

Stress as a major determinant of migraine in women aged 25-65 years

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ABSTRACT

BACKGROUND

Migraine is a primary headache causing substantial disability in patients. The prevalence of migraine in women is still high. Menarche, menstruation, pregnancy, menopause, and the use of hormonal contraceptives and hormone replacement treatment may influence migraine occurrence. The aim of this study was to determine the major determinants of migraine in adult women aged 25-65 years.

METHODS

A cross-sectional study of 2,747 women from the baseline study "Cohort Study of Risk Factors for Non-Communicable Diseases". The dependent variable was migraine based on the diagnosis of health providers or symptoms. Independent variables were demographic (age, marital status, education) and behavioral (smoking, diet, and stress) characteristics, metabolic disorders (obesity, hypertension, dyslipidemia), and hormonal factors (contraception and hormone therapy). Data were collected through interviews (characteristics, health and hormonal status, diet), measurement (anthropometrics, blood pressure), and health examination (blood specimens, neurology). Data were analyzed by chi-square test and multiple logistic regression.

RESULTS

Migraine in adult women was found in 710 cases (25.8%) with symptoms of worsening with activity (15%), nausea and vomiting (13%), and photophobia/phonophobia (4.1%). The main determinant of migraine in adult women was stress with a 2.47-fold risk [95% CI = 2.07 to 2.95] as compared with no stress, after controlling for smoking, menstruation and hormonal drug consumption.

CONCLUSION

Stress is a major determinant of migraine in adult women, therefore health programs should be instituted through health promotion, prevention and education to control stress.

Key words: Migraine, stress, risk factors, adult women

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Stres sebagai determinan utama terjadinya migren pada perempuan umur 25-65 tahun

ABSTRAK

LATAR BELAKANG

Migrain merupakan nyeri kepala primer yang menyebabkan disabilitas secara substansial bagi penderita. Proporsi migrain pada perempuan masih tinggi. Faktor menarke, haid, kehamilan, menopause, dan penggunaan obat kontrasepsi hormonal serta pengobatan sulih hormon dapat mempengaruhi kejadian migren. Tujuan penelitian ini untuk menentukan determinan utama penyakit migren pada perempuan dewasa berusia 25-65 tahun.

METODE

Desain penelitian potong-lintang pada 2747 perempuan dari data baseline penelitian “Studi Kohor Faktor Risiko Penyakit Tidak Menular”. Variabel dependen adalah migren berdasarkan hasil diagnosis tenaga kesehatan atau gejala. Variabel independen meliputi karakteristik demografi (umur, status kawin, pendidikan), perilaku (merokok, konsumsi makanan berisiko, dan stres), gangguan metabolik (kegemukan, hipertensi, dislipidemia) dan faktor hormonal (kontrasepsi dan terapi hormon). Data dikumpulkan dengan metode wawancara (karakteristik, status kesehatan dan hormonal, diet), pengukuran (antropometri, tekanan darah) dan pemeriksaan (spesimen darah, neurologi). Data dianalisis dengan uji chi-square dan uji regresi logistik ganda.

HASIL

Penyakit migren pada perempuan ditemukan pada 710 orang (25,8%), gejala penyerta nyeri kepala semakin hebat dengan aktivitas 15%, mual dan muntah 13% serta fotofobia/fonofobia 4,1%. Determinan utama penyakit migren pada perempuan adalah stres dengan risiko 2,47 kali [95% CI = 2,07 – 2,95] dibandingkan tanpa stres, dengan mengontrol faktor merokok, menruasi dan konsumsi obat hormon.

KESIMPULAN

Determinan yang paling berperan terhadap migren adalah stres, sehingga program terkait perlu segera melakukan upaya promotif dan preventif melalui edukasi untuk mengendalikan faktor stres pada perempuan usia 25-65 tahun.

