Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Arch Neurol. Author manuscript; available in PMC 2015 May 11.

Published in final edited form as:

Arch Neurol. 2010 January ; 67(1): 87–92. doi:10.1001/archneurol.2009.308.

Association of C-Reactive Protein to Cognitive Impairment

James M Noble, MD MS[1,2,3], **Jennifer J Manly, PhD**[2,3], **Nicole Schupf, PhD**[2,3,4], **Ming Xing Tang, PhD**[2,5], **Richard Mayeux, MD MS**[1,2,3,4,6], and **José A. Luchsinger, MD MPH**[2,3,4,7]

[1]Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY.

[2]Gertrude H. Sergievsky Center, Columbia University, New York, NY.

[3]Taub Institute for Research of Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY.

[4]Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

[5]Department of Biostatistics, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

[6]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY.

[7]Division of General Medicine, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY.

Abstract

Background—High sensitivity C-reactive protein (hsCRP) is a biomarker of cardiovascular risk suggested as a biomarker for cognitive impairment.

Objective—To explore the association between hsCRP and cognitive impairment

Design—Cross-sectional analysis of a population-based community aging study

Setting—Northern Manhattan, New York

Subjects—1331 participants from a longitudinal study of aging without dementia and available hsCRP and neuropsychological testing at baseline.

Main Outcome Measures—Four cognitive scores (memory, visuospatial, executive, language) derived from a neuropsychological battery. Cognitive impairment was defined by scores below 1.5 SD of demographically corrected means.

Results—Participants with the highest hsCRP tertile had higher adjusted odds of impaired memory (OR=1.5, 95%CI: 1.0–2.1; p for trend = 0.03) than participants with the lowest tertile Subjects in the highest hsCRP tertile also had greater odds of visuospatial impairment (OR=1.6, 95% CI: 1.0–2.3; p for trend-0.03). Higher hsCRP was not associated with executive or language

Correspondence/Requests for reprints: José A. Luchsinger, MD, 630 West 168th St., PH9E-105, New York, NY 10032, Telephone: 212-3054730, Fax: 212-3059349, jal94@columbia.edu.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

impairment. Persons with at least one APOE-ε4 allele and hsCRP in the highest tertile had the greatest odds of impaired memory (OR=2.7, 95% CI: 1.6–4.4).

Conclusion—High hsCRP may be a marker of memory and visuspatial impairment in the elderly. The role of APOE-ε4 requires further exploration.

Background

C-reactive protein (CRP) is known to be elevated in risk factors common to stroke and dementia, including diabetes,[1, 2] obesity,[3] and smoking,[4] and is associated with adverse risk of cardiovascular disease,[5] increased risk for primary stroke,[6] and increased stroke severity.[7] High sensitivity CRP (hsCRP) is increasingly used in clinical practice as a marker of cardiovascular risk and to guide therapy[8]. Cardiovascular disease[9] and inflammation may also be important in Alzheimer's disease (AD)[10] and hsCRP has been suggested as an AD biomarker[11].

We sought to investigate the cross-sectional relation between hsCRP and impairment in specific cognitive domains, among a multiethnic non-demented elderly population in Northern Manhattan.

Methods

Subjects

The source sample is 2776 participants from a prospective study of aging and dementia in Medicare-eligible northern Manhattan residents, age 65 years and older (Washington/Hamilton Heights-Inwood Columbia Aging Project: WHICAP II). The WHICAP II cohort represents a combination of continuing members of a cohort originally recruited in 1992 (WHICAP I; n=602) and members of a new cohort recruited between 1999 and 2001 (n=2,174). The sampling strategies and recruitment outcomes of these two cohorts have been described in detail elsewhere[12]. The population from which participants were drawn comprises individuals from three broadly defined ethnic categories (i.e., Hispanic, African American, and non-Hispanic White). Participants have been followed at approximately 18-month intervals with similar assessments at each interval. Ethnic group was determined by self-report using the format of the 2000 US Census[13]. All individuals were first asked to report their race (i.e., American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black or African American, or White), then, in a second question, were asked whether or not they were Hispanic. Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute.

