nature publishing group

Predictive Value of Prehypertension for Metabolic Syndrome, Diabetes, and Coronary Heart Disease Among Turks

Altan Onat[1,2], Mehmet Yazici[3], Günay Can[4], Zekeriya Kaya[5], Serkan Bulur[3], Gülay Hergenç[6]

BACKGROUND
Predictors of prehypertension and the latter's significance in predicting metabolic syndrome (MetS), type 2 diabetes (DM), and incident coronary heart disease (CHD) need further exploration.

METHODS
Individuals with or without prehypertension (blood pressure (BP) 120–139 systolic or 80–89 mm Hg diastolic) were studied prospectively in a representative sample of Turkish adults.

RESULTS
Mean age of 1,501 men and 1,533 women was 48 ± 12 years at baseline. Prehypertension, identified in 32.8% of the sample, differed from the normotensive group mainly by age-adjusted obesity measures and C-reactive protein (CRP) and progressed to hypertension at more than twofold annual incidence as normotension did. In logistic regression analysis, adjusted for sex, age, heart rate, and smoking status, prehypertension was predictive for risk of MetS in both genders (relative risk (RR) 1.55 (95% confidence interval (CI) 1.21; 1.99)) compared with normotensives. However, DM and CHD were significantly predicted by prehypertension only in women (RR 2.06 and 1.98, respectively, for outcomes). Cardiometabolic risks in women were largely independent of obesity. Body mass index (BMI) at baseline predicted significantly subsequent development of new prehypertension in both genders (hazard ratio 1.39 (95% CI 1.17; 1.65)) and CRP tended to contribute to this risk.

CONCLUSIONS
Prehypertension, compared with normotension, approximately doubles the risk for DM, MetS, and CHD in women without conferring substantial risk in Turkish men, except toward MetS. Excess cardiometabolic risk of prehypertension in women is independent of obesity. BMI is a determinant of prehypertension.

Am J Hypertens 2008; **21**:890-895 © 2008 American Journal of Hypertension, Ltd.

The term "prehypertension" was used by the USA Joint National Committee Guidelines (JNC 7) on hypertension[1] to unify normal and high-normal blood pressure (BP) as a single entity. This designation was chosen to identify individuals (with systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg) believed to be at higher risk of developing hypertension than in those with an optimal BP (<120/80 mm Hg).[2,3] This terminology is not used by the European Society of Hypertension/European Society of Cardiology Committee for several reasons, mainly because risk increases gradually without a threshold and depends on the concomitant risk profile of the subject.[4]

Risk factor–adjusted risk of cardiovascular disease (CVD) also have been found to be higher in subjects with high-normal BP (130–139/85–89 mm Hg) than in those with optimal BP in the Framingham study, particularly in women.[5] In the past few years, several prospective[6–8] and cross-sectional[9] studies reported an elevated CVD risk among prehypertensive subjects. Hsia *et al.*[10] found the persistence of a graded relationship between BP and cardiovascular events in the Women's Health Initiative when BP was categorized as optimal, normal, high normal, and hypertensive. Progression to stage I hypertension over a 4-year period was demonstrated in nearly two-thirds of patients with untreated prehypertension.[11]

Metabolic syndrome (MetS) has been reported to be associated with prehypertension among Japanese[12] and Spanish subjects[13] in cross-sectional studies. Nonetheless, whether and to what extent prehypertension is related to subsequent development of metabolic disturbances such as MetS or type 2 diabetes (DM) has been scarcely examined prospectively.

Moreover, the CVD risk related to separate genders has not been conclusively delineated. In some reports, discrepant findings exist pertaining to higher CVD risk in women[5] and in men.[7] Body mass index (BMI) or waist circumference as determinants of prehypertension was found to be modulated by gender,[14] and ethnic differences among Americans

[1]Turkish Society of Cardiology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [2]Department of Cardiology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [3]Department of Cardiology, Düzce University Medical Faculty, Düzce, Turkey; [4]Department of Public Health, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey; [5]Koşuyolu Heart Hospital, Kartal, Istanbul, Turkey; [6]Biology Department, Yildiz Technical University, Istanbul, Turkey. Correspondence: Altan Onat (alt_onat@yahoo.com.tr)

