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C-reactive protein and rate of dementia in carriers and non carriers of Apolipoprotein APOE4 genotype

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Abstract

Background—Those with an apolipoprotein APOE4 allele (APOE4) have lower C-reactive protein (CRP) than those without APOE4. Whether APOE4 modifies the effects of CRP on rate of all cause dementia, cognitive impairment or Alzheimer's disease (AD) is not established.

Methods—All cause dementia and cognitive impairment without dementia (CIND) was determined over five follow up visits from 1998–2006 in an ongoing cohort of older Latinos. The association between high sensitivity CRP and dementia/CIND, all cause dementia and Alzheimer's disease by APOE4 status was examined in semi-parametric survival models with covariate adjustments.

Results—CRP was significantly lower among those with APOE4 than in those without. Among those with APOE4, CRP was associated with lower rates of combined dementia/CIND (HR: 0.60, 95% CL: 0.20–0.91, $p=0.03$) from a fully adjusted model. Among those with no APOE4, there was no effect of CRP on dementia/CIND rates (HR: 0.94, 95% CL: 0.67–1.33).

Conclusions—Lower CRP in those with APOE4 may reflect immune effects of the APOE4 genotype. Higher CRP in those with APOE4 may be a marker of better immune function, leading to lower rate of dementia and AD.

Keywords

Apolipoprotein E; c-reactive protein; cognitive impairment; dementia incidence; Latino aging

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Disclosure Statement

Mary N. Haan is the principal investigator for this study and conceptualized the design and conduct, supervised data collection, analyzed the data and wrote the paper. Allison E Aiello conceptualized the work to do analyses of c-reactive protein and contributed funding to that end, reviewed paper drafts and contributed interpretation of the findings. William J Jagust conceptualized the study in collaboration with Dr. Haan, supervised diagnoses of cognitive impairment and dementia. Nancy A. West reviewed paper drafts and contributed interpretations of the findings. None of the authors had any conflict of interest related to employment, stock ownership, honoraria, paid testimony, patent applications, grants or other funding. All procedures and approvals required for human subjects' research were obtained from the University of Michigan, the University of California, Berkeley and Davis. The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging

1. Introduction

Serum C-reactive protein (CRP) is widely reported to be associated with increased risk of cardiovascular disease [Ridker, Haughe, 1998] [Ridker, Buring, et al. 1998]. Although immune and inflammatory factors such as CRP may influence the development of dementia and cognitive impairment, research examining the influence on dementia risk of this acute phase reactant has produced varied results [Ravaglia, Forti, et al. 2006] [Dik, Jonker, et al. 2005] [van Oijen, de Maat, et al. 2006]. APOE is often found to modify the effects of exposure on neurodegenerative processes [Haan, Shemanski, et al. 1999]. Recent work in a variety of populations shows that the Apolipoprotein APOE4 allele, a major risk factor for dementia, Alzheimer's and vascular dementia, may modify CRP such that it is lower among carriers of the '4' allele than in non carriers [Judson, Brain, et al. 2004] [van Oijen, de Maat, et al. 2006] [Chasman, Kozlowski, et al. 2006] [Eiriksdottir, Aspelund, et al. 2006] [Marz, Scharnagl, et al. 2004] [Rontu, Ojala, et al. 2006]. Although this suggests that the influence of CRP on dementia rate could vary by APOE4 status, none of the studies of CRP and dementia or cognitive impairment have addressed potential modification of the association between CRP and dementia by APOE4.

The goals of the present analysis are to examine the variation in high sensitivity CRP by APOE genotype, to test the overall association between CRP and incidence of all cause dementia or cognitive impairment without dementia (CIND) and to evaluate whether this association is different in carriers of the '4' allele than in non-carriers.

