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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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3 1 **CORRELATION OF SERUM URIC ACID, MORNING HOME BLOOD PRESSURE**
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5 2 **AND CARDIOVASCULAR RISK FACTORS OVER 10 YEARS**
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7 3 **IN A PREHYPERTENSIVE POPULATION**
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59 27 **Word count: 3153**
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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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3 52 body mass index, fasting blood glucose, and serum uric acid levels, whereas in men, blood
4
5 53 pressure was only associated with body mass index and fasting blood glucose.
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10 55 **Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences
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13 14 15 57 **STRENGTH AND LIMITATION OF THIS STUDY**

- 16
17 58 • This study followed up the changes of blood pressure on subjects for over 10 years.
18
19 59 • The association between serum uric acid, blood pressure, and cardiovascular risk factors
20
21 60 were analyzed based on gender.
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24 61 • The analysis' were also performed by using both JNC 7 and 2017 ACC/AHA guideline.
25
26 62 • This study could not present the changes of all measured value over 10 year period
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28 63 because in the prior study in 2007, these laboratory value were not examined, except for
29
30 64 blood pressure.
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66 INTRODUCTION

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

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3 90 least 30% of prehypertensive patients will eventually develop hypertension and that it is
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5 91 associated with SUA.
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93 **METHODS**

94 ***Study Design***

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

99 ***Study Population***

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

112 ***Patient and Public Involvement***

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

114 ***Data Collection***

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3 115 The data collection was conducted twice during the study period. The first data
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5 116 collection was conducted in 2007 to collect the prehypertension population (n=4,190). The
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8 117 second data collection was performed in 2017 to collect samples from the Mlati Study Database
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10 118 by the random sampling method (n=733).

12 119 In 2007, interviews were conducted on 12,073 subjects to obtain family history and to
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14 120 perform physical and laboratory examinations. Physical examinations, which included
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17 121 measurements of morning home BP, body weight, body height, upper-hand circumference,
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19 122 wrist circumference, abdominal circumference and hip circumference, were conducted on day
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21 123 1. On day 2, we examined morning home BP and took urine and blood samples.

24 124 In 2017, we collected data from 733 subjects, including physical and laboratory
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26 125 examinations. On the first day, subjects were interviewed, physically examined, and given
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28 126 urine containers for one-time urine samples as well as for a 24-h urine collection that had to be
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31 127 submitted on day 2. The physical examination consisted of a morning home BP measurement
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33 128 using the Omron HEM-907 monitor (digital automatic blood pressure monitoring) and
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35 129 measurements of body weight, body height, upper-hand circumference, wrist circumference,
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38 130 abdominal circumference and hip circumference. On the second day, subjects came while
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40 131 fasting and were physically examined for BP again. Urine and blood samples were examined
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42 132 in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine sample was
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44 133 collected to measure uric acid excretion and creatinine, and a blood sample was collected to
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46
47 134 measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol, low density
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49 135 lipoprotein/LDL-C, high density lipoprotein/HDL-C and triglycerides), and fasting blood
50
51 136 glucose levels.

54 137 ***Definition of Prehypertension and Hypertension***

56 138 The definitions of prehypertension and hypertension were based on the Seventh Report
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58 139 of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only their
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1
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3 140 treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of 80–89
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5 141 mmHg are defined as prehypertension, while SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg
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8 142 are defined as hypertension.[10]
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10 143 For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as
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12 144 follows: (1) normal BP = SBP < 120 mmHg and DBP < 80 mmHg, (2) elevated BP = SBP 120-
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14 145 129 mmHg and DBP < 80 mmHg, (3) stage 1 hypertension = SBP 130-139 mmHg or DBP 80-
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16 146 89 mmHg, and (4) stage 2 hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.[11]
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19 147 ***Serum Uric Acid Cut-off Point***

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21 148 Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3
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23 149 categories: normal (< 5 mg/dL), high-normal (5–7 mg/dL), and high (≥ 7 mg/dL).[12]
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26 150 ***Statistical Analysis***

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28 151 The data consisted of continuous and categorical data, which were expressed as the
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30 152 mean (SD) for continuous data and as numbers and percentages for categorical data. The
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32 153 continuous variables were analysed and compared by independent samples t-tests and
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34 154 nonparametric Mann-Whitney U tests. The categorical variables were analysed and compared
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36 155 by Pearson chi-square tests. Multivariable analysis was performed using multiple linear
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38 156 regression. The significance of associations between categorical variables and numerical
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40 157 variables were determined using 95% confidence intervals (CIs).
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158 **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)

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

168 After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to
 169 normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%)
 170 became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal, and
 171 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	0.87 – 1.16
High	164 (22.4)	167 (22.8)			

* reference category

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

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)		

^aBP was categorized using the JNC 7 Guideline

^bBP was categorized using the 2017 ACC/AHA Guideline

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3 184 The associations between gender and SUA levels on BP are shown in Table 3. There
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6 185 was no significant association between gender and BP ($p=0.584$). To examine the association
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8 186 between uric acid and hypertension, we compared SUA levels and morning home BP. The
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10 187 association between SUA levels and BP was statistically significant ($p=0.008$, $RR=1.12$, 95%
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12 188 $CI=1.03-1.22$). The risk of high-normal and high SUA levels becoming prehypertension or
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14 189 hypertension was 1.12 times higher than that of normal SUA levels. Furthermore, the
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16 190 association between SUA levels and BP in men and women is also described in Table 3. In
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18 191 men, SUA levels were not significantly associated with BP ($p=0.805$, $RR=1.02$, 95% $CI=0.88-$
19
20 192 1.19). However, there was a significant association between SUA levels and BP in women
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22 193 ($p=0.001$, $RR=1.21$, 95% $CI=1.09-1.34$). In women, the risk of having prehypertension or
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24 194 hypertension was 1.21 times higher in those who had high-normal and high SUA levels than
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26 195 those with normal SUA levels. Additional analysis using 2017 ACC/AHA guideline for
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28 196 observing the associations between gender and SUA levels on BP also showed similar results
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30 197 with the previous analysis using JNC 7 guideline regarding the significant associations between
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32 198 SUA levels and BP.

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37 199 Figure 1 shows the association between SUA and cardiovascular risk factors. The SUA
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39 200 levels were significantly associated with total cholesterol ($p=0.001$), LDL ($p=0.002$), HDL
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41 201 ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$). Subjects with high-
42
43 202 normal and high SUA levels had significantly higher total cholesterol, LDL, and triglyceride
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45 203 levels than subjects with normal SUA levels. On the other hand, HDL and fasting blood glucose
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47 204 were statistically lower among subjects with high-normal and high SUA levels than among
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49 205 those with normal SUA levels.

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53 206 The relationships between SUA levels and cardiovascular risk factors among men and
54
55 207 women are presented in Figure 2. In men, there were significant differences in BMI ($p<0.001$)
56
57 208 and triglycerides ($p=0.002$) between subjects with normal SUA levels and those with high-
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209 normal and high SUA levels. In women, there was no significant differences in all
 210 cardiovascular risk factors ($p>0.05$) between subjects with normal SUA levels and those with
 211 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 ($p<0.05$)

212
 213 Multivariable analysis was conducted to describe the association between SUA levels
 214 and BP, with adjustment for cardiovascular risk factors. Cardiovascular risk factors such as
 215 BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all taken into
 216 account for adjustment in multiple linear regression (Table 4). BMI, fasting blood glucose, and
 217 SUA levels were significantly associated with BP. BMI was significantly associated with SBP
 218 and DBP both in men ($p<0.001$ and $p<0.001$) and women ($p=0.001$ and $p<0.001$). In addition,
 219 fasting blood glucose was found to be associated with SBP in men ($p=0.036$) and women
 220 ($p<0.001$) and was also associated with DBP in women ($p=0.020$). Regarding SUA levels, SUA
 221 was significantly associated with both SBP and DBP in women ($p<0.001$ and $p<0.001$,
 222 respectively) but not in men.

226 DISCUSSION

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

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

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

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3 251 Similar finding was also found by Zhang, *et al.* which reported that SUA levels were
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5 252 statistically higher in men than in women, though the SUA level did not increase with the age
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7 253 both in men and women.[16] These studies results were consistent with our finding which
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9 254 stated that SUA level was significantly higher in men and SUA level was significantly
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11 255 associated with higher BMI also in men. However, the study population in this study and in the
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13 256 study by Kawabe, *et al.* was different in the age group which were adults (30-59 years) and
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15 257 elderly, respectively.

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19 258 Chen *et al.* reported a different result in a cross-sectional analysis regarding the
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21 259 association between SUA levels and the presence of hypertension when analysed by gender.
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23 260 For the total population, SUA levels had significant associations with hypertension. The levels
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25 261 of SUA had a significant relationship with hypertension in men aged <30 years, 30–40 years,
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27 262 and >40 years but only in women aged >40 years.[8] This situation could be explained with
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29 263 Table 2, which provides the age distribution of women and its association with SUA levels. In
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31 264 Table 2, the proportion of women aged 40–49 years combined with those aged 50–59 years
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33 265 having high-normal and high SUA levels was 24.6%. This age range in women is associated
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35 266 with menopausal problems. A study by Hak *et al.* stated that menopause was associated with
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37 267 an increased risk of incident gout, which may help explain why the age of the women in this
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39 268 study could play a significant role in their SUA levels.[17]

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43 269 Regarding the cardiovascular risk factors, the result of this study found that the SUA
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45 270 levels were significantly associated with total cholesterol ($p=0.001$), LDL ($p=0.002$), HDL
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47 271 ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$), regardless of gender.
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49 272 When the data were analysed by gender, significant differences were found only in BMI and
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51 273 triglycerides and only in men ($p<0.001$ and $p=0.002$, respectively). Another study has shown
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53 274 a stronger association between the increasing of SUA level and cardiovascular mortality among
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55 275 women in healthy subjects compared to men.[18] Meta-analysis showed that there was
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1
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3 276 significant association between hyperuricemia and cardiovascular mortality in women, but not
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5 277 in men.[19] Chen *et al.* reported that SUA levels were significantly associated with the
6
7 278 occurrence of metabolic syndrome and hypertension in the total population. In men, SUA levels
8
9 279 had a positive association with the occurrence of metabolic syndrome in the age groups of <30
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11 280 and 30–40. In women, SUA levels were significantly associated with the occurrence of
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13 281 metabolic syndrome in the age groups of <30 and >40.[8]
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16
17 282 In this study, BMI was associated with blood pressure by both gender and SUA levels
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19 283 in men. This finding was in line with those of a previous study by Droyvold *et al.*, in which the
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21 284 authors reported that an increase in BMI was associated with increased BP in men and
22
23 285 women.[20] With regard to the association between BMI and SUA levels, our findings were
24
25 286 different from those of a report by Rodrigues *et al.*, in which the authors reported a significant
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27 287 correlation between BMI and SUA levels in both men and women.[21] The link between BMI
28
29 288 and hyperuricaemia has not been well elucidated; however, insulin resistance might be the
30
31 289 bridging gap. Obese people are more likely to have metabolic syndrome, and metabolic
32
33 290 syndrome itself is associated with insulin resistance. It is thought that insulin resistance impairs
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35 291 the ability of the kidney to excrete uric acid and therefore leads to hyperuricaemia.[22]
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40 292 This study found that fasting blood glucose was associated with SBP in both genders
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42 293 and with DBP only in women. The same result was observed in a study by Yan *et al.*, which
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44 294 revealed that fasting plasma glucose was independent of both SBP and DBP.[23] Moreover,
45
46 295 fasting blood glucose was also associated with SUA levels, but only in men. This finding is
47
48 296 contradictory to those of a study by Kawamoto *et al.*, which revealed that SUA levels were
49
50 297 associated with fasting plasma glucose in females but not in males.[24] The mechanism of how
51
52 298 this phenomenon occurred remains unclear, and further study is needed to observe a cause-
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54 299 effect relationship. Serum triglycerides were also associated with SUA levels in this study. The
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56 300 relationship between SUA levels and lipid profiles has been described in various studies, but
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3 301 the exact mechanism remains unclear. A study by Peng *et al.* revealed that all lipid profile
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5 302 parameters, including triglycerides but not HDL cholesterol, were associated with SUA
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7 303 levels.[25] SUA levels were associated with both SBP and DBP but only in women. This result
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9
10 304 is similar to those of previous studies.[24, 26] It has been suggested that the mechanism by
11
12 305 which uric acid causes hypertension is due to endothelial dysfunction after oxidative stress
13
14 306 damage to the endothelium during excessive uric acid formation.[26]
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18 19 308 **CONCLUSION**

20
21 309 In conclusion, after 10 years of follow-up, the SUA levels in men are significantly
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23 310 higher than those in women. Moreover, high-normal and high SUA levels were significantly
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25 311 associated with prehypertension and hypertension in women but not in men. For the total
26
27 312 population, SUA levels were significantly associated with the levels of total cholesterol, LDL,
28
29 313 HDL, triglycerides and fasting blood glucose. The BMI was found to be significantly
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31 314 associated with BP in both men and women. Fasting blood glucose is significantly associated
32
33 315 with SBP in men and with SBP and DBP in women; meanwhile, SUA levels were significantly
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35 316 associated with BP only in women.
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40 317 41 42 318 **ACKNOWLEDGEMENTS**

43
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46 320 like to thank Prodia Laboratory for performing laboratory examinations.
47
48

49 321 **CONTRIBUTORS**

50
51 322 LAB and MS composed the idea of the study and arranged the study's design. MS, FI, AW,
52
53 323 and AK obtained the data. ZZ led the statistical analysis with the supervision of MS. MS, LAB
54
55 324 and ZZ wrote the first draft of this paper and all authors read, revised, and approved the final
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57 325 manuscript.
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4

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6
7
8 328 Gadjah Mada, Indonesia.
9

10 329 **DISCLOSURE**
11

12 330 There were no conflicts of interest to disclose.
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15 331 **DATA SHARING STATEMENT**
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17 332 Data may be obtained from the corresponding author upon reasonable request.
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24 335 **REFERENCES**
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3 **410 Figure Legend**
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6 411 Figure 1. The SUA/serum uric acid levels were significantly associated with total cholesterol
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8 412 (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001),
9
10 413 triglycerides (p<0.001) and fasting blood glucose (p=0.030).