Received 21 September 2007; first decision 3 November 2007; accepted 5 May 2008; advance online publication 12 June 2008. doi:10.1038/ajh.2008.212

were shown to play a role in the population-attributable risk of prehypertension.[15] This paper, therefore, investigates longitudinally the following aspects of prehypertension in a cohort representative of Turkish adults in whom MetS and diabetes is highly prevalent:[16] (i) which risk variables determine risk for developing prehypertension? (ii) To what extent does prehypertension predict the risk of the stated metabolic disorders and coronary heart disease (CHD), and whether a gender difference exists? In addition, progression to hypertension is analyzed from prehypertensive state as compared to normotensive state.

METHODS

Population sample. The Turkish Adult Risk Factor Study is a prospective survey on the prevalence of cardiac disease and risk factors in adults in Turkey carried out periodically since 1990 in 59 communities throughout the geographical regions.[17] It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions, and for rural–urban distribution.[17] At least two sets of BP measurements at different periods were available in 3,034 subjects free of diabetes and prevalent CHD of whom baseline values existed in 2,860 participants of the 1997-98 survey and 174 subjects enrolled in 2002. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. Individuals of the cohort signed consent for participation after having read an explanatory note. Data were obtained by history of the past years by a questionnaire, physical examination of the cardiovascular system, sampling of blood, and recording of a resting electrocardiogram.

Measurements of risk variables. BP was measured in the sitting position on the right arm, and the mean of two recordings at least 3 min apart was recorded. Waist circumference was measured using a tape (Roche LI95 63B 00; Roche Diagnostics, Mannheim, Germany), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. BMI was computed as weight divided by height squared (kg/m^2).

Serum concentrations of cholesterol, fasting triglycerides, HDL-cholesterol, and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus. In the final three surveys, the stated parameters, as well as creatinine, C-reactive protein (CRP), insulin values, and sex hormones were assayed in a single central laboratory. Blood samples collected into dry vacutainers were spun and sera shipped on cooled gel packs to Istanbul to be stored in deep-freeze at −75 °C, until analyzed at a central laboratory. Concentrations of creatinine were measured using Roche enzymatic kits and those of insulin, total testosterone, and sex hormone–binding globulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of serum apolipoprotein B and CRP were measured by the Behring nephelometry (Behring Diagnostics, Marburg, Germany).

Definitions and outcomes. Hypertension was defined as a BP ≥140 mm Hg and/or ≥90 mm Hg, and/or use of antihypertensive medication. Prehypertension was defined as a BP 120–139 mm Hg or 80–89 mm Hg. Individuals with diabetes were diagnosed with criteria of the American Diabetes Association,[18] namely when plasma fasting glucose was ≥126 mg/dl (or 2-h postprandial glucose >200 mg/dl) and/or the current use of diabetes medication. Individuals with MetS were identified when three of the five criteria of the National Cholesterol Education Program (ATP III)[19] were met, modified for prediabetes (fasting glucose 100–125 mg/dl[20]) and further for abdominal obesity using as cutoff point ≥95 cm in men, as recently assessed in the Turkish Adult Risk Factor study.[21] Missing data on triglycerides in one of the nine samples did not preclude the identification of MetS as availability of no more than three criteria was required, and the MetS status of the subsequent survey was adopted in few individuals presenting two positive criteria. HOMA was calculated using the following formula:[22] insulin (mIU/l) × glucose (in mmol/l)/22.5. Values of the baseline examination were used to evaluate prospective developments. Diagnosis of nonfatal CHD was based on the presence of angina pectoris, of a history of myocardial infarction with or without accompanying Minnesota codes of the ECG[23] or on a history of myocardial revascularization. Typical angina and, in women, age >45 years were prerequisites for a diagnosis when angina was isolated. ECG changes of "ischemic type" of greater than minor degree (Codes 1.1–2, 4.1–2, 5.1–2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively. CHD diagnosis did not include chronic heart failure or isolated atrial fibrillation.

