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PENGUSUL: Dr. dr. Mahalul Azam, M.Kes

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Lipid Profiles and Postprandial Glucose Status of Hypertensive Individuals with Stroke in Indonesia

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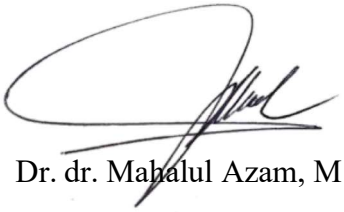

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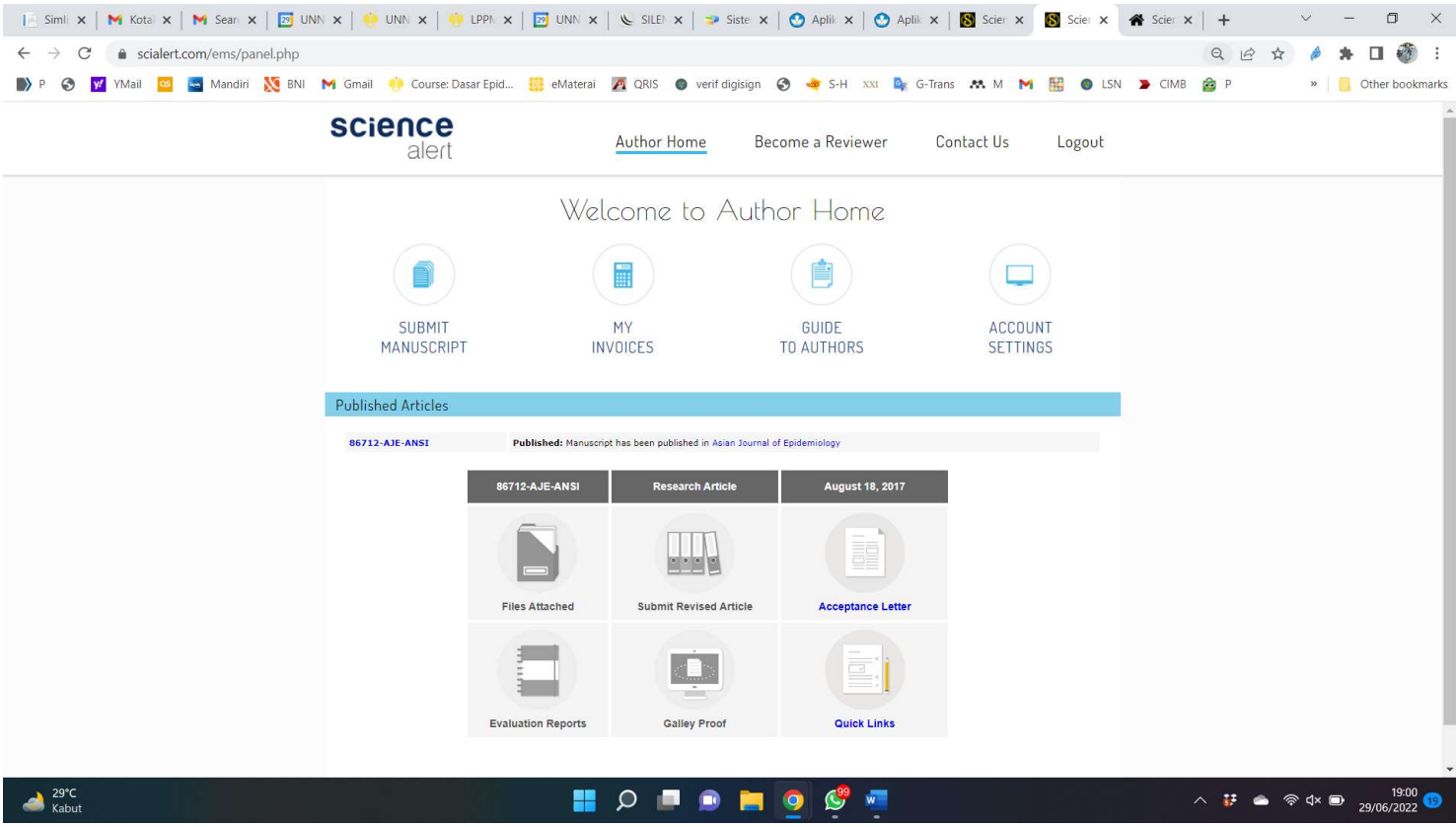

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LIPID PROFILE AND PPG OF HYPERTENSIVE PEOPLE WITH STROKE IN INDONESIA

Running Title:

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significance statement

Mahalul Azam[1,2*], Fatkhiatun Nida[1], Oktia Woro Kasmini Handayani[1], Arulita Ika Fibriana[1]

Author information:

[1]Department of Public Health, Sports Science Faculty, Universitas Negeri Semarang, Indonesia

[2]Doctoral Program in Medicine and Health Sciences, Faculty of Medicine Universitas Diponegoro, Semarang, Indonesia

[*]corresponding author: address: Gedung F5, Kampus UNNES, Sekaran, Gunungpati, Semarang, Indonesia 50229; email: mahalul.azam@mail.unnes.ac.id

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Abstract

Background and Objective: Stroke is the second leading cause of death worldwide. Stroke caused 23.48% of all deaths in Indonesia, a country with the highest prevalence of stroke in the world. The main risk factor for stroke is hypertension. In Indonesia, hypertension is the most prevalent non-communicable disease (25.8%). ~~We~~ The aim of this study was to ~~conducted this study to~~ determine lipid profile and postprandial (PPG) status among hypertensive people with stroke in Indonesia. **Material and Method:** ~~We~~ ~~used~~ In this study cross-sectional study design was used , and obtained data from secondary data of Riskesdas 2013. The number of respondents was 8,511. Data were analyzed using Cohran's and Mantel-Haenzel test. **Results:** Prevalence of stroke cases in people with hypertension was 9%. Most of stroke respondents have high T-Chol, LDL-C, triglyceride, and PPG. Factors related to stroke are: age, LDL-C level (PR=1.21; 95% CI=1.026-1.431), and PPG status ((PR=1.28; 95% CI=. After adjusting for gender and age, PPG was associated with stroke incident in hypertensive people in Indonesia. **Conclusion**: Prevalence of high LDL-C and PPG levels in hypertensive people with stroke is high. Those related with stroke incident among hypertensive people. It needs an educational effort to the stroke group to control LDL cholesterol levels for prevention of recurrent stroke and other impacts.

