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# Correlation of Serum Uric Acid, Morning Home Blood Pressure and Cardiovascular Risk Factors over 10 Years in a Prehypertensive Population



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# CORRELATION OF SERUM URIC ACID, MORNING HOME BLOOD PRESSURE AND CARDIOVASCULAR RISK FACTORS OVER 10 YEARS IN A PREHYPERTENSIVE POPULATION

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## ABSTRACT

**Objective**: To investigate significant changes, mainly in serum uric acid levels, blood pressure and cardiovascular risk factors, that occurred over 10 years in the epidemiological data of a target group of prehypertensive patients.

**Design:** cross-sectional cohort study

**Setting:** Mlati Sub-district, Sleman District, Yogyakarta Province, Indonesia

**Participants**: Prehypertension population dataset (n=4190) were used from the 2007 "Mlati Study Database". A total of 733 patients were selected by simple random sampling using statistical software. Subjects had both physical and laboratory examinations.

**Outcome measures:** Morning home blood pressure and laboratory examination of urine (uric acid excretion and creatinine) and blood samples (SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol, low density lipoprotein/LDL-C, high density lipoprotein/HDL-C and triglycerides), and fasting blood glucose levels)

**Results**: Serum uric acid levels were significantly higher in men than in women (5.78 (1.25) mg/dL vs 4.52 (1.10) mg/dL, $p<0.001$). Furthermore, men tended to have high-normal and high serum uric acid levels compared to women ($p<0.001$, RR=2.60). High-normal and high serum uric acid levels were significantly associated with prehypertension and hypertension only in women ($p=0.001$, RR=1.21). Body mass index was found to be significantly associated with blood pressure in the sample group. Fasting blood glucose was significantly associated with systolic blood pressure in men and with systolic and diastolic blood pressure in women; meanwhile, serum uric acid was significantly associated with blood pressure only in women.

**Conclusion**: We concluded that serum uric acid levels were significantly associated with prehypertension and hypertension only in women. Here, blood pressure was associated with


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body mass index, fasting blood glucose, and serum uric acid levels, whereas in men, blood pressure was only associated with body mass index and fasting blood glucose.

**Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences

## STRENGTH AND LIMITATION OF THIS STUDY

- This study followed up the changes of blood pressure on subjects for over 10 years.
- The association between serum uric acid, blood pressure, and cardiovascular risk factors were analyzed based on gender.
- The analysis' were also performed by using both JNC 7 and 2017 ACC/AHA guideline.
- This study could not present the changes of all measured value over 10 year period because in the prior study in 2007, these laboratory value were not examined, except for blood pressure.

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## INTRODUCTION

Hypertension is still a major problem worldwide, as reflected by a meta-analysis report in 2016 stating that in 2010, 40% of the world's population was hypertensive and that approximately 17 million people worldwide died due to hypertension.[1] In Indonesia, the prevalence of hypertension in 2013 was 25.8%, based on the Indonesian Ministry of Health report.[2] Therefore, it is important to facilitate the early recognition and treatment of hypertension and its possible effects. This study was important due to its cohort design, such that patients were followed for 10 years. Patients with prehypertension were hypothesized to eventually become hypertensive after 10 years and thus have a poorer quality of life. During the last two decades, it has been repeatedly published that the incidence of hypertension is associated with even moderate increases in levels of serum uric acid (SUA) and an increased risk of cardiovascular diseases (CVD).[3,4] The Framingham Heart Study reported an increased risk of blood pressure (BP) progression in 3157 subjects with hyperuricaemia. SUA was positively associated with increases in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) after 4 years with no antihypertensive treatment.[5] Current findings based on a large-scale cohort study suggested that uric acid is a predictive factor of the development of prehypertension in adults.[6] A meta-analysis by Jiang *et al.* indicated that SUA was possibly associated with prehypertension but still found conflicting results.[7] The associations among SUA, hypertension, cardiovascular risk factors and gender remain controversial.[8, 9] Therefore, this study was conducted as a cohort study of ten years of follow-up (2007–2017) in a population with homogenous characteristics in the Mlati Subdistrict, Sleman District, Yogyakarta, Java Island, Indonesia. The aim of this study was to observe the progression from prehypertension to hypertension after 10 years of follow-up and its association with SUA as well as other cardiovascular risk factors. We hypothesized that at

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least 30% of prehypertensive patients will eventually develop hypertension and that it is associated with SUA.

## METHODS

### *Study Design*

This study was a cross-sectional cohort study conducted in Mlati Sub-district, Sleman District in the Yogyakarta Special Region, Indonesia. The protocol of this study was approved by Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with the ID approval of KE/FK/0961/EC/2017.

### *Study Population*

We pooled data from participants enrolled in the 2007 Mlati Study Database. The sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion criteria for the prehypertensive subgroup of the study sample were negative proteinuria, negative urine reduction, and age between 20 and 49 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected as participants in the current study by simple random sampling using statistical software. All 1500 subjects were invited to have a physical and laboratory examination; however, only 733 subjects who participated in the sampling were examined (the other subjects who did not show up during the laboratory examination were due to the change of residential area or death or any other unknown reasons). All subjects provided informed consent at the beginning of the study.

### *Patient and Public Involvement*

Patient were not involved in any of the design, analysis, and presentation of the study results.

### *Data Collection*

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The data collection was conducted twice during the study period. The first data collection was conducted in 2007 to collect the prehypertension population (n=4,190). The second data collection was performed in 2017 to collect samples from the Mlati Study Database by the random sampling method (n=733).

In 2007, interviews were conducted on 12,073 subjects to obtain family history and to perform physical and laboratory examinations. Physical examinations, which included measurements of morning home BP, body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference and hip circumference, were conducted on day 1. On day 2, we examined morning home BP and took urine and blood samples.

In 2017, we collected data from 733 subjects, including physical and laboratory examinations. On the first day, subjects were interviewed, physically examined, and given urine containers for one-time urine samples as well as for a 24-h urine collection that had to be submitted on day 2. The physical examination consisted of a morning home BP measurement using the Omron HEM-907 monitor (digital automatic blood pressure monitoring) and measurements of body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference and hip circumference. On the second day, subjects came while fasting and were physically examined for BP again. Urine and blood samples were examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine sample was collected to measure uric acid excretion and creatinine, and a blood sample was collected to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol, low density lipoprotein/LDL-C, high density lipoprotein/HDL-C and triglycerides), and fasting blood glucose levels.

***Definition of Prehypertension and Hypertension***

The definitions of prehypertension and hypertension were based on the Seventh Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only their

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treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of 80–89 mmHg are defined as prehypertension, while SBP of ≥140 mmHg and/or DBP of ≥90 mmHg are defined as hypertension.[10]

For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as follows: (1) normal BP = SBP <120 mmHg and DBP <80 mmHg, (2) elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, (3) stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, and (4) stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg.[11]

***Serum Uric Acid Cut-off Point***

Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3 categories: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).[12]

***Statistical Analysis***

The data consisted of continuous and categorical data, which were expressed as the mean (SD) for continuous data and as numbers and percentages for categorical data. The continuous variables were analysed and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The categorical variables were analysed and compared by Pearson chi-square tests. Multivariable analysis was performed using multiple linear regression. The significance of associations between categorical variables and numerical variables were determined using 95% confidence intervals (CIs).

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## RESULTS

**Table 1.** Characteristic of Subjects by Gender Presented in Mean (SD)

| Variables | Men n=306 | Women n=427 | p-value |
|---|---|---|---|
| Age (years) | 46 (7.71) | 46 (7.76) | 0.431 |
| 30 – 39 years | 35 (2.86) | 36(2.63) | 0.093 |
| 40 – 49 years | 45 (2.89) | 45 (2.67) | 0.372 |
| 50 – 59 years | 54 (3.18) | 54 (2.77) | 0.779 |
| BMI (kg/m$^2$) | 23.5 (3.70) | 25.7 (4.81) | <0.001* |
| SBP (mmHg) | 132 (17.26) | 134 (21.62) | 0.595 |
| DBP (mmHg) | 78 (11.96) | 79 (12.32) | 0.091 |
| Uric Acid (mg/dL) | 5.8 (1.25) | 4.5 (1.10) | <0.001* |
| Total cholesterol (mg/dL) | 167 (36.86) | 166 (41.59) | 0.559 |
| LDL (mg/dL) | 109 (29.59) | 106 (33.27) | 0.155 |
| HDL (mg/dL) | 41 (10.02) | 47 (12.20) | <0.001* |
| Triglyceride (mg/dL) | 129 (79.09) | 103 (63.84) | <0.001* |
| Fasting Blood Glucose (mg/dL) | 100 (37.22) | 97 (33.70) | 0.101 |

*Significant ($p<0.05$)

The subjects of this study consisted of 733 adults (aged 30–59 years) living in the Mlati Subdistrict; 306 (41.75%) and 427 (58.25%) were men and women, respectively. The characteristics of the subjects (by gender) are presented in Table 1. There was no significant difference in age, SBP, DBP, total cholesterol, low density lipoprotein (LDL) and fasting blood glucose between men and women ($p>0.05$). Significant differences were found in body mass index (BMI) ($p<0.001$), SUA levels ($p<0.001$), high density lipoprotein (HDL) ($p<0.001$) and triglycerides ($p<0.001$). BMI and HDL were significantly higher in women, whereas SUA levels and triglycerides were significantly higher in men.

After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal, and only 6.6% had high SUA levels.

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**Table 2.** Association between Gender, Age, BMI, Uric Acid Excretion, and Uric Acid Concentration to Serum Uric Acid Level

| Variables | SUA | | p value | RR | 95% CI |
|---|---|---|---|---|---|
| | High-normal and high (%) | Normal (%) | | | |
| Gender | | | | | |
| Men | 237 (32.3) | 69 (9.4) | <0.001 | 2.60 | 2.22-3.05 |
| Women | 127 (17.3) | 300 (40.9) | | | |
| Age | | | | | |
| Men | | | | | |
| 30 – 39 years* | 52 (17.0) | 11 (3.6) | - | 1 | - |
| 40 – 49 years | 104 (34.0) | 22 (7.2) | 1,000 | 1.00 | 0.87-1.15 |
| 50 – 59 years | 81 (26.5) | 36 (11.8) | 0.053 | 0.84 | 0.71-0.99 |
| Women | | | | | |
| 30 – 39 years* | 22 (5.2) | 85 (19.9) | - | 1 | - |
| 40 – 49 years | 40 (9.4) | 128 (30.0) | 0.530 | 1.16 | 0.73-1.84 |
| 50 – 59 years | 65 (15.2) | 87 (20.4) | <0.001 | 2.08 | 1.37-3.15 |
| BMI | | | | | |
| Overweight-Obese | 171 (23.3) | 154 (21.0) | 0.153 | 1.13 | 0.96 - 1.32 |
| Underweight-normal | 193 (26.3) | 215 (29.3) | | | |
| Uric Acid Excretion (24-h) | | | | | |
| High | 169 (23.1) | 130 (17.7) | 0.002 | 1.32 | 1.10 - 1.57 |
| Normal | 195 (26.6) | 239 (32.6) | | | |
| Uric Acid Concentration | | | | | |
| Normal | 200 (27.3) | 202 (27.5) | 0.956 | 1.00 | 087 – 1.16 |
| High | 164 (22.4) | 167 (22.8) | | | |

* reference category

In men, 32.3% of the subjects had high-normal or high levels of SUA, while in women, only 17.3% had high-normal or high levels of SUA. There was a significant difference in SUA between men and women (p<0.001, RR=2.60, 95% CI=2.22–3.05). When gender was further analysed by age distribution, age was significantly associated with SUA levels only in women aged 50–59 years (p<0.001, RR=2.08, 95% CI=1.36–3.15). Additionally, there was a significant association between SUA levels and uric acid excretion by 24-h urine (p=0.002, RR=1.32, 95% CI=1.10–1.57). On the other hand, no significant association was observed between SUA levels and BMI (p=0.153, RR=1.1, 95% CI=0.96–1.32) or between SUA levels and uric acid concentration (p=0.100, RR=0.786, 95% CI=0.59–1.05) (Table 2).

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**Table 3.** Association between Gender and Serum Uric Acid on Blood Pressure

| Variables | Blood Pressure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | JNC 7[a] | | | | 2017 ACC/AHA[b] | | | |
| | Pre-HT and HT (%) | Normal (%) | p | RR (95%CI) | HT-1 and HT-2 (%) | Normal and elevated (%) | p | RR (95%CI) |
| Gender | | | | | | | | |
| Men | 234 (31.9) | 72 (9.8) | 0.584 | 1.02 (0.94 – 1.11) | 159 (21.7) | 147 (20.1) | 0.129 | 0.9 (0.79 - 1.03) |
| Women | 319 (43.5) | 108 (14.7) | | | 246 (33.6) | 181 (24.7) | | |
| SUA | | | | | | | | |
| High-normal and High | 290 (39.6) | 74 (10.1) | 0.008* | 1.12 (1.03 - 1.22) | 224 (30.6) | 140 (19.1) | 0.001* | 1.26 (1.10 - 1.43) |
| Normal | 263 (35.9) | 106 (14.5) | | | 181 (24.7) | 188 (25.6) | | |
| SUA | | | | | | | | |
| Men | | | | | | | | |
| High-normal and High | 182 (59.5) | 55 (18.0) | 0.805 | 1.02 (0.88 – 1.19) | 129 (42.2) | 108 (35.3) | 0.109 | 1.25 (0.93 – 1.68) |
| Normal | 52 (17.0) | 17 (5.6) | | | 30 (9.8) | 39 (12.7) | | |
| Women | | | | | | | | |
| High-normal and High | 108 (25.3) | 19 (4.4) | 0.001* | 1.21 (1.09 – 1.34) | 95 (22.2) | 32 (7.5) | 0.000* | 1.49 (1.28 – 1.73) |
| Normal | 211 (49.4) | 89(20.8) | | | 151 (35.4) | 149 (34.9) | | |

[a] BP was categorized using the JNC 7 Guideline

[b] BP was categorized using the 2017 ACC/AHA Guideline

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The associations between gender and SUA levels on BP are shown in Table 3. There was no significant association between gender and BP (p=0.584). To examine the association between uric acid and hypertension, we compared SUA levels and morning home BP. The association between SUA levels and BP was statistically significant (p=0.008, RR=1.12, 95% CI=1.03–1.22). The risk of high-normal and high SUA levels becoming prehypertension or hypertension was 1.12 times higher than that of normal SUA levels. Furthermore, the association between SUA levels and BP in men and women is also described in Table 3. In men, SUA levels were not significantly associated with BP (p=0.805, RR=1.02, 95% CI=0.88–1.19). However, there was a significant association between SUA levels and BP in women (p=0.001, RR=1.21, 95% CI=1.09–1.34). In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal and high SUA levels than those with normal SUA levels. Additional analysis using 2017 ACC/AHA guideline for observing the associations between gender and SUA levels on BP also showed similar results with the previous analysis using JNC 7 guideline regarding the significant associations between SUA levels and BP.

Figure 1 shows the association between SUA and cardiovascular risk factors. The SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030). Subjects with high-normal and high SUA levels had significantly higher total cholesterol, LDL, and triglyceride levels than subjects with normal SUA levels. On the other hand, HDL and fasting blood glucose were statistically lower among subjects with high-normal and high SUA levels than among those with normal SUA levels.

The relationships between SUA levels and cardiovascular risk factors among men and women are presented in Figure 2. In men, there were significant differences in BMI (p<0.001) and triglycerides (p=0.002) between subjects with normal SUA levels and those with high-

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normal and high SUA levels. In women, there was no significant differences in all cardiovascular risk factors (p>0.05) between subjects with normal SUA levels and those with high-normal and high SUA levels.

**Table 4.** Multiple Linear Regression of Association of Cardiovascular Risk Factors and SUA on Blood Pressure

| Variables | Blood Pressure of Men | | | | Blood Pressure of Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Systolic | | Diastolic | | Systolic | | Diastolic | |
| | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value |
| SUA | -0.184 | 0.817 | 0.612 | 0.253 | 5,588 | <0.001* | 2,196 | <0.001* |
| BMI | 1,428 | <0.001* | 1,208 | <0.001* | 0.757 | 0.001* | 0.727 | <0.001* |
| Total Cholesterol | 0.027 | 0.819 | 0.034 | 0.670 | 0.130 | 0.253 | 0.029 | 0.645 |
| LDL | -0.037 | 0.762 | -0.019 | 0.815 | -0.09 | 0.438 | -0.015 | 0.824 |
| HDL | 0.190 | 0.181 | 0.047 | 0.624 | -0.002 | 0.988 | -0.051 | 0.469 |
| Triglyceride | 0.000 | 0.991 | 0.002 | 0.929 | -0.024 | 0.377 | 0.005 | 0.726 |
| Fasting Blood Glucose | 0.056 | 0.036* | 0.010 | 0.562 | 0.117 | <0.001* | 0.039 | 0.020* |

*Significant (p<0.05)

Multivariable analysis was conducted to describe the association between SUA levels and BP, with adjustment for cardiovascular risk factors. Cardiovascular risk factors such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all taken into account for adjustment in multiple linear regression (Table 4). BMI, fasting blood glucose, and SUA levels were significantly associated with BP. BMI was significantly associated with SBP and DBP both in men (p<0.001 and p<0.001) and women (p=0.001 and p<0.001). In addition, fasting blood glucose was found to be associated with SBP in men (p=0.036) and women (p<0.001) and was also associated with DBP in women (p=0.020). Regarding SUA levels, SUA was significantly associated with both SBP and DBP in women (p<0.001 and p<0.001, respectively) but not in men.