11
12 414 Figure 2. Significant differences were found in BMI (p<0.001) and triglycerides (p=0.002)
13
14 415 between subjects with normal SUA levels and those with high-normal and high SUA levels in
15
16 416 men. No significant difference was found (p>0.05) between subjects with normal SUA levels
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18 417 and those with high-normal and high SUA levels in women.
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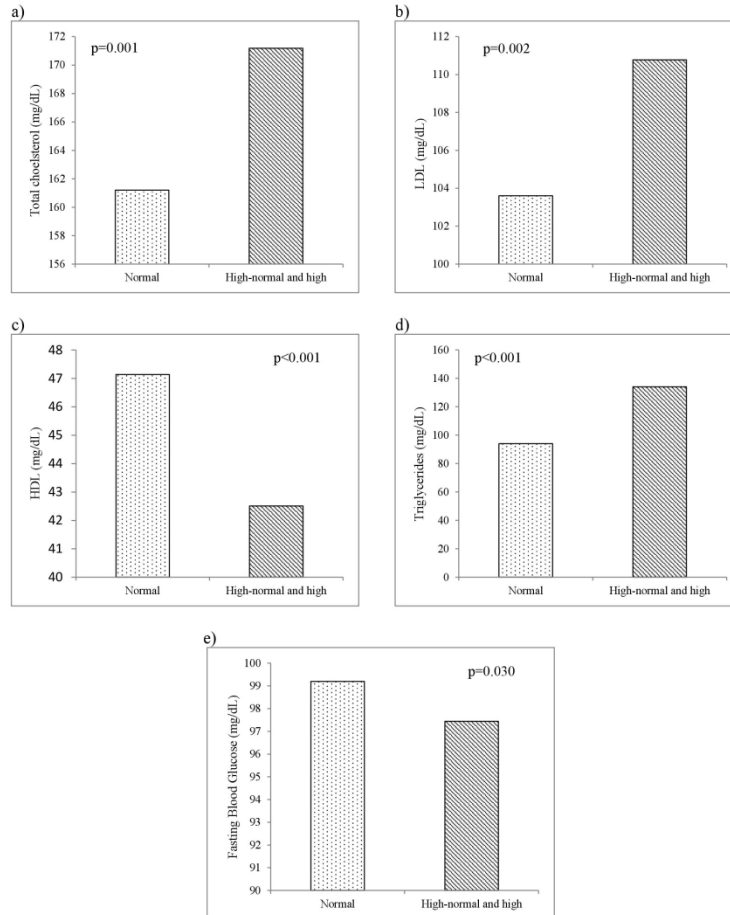


Fig. 1. Mean of cardiovascular risk factors in different serum uric acid levels

210x297mm (300 x 300 DPI)

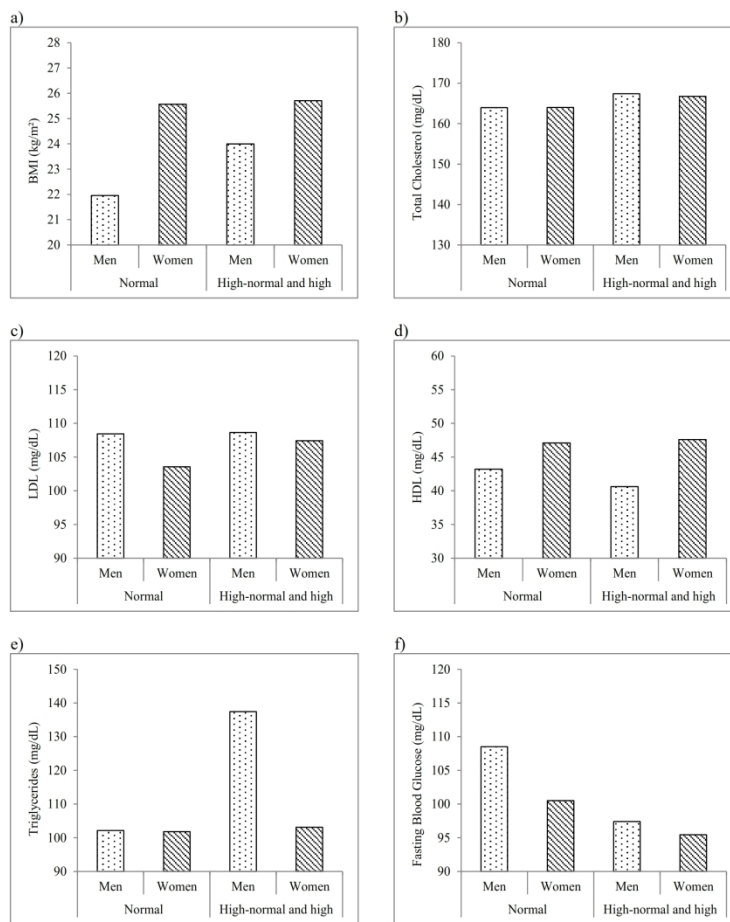


Fig. 2. Mean of cardiovascular risk factors in men and women between normal and high-normal/high SUA levels. In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests. In 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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3 1 **ASSOCIATION OF SERUM URIC ACID, MORNING HOME BLOOD PRESSURE**
4
5 2 **AND CARDIOVASCULAR RISK FACTORS IN A PREHYPERTENSIVE**
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7 3 **POPULATION**
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12 5 **Lucky A Bawazier^{1,2}, Mochammad Sja'bani¹, Freddie Irijanto^{1,3}, Zulaela^{1,4}, Agus**
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14 6 **Widiatmoko^{1,5}, Abdul Kholiq^{1,6}, Yasuhiko Tomino⁷**
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59 27 **Word count: 3537**
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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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3 52 **Conclusion:** We concluded that serum uric acid levels were significantly associated with
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5 53 prehypertension and hypertension only in women. Blood pressure was associated with age,
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7 54 body mass index, serum uric acid levels and fasting blood glucose in women, whereas in
8
9 55 men, blood pressure was only associated with age body mass index.
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15 57 **Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences
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19 59 **STRENGTH AND LIMITATION OF THIS STUDY**

- 20
21 60 • This study followed up the changes of blood pressure on subjects for over 10 years.
22
23 61 • The association between serum uric acid, blood pressure, and cardiovascular risk factors
24
25 62 were analyzed based on gender.
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27 63 • The analysis' were also performed by using both JNC 7 and 2017 ACC/AHA guideline.
28
29 64 • This study could not present the changes of all measured value over 10 year period
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31 65 because in the prior study in 2007, these laboratory value were not examined, except for
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33 66 blood pressure.
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68 INTRODUCTION

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

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3 93 predictive factor for cardiovascular risk in individual without hypertension and diabetic.[17]
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5 94 SUA also being reported to have stronger association on cardiovascular risk [18] and risk of
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8 95 cardiovascular disease mortality [19,20] in women than in men.

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10 96 Therefore, the aim of this study was to observe the progression from prehypertension
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12 97 to hypertension after 10 years of follow-up and its association with SUA as well as other
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15 98 cardiovascular risk factors.

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100 **METHODS**

101 *Study Design*

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

107 *Study Population*

108 We pooled data from participants enrolled in the 2007 Mlati Study Database. The
109 sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages
110 in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion
111 criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg
112 and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49
113 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of
114 the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected
115 as participants in the current study by simple random sampling using statistical software. All
116 1500 subjects were invited to have a physical and laboratory examination; however, only 733
117 subjects who participated in the sampling were examined (the other subjects who did not

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3 118 show up during the laboratory examination were due to the change of residential area or
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5 119 death or any other unknown reasons and were excluded from this study). All subjects did not
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8 120 take any drugs lowering BP and SUA. All subjects were provided informed consent at the
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10 121 beginning of the study (Figure 1).

12 122 ***Patient and Public Involvement***

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15 123 Patient were not involved in any of the design, analysis, and presentation of the study results.

16 124 ***Definition of Prehypertension and Hypertension***

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19 125 The definitions of prehypertension and hypertension were based on the Seventh
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21 126 Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only
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23 127 their treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of
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25 128 80–89 mmHg are defined as prehypertension, while SBP of ≥ 140 mmHg and/or DBP of ≥ 90
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27 129 mmHg are defined as hypertension.[21]

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30 130 For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as
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32 131 follows: (1) normal BP = SBP < 120 mmHg and DBP < 80 mmHg, (2) elevated BP = SBP
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34 132 120–129 mmHg and DBP < 80 mmHg, (3) stage 1 hypertension = SBP 130–139 mmHg or
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36 133 DBP 80–89 mmHg, and (4) stage 2 hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.[22]

37 134 ***Serum Uric Acid Cut-off Point***

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40 135 Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3
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42 136 categories: normal (< 5 mg/dL), high-normal (5–7 mg/dL), and high (≥ 7 mg/dL).[23]

43 137 ***Data Collection***

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46 138 The data collection was conducted twice during the study period. The first data
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48 139 collection was conducted in 2007 to collect the prehypertension population (n=4,190). The
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50 140 second data collection was performed in 2017 to collect samples from the Mlati Study
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52 141 Database by the random sampling method (n=733).

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3 142 In 2007, interviews were conducted on 12,073 subjects to obtain demographic data
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5 143 (e.g. sex and age), family history and to perform physical and laboratory examinations.
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7 144 Physical examinations, which included measurements of morning home BP (measured by
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9 145 using sphygmomanometer), body weight, body height, upper-hand circumference, wrist
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11 146 circumference, abdominal circumference and hip circumference, were conducted on day 1 in
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13 147 subject's house or their neighbor. BP measurements were performed in the morning (at 6 – 8
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15 148 a.m) by the medical team for 2 times (or until stable BP were obtained) while subjects in
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17 149 sitting position. On day 2, we examined morning home BP and took urine and blood samples.
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22 150 In 2017, we collected data from 733 subjects, including interviews of demographic
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24 151 data, physical and laboratory examinations. On the first day, subjects were interviewed,
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26 152 physically examined, and given urine containers for one-time urine samples, as well as for a
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28 153 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The
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30 154 physical examination was performed by medical team, consisted of a morning home BP
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32 155 measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained),
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34 156 while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure
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36 157 monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan) and measurements of
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38 158 body weight, body height, upper-hand circumference, wrist circumference, abdominal
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40 159 circumference and hip circumference. On the second day, subjects who were in fasting
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42 160 condition were invited to come to the neighbor's hall in the morning and physically examined
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44 161 for BP again (at 6 – 8 a.m) and drawn for their blood. Urine and blood samples were
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46 162 examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine sample
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48 163 was collected to measure uric acid excretion and creatinine, and a blood sample was collected
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50 164 to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol, low density
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52 165 lipoprotein/LDL-C, high density lipoprotein/HDL-C and triglycerides), and fasting blood
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54 166 glucose levels.
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3 167 ***Statistical Analysis***
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5 168 All data presented later in results section were from data collection in 2017. Data were
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7
8 169 analysed using IBM SPSS Statistics 20. The data consisted of continuous and categorical
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10 170 data, which were expressed as the mean (SD) for continuous data and as numbers and
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12 171 percentages for categorical data. The continuous variables were analysed and compared by
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14 172 independent samples t-tests and nonparametric Mann-Whitney U tests. The categorical
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16 173 variables were analysed and compared by Pearson chi-square tests. Multivariable analysis
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18 174 was performed using multiple linear regression to describe the association between SUA
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20 175 levels and BP, with adjustment for age and cardiovascular risk factors. The significance of
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22 176 associations between categorical variables and numerical variables were determined using
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24 177 95% confidence intervals (CIs).
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178 **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

179 The subjects of this study consisted of 733 adults (aged 30–59 years) living in the
 180 Mlati Subdistrict; 306 (41.75%) and 427 (58.25%) were men and women, respectively. The
 181 characteristics of the subjects (by gender) are presented in Table 1. There was no significant
 182 difference in age, SBP, DBP, total cholesterol, LDL and fasting blood glucose between men
 183 and women (p>0.05). Significant differences were found in body mass index (BMI)
 184 (p<0.001), SUA levels (p<0.001), HDL (p<0.001) and triglycerides (p<0.001). BMI and
 185 HDL were significantly higher in women, whereas SUA levels and triglycerides were
 186 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)