hsCRP was measured in 2008 in frozen plasma obtained in 1999–2001 in the WHICAP II baseline examination. Participants without prevalent dementia at baseline and at least one follow-up examination were chosen. Of the total of 2776 participants, 356 were excluded due to prevalent dementia, 544 were excluded due to lack of follow-up, and 542 were excluded for lack of a frozen plasma sample; hsCRP was measured in 1352 persons. Persons with hsCRP measured were younger than those excluded, had a lower proportion of women

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

than those with prevalent dementia and without blood, had a higher proportion of Whites than those with prevalent dementia, a lower proportion of non-Hispanic Blacks than those with no bloods, and a lower proportion of Hispanics than those with prevalent dementia (Supplemental Table 1). Of the 1352 persons with hsCRP measured, 1330 had sufficient information on memory scores, 1328 for visuospatial scores, 1331 for language and executive scores, 906 had color trails 1, and 854 color trails 2.

Measurement of hsCRP and other covariates

C-reactive protein was measured with an ultra-sensitive ELISA (Diagnostic systems Laboratory, Inc). Sociodemographic covariates included age, gender, race-ethnicity using the format of the 1990 census[14] (subjects were categorized as Hispanic, non-Hispanic White, or non-Hispanic Black), education (recorded as a continuous variable and categorized for the purposes of these analyses as 0–6, 7–12, 13–16, and >16 years of education). APOE genotypes were determined as described by Hixson and Vernier[15] with slight modification[16]. We classified persons by the presence (homozygous or heterozygous) or absence of the APOE ε4 allele.

Vascular risk factors have been found to be predictors of cognitive impairment in our cohort[17]. Thus, we included them as covariates. Vascular covariates included type 2 diabetes, hypertension, heart disease, stroke, smoking, and use of lipid-lowering medications. Determination of the presence of diabetes was based upon self-report or by medications indicated for the treatment of diabetes. Hypertension was defined also based upon self-report or medication use, but also by blood pressure measurements. Based upon standardized criteria[18], hypertension was defined by a systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg. Blood pressure measurements did not significantly affect the predictive value over self-report, and results included in this study only reflect self-report/medication use. Heart disease was defined by a history of atrial fibrillation or other arrhythmias, coronary artery disease including myocardial infarction or angina pectoris, or congestive heart failure. Stroke was defined according to the WHO criteria[19], and was based upon questioning of the participant or relatives, supplemented by a neurological examination or review of medical records. Smoking was also determined by self report, and classified as current smokers, former smokers, or non-smokers. Lipid lowering medications significantly reduce hsCRP[5]. Thus, we included them as a covariate. The use of lipid-lowering medications was based on self-report or review of medications.

Cognitive measures

Learning and Memory was assessed with the Selective Reminding Test[20] (SRT) including delayed recall and delayed recognition, and Recognition from the Benton Visual Retention Test (BVRT)[21, 22]. Visuospatial Ability was assessed with the Rosen Drawing Test[23], and the BVRT Matching[24]. Language was assessed with the Boston Naming Test[25], the Controlled Oral Word Association Test[26], and Category Fluency Test[27]. Psychomotor speed was assessed with the Color Trails Test 1[28]. Executive Functioning was assessed with the Similarities subtest from the Wechsler Adult Intelligence Scale - Revised[29] and the Color Trails 2.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The normative sample used to define cognitive impairment was selected from participants recruited in 1992 and 1999 by means of the robust norms approach[30]. Details of the normative sample are published elsewhere[31]. Demographically corrected T scores were developed on the basis of the Heaton et al[32] regression method. Influences of age, years of education, race/ethnicity, and sex on each cognitive test score were assessed by performing multiple linear regression analyses. Racial-ethnic group and language (ie, Spanish vs English) were highly related, since most of the Hispanics were tested in Spanish and all of the Whites and African Americans were tested in English; therefore, we did not add language into the model. Each of the 4 cognitive domain scores were included as dependent variables: memory (average composite of total raw scores for immediate recall and delayed recall from the Selective Reminding Test and BVRT recognition); language (average composite of total correct on the 15-item Boston Naming Test, number of phrases correctly produced on BDAE repetition, and number correct on BDAE comprehension); executive function (average composite of total correct on the Mattis Identities and Oddities, raw score on Wechsler Adult Intelligence Scale–Revised Similarities subtest, and mean number of words generated during three 60-second trials for category and letter fluency); and visuospatial skill (average composite of number correct on the Rosen Drawing Test and BVRT matching). Continuous predictors were age and years of education. Sex was a categorical predictor, as was racial-ethnic classification (ie, non-Hispanic black, non-Hispanic white, and Hispanic). For each of the 4 regression analyses, we first included all 4 predictors in the model, retaining only the variables that significantly contributed to prediction of cognitive test score. The βweights of each of these predictors in the final model, as well as the standard error of each regression model, were used to calculate predicted scores on each test. These predicted scores were subtracted from each participant's actual composite score to calculate residual scores. Residual scores were converted to T scores according to the following formula:

