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Serum uric acid to creatinine ratio as a predictor of insulin resistance, β cell function, and metabolic syndrome in normal Korean adults: a cross-sectional study

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Abstract

Background This study aimed to determine the relations between serum uric acid to creatinine ratio(SUA/Cr) and insulin resistance, pancreatic β cell function, and outbreak of metabolic syndrome (MetS) in normal Korean participants.

Materials and methods This study included 14,984 participants without diabetes mellitus or gout who participated in the 2019–2021 Korea National Health and Nutrition Examination Survey. To evaluate insulin resistance and β cell function, the homeostasis model assessment (HOMA) was used. Insulin resistance was suggested by HOMA-IR, and β cell function was presented as HOMA-β. Multivariate logistic linear regression analysis was used to identify the factors affecting HOMA-IR, HOMA-β, and MetS. Cut-off values of SUA/Cr to predict insulin resistance, β cell dysfunction, and MetS risk were also been suggested.

Results Consequent to dividing SUA/Cr into tertiles, the higher the SUA/Cr, the higher the HOMA-IR and dysfunction of β cell, and the rate of MetS increased ($p < 0.05$). SUA/Cr was associated with insulin resistance, β cell function, and existence of MetS (adjusted odds ratio [OR]; 1.231 [95% confidence interval [CI]; 1.204–1.259], 1.033 [1.011–1.057], and 1.065 [1.026–1.106], respectively). In addition, the group with the clinical significance was the 3rd tertile. In this group, insulin resistance, β cell dysfunction, and MetS risk could be predicted when SUA/Cr value was 8.2716, 8.8710, and 7.9762, respectively. Based on the total number of people, meaningful SUA/Cr values were 7.0175, 6.7925, and 6.9369.

Conclusions The SUA/Cr may be a useful marker for predicting the insulin resistance, β cell function and incidence of MetS in normal Korean participants.

Keywords Serum uric acid to creatinine ratio, Metabolic syndrome, Insulin resistance, β cell function, HOMA-IR, HOMA-β

Introduction

The increase in the incidence of diabetes mellitus (DM) has become a global issue. Based on an analysis of the global burden of disease research data from 1990 to 2021, researchers at the University of Washington reported that the number of patients with DM worldwide is expected

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to reach 1.3 billion by 2050, which is more than double the current number [1].

DM is caused by two mechanisms; pancreatic β cell dysfunction that reduces insulin secretion and insulin resistance. Among the methods to measure them, the homeostasis model assessment (HOMA) is widely used epidemiologically [2]. The HOMA model needs fasting glucose and basal insulin concentration to evaluate insulin resistance represented by HOMA-IR and β cell function called HOMA-β [3].

Metabolic syndrome (MetS) is a major global public health concern. There is limited evidence that these serum biomarkers can be used to detect MetS onset [4].

Serum creatinine is an indicator of renal function, and research has shown that serum uric acid (SUA) levels can influence the risk of DM, hypertension, and MetS [5]. Previous studies have suggested that the serum uric acid to creatinine ratio (SUA/Cr) may predict the complication incidence of type 2 DM better than SUA alone [6]. Since insulin resistance and residual β cell function are triggers for DM, the possibility that they are related to SUA/Cr cannot be ruled out. As there have been no studies in Korea that have investigated the relationship between the HOMA model and SUA/Cr in the normal population, this study aimed to determine the relations between SUA/Cr and insulin resistance, pancreatic β cell function, and outbreak of metabolic syndrome (MetS) in Korean participants.

Materials and methods

Study population

This cross-sectional study included 18,552 participants who underwent the 2019–2021 Korea National Health and Nutrition Examination Survey (KNHANES). The exclusion criteria were as follows; (i) age < 20 years or > 80 years, (ii) diagnosis of DM before the survey or on medication, (iii) diagnosis of gout before the survey or on medication, and (iv) incomplete clinical data. Patients taking DM or gout medication were excluded as it may affect insulin secretion and SUA/Cr values. This study was approved by the institutional review board of Korea Centers for Disease Control and Prevention (Ethics Committee reference number 2018-01-03–5 C-A). All participants in the survey provided written informed consent. Figure 1 shows a flowchart of the study population.

