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C-Reactive Protein and Cardiovascular Disease in East Asians: A Systematic Review

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ABSTRACT: Elevated C-reactive protein (CRP) levels are associated with an increased risk of cardiovascular disease (CVD) in Caucasians; however, evidence is lacking for East Asians, who have low CRP levels. PubMed and Google Scholar searches were conducted (1966 through September 2014), and eight prospective studies in East Asian countries (China, Hong Kong, Japan, Korea, Macao, Mongolia, and Taiwan) that documented risk ratios of elevated CRP for CVD were included for meta-analysis with random-effects models. The overall association between CRP levels and stroke was significant in six studies (risk ratio = 1.40 [95% confidence interval {CI}, 1.10–1.77], $P = 0.008$). The association with ischemic stroke was more evident in subgroup analyses. For coronary heart disease (CHD) and CVD, the risk ratio was 1.75 (95% CI, 0.96–3.19, $P = 0.07$) and 1.76 (95% CI, 1.29–2.40, $P < 0.001$), respectively. Although East Asians have low CRP levels, this meta-analysis shows that elevated CRP levels were significantly associated with an increased risk of stroke, primarily ischemic stroke.

KEYWORDS: C-reactive protein, cardiovascular disease, East Asia, systematic review

SUPPLEMENT: Inflammation, Atherosclerosis and Coronary Artery Disease

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Introduction

The inflammatory hypothesis states that endothelial cell damage promotes atherogenesis, linking the complex inflammatory process with cardiovascular events.[1,2] Among several parameters of inflammation, C-reactive protein (CRP) measurements have great benefits from the viewpoints of cost and quality. Considerable evidences, including data from clinical intervention trials, also confirm that CRP measurements are useful for identifying individuals at high risk for cardiovascular disease (CVD).[3,4]

To date, a meta-analysis has documented strong evidence for adding CRP measurements to the measurement of traditional risk factors for predicting coronary heart disease (CHD). The prediction model that included CRP levels indicated a better fit in comparison with a common model using the Framingham risk score. A US clinical guideline concluded that CRP assessment was beneficial in a clinical setting for detecting high-risk individuals.[3]

Regardless of such a favorable recommendation, aggregated evidence is lacking for Asian individuals. In particular, East Asian populations have low levels of CRP and lower rates of CHD[5,6] compared with Western populations.[7] The meta-analysis included some Asian cohorts, but the overall analysis concealed the Asian characteristics when the data were pooled.

The difference in CRP levels among varied ethnic groups was substantial; therefore, it may not be acceptable to apply the findings from most Western countries to Asian individuals.

Methods

Data sources and searches. We searched the PubMed database for prospective cohort studies of CRP and CVD between 1966 and September 2014 with the following MeSH terms: C-reactive protein, cohort studies, cardiovascular diseases, and Far East. Publications were limited to those written in English. We also examined recent articles published in 2014 from a search of Google Scholar ($n = 270$).

Study selection. Inclusion criteria for this analysis were as follows: (1) cohort study, including nested case–control study, (2) community-based study in East Asian countries (China, Hong Kong, Japan, Korea, Macao, Mongolia, and Taiwan), and (3) study to estimate the association between CRP and CVD outcomes in adults, defined as incidence or mortality with long-term follow-up. All studies were required to measure standardized CRP by immunoassay. We excluded studies carried out in clinical settings to evaluate the prognosis of diseases or the effect of medications and studies that were conducted with Asian immigrants in the US or other Western countries.

Data extraction and quality assessment. Three researchers evaluated articles in accordance with the inclusion criteria mentioned above. First, after skimming the title and abstract of articles retrieved from the database search, the researchers initially selected the primary articles. Second, potential articles for meta-analysis were retrieved on the basis of evaluation of the full text of the paper. Quality assessment was carried out based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[8] All the selected articles adequately defined outcomes and mentioned the study design, and each had a sufficient follow-up period.

Data synthesis and analysis. Most studies provided hazard ratios or odds ratios for stroke, CHD, and CVD outcomes grouped in accordance with tertiles, quartiles, or quintiles of CRP distribution after adjustment for established CVD risk factors. Although cut-off points differed among studies, we used the risk ratios published in the articles because they appeared to be similar among homogeneous Asian populations. When studies provided only sex-specific associations, we calculated summarized risk ratios that combined both sexes using the fixed-effect model in each study.

