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## Original Contribution

# Hyperuricemia in Young Adults and Risk of Insulin Resistance, Prediabetes, and Diabetes: A 15-Year Follow-up Study

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The objective of this study was to assess the utility of hyperuricemia as a marker for diabetes and prediabetes (impaired fasting glucose) and insulin resistance in young adults. Using Cox proportional hazards regression models, the authors analyzed 15-year follow-up data on 5,012 persons in 4 US cities who were aged 18–30 years and diabetes-free at the time of enrollment. At baseline (1986), 88% of participants had a body mass index (weight (kg)/height $(m)^2$) less than 30. During the follow-up period (through 2001), the incidence rates of diabetes and prediabetes (insulin resistance and impaired fasting glucose) were higher among persons with greater serum urate concentrations. In multivariable Cox regression analyses that adjusted for age, gender, race, body mass index, family history of diabetes, diastolic blood pressure, total cholesterol, smoking, and alcohol use, the hazard ratios for diabetes, insulin resistance, and prediabetes among persons with hyperuricemia (serum urate level >7 mg/dL vs. ≤7.0 mg/dL) were 1.87 (95% confidence interval (CI): 1.33, 2.62), 1.36 (95% CI: 1.23, 1.51), and 1.25 (95% CI: 1.04, 1.52), respectively. This observation was generally consistent across subgroups. The authors conclude that hyperuricemia in the midtwenties is an independent marker for predicting diabetes and prediabetes among young adults in the subsequent 15 years.

diabetes mellitus, type 2; follow-up studies; hyperuricemia; insulin resistance; prediabetic state; risk factors

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval.

Insulin resistance and type 2 diabetes mellitus (diabetes) have become a leading public health problem around the world. In the United States, 25.6 million persons (11.3% of the adult population) had this disease in 2010, of which there were 1.9 million newly diagnosed cases (1). These numbers are likely to rise over time (2). Diabetes doubles all-cause mortality risk and is the seventh-leading cause of death in the United States (1). In the year 2007, the total cost of this disease was estimated to be US$174 billion (3).

Diabetes may be preventable with targeted lifestyle modification interventions in high-risk individuals, but reliably identifying such people early in life is difficult (4). However, the population attributable risk for obesity, a known risk factor, is no more than 38% (5). Candidate genetic markers have been evaluated, but studies of their ability to provide additional predictive value to the existing risk scores have been inconclusive (6–8), highlighting the need for additional markers of diabetes. Many available risk scoring methods incorporate obesity and were developed in clinic-based, primarily Caucasian populations over age 35 years that were followed up for a relatively short time (9–13). These risk stratification models do not correspond to the risk models in children, an increasingly recognized age category of persons at risk for diabetes (14). From the perspective of diabetes prevention, it is important to establish risk factors at an age where mitigation might have the greatest impact.

Recently, hyperuricemia and gout have been proposed as novel risk factors for diabetes, but the results from epidemiologic studies have been mixed (15–21), and none examined the age group 18–30 years, in whom lifestyle interventions may be most important. In the present analysis,

we prospectively studied the relation between hyperuricemia and the risk of subsequent diabetes, insulin resistance, and impaired fasting glucose (prediabetes) in young adults.

## MATERIALS AND METHODS

### Design

This study was designed as a post-hoc analysis of 15-year prospective observational data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The primary objective of that study, started in 1986, has been to examine the development and determinants of cardiovascular disease and its risk factors (22).

### Settings

The study participants were enrolled from 4 cities in the United States: Minneapolis, Minnesota; Birmingham, Alabama; Chicago, Illinois; and Oakland, California.

### Data source

The data presented in this study were collected as part of the CARDIA research program and were made available in de-identified form by the National Heart, Lung, and Blood Institute as a part of the Limited Access Program. Participants in the CARDIA cohort have provided informed consent that allows post-hoc analyses such as those conducted in the present study. The CARDIA Study is ongoing and is supervised by the institutional review boards of the institutions at the 4 enrolling sites.

### Participants

The original cohort was a group of 5,115 black and white men and women aged 18–30 years. The participants were selected so that there would be approximately the same numbers of people in subgroups of race, gender, education (high school or less and more than high school), and age (18–24 years and 25–30 years). The Limited Access Program enabled access to 5,113 participants who had data from more than 1 time point.