Clinical and laboratory data

Waist circumference (WC) was measured at the level of the umbilicus while the participants are standing [7]. Blood pressure (BP) in the upper arm was measured using an automatic BP monitor. Blood tests were performed after an overnight fast. Fasting glucose levels were presented in units of mass (mg/dL). Insulin levels were measured through blood samples using the Electrochemiluminescence Immunoassay (ECLIA) method, which was performed with the Roche Modular E801 system and Elecsys Insulin reagent from Roche, Germany.

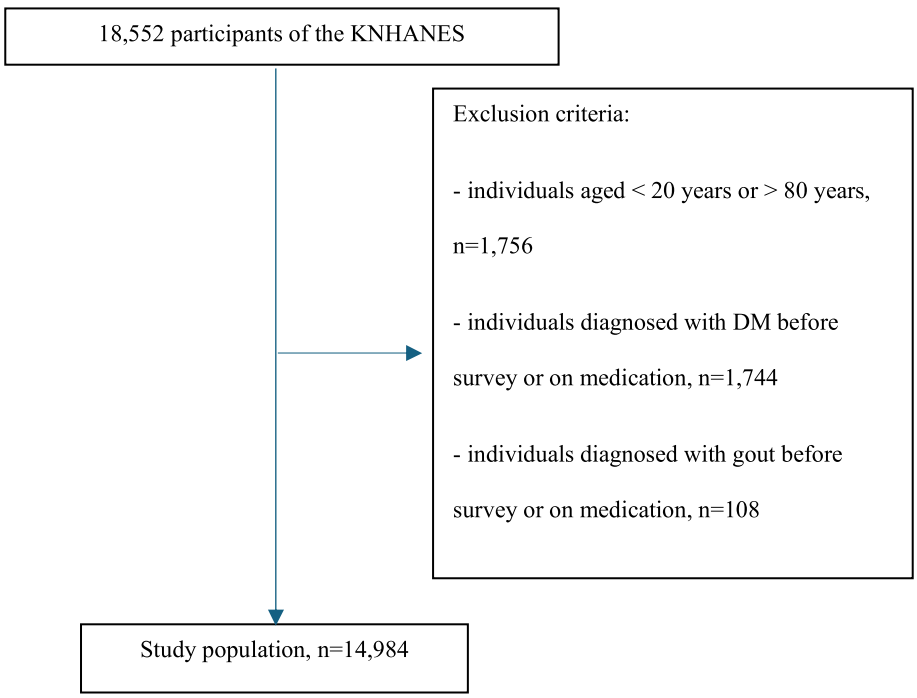

Fig. 1 Flowchart of the study population. *Abbreviations*: DM, diabetes Mellitus; KNHANES, Korea National Health and Nutrition Examination Survey

Insulin resistance index HOMA-IR was calculated as fasting glucose (mg/dL) x insulin (mU/L)/405, and β cell function index HOMA-β was calculated as 360 x insulin (mU/L)/(fasting glucose [mg/dL]-63) [8].

Reference values

Previous studies suggested that prognostic values of insulin resistance and normal β cell function are defined by HOMA-IR ≥ 2.5 and HOMA-β 60 − 100, respectively [9, 10]. Therefore, these criteria were applied in this study.

Definition of MetS

MetS was diagnosed based on the presence of at least three of the following criteria; (i) central obesity defined as WC (≥ 90 cm in men, ≥ 85 cm in women) [11] (ii) fasting glucose level (≥ 100 mg/dL), (iii) high-density lipoprotein-cholesterol (HDL-C) levels (< 40 mg/dL in men, < 50 mg/dL in women), (iv) triglyceride (TG) levels ≥ 150 mg/dL, and (v) systolic BP (SBP) ≥ 130 mmHg or diastolic BP (DBP) ≥ 85 mmHg [12].

The criteria in the definition of MetS were scored as 1 if met and 0 if not met. Then, the total score of the five criteria in MetS was named the MetS score.

Criteria for smoking, drinking, and exercising

A smoker was defined as an individual who had smoked > 100 cigarettes in their lifetime. A person who drank alcohol was defined as someone who had consumed any type of alcohol in their lifetime. Individuals who exercise are defined as those who engage in high-intensity exercise daily (at an intensity that causes sweating for > 30 min).

Statistical analysis

We calculated odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) using SPSS™ statistics version 25.0 (IBM, Armonk, NY, USA). The analysis included demographic information, traditional DM, and MetS risk factors.