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## DISCUSSION

This study consisted of two parts of data collection. The first data collection was performed in 2007 to gather data on the prehypertension population (n=4,190); this study was later called the "Mlati Study Database". In 2017, after 10 years, the second data collection was performed to gather samples from the Mlati Study Database by a random sampling method (n=733) to show the change in BP status from prehypertension to hypertension. The data collection in 2017 also aimed to show the association between uric acid (serum, urinary excretion, and concentrate) and hypertension.

The results of our study showed that gender and uric acid excretion (by 24-h urine) were significantly associated with SUA levels. The mean SUA levels in men were significantly higher than those in women. In addition, subjects with high-normal and high SUA levels had a risk of developing prehypertension and hypertension that was 1.12 times higher than those with normal SUA levels. When analysed by gender, high-normal and high SUA levels were significantly associated with prehypertension and hypertension only in women. The relationship between SUA levels and the development of hypertension or renal disease has been shown in several previous studies. This relationship was significantly higher in women than in men.[13,14]

The study by Kawabe *et al.* revealed that in women, the older the age was, the higher the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an increase in the quartile of SUA along with higher BMI was only found in men but not in women. Additionally, the mean value of SUA in men was higher than in women.[15] These results were consistent with our finding that SUA levels were significantly higher in men and that SUA levels were significantly associated with higher BMI in men. However, the study populations in this study and in the study by Kawabe *et al*. were different in terms of the age group examined, which were adults (30–59 years old) and elderly adults, respectively.[15]

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Similar finding was also found by Zhang, *et al*. which reported that SUA levels were statistically higher in men than in women, though the SUA level did not increase with the age both in men and women.[16] These studies results were consistent with our finding which stated that SUA level was significantly higher in men and SUA level was significantly associated with higher BMI also in men. However, the study population in this study and in the study by Kawabe, *et al*. was different in the age group which were adults (30-59 years) and elderly, respectively.

Chen *et al.* reported a different result in a cross-sectional analysis regarding the association between SUA levels and the presence of hypertension when analysed by gender. For the total population, SUA levels had significant associations with hypertension. The levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40 years, and >40 years but only in women aged >40 years.[8] This situation could be explained with Table 2, which provides the age distribution of women and its association with SUA levels. In Table 2, the proportion of women aged 40–49 years combined with those aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in women is associated with menopausal problems. A study by Hak *et al*. stated that menopause was associated with an increased risk of incident gout, which may help explain why the age of the women in this study could play a significant role in their SUA levels.[17]

Regarding the cardiovascular risk factors, the result of this study found that the SUA levels were significantly associated with total cholesterol ($p=0.001$), LDL ($p=0.002$), HDL ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$), regardless of gender. When the data were analysed by gender, significant differences were found only in BMI and triglycerides and only in men ($p<0.001$ and $p=0.002$, respectively). Another study has shown a stronger association between the increasing of SUA level and cardiovascular mortality among women in healthy subjects compared to men.[18] Meta-analysis showed that there was

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significant association between hyperuricemia and cardiovascular mortality in women, but not in men.[19] Chen *et al*. reported that SUA levels were significantly associated with the occurrence of metabolic syndrome and hypertension in the total population. In men, SUA levels had a positive association with the occurrence of metabolic syndrome in the age groups of <30 and 30–40. In women, SUA levels were significantly associated with the occurrence of metabolic syndrome in the age groups of <30 and >40.[8]

In this study, BMI was associated with blood pressure by both gender and SUA levels in men. This finding was in line with those of a previous study by Droyvold *et al*., in which the authors reported that an increase in BMI was associated with increased BP in men and women.[20] With regard to the association between BMI and SUA levels, our findings were different from those of a report by Rodrigues *et al*., in which the authors reported a significant correlation between BMI and SUA levels in both men and women.[21] The link between BMI and hyperuricaemia has not been well elucidated; however, insulin resistance might be the bridging gap. Obese people are more likely to have metabolic syndrome, and metabolic syndrome itself is associated with insulin resistance. It is thought that insulin resistance impairs the ability of the kidney to excrete uric acid and therefore leads to hyperuricaemia.[22]

This study found that fasting blood glucose was associated with SBP in both genders and with DBP only in women. The same result was observed in a study by Yan *et al*., which revealed that fasting plasma glucose was independent of both SBP and DBP.[23] Moreover, fasting blood glucose was also associated with SUA levels, but only in men. This finding is contradictory to those of a study by Kawamoto *et al*., which revealed that SUA levels were associated with fasting plasma glucose in females but not in males.[24] The mechanism of how this phenomenon occurred remains unclear, and further study is needed to observe a cause-effect relationship. Serum triglycerides were also associated with SUA levels in this study. The relationship between SUA levels and lipid profiles has been described in various studies, but

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the exact mechanism remains unclear. A study by Peng *et al*. revealed that all lipid profile parameters, including triglycerides but not HDL cholesterol, were associated with SUA levels.[25] SUA levels were associated with both SBP and DBP but only in women. This result is similar to those of previous studies.[24, 26] It has been suggested that the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after oxidative stress damage to the endothelium during excessive uric acid formation.[26]

## CONCLUSION

In conclusion, after 10 years of follow-up, the SUA levels in men are significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men. For the total population, SUA levels were significantly associated with the levels of total cholesterol, LDL, HDL, triglycerides and fasting blood glucose. The BMI was found to be significantly associated with BP in both men and women. Fasting blood glucose is significantly associated with SBP in men and with SBP and DBP in women; meanwhile, SUA levels were significantly associated with BP only in women.

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## CONTRIBUTORS

LAB and MS composed the idea of the study and arranged the study's design. MS, FI, AW, and AK obtained the data. ZZ led the statistical analysis with the supervision of MS. MS, LAB and ZZ wrote the first draft of this paper and all authors read, revised, and approved the final manuscript.

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## DISCLOSURE

There were no conflicts of interest to disclose.

## DATA SHARING STATEMENT

Data may be obtained from the corresponding author upon reasonable request.

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**Figure Legend**

Figure 1. The SUA/serum uric acid levels were significantly associated with total cholesterol (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030).

Figure 2. Significant differences were found in BMI (p<0.001) and triglycerides (p=0.002) between subjects with normal SUA levels and those with high-normal and high SUA levels in men. No significant difference was found (p>0.05) between subjects with normal SUA levels and those with high-normal and high SUA levels in women.

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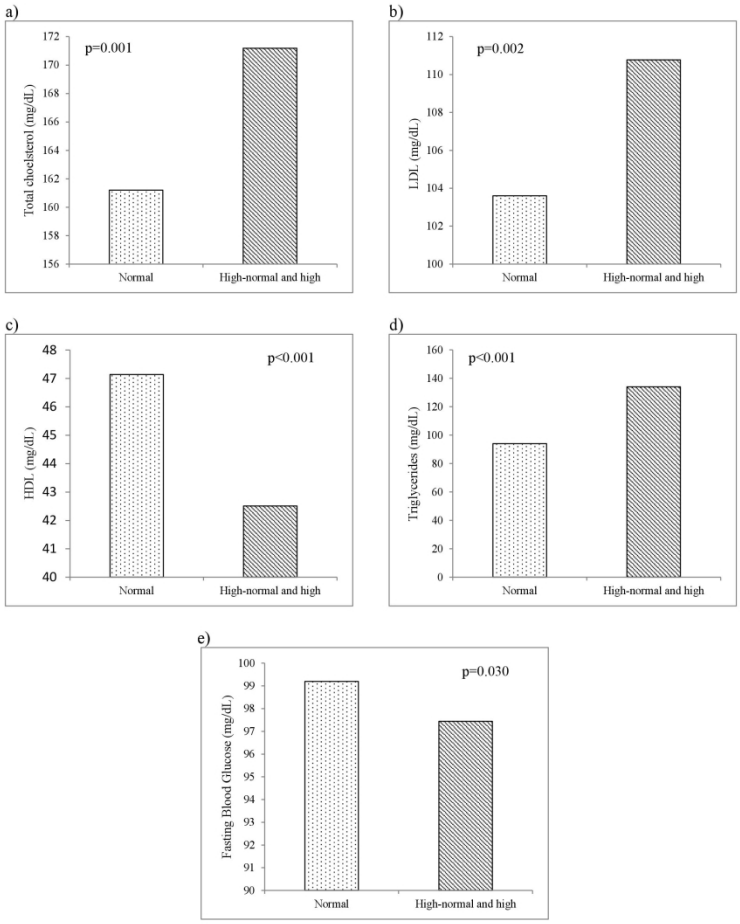


**Fig. 1.** Mean of cardiovascular risk factors in different serum uric acid levels

210x297mm (300 x 300 DPI)

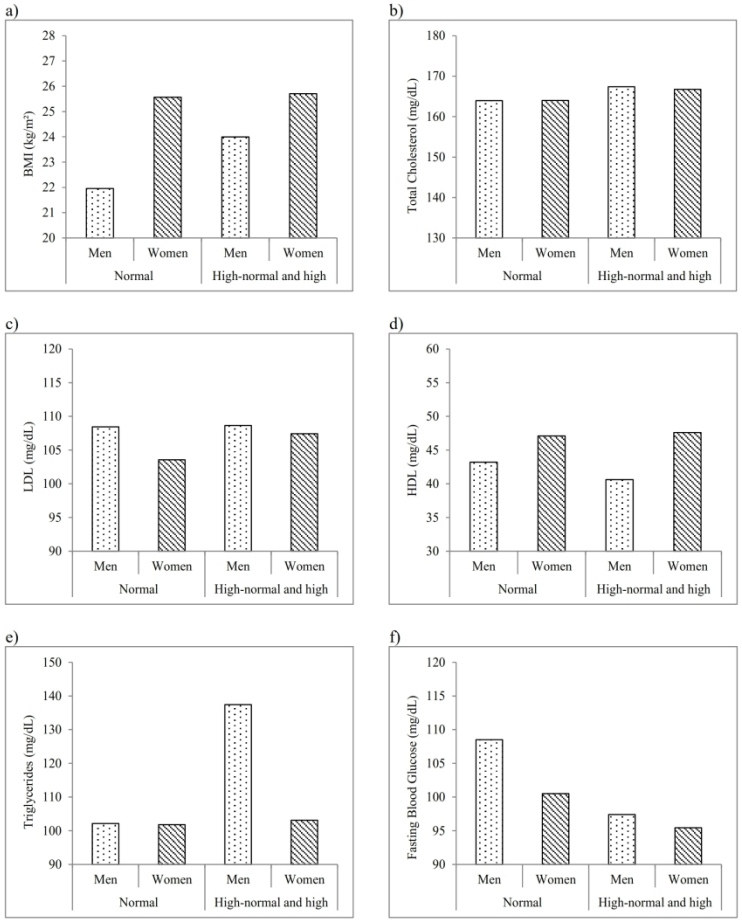


**Fig. 2.** Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.
In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests.
In women, BMI, total cholesterol, LDL, HDL and triglyceride levels were analysed using the Mann-Whitney U test; fasting blood glucose was analysed using independent samples t-tests.

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# Association of Serum Uric Acid, Morning Home Blood Pressure and Cardiovascular Risk Factors in a Prehypertensive Population



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# ASSOCIATION OF SERUM URIC ACID, MORNING HOME BLOOD PRESSURE AND CARDIOVASCULAR RISK FACTORS IN A PREHYPERTENSIVE POPULATION

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## ABSTRACT

**Objective**: To observe the changes in blood pressure (BP) over 10 years and to investigate its association to serum uric acid (SUA) levels and cardiovascular risk factors in the epidemiological data of a target group of prehypertensive patients in 2007.

**Design:** cross-sectional cohort study

**Setting:** Mlati Sub-district, Sleman District, Yogyakarta Province, Indonesia

**Participants**: Prehypertension population dataset (n=4190), with blood pressure classification of SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, were used from the 2007 "Mlati Study Database". A total of 733 patients were selected by simple random sampling using statistical software. Subjects had both physical and laboratory examinations.

**Outcome measures:** Morning home blood pressure and laboratory examination of urine (uric acid excretion and creatinine) and blood samples (SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol, low density lipoprotein/LDL-C, high density lipoprotein/HDL-C and triglycerides), and fasting blood glucose levels)

**Results**: Mean (SD) of SUA levels were significantly higher in men than in women (5.78 (1.25) mg/dL vs 4.52 (1.10) mg/dL, $p<0.001$). Furthermore, men tended to have high-normal (5–7 mg/dL) and high serum uric acid levels (≥7 mg/dL) compared to women ($p<0.001$, RR=2.60). High-normal and high SUA levels were significantly associated with prehypertension and hypertension only in women ($p=0.001$, RR=1.21). Age and body mass index was found to be significantly associated with both systolic and diastolic BP in men, but only with systolic BP in women. Fasting blood glucose was significantly associated with systolic and diastolic BP in women; meanwhile, SUA was significantly associated with BP only in women.


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**Conclusion**: We concluded that serum uric acid levels were significantly associated with prehypertension and hypertension only in women. Blood pressure was associated with age, body mass index, serum uric acid levels and fasting blood glucose in women, whereas in men, blood pressure was only associated with age body mass index.

**Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences

## STRENGTH AND LIMITATION OF THIS STUDY

- This study followed up the changes of blood pressure on subjects for over 10 years.
- The association between serum uric acid, blood pressure, and cardiovascular risk factors were analyzed based on gender.
- The analysis' were also performed by using both JNC 7 and 2017 ACC/AHA guideline.
- This study could not present the changes of all measured value over 10 year period because in the prior study in 2007, these laboratory value were not examined, except for blood pressure.

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## INTRODUCTION

Hypertension is still a major problem worldwide, as reflected by a meta-analysis report in 2016 stating that in 2010, 40% of the world's population was hypertensive and that approximately 17 million people worldwide died due to hypertension.[1] In Indonesia, the prevalence of hypertension in 2013 was 25.8%, based on the Indonesian Ministry of Health report.[2] Therefore, it is important to facilitate the early diagnosis and treatment of hypertension and its possible effects. Patients with prehypertension were hypothesized to eventually become hypertensive after 10 years, and thus have a poorer quality of life [3,4]. During the last two decades, it has been repeatedly published that the incidence of hypertension is associated with even moderate increases in levels of serum uric acid (SUA) and an increased risk of cardiovascular diseases (CVD).[5,6] The Framingham Heart Study reported an increased risk of blood pressure (BP) progression in 3157 subjects with hyperuricaemia. SUA was positively associated with increases in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) after 4 years with no antihypertensive treatment.[7] Current findings based on a large-scale cohort study suggested that uric acid is a predictive factor of the development of prehypertension in adults.[8] A meta-analysis by Jiang *et al.* indicated that SUA was possibly associated with prehypertension but still found conflicting results.[9] The associations among SUA, hypertension, cardiovascular risk factors and gender remain controversial. Serum uric acid levels has been known to have an association with blood pressure and hypertension.[10-12] Some studies reported that hyperuricemia have higher susceptibility of developing hypertension especially in men [10,13], while the other study reported vice versa.[14] Lee *et al.* also showed that hyperuricemia in women led to higher risk of developing hypertension than in men.[15] In term of the association of SUA and cardiovascular risk, SUA did not have a causal role in the development of cardiovascular outcomes.[16] Another study stated that the serum uric acid level was an independent

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predictive factor for cardiovascular risk in individual without hypertension and diabetic.[17] SUA also being reported to have stronger association on cardiovascular risk [18] and risk of cardiovascular disease mortality [19,20] in women than in men.

Therefore, the aim of this study was to observe the progression from prehypertension to hypertension after 10 years of follow-up and its association with SUA as well as other cardiovascular risk factors.

## METHODS

### *Study Design*

This study was a cross-sectional cohort study of ten years of follow-up (2007–2017) conducted in Mlati Sub-district, Sleman District in the Yogyakarta Special Region, Indonesia. The protocol of this study was approved by Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with the ID approval of KE/FK/0961/EC/2017.

### *Study Population*

We pooled data from participants enrolled in the 2007 Mlati Study Database. The sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected as participants in the current study by simple random sampling using statistical software. All 1500 subjects were invited to have a physical and laboratory examination; however, only 733 subjects who participated in the sampling were examined (the other subjects who did not

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show up during the laboratory examination were due to the change of residential area or death or any other unknown reasons and were excluded from this study). All subjects did not take any drugs lowering BP and SUA. All subjects were provided informed consent at the beginning of the study (Figure 1).

