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Lifestyle and Metabolic Determinants of Incident Hypertension, With Special Reference to Cigarette Smoking: A Longitudinal Population-Based Study

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BACKGROUND
Lifestyle and metabolic determinants of incident hypertension in a population with a high prevalence of metabolic syndrome (MetS) need to be further assessed.

METHODS
A representative sample of middle-aged and elderly Turkish adults was prospectively evaluated over a mean 7.4 years, after exclusion of prevalent hypertension and major renal dysfunction.

RESULTS
In 2,427 men and women, aged 45.8 ± 11.7 years, Kaplan–Meier analysis showed in combined genders mean time to incident hypertension to be 7.23 years in never, 7.78 years in current smokers ($P < 0.001$). Age and female sex were major determinants of subsequent hypertension after adjustment for physical activity grade, family income bracket, smoking status, usage of alcohol and of hormone replacement or birth control pill. Relative risk (RR) for incident hypertension of current vs. never smoking was reduced in women ($P = 0.058$) and both genders combined ($P = 0.054$). Former smokers uniformly exhibited significantly higher risk for the development of hypertension than both never ($P = 0.054$) and current ($P < 0.001$) smokers, whereby abdominally obese individuals were at increased risk. In further multivariable models, circulating C-reactive protein (CRP) and fasting insulin emerged as modest independent determinants and waist girth, modulated by current smoking, as a major determinant of subsequent hypertension.

CONCLUSIONS
Age, female sex, and waist circumference are major and serum insulin and CRP modest determinants of incident hypertension in middle-aged Turkish adults in whom current cigarette smoking plays a protective role at borderline significance, largely by modulating waist girth. Former smokers with abdominal obesity are under higher risk of subsequent hypertension than current smokers.

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The pathophysiology of hypertension is well known to be multifactorial. Gender, varying at different periods of life,[1] and age[2] are two of its main determinants. Apart from genetic determinants,[3] changes in renin–angiotensin system,[4] certain behavioral variables such as physical inactivity, alcohol or cigarette consumption,[5] use of oral contraceptives, or receiving hormone replacement therapy[6] influence risk of incident hypertension. Obesity, insulin resistance and a proinflammatory state have been further recognized determinants.[7] The proinflammatory state, known to be interrelated with obesity and smoking habit, was reported to antidate at least by several years the onset of overt hypertension.[8]

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Investigations have been abundant on cigarette smoking being an established risk factor for cardiovascular disease;[9,10] yet the relationship between smoking and the development of hypertension is unclear. Results have been inconclusive and prospective epidemiological studies have been scarce. Recent reports on the long-term influence of smoking status to the new development of hypertension indicated a positive association of modest strength in men[11] and a still more modest one among women.[12] A nonsignificant association was obtained among current smokers in the small-sized prospective ATTICA study.[13]

The relationship between insulin resistance and blood pressure (BP) may be mediated by mechanisms related to racial[14] and ethnic differences. We have previously provided evidence in prospective epidemiological analyses that cigarette smoking Turkish women tend to be protected from metabolic syndrome (MetS) and type 2 diabetes[15] and that they differ from men in not disclosing elevation in C-reactive protein (CRP) in the follow-up.[16]

We, therefore, aimed to investigate prospectively the lifestyle determinants of hypertension, with special reference to the smoking habit, in a population sample representative of

Turkish adults in whom MetS highly prevails.[17] Because both smoking and hypertension are intrinsically related to certain metabolic states such as abdominal obesity, insulin resistance, and proinflammatory state, these will also be taken into consideration.

METHODS

Population sample. The Turkish Adult Risk Factor Study is a longitudinal population-based cohort study on the prevalence of cardiac disease and risk factors in adults in Turkey carried out biennially in 59 communities scattered throughout all geographical regions of the country.[18] It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural–urban distribution.[18] Because combined measurements of waist circumference and high-density lipoprotein cholesterol were first performed at the follow-up visit in 1997/98, the latter examination formed the baseline. Participants, being ≥28 years of age at baseline, were examined initially and biennially over a period of 9 years, up to the survey 2006/07. Of 3,202 individuals examined at baseline, 754 subjects (23.6%) with hypertension and/or using antihypertensive drugs, and further 21 men and women with serum creatinine values ≥1.5/>1.3 mg/dl at baseline were excluded; thus, 2,427 subjects composed the cohort of the current study. 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 were visited in their addresses on the eve of the examination and gave written consent for participation. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting 12-lead electrocardiogram.

