PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of serum uric acid, morning home blood pressure and cardiovascular risk factors in a population with previous prehypertension : a cross-sectional study
AUTHORS	Bawazier, Lucky; Sja'bani, Mochammad; Irijanto, Fredie; Zulaela, Zulaela; Widiatmoko, Agus; Kholiq, Abdul; Tomino, Yasuhiko

VERSION 1 – REVIEW

REVIEWER	Stefano Omboni Italian Institute of Telemedicine Italy
REVIEW RETURNED	14-Mar-2020

GENERAL COMMENTS	In this study, the authors evaluated a group of prehypertensive patients over ten years to verify the proportion of subjects turning into hypertensive and the association of this evolution with serum uric acid levels and other CV risk factors. The presentation is not very clear, though I guess the results presented in the paper refer to the 2017 dataset only. The article must be revised to make this aspect more clearly. The abstract does not reflect the content of the paper and must be rewritten. The primary issue is that it is not clear whether the data that the authors are showing are related to changes over the years or others. Abstract. Page 3, line 35. Please, define prehypertension Abstract. Page 3, lines 44-45. Please, define high-normal and high serum uric acid levels. Methods. Page 6. Prehypertension is defined based on several criteria, with no inclusion of BP levels. The definition of prehypertension is given in a next section and should be moved here because it is an inclusion criterion. There is no mention of the exclusion criteria. Please, update the paper with this information. Methods. Page 7. It is not clear whether morning home blood pressure was self-measured by the patient or by a nurse visiting the patient. It seems that all the data collection was done by visiting the patients at home. In some parts of the text, the fact that the patient came to the office is also mentioned. The site where the visits were made and the details of the methodology employed for the measurements must be indicated (e.g., number of BP readings, etc.).

	In 2017 an Omron HEM-907 BP monitor was used for measuring home BP. Was this the same used in 2007? This is important to check for the consistency of BP categorization. If home BP was taken by a nurse visiting the patient at home, thus this is not self-measured home BP. In this case, the term home must be removed in all situations where it is associated with BP. The same applies to the morning. Please, use the term “blood pressure” and remove “morning home.” The drop out rate of the initial subjects screened in 2007 is high 1550 randomly selected end up in 733 subjects showing up for a visit. Please discuss it as a limitation. Table 1. I guess these data refer to the initial visit in 2007. This must be specified in the legend. I recommend expanding table 1 and add the same data for the last observation (2017). Table 1 must report for both 2007 and 2017 the proportion of prehypertensives (100% in 2007), that of normotensives and hypertensives, the percentage of subjects with normal, high-normal, and high SUA. A column with all subjects (men+ women) must be included for each period I am confused. Do the results of Tables 2 and 3 refer to 2007 or 2017? During the ten years of follow-up, 228 became hypertensives. Did these patients take any drug? This is not mentioned, and it is relevant. If antihypertensive medications have been administered, this must be reported in the study, and adjustment of results must be made. Where SUA-lowering drugs administered to any patients? Discussion. Association of BP with CV risk factors such as blood glucose, SUA, BMI is not a new finding. The authors had the chance of studying over ten years patients who have initially been in a prehypertensive state and tracking the factors possibly related to the risk of developing hypertension. They missed the target. I understand that not all laboratory values were available for 2007. Thus the paper must change the title (and the authors must amend most of the text) because the term “correlation…” “…over ten years” is misleading.

REVIEWER	Georgios Mourtzinis Sahlgrenska University Hospital, Gothenburg, Sweden
REVIEW RETURNED	15-Mar-2020

GENERAL COMMENTS	Thank you for giving me the opportunity to review this interesting manuscript of Lucky A Bawazier et al. This is a well conducted field study where individuals in 3 villages in Mlati, Indonesia examined 2007 and 2017. The investigators identified a subgroup of 4190 individuals with prehypertension in 2007, and examined 733 of them again 10 years later in 2017. The aim of this study was to "observe the progression from prehypertension to hypertension after 10 years of follow-up and its association with serum uric acid as well as other cardiovascular risk factors." The abstract describes a cross-sectional cohort study, while the title and the objective suggest a “correlation over 10 years”. After reading

	the manuscript I realized that this is a cross-sectional study conducted 2017, and therefore the title needs to be changed. The study population, however, is identified from the prehypertensive subgroup in the Mlati Study Database from 2007. So the whole study population has been prehypertensive back in 2007. A missing information is how prehypertensive was defined 2007. Overall it is not very clear how the study is designed. Therefore I believe that the use of a flow-chart is needed in order to give a better picture of the study design. A major shortcoming is that the authors clustered together prehypertension and hypertension as endpoint in the analyses. It is, though, impossible to "observe the progression from prehypertension to hypertension" that was the aim of this study. The authors categorize the study population to normotensive/prehypertensive/hypertensive just after a single blood pressure measurement. That is by far less robust than multiple measurements or 24h measurement in order to identify the true normotensive/ prehypertensive/ hypertensive individuals. I hade expected me that the authors compared serum uric acid in 2007 with the development of hypertension in 2017 to get the 10 years follow-up , but no information about the 2007 subgroup is given. The statement in line 193 that "In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal and high SUA levels than those with normal SUA levels." can not be justified. This cross-sectional study can give information about association but not "risk of development". Furthermore I have the following comments for the authors: Line 39; SUA needs to be explained Line 42; "Serum uric acid levels were significantly higher in men than in women (5.78 (1.25) 43 mg/dL vs 4.52 (1.10) mg/dL, p<0.001)", what is 5.78 and 1.25? I guess that one of them is the mean uric acid level among men in the studied population. The same with 4.52 and 1.10 for women. This needs to be clarified. Line 50; "We concluded that serum uric acid levels were significantly associated with prehypertension and hypertension only in women", but the population was described as prehypertensive. How is an association with hypertension possible in a cross-sectional study in a prehypertensive population? Line 51; "Here" doesn't make sense. Line 71; Consider to use "diagnosis" instead of "recognition" Line 72; "This study was important due to its cohort design, such that patients were followed for 10 years." Doesn't belong in the introduction but in the methods. Besides I believe that the authors want to tell that a strength with this study is the longitudinal design and the long follow-up time, thus I suggest revising this sentence. Line 74; "thus have poorer quality of life". The association of hypertension and poor quality of life needs a reference; furthermore hypertensive patients have a higher risk for cardiovascular morbidity

