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Uric Acid and Insulin Sensitivity and Risk of Incident Hypertension

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Abstract

Background—Uric acid, insulin sensitivity, and endothelial dysfunction may be important in the development of hypertension. Corresponding circulating biomarkers are associated with risk of hypertension in many studies. However, because these factors may be interrelated, whether they independently influence risk is unknown.

Methods—Among 1,496 young women who did not have hypertension at baseline, we prospectively analyzed the association between fasting plasma levels of uric acid, insulin, triglycerides, the insulin sensitivity index, two biomarkers associated with endothelial dysfunction (homocysteine and soluble intercellular adhesion molecule-1), and the odds of incident hypertension. Odds ratios were adjusted for standard risk factors, and then for all biomarkers, plus estimated glomerular filtration rate and total cholesterol. The population attributable risk was estimated for biomarkers significantly associated with hypertension.

Results—All biomarkers were associated with incident hypertension after adjustment for standard hypertension risk factors. However, after simultaneously controlling for all biomarkers, eGFR, and total cholesterol, only uric acid and insulin were independently associated with incident hypertension. Comparing the highest to lowest quartile of uric acid, the OR was 1.89 (1.26-2.82). A similar comparison yielded an OR=2.03 (1.35-3.05) for insulin. Using an estimated basal incidence rate of 14.6 per 1000/year, 30.8% of all hypertension occurring in young women annually is associated with uric acid levels ≥3.4 mg/dL. For insulin levels ≥2.9 μIU/mL, this proportion is 24.2%.

Conclusions—Differences in uric acid and insulin robustly and substantially influence the risk of developing hypertension among young women. Measuring these biomarkers in clinical practice may identify higher risk individuals.

Introduction

Hypertension is highly prevalent, affecting approximately one-third of Americans.[1] and is a leading cause of morbidity and mortality.[2] The etiology of hypertension is unclear in the vast majority of cases.[3] Proposed pathophysiologic mechanisms include: 1) uric acid induced activation of the renin angiotensin system (RAS) and injury to preglomerular renal vessels;[4] 2) reduced insulin sensitivity and hyperinsulinemia with altered renal sodium handling and enhanced sympathetic tone;[5-7] and 3) endothelial dysfunction with altered vascular tone and

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function.[8-11] Measurement of these potential pathophysiologic factors may ultimately lead to identification of high-risk individuals and improved prevention.

Circulating biomarkers related to these three pathophysiologic processes, specifically uric acid,[12-25] insulin,[26, 27] and homocysteine,[28, 29] have been associated with risk of hypertension in most studies. However, because these factors may be interrelated, it is unknown whether they are independently associated with risk of hypertension. Therefore, we measured uric acid, insulin and triglycerides (to compute the insulin sensitivity index),[30] and homocysteine and soluble intercellular adhesion molecule-1 (both associated with endothelial dysfunction)[31-36] in a prospective nested case-control study of 1,496 young, healthy women from the second Nurses' Health Study (NHS2) to determine whether differences in these biomarkers precede and independently predict the onset of hypertension.

Methods

Study Population

The NHS2 is an ongoing prospective cohort of 116,671 female registered nurses that began in 1989. Participants are followed via biennial questionnaires that gather information on health-related behaviors and medical events. Follow-up of participants was >90% through 2005. During the years 1997-1999, 29,616 participants contributed blood samples that were stored in liquid nitrogen (-130 C). We conducted a nested case-control study of incident hypertension among those women who contributed blood samples and who did not have prevalent hypertension at the time of blood collection. The institutional review board at Brigham and Women's Hospital approved this study.

