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Dietary inflammation factor rating™ system and risk of Alzheimer's disease in elders

Yian Gu, PhD[1], **Jeri W Nieves, PhD**[2,3], **Jose A Luchsinger, MD, MPh**[1,3,4,5], and **Nikolaos Scarmeas, MD, MS**[1,4,6]

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

[2] Clinical Research Center, Helen Hayes Hospital, Route 9W, West Haverstraw, NY, 10994, United States

[3] Department of Epidemiology, Columbia University, New York, NY

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

[5] Department of Medicine, Columbia University, New York, NY

[6] Department of Neurology, Columbia University, New York, NY

Abstract

It has been suggested that inflammation is involved in Alzheimer's disease (AD) pathogenesis. The aim of this study is to evaluate the association between inflammatory aspects of diet and incident AD risk. 2258 non-demented elderly (age ≥ 65) in New York who provided dietary information at baseline were followed-up prospectively for AD development. We examined the composite total Inflammation Factor Rating (tIFR), as a measure of inflammatory impact of foods, in relation with (i) serum level of high-sensitivity C-reactive protein (hsCRP) and (ii) risk of incident AD using Cox proportional hazards model. The tIFR was not associated with serum hsCRP level. After an average of 4.0 years of follow-up, 262 subjects developed incident AD. The tIFR was not associated with AD risk: compared to the lowest tertile of tIFR (most pro-inflammatory), HRs (95% CI) for the highest tertile (most anti-inflammatory) was 0.97(0.69–1.35) (*p*-for-trend=0.84), in the adjusted model. We conclude that tIFR might not be a biologically relevant measure of the inflammatory impact of the diet. Additionally, although it remains possible that tIFR might be related with some other aspects of inflammation not captured by hsCRP, lack of association with AD risk suggests its limited clinical utility.

Keywords

Alzheimer's disease; Dementia; Diet; Inflammation; Epidemiology; Cohort Studies

1. Introduction

There is growing evidence from observational studies that dietary factors are related to the risk of Alzheimer's disease (AD) (1). AD is caused by the deposition of amyloid β in the brain, and inflammation, oxidative stress, vascular and metabolic diseases have been

Corresponding author: Nikolaos Scarmeas, MD, MS, Columbia University Medical Center, 622 W 168th St., PH 19th floor, New York, NY 10032, Phone: 212-342-1350, Fax: 212-342-1838, ns257@columbia.edu.

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suggested as potentially important in the pathogenesis of AD (2). Thus, the diet-AD association could be mediated via any of the above biological pathways.

The role of inflammation in the etiology and pathology of AD has been supported by several lines of evidence (3–6). An association between inflammatory markers and performance on cognitive function tests (7–10) or AD risk (11–15) has been reported in a number of population-based studies.

At the same time, various dietary factors have been shown to either retard or promote inflammation. For instance, the western-type dietary pattern has been found to be positively associated with pro-inflammatory markers including C-reactive protein (CRP) and IL-6 (16–17), while reduced levels of pro-inflammatory markers were found in people adhering to a Mediterranean-type diet (18–23). This is important since, in our study population, higher adherence to the Mediterranean type diet has been found to reduce the risk of AD (24).

Taken together, there has been cumulative evidence suggesting a potential association between inflammation and AD risk on one hand, and dietary factors and inflammation on the other hand. Collectively, this evidence supports the hypothesis that the protection of dietary factors against AD could be partly explained by their effect on reducing inflammation. Intake of anti-inflammatory foods or diet is therefore oftentimes claimed to be able to help prevent AD. However, the inflammatory impact of foods on risk of incident AD has never been directly examined, which may be partly due to the difficulty in measuring the overall inflammatory impact of foods. Measuring the overall inflammatory impact of foods, however, has been made possible recently with the introduction of the Inflammation Factor Rating (IFR) system(25). Nevertheless, whether the IFR of foods correlate with inflammatory biomarkers and whether it can be of any predictive value for diseases, has never been scientifically evaluated.