	and mortality that might be of value to be mentioned. Line 85; “Therefore, this study was conducted as a cohort study of ten years of follow-up (2007–2017) in a population with homogenous characteristics in the Mlati Subdistrict, Sleman District, Yogyakarta, Java Island, Indonesia.” Belongs to the methods, not the introduction. Line 89; “We hypothesized that at least 30% of prehypertensive patients will eventually develop hypertension and that it is associated with SUA.” Is this statement needed in the introduction? In that case where the authors do based this assumption? Line 95; Is this study a cross-sectional one or has a longitudinal 10 years follow-up design? Line 100; Was the Mlati Study a population based study that included the whole population aged 20-69 in these 3 villages in Mlati, Indonesia? I miss a brief description of Mlati Study as well as a reference. Line 102; There were no blood pressure criteria for the inclusion in the “prehypertensive subgroup”. How could this group be named prehypertensive? Line 103; Consider to use the term no proteinuria or without proteinuria instead of “negative proteinuria”. Line 104; I am not familiar with the term “negative urine reduction”, please clarify. Line 105; “current age was 30–59 years” is misleading as the “current”is not defined. The authors do not need to state that the population of 20-49 years old in 2007 became 30-59 years old ten years later. Line 121; Where the examinations conducted at the individuals’ homes? The blood pressure measured by nursing stuff or was it self measured by the study individuals? The definitions of prehypertension/hypertension that the authors used consider office blood pressure. It is of importance to point out under what conditions the blood pressure was measured. Is a single morning blood pressure measurement enough in order to categorize an individual as normotensive/prehyperensive/hypertensive? Line 158; Table 1. Please state in the table heading if these data are from 2007 or 2017. Line 158; Table 1. Is there any information about individuals’ co-morbidity? It is of interest to see the prevalence of diabetes, cardiovascular disease, history of stroke/TIA, heart failure in the study population. Furthermore it is of interest to present the ongoing medication (for diabetes, cholesterol, blood pressure etc). Line 163; LDL-C in already defined on line 135. Line 165; HDL-C is already defined on line 135. Line 173; Table 2. Why did the authors cluster together high and high-normal SUA?

	Line 173; Table 2. Please define the cut-off values for BMI (Overweight-Obese Underweight-normal), Uric Acid Excretion (24-h) (high-normal) Line 173; Table 2. Please explain the difference between Uric Acid Concentration and SUA. I miss a definition and cut-off values for uric acid concentration. ¼ or the individuals with high SUA have normal uric Acid Concentration and vice versa, any comments? Line 184; table 3. Please state the blood pressure cut-off values, not enough to just say according to JNC 7 and AHA/ACC 2017. Line 184; table 3. Why did the authors choose to categorize together pre-HT and HT in the JNC 7 analysis? Why did the authors choose to categorize together normal and elevate blood pressure in the 2017 AHA/ACC analysis? Line 186; “The association between SUA levels and BP was statistically significant”. There is rather an association between SUA levels and the chosen BP categories. It would be interesting to see an analysis with blood pressure as a continuous variable. Line 188; “The risk of high-normal and high SUA levels becoming prehypertension or hypertension was 1.12 times higher than that of normal SUA levels.”, this sentence is difficult to make sense, please consider to revise it. Line 193; “In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal and high SUA levels than those with normal SUA levels.” It should be high-normal OR high SUA instead of high-normal AND high SUA. And once again, why did the authors choose to categorize together high-normal and high SUA? It would be better to see a presentation with 3 categories or the SUA as a continuous variable. Line 212; Table 4. The tables should be able to stand alone without the main text, please define SUA etc. Line 236; “In addition, subjects with high-normal and high SUA levels had a risk of developing prehypertension and hypertension that was 1.12 times higher than those with normal SUA levels.” All those individuals had prehypertension already, they where in the prehypertension subgroup 2007. Therefore it is strange to state that they had greater risk of developing prehypertension. Line 410. Figure legend. The figures should be able to stand alone without the main text, and therefore the figure legends should include the definitions of normal, high-normal, high SUA. I had expected me the authors to discuss a little bit about the different normal blood pressure/prehypertenson definitions. Maybe of interest to mention and compare to the 2018 ESC/ESH guidelines that define SBP 120-129 as normal and SBP 130-139 as high normal. [European Heart Journal (2018) 39, 3021–3104].

REVIEWER	Caress Dean Oakland University
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	Objective: Written clear and concise, however, it does not illustrate that your study focus is to assess the associations by gender. Introduction: 1. Line 72: 'This study was important due to…' It appears the authors were discussing their research study here. Recommend moving this later in the introduction after discussing the literature. 2. The introduction is well written and provides great background on the significance of cardiovascular disease and uric acid; however, it does not discuss in detail contrasting studies on the association between SUA, hypertension, and gender. Methods: 1. Methods section states family history information was collected, but specific measures was not stated in the methods section and the related results were not stated in the results section. 2. Demographic characteristics (e.g., age) were collected and not stated in the method section. 3. Authors state that multiple linear regression analyses were performed but did not state what is assessed until results section, line 213: 'Multivariable analysis was conducted to describe…'. This sentence should be moved to methods section. 4. In regression analysis, the model was adjusted for cardiovascular risk factors. Is there a reason why models were not adjusted for age? The research shows that one's blood pressure level increases with age. Also, research shows men and women's risk vary by age. 5. Methods section does not state what statistical software was utilized to perform the analyses. Limitations: I did not see a limitations section.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Stefano Omboni
Institution and Country
Italian Institute of Telemedicine
Italy

1. In this study, the authors evaluated a group of prehypertensive patients over ten years to verify the proportion of subjects turning into hypertensive and the association of this evolution with serum uric acid levels and other CV risk factors. The presentation is not very clear, though I guess the results presented in the paper refer to the 2017 dataset only. The article must be revised to make this aspect more clearly.
The study based on 2007 data of 4190 prehypertension population with no glycosuria, no proteinuria. The data in 2007 was randomized from 1500 samples get 733 samples and analysis the association of the changes blood pressure categorizes with serum uric acid levels and other CV risk factors in 2017. Observational the changes blood pressure categorize to normal, prehypertension and hypertension

2. The abstract does not reflect the content of the paper and must be rewritten. The primary issue is that it is not clear whether the data that the authors are showing are related to changes over the years

or others.
We have revised the abstract

3. Abstract. Page 3, line 35. Please, define prehypertension
We have added prehypertension definition on the abstract (line 36). The content is also listed below.
“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””

4. Abstract. Page 3, lines 44-45. Please, define high-normal and high serum uric acid levels.
We have added SUA level cut off point for high-normal and high (line 44-45). The content is also listed below.
“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).”

5. Methods. Page 6. Prehypertension is defined based on several criteria, with no inclusion of BP levels. The definition of prehypertension is given in a next section and should be moved here because it is an inclusion criterion.
We have added BP levels for inclusion criteria (line 110-113). The content is also listed below.
“The inclusion criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49 years; this subgroup included 4,190 participants (current age was 30–59 years).”

6. There is no mention of the exclusion criteria. Please, update the paper with this information.
Exclusion criteria have been added in the method section (line 117-119).The content is also listed below.
“… (the other subjects who did not show up during the laboratory examination were due to the change of residential area or death or any other unknown reasons and were excluded from this study).”

