Published in final edited form as:

Parkinsonism Relat Disord. 2012 March ; 18(3): 274–278. doi:10.1016/j.parkreldis.2011.11.003.

Markers of Inflammation in Prevalent and Incident Parkinson's Disease in the Cardiovascular Health Study

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Abstract

Background—Studies demonstrate existence of inflammation in prevalent Parkinson's disease (PD). We assessed associations of baseline levels of inflammatory markers with prevalent PD at baseline (1989) and incident PD identified over 13 years of follow-up of the Cardiovascular Health Study.

Methods—Blood samples at baseline were measured for fibrinogen, interleukin-6, tumor necrosis factor- α , C-reactive protein, albumin, and white blood cells. The analysis included 60 prevalent and 154 incident PD cases.

Results—Risk of prevalent PD was significantly higher per doubling of IL-6 among women (odds ratio [OR] = 1.5, 95% confidence interval [CI]: 1.0, 2.4) and WBC among men (OR: 2.4, 95% CI: 1.2, 4.9) in multivariate models. Risk of incident PD was not associated with higher levels of any biomarker after adjusting for age, smoking, African American race, and history of diabetes. Inverse associations with incident PD were observed per doubling of C-reactive protein (OR=0.9; 95% CI: 0.8, 1.0) and of fibrinogen among women (OR=0.4; 95% CI: 0.2, 0.8).

Conclusions—Although inflammation exists in PD, it may not represent an etiologic factor. Our findings suggest the need for larger studies that measure inflammatory markers before PD onset.

Keywords

albumins; C-reactive protein; inflammation; interleukin-6; odds ratio; Parkinson's disease; tumor necrosis factor- α

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INTRODUCTION

The inflammatory hypothesis, which has received considerable attention in Parkinson's disease (PD), posits that microglia-activated neuroinflammatory processes are involved in the progressive degeneration of the nigrostriatal pathway in PD [1–2]. Accumulation of inflammatory cytokines such as tumor necrosis factor (TNF) and interleukins (IL) has been observed in experimental animal models of PD and in post-mortem and clinical studies in humans [3–4]. In particular, studies have reported elevated inflammatory cytokines in the cerebral spinal fluid [5] and in plasma of PD patients [6–8]. Because these studies determined cytokine levels in patients with prevalent PD, they cannot rule out the possibility of reverse causation in which inflammatory markers become elevated as a result of the disease. Two recent studies have attempted to determine the predictive value of pre-diagnostic levels of inflammation on future PD risk. In one study [9], investigators observed an association between greater IL-6 concentrations and higher PD risk but found no associations for other markers of inflammation including C-reactive protein (CRP), fibrinogen, or TNF- α . In the other study, higher levels of fibrinogen were associated with higher PD risk among men of Japanese ancestry [10].

In this study, we examined several inflammatory markers in relation to prevalent and incident PD in the Cardiovascular Health Study (CHS). Our aim was to assess whether baseline inflammatory markers are significantly more prevalent among those with PD at baseline, and whether they are associated with increased risk of PD over 13 years of follow-up.

MATERIALS AND METHODS

Subjects

The CHS is a prospective cohort study of coronary heart disease and stroke in adults aged 65 years and older. The CHS recruited 5,888 elderly men and women from four communities in the US. Details about recruitment are described elsewhere [11]. In brief, 5,201 men and women were recruited into the original cohort in 1989–90, and an additional 687 African Americans were recruited in 1992–93. Extensive evaluations were performed at baseline to identify the presence and severity of cardiovascular risk factors. Participants were contacted twice per year for new diagnoses, hospitalizations, and medical procedures. Examinations continued annually from 1989 through 1999, after which telephone follow-up was continued. Reports of hospitalizations were cross-examined in the Health Care Finance Administration records to help enhance surveillance of events and deaths. The institutional review board at each site approved the study methods, and all participants gave written informed consent.

Laboratory analysis

Blood samples were drawn at enrollment after an overnight fast and stored at -70°C using standardized protocols. Methods and quality assurance results for procurement, processing, shipping, storage and sample analysis for albumin, uric acid, creatinine, white blood cell count (WBC), and fibrinogen have been described in detail [12]. IL-6 was measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA) with a coefficient of variation of 6.3% [13–14]. Baseline CRP was measured by colorimetric competitive ELISA developed in the CHS central lab at the University of Vermont [15]. In the final analyses, measures of IL6 were available for 5382 participants, fibrinogen for 5788, albumin for 5808, CRP for 5796, and WBC for 5797.

