

Observational Study

Metabolic biomarkers and long-term blood pressure variability in military young male adults

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Abstract**BACKGROUND**

Metabolic syndrome is a cluster of cardiovascular risk factors, including central obesity, high blood pressure, elevated plasma glucose, reduced high-density lipoprotein and elevated triglyceride levels.

AIM

To investigate the relationship between metabolic biomarkers and long-term blood pressure variability (BPV) in young males.

METHODS

A cohort of 1112 healthy military males aged 18-40 years from the cardiorespiratory fitness and hospitalization events in armed forces study in eastern Taiwan was prospectively included. The following metabolic biomarkers were used: Waist circumference, serum uric acid (SUA), triglycerides, high density lipoprotein, triglycerides, and fasting glucose. BPV was assessed by average real variability (ARV) and standard deviation (SD) across 4 clinic visits during the study period (2012-14, 2014-15, 2015-16, and 2016-18). Multivariable linear regression analysis was used to determine the association after adjusting for age, body mass index, systolic and diastolic blood pressure (SBP and DBP),

data were confidential and not allowed to be opened in public. If there are any needs for clarification, the readers can contact Colonel Dr. Gen-Min Lin, the corresponding author for sharing the data.

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lipid profiles, physical activity, alcohol intake and tobacco smoking status.

RESULTS

In the unadjusted model, waist circumference was significantly and positively correlated with ARV_{DBP} and SD_{DBP} [β (standard errors) = 0.16 (0.049) and 0.22 (0.065), respectively], as was SUA [β = 0.022 (0.009) and 0.038 (0.012), respectively]. High-density lipoprotein was negatively correlated with ARV_{SBP} [β = -0.13 (0.063)]. There were no associations with the other metabolic biomarkers. In contrast, only SUA was significantly correlated with SD_{SBP} and SD_{DBP} [β = 0.019 (0.011) and 0.027 (0.010), respectively] in the adjusted model.

CONCLUSION

Our findings showed that of traditional metabolic biomarkers, SUA had the strongest positive correlation with long-term systolic and diastolic BPV in young male adults, and the clinical relevance needs further investigation.

Key words: Blood pressure variability; Metabolic syndrome; Serum uric acid; Young males

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Core tip: This study examined the relationship between metabolic biomarkers and long-term blood pressure variability (BPV) in a military population of 1112 young males across 4 visits during a 7-year period. We found that serum uric acid and waist circumference were positively correlated with long-term BPV, whereas high-density lipoprotein was inversely correlated with long-term BPV in the unadjusted model. Only serum uric acid was positively correlated with long-term BPV in the fully adjusted model. Serum uric acid, which may reflect arterial stiffness, is likely one of the strongest metabolic biomarkers for long-term BPV and related cardiovascular risk in young male adults.

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INTRODUCTION

Metabolic syndrome is a cluster of cardiovascular risk factors, including central obesity, high blood pressure, elevated plasma glucose, reduced high-density lipoprotein and elevated triglyceride levels. In 2004 and 2006, the National Cholesterol Education Program's Adult Treatment Panel III^[1] and the International Diabetes Federation^[2] revised the definition of metabolic syndrome. In these fundamental statements, several other components, such as hyperuricemia, coagulation disorder and increased PAI-1, were described, though none of them were obligatory for diagnosing metabolic syndrome. Recent studies have shown that hyperuricemia could predict metabolic syndrome in elderly individuals, adolescents and even children^[3-5]. In particular, the association of hyperuricemia with cardiovascular diseases has been reported since the 1950s in numerous epidemiological studies^[6-10]. Whether serum uric acid (SUA) is merely a risk factor for cardiovascular disease or whether hypouricemic agents affect the outcome remains elusive^[11].

Short-term and long-term blood pressure variability (BPV) are independently associated with cardiovascular events and renal damage^[12]. In addition, long-term BPV, visit-to-visit variability in systolic blood pressure (SBP) and maximal SBP have been shown to be strongly prognostic for stroke and coronary events independent of mean blood pressure in a 2010 post hoc analysis of four large clinical trials on hypertension^[12,13]. Of particular interest are that while several factors involved in short-term BPV have been recognized, information on the factors contributing to long-term BPV, particularly in younger adults, remains speculative^[14,15]. Behavioral

changes, seasonal changes, reduced dosing or adherence to antihypertensive treatment, and increased arterial stiffness have previously been proposed as possible mechanisms for long-term BPV^[15-17]. These studies were conducted on middle-aged/older individuals or high-risk populations undergoing antihypertensive treatment, suggesting that BPV itself might be intertwined with these factors. Among young adults, greater body mass index levels were associated with higher long-term BPV in the Coronary Artery Risk Development in Young Adults study^[18].