7. Methods. Page 7. It is not clear whether morning home blood pressure was self-measured by the patient or by a nurse visiting the patient. It seems that all the data collection was done by visiting the patients at home. In some parts of the text, the fact that the patient came to the office is also mentioned. The site where the visits were made and the details of the methodology employed for the measurements must be indicated (e.g., number of BP readings, etc.).
We have added an explanation about the collection of BP data in the method section (line 142-157). The content is also listed below.
“In 2007, interviews were conducted on 12,073 subjects to obtain demographyc data (e.g. sex and age), family history and to perform physical and laboratory examinations. Physical examinations, which included measurements of morning home BP (measured by using sphygmomanometer), body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference and hip circumference, were conducted on day 1 in subject’s house or their neighbor. BP measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times (or until stable BP were obtained) while subjects in sitting position. On day 2, we examined morning home BP and took urine and blood samples.
In 2017, we collected data from 733 subjects, including interviews of demographic data, physical and laboratory examinations. On the first day, subjects were interviewed, physically examined, and given urine containers for one-time urine samples, as well as for a 24-h urine collection that had to be submitted on day 2, in their home or neighbour. The physical examination was performed by medical team, consisted of a morning home BP measurement in the morning (at 6 – 8 a.m) for 2 times (or until stable BP were obtained), while subjects in sitting position, using the Omron HEM-907 digital automatic blood pressure monitor (manufactured by Omron Healthcare Co., Ltd, Kyoto, Japan)

8. In 2017 an Omron HEM-907 BP monitor was used for measuring home BP. Was this the same

used in 2007? This is important to check for the consistency of BP categorization.
In 2007, we used sphygmomanometer (line 144-145), and in 2017, we used Omron HEM-907 digital BP monitor (line 156-157).

9. If home BP was taken by a nurse visiting the patient at home, thus this is not self-measured home BP. In this case, the term home must be removed in all situations where it is associated with BP. The same applies to the morning. Please, use the term “blood pressure” and remove “morning home.”
The term of morning home blood pressure was still be used in this report because the BP measurements were done in the morning (at 6-8 a.m) in subject’s house or neighbor.

10. The drop out rate of the initial subjects screened in 2007 is high 1550 randomly selected end up in 733 subjects showing up for a visit. Please discuss it as a limitation.
We have added this in the limitation (line 325-329). The content is also listed below.
“First, subject in this study were collected from database made in 2007. From 1500 subjects randomly selected in the beginning of this study, only 733 subjects joined and attend the 2-days examination. More than half of the selected subjects did not attend the examination invitation due to several reasons, thus, this had lessened the total samples of subjects of this study.”

11. Table 1. I guess these data refer to the initial visit in 2007. This must be specified in the legend. I recommend expanding table 1 and add the same data for the last observation (2017). Table 1 must report for both 2007 and 2017 the proportion of prehypertensives (100% in 2007), that of normotensives and hypertensives, the percentage of subjects with normal, high-normal, and high SUA. A column with all subjects (men+ women) must be included for each period
We have been added one more table (Table 2) to describe blood pressure changes over 10 years.
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)

12. I am confused. Do the results of Tables 2 and 3 refer to 2007 or 2017?
Results in table 2 and 3 referred to 2017 data.

13. During the ten years of follow-up, 228 became hypertensives. Did these patients take any drug? This is not mentioned, and it is relevant. If antihypertensive medications have been administered, this must be reported in the study, and adjustment of results must be made.
The patient did not take any drugs lowering blood pressure (line 119-120). The content is also listed below.
“All subjects did not take any drugs lowering BP and SUA.”
14. Where SUA-lowering drugs administered to any patients?
The patient did not take any drugs lowering uric acid (line 119-120). The content is also listed below.
“All subjects did not take any drugs lowering BP and SUA.”

15. Discussion. Association of BP with CV risk factors such as blood glucose, SUA, BMI is not a new finding. The authors had the chance of studying over ten years patients who have initially been in a prehypertensive state and tracking the factors possibly related to the risk of developing hypertension.

They missed the target. I understand that not all laboratory values were available for 2007. Thus the paper must change the title (and the authors must amend most of the text) because the term “correlation…” “…over ten years” is misleading.
We have revised our manuscript title to avoid misleading. Therefore, our manuscript is now entitled “Association of Serum Uric Acid, Morning Home Blood Pressure and Cardiovascular Risk Factors in a Prehypertension Population”

Reviewer: 2
Reviewer Name
Stefano Omboni
Institution and Country
Italian Institute of Telemedicine
Italy

Thank you for giving me the opportunity to review this interesting manuscript of Lucky A Bawazier et al. This is a well conducted field study where individuals in 3 villages in Mlati, Indonesia examined 2007 and 2017. The investigators identified a subgroup of 4190 individuals with prehypertension in 2007, and examined 733 of them again 10 years later in 2017. The aim of this study was to "observe the progression from prehypertension to hypertension after 10 years of follow-up and its association with serum uric acid as well as other cardiovascular risk factors."

1. The abstract describes a cross-sectional cohort study, while the title and the objective suggest a “correlation over 10 years”. After reading the manuscript I realized that this is a cross-sectional study conducted 2017, and therefore the title needs to be changed. The study population, however, is identified from the prehypertensive subgroup in the Mlati Study Database from 2007. So the whole study population has been prehypertensive back in 2007. A missing information is how prehypertensive was defined 2007. Overall it is not very clear how the study is designed. Therefore I believe that the use of a flow-chart is needed in order to give a better picture of the study design.
We added one more figure to show the study flow chart (Figure 1).

2. A major shortcoming is that the authors clustered together prehypertension and hypertension as endpoint in the analyses. It is, though, impossible to “observe the progression from prehypertension to hypertension” that was the aim of this study.
The authors categorize the study population to normotensive/prehypertensive/hypertensive just after a single blood pressure measurement. That is by far less robust than multiple measurements or 24h measurement in order to identify the true normotensive/ prehypertensive/ hypertensive individuals.
The BP measurement was done at a minimum of twice (or more until stable BP was obtained) a day for 2 days (line 147-157)

3. I hade expected me that the authors compared serum uric acid in 2007 with the development of hypertension in 2017 to get the 10 years follow-up , but no information about the 2007 subgroup is given.
We did not compared serum uric acid between 2007 and 2017 data because serum uric acid data were not collected in 2007. Therefor, a comparison for serum uric acid between 2007 and 2017 data cannot be made.

4. The statement in line 193 that “In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal and high SUA levels than those with normal SUA levels.” can not be justified. This cross-sectional study can give information about association but not “risk of development”.

We have read an article from Schmidt and Kohlmann (2008). It said that “The relative risk (RR) and the odds ratio (OR) are the two most widely used measures of association in epidemiology. The direct computation of relative risks is feasible if meaningful
prevalences or incidences are available. Cross-sectional data may serve to calculate relative risks from prevalences. Cohort study designs allow for the direct calculation of relative risks from incidences.”. Thus, we were still using RR for showing this study results.

