

# Effects of Bio-Psycho-Socio-Spiritual Factors on Biomarkers of Cardiovascular Inflammation in Elderly Indonesian Muslim

Yusuf Alam Romadhona<sup>1</sup>, Bambang Purwantob<sup>2</sup>, Rochmad Romdonic<sup>3</sup>, Surotod<sup>4</sup>

<sup>1</sup>Doctoral Student of Medical Science, Sebelas Maret University of Surakarta / Family Medicine and Public Health Department, Faculty of Medicine, Muhammadiyah University of Surakarta, <sup>2</sup>Internal Medicine Department, Faculty of Medicine, Sebelas Maret University of Surakarta, <sup>3</sup>Cardiology Department, Faculty of Medicine, Airlangga University, <sup>4</sup>Neurology Department, Faculty of Medicine, Sebelas Maret University of Surakarta.

## Abstract

**Background:** The evaluation of bio-psycho-socio-spiritual factors on cardiovascular inflammatory biomarkers has not been widely studied in Indonesia. Accumulated evidence that biological, psychosocial and spiritual factors were related to the incidence, severity and cure of cardiovascular disease through psycho-neuro-immunological pathways. Objective: This study was conducted to analyze the effect of bio-psycho-socio-spiritual factors on cardiovascular risk and inflammatory biomarkers. **Subjects and Methods:** A total of 121 subjects voluntarily participated in the study, were recruited using the cluster random sampling method from Posyandu (Indonesian health service). Each subject was examined for ELISA blood examination of the high sensitive C-reactive protein, transforming growth factor- $\beta$ , intracellular adhesion molecule-1 and interferon- $\gamma$ . The subjects filled out the depression anxiety stress scale-42 questionnaire for stress, anxiety and depression; WHOQOL BREF for quality of life and the solemnity questionnaires for the solemnity in Islamic prayer measurement. The assessment for cardiovascular risk using the Jakarta score method. **Results:** The biophysical factors which influence inflammatory biomarker include blood pressure on ICAM-1 and hs-CRP, body mass index on TGF- $\beta$ , and fasting blood glucose on hs-CRP. The influence of psychosocial factors include educational degree on ICAM-1 and hs-CRP, marital status on cardiovascular risk and depression on blood pressure. The solemnity in Islamic prayer is a spiritual coping that have effect on improving the quality of life. **Conclusion:** The biophysical factors having influence on inflammatory biomarker are blood pressure, body mass index and fasting blood glucose. The contribution from psycho-socio-spiritual factors include educational degree, marital status and depression.

**Keywords:** Biological, psychosocial, spiritual factors, inflammatory biomarkers.

**Corresponding Author:** Dr. Yusuf Alam Romadhon, Doctoral Student of Medical Science, Sebelas Maret University of Surakarta / Family Medicine and Public Health Department, Faculty of Medicine, Muhammadiyah University of Surakarta.

**Received:** November 2019

**Accepted:** November 2019

## Introduction

According to the World Health Organization (WHO), cardiovascular disease is one of the global causes of death, with a 31% rate across the world today.<sup>[1]</sup> In 2018, its risk factors in Indonesia were 34% for hypertension and the prevalence of impaired lipid profile and 1.5% for heart diseases. Meanwhile adherence to its anti-hypertensive medication was 54.4%, 12 % checked their blood pressure regularly, 10.9% were prevalent to stroke, 39.4% were in control of their body parts, and the prevalence of chronic kidney failure 0.38%.<sup>[2]</sup> From the point of view of health costs, cardiovascular diseases in the category of catastrophic diseases have accounted for 21.07% of the total health budget in Indonesia. The cost of an invasive action for cardiovascular disease is borne by the contributions of 3,717 healthy participants.<sup>[3-5]</sup> Efforts have been made to anticipate the development of cardiovascular disease, through risk screening. The Jakarta cardiovascular score is a risk screening tool developed after 13 years of cohort research and was first published by Kusmana.<sup>[6]</sup> It is currently used by the Ministry of Health in Indonesia to

screen cardiovascular disease.<sup>[7]</sup> Some publications use this tool for their studies.<sup>[8-12]</sup> In a cross-sectional study of 107 respondents with workers backgrounds, it was found that the Framingham score correlated strongly with the Jakarta cardiovascular scores using a coefficient of 0.592 and  $p = 0.000$ .<sup>[13]</sup>

Cardiovascular disease, which includes coronary heart and cerebrovascular diseases has a common basic mechanism, namely atherosclerosis. It is a disorder of lipid accumulation in the arterial wall and chronic inflammatory disease.<sup>[14,15]</sup> Long-term systemic inflammatory conditions have been shown to increase the risk of cardiovascular disease.<sup>[16]</sup> Inflammation previously proceeded by lipid accumulation, are both related to the innate and adaptive immune system's contribution to initiating and exacerbating the progression of atherosclerosis.<sup>[17]</sup> High sensitive C-reactive protein (hs-CRP) is the first inflammatory biomarker often used as a predictor of future cardiovascular events or changes in blood vessel structure. Its main role in atherosclerotic lesions is to trigger endothelial dysfunction.<sup>[16-24]</sup> The level of hs-CRP reflects the systemic inflammatory state, while the intracellular adhesion molecule-1 [ICAM-1] is the