Kata kunci: *Migren, stress, faktor risiko, perempuan dewasa*

INTRODUCTION

Migraine is a primary headache that is frequently misunderstood, poorly diagnosed, and seldom treated in clinical practice.⁽¹⁾ The symptoms of migraine are commonly accompanied by nausea, vomiting, or excessive sensitiveness to light (photophobia). In many people, migraine causes pulsations occurring only on one side of the head.⁽²⁾ Migraine may cause substantial disability to the patients, their family, and the community, as a result of its high prevalence in the general population.⁽³⁾

The respective prevalences of migraine in both males and females in Spain,⁽³⁾ Taiwan,⁽⁴⁾ and China⁽⁵⁾ are 11.20%, 25.01%, and 9.3%.⁽⁴⁾ Its prevalences in Taiwanese and Spanish women are 15.07%⁽³⁾ and 15.94%, respectively.⁽⁴⁾ The Spanish study showed that females have a 3.02-fold greater risk for migraine than males.⁽³⁾ The prevalences of migraine by gender are said to be 43% for females and 18% for males, with a significant correlation being found between gender and migraine.⁽⁶⁾ The main cause of migraine is still not known with certainty. It is believed that

migraine is caused by a combination of genetic and environmental factors. Migraine is also influenced by several other factors, such as physiological (stress, fatigue, hunger, hormones) and dietary factors.⁽⁷⁾

The main determinant of migraine in women has not been extensively studied. Studies on migraine in women are few in number and do not completely reveal its determinants or factors. The existing studies state that the main factor influencing migraine is variation in female sex hormone levels.⁽⁸⁾ Genetic factors also influence the occurrence of migraine in women.⁽⁹⁾ The aim of the present study was to find the main determinant of migraine in women aged 25–65 years.

METHODS

Research design

This was a study of cross-sectional design carried out in 5 *kelurahan* [villages] of Central Bogor District [*Kecamatan Bogor Tengah*], Bogor City, in 2011–2012.

Study subjects

Women aged 25–65 years were recruited into the study if they met the inclusion criteria (permanent resident, capable of communication, and independent) and the exclusion criteria (pregnant, refusing to participate). A subject was categorized as having migraine if she had been diagnosed by health providers or had unilateral headache accompanied by at least 1 of these 3 symptoms: aggravation by physical activity, nausea, and vomiting, and photophobia or phonophobia.

The sample size was determined from the formula for estimation of proportions. After adjusting by a drop-out factor of 20%, the required sample size was 2747.⁽¹⁰⁾ The sample was obtained by consecutive sampling (voluntary until the required size was reached) among households (permanent residents) selected from all *Rukun Tetangga* (RT) in all *Rukun Warga* (RW) of 5 *kelurahan* (Kebon

Kalapa, Babakan Pasar, Babakan, Ciwaringin, and Panaragan) in Central Bogor District [*Kecamatan Bogor Tengah*], Bogor City.

Data collection

The selected study subjects were interviewed using questionnaires, consisting of public health questionnaires on demographic characteristics, health status (including mental or stress status), and nutritional questionnaires, comprising recall questionnaire and food frequency questionnaire (FFQ). Physical examination comprised determination of anthropometric measures (weight, height, and abdominal circumference) and blood pressure, in addition to laboratory investigations for fasting blood glucose and 2-hour blood glucose after a glucose load of 75 grams.⁽¹¹⁾

Interviews

The variables collected by interviews comprised the characteristics of the respondents (age, gender, marital status, education, occupation), behavior (smoking, and consumption of migraine trigger foods), mental health (stress), migraine status, and hormonal factors (consumption of hormonal drugs or hormone replacement therapy). Age was categorized into 2 age groups, i.e. 25–44 years and 45–65 years. Marital status was categorized into unmarried, married, and divorced/widowed. Educational status of the respondents, based on length of education until completion, was categorized into 3 categories, viz. low (no education and primary school), intermediate (junior and senior high school) and high (*D3* and *Sarjana*). Smoking habit was categorized into smoker (including ex-smokers) and non-smoker. Mental health status was assessed by symptoms of emotional disorder (stress), by the respondents themselves answering questions on emotional disorder contained in the Self Reporting Questionnaire (SRQ). Respondents were considered to have symptoms of emotional disorder (stress) if they had at least 6 of the 20 symptoms.

