

## Absence of Association Between Serum Folate and Blood Pressure on Fisherman in Bulak District

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### Abstract

Folate deficiency induces homocysteine efflux into the circulation by inhibiting remethylation pathway. That matter cause increasing circulating homocysteine levels, which commonly called hyperhomocysteinemia. Hyperhomocysteinemia is fully recognised as an independent risk factor for cardiovascular disease. This cross-sectional study examined association between serum folate and blood pressure on fisherman in Bulak District. An observational analytic with cross sectional design on 95 fishermen aged 26-≤60 years. After adjusted with inclusion and exclusion criteria then 31 fishermen participated in this study. The sample frame on this study is the list of fishermen names who still on duty, owned by the fisherman chief. Binary logistic regression test showed no correlation between serum folate level with prehypertension and hypertension by means of significance value  $p = 0,573$ . The incidence of hypertension and prehypertension occurred in fishermen aged  $\geq 40$  years, in poor fishermen with limited education. Serum folate of respondent was normal ( $>3\text{ng/mL}$ ) but folate intake of respondents inadequate compared to Recommended Dietary Allowance (RDA). We conclude that there is no association between serum folate with high blood pressure. Respondent's folate serum was normal despite low of folate intake because supporting nutritional intake of vitamins  $B_{12}$  and  $B_6$  were adequate.

**Keywords:** Blood pressure, folate, homocystein, dietary intake, nutrition

### I. INTRODUCTION

Folate is a term used as a generic descriptors for folic acid (*pteroylmonoglutamic acid*) and related compounds that demonstrate the biological activity of folic acid [1]. Folate is important for DNA synthesis, methylation and repair in all cells [2]. Main sources of folate are vegetables and fruits, but 93% of Indonesian people consume less vegetables and fruits [3]. Adequate intake of fruits and vegetables is believed to prevent the risk of cardiovascular disease [4].

Nowadays, more people recognize that folate can play a role in the prevention of cardiovascular disease. Over the last few years, several studies have reported beneficial effects of folate on endothelial function, which is a surrogate endpoint for cardiovascular risk. Consistently, observational studies have demonstrated an association between folate levels and morbidity and mortality of cardiovascular disease [5], one of them, in the deficiency condition being the main cause of hyperhomocysteinemia, which is a hypertensive risk factor.

In vivo and in vitro experimental data describe the associated between folate deficiency and increasing homocysteine levels because it efflux into circulation [6]. The process of decreasing folate in tissues coincides with decreasing the production of methionine. Methionine is a recycled form of homocysteine, if methionine decreases then the number of homocysteine will increase [7]. Some studies focus on increasing homocysteine on elevated blood pressure or hypertension [8], but since the study used a retrospective design, elevated homocysteine levels is only a marker rather than a causal factor of hypertension [9].

The prevalence of hypertension in Indonesia is still quite high. Results of Basic Health Research or RISKESDAS 2007 showed that the highest proportion cause of death was non communicable disease, ie cardiovascular disease (31.9%) including hypertension (6.8%) and stroke (15.4%). The RISKESDAS 2013 data provides prevalence on hypertension was 23.2%, 20.2% in males and 26.2% in females [3]. Prevention and control of hypertension is necessary to reduce the prevalence of hypertension and prevent its complications to the community. Therefore, the purpose of this study to examine the relationship between serum folate and blood pressure in fishermen in Bulak District.

## II. METHODS

### A. Study design

This quantitative study used an observational analytic with cross sectional design. This research was conducted in Kelurahan Kedung Cowek in Bulak District. The data collection conducted in May - August 2017. Population in this study was all fishermen in Bulak District.

### B. Subjects

The subjects used for this study consisted of fisherman that has fulfilled inclusion and exclusion criteria. The inclusion criteria were 26-≤60 years old, still actively working, willing to participated on whole procedure and sign informed consent. The number of fishermen in the sample frame was 95 people, but eligible participant after adjusted inclusion and exclusion criteria remains 31 people. Sampling was done by simple random sampling (SRS) by randomized the name on the list given by the fisherman's chief. The study protocol was approved by the Ethics Committee of the Faculty of Public Health, Airlangga University, Indonesia, and informed consent was obtained from each participant.

### C. Statistical methods

Statistical analysis was conducted include univariate and multivariate test. Univariate analysis presented in the tables about characteristics of participants, average blood pressure and serum folate. It also presented a cross-tabs described average serum folate among those who had pre or hypertensive and normal. Multivariate analysis used binary logistic regression test to determine the relationship between dependent and independent variables and confounding variables.