manifestation of endothelial dysfunction.<sup>[25-27]</sup> Nuclear transcription factors in various leukocyte cells and this affects the production of various cytokines such as interleukin [IL] 1, IL4, IL6, tumor necrosis factor- $\kappa$  [TNF- $\kappa$ ], interferon- $\kappa$  [IFN- $\kappa$ ] and transforming growth factor- $\kappa$  [TGF- $\kappa$ ] which works on various molecular targets to form and worsen atherosclerotic plaque conditions.<sup>[28,29]</sup> Interferon- $\kappa$  and TGF- $\kappa$  are used to measure the performance of the adaptive immune system.<sup>[30]</sup> It increases the number of TGF- $\kappa$  receptors, ie endoglin, reduces atherosclerotic lesions by inhibiting the proliferation and migration of smooth muscle cells with an impact on plaque stabilization in experimental animal models, to ensure it achieves the TGF- $\kappa$  its serves as an anti-atherogenic.<sup>[31-33]</sup> Nevertheless, serum TGF- $\kappa$  levels above 200 ng/mL, is used to differentiate between normal individuals and those with coronary heart diseases.<sup>[34]</sup> TGF- $\kappa$  in levels of 300 ng/mL increases adhesion and migration by depending on the endothelial anchoring, though it is inhibitory when in concentrations of 1 ng/ml.<sup>[35]</sup> IL-6 is used as a general index of the degree of chronic inflammation, while TGF- $\kappa$  is commonly used to measure the degree of fibrosis and calcification in the micro-region of the heart and blood vessels.<sup>[36,37]</sup> Interferon- $\kappa$  is a pro-inflammatory cytokine produced by T cells, and expressed in high levels of atherosclerotic lesions, by contributing to the formation and release of free radical oxygen which further increases the expression of adhesion molecules and tissue destruction.<sup>[38-41]</sup> Interferon- $\kappa$  is positively correlated with the triglyceride levels were  $r = 0.560$ ,  $p \leq 0.05$ .<sup>40</sup> The involvement of adaptive immunity through the activation of T cells, suddenly changes to coronary instability, thereby, making interferon- $\kappa$  one of its performance products.<sup>[41]</sup> Psychosocial factors such as maladaptive coping strategies or anxiety conditions, post-traumatic stress disorder [PTSD] and depression, increases the risk of future cardiovascular diseases.<sup>[42-47]</sup> Mechanisms that mediate psychosocial factors with cardiovascular risk which are commonly proposed include low-level systemic inflammation from various biomarkers previously mentioned, autonomic nervous system disorders related to stress and abnormal hypothalamic pituitary adrenal axis pathways, with negative impact on the occurrence of endothelial dysfunction.<sup>48</sup> Exposure to acute stressors temporarily triggers the first wave reaction such as the activation of sympathetic nervous system which results in the release of adrenaline and noradrenaline catecholamines from the adrenal medulla. The second wave of stress response is the activation of the hypothalamic - pituitary - adrenal axis [HPA axis] followed by a slow increase in circulating cytokines such as IL-6 and IL-1.<sup>[49]</sup> Initially, the glucocorticoids produced via the HPA axis pathway suppressed inflammation, but with prolonged stress, it decreased in sensitivity during and continued to produce cytokines.<sup>[50]</sup> IL-6 and hs-CRP are increased biomarkers associated with psychosocial stressors

especially financial problems through psychological well-being, interpersonal distress, and stress adaptation.<sup>[51,52]</sup> Stress reactions activate key inflammatory pathways in peripheral white blood cells and nuclear factor -  $\kappa$ B [NF -  $\kappa$ B] resulting in a marked increase in pro-inflammatory cytokines such as IL-6 and hs-CRP.<sup>[53]</sup>

Factors of Islamic spirituality such as the solemnity [khusyuk] prayer [salat], has never been explored regarding the level of cardiovascular inflammatory biomarkers. Khusyuk is a unique Islamic spiritual factor, which consists of four constructs namely: 1) change of consciousness such as how much someone involves their consciousness during prayers, the level of qualitative consciousness, and the success of induction consciousness change associated with the intention [niyat]. Furthermore, enables factors that change of qualitative consciousness triggered by understanding the meaning of chanting and prayer movements, and due to life problems by complaining to God. Another sub construct in change of consciousness is the level of mind wandering control, 2) attachment to God such as how much a person feels calm and dependent when praying, 3) the spiritual atmosphere previously created during and after prayer, which includes spiritual maturity and conditioning 4) immediate relaxation during prayer.<sup>[54,55]</sup>

Until now, there has been no comprehensive research that examined these bio-psycho-socio-spiritual factors in relation to cardiovascular inflammatory biomarkers. Therefore, a good understanding of the relationship has the ability to provide a more effective and holistic approach to prevention, treatment and rehabilitation in cardiovascular disease management.

This research is intended to explore the influence of biological, psychosocial and Islamic spiritual (solemnity/khusyuk) factors on cardiovascular inflammatory biomarkers which include hs-CRP, TGF- $\kappa$ , ICAM-1 and interferon- $\kappa$ . Secondly, it examines the correlation between Jakarta cardiovascular scores and the inflammatory biomarkers.

## Subjects and Methods

### Study participants

Research subjects were elderly members of the Indonesian health service (Posyandu) in a working area of Kartasura Sukoharjo, Central Java, Indonesia. We first enrolled 121 subjects who did not suffer any clinical related disease between November 2018 and January 2019. The enrolment was using cluster random sampling technique.

### Measurement

The depression, anxiety, and stress level of each participant were measured using the DASS 42 questionnaire. While the WHOQOLBREF questionnaire was used to measure the quality of life, with a solemn questionnaire used to measure the level of solemnity [khusyuk] in Islamic prayer. The solemnity questionnaire was tested for the theoretical

validity through a review of psychology and religion experts, and tested for reliability on 90 medical students with Cronbach alpha 0.945.

Cardiovascular risk was determined by the Jakarta Score, while the inflammation biomarker was examined by measuring the serum levels of each biomarker using the ELISA method. The hs-CRP ELISA examination was using commercial reagents by Calbiotech, Inc., USA, and ICAM-1, TGF-β, and Interferon-γ by Wuhan Fine Biotech Co. China. The laboratory examination procedures are under the guidelines provided by the company.

Furthermore, the venous blood sampling from participants was carried out from 06.30 am until 08.30 am, after the participants had finished fasting for 10-12 hours. Blood were drawn from participants in a seated position through the anterior cubital vein by using a 3 cc syringe and stored in a non-heparinized tube before being taken to the laboratory. The samples were centrifuged at 3000 RPM for 10 minutes to separate the serum elements. Further, inflammatory biomarkers was examined by ELISA in the Laboratory of Molecular Biology, Faculty of Pharmacy, Muhammadiyah University of Surakarta.