### Follow-up

Data were available from follow-up examinations conducted during 1987–1988 (year 2), 1990–1991 (year 5), 1992–1993 (year 7), 1995–1996 (year 10), and 2000–2001 (year 15).

### Study assessments

At baseline and during subsequent visits, participants were evaluated for coronary artery disease, stroke, renal disease, and diabetes through review of medical history, clinician assessment, and other clinical measures as appropriate. Information on risk factors that could potentially confound the serum urate-diabetes relation, identified from the literature (age, gender, body mass index (weight (kg)/height $(m)^2$), waist circumference, low density lipoprotein cholesterol, alcohol use, physical activity (CARDIA physical activity score (range, 0–5)), smoking, history of gestational diabetes, and polycystic ovarian disease), was available (22, 23). These data were collected as self-reported data via questionnaires (alcohol, tobacco, physical activity, medications, and diet), physician examinations (anthropometry, blood pressure), and fasting phlebotomy (for serum urate, glucose, insulin, lipids, and creatinine). Detailed information on an individual's use of medications for diabetes or hypertension, such as drug name, dosage, and duration of treatment, was not available for the present analyses. All participants provided informed consent at individual study centers. The presence of the metabolic syndrome was determined using World Health Organization criteria (24).

### Outcome assessment

Incidence of type 2 diabetes mellitus was the primary outcome. Fasting phlebotomy was performed during all visits, and glucose measures were available for baseline and years 7, 10, and 15. Study definitions for type 2 diabetes and prediabetes used the fasting glucose criteria of the American Diabetes Association (25). Participants using antidiabetic medication were considered to be diabetic regardless of their fasting plasma glucose concentration. Hemoglobin $A_{1c}$ concentrations were not available and therefore were not utilized for our analyses. Insulin resistance was defined as ≥75th percentile of homeostasis model assessment of insulin resistance among nondiabetic subjects at baseline (26). This corresponded to a value of 2.64 units in this cohort. A self-report variable was not considered in our case definition.

### Assessment of serum urate concentration

Serum urate, assayed using the uricase method, was analyzed as both a continuous variable and a categorical (quartile) variable. Additionally, we used serum urate levels ≤7.0 mg/dL and >7.0 mg/dL to define normouricemia and hyperuricemia, respectively, consistent with prior epidemiologic studies examining hyperuricemia and cardiovascular outcomes (27).

### Participants

For all analyses, subjects were excluded if they had diabetes at baseline or if their serum urate levels were not measured at baseline. Persons with gout, defined as a self-reported physician's diagnosis of gouty arthritis, were not excluded, since there were few of them ($n = 7$) and the diagnoses could not be confirmed. For the analyses of the primary outcome, there were 5,012 eligible participants.

### Statistical analyses

All statistical analyses were performed in SAS 9.2 (SAS Institute Inc., Cary, North Carolina) and STATA 10 (StataCorp LP, College Station, Texas). Proportions and mean values across categories of serum urate concentration were

**Table 1.** Baseline Characteristics of the Study Population by Quartile of Baseline Serum Urate Concentration ($n = 5{,}012$[a]), Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001