187 After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to
 188 normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%)
 189 became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal,
 190 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	0.87 – 1.16
High	164 (22.4)	167 (22.8)			

* reference category

^aBMI= body mass index, <18.5kg/m² = underweight, 18.5-24.9 kg/m² = normal, 25-29.9 kg/m² = overweight, >30 kg/m² = obese

^bUric acid excretion, <435.08 mg/day = normal, ≥435.08 mg/day = high

^cUric acid concentration (mg per 100 ml of urine), <46.63 mg% = normal, ≥46.63 mg% = high

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

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3 196 levels only in women aged 50–59 years ($p < 0.001$, $RR = 2.08$, 95% $CI = 1.36–3.15$).
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5 197 Additionally, there was a significant association between SUA levels and uric acid excretion
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7 198 by 24-h urine ($p = 0.002$, $RR = 1.32$, 95% $CI = 1.10–1.57$). On the other hand, no significant
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9 199 association was observed between SUA levels and BMI ($p = 0.153$, $RR = 1.1$, 95% $CI = 0.96–$
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11 200 1.32) or between SUA levels and uric acid concentration ($p = 0.100$, $RR = 0.786$, 95%
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13 201 $CI = 0.59–1.05$) (Table 3).
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17 202 The associations between gender and SUA levels on BP are shown in Table 4. There
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19 203 was no significant association between gender and BP ($p = 0.584$). To examine the association
20
21 204 between uric acid and hypertension, we compared SUA levels and morning home BP. The
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23 205 association between SUA levels and BP was statistically significant ($p = 0.008$, $RR = 1.12$, 95%
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25 206 $CI = 1.03–1.22$). The risk of subjects with high-normal or high SUA levels for becoming
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27 207 prehypertension or hypertension was 1.12 times higher than those who has normal SUA
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29 208 levels. Furthermore, the association between SUA levels and BP in men and women is also
30
31 209 described in Table 4. In men, SUA levels were not significantly associated with BP ($p = 0.805$,
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33 210 $RR = 1.02$, 95% $CI = 0.88–1.19$). However, there was a significant association between SUA
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35 211 levels and BP in women ($p = 0.001$, $RR = 1.21$, 95% $CI = 1.09–1.34$). In women, the risk of
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37 212 having prehypertension or hypertension was 1.21 times higher in those who had high-normal
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39 213 or high SUA levels than those with normal SUA levels. Additional analysis using 2017
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41 214 ACC/AHA guideline for observing the associations between gender and SUA levels on BP
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43 215 also showed similar results with the previous analysis using JNC 7 guideline regarding the
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45 216 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 \geq 140 mmHg and/or DBP of \geq 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 \geq 140 mmHg or DBP \geq 90 mmHg)

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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3 234 such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all
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5 235 taken into account for adjustment in multiple linear regression (Table 5). Age, BMI, fasting
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7 236 blood glucose, and SUA levels were significantly associated with BP. Significant association
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10 237 were found between age and SBP both in men ($p<0.001$) and women ($p<0.001$), and DBP
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12 238 only in men ($p<0.001$). BMI was significantly associated with SBP and DBP both in men
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14 239 ($p<0.001$ and $p<0.001$) and women ($p<0.001$ and $p<0.001$). In addition, fasting blood glucose
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16 240 was found to be associated with SBP and DBP in women ($p=0.001$ and $p=0.020$). Regarding
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18 241 SUA levels, SUA was significantly associated with both SBP and DBP in women ($p<0.001$
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20 242 and $p<0.001$, respectively) but such association was not found in men.
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27 244 **DISCUSSION**

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30 245 This study consisted of two parts of data collection. The first data collection was
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32 246 performed in 2007 to gather data on the prehypertension population ($n=4,190$); this study was
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34 247 later called the “Mlati Study Database”. In 2017, after 10 years, the second data collection
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36 248 was performed to gather samples from the Mlati Study Database by a random sampling
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38 249 method ($n=733$) to show the change in BP status from prehypertension to hypertension. The
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40 250 data collection in 2017 also aimed to show the association between uric acid (serum, urinary
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42 251 excretion, and concentrate) and hypertension.
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46 252 The results of our study showed that gender and uric acid excretion (by 24-h urine)
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48 253 were significantly associated with SUA levels. The mean SUA levels in men were
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50 254 significantly higher than those in women. In addition, subjects with high-normal and high
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52 255 SUA levels had a risk of having prehypertension and hypertension that was 1.12 times higher
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54 256 than those with normal SUA levels. When analysed by gender, high-normal and high SUA
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56 257 levels were significantly associated with prehypertension and hypertension only in women.
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58 258 The relationship between SUA levels and the development of hypertension or renal disease
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3 259 had been shown in several previous studies. This relationship was significantly higher in
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5 260 women than in men.[15,24]
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8 261 The study by Kawabe *et al.* revealed that in women, the older the age was, the higher
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10 262 the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an
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12 263 increase in the quartile of SUA along with higher BMI was only found in men but not in
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14 264 women. Additionally, the mean value of SUA in men was higher than in women.[25] These
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16 265 results were consistent with our finding that SUA levels were significantly higher in men and
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18 266 that SUA levels were significantly associated with higher BMI in men. However, the study
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20 267 populations in this study and in the study by Kawabe *et al.* were different in terms of the age
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22 268 group examined, which were adults (30–59 years old) and elderly adults, respectively.[25]
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24 269 Similar finding was also found by Zhang, *et al.* which reported that SUA levels were
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26 270 statistically higher in men than in women, though the SUA level did not increase with the age
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28 271 both in men and women.[26] These studies results were consistent with our finding which
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30 272 stated that SUA level was significantly higher in men and SUA level was significantly
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32 273 associated with higher BMI also in men. However, the study population in this study and in
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34 274 the study by Kawabe, *et al.* was different in the age group which were adults (30-59 years)
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36 275 and elderly, respectively.
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42 276 Chen *et al.* reported a different result in a cross-sectional analysis regarding the
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44 277 association between SUA levels and the presence of hypertension when analysed by gender.
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46 278 For the total population, SUA levels had significant associations with hypertension. The
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48 279 levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40
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50 280 years, and >40 years but only in women aged >40 years.[10] This situation could be
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52 281 explained with Table 3, which provides the age distribution of women and its association
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54 282 with SUA levels. In Table 3, the proportion of women aged 40–49 years combined with those
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56 283 aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in
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3 284 women is associated with menopausal problems. A study by Hak *et al.* stated that menopause
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5 285 was associated with an increased risk of incident gout, which may help explain why the age
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7 286 of the women in this study could play a significant role in their SUA levels.[27]
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10 287 Regarding the cardiovascular risk factors, the result of this study found that the SUA
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12 288 levels were significantly associated with total cholesterol ($p=0.001$), LDL ($p=0.002$), HDL
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14 289 ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$), regardless of gender.
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16 290 When the data were analysed by gender, significant differences were found only in BMI and
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18 291 triglycerides and only in men ($p<0.001$ and $p=0.002$, respectively). Another study has shown
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20 292 a stronger association between the increasing of SUA level and cardiovascular mortality
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22 293 among women in healthy subjects compared to men.[28] Meta-analysis showed that there
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24 294 was significant association between hyperuricemia and cardiovascular mortality in women,
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26 295 but not in men.[29] Chen *et al.* reported that SUA levels were significantly associated with
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28 296 the occurrence of metabolic syndrome and hypertension in the total population. In men, SUA
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30 297 levels had a positive association with the occurrence of metabolic syndrome in the age groups
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32 298 of <30 and $30-40$. In women, SUA levels were significantly associated with the occurrence
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34 299 of metabolic syndrome in the age groups of <30 and >40 .[10]
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40 300 In this study, BMI was significantly associated with SBP and DBP in both gender.
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42 301 This finding was in line with those of a previous study by Droyvold *et al.*, in which the
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44 302 authors reported that an increase in BMI was associated with increased BP in men and
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46 303 women.[30] With regard to the association between BMI and SUA levels, our findings were
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48 304 different from those of a report by Rodrigues *et al.*, in which the authors reported a
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50 305 significant correlation between BMI and SUA levels in both men and women.[31] The link
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52 306 between BMI and hyperuricaemia has not been well elucidated; however, insulin resistance
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54 307 might be the bridging gap. Obese people are more likely to have metabolic syndrome, and
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56 308 metabolic syndrome itself is associated with insulin resistance. It is thought that insulin
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3 309 resistance impairs the ability of the kidney to excrete uric acid and therefore leads to
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5 310 hyperuricaemia.[32]
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8 311 This study found that fasting blood glucose was associated with SBP and DBP only in
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10 312 women. The same result was observed in a study by Yan *et al.*, which revealed that fasting
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12 313 plasma glucose was independent of both SBP and DBP.[33] Fasting blood glucose was also
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14 314 associated with SUA levels, but when analysed by gender, no significant different was found.
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16 315 This finding is contradictory to those of a study by Kawamoto *et al.*, which revealed that
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18 316 SUA levels were associated with fasting plasma glucose in females.[34] The mechanism of
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20 317 how this phenomenon occurred remains unclear, and further study is needed to observe a
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22 318 cause-effect relationship. Serum triglycerides were also associated with SUA levels in this
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24 319 study. The relationship between SUA levels and lipid profiles has been described in various
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26 320 studies, but the exact mechanism remains unclear. A study by Peng *et al.* revealed that all
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28 321 lipid profile parameters, including triglycerides but not HDL cholesterol, were associated
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30 322 with SUA levels.[35] SUA levels were associated with both SBP and DBP but only in
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32 323 women. This result is similar to those of previous studies.[34, 36] It has been suggested that
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34 324 the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after
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36 325 oxidative stress damage to the endothelium during excessive uric acid formation.[36]
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42 326 There were several limitations in this study. First, subject in this study were collected
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44 327 from database made in 2007. From 1500 subjects randomly selected in the beginning of this
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46 328 study, only 733 subjects joined and attend the 2-days examination. More than half of the
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48 329 selected subjects did not attend the examination invitation due to several reasons, thus, this
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50 330 had lessened the total samples of subjects of this study. Second, this study could not present
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52 331 the changes of all measured value over 10-year period because in the prior study in 2007,
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54 332 these laboratory value were not examined, except for blood pressure. Therefore, only the
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56 333 changes on blood pressure which can be presented on the results. Third, the instruments used
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3 334 to measure blood pressure in 2007 and 2017 were different. In 2007, we used
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5 335 sphygmomanometer, whereas in 2017 we used digital automatic blood pressure monitor.
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8 336 Thus, this may lead bias in blood pressure data measurement between 2007 and 2017.
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11 338 **CONCLUSION**

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14 339 In conclusion, after 10 years of follow-up, the SUA levels in men are significantly
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16 340 higher than those in women. Moreover, high-normal and high SUA levels were significantly
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18 341 associated with prehypertension and hypertension in women but not in men. For the total
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20 342 population, SUA levels were significantly associated with the levels of total cholesterol,
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22 343 LDL, HDL, triglycerides and fasting blood glucose. The BMI was found to be significantly
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24 344 associated with BP in both men and women. Fasting blood glucose is significantly associated
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26 345 with SBP in men and with SBP and DBP in women; meanwhile, SUA levels were
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28 346 significantly associated with BP only in women.
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34 348 **ACKNOWLEDGEMENTS**

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38
39 350 also like to thank Prodia Laboratory for performing laboratory examinations.
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41

42 351 **CONTRIBUTORS**

43
44 352 LAB and MS composed the idea of the study and arranged the study's design. MS, FI, AW,
45
46 353 and AK obtained the data. ZZ led the statistical analysis with the supervision of MS. MS,
47
48 354 LAB and ZZ wrote the first draft of this paper and all authors read, revised, and approved the
49
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58 358 Gadjah Mada, Indonesia.
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3 359 **COMPETING INTEREST**
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5 360 There were no conflicts of interest to disclose.
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8 361 **DATA SHARING STATEMENT**
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10 362 Data may be obtained from the corresponding author upon reasonable request.
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3 **471 Figure Legend**
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6 472 Figure 2. The SUA/serum uric acid levels were significantly associated with total cholesterol
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8 473 ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$),
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10 474 triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$). The SUA category: normal (<5
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12 475 mg/dL), high-normal ($5-7$ mg/dL), and high (≥ 7 mg/dL).