Despite a growing body of evidence revealing the benefits of long-term BPV control, before being integrated into clinical practices as an additional goal of antihypertensive treatment, an improved understanding of BPV is mandatory. Therefore, we aimed to investigate whether long-term BPV throughout young adulthood is associated with metabolic biomarkers, including the components of metabolic syndrome, in a cohort of young military males.

MATERIALS AND METHODS

Study population

The study cohort included 1112 military males aged 18-40 years from the cardiorespiratory fitness and hospitalization events in armed forces study in Taiwan who were not undergoing antihypertensive treatment^[19]. All military participants self-reported their medical history and the status for tobacco smoking (current *vs* former or never), alcohol intake (current *vs* former or never) and physical activity. A physical examination including anthropometric and hemodynamic measurements and blood biochemical tests were performed at each clinic visit at the Hualien Armed Forces General Hospital of Taiwan every two years from 2012 to 2018 (2012-14, 2014-15, 2015-16, and 2016-18)^[20].

Anthropometric measurements and biochemical blood tests

With regard to the anthropometric parameters, the body height, body weight and waist circumference of each participant were measured in a standing position. Body mass index was calculated as the ratio of body weight (kg) to body height squared (m²). Waist circumference was measured midway between the lower rib margin and the iliac crest. Blood biochemical tests regarding concentrations of total cholesterol, high-density lipoprotein, triglycerides, fasting plasma glucose, creatinine and SUA were enzymatically measured on an autoanalyzer (AU640, Olympus, Kobe, Japan). The estimated glomerular filtration rate (eGFR) was calculated according to the equation of chronic kidney disease epidemiology collaboration^[21]. All blood samples were collected from the participants after an overnight 12-hour fast in the early morning by well-trained phlebotomists at the same blood draw station^[22-26].

Measurements of long-term BPV

Sympathomimetic agents such as theophylline or caffeine-containing materials were prohibited for 12 h before each participant's visit to the hospital. To avoid the temporary effects of pain, anxious mood, and cold temperature on blood pressure, the measurements of systolic and diastolic blood pressure (SBP and DBP, respectively) of each participant were performed in a room with an air conditioner, which maintained a constant indoor temperature of 24 °C. The blood pressure of each participant was checked once on the right upper arm in a sitting position after resting for at least 15 min using an FT-201 automated blood pressure monitor (Parama-Tech Co Ltd, Fukuoka, Japan) at each visit. Long-term BPV was assessed by standard deviation (SD) and average real variability (ARV) for both SBP and DBP across 4 visits for the period of 2012-2018. SD_{SBP} and ARV_{SBP} are illustrated in **Figure 1** and are represented by dotted and solid lines, respectively. ARV is calculated as an average of the sum of absolute differences between successive measurements of blood pressure, which takes the order of measurements into account $(|\Delta 1| + |\Delta 2| + |\Delta 3|)/3$ ^[20].

Statistical analysis

Metabolic biomarkers in this study included SUA and the central components of metabolic syndrome: Waist circumference, serum triglycerides, high-density lipoprotein, and fasting glucose. Metabolic syndrome was defined according to the clinical criteria of the International Diabetes Federation^[2]. The characteristics of participants with metabolic syndrome ($n = 112$) and those without ($n = 1000$) were expressed as numbers (%) and compared using a chi-square test for categorical data and as the mean \pm SD and compared using a two-sample *t* test for continuous data. The range of each BPV index was divided by quantile to reveal the distribution of BPV in all study subjects. Differences in the levels of each metabolic biomarker among the quantile groups were assessed by analysis of covariance with adjustment for