$$\text{T score} = [(\text{Residual Score}/\text{SE of Estimate for the Regression Equation}) \times 10] + 50.$$

T scores have a mean of 50 and an SD of 10, allowing a T score of 35 to be the –1.5-SD mark for each of the 4 composite scores. We defined cognitive impairment as scores in specific cognitive domains < 1.5 SD below these demographically corrected means[31], as previously done in our cohort for the diagnosis of mild cognitive impairment (MCI)[33]. This definition of cognitive impairment differs from the definition of MCI in that it did not require the memory complaint or the functional impairment criteria. The Color Trails 1 and 2 were not originally part of the cognitive scores in our cohort[31] and were not available in all participants. Thus, we defined impairment in the Color Trails 1 and 2 separately also using the 1.5 SD cutoff and conducted secondary analyses with these tests.

Statistical analyses

First, we examined the distribution of all variables. hsCRP was not normally distributed, but was normally distributed after log transformation. We used chi-square in bivariate analyses of dichotomous variables and t-test for continuous variables. For multivariable analyses we used logistic regression relating hsCRP to the presence of cognitive impairment. Models were constructed for each of the cognitive scores. We report several models for the multivariable analyses in the tables: one adjusted for age and gender, one further adjusted

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

for education, ethnic group and APOE-ε4, and another one adjusted for vascular risk factors. We report the second model in the text unless otherwise indicated. We decided a-priori that changes in the OR in the model adjusted for vascular risk factors would be evidence of mediation and not confounding since vascular risk factors and hsCRP are in the same hypothetical causal pathway[34]. All analyses were conducted using SAS. 9.1 for Windows.

Results

Table 1 shows the general characteristics of the sample and compares characteristics among hsCRP tertiles. Compared to the first tertile, persons in the third tertile where younger, more likely to be women, Black, Hispanic, less likely to be White, less likely to have APOE-ε4, more likely to be current or past smokers, have hypertension, and have memory or visuospatial impairment.

We conducted multivariable analyses first relating log transformed hsCRP as a continuous variable with the cognitive scores. hsCRP was associated with memory impairment (adjusted OR=1.1, 95% CI: 1.0–1.3) and this association was not attenuated by adjustment for vascular risk factors and stroke. Log-hsCRP was also associated with visuospatial impairment (OR=1.2, 95% CI: 1.0–1.34) after adjusting for sociodemographics and APOE, but was modestly attenuated and became non-significant after adjusting for vascular factors (OR=1.1, 95% CI: 0.96–1.27). We found no association between hsCRP and language, executive, or impairment in the Color Trails 1 and 2.

We explored the relation between hsCRP tertiles and cognitive impairment in order to examine thresholds for the associations (Table 2). In comparison to participants with the lowest hsCRP tertile, participants in the highest hsCRP tertile had a 50% greater odds of impaired memory that was not attenuated after adjustment for vascular risk factors. The OR for the second tertile was 1 and not statistically significant, suggesting a threshold for the association between hsCRP and memory impairment.