Hormonal factors were defined as factors associated with a reproductive condition or status (menstruation) and use of hormonal contraceptives, hormonal drugs, and hormone replacement therapy. Menstrual status was categorized as “yes” (if still menstruating) and “no” (if in menopause/ceased to menstruate). Contraceptive use was categorized as “yes” (if using hormonal contraceptive pills, injections, or implants, and “no” (if not using them). Hormonal therapy was defined as treatment or prevention by hormonal drugs or hormone replacement therapy. The categories were “yes” (if taking hormonal drugs or hormone replacement therapy) and “no” (if not taking hormonal drugs or hormone replacement therapy).

Measurements

These comprised height and weight for calculation of body mass index (BMI) using the formula $\text{weight (kg)}/\text{height}^2$ (height in meters). BMI was categorized according to the classification of the World Health Organization into 4 categories, i.e. underweight (BMI <18.5), normal (BMI 18.5–22.9), overweight (BMI 23–24.9) and obese (BMI >25). In the multivariate analysis obesity was categorized as obese (BMI >25) and non-obese (BMI <25). Hypertension was defined as the condition of a systolic blood pressure of >140 mmHg and/or a diastolic blood pressure of >90 mmHg, based on the 2007 standards of the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.⁽¹²⁾ Metabolic abnormality was defined as the presence of metabolism-related disorders in an individual, comprising obesity, hypertension, dyslipidemia, and hyperglycemia.

Laboratory tests

The laboratory tests were performed by regional private laboratories with ISO 15189 and ISO 9001 accreditation. All determinations were done on an automatic analyzer. Total cholesterol concentration was determined by the colorimetric enzymatic hexokinase method. Determination of

high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol in the blood was by direct homogeneous enzymatic method. Triglyceride concentration was by the colorimetric enzymatic glycerol-3-phosphate method. Determination of fasting blood glucose and 2-hour blood glucose after glucose loading was by the glucose hexokinase II (GLUH) method.

Dyslipidemia was defined as the condition in which blood total cholesterol, LDL cholesterol, and triglycerides were higher than normal, while HDL cholesterol was lower than normal. Total cholesterol was categorized as “high” if >200 mg/dL and “normal” if <200 mg/dL. LDL cholesterol was categorized as “high” if >100 mg/dL and “normal” if <100 mg/dL. Triglyceride level was categorized as “high” if >150 mg/dL and “normal” if <150 mg/dL. HDL cholesterol was categorized as “low” if <40 mg/dL in males and <50 mg/dL in females, while it was categorized as “normal” if >40 mg/dL (males) and >50 mg/dL (females).

Hyperglycemia was defined as the condition of the blood glucose level exceeding the standard. Determination of hyperglycemia was based on blood glucose levels with a loading dose of 75 gram glucose. Hyperglycemia was categorized as diabetes mellitus (DM) if the blood glucose was >200 mg/dL, as impaired glucose tolerance if the blood glucose was 140–199 mg/dL, and as normal if the blood glucose was <140 mg/dL.

Dietary intake

The habit of consumption of migraine trigger foods was determined on the basis of frequency of consumption of foods categorized as migraine triggers, such as milk, coconut milk (*santan*) and legumes. The dietary consumption was obtained by 24-hour recall and Food Frequency Questionnaire (FFQ). FFQ is a recall interview method asking about habitual consumption on the basis of frequency of food consumption per week. The variable habitual consumption of trigger foods was categorized as “yes” (if consumed) or “no” (if not).

Data analysis

The data were analyzed using the chi-square test, for differences in proportions and crude odds ratio. Multiple logistic regression was used to find the main determinant associated with migraine in women after controlling for other determinants and calculating the adjusted odds ratio.

Ethical clearance

This study was approved for ethical clearance by the Commission on Health Research Ethics of the Health Research and

Development Board, Ministry of Health, Republic of Indonesia (*Litbangkes Kemenkes RI*).

RESULTS

A total of 2747 respondents were successfully recruited into the study, among whom 710 respondents (25.8%) were diagnosed as having migraine. The accompanying symptom of headache aggravated by increasing activity was experienced by 15% respondents, nausea or vomiting by around 13.2%, and phonophobia or photophobia by 4.2%.

