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Letter to the Editor

Overall and Gender-specific Associations between C-reactive Protein and Stroke Occurrence: A Cross-sectional Study in US

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Dear Sir:

C-reactive protein (CRP), a marker of systemic inflammation, has been proposed to increase the risk of stroke, a common cardiovascular disease, in multiple cross-sectional and prospective studies.[1,2] While, a few reports found CRP had no apparent value for stroke predictions.[3] Furthermore, the gender-specific associations between CRP concentration and stroke occurrence are not well clarified. We used data collected from the National Health and Nutrition Examination Survey (NHANES), a large representative US national dataset, to testify the overall and gender-specific associations between CRP level and stroke prevalence.

NHANES has a complex multistage sample design to provide a nationally representative sample of the non-institutionalized US general population. We conducted our study based on the public-access data of adults aged 20 years or older from 1999-2010 NHANES dataset. All participants provided written informed consent and the National Center for Health Statistics Research Ethics Review Board approved all protocols. The subjects were considered to have stroke if they answered "yes" to the question "Has a doctor or other profession ever told you have a stroke?". Those with answer of "don't know" or incomplete answers were excluded from our study. The subjects were categorized into high CRP group (CRP > 3 mg/L) and normal CRP group (CRP ≤ 3 mg/L). Age, race/ethnicity, body mass index, low-density lipoprotein cholesterol, diabetes and smoking status were included as covariates in our study, and they were adjusted in multivariate models because they are regarded as traditional stroke risk factors. Data are summarized as mean (standard deviation) or median (interquartile range) in the case of continuous variables and as percentages in the case of categorical variables. Logistic regression analyses were used to explore the relationship of higher CRP concentration and the strengths of the association were estimated by odds ratios along with their corresponding 95% confidential intervals (CIs). In addition, population attributable fractions were computed to determine the proportion of stroke occurrence attributable to higher CRP level. All analyses were performed by Stata software, version 14.1 (Stata Corp, College Station, TX). All tests were 2 tailed, and a P value < 0.05 was considered statistically significant.

A total of 32,408 participants were enrolled in our study, including 15,495 men and 16,913 women. The overall prevalence of stroke is 4.0% (1,284/32,408). Baseline characteristics of the participants are presented in Table 1. According to the multivariate logistic analysis, higher CRP concentration is related to greater odds of stroke in the overall population (odds ratio = 1.38; 95% CI: 1.11-1.71; P = 0.004). Multivariate analyses stratified by gender revealed a non-significant association between higher CRP level and stroke in males (odds ratio = 1.32; 95% CI: 0.97-1.79; P = 0.079). While, the association remained significant in females (odds ratio = 1.42; 95% CI: 1.04-1.94; P = 0.026). In the overall population, 13% of stroke was attributable to higher CRP concentration (95% CI: 0.04-0.21). However, the population attributable risk of elevated CRP for stroke was not significant in male, with population attributable fractions of 10% (95% CI: -0.02-0.20). Removal of higher CRP level was

Table 1. Basic characteristics of participants.

Factors	Males (n = 15,495)	Females (n = 16,913)	Total (n = 32,408)
Stroke (%)	4.1	3.8	4.0
C-reactive protein (CRP), mg/L [median (IQR)]	1.7 (3.1)	2.8 (5.2)	2.2 (4.2)
Age, year [median (IQR)]	50.0 (31.0)	48.0 (32.0)	49.0 (31.0)
Race/ethnicity (%)			
Non-Hispanic White	20.0	20.2	20.1
Non-Hispanic Black	6.6	7.5	7.1
Mexican American	49.3	47.8	48.5
Other Race	19.8	20.0	19.9
Other Hispanic	4.3	4.5	4.4
Body mass index, kg/m^2 [median (IQR)]	27.5 (6.6)	27.8 (9.0)	27.7 (7.7)
Low-density lipoprotein cholesterol, mg/dL [median (IQR)]	117.0 (46.0)	114.0 (47.0)	115.0 (47.0)
Diabetes (%)	15.3	13.5	14.3
Smoking status (%)			
Current smoker	25.8	18.0	21.7
Former smoker	31.8	20.1	25.7
Non smoker	42.4	61.9	52.6

IQR, interquartile range.

linked with 16% of stroke risk reduction in females (95% CI: 0.01-0.28).

Our findings of the overall association between CRP level and risk of stroke are in line with several previous reports. In a large US case-cohort study, the highest CRP category was associated with an increased risk of stroke by a 1.87-fold.[4] A similar association was noted in a US cohort study, with a 3.08-fold of stroke occurrence in elevated CRP group.[5] However, the correlation was not significant in a prospective study, which was conducted in the Netherlands.[3] It is still uncertain whether the differences of the association are due to geography, genetic or hormone level, which need further explorations. It is noteworthy that increased CRP was a significant risk factor of stroke among women rather than men, which was confirmed in our multivariate logistic analysis results and further supported by population attributable fractions analysis results. Our findings are consistent with several prior studies. The Framingham study observed that the highest quartile CRP level was linked with significant increase of ischemic stroke or transient ischemic attack among females (risk ratio = 2.1; 95% CI: 1.19-3.83), whereas the association disappeared among males (risk ratio = 1.6; 95% CI: 0.87-3.13).[6] In another cohort study, the risks of cardiovascular diseases associated with CRP concentration were greater for females than for males (risk ratio: 1.60 vs. 1.07).[7] A similar pattern was also confirmed by comparison of the association strengths of two cohort studies that were conducted in females and males, respectively (risk ratio: 5.5 vs. 2.8).[8,9] While, a Chinese study revealed that gender modified the association in an opposite way. They observed elevated CRP had significant effect on male instead of females subjects.[10] Inconsistent findings of the gender differences may be partly due to hormone and/or genetic distinctions among women and men, although the underlying mechanisms are still unclear and require deeper investigations.

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