**Statistics**

The independent variable with categorical scale, include age, occupation, gender, education, revenue, marital status, body mass index, blood pressure, fasting blood glucose, physical activity, TGF-β, ICAM-1, stress, depression, anxiety, quality of life, level of solemnity in Islamic prayer, and cardiovascular risk. The dependent variable in this study are inflammatory biomarker include hs-CRP, TGF-β, ICAM-1 and interferon-γ all in continuous scale, and data distribution are non-parametric. We used Mann Whitney to test mean different these variable for every attribute of

independent variable.

In testing for the factors that have influence on biopsychosocial indicators, the data distribution are normal in variables like level of solemnity, quality of life, cardiovascular risk and body mass index. The other variables like systolic blood pressure, diastolic blood pressure, fasting glucose level, stress, depression, anxiety and revenue have non-parametric data distribution. When testing mean different for normal distribution data, we apply independent t test, and the others using Mann Whitney.

In testing the correlation between cardiovascular risk and inflammatory biomarker, all variables in continuous scale and the data distribution in non-parametric, we apply Spearman correlation test.

**Results**

In general, the characteristics of the subjects are presented in table I The elderly Posyandu, in this study had similar pattern and was dominated by women. Although this activity is solely made for the elderly, it turned out that the active ones were those in their middle ages. Majority were high school graduates, married, not working, had an income above the regional minimum wage, normal body weight, mild physical activity, with psychological status of subjects in terms of anxiety, depression and stress, majorly witnessed under normal circumstances. However, cardiovascular risk, based on Jakarta's score, analyzed that most respondents were in the moderate and high categories. For hs-CRP inflammatory biomarkers, all participants were categorized as being at low risk, while interferon-γ was still within the normal range. In this study, although some respondents higher levels of TGF-β and ICAM-1, majority were normal.

**Table 1: Demographic characteristics of study subjects (n = 121)**

No	Variable	Mean	SD	Min	Max	Attribute	Σ	%
1	Age	52.93	7.21	40	73	Pre-elderly	95	79
						Elderly	26	21
2	Occupation	-	-	-	-	Work	46	38
						Does not work	75	62
3	Gender	-	-	-	-	Male	15	12
						Female	106	88
4	Education	-	-	-	-	≥ 12 years	97	80
						< 12 years	24	20
5	Revenue (Rupiah)	2,346,860	1,508,271	3,00,000	7,000,000	>regional minimum wage	70	58
						≤regional minimum wage	51	42
6	Marital status	-	-	-	-	Married	108	89
						Not married	13	11
7	Body mass index (kg w/m <sup>2</sup> h)	24.81	3.85	14.88	36.64	≤ Normoweight	68	56
						Overweight/obese	53	44
8	Blood pressure					Normotension	81	67
						Borderline/hypertension	40	33
9	Fasting blood glucose (mg/dL)	106.94	34.17	61	315	Normal	102	84
						High	19	16
10	Physical activity	-	-	-	-	Moderate/heavy	31	26
						Light	90	74
11	hs-CRP (mg/L)	0.021	0.010	0.00	0.05	-	-	-
12	TGF-β (pg/mL)	51.380	102.79	0.000	412.00	Normal	104	86
						Higher	17	14

13	ICAM-1 (ng/mL)	176.31	496.79	0.000	3089.99	Normal	107	88
						Higher	14	12
14	IFN- $\gamma$ (pg/mL)	0.605	2.263	0.000	16.76	-	-	-
15	Stress	6.372	5.485	0.000	20.00	Normal	106	88
						Stress	15	12
16	Depression	3.124	3.671	0.000	13.00	Normal	107	88
						Depression	14	12
17	Anxiety	4.694	4.399	0.000	28.00	Normal	90	74
						Anxiety	31	26
18	Quality of life	404.36	53.45	306.25	593.75	< Median	60	50
						$\geq$ Median	61	50
19	Level of solemnity in Islamic prayer	250.21	25.56	170	294	< Median	60	50
						$\geq$ Median	61	50
20	Cardiovascular risk	3.47	2.55	-2	12	Low	41	34
						Moderate	49	40
						High	31	26

**Table 2: Differences in mean levels of inflammatory biomarkers from various categorical variables**

Variable	Attribute	N	Mean	SD	P
<b>ICAM-1</b>					
Education	$\geq$ 12 years	97	109.030	336.536	0.042
	< 12 years	24	448.239	847.755	
Blood pressure	Normotension	82	141.29	408.90	0.038
	Borderline/hypertension	39	249.94	644.02	
<b>TGF-<math>\beta</math></b>					
Body mass index	$\leq$ Normoweight	80	46.50	104.65	0.051
	Overweight/obese	41	60.90	99.62	
<b>hs-CRP</b>					
Blood pressure	Normotension	82	0.019	0.009	0.038
	Borderline/hypertension	39	0.023	0.011	
Fasting blood glucose	Normal	102	0.020	0.009	0.048
	High	19	0.025	0.013	
Level of solemnity in Islamic prayer	< Median	60	0.018	0.009	0.006
	$\geq$ Median	61	0.023	0.010	

**Table 3: Difference in mean bio-psycho-socio-spiritual indicators from various categorical variables**

Variabel	Atribut	N	Mean	SD	P
<b>Jakarta cardiovascular score</b>					
Marital status	Married	108	3.67	2.51	0.014
	Not married	13	1.85	2.38	
<b>Systolic blood pressure (mmHg)</b>					
Depression	Normal	107	122.48	17.58	0.037
	Depression	14	115.00	22.79	
<b>Quality of life</b>					
Age	Pre-elderly	95	398.97	52.42	0.034
	Elderly	26	424.04	53.55	
Marital status	Married	108	408.29	53.99	0.019
	Not married	13	371.64	35.69	
Level of solemnity in Islamic prayer	< Median	60	392.19	43.65	0.016
	$\geq$ Median	61	416.33	59.55	
<b>Level of solemnity in Islamic prayer</b>					
Fasting blood glucose	Normal	102	248.17	25.66	0.041
	High	19	261.16	22.61	
<b>Revenue (Rupiah)</b>					
Education	$\geq$ 12 years	97	2,557,010	1,502,389	0.000
	< 12 years	24	1,497,500	1,228,279	
Khusyuk in Islamic prayer	< Median	60	2,691,167	1,628,277	0.016
	$\geq$ Median	61	2,008,197	1,306,719	