2. Methods

2.1 Population

The analysis presented here is based on an ongoing cohort study (n=1779) of Latinos aged 60 to 101 at baseline, who are primarily Mexican American in ancestry and were residing in the Sacramento Valley of California when recruited in 1998–99. Details of the recruitment and baseline assessment and the protocols for diagnosing baseline dementia and CIND have been published elsewhere [Haan, Mungas, et al. 2003] [Mungas, Reed, et al. 2004]. Informed consent procedures were followed and approved by the University of California, Davis and the University of Michigan, Institutional Review Boards. The analyses for this paper are restricted to a five year follow up period after baseline (1999–2006) and to those who were free of dementia or CIND at baseline. To date, participants have been evaluated five times since baseline at 12 to 15 months intervals. Those with dementia or CIND at baseline were excluded from these analyses. A total of 1,435 observations were included in this analysis that had complete values for LDL, CRP and APOE lipoprotein. As of the end of the fifth follow-up visit, there were 1,118 people still active in the study, there had been 404 deaths (23%), 153 (9%) refusals (still alive), and 114 (6%) lost to follow up.

2.2 Measurement

Diagnosis of all cause dementia and CIND and Alzheimer's disease—After baseline assessment, the cognitive screening protocol required that referral for further evaluation for participants who declined from the baseline score by more than 3 points (standard error of measurement) on the Verbal Episodic Memory (VEM) test or by more than 8 points on the Modified Minimental State Exam (3MSE) [Mungas, Reed, et al. 2004], and whose current 3MSE or VEM score was <20th percentile on either test. These referrals underwent an expanded neuropsychological test battery and a standard neurological examination by a geriatrician. Case adjudication was done by an expert panel including a neurologist, a geriatrician and a neuropsychologist. Dementia cases were referred for MRI for use in assigning etiology. Cases were classified as demented if they failed one or more cognitive tests on the

battery (including one memory test) at the 10th percentile, were limited in daily independent function as measured by the IQCODE, a standard interview done with informants and were judged by the expert panel to meet DSM IVR criteria for dementia. Alzheimer's disease diagnosis was established using standard criteria from NINDS-ADRDA. Cases were categorized as CIND if they failed ($\leq 10^{\text{th}}$ percentile) one or more cognitive tests after screening but did not meet criteria for dementia. This usually occurred because of impairment in only one cognitive domain or non-memory multi-domain impairment that was judged by the review panel as clinically questionable or insignificant, usually because of maintained daily function. Thirteen (13) dementia cases that were not previously diagnosed by the study were identified from a mortality search that obtained multiple causes from death certificates. These were assigned a diagnosis of dementia after case review using available study records and the year of death was given as the year of diagnosis.

Biomarkers—At baseline, fasting blood was collected from each participant by standard venipuncture into evacuated tubes with and without EDTA. The blood was transported on ice to the Medical Center Clinical Laboratory at the University of California, Davis, for processing within 4 hours of collection and isolated and stored at -80°C until they were analyzed. **CRP.** The Genzyme Diagnostics from Roche Diagnostics (formerly Equal Diagnostics) High sensitivity CRP kit was used for testing the samples which is a latex-enhanced turbidimetric in vitro immunoassay. The actual concentration is determined by interpolation from a calibration curve prepared from calibrators of known concentrations. The Coefficient of Variation (CV) for CRP at QC level 1 (low control) was: Mean = 1.23, SD = 0.09, CV = 7.2%, Range = 0.3 and at QC Level 2 (high control): Mean = 8.74, SD = 0.31, CV = 3.6%, Range = 2.1. These CVs are all below 10% and indicate that the quality of the CRP measurements is quite good. **Low Density Lipoprotein cholesterol (LDL-C):** The LDL-C Direct Liquid Select from Equal Diagnostics (No. 7120) is a homogeneous method for directly measuring LDL-C in serum or plasma, without the need for any off-line pretreatment or centrifugation steps. Inter-assay variations were 3.1% at 110 mg/dL, 2.6 at 155 mg/dL and 2.7 at 205 mg/dL.

Apolipoprotein E—DNA for APOE genotyping was derived from buccal cell swabs 391 participants and from serum samples in 1059 participants, for a total of 1450. Allele frequencies were E23 (n=111), E24 (n=10), E33 (n=1096), E34 (n=171), E44 (n=10), among those who had a CRP result and were not demented or CIND at baseline. There were no participants with a E22. The APOE genotype was in Hardy-Weinberg equilibrium ($p=0.14$).