Outcome Definitions

Detailed methods to define PD in the CHS are described elsewhere [16]. In general, because clinical information to diagnose PD are not available in the CHS and because collection of new data is not possible in the cohort, we developed an algorithm to identify PD in the CHS using available data sources including self-report, an annual inventory of medications, and ICD-9 codes from hospital discharge records. Participants were asked to report a physician diagnosis of PD at the first follow-up examination (at baseline for the African American cohort) and at the 1998–99 (Year 11) examination. The medication inventory, obtained annually, contains information on prescription medications, and was screened for PD medications. Hospitalization discharge codes were abstracted for participants who were hospitalized during follow-up and were screened for ICD-9 code of 332.0. By 2002, 85% of participants in the CHS were hospitalized.

We defined prevalent PD as evidence from any data source at baseline or at first year of follow-up. We defined incident PD as those whose first evidence of PD occurred after the first year of follow-up through 2002. Participants who used parkinsonism-inducing medications before the first evidence of PD were classified as secondary parkinsonism and were not classified as incident PD. To assess disease misclassification, we used a secondary outcome definition in which only participants with corroborating evidence from two or more data sources were considered to have PD. We repeated our analyses after excluding incident PD identified within 5 years of baseline.

Statistical Analyses

Because “date of first evidence of PD” using three disparate data sources provided inaccurate measures of person-time [16], we used unconditional logistic regression as the primary method of analysis from which we obtained odds ratios (OR) and 95% confidence intervals (CI). As a secondary analysis, we repeated our analysis of incident PD using Cox regression models and compared the estimates of association to those obtained in logistic models. We conducted two sets of analysis: for prevalent PD and for incident. In univariate analyses, we used Pearson's χ^2 statistic (categorical variables) and Student's t-test (continuous variables) to compare baseline characteristics with each outcome. In multivariate analyses, we characterized biomarker levels into quartiles based on cutoffs among men and women separately at baseline, and stratified our analyses according to gender. We adjusted all analyses for factors known to be associated with PD such as age and smoking (parameterized as years since quitting smoking), and assessed effects of other potential confounders such as pack-years of smoking, coffee drinking, and baseline uric acid concentration. For incident PD, we additionally adjusted for African American race, and history of diabetes. All analyses for incident PD excluded participants with prevalent PD at baseline. Because baseline creatinine and uric acid levels were not associated with incident PD and did not appreciably alter the estimates in the multivariate model, they were not retained in the final model for incident PD. The models for prevalent PD were additionally adjusted for baseline levels of creatinine and uric acid. The use of NSAIDs at baseline was not related to either prevalent or incident PD. Further adjustment for smoking intensity (pack-years) did not affect the primary association in prevalent PD models; adjustment for smoking intensity and baseline uric acid did not appreciably alter the estimates in incident PD models. We used Wald's test to assess linear trends in the OR associated with quartiles of exposure. For ease of clinical interpretation, we also transformed raw baseline levels of biomarkers using a logarithmic base 2 scale to allow for an estimate of association per doubling of baseline biomarker levels. To minimize the effect of reverse causality on our results, we repeated our analyses of incident PD excluding incident cases identified within 5 years of the baseline. To minimize disease misclassification, we conducted a secondary analysis restricting our definition of incident PD to those with two or more corroborating

data sources. All tests were two-tailed, with a significant level set at $\alpha = 0.05$. We conducted all analyses in Stata [17].

RESULTS

We identified 60 participants who had prevalent PD, and an additional 154 participants who had incident PD over 13 years of follow-up as indicated by at least one data source. Of these 154 participants, 63 (40.9%) had corroborating evidence of PD from two or more data sources. Participants with prevalent PD differed significantly from those without PD (Table 1). Those with prevalent PD at baseline were significantly older, more likely to be men, less likely to be African American, more likely to have a history of diabetes, and had higher mean baseline levels of plasma creatinine, uric acid, CRP, and WBC. Baseline characteristics that were significantly associated with incident PD included male gender and history of diabetes. We observed a weak inverse trend of smoking with both prevalent and incident PD ($P=0.08$). Age-adjusted correlations between biomarkers are summarized in Table 2. The correlations for IL-6, CRP, and fibrinogen were inversely related to baseline albumin levels. Correlations between inflammatory markers and uric acid were only modest.