Table 1. Distribution of migraine by respondent characteristics and risk behavior

Characteristic	M igraine				p v alue
	Yes (n=710)		No (n=2037)		
Age (years)					
25 –44	407	28.5	1019	71.5	0.001 *
45 –65	303	22.9	1018	77.1	
Marital status					
Unmarried	18	19.4	75	80.6	0.242
Married	610	26.3	1705	73.7	
Divorced/widowed	82	24.0	257	76.0	
Education					
Low	288	24.8	875	75.2	0.214
Intermediate	388	27.1	1042	72.9	
High	34	22.1	120	77.9	
Risk behavior					
Smoking					
Smoker	99	35.1	183	64.9	0.000 *
Non-smoker	611	24.8	1854	75.2	
Stress					
Yes	334	38.5	534	61.5	0.000 *
No	376	20.0	1503	80.0	
Consumption of legumes					
Yes	677	25.7	1953	74.3	0.589
No	33	28.2	84	71.8	
Consumption of milk					
Yes	308	27.0	831	73.0	0.233
No	402	25.0	1206	75.0	
Consumption of coconut milk					
Yes	360	26.2	1012	73.8	0.663
No	350	25.5	1025	74.5	

*Significant at $p < 0.05$

The distribution of women with migraine by respondent characteristics is presented in Table 1. Table 1 shows that characteristics and risk behavior have significant differences in the proportions ($p < 0.05$) of the variables age, smoking, and emotional disorder (stress). The

Table 2. Distribution of migraine by metabolic disorder and hormonal factors of respondents

Metabolic disorder	Migraine				p value
	Yes (n=710)		No (n=2037)		
Hypertension					
Yes	241	25.3	710	74.7	0.680
No	469	26.1	1327	73.9	
BMI					
Obesity	382	24.6	1109	75.4	0.466
Overweight	126	27.2	338	72.8	
Normal	189	27.4	500	72.6	
Underweight	33	26.8	90	73.2	
Total cholesterol					
High	361	24.7	1098	75.3	0.163
Normal	349	27.1	939	72.9	
LDL cholesterol					
High	576	25.9	1648	74.1	0.912
Normal	134	25.6	389	74.4	
HDL cholesterol					
Low	299	24.9	903	75.1	0.313
Normal	411	26.6	1134	73.4	
Triglycerides					
High	101	24.3	314	75.7	0.466
Normal	609	26.1	1723	73.9	
Blood glucose					
DM	49	23.0	164	77.0	0.078
IGT	143	22.9	464	77.1	
Normal	523	27.1	1409	72.9	
Menstrual status					
Yes	503	28.1	1286	71.9	0.000*
No	207	21.6	751	78.4	
Hormonal contraceptives					
Yes	456	26.5	1264	73.5	0.322
No	254	24.7	773	75.3	
Hormonal replacement therapy					
Yes	14	27.5	37	72.5	0.749
No	696	25.8	2000	74.2	
Consumption of hormonal drugs					
Yes	27	37.5	683	25.5	0.028*
No	683	25.5	1992	74.5	

BMI = body mass index; HDL = high density lipoprotein; LDL = low density lipoprotein; DM = diabetes mellitus; IGT = impaired glucose tolerance; *Significant at $p < 0.05$

younger or young adult age group (25-44 years) had a higher proportion of migraine than did the 45+ age group ($p=0.001$). Respondents with smoking habits had a higher proportion of migraine than non-smokers ($p=0.000$). Respondents with migraine had more symptoms of emotional disorder (stress) than those without migraine ($p=0.000$).

The distribution of migraine by metabolic disorder is presented in Table 2. Table 2 shows that all variables of metabolic disorders were not associated with migraine ($p>0.05$). This signifies that the factors of metabolic disorders (hypertension, obesity, total, LDL, and HDL cholesterol, triglycerides, and blood glucose) were not correlated with migraine prevalence.

Hormonal factors in women play an important role in body metabolism, such as the occurrence of a regular menstrual cycle at reproductive age. Table 2 shows that among the hormonal factors (menstrual status, use of hormonal contraceptives, hormone replacement therapy, and consumption of hormonal drugs), the variables menstrual status and consumption of hormonal drugs had significantly different proportions ($p<0.05$). Women who still had a menstrual cycle (were reproductive) had a higher proportion of migraine than those in menopause, while women taking hormonal drugs had a higher proportion of migraine than those

not taking hormonal drugs.

