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ORIGINAL ARTICLE

High sensitivity C-reactive protein (hsCRP): Its relationship with metabolic syndrome and Framingham Risk Score

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Abstract

Introduction: Cardiovascular disease (CVD) remains the leading cause of death in Malaysia. Identification of asymptomatic at-risk individuals is often achieved by means of a risk prediction algorithm. Traditional CVD risk factors and their associated algorithms are, however, limited by residual CVD risk. High sensitivity C-reactive protein (hsCRP) has emerged as a novel CVD risk factor. This study aimed to evaluate hsCRP as an adjunct CVD risk marker among the adult Malaysian population by determining its correlation with the Framingham Risk Score (FRS). Comparison analyses were done according to sociodemographic, clinical and laboratory factors and between subjects with and without Metabolic Syndrome (MetS). *Method*: This cross-sectional study involved eighty-three (n=83) adults attending a health screening program at Universiti Putra Malaysia (UPM). Demographic data, anthropometric measurements and blood samples for fasting blood glucose (FBG), fasting lipid profile (FSL), glycated haemoglobin (HbA1c) and hsCRP were taken. Respondents were grouped according to FRS and the Joint Interim Statement into 10-year CVD risk categories (low, intermediate and high) and MetS, respectively. *Results*: hsCRP was significantly increased in patients with high body mass index (BMI) (p=0.001), at-risk waist circumference (WC) (p=0.001) and MetS (p=0.009). Spearman's correlation coefficient showed a significant positive correlation between hsCRP level and total FRS score (r=0.26, p<0.05) and HDL-C score (r=0.22, p<0.05). *Conclusion*: The significant difference of hsCRP levels across obesity levels and MetS with its modest correlation with FRS scores supported the adjunctive role of hsCRP in CVD risk prediction, most likely capturing the inflammatory pathological aspect and thus partly accounting for the residual CVD risk.

Keywords: High sensitivity C-reactive protein (hsCRP), Cardiovascular disease (CVD), Framingham Risk Score (FRS), Metabolic Syndrome (MetS)

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in Malaysia; with ischaemic heart disease being the principal cause of mortality.[1] Accurate identification of asymptomatic at-risk individuals, therefore, presents an opportunity to intensify risk factor modification prior to such event. Often, this is achieved by means of CVD risk prediction algorithms, which subsequently dictates one's management. The four major modifiable traditional CVD risk factors, namely smoking, hyperlipidaemia, diabetes mellitus (DM) and hypertension (HPT), plus age and gender form the Framingham Risk Score (FRS)[2], one of the most widely used algorithms to assess an individual's 10-years global CVD risk.

However, studies have demonstrated the limitations of these traditional factors and hence their associated algorithms.[3-6] A closer look at a compiled data from 14 clinical trials showed that up to 50% and 60% of coronary events in women and men, respectively, occurred in those with one or none of the four main CVD risk

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factors[3], whilst up to 20% of events occurred in the absence of any.[3,4] In women, almost 50% of CVD events occurred in women with low-density lipoprotein (LDL)-cholesterol below the recommended treatment threshold.[5] It has also been shown that 40% of coronary deaths happened in patients with total cholesterol levels below the population average.[6]

Thus, despite their established roles in primary and secondary CVD preventions, residual CVD risks remain, unexplained by these CVD traditional risk factors. Interest has since moved towards the inflammatory aspect of CVD pathogenesis.[7,8] Detection of a lower level of C-reactive protein (CRP), an acute-phase protein of hepatic origin by a high sensitivity assay, reflects low-grade systemic inflammation, which plays pathological roles, particularly in rupturing atherosclerotic plaques and its associated vascular thrombosis.[8] Not until recently, high sensitivity CRP (hsCRP) has been recognised as a surrogate biomarker for the upstream activities of two main inflammatory cytokines, namely interleukin-1beta (IL-1β) and interleukin-6 (IL-6).[9]

Evidence supporting the hsCRP role as a novel CVD risk factor has been growing, from earlier[10,11] to more recent studies.[12] Currently, hsCRP has been adopted mostly as an adjunct for statin therapy in equivocal risk categories by several CVD risk predictive algorithms.[13] Thus far, only one algorithm has incorporated hsCRP as a non-traditional CVD risk factor. In Malaysia, hsCRP is given a Class IIa level of recommendation for its possible role in a reclassification of intermediate-risk categories to high risk.[14] Association of hsCRP with known cardiovascular risks has been studied locally.[15] This study aimed to examine its association with FRS, findings of which may provide supportive evidence to utilising hsCRP as an adjunct to traditional CVD risk factors. Comparison analyses were also done in subjects with and without MetS.