We selected cases and controls from among those who met the following criteria at the time of blood collection: 1) blood sample collected after fasting for at least 8 hours; 2) no diagnosis of hypertension; 3) no use of anti-hypertensive medications; 4) no diagnosis of cancer (except non-melanoma skin cancer); 5) no diagnosis of either coronary heart disease or diabetes; and 6) BMI < 30 kg/m^2. This last eligibility criterion was imposed because high BMI is a powerful predictor of hypertension[37, 38] and the biomarkers under study.[39-43]

Using risk-set sampling, we selected 750 cases who subsequently developed hypertension and 750 controls who did not develop hypertension. Controls were matched to cases on the following factors: age (within 1 year), race, date of blood sample collection (within 1 month), day of menstrual cycle if pre-menopausal (within 2 days), and time of day of the blood collection (within 2 hours). In addition, controls were required to have had at least one clinician examination during the two years prior to being selected as a control. After excluding 2 pairs with missing biomarker data, the final study population included 748 case-control pairs (N=1,496).

Biomarker Measurement

Uric acid was determined by oxidization with the specific enzyme uricase to form allantoin and H_2O_2 (Roche Diagnostics, Indianapolis, IN). The coefficient of variation (CV) using quality control samples was 3.4%.

Insulin and triglyceride levels were used as biomarkers of insulin sensitivity, and were measured using a radio-immunoassay and standard enzymatic methods, respectively (Roche Diagnostics); the CVs were 10.4% and 14.1%. The insulin sensitivity index (glucose disposal rate [M] corrected for fat-free mass; i.e., MFFM) was calculated for participants using the following prediction equation that includes fasting insulin and triglyceride levels (triglyceride levels converted to mmol/L):

$$\text{MFFM} = e^{\{2.63 - [0.28 \times \ln(\text{insulin})] - [0.31 \times \ln(\text{triglycerides})]\}}$$

This calculated MFFM value has been validated [30], and has been accepted as an index of insulin sensitivity.[44]

Homocysteine Hcy was measured using an enzymatic assay (Roche Diagnostics; CV = 7.4%), and sICAM was measured using an enzyme-linked immunoabsorbant assay (R & D Systems, Minneapolis, MN; CV = 8.8%).

Total cholesterol was measured with a standard esterase-oxidase method (CV = 5.3%), and creatinine was assayed using a modified Jaffe method (CV = 6.5%). Estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation.[45]

$$186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (female correction factor)}$$

Ascertainment of Other Covariates

Age and BMI (weight in kilograms divided by the height in meters squared) were obtained from the supplemental questionnaire that accompanied the submitted blood samples. Smoking status (never, past, current), physical activity (metabolic equivalent task scores; METS), and alcohol intake (g/d) were ascertained from the biennial questionnaire that immediately followed submission of the blood sample (typically the 1999 biennial questionnaire). Family history of hypertension was obtained from the 1989 questionnaire; race was self-classified. Blood pressure (BP) was reported on the 1999 questionnaire in 9 systolic (SBP) categories (<105, 105-114, 115-124, 125-134, 135-144, 145-154, 155-164, 165-174, and ≥175 mmHg) and 7 diastolic (DBP) categories (<65, 65-74, 75-84, 85-89, 90-94, 95-104, and ≥105 mmHg). Based upon these categories, we assigned participants a baseline BP using the middle value of each category; for example, if a participant reported her SBP and DBP as 125-134 and 75-84, respectively, she was assigned a BP of 130/80 mmHg. Self-reported BP in nurses has been previously validated as predictive of future cardiovascular events.[46]

Ascertainment of Hypertension

Clinician-diagnosed hypertension was self-reported by these health professionals on biennial questionnaires. Self-reported hypertension was highly reliable amongst participants in a similar cohort of nurses; specifically, the accuracy was 100% among a sub-study of randomly selected participants who reported the diagnosis.[47]

Women were considered to have prevalent hypertension at the time of blood collection if they reported hypertension on the biennial questionnaire immediately following their blood collection or on any prior questionnaire. For this study of incident hypertension, women with prevalent hypertension were excluded. In addition, women who reported taking anti-hypertensive medications on the questionnaire immediately following blood collection were also excluded.

Statistical Analyses

Because the continuous baseline variables, including the biomarker levels, were not normally distributed, differences between these variables among cases and controls were analyzed using

the Wilcoxon rank-sum test. Differences in categorical variables between cases and controls were compared using the chi square test.