Measurements of risk variables. BP was measured using a sphygmomanometer (Erka, Bad Tölz, Germany) after 10 min of rest in the sitting position on the right arm, unless a specific reason was apparent in which case the arm with the higher value; and the mean of two recordings at least 3 min apart was recorded. Weight was measured without shoes in light indoor clothes using a scale. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index was calculated as weight divided by height squared (kg/m^2). Participants categorized themselves at baseline into four predefined increasing family income brackets.[18] Self-reported cigarette smoking was categorized into never smokers, former smokers (discontinuance of ≥3 months) and current smokers (regularly ≥1 cigarettes daily), as elicited in interview during examination. Pipe or cigar smokers are very rare among Turks and none existed in this cohort. Anyone consuming alcohol once a week or more was considered as alcohol user. Physical activity was graded by the participant himself into four categories of increasing order with the aid of the following scheme: grade 1: white-collar worker, sewing-knitting, walking ≤1 km daily; grade 2: repair worker, house work, walking 1–2 km daily; grade 3: mason, carpenter, truck driver, cleaning floors and windows, walking 4 km daily; grade 4: heavy labor, farming, regular sports activity.[18]

Plasma concentrations of cholesterol, fasting triglycerides, high-density lipoprotein cholesterol, and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus. Low-density lipoprotein cholesterol values were computed according to the Friedewald formula. In the final four surveys, the stated parameters, as well as insulin and CRP values were assayed in a single central laboratory. Blood samples were spun at 1,000*g* for 10 min and shipped on cooled gel packs at 2–5 °C to Istanbul to be stored in deep-freeze at −75 °C, until analyzed at a central laboratory in the same city. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of serum CRP were measured by the Behring nephelometry, using an N high-sensitivity CRP kit (Behring Diagnostics, Marburg, Germany) the lower detection limit of which was 0.0175 mg/l. Within run and day-to-day coefficients of variation for CRP were 1.3 and 2.9%, respectively. Plasma fibrinogen was assayed by the modified Clauss method using Behring Fibrintimer II coagulometer and Multifibren U kit. Data on baseline insulin and CRP were available in 55 and 84% of participants, respectively. Homeostatic model assessment (HOMA) was calculated with the following formula: insulin (mIU/l) × glucose (in mmol/l)/22.5.

Definitions and outcomes. Hypertension was defined as a BP ≥140 mm Hg and/or ≥90 mm Hg, and/or use of antihypertensive medication. Individuals with diabetes were diagnosed with criteria of the American Diabetes Association,[19] 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 3 of the 5 criteria of the National Cholesterol Education Program (ATP III)[20] were met, modified for prediabetes (fasting glucose 100–125 mg/dl[21] and further for abdominal obesity using as cutpoint ≥95 cm in men, as recently assessed in the Turkish Adult Risk Factor study.[22]

Data analysis. Descriptive parameters were shown as mean ± s.d. for age, or as age-adjusted estimated mean ± s.e. and in percentages. Because of the skewed distribution of concentrations of insulin and CRP, these were log-transformed for calculations. Two-sided *t*-tests and Pearson's χ^2-tests were used to analyze the differences between means and proportions of two groups. Analysis of variance comparisons and pairwise comparisons with Bonferroni adjustment were made to detect significance between groups of estimated means. Development of future hypertension was estimated with the Kaplan–Meier method taking into account the last examination data of the participants. In predicting future hypertension from multivariate analyses at baseline examination, in addition, estimates (and 95% confidence intervals) for relative risk (RR) of a dependent variable were obtained by use of logistic regression analysis in three models. A basic one comprised

sex, age, physical activity grade, family income bracket, alcohol usage, and smoking status, in women, additionally for use of hormone replacement or birth control pill. With the purpose of assessing the role of certain mediators, waist circumference, insulin, and CRP were added (Model 2), and finally smoking status was analyzed jointly with the dichotomized important covariant waist circumference (Model 3). Hazard ratios were calculated using the given RRs for 1 s.d. (s.d. = 2.85-fold concentration of CRP). A possible interaction between current smoking and abdominal obesity was examined by dichotomizing waist circumference using cutoff values of 95 and 88 cm in men and women, respectively, which also coincide with thresholds for abdominal obesity among Turks as stated above. 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

At baseline examination, 1,278 men (52.6%, mean age 46.5 ± 11.8 years) and 1,149 women (45.0 ± 11.5 years, $P = 0.001$) were available. Only 40 subjects (1.6%) had prevalent CHD. Mean follow-up consisted of 7.4 years (total 18,004 person-years) during which hypertension developed in 775 cases (3.8% per year).

