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Escuela Profesional de Medicina Humana

Association of serum uric acid and metabolic syndrome among health personnel from a public hospital in Peru

Trabajo de Investigación para obtener el Grado Académico de Bachiller en Medicina Humana

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Lima, marzo del 2021

DECLARACIÓN JURADA DE AUTORÍA DEL TRABAJO DE INVESTIGACIÓN

Anderson Nelver Elias Soriano Moreno, de la Facultad de Ciencias de la Salud , Escuela Profesional de Medicina Humana, de la Universidad Peruana Unión.

DECLARO:

Que la presente investigación titulada: **"Association of serum uric acid and metabolic syndrome among health personnel from a public hospital in Peru"** constituye la memoria que presenta la estudiante Brenda Mireya Galindo Yllu para obtener el Grado Académico de Bachiller en Medicina Humana, cuyo trabajo de investigación ha sido realizado en la Universidad Peruana Unión bajo mi dirección.

Las opiniones y declaraciones en este informe son de entera responsabilidad del autor, sin comprometer a la institución.

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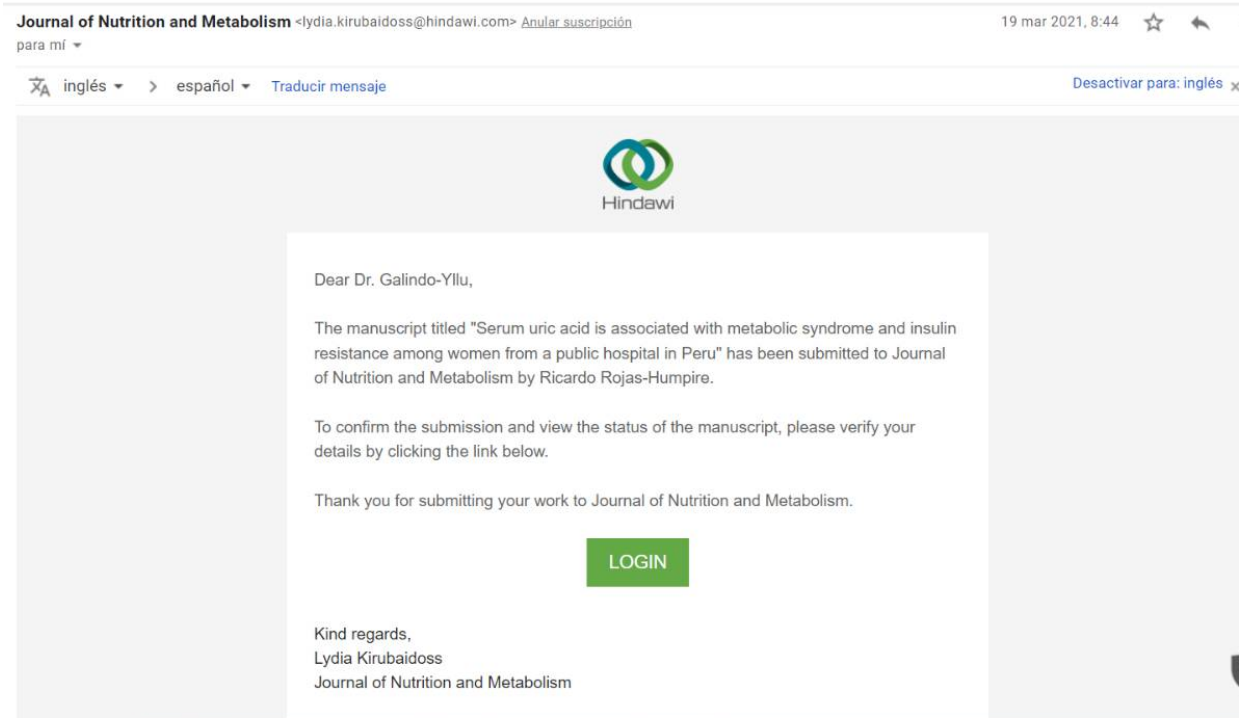

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Serum uric acid is associated with metabolic syndrome and insulin resistance among women from a public hospital in Peru