### D. Data Collection Procedures

Blood pressure measurement was performed by health workers at Puskesmas Kenjeran, whereas blood sampling was done by doctor from Faculty of Medicine, Airlangga University . The collected blood serum was stored in an EDTA tube and given 0.5% sodium ascorbic acid at a ratio of 1:20 to avoid oxidation, then it was tested using the *Gas Chromatography* method at the Pharmacy Laboratory of Airlangga University. Data of confounding variable was obtained by interview using questionnaire while data of folate intake was obtained by interview using semi quantitative food frequency questionnaire (SQ-FFQ) form.

## III. RESULT

Table 1 illustrates participants's characteristics by normal and abnormal blood pressure (prehypertension and hypertension) which included age, education level, income level, history of disease, and smoking behavior.

Table1. Percentage of respondent characteristics by blood pressure category

Characteristic	Blood Pressure Category			
	Normal		Abnormal (Pre/Hypertension)	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
<b>Age</b>				
<40 y.o	6	54.5	3	15.0
≥40 y.o	5	45.5	17	85.0
<b>Level of Education</b>				
Never go to school	0	0	1	5.0
< 6 <sup>th</sup> grade	3	27.3	6	30.0
6 <sup>th</sup> grade	3	27.3	11	55.0
Junior high school	3	27.3	1	5.0
High secondary school	2	18.2	1	5.0
College	0	0	0	0
<b>Monthly Income</b>				
< Rp 3.200.000	7	63.6	15	75.0
≥Rp 3.200.000	4	36.4	5	25.0
<b>Hospital chart</b>				
Yes	3	27.3	10	50.0
No	8	72.7	10	50.0
<b>Smoking</b>				
Yes	9	81.8	10	50.0
No	2	18.2	10	50.0

The table illustrated that the greatest prevalence in participant whose blood pressure was abnormal or had prehypertension and hypertension aged ≥40 years was 85%. The education level of respondents who had abnormal blood pressure is 6<sup>th</sup> grade equal to the percentage of 55% and had income below Regional Minimum

Wage in Surabaya that was < Rp 3,200,000.00 equal to 75%. Based on variable of hospital chart and smoking behavior, participants who had prehypertension and hypertension as much as 50% had hospital chart and 50% smoking.

Table 2. Distribution of frequency participant's blood pressure

Blood Pressure	Frequency (n)	Percentage (%)
Hypertension	5	16.1
Pre Hypertension	15	48.4
Normal	11	35.5

Most participants experienced prehypertension as listed in table 2, that the percentage of participants who experienced prehypertension that was as much as 48.4% while those with hypertension was 16.1%.

Table 3. The average serum folate of participants by blood pressure category

Blood Pressure	Frequency (n)	Serum folate (ng/mL)			
		Mean	SD	Minimum	Maksimum
Hypertension	5	9.7	1.3	7.5	10.9
Pre Hypertension	15	9.6	1.8	6.2	12.5
Normal	11	9.8	2.3	6.1	12.9

The average serum folate level based on the categorization of participant's blood pressure as listed in table 3 was well over the threshold for deficiency of > 3ng / mL and the value was almost the same in each group. That was in line with the average number of folate intake of participants in each category was also almost the same. The average number of folate intake of participants in the hypertension group, prehypertension and normal was  $112.45 \pm 46.16 \mu\text{g}$ ,  $166.16 \pm 60.82 \mu\text{g}$  and  $147.01 \pm 59.09 \mu\text{g}$ . That number only meets 37.46% of RDA.

Table 4. Summary Binary Logistic Test by 95% Confident Interval

Dependent Variable	Independent Variable	Coefisient	P	OR
Blood pressure	Age			
	≥40 y.o.		0.110	
	<40 y.o.			
	Monthly income			
	<Rp 3,200,000.00		0.084	
	≥Rp 3,200,000.00			
	Never go to school			
	< 6 <sup>th</sup> grade		1.000	
	6 <sup>th</sup> grade		0.120	
	Junior high school		0.178	
	High secondary school		0.918	
	College		0.594	
	Smoking			
	Yes		0.675	
	No			
Hospital Chart				
Yes		0.072		
No				
Serum Folate		0.573		
Total Folate Intake		0.384		

Folate serum values of participants listed on table 3 described the results of the analysis using multiple logistic regression on table 4, that after adjusted for other confounding variables (age, level of education, monthly income), hospital chart and folate intake there was no correlation between serum folate with blood pressure because the value of significance was more than the value of  $\alpha$  ie  $p = 0.573$ .

#### IV. DISCUSSION

##### **A. Characteristic of Participant**

Characteristics of participants that includes age, level of education and monthly income. The results of this study found that most respondents who experienced abnormal blood pressure, namely prehypertension and hypertension aged  $\geq 40$  years. This was in line with the statement of National Health, Lung And Blood Institute (2014) that age 40-60 years have a greater risk of cardiovascular disease [10]. Previous study also confirmed that the prevalence of hypertension at age 45-54 years or older is always higher [11].