5. Line 39; SUA needs to be explained
The first SUA abbreviation has been explained line 31. The content is also listed below.
“… association to serum uric acid (SUA) levels…”

6. Line 42; “Serum uric acid levels were significantly higher in men than in women (5.78 (1.25) 43 mg/dL vs 4.52 (1.10) mg/dL, p<0.001)”, what is 5.78 and 1.25? I guess that one of them is the mean uric acid level among men in the studied population. The same with 4.52 and 1.10 for women. This needs to be clarified.
We have made it more clear by adding “Mean (SD)” in the sentence (line 43). The content is also listed below.
“Mean (SD) of SUA levels were significantly higher in men than in women…”

7. Line 50; “We concluded that serum uric acid levels were significantly associated with prehypertension and hypertension only in women”, but the population was described as prehypertensive. How is an association with hypertension possible in a cross-sectional study in a prehypertensive population?
Prehypertensive population was the initial population we used to collect study sample. It was prehypertensive population in 2007, but over 10 years, there were changes in their blood pressure, some remained with prehypertension, and the other became normotensive or hypertensive.

8. Line 51; “Here” doesn’t make sense.
We have erased the word “here”.

9. Line 71; Consider to use “diagnosis” instead of “recognition”
The word “recognition” has been replaced by “diagnosis” (line 73)

10. Line 72; “This study was important due to its cohort design, such that patients were followed for 10 years.” Doesn’t belong in the introduction but in the methods. Besides I believe that the authors want to tell that a strength with this study is the longitudinal design and the long follow-up time, thus I suggest revising this sentence.
The sentence has been erased from introduction section and added in method section (line 102). The content is listed below
“This study was a cross-sectional cohort study of ten years of follow-up (2007–2017) conducted in Mlati Sub-district, Sleman District in the Yogyakarta Special Region, Indonesia.”

11. Line 74; “thus have poorer quality of life”. The association of hypertension and poor quality of life needs a reference; furthermore hypertensive patients have a higher risk for cardiovascular morbidity and mortality that might be of value to be mentioned.
Revised. References have been added (ref. 3 and 4)
3. Ruchira P, Gajendra Singh M. PS 15-11 Impact of Hypertension on Quality of Life among People Living in an Urban Area of Delhi, India. J Hypertens 2016; 34:e462. doi: 10.1097/01.hjh.0000501221.33083.08
4. de Carvalho MV, Siqueira LB, Sousa ALL, et al. The Influence of Hypertension on Quality of Life. Arq Bras Cardiol 2013; 100(2):164-174. doi: 10.5935/abc.20130030

12. Line 85; “Therefore, this study was conducted as a cohort study of ten years of follow-up (2007–2017) in a population with homogenous characteristics in the Mlati Subdistrict, Sleman District, Yogyakarta, Java Island, Indonesia.” Belongs to the methods, not the introduction.
It has been moved to method section (line 102)

13. Line 89; “We hypothesized that at least 30% of prehypertensive patients will eventually develop hypertension and that it is associated with SUA.” Is this statement needed in the introduction? In that case where the authors do based this assumption?
It has been removed from introduction section

14. Line 95; Is this study a cross-sectional one or has a longitudinal 10 years follow-up design?
This is a combination design of cross-sectional and cohort study over 10 years follow up. Therefore, named as cross-sectional cohort study design.

15. Line 100; Was the Mlati Study a population based study that included the whole population aged 20-69 in these 3 villages in Mlati, Indonesia? I miss a brief description of Mlati Study as well as a reference.
Yes, Mlati Study included whole population aged 20-69 years in 3 village in Mlati.

16. Line 102; There were no blood pressure criteria for the inclusion in the “prehypertensive subgroup”. How could this group be named prehypertensive?
Inclusion criteria for blood pressure has been added (line 110-112). The content is also listed below.
“The inclusion criteria for the prehypertensive subgroup of the study sample were SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, no proteinuria, no glycosuria, and age between 20 and 49 years; this subgroup included 4,190 participants (current age was 30–59 years).”

17. Line 103; Consider to use the term no proteinuria or without proteinuria instead of “negative proteinuria”.
Have been replaced with no proteinuria (line 112)

18. Line 104; I am not familiar with the term “negative urine reduction”, please clarify.
Have been replaced with no glycosuria (line 112)

19. Line 105; “current age was 30–59 years” is misleading as the “current”is not defined. The authors do not need to state that the population of 20-49 years old in 2007 became 30-59 years old ten years later.
Have been removed from method section

20. Line 121; Where the examinations conducted at the individuals’ homes? The blood pressure measured by nursing stuff or was it self measured by the study individuals? The definitions of prehypertension/hypertension that the authors used consider office blood pressure. It is of importance to point out under what conditions the blood pressure was measured. Is a single morning blood pressure measurement enough in order to categorize an individual as normotensive/prehyperensive/hypertensive?
The clearer explanation about blood pressure measurement has been added in method section (line 142-161). The content is also listed below.
“In 2007, interviews were conducted on 12,073 subjects to obtain demographyc data (e.g. sex and age), family history and to perform physical and laboratory examinations. Physical examinations, which included measurements of morning home BP (measured by using sphygmomanometer), body weight, body height, upper-hand circumference, wrist circumference, abdominal circumference and hip circumference, were conducted on day 1 in subject’s house or their neighbor. BP measurements were performed in the morning (at 6 – 8 a.m) by the medical team for 2 times (or until stable BP were

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

21. Line 158; Table 1. Please state in the table heading if these data are from 2007 or 2017.
Has been added in Table 1.

22. Line 158; Table 1. Is there any information about individuals' co-morbidity? It is of interest to see the prevalence of diabetes, cardiovascular disease, history of stroke/TIA, heart failure in the study population. Furthermore it is of interest to present the ongoing medication (for diabetes, cholesterol, blood pressure etc).
No information obtained about subject's comorbidity because all subjects in this study were having essential prehypertension without any other comorbidity.

23. Line 163; LDL-C in already defined on line 135.
Has been removed

24. Line 165; HDL-C is already defined on line 135. ,.
Has been removed

25. Line 173; Table 2. Why did the authors cluster together high and high-normal SUA?
Because, we want to classified those who did not have abnormal changes in SUA level and those who have abnormal SUA levels, which were high normal and high SUA levels.