Other covariates—Type 2 diabetes at baseline was based on a fasting glucose level of >125 mg/dL, use of a diabetic medication and/or self-report of a physician diagnosis. Stroke was based upon a self-report of a physician diagnosis of stroke. A medication inventory is taken in every year where the medication type and dose are recorded from the bottle and coded using the CDC Ambulatory Drug Database system [CDC 2006].

2.2.3 Statistical approach

Incidence rates for all cause dementia and CIND and AD were calculated using an approach in which the cumulative number of cases was the numerator and cumulative person years of follow up were the denominator. Person years were calculated by gender and age group of diagnosis in those with CIND, AD, or dementia, or age at last contact or age at death in those not diagnosed with AD, dementia or CIND. Cases that were judged as CIND before becoming demented were treated as CIND in the combined analysis. CRP was not normally distributed and was log-transformed in multivariate analyses. APOE lipoprotein alleles were combined so that 'any E4' was given a value of '1' and no APOE4 was given a value of '0'.

A series of proportional hazards models were fit using progressive adjustment for covariates. The time variable in these models was the interval between age at baseline and age at diagnosis or censoring. A multiplicative effect modification term was created for APOE4 and CRP. Model fit was tested using the difference between the -2 log likelihood (-2 LL) for each model compared to the next and the Akaike Information criterion (AIC) [Akaike 1974] [Burnham 2002] to judge the overall fit of the model. Covariates were selected based on their influence on the magnitude and statistical significance of the associations of interest and on the fit of the overall model. LDL-C was included in analyses because of its known relationship with APOE and the possibility that the effects of APOE on CRP are mediated by LDL-C. HDL-C and total cholesterol did not differ by APOE status and were not associated with dementia/CIND so were not included in these analyses.

A multiplicative interaction term between baseline age and age at risk was tested and found to improve model fit and was retained in the model. The hazard ratio and 95% confidence limits for the interaction terms were calculated using a published formula [Hosmer 1999] that produced estimates of the effect of CRP on dementia/CIND rates for those with and without APOE4. To evaluate the role of selective survival in these analyses (death compared to dementia/CIND), a proportional hazards model using a competing risk approach was used and the same analyses were repeated. Since this did not change the results, these are not included in detail in this paper.

3. Results

Table 1 shows gender-specific incidence rates for combined dementia/CIND by age group at censoring or failure. There were 104 cases of which 42 were CIND cases and 62 were dementia cases, of which 37 were AD. The overall crude dementia/CIND incidence rate was 12.5 per 1,000 py and the highest rates were among people over age 80. The hazard ratio for gender (women vs. men) was 1.10 (95% CI: 0.77–1.59) from an unadjusted proportional hazards model so gender was not included in further models. Rates are also shown by presence or absence of ApoE4, indicating that the crude rate ratio for dementia or CIND vs. no disease was 70% higher among those with any E4. Dementia/CIND rates by tertile of CRP are shown. Twenty-two percent (22%) of the dementia/CIND cases had any APOE4 allele compared to 13.2% of the eligible sample ($\chi^2_{(1)} p=0.005$).

Approximately 53% of the dementia cases were assigned a diagnosis of Alzheimer's, 14.5% were vascular, 14.5% were mixed vascular and AD, and 17.7% were other dementias (including Lewy body, Frontotemporal Lobar Degeneration and undetermined). For this analysis, all dementias were combined.

Table 2 shows the median and interquartile values for CRP by APOE genotype. These varied such that CRP in participants with any 'APOE4' allele was significantly lower than in those without a '4' allele. Those with '3-4' and '4-4' allele combinations had the lowest CRP levels and those with '3-3' had the highest. CRP was significantly higher in those with type 2 diabetes or stroke at baseline. There was not a significant difference in CRP by dementia/CIND (incident cases) status. Median CRP was lowest in those with dementia/CIND and an APOE4 allele. Figure 1 shows three scatter plots of CRP by the presence of the APOE4, APOE3 or APOE2 genotype.

LDL-C varied by allele combination so that LDL-C was higher in those with a '4' allele. LDL-C did not differ by dementia/CIND status. LDL-C was significantly lower in type 2 diabetics than non-diabetics but there no differences existed for stroke, dementia/CIND or dementia/CIND by APOE4 status. LDL-C and CRP were weakly correlated ($r=-0.10$, $p=.0001$). Among

those with both APOE4 and dementia/CIND, this correlation was higher ($r=-0.28$, $p=0.17$) but not significant.