Keyword: Stroke, T-Cholesterol, LDL-C, HDL-C, Triglyceride, Postprandial glucose

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1. INTRODUCTION

Stroke is an important issue in the world~~,~~ and Indonesia as well. Stroke is the second leading cause of death worldwide, causing 11.3% of all deaths[1]. In 2011, the prevalence of stroke reached 30.7 million people globally. A total of 12.6 million had moderate to severe disability[2]. Stroke burden increased from 38 to 61 million disability-adjusted life years (DALYs) in 1990 to 2020 globally. In addition, stroke has also been the single largest cause of disability in the UK[3]. In the United States, stroke and coronary heart disease (CHD) related health service cost was the most expensive and reached more than USD 320.1 billion[1].

Riset Kesehatan Dasar (Riskesdas), the Indonesian Basic Health Research 2007, reported the prevalence of stroke is 8.3 per 1000 population. It increased to 12.1 per 1000 population in 2013[4,5]. It is in concordance with mortality rate due to stroke in Indonesia that

reached 200.16 cases per 100,000 populations. Stroke is the leading cause of death in Indonesia based on WHO data in 2014, with the number of deaths reaching 328,525 or 23.48% of all deaths in Indonesia. It makes Indonesia the country with the highest case of stroke in the world [6] and the risk is increasing in people with poor health and quality of life[7]. According to *Jaminan Kesehatan Nasional* (JKN, National Health Insurance) data, stroke was the most costly case in hospital in Indonesia with finance totaling USD 115.35 million[8].

Hypertension is a major risk factor of stroke. Hypertension increased the risk of stroke to 3.89 (99% CI=3.33-4.54) times the risk in non-hypertensive[9]. Hypertension is also the most prevalent non-communicable disease in Indonesia with a prevalence of 25.8%[5].

Relationship between lipid profile and postprandial glucose (PPG) status with stroke are well known. Risk of stroke increases 3.75 (95% CI 1.83-7.7) for higher total cholesterol[10], 2.29 (95% CI1.1-4.8) for high LDL-C[10], 0.52 (95% CI 0.28-0.96) for lower HDL-C[10],0.97 (95% CI 0.956-0.978) for higher triglyceride[11], and 2.71 (95% CI 1.24-5.91) for higher PPG.[12] Lipid profile[13] and PPG[14] status also play a pivotal role in prevention of recurrent stroke. However, there is lack of information about lipid profile and PPG status in hypertensive people with stroke. According to our knowledge, lipid profile and PPG status in hypertensive people with stroke in Indonesia has not been reported yet. The objective of this study was to determine the prevalence of stroke in hypertensive people in Indonesia and their lipid profile and PPG status based on Riskesdas 2013.

2. MATERIAL AND METHOD

2.1. Design and Sample Research

This cross-sectional study used secondary data from Riskesdas 2013. Population in this study was hypertensive respondents of Riskesdas 2013. Subjects with incomplete data were excluded. Total numbers of participants were 8,511 respondents. Detailed information about method and other related data on this survey could be accessed in Riskesdas 2013 report[5] and *Riskesdas Biomedis* 2013 for biomedical measurement report[15].

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2.2. Data Collection

Riskesdas 2013 was a community-based survey covering all regions in Indonesia. Riskesdas collected baseline data and health indicators that represent a national, provincial, and district/city description. Riskesdas is planned to be implemented every 3 years and the

latest survey was conducted in 2013. The design used in this study was cross-sectional with respondents from 33 provinces and 497 districts/cities in Indonesia, total~~ing~~ 1,027,763 respondents. This study was approved by the Ethics Committee, National Institute of Health Research and Development (NIHRD), Health Ministry of Indonesia in 2013.

Respondents with hypertension were defined by having: blood pressure ≥140 mmHg (systolic pressure) and/or ≥90 mmHg (diastolic pressure),[16] been diagnosed with hypertension by health professional, or prescribed antihypertensive medication. Case of stroke was determined by asking respondents whether or not they had been diagnosed by a health professional (doctor or nurse) or suddenly showing symptoms of a stroke. Symptoms shown were: 1) experiencing paralysis on one side of the body, 2) tingling or numbness on one side of the body, 3) mouth droops without eye muscle paralysis, 4) slurred speech, 5) difficulty speaking and/or understanding conversation accessed in Riskesdas 2013[5]. Factors that have been analyzed were limited to age and biomedical parameters i.e.; total cholesterol, LDL-C, HDL-C, triglyceride, and PPG. Total cholesterol, LDL-C, HDL-C, and triglyceride were measured by auto analyzer TRX 7010®. And postprandial glucose was measured by Accu check performa®.

Age was classified to young (< 45 years), middle age (45-65 years), and elderly (>65 years). Total cholesterol, LDL-C, HDL-C, and triglyceride level were determined based on the dyslipidemia guideline according to *Perhimpunan Endokrinologi Indonesia* (PERKENI, The Indonesia Society of Endocrinology)[17]. Level of PPG was determined according to the monitoring guideline of risk factors for non-communicable diseases of the Health ministry of Indonesia[18]. Total cholesterol level was determined to be at risk if the concentration is ≥190 mg/dl. LDL level was determined to be at risk if the concentration is ≥110 mg/dl. HDL level was determined to be at risk if the concentration is <40 mg/dl for men and <45 mg/dl for women. Triglyceride level was determined to be at risk if the concentration is ≥150 mg/dl. PPG level was determined to be abnormal if the concentration is ≥180 mg/dl.

2.3 Statistical ~~Data~~ Analysis

Characteristics of respondents were presented in frequency and proportion. We explored lipid profie and PPG that was related to stroke prevalence adjusted for age and gender in hypertension using Cohran's and mantel-haenszel analysis. Statistically significant

was considered at p<0.05. All statistical analysis were performed using the IBM SPSS Statistic 21 program.

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3. RESULT

The number of respondents analyzed was 8,511 and the number of stroke cases was 767 respondents. It showed that prevalence of stroke cases among people with hypertension based on Riskesdas 2013 in Indonesia was 9%.

Most of the respondents were female (65.5%), aged 45-55 years (51.1%), have total cholesterol at risk (57.3%), LDL-C at risk (75.5%), HDL-C not at risk (70%), triglyceride level not at risk (71.8%)~~,~~ and normal PPG level (77.9%). Respondent distribution by characteristics was presented in Table 1.

Out of 7 variables assessed, bivariate analysis found 3 related variables, i.e.; age, LDL level, and postprandial glucose level. The result of bivariate analysis was presented in table 2. ~~Table 2 shows that~~ the prevalence of stroke was more common in women (9.2%) than in men (8.6%) as shown in table 2. However, gender was not associated with stroke prevalence in hypertensive people in Indonesia. This result was based on a p value of 0.347.