26. Line 173; Table 2. Please define the cut-off values for BMI (Overweight-Obese Underweight-normal), Uric Acid Excretion (24-h) (high-normal)
We have added cut-off values for BMI, Uric acid excretion (24-h), and Uric acid concentration (per 100 ml urine) in Table 3 (Table 2 in the previous manuscript has been changed in to Table 3). Here are the cut-off values:
• BMI, <18.5kg/m2 = underweight, 18.5-24.9 kg/m2 = normal, 25-29.9 kg/m2 = overweight, >30 kg/m2 = obese
• Uric acid excretion (24-h urine), <435.08 mg/day = normal, ≥435.08 mg/day = high
• Uric acid concentration (mg per 100 ml of urine), <46.63 mg% = normal, ≥46.63 mg% = high

27. Line 173; Table 2. Please explain the difference between Uric Acid Concentration and SUA. I miss a definition and cut-off values for uric acid concentration. ¼ or the individuals with high SUA have normal uric Acid Concentration and vice versa, any comments?
Uric acid concentration was a concentration of uric acid obtained from total 24-h urine, while SUA obtained from blood samples.
As for the individuals with high SUA levels have normal uric acid concentration, this could be affected by many other variables, e.g. total 24-h urine volume. Although individuals have normal renal function, we cannot predict that those who have high SUA levels would certainly have uric acid concentration,

because uric acid concentration is very affected by 24-h urine volume.

28. Line 184; table 3. Please state the blood pressure cut-off values, not enough to just say according to JNC 7 and AHA/ACC 2017.
Cut-off values for blood pressure according to JNC 7 and AHA/ACC 2017 have been added in Table 4 (Table 3 in the previous manuscript has been changed in to Table 4).
• JNC 7 blood pressure category:
prehypertension: SBP of 120–139 mmHg and/or DBP of 80–89 mmHg, hypertension: SBP of ≥140 mmHg and/or DBP of ≥90 mmHg
• AHA/ACC 2017 blood pressure category:
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

29. Line 184; table 3. Why did the authors choose to categorize together pre-HT and HT in the JNC 7 analysis? Why did the authors choose to categorize together normal and elevate blood pressure in the 2017 AHA/ACC analysis?
Same reason with the classification in the analysis of SUA levels, that we want to classified those who had normal tension and those with abnormal tension.

30. Line 186; “The association between SUA levels and BP was statistically significant”. There is rather an association between SUA levels and the chosen BP categories. It would be interesting to see an analysis with blood pressure as a continuous variable.
Analysis of blood pressure and SUA levels as a continuous variable was presented in multiple linear regression (Table 4, now is in Table 5)

31. Line 188; “The risk of high-normal and high SUA levels becoming prehypertension or hypertension was 1.12 times higher than that of normal SUA levels.”, this sentence is difficult to make sense, please consider to revise it.
It has been revised (line 206). The content is also listed below.
“ The risk of subjects with high-normal or high SUA levels for becoming prehypertension or hypertension was 1.12 times higher than those who has normal SUA levels.”

32. Line 193; “In women, the risk of having prehypertension or hypertension was 1.21 times higher in those who had high-normal and high SUA levels than those with normal SUA levels.” It should be high-normal OR high SUA instead of high-normal AND high SUA. And once again, why did the authors choose to categorize together high-normal and high SUA? It would be better to see a presentation with 3 categories or the SUA as a continuous variable.
We have changed “and” in to “or” (line 212-213). The content is also listed below.
“…. having prehypertension or hypertension was 1.21 times higher in those who had high-normal or high SUA levels than those with normal SUA levels.”

33. Line 212; Table 4. The tables should be able to stand alone without the main text, please define SUA etc.
Definition of abbreviation of SUA, BMI, LDL, and HDL have been added in Table 5 (Table 4 in the previous manuscript has been changed in to Table 5)

34. Line 236; “In addition, subjects with high-normal and high SUA levels had a risk of developing prehypertension and hypertension that was 1.12 times higher than those with normal SUA levels.” All those individuals had prehypertension already, they where in the prehypertension subgroup 2007. Therefore it is strange to state that they had greater risk of developing prehypertension.
It has been revised, the phrase “developing prehypertension and hypertension” has been changed in

to “having prehypertension and hypertension” (line 256)

35. Line 410. Figure legend. The figures should be able to stand alone without the main text, and therefore the figure legends should include the definitions of normal, high-normal, high SUA.
Definition of SUA levels have been added in figure legend (line 472-481)

36. I had expected me the authors to discuss a little bit about the different normal blood pressure/prehypertenson definitions. Maybe of interest to mention and compare to the 2018 ESC/ESH guidelines that define SBP 120-129 as normal and SBP 130-139 as high normal. [European Heart Journal (2018) 39, 3021–3104].
In this study, we use JNC 7 as the guideline for defining prehypertension and hypertension because the first data collection was done in 2007. So that, we used JNC 7 for the guideline. We also analyzed the data using ACC/AHA 2017 guideline (in Table 4) in addition to JNC 7 because the second data collection was done in 2017, when in 2017, the hypertension guideline has been updated in to ACC/AHA 2017.
JNC 7 ACC/AHA 2017
Normal SBP < 120 mmHg Normal SBP < 120 mmHg
Prehypertension SBP : 120 – 139 mmHg Elevated SBP : 120 – 129 mmHg
HT stage 1 SBP : 130 – 139 mmHg
Hypertension ≤ 140 mmHg HT stage 2 ≤ 140 mmHg

Reviewer: 3
Reviewer Name
Caress Dean
Institution and Country
Oakland University

Objective:
Written clear and concise, however, it does not illustrate that your study focus is to assess the associations by gender.

Introduction:
1. Line 72: ‘This study was important due to…’ It appears the authors were discussing their research study here. Recommend moving this later in the introduction after discussing the literature.
It has been revised and removed to method section (line 102). The content is also listed below.
“This study was a cross-sectional cohort study of ten years of follow-up (2007–2017) conducted in Mlati Sub-district, Sleman District in the Yogyakarta Special Region, Indonesia.”

2. The introduction is well written and provides great background on the significance of cardiovascular disease and uric acid; however, it does not discuss in detail contrasting studies on the association between SUA, hypertension, and gender.
We have added more literature about some studies with conflicting result about SUA leves, hypertension, cardiovascular, and gender (line 83-95)

Methods:
1. Methods section states family history information was collected, but specific measures was not stated in the methods section and the related results were not stated in the results section.
Family history were not analysed in this study, therefore, we did not state it in the results section.

2. Demographic characteristics (e.g., age) were collected and not stated in the method section.
These have been added in method section (line 142-143). The content is also listed below.
“In 2007, interviews were conducted on 12,073 subjects to obtain demographyc data (e.g. sex and age), ….”

3. Authors state that multiple linear regression analyses were performed but did not state what is assessed until results section, line 213: ‘Multivariable analysis was conducted to describe…’. This sentence should be moved to methods section.
We have added this sentence in method section (line 173-175). The content is also listed below.
“Multivariable analysis was performed using multiple linear regression to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors.”

4. In regression analysis, the model was adjusted for cardiovascular risk factors. Is there a reason why models were not adjusted for age? The research shows that one’s blood pressure level increases with age. Also, research shows men and women’s risk vary by age.
We have re-analyzed the multiple linier regression and added variable age to the analysis (presented in Table 5)

5. Methods section does not state what statistical software was utilized to perform the analyses.
It has been revised (line 168-169). The content is also listed below.
“All data presented later in results section were from data collection in 2017. Data were analysed using IBM SPSS Statistics 20.”