***Patient and Public Involvement***

Patient were not involved in any of the design, analysis, and presentation of the study results.

***Definition of Prehypertension and Hypertension***

The definitions of prehypertension and hypertension were based on the Seventh Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only their treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of 80–89 mmHg are defined as prehypertension, while SBP of ≥140 mmHg and/or DBP of ≥90 mmHg are defined as hypertension.[21]

For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as follows: (1) normal BP = SBP <120 mmHg and DBP <80 mmHg, (2) elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, (3) stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, and (4) stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg.[22]

***Serum Uric Acid Cut-off Point***

Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3 categories: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).[23]

***Data Collection***

The data collection was conducted twice during the study period. The first data collection was conducted in 2007 to collect the prehypertension population (n=4,190). The second data collection was performed in 2017 to collect samples from the Mlati Study Database by the random sampling method (n=733).

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In 2007, interviews were conducted on 12,073 subjects to obtain demographyc data (e.g. sex and age), family history and to perform physical and laboratory examinations. Physical examinations, which included measurements of morning home BP (measured by using sphygmomanometer), body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference and hip circumference, were conducted on day 1 in subject's house or their neighbor. BP measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times (or until stable BP were obtained) while subjects in sitting position. On day 2, we examined morning home BP and took urine and blood samples.

In 2017, we collected data from 733 subjects, including interviews of demographic data, physical and laboratory examinations. On the first day, subjects were interviewed, physically examined, and given urine containers for one-time urine samples, as well as for a 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The physical examination was performed by medical team, consisted of a morning home BP measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained), while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan) and measurements of body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference and hip circumference. On the second day, subjects who were in fasting condition were invited to came to the neighbor's hall in the morning and physically examined for BP again (at 6 – 8 a.m) and drawn for their blood. Urine and blood samples were examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine sample was collected to measure uric acid excretion and creatinine, and a blood sample was collected to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol, low density lipoprotein/LDL-C, high density lipoprotein/HDL-C and triglycerides), and fasting blood glucose levels.

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### *Statistical Analysis*

All data presented later in results section were from data collection in 2017. Data were analysed using IBM SPSS Statistics 20. The data consisted of continuous and categorical data, which were expressed as the mean (SD) for continuous data and as numbers and percentages for categorical data. The continuous variables were analysed and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The categorical variables were analysed and compared by Pearson chi-square tests. Multivariable analysis was performed using multiple linear regression to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. The significance of associations between categorical variables and numerical variables were determined using 95% confidence intervals (CIs).

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## RESULTS

**Table 1.** Characteristic of Subjects by Gender Presented in Mean (SD)[a]

| Variables | Men n=306 | Women n=427 | p-value |
|---|---|---|---|
| Age (years) | 46 (7.71) | 46 (7.76) | 0.431 |
| 30 – 39 years | 35 (2.86) | 36(2.63) | 0.093 |
| 40 – 49 years | 45 (2.89) | 45 (2.67) | 0.372 |
| 50 – 59 years | 54 (3.18) | 54 (2.77) | 0.779 |
| BMI (kg/m$^2$) | 23.5 (3.70) | 25.7 (4.81) | <0.001* |
| SBP (mmHg) | 132 (17.26) | 134 (21.62) | 0.595 |
| DBP (mmHg) | 78 (11.96) | 79 (12.32) | 0.091 |
| Uric Acid (mg/dL) | 5.8 (1.25) | 4.5 (1.10) | <0.001* |
| Total cholesterol (mg/dL) | 167 (36.86) | 166 (41.59) | 0.559 |
| LDL (mg/dL) | 109 (29.59) | 106 (33.27) | 0.155 |
| HDL (mg/dL) | 41 (10.02) | 47 (12.20) | <0.001* |
| Triglyceride (mg/dL) | 129 (79.09) | 103 (63.84) | <0.001* |
| Fasting Blood Glucose (mg/dL) | 100 (37.22) | 97 (33.70) | 0.101 |

*Significant ($p<0.05$)
[a] Characteristic of subjects collected in 2017

The subjects of this study consisted of 733 adults (aged 30–59 years) living in the Mlati Subdistrict; 306 (41.75%) and 427 (58.25%) were men and women, respectively. The characteristics of the subjects (by gender) are presented in Table 1. There was no significant difference in age, SBP, DBP, total cholesterol, LDL and fasting blood glucose between men and women ($p>0.05$). Significant differences were found in body mass index (BMI) ($p<0.001$), SUA levels ($p<0.001$), HDL ($p<0.001$) and triglycerides ($p<0.001$). BMI and HDL were significantly higher in women, whereas SUA levels and triglycerides were significantly higher in men.

**Table 2.** Blood Pressure after 10 years and Serum Uric Acid Frequency Distribution

| Variables | Frequency (%) | |
|---|---|---|
| | 2007 | 2017 |
| BP (n=733) | | |
| Normal | 0 | 180 (24.6) |
| Prehypertension (Pre-HT) | 733 (100) | 325 (44.3) |
| Hypertension (HT) | 0 | 228 (31.1) |
| Uric Acid (n=733) | | |
| Normal | - | 369 (50.3) |
| High-normal | - | 316 (43.1) |
| High | - | 48 (6.6) |

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After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal, and only 6.6% had high SUA levels (Table 2).

**Table 3.** Association between Gender, Age, BMI, Uric Acid Excretion, and Uric Acid Concentration to Serum Uric Acid Level

| Variables | SUA | | p value | RR | 95% CI |
|---|---|---|---|---|---|
| | High-normal and high (%) | Normal (%) | | | |
| Gender | | | | | |
| Men | 237 (32.3) | 69 (9.4) | <0.001 | 2.60 | 2.22-3.05 |
| Women | 127 (17.3) | 300 (40.9) | | | |
| Age | | | | | |
| Men | | | | | |
| 30 – 39 years* | 52 (17.0) | 11 (3.6) | - | 1 | - |
| 40 – 49 years | 104 (34.0) | 22 (7.2) | 1,000 | 1.00 | 0.87-1.15 |
| 50 – 59 years | 81 (26.5) | 36 (11.8) | 0.053 | 0.84 | 0.71-0.99 |
| Women | | | | | |
| 30 – 39 years* | 22 (5.2) | 85 (19.9) | - | 1 | - |
| 40 – 49 years | 40 (9.4) | 128 (30.0) | 0.530 | 1.16 | 0.73-1.84 |
| 50 – 59 years | 65 (15.2) | 87 (20.4) | <0.001 | 2.08 | 1.37-3.15 |
| BMI[a] | | | | | |
| Overweight-Obese | 171 (23.3) | 154 (21.0) | 0.153 | 1.13 | 0.96 - 1.32 |
| Underweight-normal | 193 (26.3) | 215 (29.3) | | | |
| Uric Acid Excretion (24-h)[b] | | | | | |
| High | 169 (23.1) | 130 (17.7) | 0.002 | 1.32 | 1.10 - 1.57 |
| Normal | 195 (26.6) | 239 (32.6) | | | |
| Uric Acid Concentration[c] | | | | | |
| Normal | 200 (27.3) | 202 (27.5) | 0.956 | 1.00 | 087 – 1.16 |
| High | 164 (22.4) | 167 (22.8) | | | |

* reference category
[a]BMI= body mass index, <18.5kg/m$^2$ = underweight, 18.5-24.9 kg/m$^2$ = normal, 25-29.9 kg/m$^2$ = overweight, >30 kg/m$^2$ = obese
[b]Uric acid excretion, <435.08 mg/day = normal, ≥435.08 mg/day = high
[c]Uric acid concentration (mg per 100 ml of urine), <46.63 mg% = normal, ≥46.63 mg% = high

In men, 32.3% of the subjects had high-normal or high levels of SUA, while in women, only 17.3% had high-normal or high levels of SUA. There was a significant difference in SUA between men and women (p<0.001, RR=2.60, 95% CI=2.22–3.05). When gender was further analysed by age distribution, age was significantly associated with SUA

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levels only in women aged 50–59 years (p<0.001, RR=2.08, 95% CI=1.36–3.15). Additionally, there was a significant association between SUA levels and uric acid excretion by 24-h urine (p=0.002, RR=1.32, 95% CI=1.10–1.57). On the other hand, no significant association was observed between SUA levels and BMI (p=0.153, RR=1.1, 95% CI=0.96–1.32) or between SUA levels and uric acid concentration (p=0.100, RR=0.786, 95% CI=0.59–1.05) (Table 3).

The associations between gender and SUA levels on BP are shown in Table 4. There was no significant association between gender and BP (p=0.584). To examine the association between uric acid and hypertension, we compared SUA levels and morning home BP. The association between SUA levels and BP was statistically significant (p=0.008, RR=1.12, 95% CI=1.03–1.22). The risk of subjects with high-normal or high SUA levels for becoming prehypertension or hypertension was 1.12 times higher than those who has normal SUA levels. Furthermore, the association between SUA levels and BP in men and women is also described in Table 4. In men, SUA levels were not significantly associated with BP (p=0.805, RR=1.02, 95% CI=0.88–1.19). However, there was a significant association between SUA levels and BP in women (p=0.001, RR=1.21, 95% CI=1.09–1.34). In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal or high SUA levels than those with normal SUA levels. Additional analysis using 2017 ACC/AHA guideline for observing the associations between gender and SUA levels on BP also showed similar results with the previous analysis using JNC 7 guideline regarding the significant associations between SUA levels and BP.

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**Table 4.** Association between Gender and Serum Uric Acid on Blood Pressure

| Variables | Blood Pressure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | JNC 7[a] | | | | 2017 ACC/AHA[b] | | | |
| | Pre-HT and HT (%) | Normal (%) | p | RR (95%CI) | HT-1 and HT-2 (%) | Normal and elevated (%) | p | RR (95%CI) |
| Gender | | | | | | | | |
| Men | 234 (31.9) | 72 (9.8) | 0.584 | 1.02 (0.94 – 1.11) | 159 (21.7) | 147 (20.1) | 0.129 | 0.9 (0.79 - 1.03) |
| Women | 319 (43.5) | 108 (14.7) | | | 246 (33.6) | 181 (24.7) | | |
| SUA | | | | | | | | |
| High-normal and High | 290 (39.6) | 74 (10.1) | 0.008* | 1.12 (1.03 - 1.22) | 224 (30.6) | 140 (19.1) | 0.001* | 1.26 (1.10 - 1.43) |
| Normal | 263 (35.9) | 106 (14.5) | | | 181 (24.7) | 188 (25.6) | | |
| SUA | | | | | | | | |
| Men | | | | | | | | |
| High-normal and High | 182 (59.5) | 55 (18.0) | 0.805 | 1.02 (0.88 – 1.19) | 129 (42.2) | 108 (35.3) | 0.109 | 1.25 (0.93 – 1.68) |
| Normal | 52 (17.0) | 17 (5.6) | | | 30 (9.8) | 39 (12.7) | | |
| Women | | | | | | | | |
| High-normal and High | 108 (25.3) | 19 (4.4) | 0.001* | 1.21 (1.09 – 1.34) | 95 (22.2) | 32 (7.5) | 0.000* | 1.49 (1.28 – 1.73) |
| Normal | 211 (49.4) | 89(20.8) | | | 151 (35.4) | 149 (34.9) | | |

[a] BP was categorized using the JNC 7 Guideline (prehypertension: SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, hypertension: SBP of ≥140 mmHg and/or DBP of ≥90 mmHg)
[b] BP was categorized using the 2017 ACC/AHA Guideline (normal BP = SBP <120 mmHg and DBP <80 mmHg, elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg)

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Figure 2 shows the association between SUA and cardiovascular risk factors. The SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030). Subjects with high-normal and high SUA levels had significantly higher total cholesterol, LDL, and triglyceride levels than subjects with normal SUA levels. On the other hand, HDL and fasting blood glucose were statistically lower among subjects with high-normal and high SUA levels than among those with normal SUA levels.

The relationships between SUA levels and cardiovascular risk factors among men and women are presented in Figure 3. In men, there were significant differences in BMI (p<0.001) and triglycerides (p=0.002) between subjects with normal SUA levels and those with high-normal and high SUA levels. In women, there was no significant differences in all cardiovascular risk factors (p>0.05) between subjects with normal SUA levels and those with high-normal and high SUA levels.

**Table 5.** Multiple Linear Regression of Association of Age, Cardiovascular Risk Factors and SUA on Blood Pressure

| Variables | Blood Pressure of Men | | | | Blood Pressure of Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Systolic | | Diastolic | | Systolic | | Diastolic | |
| | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value |
| Age | 0.704 | <0.001* | 0.336 | <0.001* | 0.674 | <0.001* | -0.017 | 0.817 |
| SUA | -0.247 | 0.745 | 0.582 | 0.267 | 4.527 | <0.001* | 2.223 | <0.001* |
| BMI | 1.602 | <0.001* | 1.295 | <0.001* | 0.929 | <0.001* | 0.722 | <0.001* |
| Total Cholesterol | 0.044 | 0.696 | 0.042 | 0.591 | 0.119 | 0.279 | 0.030 | 0.643 |
| LDL | -0.074 | 0.529 | -0.036 | 0.657 | -0.102 | 0.365 | -0.014 | 0.828 |
| HDL | 0.184 | 0.174 | 0.042 | 0.653 | -0.054 | 0.656 | -0.049 | 0.483 |
| Triglycerides | -0.005 | 0.828 | -0.001 | 0.941 | -0.029 | 0.280 | 0.006 | 0.721 |
| Fasting Blood Glucose | 0.032 | 0.213 | -0.001 | 0.941 | 0.098 | 0.001* | 0.040 | 0.020* |

*Significant (p<0.05)
SUA=Serum uric acid, BMI=Body mass index, LDL=Low density lipoprotein, HDL=High density lipoprotein

Multivariable analysis was conducted to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. Cardiovascular risk factors

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such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all taken into account for adjustment in multiple linear regression (Table 5). Age, BMI, fasting blood glucose, and SUA levels were significantly associated with BP. Significant association were found between age and SBP both in men ($p<0.001$) and women ($p<0.001$), and DBP only in men ($p<0.001$). BMI was significantly associated with SBP and DBP both in men ($p<0.001$ and $p<0.001$) and women ($p<0.001$ and $p<0.001$). In addition, fasting blood glucose was found to be associated with SBP and DBP in women ($p=0.001$ and $p=0.020$). Regarding SUA levels, SUA was significantly associated with both SBP and DBP in women ($p<0.001$ and $p<0.001$, respectively) but such association was not found in men.

## DISCUSSION

This study consisted of two parts of data collection. The first data collection was performed in 2007 to gather data on the prehypertension population (n=4,190); this study was later called the "Mlati Study Database". In 2017, after 10 years, the second data collection was performed to gather samples from the Mlati Study Database by a random sampling method (n=733) to show the change in BP status from prehypertension to hypertension. The data collection in 2017 also aimed to show the association between uric acid (serum, urinary excretion, and concentrate) and hypertension.

The results of our study showed that gender and uric acid excretion (by 24-h urine) were significantly associated with SUA levels. The mean SUA levels in men were significantly higher than those in women. In addition, subjects with high-normal and high SUA levels had a risk of having prehypertension and hypertension that was 1.12 times higher than those with normal SUA levels. When analysed by gender, high-normal and high SUA levels were significantly associated with prehypertension and hypertension only in women. The relationship between SUA levels and the development of hypertension or renal disease

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had been shown in several previous studies. This relationship was significantly higher in women than in men.[15,24]

The study by Kawabe *et al.* revealed that in women, the older the age was, the higher the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an increase in the quartile of SUA along with higher BMI was only found in men but not in women. Additionally, the mean value of SUA in men was higher than in women.[25] These results were consistent with our finding that SUA levels were significantly higher in men and that SUA levels were significantly associated with higher BMI in men. However, the study populations in this study and in the study by Kawabe *et al*. were different in terms of the age group examined, which were adults (30–59 years old) and elderly adults, respectively.[25] Similar finding was also found by Zhang, *et al*. which reported that SUA levels were statistically higher in men than in women, though the SUA level did not increase with the age both in men and women.[26] These studies results were consistent with our finding which stated that SUA level was significantly higher in men and SUA level was significantly associated with higher BMI also in men. However, the study population in this study and in the study by Kawabe, *et al*. was different in the age group which were adults (30-59 years) and elderly, respectively.