Baseline characteristics of the sample according to smoking status

Table 1 shows the distribution of certain sex- and age-adjusted risk variables of this nonhypertensive study sample according to smoking status. A relatively high waist girth, low total and high-density lipoprotein cholesterol and high fasting glucose levels are notable. Current smokers were distinguished from never smokers by significantly lower waist girth (4 cm) and BPs (5/2 mm Hg), higher low-density lipoprotein cholesterol (5 mg/dl) and fibrinogen (0.27 g/l). Fasting glucose tended to be lower among current smokers.

Though HOMA index and CRP concentrations did not differ significantly across smoking status in combined genders, genders differed from each other in these relations (**Supplementary Table S1** online). Compared with never smokers, current smoking women had significantly lower (1.70 vs. 1.97 mg/l, $P = 0.04$), whereas men had higher CRP levels (2.09 vs. 1.56 mg/l, $P = 0.002$). Whereas HOMA was similar among women across the smoking status, smoking men had lower HOMA than both never ($P = 0.078$) and former smokers ($P = 0.050$).

CRP and HOMA values in current smokers were compared with never smokers by a stratified approach depending on the development of hypertension in the follow-up (**Supplementary Table S1** online). Though individuals who developed hypertension tended to disclose higher CRP levels, this reached significance only in male current smokers. In all the other subgroups including HOMA values (not shown in detail), no significant difference was noted in the stratified analyses.

Kaplan–Meier analysis for remaining free of hypertension

By Kaplan–Meier analysis for the whole study sample, mean time to development of hypertension was 7.23 years in never smok-

Table 1 | Sex- and age-adjusted[a] baseline characteristics of the sample free of hypertension, by smoking status

	Never smokers ($n = 1,165$)		Past smokers ($n = 283$)		Current smokers ($n = 979$)		
$n = 2,427$ subjects	Mean	s.e.	Mean	s.e.	Mean	s.e.	*F* value
Crude age, years	46.7	12.3[b]	50.5	12.1[b]	43.3	11[b]	<0.001
Sex (male) % (53)	26.4		84.5		74.7		<0.001
Body mass index (kg/m^2)	27.5	0.2	27.8	0.4	26.2	0.2	<0.001
Waist circumference (cm)	92.2	0.35	92.1	0.69	88.2[c**]	0.38	<0.001
Fasting triglycerides (mg/dl) ($n = 2,001$)	136.3	3.2	149.6	6.2	138.9	3.4	0.17
HDL-cholesterol (mg/dl)	40.7	0.43	43[c*]	0.76	40.1	0.42	0.003
LDL-cholesterol (mg/dl) ($n = 2,000$)	113.5	1.1	114.2	2	118.5[d*]	1.2	0.011
Total cholesterol (mg/dl)	177.3	1.2	183.8	2.3	184.5	1.3	0.001
Fasting glucose (mg/dl) ($n = 2,069$)	98	0.9	99.2	1.7	95.6	0.9	0.062
Fasting insulin (mIU/l)[e] ($n = 1,340$)	7.5	1.03	7.6	1.06	6.9	1.04	0.15
C-reactive protein (mg/l) ($n = 2,032$)	1.83	1.04	1.79	1.08	2.02	1.04	0.17
Fibrinogen (g/dl) ($n = 1,661$)	2.89	0.03	3.02	0.06	3.16[d*]	0.03	<0.01
Systolic blood pressure (mm Hg)	122	0.45	122	0.9	117[c**]	0.48	<0.001
Diastolic blood pressure (mm Hg)	78	0.31	79	0.6	76[c**]	0.33	<0.001
Physical activity grade (I to IV)	2.42	0.03	2.35	0.06	2.45	0.03	0.26
Alcohol usage, %	10.6		23.7		27.1		<0.001
Presence of diabetes mellitus (%)	4.5		3.9		2.7		0.09
Presence of metabolic syndrome (%)	36.1		43.7		26[c**]		<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Adjusted to age 46 years. [b]Standard deviation. [c]Compared with both remaining values, [d]Compared with the remaining lower value. [e]Log-transformed values.
*$P < 0.05$, **$P < 0.001$.