| | Quartile of Serum Urate Concentration | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall | | Quartile 1[c] | | Quartile 2[d] | | Quartile 3[e] | | Quartile 4[f] | | *P* Value[b] |
| | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | |
| Age, years | | 24.84 (3.6) | | 24.74 (3.6) | | 24.84 (3.6) | | 24.84 (3.6) | | 24.92 (3.6) | 0.643 |
| Male gender | 45.6 | | 45.3 | | 48.4 | | 44.7 | | 44.5 | | 0.194 |
| African-American race/ethnicity | 51.2 | | 59.0 | | 50.0 | | 46.6 | | 48.0 | | <0.0001 |
| Smoker | 43.1 | | 42.9 | | 41.0 | | 43.1 | | 45.0 | | 0.199 |
| Body mass index[g] | | 24.42 (4.8) | | 22.91 (3.5) | | 23.82 (4.2) | | 24.47 (4.7) | | 26.48 (5.7) | <0.0001 |
| Waist circumference, cm | | 77.56 (10.8) | | 74.03 (8.3) | | 76.37 (9.9) | | 77.81 (10.5) | | 82.11 (12.5) | <0.0001 |
| Systolic blood pressure, mm Hg | | 110.41 (10.9) | | 108.96 (10.5) | | 110.14 (10.9) | | 110.1 (10.5) | | 112.48 (11.5) | <0.0001 |
| Diastolic blood pressure, mm Hg | | 68.58 (9.6) | | 67.37 (9.1) | | 68.33 (9.6) | | 68.47 (9.5) | | 70.17 (10.1) | <0.0001 |
| Insulin level, uU/mL | | 10.82 (7.9) | | 9.46 (6.5) | | 9.70 (6) | | 10.48 (6.6) | | 13.61 (10.8) | <0.0001 |
| Plasma glucose level, mg/100 mL | | 81.70 (8.3) | | 81.06 (7.7) | | 81.44 (8) | | 81.58 (8.3) | | 82.74 (9) | <0.0001 |
| Serum creatinine level, mg/dL | | 1.04 (0.3) | | 0.99 (0.2) | | 1.03 (0.2) | | 1.03 (0.2) | | 1.10 (0.6) | <0.0001 |
| Serum albumin level, g/dL | | 4.63 (0.3) | | 4.59 (0.3) | | 4.63 (0.3) | | 4.63 (0.3) | | 4.65 (0.3) | <0.0001 |
| Total cholesterol level, mg/dL | | 176.65 (33.4) | | 172.69 (33.4) | | 175.62 (32.3) | | 176.84 (31.9) | | 181.54 (35.2) | <0.0001 |
| Low density lipoprotein cholesterol level, mg/dL | | 108.96 (31.2) | | 105.04 (31) | | 108.39 (30.3) | | 109.49 (30.1) | | 113.03 (32.9) | <0.0001 |
| Triglyceride level, mg/dL | | 72.66 (47) | | 61.05 (29.1) | | 66.21 (35.8) | | 74.45 (45.2) | | 88.87 (64.9) | <0.0001 |
| Physical activity[h] during past year | | 3.30 (1.1) | | 3.34 (1.1) | | 3.32 (1.2) | | 3.32 (1.1) | | 3.24 (1.2) | 0.110 |
| Alcohol use, mL/day | | 12.02 (21.7) | | 9.19 (16) | | 10.66 (19.6) | | 12.80 (22.9) | | 15.47 (26.6) | <0.0001 |
| Serum urate level, mg/dL | | 5.24 (1.4) | | 3.99 (0.9) | | 4.92 (0.9) | | 5.48 (0.9) | | 6.61 (1.2) | <0.0001 |
| Self-reported gestational diabetes[i] | 0.29 | | 0.42 | | 0.10 | | 0.35 | | 0.20 | | 0.528 |

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; SD, standard deviation.

[a] Excluded from the original cohort were persons with diabetes and observations without serum urate information.

[b] *P* values were based on analysis of variance for continuous variables and the chi-square test for categorical variables.

[c] Quartile 1: 0.4–5.3 mg/dL for males; 0.6–3.7 mg/dL for females.

[d] Quartile 2: 5.4–6.0 mg/dL for males; 3.8–4.3 mg/dL for females.

[e] Quartile 3: 6.1–6.7 mg/dL for males; 4.4–5.0 mg/dL for females.

[f] Quartile 4: 6.8–13.3 mg/dL for males; 5.1–9.3 mg/dL for females.

[g] Weight (kg)/height $(m)^2$.

[h] Physical activity was assessed by means of the CARDIA physical activity score (range, 0–5) (23).

[i] Information on gestational diabetes was obtained from the year 2 visit.