Chen *et al.* reported a different result in a cross-sectional analysis regarding the association between SUA levels and the presence of hypertension when analysed by gender. For the total population, SUA levels had significant associations with hypertension. The levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40 years, and >40 years but only in women aged >40 years.[10] This situation could be explained with Table 3, which provides the age distribution of women and its association with SUA levels. In Table 3, the proportion of women aged 40–49 years combined with those aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in

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women is associated with menopausal problems. A study by Hak *et al*. stated that menopause was associated with an increased risk of incident gout, which may help explain why the age of the women in this study could play a significant role in their SUA levels.[27]

Regarding the cardiovascular risk factors, the result of this study found that the SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030), regardless of gender. When the data were analysed by gender, significant differences were found only in BMI and triglycerides and only in men (p<0.001 and p=0.002, respectively). Another study has shown a stronger association between the increasing of SUA level and cardiovascular mortality among women in healthy subjects compared to men.[28] Meta-analysis showed that there was significant association between hyperuricemia and cardiovascular mortality in women, but not in men.[29] Chen *et al*. reported that SUA levels were significantly associated with the occurrence of metabolic syndrome and hypertension in the total population. In men, SUA levels had a positive association with the occurrence of metabolic syndrome in the age groups of <30 and 30–40. In women, SUA levels were significantly associated with the occurrence of metabolic syndrome in the age groups of <30 and >40.[10]

In this study, BMI was significantly associated with SBP and DBP in both gender. This finding was in line with those of a previous study by Droyvold *et al*., in which the authors reported that an increase in BMI was associated with increased BP in men and women.[30] With regard to the association between BMI and SUA levels, our findings were different from those of a report by Rodrigues *et al*., in which the authors reported a significant correlation between BMI and SUA levels in both men and women.[31] The link between BMI and hyperuricaemia has not been well elucidated; however, insulin resistance might be the bridging gap. Obese people are more likely to have metabolic syndrome, and metabolic syndrome itself is associated with insulin resistance. It is thought that insulin

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resistance impairs the ability of the kidney to excrete uric acid and therefore leads to hyperuricaemia.[32]

This study found that fasting blood glucose was associated with SBP and DBP only in women. The same result was observed in a study by Yan *et al*., which revealed that fasting plasma glucose was independent of both SBP and DBP.[33] Fasting blood glucose was also associated with SUA levels, but when analysed by gender, no significant different was found. This finding is contradictory to those of a study by Kawamoto *et al*., which revealed that SUA levels were associated with fasting plasma glucose in females.[34] The mechanism of how this phenomenon occurred remains unclear, and further study is needed to observe a cause-effect relationship. Serum triglycerides were also associated with SUA levels in this study. The relationship between SUA levels and lipid profiles has been described in various studies, but the exact mechanism remains unclear. A study by Peng *et al*. revealed that all lipid profile parameters, including triglycerides but not HDL cholesterol, were associated with SUA levels.[35] SUA levels were associated with both SBP and DBP but only in women. This result is similar to those of previous studies.[34, 36] It has been suggested that the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after oxidative stress damage to the endothelium during excessive uric acid formation.[36]

There were several limitations in this study. First, subject in this study were collected from database made in 2007. From 1500 subjects randomly selected in the beginning of this study, only 733 subjects joined and attend the 2-days examination. More than half of the selected subjects did not attend the examination invitation due to several reasons, thus, this had lessened the total samples of subjects of this study. Second, this study could not present the changes of all measured value over 10-year period because in the prior study in 2007, these laboratory value were not examined, except for blood pressure. Therefore, only the changes on blood pressure which can be presented on the results. Third, the instruments used

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to measure blood pressure in 2007 and 2017 were different. In 2007, we used sphygmomanometer, whereas in 2017 we used digital automatic blood pressure monitor. Thus, this may lead bias in blood pressure data measurement between 2007 and 2017.

## CONCLUSION

In conclusion, after 10 years of follow-up, the SUA levels in men are significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men. For the total population, SUA levels were significantly associated with the levels of total cholesterol, LDL, HDL, triglycerides and fasting blood glucose. The BMI was found to be significantly associated with BP in both men and women. Fasting blood glucose is significantly associated with SBP in men and with SBP and DBP in women; meanwhile, SUA levels were significantly associated with BP only in women.

## ACKNOWLEDGEMENTS

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## CONTRIBUTORS

LAB and MS composed the idea of the study and arranged the study's design. MS, FI, AW, and AK obtained the data. ZZ led the statistical analysis with the supervision of MS. MS, LAB and ZZ wrote the first draft of this paper and all authors read, revised, and approved the final manuscript.

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## COMPETING INTEREST

There were no conflicts of interest to disclose.

## DATA SHARING STATEMENT

Data may be obtained from the corresponding author upon reasonable request.

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## Figure Legend

Figure 2. The SUA/serum uric acid levels were significantly associated with total cholesterol ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$). The SUA category: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).

Figure 3. Significant differences were found in BMI ($p<0.001$) and triglycerides ($p=0.002$) between subjects with normal SUA levels and those with high-normal and high SUA levels in men. No significant difference was found ($p>0.05$) between subjects with normal SUA levels and those with high-normal and high SUA levels in women. The SUA category: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).

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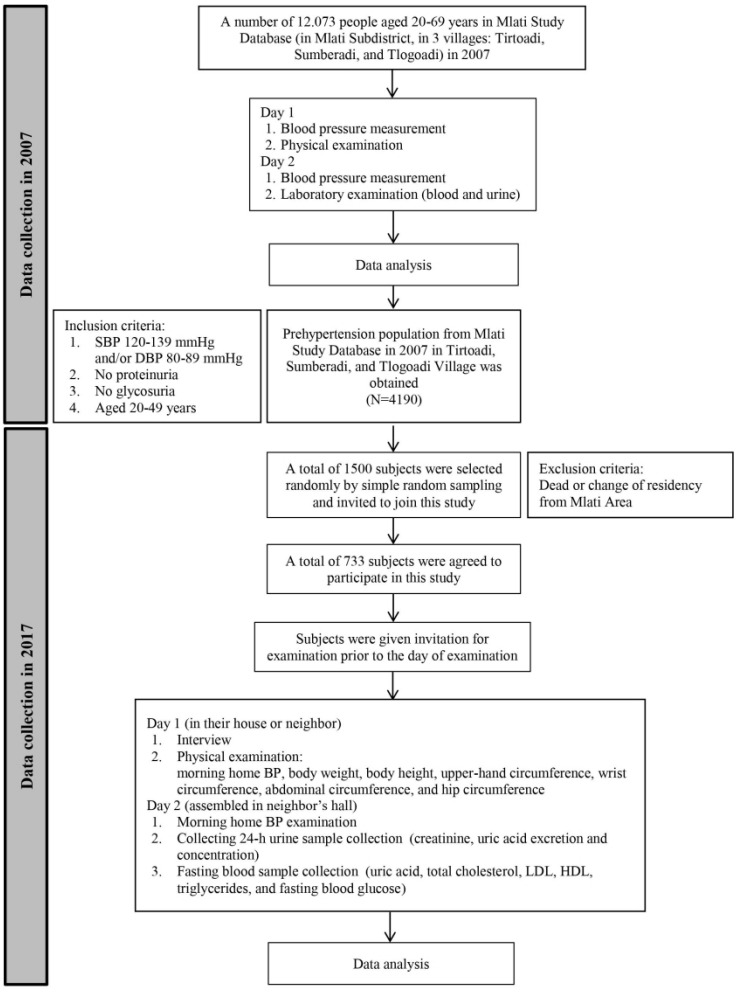


Fig 1. Study Flow Chart

Fig 1. Study Flow Chart

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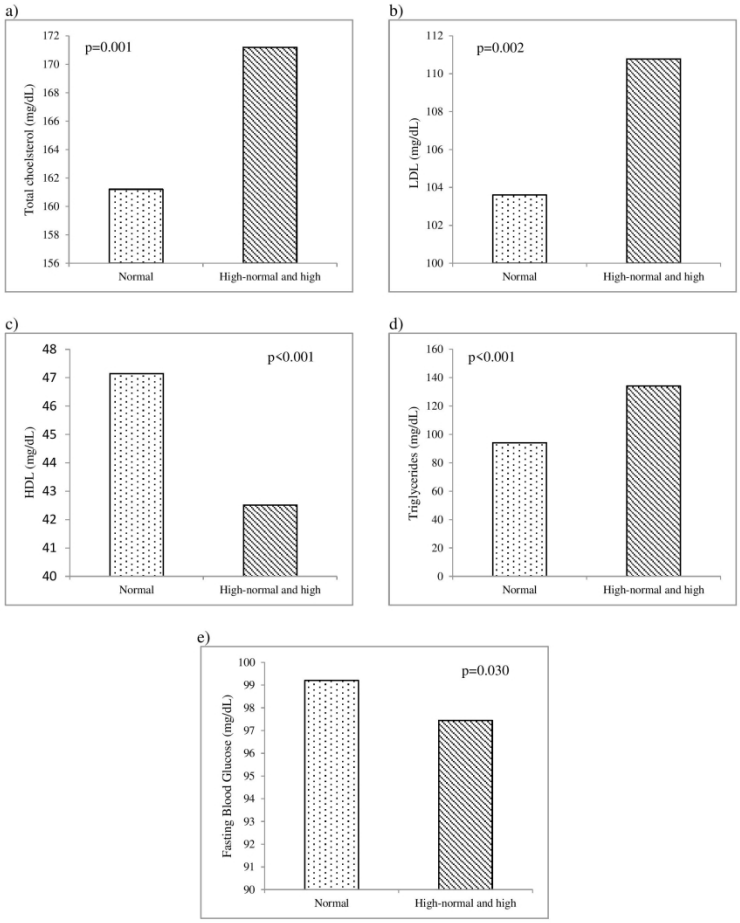


**Fig. 2.** Mean of cardiovascular risk factors in different serum uric acid levels
The SUA/serum uric acid levels were significantly associated with total cholesterol (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030).

Figure 2. Mean of cardiovascular risk factors in different serum uric acid levels

210x297mm (300 x 300 DPI)

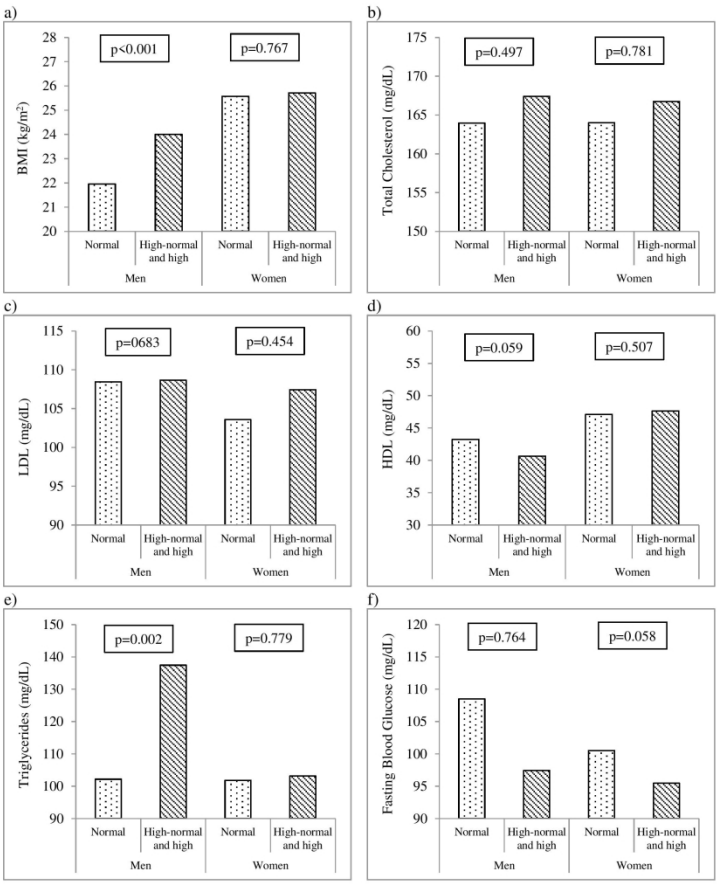


**Fig. 3.** Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.
In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests.
In women, BMI, total cholesterol, LDL, HDL and triglyceride levels were analysed using the Mann-Whitney U test; fasting blood glucose was analysed using independent samples t-tests.

Figure 3. Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.

210x297mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | N/A |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | N/A |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | N/A |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |

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| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures | N/A |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Written on each table |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 17 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 14-17 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | N/A |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 18 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Association of Serum Uric Acid, Morning Home Blood Pressure and Cardiovascular Risk Factors in a Population with Previous Prehypertension



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# ASSOCIATION OF SERUM URIC ACID, MORNING HOME BLOOD PRESSURE AND CARDIOVASCULAR RISK FACTORS IN A POPULATION WITH PREVIOUS PREHYPERTENSION

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## ABSTRACT

**Objective**: To observe the changes in blood pressure (BP) over 10 years and to investigate current BP association to serum uric acid (SUA) levels and cardiovascular risk factors in the epidemiological data of a target group of prehypertensive patients in 2007.

**Design:** cross-sectional study

**Setting:** Mlati Sub-district, Sleman District, Yogyakarta Province, Indonesia

**Participants:** A total of 733 patients from "Mlati Study Database" in 2007 were selected by simple random sampling using statistical software. Subjects had both physical and laboratory examinations.

**Outcome measures:** Morning home blood pressure and laboratory examination of urine (uric acid excretion and creatinine) and blood samples (SUA, blood urea nitrogen, creatinine, a lipid profile, and fasting blood glucose levels)

**Results**: About 31,1% of 733 prehypertensive subjects became hypertension after 10 years, 24,6% returned to normal tension, and the rest of it remained in prehypertensive state. Mean (SD) of SUA levels in 2017 were significantly higher in men than in women (5.78 (1.25) mg/dL vs 4.52 (1.10) mg/dL, $p<0.001$). Furthermore, men tended to have high-normal (5–7 mg/dL) or high SUA levels (≥7 mg/dL) compared to women ($p<0.001$, RR=2.60). High-normal and high SUA levels in population with a history of prehypertension were significantly associated with current prehypertension and hypertension only in women ($p=0.001$, RR=1.21). Age and body mass index was found to be significantly associated with both systolic and diastolic BP in men, but only with systolic BP in women. Fasting blood glucose and SUA levels were significantly associated with systolic and diastolic BP only in women.


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**Conclusion**: We concluded that after 10 years, of 733 prehypertensive subjects, 31.1% became hypertensive. The SUA levels in men are significantly higher than those in women. Moreover, High-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men.

**Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences

## STRENGTH AND LIMITATION OF THIS STUDY

- This study followed up the changes in blood pressure on subjects for over 10 years.
- The association between serum uric acid, blood pressure, and cardiovascular risk factors were analysed based on gender.
- The analysis' was also performed by using both JNC 7 and 2017 ACC/AHA guideline.
- This study could not present the changes of all measured values over 10 year period because, in the prior study in 2007, these laboratory values were not examined, except for blood pressure.

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## INTRODUCTION

Hypertension is still a major problem worldwide, as reflected by a meta-analysis report in 2016 stating that in 2010, 40% of the world's population was hypertensive and that approximately 17 million people worldwide died due to hypertension.[1] In Indonesia, the prevalence of hypertension in 2013 was 25.8%, based on the Indonesian Ministry of Health report.[2] Therefore, it is important to facilitate the early diagnosis and treatment of hypertension and its possible effects. Patients with prehypertension were hypothesized to eventually become hypertensive after 10 years, and thus have a poorer quality of life [3,4]. During the last two decades, it has been repeatedly published that the incidence of hypertension is associated with even moderate increases in levels of serum uric acid (SUA) and an increased risk of cardiovascular diseases (CVD).[5,6] The Framingham Heart Study reported an increased risk of blood pressure (BP) progression in 3157 subjects with hyperuricemia. SUA was positively associated with increases in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) after 4 years with no antihypertensive treatment.[7] Current findings based on a large-scale cohort study suggested that uric acid is a predictive factor of the development of prehypertension in adults.[8] A meta-analysis by Jiang *et al.* indicated that SUA was possibly associated with prehypertension but still found conflicting results.[9] The associations among SUA, hypertension, cardiovascular risk factors and gender remain controversial. Serum uric acid levels have been known to have an association with blood pressure and hypertension.[10-12] Some studies reported that hyperuricemia has higher susceptibility of developing hypertension especially in men [10,13], while the other study reported vice versa.[14] Lee *et al.* also showed that hyperuricemia in women led to a higher risk of developing hypertension than in men.[15] In terms of the association of SUA and cardiovascular risk, SUA did not have a causal role in the development of cardiovascular outcomes.[16] Another study stated that the serum uric acid level was an independent

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predictive factor for cardiovascular risk in individuals without hypertension and diabetes.[17] Serum uric acid also being reported to have a stronger association with cardiovascular risk [18] and risk of cardiovascular disease mortality [19,20] in women than in men.

Therefore, the aim of this study was to observe the progression from prehypertension to hypertension after 10 years (2007-2017) and the association of BP with SUA as well as other cardiovascular risk factors in 2017.

## METHODS

### *Study Design*

This study was a cross-sectional study conducted in Mlati Sub-district, Sleman District in the Yogyakarta Special Region, Indonesia. The protocol of this study was approved by the Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with the ID approval of KE/FK/0961/EC/2017.

