ORIGINAL ARTICLE

Metabolic Syndrome as a Risk for Coronary Heart Disease in Indonesia: A Longitudinal Study 2007-2014

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ABSTRACT

Introduction: Indonesia has a serious burden of cardiovascular disease, especially coronary heart disease (CHD). The prevalence of CHD has not in fact increased; however, there has been a significant increase in the prevalence of CHD risk factors. Several of these occurring together could cause metabolic syndrome, whose prevalence is relatively high in Indonesia, and consequently increase the risk of CHD. This study aims to obtain the risk of CHD in patients with metabolic syndrome in Indonesia. **Methods:** This is a retrospective cohort study with a median followed up of 6.8 years, secondary data from the Indonesian Family Life Survey (IFLS) waves 4 and 5 (2007-2014), and a study population of 6,571 respondents aged 40-69 years. The Joint Interim Statement criteria were used to define metabolic syndrome, with the omission of one component. **Results:** The prevalence of metabolic syndrome was 20%; the highest component was low HDL at 69.1%, followed by hypertension at 59.7%, and central obesity at 39.7%. The incidence of CHD was 2.72%, with an incidence rate 34per 100,000 person-years. Multivariate analysis found that the relative risk (RR) hazard ratio (HR) was 2.16 (95% CI 1.564-2.985). **Conclusion:** Subjects with metabolic syndrome had a two times higher risk of developing CHD, as adjusted by sex, age, smoking status, and physical activity.
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INTRODUCTION

Coronary heart disease (CHD) is the main cause of death among the non-communicable disease (NCD) group in Indonesia. The preliminary analysis of the Sample Registration Survey (SRS) conducted by the National Institute of Health Research and Development in 2015 showed that nationally CHD was one of the five highest causes of death (12.9%) (1). In addition, the prevalence of CHD based on National Basic Health Survey (Riskesdas) 2018 data is 1.5% (2).

Based on data from Riskesdas 2013 to Riskesdas 2018, as reviewed by Kusuma (3), there was an increase in CHD risk factors. Several of these risk factors occurring together can result in a condition called metabolic syndrome (4), whose prevalence in Indonesia is relatively high. Based on a study using Riskesdas 2013 data, the prevalence of metabolic syndrome in men and women was 28% and 46% respectively (5). In addition, based on a study using IFLS wave 4, the prevalence of the syndrome was 21.66%, rising to 50% in several provinces (6).

The correlation between metabolic syndrome and the risk of developing CHD has been examined in several studies. In a cohort study conducted in South Carolina, men with metabolic syndrome had a greater risk than women of the occurrence of CHD, with a relative risk (RR) of 2.54 (95% CI 1.62 to 3.98) and 1.54 (95% CI 0.68 to 3.53) respectively (7). In addition, a cohort study in Finland and Sweden which analyzed the cardiovascular risk associated with the metabolic syndrome showed an RR of 2.96 (95% CI 2.36–3.72) (8). Studies in Taiwan have also found that the hazard ratio (HR) increases with the number of components in the metabolic syndrome (9).

Research on each CHD risk factor or the interaction between two factors has been extensively conducted, but studies on the metabolic syndrome, which is a group of interrelated risk factors in the occurrence of CHD, using national coverage data, are still limited in Indonesia. This study therefore aims to obtain the risk of metabolic syndrome on the incidence of CHD in the country. It is important to ascertain the magnitude of the risk when establishing comprehensive programs to control CHD in Indonesia based on evidence using national data.

MATERIALS AND METHODS

Subject

The Indonesian Family Life Survey (IFLS) is a survey to assess socioeconomic and health designed to accommodate data in studying behavior and outcomes, and has been conducted longitudinally since 1993, IFLS wave 4 taking place in 2007-2008 (10). IFLS5 was conducted in 2014-2015. Provinces were chosen to maximize the population representation and capture Indonesia's cultural and socioeconomic diversity, as well as on the basis of cost-effectiveness, so the sample included 13 of the 27 provinces in Indonesia, covering 83% of the population (11).