Quantitative data are presented as mean ± standard deviation, while categorical variables are expressed as absolute values (percentages). Chi-square test was used to compare participants according to the SUA/Cr tertiles and sex as categorical variables. Kruskal-Wallis test and Mann-Whitney test were used to compare groups divided according to SUA/Cr values. Spearman's correlation analysis was used to determine the relation between SUA/Cr and HOMA-IR, HOMA-β, and MetS score. Binary logistic regression models were used to evaluate the association between SUA/Cr and HOMA-IR, HOMA-β, and MetS. Cut-off values of SUA/Cr to predict insulin resistance, β cell dysfunction, and MetS risk were also been suggested.

Results

Table 1 shows the participants' baseline characteristics stratified according to SUA/Cr tertiles. The participants' mean age, UA levels, and creatinine levels were 51.1years, 5.1 mg/dL, and 0.8 mg/dL, respectively. Consequent to dividing SUA/Cr into tertiles, the higher the age, the lower the value. Additionally, the higher the SUA/Cr, the higher the HOMA-IR and HOMA-β, and the rate of MetS increased ($p < 0.05$).

The relationship between SUA/Cr and HOMA-IR, HOMA-β, and MetS scores in each SUA/Cr tertile was investigated. This was done using Spearman correlation analysis. Table 2 shows that especially in the 3rd tertile, SUA/Cr and HOMA-IR, and HOMA-β are proportional to each other.

Multivariate logistic regression analysis was conducted to show the association between SUA/Cr and HOMA-IR, HOMA-β, and MetS. The independent variables are SUA/Cr, and the dependent variables are the presence of insulin resistance, the presence of β cell dysfunction, and the occurrence of MetS. To reduce the occurrence of multicollinearity, important factors were analyzed among those that were closely related to each other.

In Tables 3, age, WC, HbA1c, low-density lipoprotein-cholesterol (LDL-C), and SUA/Cr were associated with HOMA-IR and HOMA-β (p <0.01). The participants' smoking and drinking were related to HOMA-IR but not HOMA- β (p <0.01). The higher the SUA/Cr, the more often there was insulin resistance and abnormal β cell function (adjusted OR; 1.231 [95% confidence interval [CI]; 1.204-1.259, p<0.001] and 1.033 [95% CI; 1.011–1.057, p=0.004], respectively). Furthermore, the presence of MetS was related with SUA/Cr (adjusted OR; 1.065 [95% CI; 1.026–1.106,p=0.001]).

Age, men, smoking, exercise, SBP, DBP, WC, HbA1c, HDL-C, LDL-C, TG, and SUA/Cr were associated with the presence of MetS (Table 3).

A receiver operating characteristic(ROC) curve was drawn and analyzed to determine the cut-off value of SUA/Cr required to predict insulin resistance, β cell function, and incidence of metabolic syndrome. This analysis according to the SUA/Cr tertiles and the overall sample are included in Table 4 and Fig. 2.

The group with the clinical significance was the 3rd tertile. In this group, insulin resistance, β cell dysfunction, and MetS risk could be predicted when SUA/