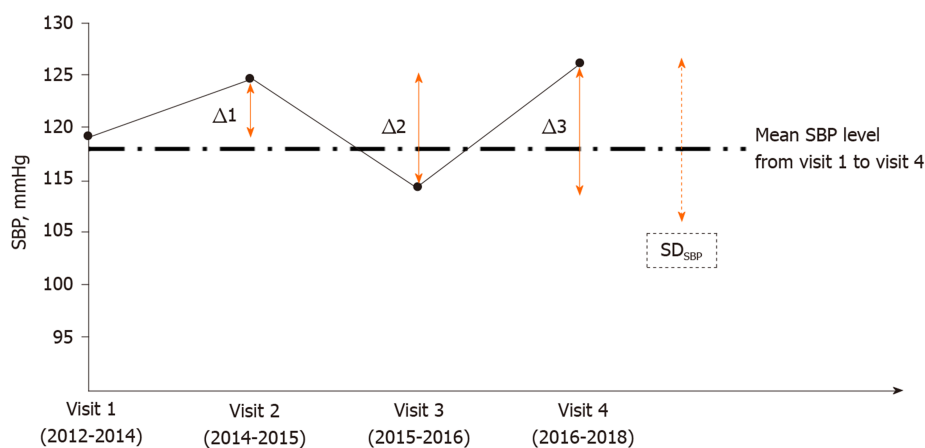


Figure 1 Long-term blood pressure variability was assessed by standard deviation and average real variability across 4 visits in the study period (2012-2018). (Standard deviation)_{SBP} and [average real variability (ARV)]_{SBP} were illustrated by dotted and solid lines, respectively. ARV_{SBP} is calculated as an average of absolute differences between successive systolic blood pressure measurements, taking the order of measurements into account: $(|\Delta 1| + |\Delta 2| + |\Delta 3|)/3$. SD: Standard deviation; SBP: Systolic blood pressure.

baseline age, body mass index, tobacco smoking status, alcohol intake status, total cholesterol levels, physical activity, SBP, and DBP. Unadjusted and multivariable adjusted linear regression models were used to determine the relationship between each biomarker and long-term BPV. Model 1 was adjusted for the baseline SBP and DBP. Model 2 was additionally adjusted for age, body mass index, smoking status, alcohol intake status, total cholesterol levels, and physical activity. This study protocol was reviewed and approved by the Institutional Review Board of Mennonite Christian Hospital (No. 16-05-008), and written informed consent was obtained from all participants. A $P < 0.05$ was considered significant. SAS statistical software (SAS version 9.4; SAS Institute, Cary, NC, United States) was used for all statistical analyses.

RESULTS

The baseline characteristics of the study participants (2012-2014) are shown in [Table 1](#). Those males with metabolic syndrome had notably greater baseline levels of waist circumference, body mass index, total cholesterol, triglycerides, fasting glucose and blood pressure than those without metabolic syndrome. However, there were no differences in eGFR, physical activity, smoking status, or alcohol intake between those with metabolic syndrome and those without.

[Figure 2](#) demonstrates the mean (95% confidence intervals) levels of each metabolic biomarker, with adjustment for the baseline SBP and DBP, in quantiles of SD_{BP} and ARV_{BP} . There was only a significant difference in the means of SUA among quartiles of ARV_{DBP} ($P = 0.03$) and a borderline significant difference among quartiles of SD_{DBP} ($P = 0.06$). In contrast, there were no significant differences in waist circumference, fasting glucose, triglycerides, or high-density lipoprotein against any indexes of BPV with adjustment.

The results of the linear regression models are shown in [Table 2](#). In the unadjusted model, waist circumference and SUA were positively and significantly correlated with ARV_{DBP} [β and standard errors = 0.16 (0.049) and 0.022 (0.009), respectively] and SD_{DBP} [$\beta = 0.22$ (0.065) and 0.038 (0.012), respectively]. In contrast, high-density lipoprotein was negatively and significantly correlated with ARV_{SBP} [$\beta = -0.13$ (0.063)]. With adjustment for the baseline SBP and DBP in model 1, the positive correlation between waist circumference and ARV_{DBP} decreased and was not significant, and neither was in the fully adjusted model 2. The positive correlation of SUA with SD_{DBP} and the inverse correlation of high-density lipoprotein with ARV_{SBP} remained significant in model 1. In the fully adjusted model 2, SUA was positively and significantly correlated with SD_{SBP} and SD_{DBP} [$\beta = 0.019$ (0.010) and 0.027 (0.012), respectively], whereas the inverse correlation of high-density lipoprotein with ARV_{SBP} was no longer significant.