Subjects with the highest hsCRP tertile had a 60% greater odds of visuospatial impairment (Table 2). Additionally adjusting for vascular factors, heart disease, diabetes, hypertension, smoking, stroke, and use of lipid-lowering medications led to marked attenuation of the relationship between hsCRP and the visuospatial factor, suggesting that vascular factors may be mediators in this relationship. Similar to memory, in all models the OR relating the middle tertile of hsCRP and visuospatial impairment was not significant; furthermore, crude models of hsCRP and visuospatial factor, as well as models adjusted for sociodemographic factors suggested a dose-response relationship between hsCRP and visuospatial impairment.

HsCRP was not related with executive function language. We conducted secondary analyses in a subset of participants with data on Color Trails 1 and 2, but there was no relation with either. The OR for the 3rd tertile of hsCRP of the Color Trails 1 was 1.1 (95% CI: 0.8–1.5; p for trend = 0.62) and 0.9 for Color trails 2 (95% CI: 0.7–1.3; p for trend = 0.75).

We examined effect modification by APOE-ε4 by constructing strata of APOE-ε4 and hsCRP levels as suggested for the examination of gene-environment interactions[35] (Table 3). Since only the third tertile of hsCRP was associated with memory and visuospatial

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

impairment, we created a dichotomous variable defining high hsCRP as the third tertile. The interaction term of APOE-ε4 and high hsCRP was of borderline statistical significant (p=0.06). Persons with both the highest tertile of hsCRP and APOE-4ε had a higher risk of memory impairment compared to those with neither. Persons with either risk factor alone did not have a higher risk of memory impairment. These findings are suggestive of an additive interaction. Both risk factors were associated with a higher risk of visuospatial impairment in isolation, with only a modest increase in risk with their joint presence.

Comment

In cross-sectional analyses of a large, elderly, multiethnic, community-based cohort, we found that high hsCRP was related to memory and visuospatial impairment. The association between high hsCRP and memory seemed to occur in the presence of APOE-ε4.

There are several mechanisms through which inflammation could affect cognition. Endothelial function depends on the sum of all factors contributing to and attenuating atherogenesis and is an important risk factor for cardiovascular outcomes.[36, 37] Diseases associated with systemic inflammation may lead to impaired endothelial function, which has been associated with cerebral white matter hyperintensities,[38, 39] vascular dementia, and AD.[40–42] Non-infectious systemic inflammatory markers have been independently associated with impaired cerebral blood flow[43] and animal inflammatory models suggest focal dysregulation in cerebrovascular flow in areas important to memory such as the hippocampus.[44]. It can be postulated that high systemic inflammation could be a marker of vascular disease[8], but could also directly affect the amyloid cascade.[45] Recent findings suggest that CRP is a marker of vascular disease, but its elevation does not have direct effects on vascular outcomes[46, 47]. We found that the inclusion of vascular risk factors in multivariable models attenuated the relationship between hsCRP and visuospatial abilities, but not memory. Acknowledging the limitations of our cross-sectional analyses, one could speculate that the relation of hsCRP with visuospatial abilities, affected most by cerebrovascular disease and disruption of frontal subcortical pathways[48], is mediated by vascular disease, while the association with memory is explained by non-vascular mechanisms. Surprisingly, we did not find an association of hsCRP with a “subcortical pattern” of cognitive impairment, with hallmarks of impaired executive function, processing speed, and attention as described in patients with vascular cognitive impairment.[49]

Several studies have examined the relation of several markers of inflammation and incident cognitive decline.[50–52] Although some longitudinal studies have found associations specifically between hsCRP and incident cognitive decline,[51] others have revealed conflicting results, including minimal or no overall association with incident decline in memory[53–55] dementia,[52] or neuropsychological test performance,[56.57] In comparison with other studies of cognition and hsCRP, our threshold level of the highest hsCRP tertile was much higher in this population than in some other studies of dementia and memory. Studies examining hsCRP and cognition have classified high hsCRP as higher than 1.0–4.1 mg/L[50–52, 54, 58, 59] or at least 5.3 mg/L,[56]. However, levels of hsCRP in our study are comparable to other reports in northern Manhattan[7] as well as elderly Latinos in California.[7, 60]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Among the oldest old, persons with high hsCRP and Apolipoprotein-E (APOE) ε4 carriers may be at greatest risk for impaired memory,[53] but this has not previously been found in other studies with wider age ranges[59, 60]. Our findings suggest an additive interaction between APOEε4 and hsCRP for memory impairment, but this observation is limited by the cross-sectional nature of the study.

hsCRP is currently being used as a marker of cardiovascular risk[8] and lipid lowering treatments[61]. Our results suggest that it could also be used as a marker of cognitive impairment in persons without dementia, and could serve as the basis for interventions. This possibility requires further exploration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

Drs. Noble had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest and sources of funding:

Support for this work was provided by grants from the National Institutes of Health P01AG07232.