In multivariate models for prevalent PD (Table 3), women had a 50% increased risk of PD per doubling of baseline IL-6 levels (OR=1.5; 95% CI: 1.0, 2.4). We did not observe any statistically significant associations between IL-6 and prevalent PD among men. For WBC, we observed an 80% higher risk of prevalent PD per doubling of baseline WBC in the pooled analysis, which was primarily influenced by results for men who had a greater than 2-fold likelihood of having PD per doubling of their WBC (OR=2.4; 95% CI: 1.2, 4.9), and displayed a linear trend in estimates of association across quartiles of WBC ($p=0.038$). No association with WBC was observed among women. Although there was a suggestion of increased risk of PD among women with increasing levels of fibrinogen, none of the OR estimates reached statistical significance.

Results for incident PD are presented in Table 4. In the pooled analysis, we observed a significant decreasing linear trend for PD risk from low to high quartiles of baseline CRP ($p=0.03$) as well as a significant 10% reduction in risk per doubling of CRP levels (OR=0.9; 95% CI: 0.8, 1.0). We also observed an inverse association between baseline fibrinogen levels and risk of PD among women, with a significant trend across quartiles of fibrinogen ($p=0.03$) and a significantly decreased risk per doubling of baseline fibrinogen level (OR=0.4; 95% CI: 0.2, 0.8). Associations with fibrinogen levels were not evident among men. Logarithmic estimates for baseline WBC were not clearly significant but suggest a 30–40% higher PD risk per doubling of baseline WBC levels. Unlike for prevalent PD, an association between IL-6 and incident PD was not clearly evident among either men or women. We also observed no clear association for baseline albumin levels and development of PD.

When we restricted our incident PD group to those with two or more corroborating sources, we observed stronger risk estimates associated with a doubling of fibrinogen levels among women (OR=0.2; 95% CI: 0.03, 0.6) and for linear trend in quartiles of CRP ($p=0.023$). Although point estimates for IL-6 moved away from the null, the corresponding confidence intervals did not exclude 1.0 (data not shown). When we excluded 39 incident outcomes within the first five years of follow-up, our results did not change appreciably. However, we continued to observe an inverse association per doubling in fibrinogen levels among women, which remained statistically significant (OR=0.3; 95% CI: 0.1, 0.8).

Results were unchanged when we additionally adjusted our prevalent PD models for pack-years and coffee drinking, and our incident PD models for pack-years, coffee drinking, and

baseline uric acid. Estimates of association obtained by time-to-event analysis using Cox regression models were similar to those obtained from our primary analyses using logistic models (data not shown).

DISCUSSION

For prevalent PD, we observed significantly higher risk among those with higher levels of IL-6, and WBC. We also observed higher risk of prevalent PD per doubling of baseline WBC. For development of PD, clear associations for IL-6 or CRP were not evident. Curiously, we observed that women with higher levels of fibrinogen were significantly less likely to develop PD. A similarly significant inverse association was evident for baseline CRP and incident PD.

Our results for prevalent PD are consistent with the mounting evidence from studies in humans indicating the existence of inflammation among individuals with PD [18–19]. Case series and case-control studies of idiopathic PD and parkinsonism report higher levels of CRP, IL-2, IL-6, TNF- α , fibrinogen, as well as higher markers of humoral immune activity when measured in prevalent disease or post-mortem brain tissue [6–8, 10, 20–22].

Whether inflammation represents an etiologic factor for development of PD remains unclear in light of conflicting evidence. Only two studies have attempted to assess inflammatory markers measured before diagnosis of incident PD. Chen and colleagues conducted a nested case-control study of 84 men with incident PD and 165 matched controls within the Health Professionals Study [9]. They determined that pre-diagnostic levels of IL-6 were linearly associated with higher risk of PD ($p=0.03$) after controlling for age, smoking, caffeine intake, uric acid level and creatinine level. They did not observe associations for PD risk with other inflammatory markers such as CRP, fibrinogen, TNF-R1, and TNF-R2. Results from another recent study of incident PD among Japanese-American men between 76 and 93 years old reported an association between high fibrinogen levels and PD risk [10]. Our results do not suggest that higher levels of IL-6 or fibrinogen are associated with development of PD; on the contrary, men with high levels of CRP and women with high levels of fibrinogen had significantly decreased risk of developing PD in our study. The inverse association we observed among women for high fibrinogen levels in our study does not necessarily conflict with these two previous studies which only included men [9–10]. Additional prospective studies are needed to help reconcile conflicting evidence regarding the role of IL-6 and CRP on risk of incident PD.