The results of multivariate analysis to find the main determinant of migraine in women are shown in Table 3. Table 3 shows from the results of bivariate (crude OR) and multivariate analyses (adjusted OR) that the major determinants of migraine comprise stress (emotional disorders), smoking habit, menstrual status, and consumption of hormonal drugs. These determinants already showed a risk (crude OR) in the bivariate analysis, and were again significantly correlated in the multivariate analysis. The results show that among the four determinants entering the multivariate analysis, the determinant smoking showed a decrease in risk from 1.87 (c OR) to 1.53 (a OR). The results may be summarized as indicating that the major determinants of migraine in women comprise stress, with a 2.47-fold risk (95% CI 2.07 – 2.95), smoking habit, with a 1.53-fold risk (95% CI 1.17 – 2.01), active menstrual cycle, with a 1.44-fold risk (95% CI 1.19 – 1.74), and consumption of hormonal drugs, with a 1.79-fold risk (95% CI 1.09 – 2.96).

DISCUSSION

In the present study, the proportion of migraine in women was around 25.8%, which agrees with the finding of a similar proportion

Table 3. Determinants of migraine in women

Determinant	Migraine				p value
	Crude odds ratio (c OR)	95% Confidence interval	Adjusted odds ratio (a OR)	95% Confidence interval	
Stress					
Yes	2.50	2.00 – 2.98	2.47	2.07 – 2.95	0.000
No	1	Reference	1	Reference	
Smoking					
Yes	1.87	0.26 – 13.45	1.53	1.17 – 2.01	0.002
No	1	Reference	1	Reference	
Menstrual status					
Yes	1.42	1.18 – 1.71	1.44	1.19 – 1.74	0.000
No	1	Reference	1	Reference	
Consumption of hormonal drugs					
Yes	1.75	1.08 – 2.84	1.79	1.09 – 2.96	0.022
No	1	Reference	1	Reference	

(25.01%) in the Taiwanese study.⁽⁴⁾ This is in contrast with the studies conducted in Spain and China, which found the lower prevalences of 11.02% and 9.3%, respectively.^(3,5)

The accompanying symptom most frequently experienced by migraine patients was headache aggravated by activity (15%), followed by nausea and vomiting (13.2%), while the least frequent symptoms were phonophobia and photophobia (4.2%). These are all symptoms commonly developing in migraine without aura. In contrast, the headache in migraine with aura is usually accompanied by disturbances of vision and sensory equilibrium.⁽¹³⁾ The number of accompanying symptoms apparently determine the severity of migraine without aura. Studies have shown a significant correlation between severity of migraine and accompanying symptoms (photophobia, phonophobia, and nausea), which disturbs the functioning and quality of life of the patient.⁽¹⁴⁾ Characteristically, migraine of moderate degree is aggravated by increased activity and is associated with nausea, photophobia, and phonophobia.⁽¹⁵⁾

According to subject characteristics and risk behavior, the determinants showing significant differences in proportions were age, smoking, and emotional disorder (stress). Women in the age group of 25-44 years showed a higher proportion of migraine than those in the 45+-year age group. A number of previous studies state that younger age is a predictor of migraine onset.⁽¹⁶⁾

With regard to smoking habit, women smokers in our study had a higher proportion of migraine than non-smokers. This is in accord with previous studies reporting the presence of an association between smoking habit and migraine, stating that the risk of migraine increases significantly with low educational level, unemployment, and smoking.⁽¹⁷⁾

Our migraineurs had more emotional symptoms than non-migraineurs. Emotional disorders, such as stress or depression was associated with migraine onset, especially in women. Similar findings were obtained by

Peterlin et al. in Spain,⁽¹⁸⁾ showing that depressive individuals with stress frequently suffered from migraine (25.71%), with a 3.64-fold greater chance of experiencing migraine. Stress activates the sympathetic nervous system and the hypothalamic pituitary adrenal axis, which are both associated with the feelings of an individual towards internal and external threats. A study carried out in Sweden also states that stress is an important factor for the occurrence of migraine. Anxiety and depression occurs twice as frequent in females as in males.⁽¹⁸⁾