About 10.5% of stroke prevalence was found in age group of >65 years, 10% in age group 45-65 years~~,~~ and 6.7% in age group < 45 years. Statistical analysis showed there was a significant relationship between age and stroke prevalence in hypertensive people in Indonesia in all age groups compared to reference (<45 years). Respondents aged > 65 years are at risk of stroke by as much as 1.57 times greater than respondents aged < 45 years ~~(reference).~~ Respondents aged 45-65 years were at risk of stroke by 1.48 times greater than reference.

The prevalence of stroke was found to be higher in the risk group of total cholesterol levels (9.5%) than the non-risk group (8.4%). However, there was no significant association between total cholesterol level and stroke prevalence in hypertensive people in Indonesia, with p value 0.087 at α=0.05.

Higher stroke prevalence was found in the risk group of LDL-C level (9.4%) than in non-risk group (7.2%). Statistical analysis revealed a significant association between LDL-C level and stroke prevalence in hypertensive people in Indonesia, with p value 0.025 at

α=0.05. Respondents with LDL-C level that was at risk were 1.21 times greater to have stroke than respondents who have LDL-C level that was not at risk.

Stroke prevalence was found to be higher in non-risk group of HDL-C (9.2%) than in the risk group (8.6%). ~~So,~~ there was no significant relationship between HDL level and stroke prevalence in hypertensive people in Indonesia, with p value 0.465 at α=0.05.

The prevalence of stroke was found to be higher in the risk group (9.8%) of triglyceride than in the non-risk group (8.7%). However, there was no significant association between triglyceride level and stroke prevalence in hypertensive people in Indonesia, with a p value of 0.120 at α=0.05.

Stroke prevalence was also found to be higher in the abnormal PPG group (10.9%) than the normal group (8.5%). Statistical analysis revealed a significant relationship between PPG level with stroke prevalence in hypertensive people in Indonesia, with p value 0.002 at α=0.05. Respondents with abnormal postprandial glucose level have a 1.28 times greater risk of stroke than respondents who have normal postprandial glucose level.

~~Table 3 shows~~ the comparison of prevalence ratio in each model as shown in table 3. Before adjusting for other variables, LDL-C and PPG were significantly related to stroke prevalence among people with hypertension in Indonesia (Model 1). Similarly, after adjusted for gender, LDL-C and PPG were significantly related to stroke incident among hypertensive people in Indonesia (Model 2). However, the prevalence ratio (PR) of LDL-C increased from 1.21 to 1.23. Prevalence ratio of PPG increased from 1.28 to 1.31. Model 3 shows that after adjusting for age, only PPG had relationship with stroke prevalence among people with hypertension in Indonesia. The PR decreased from 1.28 (Model 1) to 1.25 (Model 3). Similarly, after adjusted for age and gender, only postprandial glucose had relationship with stroke prevalence among people with hypertension in Indonesia. The PR decreased from 1.28 (Model 1) to 1.24 (Model 4).

4. DISCUSSION

~~Our~~ This study found 9% of hypertension with stroke. This figure less than in Nigerian study[19]. This study shows that age, LDL-C~~,~~ and PPG status associated with stroke incident among hypertensive people in Indonesia. But there are no association for gender, total cholesterol, HDL-C, and Triglyceride. Reports of lipid profile and PPG status among

hypertensive people with stroke are limited. Nigerian Study shows that modifiable factors signicantly wih stroke occurrence included higher maximum and minimum blood pressure in preceding 3 months, higher fasting plasma glucose, ~~ge rater~~ large alcohol consumption, lesser physical activity and increased CIMT. But this research only determined lipid profile and PPG status as object of research.

~~Our~~ This study showed a significant relationship between age and the prevalence of stroke in hypertensive people in Indonesia. The risk of stroke increases with increasing age. The prevalence of stroke at young (< 45 years) were found to be 6.7%. The most cases were found at age >65 years (10.5%). Generally, stroke occurs due to aging. Naturally, the blood vessels will become more rigid as a result of plaque[20]. In young adults, increased risk of infarction and vascular risk factors in developing countries is associated with increased smoking and urbanization behavior[21]. Although the relationship between age and stroke incident has been well known, that there is a significant relationship between age and stroke incident among hypertensive people especially in Indonesia provided valuable information.

~~Our~~ this study showed a significant relationship between LDL level and the prevalence of stroke in hypertensive people in Indonesia. Respondents who had LDL levels >100 mg/dL have a 1.30 times greater risk of getting stroke than respondents with LDL levels <100 mg/dL. However, after adjusted for age and gender, LDL was not a significant variable related to stroke incident among hypertensive people in Indonesia.

The association between LDL level and coronary heart disease has been proven with certainty. However, the relationship between LDL level and the prevalence of stroke is controversial. Our study was in line with a study in Kerala, India[10] which reported respondents with cholesterol level greater than 200 mg/dl were 2.29 times more likely to have a stroke than those with normal cholesterol level, with p value = 0.009 (1.27-4.15). Likewise, a study in the Neurology Department of Sina Hospital[11] also revealed similar finding. LDL was a predictor of hemorrhagic stroke. Increased cholesterol and LDL level were associated with a high risk of ischemic stroke. It concluded that LDL is a risk factor in both ischemic and hemorrhagic stroke[11]. LDL level was also associated with death after long-term stroke, but was not a prognostic factor[22]. It was different with an Indonesian cohort study[12] in common population and Nigerian-African study[19] in hypertensive population. This difference may be due to differences in the number of respondents, control

of other confounding factors, or data weaknesses. Research with cross-sectional design measures exposure and effects in the same time, so it is not known exactly which events occurred earlier. Whether respondents have hypertension, stroke, or have risky LDL levels first. This study also can't explain the LDL status before the data collection. However, from Table 2 it is known that in most stroke patients still have LDL levels at risk (≥100 mg / dl) of 9.4%. This means that controlling LDL in the stroke group is still low, so it needs an educational effort to the stroke group to control LDL cholesterol levels for prevention of recurrent stroke and other impacts.

~~Our~~ This study showed a significant relationship between PPG level and stroke prevalence in hypertensive people in Indonesia. Respondents with abnormal PPG level have a 1.28 times greater risk of having stroke than respondents with normal PPG level. However, after adjusted for age and gender, PPG was a significant variable related to stroke incident among hypertensive people in Indonesia. The PR decreased from 1.28 (Model 1) to 1.24 (Model 4).