We calculated the I^2 statistics to evaluate the statistical heterogeneity among the studies. We used random-effect meta-regression to evaluate the overall association between CRP and CVD and presented risk ratios and 95% confidence intervals (CIs) stratified by outcomes. The publication bias of selected articles was tested by using funnel plots and the Egger test. All analyses were conducted with Review Manager (RevMan) 5.0 software.

Results

Search results and study inclusion. Our searches retrieved 208 PubMed citations and 2 Google Scholar citations. In all, 22 of them met our inclusion criteria without duplicates (Fig. 1). We excluded 14 articles after a more detailed evaluation, and finally, 8 articles were acceptable for the meta-analysis.[9–16]

The remaining articles were excluded primarily because they described studies that were performed in a clinical setting

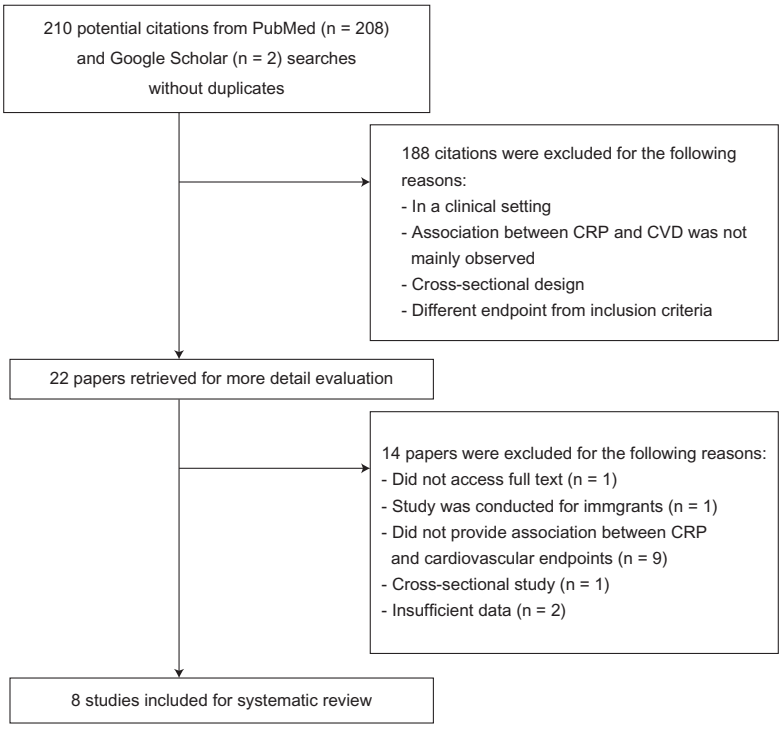

Figure 1. Flow of study selection.

($n = 91$). The aim of studies was not different from this review purpose ($n = 85$). The study outcomes were not CVD onset or mortality, or the study design was cross-sectional ($n = 12$). Though two studies met the inclusion criteria, it was difficult to include them in the meta-analysis, because one was conducted only in men[17] and another large population study used a different cut-off point for CRP compared with the other studies, and the distribution of CRP and the incidence of stroke were heterogeneous.[18]

Of the selected articles, 5 were about the Japanese, 1 about the Chinese, 1 about the Taiwanese, and 1 about the Korean population (Table 1). Of these studies, three provided sex-specific risk ratios for CVD, which were combined into a risk ratio for both sexes with a fixed-effects model.

CRP levels among populations. Figure 2 shows the CRP levels (median/geometric mean) among the populations we included for meta-analysis. Most median levels of CRP were very low (less than 1 mg/L).

CRP and CVDs outcomes. The overall association between elevated CRP levels and stroke was significant using the random-effects model with the six stroke studies (risk ratio = 1.39 [95% CI, 1.09–1.77], $P = 0.008$) (Fig. 3). We did not find significant heterogeneity of effect among the studies ($I^2 = 32\%$, $P = 0.19$). Only one study measured mortality as an outcome, but the association was unchanged if the study was excluded from the analysis. Regarding CHD, the random-effects association was not significant, with wide CIs, when including four studies (risk ratio = 1.75 [95% CI, 0.96–3.19], $P = 0.07$). There was significant heterogeneity of effect ($I^2 = 72\%$, $P = 0.01$). The risk ratio for CVD was 1.76 (95% CI, 1.29–2.40, $P < 0.001$), and we found no heterogeneity of effect ($I^2 = 49\%$, $P = 0.14$) among studies.