In this study, we evaluated the validity of the IFR by examining its relationship with a known inflammatory marker, high-sensitivity CRP (hsCRP), in the Washington Heights-Inwood Columbia Aging Project (WHICAP) population. Furthermore, we examined the inflammatory impact of foods, as measured by IFR, on risk of incident AD in the WHICAP population.

2. Materials and Methods

2.1 Study population

The study included participants of two related cohorts recruited in 1992 (WHICAP 1992) and 1999 (WHICAP 1999) which were identified (via ethnicity and age stratification processes) from a probability sample of Medicare beneficiaries residing in an area of 3 contiguous census tracts within a geographically defined area of northern Manhattan (26). At entry, a physician elicited each subject's medical and neurological history and conducted a standardized physical and neurological examination. Each subject also underwent a structured in-person interview including an assessment of health and function and a neuropsychological battery (27). The neuropsychological battery contained tests of memory, orientation, abstract reasoning, language, and construction. Subjects were followed at intervals of approximately 1.5 years, repeating the baseline examination and consensus diagnosis at each follow-up. 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.

The process for diagnosing AD patients has been previously reported (28). Briefly, a consensus diagnosis for the presence or absence of dementia was made at a diagnostic

conference of neurologists and neuropsychologists where information of all the above evaluations was presented. Evidence of cognitive deficit, evidence of impairment in social or occupational function, and evidence of cognitive and social-occupational function decline as compared to the past were the criteria used for the diagnosis of dementia as required by the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R). The type of dementia was subsequently determined. For the diagnosis of probable or possible AD, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (29) were used. Dietary data were not available to the consensus panel and were not considered in the diagnostic process.

2.2 Dietary data

Dietary data regarding average food consumption over the year before the baseline assessment was obtained using a 61-item version of Willett's semi-quantitative food frequency questionnaire (FFQ) (Channing Laboratory, Cambridge, MA) (30) administered by trained interviewers. FFQs have been used and validated for the determination of nutrient intake in the elderly (31). The validity and reliability of various components of the FFQ in WHICAP have been previously reported, with intraclass correlations generally above 0.3 (26,32–33). Responses of the 61 food items were converted from "portions/day" into "grams/day". As recommended by Willet and Stampfer (34), we regressed caloric intake (measured in kilocalories) and calculated the derived residuals of daily gram intake for each food to get "gram residuals/day".

The Inflammation Factor Rating (IFR) system has recently been introduced in a book to the general population as a tool to measure the inflammatory impact of more than 1600 foods (see also http://www.nutritiondata.com/) and as a guide to plan an anti-inflammatory diet (25). The IFR is formulated by taking into account the effects of more than 20 nutritional factors (including amount and type of fat, essential fatty acids, vitamins, minerals and antioxidants, glycemic index, and anti-inflammatory compounds) that determine a food's inflammatory or anti-inflammatory potential (25).

The IFR per portion size ("IFR/portion") has a wide range of values without upper or lower limits. An IFR of 0 indicates a neutral food, negative values a pro-inflammatory food, and positive values an anti-inflammatory food, with a higher number corresponding to a stronger effect (Table 1). For example, fish (3–5oz) ranks the highest (IFR= 300) among all the foods included in FFQ, followed by spinach or collard greens (IFR=246 per ½ cup), cooked carrots (IFR=131.8 per ½ cup), raw carrots (IFR=60 per ½ cup), and yellow squash (IFR=54 per ½ cup). Baked potatoes is the most pro-inflammatory as it has the lowest IFR (−255.5 per 1 cup), followed by rice or pasta (IFR= −237 per 1 cup), carbonated beverage with sugar (IFR= −215 per can), french fried potatoes (IFR= −213 per 4 oz), and candy without chocolate (IFR= −168 per 1 oz) (Table 1). We further converted "IFR/portion" into "IFR/grams". Hence, a calorie-adjusted IFR could be calculated by multiplying "gram residuals/day" by "IFR/grams".