14 476 Figure 3. Significant differences were found in BMI ($p<0.001$) and triglycerides ($p=0.002$)
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16
17 477 between subjects with normal SUA levels and those with high-normal and high SUA levels in
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19 478 men. No significant difference was found ($p>0.05$) between subjects with normal SUA levels
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21 479 and those with high-normal and high SUA levels in women. The SUA category: normal (<5
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23 480 mg/dL), high-normal ($5-7$ mg/dL), and high (≥ 7 mg/dL).
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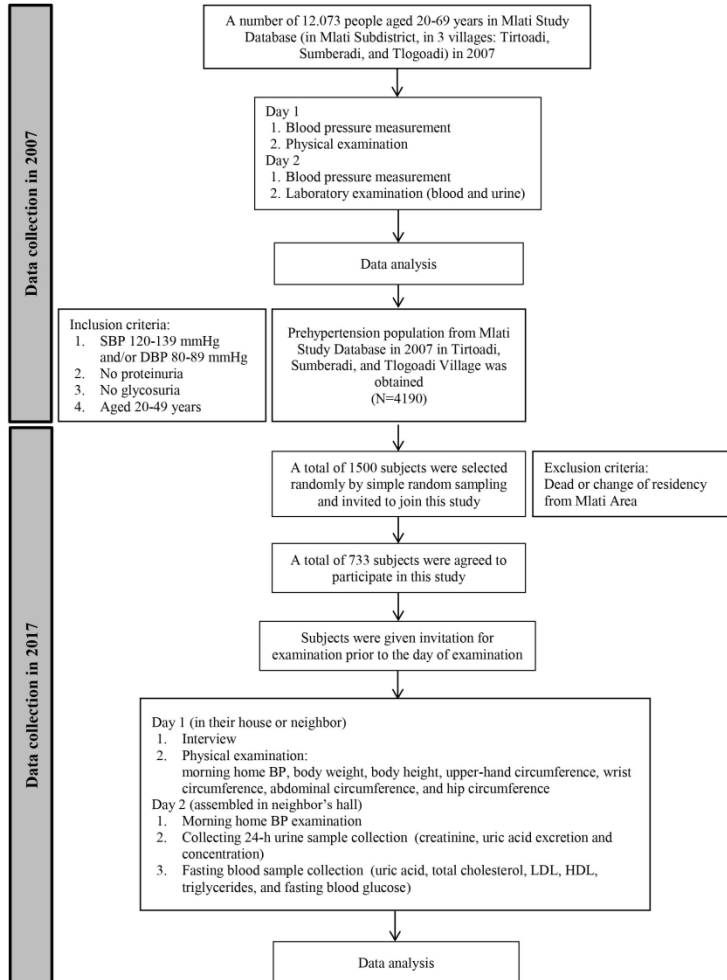


Fig 1. Study Flow Chart

Fig 1. Study Flow Chart

210x297mm (300 x 300 DPI)

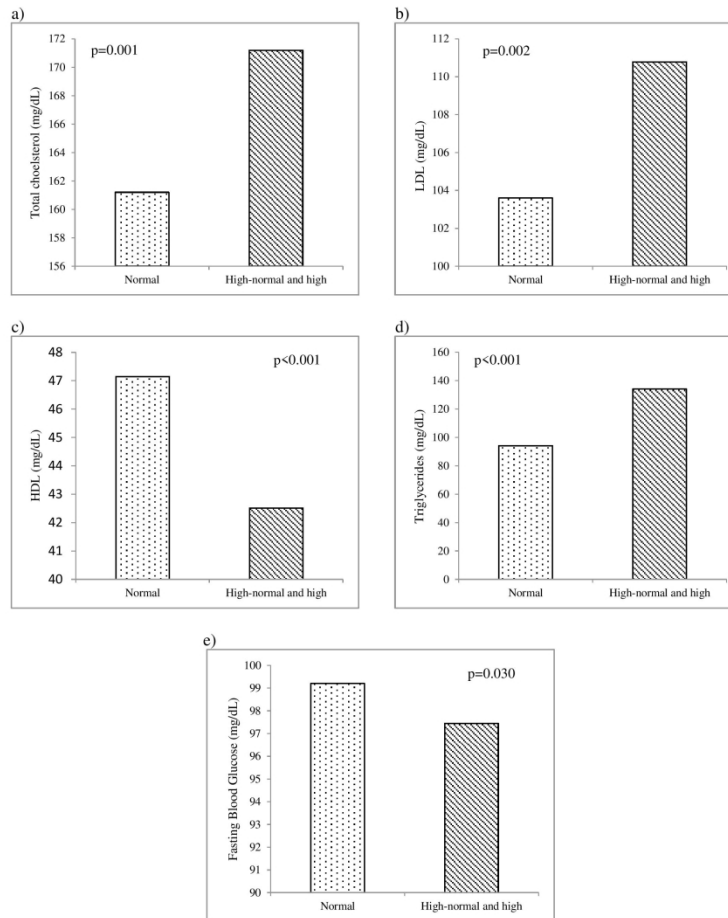


Fig. 2. Mean of cardiovascular risk factors in different serum uric acid levels
The SUA/serum uric acid levels were significantly associated with total cholesterol ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$), triglycerides ($p<0.001$) and fasting blood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

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

210x297mm (300 x 300 DPI)

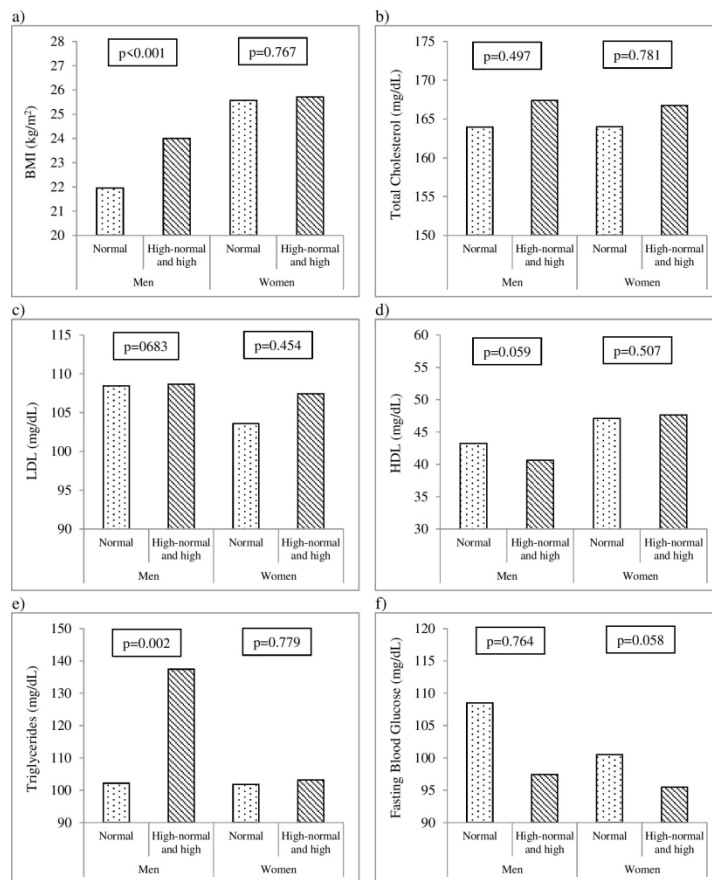


Fig. 3. Mean of cardiovascular risk factors in men and women between normal and high-normal/high SUA levels. In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests. In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

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.

BMJ Open

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

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Hypertension < CARDIOLOGY, PUBLIC HEALTH, EPIDEMIOLOGY

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3 1 **ASSOCIATION OF SERUM URIC ACID, MORNING HOME BLOOD PRESSURE**
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5 2 **AND CARDIOVASCULAR RISK FACTORS IN A POPULATION WITH PREVIOUS**
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7 **PREHYPERTENSION**
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12 5 **Lucky A Bawazier^{1,2}, Mochammad Sja'bani¹, Freddie Irijanto^{1,3}, Zulaela^{1,4}, Agus**
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14 6 **Widiatmoko^{1,5}, Abdul Kholiq^{1,6}, Yasuhiko Tomino⁷**
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59 27 **Word count: 3801**
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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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3 52 **Conclusion:** We concluded that after 10 years, of 733 prehypertensive subjects, 31.1%
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6 53 became hypertensive. The SUA levels in men are significantly higher than those in women.
7
8 54 Moreover, High-normal and high SUA levels were significantly associated with
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10 55 prehypertension and hypertension in women but not in men.
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15 57 **Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences
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19 59 **STRENGTH AND LIMITATION OF THIS STUDY**

- 20
21 60
- 22 • This study followed up the changes in blood pressure on subjects for over 10 years.
 - 23
 - 24 61 • The association between serum uric acid, blood pressure, and cardiovascular risk factors
25
26 62 were analysed based on gender.
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 - 29 63 • The analysis' was also performed by using both JNC 7 and 2017 ACC/AHA guideline.
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31 64 • This study could not present the changes of all measured values over 10 year period
32
33 65 because, in the prior study in 2007, these laboratory values were not examined, except
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35 66 for blood pressure.
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68 INTRODUCTION

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

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3 93 predictive factor for cardiovascular risk in individuals without hypertension and diabetes.[17]
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5 94 Serum uric acid also being reported to have a stronger association with cardiovascular risk
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7 [18] and risk of cardiovascular disease mortality [19,20] in women than in men.
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10 96 Therefore, the aim of this study was to observe the progression from prehypertension
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12 97 to hypertension after 10 years (2007-2017) and the association of BP with SUA as well as
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14 98 other cardiovascular risk factors in 2017.
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100 **METHODS**

101 *Study Design*

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

107 *Study Population*

108 We pooled data from participants enrolled in the 2007 Mlati Study Database. The
109 sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages
110 in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion
111 criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg
112 and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49
113 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of
114 the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected
115 as participants in the current study by simple random sampling using statistical software. All
116 1500 subjects were invited to have a physical and laboratory examination; however, only 733
117 subjects who participated in the sampling were examined (the other subjects who did not
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3 118 show up during the laboratory examination were due to the change of residential area or
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5 119 death or any other unknown reasons and were excluded from this study). All subjects did not
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8 120 take any drugs lowering BP and SUA. All subjects were provided informed consent at the
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10 121 beginning of the study (Figure 1).

12 122 ***Patient and Public Involvement***

14 123 Patients were not involved in any of the design, analysis, and presentation of the study
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16
17 124 results.

19 125 ***Definition of Prehypertension and Hypertension***

21 126 The definitions of prehypertension and hypertension were based on the Seventh
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24 127 Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only
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26 128 their treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of
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28 129 80–89 mmHg are defined as prehypertension, while SBP of ≥ 140 mmHg and/or DBP of ≥ 90
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30 130 mmHg are defined as hypertension.[21]

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33 131 For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as
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35 132 follows: (1) normal BP = SBP < 120 mmHg and DBP < 80 mmHg, (2) elevated BP = SBP
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37 133 120–129 mmHg and DBP < 80 mmHg, (3) stage 1 hypertension = SBP 130–139 mmHg or
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39 134 DBP 80–89 mmHg, and (4) stage 2 hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.[22]

42 135 ***Serum Uric Acid Cut-off Point***

44 136 Based on the study by Sja'bani (2014), the cut-off point of SUA was divided into 3
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46 137 categories: normal (< 5 mg/dL), high-normal (5–7 mg/dL), and high (≥ 7 mg/dL).[23]

49 138 ***Data Collection***

51 139 The data collection was conducted twice during the study period. The first data
52
53 140 collection was conducted in 2007 to collect the prehypertension population (n=4,190). The
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55 141 second data collection was performed in 2017 to collect samples from the Mlati Study
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58 142 Database by the random sampling method (n=733).

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3 143 In 2007, interviews were conducted on 12,073 subjects to obtain demographic data
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5 144 (e.g. sex and age), family history of hypertension and diabetes mellitus, patients' history of
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7 145 diabetes mellitus, patients' history of consuming hypertension and uric acid drugs, and to
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9 146 perform physical and laboratory examinations. Physical examinations, which included
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11 147 measurements of morning home BP (measured by using sphygmomanometer), body weight,
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13 148 body height, upper-hand circumference, wrist circumference, abdominal circumference, and
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15 149 hip circumference, were conducted on day 1 in subject's house or their neighbor. BP
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17 150 measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times
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19 151 (or until stable BP were obtained) while subjects in sitting position. On day 2, we examined
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21 152 morning home BP and took urine and blood samples.
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26 153 In 2017, we collected data from 733 subjects, including interviews of demographic
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28 154 data, physical and laboratory examinations. On the first day, subjects were interviewed,
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30 155 physically examined, and given urine containers for one-time urine samples, as well as for a
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32 156 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The
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34 157 physical examination was performed by the medical team, consisting of a morning home BP
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36 158 measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained),
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38 159 while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure
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40 160 monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan) and measurements of
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42 161 body weight, body height, upper-hand circumference, wrist circumference, abdominal
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44 162 circumference, and hip circumference. On the second day, subjects who were in fasting
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46 163 condition were invited to come to the neighbour's hall in the morning and physically
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48 164 examined for BP again (at 6 – 8 a.m) and drawn for their blood. Urine and blood samples
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50 165 were examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine
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52 166 sample was collected to measure uric acid excretion and creatinine, and a blood sample was
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54 167 collected to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol,
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3 168 low-density lipoprotein/LDL-C, high-density lipoprotein/HDL-C and triglycerides), and
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5 169 fasting blood glucose levels.
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8 170 *Statistical Analysis*