Participants who experienced abnormal blood pressure ie prehypertension and hypertension mostly had 6<sup>th</sup> grade education and < 6<sup>th</sup> grade education and earning less than Regional Minimum Wage. The results of this study are consistent with the findings of Mendez *et. al.*, (2003) that hypertension is related to education and income but the pattern of relationships is negative for poor men and limited education [12]. The socio-cultural transition during the economic development process is thought to affect the rate of hypertension and cardiovascular risk factors present in developing countries [13]. A lot of research has been done, but the results are diverse and inconsistent. There is still unknown cause of the inconsistent results, but one explanation assumes that heterogeneity in the stage of modernization and economic development [14-15].

This study found no association between age, level of education and monthly income with blood pressure, but in table 4 illustrates that monthly income variable less than the Regional Minimum Wage is a variable that potentially has a relationship with blood pressure with a *p value* = 0.084 approaching 95% CI. This can be caused because the number of participants in this study is too small so the relationship between variable can't read statistically.

##### **B. Prehypertension and hypertension, smoking behavior and hospital chart**

The results of this study found that most participants experienced prehypertension that is 48.4%. Participants who had prehypertension and hypertension were have a smoking status fifty-fifty and hospital chart status fifty-fifty too, so in table 4 it was shown that there was no correlation between smoking behavior and hospital chart with blood pressure. This is not in line with some previous research that proves that smoking behavior is related to blood pressure.

Many studies have found that smoking affects a variety of cardiovascular diseases that harm and act synergistically with hypertension and dyslipidemia to increase the risk of coronary heart disease [16]. More than 4000 toxic substances are identified on a cigarette, at least there is evidence that there are two major toxic substances, nicotine and carbon monoxide, which give toxic effects to the heart and blood vessels [17]. Smoking behavior is one of hypertension risk factors, but there are many other factors such as obesity, vegetable and fruit intake, lifestyle, physical activity and dietary intake of respondents [11] discussed in other papers.

In addition to smoking behavior, the hospital chart variables are also not associated with blood pressure. Hospital chart referred to in this study is a history disease that had suffered by participant both infectious and degenerative diseases. As many as 50% of participants who have prehypertension and hypertension have a history of certain diseases including thypus, gout, diabetes, hypertension and stroke. One or other history of participant's disease are metabolic syndrome, such as diabetes, contributes to the increase in blood pressure [18].

##### **C. Serum folate, total folate intake and blood pressure**

Table 4 shows that the serum folate as well as total folate intake were not related to the participant's blood pressure. The results are supported by data in the previous table that describes the average serum folate of participant based on blood pressure category is normal and almost the same in each group. Although the average of total of folate is still 37.8% of the RDA but the average serum folate > 3ng / mL, which means normal. However, the results of the respondent's blood pressure tend to be high or abnormal so that it is included in the category of having prehypertension (systolic  $\geq 120$  or diastolic  $\geq 80$ ) and hypertension (systolic  $\geq 140$  or diastolic  $\geq 90$ ).

Folate plays a role in endothelial function, endothelial dysfunction increases cardiovascular risk and is closely related to ischaemia [5]. In addition, folate also plays a role in homocysteine metabolism, which recycles homocysteine into methionine, folate deficiency is associated with increasing homocystein concentration levels that marks the occurrence of hypertension [19].

The results of this study are not in consistent with the hypothesis, but similar to the results of the study conducted by Thériault, *et. al.* (2013) that serum folate in participants was high but there was no different serum folate in participants who have hypertension and normotension. The study also did not measure the levels of homocysteine participants besides the incidence of high homocysteine level or hyperhomocysteinemia that became a direct marker of the incidence of hypertension mediated by folate deficiency [20].

#### **D. The role of other nutritional intake towards folate serum levels**

The total folate intake of participants only meets 37.8% of RDA but serum folate of participants is well over the threshold for deficiency. This is because the metabolism of folate is influenced by two other B vitamins namely vitamin B<sub>6</sub> and vitamin B<sub>12</sub> [21]. Low levels of vitamin B<sub>12</sub> in the tissues will inhibit the formation of 5-methyltetrahydrofolate into folate [2]. The study also analyzed the amount of vitamin B<sub>6</sub> and vitamin B<sub>12</sub> intake and the results showed that the intake of these two nutrients was high. The average percentage of adequate intake of vitamin B<sub>6</sub> and vitamin B<sub>12</sub> was 108.82% and 107.71% of RDA. It is answering the results of this study that although total folate intake of participants was low but serum folate was high.