Table 1 Clinical characteristics of study cohort, (*n* = 1112)

Characteristics	With metabolic syndrome(<i>n</i> = 112)	Without metabolic syndromes (<i>n</i> = 1000)	P value
Age	33.45 ± 3.93	32.08 ± 3.86	< 0.001
Body mass index (kg/m ²)	28.02 ± 2.03	24.82 ± 2.81	< 0.001
Waist circumference (cm)	91.94 ± 5.04	83.49 ± 6.95	< 0.001
Systolic blood pressure (mm Hg)	126.95 ± 14.90	117.39 ± 12.87	< 0.001
Diastolic blood pressure (mm Hg)	78.12 ± 12.45	70.88 ± 9.53	< 0.001
Heart rate (beats per min)	78.65 ± 10.55	74.62 ± 10.54	< 0.001
High blood pressure	31 (27.7)	47 (4.7)	< 0.001
Total cholesterol (mg/dL)	194.68 ± 38.61	178.53 ± 31.66	< 0.001
Serum triglyceride (mg/dL)	250.67 ± 232.27	108.71 ± 66.01	< 0.001
Fasting plasma glucose (mg/dL)	104.71 ± 27.08	93.36 ± 10.30	< 0.001
Serum uric acid (mg/dL)	7.22 ± 1.42	6.64 ± 1.28	< 0.001
(Minimum-Maximum)	(3.9-12.7)	(2.8-13.2)	
High-density lipoprotein (mg/dL)	47.12 ± 10.19	48.50 ± 9.77	< 0.001
Low-density lipoprotein (mg/dL)	114.74 ± 28.51	109.56 ± 28.44	0.06
eGFR (mL/min per 1.73 m ²)	97.18 ± 12.79	97.97 ± 13.74	0.56
Physical activity			
Never or occasionally	23 (20.5)	162 (16.2)	0.40
1-2 times/wk	38 (33.9)	389 (38.9)	
≥ 3-5 times/wk	51 (45.6)	449 (44.9)	
Current alcohol drinkers, <i>n</i> (%)	53 (47.3)	464 (46.4)	0.85
Current tobacco smokers, <i>n</i> (%)	45 (40.2)	386 (38.6)	0.74

Continuous variables are expressed as mean ± standard deviation, and categorical variables as *n* (%); eGFR: Estimated glomerular filtration rate.

DISCUSSION

Our principal findings were that among young males who were not undergoing antihypertensive therapy, SUA and waist circumference were associated with a greater long-term diastolic BPV index, whereas high-density lipoprotein was associated with a lower systolic BPV index. With adjustment for the baseline confounders, SUA was the only metabolic biomarker associated with higher systolic and diastolic BPV indexes, indicating that SUA might be one of the strongest metabolic biomarkers related to long-term BPV.

Uric acid is the final enzymatic product of purine metabolism in the human body. Elevated SUA is mostly due to reduced urinary excretion or comes from high oral intake of purine-rich foods^[27]. Uric acid, which is partly produced by vascular endothelial cells, has been regarded as an antioxidant in plasma with anti-atherosclerotic effects^[28]. In contrast, higher SUA may also increase peroxynitrite-mediated oxidation of low-density lipoprotein and stimulate the production of free radicals that have proinflammatory effects on vascular smooth muscle cells^[29], resulting in insulin resistance and arterial stiffness^[30,31]. Hyperuricemia is a potent risk factor for gout flares^[32], and several previous population studies have shown that there is an association with hypertension^[33] and other metabolic disorders, such as type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease^[29,30,32]. Given that greater SUA has been shown to be longitudinally associated with increased arterial stiffness and the development of hypertension in men or women without hypertension^[34,35], the implication of the role of hyperuricemia in BPV would remain.