Of the six stroke studies, four studies that were carried out in Japan provided risk ratios by subtype of stroke (Fig. 4). The subgroup analysis revealed that the overall risk ratio of elevated CRP was increased primarily for ischemic stroke (risk ratio = 1.40 [95% CI, 1.08–1.81], $P = 0.01$) and was not increased for hemorrhagic stroke (risk ratio = 1.04 [95% CI, 0.66–1.65], $P = 0.85$), although the heterogeneity of their risk ratios was not significant ($I^2 = 16.9\%$, $P = 0.27$).

Discussion

Main findings. The meta-analysis confirmed that elevated CRP levels were significantly associated with an increased risk of stroke among East Asian populations, primarily for ischemic stroke. The association with CHD was likely to be the same, though the studies were few, and it did not reach a statistically significant level ($P = 0.07$). Despite lower average levels of CRP in Asians compared with Caucasians, individuals in the highest quartiles or quintiles of CRP were at increased risk of CVD.

Previous meta-analyses among US or European studies reported a strong association of elevated CRP levels with CHD, ischemic stroke, cardiovascular mortality, and death

Table 1. A summary of studies in East Asian cohorts included in the analysis.

OUTCOME	STUDY	SURVEY YEAR, SAMPLE SIZE, LOCATION	STUDY DESIGN	CONTROLLED VARIABLES	ENDPOINT	RISK RATIOS AND 95% CIS
Stroke	Wakugawa et al, 2006[13]	1988 n = 2,692 Japan	Cohort	Age, SBP, ECG abnormalities, diabetes, BMI, TC, HDL, smoking, alcohol drinking, and physical activity.	Incidence	3.11 (1.04–9.32) in men and 1.34 (0.61–2.91) in women for ischemic stroke; and 0.68 (0.21–2.26) and 1.74 (0.51–5.85) for hemorrhagic stroke, respectively, grouped in the highest vs the lowest quintiles.
	Iso et al, 2009[11]	1988–1990 n = 39,242 Japan	Nested	Age, BMI, hypertension, hyperlipidemia, smoking, and drinking status.	Mortality	1.60 (0.90–2.85) in men and 1.07 (0.58–1.97) in women for total stroke; 2.04 (0.95–4.37) and 1.00 (0.39–2.61) for ischemic stroke; and 1.85 (0.40–8.72) and 1.78 (0.61–5.22) for hemorrhagic stroke, respectively, grouped in the highest vs the lowest quartiles.
	Jiang et al, 2009[16]	1998–2001 n = 2,919 China	Cohort	Age, sex, SBP, DBP, diabetes, TC, HDL, BMI, and smoking.	Incidence	1.58 (1.08–2.31) of CRP >2.0 mg/dl for total stroke in both sexes.

(Continued)

Table 1. (*Continued*)