Table 3 shows the results of a series of three proportional hazards models that tested the association between an interquartile difference for log transformed CRP (1.69) and incidence of dementia/CIND. Table 3 also shows the AIC and $-2\text{Log Likelihood (LL)}$ tests for model fit that compares the current model to the previous model. An interaction term for age at baseline and age at risk was included in all models as this improved model fit. Table 3 also shows the hazard ratio (HR) and 95% confidence limits for the effect of CRP on dementia/CIND in carriers of the '4' allele calculated from the interaction term between CRP. In **Model 1** CRP was not associated with dementia/CIND. In **Model 2**, the addition of an interaction term for any APOE4 and CRP and LDL-C improved the model fit ($p=0.04$ for the interaction term). LDL-C was associated with a increase in rates of dementia/CIND so that an interquartile difference ($\text{LDL-C}=45$) would yield an HR of 1.42 ($p=0.01$). **Model 3** added adjustment for type 2 diabetes and stroke at baseline to Model 2, which did not affect the significance level of the interaction term between APOE4 and CRP. In **Model 3**, among those with a '4' allele, an interquartile difference in CRP was associated with a 40% reduction in rates of dementia/CIND. Among those with no '4', there was no effect of CRP on dementia/CIND. The analyses were restricted to all cause dementia (HR for CRP with $E4=1$: 0.59; 95% CL: 0.24–1.49, $p=$ for interaction = 0.06), and to Alzheimer's cases (HR for CRP with $E4=1$: 0.74, 95% CL: 0.35–0.90, p for interaction = 0.07). Among those without an E4, CRP was associated with increased risk for AD (HR for interquartile difference of CRP: HR: 1.24; 95% CL: 1.29–1.40). Figure 2 displays the survival curves by APOE4 strata, for low vs. high CRP (1.69 is the interquartile range of log transformed CRP).

There was a possibility that selective survival by APOE status might influence these results. However, compared to those without an APOE4, those with an APOE4 were *less likely* to die (12.4% vs. 23.7%), refuse (6.9% vs. 10.1%), or be lost to follow up (5.1% vs. 7.25%). We used a competing risks proportional hazards model to simultaneously estimate the rates of death and dementia/CIND. In a fully adjusted model evaluating the association between APOE4 and either dementia/CIND or death, APOE4 was associated with an increased rate of dementia (HR: 3.14, $p<0.0001$). APOE4 was not associated with mortality (HR: 0.68, $p=0.18$). We also evaluated the interaction between CRP and APOE4 with both dementia/CIND and death in the competing risks model. For the dementia/CIND outcome, CRP remained protective in those with an E4: HR = 0.46 (p for $E4*CRP$ interaction=0.016). For the mortality outcome, the interaction between APOE4 and CRP was not significant ($p=0.18$). Thus, selective survival by APOE4 status does not seem to affect the effects of CRP on dementia/CIND in those with an APOE4 allele.

4. Discussion

We have found that CRP is lower among older Mexican Americans with an 'APOE4' allele for the APOE lipoprotein genotype compared to those without an APOE4. CRP was lowest among those with a '3-4' or '4-4' combination compared to the other allele combinations. Among those with APOE4, *higher* CRP appears to be associated with *lower* rates of combined dementia/CIND, 'all cause' dementia and Alzheimer's disease. Among those without any APOE4, CRP is associated with higher rates for all these outcomes. Adjustment for metabolic disease and stroke at baseline slightly reduced the dementia/CIND rates related to CRP in those with any APOE4 vs. none but had little effect on the association between CRP and AD, which remained statistically significant. The same pattern of results is seen for the 'all cause' dementia group but the association in the fully adjusted model was not significant. There were too few cases of vascular dementia to evaluate this subtype separately.