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Abstract

We explored the association between serum uric acid (SUA) to metabolic syndrome (MetS) and insulin resistance (IR) among health personnel from a public hospital in Peru in a cross-sectional study with data from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases of Huaycán Hospital. MetS was defined according to Latin American Diabetes Association (ALAD) criteria and IR with surrogate IR markers, triglycerides to HDL-C ratio (TG/HDL-C), and triglycerides to glucose index (TyG). The association between SUA to MetS and IR was determined using Poisson regression models in a sample of 292 participants with an average age of 46.2 ± 10.6 years. The total prevalence of MetS was 38% and the adjusted regression models showed that women with SUA in the high tertile increased the prevalence of MetS (aRP:1.71, 95%CI: 1.07 – 2.74), hypertriglyceridemia (aRP:2.02, 95%CI: 1.13 – 3.62) and elevated TyG (aRP:1.90, 95%CI: 1.12 – 3.21) compared to low tertile of SUA. We concluded that SUA is stronger associated with MetS and IR in women than the overall population of health personnel. On the other hand, more research is required and lifestyle interventions to control risk factors to MetS and IR in women.

Keywords: *Metabolic Syndrome, Insulin Resistance, Serum Uric Acid, Life Style, women.*

Introduction

In recent decades, metabolic syndrome (MetS) has increased dramatically and is considered one of the most important risk factors for cardiovascular disease [1]. MetS is a set of interrelated clinical disorders, including dyslipidemia, central obesity, glucose intolerance, and high blood pressure [2]. Its presence is involved in the development of various diseases such as fatty liver, diabetes mellitus (DM), cancer, as well as cardiovascular and infectious diseases [3,4]. Prior research indicates that insulin resistance (IR) plays an important role in the pathophysiology of this condition [5]. Considering this, TyG and TG/HDL ratio are simple and practical surrogate markers for insulin resistance that can be used in primary health care[6].

Serum uric acid (SUA) is an excretory metabolite produced by the metabolism of the purines [7]. It can be elevated as a result of the low renal filtration rate, overproduction of purine precursors, and diet [8]. SUA regulates proinflammatory pathways in vascular smooth muscle cells and oxidative stress at the mitochondrial level [9]. Additionally, it is involved in the mechanisms of metabolic dysregulation mediated by excess fructose [10]. Previous studies have reported the association of SUA concentrations and MetS, IR, DM, and other cardiometabolic diseases [11,12].

Several Latin American countries have exhibited a high prevalence of MetS (>20%) [13]. The biological diversity of the Latino population leads to changes in the prevalence and development of certain diseases such as metabolic diseases [14]. In this regard, a study developed in a group of Brazilian women found that afro-descendant, lower handgrip strength/Body Mass Index (BMI), and lower levels of estradiol were associated with MetS. However, SUA was not evaluated [15]. On the other hand, healthcare personnel are important agents of public health and quality of life in communities [16]. Moreover, they are exposed to different risk factors that could trigger metabolic disorders [17]. For this reason, we found it appropriate to conduct a study in a Latin population, specifically in a Peruvian hospital, to analyze the association of MetS with SUA and IR stratified by sex.

Methods

Design of the primary study

We conducted a cross-sectional analytical study using data from adult workers of both sexes who were part of the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases at the *Hospital de Huaycán* II-1, Lima, Peru, in 2019. In this prevention plan, clinical evaluation and laboratory tests are performed to prevent and diagnose diseases in workers. Trained personnel collected data on demographic characteristics, lifestyle behaviors, anthropometric measurements, and laboratory data using questionnaires. Likewise, workers were explained that their medical data would be used for future research, and written informed consent was obtained from all participants.

Eligibility criteria

We included Health Personnel Data from *Hospital de Huaycan*. Pregnant women, participants who did not fill out the form, participants who did not do laboratory tests, and those who did not present plausible data for the study were excluded. We eliminated 75 observations due missing

data (n = 46,12.5%) and implausible data (n = 29, 7.9%) (Table S1 in the Supplementary Appendix).