The rationale for using BMI cutoffs of 27 kg/m^2 in men and 29.5 kg/m^2 for obesity is based on the knowledge that the best surrogate of visceral adiposity among Turks is waist circumference and that lower BMI at a given waist circumference in men suggests the existence of a higher visceral adipose tissue area.[24]

Prospective evaluation of prehypertension from the baseline examination aimed at assessing overall relative risk (RR) for metabolic disorders and CVD. Cross-sectional assessment of the final screening served to examine additional characteristics of prehypertension such as associations with creatinine and sex hormones not assayed at baseline, and these were compared with those of normotensives and hypertensives.

Data analysis. Descriptive parameters were shown as mean ± s.d. or as age-adjusted mean estimate and in percentages. Log-transformed values were used for CRP, insulin, sex hormone–binding globulin, and total testosterone due to their skewed distribution. Two-sided *t*-tests and Pearson's χ^2-tests served to analyze the differences in means and proportions between groups. ANOVA comparisons and pairwise comparisons with Bonferroni adjustment were made to detect significance between groups of estimated means. After exclusion of the cohort with the dependent variable at baseline examination, estimates (and 95% confidence intervals (CIs) for RR) of a dependent variable were obtained using logistic regression

analyses in models that controlled for potential confounders. Among men and women, 1 s.d. of BMI corresponded to 4 and 5.6 kg/m^2 and waist circumference to 11 and 12.4 cm, respectively. A value of $P < 0.05$ on the two-sided test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (SPSS, Chicago, IL; No. 9026510).

RESULTS

Cross-sectional evaluation

Estimated marginal means of certain age-adjusted risk variables related to prehypertensives were compared with those of normotensives and hypertensives in Table 1. Prehypertensive subjects were 3.6 years older than normotensives but 7.3 younger than hypertensive subjects (both $P < 0.001$), and differed from normotensives in waist circumference and BMI in both genders ($P < 0.01$). It is noteworthy that prehypertensive women were otherwise not distinguished from normotensive women, whereas prehypertensive men differed significantly with respect to having higher serum triglycerides and total testosterone. Compared with normotensive men and women combined (1.77 ± 1.045 mg/l), age-adjusted CRP levels were higher among prehypertensives (2.05 ± 1.045 mg/l, $P = 0.047$). Hypertensive subjects had significantly different values from prehypertensives regarding various risk parameters. It may be worth pointing out that current smoking—compared with never smoking—is associated with higher prevalence of normotension in both genders among Turks, regardless of the dichotomized BMI (P trend <0.001). Among obese women, the proportion of current smokers in prehypertensives was lower (14.1% vs. 23.4%, $P = 0.068$) than in normotensives (Table 1).

Prospective evaluation

At baseline examination in 1997–1998, 3,034 participants (of whom 1,501 were men) free of diabetes and prevalent CHD formed the study sample. Mean age of participants was 48 ±12 years, and mean follow-up constituted 6.6 years (total 20,020 person-years). Normotensives ($n = 978$), prehypertensives (996), and hypertensives (1,060) were fairly evenly distributed. Mean ages for these groups were 42.6 (±10.4), 46.2 (±11.4), and 53.5 (±12.1) years, respectively, with age in prehypertensives differing ($P < 0.001$) from the other two groups. A total of

Table 1 | Estimated marginal means of various age-adjusted risk variables, stratified by gender and blood pressure groups at final screening