MATERIALS AND METHODS

Subjects

A total of 103 self-declared healthy adults with no history of CVD, including diabetes mellitus or hypertension, were recruited in a one-day event of a health screening program on the 24th March 2016 at the Faculty of Medicine and Health Sciences (FMHS), UPM. The sample size was estimated using a formula for proportion in hypothesis testing type of study, as follows: $n=\{Z-((1-\propto/2))\sqrt{(2P(1-P)}+Z-((1-\beta))\sqrt{(P1(1-P1)}+P2(1-P2))\}^2/(P1-P2)^2$, whereby P1 and P2 are percentages of individuals with Metabolic Syndrome with hsCRP>3mg/L and hsCRP<3mg/L[16], respectively; significant level, $\alpha=0.05$; $z-(1-\alpha/2) = 95\%$ CI= 1.96; power, $\beta=80\%$; $z\_(1-\beta) = 0.842$; $P = (P1+P2)/2$. The minimum estimated sample size was 56. Allowing for a non-response rate of 20%, and a non-eligibility rate of 10%, the adjusted sample size was 78 participants. The study protocol was approved by the Ethics Committee for Research Involving Human Subjects, UPM [FPSK (FR15) PO23].

Sampling method

Invitation emails containing the information sheet were sent to all faculty staff. Eligible respondents who fulfilled the inclusion criterion of being Malaysian adult aged between 30 and 60 years old were requested to fast a minimum of 8 hours prior to blood sampling. Exclusion criteria included women on hormone replacement therapy (HRT), pregnant or lactating; current acute illness and active inflammatory conditions. hsCRP level of more than 10 mg/L was excluded as it may due to acute infection.[17] Informed written consent was obtained from the respondents.

Data and sample collection

Demographic and anthropometric data [weight, height, waist circumference (WC)] and blood pressure (BP)] were recorded. A minimum of 7 mls of blood was drawn from each participant for laboratory investigations.

Biochemical assay

Blood samples were assayed in Pathology Laboratory, Hospital Kuala Lumpur (HKL). Analyses for fasting blood glucose (FBG) and fasting lipid profile (FSL) were done on the day of collection. Aliquots of HbA1c and hsCRP were stored at -20°C until batch analyses. FBG, FSL and hsCRP analyses were done on Cobas 6000 Analyser (Hitachi Roche, Germany); and HbA1c analysis on VariantTM II TURBO System (Bio-rad, CA, USA).

Definitions

hsCRP levels >3 mg/L, indicating higher vascular risk in the context of other risk factors[8,17] was used for the outcome analyses. Diagnosis of MetS was based on the Joint Interim Statement[18],

fulfilling 3 out of 5 criteria [WC, BP, FBG, triglyceride (TG) and high-density lipoprotein-cholesterol (HDL-C)]. The Hba1c cut-off of 6.3% for the diagnosis of T2DM was based on the Clinical Practice Guideline (CPG) on Management of Type 2 Diabetes Mellitus 5th edition.[19] FRS was calculated using the online calculator (https://www.framinghamheartstudy.org/risk-functions/cardiovascular- disease/10-year-risk.php). Individuals with <10%, 10-20% and >20% 10-year CVD risk were categorised as low, intermediate and high risks, respectively.

Statistical analysis

Statistical calculations were performed using the standard statistical software package, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. The statistically significant value was accepted at $p<0.05$. Data were tested for normality using the Shapiro-Wilk test. Comparisons between groups were performed using the Mann-Whitney U test or Kruskal Wallis test for continuous variables. The Spearman correlation test was used to determine the relationship between the hsCRP levels and the FRS total and individual components scores.

RESULTS

103 subjects participated in the health screening programme. However, 14 subjects were excluded due to insufficient data and six were due to hsCRP >10 mg/L. A total of 83 subjects, of which 78.3% were females with a median age of 35 years [Interquartile range (IQR) (8)] were included in this study.