Nicole Schupf has provided consultation to Elan pharmaceuticals.

References

1. Craft S. Insulin resistance syndrome and Alzheimer's disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol Aging. 2005 Dec; 26(Suppl 1):65–69. [PubMed: 16266773]
2. de Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Lett. 2008 Jan 9; 582(1):97–105. [PubMed: 18053812]
3. Singer G, Granger DN. Inflammatory responses underlying the microvascular dysfunction associated with obesity and insulin resistance. Microcirculation. 2007 Jun-Jul;14(4–5):375–387. [PubMed: 17613809]
4. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest. 2007 May; 131(5):1557–1566. [PubMed: 17494805]
5. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002 Nov 14; 347(20):1557–1565. [PubMed: 12432042]
6. Rost NS, Wolf PA, Kase CS, et al. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. Stroke. 2001 Nov; 32(11):2575–2579. [PubMed: 11692019]
7. Elkind MS, Tai W, Coates K, Paik MC, Sacco RL. High-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and outcome after ischemic stroke. Arch Intern Med. 2006 Oct 23; 166(19):2073–2080. [PubMed: 17060536]
8. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. American Heart Journal. 2004; 148(1, Supplement 1):S19–S26. 2004/7. [PubMed: 15211329]
9. Luchsinger J, Mayeux R. Cardiovascular risk factors and Alzheimer's disease. Curr Atheroscler Rep. 2004; 6(4):261–266. [PubMed: 15191699]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

10. Gupta A, Pansari K. Inflammation and Alzheimer's disease. Int J Clin Pract. 2003; 57:36–39. [PubMed: 12587940]
11. Frank RA, Galasko D, Hampel H, et al. Biological markers for therapeutic trials in Alzheimer's disease. Proceedings of the biological markers working group; NIA initiative on neuroimaging in Alzheimer's disease. Neurobiol Aging. 2003 Jul-Aug;24(4):521–536. [PubMed: 12714109]
12. Tang MX, Cross P, Andrews H, et al. Incidence of Alzheimer's disease in African-Americans, Caribbean Hispanics and Caucasians in northern Manhattan. Neurology. 2001; 56:49–56. 2001///. [PubMed: 11148235]
13. Census PaH. Census of Population and Housing Summary Tape File1, Technical Documentation. WAshington, DC: Bureau of the Census; 1991.
14. 1990 Census of populations and housing: summary tape file 1, technical documentation (computer diskette). [computer program]. Version. Washington, CD: Bureau of the Census; 1991.
15. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res. 1990 Mar; 31(3):545–548. [PubMed: 2341813]
16. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 1995 Mar; 45(3 Pt 1): 555–557. [PubMed: 7898715]
17. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. 2005 Aug 23; 65(4):545–551. 2005. [PubMed: 16116114]
18. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. [see comment][erratum appears in JAMA. 2003 Jul 9;290(2):197]. Jama. 2003; 289(19):2560–2572. [PubMed: 12748199]
19. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ. 1976; 54(5):541–553. [PubMed: 1088404]
20. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology. 1974; 24(11):1019–1025. [PubMed: 4473151]
21. Benton, AL. The Visual Retention Test. New York, NY: The Psychological Corporation; 1955.
22. Benton, AL. Revised Visual Retention Test. 4th ed.. 1974.
23. Rosen, W. The Rosen Drawing Test. Odessa: Psychological Assessment Resources; 1981.
24. Benton, A. The Visual Retention Test. New York: The Psychological Corporation; 1955.
25. Kaplan, E.; Goodglass, H.; Weintraub, S. Boston Naming Test. Philadelphia, PA: Lea & Febiger; 1983.
26. Benton, AL.; Hamsher, K. Multilingual Aphasia Examination. 1983.
27. Goodglass, H.; Kaplan, D. The assessment of aphasia and related disorders. 2nd ed.. Philadelphia: Lea and Febiger; 1983.
28. D'Elia, LF.; Satz, P.; Uchiyama, CL.; White, T. Color Trails Test Professional Manual. Odessa, FL: Psychological Assessment Resources; 1994.
29. Wechsler, D. Wechsler Adult Intelligence Scale-Revised. New York, NY: The Psychological Corporation; 1981.
30. Sliwinski M, Lipton RB, Buschke H, Stewart W. The effects of preclinical dementia on estimates of normal cognitive functioning in aging. J Gerontol B Psychol Sci Soc Sci. 1996 Jul; 51(4):P217–P225. [PubMed: 8673642]
31. Manly JJ, Bell-McGinty S, Tang MX, Schupf N, Stern Y, Mayeux R. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. Arch Neurol. 2005 Nov; 62(11):1739–1746. [PubMed: 16286549]
32. Heaton, RK.; I, G.; Matthews, CG. Comprehensive Norms for an Expanded Halstead-Reitan Battery. Odessa: FlaPsychological Assessment Resources Inc; 1991.
33. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001; 58(12):1985–1992. [PubMed: 11735772]
34. Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-Reactive protein in risk assessment. The American Journal of Medicine. 2004; 116(6, Supplement 1):9–16. 2004/3/22.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

35. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 1995; 45(3 Pt 1):555–557. [PubMed: 7898715]
36. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003 Feb 1; 23(2):168–175. [PubMed: 12588755]
37. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation. 2005 Jan 25; 111(3):363–368. [PubMed: 15668353]
38. Hoth KF, Tate DF, Poppas A, et al. Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. Stroke. 2007 Feb; 38(2):308–312. [PubMed: 17204686]
39. Markus HS, Hunt B, Palmer K, Enzinger C, Schmidt H, Schmidt R. Markers of endothelial and hemostatic activation and progression of cerebral white matter hyperintensities: longitudinal results of the Austrian Stroke Prevention Study. Stroke. 2005 Jul; 36(7):1410–1414. [PubMed: 15905468]
40. Vicenzini E, Ricciardi MC, Altieri M, et al. Cerebrovascular reactivity in degenerative and vascular dementia: a transcranial Doppler study. Eur Neurol. 2007; 58(2):84–89. [PubMed: 17565221]
41. Silvestrini M, Pasqualetti P, Baruffaldi R, et al. Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. Stroke. 2006 Apr; 37(4):1010–1015. [PubMed: 16497984]
42. Lavi S, Gaitini D, Milloul V, Jacob G. Impaired cerebral CO2 vasoreactivity: association with endothelial dysfunction. Am J Physiol Heart Circ Physiol. 2006 Oct; 291(4):H1856–H1861. [PubMed: 16766649]
43. Novak V, Last D, Alsop DC, et al. Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. Diabetes Care. 2006 Jul; 29(7):1529–1534. [PubMed: 16801574]
44. Semmler A, Okulla T, Sastre M, Dumitrescu-Ozimek L, Heneka MT. Systemic inflammation induces apoptosis with variable vulnerability of different brain regions. J Chem Neuroanat. 2005 Oct; 30(2–3):144–157. [PubMed: 16122904]
45. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. Nat Rev Immunol. 2007 Feb; 7(2):161–167. [PubMed: 17220915]
46. Schunkert H, Samani NJ. Elevated C-reactive protein in atherosclerosis--chicken or egg? N Engl J Med. 2008 Oct 30; 359(18):1953–1955. [PubMed: 18971498]
47. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med. 2008 Oct 30; 359(18):1897–1908. [PubMed: 18971492]
48. Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. Neurobiology of Aging. 2002; 23(3):421–431. [PubMed: 11959405]
49. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurol. 2003; 2(2):89–98. [PubMed: 12849265]
50. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. Jama. 2004 Nov 10; 292(18):2237–2242. [PubMed: 15536110]
51. Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003 Jul 8; 61(1):76–80. [PubMed: 12847160]
52. Tan ZS, Beiser AS, Vasan RS, et al. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. Neurology. 2007 May 29; 68(22):1902–1908. [PubMed: 17536046]
53. Schram MT, Euser SM, de Craen AJ, et al. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc. 2007 May; 55(5):708–716. [PubMed: 17493190]
54. Ravaglia G, Forti P, Maioli F, et al. Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. Neurobiol Aging. 2007 Dec; 28(12):1810–1820. [PubMed: 17011077]
55. Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. Arch Neurol. 2004 May; 61(5):668–672. [PubMed: 15148142]
56. Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, Eikelenboom P. Serum inflammatory proteins and cognitive decline in older persons. Neurology. 2005 Apr 26; 64(8):1371–1377. [PubMed: 15851726]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

