Published in final edited form as:
J Geriatr Psychiatry Neurol. 2010 March ; 23(1): 49–53. doi:10.1177/0891988709351832.

Decreased C-Reactive Protein Levels in Alzheimer Disease

Sid E. O'Bryant, PhD[1], **Stephen C. Waring, DVM, PhD**[2], **Valerie Hobson, MA**[3], **James R. Hall, PhD**[4], **Carol B. Moore, MA**[5], **Teodoro Bottiglieri, PhD**[6], **Paul Massman, PhD**[7,8], and **Ramon Diaz-Arrastia, MD, PhD**[5]

[1]Department of Neurology, F. Marie Hall Institute for Rural & Community Health, Texas Tech University Health Sciences Center, Lubbock, Texas

[2]Marshfield Clinic Research Foundation, Epidemiology Research Center, Marshfield, Wisconsin

[3]Department of Psychology, Texas Tech University, Lubbock, Texas

[4]Department of Psychiatry, University of North Texas Health Science Center, Fort Worth, Texas

[5]Department of Neurology, University of Texas Southwestern Medical Center, Dallas, Texas

[6]Institute for Metabolic Disease, Baylor University Medical Center, Dallas, Texas

[7]Department of Neurology, Baylor College of Medicine, Houston, Texas

[8]Department of Psychology, University of Houston, Houston, Texas

Abstract

C-reactive protein (CRP) is an acute-phase reactant that has been found to be associated with Alzheimer disease (AD) in histo-pathological and longitudinal studies; however, little data exist regarding serum CRP levels in patients with established AD. The current study evaluated CRP levels in 192 patients diagnosed with probable AD (mean age = 75.8 ± 8.2 years; 50% female) as compared to 174 nondemented controls (mean age = 70.6 ± 8.2 years; 63% female). Mean CRP levels were found to be significantly decreased in AD (2.9 μg/mL) versus controls (4.9 μg/mL; *P* = .003). In adjusted models, elevated CRP significantly predicted poorer (elevated) Clinical Dementia Rating Scale sum of boxes (CDR SB) scores in patients with AD. In controls, CRP was negatively associated with Mini-Mental State Examination (MMSE) scores and positively associated with CDR SB scores. These findings, together with previously published results, are consistent with the hypothesis that midlife elevations in CRP are associated with increased risk of AD development though elevated CRP levels are not useful for prediction in the immediate prodrome years before AD becomes clinically manifest. However, for a subgroup of patients with AD, elevated CRP continues to predict increased dementia severity suggestive of a possible proinflammatory endophenotype in AD.

Keywords

Alzheimer disease; C-reactive protein; inflammation; treatment; primary prevention

Sid E. O'Bryant, Department of Neurology, Texas Tech University Health Science Center, 3601 4th St. STOP 8321, Lubbock, TX 79430. sid.obryant@ttuhsc.edu.

Declaration of Conflicting Interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Introduction

C-reactive protein (CRP) is an acute-phase reactant that is synthesized by the liver in response to acute injury, infection, or other inflammatory stimuli. Prospective studies suggest that CRP levels in the highest tertile put one at increased risk of developing cardiovascular disease (CVD). This risk holds for men,[1,2] women,[3,4] and the elderly population[5,6] and does not appear to be moderated by race or ethnicity.[7] As a result of this accumulated evidence, the Centers for Disease Control and Prevention and the American Heart Association presented interpretive guidelines for high-sensitivity CRP (hs-CRP) with a cutoff score of <1.0 mg/L reflecting a low risk, 1.0 to 3.0 mg/L reflecting an average risk, and >3.0 mg/L corresponding to a high risk in the adult population. The highest risk tertile has approximately a 2-fold increased risk of developing CVD when compared to the lowest risk tertile. Very highly elevated levels (>10 mg/L) may be due to noncardiovascular causes of inflammation.[8]