Definition of variables

Exposure: SUA

SUA concentration was categorized into tertiles according to sex-specific distribution: T1 (2.5 - 4.4 mg/dL), T2 (4.5 - 5.0 mg/dL) and T3 (5.1 - 6.3 mg/dL) for men, and T1 (1.2 - 3.1 mg/dL), T2 (3.2 - 3.8 mg/dL) and T3 (3.9 - 6.8 mg/dL) for women.

Outcome: MetS

MetS was defined according to the criteria of the Latin American Diabetes Association (ALAD) 2010 [18], including waist circumference (WC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose (FG), glycosylated hemoglobin (HbA1c) and some data from the workers' registry. The criteria for SM were central obesity (WC ≥ 94 cm in men and ≥ 88 cm in women) and two or more of the following: hypertriglyceridemia (TG >150 mg/dL or in specific hypolipidemic therapy), low HDL-C (HDL-C < 40 mg/dL in men and < 50 mg/dL in women), high blood pressure (SBP ≥ 130 mmHg and/or SBP ≥ 85 mmHg or on antihypertensive treatment) or impaired glucose regulation (SBP ≥ 100 mg/dL, HbA1c > 5.6% or in treatment for DM).

Other Variables

Triglycerides to HDL-cholesterol ratio (TG/HDL-C) and triglycerides to glucose index (TyG) were selected as insulin resistance indexes because they are accurate indicators of insulin resistance diagnosis in many populations [19]. TG/HDL-C was calculated using the following formula: fasting TG (mg/dL) / fasting HDL-cholesterol (mg/dL), and categorized into elevated (≥ 3) and normal TG/HDL-C [20]. TyG was calculated using the formula: Ln[fasting TG (mg/dL) × fasting plasma glucose (mg/dL)/2], and categorized into elevated (≥ 8.65) and normal TyG [21].
Nutrition, smoking, alcohol consumption, and physical activity were extracted from the FANTASTICO, a healthy lifestyle questionnaire, validated in Peru [30]. The variables were categorized into "good" nutrition (balanced diet almost always and no consumption of sugar, salt, junk food or high fat) and "bad" nutrition (balanced diet sometimes or rarely and consumption of sugar, salt, junk food and/or high fat), “physically active" (active exercise at least 20 min four or more times per week) and "physically inactive" (active exercise at least 20 min one to three times per week or less than one time per week), "low-moderate alcohol consumption" (0-7 drinks per week) and "high alcohol consumption" (8-12 or more drinks per week), "non-smoking" (no smoking in last year) and "smoking" (smoked this year or smokes 1-10 cigarettes per day or more than 10 per day). The family history of DM was extracted from the FINDRISC questionnaire and was categorized as "Yes" and "No". The variables of age, sex, type of employee, BMI, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), total cholesterol, and body fat percentage were also included.

Statistical Analysis

Data analysis was performed with RStudio V1.3 software. Categorical variables were described in absolute and relative frequencies. Numerical variables were described with mean and standard deviation. To assess the association between SUA level (as a numerical value and categorized by tertiles) and metabolic syndrome, prevalence ratios (PR) and their respective 95% confidence intervals (95% CI) were determined using Poisson regression models with robust variance. The first model examined the bivariate association between SUA and metabolic syndrome. The second model was adjusted for age and sex in the overall population and by age in the sex-stratified population. The third model was additionally adjusted for BMI variables, nutrition, smoking, alcohol consumption, physical activity, and family history of DM. In the same way, the analysis of MetS components and insulin resistance markers had adjustments for these potential confounders. The association analysis was stratified by sex and a p-value <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board of the *Hospital de Huaycán* (N°023-2020) and of the Faculty of Health Sciences of the Universidad Peruana Unión (No. 00136-2020).