There were no significant differences in median hsCRP levels for sociodemographic factors, and most of the clinical characteristics and laboratory parameters (Table 1). Since hsCRP levels were not significant between genders, data for male and female were combined for further analyses. There was a statistically significant difference in hsCRP level across the three BMI groups ($\chi 2 = 13.713$, $p = 0.001$) with the highest median hsCRP seen in obese (3.23 mg/L) followed by overweight (1.51 mg/L) and normal (1.02 mg/L). hsCRP level in the at-risk WC group was significantly higher than the low-risk WC group ($z = -3.315$, $p = 0.001$). Median hsCRP level was significantly higher in those with MetS compared to those without ($z = -2.625$, $p = 0.009$) as shown on Table 2.

The majority (98%) of the subjects had low 10-year CVD risk and only 2% had intermediate risk. No subject had a high 10-year CVD risk. hsCRP level in the intermediate-risk group was almost double that of low-risk group, although non-significant. (Table 3)

As shown in Table 4, Spearman's rank-order correlation indicated the presence of modest positive correlations between hsCRP and total FRS ($r = 0.27$, $p <0.05$) and between hsCRP and HDL-C score ($r = 0.22$, $p < 0.05$).

DISCUSSION

In this study, comparison analyses showed no difference between hsCRP levels and most of the sociodemographic, clinical and laboratory parameters (Table 1), including between genders, as similarly shown by Norshafawati *et al*.[15] In contrast, Albert *et al*. found a significantly higher hsCRP among previously healthy women than men which was, however, accounted for by HRT usage.[20] Interestingly, in a cohort with known DM or CVD diseases, Seo *et al*. showed higher hsCRP levels in Korean men compared to women, not on HRT.[21] It has been shown that without HRT, hsCRP levels are generally similar between genders and modestly increase with age.[8] Thus, in Seo *et al*., in which males were younger than females, higher hsCRP levels in men were more likely attributed to their higher CVD risk category, as reflected by a higher incidence of CHD among them compared to women in that study.

The present study showed significant increase in hsCRP levels in subjects with high BMI ($p=0.001$), at-risk WC ($p=0.001$) (Table 1) and MetS ($p=0.009$) (Table 2). These findings closely mirrored what was shown previously[15,22-24] despite differences in CRP assays and BMI and WC cut-offs. Using conventional CRP, Aronson *et al*. showed that the association between MetS and CRP was mainly related to overall obesity as BMI accounted for 15% of the variability in log-CRP levels.[22] Similarly, Kao *et al*. showed significant difference and associations between CRP levels with BMI and WC categories.[23] In a more recent study utilising hsCRP, its correlations with BMI and WC were demonstrated by Norshafawati *et al*., who also showed that BMI was the only predictor of hsCRP, accounting for 24% of the log-hsCRP variability.[15] In a similar study among healthy adult Indians, in which Asian BMI categories were used, as in this present study, Lavanya *et al*. showed similar significant difference and positive correlations.[24]

The findings of higher body fat content in Asians than in the White population[25] of the

Table 1: Comparison of hsCRP levels according to sociodemographic factors, clinical characteristics and laboratory parameters

