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ORIGINAL ARTICLE

Metabolic syndrome is associated with visit-to-visit systolic blood pressure variability in the US adults

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Epidemiological studies have shown that blood pressure is not a constant variable. Evidence has accumulated showing that the blood pressure variability is associated with organ damage. A substantial increase in the prevalence of the metabolic syndrome has been documented globally. We examined the association of visit-to-visit blood pressure variability with the metabolic syndrome and its components, using data collected in the Third National Health and Nutrition Examination Survey. A multivariable generalized linear model was performed. The metabolic syndrome and its components, particularly hypertension, increased waist circumference and hyperglycemia, were significantly associated with systolic blood pressure variability across study visits ($P<0.05$). After adjusting for the effect of age, gender, race and antihypertensive medication, the multivariable analyses did not show significant relationships between the metabolic syndrome and diastolic blood pressure variability (P-values >0.05). Additional research is required to verify the observed results in prospective studies and evaluate approaches to reduce blood pressure variability observed in clinical settings among persons with the metabolic syndrome to reduce its subsequent complications.
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Keywords: blood pressure; blood pressure variability; metabolic syndrome; waist circumference

INTRODUCTION

Hypertension is an important global public health problem as it affects approximately 25% of the adult population in western countries and over one billion people worldwide.[1] Additionally, it is a major risk factor for many causes of morbidity and mortality in the general population, including ischemic heart disease and stroke.[2] Epidemiological studies, which used the National Health and Nutrition Examination Survey (NHANES), have reported that the age-adjusted prevalence of hypertension in the population 18 years and older is 39.1% and 28.5% in non-Hispanic blacks and non-Hispanic whites, respectively.[3] Epidemiological studies have also shown that blood pressure is not stationary and it undergoes profound and spontaneous oscillations over short- and long-term periods.[4] Evidence has accumulated showing that blood pressure variability is associated with organ damage.[5] Several observational studies have documented that the harmful cardiovascular (CV) consequences of high blood pressure not only depend on absolute blood pressure values but also on blood pressure variability.[6,7] Therefore, blood pressure fluctuations are strongly associated with CV disease and mortality.[6] A *post hoc* analysis of large studies has shown that visit-to-visit blood pressure variability, that is, visits to a physician's office is strongly prognostic for cerebrovascular diseases.[8] Comparing the highest to lowest decile of standard deviation of systolic blood pressure, the hazard ratio for stroke over seven visits in the United Kingdom Transient Ischemic Attack trial (UK-TIA) was 6.22, 95% confidence interval: 4.16–9.29, $P<0.0001$ and in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) the hazard ratio for stroke was 4.29, 95% confidence interval: 1.78–10.4, $P<0.0001$.[8] Thus, visit-to-visit variability of blood pressure has emerged as a promising area of research.

The metabolic syndrome (MetS), a common complex disease, is a major worldwide public health problem. In the United States, the prevalence of the MetS has risen from an overall age-adjusted prevalence of 23.7% to 34.5% between 1988 and 2002.[9] There have been a number of different definitions of the MetS but all revolve around the metabolic abnormalities of central obesity, hypertension, decreased high-density lipoproteins and elevated triglycerides and blood glucose. An individual possessing three or more of these risk factors would be classified as having this syndrome. The importance of the MetS stems from the fact that it is a very strong risk factor for CV disease.[10,11] Additionally, the large number of individuals with the MetS places economic burdens on both the individual and society.[12] To our knowledge, no population studies have evaluated the association between the MetS and blood pressure variability (visit-to-visit variability). Therefore, this study's objective was to assess the

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relationship of the MetS with visit-to-visit blood pressure variability in the American population for the first time.

METHODS

Between 1988 and 1994, the National Center for Health Statistics conducted the Third National Health and Nutrition Examination Survey (NHANES III). This cross-sectional study consisted of a multistage, stratified, clustered probability sample of the civilian non-institutionalized US population. Because NHANES III is based on a complex multistage probability sample design, appropriate probability sampling weights were assigned to produce correct population estimates. The sampling weights were used in all analyses to produce an unbiased national estimate.