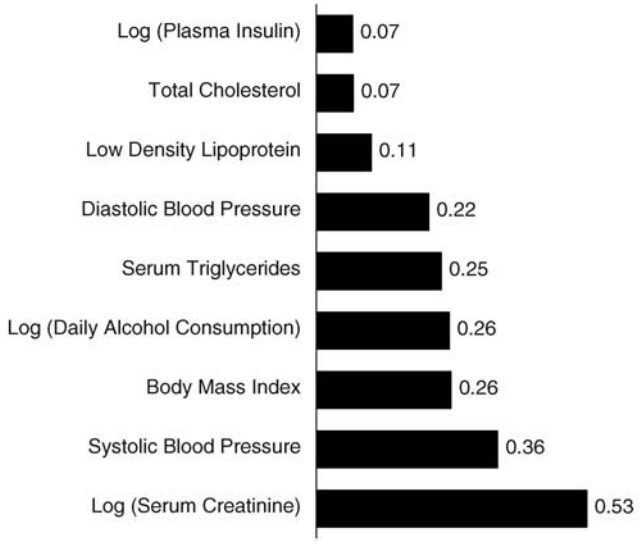


**Figure 1.** Spearman correlations between baseline serum urate level and other cardiometabolic risk factors, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001. Plasma insulin level, serum creatinine level, and daily alcohol use were log-transformed to normalize the distribution. Specific correlation coefficients are shown at the end of each bar. All correlations were statistically significant at $P < 0.01$.

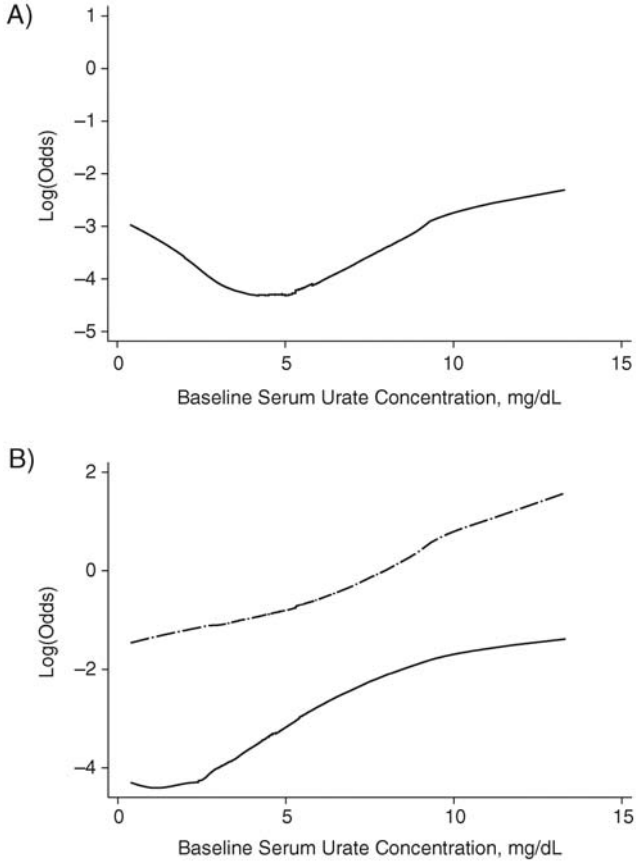


**Figure 2.** Increase in the risks (log odds) of A) diabetes and B) insulin resistance (dotted-dashed line) and prediabetes (solid line) according to baseline serum urate concentration, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001. The risk of each of these outcomes was plotted against serum urate concentration using locally weighted scatterplot smoothing regression. Centered subsets of bandwidth of 0.9 times the total number of observations were used for calculating smoothed values for each point in the data, except for endpoints, where smaller, uncentered subsets were used. Diabetes and prediabetes were defined according to the fasting glucose criteria of the American Diabetes Association guidelines (26). Participants using antidiabetic medication were considered to be diabetic regardless of their fasting plasma glucose concentration. Insulin resistance was defined as ≥75th percentile of homeostasis model assessment of insulin resistance among nondiabetic subjects at baseline (2.64 units in this cohort) (27).

compared using Pearson chi-square tests and Student's *t* tests, respectively. Bivariate correlations were measured by means of Spearman's rank correlation coefficient. Ordinary least squares regression models were used to assess the baseline association between insulin and urate concentrations. All *P* values presented are 2-tailed.

Baseline data were cross-sectionally analyzed using ordinary least squares regression to examine the relation between serum urate and plasma insulin concentrations. These regression analyses adjusted for age, gender, race, body mass index, systolic blood pressure, alcohol use, serum creatinine level, and physical activity level as continuous measures.

Incidence rates were calculated as the number of new cases per 1,000 person-years of observation. Regression analyses of longitudinal data were performed using Cox regression models, where proportionality assumptions were verified by plotting Schoenfeld residuals of fitted Cox regressions against the time variable and visually and statistically examining the slope of the curve. A nonzero slope was considered a violation of proportionality specification (28). Confidence intervals were measured using robust variance estimators (29). Model fit was assessed using likelihood ratio tests, as described by Rothenberg (30).

