Association between Hs-CRP and other Cardiovascular Risk Factors with Blood Pressure in Young Adults

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ABSTRACT

INTRODUCTION: Hypertension remains the leading preventable risk factor for premature mortality and morbidity worldwide. The use of high-sensitivity C-reactive protein (hs-CRP) as the global risk prediction assessment for cardiovascular diseases (CVD) in asymptomatic individuals suggests the possibility that higher hs-CRP, or subclinical inflammation, maybe one of the causal factors contributing to an increased risk of CVD in young hypertensive patients. Most studies of hypertension and hs-CRP association were conducted regionally, whereby most of the participants were Caucasians with age beyond 40 years old. Studies of this association among young adults in Asian populations are lacking, therefore, a generalization of data might be limited to certain ages and populations only. **MATERIALS AND METHOD:** This comparative cross-sectional study analysed the association between hs-CRP and other cardiovascular risk factors with three different blood pressure statuses categorised into Normotensive (NT), Pre-hypertensive (PHT), and Hypertensive (HPT) groups among young adults in Kuantan, Pahang, Malaysia. **RESULTS:** Independently, the association was significant only in males and subjects with parental history of hypertension in the prehypertensive group. However, in the hypertensive group, the relationships were significant not only in males and individuals with parental histories of hypertension but also in obese subjects. Hs-CRP was not associated with blood pressure status in the present study. **CONCLUSION:** The hypothesis that hs-CRP has an independent association with blood pressure status was not demonstrated in the present study. However, the observed association between circulating hs-CRP and blood pressure status is likely to be driven by confounders namely age, gender, genetic factors, and BMI status.

KEYWORDS: High sensitivity C-Reactive Protein; Hypertension; Cardiovascular Risk Factors, Young adult

INTRODUCTION

Hypertension remains the leading preventable risk factor for premature mortality and morbidity worldwide [1]. It shows a substantial variation between ethnic groups with the highest rates among African-American women. Data from the National Health and Nutrition Examination Survey (NHANES) for 2011 to 2014 showed that the prevalence of hypertension was highest among non-Hispanic black adults (41.2%) compared to other ethnicities namely non-Hispanic whites (28.0%), Asian (24.9%), and Hispanic (25.9%) adults [2]. Hypertension is usually preceded by prehypertension, and without intervention, prehypertension may lead to hypertension at an accelerated rate [3,4].

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The prominent Framingham Heart Study led to the identification of multiple risk factors of cardiovascular diseases (CVD). Age, sex, ethnicity, genetic factors, elevated blood pressure, hyperglycaemia, hyperlipidaemia or dyslipidaemia, and being overweight or obese are some of the more established cardiovascular risk factors.[5–7] Newer risk factors such as biochemical and subclinical disease markers for instance lipoprotein (a), C-Reactive Protein, homocysteine, and markers of fibrinolytic and hemostatic function such as fibrinogen, D-dimer, tissue plasminogen activator, and plasminogen activator inhibitor-1 antigen, are also identified as risk factors for these diseases [8,9]. Based on many reports [10–14], CRP is regarded as an independent risk factor in the development of CVD through its active participation in atherosclerosis. This involves its influence to activate the complement system, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation, and thrombosis by both isoforms, mCRP and pCRP.[15]

Numerous large studies have been conducted to view the association between hypertension and CRP. The study by Sesso et al. (2003) concluded that hs-CRP levels are associated with future development of hypertension suggesting involvement of inflammation in the process. However, most studies were conducted among western populations in which, most of the participants are Caucasians aged beyond 40 years old. The relationship is not reported in younger Asian people, so the generalization of existing data can only be limited to specific ages and demographics. This study aimed to assess the association between hs-CRP and other cardiovascular risk factors with blood pressure status, among young adults in Kuantan, Pahang Malaysia.