Inflammation has been shown to play a role in cognitive decline,[9,10] Alzheimer disease (AD),[11,12] and vascular dementia (VaD).[11] There have been numerous studies linking CRP levels specifically to AD. Histopathologically, CRP has been found in association with both neurofibrillary tangles[13] and senile plaques[14] in AD tissue. Longitudinally, Schmidt et al[12] analyzed data from the Honolulu-aging study and Honolulu-heart study and found that increased CRP levels at midlife were associated with increased risk of the development of AD, as well as VaD 25 years later. However, CRP levels did not predict AD development in the Conselice Study of Brain Aging over a 4-year period.[15] Similarly, over an average of a 5.7-year follow-up period, CRP levels did not predict the development of AD among participants from the Rotterdam Study.[16] A separate analysis of a subgroup of the Rotterdam Study found a weak relationship between CRP and AD development through a strong relationship with VaD development.[11] Cross-sectionally, very little data exist regarding serum CRP levels in patients with established AD. A small study[17] found that CRP levels were elevated in AD and VaD. Locascio et al[18] recently found that lower levels of CRP were associated with more rapid cognitive and functional decline over time in patients diagnosed with AD. The current study sought to evaluate serum CRP levels in clinically diagnosed patients with AD as compared to nondemented control participants and to evaluate the relationship of CRP with scores of global cognition (Mini-Mental State Examination [MMSE]) and dementia severity (Clinical Dementia Rating [CDR] Scale). Based on the recent study by Locascio et al[18], it was hypothesized that CRP levels would be decreased in patients with AD relative to controls.

Materials and Methods

Participants

Participants in this study represent a combined pool of 192 patients diagnosed with probable AD and 174 nondemented controls; participants were recruited through 3 different research projects each designed to examine the relation between biomarkers (including CRP) and AD. Data on 198 participants (99 patients with AD and 99 controls) were collected as part of the longitudinal study on genetic and biomarkers of AD being conducted by the Texas Alzheimer's Research Consortium (TARC). The methodology of the TARC project has been described previously.[19] Data on 30 patients with AD and 17 controls were extracted from the University of Texas-Southwestern Medical Center (UTSW) Alzheimer's Disease Research Center (ADRC) database. Finally, data on 63 patients with AD and 58 controls were collected from a separate research project examining the link between homocysteine and AD at UTSW. Cases and controls were similar across recruitment methodologies with regard to demographics (age, sex, education), and mean CRP and ranges were similar within groups (case or control) across the 3 sites (analysis not shown). Therefore, samples were

combined for analyses. All participants met consensus-based diagnoses for probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[20] and controls performed within normal limits on psychometric assessment and were assigned a CDR Scale global score of 0.0. All participants signed written informed consent under IRB approved research protocols.

Measures

In addition to other clinical and neuropsychological measures, each participant was administered the MMSE[21] and rated on the CDR scale[22] by an AD specialist as part of his or her clinical examination.

Assays

C-reactive protein levels were assessed in serum that was stored at −80°C. C-reactive protein levels from the TARC cohort were analyzed by rules based medicine (www.rulesba-sedmedicine.com) via multiplexed immunoassay on their human multianalyte profile (human MAP); the least detectable dose (LDD) was 0.0015 μg/mL. Assays conducted by this company using the human MAP platform, including TARC samples, have been previously published.[23,27] High-sensitivity CRP assays for all other participants were conducted under Clinical Laboratory Improvement Amendments (CLIA) standardized conditions using commercially available kits (Dade-Behring Inc, Newark, DE, USA, dadebehring.com).

Analyses

Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina). Analyses comparing demographic variables and log-transformed CRP levels between clinical groups were carried out using *t* test for continuous variables and χ^2 test for discrete variables. Analyses were also examined using a subset of participants with all available data on the relation between CRP levels, MMSE, and CDR sum of boxes scores using linear regression adjusted for significant covariates.