**Table 4: Correlation between Jakarta cardiovascular scores and levels of inflammatory biomarkers**

		hs-CRP	TGF- $\beta$	ICAM1	IFN- $\gamma$
Jakarta cardiovascular score	r	0.038	-0.099	0.052	-0.125
	p	0.681	0.282	0.570	0.173

In [Table 2], it was found that the mean ICAM-1 level was statistically significant higher in subjects with low

education and hypertension. Subjects with higher mean TGF- $\beta$  levels were found in the overweight/obese group,



while higher mean hs-CRP levels were found in the groups with high blood pressure, high glucose levels, and high score of *khushyuk*. Mean interferon- $\gamma$  levels were not found statistically significant in all groups of categorical variables. In [Table 3], it was found that married subjects had higher Jakarta cardiovascular scores, and systolic blood pressure tended to be lower in individuals with higher depressive scores. The marital status (married), age (elderly) and high solemn score had a better mean quality of life, and are statistically significant. Individuals with higher blood glucose levels had higher solemn scores, while those with high income have lower rates of solitude. Highly educated subjects have a higher average income.

In [Table 4], Jakarta's cardiovascular scores do not have a statistical correlation with all inflammatory biomarkers tested in this study.

## Discussion

### Inflammatory biomarkers

All subjects of the study had low hs-CRP levels (below 1 mg/L), although in Jakarta cardiovascular score calculations two-thirds had moderate and high cardiovascular risk. From the literature it is mentioned that, levels of hs-CRP are categorized as low risk if the levels are 0 – <1 mg/L, moderate risk 1 – 3 mg/L and high risk > 3 mg/L. The increase is due to non-specific processes when the levels are > 10 mg/L.<sup>[56-58]</sup> When this is compared with other studies, such as blacks and whites in America in terms of BMI, hs-CRP and ICAM-1, there is an upward trend in BMI followed by increases in hs-CRP and ICAM-1.<sup>[59]</sup> In terms of hs-CRP levels in the current study population, compared with other studies.<sup>[24,59,60]</sup> All subjects, regardless of cardiovascular risk, hs levels -CRP less than 1 mg/L, however, further investigation is required for polymorphism. The implication of the classification of cardiovascular risk based on hs-CRP levels needs to be reviewed for the Javanese populations. Secondly, the possibility, stress, depression and anxiety levels are mostly normal - moderate subjects, therefore, there is not enough dose as an allostatic burden to trigger an increase in hs-CRP production. According to the literature, the level of hs-CRP is the most consistent biomarker associated with stress levels and other psycho-emotional disorders.<sup>[61-63]</sup>

In this study, ICAM-1 levels were influenced by education level and blood pressure. Overweight/obese have a tendency to increase TGF- $\beta$  levels, with the hs-CRP levels affected by high blood pressure, high blood glucose levels and high solitude [*khushyuk*]. In another study ICAM-1 levels were affected by stress and exercise with high intensity.<sup>64</sup> The ICAM-1 levels is reduced by administering atorvastatin, which shows the role of lipid profiles in modulating inflammation of the endothelial dysfunction pathway.<sup>[65,66]</sup>

The effect of education on ICAM-1 levels is explained through its relationship with income level. The short formal education period affects the level of income, where the short formal education period and average income is lower

than the longer education period. Short formal education period makes ICAM-1 levels higher than longer ones, which is interpreted as an education resulting in a "low" self-efficacy in meeting the demands of life, thereby, leading to higher stress level. This is achieved through the psychoneuroimmunology explanation pathway, from the hypothalamus-pituitary-adrenal axis [HPA axis] pathway and the sympathetic nervous system. It leads to an increase in inflammatory biomarkers, and further triggers endothelial dysfunction, with one of the biomarkers as ICAM-1.

The absence of variables that affect interferon- $\gamma$  in this study, explains that the hs-CRP levels are still below one, which is categorized as having a low alostatic load. Therefore the degree of endothelial dysfunction is not yet sufficient to generate an adaptive immune response. One of the products of the adaptive immune response which influences the pathogenesis of atherosclerosis is interferon- $\gamma$ .

The TGF- $\beta$  in this research is influenced by biological factors and body mass index due to increasing levels of hs-CRP through levels of IL-6 which triggers the liver to produce further CRP.<sup>[67]</sup> In other studies, obese subjects carried out high-intensity exercise which increased ICAM-1 levels.<sup>64</sup> Clinical conditions that affect TGF- $\beta$  levels are post-traumatic stress disorders [PTSD].<sup>[68]</sup> By looking at the role of TGF- $\beta$  in post-destructive inflammatory remodeling, hypertrophic cardiomyopathy, high levels of TGF- $\beta$  in serum indicates an inflammatory "relief" process.<sup>[28,37]</sup> It can be interpreted that, the subjects of this study have not experienced "damage" that requires "damping" TGF- $\beta$ .

### Biophysical Marker

Two biophysical markers in this study, which found a significant mean difference, were Jakarta cardiovascular scores and systolic blood pressure. Married subjects had higher cardiovascular scores than unmarried. This condition can be explained that in this study population there was a tendency (although not statistically significant), married subjects had higher in incomes, body mass index, blood pressure systole or diastole and fasting blood glucose levels. So these factors make their cardiovascular scores higher. While psychosocial factors such as stress, depression and anxiety are found to be higher in those who are not married. It can be interpreted that, biophysical factors more dominance on cardiovascular risk than psychosocial factors in this population.