### *Study Population*

We pooled data from participants enrolled in the 2007 Mlati Study Database. The sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected as participants in the current study by simple random sampling using statistical software. All 1500 subjects were invited to have a physical and laboratory examination; however, only 733 subjects who participated in the sampling were examined (the other subjects who did not

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show up during the laboratory examination were due to the change of residential area or death or any other unknown reasons and were excluded from this study). All subjects did not take any drugs lowering BP and SUA. All subjects were provided informed consent at the beginning of the study (Figure 1).

***Patient and Public Involvement***

Patients were not involved in any of the design, analysis, and presentation of the study results.

***Definition of Prehypertension and Hypertension***

The definitions of prehypertension and hypertension were based on the Seventh Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only their treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of 80–89 mmHg are defined as prehypertension, while SBP of ≥140 mmHg and/or DBP of ≥90 mmHg are defined as hypertension.[21]

For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as follows: (1) normal BP = SBP <120 mmHg and DBP <80 mmHg, (2) elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, (3) stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, and (4) stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg.[22]

***Serum Uric Acid Cut-off Point***

Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3 categories: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).[23]

***Data Collection***

The data collection was conducted twice during the study period. The first data collection was conducted in 2007 to collect the prehypertension population (n=4,190). The second data collection was performed in 2017 to collect samples from the Mlati Study Database by the random sampling method (n=733).

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In 2007, interviews were conducted on 12,073 subjects to obtain demographic data (e.g. sex and age), family history of hypertension and diabetes mellitus, patients' history of diabetes mellitus, patients' history of consuming hypertension and uric acid drugs, and to perform physical and laboratory examinations. Physical examinations, which included measurements of morning home BP (measured by using sphygmomanometer), body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference, and hip circumference, were conducted on day 1 in subject's house or their neighbor. BP measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times (or until stable BP were obtained) while subjects in sitting position. On day 2, we examined morning home BP and took urine and blood samples.

In 2017, we collected data from 733 subjects, including interviews of demographic data, physical and laboratory examinations. On the first day, subjects were interviewed, physically examined, and given urine containers for one-time urine samples, as well as for a 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The physical examination was performed by the medical team, consisting of a morning home BP measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained), while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan) and measurements of body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference, and hip circumference. On the second day, subjects who were in fasting condition were invited to came to the neighbour's hall in the morning and physically examined for BP again (at 6 – 8 a.m) and drawn for their blood. Urine and blood samples were examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine sample was collected to measure uric acid excretion and creatinine, and a blood sample was collected to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol,

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low-density lipoprotein/LDL-C, high-density lipoprotein/HDL-C and triglycerides), and fasting blood glucose levels.

***Statistical Analysis***

The outcomes of this study were presented in two primary analyses which were (1) blood pressure changes during the period of 2007-2017 to measure the progression from prehypertension (2007) to hypertension (2017) (Table 2), and (2) the association of current BP with SUA levels and cardiovascular risk factors (Table 4 and Table 5). Additional analyses were also being performed to observed the SUA association with cardiovascular risk factors (Figure 2 and Figure 3). The data analyses were mostly performed based on gender in order to know about the gender differences in the analyses mentioned above.

Data presented later in the results section were collected in 2007 and 2017. Data were analysed using IBM SPSS Statistics for Windows, Version 22.0.[24] The data consisted of continuous and categorical data, which were expressed as the mean (SD) for continuous data and as numbers and percentages for categorical data. The continuous variables were analysed and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The categorical variables were analysed and compared by Pearson chi-square tests. Multivariable analysis was performed using multiple linear regressions to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. The significance of associations between categorical variables and numerical variables was determined using 95% confidence intervals (CIs).

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## RESULTS

**Table 1.** Characteristics of Subjects by Gender in 2017 in Mean (SD)

| Variables | Men n=306 | Women n=427 | p-value |
|---|---|---|---|
| Age (years) | 46 (7.71) | 46 (7.76) | 0.431 |
| 30 – 39 years | 35 (2.86) | 36(2.63) | 0.093 |
| 40 – 49 years | 45 (2.89) | 45 (2.67) | 0.372 |
| 50 – 59 years | 54 (3.18) | 54 (2.77) | 0.779 |
| BMI (kg/m$^2$) | 23.5 (3.70) | 25.7 (4.81) | <0.001* |
| SBP (mmHg) | 132 (17.26) | 134 (21.62) | 0.595 |
| DBP (mmHg) | 78 (11.96) | 79 (12.32) | 0.091 |
| Uric Acid (mg/dL) | 5.8 (1.25) | 4.5 (1.10) | <0.001* |
| Total cholesterol (mg/dL) | 167 (36.86) | 166 (41.59) | 0.559 |
| LDL (mg/dL) | 109 (29.59) | 106 (33.27) | 0.155 |
| HDL (mg/dL) | 41 (10.02) | 47 (12.20) | <0.001* |
| Triglyceride (mg/dL) | 129 (79.09) | 103 (63.84) | <0.001* |
| Fasting Blood Glucose (mg/dL) | 100 (37.22) | 97 (33.70) | 0.101 |

*Significant (p<0.05)

The subjects of this study consisted of 733 adults (aged 30–59 years) living in the Mlati Subdistrict; 306 (41.75%) and 427 (58.25%) were men and women, respectively. The characteristics of the subjects (by gender) are presented in Table 1. There was no significant difference in age, SBP, DBP, total cholesterol, LDL, and fasting blood glucose between men and women (p>0.05). Significant differences were found in body mass index (BMI) (p<0.001), SUA levels (p<0.001), HDL (p<0.001) and triglycerides (p<0.001). BMI and HDL were significantly higher in women, whereas SUA levels and triglycerides were significantly higher in men.

**Table 2.** Blood Pressure changes after 10 years and Serum Uric Acid Frequency Distribution (n=733)

| Variables | Frequency (%) | |
|---|---|---|
| | 2007 | 2017 |
| BP[a] | | |
| Normal | 0 | 180 (24.6) |
| Prehypertension (Pre-HT) | 733 (100) | 325 (44.3) |
| Hypertension (HT) | 0 | 228 (31.1) |
| SUA[b] | | |
| Normal | - | 369 (50.3) |
| High-normal | - | 316 (43.1) |

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| | | |
|---|---|---|
| High | - | 48 (6.6) |

[a] BP (blood pressure), normal: SBP < 120 mmHg and DBP < 80 mmHg, prehypertension: SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, hypertension: SBP of ≥140 mmHg and/or DBP of ≥90 mmHg)
[b] SUA (serum uric acid), normal <5 mg/dL, high-normal = 5–7 mg/dL, and high ≥7 mg/dL

After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal, and only 6.6% had high SUA levels (Table 2).

**Table 3.** Association between Gender, Age, BMI, Uric Acid Excretion, and Uric Acid Concentration to Serum Uric Acid Level

| Variables | SUA[a] | | p value | RR | 95% CI |
|---|---|---|---|---|---|
| | High-normal and high (%) | Normal (%) | | | |
| Gender | | | | | |
| Men | 237 (32.3) | 69 (9.4) | <0.001 | 2.60 | 2.22-3.05 |
| Women | 127 (17.3) | 300 (40.9) | | | |
| Age | | | | | |
| Men | | | | | |
| 30 – 39 years* | 52 (17.0) | 11 (3.6) | - | 1 | - |
| 40 – 49 years | 104 (34.0) | 22 (7.2) | 1,000 | 1.00 | 0.87-1.15 |
| 50 – 59 years | 81 (26.5) | 36 (11.8) | 0.053 | 0.84 | 0.71-0.99 |
| Women | | | | | |
| 30 – 39 years* | 22 (5.2) | 85 (19.9) | - | 1 | - |
| 40 – 49 years | 40 (9.4) | 128 (30.0) | 0.530 | 1.16 | 0.73-1.84 |
| 50 – 59 years | 65 (15.2) | 87 (20.4) | <0.001 | 2.08 | 1.37-3.15 |
| BMI[b] | | | | | |
| Overweight-Obese | 171 (23.3) | 154 (21.0) | 0.153 | 1.13 | 0.96 - 1.32 |
| Underweight-normal | 193 (26.3) | 215 (29.3) | | | |
| Uric Acid Excretion (24-h)[c] | | | | | |
| High | 169 (23.1) | 130 (17.7) | 0.002 | 1.32 | 1.10 - 1.57 |
| Normal | 195 (26.6) | 239 (32.6) | | | |
| Uric Acid Concentration[d] | | | | | |
| Normal | 200 (27.3) | 202 (27.5) | 0.956 | 1.00 | 087 – 1.16 |
| High | 164 (22.4) | 167 (22.8) | | | |

* reference category
[a] SUA, normal <5 mg/dL, high-normal = 5–7 mg/dL, and high ≥7 mg/dL
[b] BMI= body mass index, <18.5kg/m$^2$ = underweight, 18.5-24.9 kg/m$^2$ = normal, 25-29.9 kg/m$^2$ = overweight, >30 kg/m$^2$ = obese
[c] Uric acid excretion, <435.08 mg/day = normal, ≥435.08 mg/day = high
[d] Uric acid concentration (mg per 100 ml of urine), <46.63 mg% = normal, ≥46.63 mg% = high

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In men, 32.3% of the subjects had high-normal or high levels of SUA, while in women, only 17.3% had high-normal or high levels of SUA. There was a significant difference in SUA between men and women (p<0.001, RR=2.60, 95% CI=2.22–3.05). When gender was further analysed by age distribution, age was significantly associated with SUA levels only in women aged 50–59 years (p<0.001, RR=2.08, 95% CI=1.36–3.15). Additionally, there was a significant association between SUA levels and uric acid excretion by 24-h urine (p=0.002, RR=1.32, 95% CI=1.10–1.57). On the other hand, no significant association was observed between SUA levels and BMI (p=0.153, RR=1.1, 95% CI=0.96–1.32) or between SUA levels and uric acid concentration (p=0.100, RR=0.786, 95% CI=0.59–1.05) (Table 3).

The associations between gender and SUA levels on BP are shown in Table 4. There was no significant association between gender and BP (p=0.584). To examine the association between uric acid and hypertension, we compared SUA levels and morning home BP. The association between SUA levels and BP was statistically significant (p=0.008, RR=1.12, 95% CI=1.03–1.22). In subjects with previous history of prehypertension, high-normal SUA or high SUA levels were associated with current prehypertension or hypertension. Furthermore, the association between SUA levels and BP in men and women is also described in Table 4. In men, SUA levels were not significantly associated with BP (p=0.805, RR=1.02, 95% CI=0.88–1.19). However, there was a significant association between SUA levels and BP in women (p=0.001, RR=1.21, 95% CI=1.09–1.34). In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal or high SUA levels than those with normal SUA levels. Additional analysis using the 2017 ACC/AHA guideline for observing the associations between gender and SUA levels on BP also showed similar results with the previous analysis using JNC 7 guideline regarding the significant associations between SUA levels and BP.

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**Table 4.** Association between Gender and Serum Uric Acid on Blood Pressure

| Variables | Blood Pressure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | JNC 7[a] | | | | 2017 ACC/AHA[b] | | | |
| | Pre-HT and HT (%) | Normal (%) | p | RR (95%CI) | HT-1 and HT-2 (%) | Normal and elevated (%) | p | RR (95%CI) |
| Gender | | | | | | | | |
| Men | 234 (31.9) | 72 (9.8) | 0.584 | 1.02 (0.94 – 1.11) | 159 (21.7) | 147 (20.1) | 0.129 | 0.9 (0.79 - 1.03) |
| Women | 319 (43.5) | 108 (14.7) | | | 246 (33.6) | 181 (24.7) | | |
| SUA[c] | | | | | | | | |
| High-normal and High | 290 (39.6) | 74 (10.1) | 0.008* | 1.12 (1.03 - 1.22) | 224 (30.6) | 140 (19.1) | 0.001* | 1.26 (1.10 - 1.43) |
| Normal | 263 (35.9) | 106 (14.5) | | | 181 (24.7) | 188 (25.6) | | |
| SUA | | | | | | | | |
| Men | | | | | | | | |
| High-normal and High | 182 (59.5) | 55 (18.0) | 0.805 | 1.02 (0.88 – 1.19) | 129 (42.2) | 108 (35.3) | 0.109 | 1.25 (0.93 – 1.68) |
| Normal | 52 (17.0) | 17 (5.6) | | | 30 (9.8) | 39 (12.7) | | |
| Women | | | | | | | | |
| High-normal and High | 108 (25.3) | 19 (4.4) | 0.001* | 1.21 (1.09 – 1.34) | 95 (22.2) | 32 (7.5) | 0.000* | 1.49 (1.28 – 1.73) |
| Normal | 211 (49.4) | 89(20.8) | | | 151 (35.4) | 149 (34.9) | | |

[a] BP was categorized using the JNC 7 Guideline (prehypertension: SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, hypertension: SBP of ≥140 mmHg and/or DBP of ≥90 mmHg)
[b] BP was categorized using the 2017 ACC/AHA Guideline (normal BP = SBP <120 mmHg and DBP <80 mmHg, elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg)
[c] SUA, normal <5 mg/dL, high-normal = 5–7 mg/dL, and high ≥7 mg/dL

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Figure 2 shows the association between SUA and cardiovascular risk factors. The SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030). Subjects with high-normal and high SUA levels had significantly higher total cholesterol, LDL, and triglyceride levels than subjects with normal SUA levels. On the other hand, HDL and fasting blood glucose were statistically lower among subjects with high-normal and high SUA levels than among those with normal SUA levels.

The relationships between SUA levels and cardiovascular risk factors among men and women are presented in Figure 3. In men, there were significant differences in BMI (p<0.001) and triglycerides (p=0.002) between subjects with normal SUA levels and those with high-normal and high SUA levels. In women, there was no significant differences in all cardiovascular risk factors (p>0.05) between subjects with normal SUA levels and those with high-normal and high SUA levels.

**Table 5.** Multiple Linear Regression of Association of Age, Cardiovascular Risk Factors and SUA on Blood Pressure

| Variables | Blood Pressure of Men | | | | Blood Pressure of Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Systolic | | Diastolic | | Systolic | | Diastolic | |
| | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value |
| Age | 0.704 | <0.001* | 0.336 | <0.001* | 0.674 | <0.001* | -0.017 | 0.817 |
| SUA | -0.247 | 0.745 | 0.582 | 0.267 | 4.527 | <0.001* | 2.223 | <0.001* |
| BMI | 1.602 | <0.001* | 1.295 | <0.001* | 0.929 | <0.001* | 0.722 | <0.001* |
| Total Cholesterol | 0.044 | 0.696 | 0.042 | 0.591 | 0.119 | 0.279 | 0.030 | 0.643 |
| LDL | -0.074 | 0.529 | -0.036 | 0.657 | -0.102 | 0.365 | -0.014 | 0.828 |
| HDL | 0.184 | 0.174 | 0.042 | 0.653 | -0.054 | 0.656 | -0.049 | 0.483 |
| Triglycerides | -0.005 | 0.828 | -0.001 | 0.941 | -0.029 | 0.280 | 0.006 | 0.721 |
| Fasting Blood Glucose | 0.032 | 0.213 | -0.001 | 0.941 | 0.098 | 0.001* | 0.040 | 0.020* |

*Significant (p<0.05)
SUA=Serum uric acid, BMI=Body mass index, LDL=Low density lipoprotein, HDL=High density lipoprotein

Multivariable analysis was conducted to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. Cardiovascular risk factors

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such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all taken into account for adjustment in multiple linear regression (Table 5). Age, BMI, fasting blood glucose, and SUA levels were significantly associated with BP. Significant associations were found between age and SBP both in men ($p<0.001$) and women ($p<0.001$), and DBP only in men ($p<0.001$). BMI was significantly associated with SBP and DBP both in men ($p<0.001$ and $p<0.001$) and women ($p<0.001$ and $p<0.001$). In addition, fasting blood glucose was found to be associated with SBP and DBP in women ($p=0.001$ and $p=0.020$). Regarding SUA levels, SUA was significantly associated with both SBP and DBP in women ($p<0.001$ and $p<0.001$, respectively) but such association was not found in men.

## DISCUSSION

This study consisted of two parts of data collection. The first data collection was performed in 2007 to gather data on the prehypertension population (n=4,190); this study was later called the "Mlati Study Database". In 2017, after 10 years, the second data collection was performed to gather samples from the Mlati Study Database by a random sampling method (n=733) to show the change in BP status from prehypertension to hypertension. The data collection in 2017 also aimed to show the association between uric acid (serum, urinary excretion, and concentrate) and hypertension.