OUTCOME	STUDY	SURVEY YEAR, SAMPLE SIZE, LOCATION	STUDY DESIGN	CONTROLLED VARIABLES	ENDPOINT	RISK RATIOS AND 95% CIS
	Chen et al, 2009[15]	1994–1995 n = 3,602 Taiwan	Nested	Age, sex, waist circumference, TC, history of hypertension, history of diabetes.	Incidence	2.63 (1.06–6.53) for total stroke in both sexes grouped in the highest vs the lowest tertiles.
	Chei et al, 2011[10]	1984–2001 n = 13,521 Japan	Nested	Age, sex, community, SBP, antihypertensive medication, BMI, smoking, alcohol intake, TC, TG, and GLU	Incidence	1.49 (0.93–2.41) for total stroke; 1.57 (0.85–2.91) for ischemic stroke; and 1.39 (0.60–3.19) for hemorrhagic stroke in both sexes grouped in the highest vs the lowest quintiles.
	Iso et al, 2012[12]	1990–1993 n = 29,876 Japan	Nested	Age, sex, community, SBP, antihypertensive medication, BMI, smoking, alcohol intake, TC, lipid-lowering medication and GLU.	Incidence	0.93 (0.71–1.23) for total stroke; 1.19 (0.82–1.73) for ischemic stroke; and 0.70 (0.46–1.04) for hemorrhagic stroke in both sexes, grouped in the highest vs the lowest quartiles.
Coronary heart disease						
	Arima et al, 2008[9]	1988 n = 2,589 Japan	Cohort	Age, sex, SBP, ECG abnormalities, diabetes, BMI, TC, HDL, smoking, alcohol intake, and regular exercise.	Incidence	2.98 (1.53–5.82) in both sexes grouped in the highest vs the lowest quartiles.
	Jiang et al, 2009[16]	1998–2001 n = 2,919 China	Cohort	the same as the above	Incidence	1.13 (0.70–1.83) of CRP >2.0 mg/dl for coronary heart disease in both sexes.
	Iso et al, 2009[11]	1988–1990 n = 39,242 Japan	Nested	the same as the above	Mortality	3.68 (1.02–13.3) in men and 3.74 (0.91–15.3) in women grouped in the highest vs the lowest quartiles.
	Iso et al, 2012[12]	1990–1993 n = 29,876 Japan	Nested	the same as the above	Incidence	1.02 (0.58–1.72) in both sexes grouped in the highest vs the lowest quartiles.
Cardiovascular disease						
	Jiang et al, 2009[16]	1998–2001 n = 2,919 China	Cohort	Same as above	Incidence	1.39 (1.04–1.87) of CRP >2.0 mg/dl for coronary heart disease in both sexes.
	Iso et al, 2009[11]	1988–1990 n = 39,242 Japan	Nested	Same as above	Mortality	2.31 (1.49–3.59) in men and 1.69 (1.06–2.68) in women grouped in the highest vs the lowest quartiles.
	Sung et al, 2014[14]	2002–2009 n = 268,803 Korea	Cohort	Age, sex, BMI, smoking, alcohol intake, regular exercise, history of hypertension, history of diabetes, history of coronary heart disease, glucose, LDL, HDL, and SBP.	Mortality	3.48 (1.71–7.10) in men and 0.92 (0.28–3.00) in women grouped in the highest vs the lowest quartiles.

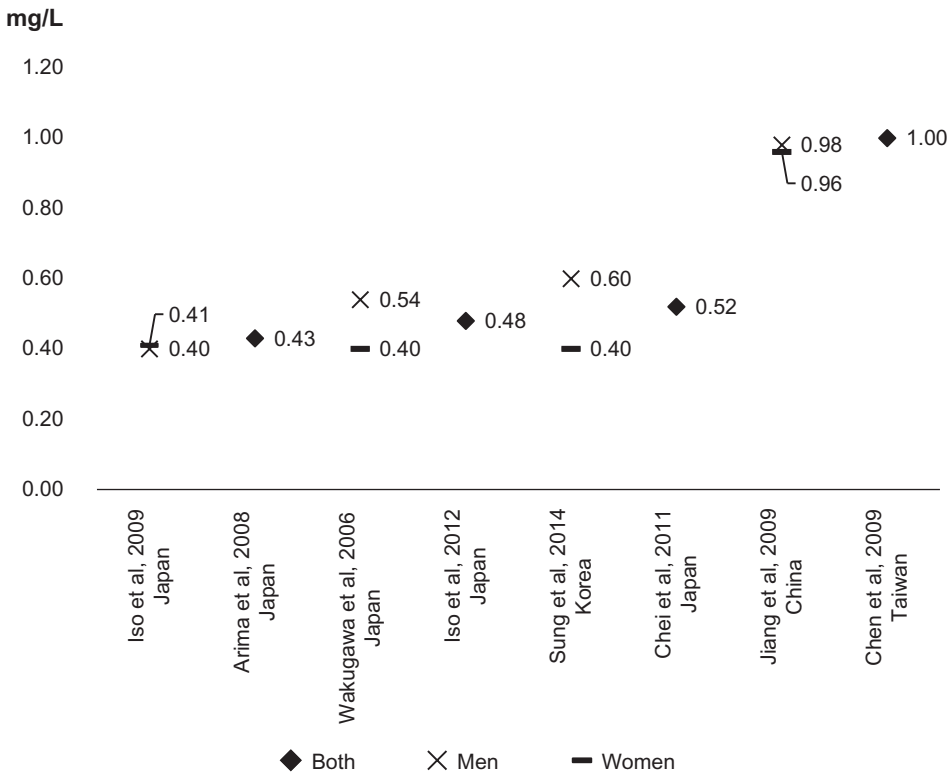

Figure 2. CRP levels among selected Asian studies.

from cancer.[4] The results of our systematic review were almost consistent with those in Caucasian populations.