Research on the relationship between PPG levels and stroke incident both general and hypertension population is limited. Most studies use fasting blood sugar (FBG) levels as a research variable. The cohort study in Indonesia[12] showed a significant association between PPG levels and stroke incidence in the general population, but after controlled with other variables, PPG was not the dominant variable causing stroke.[12] While the study in Nigeria (2013)[19] using fasting blood glucose levels as a parameter to show a relationship of FBG with stroke incidence in patients with hypertension. These results indicate a significant relationship between FBG with the incidence of stroke in patients with hypertension. However, when controlled with other variables, FBG levels are not the dominant variable of stroke incidence in hypertensive patients.[19] The San Luigi diabetes study showed that postprandial blood glucose was a strong cardiovascular predictor of fasting blood glucose in type 2 diabetes mellitus, especially in women.[23] High PPG levels or postprandial hyperglycemia are characterized by hyperglycemic spikes that cause endothelial dysfunction, inflammatory reactions and oxidative stress, which can lead to the development of atherosclerosis and the occurrence of cardiovascular events. Research has shown that postprandial hyperglycemia may predispose to the development of atherosclerosis and cardiovascular events[24].

With a larger number of respondents and different data collection from the study in Nigeria, this study showed a significant association between PPG levels and stroke incidence in hypertensive patients in Indonesia. Patients with hypertension who have abnormal levels of PPG at risk of stroke 1.28 times greater than hypertensive respondents who have normal PPG levels. After controlled by age variables, this risk decreases to from 1.28 to 1.25 times. Thus, this provides new insights, that there is a significant relationship between PPG levels and the incidence of stroke in hypertensive people, especially in Indonesia.

Future Recommendation; However, further research is needed to explain the role of PPG levels in increasing the risk of stroke.

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5. CONCLUSION

Most of hypertensive people with stroke have high LDL and PPG levels. There was a significant relationship between age, LDL level, and PPG levels and stroke prevalence in hypertensive people in Indonesia. After adjusted for gender and age, PPG level was found to be a significant variable for stroke prevalence in hypertension in Indonesia. It needs an educational effort to the stroke group to control LDL-C levels for prevention of recurrent stroke and other impacts.

6. ACKNOWLEDGEMENT

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7. CONFLICT OF INTEREST

The authors declared that there are no conflict of interest.

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Table 1. Characteristics of the subjects included in the analysis

Characteristic	Frequency (n)	Proportion (%)
Gender		
- Male	2,933	34.5
- Female	5,578	65.5
Age group		
< 45 years	1,386	16.3
45-65 years	4,345	51.1
>65 years	2,780	32.7
Total Cholesterol Levels		
-≥190 mg/dl	4,873	57.3
- < 190 mg/dl	3,638	42.7
LDL-C Levels		
- ≥100 mg/dl	6,426	75.5
- < 100 mg/dl	2,085	24.5
HDL-C Levels		
-At risk (M < 40 mg/dl ; F < 45 mg/dl)	2,556	30.0
-No risk (M ≥ 40 mg/dl ; F ≥ 45 mg/dl)	5,955	70.0
Triglyceride Levels		
- ≥150 mg/dl	2,397	28.2
- < 150 mg/dl	6,114	71.8
Postprandial glucose		
- ≥180 mg/dl	1,885	22.1
- < 180 mg/dl	6,626	77.9
Stroke		
-Yes	**767**	**9%**
-No	**7744**	**91%**

LDL-C : Low Density Lipoprotein Cholesterol
HDL-C : High Density Lipoprotein Cholesterol

Table 2. Relationship between parameters and stroke among respondents with hypertension

Parameter	Stroke (n = 747)		No Stroke (n = 7744)		P Value	PR	95% CI
	N	%	n	%			
Gender							
- Male	252	8.6	2,681	91.4	0.347	0.93	0.806-1.075
- Female	515	9.2	5,063	90.8			
Age Group							
>65 years	146	10.5	1,240	89.5	0.0001	1.57	1.274-1.925
45-65 years	434	10.0	3,911	10.0	0.0001	1.48	1.259-1.751
<45 years	187	6.7	2,593	93.3	*Reference*		
Total Cholesterol Levels							
≥190 mg/dl	462	9.5	4,411	90.5	0.087	1.13	0.985-1.298
< 190 mg/dl	305	8.4	3,333	91.6			
LDL-C Levels							
≥100 mg/dl	605	9.4	5,821	90.6	0.025	1.21	1.026-1.431
< 100 mg/dl	162	7.8	1,923	92.2			
HDL-C Levels							
-At Risk (M < 40 mg/dl ; F < 45 mg/dl)	221	8.6	2,335	91.4	0.465	0.94	0.812-1.095
-No Risk (M ≥ 40 mg/dl ; F ≥ 45 mg/dl)	546	9.2	5,409	90.8			
Triglyceride Levels							
≥150 mg/dl	235	9.8	2,162	90.2	0.12	1.13	0.974-1.304
< 150 mg/dl	532	8.7	5,582	91.3			
Postprandial glucose ≥180 mg/dl							
< 180 mg/dl	205	10.9	1,680	89.1	0.002	1.28	1.102-1.1492
	562	8.5	6,064	91.5			

Table 3. Comparison of Prevalence Ratio

Parameters	Model 1[+] PR (95% CI)	Model 2 [++] PR (95% CI)	Model 3 [+++] PR (95% CI)	Model 4 [++++] PR (95% CI)
Total Cholesterol	1,13 (0,985-1,298)	1,14 (0,976 – 1,325)	1,10 (0,941 – 1,277)	1,09 (0,937 -1,277)
LDL-C	1,30 * (1,054-1,597)	1,23 * (1,024 – 1,473)	1,20 (0,996 – 1,433)	1,20 (0,997 -1,439)
HDL-C	0,94 (0,812-1,095)	0,94 (0,798 – 1,108)	0,98 (0,830 – 1,153)	0,99 (0,840 -1,168)
Triglyceride – C	1,13 (0,974-1,304)	1,15 (0,976 – 1,349)	1,12 (0,954 – 1,319)	1,16 (0,981 – 1359)
Postprandial blood glucose	1,28 * (1,102-1,1492)	1,31 * (1,107 – 1,552)	1,25 * (1,057 – 1,483)	1,24 * (1,043 – 1,464)

*) significant p value at <0,05

[+]) Model 1 : Crude Prevalence Ratio

[++]) Model 2 : Prevalence ratio after adjusted by gender

[+++]) Model 3 : Prevalence ratio after adjusted by age

[++++]) Model 4 : Prevalence ratio after adjusted by gender and age

COVER LETTER FOR SUBMISSION OF REVISED MANUSCRIPTS

Dear Prof. Raafat Mohamed Shaapan Sayed
Editor in Chief Asian Journal of Epidemiology

Subject:
RE-SUBMISSION OF REVISED MANUSCRIPT FOR FURTHER EVALUATION

We would like to thank very much for the editor that have been making review for our manuscript so that we can improve our paper better.