One possible explanation for differences in results for IL-6 between our study and that conducted by Chen and colleagues is in the number of years between blood collection and diagnosis of incident PD. Whereas Chen and colleagues reported an average of 4.3 years between blood collection and PD diagnosis with 50% of outcomes occurring after 4 years, participants in our study were identified with PD an average of 10.2 years after blood collection. Because PD has a lengthy latent period, those presumed to have incident PD in the early years of follow-up during a cohort study may, in fact, be prevalent PD cases with disease-associated inflammation. In a nested case-control study of PD such as that conducted by Chen and colleagues, an average of 4.3 years between blood collection and diagnosis of incident PD may not be sufficient to rule out reverse causality. As a result, higher risk associated with higher levels of IL-6 reported by Chen and colleagues may reflect reverse causality in which the underlying pre-diagnostic prevalent disease gave rise to inflammation. When we attempted to reduce the effect of reverse causality on our results, the inverse association with fibrinogen among women persisted, and our conclusions for other biomarkers remained unchanged.

We acknowledge several limitations. First, PD may be misclassified in our study because no neurological exams to diagnose PD were performed [16]. We attempted to reduce disease misclassification by restricting our analysis to those with two or more corroborating sources of evidence for PD. The resulting estimates moved away from the null and stronger inverse associations emerged for certain biomarkers in relation to incident PD. Second, our study had a small sample size would likely not detect more subtle associations that may exist. Despite the even smaller prevalent group, however, significant associations emerged for WBC, fibrinogen, and IL-6. Nonetheless, results from a small study such as this one should be viewed as preliminary and should serve as a platform for future studies. In addition, our results may also be affected by unmeasured or residual confounding. Furthermore, the CHS represents a volunteer survival cohort in which individuals with prevalent disease, by definition, volunteer for the study. As a result, our results may be biased by selection factors. Finally, our results may be influenced by competing risks. Those who died without evidence of PD were classified into the non-PD group. Because inflammatory markers are associated with cardiovascular disease and mortality [23] and because those who died during follow-up may be more likely to be classified as non-PD by Year 13, our results for incident PD may be attenuated towards the null due to this bias.

Although evidence supports the existence of inflammation in PD patients, the precise role of inflammation as an etiologic risk factor remains unclear. The inflammatory response has been deemed a “double edged sword” [19, 24–25], which can have both beneficial and detrimental effects. Activated microglia, which are implicated in aggravating the neurodegenerative process in PD, also secrete a number of neurotrophic factors that promote healing and participate in defense mechanisms, protective responses, and regulation of inflammation [19, 26]. The autotoxic hypothesis suggests that detrimental effects emerge when the concentration and degree of microglial activation overcomes the system’s ability to balance between beneficial and pathologic responses [25], representing a process that has “spiral[ed] out of control” [27]. Finally, the differences in findings between incident and prevalent PD in relation to baseline levels of inflammation underscore the importance of accounting for the timing of exposure in relation to disease during interpretation of results. Given that inflammation is a dynamic process over time and that the latent period of PD is likely a lengthy one, a greater understanding of whether the inflammatory process is an etiologic contributor must come from longitudinal studies of repeated measures of inflammation that precede the onset of disease.

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Table 1

Baseline Characteristics of Prevalent and Incident Parkinson's Disease in the Cardiovascular Health Study, United States, 1989–90.