Stroke is the most common disease among CVD events in Japan. It is well known that Japan is one of the countries with the highest stroke incidence, mainly because of hypertension and high salt intake, regardless of obesity.[6] The explanations associated with frequent incident stroke and traditional risk factors and trends among Japanese adults have been reviewed elsewhere. Moreover, of the six studies we included in the present analysis, four showed risk ratios by stroke subtype, ie, ischemic stroke and hemorrhagic stroke. The association of CRP was more evident for ischemic stroke and was not apparent for hemorrhagic stroke. The findings implied that increased CRP levels are linked with atherosclerosis and thrombosis that are closely related to obesity and the metabolic syndrome.[1]

Ethnic differences in CRP levels and cut-off points. When compared with previous findings from various studies, the level of CRP in Asian populations was approximately one-third of the median value in Caucasians.[5] As shown in Figure 2, it seemed to be true that East Asian individuals had low levels of CRP, and that in most populations, the levels were less than 1 mg/L. CRP levels varied among East Asian populations and were relatively higher in Chinese individuals compared with Korean and Japanese individuals. Some polymorphisms were reported to determine the CRP concentrations in the Chinese population[19,20]; however, it was unclear why CRP concentrations were higher in Chinese individuals. Although CRP levels in Chinese individuals were still low when compared with those in Caucasians, the heterogeneity among Far East countries might be caused by factors related to genetics, lifestyle, or environmental conditions.

The majority of studies in Western countries reported CRP average levels more than 1 mg/L, and the levels varied greatly among ethnic groups. For example, the Women's Health Study reported that median CRP values in black women (2.96 mg/L) were significantly higher than in Hispanics (2.06 mg/L), whites (2.02 mg/L), and Asians (1.12 mg/L) in the US.[21] The Dallas Heart Study also pointed out significant race and gender differences in the population distribution of CRP levels, with the highest median values in black women (3.5 mg/L).[22]

The Asian studies in the present meta-analysis set up quartile or quintile levels of CRP as cut-off points to evaluate risk ratios for CVD, corresponding with approximately 1 mg/L of CRP. This implied that CRP levels >1.0 mg/L were associated with an increased risk of CVD in the Asian population.[18]

The Multiethnic Study of Atherosclerosis (MESA) study investigated CRP levels across four ethnic groups living in the US.[23] In that study, the median CRP levels of Chinese men and women were 0.80 and 0.99 mg/L, respectively, which were roughly consistent with the baseline data we found in the present study. This fact indicated that CRP levels in Asians who live in the Far East might be essentially equal to those in Asians who live in the US. Therefore, CRP levels were greatly influenced by ethnic background, and the cut-off