		Men ($n = 1,501$)								Women ($n = 1,533$)					
		Normotensive ($n = 425$)		Prehypertensive ($n = 393$)		Hypertensive ($n = 683$)		P trend		Normotensive ($n = 362$)		Prehypertensive ($n = 328$)		Hypertensive ($n = 843$)	
	n	Mean	s.e.	Mean	s.e.	Mean	s.e.	Men	Women	Mean	s.e.	Mean	s.e.	Mean	s.e.
Waist circumference, cm	3,034	90.1***	0.55	93.3	0.56	98.1***	0.44	***	***	85.5**	0.65	88.1	0.66	94.8***	0.43
Body mass index, kg/m^2	3,034	25.6***	0.20	26.9	0.20	28.9***	0.16	***	***	27.4**	0.30	28.7	0.30	31.9***	0.19
Systolic BP, mm Hg	3,034	106***	0.8	122	0.8	137***	0.6	***	***	106***	1.00	124	1.0	141***	0.7
Diastolic BP, mm Hg	3,034	68***	0.4	79	0.4	85***	0.4	***	***	67***	0.55	79	0.6	87***	0.4
Heart rate, per min	3,034	73**	0.5	76	0.6	80**	0.5			75**	0.5	77	0.7	81*	0.6
Total cholesterol, mg/dl	3,034	187.5	2.1	187.9	2.1	191.8	1.6	0.21	***	188.9	2.3	194.7	2.4	202.5**	1.5
LDL-cholesterol, mg/dl	2,516	115.3	1.9	112	1.9	115.5	1.5	0.31	*	115.6	2.0	117.4	2.0	122.3	1.3
HDL-cholesterol, mg/dl	3,034	39.4	0.56	40.1	0.57	39.5	0.44	0.63	*	47.1	0.68	48.6	0.70	46.2**	0.45
Fast triglycerides, mg/dl	2,584	147.3*	5.7	170.1	5.7	177	4.4	***	***	128.7	5.0	132.3	5.1	157.5**	3.3
Apolipoprotein B, mg/dl	2,421	105.5	1.9	105.7	1.9	110.9*	1.5	*	***	101	1.9	106.2	2.29	111	1.4
Apolipoprotein A-I, mg/dl	2,290	130.4	1.5	131.8	1.5	134.4	1.2	0.12	0.19	143.5	1.8	144.5	1.8	147.3	1.2
Fasting glucose, mg/dl	2,584	91.4	1.7	92.2	1.7	98.4**	1.3	**	***	89	1.5	89.3	1.5	95.2**	1.0
Fasting insulin[a]	2,019	7.10	1.05	6.95	1.05	9.29***	1.04	***	***	7.18	1.05	7.36	1.05	9.55***	1.03
HOMA index[a]	2,019	1.49	1.05	1.50	1.06	2.13***	1.04	***	***	1.51	1.05	1.57	1.05	2.17***	1.03
Creatinine, mg/dl	1,828	0.97	0.02	1.00	0.02	1.02	0.01	0.06	*	0.76	0.02	0.76	0.02	0.81*	0.01
SHBG,[a] nmol/l	798	48.8	1.05	48.6	1.05	41.6*	1.03	**	0.17	53.5	1.07	59.4	1.07	51.4	1.04
Total testosterone,[a] nmol/l	1,149	6.90*	1.08	9.55	1.09	8.53	1.05	*	**	0.28	1.12	0.28	1.11	0.38*	1.06
C-reactive protein, mg/l[a]	2,595	1.77	1.06	2.10	1.06	2.30	1.05	**	***	1.79	1.07	2.01	1.07	2.74***	1.04
Current smokers															
Obese	1,586	55.8		45.2		28.7		***	***	23.4[b]		14.1		7.6	
Nonobese,[b] %	1,448	60.9		54.6		40.2		**	***[b]	33.3		28.1		11.3	

BP, blood pressure; HOMA, homeostatic model assessment; SHBG, sex hormone–binding globulin.
[a]log-transformed. [b]$P = 0.068$ vs. prehypertensives.
Difference from the prehypertensive group, *<0.05, **<0.01, ***<0.001 P trend by Pearson χ^2-test.

165 men and 154 women developed incident CHD at follow-up (15.9 per 1,000 person-years). Incident CHD occurred in 46 cases of normotensives (4.7%), 81 cases of prehypertensives (8.1%), and 192 cases of hypertensives (18.1%). At baseline, 605 men and 618 women were identified to have MetS (prevalences 39.9 and 40.7%, respectively). These participants were excluded from subsequent analyses. During the follow-up, 454 incident MetS (38.1 per 1,000 person-years) occurred.

Prediction of incident CHD, diabetes, and new MetS by prehypertension at baseline

Sex-stratified incidences in Table 2 disclose significantly higher crude rates of all three outcomes in prehypertensive than normotensive women but significantly lower rates than in hypertensive women. In contrast, prehypertensive men, though exhibiting lower rates of diabetes and CHD than hypertensive men, showed rates similar to normotensive men ($P > 0.16$), whereas they had significantly higher MetS rates than normotensive men but MetS rates similar to hypertensive men.