The improving interMediAte RiSk management (MARK) study revealed that waist size was linearly correlated with the cardio-ankle vascular index (CAVI), a marker of central arterial stiffness, but not with brachial-ankle pulse wave velocity (baPWV), a marker of peripheral arterial stiffness, among middle- and old-aged males and females with intermediate risk for cardiovascular disease^[36], which was in line with the present study finding that waist circumference was not an independent risk factor for long-term peripheral BPV in young male adults. In contrast, high-density lipoprotein was linearly correlated with baPWV but not CAVI among middle- and old-aged male adults in the MARK study^[36], which could be the reason why the relationship between high-density lipoprotein and peripheral BPV remained after adjustment for the baseline SBP and DBP in young male adults in the present study.

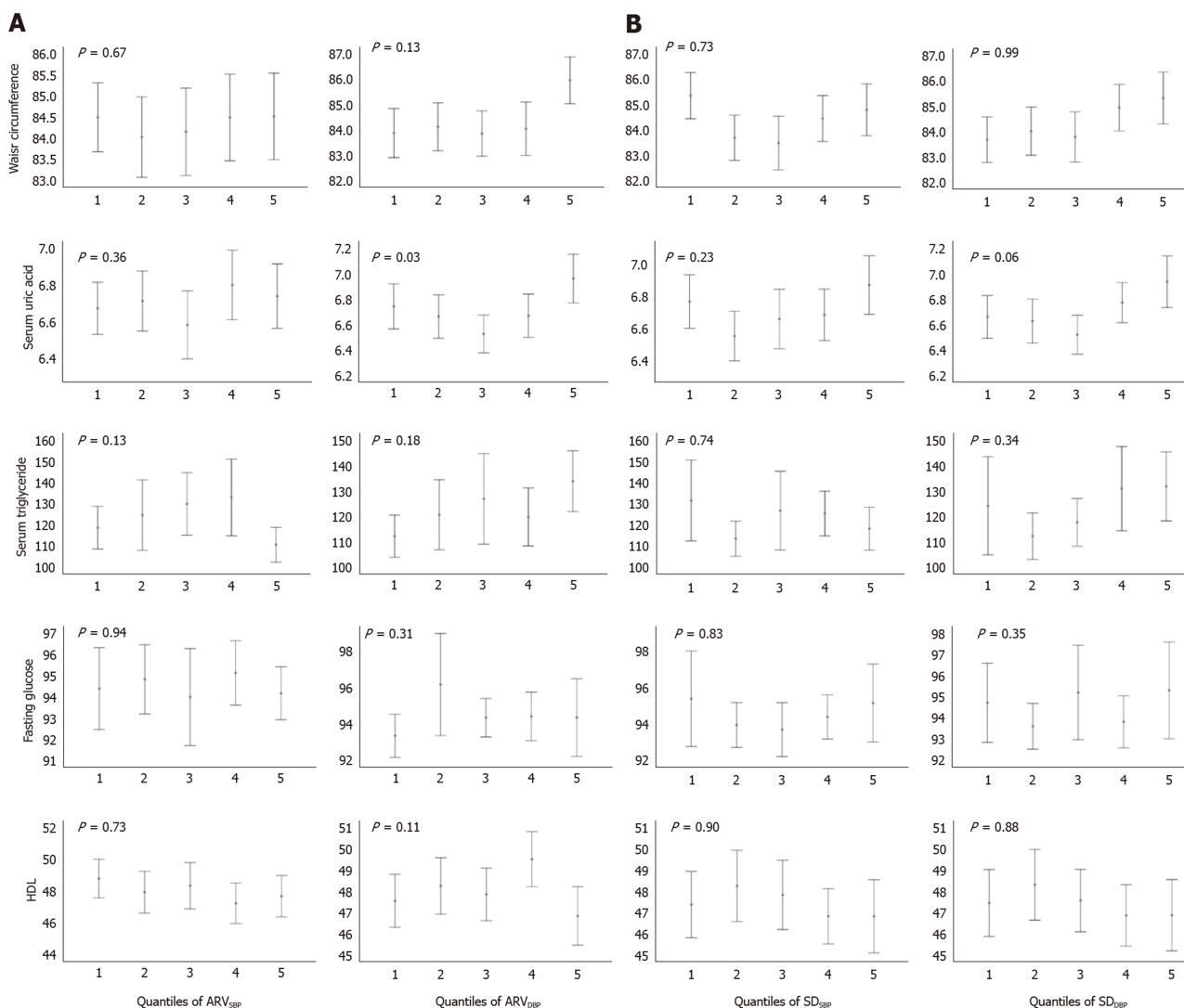


Figure 2 Levels of metabolic biomarkers in quantiles of (average real variability)_{SBP} and (standard deviation)_{SBP}. Bars represent means (95% confidence intervals) with adjustment for systolic blood pressure and diastolic blood pressure, age, body mass index, total cholesterol levels, physical activity, tobacco smoking status, alcohol intake status. HDL: High-density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ARV: Average real variability; SD: Standard deviation. *P* values were calculated by analysis of covariance.

With regard to other components of metabolic syndrome, such as serum triglycerides and fasting plasma glucose, although both of them were linearly correlated with baPWV among middle- and old-aged male adults, high serum triglycerides and fasting glucose were not significantly associated with a higher risk of criteria-defined peripheral arterial stiffness in the MARK study^[36]. We could speculate that among young male adults, the ranges of serum triglyceride and fasting glucose levels were relatively limited, and thus, the relationship with the peripheral arterial stiffness index or related BPV might not be significant. In another study of southern Chinese adults^[37], the baseline BP level was found to be the strongest predictor of baPWV among the metabolic biomarkers, and only high-density lipoprotein and SUA were not correlated with baPWV. This finding could also be explained by our result that after adjustment for the baseline BP, the association between waist circumference and BPV was absent.