Table 1 Baseline characteristics of the study population according to the SUA/Cr

SUA/Cr					
	Total (*n* = 14,984)	**1st tertile (< 5.87) (*n* = 4,942)**	**2nd tertile (5.87 ~ 7.11) (*n* = 4,941)**	**3rd tertile (> 7.11) (*n* = 5,101)**	***P*-Value**
Age(years)	51.1 ± 16.8	54.0 ± 16.7	50.7 ± 16.6	48.6 ± 16.7	< 0.001
Sex(men)	6,560(43.8%)	2,102(42.5%)	2,138(43.3%)	2,320(45.5%)	0.459
Smoking	463(3.1%)	165(3.4%)	144(2.9%)	154(3.0%)	0.603
Drinking	1,691(11.3%)	648(13.1%)	534(10.8%)	509(10.0%)	0.004
Exercising	220(1.5%)	52(1.1%)	66(1.3%)	102(2.0%)	0.011
MetS	3,181(21.2%)	788(15.9%)	978(19.8%)	1,415(27.7%)	< 0.001
SBP(mmHg)	119.1 ± 16.3	118.5 ± 16.8	118.5 ± 16.0	120.1 ± 15.9	0.623
DBP(mmHg)	75.4 ± 9.9	74.3 ± 9.7	75.1 ± 9.6	76.5 ± 10.2	< 0.001
WC(cm)	83.7 ± 10.5	81.7 ± 10.1	83.0 ± 10.0	86.2 ± 10.7	< 0.001
BMI(kg/m2)	24.0 ± 3.6	23.2 ± 3.3	23.7 ± 3.4	25.0 ± 4.0	< 0.001
FPG(mg/dl)	98.4 ± 17.0	98.3 ± 19.5	97.7 ± 15.0	99.2 ± 16.1	0.076
HbA1c(%)	5.7 ± 0.6	5.7 ± 0.7	5.6 ± 0.5	5.7 ± 0.6	0.309
Insulin(mU/L)	9.2 ± 9.1	8.1 ± 7.1	8.6 ± 7.2	10.8 ± 11.8	< 0.001
HOMA-IR	2.3 ± 3.1	2.0 ± 2.2	2.2 ± 2.3	2.8 ± 4.1	< 0.001
HOMA-β	97.4 ± 88.3	86.9 ± 82.8	92.3 ± 68.1	112.5 ± 106.8	< 0.001
TC(mg/dl)	194.1 ± 37.3	190.7 ± 36.8	194.3 ± 37.5	197.2 ± 37.3	< 0.001
HDL-C(mg/dL)	52.8 ± 12.8	54.5 ± 13.2	52.9 ± 12.6	51.0 ± 12.3	< 0.001
LDL-C(mg/dL)	115.7 ± 34.9	114.1 ± 33.2	116.8 ± 34.7	116.1 ± 36.5	< 0.001
TG(mg/dL)	128.3 ± 103.9	110.2 ± 72.0	123.2 ± 92.7	150.7 ± 132.4	< 0.001
Creatinine(mg/dL)	0.8 ± 0.2	0.9 ± 0.3	123.2 ± 92.7	0.7 ± 0.2	< 0.001
SUA(mg/dL)	5.1 ± 1.4	4.3 ± 1.1	5.2 ± 1.1	6.1 ± 1.3	< 0.001

Kruskal-Wallis test and Mann-Whitney test were used to compare groups divided according to SUA/Cr values

Quantitative data are presented as mean ± standard deviation, and categorical variables are expressed as absolute values (percentages)

Abbreviations: *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting glucose, *HDL-C* high-density lipoprotein-cholesterol, *HOMA-β* homeostasis model assessment-beta cell secretory function, *HOMA-IR* homeostasis model assessment-insulin resistance, *LDL-C* low-density lipoprotein-cholesterol, *MetS* metabolic syndrome, *SUA* serum uric acid, *SUA/Cr* serum uric acid to creatinine ratio, *TC* total cholesterol, *TG* Triglyceride

Table 2 The relationship between SUA/Cr and HOMA-IR, HOMA-β, and MetS in each SUA/Cr tertiles

	SUA/Cr	
	r	***P*-value**
1st tertile		
HOMA-IR	−0.040	0.005
HOMA-β	−0.003	0.852
MetS score	−0.025	0.079
2nd tertile		
HOMA-IR	0.022	0.020
HOMA-β	0.021	0.029
MetS score	0.038	< 0.001
3rd tertile		
HOMA-IR	0.142	< 0.001
HOMA-β	0.117	< 0.001
MetS score	0.119	< 0.001

Spearman's correlation analysis was used

The total score of the five criteria in MetS was named the MetS score

Abbreviations: *HOMA-β* homeostasis model assessment-beta cell secretory function, *HOMA-IR* homeostasis model assessment-insulin resistance, *MetS* metabolic syndrome

Cr value was 8.2716, 8.8710, and 7.9762, respectively. Based on the total number of people, meaningful SUA/Cr values were 7.0175, 6.7925, and 6.9369.

Discussion

Type 2 DM can easily cause severe complications; therefore, primary prevention of DM is required globally. MetS contributes to the onset of cardiovascular diseases [13]. Therefore, screening healthy participants with risk factors for DM and MetS, and recommending proper lifestyle modifications are useful ways to prevent early DM and MetS incidence [14].