The prediction of new MetS, diabetes, and incident CHD by prehypertension compared to normotensives at baseline is shown in Table 3. Prehypertensive women had roughly twofold RRs for these conditions whereas prehypertensive men had higher risk of developing only MetS (RR 1.45, 95% CI 1.03; 2.04). The adjusted risk of developing diabetes or incident CHD by prehypertension was not increased in men with prehypertension. When adjustment was made in these models for obesity cutoffs (27 kg/m^2 in men and 29.5 kg/m^2), the associations of prehypertension with new MetS disappeared in men, being consistent with partial confounding by obesity. Women, in contrast, exhibited evidence of only moderate mediation by obesity regarding diabetes, and associations hardly attenuated with respect to MetS (RR 1.62, 95% CI 1.09; 2.38) and CHD (RR 1.95, 95% CI 1.04; 3.66), suggesting largely independence of obesity.

Predictors of prehypertension

Prehypertension developed in 317 of 845 initially nonhypertensive participants (corresponding to an incidence of 5.0% per annum). In seeking predictors of newly developing prehypertension in a multiple logistic regression, total and HDL-cholesterol, triglycerides, and log HOMA did not approach significance when analyzed in conjunction with waist circumference, which was a significant predictor in both genders (RR 1.027, 95% CI 1.013; 1.041). BMI predicted likewise prehypertension (RR 1.07, 95% CI 1.03; 1.11) when substituted for waist circumference in this model (Table 4). Sex-, age-, and BMI-adjusted logistic regression analysis for prehypertension demonstrated an RR of 1.064 (95% CI 0.996; 1.14, $P = 0.067$) for a twofold increment in CRP.

Progression to hypertension

Of 996 men and women who were prehypertensive at baseline, 333 developed hypertension at follow-up (corresponding to an incidence of 4.5% per annum), and 404 remained prehypertensive. This may be compared with 978 normortensives of whom 133 developed hypertension at follow-up (incidence 1.9% per

Table 2 | Incidence (in %) of new metabolic syndrome, diabetes and cardiovascular disease in 3,034 participants,[a] by blood pressure groups at baseline and gender

		Normotensives		Prehypertensives		Hypertensives	
Outcome	*n*	Men	Women	Men	Women	Men	Women
Metabolic syndrome	454	21.2*	16.5***	27.7	26.4	34.5	38.5**
Type 2 diabetes	258	5.0[†]	3.7**	7.1	8.1	15.1***	11.8*
Coronary heart disease	319	5.6[‡]	3.7**	7.6	8.7	21***	15.9***

Difference from the prehypertensive group, by Pearson χ^2-test: *<0.05, **<0.01, ***<0.001.
[†]$P = 0.17$, [‡]$P = 0.19$.
[a]Before exclusion of conditions at baseline.

Table 3 | Predictive value of adjusted* prehypertension for new-onset metabolic syndrome, diabetes and incident CHD at baseline, in two models

	Total		Men		Women	
	RR	95% CI	RR	95% CI	RR	95% CI
Metabolic syndrome (*n*)		1,811		910		901
Model 1						
Prehypertensives	**1.55**	1.21; 1.99	**1.45**	1.03; 2.04	**1.70**	1.17; 2.48
Model 2						
Prehypertensives	**1.40**	1.08; 1.82	1.24	0.86; 1.78	**1.62**	1.09; 2.38
BMI >27/>29.5	**2.98**	2.34; 3.79	**3.61**	2.58; 5.05	**2.29**	1.61; 3.26
Diabetes (*n*)		3,034		1,501		1,533
Model 1						
Prehypertensives	**1.52**	1.03; 2.25	1.18	NS	**2.05**	1.13; 3.72
Model 2						
Prehypertensives	1.26	0.84; 1.89	1.02	NS	1.65	0.90; 3.03
BMI >27/>29.5	**2.46**	1.85; 3.28	**2.54**	1.68; 3.82	**2.44**	1.62; 3.66
Incident CHD (*n*)		3,034		1,501		1,533
Model 1						
Prehypertensives	1.41	0.96; 2.07	1.10	NS	**1.98**	1.09; 3.59
Model 2						
Prehypertensives	1.34	0.90; 2.00	1.04	NS	**1.95**	1.04; 3.66
BMI >27/>29.5	**1.35**	1.03; 1.76	1.36	0.94; 1.97	1.36	0.94; 1.96