The results of our study showed that gender and uric acid excretion (by 24-h urine) were significantly associated with SUA levels. The mean SUA levels in men were significantly higher than those in women. In addition, subjects with high-normal and high SUA levels had a risk of having prehypertension and hypertension that was 1.12 times higher than those with normal SUA levels. When analysed by gender, high-normal and high SUA levels were significantly associated with prehypertension and hypertension only in women. The relationship between SUA levels and the development of hypertension or renal disease

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had been shown in several previous studies. This relationship was significantly higher in women than in men.[15,25]

The study by Kawabe *et al.* revealed that in women, the older the age was, the higher the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an increase in the quartile of SUA along with higher BMI was only found in men but not in women. Additionally, the mean value of SUA in men was higher than in women.[26] These results were consistent with our finding that SUA levels were significantly higher in men and that SUA levels were significantly associated with higher BMI in men. However, the study populations in this study and the study by Kawabe *et al*. were different in terms of the age group examined, which were adults (30–59 years old) and elderly adults, respectively.[26] A similar finding was also found by Zhang, *et al*. which reported that SUA levels were statistically higher in men than in women, though the SUA level did not increase with the age both in men and women.[27] These studies' results were consistent with our finding which stated that SUA level was significantly higher in men and SUA level was significantly associated with higher BMI also in men. However, the study population in this study and the study by Kawabe, *et al*. was different in the age group which was adults (30-59 years) and elderly, respectively.

Chen *et al.* reported a different result in a cross-sectional analysis regarding the association between SUA levels and the presence of hypertension when analysed by gender. For the total population, SUA levels had significant associations with hypertension. The levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40 years, and >40 years but only in women aged >40 years.[10] This situation could be explained in Table 3, which provides the age distribution of women and its association with SUA levels. In Table 3, the proportion of women aged 40–49 years combined with those aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in

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women is associated with menopausal problems. A study by Hak *et al*. stated that menopause was associated with an increased risk of incident gout, which may help explain why the age of the women in this study could play a significant role in their SUA levels.[28]

Regarding the cardiovascular risk factors, the result of this study found that the SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030), regardless of gender. When the data were analysed by gender, significant differences were found only in BMI and triglycerides and only in men (p<0.001 and p=0.002, respectively). Another study has shown a stronger association between the increase of SUA level and cardiovascular mortality among women in healthy subjects compared to men.[29] Meta-analysis showed that there was a significant association between hyperuricemia and cardiovascular mortality in women, but not in men.[30] Chen *et al*. reported that SUA levels were significantly associated with the occurrence of metabolic syndrome and hypertension in the total population. In men, SUA levels had a positive association with the occurrence of metabolic syndrome in the age groups of <30 and 30–40. In women, SUA levels were significantly associated with the occurrence of metabolic syndrome in the age groups of <30 and >40.[10]

In this study, BMI was significantly associated with SBP and DBP in both genders. This finding was in line with those of a previous study by Droyvold *et al*., in which the authors reported that an increase in BMI was associated with increased BP in men and women.[31] With regard to the association between BMI and SUA levels, our findings were different from those of a report by Rodrigues *et al*., in which the authors reported a significant correlation between BMI and SUA levels in both men and women.[32] The link between BMI and hyperuricemia has not been well elucidated; however, insulin resistance might be the bridging gap. Obese people are more likely to have metabolic syndrome, and the metabolic syndrome itself is associated with insulin resistance. It is thought that insulin

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resistance impairs the ability of the kidney to excrete uric acid and therefore leads to hyperuricemia.[33]

This study found that fasting blood glucose was associated with SBP and DBP only in women. The same result was observed in a study by Yan *et al*., which revealed that fasting plasma glucose was independent of both SBP and DBP.[34] Fasting blood glucose was also associated with SUA levels, but when analysed by gender, no significant difference was found. This finding is contradictory to those of a study by Kawamoto *et al*., which revealed that SUA levels were associated with fasting plasma glucose in females.[35] The mechanism of how this phenomenon occurred remains unclear, and further study is needed to observe a cause-effect relationship. Serum triglycerides were also associated with SUA levels in this study. The relationship between SUA levels and lipid profiles has been described in various studies, but the exact mechanism remains unclear. A study by Peng *et al*. revealed that all lipid profile parameters, including triglycerides but not HDL cholesterol, were associated with SUA levels.[36] SUA levels were associated with both SBP and DBP but only in women. This result is similar to those of previous studies.[35, 37] It has been suggested that the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after oxidative stress damage to the endothelium during excessive uric acid formation.[37]

There were several limitations to this study. First, subjects in this study were collected from the database made in 2007. From 1500 subjects randomly selected at the beginning of this study, only 733 subjects joined and attend the 2-days examination. More than half of the selected subjects did not attend the examination invitation due to several reasons, thus, this had lessened the total samples of subjects of this study. However, a total sample of 733 has met the minimum sample requirement for this study based on sample size calculation (a minimum sample size of 661 subjects are needed for this study). We invited 1500 subjects at the beginning of this study to anticipate any subjects that could not participate in this study

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due to any reasons, so that the minimum number of samples could still be met. This was one of the difficulties we met since this study was a community-based study. The findings of this study were expected to be generalized to the 4190 prehypertensive patients whom collected from "Mlati Study" database in 2007. Second, this study could not present the changes of all measured values over a 10-year period because, in the prior study in 2007, these laboratory values were not examined, except for blood pressure. Therefore, only the changes in blood pressure can be presented on the results. Third, the instruments used to measure blood pressure in 2007 and 2017 were different that might cause instrument bias. In 2007, we used sphygmomanometers, whereas in 2017 we used digital automatic blood pressure monitors. Thus, this may lead to bias in blood pressure data measurement between 2007 and 2017. Nevertheless, we tried to minimize the bias by calibrating both the sphygmomanometers and digital automatic blood pressure monitors before data collection, so that, the blood pressure data were all accurate.

## CONCLUSION

In conclusion, after 10 years of follow-up (2007-2017), of 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) got hypertension. In the cross-sectional analyses of SUA in 2017, the SUA levels in men were significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men.

## ACKNOWLEDGMENTS

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## CONTRIBUTORS

LAB, MS and YT composed the idea of the study and arranged the study's design. MS, FI, AW, and AK obtained the data. ZZ led the statistical analysis with the supervision of MS. MS, LAB and ZZ wrote the first draft of this paper and all authors read, revised, and approved the final manuscript.

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## COMPETING INTEREST

There were no conflicts of interest to disclose.

## DATA SHARING STATEMENT

Data may be obtained from the corresponding author upon reasonable request.

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## Figure Legend

Figure 1. Data collection was conducted twice in 2007 (resulting in a collection of prehypertensive population of 4190 patients) and 2017 (to collect the study sample of 733 and obtained physical and laboratory examinations data)

Figure 2. The SUA/serum uric acid levels were significantly associated with total cholesterol ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$). The SUA category: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).

Figure 3. Significant differences were found in BMI ($p<0.001$) and triglycerides ($p=0.002$) between subjects with normal SUA levels and those with high-normal and high SUA levels in men. No significant difference was found ($p>0.05$) between subjects with normal SUA levels and those with high-normal and high SUA levels in women. The SUA category: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).

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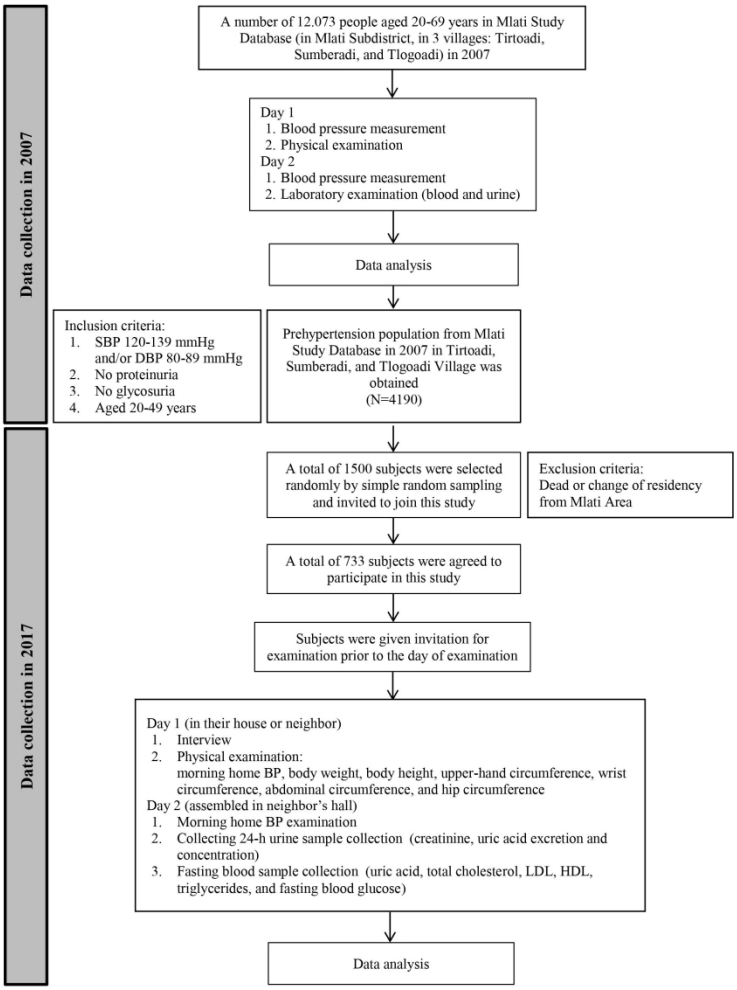


Fig 1. Study Flow Chart

Fig 1. Study Flow Chart

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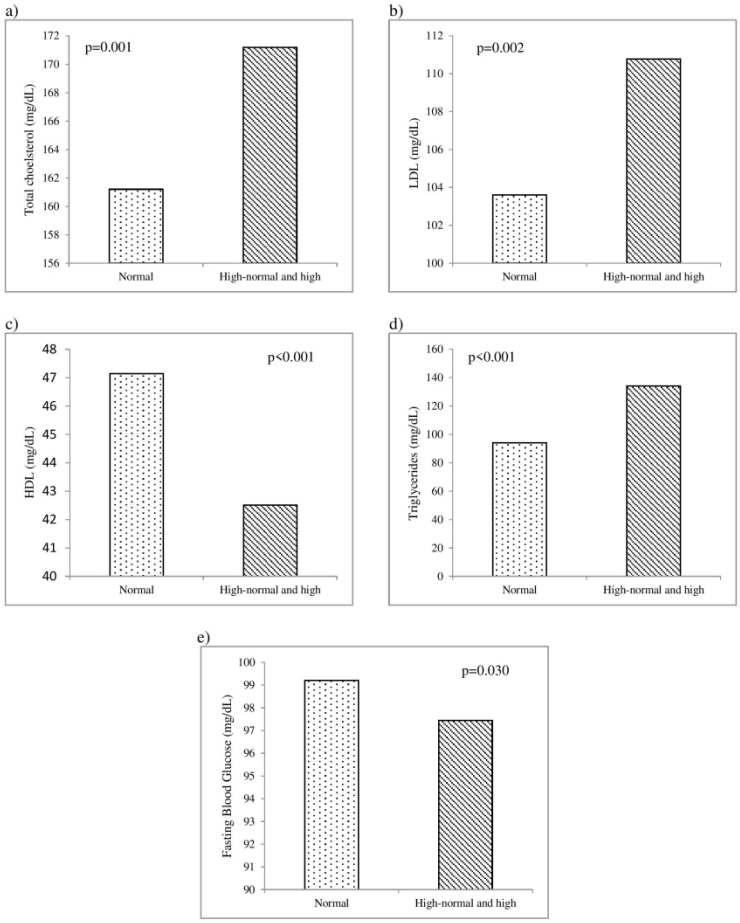


**Fig. 2.** Mean of cardiovascular risk factors in different serum uric acid levels
The SUA/serum uric acid levels were significantly associated with total cholesterol (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030).

Figure 2. Mean of cardiovascular risk factors in different serum uric acid levels

210x297mm (300 x 300 DPI)

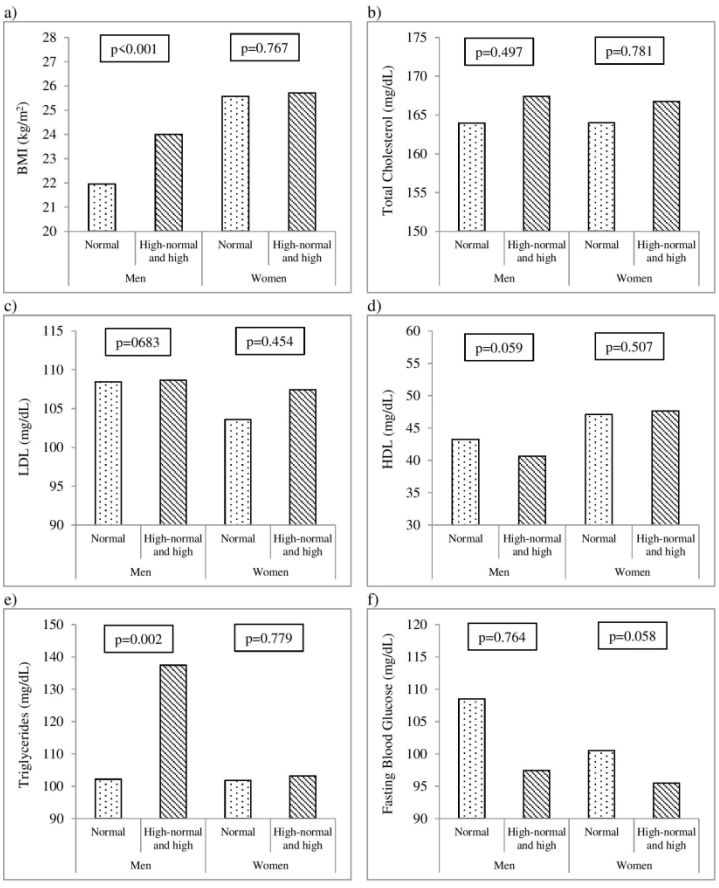


**Fig. 3.** Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.
In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests.
In women, BMI, total cholesterol, LDL, HDL and triglyceride levels were analysed using the Mann-Whitney U test; fasting blood glucose was analysed using independent samples t-tests.

Figure 3. Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.

210x297mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 17-18 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | N/A |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |

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| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Written on each table |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 17 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 14-17 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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# Association of serum uric acid, morning home blood pressure and cardiovascular risk factors in a population with previous prehypertension : a cross-sectional study

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# Association of serum uric acid, morning home blood pressure and cardiovascular risk factors in a population with previous prehypertension : a cross-sectional study

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## ABSTRACT

**Objective**: To observe the changes in blood pressure (BP) over 10 years and to investigate current BP association to serum uric acid (SUA) levels and cardiovascular risk factors in the epidemiological data of a target group of prehypertensive patients in 2007.

**Design:** cross-sectional study

**Setting:** Mlati Sub-district, Sleman District, Yogyakarta Province, Indonesia

**Participants:** A total of 733 patients from "Mlati Study Database" in 2007 were selected by simple random sampling using statistical software. Subjects had both physical and laboratory examinations.

**Outcome measures:** Morning home blood pressure and laboratory examination of urine (uric acid excretion and creatinine) and blood samples (SUA, blood urea nitrogen, creatinine, a lipid profile, and fasting blood glucose levels)

**Results**: About 31.1% of 733 prehypertensive subjects became hypertension after 10 years, 24.6% returned to normal tension, and the rest of it remained in prehypertensive state. Mean (SD) of SUA levels in 2017 were significantly higher in men than in women (5.78 (1.25) mg/dL vs 4.52 (1.10) mg/dL, $p<0.001$). Furthermore, men tended to have high-normal (5–7 mg/dL) or high SUA levels (≥7 mg/dL) compared to women ($p<0.001$, RR=2.60). High-normal and high SUA levels in population with a history of prehypertension were significantly associated with current prehypertension and hypertension only in women ($p=0.001$, RR=1.21). Age and body mass index was found to be significantly associated with both systolic and diastolic BP in men, but only with systolic BP in women. Fasting blood glucose and SUA levels were significantly associated with systolic and diastolic BP only in women.


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**Conclusion**: We concluded that after 10 years, of 733 prehypertensive subjects, 31.1% became hypertensive. The SUA levels in men are significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men.

**Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences

## STRENGTH AND LIMITATION OF THIS STUDY

- This study followed up the changes in blood pressure on subjects for over 10 years.
- The association between serum uric acid, blood pressure, and cardiovascular risk factors were analysed based on gender.
- The analysis' was also performed by using both JNC 7 and 2017 ACC/AHA guideline.
- This study could not present the changes of all measured values over 10 year period because, in the prior study in 2007, these laboratory values were not examined, except for blood pressure.