Limitations:
I did not see a limitations section.
We have added limitations on the manuscript (line 325-335). The content is also listed below.
“There were several limitations in this study. First, subject in this study were collected from database made in 2007. From 1500 subjects randomly selected in the beginning of this study, only 733 subjects joined and attend the 2-days examination. More than half of the selected subjects did not attend the examination invitation due to several reasons, thus, this had lessened the total samples of subjects of this study. Second, this study could not present the changes of all measured value over 10-year period because in the prior study in 2007, these laboratory value were not examined, except for blood pressure. Therefore, only the changes on blood pressure which can be presented on the results. Third, the instruments used to measure blood pressure in 2007 and 2017 were different. In 2007, we used sphygmomanometer, whereas in 2017 we used digital automatic blood pressure monitor. Thus, this may lead bias in blood pressure data measurement between 2007 and 2017.”

VERSION 2 – REVIEW

REVIEWER	Stefano Omboni Italian Institute of Telemedicine Italy
REVIEW RETURNED	21-May-2020

GENERAL COMMENTS	The authors have clarified the issues raised by my previous comments. However, this work is still weak. Definitively, it is not a prospective study because relevant data (e.g., SUA) is missing at the first examination (2007). It is not a study in pre-hypertensive subjects because at the last examination (2017), when all relevant data were available, only a fraction of subjects were in the pre-hypertensive status. Nothing can be told about the relation between BP changes and changes in SUA and CV risk factors.

REVIEWER	Georgios Mourtzinis Sahlgrenska University Hospital, Sweden
REVIEW RETURNED	21-May-2020

GENERAL COMMENTS	The authors' revision has obviously improved the manuscript. However, I have the following (minor) concerns that I believe can lead to an even better version of the manuscript. ABSTRACT No need to specify in the abstract that the studied population of 773 derived from a database of 4190. It is enough to describe this in the methods. In the abstract it is enough to say that the studied population in the current study is 733. METHODS "The study was a cross-sectional cohort study of ten years of follow up (207-2017)" is a conflicting statement. After reading the manuscript a lot of times I understood that the study has a 10 years follow-up regarding the blood pressure levels. On the other hand all the SUA analyses (and BMI, Cholesterol, glucose) are cross-sectional. I believe that this study is well conducted and has a lot of strength-points, but is presented in a kind of complicated way. It would be preferred to present the study in amore easy and concrete way with only 2 primary analyses (development from prehpertension between 2007 and 2017, and correlation to SUA in 2017). RESULTS Table 2: I believe that the tables should be able to stand alone without the text; therefore it is good if the authors add the definitions of normal BR/pre-HT/HT and uric acid levels in the table. "The risk of subjects with high-normal or high SUA levels for becoming prehypertension or hypertension was 1.12 times higher than those who have normal SUA levels." This statement means that prehypertensive subjects with high-normal SUA or high SUA have a 1.12 higher risk to stay pre-hypertensive or to develop hypertension, and this is not really correct since the SUA was not from 2007 but from 2017. If SUA was measured prospectively in 2007 we could now say that the subjects with high-normal och high SUA had higher risk. Now that the SUA is taken retrospectively (2017) we can say that in a previous prehypertensive population high-normal SUA or high SUA levels were associated with current prehypertension or hypertension. CONCLUSION It is confusing to read in the conclusion that "after 10-years of follow-up the SUA levels..." since SUA analyses were cross-sectional. The authors missed to mention their main finding in the conclusion, namely that " After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive.". Furthermore, I think that the short information "733 prehypertensive subjects" should stated in the conclusion. My personal opinion is that the results of BMI glucose and lipids do not need to stay in the occlusion. I believe it would be much better to present the occlusions as two parts. For instance: A. "After 10 years of follow-up (2007-2017) of 733 prehypertensive

	subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive." B. In the cross-sectional analyses of SUA in 2017 "the SUA levels in men are significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men".

REVIEWER	Caress Dean Oakland University, USA
REVIEW RETURNED	02-Jun-2020

GENERAL COMMENTS	I want to commend the authors for revising the manuscript. The changes made provide clarification into the methods and study findings; however, additional revisions are warranted. Spelling and grammar: There are a few spelling and grammatical errors through out the manuscript. For instance, line 142, under the data collection section states 'demographyc data". Recommend reviewing the entire document with a spelling/grammatical software. Abstract: The results section, line 43, states the mean (SD) of SUA levels were significantly higher….Recommend adding the year 2017, so the reader does not misinterpret it to be findings from 2007. Conclusion section, another grammatical error, line 55, should be ' with age and body mass index'. Methods: Line 114, authors state that subjects did not take drugs to lower their BP or SUA. How was this known, was this asked in a questionnaire or during the interview? Per my previous comment from the first review, details on measures collected are not stated. For instance, line 143 states family history information was collected, but the manuscript does not state what family history information. For instance, was family history of heart disease collected? Family history of diabetes? Statistical analysis section— Line 168, states "all data presented in results section were from data collection in 2017" recommend rephrasing because it indicates that the results only depict data from 2017 and there is data from 2007 and 2017. The SPSS software should be referenced. Add the in-text citation for the SPSS software used. Results: Superscript 'a' can be removed and the year can be placed in the title of the table. This would enhance the organization of your table, Per Table 2, the total sample for both measures were 733, therefore, the sample size can be placed in the title of the table and removed from next to BP and Uric acid. Discussion: The authors have added the limitations section; however, the limitations section is missing additional details. For instance, the author states that their number of participants decreased from 1,500 to 733 subjects, but the author does not state how this impacted their findings. Similarly, when discussing the limitations of using sphygmomanometer and the Omron, the authors states that there is

	a bias, but do not state the type of bias and the impact of this bias on their findings. Last, prominent limitations are missing. First the authors do not discuss the limitations of using a cross-sectional cohort study design. Second, the authors also do not discuss the generalizability of their results to their sampling method.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Stefano Omboni
Institution and Country
Italian Institute of Telemedicine
Italy

The authors have clarified the issues raised by my previous comments. However, this work is still weak. Definitively, it is not a prospective study because relevant data (e.g., SUA) is missing at the first examination (2007). It is not a study in pre-hypertensive subjects because at the last examination (2017), when all relevant data were available, only a fraction of subjects were in the pre-hypertensive status. Nothing can be told about the relation between BP changes and changes in SUA and CV risk factors.
Thank you so much for your kind advice and review. We decided to change the study design from cross-sectional cohort study into a cross-sectional study only, and make some corrections in the abstract and method section regarding the cross-sectional study design. The contents are also listed below.

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

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

Reviewer: 2
Reviewer Name
Georgios Mourtzinis
Institution and Country
Sahlgrenska University Hospital, Sweden

The authors' revision has obviously improved the manuscript. However, I have the following (minor) concerns that I believe can lead to an even better version of the manuscript.