Characteristic	Prevalent PD at baseline			Incident PD during follow-up		
	PD (n=60)	No PD (n=5674)	P- value	PD (n=154)	No PD (n=5674)	P- value
Age at baseline, n(%)			0.002			0.26
65–74	27 (45.0)	3867 (66.4)		108 (70.1)	3759 (66.3)	
75–85	29 (48.3)	1740 (29.9)		42 (27.3)	1698 (29.9)	
85+	4 (6.7)	221 (3.8)		4 (2.6)	217 (3.8)	
Male sex, n(%)	37 (61.7)	2458 (42.2)	0.002	84 (54.6)	2374 (41.8)	0.002
Education, n(%)			0.26			0.6
<HS	14 (23.3)	1718 (29.6)		42 (27.3)	1676 (29.6)	
HS	14 (23.3)	1606 (27.6)		44 (28.6)	1562 (27.6)	
>HS	32 (53.3)	2487 (42.8)		68 (44.2)	2419 (42.8)	
African American race, n(%)	3 (5.0)	921 (15.8)	0.02	24 (15.6)	897 (15.8)	0.9
Smoking status, n(%)			0.12			0.19
Never	34 (56.7)	2704 (46.4)		75 (48.7)	2629 (46.4)	
Former	21 (35.0)	2423 (41.6)		68 (44.2)	2355 (41.5)	
Current	5 (8.3)	695 (11.9)		11 (7.1)	684 (12.1)	
Total pack-years‡, n(%)			0.21			0.26
Never smoker	34 (56.7)	2704 (48.0)		75 (50.0)	2630 (48.0)	
1 st quartile (0–13)	9 (15.0)	856 (15.2)		22 (14.7)	743 (13.6)	
2 nd quartile (14–27)	3 (5.0)	660 (11.7)		21 (14.0)	675 (12.3)	
3 rd quartile (28–49)	8 (13.3)	515 (9.1)		18 (12.0)	720 (13.1)	
4 th quartile (50)	6 (10.0)	898 (15.9)		14 (9.3)	716 (13.0)	
Years since quitting, n(%)			0.08			0.08
Never smokers	34 (56.7)	2704 (47.0)		75 (49.3)	2629 (47.0)	
30+	7 (11.7)	626 (10.9)		21 (13.8)	605 (10.8)	
20–29	4 (6.7)	579 (10.1)		18 (11.8)	561 (10.0)	
10–19	8 (13.3)	595 (10.4)		15 (9.9)	580 (10.4)	
<10	3 (3.3)	549 (9.6)		12 (7.9)	537 (9.6)	
Current smoker	5 (8.3)	695 (12.1)		11 (7.2)	684 (12.2)	

Characteristic	Prevalent PD at baseline			Incident PD during follow-up		
	PD (n=60)	No PD (n=5674)	P- value	PD (n=154)	No PD (n=5674)	P- value
Coffee Consumption ^a , n(%)	19 (31.7)	1775 (30.5)	0.8	53 (34.4)	1772 (30.4)	0.3
Use of NSAID or ASA, n(%)	12 (20.0)	938 (16.1)	0.4	22 (14.3)	916 (16.1)	0.5
History of diabetes, n(%)	15 (25.0)	938 (16.3)	0.07	36 (23.4)	902 (16.1)	0.015
History of hypertension, n(%)	31 (51.7)	2583 (44.4)	0.25	67 (43.5)	2516 (44.4)	0.8
Biomarkers, mean (SD)						
Plasma creatinine (mg/dl)	1.2 (0.5)	1.1 (0.4)	0.006	1.1 (0.4)	1.1 (0.4)	0.38
Uric Acid (mg/dl)	6.2 (1.9)	5.7 (1.5)	0.01	5.8 (1.6)	5.7 (1.5)	0.6
Inflammatory markers, mean (SD)						
Fibrinogen (mg/dl)	323.8 (67.3)	328.5 (69.9)	0.6	317.8 (65.2)	323.9 (67.4)	0.26
Interleukin-6 (pg/ml)	2.4 (1.9)	2.2 (1.9)	0.4	2.2 (2.2)	2.2 (1.9)	0.8
C-reactive protein (mg/l)	7.1 (16.0)	4.8 (8.2)	0.037	4.1 (8.8)	4.8 (8.2)	0.28
Albumin (g/dl)	4.0 (0.3)	4.0 (0.3)	0.9	4.0 (0.3)	4.0 (0.3)	1.0
WBC ($\times 1000/\text{mm}^3$)	6.3 (2.1)	6.9 (1.9)	0.036	6.9 (1.9)	6.4 (1.6)	0.5

CI, confidence interval; dl, deciliter; g, grams; mg, milligrams; mm, millimeter; n, number; OR, odds ratio; PD, Parkinson's disease; pg, picograms

^a only among original CHS cohort

Age-Adjusted Correlation Coefficients for Baseline Biomarkers Among Participants Without Prevalent PD at Baseline, the Cardiovascular Health Study, United States, 1989–90.