In these Cox regression analyses, baseline serum urate level as a continuous variable was the main independent variable of interest, and the dependent variables of interest were diabetes, insulin resistance, and prediabetes. The analyses were then repeated using quartiles of serum urate for analyzing overall trends. Additionally, serum urate was also analyzed as a dichotomous variable signifying hyperuricemia. The covariates used for adjustment were identified primarily on the basis of published literature on the risk factors for diabetes; these were: age, diastolic blood pressure, body mass index, physical activity score, fasting serum creatinine level, and total cholesterol level (as continuous variables) and gender, family history of diabetes, systolic blood pressure, current smoking, and current alcohol use (as categorical variables). In all regression models, the values of each covariate were updated at each visit (i.e., time-varying covariates) unless otherwise specified. Subgroup analyses were performed for men and women and for whites and African Americans.

**Table 2.** Incidence Rates of Diabetes and Prediabetes by Quartile of Serum Urate Concentration,[a] Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001

| Outcome and Quartile of Serum Urate Concentration | No. of Cases | Person-Years of Observation | Incidence Rate (per 1,000 Person-Years) | 95% CI | Hazard Ratio | 95% CI |
|---|---|---|---|---|---|---|
| Diabetes[b] | | | | | | |
| Quartile 1 | 49 | 16,688.0 | 2.9 | 2.2, 3.9 | 1 | |
| Quartile 2 | 48 | 15,748.1 | 3.0 | 2.3, 4.0 | 1.10 | 0.74, 1.64 |
| Quartile 3 | 67 | 14,677.1 | 4.6 | 3.6, 5.8 | 1.71 | 1.18, 2.48 |
| Quartile 4 | 105 | 14,935.1 | 7.0 | 5.8, 8.5 | 2.69 | 1.91, 3.79 |
| Insulin resistance[c] | | | | | | |
| Quartile 1 | 553 | 11,770.2 | 47.0 | 43.2, 51.1 | 1 | |
| Quartile 2 | 712 | 10,757.3 | 66.2 | 61.5, 71.2 | 1.28 | 1.15, 1.43 |
| Quartile 3 | 787 | 9,314.4 | 84.5 | 78.8, 90.6 | 1.55 | 1.39, 1.73 |
| Quartile 4 | 940 | 7,352.6 | 127.8 | 119.9, 136.3 | 2.09 | 1.88, 2.33 |
| Prediabetes[b] | | | | | | |
| Quartile 1 | 136 | 16,014.0 | 8.5 | 7.2, 10.0 | 1 | |
| Quartile 2 | 133 | 15,061.1 | 8.8 | 7.5, 10.5 | 0.99 | 0.77, 1.26 |
| Quartile 3 | 190 | 13,865.1 | 13.7 | 11.9, 15.8 | 1.51 | 1.21, 1.88 |
| Quartile 4 | 281 | 13,787.1 | 20.4 | 18.1, 22.9 | 2.26 | 1.83, 2.78 |

Abbreviation: CI, confidence interval.

[a] See Table 1 for definitions of urate quartiles.

[b] Diabetes and impaired fasting glucose (prediabetes) were defined as meeting the fasting glucose criteria of the American Diabetes Association guidelines (26). All participants using antidiabetes medication were considered to be diabetic.

[c] Insulin resistance was defined as ≥75th percentile of homeostasis model assessment of insulin resistance among nondiabetic subjects at baseline (27). This corresponded to a value of 2.64 units in this cohort.

## RESULTS

### Study participants

The baseline characteristics of participants by stratum of serum urate level are provided in Table 1. The prevalence of obesity (body mass index ≥30) was 12%. Figure 1 shows the bivariate relation between serum urate concentration, plasma insulin level, and other cardiometabolic risk factors at the first visit. At baseline, serum urate level was weakly but inversely correlated with the logarithm of plasma insulin concentration. In addition, increasing baseline mean serum urate level was associated with significantly higher body mass index, systolic and diastolic blood pressure, and serum lipid levels ($P < 0.0001$). In multiple linear regression analyses, after adjustment for the effects of baseline age, gender, race, body mass index, systolic blood pressure, alcohol use, serum creatinine level, and physical activity level, each standard-deviation (1.4-mg/dL) increase in serum urate level was associated with a 0.92-μU/mL increase in plasma insulin concentration (95% confidence interval (CI): 0.66, 1.18; adjusted $R^2 = 28\%$). In the subgroup analysis among subjects without metabolic syndrome, no significant association between baseline serum urate level and baseline plasma insulin level was observed ($\beta = 0.05$, 95% CI: −0.4, 0.14; adjusted $R^2 = 12\%$).