Criteria		hsCRP		
	n (%)	Median (IQR) (mg/L)	z / $\chi 2$	*p value
Age (years)				
≤ 35	45(54)	1.29 (2.28)	-1.015	0.31
>35	38(46)	1.45 (1.88)		
Gender				
Male	18(22)	0.99 (2.17)	-1.138	0.255
Female	65(78)	1.42 (2.09)		
Race				
Malay	66(80)	1.31 (1.95)	5.648[a]	0.13
Chinese	9 (11)	0.82 (2.03)		
Indian	6 (7)	2.74 (2.23)		
Others	2 (2)	4.10 (1.58)		
Smoking				
No	81(98)	1.37 (2.09)	-0.386	0.699
Yes	2 (2)	1.52 (1.00)		
BP (mmHg)				
Normal (≤ 130/80)	56(67)	1.19 (1.95)	-1.813	0.07
Above normal (>130/80)	27(33)	2.07 (2.86)		
BMI[b] (kg/m^2)				
Normal (<23)	53(64)	1.02 (1.81)	13.713[a]	0.001*
Overweight (23-24.9)	18(22)	1.51 (2.66)		
Obese (≥ 25)	12(14)	3.23 (3.47)		
WC[c]				
Low risk	54(65)	1.04 (1.83)	-3.315	0.001*
At-risk	29(35)	2.52 (3.64)		
TC (mmol/L)				
Desirable (< 5.2)	43(52)	1.32 (2.00)	-0.633	0.526
Above desirable (≥ 5.2)	40(48)	1.45 (5.53)		
TG (mmol/L)				
Normal (<1.7)	76(92)	1.33 (2.11)	-0.426	0.67
Above normal (≥1.7)	7 (8)	1.87 (1.89)		
HDL-C[d] (mmol/L)				
Normal	15(18)	1.59 (2.71)	-1.474	0.141
At risk	68(82)	1.26 (2.08)		
LDL-C (mmol/L)				
Optimal (<2.6)	13(16)	1.21 (1.93)	-0.169	0.866
Above optimal (≥ 2.6)	70(84)	1.42 (2.14)		
FBG[e] (mmol/L)				
Normal (<5.6)	71(85)	1.37 (2.02)	-0.758	0.449
Abnormal (≥ 5.6)	12 (15)	1.46 (2.68)		
HbA1c[f, g] (%)				
Normal (<6.3)	76 (99)	1.42 (2.11)	-0.337	0.736
High (≥ 6.3)	1 (1)	1.06 (0)		

[a] Kruskal-Wallis statistical test ($\chi 2$); Mann Whitney statistical test (z); [b] Classification based on WHO/IASO/IOTF (2000)[26]; [c] WC defined as, low risk, for male ≤ 90 cm; for female ≤80 cm; at risk, for male > 90 cm; for female> 80 cm based on WHO/IASO/IOTF (2000)[26]; [d] HDL-C defined as, normal, for male ≥ 1.0 mmol/L; for female ≥ 1.3 mmol/L; at risk, for male <1.04 mmol/L; for female <1.29 mmol/L based on the Joint Interim Statement[18]; [e] Classification based on the Joint Interim Statement[18]; [f] Classification based on CPG Management of Type 2 DM, 2015[19] ; [g] six (6) data were excluded due to error in measurement; * p<0.05 is statistically significant

Table 2: hsCRP level in subjects with and without MetS

MetS	n (%)	hsCRP(mg/L)	z statistic	*p value
		Median (IQR)		
No	69 (83)	1.16 (1.95)	-2.901	0.004
Yes	14 (17)	2.67 (3.48)		

*p<0.05 is statistically significant; Mann-Whitney U test (z)

Table 3: hsCRP level based on FRS risk

FRS risk	n (%)	hsCRP(mg/L)	z statistic	*p value
		Median (IQR)		
Low	81(98)	1.33 (2.07)	-1.440	0.150
Intermediate	2 (2)	2.52 (1.1)		

Notes: High risk was not included as there was no subject in this group.
*p<0.05 is statistically significant; Mann-Whitney U test (z)

same age, gender and BMI had previously led to jointly proposed Asian BMI cut-off values.[26] For public health intervention, the World Health Organization (WHO) added thresholds while maintaining the international BMI cut-offs in the Asian population.[25] Yet, most authorities believe that the same degree of obesity is projected by different BMI values in different ethnic groups.[25] Thus, the continuing use of Asian BMI categories[23,24,27], as adopted in this present study.

Cardio-metabolic complications of obesity and therefore CVD risk is more closely related to the distribution of adiposity, of which visceral or central adiposity is the most pathological type, rather than the overall degree of adiposity, reflected by WC and BMI, respectively. Comparing these measures of adiposity, Lam *et al*. showed that despite their apparent differences, BMI and WC are, however, comparable in their associations with traditional CVD risk factors.[28]

Prospective studies have independently shown that hsCRP levels were significantly higher in subjects than those without MetS, both in men[29] and women.[5] In view of hsCRP being an independent predictor of coronary heart disease (CHD) and DM, Sattar *et al*. suggested that it could improve future revision of MetS criteria.[29] Collectively, it was demonstrated that elevated baseline hsCRP >3mg/L added prognostic information for future CHD and DM[23] as well as CVD events[5], in men and women, respectively, with and without MetS. Interestingly, these studies have also shown that the findings were minimally impacted using different MetS criteria.[5,29]