We have making any changes according to the editor review. Some minor error like typos and grammatically correction have been accepted and English Editing was done by Editage (Certificate attached)

Some fundamental changes for running tittle, author ID & author contribution, significance statement, and refference style have been added.

Fundamental clarification have been stated, i.e. justification of the review "how this almost 4 years previous study contributes in the advancement of knowledge meanwhile justify the significance of the study as it is only based on the secondary data" have done in page 3 paragraph 2; Sentence 5 and 6 (Introduction section)

List of detailed changes provide in table below.

Serial No.	Part of the Manuscript	Reviewer's Comments	Response of Author
	Running Title	Provide the running title of the article as it is necessary according to the format of the journal.	Added: Lipid Profile and PPG of Hypertensive People with Stroke in Indonesia
	Author Contributi	There is a series of questions that will enable you to state the contributions of each author. Each author listed on the manuscript should have a real and concrete contribution to	Added in page 1

	on	the submission. Every single person who contributed to the manuscript should be listed. More information about authorship can be collected from *Editorial Policies*	
	Correspon ding Author	Do provide the Contact details(Mobile Number) of Corresponding Author for faster communication and updation. From January 1, 2017, its compulsory for all corresponding authors submitting papers to any Science Alert Journal to provide LiveDNA iDs (livedna.net) before final publication of their articles. With this standard identifier, you can create a profile of your research activities to distinguish yourself from other researchers with similar names, and make it easier for your colleagues to find your publications. To get LiveDNA, please go to the link: http://livedna.net/form.php.	Added corresponding author: address: Gedung F5, Kampus UNNES, Sekaran, Gunungpati, Semarang, Indonesia 50229; email: mahalul.azam@mail.unnes.ac.id Phone: +62 812-2853-982 LiveDNA ID: http://livedna.org/62.16978
	Introducti on		
	Material and Method	justify how this almost 4 years previous study contributes in the advancement of knowledge meanwhile justify the significance of the study as it is only based on the secondary data Please indicate both the manufacturer's name and location (including city, state, and country) for all specialized software used in the experiment.E:g Social Sciences (SPSS) software (version 13.0 for Windows; SPSS Inc., Chicago, IL)	Justification added in page 3 paragraph 3; Sentence 5 and 6 (Introduction section) Be corrected in page 5 paragraph 3
	Discussion		

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From January 1, 2017, its compulsory for all corresponding authors submitting papers to any Science Alert Journal to provide LiveDNA iDs (livedna.net) before final publication of their articles. With this standard identifier, you can create a profile of your research activities to distinguish yourself from other researchers with similar names, and make it easier for your colleagues to find your publications. To get LiveDNA, please go to the link: http://livedna.net/form.php.

	References	The formatting to reference list was not according to the Journal format. Please visit the link below and set the reference list accordingly. http://scialert.net/guide2.php?issn=2150-4210&id=28	Be corrected in Refferences section
	Significance statement	A statement about the significance of this research work should be included in the manuscript. The significance statement should provide the novelty aspect and significance of this research work with respect to the existing literature and more generally to the society. It should be a short summary which describe what this paper adds to and what was already known. **Start this statement with the following words:** This study discover the ---------- that can be beneficial for …… **And the last sentence of this statement could be such as:** This study will help the researcher to uncover the critical areas of ---------- that many researchers were not able to explore. Thus a new theory on ---------- may be arrived at. **A Model Significance Statement:** This study discovers the possible synergistic effect of vitamin E, calcium, and vitamin D combination that can be beneficial for osteoporosis-induced ovariectomized rats. This study will help the researcher to uncover the critical area of postmenopausal bone loss that many researchers were not able to explore. Thus, a new theory on these micronutrients combination, and possibly other combinations, may be arrived at.	Added in page 1 And Section number 7 Significance Statement
	abstract	Please verify whether the edited sentence is correct as the original wording did not make sense	Edited sentences accepted in page 2 (abstract section)

Original review

Lipid Profile and PPG of Hypertensive People with Stroke in Indonesia

Running Title:

Lipid Profile and PPG of Hypertensive People with Stroke in Indonesia

Author Contribution:

Mahalul Azam: Principle Investigator

Fatkhiatun Nida: Collecting data and preparing manuscript submission

Oktia Woro Kasmini Handayani: Designing study

Arulita Ika Fibriana: Analyzing data and preparing manuscript submission

Significance statement:

This study discovers the LDL-C and PPG levels related to hypertensive people with stroke. This study will help the researcher to uncover the critical area risk factors of stroke, especially lipid profile and PPG levels in people with hypertension that many researchers were not able to explore. Thus, a new theory on LDL-C and PPG were the main parameters that related to stroke in hypertensive people, may be arrived at.

Mahalul Azam[1,2*], Fatkhiatun Nida[1], Oktia Woro Kasmini Handayani[1], Arulita Ika Fibriana[1]

Author information:

[1]Department of Public Health, Sports Science Faculty, Universitas Negeri Semarang, Indonesia

[2]Doctoral Program in Medicine and Health Sciences, Faculty of Medicine Universitas Diponegoro, Semarang, Indonesia

[*]corresponding author: address: Gedung F5, Kampus UNNES, Sekaran, Gunungpati, Semarang, Indonesia 50229; email: mahalul.azam@mail.unnes.ac.id

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A Model Significance Statement: This study discovers the possible synergistic effect of vitamin E, calcium, and vitamin D combination that can be beneficial for osteoporosis-induced ovariectomized rats. This study will help the researcher to uncover the critical area of postmenopausal bone loss that many researchers were not able to explore. Thus, a new theory on these micronutrients combination, and possibly other combinations, may be arrived at.

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Abstract

Background and Objective: Stroke is the second leading cause of death worldwide. Stroke caused 23.48% of all deaths in Indonesia, a country with the highest prevalence of stroke in the world. The main risk factor for stroke is hypertension. In Indonesia, hypertension is the most prevalent non-communicable disease (25.8%). The aim of this study was to determine lipid profile and postprandial (PPG) status among hypertensive people with stroke in Indonesia. **Material and Method:** In this study cross-sectional study design was used , and obtained data from secondary data of Riskesdas 2013. The number of respondents was 8,511. Data were analyzed using Cohran's and Mantel-Haenzel test. **Results:** Prevalence of stroke cases in people with hypertension was 9%. Most of stroke respondents have high T-Chol, LDL-C, triglyceride, and PPG. Factors related to stroke are: age, LDL-C level (PR=1.21; 95% CI=1.026-1.431), and PPG levels ((PR=1.28; 95% CI=1.102-1.1492). After adjusting for gender and age, PPG was associated with stroke prevalence in hypertensive people in Indonesia. **Conclusion**: Prevalence of high LDL-C and PPG levels in hypertensive people with stroke is high. Those related to stroke incident among hypertensive people. It needs an educational effort to the stroke group to control LDL-C levels for prevention of recurrent stroke and other impacts.