The mechanism that causes DM is β cell dysfunction and insulin resistance [15]. The HOMA model is a convenient and economical way to measure insulin resistance and β cell function by simple blood test. In a large-scale study conducted in healthy individuals without DM, Song et al. followed 82,069 women for approximately six years. HOMA-IR and HOMA-β were found to be independent tools for predicting the development of DM in the research [16]. The incidence risk of DM was

Table 3 Factors affecting insulin resistance(HOMA-IR), β cell dysfunction(HOMA-β), and incidence of MetS investigated by binary logistic regression analysis

	Insulin resistance(HOMA-IR)			β cell dysfunction(HOMA-β)			Incidence of MetS		
	P-Value	Odds ratio	95% CI	*P*-Value	Odds ratio	95% CI	*P*-Value	Odds ratio	95% CI
Age(years)	0.026	1.002	1.000–1.005	< 0.001	0.995	0.993–0.997	< 0.001	1.014	1.009–1.019
Sex(men)	0.013	1.096	1.019–1.178				< 0.001	4.705	4.126–5.365
Smoking	< 0.001	1.493	0.960–2.323				0.023	0.378	0.163–0.876
Drinking	< 0.001	0.966	0.631–1.478						
Exercising	< 0.001	0.785	0.591–1.043						
SBP(mmHg)	< 0.001	1.020	1.018–1.023				< 0.001	1.013	1.008–1.018
DBP(mmHg)	< 0.001	1.035	1.032–1.039				< 0.001	1.062	1.053–1.071
WC(cm)	< 0.001	1.121	1.115–1.126	< 0.001	1.009	1.005–1.013	< 0.001	1.124	1.115–1.133
HbA1c(%)	< 0.001	3.627	3.326–3.956	< 0.001	1.359	1.260–1.466	< 0.001	2.239	1.999–2.509
HDL-C(mg/dL)	< 0.001	0.950	0.947–0.953				< 0.001	0.901	0.895–0.908
LDL-C(mg/dL)	< 0.001	0.998	0.997–0.999	0.001	0.998	0.997–0.999	0.005	1.002	1.001–1.004
TG(mg/dL)	< 0.001	1.007	1.007–1.008				< 0.001	1.012	1.011–1.013
SUA/Cr	< 0.001	1.231	1.204–1.259	0.004	1.033	1.011–1.057	0.001	1.065	1.026–1.106

Multivariate logistic regression analysis was conducted to show the association between SUA/Crand HOMA-IR, HOMA-β, and MetS

Only statistically significant variables were presented in the table

Abbreviations: *CI* confidence interval, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein-cholesterol, *HOMA-β* homeostasis model assessment-beta cell secretory function, *HOMA-IR* homeostasis model assessment-insulin resistance, *LDL-C* low-density lipoprotein-cholesterol, *MetS* metabolic syndrome, *SBP* systolic blood pressure, *SUA/Cr* serum uric acid to creatinine ratio, *TG* Triglyceride

highest with high insulin resistance and low β cell dysfunction. Additionally, as stated in the Reference values section, if we can determine an opinion on the normal values of HOMA-IR and HOMA- β, early DM could be found more precisely.

SUA, a product of purine metabolism, is synthesized in the liver and excreted in the urine [17]. The production and excretion rates of UA are relatively constant in healthy individuals [18]. Circulating SUA is filtered from the glomeruli into the renal tubule [19]. If SUA levels exceed the norm, the body becomes acidic, which blocks the function of human cells and leads to metabolic diseases [20]. Kidney function is known to influence SUA levels [21]. As SUA and creatinine levels reflect kidney status, the use of SUA/Cr reduces interference due to renal function [22].

Table 4 Cut-off values of SUA/Cr to predict insulin resistance, β cell dysfunction, and MetS risk

	Cut-off value	AUC	*P*-value	Sensitivity(%)	Specificity(%)
1st tertile					
Insulin resistance (HOMA-IR)	4.9533	0.524	0.017	43.4	61.4
β cell dysfunction (HOMA-β)	4.8246	0.517	0.044	34.3	69.4
Incidence of MetS	5.4795	0.503	0.815	31.7	71.9
2nd tertile					
Insulin resistance (HOMA-IR)	6.3393	0.528	0.003	65.2	40.8
β cell dysfunction (HOMA-β)	6.7925	0.512	0.161	25.0	79.0
Incidence of MetS	5.4795	0.503	0.815	31.7	71.9
3rd tertile					
Insulin resistance (HOMA-IR)	8.2716	0.574	< 0.001	47.5	64.3
β cell dysfunction (HOMA-β)	8.8710	0.526	0.002	25.4	79.1
Incidence of MetS	7.9762	0.558	< 0.001	57.4	52.3
Total					
Insulin resistance (HOMA-IR)	7.0175	0.593	< 0.001	47.0	68.0
β cell dysfunction (HOMA-β)	6.7925	0.520	< 0.001	43.3	60.9
Incidence of MetS	6.9369	0.590	< 0.001	49.2	64.8