NHANES III consisted of a standardized questionnaire administered in the home by a trained interviewer followed by a detailed physical examination at a Mobile Examination Center (MEC). Blood pressure was measured using a mercury sphygmomanometer, whereas the study participant was sitting all the way to the back of the chair so that his/her spine is straight, according to the standardized blood pressure measurement protocols recommended by the American Heart Association. Blood pressure was measured three times during the in-home interview (1st visit) and three additional times during the MEC visit (second visit). The research assistant/physician waited at least 1 min between readings. The MEC visit was scheduled within 1 month of the in-home interview. Additional details regarding blood pressure measurement and quality-control procedures are provided in the NHANES III manual of operations (http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/bpqc.pdf).

During the visit to the MEC, a fasting venous blood specimen was drawn from each participant according to a standardized protocol.[13] Plasma glucose was measured at the University of Missouri Diabetes Diagnostic Laboratory using a hexokinase enzymatic method. Fasting serum insulin, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol and triglycerides were measured at other centralized laboratories. The Adult Treatment Panel III guidelines were used to define the MetS as the presence of three or more of the following:[14]

- Systolic blood pressure >130 mm Hg and/or diastolic blood pressure >85 mm Hg.
- HDL <40 mg dl^{-1} for men and <50 mg dl^{-1} for women.
- Triglycerides >150 mg dl^{-1}.
- Fasting blood glucose >100 mg dl^{-1}.
- Waist circumference >102 cm for men and >88 cm for women.

Cotinine concentration in the blood, a metabolite of nicotine, was used as a biomarker to classify participants into groups of current and non-current smokers.[15] Current smokers were defined as those who had cotinine levels >3 ng ml^{-1}, whereas those with serum cotinine $\leqslant 3$ ng ml^{-1} were classified as non-current smokers.[15] Self-reported data collected at the home interview relevant to the proposed analysis include demographics (age, race and gender) and a history of medication use.

Statistical analysis

To be included in the analysis, the study subject had to have complete information on his/her three arterial blood pressure readings obtained during the in-home visit and the additional three readings that were documented in the MEC visit. All analyses were performed using Stata version 12, which took into account the complex sampling designs used in NHANES III. Observations were weighted using weights calculated for that purpose by the National Center for Health Statistics to reflect the general US population. To determine the appropriate distribution that fits the study outcomes (systolic and diastolic blood pressure variability), normal, gamma and log-normal distributions were fitted. Goodness-of-fit tests showed that the gamma distribution was the best distribution that fit our data. The mean systolic blood pressure variability (standard deviations) was calculated under the gamma distribution. We conducted univariate generalized linear model (family = gamma; link = identity) to evaluate the effect of age, gender, race, smoking, antihypertensive medication intake, the MetS and its components on systolic blood pressure variability.

The covariates, age, gender, race, antihypertensive medication intake, and smoking, were included in a multivariable generalized linear model (family = gamma; link = identity) to adjust for their effect while assessing the effect of the MetS on systolic blood pressure variability. We separately evaluated the relationship between each MetS component, namely high blood pressure, large waist circumference, hyperglycemia, low HDL and high triglycerides and visit-to-visit systolic blood pressure variability after adjusting for the effect of the listed covariates (age, gender, race, antihypertensive medication intake and smoking). We decided to test the effect of each component individually because the MetS components are highly correlated with each other (collinearity). Finally, we conducted a test of trend to detect a dose–response relationship between the number of MetS components and systolic blood pressure variability. The significance level of all the performed analyses was set at 5%. The previous statistical analyses were reperformed and systolic blood pressure variability was replaced with diastolic blood pressure variability as an outcome.

RESULTS

The study included participants who fasted for at least 8 hours (h) ($N = 9140$). The participants' mean age was 43.11 years. The mean of the standard deviation of systolic blood pressure across study visits was 6.82 mm Hg. The mean standard deviation of systolic blood pressure across visits was more likely to be higher among smokers and individuals on antihypertensive medications (Table 1). Additionally, individuals with higher standard deviation of systolic blood pressure across study visits were more likely to have a large waist circumference (Table 1). The mean systolic blood pressure variability was higher among participants who had the MetS, central obesity, hypertension, hyperglycemia and low HDL (Table 1). In the unadjusted analysis, the mean standard deviation of systolic blood pressure across visits was associated with the MetS, central obesity, hypertension, hyperglycemia and low HDL (Table 1).