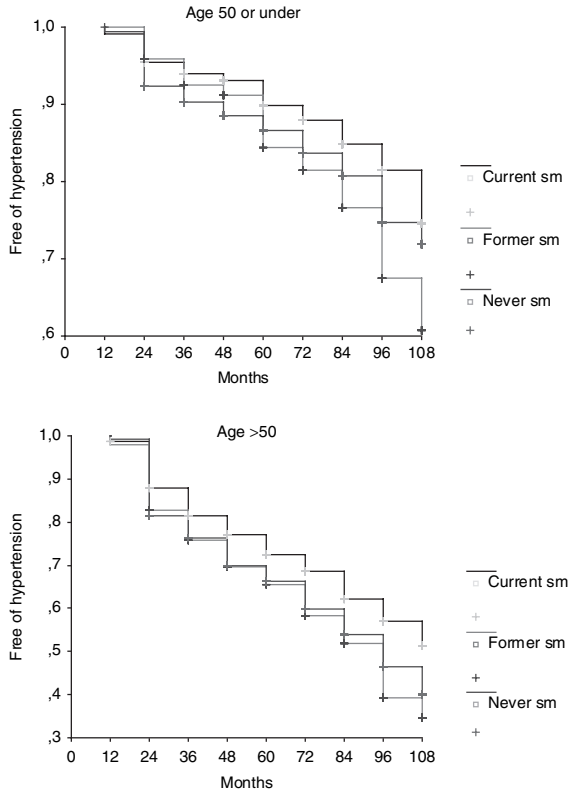

Figure 1 | Kaplan–Meier survival curves remaining free of hypertension by smoking status in combined genders at ages ≤50 and >50 years (*P* for log rank between current and never smokers 0.034 and 0.002, respectively). In 1,270 younger subjects, while 124 developed hypertension among 575 never smokers at a mean 78.4 months, 100 developed hypertension among 597 current smokers at a mean 83.3 months. In the older group of 1,157 subjects, whereas 291 developed hypertension among 590 never smokers at a mean 50.7 months, 142 developed hypertension among 382 current smokers at a mean 54.5 months.

ers, 7.78 years in current smokers ($P < 0.001$), and 6.91 years in former smokers. **Figure 1** shows crude survival curves remaining free of hypertension by smoking status in both genders, by age ≤50 and >50 years. The curves separate steadily throughout the entire follow-up period, without a higher proportion of early vs. late hypertensive subjects ($P = 0.034$ in current vs. never smoking subjects ≤50 years and 0.002 in those older).

Multivariate analyses of predictors of newly developing hypertension

These were carried out in three logistic regression models (**Table 2**). Aside from female sex (odds ratio 1.4) and age (1.68 per decade), waist circumference was the strongest studied determinant of subsequent hypertension (1.52 for an increment of 11 cm), independent of other confounders. The nonsignificant variables family income, physical activity grade, and usage of lipid-lowering medication are not shown in the remaining models.

In the basic model, current smoking predicted hypertension inversely at a borderline significance in both genders combined ($P = 0.054$) and among women ($P = 0.058$). A twofold increment in insulin was modestly associated with future hypertension, and a twofold increment in CRP predicted hypertension, especially in women (Model 2). RR of current smoking was largely attenuated to 0.89 in this (half-sized) model indicating that the association of smoking was largely mediated by waist circumference and the covariates. Model 3 discloses that, compared with nonsmoking slim persons, abdominal obesity predicted hypertension with an RR 1.8 regardless of gender and smoking status; furthermore, both slim and abdominally obese female smokers exhibited a nonsignificant tendency to lower (not higher) RR of hypertension. Thus, no evidence of an interaction between smoking and abdominal obesity was observed.