Results

Demographic characteristics of the study population are shown in Table 1. Patients with AD were significantly older ($P < .001$) and less educated ($P = .049$) than control participants. There were significantly more women in the control group ($P = .011$). The control group performed significantly better on the MMSE ($P < .001$) and received lower scores on the CDR global ($P < .001$) and sum of boxes ($P < .001$) scores.

Due to a nonnormal distribution, CRP levels were log transformed for analysis. Log-transformed CRP levels passed the Anderson-Darling test for normality ($P = .073$) so comparison between AD and control groups was conducted via *t* test, which was significant ($P < .0001$; see Table 1).

Next, linear regression models were conducted to analyze the relation between CRP levels, MMSE, and CDR SB scores. Analyses were conducted separately for cases and controls (see Tables 2 and 3). For patients with AD, age contributed significantly to the model and was entered as a covariate whereas sex, education, and ethnicity were not significant contributors. In the adjusted model, elevated CRP levels significantly predicted higher (poorer) CDR SB scores ($P = .04$). In controls, no demographic variables (age, sex, education, or ethnicity) contributed significantly to the models. In unadjusted models, CRP levels were associated with poorer MMSE ($P < .01$) and CDR SB ($P = .02$) scores (Table 2).

Discussion

The current findings suggest that CRP levels are decreased in patients with AD when compared to non-AD controls. Taken in light of previously published findings, it appears that midlife elevations in CRP are a risk factor for the development of AD; however, this elevation appears to reduce and even fall below that of nondemented controls once the disease becomes clinically manifest.

These findings, together with published results from epidemiologic studies[11,12,15,16] are consistent with the hypothesis that midlife CRP elevations are associated with increased risk of AD, though elevated CRP levels are not useful for prediction in the immediate prodromal phase years before AD becomes clinically evident. Consistent with earlier studies,[28] these findings suggest that CRP levels, such as other physiologic parameters (eg, hypertension[29]) and serum biomarkers associated with AD development (eg, MCP-1[30]), might decrease prior to or during the development of AD.

This trend of increased CRP levels prior to AD manifestation followed by a decline in CRP levels once AD is clinically evident, if confirmed, has profound implications for treatment studies. This hypothesis may potentially explain the conflicting evidence between epidemiological studies supporting the protective effect of anti-inflammatory compounds and the failure of treatment studies using these same drugs. There is a large base of epidemiological evidence supporting the notion that anti-inflammatory compounds reduce the risk of developing AD. In a prospective, population-based cohort study of nearly 7000 individuals 55 years of age and older, all of whom were dementia free at baseline, long-term use of nonsterodial anti-inflammatory drugs (NSAIDs) was associated with a reduced risk of developing AD (relative risk = 0.20, confidence interval [CI] = 0.05–0.83).[31] When analyzing data from the Cache County Study, Anthony et al[32] found that the use of nonaspirin NSAIDs alone reduced the risk of developing AD (odds ratio [OR] = 0.43, CI = 0.23–0.75) and that the use of nonaspirin NSAIDs and aspirin reduced that risk even further (OR = 0.17, CI = 0.04–0.48). A meta-analysis of 9 published studies (pooled sample size = 14 654) further supported the notion of a protective effect of NSAID use in terms of AD development with the relative risk of 0.27 (95% CI = 0.13–0.58) associated with long-term use,[33] though a more recent study failed to find such a protective effect.[34] However, treatment studies have failed to demonstrate a benefit of NSAIDs in slowing the progression of AD,[35] reducing rates of progression from mild cognitive impairment (MCI) to AD,[36] or preventing the development of AD in elders at risk of the disease.[37]