57. Weuve J, Ridker PM, Cook NR, Buring JE, Grodstein F. High-sensitivity C-reactive protein and cognitive function in older women. Epidemiology. 2006 Mar; 17(2):183–189. [PubMed: 16477259]

58. Jordanova V, Stewart R, Davies E, Sherwood R, Prince M. Markers of inflammation and cognitive decline in an African-Caribbean population. Int J Geriatr Psychiatry. 2007 Oct; 22(10):966–973. [PubMed: 17343293]

59. Laurin D, David Curb J, Masaki KH, White LR, Launer LJ. Midlife C-reactive protein and risk of cognitive decline: A 31-year follow-up. Neurobiol Aging. 2008 Mar 1.

60. Haan MN, Aiello AE, West NA, Jagust WJ. C-reactive protein and rate of dementia in carriers and non carriers of Apolipoprotein APOE4 genotype. Neurobiol Aging. 2007 May 29.

61. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events. N Engl J Med. 2002 Nov 14; 347(20):1557–1565. 2002. [PubMed: 12432042]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

General characteristics of the study sample (second column) and comparison of pertinent characteristics among hsCRP tertiles (third, fourth, and fifth columns). For all comparisons, a global test of significance was first obtained with ANOVA for continuous variables or χ^2 for proportions. If this global test was significant, pairwise comparison of tertiles was conducted with the first tertile as the reference.

	Study sample	hsCRP Tertile 1 (≤3.6 mg/L)	hsCRP Tertile 2 (3.7–9.9 mg/L)	hsCRP Tertile 3 (>9.9 mg/L)
	N = 1331	N=443	N=444	N=444
Age, median (IQR)	76.1 (71.5–81.0)	77.1 (72.2–81.6)	75.9 (71.3–80.8)	75.8 (71.3–80.4)*
Women, n (%)	893 (67.1)	273 (61.6)	307 (69.1)*	313 (70.5)**
Years of education, mean (SD)	10.4 (4.8)	10.8 (4.8)	10.5 (4.7)	10.1 (4.8)
Non-Hispanic Whites, n (%)	422 (31.7)	178 (40.2)	138 (31.1)	106 (23.9)
Non-Hispanic Blacks, n (%)	397 (29.8)	117 (26.4)	128 (28.8)*	152 (34.2)***
Hispanics, n (%)	512 (38.4)	148 (33.4)	178 (40.1)**	186 (41.9)***
APOE ε4, n (%) †	343 (26.0)	135 (30.8)	119 (27.1)	89 (20.1)***
Current Smoking, n (%)	101 (7.6)	23 (5.2)	23 (5.2)	55 (12.4)***
Former Smoking, n (%)	425 (31.9)	123 (27.8)	151 (34.0)*	151 (34.0)**
Stroke, n (%)	133 (10.0)	38 (8.6)	41 (9.2)	54 (12.2)
Heart Disease, n (%)	346 (26.0)	115 (26.0)	116 (26.1)	115 (25.9)
Hypertension, n (%)	825 (62.0)	240 (54.2)	285 (64.2)**	300 (67.6)***
Type 2 Diabetes, n (%)	218 (16.4)	57 (12.9)	73 (16.4)	88 (19.8)**
Lipid-lowering medication, n (%)	262 (19.7)	85 (19.2)	92 (20.7)	85 (19.1)
hsCRP (mg/L), median (IQR)	5.4 (2.8, 13.9)	1.9 (1.2–2.8)	5.4 (4.4–7.3)***	20.3 (13.9–32.2)***
Memory impairment, n (%) ‡	234 (17.6)	72 (16.3)	68 (15.4)	94 (21.2)*
Language impairment, n (%)‡	195 (14.7)	67 (15.1)	65 (14.6)	63 (14.2)
Executive impairment, n (%)‡	156 (11.7)	50 (11.3)	49 (11.0)	57 (12.8)
Visuospatial impairment, n %) ‡	197 (14.8)	52 (11.8)	64 (14.5)	81 (18.3)**