Regarding metabolic disorders in women, such as hypertension, obesity, hyperglycemia, and dyslipidemia, in the present study no correlation was found between the metabolic syndrome and migraine upon further analysis. There is a study reporting significant differences between the metabolic syndrome and migraine for diabetes, abdominal circumference, and obesity, but not for hypertension and dyslipidemia.⁽¹⁹⁾ These differing findings are presumably due to the facts that in the abovementioned study the population consisted of males and females, that hyperglycemia was categorized on the basis of diabetic status, and that obesity was categorized on the basis of a BMI value of 30.

Migraine is strongly associated with hormonal factors, especially in women. In the case of hormonal factors, the present study shows that women with an active menstrual cycle (reproductive women) had more frequent migraine attacks than those in menopause. In women, migraine is associated with the menstrual period, resulting in the complication of headache associated with menstruation, usually at the time of ovulation, frequently during the menstrual period and seldom in the premenstrual period.⁽²⁰⁾ Fluctuations in estrogen levels is said to be capable of triggering headache in women, especially migraine. Migraine occurs (1) before or during the menstrual period (in which there is a large decrease in estrogen levels); (2) in pregnancy or menopause; (3) after consumption

of hormonal drugs, such as oral contraceptives and hormone replacement therapy.⁽²¹⁾

Women who use hormonal contraceptives (pills, injections, implants) and hormone replacement therapy, showed a significantly higher proportion of migraine than those who do not use these treatments. In the case of hormonal contraceptives, it has been shown that their use positively affects the occurrence of migraine, as a number of recent cross-sectional studies on large populations found that the use of combined oral contraceptives was significantly correlated with migraine.^(22,23) Hormonal drug and hormone replacement therapy showed a higher proportion of migraine in comparison with no hormonal therapy.

Our study also shows that the main determinants of migraine in women comprise stress (emotional disorders), smoking habit, menstrual status, and consumption of hormonal drugs. Stress appears to have the highest risk than the other factors, as migraine in women is associated with stress with a 2.47-fold risk (95% CI 2.07 – 2.95). Several previous studies reported that stress affects migraine and more frequently appears in women, since these are more susceptible to stressors.⁽²⁴⁻²⁶⁾

The number of women smokers in our study was approximately 10%. Our analyses showed that women smokers had a 1.53-fold increased risk (95% CI 1.17 – 2.01) of suffering from migraine than non-smokers. Nicotine in cigarettes increases the risk of migraine with aura 1.8-fold (95% CI 1.0 – 3.2) and of migraine without aura 2.3-fold (95% CI 1.3 – 3.8).⁽²⁷⁾ Smoking increases the risk of migraine 6.6-fold (95% CI 2.2 – 19.6) in comparison with no smoking, after controlling for the factors of alcohol consumption, lack of sleep, stress, and number of household members.

In the present study, migraine was also associated with menstrual status, women with active menstrual cycle having a 1.44-fold greater risk of migraine (95% CI 1.19 – 1.74) in comparison with women in menopause. In the case of hormonal drugs, women who consume


hormonal drugs showed a 1.79-fold (95% CI 1.09 – 2.96) risk of suffering from migraine than women who were not on hormonal drugs. A previous study reported that the risk factors affecting migraine occurrence in women are associated with menarche, menstruation, pregnancy, use of hormonal contraceptives and hormone replacement therapy.⁽²⁸⁾

The present study has several limitations. The method of recall interview is constrained by the recall ability of the respondents and was not confirmed by special medical examination for the diagnosis of migraine. Other limitations are the lack of diagnostic subcategories for migraine, such as episodic migraine, periodic migraine, migraine with aura and migraine without aura, the lack of a measure of dose response for the variables of concentration and duration, e.g. for smoking and hormonal drug consumption.

CONCLUSIONS

The prevalence of migraine in women aged 25-65 years is 25.8% and a major determinant of migraine is stress. Integrated programs should be instituted as promotive and preventive measures for migraine, through education of the community, with a focus on the control of stress (emotional disorder).

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