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10 171 The outcomes of this study were presented in two primary analyses which were (1)
11
12 172 blood pressure changes during the period of 2007-2017 to measure the progression from
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14 173 prehypertension (2007) to hypertension (2017) (Table 2), and (2) the association of current
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16 174 BP with SUA levels and cardiovascular risk factors (Table 4 and Table 5). Additional
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18 175 analyses were also being performed to observed the SUA association with cardiovascular risk
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20 176 factors (Figure 2 and Figure 3). The data analyses were mostly performed based on gender in
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22 177 order to know about the gender differences in the analyses mentioned above.
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26 178 Data presented later in the results section were collected in 2007 and 2017. Data were
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28 179 analysed using IBM SPSS Statistics for Windows, Version 22.0.[24] The data consisted of
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30 180 continuous and categorical data, which were expressed as the mean (SD) for continuous data
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32 181 and as numbers and percentages for categorical data. The continuous variables were analysed
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34 182 and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The
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36 183 categorical variables were analysed and compared by Pearson chi-square tests. Multivariable
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38 184 analysis was performed using multiple linear regressions to describe the association between
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40 185 SUA levels and BP, with adjustment for age and cardiovascular risk factors. The significance
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42 186 of associations between categorical variables and numerical variables was determined using
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44 187 95% confidence intervals (CIs).
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189 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)

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

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199 After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to
200 normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%)
201 became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal,
202 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	0.87 – 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/m² = underweight, 18.5-24.9 kg/m² = normal, 25-29.9 kg/m² = overweight, >30 kg/m² = 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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3 204 In men, 32.3% of the subjects had high-normal or high levels of SUA, while in
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6 205 women, only 17.3% had high-normal or high levels of SUA. There was a significant
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8 206 difference in SUA between men and women ($p < 0.001$, $RR = 2.60$, $95\% \text{ CI} = 2.22\text{--}3.05$). When
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10 207 gender was further analysed by age distribution, age was significantly associated with SUA
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12 208 levels only in women aged 50–59 years ($p < 0.001$, $RR = 2.08$, $95\% \text{ CI} = 1.36\text{--}3.15$).
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14 209 Additionally, there was a significant association between SUA levels and uric acid excretion
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16 210 by 24-h urine ($p = 0.002$, $RR = 1.32$, $95\% \text{ CI} = 1.10\text{--}1.57$). On the other hand, no significant
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18 211 association was observed between SUA levels and BMI ($p = 0.153$, $RR = 1.1$, $95\% \text{ CI} = 0.96\text{--}$
19
20 212 1.32) or between SUA levels and uric acid concentration ($p = 0.100$, $RR = 0.786$, 95%
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22 213 $\text{CI} = 0.59\text{--}1.05$) (Table 3).

26 214 The associations between gender and SUA levels on BP are shown in Table 4. There
27
28 215 was no significant association between gender and BP ($p = 0.584$). To examine the association
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30 216 between uric acid and hypertension, we compared SUA levels and morning home BP. The
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32 217 association between SUA levels and BP was statistically significant ($p = 0.008$, $RR = 1.12$, 95%
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34 218 $\text{CI} = 1.03\text{--}1.22$). In subjects with previous history of prehypertension, high-normal SUA or
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36 219 high SUA levels were associated with current prehypertension or hypertension. Furthermore,
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38 220 the association between SUA levels and BP in men and women is also described in Table 4.
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40 221 In men, SUA levels were not significantly associated with BP ($p = 0.805$, $RR = 1.02$, 95%
41
42 222 $\text{CI} = 0.88\text{--}1.19$). However, there was a significant association between SUA levels and BP in
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44 223 women ($p = 0.001$, $RR = 1.21$, $95\% \text{ CI} = 1.09\text{--}1.34$). In women, the risk of having
45
46 224 prehypertension or hypertension was 1.21 times higher in those who had high-normal or high
47
48 225 SUA levels than those with normal SUA levels. Additional analysis using the 2017
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50 226 ACC/AHA guideline for observing the associations between gender and SUA levels on BP
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52 227 also showed similar results with the previous analysis using JNC 7 guideline regarding the
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54 228 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

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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3 246 such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all
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5 247 taken into account for adjustment in multiple linear regression (Table 5). Age, BMI, fasting
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7 248 blood glucose, and SUA levels were significantly associated with BP. Significant
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9 249 associations were found between age and SBP both in men ($p<0.001$) and women ($p<0.001$),
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11 250 and DBP only in men ($p<0.001$). BMI was significantly associated with SBP and DBP both
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13 251 in men ($p<0.001$ and $p<0.001$) and women ($p<0.001$ and $p<0.001$). In addition, fasting blood
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15 252 glucose was found to be associated with SBP and DBP in women ($p=0.001$ and $p=0.020$).
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17 253 Regarding SUA levels, SUA was significantly associated with both SBP and DBP in women
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19 254 ($p<0.001$ and $p<0.001$, respectively) but such association was not found in men.
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27 256 **DISCUSSION**

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30 257 This study consisted of two parts of data collection. The first data collection was
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32 258 performed in 2007 to gather data on the prehypertension population ($n=4,190$); this study was
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34 259 later called the “Mlati Study Database”. In 2017, after 10 years, the second data collection
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36 260 was performed to gather samples from the Mlati Study Database by a random sampling
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38 261 method ($n=733$) to show the change in BP status from prehypertension to hypertension. The
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40 262 data collection in 2017 also aimed to show the association between uric acid (serum, urinary
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42 263 excretion, and concentrate) and hypertension.
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46 264 The results of our study showed that gender and uric acid excretion (by 24-h urine)
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48 265 were significantly associated with SUA levels. The mean SUA levels in men were
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50 266 significantly higher than those in women. In addition, subjects with high-normal and high
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52 267 SUA levels had a risk of having prehypertension and hypertension that was 1.12 times higher
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54 268 than those with normal SUA levels. When analysed by gender, high-normal and high SUA
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56 269 levels were significantly associated with prehypertension and hypertension only in women.
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59 270 The relationship between SUA levels and the development of hypertension or renal disease
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3 271 had been shown in several previous studies. This relationship was significantly higher in
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5 272 women than in men.[15,25]
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8 273 The study by Kawabe *et al.* revealed that in women, the older the age was, the higher
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10 274 the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an
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12 275 increase in the quartile of SUA along with higher BMI was only found in men but not in
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14 276 women. Additionally, the mean value of SUA in men was higher than in women.[26] These
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16 277 results were consistent with our finding that SUA levels were significantly higher in men and
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18 278 that SUA levels were significantly associated with higher BMI in men. However, the study
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20 279 populations in this study and the study by Kawabe *et al.* were different in terms of the age
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22 280 group examined, which were adults (30–59 years old) and elderly adults, respectively.[26] A
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24 281 similar finding was also found by Zhang, *et al.* which reported that SUA levels were
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26 282 statistically higher in men than in women, though the SUA level did not increase with the age
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28 283 both in men and women.[27] These studies' results were consistent with our finding which
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30 284 stated that SUA level was significantly higher in men and SUA level was significantly
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32 285 associated with higher BMI also in men. However, the study population in this study and the
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34 286 study by Kawabe, *et al.* was different in the age group which was adults (30-59 years) and
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36 287 elderly, respectively.
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42 288 Chen *et al.* reported a different result in a cross-sectional analysis regarding the
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44 289 association between SUA levels and the presence of hypertension when analysed by gender.
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46 290 For the total population, SUA levels had significant associations with hypertension. The
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48 291 levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40
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50 292 years, and >40 years but only in women aged >40 years.[10] This situation could be
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52 293 explained in Table 3, which provides the age distribution of women and its association with
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54 294 SUA levels. In Table 3, the proportion of women aged 40–49 years combined with those
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56 295 aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in
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3 296 women is associated with menopausal problems. A study by Hak *et al.* stated that menopause
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5 297 was associated with an increased risk of incident gout, which may help explain why the age
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7 298 of the women in this study could play a significant role in their SUA levels.[28]
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10 299 Regarding the cardiovascular risk factors, the result of this study found that the SUA
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12 300 levels were significantly associated with total cholesterol ($p=0.001$), LDL ($p=0.002$), HDL
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14 301 ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$), regardless of gender.
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16 302 When the data were analysed by gender, significant differences were found only in BMI and
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18 303 triglycerides and only in men ($p<0.001$ and $p=0.002$, respectively). Another study has shown
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20 304 a stronger association between the increase of SUA level and cardiovascular mortality among
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22 305 women in healthy subjects compared to men.[29] Meta-analysis showed that there was a
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24 306 significant association between hyperuricemia and cardiovascular mortality in women, but
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26 307 not in men.[30] Chen *et al.* reported that SUA levels were significantly associated with the
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28 308 occurrence of metabolic syndrome and hypertension in the total population. In men, SUA
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30 309 levels had a positive association with the occurrence of metabolic syndrome in the age groups
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32 310 of <30 and $30-40$. In women, SUA levels were significantly associated with the occurrence
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34 311 of metabolic syndrome in the age groups of <30 and >40 .[10]
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40 312 In this study, BMI was significantly associated with SBP and DBP in both genders.
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42 313 This finding was in line with those of a previous study by Droyvold *et al.*, in which the
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44 314 authors reported that an increase in BMI was associated with increased BP in men and
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46 315 women.[31] With regard to the association between BMI and SUA levels, our findings were
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48 316 different from those of a report by Rodrigues *et al.*, in which the authors reported a
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50 317 significant correlation between BMI and SUA levels in both men and women.[32] The link
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52 318 between BMI and hyperuricemia has not been well elucidated; however, insulin resistance
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54 319 might be the bridging gap. Obese people are more likely to have metabolic syndrome, and the
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56 320 metabolic syndrome itself is associated with insulin resistance. It is thought that insulin
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3 321 resistance impairs the ability of the kidney to excrete uric acid and therefore leads to
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5 322 hyperuricemia.[33]
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8 323 This study found that fasting blood glucose was associated with SBP and DBP only in
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10 324 women. The same result was observed in a study by Yan *et al.*, which revealed that fasting
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12 325 plasma glucose was independent of both SBP and DBP.[34] Fasting blood glucose was also
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14 326 associated with SUA levels, but when analysed by gender, no significant difference was
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16 327 found. This finding is contradictory to those of a study by Kawamoto *et al.*, which revealed
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18 328 that SUA levels were associated with fasting plasma glucose in females.[35] The mechanism
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20 329 of how this phenomenon occurred remains unclear, and further study is needed to observe a
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22 330 cause-effect relationship. Serum triglycerides were also associated with SUA levels in this
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24 331 study. The relationship between SUA levels and lipid profiles has been described in various
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26 332 studies, but the exact mechanism remains unclear. A study by Peng *et al.* revealed that all
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28 333 lipid profile parameters, including triglycerides but not HDL cholesterol, were associated
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30 334 with SUA levels.[36] SUA levels were associated with both SBP and DBP but only in
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32 335 women. This result is similar to those of previous studies.[35, 37] It has been suggested that
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34 336 the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after
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36 337 oxidative stress damage to the endothelium during excessive uric acid formation.[37]
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42 338 There were several limitations to this study. First, subjects in this study were collected
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44 339 from the database made in 2007. From 1500 subjects randomly selected at the beginning of
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46 340 this study, only 733 subjects joined and attend the 2-days examination. More than half of the
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48 341 selected subjects did not attend the examination invitation due to several reasons, thus, this
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50 342 had lessened the total samples of subjects of this study. However, a total sample of 733 has
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52 343 met the minimum sample requirement for this study based on sample size calculation (a
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54 344 minimum sample size of 661 subjects are needed for this study). We invited 1500 subjects at
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56 345 the beginning of this study to anticipate any subjects that could not participate in this study
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3 346 due to any reasons, so that the minimum number of samples could still be met. This was one
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5 347 of the difficulties we met since this study was a community-based study. The findings of this
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7 348 study were expected to be generalized to the 4190 prehypertensive patients whom collected
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9 349 from “Mlati Study” database in 2007. Second, this study could not present the changes of all
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11 350 measured values over a 10-year period because, in the prior study in 2007, these laboratory
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13 351 values were not examined, except for blood pressure. Therefore, only the changes in blood
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15 352 pressure can be presented on the results. Third, the instruments used to measure blood
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17 353 pressure in 2007 and 2017 were different that might cause instrument bias. In 2007, we used
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19 354 sphygmomanometers, whereas in 2017 we used digital automatic blood pressure monitors.
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21 355 Thus, this may lead to bias in blood pressure data measurement between 2007 and 2017.
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23 356 Nevertheless, we tried to minimize the bias by calibrating both the sphygmomanometers and
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25 357 digital automatic blood pressure monitors before data collection, so that, the blood pressure
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27 358 data were all accurate.
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34 35 360 **CONCLUSION**

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37 361 In conclusion, after 10 years of follow-up (2007-2017), of 733 prehypertensive
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39 362 subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a
40
41 363 prehypertensive state, and 228 (31.1%) got hypertension. In the cross-sectional analyses of
42
43 364 SUA in 2017, the SUA levels in men were significantly higher than those in women.
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45 365 Moreover, high-normal and high SUA levels were significantly associated with
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47 366 prehypertension and hypertension in women but not in men.
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52 53 368 **ACKNOWLEDGMENTS**