Former smoking revealed significantly increased risk for hypertension in men compared with *never* smoking and uniformly significantly increased risk compared with *current* smoking in all models of combined genders, regardless of adjustment for lipids, insulin, or CRP levels (**Table 3**). When subjects were stratified by the presence of abdominal obesity, only abdominally obese male and total former smokers but not slim former smokers were found to be at significantly elevated risk of hypertension. In paired sample tests, waist girth increased by 4.4 (95% confidence interval 3.5; 5.4) cm at the final survey among 206 adults who ceased to smoke after the baseline examination, whereas it increased by 2.0 (95% confidence interval 1.5; 2.5) cm at the final survey among 714 adults who continued to smoke.

DISCUSSION

In a representative sample of a middle-aged population having a high prevalence of MetS and being free of hypertension or renal failure, a follow-up of 5–9 years demonstrated female sex, aging, and waist circumference as important determinants of newly developing hypertension. Current smoking, significantly associated with waist girth, serum CRP and fasting insulin levels, was found to be a further independent (inverse) determinant mediated by waist girth, particularly among women. Abdominally obese former smokers disclosed a significantly increased (1.6-fold) RR for the development of hypertension compared with abdominally obese never smokers.

We confirmed that age and gender are salient determinants of subsequent hypertension. Though male sex is more predisposed to hypertension before age 50 years, female sex is so after this age.[1] We have selected to investigate the role of waist circumference rather than body mass index as a determinant of hypertension, because it is a better indicator of visceral adiposity among Turks than body mass index, particularly in men[23] which was reported to be valid in Western populations[24] as well.

Abdominal obesity stronger predictor of hypertension than hyperinsulinemia or elevated CRP

Our observations on fasting insulin being a more modest determinant of future hypertension in joint analysis with waist circumference were rather in agreement with those of Poirier[7] and at some variance with the EGIR Study.[25] The strength of the multivariably adjusted association of CRP with subsequent hypertension was ~1.12–1.15 per s.d.

Table 2 | Multivariably adjusted predictors of newly developing hypertension

	Total (n = 2,393)		Men (n = 1,261)		Women[a] (n = 1,132)	
Model 1	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Sex, female	**1.41****	1.13; 1.75				
Age (years)	**1.053*****	1.044; 1.062	**1.043*****	1.031; 1.055	**1.064*****	1.05; 1.08
Physical activity grade I–IV	0.96†	0.86; 1.06	0.96†	0.85; 1.09	0.95†	0.79; 1.14
Family income I–IV	1.07†	0.98; 1.16	1.05†	0.93; 1.19	1.12††	0.99; 1.25
Former smokers	1.33†	0.98; 1.81	**1.52***	1.05; 2.20	1.20†	0.62; 2.33
Current smokers	0.80††	0.64; 1.007	0.89†	0.65; 1.22	0.74††	0.52; 1.05
Model 2	**Total (n = 1,295)**		**Men (n = 628)**		**Women (n = 667)**	
Fasting insulin[a]	**1.11***	1.02; 1.21	**1.13***	1.004; 1.27	1.065†	0.94; 1.21
C-reactive protein[a]	**1.081****	1.024; 1.14	1.067†	0.986; 1.15	**1.10***	1.02; 1.19
Waist circumference, cm	**1.025*****	1.012; 1.038	**1.03****	1.01; 1.05	**1.021***	1.005; 1.038
Current smokers	0.89	0.64; 1.23	0.84	0.53; 1.31	1.01	0.66; 1.57
Model 3	**Total (n = 2,388)**		**Men (n = 1,257)**		**Women (n = 1,131)**	
Smoker + slim	0.80†	0.59; 1.10	0.84†	0.53; 1.34	0.73†	0.44; 1.19
Nonsmoker + abdominally obese obese	**1.85*****	1.42; 2.41	1.65††	0.98; 2.78	**1.88*****	1.38; 2.56
Smoker + abdominally obese	**1.83*****	1.32; 2.53	**1.85***	1.15; 2.99	**1.69***	1.001; 2.85
Former smokers	1.33†	0.976; 1.82	**1.49***	1.02; 2.17	1.16†	0.55; 2.45