The composite daily total IFR (tIFR) was generated for each participant by summing the IFRs of food items consumed, with higher tIFR indicating a more anti-inflammatory diet. If several food components, with different IFRs, were listed as a single food item in the questionnaire, the average IFR of the food components was assigned to the food item. For example, 1 tsp of regular butter and 1 tsp of whipped butter have −45 and −25 IFR, respectively, so −35 was assigned to the food item "butter". A total of 9 of 61 food items were excluded from the tIFR calculation due to the following reasons: (i) Subtypes of the foods that have very wide range of IFRs, making it difficult to assume an average IFR value (yogurt, yams or sweet potatoes, cold breakfast cereal, and punch). For example, the IFR for

½ cup of baked yams is −52, while it is +228 for ½ cup of sweet potatoes. (ii) The IFR is zero (coffee, beer, wine, and liquor) or not available (low calorie carbonated beverage).

2.3 Covariates evaluation

Information about age at baseline (years), enrollment time (enrolled in 1992 as reference), gender (men as reference), ethnicity (including White, Black, Hispanic, and others, with White as reference), education (years), smoking status at baseline (no smoking as reference), and body mass index (BMI, weight in kilograms divided by height in square meters [kg/m^2]) was obtained from baseline or follow-up interviews. Caloric intake (kilocalories [kcal]) and alcohol consumption (non-drink [0 gram/day] or heavy-drink [>30 gram/day] vs. moderate-drink intake [>0 and ≤30 gram/day], with moderate drink as the reference) were calculated from the FFQ. Apolipoprotein E (APOE) genotypes were determined using the method of Hixson and Vernier (35) with some modification (36), and was used as a dichotomous variable: absence of (as reference) vs. presence of either 1 or 2 ε4 alleles. A modified version (37) of the Charlson Index of Comorbidity (38) (hereafter referred to as ‘medical comorbidity index’) was included as a continuous variable, with a higher index indicating more comorbid diseases.

2.4 hsCRP measurement

Baseline plasma hsCRP level was measured using ELISA (Diagnostic systems laboratories, INC, Webster, Texas) in a total of 1172 subjects (52% of the analytic sample), who had frozen plasma samples available. The assay sensitivity was 1.6 ng/ml, the inter-assay coefficient of variation (CV) was 11.7%, and the intra-assay CV was 4.6%.

2.5 Statistical analysis

Characteristics of study subjects were compared according to tertiles of tIFR, using Chi-square test for categorical variables, and linear regression model for continuous variables by entering tIFR tertiles into the model as an ordinal independent variable.

To evaluate whether the tIFR of foods was associated with circulating levels of a standard systemic inflammatory marker, hsCRP (39), Spearman correlation analysis was run between tIFR and hsCRP in the subset where hsCRP was available.

To evaluate whether the tIFR was associated with risk of AD in the WHICAP population, Cox proportional hazards models were used with AD as the dichotomous outcome. The time-to-event variable was time from recording of baseline diet to first visit of AD diagnosis for incident cases, or to the time of the last follow-up for subjects who did not develop dementia. The exposure-of-interest was the baseline tIFR evaluated as a continuous variable or in tertiles. Tests for trend were evaluated by entering the tertile terms as an ordinal variable in the COX model. Each model was simultaneously adjusted for: age, enrollment time, gender, ethnicity, education, smoking status, BMI, alcohol drinking, caloric intake, medical comorbidity index, and APOE genotype. All variables were used as time-constant covariates. The proportional hazard assumption for Cox models were satisfied based on the martingale residuals method(40).