54
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56
57 370 also like to thank Prodia Laboratory for performing laboratory examinations.
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3 371 **CONTRIBUTORS**
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5 372 LAB, MS and YT composed the idea of the study and arranged the study's design. MS, FI,
6
7 373 AW, and AK obtained the data. ZZ led the statistical analysis with the supervision of MS.
8
9 374 MS, LAB and ZZ wrote the first draft of this paper and all authors read, revised, and
10
11 375 approved the final manuscript.
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13

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17
18 378 Gadjah Mada, Indonesia.
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21 379 **COMPETING INTEREST**

22
23 380 There were no conflicts of interest to disclose.
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26 381 **DATA SHARING STATEMENT**

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28 382 Data may be obtained from the corresponding author upon reasonable request.
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3 **493 Figure Legend**
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6 494 Figure 1. Data collection was conducted twice in 2007 (resulting in a collection of
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8 495 prehypertensive population of 4190 patients) and 2017 (to collect the study sample of 733
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10 496 and obtained physical and laboratory examinations data)

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12 497 Figure 2. The SUA/serum uric acid levels were significantly associated with total cholesterol
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14 498 (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001),
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16 499 triglycerides (p<0.001) and fasting blood glucose (p=0.030). The SUA category: normal (<5
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18 500 mg/dL), high-normal (5–7 mg/dL), and high (\geq 7 mg/dL).
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21 501 Figure 3. Significant differences were found in BMI (p<0.001) and triglycerides (p=0.002)
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23 502 between subjects with normal SUA levels and those with high-normal and high SUA levels in
24
25 503 men. No significant difference was found (p>0.05) between subjects with normal SUA levels
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27 504 and those with high-normal and high SUA levels in women. The SUA category: normal (<5
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29 505 mg/dL), high-normal (5–7 mg/dL), and high (\geq 7 mg/dL).
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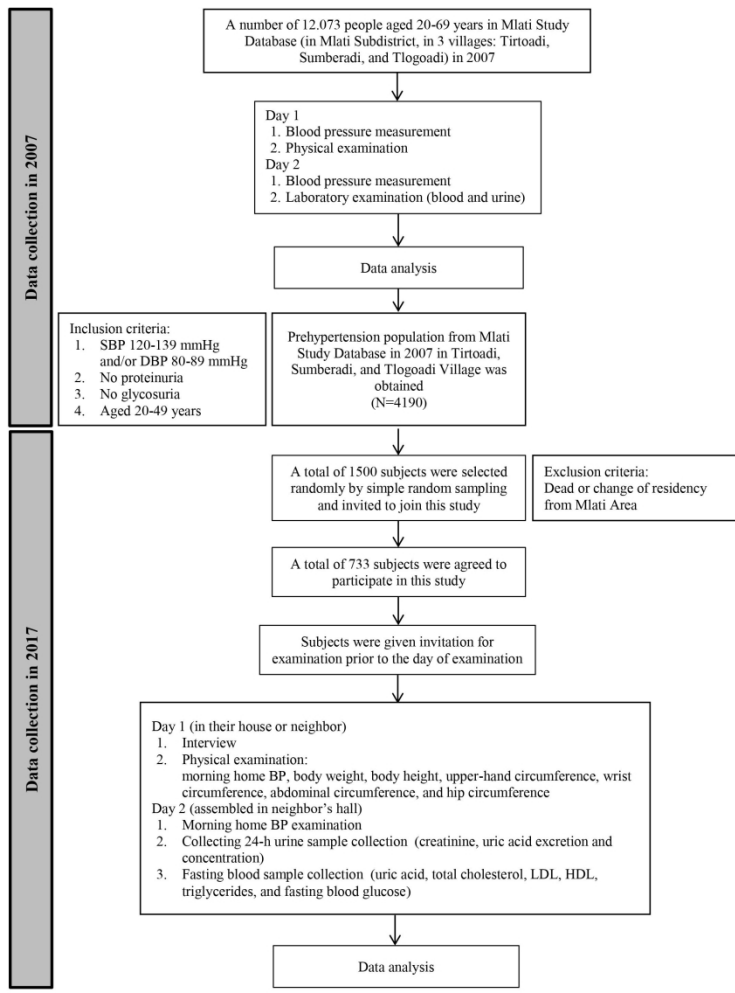


Fig 1. Study Flow Chart

Fig 1. Study Flow Chart

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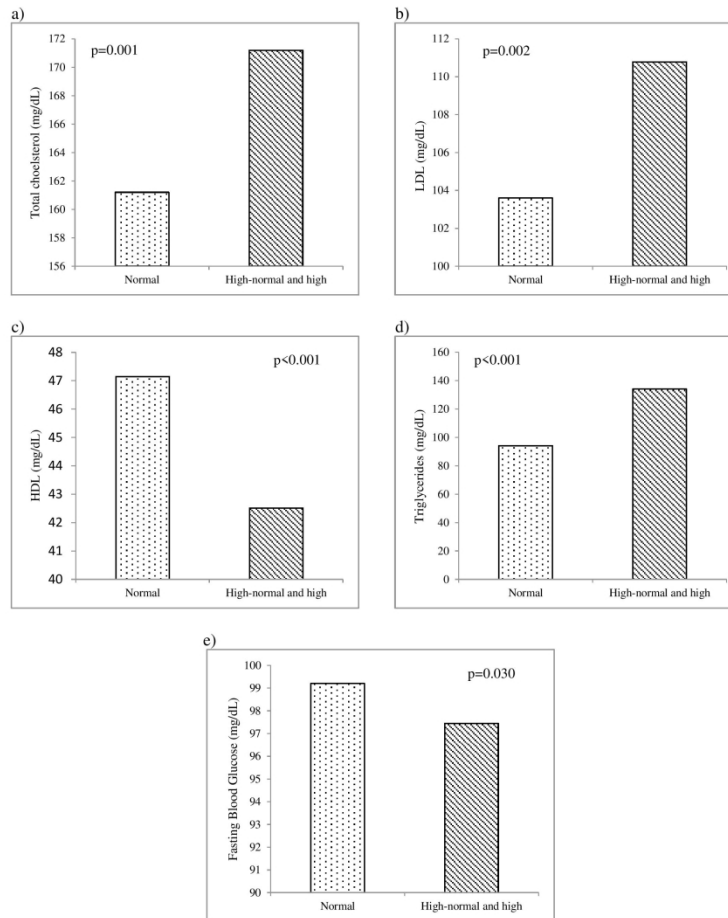


Fig. 2. Mean of cardiovascular risk factors in different serum uric acid levels
 The SUA/serum uric acid levels were significantly associated with total cholesterol ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$), triglycerides ($p<0.001$) and fasting blood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

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

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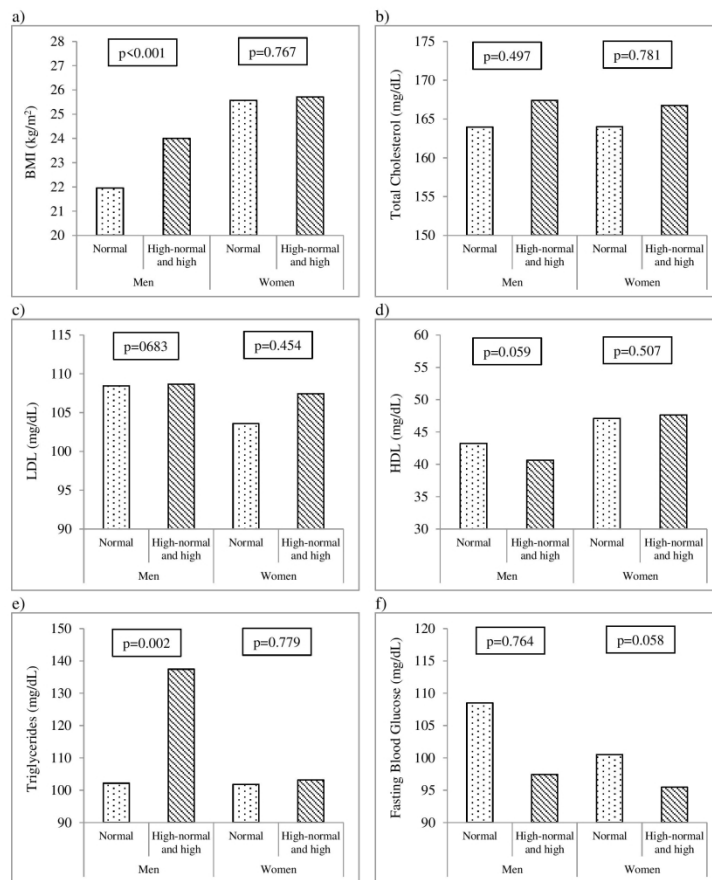


Fig. 3. Mean of cardiovascular risk factors in men and women between normal and high-normal/high SUA levels. In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests. In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

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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			

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.

BMJ Open

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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Keywords:	Hypertension < CARDIOLOGY, PUBLIC HEALTH, EPIDEMIOLOGY

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3 1 **Association of serum uric acid, morning home blood pressure and cardiovascular risk**
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5 2 **factors in a population with previous prehypertension : a cross-sectional study**
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10 4 **Lucky A Bawazier^{1,2}, Mochammad Sja'bani¹, Freddie Irijanto^{1,3}, Zulaela^{1,4}, Agus**
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12 5 **Widiatmoko^{1,5}, Abdul Kholiq^{1,6}, Yasuhiko Tomino⁷**
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56 26 **Word count: 3845**
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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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2
3 51 **Conclusion:** We concluded that after 10 years, of 733 prehypertensive subjects, 31.1%
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6 52 became hypertensive. The SUA levels in men are significantly higher than those in women.
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8 53 Moreover, high-normal and high SUA levels were significantly associated with
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10 54 prehypertension and hypertension in women but not in men.
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14 56 **Keywords:** blood pressure, serum uric acid, cardiovascular risk factor, gender differences
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19 58 **STRENGTH AND LIMITATION OF THIS STUDY**

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21 59
- 22 • This study followed up the changes in blood pressure on subjects for over 10 years.
 - 23 • The association between serum uric acid, blood pressure, and cardiovascular risk factors
24 60 were analysed based on gender.
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26 61
 - 27 • The analysis' was also performed by using both JNC 7 and 2017 ACC/AHA guideline.
28
29 62
 - 30 • This study could not present the changes of all measured values over 10 year period
31 63 because, in the prior study in 2007, these laboratory values were not examined, except
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33 64 for blood pressure.
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67 INTRODUCTION

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

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3 92 predictive factor for cardiovascular risk in individuals without hypertension and diabetes.[17]
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5 93 Serum uric acid also being reported to have a stronger association with cardiovascular risk
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7 94 [18] and risk of cardiovascular disease mortality [19,20] in women than in men.
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10 95 Therefore, the aim of this study was to observe the progression from prehypertension
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12 96 to hypertension after 10 years (2007-2017) and the association of BP with SUA as well as
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14 97 other cardiovascular risk factors in 2017.
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19 99 **METHODS**

21 100 *Study Design*

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24 101 This study was a cross-sectional study conducted in Mlati Sub-district, Sleman
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26 102 District in the Yogyakarta Special Region, Indonesia. The protocol of this study was
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28 103 approved by the Medical and Health Research Ethics Committee of Faculty of Medicine,
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30 104 Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia with the ID
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32 105 approval of KE/FK/0961/EC/2017.
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35 106 *Study Population*

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37 107 We pooled data from participants enrolled in the 2007 Mlati Study Database. The
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39 108 sample of the Mlati Study included 12,073 people aged 20–69 years who lived in 3 villages
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41 109 in Mlati (Tirtoadi, Sumberadi, and Tlogoadi), Sleman, Yogyakarta, Indonesia. The inclusion
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43 110 criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg
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45 111 and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49
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47 112 years; this subgroup included 4,190 participants (current age was 30–59 years). In 2017, of
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49 113 the 4,190 individuals with a history of prehypertension in 2007, 1500 subjects were selected
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51 114 as participants in the current study by simple random sampling using statistical software. All
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53 115 1500 subjects were invited to have a physical and laboratory examination; however, only 733
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55 116 subjects who participated in the sampling were examined (the other subjects who did not
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3 117 show up during the laboratory examination were due to the change of residential area or
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5 118 death or any other unknown reasons and were excluded from this study). All subjects did not
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8 119 take any drugs lowering BP and SUA. All subjects were provided informed consent at the
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10 120 beginning of the study (Figure 1).

121 ***Patient and Public Involvement***

122 Patients were not involved in any of the design, analysis, and presentation of the study
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17 123 results.