There have not been any other published studies in this age and ethnic group that address the interaction between CRP and APOE4 with respect to dementia or cognitive outcomes. A recent study by Schmidt reported that elevated CRP was associated with dementia incidence but did not examine the modifying effects of APOE4 on this association [Schmidt, Schmidt, et al. 2002]. Our finding that CRP is lower among those with any APOE4 is consistent with most reports for other populations. Another published study in a population-based study of the association between dementia incidence and CRP [Dik, Jonker, et al. 2005], found no association between CRP and dementia but, in a recent analysis of three CRP genotypes [van Oijen, de Maat, et al. 2006] the authors found one haplotype that was associated with *increased* rate of dementia. This was not evaluated in relation to APOE. Other research relating CRP to cognition [Kuo, Yen, et al. 2005] [Yaffe, Lindquist, et al. 2003] [Dik, Jonker, et al. 2005] [Tilvis, Kahonen-Vare, et al. 2004] [Yaffe, Lindquist, et al. 2003] has produced conflicting results. Elevated CRP has been linked to cardiovascular disease, atherosclerosis and ischemic stroke [Ridker, Haughe 1998] [Kuo, Yen, et al. 2005] [van Dijk, Prins, et al. 2005] which are themselves associated with higher risk of cognitive impairments. We have adjusted for confounding by stroke and diabetes. However, it is possible that there is residual confounding not accounted for in these analyses. We are limited by the number of cases from examining the vascular dementia subtype.

Clinical treatment implications of elevated CRP for vascular outcomes are still controversial, but there is evidence that statins can reduce CRP levels [Ridker, Rifai, et al. 2002]. We found a weak negative overall correlation between LDL-C and CRP that was still negative, but larger, among those with dementia/CIND and APOE4. It is not known whether CRP would be increased by lowering lipids in those with APOE4. Stankovic [Stankovic & Sparks 2006] [Sparks, Sabbagh, et al. 2006] recently reported a lack of effect on CRP in relation to Atorvastatin treatment of dementia patients but that analysis did not consider APOE4 status. A recent small randomized trial of Atorvastatin in AD patients produced some improvement in cognitive function, but this was conditional upon previous statin treatment and no genetic information was considered [Sparks, Sabbagh, et al. 2006]. A recent report from the same study reported that the statin mechanism for neurodegeneration may not be related to reductions in CRP [Stankovic & Sparks 2006].

The evidence presented here provides evidence that individuals with APOE4 have lower CRP levels and that higher CRP levels in those individuals are associated with fewer cognitive deficits. CRP plays an important role in immunological regulation.^{1, 2} Our findings suggest that a deficit in CRP is detrimental among APOE4 positive subjects which might indicate that these individuals are lacking an important component of immune protection [Du Clos 2000] [Du Clos & Mold 2004]. However, the immune mechanism by which CRP may affect neurodegeneration may not be the same pathway by which statin treatment influences neurodegeneration [Eiriksdottir, Aspelund, et al. 2006]. These findings imply that reduction of CRP might be more efficacious against neurodegeneration in those without any 'APOE4'. Colton [Colton, Needham, et al. 2004] addressed the relationship between APOE4, monocyte derived macrophages and an increase in NO production in AD patient compared to age matched controls with APOE 3/3. These findings provide insight into CNS immune mechanism associated with APOE alleles and build upon a growing body of literature showing that APOE may moderate aspects of immunity [Laskowitz, Lee, et al. 2000] [Tenger, Zhou 2003]. One interesting connection between our study and those findings is the fact that CRP has been shown to inhibit NO synthase [Venugopal, Devaraj, et al. 2002]. It is possible that through APOE4 effects on CRP, individuals with lower CRP are at increased risk of higher NO production in the CNS and greater risk of AD. However, our CRP measurements were gathered solely from the periphery, not from CNS and we cannot directly evaluate the effects of CRP on inflammation occurring in the CNS.

The association between CRP and neurodegeneration among APOE4 carriers appears counter intuitive since CRP is often positively associated with vascular disease. However, our study and a number of others have consistently reported lower CRP in those with APOE4. This consistency lends weight to the notion that neurodegeneration associated with CRP may be modified by this genotype. Since APOE is often found to modify the effects of exposure variables on neurodegeneration, it is not very surprising that it operates in this manner here [Haan, Shemanski, et al. 1999]. What requires further examination is the reason why CRP appears to have a protective effect in the presence of a genotype that is generally found to increase neurodegeneration. Higher CRP in those with APOE4 may be a marker of better immune function, hence leading to lower risk of dementia and AD.