The association of hyperglycemia, elevated blood pressure and larger waist circumference with the increased standard deviation of systolic blood pressure remained significant after adjusting for the effect of the confounders, but the relationship between low HDL and systolic blood pressure variability became insignificant (Table 2). A dose–response relation between systolic blood pressure variability and the number of the MetS components was noticed (Table 2 and Figure 1). When the MetS variable was included alone in the generalized linear model, a significant relationship between the MetS and diastolic blood pressure variability was observed (Supplementary Table 1). However, after adjusting for the effect of gender, race, age, smoking and antihypertensive medication intake, the significant relationships between the MetS and diastolic blood pressure variability became insignificant (P-value >0.05) (Supplementary Table 2).

DISCUSSION

This study revealed a significant relationship between the MetS and its components, particularly high blood pressure, large waist circumference, hyperglycemia and visit-to-visit blood pressure variability. The MetS was not a significant risk factor for visit-to-visit diastolic blood pressure variability. Human and animal studies have linked the MetS and its components, especially, hypertension, hyperglycemia and obesity to arterial stiffness via some metabolic changes such as insulin resistance and high free fatty acids concentration.[16–26] Arterial stiffness has been postulated as an important cause for systolic arterial blood pressure variability.[27] Therefore, we hypothesize that the noticed significant relationship between the MetS and visit-to-visit blood pressure variability in this study may be explained by arterial

Table 1 The relationship between the metabolic syndrome and its components with systolic blood pressure variability (unadjusted analysis)

	Mean systolic blood pressure variability (s.d.) (mm Hg)	β-*Coefficient*	*s.e.*	P-*value*
Age (years)	6.70[a]	0.09	3×10^{-3}	<0.01
Gender				
Male ($n=4330$)	6.24	Reference		
Female ($n=4810$)	6.61	0.37	0.18	0.04
Race				
White ($n=6230$)	6.82	Reference		
Black ($n=2582$)	6.62	−0.20	0.16	0.20
Hispanics ($n=328$)	6.49	−0.33	0.45	0.13
Smoking				
No ($n=3007$)	6.82	Reference		
Yes ($n=6133$)	7.10	0.28	0.19	<0.01
Antihypertensive medication				
No ($n=7528$)	6.23	Reference		
Yes ($n=1612$)	10.07	3.84	0.32	<0.01
Hypoglycemic medication				
No ($n=8849$)	6.76	Reference		
Yes ($n=291$)	9.49	2.73	0.63	<0.01
Blood lipid-lowering medication				
No ($n=8908$)	6.75	Reference		
Yes ($n=232$)	8.55	1.80	0.45	<0.01
Metabolic syndrome				
No ($n=6430$)	5.62	Reference		
Yes ($n=2710$)	8.95	3.33	0.23	<0.01
Hypertension				
No ($n=5306$)	5.58	Reference		
Yes ($n=3834$)	8.76	3.17	0.20	<0.01
Large waist circumference				
No ($n=5469$)	6.22	Reference		
Yes ($n=3671$)	7.89	1.67	0.19	<0.01
Hyperglycemia				
No ($n=6524$)	6.30	Reference		
Yes ($n=2616$)	8.45	2.15	0.23	<0.01
Low high-density lipoprotein				
No ($n=5812$)	6.60	Reference		
Yes ($n=3328$)	7.15	0.55	0.19	<0.01
High triglycerides				
No ($n=6580$)	6.44	Reference		
Yes ($n=2560$)	7.75	1.31	0.22	<0.01
Number of metabolic syndrome components				
0 ($n=2149$)	5.37	Reference		
1 ($n=2293$)	5.93	0.56	0.20	<0.01
2 ($n=1988$)	7.17	1.81	0.23	<0.01
3 ($n=1461$)	8.41	3.05	0.31	<0.01
4 ($n=888$)	8.67	3.31	0.40	<0.01
5 ($n=361$)	10.07	4.79	0.64	<0.01
				P-value for trend <0.01

Abbreviation: s.d., standard deviation.
The National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP III). Participants defined as 'with metabolic syndrome' had three or more of the following metabolic syndrome component: large waist circumference—male, >102 cm and female, >88 cm; elevated systolic blood pressure: ⩾130 mm Hg or diastolic blood pressure: ⩾85 mm Hg or taking antihypertension medication; elevated triglycerides: ⩾150 mg dl^{-1}; low high-density lipoprotein—male <40 mg dl^{-1} and female: <50 mg dl^{-1}; fasting blood glucose level—⩾100 mg dl^{-1} or taking antidiabetes treatment.
Smokers were defined as those with serum cotinine >3 ng ml^{-1}, whereas those with a serum cotinine of ⩽3 ng ml^{-1} were classified as non-smokers.
[a]Systolic blood pressure variability for 43.11 years old (mean age of the study population).

stiffness. However, we were unable to test the role of arterial stiffness as a possible mechanism that links the MetS to systolic blood pressure variability because data on arterial stiffness were not collected by the survey.