Model 1
Included were 372 men (29.5%) and 393 women (34.7%) with new hypertension. 723/234 men (57.4%) and 245/43 women (21.6%) current/former smokers. Reference category for RRs of smokers is never smokers in all models. Significant values are highlighted in boldface.
[a]Also adjusted for alcohol usage, lipid-lowering drugs (30 persons), usage of hormone replacement or birth control pill in 95 women (all $P > 0.05$).
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, †$P > 0.05$, ††0.054–0.09.
Model 2
Included were 196 men (31.2%) and 220 women (33%) with new hypertension. 344/120 men and 133/22 women current/former smokers.
[a]Log-transformed and expressed in terms of a twofold increment. Also adjusted for sex, age, family income, physical activity, usage of alcohol, lipid-lowering drugs (9 persons), use of hormone replacement or birth control pill and smoking status (attenuated in females in this model, RR just over 1).
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, †$P > 0.05$.
Model 3
Included were 372 men (29.5%) and 393 women (34.7%) with new hypertension. Referent nonsmoking slim (<95/88 cm) subjects encoded 145 men and 379 women. 445 men and 159 women were encoded as smoking + slim. 720/234 men and 245/43 women current/former smokers. Also adjusted for sex, age, physical activity, family income, usage of alcohol, lipid-lowering drugs (30 persons), use of hormone replacement or birth control pill.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, †$P > 0.05$, ††$P = 0.060$.

Table 3 | Relative risk for incident hypertension of former smokers at baseline, with reference to current smokers

	Total		Men		Women	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Model 1	**1.66**	1.24; 2.23	**1.70**	1.23; 2.35	1.63	0.80; 3.33
Model 2 Trg, HDL-C	**1.75**	1.25; 2.46	**1.81**	1.24; 2.63	1.73	0.79; 3.78
Model 3 Waist, ins., CRP	**1.56**	1.02; 2.37	**1.78**	1.11; 2.86	0.78	0.27; 2.29
Model 4						
Waist ≥95/88 cm	**1.62**	1.08; 2.41	**1.64**	1.06; 2.53	1.41	0.50; 3.95
Waist <95/88 cm	1.17	0.70; 1.94	1.24	0.71; 2.15	1.003	0.26; 3.91

All models were also adjusted for sex, age, physical activity, family income, usage of alcohol and, in women, of hormone replacement or birth control pill. Significant values are highlighted in boldface.
CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; Ins, insulin; Trg, triglycerides.

increment, less than the odds of 1.26 found in the analysis by Wang *et al.*[8]

Some *gender differences* existed regarding risk for hypertension. In women, CRP appeared to behave partly independently of waist girth, whereas among men, insulin levels were to a large part independent of waist girth and contributed more than CRP to the risk of hypertension.

The paradox of effect of cigarette smoking in risk of hypertension

Current smoking was identified in this population sample as an independent inverse determinant mediated by waist girth, CRP, and insulin levels, especially among women. And former smoking clearly predicted subsequent development of hypertension, notably in abdominally obese adults. This

novel finding is at variance with related findings obtained in Western populations. A new analysis of the Physicians' Health Study evaluated in 13,529 men the role of smoking status in the risk of incident hypertension.[11] Over a median follow-up of 14.5 years, current smokers compared with never smokers had a modestly increased RR of 1.15 of developing self-reported hypertension. Multivariably adjusted risk of smokers among the 28,236 women in the Women's Health Study followed up over a median 9.8 years was of similar magnitude, namely 1.12 (95% confidence interval 1.03; 1.21) in those who smoked ≥15 cigarettes daily but did not significantly differ from never smokers in women smoking <15 cigarettes daily.[12] Cross-sectional analysis of a large French sample concluded that current smokers were associated with increased likelihood of systolic hypertension, this being independent of body mass index.[26]

Present findings appear to confirm our previous observations[15,16,22,27] and extend the "favorable" influence of cigarette smoking to the development of hypertension in this population, after multivariable adjustment. It should be mentioned that smoking up to 20 cigarettes daily among lean men reduced the risk of developing diabetes also in a large Japanese male population sample.[28]

Though the multivariably reduced RR in smoking females (0.74) and combined genders (0.80) just fell short of attaining full significance ($P = 0.058$ and 0.054, respectively) in the current study, following points strongly argue against this being a chance finding. The Kaplan–Meier analysis was highly significant. Former smoking compared with never smoking demonstrated a uniformly increased risk compared with current smokers in all models and both genders, particularly in individuals with abdominal obesity. Finally, the fact that these are in line with previous findings related to aspects other than hypertension underlines the consistency of the results.