MATERIALS AND METHODS

This comparative cross-sectional study analyses the association between hs-CRP and other cardiovascular risk factors with three different blood pressure statuses categorized into Normotensive (NT), Pre-hypertensive (PHT), and Hypertensive (HPT) groups. The categorization is in accordance with The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood

Pressure (JNC 7) produced in 2003. The Normotensive (NT) group is categorised as systolic blood pressure (SBP) of below 120 mm Hg and diastolic blood pressure (DBP) less than 80 mm Hg. Subjects with SBP between 120 to 140 mm Hg and/ or DBP with a range of 80 to 90 mm Hg are classified as Pre-hypertensive (PHT) group. Whilst subjects with SBP and/ or DBP of (or more than) 140- and 90-mm Hg respectively, are classified into mild hypertensive (HPT) group. Ethics approval was obtained from the Institutional (International Islamic University Malaysia, IIUM) Research Ethics Committee (IREC ID No: 544) and the Malaysian Medical Research Ethics Committee (MREC, NMRR 16-2572-32869) which operates following the Declaration of Helsinki. Written informed consent was obtained from each patient.

Subject recruitment and the study protocol

A total of 315 young adults (age range between 18 and 45 years old) from Kuantan, Pahang were involved in the study. Recruitment was carried out from January 2016 to November 2017. 43 subjects were excluded due to multiple reasons leaving a total of 272 subjects for analysis. The main inclusion criterion was subjects aged 18 to 45, which is considered young adults[11,12]. Subjects other than those defined as a young adult; or with end-organ damage or hypertensive complications; alcoholic; pregnant and lactating females or those on regular oral contraceptive were excluded from this study. Diabetics, as well as subjects with the previous diagnosis of hypertension or, has been on anti-hypertensive medications were also excluded. All subjects were ensured to be free of any type of infection, inflammation, or traumatic injury at least two weeks prior to appointment and followed a pre-test, ten-hour fasting protocol prior to sample collection.

Full history with particular emphasis on own medical and family history as well as other social-demographic data were elicited, together with anthropometry measurements such as weight, height, and waist circumference and followed by blood pressure and pulse rate measurements. Blood pressure was measured using a recently validated automated digital blood pressure monitor (Omron HEM-7130). Three different blood pressure measurements were taken at different

occasions (screening, time of sample collection, and consultation day) to confirm genuine cases. The average blood pressure on each occasion was used to categorize the subjects. On average, the interval between the screening, time of sample collection, and consultation day during result presentation was seven days.

Biochemical analyses

All biochemical profiles were outsourced to an accredited pathology laboratory and analysed using Advia 2400 Chemistry Analyser, following the well-documented Advia 2400 User Manual for the biochemical parameters involved.

Statistical analysis

Data were analysed using SPSS statistical software Version 23.0. Multinomial Logistic Regression Analysis was conducted to describe the association of the cardiovascular risk factors with blood pressure status both in unadjusted and adjusted models.

RESULTS

From 272 subjects, males outnumbered females by more than 20%. The majority of the participants were Malays

Table 1 Overall baseline characteristics of the study subjects

Variables	N, (n= 272)	Mean (SD) or %
Age, year		33.5 (7.1)
Gender	Male	65.4
	Female	34.6
Race	Malay	91.9
	Chinese	6.6
	Indian	0.7
	Others	0.7
BMI status	Normal	21
	Overweight	32
	Obese	47
Smoking status	Yes	20.6
	No	79.4
Alcohol consumption	Yes	3.7
	No	96.3
Family history of hypertension	Yes	69.9
	No	30.1
Blood pressure status	NT	33.5
	PHT	38.2
	HPT	28.3

Note. Data are expressed as mean (SD) for continuous variables and percentage for categorical variables; SD = standard deviation.

Table 2 Overall mean (SD) for SBP, DBP, and other biochemical profiles of the study subjects

Variables	Mean (SD)
SBP, mm Hg	126.72 (16.01)
DBP, mm Hg	84.45 (11.34)
FBS, mmol/L	5.03 (0.97)
TC, mmol/L	5.78 (1.04)
TG, mmol/L	1.46 (0.8)
HDL-C, mmol/L	1.33 (0.32)
LDL--C, mmol/L	3.77 (0.94)
Hs-CRP, mg/L	2.79 (2.65)

Note. SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood sugar; TC = total cholesterol; TG = triglycerides; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; hs-CRP = high sensitivity C-Reactive Protein

(91.9%). More than half of the subjects were non-smokers and non-alcohol consumers. When categorised according to the BMI status, almost half of the subjects recruited in this study were obese. The range of SBP in subjects with normal BMI status was from 93 mm Hg to 157 mm Hg. While for overweight subjects, the

