

## Factors Influencing Hyperuricemia: Evidence from Sukoharjo, Central Java, Indonesia

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### ABSTRACT

**Background:** Hyperuricemia is an elevated serum uric acid level. It causes urate deposits in the joints, tendons, and other tissues as physiological prerequisites for gout. Hyperuricemia is also related to the existence and severity of several comorbidities, such as hypertension, cardiovascular disease, diabetes, and metabolic syndrome. The result of basic health research in 2018 showed that the prevalence of joint disease in Indonesia based on a doctor's diagnosis was 7.3%. The highest prevalence was in Aceh (13.3%). The lowest prevalence was in West Sulawesi (3.2%). This study aimed to examine factors associated with hyperuricemia.

**Subjects and Method:** This was an analytical observational study with a case control design. The study was conducted in Sukoharjo, Central Java, from January to April, 2018. A sample of 90 study subjects was selected by consecutive sampling. The dependent variable was hyperuricemia. The independent variables were age, sex, stress, purine-rich foods intake, and family history of gout. Stress was measured by depression, anxiety, and stress scale (DASS 42). The other variables were collected by questionnaire. The data were analyzed by a multiple logistic regression.

**Results:** Older age (OR= 13.80; 95% CI= 3.36 to 56.66;  $p < 0.001$ ), female (OR= 1.94; 95% CI= 3.36 to 7.62;  $p = 0.345$ ), purine-rich foods intake (OR= 5.01; 95% CI= 1.48 to 16.97;  $p = 0.010$ ), and stress (OR= 6.14; 95% CI= 1.83 to 20.60;  $p = 0.003$ ) increased the risk of hyperuricemia. Family history of gout (OR= 1.47; 95% CI= 0.43 to 5.04;  $p = 0.537$ ) increased the risk of hyperuricemia, but it was statistically non-significant.

**Conclusion:** Age, female, purine-rich foods intake, and stress increase the risk of hyperuricemia. Family history of gout increases the risk of hyperuricemia, but it was statistically non-significant.

**Keywords:** hyperuricemia, purine-rich food, stress

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### BACKGROUND

Uric acid is the final product of purine metabolism in humans. The normal reference of uric acid in human blood is 1.5-6 mg/dL in women and 2.5 -7 mg/dL in men (Wardhana, 2018). Hyperuricemia is defined as an elevated serum uric acid level which. It causes urate deposits in the joints, tendons, and other tissues as physiological prerequisites for gout. Hyperuricemia is also associated with the existence and severity of several co-morbidities, such as hypertension, cardiovascular disease, diabe-

tes, dyslipidemia, chronic kidney disease, atrial fibrillation, and metabolic syndrome (Ichida et al., 2012; Maruhashi et al., 2018). Hyperuricemia can occur due to increased uric acid metabolism (over production), decreased uric acid excretion (under excretion), or a combination of them (Kurniari, 2011)

Hyperuricemia is very common in developed countries. Based on the result of the National Health and Nutrition Examination Survey (NHANES), around 21% (or 43 million) American adults aged 20

years and above experienced hyperuricemia. Compared to developed countries, the prevalence of hyperuricemia tends to be lower in developing countries. For example, the prevalence of hyperuricemia was 10.6% in Thailand and 8.4% in Saudi Arabia (Song et al., 2018). A recent meta-analysis of 36 articles from 2000 to 2014 showed that the prevalence of hyperuricemia in Mainland China was 13.3%, while in Tibet China reached 37.2% (Zhang et al., 2018).

The prevalence of hyperuricemia in Indonesia is still unclear. The prevalence of hyperuricemia in residents of Central Java was 24.3% in men and 11.7% in women. Based on a preliminary study of hyperuricemia in Sembiran Village, Bali Province, the prevalence of hyperuricemia was 18.9%. Meanwhile, based on a field study, the prevalence of hyperuricemia in residents of Denpasar city was 18.2%. In addition, the prevalence of hyperuricemia in residents of Nusa Ceningan, Nusa Penida District, was 17%. Based on a study conducted in rural tourism areas in Ubud District, the prevalence of hyperuricemia was 12% (Kurniari, 2011).

Based on the result of the Basic Health Research (Ministry of Health RI, 2018), the prevalence of joint disease in Indonesia, based on a doctor's diagnosis was 7.3%. The highest prevalence was in Aceh (13.3%) and the lowest was in West Sulawesi (3.2%). The prevalence of joint disease at the age of 15-24 years was 1.2%; 25-34 years was 3.1%; 35-44 years was 6.3%; 45-54 years was 11.1%; 55-64 years was 15.5%; 65-74 years was 18.6%; and 75 years and above was 18.9%. The prevalence of joint disease in women was 8.5%; in men was 6.1%; in urban residents was 6.9% and in rural residents was 7.8%. The highest prevalence occurred in farmers, which was 9.90.