The baseline population in this study were subjects aged 40-69 years who free from CHD in IFLS wave 4 (n=9,667). These population subjects were excluded if they were diagnosed with CHD in IFLS wave 4 (n=256); if there were incomplete data on the metabolic syndrome components (n=1,343); if they had been diagnosed with CHD before 2007 in IFLS wave 5 (n=16); and if they had an unknown CHD status (n=1,481) in IFLS wave 5. Consequently, the eligible population that met the inclusion and exclusion criteria was 6,571 subjects, the same number for the study population. Exposure status was assessed in IFLS wave 4 in 2007 to obtain the metabolic syndrome group (n=1,334) and the group without metabolic syndrome (n=5,237). This population was then followed during the observation period and assessed for outcome status in IFLS wave 5 in 2014, thus obtaining a group with CHD (n=179), and one without CHD (n=6,392). The sampling flow is shown in figure 1.

Study design

A fixed retrospective cohort design was used to assess the risk of metabolic syndrome on the occurrence of CHD. The status of metabolic syndrome was determined based on IFLS wave 4 in 2007, then followed up and assessed for disease status based on IFLS wave 5 in 2014. Demographic data and other risk factors, i.e. sex, age, marital status, occupation, level of education, residence, ethnicity, smoking status, physical activity, and family history of CHD, were assessed in IFLS wave 4 in 2007.

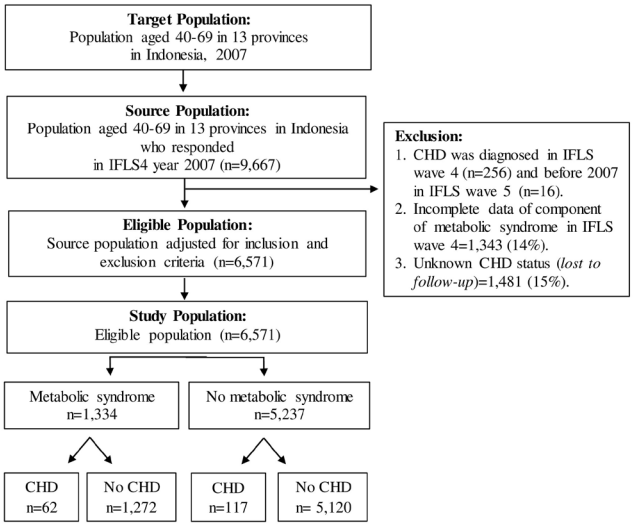

Figure 1: Study flow

Data collection

The IFLS collected data using household questionnaires in Indonesian, with interviews conducted by trained enumerators. Assessment of CHD was obtained through interviews based on the IFLS5 questionnaire, the interviewers asked whether the respondents had ever been a heart attack, coronary heart disease, angina, or other heart problems diagnosed by a doctor/paramedic/nurse/midwife.

The diagnosis of metabolic syndrome was defined by The Joint Interim Statement year 2009, which requires the presence of three of five risk factors for the diagnosis of metabolic syndrome, including 1) central obesity, with a high waist circumference, with the WHO-based circumference limit for the Asian population being 90cm for men and 80cm for women; 2) escalation of blood pressure, systolic 130 mmHg and/or diastolic 85 mmHg, or consumption of antihypertensive drug treatment in a patient with a history of hypertension as an alternative indicator; 3) escalation of triglycerides of >150 mg/dL, or consumption of drug for the condition as an alternate indicator; 4) degression HDL-C, <40 mg/dL in men and <50mg/dL in women, or drug treatment for reduced HDL-C is an alternate indicator; and 5) escalation of fasting glucose of 100 mg/dL, or consumption of drug treatment for elevated glucose is an alternative indicator (4). However, due to the unavailability of data for measuring triglyceride levels, the criteria were reduced to three of the four risk factors in the definition of metabolic syndrome. Likewise, there are no data on the measurement of elevated fasting glucose, so the status of having been diagnosed with diabetes mellitus or taking medication for diabetes was used a substitute for assessing elevated fasting glucose.