Table 3 Association between cardiovascular risk factors with blood pressure groups in the unadjusted model

	Prehypertensive (n= 109)					
Variables	B	SE	P	OR	95% CI	
					Lower	Upper
Age	0.025	0.021	0.234	1.026	0.984	1.069
Male[a]	1.028	0.316	0.001*	2.796	1.505	5.194
Smoking[b]	0.588	0.400	0.142	1.8	0.821	3.945
Alcohol consumption[c]	0.399	1.234	0.747	1.49	0.133	16.738
Parent's history of HPT[d]	0.663	0.318	0.037*	1.94	1.041	3.614
BMI status[e]						
Obese	1.656	0.399	<0.001*	5.238	2.394	11.46
Over weight	0.386	0.386	0.317	1.471	0.69	3.136
FBS	0.655	0.277	0.018*	1.924	1.118	3.314
Total cholesterol	0.061	0.148	0.678	1.063	0.796	1.421
TG	1.376	0.281	<0.001*	3.957	2.28	6.866
HDL-C	-2.24	0.521	<0.001*	0.107	0.038	0.297
LDL-C	0.102	0.162	0.531	1.107	0.805	1.522
Hs-CRP	0.163	0.066	0.014*	1.177	1.034	1.341

Con't

	Hypertensive (n= 86)					
Variables	B	SE	P	OR	95% CI	
					Lower	Upper
Age	0.087	0.023	<0.001*	1.091	1.042	1.143
Male[a]	1.049	0.327	0.001*	2.854	1.502	5.422
Smoking[b]	0.588	0.41	0.152	1.8	0.806	4.019
Alcohol consumption[c]	1.846	1.081	0.088	6.333	0.762	52.66
Parent's history of HPT[d]	0.979	0.342	0.004*	2.663	1.361	5.207
BMI status[e]						
Obese	3.296	0.602	<0.001*	27	8.299	87.84
Overweight	2.209	0.588	<0.001*	9.103	2.874	28.83
FBS	0.667	0.279	0.017*	1.948	1.127	3.367
Total	0.283	0.152	0.062	1.327	0.986	1.786
TG	1.043	0.275	<0.001*	2.839	1.655	4.87
HDL-C	-2.412	0.549	<0.001*	0.09	0.031	0.263
LDL-C	0.259	0.169	0.124	1.296	0.931	1.804
Hs-CRP	0.246	0.067	<0.001*	1.279	1.122	1.459

Note. Multinomial Logistic Regression; Normotensive was set as the reference group; B = estimated coefficient; SE = standard error; P = P-value; OR = odds ratio; CI = confidence interval; [a]Compared to female, [b]compared to non-smoker, [c]compared to non-alcohol consumer, [d]compared to subjects without a parental history of hypertension, [e]compared to Normal BMI status; *statistically significant at P<0.05, 95% confidence interval.

minimum SBP was 94 mm Hg, and the maximum SBP was 176 mm Hg. The obese subjects had a range of SBP from 95 mm Hg to 174 mm Hg. Meanwhile, the range of DBP in normal, overweight, and obese status were from 59 mm Hg to 109 mm Hg, 61 mm Hg to 105 mm Hg, and 63 mm Hg to 121 mm Hg respectively. The baseline characteristics of the study subjects and the overall mean (SD) of SBP and DBP; and other biochemical profiles in the study population are presented in Tables 1 and 2 respectively.

In the crude model, it was found that all parameters except smoking, alcohol consumption, total cholesterol, and LDL-C were significantly associated with either prehypertensive or hypertensive groups. On the other hand, only parental history, FBS, triglyceride, HDL-C, and hs-CRP were significantly associated with blood pressure status in both groups.

It was also observed that age and overweight subjects were not significantly associated with prehypertension, but the association was significant in hypertensive subjects as shown in Table 3.

Once the model was adjusted for all the significant covariates, the analysis showed that in the prehypertensive group, the association between gender and parents' history of hypertension were statistically significant (*P*= 0.042 and *P*= 0.040 respectively). In men, the risk of developing prehypertension was greater than in females; concurrently, compared to subjects with non-hypertensive parents, it was even stronger in subjects with only one or both parents experiencing hypertension.