Results

General characteristics of the study population

We analyzed the data from a total of 292 individuals (202 women and 90 men). The mean age of the participants was 46.2 ± 10.6 years, the largest proportion of the workers were in healthcare positions (66.5%), were non-smokers (87.7%), had good nutrition (71.6%), had no family history of DM (65.1%), reported low-moderate alcohol consumption (93.5%) and were physically active (81.5%). The mean concentration of SUA was 3.9 ± 1.0 mg/dL in the general population, 3.49 ± 0.88 mg/dL in women, and 4.70 ± 0.85 mg/dL in men. The characteristics of both MetS and no-MetS groups are presented in Table S2 in the Supplementary Appendix.
The highest proportion in the group with MetS was healthcare workers between 50 to 60 years of age. The MetS group showed a higher mean of VLDL-C, SBP, DBP, BMI, waist circumference, body fat, cholesterol, triglycerides, and HbA1c compared to the no-MetS group in both sexes. However, glucose, HDL-C, and LDL-C revealed different behavior by sex (Table S2 in the Supplementary Appendix).

MetS prevalence by tertiles of SUA concentration

The prevalence of MetS in the total population was 38%, 36.7% in men, and 38.6% in women. The components of MetS changed by each SUA tertile. In this way, more MetS components were pooled in the high tertile than in the low tertile in both men (24.1 vs 12.1%) and women (31.3 vs 6.8%), as shown in Figure 1.

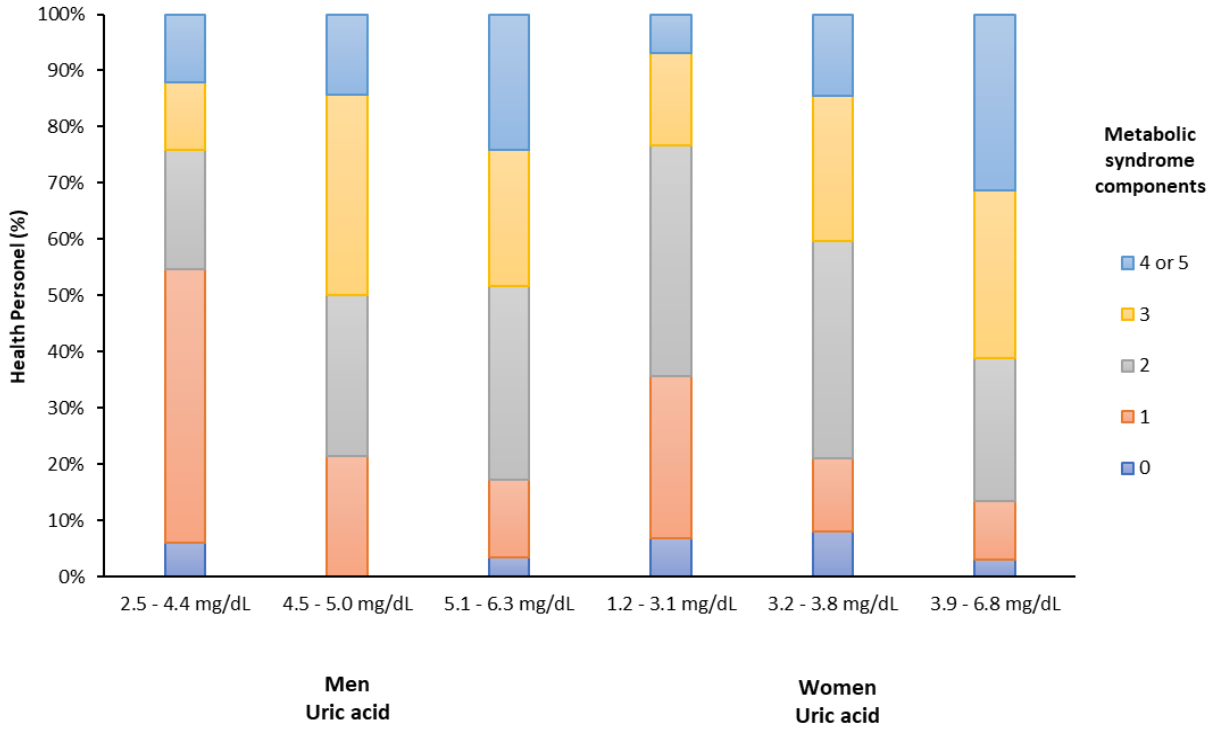

Figure 1: Components of metabolic syndrome frequency according to tertiles of uric acid. T1 (2.5 - 4.4 mg/dL), T2 (4.5 - 5.0 mg/dL) and T3 (5.1 - 6.3 mg/dL) in men; T1 (1.2 - 3.1 mg/dL), T2 (3.2 - 3.8 mg/dL) and T3 (3.9 - 6.8 mg/dL) in women.