Keyword: Stroke, T-Cholesterol, LDL-C, HDL-C, Triglyceride, Postprandial glucose

1. INTRODUCTION

Stroke is an important issue in the world and Indonesia as well. Stroke is the second leading cause of death worldwide, causing 11.3% of all deaths[1]. In 2011, the prevalence of stroke reached 30.7 million people globally. A total of 12.6 million had moderate to severe disability[2]. Stroke burden increased from 38 to 61 million disability-adjusted life years (DALYs) in 1990 to 2020 globally. In addition, stroke has also been the single largest cause of disability in the UK[3]. In the United States, stroke and coronary heart disease (CHD) related health service cost was the most expensive and reached more than USD 320.1 billion[1].

Riset Kesehatan Dasar (Riskesdas), the Indonesian Basic Health Research 2007, reported the prevalence of stroke is 8.3 per 1000 population. It increased to 12.1 per 1000 population in 2013[4,5]. It is in concordance with mortality rate due to stroke in Indonesia that reached 200.16 cases per 100,000 populations. Stroke is the leading cause of death in

Indonesia based on WHO data in 2014, with the number of deaths reaching 328,525 or 23.48% of all deaths in Indonesia. It makes Indonesia the country with the highest case of stroke in the world [6] and the risk is increasing in people with poor health and quality of life[7]. According to *Jaminan Kesehatan Nasional* (JKN, National Health Insurance) data, stroke was the most costly case in hospital in Indonesia with finance totaling USD 115.35 million[8].

Hypertension is a major risk factor of stroke. Hypertension increased the risk of stroke to 3.89 (99% CI=3.33-4.54) times the risk in non-hypertensive[9]. Hypertension is also the most prevalent non-communicable disease in Indonesia with a prevalence of 25.8%[5].

Relationship between lipid profile and postprandial glucose (PPG) status with stroke are well known. Risk of stroke increases 3.75 (95% CI 1.83-7.7) for higher total cholesterol[10], 2.29 (95% CI1.1-4.8) for high LDL-C[10], 0.52 (95% CI 0.28-0.96) for lower HDL-C[10],0.97 (95% CI 0.956-0.978) for higher triglyceride[11], and 2.71 (95% CI 1.24-5.91) for higher PPG.[12] Lipid profile[13] and PPG[14] status also play a pivotal role in prevention of recurrent stroke. However, there is lack of information about lipid profile and PPG status in hypertensive people with stroke. Riskesdas 2013 was the latest survey of Indonesian Basic Health Research. This survey support comprhensive health data, nevertheless analyzing in lipid profile and PPG levels in hypertensive people with stroke in Indonesia has not been reported yet. The objective of this study was to determine the prevalence of stroke in hypertensive people in Indonesia and their lipid profile and PPG status based on Riskesdas 2013.

2. MATERIAL AND METHOD

2.1. Design and Sample Research

This cross-sectional study used secondary data from Riskesdas 2013. Population in this study was hypertensive respondents of Riskesdas 2013. Subjects with incomplete data were excluded. Total numbers of participants were 8,511 respondents. Detailed information about method and other related data on this survey could be accessed in Riskesdas 2013 report[5] and *Riskesdas Biomedis* 2013 for biomedical measurement report[15].

Commented [U6]: justify how this almost 4 years previous study contributes in the advancement of knowledge meanwhile justify the significance of the study as it is only based on the secondary data

2.2. Data Collection

Riskesdas 2013 was a community-based survey covering all regions in Indonesia. Riskesdas collected baseline data and health indicators that represent a national, provincial,

and district/city description. Riskesdas is planned to be implemented every 3 years and the latest survey was conducted in 2013. The design used in this study was cross-sectional with respondents from 33 provinces and 497 districts/cities in Indonesia, total 1,027,763 respondents. This study was approved by the Ethics Committee, National Institute of Health Research and Development (NIHRD), Health Ministry of Indonesia in 2013.

Respondents with hypertension were defined by having: blood pressure ≥140 mmHg (systolic pressure) and/or ≥90 mmHg (diastolic pressure),[16] been diagnosed with hypertension by health professional, or prescribed antihypertensive medication. Case of stroke was determined by asking respondents whether or not they had been diagnosed by a health professional (doctor or nurse) or suddenly showing symptoms of a stroke. Symptoms shown were: 1) experiencing paralysis on one side of the body, 2) tingling or numbness on one side of the body, 3) mouth droops without eye muscle paralysis, 4) slurred speech, 5) difficulty speaking and/or understanding conversation accessed in Riskesdas 2013[5]. Factors that have been analyzed were limited to age and biomedical parameters i.e.; total cholesterol, LDL-C, HDL-C, triglyceride, and PPG. Total cholesterol, LDL-C, HDL-C, and triglyceride were measured by auto analyzer TRX 7010®. And postprandial glucose was measured by Accu check performa®.

Age was classified to young (< 45 years), middle age (45-65 years), and elderly (>65 years). Total cholesterol, LDL-C, HDL-C, and triglyceride level were determined based on the dyslipidemia guideline according to *Perhimpunan Endokrinologi Indonesia* (PERKENI, The Indonesia Society of Endocrinology)[17]. Level of PPG was determined according to the monitoring guideline of risk factors for non-communicable diseases of the Health ministry of Indonesia[18]. Total cholesterol level was determined to be at risk if the concentration is ≥190 mg/dl. LDL-C level was determined to be at risk if the concentration is ≥110 mg/dl. HDL level was determined to be at risk if the concentration is <40 mg/dl for men and <45 mg/dl for women. Triglyceride level was determined to be at risk if the concentration is ≥150 mg/dl. PPG level was determined to be abnormal if the concentration is ≥180 mg/dl.

2.3 Statistical Analysis

Characteristics of respondents were presented in frequency and proportion. We explored lipid profie and PPG that was related to stroke prevalence adjusted for age and gender in hypertension using Cohran's and mantel-haenszel analysis. Statistically significant

was considered at $p<0.05$. All statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) software (version 13.0 for Windows; IBM SPSS Inc., Chicago, IL).

3. RESULT

The number of respondents analyzed was 8,511 and the number of stroke cases was 767 respondents. It showed that prevalence of stroke cases among people with hypertension based on Riskesdas 2013 in Indonesia was 9%.

Most of the respondents were female (65.5%), aged 45-55 years (51.1%), have total cholesterol at risk (57.3%), LDL-C at risk (75.5%), HDL-C not at risk (70%), triglyceride level not at risk (71.8%) and normal PPG level (77.9%). Respondent distribution by characteristics was presented in Table 1.