Hyperuricemia is affected by several factors, including sex, BMI (Body Mass Index), purine intake, and carbohydrate intake (Setyoningsih, 2009). Factors associated to the suspected occurrence of hyperuricemia are family history, obesity, fructose intake, purine intake, and fluid intake (Khoirina, 2016). Based on a study conducted by Diantari in 2012, purine intake affects uric acid level; however, fluid did not affect uric acid level in women aged 50-60 years.

Based on a study conducted in Tibet, China, the characteristics associated with hyperuricemia were farmer (OR= 1.75; 95% CI= 1.02 to 2.99), low education level (OR= 1.57, 95% CI= 1.10 to 2.24), alcohol consumption (OR= 1.80; 95% CI= 1.19 to 2.70), hypertension (OR= 1.48; 95% CI= 1.09 to 2.01), BMI (OR= 1.12; 95% CI= 1.08 to 1.16) and serum creatinine (OR= 1.05; 95% CI= 1.03 to 1.06) (Zhang et al., 2018).

Based on a study conducted by Song et al., in 2018, hyperuricemia was more common in men than women (7.9% vs. 4.9%). The risk of hyperuricemia increased in both sexes as getting older. Men who consumed alcohol, had obesity, and had dyslipidemia were positively associated with hyperuricemia. Besides, single men and men who lived in North China had lower chance of having hyperuricemia. Women or single women at a higher economic level who lived in Southwest China, who smoke, had obesity, had diabetes, had hypertension, and had dyslipidemia were significantly associated with the risk factors of hyperuricemia. Women who lived in North China and North-West China had lower prevalence of hyperuricemia than women in East China. According to demographic, socio-economic, and geographical factors, the prevalence of hyperuricemia in China varies greatly.

This study aimed to analyze the factors influencing hyperuricemia.

## SUBJECTS AND METHOD

### 1. Study Design

This was an observational analytic study with a case control design. The study was conducted in Sukoharjo, Central Java, from January to April 2018.

### 2. Study Sample

A sample of 90 study subjects was selected for this study by consecutive sampling.

### 3. Study Variables

The dependent variable was hyperuricemia. The independent variables were age, sex,

family history of gout, stress, and purine-rich foods intake.

### 4. Study Instrument

Data on stress was measured by Depression, Anxiety, and Stress Scale (DASS 42) questionnaire. Purine level was measured by uric acid meter.

### 5. Data analysis

This study was analyzed using univariate, bivariate, and a multiple logistic regression.

## RESULTS

### 1. Sample characteristics

The characteristics of the study subjects can be seen in Table 1.

**Table 1. The distribution of study subjects of factors influencing hyperuricemia**

Characteristics	Case		Control	
	N	%	N	%
<b>Age</b>				
40 - 70 years	41	91	19	42
20 - 39 years	4	9	26	58
<b>Sex</b>				
Male	18	40	9	20
Female	27	60	36	80
<b>Family History of Gout</b>				
With history	7	16	5	11
Without history	38	84	40	89
<b>Purine-Rich Foods Intake</b>				
High	35	78	14	31
Low	10	22	31	69
<b>Stress</b>				
High	31	69	11	24
Low	14	31	34	76

Based on the characteristics of the study subjects, the majority of subjects in the case group (91%) were 40-70 years of age, while in the control group (58%) were 20-39 years of age. The majority of subjects were female (60% in the case group and 80% in the control group). Only a small number of subjects had family history of gout (16% in the case group and 11% in the control group).

Most of the subjects in the case group (78%) consumed purine-rich foods with high intensity. Meanwhile, most of the sub-

jects in the control group (69%) consumed purine-rich foods with low intensity. Most of the subjects in the case group (69%) had high stress level. In addition, most of the subjects in the control group (76%) had low stress level.

### 2. Bivariate Analysis

Table 2 shows that the results of the bivariate analysis of factors influencing hyperuricemia. Variable of family history of gout did not have any influence on hyperuricemia. Hyperuricemia increased with age (OR= 14.03; 95% CI= 4.29 to 45.87; p

<0.001), and female (OR= 2.67; 95% CI= 1.04 to 6.85; p= 0.041).