A significant dose–response relationship was observed between the number of the components and visit-to-visit systolic blood pressure variability. Each component of the MetS enhances the pathophysiological changes, for example, arterial stiffness, that are intermediate steps between the MetS components and systolic blood pressure variability. Thus, as the number of the MetS components increases blood pressure variability increases. In other words, individuals with a larger number of the MetS components will have a greater additive stimulatory effect on the mechanisms that lead to systolic blood pressure variability. The mechanical stress that is placed on the vasculature as a result of increased variability of blood flow pursuant to blood pressure variability may induce a subclinical inflammatory vascular response that leads to endothelial cell damage.[28] The consequent vascular endothelial dysfunction due to endothelial damage can impair the vasodilatory mechanisms of the arteries supplying different important organs such as the heart and brain, and therefore the CV disease risk increases.[29]

Blood pressure variability increases when blood pressure increases. This association can be also clearly noticed when normotensive, mild, moderate and severe hypertensive subjects are compared.[30] In this study, a significant relationship between antihypertensive medication use and increased systolic blood pressure variability was observed. In observational studies, such as our study, antihypertensive medication is more likely to be given to individuals with more severe disease (with higher blood pressure readings and complications such as organ damage) and hence worse prognosis. Therefore, antihypertensive medications were associated with greater blood pressure variability because of their association with hypertension severity. Unlike observational studies, experimental studies do not have this limitation, mainly because randomization balances the severity distribution of the compared groups. The second possible reason to explain the observed relationship between antihypertensive medication use and higher visit-to-visit blood pressure variability is low medication adherence. Low medication adherence is a risk factor

Table 2 The relationship between the metabolic syndrome and its components with systolic blood pressure variability (multivariable analysis)

	β-*Coefficient*	*s.e.*	P-*value*
Metabolic syndrome (Model 1)			
No ($n=6430$)	Reference		
Yes ($n=2710$)	0.92	0.25	<0.01
Hypertension (Model 2)			
No ($n=5306$)	Reference		
Yes ($n=3834$)	1.04	0.18	<0.01
Large waist circumference (Model 3)			
No ($n=5469$)	Reference		
Yes ($n=3671$)	0.41	0.14	0.02
Hyperglycemia (Model 4)			
No ($n=6524$)	Reference		
Yes ($n=2616$)	0.62	0.23	0.01
Low HDL (Model 5)			
No ($n=5812$)	Reference		
Yes ($n=3328$)	0.13	0.09	0.16
High triglycerides (Model 6)			
No ($n=6580$)	Reference		
Yes ($n=2560$)	0.21	0.19	0.29
Number of metabolic syndrome components (Model 7)			
0 ($n=2149$)	Reference		
1 ($n=2293$)	0.10	0.07	1.00
2 ($n=1988$)	0.40	0.04	0.01
3 ($n=1461$)	0.79	0.06	0.01
4 ($n=888$)	1.00	0.04	<0.01
5 ($n=361$)	1.83	0.07	<0.01
			P-value for trend <0.01

Abbreviation: HDL, high-density lipoprotein.
Model 1: Metabolic syndrome + age + gender + race + smoking + antihypertensive medication.
Model 2: Hypertension + age + gender + race + smoking: antihypertensive medication intake was included in the definition of hypertension.
Model 3: Large waist + age + gender + race + smoking + antihypertensive medication.
Model 4: Hyperglycemia + age + gender + race + smoking + antihypertensive medication.
Model 5: Low HDL + age + gender + race + smoking + antihypertensive medication.
Model 6: High triglycerides + age + gender + race + smoking + antihypertensive medication.
Model 7: Number of metabolic syndrome components + age + gender + race + smoking + antihypertensive medication.