Taken together, the currently available data would suggest that anti-inflammatory compounds may have therapeutic potential in primary prevention of the disease; however, administration of these compounds may have little or no benefit once the disease is present —clinically manifest or not. The AD Anti-inflammatory Prevention Trial (ADAPT)[37] was the first attempt at primary prevention using NSAID compounds in AD. The ADAPT study randomized 2528 nondemented participants at risk of AD to test the hypothesis that anti-inflammatory compounds would reduce the risk of developing AD. To be included into the study, individuals had to be at least 70 years of age and have at least 1 first-degree relative with AD. However, given the above-mentioned findings,[15,16,36] it seems possible that the inflammatory cascade had already declined in those individuals at risk of developing AD in a short period of time and who were likely already in the pre-MCI stages. Our findings that elevated CRP continued to predict increased dementia severity, despite the overall lower level as compared to controls, suggest the presence of a proinflammatory endophenotype or subgroup that may benefit from NSAID (or other anti-inflammatory) administration and such a group would have been obscured by the analyses used in the ADAPT and other trials. The challenge will be to develop an appropriately powered and statistically designed

research protocol to test the epidemiological evidence and look for a proinflammatory endophenotype of patients with AD that might respond differentially to preventative and therapeutic measures. Such analyses are currently ongoing in the TARC cohort.

It is possible that medication status of the current AD group contributed to the overall finding of lower CRP levels as compared to controls as many drugs commonly taken by elders have anti-inflammatory qualities (eg, NSAIDs, statins) and medication status was not available for all patients in this sample, which reflects a limitation of the current study. However, there is no a priori reason to assume that the medication status of these patients with AD would be different from others though follow-up analyses are needed and are being conducted in the larger TARC cohort. Another limitation to the current study is the cross-sectional nature of the analyses; however, longitudinal follow-up of the TARC cohort are ongoing and future studies will be able to examine changes in inflammatory markers across dementia stages as well us during the transition from normal control to AD.

Acknowledgments

Funding

The authors disclosed receipt of the following financial support for the research and/or authorship of this article: National Institutes of Health (NIH) RO1 AG17869 and P30 AG12300 and the Texas Alzheimer's Research Consortium (TARC) and the state of Texas through the Texas Council on Alzheimer's Disease and Related Disorders.

References

1. Ridker PM, Haughie P. Prospective studies of C-reactive protein as a risk factor for cardiovascular disease. J Investig Med. 1998; 46(8):391–395.
2. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trail. Am J Epidemiol. 1996; 144(6):537–547. [PubMed: 8797513]
3. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardio-vascular events among apparently healthy women [see comment]. Circulation. 1998; 98(8):731–733. [PubMed: 9727541]
4. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000; 342(12): 836–843. [PubMed: 10733371]
5. Tracy RP, Lemaitre RN, Psaty BM, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997; 17(6):1121–1127. [PubMed: 9194763]
6. Tracy RP. Hemostatic and inflammatory markers as risk factors for coronary disease in the elderly. Am J Geriatr Cardiol. 2002; 11(2):93–100. [PubMed: 11872967]
7. Ford ES, Giles WH. Serum C-reactive protein and self-reported stroke: findings from the Third National Health and Nutrition Examination Survey. Arterioscler Thromb Vase Biol. 2000; 20(4): 1052–1056.
8. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association [see comment]. Circulation. 2003; 107(3):499–511. [PubMed: 12551878]
9. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004; 292(18):2237–2242. [PubMed: 15536110]
10. Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, Eikelenboom P. Serum inflammatory proteins and cognitive decline in older persons. Neurology. 2005; 64(8):1371–1377. [PubMed: 15851726]
11. Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: The Rotterdam Study. Arch Neurol. 2004; 61(5):668–672. [PubMed: 15148142]

12. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol. 2002; 52(2):168–174. [PubMed: 12210786]
13. Duong T, Nikolaeva M, Acton PJ. C-reactive protein-like immunoreactivity in the neurofibrillary tangles of Alzheimer's disease. Brain Res. 1997; 749(1):152–156. [PubMed: 9070642]
14. Iwamoto N, Nishiyama E, Ohwada J, Arai H. Demonstration of CRP immunoreactivity in brains of Alzheimer's disease: immunohistochemical study using formic acid pretreatment of tissue sections. Neurosci Lett. 1994; 177(1–2):23–26. [PubMed: 7824175]
15. Ravaglia G, Forti P, Maioli F, et al. Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. Neurobiol Aging. 2007; 28(12):1810–1820. [PubMed: 17011077]
16. van Oijen M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Fibrinogen is associated with an increased risk of Alzheimer disease and vascular dementia. Stroke. 2005; 36(12):2637–2641. [PubMed: 16269641]
17. Gupta A, Watkins A, Thomas P, et al. Coagulation and inflammatory markers in Alzheimer's and vascular dementia. Int J Clin Pract. 2004; 59(1):52–57. [PubMed: 15707465]
18. Locascio JJ, Fukumoto H, Yap L, et al. Plasma amyloid beta-protein and C-reactive protein in relation to the rate of progression of Alzheimer disease. Arch Neurol. 2008; 65(6):776–785. [PubMed: 18541797]
19. Waring S, O'Bryant SE, Reisch JS, Diaz-Arrastia R, Knebl J, Doody R. for the Texas Alzheimer's Research Consortium. The Texas Alzheimer's Research Consortium longitudinal research cohort: study design and baseline characteristics. Texas Public Health J. 2008; 60(3):9–13.
20. McKhann D, Drockman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. Neurology. 1984; 34(7):939–944. [PubMed: 6610841]
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]
22. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982; 140:566–572. [PubMed: 7104545]
23. O'Bryant SE, Hobson V, Hall J, Lacritz L, Massman P, Cullum M, Diaz-Arrastia R. Brain-derived neurotropic factor (BDNF) in Alzheimer's disease. A project of the Texas Alzheimer's Research Consortium (TARC). Journal of Alzheimer's Disease. 2009; 17(2):1051–1055.
24. Piccolomini F, LouWratten M, Sereni L, et al. Effects of the incubation in vitro with sorbents on serum proteomic pattern and cytokine concentration in cancer patients during chemotherapy–preliminary results. Biomed Pharmacother. 2006; 60(8):463–467. [PubMed: 16930936]
25. Gurbel PA, Kreutz RP, Bliden KP, DiChiara J, Tantry US. Biomarker analysis by fluorokine multianalyte profiling distinguishes patients requiring intervention from patients with long-term quiescent coronary artery disease: a potential approach to identify atherosclerotic disease progression. Am Heart J. 2008; 155(1):56–61. [PubMed: 18082490]
26. Duan H, Fleming J, Pritchard DK, et al. Combined analysis of monocyte and lymphocyte messenger RNA expression with serum protein profiles in patients with scleroderma. Arthritis Rheum. 2008; 58(5):1465–1474. [PubMed: 18438864]
27. Delaleu N, Immervoll H, Cornelius J, Jonsson R. Biomarker profiles in serum and saliva of experimental Sjogren's syndrome: associations with specific autoimmune manifestations. Arthritis Res Ther. 2008; 10(1):R22. [PubMed: 18289371]
28. Diaz-Arrastia, R.; Moore, CB.; Arning, E.; Bottiglieri, T. C-reactive protein in aging and Alzheimer's disease: correlation with cerebral atrophy and low plasma vitamin B6. International Conference on Alzheimer's Disease; Spain: Madrid; 2006.
29. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64(2):277–281. [PubMed: 15668425]
30. Galimberti D, Fenoglio C, Lovati C, et al. Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease. Neurobiol Aging. 2006; 27(12):1763–1768. [PubMed: 16307829]

31. In't Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. N Engl J Med. 2001; 345(21):1515–1521. [PubMed: 11794217]

32. Anthony JC, Breitner JC, Zandi PP, et al. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County study. Neurology. 2000; 54(11):2066–2071. [PubMed: 10851364]

33. Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ. 2003; 327(7407):128. [PubMed: 12869452]

34. Breitner J, Haneuse SJPA, Walker R, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology. 2009; 72(22):1899–1905. [PubMed: 19386997]

35. Aisen PS, Schafer KA, Grundman M, et al. for Alzheimer's Disease Cooperative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial [see comment]. JAMA. 2003; 289(21):2819–2826. [PubMed: 12783912]