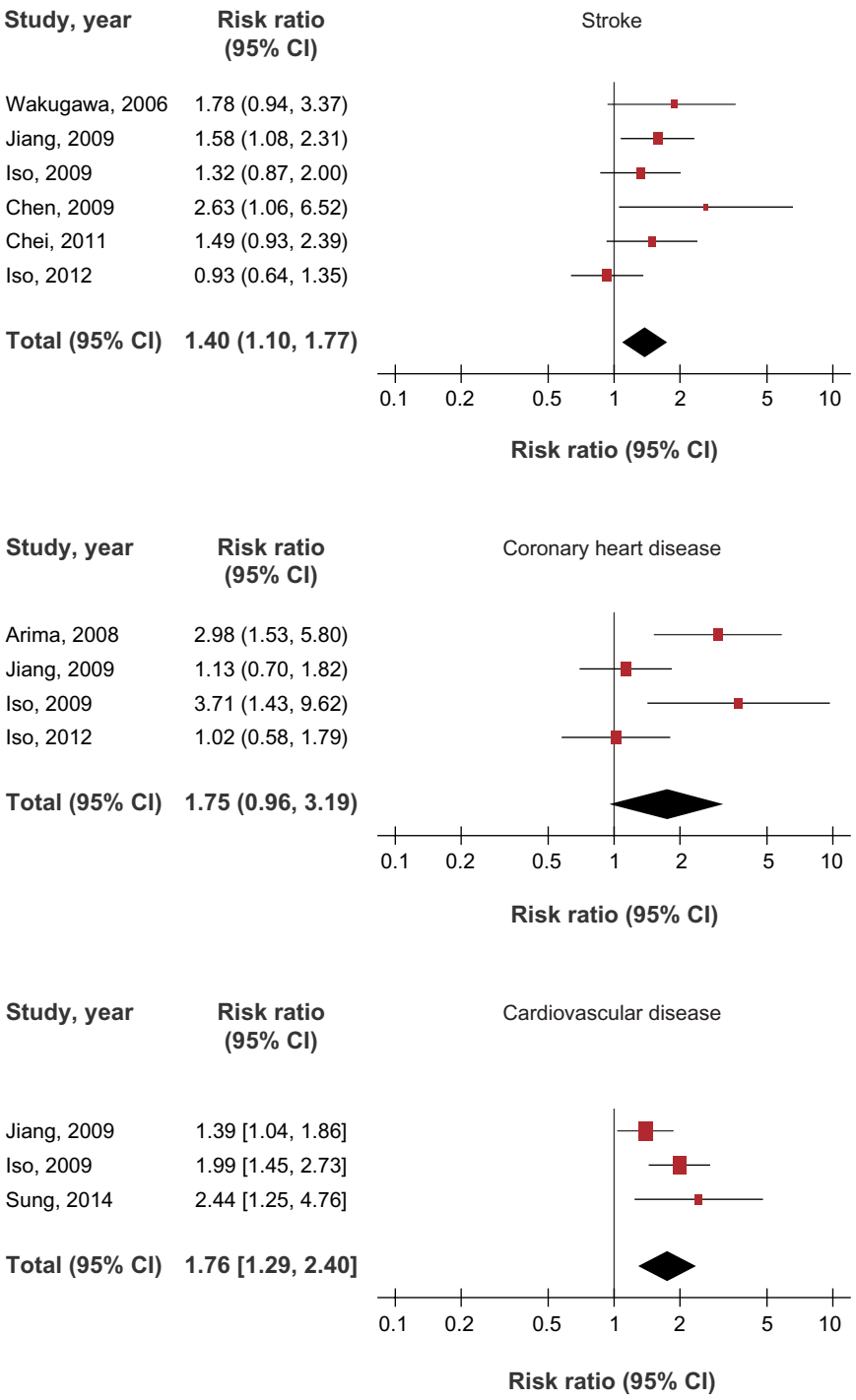

Figure 3. Risk ratios for stroke, CHD, and CVD with increased CRP levels.

points to detect high-risk individuals should be considered based on ethnicity.

Potential mechanism. It was established that CRP levels were closely related to obesity in various populations.[24,25] This may to a large extent explain the fact that CRP levels in Asians with higher BMI levels were very low in comparison with Caucasians with higher BMI levels. It is considered that adipose tissue in obesity overproduces proinflammatory cytokines, such as tissue necrosis factor (TNF)-α and interleukin (IL)-6, which stimulate hepatic CRP production. Furthermore, TNF-α in adipose tissue also inhibits insulin-stimulated autophosphorylation of the insulin receptor and causes insulin resistance.[26] Ouchi et al suggested a mechanism by showing that CRP mRNA is expressed in adipose tissue and is inversely related to adiponectin mRNA expression.[27] These mechanisms potentially connect obesity with increased CRP concentrations.