Poisson regression models with robust variance to assess the association between SUA tertiles and metabolic syndrome

All regression models are presented in table 2. In the crude Poisson regression model to calculate the association between SUA tertiles and MetS in the overall population, compared with the low tertile group, the prevalence of MetS in the intermediate and high tertile was higher (PR = 1.64, 95%CI: 1.10 - 2.46 and PR = 1.76, 95%CI: 1.19 - 2.62, respectively). Both were statistically significant. In the second model, the association maintained the direction and statistical significance (PR = 1.60, 95%CI: 1.07 - 2.39 and PR = 2.04, 95%CI: 1.33 - 3.12, respectively). In the third model, there was no statistical difference between the intermediate and high tertile compared to the low tertile (PR = 1.34, 95%CI: 0.92 - 1.95 and PR = 1.40, 95%CI: 0.96 - 2.05, respectively).

When stratified by sex in the second model, men had a higher prevalence of MetS for the intermediate tertile compared to the low tertile (PR = 2.36, 95%CI: 1.12 - 4.95), which was statistically significant. In the third model, the association maintained the pattern (PR = 1.79; 95%CI: 0.98 - 3.23), although there was no statistical difference. Women in the second model

had a higher prevalence of MetS for the high tertile compared to the low tertile (PR = 2.43; 95%CI: 1.50 - 3.93), which was statistically significant. In the third model, the association maintained the pattern and statistical significance (PR = 1.71, 95%CI: 1.07 - 2.74).

The fully adjusted PRs for each 1 mg/dl increment in SUA concentration for MetS were 1.22 (95% CI 1.04 - 1.44) in the overall population and 1.24 (95% CI 1.01 - 1.52) in women. In men, no association was found.

Table 1: Association between SUA tertiles to MetS components and insulin resistance

Metabolic Syndrome Components	**Men**			**Women**		
	T1	**T2 PR (95%CI)**	**T3 PR (95%CI)**	**T1**	**T2 PR (95%CI)**	**T3 PR (95%CI)**
Visceral Obesity	1	1.34 (0.64 – 2.82)	1.13 (0.52 – 2.43)	1	1.11 (0.64 – 2.82)	1.23 (0.79 – 1.94)
High blood pressure	1	0.94 (0.27 – 3.24)	1.00 (0.33 – 3.05)	1	0.67 (0.17 – 2.63)	1.53 (0.50 – 4.71)
Hypertriglyceridemia	1	2.28 (0.98 – 5.29)	1.94 (0.81 – 4.65)	1	1.32 (0.70 – 2.47)	2.02 (1.13 – 3.62)*
Hyperglycemia	1	1.18 (0.66 – 2.10)	1.29 (0.73 – 2.25)	1	1.02 (0.68 – 1.54)	1.02 (0.67 – 1.53)
low HDL-C	1	0.36 (0.09 – 1.46)	0.45 (0.13 – 1.60)	1	1.18 (0.69 – 2.01)	1.27 (0.75 – 2.14)
Elevated TG/HDL-C	1	1.82 (0.84 – 3.95)	1.67 (0.88 – 3.94)	1	1.24 (0.70 – 2.22)	1.44 (0.83 – 2.50)
Elevated TyG index	1	1.89 (0.83 – 4.28)	1.39 (0.59 – 3.24)	1	1.30 (0.74 – 2.30)	1.90 (1.12 – 3.21)*

PR, Prevalence ratio; 95% CI, 95% confidence interval; TG/HDL-c, Triglycerides to HDL-cholesterol ratio; TyG, Triglyceride glucose index. [a]Non adjusted; [b]Adjusted for HbA1c, LDL-c, Uric acid and alcohol consumption; *p<0.05; **p<0.01.