A sensitivity analysis was done by repeating the above analysis using a re-calculated tIFR that also included the following four food items: yogurt (IFR= −65 per 1 cup), yams or sweet potatoes (IFR= 88 per ½ cup), cold breakfast cereal (IFR=−128 per 1 cup), and punch (IFR= −104 per 1 glass). The IFRs for these four food items were calculated by taking an average of all available subtype ratings (25). We also performed analyses using the highest (e.g. +228 for ½ cup of ‘yams or sweet potatoes’), or the lowest (e.g. −52 for cup of ‘yams or sweet potatoes’), subtype rating as the IFR for each of the four food items.

All the analyses were performed using SPSS 16.0 (SPSS Inc.).

3. Results

The description of the study population has been previously reported (24). The sample for the analyses included 2258 subjects after excluding 527 subjects with missing dietary information, 24 with incomplete dietary information, and 627 lost to follow-up (1037). Compared with subjects with available dietary information, subjects with missing dietary information (n = 527) had slightly lower education (9.1 vs. 9.9 years; p = 0.001), higher proportions of dementia (17.5 vs. 11%; p < 0.001) and higher mortality (32 vs. 18%; p < 0.001).

After an average of 4.0 (±3.0; range, 0.2–13.9) years follow-up, 262 subjects developed incident AD. Compared with subjects who remained without dementia, incident AD cases were older ($p<0.001$), less educated ($p<0.001$), had a lower BMI ($p=0.005$), and were more likely Hispanics and less likely Whites ($p<0.001$) (24).

The median tIFR was −6.9 (inter-quartile range −111.2 ~ 119.8). According to Table 2, subjects who had higher tIFR (more anti-inflammatory) tended to be younger and better educated, were more likely to be enrolled in 1999, were more likely to be White or Black and less likely to be Hispanic, were less likely to be current smokers, and were more likely moderate alcohol drinkers.

Compared with subjects who had blood sample and thus had hsCRP measured (n = 1172), subjects who did not have blood sample available (n = 1086) were slightly older (76.3 vs. 78.1 years; p < 0.0001), had lower education (10.5 vs. 9.5 years; p < 0.0001), had lower total caloric intake (1477 vs. 1377 kCal, p<0.0001), and had more medical comorbidities (1.9 vs. 2.0; p =0.005); were less likely to be White (White 31%, Black 30%, Hispanic 38%, Other 2% vs. White 24%, Black 36%, Hispanic 39%, Other 1%; p < 0.0001); and were more likely to be APOE ε4 carriers (25% vs. 31%; p = 0.01). The tIFR was not associated with serum hsCRP level (Table 2), in the subsample of 1172 people with available serum samples.

The tIFR was not associated with AD risk when all the subjects were considered together. Hazard ratios (HRs, 95% CI) for the highest tertile was 0.97 (0.69–1.35) (p for trend =0.84) when compared to the lowest tertile, after adjusting for age, enrollment time, gender, education, ethnicity, smoking status, BMI, alcohol drinking, caloric intake, medical comorbidity index, and APOE genotype (Table 3).

Sensitivity analyses (adjusted for age, enrollment time, gender, education, ethnicity, smoking status, BMI, caloric intake, medical comorbidity index, and APOE genotype) with tIFR calculated including estimated average values for yogurt, yams or sweet potatoes, cold breakfast cereal, and punch showed similar results: the HRs (95% CI) for the middle and highest tertiles were 0.81 (0.59–1.12) and 0.94 (0.67–1.33), respectively, when compared to the lowest tertile (p for trend =0.62). The results did not change materially if the highest or the lowest subtype rating was assigned to the entire food item (data not shown).

4. Discussion

In this prospective study, we found the tIFR, an index summarizing the inflammatory impact of foods, was not associated with serum hsCRP level, suggesting that tIFR might not be a biologically relevant measure of the inflammatory impact of the diet (although association with aspects of inflammation not captured by hsCRP cannot be excluded). Our results also showed that the tIFR was also not associated risk of AD, adding confidence that tIFR is neither valid nor clinically significant measure of dietary inflammation.