To examine the correlations between age, BMI, and the studied biomarkers, we used Spearman partial correlations, in which pair-wise Spearman correlation coefficients were computed after adjusting for the other variables. For example, the Spearman correlation between BMI and uric acid was adjusted for age, eGFR, insulin, triglycerides, Hcy, and sICAM.

The associations between the biomarkers and incident hypertension were analyzed with biomarkers as continuous variables, and also with the biomarkers divided into quartiles with the lowest quartile defined as the reference group. We used conditional logistic regression conditioning on the matching factors to generate odds ratios (OR) and 95% confidence intervals (95% CI).

Two types of analyses were conducted. First, each biomarker was analyzed individually (i.e., without other biomarkers in the model); the primary analyses adjusted for BMI (continuous), physical activity, alcohol intake, smoking status, and family history of hypertension. Further analyses were performed after adjusting for baseline SBP and DBP. Second, each biomarker was analyzed after also adjusting for eGFR, total cholesterol, and all of the other biomarkers.

Population attributable risks were calculated for biomarkers using the adjusted quartile-specific OR from the final multivariable models and with the lowest quartile defined as the "unexposed" group. A baseline incidence rate of 14.6 cases per 1000 women annually (1.46% of the population per year) for the unexposed group was estimated using the incidence rate for the parent cohort (NHS 2).

All statistical analyses were conducted with SAS, version 9.1, Cary, North Carolina.

Results

Baseline Characteristics

The baseline characteristics of the entire study population by case status are shown in Table 1. The median age of the population was 43 years, and because this was a matching factor, did not differ. The median BMI was higher among the cases (25.1 kg/m^2) compared to controls (23.2 kg/m^2). Cases were also less physically active, had higher baseline BP values, and were more likely to have a family history of hypertension.

With the sole exception of eGFR, all of the fasting biomarkers differed between cases and controls at baseline. Cases had higher levels of uric acid, insulin, triglycerides, total cholesterol, Hcy, and sICAM; conversely, cases had lower MFFM scores.

Many of the biomarkers were correlated with each other and with age and BMI. The partial (i.e., adjusted) Spearman correlation coefficients among these variables are shown in Table 2. Besides the expected high correlation between MFFM with insulin and triglycerides (which are used to compute MFFM), the strongest correlations were: between BMI and uric acid (r = 0.22, $p<0.001$), insulin (r = 0.27, $p<0.001$), triglycerides (r = 0.19, $p<0.001$), and MFFM (r = -0.35, $p<0.001$); and between eGFR and uric acid (r = -0.17, $p<0.001$) and Hcy (r = -0.20, $p<0.001$).

Uric Acid

The median uric acid level was 3.9 mg/dL, and <1% of the population had uric acid levels that would be considered abnormally elevated (≥ 7.0 mg/dL).[48, 49] After controlling for matching factors and multivariable adjustment for BMI, physical activity, smoking, alcohol intake, and

family history of hypertension, every 1 mg/dL increase in uric acid was associated with a 1.33-fold higher odds of incident hypertension (95% CI, 1.15-1.53; Table 3). When uric acid was examined in quartiles, the OR for the highest compared to lowest quartile was 2.17 (95% CI, 1.51-3.11; Table 3). After further adjusting for baseline SBP and DBP, the same comparison remained significant (OR=1.79; 95% CI, 1.11-2.87).

Uric acid was also analyzed after further adjusting for eGFR, total cholesterol, triglycerides, insulin, Hcy, and sICAM (Table 3); the results were attenuated but remained significant. Every 1 mg/dL increase in uric acid was associated with a 1.25-fold higher odds of incident hypertension (95% CI, 1.06-1.46). The OR for women in the highest compared to lowest quartile of uric was 1.89 (95% CI, 1.26-2.82).