124 ***Definition of Prehypertension and Hypertension***

125 The definitions of prehypertension and hypertension were based on the Seventh
126 Report of Joint National Committee (JNC 7) because the newer JNC 8 report renewed only
127 their treatment targets, not their classifications. The SBP of 120–139 mmHg and/or DBP of
128 80–89 mmHg are defined as prehypertension, while SBP of ≥ 140 mmHg and/or DBP of ≥ 90
129 mmHg are defined as hypertension.[21]

130 For further analysis, we applied the 2017 ACC/AHA guideline, which classifies BP as
131 follows: (1) normal BP = SBP < 120 mmHg and DBP < 80 mmHg, (2) elevated BP = SBP
132 120–129 mmHg and DBP < 80 mmHg, (3) stage 1 hypertension = SBP 130–139 mmHg or
133 DBP 80–89 mmHg, and (4) stage 2 hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.[22]

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

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

137 ***Data Collection***

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

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3 142 In 2007, interviews were conducted on 12,073 subjects to obtain demographic data
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5 143 (e.g. sex and age), family history of hypertension and diabetes mellitus, patients' history of
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7 144 diabetes mellitus, patients' history of consuming hypertension and uric acid drugs, and to
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9 145 perform physical and laboratory examinations. Physical examinations, which included
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11 146 measurements of morning home BP (measured by using sphygmomanometer), body weight,
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13 147 body height, upper-hand circumference, wrist circumference, abdominal circumference, and
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15 148 hip circumference, were conducted on day 1 in subject's house or their neighbor. BP
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17 149 measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times
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19 150 (or until stable BP were obtained) while subjects in sitting position. On day 2, we examined
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21 151 morning home BP and took urine and blood samples.
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26 152 In 2017, we collected data from 733 subjects, including interviews of demographic
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28 153 data, physical and laboratory examinations. On the first day, subjects were interviewed,
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30 154 physically examined, and given urine containers for one-time urine samples, as well as for a
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32 155 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The
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34 156 physical examination was performed by the medical team, consisting of a morning home BP
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36 157 measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained),
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38 158 while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure
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40 159 monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan) and measurements of
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42 160 body weight, body height, upper-hand circumference, wrist circumference, abdominal
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44 161 circumference, and hip circumference. On the second day, subjects who were in fasting
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46 162 condition were invited to come to the neighbour's hall in the morning and physically
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48 163 examined for BP again (at 6 – 8 a.m) and drawn for their blood. Urine and blood samples
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50 164 were examined in the laboratory (Prodia Laboratory, Yogyakarta, Indonesia). A 24-h urine
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52 165 sample was collected to measure uric acid excretion and creatinine, and a blood sample was
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54 166 collected to measure SUA, blood urea nitrogen, creatinine, a lipid profile (total cholesterol,
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3 167 low-density lipoprotein/LDL-C, high-density lipoprotein/HDL-C and triglycerides), and
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5 168 fasting blood glucose levels.
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8 169 *Statistical Analysis*

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10 170 The outcomes of this study were presented in two primary analyses which were (1)
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12 171 blood pressure changes during the period of 2007-2017 to measure the progression from
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14 172 prehypertension (2007) to hypertension (2017), and (2) the association of current BP with
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16 173 SUA levels and cardiovascular risk factors. Additional analyses were also performed to
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18 174 observe the SUA association with cardiovascular risk factors. The data analyses were mostly
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20 175 performed based on gender to know about the gender differences in the analyses mentioned
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22 176 above.
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26 177 Data presented later in the results section were collected in 2007 and 2017. Data were
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28 178 analysed using IBM SPSS Statistics for Windows, Version 22.0.[24] The data consisted of
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30 179 continuous and categorical data, which were expressed as the mean (SD) for continuous data
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32 180 and as numbers and percentages for categorical data. The continuous variables were analysed
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34 181 and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The
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36 182 categorical variables were analysed and compared by Pearson chi-square tests. Blood
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38 183 pressure changes during the period of 2007-2017 were presented using frequencies and
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40 184 percentages. The associations of current BP with SUA levels and gender were analysed using
41
42 185 the Pearson chi-square test. Multivariable analysis was performed using multiple linear
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44 186 regressions to describe the association between SUA levels and BP, with adjustment for age
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46 187 and cardiovascular risk factors. Additional analysis to observe the association between SUA
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48 188 levels and cardiovascular risk factors and gender were performed using independent samples
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50 189 t-tests and nonparametric Mann-Whitney U tests. The significance of associations between
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52 190 categorical and numerical variables was determined using 95% confidence intervals (CIs).
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192 **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)

193 The subjects of this study consisted of 733 adults (aged 30–59 years) living in the
 194 Mlati Subdistrict; 306 (41.75%) and 427 (58.25%) were men and women, respectively. The
 195 characteristics of the subjects (by gender) are presented in Table 1. There was no significant
 196 difference in age, SBP, DBP, total cholesterol, LDL, and fasting blood glucose between men
 197 and women (p>0.05). Significant differences were found in body mass index (BMI)
 198 (p<0.001), SUA levels (p<0.001), HDL (p<0.001) and triglycerides (p<0.001). BMI and
 199 HDL were significantly higher in women, whereas SUA levels and triglycerides were
 200 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)

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

201

202 After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to
 203 normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%)
 204 became hypertensive. For SUA levels, 50.3% had normal SUA, 43.1% were high-normal,
 205 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	0.87 – 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/m² = underweight, 18.5-24.9 kg/m² = normal, 25-29.9 kg/m² = overweight, >30 kg/m² = 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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3 207 In men, 32.3% of the subjects had high-normal or high levels of SUA, while in
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6 208 women, only 17.3% had high-normal or high levels of SUA. There was a significant
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8 209 difference in SUA between men and women ($p < 0.001$, $RR = 2.60$, 95% $CI = 2.22-3.05$). When
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10 210 gender was further analysed by age distribution, age was significantly associated with SUA
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12 211 levels only in women aged 50–59 years ($p < 0.001$, $RR = 2.08$, 95% $CI = 1.36-3.15$).
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14 212 Additionally, there was a significant association between SUA levels and uric acid excretion
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16 213 by 24-h urine ($p = 0.002$, $RR = 1.32$, 95% $CI = 1.10-1.57$). On the other hand, no significant
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18 214 association was observed between SUA levels and BMI ($p = 0.153$, $RR = 1.1$, 95% $CI = 0.96-$
19
20 215 1.32) or between SUA levels and uric acid concentration ($p = 0.100$, $RR = 0.786$, 95%
21
22 216 $CI = 0.59-1.05$) (Table 3).

26 217 The associations between gender and SUA levels on BP are shown in Table 4. There
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28 218 was no significant association between gender and BP ($p = 0.584$). To examine the association
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30 219 between uric acid and hypertension, we compared SUA levels and morning home BP. The
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32 220 association between SUA levels and BP was statistically significant ($p = 0.008$, $RR = 1.12$, 95%
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34 221 $CI = 1.03-1.22$). In subjects with previous history of prehypertension, high-normal SUA or
35
36 222 high SUA levels were associated with current prehypertension or hypertension. Furthermore,
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38 223 the association between SUA levels and BP in men and women is also described in Table 4.
39
40 224 In men, SUA levels were not significantly associated with BP ($p = 0.805$, $RR = 1.02$, 95%
41
42 225 $CI = 0.88-1.19$). However, there was a significant association between SUA levels and BP in
43
44 226 women ($p = 0.001$, $RR = 1.21$, 95% $CI = 1.09-1.34$). In women, the risk of having
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46 227 prehypertension or hypertension was 1.21 times higher in those who had high-normal or high
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48 228 SUA levels than those with normal SUA levels. Additional analysis using the 2017
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50 229 ACC/AHA guideline for observing the associations between gender and SUA levels on BP
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52 230 also showed similar results with the previous analysis using JNC 7 guideline regarding the
53
54 231 significant associations between SUA levels and BP.

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 \geq 140 mmHg and/or DBP of \geq 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 \geq 140 mmHg or DBP \geq 90 mmHg)

^c SUA, normal <5 mg/dL, high-normal = 5–7 mg/dL, and high \geq 7 mg/dL

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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3 249 such as BMI, total cholesterol, LDL, HDL, triglycerides, and fasting blood glucose were all
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5 250 taken into account for adjustment in multiple linear regression (Table 5). Age, BMI, fasting
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8 251 blood glucose, and SUA levels were significantly associated with BP. Significant
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10 252 associations were found between age and SBP both in men ($p<0.001$) and women ($p<0.001$),
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12 253 and DBP only in men ($p<0.001$). BMI was significantly associated with SBP and DBP both
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14 254 in men ($p<0.001$ and $p<0.001$) and women ($p<0.001$ and $p<0.001$). In addition, fasting blood
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16 255 glucose was found to be associated with SBP and DBP in women ($p=0.001$ and $p=0.020$).
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18 256 Regarding SUA levels, SUA was significantly associated with both SBP and DBP in women
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20 257 ($p<0.001$ and $p<0.001$, respectively) but such association was not found in men.
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27 259 **DISCUSSION**

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30 260 This study consisted of two parts of data collection. The first data collection was
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32 261 performed in 2007 to gather data on the prehypertension population ($n=4,190$); this study was
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34 262 later called the “Mlati Study Database”. In 2017, after 10 years, the second data collection
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36 263 was performed to gather samples from the Mlati Study Database by a random sampling
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38 264 method ($n=733$) to show the change in BP status from prehypertension to hypertension. The
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40 265 data collection in 2017 also aimed to show the association between uric acid (serum, urinary
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42 266 excretion, and concentrate) and hypertension.
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46 267 The results of our study showed that gender and uric acid excretion (by 24-h urine)
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48 268 were significantly associated with SUA levels. The mean SUA levels in men were
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50 269 significantly higher than those in women. In addition, subjects with high-normal and high
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52 270 SUA levels had a risk of having prehypertension and hypertension that was 1.12 times higher
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54 271 than those with normal SUA levels. When analysed by gender, high-normal and high SUA
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56 272 levels were significantly associated with prehypertension and hypertension only in women.
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59 273 The relationship between SUA levels and the development of hypertension or renal disease
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3 274 had been shown in several previous studies. This relationship was significantly higher in
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5 275 women than in men.[15,25]
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8 276 The study by Kawabe *et al.* revealed that in women, the older the age was, the higher
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10 277 the quartile of SUA, but in men, the quartile of SUA did not increase with age. However, an
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12 278 increase in the quartile of SUA along with higher BMI was only found in men but not in
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14 279 women. Additionally, the mean value of SUA in men was higher than in women.[26] These
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16 280 results were consistent with our finding that SUA levels were significantly higher in men and
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18 281 that SUA levels were significantly associated with higher BMI in men. However, the study
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20 282 populations in this study and the study by Kawabe *et al.* were different in terms of the age
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22 283 group examined, which were adults (30–59 years old) and elderly adults, respectively.[26] A
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24 284 similar finding was also found by Zhang, *et al.* which reported that SUA levels were
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26 285 statistically higher in men than in women, though the SUA level did not increase with the age
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28 286 both in men and women.[27] These studies' results were consistent with our finding which
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30 287 stated that SUA level was significantly higher in men and SUA level was significantly
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32 288 associated with higher BMI also in men. However, the study population in this study and the
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34 289 study by Kawabe, *et al.* was different in the age group which was adults (30-59 years) and
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36 290 elderly, respectively.
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42 291 Chen *et al.* reported a different result in a cross-sectional analysis regarding the
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44 292 association between SUA levels and the presence of hypertension when analysed by gender.
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46 293 For the total population, SUA levels had significant associations with hypertension. The
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48 294 levels of SUA had a significant relationship with hypertension in men aged <30 years, 30–40
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50 295 years, and >40 years but only in women aged >40 years.[10] This situation could be
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52 296 explained in Table 3, which provides the age distribution of women and its association with
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54 297 SUA levels. In Table 3, the proportion of women aged 40–49 years combined with those
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56 298 aged 50–59 years having high-normal and high SUA levels was 24.6%. This age range in
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3 299 women is associated with menopausal problems. A study by Hak *et al.* stated that menopause
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5 300 was associated with an increased risk of incident gout, which may help explain why the age
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7 301 of the women in this study could play a significant role in their SUA levels.[28]
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10 302 Regarding the cardiovascular risk factors, the result of this study found that the SUA
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12 303 levels were significantly associated with total cholesterol ($p=0.001$), LDL ($p=0.002$), HDL
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14 304 ($p<0.001$), triglycerides ($p<0.001$) and fasting blood glucose ($p=0.030$), regardless of gender.
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16 305 When the data were analysed by gender, significant differences were found only in BMI and
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18 306 triglycerides and only in men ($p<0.001$ and $p=0.002$, respectively). Another study has shown
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20 307 a stronger association between the increase of SUA level and cardiovascular mortality among
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22 308 women in healthy subjects compared to men.[29] Meta-analysis showed that there was a
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24 309 significant association between hyperuricemia and cardiovascular mortality in women, but
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26 310 not in men.[30] Chen *et al.* reported that SUA levels were significantly associated with the
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28 311 occurrence of metabolic syndrome and hypertension in the total population. In men, SUA
29
30 312 levels had a positive association with the occurrence of metabolic syndrome in the age groups
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32 313 of <30 and $30-40$. In women, SUA levels were significantly associated with the occurrence
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34 314 of metabolic syndrome in the age groups of <30 and >40 .[10]
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40 315 In this study, BMI was significantly associated with SBP and DBP in both genders.
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42 316 This finding was in line with those of a previous study by Droyvold *et al.*, in which the
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44 317 authors reported that an increase in BMI was associated with increased BP in men and
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46 318 women.[31] With regard to the association between BMI and SUA levels, our findings were
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48 319 different from those of a report by Rodrigues *et al.*, in which the authors reported a
49
50 320 significant correlation between BMI and SUA levels in both men and women.[32] The link
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52 321 between BMI and hyperuricemia has not been well elucidated; however, insulin resistance
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54 322 might be the bridging gap. Obese people are more likely to have metabolic syndrome, and the
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56 323 metabolic syndrome itself is associated with insulin resistance. It is thought that insulin
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3 324 resistance impairs the ability of the kidney to excrete uric acid and therefore leads to
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5 325 hyperuricemia.[33]
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8 326 This study found that fasting blood glucose was associated with SBP and DBP only in
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10 327 women. The same result was observed in a study by Yan *et al.*, which revealed that fasting
11
12 328 plasma glucose was independent of both SBP and DBP.[34] Fasting blood glucose was also
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14 329 associated with SUA levels, but when analysed by gender, no significant difference was
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16 330 found. This finding is contradictory to those of a study by Kawamoto *et al.*, which revealed
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18 331 that SUA levels were associated with fasting plasma glucose in females.[35] The mechanism
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20 332 of how this phenomenon occurred remains unclear, and further study is needed to observe a
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22 333 cause-effect relationship. Serum triglycerides were also associated with SUA levels in this
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24 334 study. The relationship between SUA levels and lipid profiles has been described in various
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26 335 studies, but the exact mechanism remains unclear. A study by Peng *et al.* revealed that all
27
28 336 lipid profile parameters, including triglycerides but not HDL cholesterol, were associated
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30 337 with SUA levels.[36] SUA levels were associated with both SBP and DBP but only in
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32 338 women. This result is similar to those of previous studies.[35, 37] It has been suggested that
33
34 339 the mechanism by which uric acid causes hypertension is due to endothelial dysfunction after
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36 340 oxidative stress damage to the endothelium during excessive uric acid formation.[37]
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41
42 341 There were several limitations to this study. First, subjects in this study were collected
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44 342 from the database made in 2007. From 1500 subjects randomly selected at the beginning of
45
46 343 this study, only 733 subjects joined and attend the 2-days examination. More than half of the
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48 344 selected subjects did not attend the examination invitation due to several reasons, thus, this
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50 345 had lessened the total samples of subjects of this study. However, a total sample of 733 has
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52 346 met the minimum sample requirement for this study based on sample size calculation (a
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54 347 minimum sample size of 661 subjects are needed for this study). We invited 1500 subjects at
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56 348 the beginning of this study to anticipate any subjects that could not participate in this study
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3 349 due to any reasons, so that the minimum number of samples could still be met. This was one
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5 350 of the difficulties we met since this study was a community-based study. The findings of this
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7 351 study were expected to be generalized to the 4190 prehypertensive patients whom collected
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9 352 from “Mlati Study” database in 2007. Second, this study could not present the changes of all
10
11 353 measured values over a 10-year period because, in the prior study in 2007, these laboratory
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13 354 values were not examined, except for blood pressure. Therefore, only the changes in blood
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15 355 pressure can be presented on the results. Third, the instruments used to measure blood
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17 356 pressure in 2007 and 2017 were different that might cause instrument bias. In 2007, we used
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19 357 sphygmomanometers, whereas in 2017 we used digital automatic blood pressure monitors.
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21 358 Thus, this may lead to bias in blood pressure data measurement between 2007 and 2017.
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23 359 Nevertheless, we tried to minimize the bias by calibrating both the sphygmomanometers and
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25 360 digital automatic blood pressure monitors before data collection, so that, the blood pressure
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27 361 data were all accurate.
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35 363 **CONCLUSION**