Subjects with higher depression scores had lower systolic blood pressure than normal. This situation is consistent with the theory that the blood pressure of people experiencing depression has decreased.<sup>[69]</sup>

### Psycho-socio-spiritual marker

Psycho-socio-spiritual conditions with statistical significance in this study are quality of life, level of solemnity and income. The elderly, married and those with high solemn scores, have a better quality of life than the pre-elderly, not married, and those with low quality of life respectively. Subjects with higher fasting blood glucose

levels have higher solemnity scores than low score. Subjects with lower income more solemn than higher. The subjects with high solemnity scores have higher levels of hs-CRP, higher blood glucose levels, lower income levels and a better quality of life score. There is an impression that solemnity is a state of "stress" but not to the point of causing distress instead it tends to improve the quality of life. In another words, solemnity as coping strategies that has impact on improving quality of life. It means that solemnity is easier to emerge when someone is in a state of having problems. In previous qualitative study mentioned that solemn more easily arise when someone has a problem. Solemn prayer [salat khusyuk] is a media to complain to Allah. The following are three expressions in a previous study. The first subject phrase "... complains like a child complains to God ... when there is no one ... no place to complain...feels helpless". The second subject phrase "As people confide ... we feel comfortable telling ... to God". The third subject phrase "all surrendered [pasrah; Javanese phrase] to Allah truly when it was only me and Allah with the medium of prayer". Prayer [salat] is a method for cognitive and emotional restructuring. As the following fourth subject phrase. "When there is a problem, the heart is chaotic ... restless ... be it a problem that causes anger or one who drowns himself in sadness ... made prayer, the heart becomes calm, then arises in the heart of gratitude, because there is a place to complain, after that begin to see a new perspective, no longer looking at our measurements, but returning to God's measurements, why is this destined so and so ... if I acted A, would the results be as expected ... if I acted B, if the results were as expected ... if I didn't act, were the results according to expectations ... all that ruminate ("muteeer" Javanese phrase) keeps on thinking ... basically, being able to analyze one by one.<sup>[70]</sup>

Jakarta cardiovascular scores and Inflammatory Biomarkers There is no correlation between Jakarta cardiovascular scores and all inflammatory biomarkers tested in this study, because Jakarta cardiovascular score calculations do not take into account lipid profile disorders. Cohort studies were carried out using same factors with calculating LDL and hsCRP factors (cutoff point 70 mg/dL and 2 mg/L for LDL and hsCRP respectively) and was able to predict future cardiovascular events with a better degree of difference in cutoff point value of the two factors.<sup>[71,72]</sup> Studies that compared the levels of inflammatory biomarkers [hsCRP], Framingham cardiovascular risk scores with severity of non-fatty liver disease show a consistent pattern.<sup>[73]</sup>

## Conclusion

Biophysical factors that influence inflammatory biomarkers include blood pressure, body mass index, and (blood pressure and blood glucose) at ICAM-1, TGF-level, and hsCRP levels respectively. Psycho-socio-spiritual factors that influence inflammatory biomarkers include education, and solemn at ICAM1 and hsCRP levels. Biophysical factors such as Jakarta cardiovascular score are influenced by marital status, while depressing blood pressure. Khusyuk

is a spiritual coping strategy created to overcome stress capable of improving the quality of life.

## Ethical Approval

This study has been approved by Ethic Committee with Ethical Clearance number 238/UN27.6/KEPK/2018

## Author Contribution

All authors contributed equally. The first author established the concept and wrote the draft of the article. The second, third, and fourth authors revised the concept and added many improvements in method, result and discussion.

## References

1. World Health Organization (2017) Key Fact Cardiovascular diseases (CVDs), [https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) diakses pada tanggal 30 Juli 2019 jam 22.16 WIB Bartekova, M., Radosinska, J., Jelemensky, M., Dhalla, N.S. (2018) Role of cytokines and inflammation in heart function during health and disease, *Heart Failure Reviews* (2018) 23:733–758 <https://doi.org/10.1007/s10741-018-9716-x>
2. Ministry of Health of the Republic of Indonesia (2019) The National Reports Basic Health Research / Laporan Nasional Riset Kesehatan Dasar 2018, Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan Republik Indonesia
3. BPJS, (2017), Pembiayaan JKN untuk Katastropik
4. BPJS (2017) Berita BPJS pada tanggal 19 Jul 2017 17:05:05 <http://bpjs-kesehatan.go.id/bpjs/index.php/post/read/2017/475/BPJS-Kesehatan-Ajak-Pelajar-Budayakan-Pola-Hidup-Sehat-Sejak-Dini/berita>
5. BPJS (2018) Berita BPJS pada tanggal 17 – 09 – 2018 <http://bpjs-kesehatan.go.id/BPJS/index.php/arsip/detail/1068>
6. Kusmana, D (2002) The influence of smoking cessation, regular physical exercise and/or physical activity on survival: a 13 years cohort study of the Indonesian population in Jakarta, *Med J Indones* 2002; 11: 230-41
7. Kementerian Kesehatan Republik Indonesia (2017) Petunjuk Teknis Penatalaksanaan Penyakit Kardiovaskular Untuk Dokter, Sekretariat Jenderal Pusat Kesehatan Haji Kementerian Kesehatan Republik Indonesia
8. Tiksnadi, B.B (2018) Gambaran Profil Risiko Kardiovaskular Berdasarkan Skor Kardiovaskular Jakarta pada Kader Kesehatan di Desa Cilayang Kecamatan Jatinangor, *Jurnal Pengabdian Kepada Masyarakat* Vol 2, No 11
9. Yusvita, F., Nandra, N.S. (2018) Gambaran Tingkat Risiko Penyakit Jantung dan Pembuluh Darah Pada Pekerja Di PT.X, *Forum Ilmiah* Vol 15 No 2, Mei 2018
10. Subekti, I., Susatia, B., Yusrizal, (2018) Faktor Resiko Penyakit Jantung Koroner dan Senam Jantung Sehat, *Jurnal Pendidikan Kesehatan*, Vol 4, No. 1, APRIL 2015: 46-52
11. Sari, E.A., Sari, S.P., Pratiwi, S.H. (2018) Community Self-Efficacy of Coronary Heart Disease Based on Characteristic Risk Factors, *NurseLine Journal* Vol. 3 No. 2 Nov
12. Istiqomah, N.I. (2018) Risks of Coronary Heart Disease Community Lumajang, *Prosiding 1st Annual Agricultural Health Nursing Seminar: "Update Management And Prevention Related To Agricultural Activities Clinical Setting"* UPT Percetakan dan Penerbit Universitas Jember
13. Adiatmaja, I.B. (2004) Analisis Faktor Risiko yang Berpengaruh terhadap Skor Kardiovaskular Jakarta dan Skor Framingham pada Pekerja PT-X Jakarta, Thesis, Universitas Indonesia
14. Yamashita, T., Sasaki, N., Kashara, K., Hirata, K-i. (2015) Anti-inflammatory and immune-modulatory therapies for preventing atherosclerotic cardiovascular disease, *J Cardiol* 66 (2015) 1 – 8
15. Saxena, A., Russo, I., Frangogiannis, N.G. (2016) Inflammation as a therapeutic target in myocardial infarction: learning from past failures to meet future challenges, *Transl Res.* 2016 January ; 167(1): 152–166. Author manuscript; available in PMC 2017 January 01.