Insulin Sensitivity

The median values for insulin, triglyceride, and MFFM were, respectively, 4.6 μIU/mL, 78 mg/dL, and 9.6. Six percent of individuals had hyperinsulinemia (i.e., >13.1 μIU/mL).[50] Fewer than 10% of participants had elevated triglyceride levels (≥160 mg/dL), and <10% of participants had MFFM scores ≤6.3 (definition of insulin resistance).[30]

Every 2 μIU/mL higher fasting insulin concentration was associated with a 1.14-fold higher odds of incident hypertension (95% CI, 1.07-1.22; Table 3). Further controlling for baseline SBP and DBP did not attenuate the association (OR=1.19; 95% CI, 1.09-1.30). Comparing the highest to lowest quartile of insulin level, the OR was 2.41 (95% CI, 1.64-3.54) before adjusting for BP, and 2.22 (95% CI, 1.37-3.60) after controlling for SBP and DBP. When eGFR, total cholesterol, uric acid, triglycerides, Hcy, and sICAM were included in the model, the OR was 1.11 (95% CI, 1.03-1.18) for every 2 μIU/mL higher insulin level, and 2.03 (95% CI, 1.35-3.05) comparing the highest to lowest quartile (Table 3).

Although the fasting triglyceride concentration was also associated with incident hypertension in the base multivariable model (Table 3) and also after adjusting for SBP and DBP, the association did not persist when further controlling for eGFR, total cholesterol, uric acid, insulin, Hcy, and sICAM (Table 3).

Each unit increase in MFFM score, an estimate of insulin sensitivity, was associated with a lower odds of developing hypertension (OR=0.89; 95% CI, 0.84-0.93; Table 3). Those women in the highest compared to lowest quartile had a 48% reduced odds (OR=0.52; 95% CI, 0.35-0.76). This association persisted after controlling for baseline SBP and DBP; the OR was 0.88 (95% CI, 0.82-0.94) for each unit increase and 0.54 (95% CI, 0.33-0.90) comparing the highest to lowest quartile. After further adjusting for eGFR, total cholesterol, uric acid, Hcy, and sICAM (Table 3), these comparisons yielded ORs of 0.92 (95% CI, 0.87-0.97) and 0.69 (95% CI, 0.46-1.04).

Homocysteine and sICAM

The median Hcy concentration in the study population was 11.6 μmol/L; 10% of participants had elevated Hcy concentrations (> 15 μmol/L).[51] The median sICAM level was 241 ng/mL (similar to other populations).[52-55]

After multivariable adjustment, every 2 μmol/L increase in Hcy was associated with a 1.13-fold higher odds of incident hypertension (95% CI, 1.05-1.22; Table 3). When Hcy was examined in quartiles, the OR for the highest compared to lowest quartile was 1.38 (95% CI, 0.99-1.93; Table 3). After further adjusting for baseline SBP and DBP, the ORs were 1.10 (95% CI, 1.00-1.22) and 1.19 (95% CI, 0.77-1.83), respectively. When eGFR, total cholesterol, uric acid, insulin, triglycerides, and sICAM were included in the model (Table 3), the ORs

were 1.08 (95% CI, 0.99-1.18) for each 2 μmol/L increase and 1.27 (95% CI, 0.86-1.88) comparing the highest to lowest quartile.

Although the soluble-ICAM concentration was associated with incident hypertension in the base multivariable model (Table 3) and also after adjusting for SBP and DBP, the association did not persist when further controlling for eGFR, total cholesterol, uric acid, insulin, Hcy, and sICAM (Table 3).

Estimated Population Attributable Risk

We estimated the percent of incident hypertension potentially attributable to higher uric acid and insulin levels, which were the two biomarkers independently associated with hypertension (Table 4). The population attributable risk associated with the top three quartiles of uric acid (i.e., uric acid ≥ 3.4 mg/dL) was 6.5 cases of hypertension per 1000 women per year. Given an estimated baseline incidence rate of 14.6 cases per 1000 young women annually, 30.8% of hypertension occurring in young women is associated with a uric acid ≥ 3.4 mg/dL. The attributable risk associated with insulin levels ≥ 2.9 μIU/mL was 4.7 cases per 1000 young women annually. Therefore, an estimated 24.2% of hypertension occurring in young women is associated with an insulin level ≥ 2.9 μIU/mL.