36. Thal LJ, Ferris SH, Kirby L, et al. for the Rofecoxib Protocol 078 study group. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment [see comment]. Neuropsychopharmacology. 2005; 30(6):1204–1215. [PubMed: 15742005]

37. Lyketsos CG, Breitner JC, Green RC, et al. and the Adapt_Research_Group. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology. 2007; 68(21):1800–1808. [PubMed: 17460158]

Table 1

Baseline Characteristics

	AD	Control	*P* Value[a]
Number of participants	192	174	—
Sex (n, %)			.0109
Female	96 (50.0)	110 (63.2)	
Male	96 (50.0)	64 (36.8)	
Age (mean, SD)	75.8 (8.2)	70.7 (8.2)	<.0001
Range	54–100	49–93	
Race/ethnicity (n, %)			.7576
Caucasian	150 (94.3)	144 (93.5)	
Not Caucasian	9 (5.7)	10 (6.5)	
Years of education (mean, SD)	14.4 (2.8)	15.0 (2.5)	.0486
Range	6–20	8–20	
MMSE (mean, SD)[b]	20.7 (5.6)	29.3 (0.91)	<.0001
Range	5–30	25–30	
CDR global (mean, SD)[c]	1.2 (0.6)	0.0 (0.0)	<.0001
0	0	99 (100.0)	
0.5	23 (23.2)	0	
1	47 (47.5)	0	
2	29 (29.3)	0	
CDR sum of boxes (mean, SD)[d]	6.6 (3.6)	0.1 (0.2)	<.0001
Range	1.5–18	0–1.0	
CRP (μg/mL)	2.9 (4.5)	4.9 (7.7)	.003
Log CRP[e](mean, SD)	0.3 (1.3)	0.8 (1.2)	<.0001
Range	−2.8 to 3.6	−.21 to 3.9	

NOTES: AD = Alzheimer disease; CDR = clinical dementia rating; CRP = C-reactive protein; MMSE = Mini-Mental State Examination.

[a] *P* values are based on a χ^2 test for categorical variables and a *t* test for continuous variables.

[b] MMSE scores were available on 192 AD patients and 174 controls.

[c] CDR global scores were available on 99 AD patients and 99 controls.

[d] CDR sum of boxes scores were available on 128 AD patients and 115 controls.

[e] Log transformation of CRP levels passed the Anderson-Darling test for normality with a *P* value of .073, therefore comparison based on *t* test.

Table 2

Linear Regression Models for AD Patients With CRP Levels as the Independent Variable

	Crude			Adjusted[a]		
Outcome	**Coefficient (SE)**	***P* Value**	**R^2**	**Coefficient (SE)**	***P* Value**	**R^2**
MMSE	−0.0964 (0.0886)	.2776	.0062	—	—	—
CDR SB	0.1741 (0.0719)	.0169	.0444	0.1394 (0.0678)	.0419	.1696

NOTES: AD = Alzheimer disease; CDR SB = Clinical Dementia Rating sum of boxes; CRP = C-reactive protein; MMSE = Mini-Mental State Examination; R^2 = amount of total variance explained by model; SB = sum of boxes; SE = standard error.

[a] Age, sex, education, and race were included in all models as potential confounders. Only age was statistically significant in the model for CDR sum of boxes but none reached statistical significance in the MMSE model.

[b] Adjusted for age.

Table 3

Linear Regression Models for Controls With CRP Levels as the Independent Variable[a]

Outcome	Coefficient (SE)	*P* Value	R^2
MMSE	−0.0293 (0.0087)	.0010	.0614
CDR SB	0.0057 (0.0024)	.0166	.0497

NOTES: CDR SB = Clinical Dementia Rating sum of Boxes; CRP = C-reactive protein; MMSE = Mini-Mental State Examination; R^2 = amount of total variance explained by model; SB = sum of boxes; SE = standard error.

[a] Age, sex, education, and race were included in all models as potential confounders but were not statistically significant.