There are no other population based studies of dementia incidence in Mexican Americans to which we can compare

Publications by [Tang, Stern, et al. 1998] [Tang, Cross, et al. 2001] refer to Alzheimer's disease not dementia and are concerned with Caribbean Hispanics, not Mexican Hispanics. Mexican ancestry populations differ culturally and genetically from other Spanish speaking populations in the United States. This means that comparison of Mexican ancestry to other 'Hispanic' populations is not as simple as it seems. Although they share a common language, Mexican ancestry populations include significant proportions of Amerindian genetic markers (ranges from 40% to 90%). The percent of European ancestry markers are much higher in 'Hispanics' from the Caribbean (Cuba, Puerto Rico) than from Mexico. Other published data on Mexican ancestry populations largely agrees with our study's lower frequency of both the E2 and APOE4 alleles [Gamboa, Hernandez-Pacheco, et al. 2000] [Aceves, Ruiz, et al. 2006] compared to European ancestry populations. This may reflect the Amerindian ancestry of many Mexican Americans.

The influence of APOE on dementia might vary by race/ethnicity. Evans (2003) reported a 2.73-fold risk of dementia in relation to APOE4 in European ancestry participants living in Chicago. The association between APOE4 and dementia/CIND without taking CRP into account confers an approximately 2.5-fold increased risk in our study. For African ancestry participants, the OR was 1.84 and not significant. Tang [Tang, Stern, et al. 1998] reported no difference in the effect of APOE4 on Alzheimer's for African Americans, Caribbean Hispanics and Caucasians. We could not find any published study that specifically addressed the effect of APOE4 on dementia incidence in people of Mexican ancestry that was done in a population-based cohort study.

CRP does not influence dementia/CIND rates in those without an APOE4. This is consistent with other studies that have examined the effects of CRP without examining the influence of APOE4. CRP appears to confer a lower rate of dementia/CIND only in those with an APOE4. Biochemical pathways, such as NO, that could explain this need to be examined further.

These analyses should be replicated in other race and ethnic populations. Our sample was representative of the eligible population at the time of recruitment. However, they have lower education, greater poverty and higher occurrence of type 2 diabetes than European ancestry populations of the same age. Given the high prevalence of type 2 diabetes in Mexican ancestry populations [Haan, Mungas, et al. 2003], gene by gene interactions might be occurring and so this result might be most relevant for populations at high risk of diabetes.

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Figure 1.
Distribution of hs-CRP by APOE alleles

Figure 2.

Survival to dementia/CIND in participants with or without an APOE4 allele by C-reactive protein level (1,89) from a proportional hazards model including Apoe, log-CRP, age, ldl, diabetes at Baseline and interaction term for Apoe and CRP.

Likelihood ratio: X^2 205.3, $p < 0.0001$ (HR of high vs low CRP for APOE4=1: 0.45: 95% CI: 0.31–.65) (HR of high vs low CRP for E=0, HR: 1.05: 95% CI: 0.85–1.26) (P for interaction of APOE4 and log CRP = 0.016)

Table 1
Incidence rates of CIND and dementia combined through 2006 per 1,000 person years

	Age Groups (at event)	Cases (N)	Rate per 1,000 person years	Person Years (N)	Number in age group	Follow up time (years)
Male	60-69	6	4.7	1275.51	335	3.8
	70-79	14	9.1	1541.72	422	3.7
	80+	19	36.1	526.738	141	3.7
Female	Total CIND/DEM	39	11.7	3343.97	575	5.8
	60-69	7	4.0	1738.51	436	4.0
	70-79	31	12.4	2499.22	593	4.2
APOE4	80+	27	36.9	731.885	225	3.3
	Total # of CIND/DEM	65	13.1	4969.61	828	6.0
CRP tertile	Yes	24	20.7	1157.6	182	6.4
	No	80	11.2	7155.98	1221	5.9
Total	Low	45	15.7	2863.6	478	6.0
	Middle	24	8.8	2732.0	460	5.9
	High	35	12.9	2718.0	465	5.8
		104	13.1	8313.58	1403	5.9