Abbreviations: *AUC* area under the curve, *HOMA-β* homeostasis model assessment-beta cell secretory function, *HOMA-IR* homeostasis model assessment-insulin resistance, *MetS* metabolic syndrome

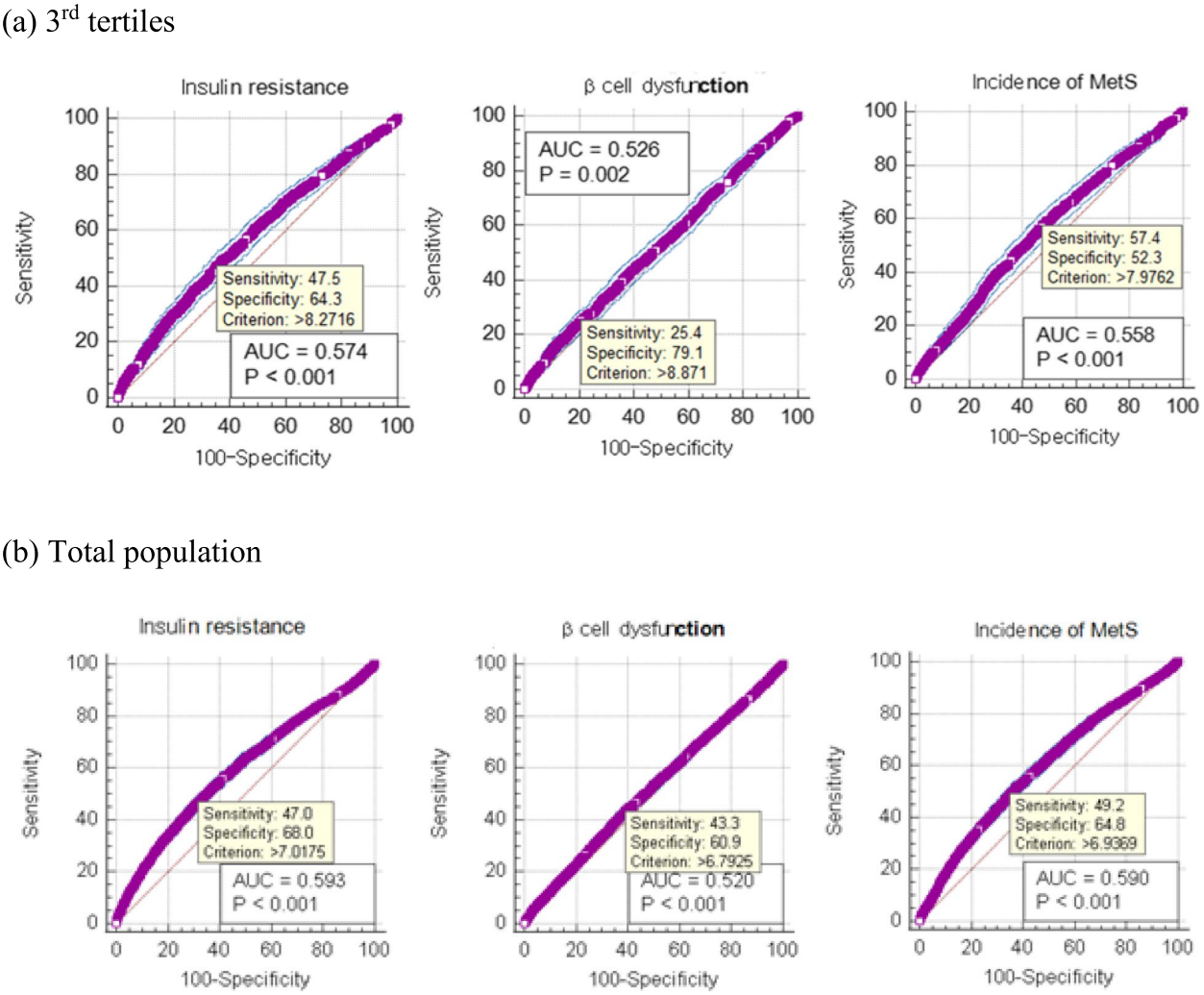

Figure 2 ROC curves of SUA/Cr to predict insulin resistance(HOMA-IR), β cell dysfunction(HOMA-β), and MetS risk in 3rd tertiles and total population. A receiver operating characteristic(ROC) curve was drawn and analyzed to determine the cut-off value of SUA/Cr required to predict insulin resistance, β cell function, and incidence of metabolic syndrome. *Abbreviations*: MetS, metabolic syndrome; ROC, receiver operating characteristic