A total of 233 men and 221 women developed MetS in 6.6-year follow-up after exclusion of 1,223 MetS cases at baseline. A total of 129 men and 125 women newly developed diabetes, 164 men and 153 women developed incident CHD in 6.6-yr follow-up in a sample free of cases of diabetes and CHD at baseline. Model 1: adjusted for sex, age, heart rate, and smoking status; Model 2: additionally for obesity as defined by a BMI of 27 in men and 29.5 kg/m^2 in women. Significant values are highlighted in boldface.
BMI, body mass index; RR, relative risk.

Table 4 | Prediction of incident prehypertension by sex- and age-adjusted waist circumference or BMI[a] at baseline, by gender

	Total (n = 839)			Men (n = 446)			Women (n = 393)		
	RR	95% CI	*P* value	RR	95% CI	*P* value	RR	95% CI	*P* value
Waist circumference, cm	**1.027**	1.013; 1.041	<0.001	**1.030**	1.01; 1.05	<0.01	**1.024**	1.005; 1.04	<0.05
BMI, kg/m^2	**1.071**	1.033; 1.11	<0.001	**1.103**	1.04; 1.17	0.001	**1.051**	1.003; 1.10	<0.05

A total of 174 and 60 men and 142 and 57 women developed prehypertension in 6.6-year follow-up after excluding cases of prehypertension at baseline and hypertension in final screening. Sex and age did not predict prehypertension significantly.
[a]Waist circumference or BMI separately analyzed in models. Significant RR values in boldface.

annum) and 528 remained normotensive. The related RR by logistic regression analysis was 2.82 (95% CI 2.24; 3.57). After additional adjustment for BMI, RR for developing hypertension from prehypertension as opposed to normotension was 2.42 (95% CI 1.90; 3.08) in the total sample, and 1.93 (95% CI 1.39; 2.70) in men and 3.05 (95% CI 2.15; 4.32) in women.

DISCUSSION

This prospective and cross-sectional population-based study provides evidence that prehypertension confers excess risk for the development of certain metabolic disturbances, CHD, and for progression to hypertension in a population having a high prevalence of MetS. It showed as a novelty that the significantly imparted excess risk for diabetes and CHD in this population sample is gender specific, confined to women. Adjusted risk for DM and CHD in prehypertensive men was similar to normotensive men. The risk predictions by prehypertension in women were largely independent of obesity. Risk for prehypertension was predicted in both genders by BMI or waist circumference.

Incidence of prehypertension and its significance in conferring CHD and cardiometabolic risk

Similar to findings in the United States[25] and Taiwan,[13] the prevalence of prehypertension in the present cohort was 32.8% at baseline in a sample having a mean age of 48 years; it gradually declined (at the expense of more hypertensives) to 23.8% at final screening at a mean age of 52 years. The incidence of prehypertension developing among middle-aged normotensives was estimated as 5.0% per annum and that of hypertension from prehypertensive individuals was more than twofold from normotensives, namely 4.5%. The latter is slightly lower than the frequency of progression to hypertension in the Framingham Study.[2]

We found prehypertension to have a significant predictive value for the risk of MetS in both genders, at an only moderate RR of 1.55, considering that roughly half of prehypertensives had by definition a given component of MetS. The significant predictive value for the risk of both diabetes and incident CHD in women at an RR twofold that of normotensives may not be totally unexpected, recognizing that high-normal BP is related to increased risk of CVD compared with optimal BP,[5] but the magnitude of risk of prehypertension for these diseases was high. The adjusted RR of prehypertension for CVD in men was found lower in men than women (1.6 vs. 2.5) in the Framingham Study.[5] Our analyses included adjustment for heart rate which was reported to influence risk of cardiovascular mortality independently from BP in an elderly Japanese population sample.[26] To our knowledge, only one prospective study demonstrated that high-normal BP predicted an increased risk of DM, after adjustment for age and BMI.[27] This is in agreement with our findings in women.