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## INTRODUCTION

Hypertension is still a major problem worldwide, as reflected by a meta-analysis report in 2016 stating that in 2010, 40% of the world's population was hypertensive and that approximately 17 million people worldwide died due to hypertension.[1] In Indonesia, the prevalence of hypertension in 2013 was 25.8%, based on the Indonesian Ministry of Health report.[2] Therefore, it is important to facilitate the early diagnosis and treatment of hypertension and its possible effects. Patients with prehypertension were hypothesized to eventually become hypertensive after 10 years, and thus have a poorer quality of life [3,4]. During the last two decades, it has been repeatedly published that the incidence of hypertension is associated with even moderate increases in levels of serum uric acid (SUA) and an increased risk of cardiovascular diseases (CVD).[5,6] The Framingham Heart Study reported an increased risk of blood pressure (BP) progression in 3157 subjects with hyperuricemia. SUA was positively associated with increases in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) after 4 years with no antihypertensive treatment.[7] Current findings based on a large-scale cohort study suggested that uric acid is a predictive factor of the development of prehypertension in adults.[8] A meta-analysis by Jiang *et al.* indicated that SUA was possibly associated with prehypertension but still found conflicting results.[9] The associations among SUA, hypertension, cardiovascular risk factors and gender remain controversial. Serum uric acid levels have been known to have an association with blood pressure and hypertension.[10-12] Some studies reported that hyperuricemia has higher susceptibility of developing hypertension especially in men [10,13], while the other study reported vice versa.[14] Lee *et al.* also showed that hyperuricemia in women led to a higher risk of developing hypertension than in men.[15] In terms of the association of SUA and cardiovascular risk, SUA did not have a causal role in the development of cardiovascular outcomes.[16] Another study stated that the serum uric acid level was an independent

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predictive factor for cardiovascular risk in individuals without hypertension and diabetes.[17] Serum uric acid also being reported to have a stronger association with cardiovascular risk [18] and risk of cardiovascular disease mortality [19,20] in women than in men.

Therefore, the aim of this study was to observe the progression from prehypertension to hypertension after 10 years (2007-2017) and the association of BP with SUA as well as other cardiovascular risk factors in 2017.

## METHODS

### *Study Design*

This study was a cross-sectional study conducted in Mlati Sub-district, Sleman District in the Yogyakarta Special Region, Indonesia. The protocol of this study was approved by the Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with the ID approval of KE/FK/0961/EC/2017.

### *Study Population*

We pooled data from participants enrolled in the 2007 Mlati Study Database. The sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected as participants in the current study by simple random sampling using statistical software. All 1500 subjects were invited to have a physical and laboratory examination; however, only 733 subjects who participated in the sampling were examined (the other subjects who did not

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show up during the laboratory examination were due to the change of residential area or death or any other unknown reasons and were excluded from this study). All subjects did not take any drugs lowering BP and SUA. All subjects were provided informed consent at the beginning of the study (Figure 1).

***Patient and Public Involvement***

Patients were not involved in any of the design, analysis, and presentation of the study results.

***Definition of Prehypertension and Hypertension***

The definitions of prehypertension and hypertension were based on the Seventh Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only their treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of 80–89 mmHg are defined as prehypertension, while SBP of ≥140 mmHg and/or DBP of ≥90 mmHg are defined as hypertension.[21]

For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as follows: (1) normal BP = SBP <120 mmHg and DBP <80 mmHg, (2) elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, (3) stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, and (4) stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg.[22]

***Serum Uric Acid Cut-off Point***

Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3 categories: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).[23]

***Data Collection***

The data collection was conducted twice during the study period. The first data collection was conducted in 2007 to collect the prehypertension population (n=4,190). The second data collection was performed in 2017 to collect samples from the Mlati Study Database by the random sampling method (n=733).

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In 2007, interviews were conducted on 12,073 subjects to obtain demographic data (e.g. sex and age), family history of hypertension and diabetes mellitus, patients' history of diabetes mellitus, patients' history of consuming hypertension and uric acid drugs, and to perform physical and laboratory examinations. Physical examinations, which included measurements of morning home BP (measured by using sphygmomanometer), body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference, and hip circumference, were conducted on day 1 in subject's house or their neighbor. BP measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times (or until stable BP were obtained) while subjects in sitting position. On day 2, we examined morning home BP and took urine and blood samples.

In 2017, we collected data from 733 subjects, including interviews of demographic data, physical and laboratory examinations. On the first day, subjects were interviewed, physically examined, and given urine containers for one-time urine samples, as well as for a 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The physical examination was performed by the medical team, consisting of a morning home BP measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained), while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan) and measurements of body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference, and hip circumference. On the second day, subjects who were in fasting condition were invited to came to the neighbour's hall in the morning and physically examined for BP again (at 6 – 8 a.m) and drawn for their blood. Urine and blood samples were examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine sample was collected to measure uric acid excretion and creatinine, and a blood sample was collected to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol,

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low-density lipoprotein/LDL-C, high-density lipoprotein/HDL-C and triglycerides), and fasting blood glucose levels.

***Statistical Analysis***

The outcomes of this study were presented in two primary analyses which were (1) blood pressure changes during the period of 2007-2017 to measure the progression from prehypertension (2007) to hypertension (2017), and (2) the association of current BP with SUA levels and cardiovascular risk factors. Additional analyses were also performed to observe the SUA association with cardiovascular risk factors. The data analyses were mostly performed based on gender to know about the gender differences in the analyses mentioned above.

Data presented later in the results section were collected in 2007 and 2017. Data were analysed using IBM SPSS Statistics for Windows, Version 22.0.[24] The data consisted of continuous and categorical data, which were expressed as the mean (SD) for continuous data and as numbers and percentages for categorical data. The continuous variables were analysed and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The categorical variables were analysed and compared by Pearson chi-square tests. Blood pressure changes during the period of 2007-2017 were presented using frequencies and percentages. The associations of current BP with SUA levels and gender were analysed using the Pearson chi-square test. Multivariable analysis was performed using multiple linear regressions to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. Additional analysis to observe the association between SUA levels and cardiovascular risk factors and gender were performed using independent samples t-tests and nonparametric Mann-Whitney U tests. The significance of associations between categorical and numerical variables was determined using 95% confidence intervals (CIs).

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## RESULTS

**Table 1.** Characteristics of Subjects by Gender in 2017 in Mean (SD)

| Variables | Men n=306 | Women n=427 | p-value |
|---|---|---|---|
| Age (years) | 46 (7.71) | 46 (7.76) | 0.431 |
| 30 – 39 years | 35 (2.86) | 36(2.63) | 0.093 |
| 40 – 49 years | 45 (2.89) | 45 (2.67) | 0.372 |
| 50 – 59 years | 54 (3.18) | 54 (2.77) | 0.779 |
| BMI (kg/m$^2$) | 23.5 (3.70) | 25.7 (4.81) | <0.001* |
| SBP (mmHg) | 132 (17.26) | 134 (21.62) | 0.595 |
| DBP (mmHg) | 78 (11.96) | 79 (12.32) | 0.091 |
| Uric Acid (mg/dL) | 5.8 (1.25) | 4.5 (1.10) | <0.001* |
| Total cholesterol (mg/dL) | 167 (36.86) | 166 (41.59) | 0.559 |
| LDL (mg/dL) | 109 (29.59) | 106 (33.27) | 0.155 |
| HDL (mg/dL) | 41 (10.02) | 47 (12.20) | <0.001* |
| Triglyceride (mg/dL) | 129 (79.09) | 103 (63.84) | <0.001* |
| Fasting Blood Glucose (mg/dL) | 100 (37.22) | 97 (33.70) | 0.101 |

*Significant ($p<0.05$)

The subjects of this study consisted of 733 adults (aged 30–59 years) living in the Mlati Subdistrict; 306 (41.75%) and 427 (58.25%) were men and women, respectively. The characteristics of the subjects (by gender) are presented in Table 1. There was no significant difference in age, SBP, DBP, total cholesterol, LDL, and fasting blood glucose between men and women ($p>0.05$). Significant differences were found in body mass index (BMI) ($p<0.001$), SUA levels ($p<0.001$), HDL ($p<0.001$) and triglycerides ($p<0.001$). BMI and HDL were significantly higher in women, whereas SUA levels and triglycerides were significantly higher in men.

**Table 2.** Blood Pressure changes after 10 years and Serum Uric Acid Frequency Distribution (n=733)

| Variables | Frequency (%) | |
|---|---|---|
| | 2007 | 2017 |
| BP[a] | | |
| Normal | 0 | 180 (24.6) |
| Prehypertension (Pre-HT) | 733 (100) | 325 (44.3) |
| Hypertension (HT) | 0 | 228 (31.1) |
| SUA[b] | | |
| Normal | - | 369 (50.3) |
| High-normal | - | 316 (43.1) |

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| | | |
|---|---|---|
| High | - | 48 (6.6) |

[a] BP (blood pressure), normal: SBP < 120 mmHg and DBP < 80 mmHg, prehypertension: SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, hypertension: SBP of ≥140 mmHg and/or DBP of ≥90 mmHg)
[b] SUA (serum uric acid), normal <5 mg/dL, high-normal = 5–7 mg/dL, and high ≥7 mg/dL

After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal, and only 6.6% had high SUA levels (Table 2).

**Table 3.** Association between Gender, Age, BMI, Uric Acid Excretion, and Uric Acid Concentration to Serum Uric Acid Level

| Variables | SUA[a] | | p value | RR | 95% CI |
|---|---|---|---|---|---|
| | High-normal and high (%) | Normal (%) | | | |
| Gender | | | | | |
| Men | 237 (32.3) | 69 (9.4) | <0.001 | 2.60 | 2.22-3.05 |
| Women | 127 (17.3) | 300 (40.9) | | | |
| Age | | | | | |
| Men | | | | | |
| 30 – 39 years* | 52 (17.0) | 11 (3.6) | - | 1 | - |
| 40 – 49 years | 104 (34.0) | 22 (7.2) | 1,000 | 1.00 | 0.87-1.15 |
| 50 – 59 years | 81 (26.5) | 36 (11.8) | 0.053 | 0.84 | 0.71-0.99 |
| Women | | | | | |
| 30 – 39 years* | 22 (5.2) | 85 (19.9) | - | 1 | - |
| 40 – 49 years | 40 (9.4) | 128 (30.0) | 0.530 | 1.16 | 0.73-1.84 |
| 50 – 59 years | 65 (15.2) | 87 (20.4) | <0.001 | 2.08 | 1.37-3.15 |
| BMI[b] | | | | | |
| Overweight-Obese | 171 (23.3) | 154 (21.0) | 0.153 | 1.13 | 0.96 - 1.32 |
| Underweight-normal | 193 (26.3) | 215 (29.3) | | | |
| Uric Acid Excretion (24-h)[c] | | | | | |
| High | 169 (23.1) | 130 (17.7) | 0.002 | 1.32 | 1.10 - 1.57 |
| Normal | 195 (26.6) | 239 (32.6) | | | |
| Uric Acid Concentration[d] | | | | | |
| Normal | 200 (27.3) | 202 (27.5) | 0.956 | 1.00 | 087 – 1.16 |
| High | 164 (22.4) | 167 (22.8) | | | |

* reference category
[a] SUA, normal <5 mg/dL, high-normal = 5–7 mg/dL, and high ≥7 mg/dL
[b] BMI= body mass index, <18.5kg/m$^2$ = underweight, 18.5-24.9 kg/m$^2$ = normal, 25-29.9 kg/m$^2$ = overweight, >30 kg/m$^2$ = obese
[c] Uric acid excretion, <435.08 mg/day = normal, ≥435.08 mg/day = high
[d] Uric acid concentration (mg per 100 ml of urine), <46.63 mg% = normal, ≥46.63 mg% = high

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In men, 32.3% of the subjects had high-normal or high levels of SUA, while in women, only 17.3% had high-normal or high levels of SUA. There was a significant difference in SUA between men and women (p<0.001, RR=2.60, 95% CI=2.22–3.05). When gender was further analysed by age distribution, age was significantly associated with SUA levels only in women aged 50–59 years (p<0.001, RR=2.08, 95% CI=1.36–3.15). Additionally, there was a significant association between SUA levels and uric acid excretion by 24-h urine (p=0.002, RR=1.32, 95% CI=1.10–1.57). On the other hand, no significant association was observed between SUA levels and BMI (p=0.153, RR=1.1, 95% CI=0.96–1.32) or between SUA levels and uric acid concentration (p=0.100, RR=0.786, 95% CI=0.59–1.05) (Table 3).

The associations between gender and SUA levels on BP are shown in Table 4. There was no significant association between gender and BP (p=0.584). To examine the association between uric acid and hypertension, we compared SUA levels and morning home BP. The association between SUA levels and BP was statistically significant (p=0.008, RR=1.12, 95% CI=1.03–1.22). In subjects with previous history of prehypertension, high-normal SUA or high SUA levels were associated with current prehypertension or hypertension. Furthermore, the association between SUA levels and BP in men and women is also described in Table 4. In men, SUA levels were not significantly associated with BP (p=0.805, RR=1.02, 95% CI=0.88–1.19). However, there was a significant association between SUA levels and BP in women (p=0.001, RR=1.21, 95% CI=1.09–1.34). In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal or high SUA levels than those with normal SUA levels. Additional analysis using the 2017 ACC/AHA guideline for observing the associations between gender and SUA levels on BP also showed similar results with the previous analysis using JNC 7 guideline regarding the significant associations between SUA levels and BP.

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**Table 4.** Association between Gender and Serum Uric Acid on Blood Pressure

| Variables | Blood Pressure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | JNC 7[a] | | | | 2017 ACC/AHA[b] | | | |
| | Pre-HT and HT (%) | Normal (%) | p | RR (95%CI) | HT-1 and HT-2 (%) | Normal and elevated (%) | p | RR (95%CI) |
| Gender | | | | | | | | |
| Men | 234 (31.9) | 72 (9.8) | 0.584 | 1.02 (0.94 – 1.11) | 159 (21.7) | 147 (20.1) | 0.129 | 0.9 (0.79 - 1.03) |
| Women | 319 (43.5) | 108 (14.7) | | | 246 (33.6) | 181 (24.7) | | |
| SUA[c] | | | | | | | | |
| High-normal and High | 290 (39.6) | 74 (10.1) | 0.008* | 1.12 (1.03 - 1.22) | 224 (30.6) | 140 (19.1) | 0.001* | 1.26 (1.10 - 1.43) |
| Normal | 263 (35.9) | 106 (14.5) | | | 181 (24.7) | 188 (25.6) | | |
| SUA | | | | | | | | |
| Men | | | | | | | | |
| High-normal and High | 182 (59.5) | 55 (18.0) | 0.805 | 1.02 (0.88 – 1.19) | 129 (42.2) | 108 (35.3) | 0.109 | 1.25 (0.93 – 1.68) |
| Normal | 52 (17.0) | 17 (5.6) | | | 30 (9.8) | 39 (12.7) | | |
| Women | | | | | | | | |
| High-normal and High | 108 (25.3) | 19 (4.4) | 0.001* | 1.21 (1.09 – 1.34) | 95 (22.2) | 32 (7.5) | 0.000* | 1.49 (1.28 – 1.73) |
| Normal | 211 (49.4) | 89(20.8) | | | 151 (35.4) | 149 (34.9) | | |

[a] BP was categorized using the JNC 7 Guideline (prehypertension: SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, hypertension: SBP of ≥140 mmHg and/or DBP of ≥90 mmHg)
[b] BP was categorized using the 2017 ACC/AHA Guideline (normal BP = SBP <120 mmHg and DBP <80 mmHg, elevated BP = SBP 120-129 mmHg and DBP <80 mmHg, stage 1 hypertension = SBP 130-139 mmHg or DBP 80-89 mmHg, stage 2 hypertension = SBP ≥140 mmHg or DBP ≥90 mmHg)
[c] SUA, normal <5 mg/dL, high-normal = 5–7 mg/dL, and high ≥7 mg/dL

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Figure 2 shows the association between SUA and cardiovascular risk factors. The SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030). Subjects with high-normal and high SUA levels had significantly higher total cholesterol, LDL, and triglyceride levels than subjects with normal SUA levels. On the other hand, HDL and fasting blood glucose were statistically lower among subjects with high-normal and high SUA levels than among those with normal SUA levels.

The relationships between SUA levels and cardiovascular risk factors among men and women are presented in Figure 3. In men, there were significant differences in BMI (p<0.001) and triglycerides (p=0.002) between subjects with normal SUA levels and those with high-normal and high SUA levels. In women, there was no significant differences in all cardiovascular risk factors (p>0.05) between subjects with normal SUA levels and those with high-normal and high SUA levels.