Health measurements were carried out by health workers who had received special related training. Waist circumferences were measured with a tape measure to the nearest millimeter. An Omron meter, HEM-7203, was used to take blood pressure, while dried blood spots from a finger prick on SPRT filter paper using the CardiochekPA system were used to measure HDL. The dried blood spot cards were Whatman 903 Protein Saver Cards. The incidence rate was calculated using survival analysis, with the duration (in months) starting from the date of interview in IFLS wave 4, until the date of re-interview in IFLS wave 5, or the date of diagnosis of CHD in respondents with CHD in IFLS wave 5.(10)

Statistical analysis

Computer software performed the statistical analyses. The Cox proportional hazards was used to obtain RR and 95% confidence interval (CI). The final model of

multivariate analysis was obtained after adjusting the confounder.

Ethics

The research was approved by the Committee for Research Ethics and Public Health Service, Faculty of Public Health, University of Indonesia, number: Ket-154/UN2.F10.D11/PPM.00.02/2021.

RESULTS

The results of the analysis provide information that the prevalence of metabolic syndrome is 20.30%, with the highest components being low HDL-C 69.1%, hypertension 59.7%, and central obesity 39.7%. The incidence of CHD was 2.72%, with a total observation of 521,250 person-time, and a median value of observation of 82 months or 6.8 years. The incidence rate was 34 per 100,000 person-years.

The results of the analysis reflected that the proportion of respondents with CHD who had metabolic syndrome was 4.65%, which was higher than those without metabolic syndrome, which was 2.23%. This difference was statistically significant with a p-value of 0.001 and a RR of 2.115 (95%CI 1.549-2.886). In this analysis, there is a significant increase in the risk of CHD based on age, occupation, and education level (Table I). The results of multivariate analysis (Table II) showed that there was a statistically significant relationship between metabolic syndrome and the occurrence of CHD with RR 2.16 (95% CI 1.564-2.985) p-value 0.001. This interprets that a person with metabolic syndrome has a two-fold higher risk of developing CHD compared to a person without metabolic syndrome adjusted by sex, age, smoking status, and physical activity.

DISCUSSION

It was found that the prevalence of metabolic syndrome in Indonesia based on IFLS4 in 2007 was 20.3%. Herningtyas' study of 2019, which used the same data set and criteria, obtained a prevalence of metabolic syndrome, of 21.7% (6). Bantas's study of 2012, using data from the National Basic Health Survey (Riskesdas) of 2007, assessed the prevalence of metabolic syndrome to be 17.5% (12), while Sirait's study of 2014, using metabolic syndrome criteria based on NCEP-ATP III and secondary data from the Bogor PTM Cohort of 2011 showed the prevalence of metabolic syndrome to be 18.7% (13). In the Framingham Offspring cohort study in South Carolina, which used the NCEP-ATP III criteria, the prevalence of metabolic syndrome was 26.8% in men and 16.6% in women (7). On the other hand, in a cohort study in Taiwan, which also used the NCEP-ATP III criteria, women had a higher prevalence of metabolic syndrome than men (28.9% versus 16.6%) (9). The reduction in metabolic syndrome components and the assessment of blood sugar only based on reports

Table I: Relationship between Metabolic Syndrome, Sex, Age, Marital Status, Occupation, Education Level, Residence, Ethnicity, Smoking Status, Physical Activity, and Family History of CHD and CHD