### Follow-up and attrition

During the 15-year follow-up period, 2.3% (115/5,012) of participants died and 25.6% (1,285/5,012) were lost to follow-up. The participants who were lost to follow-up were younger ($P < 0.05$), more likely to smoke (51% vs. 40%; $P < 0.0001$), and more likely to be African-American (62% vs. 46%; $P < 0.0001$) than those who continued in the study. The incidence rate of diabetes among persons who eventually dropped out was 6.39 cases per 1,000 person-years (95% CI: 4.91, 8.32) as compared with 4.05 cases per 1,000 person-years (95% CI: 3.55, 4.62) among those who did not.

### Unadjusted analyses

The risks of developing diabetes and prediabetes increased with serum urate concentration (Figure 2). The incidence rates of these outcomes and unadjusted hazard ratios are shown in Table 2.

### Adjusted analyses

In multivariable regression models, after adjustment for several potential confounders (age, gender, family history of diabetes, diastolic blood pressure, smoking, physical activity, body mass index, fasting serum creatinine concentration, total cholesterol level, current smoking, and alcohol use), increasing serum urate level remained a significant risk factor for diabetes, insulin resistance, and prediabetes (Table 3). The complete multivariable models are shown in Table 4. This was also evident among subgroups of race and gender, but a few results did not reach statistical significance (Figure 3).

**Table 3.** Hazard Ratios for Diabetes and Prediabetes According to Serum Urate Concentration (Cox Regression Analyses), Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001

| | Diabetes[a] | | Insulin Resistance[b] | | Prediabetes[a] | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Unadjusted HR | | | | | | |
| Per 1-mg/dL increase in serum urate level | 1.16 | 1.07, 1.26 | 1.20 | 1.16, 1.24 | 1.56 | 1.46, 1.67 |
| Serum urate level >7.0 mg/dL vs. ≤7.0 mg/dL | 1.94 | 1.43, 2.63 | 1.46 | 1.31, 1.62 | 2.15 | 1.79, 2.57 |
| Multivariable-adjusted HR[c] | | | | | | |
| Per 1-mg/dL increase in serum urate level | 1.23 | 1.08, 1.39 | 1.26 | 1.20, 1.31 | 1.21 | 1.11, 1.32 |
| Serum urate level >7.0 mg/dL vs. ≤7.0 mg/dL | 1.87 | 1.33, 2.62 | 1.36 | 1.23, 1.51 | 1.25 | 1.04, 1.52 |
| Quartile of serum urate level[d] (vs. first quartile) | | | | | | |
| Quartile 1 | 1 | | 1 | | 1 | |
| Quartile 2 | 0.98 | 0.65, 1.49 | 1.14 | 1.02, 1.22 | 1.34 | 1.05, 169 |
| Quartile 3 | 1.04 | 0.69, 1.55 | 1.26 | 1.15, 1.38 | 1.53 | 1.21, 1.91 |
| Quartile 4 | 1.65 | 1.14, 2.40 | 1.57 | 1.44, 1.71 | 1.66 | 1.32, 2.08 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Diabetes and impaired fasting glucose (prediabetes) were defined as meeting the fasting glucose criteria of the American Diabetes Association guidelines (26). All participants using antidiabetes medication were considered to be diabetic.

[b] Insulin resistance was defined as ≥75th percentile of homeostasis model assessment of insulin resistance among nondiabetic subjects at baseline (27). This corresponded to a value of 2.64 units in this cohort.

[c] Multivariable Cox regression models adjusted for the effects of age, gender, race, family history of diabetes, diastolic blood pressure, total cholesterol, current smoking status (yes/no), body mass index, and alcohol use. All continuous variables were included in the model as such in the model that updated time-varying information from visit to visit, except in the case of serum urate level, where only baseline data were used.