ABSTRACT

No need to specify in the abstract that the studied population of 773 derived from a database of 4190. It is enough to describe this in the methods. In the abstract it is enough to say that the studied population in the current study is 733.
The sentence has been revised (line 35). The content is also listed below.
“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.”

METHODS
“The study was a cross-sectional cohort study of ten years of follow up (2007-2017)” is a conflicting statement. After reading the manuscript a lot of times I understood that the study has a 10 years follow-up regarding the blood pressure levels. On the other hand all the SUA analyses (and BMI, Cholesterol, glucose) are cross-sectional. I believe that this study is well conducted and has a lot of strength-points, but is presented in a kind of complicated way. It would be preferred to present the study in amore easy and concrete way with only 2 primary analyses (development from prehypertension between 2007 and 2017, and correlation to SUA in 2017).
We have changed the study design into a cross-sectional study only as per advice from you and the other reviewer (line 33 and line 102). Design: A cross-sectional study.
For the data analyses, we have added more explanation in the method section to make it easier for the reader to understand the main content of the manuscript (especially result and discussion section) (line 171-177). The content is also listed below.
“The outcomes of this study were presented in two primary analyses which were (1) blood pressure changes during the period of 2007-2017 to measure the progression from prehypertension (2007) to hypertension (2017) (Table 2), and (2) the association of current BP with SUA levels and cardiovascular risk factors (Table 4 and Table 5). Additional analyses were also being performed to observed the SUA association with cardiovascular risk factors (Figure 2 and Figure 3). The data analyses were mostly performed based on gender in order to know about the gender differences in the analyses mentioned above.”

RESULTS
Table 2: I believe that the tables should be able to stand alone without the text; therefore it is good if the authors add the definitions of normal BR/pre-HT/HT and uric acid levels in the table.
“The risk of subjects with high-normal or high SUA levels for becoming prehypertension or hypertension was 1.12 times higher than those who have normal SUA levels.” This statement means that prehypertensive subjects with high-normal SUA or high SUA have a 1.12 higher risk to stay pre-hypertensive or to develop hypertension, and this is not really correct since the SUA was not from 2007 but from 2017. If SUA was measured prospectively in 2007 we could now say that the subjects with high-normal och high SUA had higher risk. Now that the SUA is taken retrospectively (2017) we can say that in a previous prehypertensive population high-normal SUA or high SUA levels were associated with current prehypertension or hypertension.

We have added the definitions of BP and SUA in Table 2. The content also listed below.
Table 2. Blood Pressure changes after 10 years and Serum Uric Acid Frequency Distribution (n=733)
Variables Frequency (%)
2007 2017
BPa
Normal 0 180 (24.6)
Prehypertension (Pre-HT) 733 (100) 325 (44.3)
Hypertension (HT) 0 228 (31.1)
SUAb
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

Thank you for your insightful comment on the result section. We have revised the sentence regarding the association between SUA and BP (218-219). The content also listed below.
“In subjects with previous history of prehypertension, high-normal SUA or high SUA levels were associated with current prehypertension or hypertension.”

CONCLUSION
It is confusing to read in the conclusion that “after 10-years of follow-up the SUA levels...” since SUA analyses were cross-sectional. The authors missed to mention their main finding in the conclusion, namely that “ After 10 years, among the 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive.”. Furthermore, I think that the short information “733 prehypertensive subjects” should stated in the conclusion. My personal opinion is that the results of BMI glucose and lipids do not need to stay in the occlusion.
I believe it would be much better to present the occlusions as two parts. For instance:
A. “After 10 years of follow-up (2007-2017) of 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) became hypertensive.”
B. In the cross-sectional analyses of SUA in 2017 “the SUA levels in men are significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men”.
Thank you for your advice to the writing of the conclusion. We were greatly helped by your suggestion in writing our conclusions section that is clear and to the point. We have rewritten the conclusions as per your suggestion (line 360-365) which are listed below.
“In conclusion, after 10 years of follow-up (2007-2017), of 733 prehypertensive subjects, 180 (24.6%) returned to normal blood pressure, 325 (44.3%) remained in a prehypertensive state, and 228 (31.1%) got hypertension. In the cross-sectional analyses of SUA in 2017, the SUA levels in men are significantly higher than those in women. Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men.”

Reviewer: 3

Reviewer Name
Caress Dean
Institution and Country
Oakland University, USA

I want to commend the authors for revising the manuscript. The changes made provide clarification into the methods and study findings; however, additional revisions are warranted.
Spelling and grammar:
There are a few spelling and grammatical errors through out the manuscript. For instance, line 142, under the data collection section states ‘demographyc data”. Recommend reviewing the entire document with a spelling/grammatical software.
We apologized for the issues of spelling/grammatical errors. We have tried to reread and made some revisions on the spelling/grammatical error. Hope that our latest revised manuscript has met your

requirement.

Abstract:
1. The results section, line 43, states the mean (SD) of SUA levels were significantly higher….Recommend adding the year 2017, so the reader does not misinterpret it to be findings from 2007.
We have added the year 2017 in the sentence. The content is also listed below.
“The 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).”

2. Conclusion section, another grammatical error, line 55, should be ‘ with age and body mass index’.
We have revised the conclusion part of the abstract. The content is also listed below.
“We concluded that after 10 years, of 733 prehypertensive subjects, 31.1% became hypertensive. The SUA levels in men are significantly higher than those in women. Moreover, High-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men.”

Methods:
1. Line 114, authors state that subjects did not take drugs to lower their BP or SUA. How was this known, was this asked in a questionnaire or during the interview?
Yes, the data about drug consumption were collected during the interview. We have added this matter in the method section in data collection (line 145). The content is also listed below.
“….. patient’s history of consuming hypertension and uric acid drugs, and to perform physical and laboratory examinations”

2. Per my previous comment from the first review, details on measures collected are not stated. For instance, line 143 states family history information was collected, but the manuscript does not state what family history information. For instance, was family history of heart disease collected? Family history of diabetes?
We apologized that our previous answer hasn’t met your requirement. We have added more information about data collected from interviews, including a family history of hypertension and diabetes mellitus, patient’s history of diabetes mellitus, and patient’s history of consuming hypertension and uric acid drugs (line 143-146). The content is also listed below.
“In 2007, interviews were conducted on 12,073 subjects to obtain demographic data (e.g. sex and age), family history of hypertension and diabetes mellitus, patient’s history of diabetes mellitus, patient’s history of consuming hypertension and uric acid drugs, and to perform physical and laboratory examinations”

3. Statistical analysis section—
Line 168, states “all data presented in results section were from data collection in 2017” recommend rephrasing because it indicates that the results only depict data from 2017 and there is data from 2007 and 2017.
The SPSS software should be referenced. Add the in-text citation for the SPSS software used.
The sentence has been revised (line 178), and in-text citation for SPSS software used has been added (line 178-179).
Reference for SPSS Software (ref. 24):
IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp

Results:
1. Superscript ‘a’ can be removed and the year can be placed in the title of the table. This would enhance the organization of your table,