Table 2

	IL-6	CRP	Albumin	WBC	Uric acid	Creatinine
Fibrinogen	0.31 ^a	0.48 ^b	−0.10 ^b	0.21 ^b	0.09 ^b	0.08 ^b
IL-6		0.41 ^b	−0.10 ^b	0.20 ^b	0.15 ^b	0.12 ^b
CRP			−0.16 ^b	0.19 ^b	0.10 ^b	0.07 ^b
Albumin				0.02 ^c	0.10 ^b	0.04 ^a
WBC					0.13 ^b	0.07 ^b
Uric acid						0.37 ^b

^a p < 0.001;

^b p < 0.0001;

^c not significant

CRP, C-reactive protein; IL-6, interleukin-6; WBC, white blood cells,

Association^a between baseline inflammatory markers^b and prevalent Parkinson's disease at baseline in the Cardiovascular health Study

Table 3

	Fibrinogen		Interleukin-6		CRP		Albumin		WBC	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Pooled										
1st quartile	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd quartile	1.3	0.6, 3.1	2.1	0.8, 5.8	1.4	0.6, 2.9	0.4	0.1, 1.1	1.0	0.4, 2.2
3rd quartile	2.0	0.9, 4.1	2.6	1.0, 7.2	1.0	0.5, 2.3	0.6	0.3, 1.1	1.0	0.5, 2.2
4th quartile	1.1	0.5, 2.6	1.5	0.5, 4.5	1.2	0.5, 2.5	0.8	0.4, 1.7	1.7	0.8, 3.6
P trend		0.6		0.6		0.8		0.4		0.1
Per doubling	1.2	0.5, 2.9	1.1	0.8, 1.5	1.1	0.9, 1.3	1.0	0.1, 11.9	1.8	1.0, 3.4
Men										
1st quartile	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd quartile	1.5	0.6, 3.9	1.4	0.4, 4.3	1.8	0.7, 4.6	0.8	0.2, 2.5	0.6	0.2, 2.2
3rd quartile	1.5	0.6, 3.7	1.3	0.4, 4.1	1.3	0.5, 3.6	0.8	0.3, 1.8	0.9	0.4, 2.6
4th quartile	0.8	0.3, 2.3	0.8	0.2, 2.7	0.9	0.3, 2.7	1.0	0.4, 2.1	2.0	0.8, 4.9
P trend		0.7		0.5		0.9		0.7		0.070
Per doubling	0.9	0.3, 2.6	0.8	0.5, 2.3	1.0	0.8, 1.2	0.9	0.1, 20.1	2.4	1.2, 4.9
Women										
1st quartile	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd quartile	0.9	0.1, 6.7	4.2	0.5, 36.2	0.8	0.2, 3.1	--	--	1.5	0.5, 5.1
3rd quartile	3.8	0.8, 17.3	8.7	1.1, 71.1	0.8	0.2, 3.2	0.4	0.2, 1.2	1.1	0.3, 3.8
4th quartile	2.6	0.5, 12.6	4.8	0.5, 44.2	1.9	0.6, 6.0	0.7	0.2, 2.3	1.2	0.3, 4.3
P trend		0.1		0.1		0.3		0.3		0.9
Per doubling	2.5	0.6, 10.8	1.5	1.0, 2.4	1.3	0.9, 1.7	0.9	0.1, 50.9	1.0	0.3, 3.2

^a adjusted for baseline age, years since quitting smoking, African American race, history of diabetes, baseline creatinine, baseline uric acid

^b cutoffs for pooled quartiles determined among entire cohort at baseline for fibrinogen (<281, 281–310, 311–361, 361), IL-6 (<1.1, 1.1–1.7, 1.7–2.5, 2.6), CRP (<1.26, 1.26–2.54, 2.54–4.6, 4.6), albumin (<3.8, 3.8–3.9, 4.0–4.1, 4.2), WBC (<5.1, 5.1–5.9, 6.0–7.1, 7.2); cutoffs for quartiles for men determined among men at baseline for fibrinogen (<270, 270–311, 311–361, 361), IL-6 (<1.27, 1.27–1.79, 1.80–2.73, 2.74), CRP (<1.21, 1.21–2.32, 2.33–4.28, 4.29), albumin (<3.8, 3.8–3.9, 4.0–4.1, 4.2), WBC (<5.0, 5.1–6.0, 6.1–7.1, 7.2); cutoffs for quartiles for women determined among women at baseline for fibrinogen (<285, 285–313, 314–361, 361), IL-6 (<1.09, 1.09–1.62, 1.62–2.47, 2.48), CRP (<1.32, 1.32–2.65, 2.66–4.83, 4.84), albumin (<3.8, 3.8–3.9, 4.0–4.1, 4.2), WBC (<5.0, 5.0–5.9, 6.0–7.0, 7.1)