16. Giudice, M.D., Gangestad, S.W. (2018) Rethinking IL-6 and CRP Why they are more inflammatory biomarkers and why it matters, *Brain, Behavior and Immunity* 70 (2018) 61 – 75
17. Neupane, R., Jin, X., Sasaki, T., Li, X., Murohara, T., Cheng, X.W. (2019) Immune Disorder in Atherosclerotic Cardiovascular Disease, Clinical Implications of Using Circulating T-Cell Subsets as Biomarkers, *Circulation Journal* doi: 10.1253/circj.CJ-19-0114
18. Hackam, D.G., Anand, S.S. (2003) Emerging Risk Factors for Atherosclerotic Vascular Disease A Critical Review of the Evidence, *JAMA*, August 20, 2003 - Vol 290, No. 7
19. Hermus, L., Lefrandt, J.D., Tio, R.A., Breek, J-C., Zeebregts, C.J. (2010) Carotid plaque formation and serum biomarkers, *Atherosclerosis* 213 (2010) 21 – 29
20. Thanassoulis, G., Massaro, J.M., Cury, R., Manders, E., Benjamin, E.J., Vasani, R.S., Cupple, A., Hoffmann, U., "Donnell, C.J., Kathiresan, S. (2010) Associations of Long-Term and Early Adult Atherosclerosis Risk Factors With Aortic and Mitral Valve Calcium, *Journal of the American College of Cardiology* Vol 55 No 22
21. Kablak-Ziemicka, A., Przewlocki, T., Sokolowski, A., Tracz, W., Podolec, P. (2011) Carotid intima-media thickness, hs-CRP and TNF- $\alpha$  are independently associated with cardiovascular event risk in patients with atherosclerotic occlusive disease, *Atherosclerosis* 214 (2010) 185 – 190
22. Sena, C.M., Pereira, A.M., Seica, R. (2013) Endothelial dysfunction - A major mediator of diabetic vascular disease, *Biochimica et Biophysica Acta* 1832 (2013) 2216 – 2231
23. Shrivastava, A.K., Singh, H.V., Raizada, A., Singh, S.K. (2015) C-reactive protein, inflammation and coronary heart disease, *The Egyptian Heart Journal* (2015) 67, 89 – 97
24. Verma, I., Syngle, A., Krishan, P. (2017) Predictors of endothelial dysfunction and atherosclerosis in rheumatoid arthritis in Indian population, *Indian Heart Journal* 69 (2017) 200–206
25. Tousoulis, D., Papageorgiou, N., Androulakis, E., Siasos, G., Latsios, G., Tetolouris, K., Stefanadis, C. (2013) Diabetes Mellitus - Associated Vascular Impairment, *J Am Coll Cardiol* Vol 62 No 8 2013
26. Tomey, M.L., Narula, J., Kovacic, J.C. (2014) Advances in the Understanding of Plaque Composition and Treatment Options, *J Am Coll Cardiol* Vol 63 No 16
27. Hazarika, S., Annex, B.H. (2017) Biomarkers and Genetics in Peripheral Artery Disease, *Clinical Chemistry* 63:1 236–244 (2017)
28. Bartekova, M., Radosinska, J., Jelemensky, M., Dhalla, N.S. (2018) Role of cytokines and inflammation in heart function during health and disease, *Heart Failure Reviews* (2018) 23:733–758 <https://doi.org/10.1007/s10741-018-9716-x>
29. Hori, H., Kim, Y. (2019) Inflammation and post-traumatic stress disorder, *Psychiatry and Clinical Neurosciences* 73: 143–153, 2019
30. Ketelhuth, D.F.J., Hansson, G.K. (2016) Adaptive Response of T and B Cells in Atherosclerosis, *Circ Res.* 2016;118:668-678. DOI: 10.1161/CIRCRESAHA.115.306427
31. Vecerova, L., Strasky, Z., Rathouska, J., Slanarova, M., Brcakova, E., Micuda, S., Nachtigal, P. (2012) Activation of TGF-B Receptors and Smad Proteins by Atorvastatin is Related to Reduced Atherogenesis in ApoE/LDLR Double Knockout Mice, *Journal of Atherosclerosis and Thrombosis* Vol 19 No 2
32. Dhaouadi, N., Li, J-Y., Feugier, P., Gustin, M-P., Dab, H., Kacem, K., Bricca, G., Cerutti, C. (2014) Computational identification of potential transcriptional regulators of TGF-B1 in human atherosclerotic arteries, *Genomics* 103; 357-370
33. Jang, Y-S., Choi, I-H. (2014) Contrasting Roles of Different Endoglin Forms in Atherosclerosis, *Immune Network* 2014;14(5):237-240
34. Chen, C., Lei, W., Chen, W., Zhong, J., Gao, X., Li, B., Wang, H., Huang, C. (2014) Serum TGF- $\beta$ 1 and SMAD3 levels are closely associated with coronary artery disease, *BMC Cardiovascular Disorders* 4, 14:18
35. Camaré, C., Pucelle, M., Nègre-Salvayre, A., Salvayre, R. (2017) Angiogenesis in the atherosclerotic plaque, *Redox Biology* 12 (2017) 18–34 <http://dx.doi.org/10.1016/j.redox.2017.01.007>
36. Mancini, D., Monteagudo, J., Suárez-Fariñas, M., Bander, J., Varshney, R., Gonzalez, J., Coller, B.S., Ahamed, J. (2018) New methodologies to accurately assess circulating active transforming growth factor- $\beta$ 1 levels: implications for evaluating heart failure and the impact of left ventricular assist devices, *Translational Research* 2018;192:15–29