**Table 5.** Multiple Linear Regression of Association of Age, Cardiovascular Risk Factors and SUA on Blood Pressure

| Variables | Blood Pressure of Men | | | | Blood Pressure of Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Systolic | | Diastolic | | Systolic | | Diastolic | |
| | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value | Coef. β | p-value |
| Age | 0.704 | <0.001* | 0.336 | <0.001* | 0.674 | <0.001* | -0.017 | 0.817 |
| SUA | -0.247 | 0.745 | 0.582 | 0.267 | 4.527 | <0.001* | 2.223 | <0.001* |
| BMI | 1.602 | <0.001* | 1.295 | <0.001* | 0.929 | <0.001* | 0.722 | <0.001* |
| Total Cholesterol | 0.044 | 0.696 | 0.042 | 0.591 | 0.119 | 0.279 | 0.030 | 0.643 |
| LDL | -0.074 | 0.529 | -0.036 | 0.657 | -0.102 | 0.365 | -0.014 | 0.828 |
| HDL | 0.184 | 0.174 | 0.042 | 0.653 | -0.054 | 0.656 | -0.049 | 0.483 |
| Triglycerides | -0.005 | 0.828 | -0.001 | 0.941 | -0.029 | 0.280 | 0.006 | 0.721 |
| Fasting Blood Glucose | 0.032 | 0.213 | -0.001 | 0.941 | 0.098 | 0.001* | 0.040 | 0.020* |

*Significant (p<0.05)
SUA=Serum uric acid, BMI=Body mass index, LDL=Low density lipoprotein, HDL=High density lipoprotein

Multivariable analysis was conducted to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. Cardiovascular risk factors

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such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all taken into account for adjustment in multiple linear regression (Table 5). Age, BMI, fasting blood glucose, and SUA levels were significantly associated with BP. Significant associations were found between age and SBP both in men ($p<0.001$) and women ($p<0.001$), and DBP only in men ($p<0.001$). BMI was significantly associated with SBP and DBP both in men ($p<0.001$ and $p<0.001$) and women ($p<0.001$ and $p<0.001$). In addition, fasting blood glucose was found to be associated with SBP and DBP in women ($p=0.001$ and $p=0.020$). Regarding SUA levels, SUA was significantly associated with both SBP and DBP in women ($p<0.001$ and $p<0.001$, respectively) but such association was not found in men.

## DISCUSSION

This study consisted of two parts of data collection. The first data collection was performed in 2007 to gather data on the prehypertension population (n=4,190); this study was later called the "Mlati Study Database". In 2017, after 10 years, the second data collection was performed to gather samples from the Mlati Study Database by a random sampling method (n=733) to show the change in BP status from prehypertension to hypertension. The data collection in 2017 also aimed to show the association between uric acid (serum, urinary excretion, and concentrate) and hypertension.

The results of our study showed that gender and uric acid excretion (by 24-h urine) were significantly associated with SUA levels. The mean SUA levels in men were significantly higher than those in women. In addition, subjects with high-normal and high SUA levels had a risk of having prehypertension and hypertension that was 1.12 times higher than those with normal SUA levels. When analysed by gender, high-normal and high SUA levels were significantly associated with prehypertension and hypertension only in women. The relationship between SUA levels and the development of hypertension or renal disease

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had been shown in several previous studies. This relationship was significantly higher in women than in men.[15,25]

The study by Kawabe *et al.* revealed that in women, the older the age was, the higher the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an increase in the quartile of SUA along with higher BMI was only found in men but not in women. Additionally, the mean value of SUA in men was higher than in women.[26] These results were consistent with our finding that SUA levels were significantly higher in men and that SUA levels were significantly associated with higher BMI in men. However, the study populations in this study and the study by Kawabe *et al*. were different in terms of the age group examined, which were adults (30–59 years old) and elderly adults, respectively.[26] A similar finding was also found by Zhang, *et al*. which reported that SUA levels were statistically higher in men than in women, though the SUA level did not increase with the age both in men and women.[27] These studies' results were consistent with our finding which stated that SUA level was significantly higher in men and SUA level was significantly associated with higher BMI also in men. However, the study population in this study and the study by Kawabe, *et al*. was different in the age group which was adults (30-59 years) and elderly, respectively.

Chen *et al.* reported a different result in a cross-sectional analysis regarding the association between SUA levels and the presence of hypertension when analysed by gender. For the total population, SUA levels had significant associations with hypertension. The levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40 years, and >40 years but only in women aged >40 years.[10] This situation could be explained in Table 3, which provides the age distribution of women and its association with SUA levels. In Table 3, the proportion of women aged 40–49 years combined with those aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in

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women is associated with menopausal problems. A study by Hak *et al*. stated that menopause was associated with an increased risk of incident gout, which may help explain why the age of the women in this study could play a significant role in their SUA levels.[28]

Regarding the cardiovascular risk factors, the result of this study found that the SUA levels were significantly associated with total cholesterol (p=0.001), LDL (p=0.002), HDL (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030), regardless of gender. When the data were analysed by gender, significant differences were found only in BMI and triglycerides and only in men (p<0.001 and p=0.002, respectively). Another study has shown a stronger association between the increase of SUA level and cardiovascular mortality among women in healthy subjects compared to men.[29] Meta-analysis showed that there was a significant association between hyperuricemia and cardiovascular mortality in women, but not in men.[30] Chen *et al*. reported that SUA levels were significantly associated with the occurrence of metabolic syndrome and hypertension in the total population. In men, SUA levels had a positive association with the occurrence of metabolic syndrome in the age groups of <30 and 30–40. In women, SUA levels were significantly associated with the occurrence of metabolic syndrome in the age groups of <30 and >40.[10]

In this study, BMI was significantly associated with SBP and DBP in both genders. This finding was in line with those of a previous study by Droyvold *et al*., in which the authors reported that an increase in BMI was associated with increased BP in men and women.[31] With regard to the association between BMI and SUA levels, our findings were different from those of a report by Rodrigues *et al*., in which the authors reported a significant correlation between BMI and SUA levels in both men and women.[32] The link between BMI and hyperuricemia has not been well elucidated; however, insulin resistance might be the bridging gap. Obese people are more likely to have metabolic syndrome, and the metabolic syndrome itself is associated with insulin resistance. It is thought that insulin

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resistance impairs the ability of the kidney to excrete uric acid and therefore leads to hyperuricemia.[33]

This study found that fasting blood glucose was associated with SBP and DBP only in women. The same result was observed in a study by Yan *et al*., which revealed that fasting plasma glucose was independent of both SBP and DBP.[34] Fasting blood glucose was also associated with SUA levels, but when analysed by gender, no significant difference was found. This finding is contradictory to those of a study by Kawamoto *et al*., which revealed that SUA levels were associated with fasting plasma glucose in females.[35] The mechanism of how this phenomenon occurred remains unclear, and further study is needed to observe a cause-effect relationship. Serum triglycerides were also associated with SUA levels in this study. The relationship between SUA levels and lipid profiles has been described in various studies, but the exact mechanism remains unclear. A study by Peng *et al*. revealed that all lipid profile parameters, including triglycerides but not HDL cholesterol, were associated with SUA levels.[36] SUA levels were associated with both SBP and DBP but only in women. This result is similar to those of previous studies.[35, 37] It has been suggested that the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after oxidative stress damage to the endothelium during excessive uric acid formation.[37]

There were several limitations to this study. First, subjects in this study were collected from the database made in 2007. From 1500 subjects randomly selected at the beginning of this study, only 733 subjects joined and attend the 2-days examination. More than half of the selected subjects did not attend the examination invitation due to several reasons, thus, this had lessened the total samples of subjects of this study. However, a total sample of 733 has met the minimum sample requirement for this study based on sample size calculation (a minimum sample size of 661 subjects are needed for this study). We invited 1500 subjects at the beginning of this study to anticipate any subjects that could not participate in this study

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due to any reasons, so that the minimum number of samples could still be met. This was one of the difficulties we met since this study was a community-based study. The findings of this study were expected to be generalized to the 4190 prehypertensive patients whom collected from "Mlati Study" database in 2007. Second, this study could not present the changes of all measured values over a 10-year period because, in the prior study in 2007, these laboratory values were not examined, except for blood pressure. Therefore, only the changes in blood pressure can be presented on the results. Third, the instruments used to measure blood pressure in 2007 and 2017 were different that might cause instrument bias. In 2007, we used sphygmomanometers, whereas in 2017 we used digital automatic blood pressure monitors. Thus, this may lead to bias in blood pressure data measurement between 2007 and 2017. Nevertheless, we tried to minimize the bias by calibrating both the sphygmomanometers and digital automatic blood pressure monitors before data collection, so that, the blood pressure data were all accurate.

## CONCLUSION

In conclusion, after 10 years of follow-up (2007-2017), of 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) got hypertension. In the cross-sectional analyses of SUA in 2017, the SUA levels in men were significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men.

## ACKNOWLEDGMENTS

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For peer review only

## CONTRIBUTORS

LAB, MS and YT composed the idea of the study and arranged the study's design. MS, FI, AW, and AK obtained the data. ZZ led the statistical analysis with the supervision of MS. MS, LAB and ZZ wrote the first draft of this paper and all authors read, revised, and approved the final manuscript.

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## COMPETING INTEREST

There were no conflicts of interest to disclose.

## DATA SHARING STATEMENT

Data may be obtained from the corresponding author upon reasonable request.

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**Figure Legend**

Figure 1. Data collection was conducted twice in 2007 (resulting in a collection of prehypertensive population of 4190 patients) and 2017 (to collect the study sample of 733 and obtained physical and laboratory examinations data)

Figure 2. The SUA/serum uric acid levels were significantly associated with total cholesterol ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$). The SUA category: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).

Figure 3. Significant differences were found in BMI ($p<0.001$) and triglycerides ($p=0.002$) between subjects with normal SUA levels and those with high-normal and high SUA levels in men. No significant difference was found ($p>0.05$) between subjects with normal SUA levels and those with high-normal and high SUA levels in women. The SUA category: normal (<5 mg/dL), high-normal (5–7 mg/dL), and high (≥7 mg/dL).

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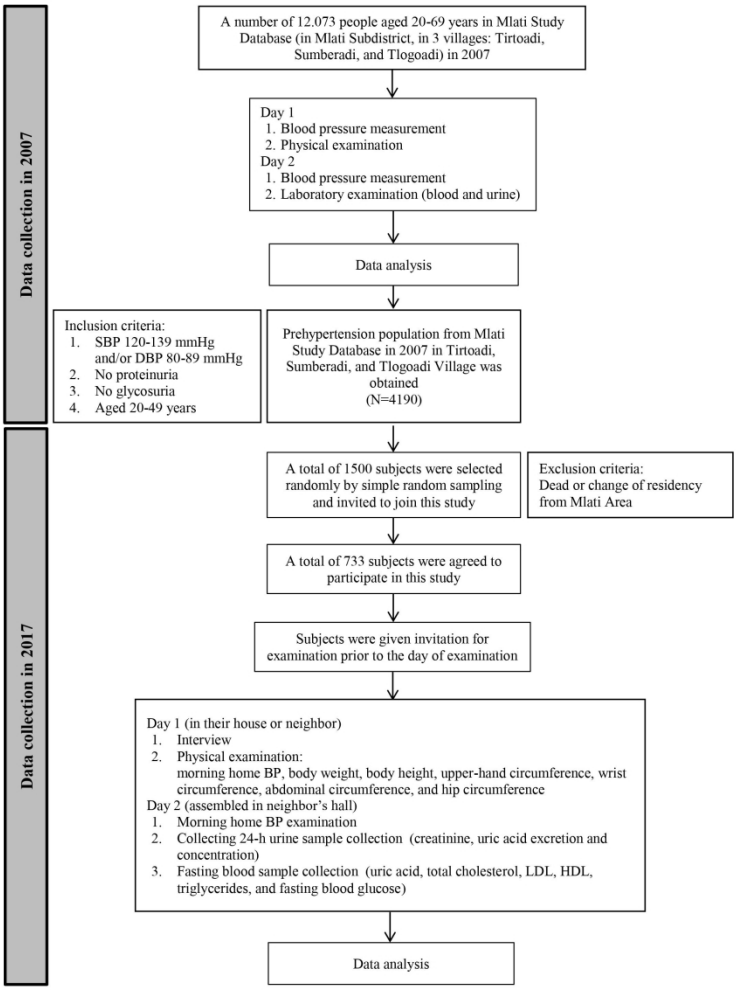


Fig 1. Study Flow Chart

Fig 1. Study Flow Chart

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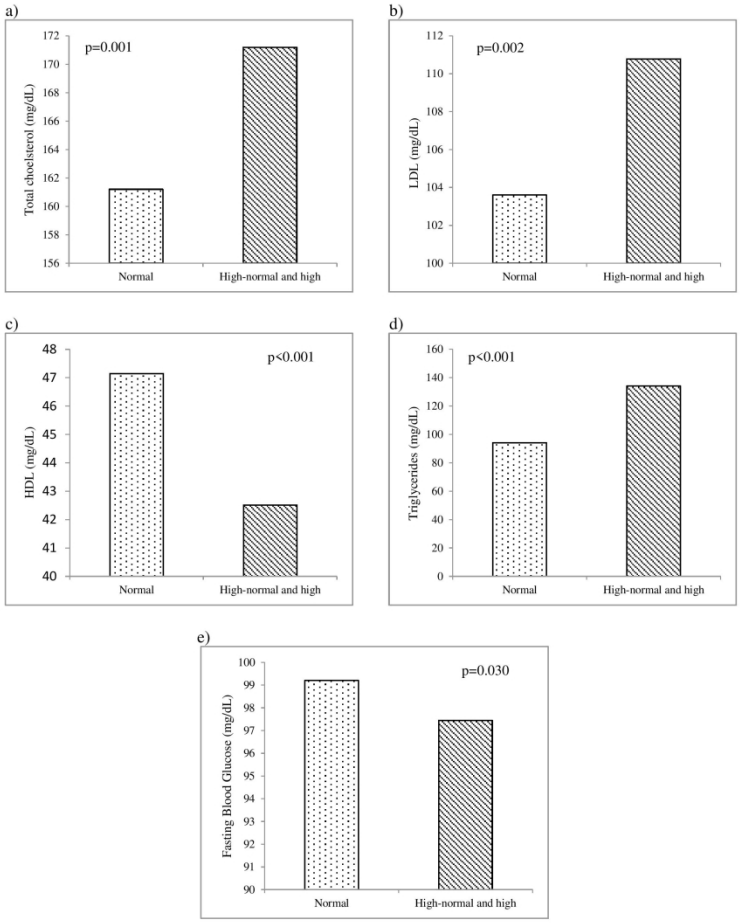


**Fig. 2.** Mean of cardiovascular risk factors in different serum uric acid levels
The SUA/serum uric acid levels were significantly associated with total cholesterol (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001), triglycerides (p<0.001) and fasting blood glucose (p=0.030).

Figure 2. Mean of cardiovascular risk factors in different serum uric acid levels

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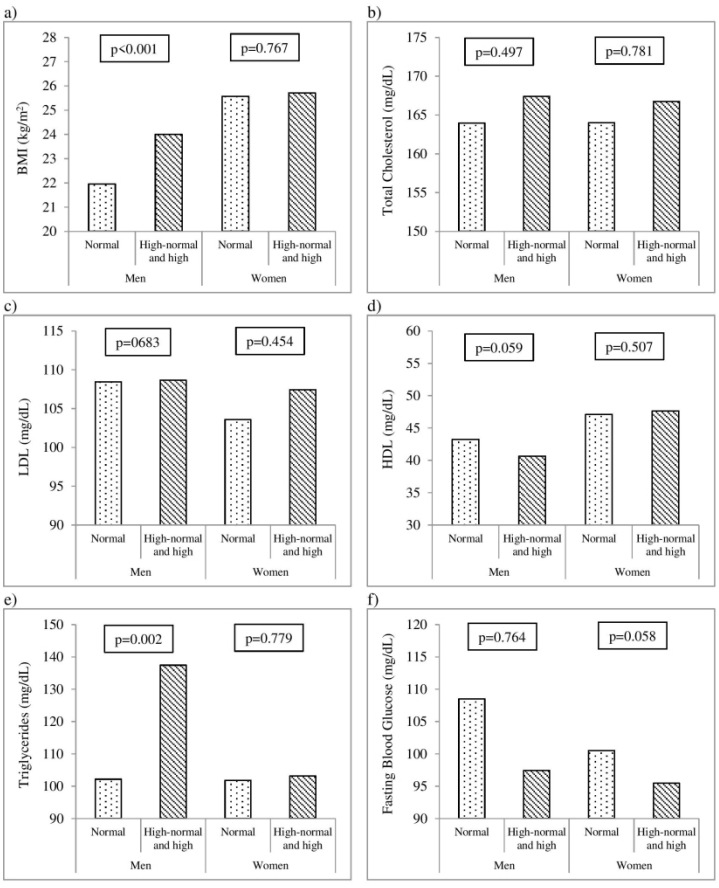


**Fig. 3.** Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.
In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests.
In women, BMI, total cholesterol, LDL, HDL and triglyceride levels were analysed using the Mann-Whitney U test; fasting blood glucose was analysed using independent samples t-tests.

Figure 3. Mean of cardiovacular risk factors in men and women between normal and high-normal/high SUA levels.

210x297mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 17-18 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | N/A |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | N/A |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |

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| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Figure 1 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | N/A |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 10-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | Written on each table |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | N/A |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 17 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 14-17 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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