Comment

Among 1,496 non-obese young women without hypertension, diabetes, or coronary disease at baseline, small differences in uric acid and insulin independently predicted clinically important increases in the odds of subsequently developing hypertension. A substantial magnitude of the population risk may be attributable to higher uric acid and insulin levels. Furthermore, these associations were observed within ranges of these biomarkers that would be considered “normal”.

Higher uric acid concentrations were independently associated with increased odds of developing hypertension. To date, 14 prospective studies have examined this association;[12-25] of these, 12 have documented a direct association with either incident hypertension or increase in BP.[12, 15-25] Most of these reports were not fully adjusted for other physiologic variables such as renal function, lipid levels, and measures of insulin resistance; controlling for these factors is important given that higher uric acid levels may be coincident with alterations in these other metabolic variables.[42, 56] Of the three studies that fully adjusted for these physiologic variables (eGFR, lipid levels, insulin or insulin resistance), all involved considerably older populations and two consisted only of men.[13, 21, 23] Thus, our study represents the only fully adjusted study to consist of young women.

The proposed mechanism linking uric acid with the onset of hypertension stems from a rat model of moderate hyperuricemia.[57-59] Johnson et al. showed that rats made hyperuricemic developed increases in BP that were reversible by lowering the uric acid concentration.[59] Furthermore, hyperuricemia was associated with endothelial dysfunction, activation of the renin-angiotensin system, and pre-glomerular vascular disease.[57-59]

However, substantial quantities of circulating uric acid are only a feature of advanced primates in whom the uricase gene is deleted; rodents, in contrast, have very low uric acid levels due to functional uricase.[60] Furthermore, uric acid is a powerful antioxidant,[61, 62] and intravenous infusion of uric acid into humans actually improves endothelial function.[63] Thus, it is not clear that the association between uric acid and hypertension is causal. Even if a randomized trial showed that uric acid lowering by xanthine oxidase inhibition decreased BP, this would not establish causality because xanthine oxidase is an important enzyme in the generation of oxidative stress and endothelial dysfunction.[64] Indeed, a recent study in patients with heart

failure demonstrated that allopurinol improved endothelial dysfunction while uric acid lowering to a similar degree with probenecid (a uricosuric) did not.[65] Nevertheless, our data demonstrate that, in relatively healthy young women, small differences in plasma uric acid levels, even within the normal range, powerfully predict the development of hypertension.

We also observed direct associations between insulin and triglyceride levels with incident hypertension, and an inverse association between a validated estimate of the insulin sensitivity index and incident hypertension. Triglyceride levels, however, were not independently associated in the final models. Several studies have examined the association between measures of insulin sensitivity (or resistance) and the risk of developing hypertension.[26, 27] In our study, even after controlling for biomarkers from other proposed pathophysiologic pathways, we observed a strong association between insulin levels (and MFFM) and risk of incident hypertension.

Several theories exist to explain how insulin may promote hypertension. First, hyperinsulinemia may disinhibit the sympathetic nervous system.[6] Several placebo controlled studies employing euglycemic clamp techniques demonstrated that insulin infusion is associated with an increase in both plasma norepinephrine concentrations and systolic BP.[5, 7] Second, insulin may stimulate the renin-angiotensin system and enhance renal sodium reabsorption. Euglycemic clamp studies have shown that insulin infusion increases both plasma renin activity and angiotensin II levels.[7, 66] Furthermore, insulin infusion into healthy individuals leads to a reduction in sodium excretion.[67-69]

Higher levels of both Hcy and sICAM are associated with endothelial dysfunction,[31-36] and in turn, endothelial dysfunction has been proposed as a risk factor for hypertension.[70] Only two prospective analyses have examined the association between Hcy concentrations and the risk of incident hypertension;[28, 29] none have examined sICAM. Neither of the Hcy studies observed an association with hypertension. Although we noted significant associations between Hcy and sICAM and incident hypertension after adjustment for standard risk factors and BP, these associations were no longer significant after the other biomarkers were considered.