[d] See Table 1 for definitions of urate quartiles.

**Table 4.** Hazard Ratios for Diabetes, Prediabetes, and Insulin Resistance According to a 1-Standard-Deviation Increase (1.38 mg/dL) in Serum Urate Concentration (Multivariable Cox Regression Models[a]), Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001

| Covariate | Diabetes[b] (*n* = 24,141) | | Insulin Resistance[c] (*n* = 17,701) | | Prediabetes[b] (*n* = 23,146) | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Baseline serum uric acid level, per-1.38 mg/dL increase | 1.32 | 1.12, 1.57 | 1.25 | 1.20, 1.31 | 1.21 | 1.11, 1.32 |
| White race (vs. African-American) | 1.02 | 0.89, 1.17 | 0.83 | 0.80, 0.86 | 0.99 | 0.93, 1.07 |
| Female gender (vs. male) | 1.21 | 1.02, 1.42 | 1.11 | 1.06, 1.15 | 0.69 | 0.64, 0.78 |
| Family history of diabetes (vs. no family history) | 1.23 | 1.10, 1.38 | 1.04 | 1.02, 1.06 | 0.99 | 0.91, 1.09 |
| Serum creatinine level, per 1.02-mg/dL increase | 0.98 | 0.94, 1.02 | 1.01 | 0.99, 1.02 | 0.99 | 0.96, 1.02 |
| Systolic blood pressure, per 12.31-mm Hg increase | 1.02 | 1.01, 1.02 | 1.01 | 1.01, 1.01 | 1.02 | 1.01, 1.02 |
| Total cholesterol level, per 34.31-mg/dL increase | 1.02 | 1.01, 1.03 | 1.01 | 1.01, 1.02 | 1.01 | 1.00, 1.02 |
| History of polycystic ovarian disease (vs. no history) | 1.00 | 1.00, 1.01 | 1.00 | 1.00, 1.00 | 1.00 | 0.99, 1.01 |
| Current smoking (vs. not currently smoking) | 1.01 | 1.00, 1.02 | 1.00 | 1.00, 1.01 | 1.02 | 1.01, 1.02 |
| Physical activity level during past year, per 1.08-unit increase in physical activity score (range, 0–5) | 0.99 | 0.98, 1.00 | 0.99 | 0.98, 0.99 | 0.99 | 0.98, 1.00 |
| Body mass index,[d] per 5.8-unit increase | 1.04 | 1.03, 1.05 | 1.05 | 1.05, 1.06 | 1.05 | 1.04, 1.05 |
| Alcohol use, per 24-mL/day increase | 0.97 | 0.94, 1.00 | 0.99 | 0.99, 1.00 | 1.01 | 1.00, 1.01 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Multivariable Cox regression models adjusted for the effects of age, gender, race, family history of diabetes, diastolic blood pressure, total cholesterol, current smoking status (yes/no), body mass index, and alcohol use. All continuous variables were included in the model as such in the model that updated time-varying information from visit to visit, except in the case of serum urate level, where only baseline data were used. For continuous variables, regression results are presented as the hazard ratio for a 1-standard-deviation change.

[b] Diabetes and impaired fasting glucose (prediabetes) were defined as meeting the fasting glucose criteria of the American Diabetes Association guidelines (26). All participants using antidiabetic medication were considered to be diabetic.

[c] Insulin resistance was defined as ≥75th percentile of homeostasis model assessment of insulin resistance among nondiabetic subjects at baseline (27). This corresponded to a value of 2.64 units in this cohort.

[d] Weight (kg)/height $(m)^2$.