Diet has been linked to circulating inflammation markers in many studies (16–22,46), and CRP is viewed as a marker of systemic inflammation (39). Therefore, tIFR, designed to reflect the inflammatory impact of diet, should be associated with the circulating CRP level. However, our data showed that the tIFR was not associated with serum hsCRP level. The lack of correlation between IFR and hsCRP might be because tIFR may not be a biologically relevant measure of inflammation, or because tIFR may not be well measured, either due to deficits in the IFR formula design or due to the brevity of the FFQ. Nevertheless, the examination of the association between IFR and hsCRP was examined in only a subset of the study population and may have limited power. In addition, as a non-specific inflammatory marker, circulating CRP level may be affected by a variety of other factors such as genetic background, medication use, and underlying unrecognized infections or other diseases (47), so the additional effect on CRP exerted by inflammatory impact of foods might be too small to be detected. Finally, to fully evaluate the validity of tIFR, future studies should extend the analysis to other inflammatory biomarkers such as IL-1, IL-6 or tumor necrosis factor-α, which might be more sensitive to the inflammatory effect of diet than CRP (16,23).

Although tIFR was not associated with serum level of hsCRP, as discussed above, tIFR might be related with other unmeasured aspects of inflammation. According to our results, tIFR was also not associated with risk of AD. While the lack of association between IFR and AD does not necessary indicate that the inflammation impact of foods is not associated with AD, it at least suggests possible aspects of inflammation captured by tIFR, if any, are not associated with AD risk, indicating a limited predicting value of tIFR.

This study has several limitations. First, the exact formula of calculating the inflammation factor for each food is not provided in the reference and the inflammation factor system has never been backed by peer-review scientific publication. The FFQ was not able to capture all foods with IFRs, several foods included in our FFQ had to be excluded from the calculation, and a few assumptions were made during the calculation. However, sensitivity analysis were performed after assuming values of IFRs for four foods that were originally excluded, and the results based on the new tIFR did not change materially. The validity for some of the FFQ elements is low and error in dietary assessment may be another explanation for the null associations. In prospective studies, however, misclassification of exposure due to limited accuracy in assessing diet using FFQ or in calculating tIFR can usually be assumed to be non-differential with respect to disease status or to covariates used to adjust the multivariate risk for AD, so the measurement error may actually bias the magnitude of the association toward null(48). Participants lacking dietary information were less educated, had higher proportions of dementia and higher mortality. Participants lacking blood specimens were older, were less educated, were less likely to be White, and had lower total caloric intake and more medical comorbidities. Although we considered these demographic and clinical factors in our models, we cannot exclude the possibility of selection bias. The analysis of the relationship between tIFR and hsCRP was based on a relatively small number of subjects. The study does not have repeated measurements of hsCRP. However, it has been shown that circulating levels of CRP are quite stable within individuals over a period of 3 years (49).

Our study has many advantages. To our knowledge, this is the first study to directly examine the inflammatory impact of foods on risk of incident AD. The study utilized the most comprehensive list of the IFR values. An important strength of the study is that it is a prospective cohort study with the diet information collected before AD diagnosis, thus ensuring a temporal sequence of exposure and disease. The diagnosis of AD took place in a University hospital and was based on comprehensive clinical and neuropsychological assessment and standard research criteria by individuals with expertise in dementia. We

believe that valid outcome assessment may have reduced measurement error and increased the study power. Finally, measures for multiple potential AD risk factors have been carefully recorded and adjusted for in the analyses. Nevertheless, residual confounding cannot be completely ruled out as an explanation of our findings.

In summary, we found that tIFR was not associated with serum level of hsCRP, nor was it associated with risk of AD, suggesting that tIFR might be neither a biologically relevant measure of the inflammatory impact of the diet, nor a valid clinical measure in relation to AD risk. Future studies are warranted to further explore other measures of dietary inflammation and to test whether diet-related inflammatory mechanisms might be important in AD.