Out of 7 variables assessed, bivariate analysis found 3 related variables, i.e.; age, LDL-C level, and postprandial glucose level. The result of bivariate analysis was presented in table 2. the prevalence of stroke was more common in women (9.2%) than in men (8.6%) as shown in table 2. However, gender was not associated with stroke prevalence in hypertensive people in Indonesia. This result was based on a p value of 0.347.

About 10.5% of stroke prevalence was found in age group of >65 years, 10% in age group 45-65 years and 6.7% in age group < 45 years. Statistical analysis showed there was a significant relationship between age and stroke prevalence in hypertensive people in Indonesia in all age groups compared to reference (<45 years). Respondents aged > 65 years are at risk of stroke by as much as 1.57 times greater than respondents aged < 45 years Respondents aged 45-65 years were at risk of stroke by 1.48 times greater than reference.

The prevalence of stroke was found to be higher in the risk group of total cholesterol levels (9.5%) than the non-risk group (8.4%). However, there was no significant association between total cholesterol level and stroke prevalence in hypertensive people in Indonesia, with p value 0.087 at $\alpha=0.05$.

Higher stroke prevalence was found in the risk group of LDL-C level (9.4%) than in non-risk group (7.2%). Statistical analysis revealed a significant association between LDL-C level and stroke prevalence in hypertensive people in Indonesia, with p value 0.025 at

α=0.05. Respondents with LDL-C level that was at risk were 1.21 times greater to have stroke than respondents who have LDL-C level that was not at risk.

Stroke prevalence was found to be higher in non-risk group of HDL-C (9.2%) than in the risk group (8.6%). there was no significant relationship between HDL level and stroke prevalence in hypertensive people in Indonesia, with p value 0.465 at α=0.05.

The prevalence of stroke was found to be higher in the risk group (9.8%) of triglyceride than in the non-risk group (8.7%). However, there was no significant association between triglyceride level and stroke prevalence in hypertensive people in Indonesia, with a p value of 0.120 at α=0.05.

Stroke prevalence was also found to be higher in the abnormal PPG group (10.9%) than the normal group (8.5%). Statistical analysis revealed a significant relationship between PPG level with stroke prevalence in hypertensive people in Indonesia, with p value 0.002 at α=0.05. Respondents with abnormal postprandial glucose level have a 1.28 times greater risk of stroke than respondents who have normal postprandial glucose level.

The comparison of prevalence ratio in each model as shown in table 3. Before adjusting for other variables, LDL-C and PPG were significantly related to stroke prevalence among people with hypertension in Indonesia (Model 1). Similarly, after adjusted for gender, LDL-C and PPG were significantly related to stroke incident among hypertensive people in Indonesia (Model 2). However, the prevalence ratio (PR) of LDL-C increased from 1.21 to 1.23. Prevalence ratio of PPG increased from 1.28 to 1.31. Model 3 shows that after adjusting for age, only PPG had relationship with stroke prevalence among people with hypertension in Indonesia. The PR decreased from 1.28 (Model 1) to 1.25 (Model 3). Similarly, after adjusted for age and gender, only postprandial glucose had relationship with stroke prevalence among people with hypertension in Indonesia. The PR decreased from 1.28 (Model 1) to 1.24 (Model 4).

4. DISCUSSION

This study found 9% of hypertension with stroke. This figure less than in Nigerian study[19]. This study shows that age, LDL-C and PPG status associated with stroke incident among hypertensive people in Indonesia. But there are no association for gender, total cholesterol, HDL-C, and Triglyceride. Reports of lipid profile and PPG status among

hypertensive people with stroke are limited. Nigerian Study shows that modifiable factors signicantly wih stroke occurrence included higher maximum and minimum blood pressure in preceding 3 months, higher fasting plasma glucose, large alcohol consumption, lesser physical activity and increased CIMT. But this research only determined lipid profile and PPG status as object of research.

This study showed a significant relationship between age and the prevalence of stroke in hypertensive people in Indonesia. The risk of stroke increases with increasing age. The prevalence of stroke at young (< 45 years) were found to be 6.7%. The most cases were found at age >65 years (10.5%). Generally, stroke occurs due to aging. Naturally, the blood vessels will become more rigid as a result of plaque[20]. In young adults, increased risk of infarction and vascular risk factors in developing countries is associated with increased smoking and urbanization behavior[21]. Although the relationship between age and stroke incident has been well known, that there is a significant relationship between age and stroke incident among hypertensive people especially in Indonesia provided valuable information.

This study showed a significant relationship between LDL-C level and the prevalence of stroke in hypertensive people in Indonesia. Respondents who had LDL-C levels >100 mg/dL have a 1.30 times greater risk of getting stroke than respondents with LDL-C levels <100 mg/dL. However, after adjusted for age and gender, LDL-C was not a significant variable related to stroke incident among hypertensive people in Indonesia.

The association between LDL-C level and coronary heart disease has been proven with certainty. However, the relationship between LDL-C level and the prevalence of stroke is controversial. Our study was in line with a study in Kerala, India[10] which reported respondents with cholesterol level greater than 200 mg/dl were 2.29 times more likely to have a stroke than those with normal cholesterol level, with p value = 0.009 (1.27-4.15). Likewise, a study in the Neurology Department of Sina Hospital[11] also revealed similar finding. LDL-C was a predictor of hemorrhagic stroke. Increased cholesterol and LDL-C level were associated with a high risk of ischemic stroke. It concluded that LDL-C is a risk factor in both ischemic and hemorrhagic stroke[11]. LDL-C level was also associated with death after long-term stroke, but was not a prognostic factor[22]. It was different with an Indonesian cohort study[12] in common population and Nigerian-African study[19] in hypertensive population. This difference may be due to differences in the number of

respondents, control of other confounding factors, or data weaknesses. Research with cross-sectional design measures exposure and effects in the same time, so it is not known exactly which events occurred earlier. Whether respondents have hypertension, stroke, or have risky LDL-C levels first. This study also can't explain the LDL-C status before the data collection. However, from Table 2 it is known that in most stroke patients still have LDL-C levels at risk (≥100 mg / dl) of 9.4%. This means that controlling LDL-C in the stroke group is still low, so it needs an educational effort to the stroke group to control LDL-C levels for prevention of recurrent stroke and other impacts.

This study showed a significant relationship between PPG level and stroke prevalence in hypertensive people in Indonesia. Respondents with abnormal PPG level have a 1.28 times greater risk of having stroke than respondents with normal PPG level. However, after adjusted for age and gender, PPG was a significant variable related to stroke incident among hypertensive people in Indonesia. The PR decreased from 1.28 (Model 1) to 1.24 (Model 4).