**Table 2. The result of the bivariate analysis of factors influencing hyperuricemia**

Independent Variables	OR	95% CI		p
		Lower limit	Upper limit	
Age	14.03	4.29	45.87	<0.001
Sex (female)	2.67	1.04	6.85	0.041
Family History of Gout	1.47	0.43	5.04	0.537
Purine-rich foods intake	7.75	3.01	19.93	<0.001
Stress	6.84	2.71	17.31	<0.001

### 3. Multivariate Analysis

**Table 3. The results of the multivariate analysis**

Independent Variables	OR	95% CI		p
		Lower limit	Upper limit	
Age	13.80	3.36	56.66	<0.001
Sex (female)	1.94	0.49	7.62	0.345
Purine-Rich Foods Intake	5.01	1.48	16.97	0.010
Stress	6.14	1.83	20.60	0.003

Table 3 showed the results of multivariate analysis. Table 3 showed that older age (OR= 13.80; 95% CI= 3.36 to 56.66; p <0.001), female (OR= 1.94; 95% CI= 3.36 to 7.62; p= 0.345), purine-rich foods intake (OR= 5.01; 95% CI= 1.48 to 16.97; p= 0.010), and stress (OR= 6.14; 95% CI= 1.83 to 20.60; p= 0.003) increased the risk of hyperuricemia. Family history of gout (OR= 1.47; 95% CI= 0.43 to 5.04; p= 0.537) increased the risk of hyperuricemia, but it was statistically non-significant.

## DISCUSSION

### 1. The influence of age on hyperuricemia

This study showed that age factor influenced hyperuricemia (OR = 13.80; 95% CI= 3.36 to 56.66; p<0.001). People aged 40 years and above had higher risk for having hyperuricemia. This probably occurred because there was a decline in kidney function at the age of 40 years and above in the process of excretion of metabolic waste in the body. It was characterized by high levels

of urea and creatinine. Other factors that cause uric acid level increases at <40 years of age are obesity, high blood pressure, abnormal blood cholesterol level, and men who are in the severity level of alcohol dependence (Choi et al., 2005). Based on the age spectrum, the risk factor of hyperuricemia in young adults (30-39 years) is hyperlipidemia; meanwhile, lifestyle and some clinical syndromes play an important role in the middle-aged people (40-59 yrs). Different risk factors between sexes in the middle age are the effects of alcohol consumption in men and the effects of menopause in women. Impaired kidney function and the use of diuretics are important factors in the elderly (≥60 years) (Lin and Chou, 2000).

The result of this study is in line with a study conducted by Kapetanovic et al. (2018) reported that in women, hyperuricemia is correlated with high BMI (r= 0.38), age (r= 0.20), systolic blood pressure (r= 0.20), triglycerides (r= 0.30), lower eGFR (r= - 0.27), total cholesterol (r= 0.18), ESR

( $r = 0.17$ ), fasting blood sugar ( $r = 0.13$ ), and the occurrence of hypertension, CVD and diabetes ( $p < 0.001$ ). Other studies show that subjects with hyperuricemia have older age, BMI, SBP, DBP, TG, and FPG in men and women (Zheng et al., 2018).

Based on a study conducted by Setyoningasih (2009), age has a positive correlation with gout ( $r = 0.85$ ;  $p < 0.001$ ). It means that the strength of correlation is moderate. The result of the linear regression analysis showed that each increase in 1 age score would increase 0.068 score of uric acid ( $b = 0.104$ ;  $p < 0.001$ ).

## **2. The influence of sex on hyperuricemia**

Based on the result of this study, men had higher risk for having hyperuricemia (OR= 1.94; 95% CI= 3.36 to 7.62;  $p = 0.345$ ). The uric acid level in men in the blood at puberty can reach 5.2 mg/dl. It will increase with age because there is no estrogen hormone as uricosuric agent. It is a chemical that assists the excretion of uric acid through the kidney. The mechanism of uricosuric agent in uric acid excretion is to inhibit URAT1 (urate transporter-1) from the lumen to the proximal tubular cells when regulating electrolyte fluid balance (Setyoningasih, 2009).

The result of this study is in line with a study conducted by Billa et al. (2018), that there is a statistically significant correlation between sexes (male vs. female;  $p < 0.0001$ ) and different age categories (<30 years vs. 31-50 years);  $p = 0.02$ ; 31-50 years vs. > 50 years;  $p < 0.0001$ ;  $\leq 30$  years and > 50 years;  $p < 0.0001$ ; chi square test). It is related to the prevalence of HU in the overall population. A study conducted by Zhang et al. (2018), showed that the prevalence of hyperuricemia in men is higher than in women (41% vs. 34.4%,  $p = 0.011$ ).

## **3. The influence of family history of gout on hyperuricemia**

This study showed that family history of gout increased the risk of hyperuricemia (OR= 1.47; 95% CI= 0.43 to 5.04;  $p = 0.537$ ). A study conducted by Kuo et al. (2015), states that the main risk factors of gout are hyperuricemia, genetics, dietary factors, drugs, comorbidities, and lead exposure.