A proinflammatory nature of prehypertension was suggested by the findings of the ATTICA study[28] which revealed an association between prehypertension and increased CRP levels linked to the atherosclerotic process. CRP levels in prehypertensive subjects in this study were also significantly higher than normotensive ones, and findings were extended that CRP tended to be predictive for the subsequent risk of prehypertension even independently of BMI.

Evidence was presented in the MONICA/KORA Augsburg case–cohort study to suggest that inflammatory processes may be of particular importance in the pathogenesis of DM in women rather than men.[29] A predictive value of prehypertension for the risk of diabetes and CHD being confined to women has not been previously reported. This might be linked to features related to the inflammatory state in Turkish men, distinct from women insofar as in men a more favorable, in women an adverse balance between anti- and proinflammatory processes might prevail and eventually lead to a sex difference in certain outcomes.

Obesity measures as determinants of prehypertension

Risk for prehypertension was significantly predicted by waist circumference and BMI in both genders, the RRs being slightly higher in men. The magnitude of the excess risk for prehypertension per 1 s.d. increment in waist circumference and BMI, respectively, corresponded to 32 and 34% in women and to 48 and 38% in men. This confirms previous studies in which obesity or adiposity was a major determinant[14] or correlate[9,10,15] of prehypertension. While confirming the findings of Sung and Ryu[30] that BMI and waist circumference were independent risk factors for high BP, at variance from some studies,[12,30] insulin resistance was associated here not independently of the anthropometric measures.

Clinical implication of present findings is apparent. Although prehypertension seems to be of minor clinical significance in men, in obese women it may assume a major public health problem, in view of its high prevalence and the demonstrated associated risk for diabetes and CHD.

Potential limitations involve the applicability of the elicited prospective findings in populations in which the prevalence of

MetS is not high. Availability of a large cohort of both genders, and the study's population-based and prospective design form its strengths.

In conclusion, prehypertension develops in middle-aged Turkish adults with normal BP at an incidence of 2.0% per year and progresses to hypertension at more than twofold annual incidence as in normotensive subjects. It is primarily determined in both genders by higher markers of obesity and, possibly, inflammatory status. It confers excess risk for the development of MetS in both genders, in addition to doubling the risk for diabetes and CHD in women. Excess risk of prehypertension for cardiometabolic risks in women is independent and added to that of obesity.

Acknowledgments: We thank the Turkish Society of Cardiology and the various pharmaceutical and nutritional companies (Pfizer, AstraZeneca, SanofiAventis, Istanbul) that have supported financially the Turkish Adult Risk Factor surveys over the years. We appreciate the dedicated works of H. Uyarel, S. Bulur, and M. Özmay, the co-workers in the survey teams.

Disclosure: The authors declared no conflict of interest.