Variable	CHD		HR (95% CI)	*P Value*
	Yes (n=179)	No (n=6.392)		
Metabolic Syndrome				
Yes	62 (4.65)	1,272 (95.35)	2.115 (1.549-2.886)	0.001*
No	117 (2.23)	5,120 (97.77)	Ref	
Sex				
Male	76 (2.54)	2,913 (97.46)	0.906 (0.672-1.222)	0.519
Female	103 (2.88)	3,479 (97.12)	Ref	
Age				
60-69 years old	47 (3.94)	1,146 (96.06)	2.014 (1.365-2.971)	0.001*
50-59 years old	72 (3.33)	2,093 (96.67)	1.781 (1.263-2.511)	0.001*
40-49 years old	60 (1.87)	3,153 (98.13)	Ref	
Marital Status				
Not married/separated	31 (2.99)	1,006 (97.01)	1.139 (0.769-1.688)	0.516
Married	148 (2.67)	5,386 (97.33)	Ref	
Occupation				
White-collar & service industry	83 (3.79)	2,105 (96.21)	2.030 (1.443-2.857)	0.001*
Blue-collar industry	56 (1.80)	3,049 (98.20)	Ref	
Education Level				
College/Academy	20 (4.24)	452 (95.76)	1.763 (1.093-2.845)	0.020*
Graduated Junior-High School	51 (3.19)	1,547 (96.81)	1.313 (0.937-1.838)	0.114
No school- elementary school	108 (2.40)	4,393 (97.60)	Ref	
Residence				
Urban	106 (3.41)	3,006 (96.59)	1.566 (1.158-2.117)	0.004
Rural	73 (2.11)	3,386 (97.89)	Ref	
Ethnicity				
Ethnicity with high PR metabolic syndrome	35 (2.48)	1,379 (97.52)	0.917 (0.633-1.328)	0.646
Ethnicity with low PR metabolic syndrome	144 (2.79)	5,013 (97.21)	Ref	
Smoking Status				
Medium-heavy smoker	44 (2.70)	1.588 (97.30)	1.026 (0.729-1.444)	0.883
Non-smoker-light smoker	135 (2.73)	4,804 (97.27)	Ref	
Physical Activity				
No-little physical activity	64 (2.90)	2,142 (97.10)	1.062 (0.778-1.449)	0.703
Sufficient physical activity	115 (2.63)	4,250 (97.37)	Ref	
Family History of CHD				
Yes	11 (3.81)	357 (97.01)	1.329 (0.702-2.516)	0.424
No	168 (2.67)	7,516 (97.81)	Ref	

*CHD: Coronary heart disease, HR: Hazard ratio, PR: Prevalence ratio

Table II: Final Model of Multivariate Analysis Metabolic Syndrome as Risk for CHD

Variable	HR	95% CI	P *value*
Metabolic Syndrome	2.160	1.564-2.985	0.001*

Adjusted for sex, age, smoking status, and physical activity *HR: Hazard ratio, CI: Confidence interval

from the respondents need to be considered because it caused the prevalence of metabolic syndrome in this study to be underestimated.

The relatively high prevalence of tmetabolic syndrome in this study was not surprising. It was caused by the prevalence of CHD risk factors in the community, which saw a fairly high increase based on Riskesdas 2013 to Riskesdas 2018; diabetes mellitus increased by 23% (from 6.9% to 8.5%); hypertension in those aged above 18 increased by 32% (from 25.8% to 34.1%); and obesity increased by 47% (from 14.8% to 21.8%) (3). These risk factors are part of the components of metabolic syndrome.

Cardiovascular diseases include diseases of the heart and blood vessels, of which CHD constitutes the majority of this group of diseases caused by the atherosclerosis process (14). In this study, the diagnosis of CHD was based only on self-reporting. Meanwhile, a study that used data from the National Basic Health Survey (Riskesdas) 2013 found the prevalence of CHD was 1.5%, based on a doctor's diagnosis or symptoms in respondents aged over 15 year in 33 provinces in Indonesia (15). In a study Riskesdas 2007, aged 40-69 years, it was found that 2% of respondents were diagnosed with cardiovascular disease (16).This study obtained a higher incidence than those studies, which was possible because the diagnosis of CHD was based on self-reporting without confirmed clinical diagnosis or records. Based on the Framingham Heart Study Offspring cohort study 2005, there were 107 new cases of CHD (3.22%) from the population aged 22-81 years with metabolic syndrome who were followed up for more than 8 years, in which the diagnosis of CHD was validated based on information from clinical examination, doctors' notes on an outpatient basis, and inpatients during the observation period (7). The prospective cohort study in Taiwan had an incidence of 3.94%, with a rate of 1.86 per 1000 person-years, with a median follow-up of 9 years (range 7.9–10 years), and with a diagnosis of CHD derived from registry data by entering data on deaths from CHD, new onset of myocardial infarction, and procedures in the treatment of CHD with the help of medical record documents on hospitalization (9). Compared to these two studies, the incidence rate in this study tends to be lower, which is because the observation time is shorter, so the outcomes have not had enough time to manifest themselves.