The mechanism underlying the favorable long-term influence of active smoking on the development of hypertension is chiefly related—though not confined—to the associated reduction of abdominal obesity in both genders.[22,27] Some improvement in the coexisting proinflammatory state among women and of insulin sensitivity in men[29] seems to be involved as well, as suggested by significantly lower age-adjusted serum insulin values among male smokers and lower age-adjusted serum CRP in female smokers.

Overall paralleling the obesity-mediated increased BP among French former vs. nonsmokers,[26] cessation of smoking led in this population sample to a rebound effect on the risk of developing hypertension in abdominally obese individuals. This is in line with smoking's beneficial influence on the development of hypertension being mainly via reducing abdominal obesity. It is not clear whether there is a concomitant overshooting of the returning abdominal obesity and/or hyperinsulinemia; our baseline values (**Supplementary Table S1** online) suggest that CRP level overshoots in female, fasting insulin in male former smokers.

Present findings provide information that the reduction in risk of incident hypertension by smoking is likely part of the effect of cigarette smoking protecting Turkish women from MetS and diabetes.[15] These observations should not deter from stating that an overall benefit of health was not obtained from active smoking, in fact, prospective multi-adjusted evaluations of incident CHD risk demonstrated a significant and moderate elevation in male, an insignificant reduction in female current smokers.[16,27] This is still consistent with reduced risks for hypertension, and stands in contrast to the significant impacts of age and BP.

Limitations and strengths

The size of the sample was relatively limited but allowed the development of hypertension in nearly 800 individuals to lead to meaningful results. The possible omission of some potential confounders such as the duration and amount of smoking in the analyses may have influenced findings though marginally. Data on salt intake of the participants were not available for inclusion in the adjustments, and the possibility of a lower salt intake among smokers was not excluded. Against arguments that conceivably narrower waist circumference *per se* rather than smoking's mediation might be responsible for the lower development of hypertension speak (i) the demonstration of cigarette smoking being an important determinant of abdominal obesity in either gender in the Turkish Adult Risk Factor Study,[22,27] (ii) the mediation shown in the development of hypertension of other factors such as fasting insulin in men (independently of waist girth) and CRP in women which were paralleled by decreased levels among current smokers, as also by prospective evaluation of smokers,[16] and (iii) the higher risk of subsequent hypertension in former than in current smokers. The composition of the population sample with a high prevalence of MetS may limit the generalizability of conclusions to populations having a low MetS prevalence. The prospective nature of the study, its being based on a representative population sample and on measurements of all studied risk variables rather than partly on questionnaire, the inclusion of women, greater extent of adjusted risk factors constitute *strengths* of the present study.

In *conclusion*, sex, age, and waist circumference were confirmed as important determinants of newly developing hypertension. Current smoking proved another independent though inverse determinant of hypertension, in particular among women, primarily mediated by changes in waist girth. Former smokers with abdominal obesity are under clearly higher risk of subsequent hypertension than their actively smoking counterparts.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ajh