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo L Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National Heart, Lung, Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252.
2. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study; a cohort study. *Lancet* 2001; 358:1682–1686.
3. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA* 2002; 287:1003–1010.
4. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 Guidelines for the management of arterial hypertension. *Eur Heart J* 2007; 28:1462–1536.
5. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001; 345:1291–1297.
6. Washio M, Tokunaga S, Yoshimasu K, Kodama H, Liu Y, Sasazuki S, Tanaka K, Kono S, Mohri M, Takeshita A, Arakawa K, Ideishi M, Nii T, Shirai K, Arai H, Doi Y, Kawano T, Nakagaki O, Takada K, Hiyamuta K, Koyanagi S. Role of prehypertension in the development of coronary atherosclerosis in Japan. *J Epidemiol* 2004; 14:57–62.
7. Qureshi AI, Suri MF, Kirmani JF, Divani AA, Mohammad Y. Is prehypertension a risk factor for cardiovascular diseases. *Stroke* 2005; 36:1859–1863.
8. Zhang Y, Lee ET, Devereux RB, Yeh J, Best LG, Fabsitz RR, Howard BV. Prehypertension, diabetes, and cardiovascular disease risk in a population-based sample: the Strong Heart Study. *Hypertension* 2006; 47:410–414.
9. Grotto I, Grossman E, Huerta M, Sharabi Y. Prevalence of prehypertension and associated cardiovascular risk profiles among young Israeli adults. *Hypertension* 2006; 48:254–259.
10. Hsia J, Margolis KL, Eaton CB, Wenger NK, Allison M, Wu L, LaCroix AZ, Black HR. Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation* 2007; 115:855–860.
11. Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N, Black HR, Grimm RH Jr, Messerli FH, Oparil S, Schork MA; Trial of Preventing Hypertension (TROPHY) Study Investigators. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med 2006; 354:1685–1697.*
12. Kanauchi M, Kanauchi K, Hashimoto T, Saito Y. Metabolic syndrome and new category 'pre-hypertension' in a Japanese population. *Curr Med Res Opin* 2004; 20:1365–1370.
13. Cordero A, Laclaustra M, Leon M, Grima A, Casasnovas JA, Luengo E, del Rio A, Ferreira I, Alegria E. Prehypertension is associated with insulin resistance state and not with an initial renal function impairment. A Metabolic Syndrome in Active Subjects in Spain (MESYS) Registry substudy. *Am J Hypertens* 2006; 19:189–196.
14. Tsai PS, Ke TL, Huang CJ, Tsai JC, Chen PL, Wang SY, Shyu YK. Prevalence and determinants of prehypertension status in the Taiwanese general population. *J Hypertens* 2005; 23:1355–1360.
15. Okosun IS, Boltri JM, Anochie LK, Chandra KM. Racial/ethnic differences in prehypertension in American adults: population and relative attributable risks of abdominal obesity. *J Hum Hypertens* 2004; 18:849–855.
16. Onat A: Risk factors and cardiovascular disease in Turkey. *Atherosclerosis* 2001; 156:1–10.
17. Onat A, Avcı GŞ, Şenocak M, Örnek E, Gözükara Y. Plasma lipids and their interrelation in Turkish adults. *J Epidem Commun Health* 1992; 46:470–476.
18. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus: The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; 26:3160–3167.
19. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486–2497.
20. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109:433–438.
21. Onat A, Uyarel H, Hergenç G, Karabulut A, Albayrak S, Can G. Determinants and definition of abdominal obesity as related to risk of diabetes, metabolic syndrome and coronary disease in Turkish men: a prospective cohort study. *Atherosclerosis* 2007; 191:182–190.
22. Mather KJ, Hunt AE, Steinberg HO, Paradisi G, Hook G, Katz A, Quon MJ, Baron AD. Repeatability characteristics of simple indices of insulin resistance: implications for research applications. *J Clin Endocrinol Metab* 2001; 86:5457–5464.
23. Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular Survey Methods*, 2nd edn. WHO: Geneva, 1982, pp. 124–127.
24. Onat A, Avcı GŞ, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes* 2004; 28:1018–1025.
25. Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new Joint National Committee guidelines: new challenges of the old problem. *Arch Intern Med* 2004; 164:2126–2134.
26. Hozawa A, Ohkubo T, Kikuya M, Ugajin T, Yamaguchi J, Ayasama K, Metoki H, Ohmori K, Hoshi H, Hashimoto J, Satoh H, Tsuji I, Imai Y. Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohasama Study. *Am J Hypertens* 2004; 17:1005–1010.
27. Hayashi T, Tsumura K, Suematsu C, Endo G, Fujii S, Okada K. High normal blood pressure, hypertension, and the risk of type 2 diabetes in Japanese men. *Diabetes Care* 1999: 22:1683–1687.
28. Chrysohoou C, Pitsavos C, Panagiotakos DB, Skoumas J, Stefanadis C. Association between prehypertension status and inflammatory markers related to atherosclerotic disease: the ATTICA Study. *Am J Hypertens* 2004; 17:568–574.
29. Thorand B, Baumert J, Kolb H, Meisinger C, Chambless L, König W, Herder K. Sex differences in the prediction of type 2 diabetes by inflammatory markers. Results from the MONICA/KORA Augsburg case-cohort study, 1984–2002. *Diabetes Care* 2007; 30:854–860.
30. Sung KC, Ryu SH. Insulin resistance, body mass index, waist circumference are independent risk factors for high blood pressure. *Clin Exp Hypertens* 2004; 26: 547–556.