Table 2
C-reactive protein and LDL-C by Apoe lipoprotein and selected covariates at baseline

	Number	C-reactive protein (mg/dL)* Median	25th	75th	Low density lipoprotein (mg/dL)* Mean	SE
Overall	1445	3.3	1.30	7.00	122.60	5.9
APOE Alleles						
2-3	111	3.00	1.00	7.00	108.80	3.25
2-4	10	3.05	1.30	5.80	109.96	10.83
3-3	1102	3.70	1.50	7.40	123.30	1.04
3-4	172	1.75	0.80	4.80	128.40	2.64
4-4	10	1.50	0.30	3.00	138.22	10.83
P value			<0.0001			
Any APOE4	192	1.80	0.80	4.80	127.93	2.5
No APOE4	1258	3.60	1.40	7.40	122.04	0.97
P value			0.006		0.03	
Baseline Diabetes						
No	974	2.90	1.10	6.50	125.80	
Yes	469	4.40	1.80	8.40	116.50	
P value			0.0003			<0.0001
Baseline Stroke						
No	116	3.30	1.30	7.00	122.91	0.94
Yes	1327	4.50	1.80	8.70	121.66	3.20
P value			0.03			0.71
Dementia/CIND (incidence)						
No	1346	3.40	1.30	7.00	123.20	0.94
Yes	104	2.70	1.10	6.70	117.70	3.4
Dementia/CIND by APOE4 status						
Yes, No e4	80	3.6	1.35	7.85	116.59	3.83
Yes, E4	25	1	0.5	3.3	120.90	6.85
No, No E4	1173	3.6	1.4	7.3	122.60	1.01
No, With E4	167	1.9	0.8	5	129.02	2.68
P value			0.54			0.79

Table 3
Association between c-reactive protein (Interquartile range (log) = 1.69) and incidence of dementia/CIND

	Variable	Coefficient	Hazard Ratio	SD	95% LCI	UCI	P-value	AIC	-2 LL
Model 1	C-reactive protein (log) (CRP)	-0.1023	0.84	0.15	0.67	1.22	0.24	1109.6	1103.6
	Age at baseline*age at risk	-1.26	0.28	0.24	0.18	0.45	<.0001		
	Age at baseline	0.013	1.01	0.00	1.01	1.02	<.0001		
Model 2	C-reactive protein (log)	0.0286	1.05	0.17	0.73	1.45	0.78	1095.2	1083.1
	Any APOE4	1.103	3.01	0.27	1.77	5.12	<.0001		5
	LDL	-0.0083	0.99	0.00	0.99	1.00	0.01		
Model 3	CRP*APOE4=1	-0.4408	0.47	0.37	0.31	1.32	0.04		
	CRP*APOE4=0	0.023	1.02	0.00	1.02	1.03	<.0001		
	Age at baseline*age at risk	-1.213	0.30	0.25	0.18	0.49	<.0001		
<i>Calculated HR and 95% CL for interaction</i>									
Model 3	CRP*APOE4=1	0.66	1.05	0.18	0.25	1.01	0.74	1075.4	1059.4
	CRP*APOE4=0	-0.034	0.94	0.18	0.73	1.45	<.0001		
	Age at baseline	1.15	3.16	0.27	1.86	5.36	0.03		
Model 3	CRP*APOE4=1	-0.0071	0.99	0.00	0.99	1.00	0.03		
	CRP*APOE4=0	-0.47	0.45	0.37	0.30	1.30	0.03		
	Age at baseline	-1.202	0.30	0.26	0.18	0.50	<.0001		
Model 3	CRP*APOE4=1	0.013	1.01	0.00	1.01	1.02	<.0001		
	CRP*APOE4=0	0.77	2.16	0.21	1.43	3.26	0.00		
	Baseline stroke	0.91	2.48	0.28	1.44	4.30	0.00		
<i>Calculated HR and 95% CL for interaction</i>									
Model 3	CRP*APOE4=1	0.60	0.60	0.20	0.20	0.91	0.74		
	CRP*APOE4=0	0.94	0.94	0.67	0.67	1.33	0.00		