Even in this study diagnosis of CHD status is only based on interviews with the questions whether the respondents had ever been a heart attack, coronary heart disease, angina, or other heart problems diagnosed by doctor/paramedic/nurse/midwife It was discussed in the theory (17) (18) that heart attacks and angina are part of the course of CHD caused by atherosclerosis, so the questionnaire were appropriate to describe the condition/disease of CHD. The term in the questionnaire "other heart problems" only refers to a small proportion of cardiovascular disease, namely diseases of the aorta and arteries (hypertension at 6.2% and peripheral vascular disease at 0.4%), rheumatic heart disease at 1.6 %, and cardiomyopathic heart muscle disorders at 1.8% (19).

In this study, the risk of metabolic syndrome on the occurrence of CHD was relatively strong. The risk is consistent with several other studies. In the Framingham Offspring cohort study in South Carolina, RR with metabolic syndrome in men was RR 2.54 (95% CI 1.62-3.98) and in women it was RR 1.54 (95%CI 0.68-3.53) for the occurrence of CHD (7). In the cohort study in Taiwan, the risk of metabolic syndrome on the occurrence of CHD was HR 1.8 (9). Although the risk in this study tends to be lower than in the Framingham study, it is slightly stronger than in the study in Taiwan, even though the incidence of CHD in this study was consistently lower than in the other two studies. This is because the observation time in this study is shorter, there is a reduction in the criteria of components from metabolic syndrome, and diagnosis of CHD and assessment of blood sugar is only based on self-reporting.

Each component of metabolic syndrome plays a role in increasing the risk of CHD. The distribution with the highest frequency of components of metabolic syndrome in this study was a 69% decrease in HDL. Low HDL levels are a reflection of chronic conditions that can increase inflammation and insulin resistance. This condition can directly affect atherosclerosis (20). This disorder is also a feature of insulin resistance-hyperinsulinemia due to abdominal obesity; an increase in plasma HDL cholesterol through weight-loss interventions, a healthy diet, increased physical activity, and if necessary, pharmacotherapy, are the optimal prevention methods of CHD in high-risk patients (21).

The increase in blood pressure in this study was the second-highest component of metabolic syndrome, at 59.7%. High blood pressure contributes to about half of all cardiovascular diseases (22). There is substantial evidence to support the notion that insulin resistance and/or compensatory hyperinsulinemia can play a role in the regulation of blood pressure and can influence a large number of indications of the development of high blood pressure. Most individuals with high blood pressure also have significant clinical abnormalities in terms of glucose, insulin, lipid metabolism, and endothelial dysfunction. This high blood pressure is a consequence of insulin resistance. Therefore, an approach to controlling hypertension alone is necessary,

but not sufficient to reduce CHD in hypertensive patients (23).

Central obesity is the main trigger for most of the pathways involved in metabolic syndrome due to a high-calorie intake being the main causative factor (24). In this study, the prevalence of central obesity was quite high, at 39.7%. Individuals with obesity changes that impair lipid metabolism tend to have an increase in fasting plasma total cholesterol, triglycerides, and a decrease in HDL levels, conditions which increase the risk of atherosclerosis (25).

The main factors of metabolic syndrome are improper nutrition and lack of physical activity, thereby leading to weight gain. Overweight and obesity are associated with insulin resistance and metabolic syndrome. Insulin resistance and hyperinsulinemia appear to be two important consequences of the lipid metabolism disorder seen in the metabolic syndrome. Hyperinsulinemia, through stimulation of arterial smooth muscle proliferation, has been implicated in the development of atherosclerotic plaque. The degree of insulin resistance is significantly correlated with coronary artery disease (25).

In obese people, waist circumference is correlated with dyslipidemia and high blood pressure. Several deleterious changes in lipid metabolism are frequently seen in obese individuals. These changes were more closely correlated with the amount of visceral fat than with total body fat. In general, obesity tends to increase fasting plasma total cholesterol, triglycerides, and reduce HDL levels, this condition increases the risk of atherosclerosis. While atherosclerosis is convinced as a major role in the pathogenesis of cardiovascular disease (25).

Risk assessment of each component of metabolic syndrome is very important, especially for developing countries such as Indonesia, because each of the components has a high prevalence in society. A review by Kusuma (3) shows that there has been a dramatic increase in the components of metabolic syndrome as a risk factor of CHD in the last five years, based on the 2018 Riskesdas report compared to the 2013 one. Without substantial policies and actions, especially for the prevention and control of NCDs, Indonesia is on the verge of an NCD epidemic, especially CHD.