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Abbreviations

APOE	Apolipoprotein E
BMI	body mass index
IFR	inflammation factor rating
CI	confidence interval
CV	coefficient of variation
HR	Hazard ratio
hsCRP	high-sensitivity C-reactive protein
SD	standard deviation
FFQ	food frequency questionnaire
WHICAP	Washington Heights-Inwood Columbia Aging Project

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Table 1

IFR per portion size of food items in FFQ

Food Item in FFQ	Average IFR
Fish (3–5 oz)	300
Spinach or collard greens, cooked (1/2 cup)	246
Carrots, cooked (1/2 cup)	131.8
Carrots, raw (1/2 cup or 2–4 sticks)	60
Yellow (winter) squash (1/2 cup)	54
Broccoli (1/2 cup)	51
Nuts (small packet or 1 oz)	36.7
Cabbage, cauliflower or brussels sprouts (1/2 cup)	27.7
Tomatoes (1, or small glass of juice)	22
Other fruits, fresh, frozen or canned (1/2 cup)	15.7
Processed meats, e.g. sausage, salami, bologna (one slice or piece)	9.7
String beans (1/2 cup)	9.5
Bacon (2 slices)	4.5
Tea (1 cup)	1
Peanut butter (1 tbsp)	0.25
Cottage or ricotta cheese (1/2 cup)	−2.7
Beef, pork or lamb as a sandwich or mixed dish e.g. stew, casserole, etc (4–6 oz)	−3.6
Beef, pork or lamb as a main dish e.g. steak, roast, ham etc (4–6 oz)	−6
Beans or lentils, baked or dried (1/2 cup)	−8
Liver (3–4 oz)	−9
Oil and vinegar dressing e.g. Italian (1 tbsp)	−11
Peas or lima beans (1/2 cup fresh, frozen, canned)	−12.7
Other cheese (1 slice or 1oz serving)	−17
Margarine (pat, i.e. 1 tsp)	−17.5
Orange (1fresh)	−19
Chocolate (1 oz)	−19
Skim or low fat milk (8oz glass)	−27
Butter (pat, i.e. 1 tsp)	−35
Cookie (1)	−38
Egg (1 large)	−43
Whole milk (8oz glass)	−44
Apple fresh; Pear (1 fresh)	−63.9
Dark bread (slice) including wheat pita bread	−68.5
Orange juice (small glass); Grapefruit juice (small glass)	−72
Peach; Apricot; Plum (1 fresh, ½ cup canned)	−73.7
White bread (slice) including pita bread	−75.5
Corn (1 ear or 1/2 cup frozen or canned)	−88

Food Item in FFQ	Average IFR
Chicken or turkey with skin (4–6 oz)	−100
Potato chips or corned chips (small bag or 1 oz)	−110
Cake (slice)	−114
Ice cream (1/2 cup)	−115.6
Banana (1fresh)	−118
Hot dog (1)	−121
Chicken or turkey without skin (4–6 oz)	−129
Hamburger (1)	−144
Pie, readymade (slice)	−146
Pie, homemade (slice)	−165
Candy without chocolate (1 oz)	−168
French fried potatoes (4 oz)	−213
Carbonated beverage with sugar (e.g. Coke) (1 can)	−215
Rice or pasta (1 cup)	−237
Potatoes, baked, boiled (1) or mashed (1 cup)	−255.5