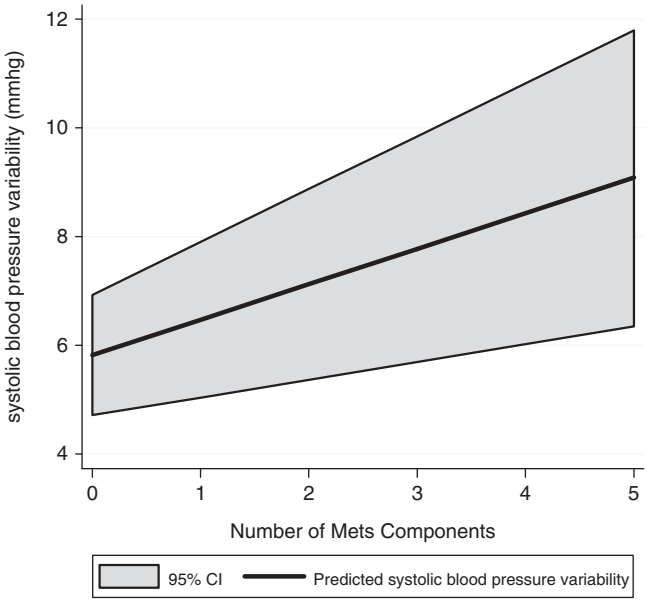

Figure 1 The relationship between the number of the metabolic syndrome (MetS) components and systolic blood pressure variability.

for blood pressure variability.[31] However, it is important to mention that only a small proportion of participants' visit-to-visit of systolic blood pressure variability can be explained by poor medication adherence.[32]

Several metrics have been used to quantify visit-to-visit blood variability in epidemiological studies.[33] We decided to use standard deviation as the only indicator for blood pressure variability because a recent study has revealed that intraindividual visit-to-visit variability gauged by standard deviation is tightly correlated with the other measures.[33] Second, calculating several metrics that capture the same aspect of visit-to-visit blood pressure variability will not convey additional data on the relationship with outcome.[33] We opted for including fasting participants only in the analysis because fasting is important to detect high triglycerides levels and impaired fasting blood glucose concentration accurately so that individuals who have one or two of these MetS components could be captured without misclassification.[34,35] Hence, participants who did not fast for 8 h or more were excluded from the analysis.

It is noteworthy to mention that the reported study estimates have small magnitudes. The difference in systolic blood pressure variability between study participants with and without the MetS that we observed was slight. However, it is important to distinguish between the implications of individual and population changes in blood pressure. At the population level, even a small upward shift in blood pressure would be expected to result in a substantial increase in CV disease and *vice versa*. The findings of this study are important because the MetS is becoming a pandemic in Western societies.[36] In the United States, the overall prevalence of the MetS is >20% in men and women over the age of 20 years and >40% in men and women over 60 years of age. Between 1988 and 1994 and between 1999 and 2000, a significant increase in the prevalence of MetS occurred among US adults aged 20 years or older.[9]

The present study has a number of important advantages. One key advantage is that the study findings can be extrapolated to US adults because NHANES III is a large probability sample of the general population. Second, the large sample size of NHANES III provided sufficient power to detect a small but important association between the MetS and blood pressure variability. Third, our study provided the opportunity to evaluate the association of the MetS syndrome with blood pressure variability for the first time in the general American population. Nevertheless, the results of this study should be interpreted with caution. First, the cross-sectional nature of these analyses did not allow for inference of causality or establishment of temporality between systolic blood pressure variability and the MetS. Second, calculation of between-visit variability of blood pressure was based on six blood pressure measurements that were taken during two visits (three blood pressure measurements in each visit). It may be possible to derive a more reliable estimate of variability, that is, standard deviation if more measurements were available. Finally, the first set of blood pressure measurements were taken during an in-home examination by research assistants, whereas the other set of measurements were obtained and recorded in a medical evaluation conducted in an

MEC by physicians. Blood pressure measurements obtained in this manner are subject to substantial error.[37] Nevertheless, a standardized study protocol and identically calibrated equipment were used to take all blood pressure measurements.

In conclusion, this study shows that the MetS can be an independent risk factor for visit-to visit systolic blood pressure variability in the general population. There is a graded relationship between the number of MetS components and visit-to-visit systolic blood pressure oscillation. Additional research is required to verify the reported results in prospective studies and develop approaches to reduce blood pressure variability observed in clinical settings among individuals who suffer from the MetS. Lowering blood pressure variability will decrease its subsequent complications.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)