Association^a between baseline inflammatory markers^b and incident Parkinson's disease over 13 years of follow-up in the Cardiovascular health Study

Table 4

	Fibrinogen		Interleukin-6		CRP		Albumin		WBC	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Pooled										
1st quartile	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd quartile	0.6	0.4, 1.0	1.1	0.7, 1.7	1.4	0.9, 2.2	0.7	0.3, 1.2	1.0	0.6, 1.7
3rd quartile	1.0	0.7, 1.5	0.9	0.6, 1.6	0.7	0.4, 1.2	0.8	0.5, 1.2	1.3	0.8, 2.0
4th quartile	0.7	0.4, 1.1	0.8	0.5, 1.3	0.7	0.4, 1.2	1.0	0.6, 1.6	1.4	0.9, 2.2
P trend	0.4		0.3		0.030		0.8		0.1	
Per doubling	0.7	0.4, 1.3	1.0	0.8, 1.1	0.9	0.8, 1.0	0.9	0.2, 4.2	1.3	0.9, 2.0
Men										
1st quartile	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd quartile	0.6	0.3, 1.2	0.8	0.4, 1.5	1.4	0.8, 2.4	0.4	0.2, 1.0	1.1	0.5, 2.3
3rd quartile	1.2	0.7, 2.2	0.8	0.4, 1.6	0.5	0.3, 1.1	0.8	0.4, 1.3	1.2	0.7, 2.3
4th quartile	1.2	0.7, 2.2	0.7	0.4, 1.5	0.6	0.3, 1.3	0.9	0.5, 1.7	1.5	0.8, 2.9
P trend	0.3		0.5		0.035		0.8		0.2	
Per doubling	1.4	0.9, 1.4	0.9	0.7, 1.3	0.9	0.7, 1.0	0.4	0.1, 3.3	1.4	0.9, 2.4
Women										
1st quartile	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference	1.0	Reference
2nd quartile	0.6	0.3, 1.2	1.3	0.7, 2.6	1.5	0.8, 2.9	1.0	0.5, 2.1	1.0	0.5, 2.0
3rd quartile	0.9	0.5, 1.6	1.1	0.5, 2.2	1.1	0.5, 2.1	0.9	0.5, 1.5	1.4	0.7, 2.6
4th quartile	0.4	0.2, 0.8	0.7	0.3, 1.6	0.9	0.5, 2.0	0.9	0.5, 1.9	1.3	0.6, 2.6
P trend	0.03		0.4		0.6		0.7		0.3	
Per doubling	0.4	0.2, 0.8	0.9	0.6, 1.3	1.0	0.8, 1.1	1.4	0.2, 14.4	1.3	0.7, 2.4

^a adjusted for baseline age, years since quitting smoking, African American race, history of diabetes

^b cutoffs for pooled quartiles determined among entire cohort at baseline for fibrinogen (<281, 281–310, 311–361, 361), IL-6 (<1.1, 1.1–1.7, 1.7–2.5, 2.6), CRP (<1.26, 1.26–2.54, 2.54–4.6, 4.6), albumin (<3.8, 3.8–3.9, 4.0–4.1, 4.2), WBC (<5.1, 5.1–5.9, 6.0–7.1, 7.2); cutoffs for quartiles for men determined among men at baseline for fibrinogen (<270, 270–311, 311–361, 361), IL-6 (<1.27, 1.27–1.79, 1.80–2.73, 2.74), CRP (<1.21, 1.21–2.32, 2.33–4.28, 4.29), albumin (<3.8, 3.8–3.9, 4.0–4.1, 4.2), WBC (<5.0, 5.1–6.0, 6.1–7.1, 7.2); cutoffs for quartiles for women determined among women at baseline for fibrinogen (<285, 285–313, 314–361, 361), IL-6 (<1.09, 1.09–1.62, 1.62–2.47, 2.48), CRP (<1.32, 1.32–2.65, 2.66–4.83, 4.84), albumin (<3.8, 3.8–3.9, 4.0–4.1, 4.2), WBC (<5.0, 5.0–5.9, 6.0–7.0, 7.1)