In this study, hsCRP levels in the intermediate FRS risk category were almost double that of the low-risk group, although this failed to reach statistical significance (Table 3). This could be due to the small number of subjects (n=2) in the former group as most respondents were young women between 30 to 56 years old, with a median age of 35 years [IQR (11)] (data not shown) with minimal CVD risk factors. In

Table 4: Correlation between hsCRP and individual component and total FRS scores

	hsCRP	
	r	*p value
Age score	0.085	0.426
Smoking score	0.051	0.636
TC score	0.165	0.123
HDL-C score	0.255	0.016
Systolic BP score	0.184	0.084
FBG score	0.099	0.357
Total FRS	0.264	0.013

*p < 0.05 is statistically significant; Spearman's rank-order correlation (r)

contrast, a significant difference in the level of hsCRP across the CVD risk groups has been shown in other studies. Albert *et al*. who utilised the Framingham Coronary Risk Score (FCRS), a closely related scoring algorithm estimating CAD rather than global CVD risk, showed a significant difference in hsCRP levels with each increasing calculated Framingham 10-year coronary risk category in both genders.[20] A careful look at their results in men, using TC or LDL-C scoring algorithm, Albert *et al*. showed that the median hsCRP levels were about 1.0 mg/L and between 1.5-2.0 mg/L in the <10% and 11-23% 10-year CAD risk categories, respectively.[20] In women not on HRT, however, these levels were higher, of 2.0 mg/L and between 2.0 to 3.0 mg/L, in the <10% and 11-20% risk groups, respectively.[20] Comparatively, in the present study, comparison analysis of hsCRP levels with FRS was done in the total study population, thus, yielding different values of 1.33 and 2.52 mg/L in the respective risk groups (Table 3). Using the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III algorithm, a similar significant difference was shown by Seo *et al*. in each risk group of the total study population, with hsCRP levels increasing from 0.15 to 0.27 and 0.47 mg/L, in the low (<10%), high (10-20%) and very high (>20%) CAD risk groups, respectively.[21]

The present study showed that despite a positive association between hsCRP and total FRS score, hsCRP levels failed to correlate significantly with most individual components of FRS, except with HDL-C score (Table 4). As HDL-C score is reciprocal of HDL-C concentration, a high score reflects high CVD risk. Thus, Seo *et al*. who showed a significant negative correlation between hsCRP and HDL-C levels had suggested that hsCRP level may be an inverse predictor of HDL-C level in their cohort of CVD or DM subjects.[21] Using FCRS in men and women, not on HRT, similar modest correlations between its total score and HDL-C score with hsCRP was shown by Albert *et al*. Similar to our study, there was a minimal association with other individual FCRS components.[20] Findings of Albert *et al*. was supported by Koenig *et al*., who estimated CAD risk among middle-aged men, using FCRS and TC/HDL-C ratio.[30] The authors concluded that CRP modulated risk estimation, particularly in the 10-20% 10-year CAD risk group.[30] Furthermore, measurement of CRP was shown to add clinically relevant information to the lipid measurement.[30]

The contradictory finding of a modest correlation between hsCRP with FRS total score and not with most of its components supported the notion that while hsCRP is linked to FRS, each may indicate different aspects of CVD risk, with hsCRP most likely capturing the inflammatory aspect of CVD pathogenesis. Local and systemic inflammations play pathological roles in atherosclerosis, the underlying pathology in CVD[9,31], from initiation, progression to plaque rupture and thrombosis, leading to acute vascular events.[9] Inflammation is also believed to be a causal factor in the progression of insulin resistance, the underlying derangement in MetS, to frank T2DM, as most inflammatory factors in T2DM are IL-1 dependent.[32] The metabolically active central adipose tissue is a major source of inflammatory cytokines, including IL-6, the key regulator of hepatic synthesis of CRP. Thus, inflammation is most likely the common ground linking MetS to increased risk of CVD and DM.