Age, gender, genetic factors, as well as BMI status (both overweight and obese) were significantly associated with blood pressure status in the hypertensive group. It revealed that with an age rise of one year in both groups, the risk of developing prehypertension and hypertension was 21% and 76% respectively (OR=1.021; 95% CI, 0.972-1.073 and OR=1.076; 1.018-1.136). In comparison, the risk of both prehypertension and hypertension in males is double as high as in females (OR=2.22; 1.029-4.808 and OR=2.46; 1.047-5.789, respectively). Overweight subjects are more likely to acquire prehypertension, however, relative to subjects with normal BMI status, obese subjects are expected to have a greater chance of developing hypertension (OR= 4.57, 1.33 - 15.78; OR= 9.46, 2.47- 36.29).

Nonetheless, after adjustment of significant variables it appeared that hs-CRP was not significantly associated with both groups thus, could not be confirmed as the risk factor for hypertension by the above results. The results are summarised in Table 4.

DISCUSSION

Hypertension is one of the major risk factors for CVD, which is responsible for at least 45 and 51 percent of total deaths due to heart disease and stroke, respectively (World Health Organization, 2013). Across the globe, the prevalence of hypertension was highest in the African Region (46%), followed by the South-East Asia Region (36%), and lowest in the Region of America at 35%.[17] There was also a substantial difference between ethnic groups where non-Hispanic black adults reported the highest prevalence of hypertension, while non-Hispanic Asian adults showed the lowest prevalence among all groups studied [2].

Table 4 Association between cardiovascular risk factors with blood pressure status in blood pressure groups in the adjusted model

Cardiovascular risk factors	PREHYPERTENSIVE						HYPERTENSIVE					
	B	SE	P	OR	95% Confidence Interval for OR		B	SE	P	OR	95% Confidence Interval for OR	
					Lower	Upper					Lower	Upper
Age	0.021	0.025	0.404	1.021	0.972	1.073	0.073	0.028	0.009*	1.076	1.018	1.136
Male[a]	0.799	0.393	0.042*	2.224	1.029	4.808	0.901	0.436	0.039*	2.46	1.047	5.789
Parental history of hypertension[b]	0.723	0.352	0.040*	2.062	1.034	4.112	0.986	0.395	0.013*	2.68	1.236	5.81
BMI[c]												
Obese	0.754	0.496	0.128	2.126	0.804	5.619	2.247	0.686	0.001*	9.46	2.467	36.288
Overweight	-0.183	0.438	0.677	0.833	0.353	1.967	1.52	0.632	0.016*	4.57	1.325	15.784
FBS	0.365	0.282	0.195	1.441	0.829	2.502	0.253	0.288	0.378	1.29	0.733	2.264
TG	0.266	0.295	0.367	1.305	0.732	2.328	0.529	0.301	0.079	1.7	0.941	3.06
HDL	-0.811	0.646	0.209	0.445	0.125	1.577	-0.12	0.722	0.871	0.89	0.216	3.662
Hs-CRP	0.087	0.08	0.273	1.091	0.933	1.276	0.134	0.084	0.108	1.14	0.971	1.348

Note. Multinomial Logistic Regression; Normotensive was set as reference group; B= estimated coefficient; SE=standard error; P = P-value; OR = odds ratio; CI = confidence interval; [a]Compared to female, [b]compared to Subjects without parent's history of hypertension, [c]compared with Normal BMI; *statistically significant at P<0.05, 95% confidence interval

In several multi-ethnic studies performed in a few regions of the world, it has also been documented that CRP levels vary by ethnicity. The link between hypertension and CRP, as well as the development and validity of cardiovascular risk assessment methods, was shown in various studies. Nonetheless, most studies have been carried out in Western populations in which most participants are Caucasians over 40 years of age. Therefore, data generalization may be applicable to such populations only.[18,19] Aggregated data from Asian countries are also lacking and thus applying similar tools using hs-CRP levels from Western countries to Asian individuals might not be justified or accurate.