### **V. CONCLUSION**

The average of participants's serum folate was normal but the prevalence of high blood pressure including prehypertension and hypertension was still higher than that of normotension, so the statistical test results also showed no relationship between serum folate and blood pressure. Although folate serum respondents are well over the threshold for deficiency but total folate intake is still below the RDA. That's because the amount of consumption of other B vitamins that support the formation of folate in the body was high and has sufficient.

### **REFERENCE**

1. Gibson RS, *Principles of Nutritional Assessment 2<sup>nd</sup> Ed.* New Zealand: Oxford University Press, 2005.
2. Okumura K & Tsukamoto H, Folate in Smoker, *Clinica Chimica Acta*, Vol. 412, pp. 521-526, 2011. Laporan RISKESDAS 2013
3. Ward M, Homocysteine, folate, and cardiovascular disease, *Int J Vitam Nutr Res*, Vol.71(3),pp. 173-8, 2001
4. Verhaar MC, Stroes E, Rabelink TJ, Foliates and Cardiovascular Disease, *Arterioscler Thromb Vasc Biol*, Vol. 22, pp.6-13, 2002.
5. Durand P, Prost M., and Blache D, Review: Folate Deficiencies and Cardiovascular Pathologies, *Clin Chem Lab Med*, Vol. 36(7), pp.419-429, 1998.
6. Tungtrongchitr R, Pongpaew P, Soonthornruengyot M, Viroonudomphol D, Vudhivai N, Tungtrongchitr A, Phonrat B, Pooudong S and Schelp FA, Relationship of Tobacco Smoking with Serum B<sub>12</sub>, Folic Acid and Haematological indices in Healthy Adults, *Public Health Nutr*, Vol.6, pp. 675-681, 2003.
7. Graham IM, Daly LE, Refsum HM, et al, Plasma Homocysteine As A Risk Factor For Vascular Disease, *European Concerted Action Project, JAMA*, Vol. 277(22), pp.1775-1781, 1997.
8. Zhong F, Zhuang L, Wang Y & Ma Y, Homocysteine Levels And Risk Of Essential Hypertension: A Meta-Analysis Of Published Epidemiological Studies, *Clinical And Experimental Hypertension*, pp. 1-7, 2017.
9. National Health, Lung and Blood Institute, *Who Is at Risk for Heart Disease?* <https://www.nhlbi.nih.gov/health/health-topics/topics/hdw/atrisk> (sitiation on 12 Agustus 2018), 2014.
10. Rahajeng, Ekowati dan Tuminah, Sulistyowati, Prevalensi Hipertensi dan Determinannya di Indonesia, *Maj Kedokt Indon*, Vol. 59(12), pp.580-58, 2009.
11. Mendez, MA, Cooper R, Wilks R, Luke A, Forrester T, Income, education, and blood pressure in adults in Jamaica, a middle-income developing country, *International Journal of Epidemiology*, Vol.32,pp. 400-408, 2003.
12. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation*, Vol. 96, pp.596-601, 1998.
13. Marmot MG, *Coronary Heart Disease: Rise and Fall of a Modern Epidemic, Coronary Heart Disease Epidemiology: From Aetiology to Public Health*, New York: Oxford University Press, pp. 3-19, 1991.
14. Perova NV, David CE, Tai S *et al*, Multi-country comparison of plasma lipid relationship to years of schooling in men and women, *Int J Epidemiol*, Vol.30, pp.371-79, 2001.
15. Primatesta P, Falaschetti E, Gupta S, Marmot MG, Poulter NR, Association Between Smoking and

- Blood Pressure : Evidence From the Health Survey for England, *Hypertension*, Vol.3, pp.187-193, 2001.
16. Leone, Aurelio, Smoking and Hypertension, *J Cardiol Curr Res*, Vol.2(2), pp. 1-7, 2015.
  17. Duvnjak, Lea, Bulum, Tomislav, Metelko, Željko, Hypertension And The Metabolic Syndrome, *Diabetologia Croatica*, Vol.37(4), pp.83-89, 2008.
  18. Wierzbicki A, Homocysteine and cardiovascular disease: a review of the evidence, *Diabetes Vasc Dis Res*, Vol.4, pp.143–149, 2007.
  19. Thériault, Sébastien, Giguère, Yves, Massé, Jacques, Lavoie, Sébastien B, Girouard, Joël, Bujold, Emmanuel, and Forest, Jean-Claude, Absence of Association Between Serum Folate and Preeclampsia in Women Exposed to Food Fortification, *OBSTETRICS & GYNECOLOGY*, VOL. 122(2), pp. 345-351,2013.
  20. Bailey LB and Gregory JF, Folate Metabolism and Requirements, *J. Nutr*, Vol.129 pp. 779–782, 1999.