Our study has limitations that deserve mention. First, we relied on self-reported hypertension and did not directly measure the BP of our participants; however, all participants are registered nurses, and hypertension reporting by nurses is highly accurate.[47] Second, controls may have been misclassified if they were unaware of existing hypertension, but because we required controls to have had a clinician examination during the follow-up period, this possibility is reduced. Furthermore, this sort of misclassification tends to produce less significant results; therefore, our findings may represent an underestimate of true associations. Third, because the coefficients of variation for the insulin and triglyceride assays were > 10%, measurement error (and as a result, misclassification of these biomarker levels) may have occurred. Because measurement error is typically random, this type of misclassification would also tend to produce less significant results; therefore, our observed associations between insulin levels, MFFM, and hypertension risk may indeed represent underestimations of the true relations. Fourth, we lacked information about the inflammatory biomarker C-reactive protein, which was observed in a previous study of women to be associated with hypertension; however, that study did not adjust for uric acid or markers of insulin sensitivity.[71] Moreover, our study included sICAM, which is also considered a prominent inflammatory biomarker.[54, 55] Fifth, we purposefully restricted our sample to women with BMI values < 30 kg/m^2. Although this limits the generalizability of our findings to non-obese women, others have suggested that the associations between a variety of these biomarkers and hypertension are stronger in leaner individuals.[20, 72, 73] Finally, our study population was almost entirely white. Therefore, our findings are not necessarily generalizable to non-whites.

In conclusion, small differences in uric acid and insulin sensitivity, even within ranges considered normal, are robustly and substantially associated with an increased risk of developing hypertension among young women. Measuring these biomarkers in clinical practice may identify higher risk individuals. Future studies are required to determine whether strategies to lower the levels of these biomarkers translate into a lower risk of developing hypertension.

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Table 1

Baseline Characteristics of the Study Population

Characteristic	All (n=1,496)	Cases (n=748)	Controls (n=748)	P-value
Physiologic/Lifestyle				
Age (y)	43 (36-49)	43 (36-49)	43 (36-49)	matching factor
BMI (kg/m^2)	24.1 (19.6-29.2)	25.1 (20.1-29.3)	23.2 (19.1-28.8)	<0.001
Physical activity (METS)	12.4 (0.9-56.9)	11.2 (0.8-51.5)	13.4 (1.0-62.1)	0.002
Current smoker (%)	5.2	5.8	4.6	0.29
Past smoker (%)	22,7	23.5	21.9	0.46
Alcohol intake (g/d)	1.6 (0-17.5)	1.5 (0-20.0)	1.8 (0-15.0)	0.78
SBP (mmHg)*	120 (100-140)	130 (110-140)	110 (100-130)	<0.001
DBP (mmHg)*	70 (60-87)	80 (70-90)	70 (60-80)	<0.001
Family history of hypertension (%)	55.1	62.8	47.3	<0.001
Fasting biomarkers				
Uric acid (mg/dL)	3.9 (2.7-5.6)	4.1 (2.8-5.8)	3.7 (2.5-5.5)	<0.001
eGFR (ml/min/1.73m^2)	85 (65-112)	86 (64-114)	84 (66-109)	0.18
Insulin (μIU/mL)	4.6 (1.2-13.2)	5.3 (1.4-15.6)	4.0 (1.1-10.1)	<0.001
Triglycerides (mg/dL)	78 (40-190)	88 (44-214)	70 (39-170)	<0.001
MFFM	9.6 (6.0-15.0)	8.9 (5.5-14.0)	10.2 (6.5-15.9)	<0.001
Total cholesterol (mg/dL)	186 (140-245)	191 (143-252)	181 (137-235)	<0.001
Homocysteine (μmol/L)	11.6 (8.2-18.3)	11.9 (8.4-19.8)	11.3 (7.9-17.0)	<0.001
sICAM (ng/mL)	241 (182-329)	245 (186-334)	238 (179-319)	<0.001

*Systolic and diastolic BPs were reported by participants in categories (see text).