In view of its assay characteristics as a robust biomarker, hs-CRP becomes a preferred clinical biomarker of CVD globally. Some of the ideal features of hs-CRP are its stability, sensitivity, reproducibility, and ease of measurement with very marginal fluctuations. In either fresh, stored, or frozen plasma or serum, the uniform high sensitivity immunoassay is capable of detecting circulating CRP levels with comparable outcomes. In addition, the hs-CRP demonstrates a relatively limited degree of intra-individual heterogeneity between sexes, age, and ethnicity, as well as diurnal variation[20]. Hs-CRP has been widely used as a predictive tool for the future development of cardiovascular events as recommended by the CDC-AHA in 2003.

In this study, despite a positive association between hs-CRP and blood pressure in crude models, the correlation did not persist after adjusting for relevant confounders. This finding was in line with a few cross-sectional studies by Pan and peers (2019) in Liangshan Yi Autonomous Prefecture of Sichuan Province, the Republic of China, and Fernandez-Real *et. al* (2001) and Bautista, Vera, Arenas, & Gamarra (2005). Several epidemiological studies also showed the unsustainability of the hs-CRP and BP relationship. A prospective cohort study conducted in Japan showed that there was no correlation between the high hs-CRP alone and the increased development of hypertension in both men and women[24]. CARDIA has shown that there has been no substantial association between hs-CRP and perimenopausal hypertension[25]. On the other hand, a large cohort study by Sesso and co-workers (2003) that hs-CRP was positively associated with hypertension which indicated that the levels of hs-CRP played crucial roles in the further development of hypertension.

The association between hs-CRP and BP status was possibly caused by the multiple confounders namely

age[26], gender [27,28], genetic factors, and BMI status.[29,30] The positive association between age and hypertension was also shown in Framingham Heart Study and other studies [31,32]. The possible mechanisms to explain these associations remain elusive. Changes in vascular stiffness might be the factors leading to arteriosclerotic structural modifications as well as calcification which results in an increment of blood pressure[31]. Males tend to have lower CRP values than females in.[27,28,33,34] The risks of hypertension and cardiovascular diseases are generally higher in men than women.[35] The mechanisms which cause gender dissimilarities in blood pressure regulation are unclear. However, androgens such as testosterone might play a significant role.[36,37]

It is well recognized that hypertension clusters in families[38]. Parikh and colleagues (2008) reported that the risk of hypertension in non-hypertensive offspring in the future highly increases with a positive family history. Thus, the presence of positive parental histories in subjects contributed to the positive association of CRP[40]. Tsai & Tsai (2008) also reported that higher BMI are associated with higher CRP values. Increased fatty tissues in obese individuals raise the vascular resistance which subsequently increases the workload on the heart. Apart from changes in renal structure and function, the activation of the sympathetic nervous system is another important mechanism that is responsible for the pathogenesis of hypertension among obese individuals.[41]

CRP was shown to be associated with several cardiovascular risk factors in the present study. Several possible mechanisms which may explain the role of CRP in the development of hypertension leading to cardiovascular diseases, mainly, renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and inflammation. In smooth muscle cells, CRP was reported to independently up-regulate angiotensin II type 1 receptor which leads to elevation of blood pressure.[42] In an acute stress response, pro-inflammatory cytokines were induced as a result of the activation of the sympathetic nervous system on cardiac myocytes causing over-activation of the β-adrenergic signalling system resulting in harmful cardiotoxic effects which are triggered by the inflammatory cascade[43]. However, the actual mechanisms are still unclear. Thus, further experimental studies are required to determine the causative effects of CRP on each cardiovascular risk factor.

There are a few limitations to this study. Firstly, it is a cross-sectional study involving a small sample size, thus, a temporal relationship between raised CRP and the development of hypertension cannot be deduced. Next, CRP role in the development of young adult hypertension is still unclear. A bigger population-based cohort study should be conducted to justify and validate the association in the population as well as to determine the causative effects of CRP on different cardiovascular risk factors.

CONCLUSION

Cumulatively, these data suggest that the observed association between circulating hs-CRP and blood pressure status is likely to be driven by all the above-mentioned factors. Nonetheless, the hypothesis that hs-CRP has an independent association with blood pressure status was not demonstrated in the present study. Early detection of hypertension status especially in young adults provides a better prognosis and prevention of progression towards CVD events. Hs-CRP predictive values for CVD among the Malaysian population may differ from other western and Asian countries. The findings of this study may suggest the need to develop our own rubric on cardiovascular risk assessment based on blood pressure and hs-CRP, especially for young adults.

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