Association between SUA tertiles and MetS components and insulin resistance markers

In the multivariable model analysis, after adjusting for confounding variables, the high tertile of SUA was significantly associated with elevated the prevalence of hypertriglyceridemia (PR: 2.02, 95%CI: 1.13 – 3.62) and high TyG index (PR: 1.90, 95%CI: 1.12 -3.21) in women. There was no significant association in the men group (Table S2 in the Supplementary Appendix).

Table 2: Prevalence ratio for MetS according to SUA tertiles by overall population and sex

	Serum uric acid (Tertiles)			Serum uric acid (mg/dL)
	T1	T2	T3	
	PR	PR (95% CI)	PR (95% CI)	PR (95% CI)
Men				
Metabolic syndrome				
Model 1[a]	1	2.19 (1.01 - 4.72)*	2.11 (0.98 - 4.57)	1.40 (0.98 - 2.00)
Model 2[b]	1	2.36 (1.12 - 4.95)*	1.73 (0.80 - 3.75)	1.29 (0.91 - 1.83)
Model 3[c]	1	1.79 (0.98 - 3.23)	1.31 (0.71 - 2.42)	1.23 (0.93 - 1.64)
Women				
Metabolic syndrome				
Model 1[a]	1	1.62 (0.94 - 2.80)	2.72 (1.69 - 4.38)**	1.49 (1.26 - 1.76)**
Model 2[b]	1	1.46 (0.85 - 2.50)	2.43 (1.50 - 3.93)**	1.45 (1.23 - 1.72)**
Model 3[c]	1	1.16 (0.68 - 1.96)	1.71 (1.07 - 2.74)*	1.24 (1.01 - 1.52)*

T1, Low tertile; T2, Middle tertile; T3, high tertile; CI, Confidence interval; PR, Prevalence ratio; * $p < 0.05$; ** $p < 0.01$; a Non adjusted; b Adjusted for age; c Adjusted for age, BMI, diabetes family history, physical activity, feeding habits, alcohol consumption, and smoking. Prevalence ratios and confidence intervals calculated with Poisson regression with robust variance

Discussion

In the present study, we evaluated the association of SUA to MetS and insulin resistance in health personnel from Peru, after adjustment by potential confounders. Our results showed that health personnel with MetS present more alterations in the laboratory and anthropometric factors compared with their no-MetS peers. In women, differences between SUA and Mets were more significant than men.

SUA is an antioxidant metabolite that maintains the stability of the vascular endothelium [7]. High SUA levels produce a pro-oxidant environment, endothelial dysfunction, and mitochondrial damage. Additionally, the increase of reactive oxygen species (ROS) and inflammatory proteins (interleukin-1, interleukin-6, and TNF-alpha) are involved in the development of IR and MetS [9]. Previous studies have shown that elevated SUA levels predispose to IR and MetS [22,23]. Some studies infer that high SUA levels may be both a risk factor and an outcome of some metabolic disorders [24,25].

The association between SUA and MetS was stronger in women than in the overall population in our results. Similarly, some studies in Asian populations show that the sex-specific association of SUA and MetS was stronger in women than in men [26,27]. Age could also explain our results

since most of our population was over 40. In this sense, a study in the Taiwanese military service population showed the risk of developing MetS was 2-fold higher in > 40 years women with high levels of SUA compared to < 40 years women [28]. Another study in an older Italian population found that women with high levels of SUA showed a 58% increased risk of MetS, while in men no association between SUA and MetS was found [29]. Aging and changes in the endocrine system may explain the susceptibility of women in the development of MetS and high levels of SUA [43]. Besides, estrogens show an inverse relationship with SUA levels, while testosterone increases them. This fact was observed in both sexes [30].

In the present study, we found the high tertile of SUA was significantly associated with hypertriglyceridemia in women. It is consistent with a longitudinal study in China that found that the highest quartile of SUA had 45.6% of cumulative incidence to hypertriglyceridemia [31]. In this sense, Jing Wu et al., showed that uric acid‐lowering therapy effectively improved serum cholesterol and triglyceride levels up to 80mg/dL [32].