Evidence in support of this hypothesis is mounting, arising from cross-sectional to subsequent prospective studies. The latter not only proved the predictive role of CRP in CVD risk but also revealed the possible beneficial anti-inflammatory effect, reflected by reduction in hsCRP in CVD risk reduction[10]; findings, which had been replicated across different cohorts.[8,11] Statin therapy soon established its independent dual actions of lipid-lowering and anti-inflammatory with greater risk reduction among those with elevated hsCRP[33] even despite normal LDL-C.[34] Subsequent studies confirmed statin's 'dual targets' of concurrently lowering LDL-C and hsCRP levels, effects seen in both mono-[35-37] and dual therapies[38] of lipid-lowering agents.

Overall, the addition of hsCRP to the existing traditional CVD risk factors only modestly improved CVD risk prediction.[13] These findings may explain the acceptance of hsCRP as an adjunct marker in deciding equivocal statin therapy.[13] However, the Reynolds Risk Score, the only algorithm incorporating hsCRP had been shown to outperform other traditional algorithms.[8,13] Nevertheless, results of ongoing trials independently testing lipid-lowering and anti-inflammatory effects, by means of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors[8], and broad[39] and narrow-spectrum[40] anti-inflammatory agents, respectively, are awaited to affirm the inflammatory role of hsCRP in CVD pathogenesis and its prevention.

To our knowledge, a similar study comparing the relationship between hsCRP and FRS has not been done in Malaysia. Although the estimated sample size was achieved in this study, recruitment of faculty staff in a tertiary institution resulted in the inclusion of mostly healthy young women with low CVD risk, with only two subjects categorised as intermediate-FRS CVD risk and no subject with high CVD risk. This may explain the non-significant difference of hsCRP level between FRS risk groups in this study. In this study, a trend towards a higher level of hsCRP in the intermediate compared to the low FRS risk category and a modest correlation between hsCRP and FRS suggest a possible statistical significance may be achieved in a future study involving a larger sample size in the general population, as shown previously in much larger studies.[20,21] Further improvement may result from the inclusion of subjects with a wider age range and of more equal gender distribution to involve all three FRS risk categories. In addition, a prospective cohort study would be able to address the causal relationship between hsCRP and FRS components.

In conclusion, a significant difference in hsCRP across MetS and obesity degree reflected by BMI and WC, together with its modest correlation with FRS shown in the present study were in keeping with previous findings in support of hsCRP as an adjunct biomarker, most likely accounting for the remaining CVD inflammatory residual risk.

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REFERENCES

1. Clinical Practice Guideline (CPG) on management of Acute ST Segment Elevation Myocardial Infarction (STEMI) 4th edition 2019. Ministry of Health Malaysia. http://www.moh.gov.my
2. D'Agostino RB, Vasan RS, Pencina MJ, *et al*. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation. 2008; 117: 743-53.
3. Khot UN, Khot MB, Bajzer CT, *et al*. Prevalence of Conventional Risk Factors in Patients with Coronary Heart Disease. JAMA. 2003; 290: 898-904.
4. Bassuk SS, Rifai N, Paul M. Ridker PM. High-Sensitivity C-Reactive Protein: Clinical Importance. Curr Probl Cardiol. 2004; 29: 439-93.
5. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels In The Prediction of First Cardiovascular Events. N Engl J Med. 2002; 347: 1557-65
6. Smith SC. Current and Future Directions of Cardiovascular Risk Prediction. Am J Cardiol. 2006; 97: 28A–32A.
7. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-Reactive Protein as a Risk Factor for Coronary Heart Disease: A Systematic Review and Meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009; 151: 483-95.
8. Ridker PM. A Test in Context. High-Sensitivity C-Reactive Protein. J Am Coll Cardiol. 2016; 67: 712–23.
9. Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1 Moving Upstream to Identify Novel Targets for Atheroprotection. Circ Res. 2016; 118: 145-56.
10. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997; 336: 973-9.
11. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000; 342: 836-43.
12. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010; 375: 132-40.
13. US Preventive Services Task Force. Risk Assessment for Cardiovascular Disease with Nontraditional Risk Factors US Preventive Services Task Force Recommendation Statement. Published online July 10, 2018.doi:10.1001/jama.2018.8359
14. Clinical Practice Guidelines on Management of Dyslipidaemia 5th edition 2017. Ministry of Health Malaysia. http://www.moh.gov.my
15. Norshafawati AA, Rosita J & Norhaizan ME. Body mass index as the predictor of high sensitivity C-reactive protein: A risk marker of cardiovascular disease. Mal J Nutr. 2014; 20(3): 291-30.
16. Ridker PM, Buring JE, Cook NR, Rifai N. C-Reactive Protein, the Metabolic Syndrome, and Risk of Incident Cardiovascular Events An 8-Year