Continuous variables are expressed as median (5^{th}-95^{th} percentile). Categorical variables are expressed as percent.
Continuous variables were analyzed using the Wicoxon rank-sum test, and categorical variables with the chi square test.

Table 2

Partial Spearman correlations among biomarkers, age, and BMI

	UA	eGFR	Ins	Trig	MFFM	Hcy	sICAM	Age	BMI
UA	1.00								
eGFR	-0.17 *	1.00							
Ins	0.09 †	0.10 †	1.00						
Trig	0.11 *	0.001	0.19 *	1.00					
MFFM	-0.15 *	-0.09 *	-0.96 *	-0.92 *	1.00				
Hcy	0.13 *	-0.20 *	-0.008	0.11 *	-0.06 ‡	1.00			
sICAM	0.19 ‡	-0.06 ‡	0.06 ‡	0.13 *	-0.14 *	0.06 ‡	1.00		
Age	-0.04	-0.12 *	-0.01	0.11 *	-0.07 ‡	0.06 ‡	-0.11 *	1.00	
BMI	0.22 *	0.03	0.27 *	0.19 *	-0.35 *	0.01	0.08 †	0.09 *	1.00

* p<0.001;

† p<0.01;

‡ p<0.05

Each correlation coefficient is adjusted for the other biomarkers except for MFFM. Correlations between MFFM and other variables are not adjusted for Ins and Trig, except for the correlations between MFFM and Ins and Trig.

UA, uric acid; eGFR, estimated Glomerular filtration rate; Ins, fasting insulin; Trig, fasting triglycerides; MFFM, glucose disposal rate (M) corrected for fat free mass (FFM); Hcy, Homocysteine; sICAM, soluble intercellular adhesion molecule-1.

Table 3

Association between Multiple Biomarkers and Risk of Incident Hypertension

Fasting Biomarker	Continuous	Quartile 1 median (range)	Quartile 2 median (range)	Quartile 3 median (range)	Quartile 4 median (range)
Uric acid	Per 1 mg/dL	3.0 (1.5-3.3)	3.7 (3.4-3.9)	4.2 (4.0-4.5)	5.1 (4.6-8.8)
No. of cases	748	134	189	185	240
Model 1	1.33 (1.15-1.53)	1.0 (ref)	1.43 (1.02-2.00)	1.72 (1.21-2.46)	2.17 (1.51-3.11)
Model 2a	1.25 (1.06-1.46)	1.0 (ref)	1.27 (0.88-1.82)	1.62 (1.10-2.40)	1.89 (1.26-2.82)
Insulin	Per 2 μIU/mL	2.0 (0.2-2.8)	3.8 (2.9-4.6)	5.8 (4.7-7.0)	9.6 (7.1-128.8)
No. of cases	718	137	159	180	242
Model 1	1.14 (1.07-1.22)	1.0 (ref)	1.08 (0.78-1.51)	1.37 (0.97-1.92)	2.41 (1.64-3.54)
Model 2c	1.11 (1.03-1.18)	1.0 (ref)	1.03 (0.73-1.45)	1.22 (0.85-1.74)	2.03 (1.35-3.05)
Triglycerides	Per 20 mg/dL	48 (12-58)	68 (59-78)	92 (79-109)	143 (110-580)
No. of cases	748	147	162	208	231
Model 1	1.07 (1.02-1.13)	1.0 (ref)	1.13 (0.81-1.58)	1.67 (1.20-2.34)	1.75 (1.22-2.50)
Model 2d	1.02 (0.96-1.08)	1.0 (ref)	1.00 (0.70-1.44)	1.39 (0.95-2.03)	1.15 (0.75-1.76)
MFFM	Per 1 unit	6.8 (2.6-7.8)	8.9 (7.9-9.5)	10.4 (9.6-11.5)	13.0 (11.6-24.3)
No. of cases	718	231	205	147	135
Model 1	0.89 (0.84-0.93)	1.0 (ref)	0.91 (0.63-1.30)	0.51 (0.35-0.74)	0.52 (0.35-0.76)
Model 2b	0.92 (0.87-0.97)	1.0 (ref)	1.00 (0.69-1.45)	0.62 (0.42-0.92)	0.69 (0.46-1.04)
Homocysteine	Per 2 μmol/L	9.0 (5.0-10.0)	10.8 (10.0-11.6)	12.6 (11.7-13.8)	15.8 (13.9-63.8)
No. of cases	748	160	186	186	216
Model 1	1.13 (1.05-1.22)	1.0 (ref)	1.15 (0.84-1.57)	1.43 (1.03-1.99)	1.38 (0.99-1.93)
Model 2e	1.08 (0.99-1.18)	1.0 (ref)	1.19 (0.85-1.68)	1.40 (0.97-2.02)	1.27 (0.86-1.88)
sICAM	Per 20 ng/mL	186 (93-217)	229 (218-241)	255 (242-269)	296 (270-697)
No. of cases	745	163	182	191	209
Model 1	1.08 (1.03-1.15)	1.0 (ref)	1.30 (0.92-1.82)	1.29 (0.91-1.84)	1.58 (1.08-2.29)
Model 2f	1.06 (0.99-1.12)	1.0 (ref)	1.18 (0.82-1.71)	1.09 (0.74-1.61)	1.18 (0.78-1.79)