37. Podolec, J., Baran, J., Siedlinski, M., Urbanczyk, M., Krupinski, M., Bartus, K., Niewiara, L., Podolec, M., Guzik, T., Tomkiewicz-Pajak, L., Komar, M., Kablak-Ziemicka, A. (2018) Serum Rantes, Transforming Growth Factor-B1 and Interleukin-6 Levels Correlates with Cardiac Muscle Fibrosis in Patients with Aortic Valve Stenosis, *Journal of Physiology and Pharmacology* 2018, 69, 4, 615 – 623
38. Voloshyna, I., Littlefield, M.J., Reiss, A.B. (2014) Atherosclerosis and interferon- $\gamma$ : New insights and therapeutic targets, *Trends Cardiovasc Med.* 2014 January; 24(1) Author manuscript; available in PMC 2015 January 01
39. Mangge, H., Becker, K., Fuchs, D., Gostner, J.M. (2014) Antioxidants, inflammation and cardiovascular disease, *World J Cardiol* 2014 June 26; 6(6): 462-477
40. Liang, K., Dong, S-R., Peng, H. (2016) Serum levels and clinical significance of IFN-g and IL-10 in patients with coronary heart disease, *Eur Rev Medic & Pharmacol Sci* 2016; 20: 1339-1343
41. Flego, D., Liuzzo, G., Weyand, C.M., Crea, F. (2016) Adaptive immunity Dysregulation in Acute Coronary Syndromes, *J Am Coll Cardiol* (2016) Vol 68 No 19
42. Dimsdale, J.E. (2010) What Does Heart Disease Have to Do With Anxiety? *Journal of the American College of Cardiology* Vol 56 No 1 2010 doi:10.1016/j.jacc.2010.04.013
43. Roohafza, H., Talaei, M., Pourmoghaddas, Z., Rajabi, F., Sadeghi, M. (2012) Association of social support and coping strategies with acute coronary syndrome: A case - control study, *Journal of Cardiology* (2012) 59, 154 – 159
44. Chauvet-Gélinier, J-C., Trojak, B., Vergès-Patois, B., Cottin, Y., Bonin, B. (2013) Review on Depression and Coronary Heart Disease, *Archives of Cardiovasc Disease* (2013) 106, 103 – 110
45. Burg, M.M., Soufer, R. (2016) Post-traumatic Stress Disorder and Cardiovascular Disease, *Curr Cardiol Rep* (2016) 18: 94
46. Chauvet-Gélinier, J.-C., Bonin, B. (2017) Stress, anxiety and depression in heart disease patients: A major challenge for cardiac rehabilitation, *Annals of Physical and Rehabilitation Medicine* 60 (2017) 6–12
47. Chiang, J.J., Turiano, N.A., Mroczek, D.K., Miller, G.E. (2018) Affective Reactivity to Daily Stress and 20-year Mortality Risk in Adults with Chronic Illness: Findings from the National Study of Daily Experiences, *Health Psychol.* 2018 February ; 37(2): 170–178 Author manuscript; available in PMC 2019 February 01
48. Pizzi, C., Santarella, L., Bugiardini, R. (2014) Epidemiology and the physiopathological link between depression and cardiovascular disease, *IJC Metabolic & Endocrine* 5 (2014) 52 – 55
49. Meyer, T., Wirtz, P.H. (2017) Mechanisms of Mitochondrial Redox Signalling in Psychosocial Stress-Responsive Systems: New Insights into an Old Story, *Antioxidants & Redox Signaling* Vo 00 No 00 2017 doi: 10.1089/ars.2017.7186
50. Straub, R.H., Cutolo, M. (2017) Psychoneuroimmunology—developments in stress research, *Wien Med Wochenschr* DOI 10.1007/s10354-017-0574-2
51. Sturgeon, J.A., Arewasikporn, A., Okun, M.A., Davis, M.C., Ong, A.D., Zautra, A.J. (2016) The psychosocial context of financial stress: Implications for inflammation and psychological health, *Psychosom Med.* 2016 ; 78(2): 134–143. doi:10.1097/PSY.0000000000000276. Author manuscript; available in PMC 2017 February 01
52. Elliot, A.J., Chapman, B.P. (2016) Socioeconomic status, psychological resources, and inflammatory markers: Results from the MIDUS Study, *Health Psychol.* 2016 November; 35(11): 1205–1213 Author manuscript; available in PMC 2016 November 01
53. Miller, A.H., Raison, C.L. (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target, *Nat Rev Immunol.* 2016 January ; 16(1): 22–34. Author manuscript; available in PMC 2017 August 03
54. Romadhon, Y.A., 2018, Shalat sebagai aktivitas kognitif kompleks: kajian teoretis dan studi kualitatif, *The 7th University Research Colloquium 2018 STIKES PKU Muhammadiyah Surakarta*
55. Romadhon, Y.A., 2019, Perilaku khusus dalam perspektif neurosains dan kedokteran pencegahan dalam Buku Pengantar Kajian Ilmu Kedokteran pada Ibadah Sholat Perspektif neurosains, kedokteran pencegahan, kronobiologi kedokteran, dan psikoneuroimmunologi, *Muhammadiyah University Press*, September pp 149 – 169
56. Ridker, P.M. (2001) High-Sensitivity C-Reactive Protein Potential Adjunct for Global Risk Assessment in the Primary Prevention of



