
- Kukull, W. A. (2006). The growing global burden of dementia. *Lancet Neurology*, 5, 199–200.

- Kuo, H. K., Yen, C. J., Chang, C. H., Kuo, C. K., Chen, J. H. and Sorond, F.** (2005). Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. *Lancet Neurology*, 4, 371–380.
- Nieuwenhuis-Mark, R. E.** (2010). The death knoll for the MMSE: has it outlived its purpose? *Journal of Geriatric Psychiatry and Neurology*, 23, 151–157.
- Petersen, R. C. et al.** (2010). Prevalence of mild cognitive impairment is higher in men. the Mayo Clinic Study of Aging. *Neurology*, 75, 889–897.
- Teunissen, C. E. et al.** (2003). Inflammation markers in relation to cognition in a healthy aging population. *Journal of Neuroimmunology*, 134, 142–150.
- Tilvis, R. S., Kahonen-Vare, M. H., Jolkonen, J., Valvanne, J., Pitkala, K. H. and Strandberg, T. E.** (2004). Predictors of cognitive decline and mortality of aged people over a 10-year period. *Journal of Gerontology Series A: Biological Sciences and Medical Sciences*, 59, 268–274.
- van Hooren, S. A., Valentijn, A. M., Bosma, H., Ponds, R. W., van Boxtel, M. P. and Jolles, J.** (2007). Cognitive functioning in healthy older adults aged 64–81: a cohort study into the effects of age, sex, and education. *Neuropsychology, Development, and Cognition Section B, Aging, Neuropsychology, and Cognition*, 14, 40–54.
- Wassel, C. L., Barrett-Connor, E. and Laughlin, G. A.** (2010). Association of circulating C-reactive protein and interleukin-6 with longevity into the 80s and 90s: The Rancho Bernardo Study. *The Journal of Clinical Endocrinology and Metabolism*, 95, 4748–4755.
- Weuve, J., Ridker, P. M., Cook, N. R., Buring, J. E. and Grodstein, F.** (2006). High-sensitivity C-reactive protein and cognitive function in older women. *Epidemiology*, 17, 183–189.
- Whitehead, A.** (2002). *Meta-Analysis of Controlled Clinical Trials*. Chichester: John Wiley & Sons.
- Yaffe, K. et al.** (2003). Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology*, 61, 76–80.