The study has limitations in terms of data incompleteness at 14% and lost to follow-up of 15%. The IFLS study is a panel, so there is a possibility of lost to follow-up when respondents in IFLS5 can no longer be contacted for various causes (died, lost contact, cannot be traced, or moved, for example). This limitation can lead to potential selection bias. However, because the sample selection in this study was made using a total sampling technique, the entire population that met the inclusion and exclusion criteria was included in the study population. Therefore, each subject had the same opportunity to be selected (probability sampling) and there was no difference in the criteria when selecting the subject's disease status based on exposure status. In this case, selection bias was minimal and the resulting estimate led to a null value or underestimation.

In this study, information bias was likely to occur in either exposure status or disease. In the former case, bias may exist as a result of a reduction in the definition of metabolic syndrome due to unavailability of data; i.e., elevated triglycerides. In addition, one component of metabolic syndrome uses a proxy variable, namely the increase in glucose, in which the assessment is based on reports of respondents having been diagnosed with diabetes or taking diabetes medication. Information bias can affect the determination of disease status. The diagnosis of CHD was based on an interview with no confirmed clinical diagnosis or records. In addition to the questionnaire, the status of CHD was asked about in one group with heart attacks, angina, or other heart problems. This made the CHD status less accurate and specific, meaning it could cause errors in grouping or misclassification between groups with and without CHD.

Although there was information bias related to both exposure and disease status, the resulting bias was non-differential because it occurred in both groups, and there were no differences in setting the criteria in the exposed and non-exposed groups and the outcome and non-outcome groups, as well as in each group using the same standard questionnaire allows the occurrence of non-differential information bias, so the estimation led to a null value.

Even though some of the data in this IFLS survey were assessed based on interviews, when the answers depended on the honesty and understanding of the respondents of the questions, the role of the data collection officers as enumerators trained in conducting direct interviews using standardized questionnaires was important, meaning respondents' misunderstanding of the questions could be minimized. The measurement of health itself was made by two trained nurses for each household member using standardized measurement tools (10).

As for the limitations in the availability of data in IFLS survey, not all confounding variable could be adjusted in this study. The risk factors that were not included were dietary patterns (high in salt, fat, calories), increased triglycerides, increased glucose, and increased LDL. These risk factors may still cause disturbances in the relationship between metabolic syndrome and the occurrence of CHD. In this study, the results of the multivariate final analysis obtained a fairly narrow confidence interval (95%CI), with a statistical

significance test p-value of 0.001. This shows that the associations found in the study are relatively precise and it is unlikely that the results obtained occurred because of chance.

With the limitations detailed, risk in this study is thought to have been underestimated, although the minimal risk is RR 2.16 (95% CI 1.564-2.985), which the relationship is strong enough, statistically significant, and with a minimal chance factor and a precise CI range, meaning these results can still obtain the minimal risk of metabolic syndrome in the incidence of CHD in Indonesia. If these limitations can be overcome in further research so that misclassification can be minimized, then the real relationships will be stronger.

The strength of this study comes from the retrospective cohort study design, in which there were no temporal ambiguity relationships. In addition, the study used data with national coverage that have not been used in other studies to assess the risk of metabolic syndrome in the occurrence of CHD.

The results of the study found that subjects with metabolic syndrome had a risk of developing CHD after adjusting the confounder. In addition, the prevalence of metabolic syndrome and its components are quite high in the community, so it is necessary to run health promotion programs and education, particularly focusing on the productive and the elderly population. In fact in Indonesia there are government programs to encourage the community to make lifestyle changes such as the Healthy Living Community Movement (GERMAS), and CERDIK programs for CHD prevention. Since central obesity is the main trigger for most of the pathways involved in metabolic syndrome, it is highly recommended that the community should be concerned about balanced diets and increased physical activity. For those with metabolic syndrome, the best approach is to educate people about compliance with medication and to provide pharmacological care.

CONCLUSION

Subjects with metabolic syndrome had a two-fold higher risk of developing CHD after adjusting for factors such as sex, age, smoking status, and physical activity.

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