* p <0.05,

** p < 0.01,

*** p < 0.001.

SD=standard deviation; IQR=inter-quartile range;

† APOE-ε4 is available in 1320 participants;

‡ n= 1330 for memory impairment, 1331 for language and executive impairment, 1328 for visuospatial impairment

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression models relating high sensitivity C-reactive protein (hsCRP) tertiles and impairment in cognitive scores.

HsCRP tertile (range in mg/L)	N	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
	1330	**Memory**		
1 (≤3.6)	443	1	1	1
2 (3.7–9.9)	443	1.0 (0.7–1.4)	1.0 (0.7–1.4)	1.0 (0.7–1.4)
3 (>9.9)	444	**1.4 (1.0–2.0)**	**1.5 (1.0–2.1)**	1.4 (1.0–2.4)
P for trend		**0.03**	**0.03**	**0.05**
	1328	**Visuospatial**		
1	442	1	1	1
2	443	1.3 (0.9–1.9)	1.2 (0.8–1.8)	1.1 (0.7–1.7)
3	443	1.7 (1.2–2.5)	1.6 (1.0–2.3)	1.3 (0.9–1.9)
P for trend		**0.005**	**0.03**	0.21
	1331	**Language**		
1	443	1	1	1
2	444	1.0 (0.7–1.5)	0.9 (0.7–1.4)	0.9 (0.6–1.3)
3	444	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.8 (0.5–1.2)
P for trend		0.96	0.61	0.23
	1331	**Executive**		
1	443	1	1	1
2	444	1.0 (0.6–1.5)	1.1 (0.7–1.6)	1.0 (0.7–1.6)
3	444	1.2 (0.8–1.8)	1.3 (0.9–1.9)	1.2 (0.8–1.9)
P for trend		0.46	0.22	0.36

Model 1: adjusted for age and gender; Model 2: additionally adjusted for education, race-ethnicity. Model 3: additionally adjusted for history of heart disease, diabetes mellitus, hypertension, smoking, stroke, and use of lipid-lowering medications.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) relating strata of hsCRP and APOE-ε4 to impairment. Model 1: adjusted for age and gender; Model 2: additionally adjusted for education, race-ethnicity. Model 3: additionally adjusted for history of heart disease, diabetes mellitus, hypertension, smoking, stroke, and use of lipid-lowering medications.

High hsCRP (>9.9 mg/L)	APOE ε4	N	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
		1319	**Memory**		
−	−	623	1.0	1.0	1.0
−	+	254	1.1 (0.8–1.7)	1.1 (0.8–1.7)	1.1 (0.8–1.7)
+	−	353	1.3 (0.9–1.8)	1.3 (0.9–1.8)	1.2 (0.9–1.7)
+	+	89	2.8 (1.7–4.6)	2.7 (1.7–4.5)	2.7 (1.6–4.4)
		1317	**Visuospatial**		
−	−	623	1.0	1.0	1.0
−	+	253	1.5 (1.00–2.3)	1.5 (1.0. –2.3)	1.5 (1.00–2.3)
+	−	352	1.7 (1.2–2.4)	1.5 (1.0–2.2)	1.3 (0.9–1.9)
+	+	89	2.0 (1.1–3.6)	1.9 (1.0–3.4)	1.7 (1.00–3.2)