There were several strengths in this study. First, since all the procedures were performed in a standard manner in the same referral hospital, the physical and laboratory examinations were performed uniformly. Second, lifestyles, such as dietary intake and physical training, were similar in the military troops, and thus, many unmeasured factors were controlled at baseline. In contrast, there were some limitations in this study. First, to our knowledge, there are remarkable sex differences in the association of metabolic biomarkers with arterial stiffness^[36], and the present results were only obtained from young male adults and might not be appropriate for young female adults. Second, although many confounders were adjusted for in the model at baseline, we could not avoid the possibility of potential confounders, which

Table 2 Association of metabolic biomarkers with long-term blood pressure variability indexes in multivariable linear regression

	Unadjusted			Model 1			Model 2		
	β (SE)	P value	R ² , %	β (SE)	P value	R ² , %	β (SE)	P value	R ² , %
Waist circumference									
ARV _{SBP}	0.046 (0.046)	0.31	0.0	0.039 (0.044)	0.38	7.9	-0.002 (0.026)	0.95	68.6
ARV _{DBP}	0.157 (0.049)	< 0.01	0.9	0.078 (0.048)	0.10	8.3	-0.004 (0.028)	0.88	68.9
SD _{SBP}	0.071 (0.060)	0.23	0.1	0.050 (0.058)	0.38	8.1	-0.021 (0.034)	0.53	68.9
SD _{DBP}	0.220 (0.065)	< 0.01	1.0	0.100 (0.064)	0.11	8.3	-0.003 (0.037)	0.92	68.9
Serum uric acid									
ARV _{SBP}	0.009 (0.008)	0.27	0.1	0.009 (0.008)	0.30	1.6	0.011 (0.008)	0.18	11.0
ARV _{DBP}	0.022 (0.009)	0.01	0.5	0.016 (0.009)	0.07	1.8	0.012 (0.008)	0.16	11.0
SD _{SBP}	0.020 (0.011)	0.06	0.3	0.019 (0.011)	0.08	1.8	0.019 (0.010)	0.05	11.1
SD _{DBP}	0.038 (0.012)	< 0.01	1.0	0.030 (0.012)	0.01	2.1	0.027 (0.011)	0.01	11.3
Serum triglycerides									
ARV _{SBP}	0.031 (0.673)	0.96	0.0	-0.014 (0.663)	0.98	3.0	0.310 (0.615)	0.61	18.2
ARV _{DBP}	1.155 (0.712)	0.10	0.2	0.473 (0.715)	0.50	3.0	0.343 (0.660)	0.60	18.2
SD _{SBP}	-0.003 (0.871)	0.99	0.0	-0.121 (0.860)	0.88	3.0	0.141 (0.796)	0.86	18.2
SD _{DBP}	1.545 (0.946)	0.10	0.2	0.493 (0.954)	0.60	3.0	0.478 (0.881)	0.58	18.2
Fasting glucose									
ARV _{SBP}	-0.008 (0.086)	0.92	0.0	-0.011 (0.086)	0.90	0.5	0.006 (0.084)	0.94	5.2
ARV _{DBP}	0.024 (0.091)	0.79	0.0	-0.014 (0.092)	0.88	0.5	-0.033 (0.090)	0.71	5.2
SD _{SBP}	0.036 (0.111)	0.74	0.0	0.029 (0.111)	0.79	0.5	0.028 (0.109)	0.79	5.2
SD _{DBP}	0.126 (0.120)	0.29	0.0	0.072 (0.123)	0.55	0.2	0.058 (0.121)	0.62	4.5
High-density lipoprotein									
ARV _{SBP}	-0.134 (0.063)	0.03	0.4	-0.131 (0.063)	0.03	0.9	-0.080 (0.060)	0.18	11.3
ARV _{DBP}	-0.062 (0.067)	0.36	0.1	-0.045 (0.068)	0.51	0.6	0.004 (0.065)	0.95	11.2
SD _{SBP}	-0.130 (0.082)	0.11	0.2	-0.121 (0.082)	0.14	0.7	-0.058 (0.078)	0.45	11.2
SD _{DBP}	-0.120 (0.089)	0.18	0.1	-0.095 (0.091)	0.29	0.3	-0.022 (0.087)	0.79	10.4