SUA is strongly associated with dyslipidemia and other metabolic disorders, having IR as a common factor, mainly in women [33]. We found that the high tertile of SUA is associated with high TyG in women. In the same way, a study performed in Korea showed that TyG index was significantly higher in the hyperuricemia than in the non-hyperuricemia group (8.96 vs. 8.54, $P<0.001$) [34]. Furthermore, a study in ST-elevation myocardial infarction (STEMI) patients demonstrated that the highest quartile of TyG had the incidence of major adverse cardiovascular and cerebral events (MACCEs) was higher[35]. On the other hand, Elizalde-Barrera et al. did not find any correlation between uric acid levels with Homeostatic model assessment of β-cell function (HOMA 1B) ($r = 0.102$, $p = 0.343$), nor with HOMA of insulin resistance (HOMA 1IR) ($r = 0.158$, $p = 0.117$), when stratified by sex women had a significant correlation with HOMA 1IR (0.278, $p = 0.01$), but not with HOMA 1B (0.138, $p = 0.257$)[36].

MetS is a group of insulin-related disorders that increase the risk of multiple diseases such as DM, hypertension, cancer, non-alcoholic fatty liver, chronic kidney disease, brain disorders, and susceptibility to infections [3,9]. For that reason, MetS risk factors research is important to establish therapeutic objectives and primary prevention. Reducing the incidence and prevalence of MetS may help to reduce the risk of developing chronic diseases that demand a high cost for the health system [1]. TyG is an obtainable and cost-effective non-insulin-based IR index that is very useful in primary health care [6]. The economic development of Peru has allowed for the adoption of some lifestyles similar to those in high-income countries, such as increased sedentarism, consumption of high-calorie foods, and development of metabolic disorders [37].

Assessing lifestyles with valid instruments is important to establish which factors are relevant to decreased incidence of MetS in susceptible populations such as health personnel, who have an environment with higher levels of stress, depression, burnout syndrome, bad sleep quality, and metabolic disorders [16,17]. On the other hand, women appear to be more susceptible to some metabolic disorders than men [27,38]. More research is necessary to establish stronger risk factors for MetS in this population.

Strengths and limitations

To the best of our knowledge, this is the first study that assessed the association between SUA and MetS conducted in health personnel from Peru. The current study provides evidence on the dose-response relationship between SUA and MetS. Other strengths of our study included the adjustment of several potential confounders. However, some limitations should be highlighted. First, it was not possible to assess causality among the variables due to the nature of the cross-sectional design of the study. Second, although several confounding factors were controlled in the present analysis, there were confounding factors that we did not consider, such as glomerular filtration rate, liver enzymes, antihyperuricemic agents, and others. Third, information collected from the Plan for the Prevention of Communicable and Non-Communicable Diseases of the *Hospital de Huaycán* was used, which could present some errors when filled in; however, a rigorous evaluation of the quality of the data was carried out to reduce the possibility of biased information.

Conclusions

We found evidence that SUA is positively associated with the prevalence of MetS in a population of health personnel at a public hospital from Peru being the association stronger in women than in the overall population. Additionally, the increased concentration of SUA is an independent factor for hypertriglyceridemia and elevated insulin resistance marker TyG. Longitudinal studies are needed to confirm these results and to determine significant risk factors for MetS considering the cultural environment of each population. More research in lifestyles with valid instruments and additional biomarkers control could decrease the prevalence of MetS and other chronic non-communicable diseases.

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A preliminary analysis of this population was presented and accepted in the 18th Annual World Congress Insulin Resistance Diabetes & Cardiovascular Disease in the abstracts meeting category.

Data Availability

The datasets used and analyzed for this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Funding

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Supplementary Appendix

S1. Title of data: Data excluded by implausible or missing values.
Description of data: Data excluded from the Plan for the Prevention and Surveillance of Communicable and Non-Communicable Diseases by implausible or missing values.

S2. Title of data: General characteristics of the healthcare personnel
Description of data: General characteristics of the healthcare personnel by sex and MetS