Recently, several genomic variants that reflected CRP concentrations were studied across ethnic groups.[28,29] The contributions of these genetic variants were not large enough to explain

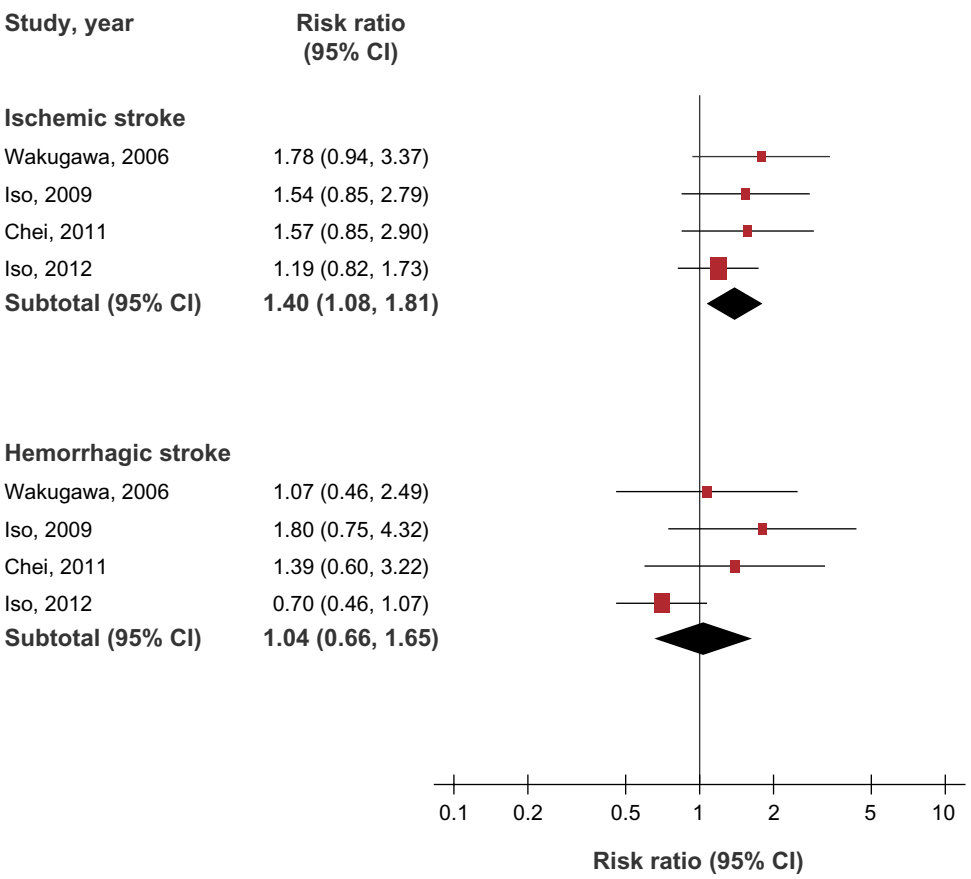

Figure 4. Subgroup analysis according to stroke subtypes.

the entire difference thus far, but low CRP concentrations in Asia may be in part a result of the genetic variants.[30]

Limitations. Although this systematic review demonstrated a significant association between CRP levels and CVD in Asians, several limitations should be noted. First, we cannot exclude a publication bias, because the funnel plot was asymmetrical and cohort studies in Asians were very limited. In particular, evidence was very scant to determine an association with CHD events. Second, the risk ratios in each study were calculated with different cut-off points, which might cause bias in estimating the true risk ratio of elevated CRP. Pooled analysis is potentially essential to determine the cut-off point of CRP for CVD prevention. Third, we did not find a sex-specific effect of CRP, because data were not available to find it in this analysis. Some studies documented a difference in the effect between men and women, and the accumulation of further evidence is desired to look at sex differences. Fourth, although risk ratios derived from various cohort studies were adjusted for established CVD risk factors, we will have to investigate whether adding the measurement of CRP levels is valuable in Asians compared with the established prediction models.[31]

Conclusion

Although East Asian adults had very low levels of CRP, a meta-analysis confirmed that elevated CRP levels were significantly associated with an increased risk of stroke, primarily ischemic stroke.

Although it is unclear whether adding CRP measurements to the measurements of traditional risk factors for predicting CHD is beneficial for Asian individuals, original evidence is urgently needed.

Author Contributions

Conceived and designed the experiments: IS. Analyzed the data: KM, EE. Wrote the first draft of the manuscript: IS. Contributed to the writing of the manuscript: IS, KM, EE. Agree with manuscript results and conclusions: IS, KM, EE. Jointly developed the structure and arguments for the paper: IS, KM, EE. Made critical revisions and approved final version: IS. All authors reviewed and approved of the final manuscript.

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