Data are presented as β (SE) using Pearson's correlation coefficient for Model 2: SBP and DBP adjustments; Model 3: The covariates in Model 2, age, BMI, total cholesterol, exercise frequency, current drinker and current smoker adjustments. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ARV: Average real variability; SD: Standard deviation; SE: Standard errors.

might lead to bias. Third, we did not have data for the amount and frequency of alcohol consumption and tobacco smoking for each subject, which might be inversely associated with long-term BPV.

In conclusion, our findings showed that of the traditional metabolic biomarkers, high-density lipoprotein might have an inverse correlation with long-term BPV, regardless of no significance in the fully adjusted model. SUA levels rather than waist circumference had the strongest positive correlation with long-term systolic and diastolic BPV in young male adults, and the clinical relevance needs further investigation.

ARTICLE HIGHLIGHTS

Research background

Short-term and long-term blood pressure variability (BPV) are associated with metabolic syndrome and cardiovascular events in middle- and old-aged adults.

Research motivation

It is unclear regarding the relationships between various metabolic biomarkers and BPV in young adults.

Research objectives

To examine the relationship of metabolic biomarkers with long-term BPV in young males.

Research methods

A cohort of 1112 healthy military males aged 18-40 years from the cardiorespiratory fitness and hospitalization events in armed forces study in eastern Taiwan was prospectively included. The

following metabolic biomarkers were used: Waist circumference, serum uric acid (SUA), triglycerides, high density lipoprotein, triglycerides, and fasting glucose. BPV was assessed by average real variability (ARV) and standard deviation (SD) across 4 clinic visits during the study period (2012-14, 2014-15, 2015-16, and 2016-18). Multivariable linear regression analysis was used to determine the association after adjusting for age, body mass index, systolic and diastolic blood pressure (SBP and DBP), lipid profiles, physical activity, alcohol intake and tobacco smoking status.

Research results

In the unadjusted model, waist circumference was significantly and positively correlated with ARV_{DBP} and SD_{DBP} [β (standard errors) = 0.16 (0.049) and 0.22 (0.065), respectively], as was SUA [β = 0.022 (0.009) and 0.038 (0.012), respectively]. High-density lipoprotein was negatively correlated with ARV_{SBP} [β = -0.13 (0.063)]. There were no associations with the other metabolic biomarkers. In contrast, only SUA was significantly correlated with SD_{SBP} and SD_{DBP} [β = 0.019 (0.011) and 0.027 (0.010), respectively] in the adjusted model.

Research conclusions

Our findings showed that of traditional metabolic biomarkers, SUA had the strongest positive correlation with long-term systolic and diastolic BPV in young male adults.

Research perspectives

Future studies should highlight the mechanism for the interplay between SUA, arterial stiffness and long-term BPV.

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