Superscript ‘a’ has been removed and the title has been revised by adding the year 2017.
Table 1. Characteristics of Subjects by Gender in 2017 in Mean (SD)
Variables Men Women p-value
n=306 n=427
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/m2) 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)

2. Per Table 2, the total sample for both measures were 733, therefore, the sample size can be placed in the title of the table and removed from next to BP and Uric acid.
The sample of 733 has been added to the title in Table 2.
Table 2. Blood Pressure changes after 10 years and
Serum Uric Acid Frequency Distribution (n=733)
Variables Frequency (%)
2007 2017
BPa
Normal 0 180 (24.6)
Prehypertension (Pre-HT) 733 (100) 325 (44.3)
Hypertension (HT) 0 228 (31.1)
SUAb
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

Discussion:
1. The authors have added the limitations section; however, the limitations section is missing additional details. For instance, the author states that their number of participants decreased from 1,500 to 733 subjects, but the author does not state how this impacted their findings.
The participants were randomly selected from 4190 patients and those who agreed to follow minimal of two examinations were only 733 patients. Although the total sample collected was decrease from 1500 to 733 subjects, it has been met the minimum sample size requirement for this study based on sample size calculation. The discussions are mentioned in line 338-346. The content is also listed below.
“From 1500 subjects randomly selected at the beginning of this study, only 733 subjects joined and attend the 2-days examination. More than half of the selected subjects did not attend the examination invitation due to several reasons, thus, this had lessened the total samples of subjects of this study. However, a total sample of 733 has met the minimum sample requirement for this study based on

sample size calculation (a minimum sample size of 661 subjects are needed for this study). We invited 1500 subjects at the beginning of this study to anticipate any subjects that could not participate in this study due to any reasons, so that the minimum number of samples could still be met. This was one of the difficulties we met since this study was a community-based study."

2. Similarly, when discussing the limitations of using sphygmomanometer and the Omron, the authors states that there is a bias, but do not state the type of bias and the impact of this bias on their findings.
We have revised the limitations of using a sphygmomanometer and digital automatic blood pressure measurement by adding the bias type (line 351-352) and its impact on our study finding (line 352-357). The content is also listed below.
"Third, the instruments used to measure blood pressure in 2007 and 2017 were different that might cause instrument bias. In 2007, we used sphygmomanometers, whereas in 2017 we used digital automatic blood pressure monitors. Thus, this may lead to bias in blood pressure data measurement between 2007 and 2017. Nevertheless, we tried to minimize the bias by calibrating both the sphygmomanometers and digital automatic blood pressure monitors before data collection, so that, the blood pressure data were all accurate."

3. Last, prominent limitations are missing. First the authors do not discuss the limitations of using a cross-sectional cohort study design. Second, the authors also do not discuss the generalizability of their results to their sampling method.
We finally decided to change the study design into a cross-sectional study only as per comments and advice from the other reviewers.
We could generalize our findings and conclusions to the previous prehypertension population (from Mlati Study Database in 2007) which amounts to 4190 patients. The discussion about generalizability has been added in line 345-347. The content is also listed below.
"The findings of this study were expected to be generalized to the 4190 prehypertensive patients whom collected from "Mlati Study" database in 2007."

VERSION 3 – REVIEW

REVIEWER	Stefano Omboni Italian Institute of Telemedicine Italy
REVIEW RETURNED	01-Jul-2020

GENERAL COMMENTS	I have no further remarks.

REVIEWER	Caress Dean Oakland University, USA
REVIEW RETURNED	14-Jul-2020

GENERAL COMMENTS	I applaud the authors for the revisions. I have very minor suggestions. Abstract • Error in the results section. Should be 31.1% instead of 31,1%. Same for 24.6% • Grammatical error in conclusion. Should be "Moreover, high-normal" Methods • Unfortunately, the changes made to the statistical analyses is confusing. The purpose of the statistical analyses section is to explain the analyses performed to meet the study's objectives.

	Tables and figures should not be discussed in this section, because they are results (therefore they should only be stated in the results section). Overall, lines 171-176 only restate the aim of the study and does not describe specific analyses (e.g., linear regression) performed. • Delete the word 'being' from line 175

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
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Italian Institute of Telemedicine
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I have no further remarks

Reviewer: 3

Reviewer Name
Caress Dean
Institution and Country
Oakland University, USA

I applaud the authors for the revisions. I have very minor suggestions.
Abstract
• Error in the results section. Should be 31.1% instead of 31,1%. Same for 24.6%
We have revised the abstract (line 41-42). The content is also listed below.
"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."

• Grammatical error in conclusion. Should be "Moreover, high-normal"
The error have been revised. The content is also listed below.
"Moreover, high-normal and high SUA levels were significantly associated with prehypertension and hypertension in women but not in men."

Methods
• Unfortunately, the changes made to the statistical analyses is confusing. The purpose of the statistical analyses section is to explain the analyses performed to meet the study's objectives. Tables and figures should not be discussed in this section, because they are results (therefore they should only be stated in the results section). Overall, lines 171-176 only restate the aim of the study and does not describe specific analyses (e.g., linear regression) performed.
• Delete the word 'being' from lina175
Thank you for your detailed review. As per your advice, we have removed table and figure from the

method section (in statistical analysis) and added specific analyses for the outcomes measured. The word ‘being’ has also been removed. The content is also listed below.
“The outcomes of this study were presented in two primary analyses which were (1) blood pressure changes during the period of 2007-2017 to measure the progression from prehypertension (2007) to hypertension (2017), and (2) the association of current BP with SUA levels and cardiovascular risk factors. Additional analyses were also performed to observe the SUA association with cardiovascular risk factors. The data analyses were mostly performed based on gender to know about the gender differences in the analyses mentioned above.
Data presented later in the results section were collected in 2007 and 2017. Data were analysed using IBM SPSS Statistics for Windows, Version 22.0.[24] The data consisted of continuous and categorical data, which were expressed as the mean (SD) for continuous data and as numbers and percentages for categorical data. The continuous variables were analysed and compared by independent samples t-tests and nonparametric Mann-Whitney U tests. The categorical variables were analysed and compared by Pearson chi-square tests. Blood pressure changes during the period of 2007-2017 were presented using frequencies and percentages. The associations of current BP with SUA levels and gender were analysed using the Pearson chi-square test. Multivariable analysis was performed using multiple linear regressions to describe the association between SUA levels and BP, with adjustment for age and cardiovascular risk factors. Additional analysis to observe the association between SUA levels and cardiovascular risk factors and gender were performed using independent samples t-tests and nonparametric Mann-Whitney U tests. The significance of associations between categorical and numerical variables was determined using 95% confidence intervals (CIs).”

VERSION 4 – REVIEW

REVIEWER	Caress Dean Oakland University, USA
REVIEW RETURNED	29-Jul-2020

GENERAL COMMENTS	No comments for the authors.