37 364 In conclusion, after 10 years of follow-up (2007-2017), of 733 prehypertensive
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39 365 subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a
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41 366 prehypertensive state, and 228 (31.1%) got hypertension. In the cross-sectional analyses of
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43 367 SUA in 2017, the SUA levels in men were significantly higher than those in women.
44
45 368 Moreover, high-normal and high SUA levels were significantly associated with
46
47 369 prehypertension and hypertension in women but not in men.
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51 370

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55
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57
58 373 also like to thank Prodia Laboratory for performing laboratory examinations.
59
60

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3 374 **CONTRIBUTORS**
4

5 375 LAB, MS and YT composed the idea of the study and arranged the study's design. MS, FI,
6
7 376 AW, and AK obtained the data. ZZ led the statistical analysis with the supervision of MS.
8
9 377 MS, LAB and ZZ wrote the first draft of this paper and all authors read, revised, and
10
11 378 approved the final manuscript.
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13

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15
16
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18
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20

21 382 **COMPETING INTEREST**

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23
24 383 There were no conflicts of interest to disclose.
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26 384 **DATA SHARING STATEMENT**

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28 385 Data may be obtained from the corresponding author upon reasonable request.
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33 387 **REFERENCES**
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3 **496 Figure Legend**
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6 497 Figure 1. Data collection was conducted twice in 2007 (resulting in a collection of
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8 498 prehypertensive population of 4190 patients) and 2017 (to collect the study sample of 733
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10 499 and obtained physical and laboratory examinations data)

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12 500 Figure 2. The SUA/serum uric acid levels were significantly associated with total cholesterol
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14 501 (p=0.001), LDL/low density lipoprotein (p=0.002), HDL/high density lipoprotein (p<0.001),
15
16 502 triglycerides (p<0.001) and fasting blood glucose (p=0.030). The SUA category: normal (<5
17
18 503 mg/dL), high-normal (5–7 mg/dL), and high (\geq 7 mg/dL).

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20
21 504 Figure 3. Significant differences were found in BMI (p<0.001) and triglycerides (p=0.002)
22
23 505 between subjects with normal SUA levels and those with high-normal and high SUA levels in
24
25 506 men. No significant difference was found (p>0.05) between subjects with normal SUA levels
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27 507 and those with high-normal and high SUA levels in women. The SUA category: normal (<5
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29 508 mg/dL), high-normal (5–7 mg/dL), and high (\geq 7 mg/dL).
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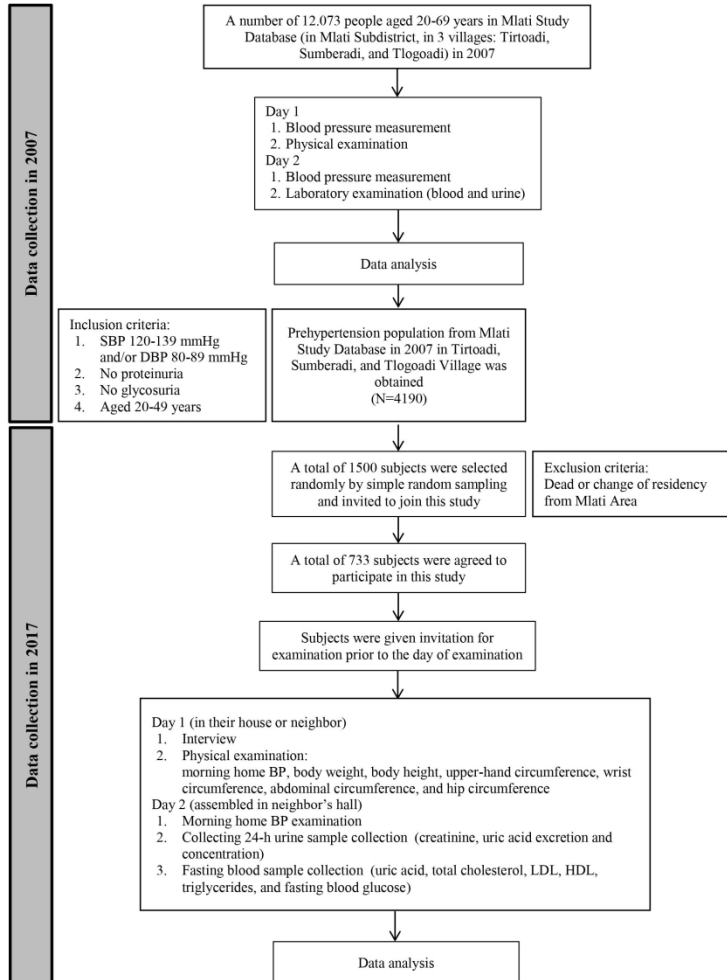


Fig 1. Study Flow Chart

Fig 1. Study Flow Chart

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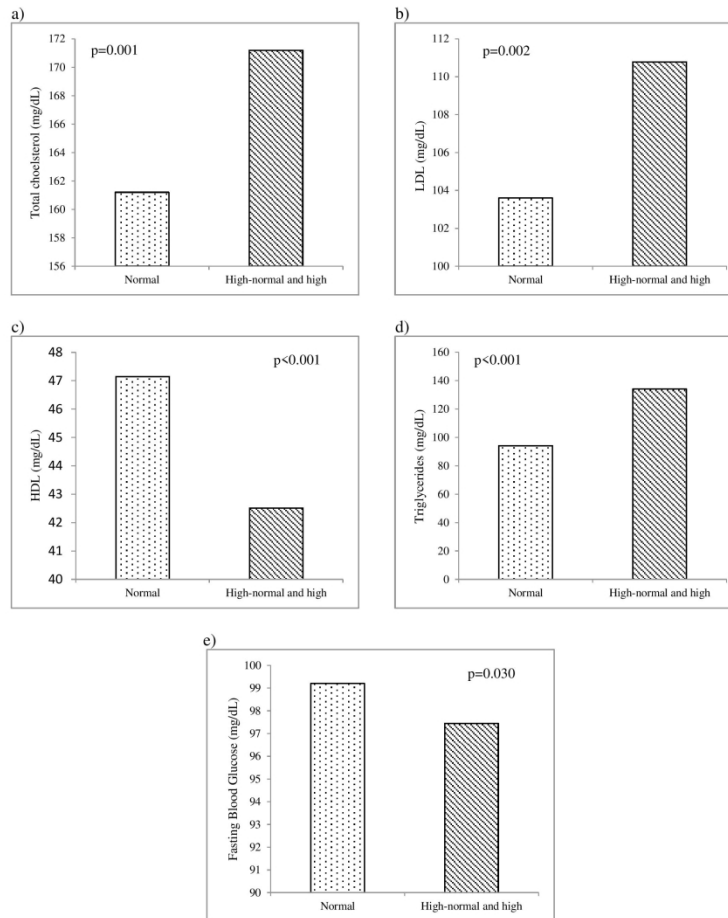


Fig. 2. Mean of cardiovascular risk factors in different serum uric acid levels
 The SUA/serum uric acid levels were significantly associated with total cholesterol ($p=0.001$), LDL/low density lipoprotein ($p=0.002$), HDL/high density lipoprotein ($p<0.001$), triglycerides ($p<0.001$) and fasting blood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

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

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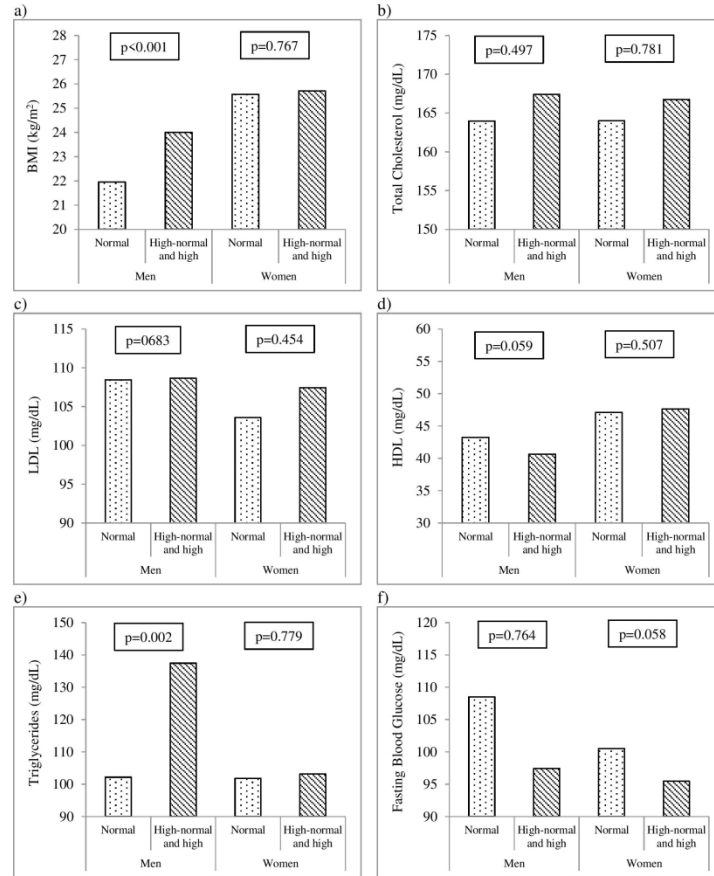


Fig. 3. Mean of cardiovascular risk factors in men and women between normal and high-normal/high SUA levels. In men, BMI, LDL, triglyceride and fasting blood glucose values were analysed using the Mann-Whitney U test; total cholesterol and HDL levels were analysed using independent samples t-tests. In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

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.