Results are OR (95% CI).

Model 1: conditioned on matching factors, and adjusted for BMI, smoking status, level of physical activity, alcohol intake, and family history of hypertension.

Model 2: conditioned on matching factors, and adjusted for all variables in Model 1 plus GFR, total cholesterol, plus:

- **a.** fasting insulin, triglycerides, homocysteine, and sICAM as continuous variables
- **b.** uric acid, homocysteine, and sICAM as continuous variables
- **c.** uric acid, triglycerides, homocysteine, and sICAM as continuous variables
- **d.** uric acid, fasting insulin, homocysteine, and sICAM as continuous variables
- **e.** uric acid, fasting insulin, triglycerides, and sICAM as continuous variables
- **f.** uric acid, fasting insulin, triglycerides, and homocysteine as continuous variables

Table 4

Estimated Population Attributable Risk of Hypertension Associated with Uric Acid and Insulin

Biomarker Level	% of Total Population	Model 2 OR	Adjusted Incidence Rate (per 1000 py)	Population Attributable Risk (per 1000 py)
Uric Acid (mg/dL)				
3.0 (1.5-3.3)	25	1.0	14.6*	0.0
3.7 (3.4-3.9)	25	1.27	18.5	0.98
4.2 (4.0-4.5)	25	1.62	23.7	2.28
5.1 (4.6-8.8)	25	1.89	27.6	3.25
≥ 3.4				**6.51**
Insulin (μIU/mL)				
2.0 (0.2-2.8)	25	1.0	14.6*	0.0
3.8 (2.9-4.6)	25	1.03	15.0	0.10
5.8 (4.7-7.0)	25	1.22	17.8	0.80
9.6 (7.1-128.8)	25	2.03	29.6	3.75
≥ 2.9				**4.65**

* Baseline incidence rate is drawn from incidence rate of the parent cohort (Nurses' Health Study II).

Adjusted incidence rate is the baseline incidence rate multiplied by the adjusted relative risk (OR).

The population attributable risk is the difference between the adjusted incidence rate and the baseline incidence rate multiplied by the % of the population.

[6.51/(14.6+6.51)] = 30.8% of hypertension occurring in young women is associated with a uric acid ≥ 3.4 mg/dL.

[4.65/(14.6+4.65)] = 24.2% of hypertension occurring in young women is associated with an insulin ≥ 2.9 μIU/mL.