Some studies have proposed that the SUA/Cr is associated with impaired insulin secretion or resistance[23]. A study by Moriyama suggested that SUA/Cr may be a positive index for components of insulin resistance and risk of MetS [24, 25]. Minchao Li et al. showed that there are relations between SUA/Cr and preserved β cell function [26]. This study, unlike Minchao Li's study, found that SUA/Cr was associated with β cell dysfunction. As most researchers have suggested, this is because SUA may suppress basal insulin release in isolated pancreatic islets and inhibit glucose-stimulated insulin secretion [27]. Our findings are consistent with these experimental results. Furthermore, out study found that the 3rd tertile with SUA/Cr higher than 7.11 was particularly likely to develop insulin resistance, decreased β cell function and metabolic syndrome. This value may be useful as an indicator of endocrine abnormalities in the future.

Other factors affecting HOMA-IR and HOMA-β were WC and LDL-C. This implies that there is a link between components of metabolic diseases, insulin resistance, and β cell function [28]. Al-Daghri et al. suggested that this finding is of considerable clinical importance, as SUA/Cr may be used as a marker in the pathogenesis of MetS [4].

So far, we have showed that SUA/Cr can affect insulin resistance, β cell function, and the development of metabolic syndrome. For groups with high SUA/Cr, active lifestyle modifications will help reduce the likelihood of developing DM or MetS in the future. Several papers

presented lifestyle habits correction methods. There is a significant tendency for the risk of insulin resistance to increase as the 'alcohol, meat pattern' score increases [29]. In the study by Song et al., which categorized participants into normal, risk, and metabolic syndrome groups, the results showed that men in the normal group and women in the risk group, who had insulin resistance, had higher intake of sugary and fatty food groups (such as oils, mayonnaise, fried foods like fried chicken, sugar, candies, jelly, and chocolate) [30]. Furthermore, a study confirmed that individuals with MetS were more likely to engage in inactive behaviors than those without MetS, and the reciprocal was true for active behaviors. This study also showed that decreased physical activity negatively affected MetS risk factors. Every additional week, which is equivalent to approximately 20 min of moderate or 10 min of vigorous activity, the odds of MetS were approximately 10% lower. Regular aerobic and resistance exercise showed that there was a reversal of MetS in 19% patients and 42% patients had improvements in at least one component of MetS at 12 months [31]. As seen in previous studies, groups with higher SUA/Cr will help prevent the increase in insulin resistance and metabolic syndrome if they reduce their intake of sugary, fatty foods, and alcohol and engage in moderate-to-vigorous physical activity every week.

This study had some limitations. First, because the present study had a Korea-based design, it did not reflect the diverse ethnicities of the study population. Furthermore, as a cross-sectional study, it did not provide sufficient information regarding causalities. Therefore, it is necessary to expand the study population in future studies. Second, the SUA levels could be affected by renal tubular injury; however, we included patients with tubular injury because of the difficulty in collecting tubular injury markers [32]. Finally, the cutoff values of SUA/Cr for predicting the HOMA model or the incidence of MetS were calculated. However, area under the curve(AUC) values were somewhat low, less than 0.6. It appears that future follow-up research should be conducted by accurately dividing the healthy adult and patient groups. In this way, it will be possible to reduce the overlap between patient and non-patient prediction distributions.

Conclusion

This study showed the association between the SUA/Cr and HOMA model, and MetS. Therefore, SUA/Cr may be a useful potential marker for predicting insulin resistance, β cell function, and risks for MetS in normal population. Considering the large annual global budget for DM and MetS, these results are expected to be helpful for early screening.

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Authors' contributions
M-SO contributed to the concept and design of the study, and analysis and interpretation of the data. S-HC contributed to the analysis of the work, data acquisition and analysis . All authors have contributed to the manuscript and approved the submitted version.

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Data availability
The datasets used and/or analyzed during the current study are available from the https://knhanes.kdca.go.kr/knhanes/sub03/sub03_02_05.do.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of Korea Centers for Disease Control and Prevention (Ethics Committee reference number 2018-01-03–5 C-A). All participants in the survey provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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