- Cardiovascular Disease, *Circulation*;103:1813-1818.
57. Pfützner, A., Forst, T. (2006) High-Sensitivity C-Reactive Protein as Cardiovascular Risk Marker in Patients with Diabetes Mellitus, *Diab Tech & Ther* Vol 8, No 1
  58. Rodriguez, E.J., Kim, E.N., Sumner, A.E., Nápoles, A.M., Pérez-Stable, E.J. (2019) Allostatic Load: Importance, Markers, and Score Determination in Minority and Disparity Populations, *J Urban Health* (2019) 96 (Suppl 1):S3–S11 <https://doi.org/10.1007/s11524-019-00345-5>
  59. Ransome, Y., Slopen, N., Karlsson, O., Williams, D.R. (2018) Elevated inflammation in association with alcohol abuse among Blacks but not Whites: results from the MIDUS biomarker study, *Journal of Behavioral Medicine* (2018) 41:374–384
  60. Tyagi, N., Kaur, C., Mohanty, A., Kabi, A., Kumari, S., Sahoo, S.S., Ramteke, A., Bagra, P., Choudhari, O.K., Kumar, R., Prasad, J., Kabi, B.C. (2019) Association of high sensitivity C-reactive Protein (hsCRP) with Coronary Artery Disease (CAD), *World Journal of Pharmacy and Pharmaceutical Sciences* Vol 8, Issue 2, 2019.
  61. Elliot, A.J., Heffner, K.L., Mooney, C.J., Moynihan, J.A., Chapman, B.P. (2018) Social Relationships and Inflammatory Markers in the MIDUS Cohort: The Role of Age and Gender Differences, *Journal of Aging and Health* 2018, Vol. 30(6) 904–923
  62. Nersesian, P.V., Han, H-R., Yenokyan, G., Blumenthal, R.S., Nolan, M.T., Hladek, M.D., Szanton, S.L. (2018) Loneliness in middle age and biomarkers of systemic inflammation: Findings from Midlife in the United States, *Social Science & Medicine* 209 (2018) 174–181
  63. Seiler, A., Murdock, K.W., Fagundes, C.P. (2018) Impaired mental health and low-grade inflammation among fatigued bereaved individuals, *J Psychosomatic Res* 112 (2018) 40–46
  64. Park, J., Willoughby, D.S., Song, J.J., Leutholtz, B.C., Koh, Y. (2018) Exercise-induced changes in stress hormones and cell adhesion molecules in obese men, *Journal of Inflammation Research* 2018:11 69–75
  65. Tousoulis D, Antoniades C, Bosinakou E, et al. Inflammatory cytokines in atherosclerosis: current therapeutic approaches. *European Heart Journal*, Volume 37, Issue 22, 2016;1723-1732
  66. Kosmas, C.E., Silverio, D., Sourlas, A., Montan, P.D., Guzman, E., Garcia, M.J. (2019) Anti-inflammatory therapy for cardiovascular disease, *Ann Transl Med* 2019;7(7):147
  67. Ong, A.D., Benson, L., Zautra, A., Ram, N. (2018) Emodiversity and Biomarkers of Inflammation, Emotion. 2018 February; 18(1): 3–14. Author manuscript; available in PMC 2019 February 01.
  68. Mellon, S.H., Gautam, A., Hammamieh, R., Jett, M., Wolkowitz, O.M. (2018) Metabolism, Metabolomics, and Inflammation in Posttraumatic Stress Disorder, *Biological psychiatry*, 83(10)
  69. Maramis, W.F., Maramis, A.A. (2009) *Catatan Ilmu Kedokteran Jiwa*, Airlangga University Press
  70. Romadhon, Y.A. (2019) Construct Solemnity in Islamic Prayer and Its Influence on Health in Indonesian, The 9th University Research Colloquium Universitas Muhammadiyah Purworejo
  71. Libby, P., Ridker, P.M., Hansson, G.K. (2009) Inflammation in Atherosclerosis From Pathophysiology to Practice, *JACC* Vol. 54, No. 23, Dec 1st:2129–38
  72. Ridker, P.M., Danielson, E., Fonseca, F.A.H., Genest, J., Gotto Jr, A.M., Kastelein, J.J.P., Koenig, W., Libby, P., Lorenzatti, A.J., MacFadyen, J.G., Nordestgaard, B.G., Shepherd, J., Willerson, J.T., Glynn, R.J. (2009) Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial, *Lancet* 2009; 373: 1175–82
  73. Yu, E., Hsu, H-Y., Huang, C-Y., Hwang, L-C. (2018) Inflammatory biomarkers and risk of atherosclerotic cardiovascular disease, *Open Med*. 2018; 13: 208-213

**Copyright:** © the author(s), 2019. It is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), which permits authors to retain ownership of the copyright for their content, and allow anyone to download, reuse, reprint, modify, distribute and/or copy the content as long as the original authors and source are cited.

**How to cite this article:** Romadhona YA, Purwantob B, Romdonic R, Surotod. Effects of Bio-Psycho-Socio-Spiritual Factors on Biomarkers of Cardiovascular Inflammation in Elderly Indonesian Muslim. *Asian J. Med. Res.* 2019;8(4):ME36-ME43.  
DOI: [dx.doi.org/10.21276/ajmr.2019.8.4.ME6](https://doi.org/10.21276/ajmr.2019.8.4.ME6)

**Source of Support:** Nil, **Conflict of Interest:** None declared.