Impaired uric acid excretion by the kidney is one of the causes of increased level of uric acid, hyperuricemia, and nephropathy. The kidney filters free circulating uric acid. It filters around 70% of the total uric acid excretion from the body. Based on a study conducted by Chittoor et al. (2017), all kidney urinary excretions were significantly inherited ( $p < 2 \times 10^{-6}$ ). Its range was from 0.41 to 0.74. The empirical threshold value for genome area significance was set at  $p < 1 \times 10^{-7}$ . There was a strong correlation ( $p < 8 \times 10^{-8}$ ) between uric acid excretion and single nucleotide polymorphism (SNP) in the 446 zinc finger protein (ZNF446) (rs20-33711 (A / G), MAF: 0.30). Minor alleles (G) were associated with increased uric acid clearance. The study also found a suggestive correlation between gout clearance and SNP in ZNF324, ZNF584, and ZNF132 (in the 72 kb area on 19q13;  $p < 1 \times 10^{-6}$ , MAFs: 0.28-0.31). This study showed the importance of the 19q13 area in regulation of uric acid excretion by the kidney in Hispanic children.

## **4. The influence of stress on hyperuricemia**

The result of the study showed that stress could increase the risk of hyperuricemia (OR= 6.14; 95% CI= 1.83 to 20.60;  $p = 0.003$ ). Psychological stress causes neuro-endocrine, inflammatory, metabolic, and transcriptional disorders that tend to affect a disease (Picard et al., 2015). Acute stress disorder can affect the activity of the HPA axis (e.g. cortisol) and the sympathetic

nervous system (e.g. heart rate and blood pressure). Even though a greater acute autonomic response has been found in adult men, but women has showed increased sensitivity to the higher adrenal cortex (Murphy and Loria, 2017).

Gout is associated with mental health, but its nervous mechanism is still unclear (Goodman et al., 2016). Cortisol hormone production increase when stress occurs. Therefore, the metabolism of carbohydrates, fats, proteins, and purines also increases. Increased purine metabolism causes an increase in uric acid level in the blood. A study by Bobaya (2016), there is a correlation between stress and gout arthritis in Tobelo Community Health Center, Tobelo District, North Halmahera.

### **5. The influence of purine-rich foods intake on hyperuricemia**

This study showed that purine-rich foods intake could increase the risk of hyperuricemia (OR= 5.01; 95% CI= 1.48 to 16.97; p= 0.010). Some purine-rich foods such as liver, intestine, red meat, sardines are often consumed by subjects in the case group. Besides, foods with low purine such as tofu, tempeh, and long beans are more often consumed by subjects in the control group. The content and bioavailability of purines in food ingredients varies. Besides, the change of purines to uric acid also depends on the relative cellularity and the transcription and cellular metabolic activity of the food. Transcription activity is the ability of cells to interpret the genetic code of one type of nucleic acid into another form. In this case, cells are able to convert purines in food into uric acid. Purines derived from animal source foods have high level of bioavailability. Besides, the amount of animal source foods is also high. Most of exogenous purines, which are derived from food, will be directly converted to uric acid without the occurrence of tissue nucleic

acids. However, guanine, hypoxanthine, and exogenous xanthine which do not combine into nucleic acids will rupture and form uric acid with the guanase enzymes assistance and oxidant xanthine in the intestinal epithelium (Choi and Curhan, 2004).

A study by Kusumayanti et al. (2015), the patterns of purine consumption and obesity had significant differences. The sequence of risk factors of hyperuricemia was obesity (OR = 2.32; 95% CI: 1.13-4.75); frequency of rich-purine foods consumption (OR= 2.16; 95% CI: 1.06 to 4.00); level of purine consumption (OR= 2.14; 95% CI= 1.02 to 4.48); and types of rich-purine foods consumed (OR = 2.12; 95% CI= 1.05 to 4.28).

A study conducted by Setyoningsih in 2009, variable of high-purine diet had a positive correlation on uric acid levels ( $r=0.82$ ;  $p<0.001$ ). The result of linear regression analysis showed that each increase in 1 high-purine diet score would increase 0.264 scores of uric acid (95% CI= 0.14 to 0.39;  $p<0.001$ ).

### **6. The influence of age, sex, high purine food intake, and stress on hyperuricemia**

The effect of age between men and women on hyperuricemia is different. At the productive age, men have a higher risk of hyperuricemia than women. After menopause, women have a higher risk of hyperuricemia than men (Song et al., 2018). This is likely related to the loss of uricosuric estrogen after menopause (Kuo et al., 2015). In other words, the difference in the prevalence of hyperuricemia in both sexes seems to be narrow as getting older. However, hyperuricemia is still a male-dominated disease as shown in several studies.

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#### **AUTHOR CONTRIBUTIONS**

Dewi Wulandari collected the data on age,

sex, stress, family history of gout, and uricemia level, did the data analysis, interpreted the results of data analysis, and wrote the manuscript.

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#### CONFLICT OF INTEREST

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We declare that we do not have any conflict of interest.

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