Follow-Up of 14 719 Initially Healthy American Women Circulation. 2003; 107: 391-7.
17. Yeh ETH & Willerson JT. Coming of age of C-reactive protein. Circulation 2003; 107: 370-2.
18. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, *et al*. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-5.
19. Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus (5th Edition) 2015. Ministry of Health Malaysia. http://www.moh.gov.my
20. Albert MA, Glynn RJ, Ridker PM, *et al*. Plasma concentration of C-reactive protein and the calculated Framingham coronary heart disease risk score. Circulation. 2003; 108: 161-5
21. Seo SM, Baek SH, Jeon HK, *et al*. Correlations between the level of high-sensitivity C-reactive protein and cardiovascular risk factors in Korean adults with cardiovascular disease or diabetes mellitus: the CALLISTO study. J Atheroscler Thromb. 2013; 20(7): 616-22.
22. Aronson D, Bartha P, Zinder O, *et al*. Obesity is the major determinant of elevated C-reactive protein in subjects with the metabolic syndrome. Inter J Obes 2004; 28: 674-9.
23. Kao TW, Lu IS, Liao KC, Lai HY, Loh CH, Kuo HK. Associations between body mass index and serum levels of C-reactive protein. S Afr Med J 2009; 99: 326-30.
24. Lavanya K, Ramamoorthi K, Acharya RV, Madhyastha SP. Association between Overweight, Obesity in Relation to Serum hs-CRP Levels in Adults 20-70 Years. Journal of Clinical and Diagnostic Research. 2017;11(12): OC32-OC35.
25. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363: 157-63.
26. WHO/IASO/IOTF (2000). The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. Health Communications Australia: Melbourne.
27. Siddiquee T, Bhowmik B, Moreira NCDV, *et al*. prevalence of obesity in rural Asian Indian (Bangladeshi) population and its determinants. BMC Public Health 2015; 15: 860.
28. Lam BC, Koh GC, Chen C, Wong MT, Fallows SJ. Comparison of Body Mass Index (BMI), Body Adiposity Index (BAI), Waist Circumference (WC), Waist-To-Hip Ratio (WHR) and Waist- To-Height Ratio (WHtR) as Predictors of Cardiovascular Disease Risk Factors in an Adult Population in Singapore. PLoS One. 2015;10(4):e0122985.
29. Sattar, N, Gaw A, Scherbakova O, et al. Metabolic Syndrome with and without C-Reactive Protein as a Predictor of Coronary Heart Disease and Diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003; 108: 414-9
30. Koenig W, Löwel H, J Baumert J, Meisinger C. C-Reactive Protein Modulates Risk Prediction Based on the Framingham Score Implications for Future Risk Assessment: Results from a Large Cohort Study in Southern Germany. Circulation. 2004; 109: 1349-53.
31. Casscells W, Hathorn B, David M, *et al*. Thermal detection of cellular infiltrates in living atherosclerotic plaques: possible implications for plaque rupture and thrombosis. Lancet 1996; 347: 1447-9.
32. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98-107.
33. Ridker PM, Rifai N, Pfeffer MA, *et al*. for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, pravastatin, and the risk of coronary events after myocardial infarctionin patients with average cholesterol levels. Circulation 1998; 98: 839-44.
34. Ridker PM, Rifai N, Clearfield M, *et al*. Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med. 2001; 344: 1959-65.
35. Ridker PM, Danielson E, Fonseca FA, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359: 2195-207.
36. Nissen SE, Tuzcu EM, Schoenhagen P, *et al*. for the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005; 352: 29-38.
37. Ridker PM, Cannon CP, Morrow D, *et al*. for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352: 20–8.
38. Cannon CP, Blazing MA, Giugliano RP, *et al*. for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 2387-97.
39. Brigham and Women's Hospital. Cardiovascular Inflammation Reduction Trial (CIRT). 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT02576067 Accessed March 3, 2020.
40. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J. 2011; 162: 597-605.