Table 2

Characteristics of study subjects and serum level of hsCRP according to tertiles of tIFR*

		tIFR Tertiles			
	Total	**Lowest**	**Middle**	**Highest**	***p* value†**
	(N=2258)	(N=791)	(N=746)	(N=721)	
Age (years), mean (SD)	77.2 96.6)	77.7 (6.7)	77.1 (6.4)	76.7 (6.5)‡‡	0.003
Enrolled in year 1999, N (%)	1221 (54)	343 (43)	390 (52)‡	488 (68)‡‡, ‡	<0.0001
Gender, N (%)	1526 (68)	522 (66)	502 (67)	502 (70)	0.31
Education < 10 years, N (%)	1097 (49)	441 (56)	368 (49)‡	288 (40)‡‡, ‡	<0.0001
Ethnicity, N (%)					
White	622 (28)	199 (25)	212 (28)‡	211 (29)‡‡, ‡	
Black	734 (33)	211 (27)	243 (33)‡	280 (39)‡‡, ‡	
Hispanic	866 (38)	347 (47)	279 (37)‡	213 (30)‡‡, ‡	
Other	36 (1.6)	7(0.9)	12 (1.6)‡	17 (2.4)‡‡, ‡	<0.0001
Current smoker, N (%)	278 (12)	102 (13)	106 (14)	70 (9.7)‡‡, ‡	0.03
Moderate alcohol drinker, N (%)	720 (32)	213 (27)	236 (32)‡	271 (38)‡‡, ‡	<0.0001
BMI (kg/m^2), mean (SD)	27.4 (5.6)	27.2 (5.3)	27.6 (6.0)	27.5 (5.4)	0.36
Daily caloric intake (kcal), mean (SD)	1428 (520)	1473 (5620)	1302 (469)	1510 (498)	0.29
Medical comorbidity index, mean (SD)	1.9 (1.4)	1.9 (1.4)	1.9 (1.4)	2.0 (1.4)	0.36
APOE-ε4+, N (%)	538 (28)	213 (31)	165 (26)	160 (26)	0.08
hsCRP (mg/L), median (inter-quartile range)	5.4 (2.8–14.0)	5.9 (3.0–14.8)	5.0 (2.5–13.3)	5.4 (3.1–14.2)	0.43

*N, number of subjects; BMI, body mass index; APOE, Apolipoprotein E; hsCRP, high-sensitivity C-reactive protein.

†*p* values were obtained from chi-square test for categorical variables, and from univariate linear regression model by treating the continuous variables as dependent variables and tIFR tertiles as a single ordinal independent variable. Pair-wise comparisons among the 3 groups were further performed for variables with a significant omnibus test, using Least Significant Difference post-hoc tests in ANOVA for continuous variables, or pair-wise chi-square tests for categorical variables.

‡p<0.05 for *post hoc* comparison between the middle and lowest tertiles of tIFR.

‡‡p<0.05 for *post hoc* comparison between the highest and lowest tertiles of tIFR.

‡p<0.05 for *post hoc* comparison between the highest and middle tertiles of tIFR.

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Table 3

HR (95% CIs) of incident AD associated with composite daily total inflammation factor rating (tIFR)

Model*	Number of AD cases/at risk	Tertiles of tIFR				Continuous tIFR	
		Tertiles	HR (95% CI)	*p*	*p*-trend	HR (95% CI)	*p*
Model 1†	260/2215	Lowest	reference				
		Middle	0.80 (0.59–1.07)	0.13			
		Highest	0.92 (0.68–1.26)	0.62	0.47	0.94 (0.81–1.11)	0.47
Model 2†	219/1759	Lowest	reference				
		Middle	0.82 (0.58–1.14)	0.23			
		Highest	0.97 (0.69–1.35)	0.84	0.71	0.99 (0.99–1.00)	0.37

*The sum of non-demented and incident AD is smaller than all subjects combined (i.e., n = 2,258) because 32 subjects who experienced development of dementia other than AD, and 4 subjects who were censored before the earliest event in a stratum are not included. Additional 7 and 463 subjects were excluding in Model 1 and Model 2, respectively, due to missing values in covariates.

†Model 1†: adjusted for age, enrollment time, gender, education, and ethnicity.

Model 2†: adjusted for covariates in Model 2 & smoking status, BMI, alcohol drinking, caloric intake, medical comorbidity index, APOE genotype.

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