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1. National Center for Health Statistics. *Health, United States*, 2005. With Chartbook on Trends in the Health of Americans. Hyattsville, MD: National Center for Health Statistics; 2005. <http://www.cdc.gov/nchs/data/hus/hus05.pdf> (2008). p. 267. Accessed 8 February 2008.
2. Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, Witteman J, Stampfer MJ. Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 1996; 27:1065–1072.
3. Yamada Y, Kato K, Yoshida T, Yokoi K, Matsuo H, Watanabe S, Ichihara S, Metoki N, Yoshida H, Satoh K, Aoyagi Y, Yasunaga A, Park H, Tanaka M, Nozawa Y. Associations of polymorphisms of ABCA1 and ROS1 with hypertension in Japanese individuals. *Int J Mol Med* 2008; 21:83–89.
4. Ichihara A, Inscho EW, Imig JD, Michel RE, Navar LG. Role of renal nerves in afferent arteriolar reactivity in angiotensin-induced hypertension. *Hypertension* 1997; 29:442–449.
5. Keil U, Chambless L, Filipiak B, Härtel U. Alcohol and blood pressure and its interaction with smoking and other behavioural variables: results from the MONICA Augsburg Survey 1984–1985. *J Hypertens* 1991; 9:491–498.
6. Gruppo di Studio Progetto Menopausa Italia. Risk factors for high blood pressure in women attending menopause clinics in Italy. *Maturitas* 2006; 53:83–88.
7. Poirier P, Lemieux I, Mauriege P, Dewailly E, Blanchet C, Bergeron J, Després J-P. Impact of waist circumference on the relationship between blood pressure and insulin: the Quebec Health Survey. *Hypertension* 2005; 45:363–367.
8. Wang TJ, Gona P, Larson MG, Levy D, Benjamin EJ, Tofler GH, Jacques PF, Meigs JB, Rifai N, Selhub J, Robins SJ, Newton-Cheh C, Vasan RS. Multiple biomarkers and the risk of incident hypertension. *Hypertension* 2007; 49:432–438.
9. Njølstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation* 1996; 93:450–456.
10. Qiao Q, Tervahauta M, Nissinen A, Tuomilehto J. Mortality from all causes and from coronary heart disease related to smoking and changes in smoking during a 35-year follow-up of middle-aged Finnish men. *Eur Heart J* 2000; 21:1621–1626.
11. Halperin RO, Gaziano JM, Sesso HD. Smoking and the risk of incident hypertension in middle-aged and older men. *Am J Hypertens* 2008; 21:148–152.
12. Bowman TS, Gaziano JM, Buring JE, Sesso HD. A prospective study of cigarette smoking and risk of incident hypertension in women. *J Am Coll Card* 2007; 50:2085–2092.
13. Panagiotakos DB, Pitsavos C, Lentzas Y, Chrysohoo C, Stefanadis S. Five-year incidence of hypertension and its determinants: the ATTICA study. *J Hum Hypertens* 2007; 21:686–688.
14. Saad MF, Lillioja S, Nyomba BL, Castillo C, Ferraro R, De Gregorio M, Ravussin E, Knowler WC, Bennett PH, Howard BV ***et al***. Racial differences in the relation between blood pressure and insulin resistance. *N Engl J Med* 1991; 324:733–739.
15. Onat A, Özhan H, Esen AM, Albayrak S, Karabulut A, Can G, Hergenç G. Prospective epidemiologic evidence of a "protective" effect of smoking on metabolic syndrome and diabetes among Turkish women—without associated overall health benefit. *Atherosclerosis* 2007; 193:380–389.
16. Onat A, Can G, Hergenç G. Serum C-reactive protein is an independent risk factor predicting cardiometabolic risk. *Metabolism* 2008;57:207–214.
17. Onat A, Ceyhan K, Başar Ö, Erer B, Toprak S, Sansoy V: Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels—a prospective and cross-sectional evaluation. *Atherosclerosis* 2002; 165:285–292.
18. 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.
19. 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. 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; 26:3160–167.
20. 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.
21. 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.
22. 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.
23. 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.
24. Pouliot MC, Déspres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994; 73:460–468.
25. Ferrannini E, Natali A, Capaldo B, Lehtovirta M, Jacob S, Yki-Järvinen H for the European Group for the Study of Insulin Resistance (EGIR). *Hypertension* 1997; 30:1144–1149.
26. Halimi JM, Giraudeau B, Vol S, Cacès E, Nivet H, Tichet J. The risk of hypertension in men: direct and indirect effects of chronic smoking. *J Hypertens* 2002; 20:171–172.
27. Onat A, Sarı I, Hergenç G, Yazıcı M, Can G, Uyarel H, Sansoy V. Predictors of abdominal obesity and high susceptibility of cardiometabolic risk to its increments among Turkish women: a prospective population-based study. *Metabolism* 2007; 56:348–356.
28. Nagaya T, Yoshida H, Takahashi H, Kawai M. Heavy smoking raises risk for type 2 diabetes mellitus in obese men; but, light smoking reduces the risk in lean men: a follow-up study in Japan. *Ann Epidemiol* 2008; 18:113–118.
29. Onat A, Hergenç G, Türkmen S, Yazıcı M, Sarı I, Can G. Discordance between insulin resistance and metabolic syndrome: features and associated cardiovascular risk in adults with normal glucose regulation. *Metabolism* 2006; 55:445–452.