Research on the relationship between PPG levels and stroke incident both general and hypertension population is limited. Most studies use fasting blood sugar (FBG) levels as a research variable. The cohort study in Indonesia[12] showed a significant association between PPG levels and stroke incidence in the general population, but after controlled with other variables, PPG was not the dominant variable causing stroke.[12] While the study in Nigeria (2013)[19] using fasting blood glucose levels as a parameter to show a relationship of FBG with stroke incidence in patients with hypertension. These results indicate a significant relationship between FBG with the incidence of stroke in patients with hypertension. However, when controlled with other variables, FBG levels are not the dominant variable of stroke incidence in hypertensive patients.[19] The San Luigi diabetes study showed that postprandial blood glucose was a strong cardiovascular predictor of fasting blood glucose in type 2 diabetes mellitus, especially in women.[23] High PPG levels or postprandial hyperglycemia are characterized by hyperglycemic spikes that cause endothelial dysfunction, inflammatory reactions and oxidative stress, which can lead to the development of atherosclerosis and the occurrence of cardiovascular events. Research has shown that postprandial hyperglycemia may predispose to the development of atherosclerosis and cardiovascular events[24].

With a larger number of respondents and different data collection from the study in Nigeria, this study showed a significant association between PPG levels and stroke incidence in hypertensive patients in Indonesia. Patients with hypertension who have abnormal levels of PPG at risk of stroke 1.28 times greater than hypertensive respondents who have normal PPG levels. After controlled by age variables, this risk decreases to from 1.28 to 1.25 times. Thus, this provides new insights, that there is a significant relationship between PPG levels and the incidence of stroke in hypertensive people, especially in Indonesia.

Future Recommendation; However, further research is needed to explain the role of PPG levels in increasing the risk of stroke.

5. CONCLUSION

Most of hypertensive people with stroke have high LDL-C and PPG levels. There was a significant relationship between age, LDL-C level and PPG levels and stroke prevalence in hypertensive people in Indonesia. After adjusted for gender and age, PPG level was found to be a significant variable for stroke prevalence in hypertension in Indonesia. It needs an educational effort to the stroke group to control LDL-C and PPG levels for prevention of recurrent stroke and other impacts.

6. ACKNOWLEDGEMENT

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7. CONFLICT OF INTEREST

The authors declared that there are no conflict of interest.

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Table 1. Characteristics of the subjects included in the analysis

Characteristic	Frequency (n)	Proportion (%)
Gender		
- Male	2,933	34.5
- Female	5,578	65.5
Age group		
< 45 years	1,386	16.3
45-65 years	4,345	51.1
>65 years	2,780	32.7
T-Cholesterol Levels		
-≥190 mg/dl	4,873	57.3
- < 190 mg/dl	3,638	42.7
LDL-C Levels		
- ≥100 mg/dl	6,426	75.5
- < 100 mg/dl	2,085	24.5
HDL-C Levels		
-At risk (M < 40 mg/dl ; F < 45 mg/dl)	2,556	30.0
-No risk (M ≥ 40 mg/dl ; F ≥ 45 mg/dl)	5,955	70.0
Triglyceride Levels		
- ≥150 mg/dl	2,397	28.2
- < 150 mg/dl	6,114	71.8
PPG Levels		
- ≥180 mg/dl	1,885	22.1
- < 180 mg/dl	6,626	77.9
Stroke		
-Yes	**767**	**9**
-No	**7744**	**91**

LDL-C : Low Density Lipoprotein Cholesterol
HDL-C : High Density Lipoprotein Cholesterol

Table 2. Relationship between parameters and stroke among respondents with hypertension

Parameter	Stroke (n = 747)		No Stroke (n = 7744)		P Value	PR	95% CI
	N	%	n	%			
Gender							
- Male	252	8.6	2,681	91.4	0.347	0.93	0.806-1.075
- Female	515	9.2	5,063	90.8			
Age Group							
>65 years	146	10.5	1,240	89.5	0.0001	1.57	1.274-1.925
45-65 years	434	10.0	3,911	10.0	0.0001	1.48	1.259-1.751
<45 years	187	6.7	2,593	93.3	*Reference*		
T-Cholesterol Levels							
≥190 mg/dl							
< 190 mg/dl	462	9.5	4,411	90.5	0.087	1.13	0.985-1.298
	305	8.4	3,333	91.6			
LDL-C Levels							
≥100 mg/dl	605	9.4	5,821	90.6	0.025	1.21	1.026-1.431
< 100 mg/dl	162	7.8	1,923	92.2			
HDL-C Levels							
-At Risk (M < 40 mg/dl ; F < 45 mg/dl)	221	8.6	2,335	91.4	0.465	0.94	0.812-1.095
-No Risk (M ≥ 40 mg/dl ; F ≥ 45 mg/dl)	546	9.2	5,409	90.8			
Triglyceride Levels							
≥150 mg/dl	235	9.8	2,162	90.2	0.12	1.13	0.974-1.304
< 150 mg/dl	532	8.7	5,582	91.3			
PPG Levels							
≥180 mg/dl							
< 180 mg/dl	205	10.9	1,680	89.1	0.002	1.28	1.102-1.1492
	562	8.5	6,064	91.5			

Table 3. Comparison of Prevalence Ratio

Parameters	Model 1[+] PR (95% CI)	Model 2 [++] PR (95% CI)	Model 3 [+++] PR (95% CI)	Model 4 [++++] PR (95% CI)
T-Cholesterol	1,13 (0,985-1,298)	1,14 (0,976 – 1,325)	1,10 (0,941 – 1,277)	1,09 (0,937 -1,277)
LDL-C	1,30 * (1,054-1,597)	1,23 * (1,024 – 1,473)	1,20 (0,996 – 1,433)	1,20 (0,997 -1,439)
HDL-C	0,94 (0,812-1,095)	0,94 (0,798 – 1,108)	0,98 (0,830 – 1,153)	0,99 (0,840 -1,168)
Triglyceride	1,13 (0,974-1,304)	1,15 (0,976 – 1,349)	1,12 (0,954 – 1,319)	1,16 (0,981 – 1359)
PPG	1,28 * (1,102-1,1492)	1,31 * (1,107 – 1,552)	1,25 * (1,057 – 1,483)	1,24 * (1,043 – 1,464)

*) significant p value at <0,05

[+]) Model 1 : Crude Prevalence Ratio

[++]) Model 2 : Prevalence ratio after adjusted by gender

[+++]) Model 3 : Prevalence ratio after adjusted by age

[++++]) Model 4 : Prevalence ratio after adjusted by gender and age

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