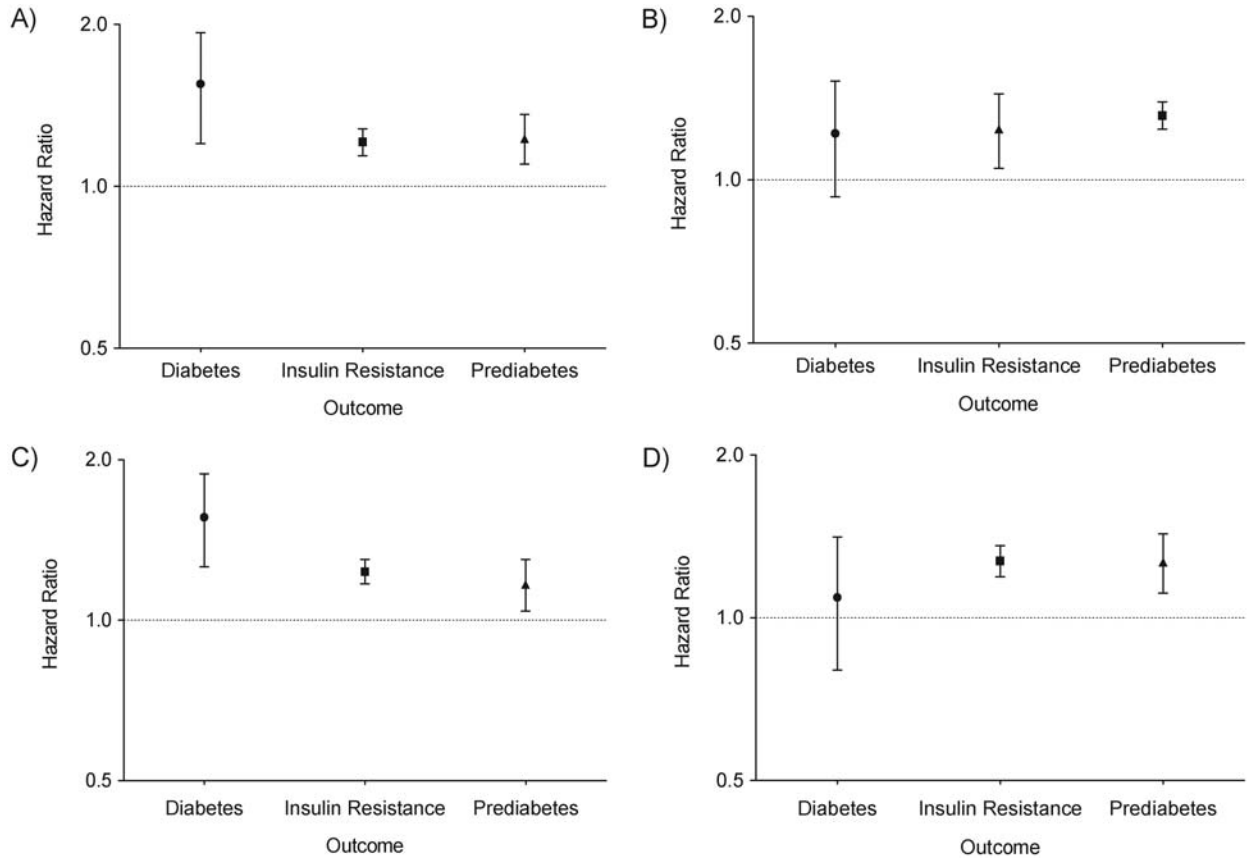


**Figure 3.** Hazard ratios for diabetes, insulin resistance, and prediabetes in A) men, B) women, C) African Americans, and D) whites among persons with hyperuricemia (serum urate level >7.0 mg/dL) versus those with a lower serum urate level (≤7.0 mg/dL), Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1986–2001. Diabetes and prediabetes were defined according to the fasting glucose criteria of the American Diabetes Association guidelines (26). Participants using antidiabetic medication were considered to be diabetic regardless of their fasting plasma glucose concentration. Insulin resistance was defined as ≥75th percentile of homeostasis model assessment of insulin resistance among nondiabetic subjects at baseline (2.64 units in this cohort) (27). Bars, 95% confidence interval.

## DISCUSSION

Obesity is a well-recognized marker and risk factor for type 2 diabetes, but a considerable proportion of individuals who develop diabetes are not obese (5), suggesting that in the absence of obesity, there are other independent risk factors. Our results suggest that elevated serum urate concentration may be one such risk factor.

To our knowledge, the present study is the longest prospective, observational analysis to have assessed the link between hyperuricemia and future diabetes and other diabetes-related outcomes in nondiabetic persons aged 18–30 years. This association was independent of obesity and other known risk factors, including age, gender, body mass index, diastolic blood pressure, smoking, fasting glucose concentration, family history of diabetes, and physical activity level. Relatively few studies have prospectively assessed the relation between serum urate level and diabetes in young adults. Results presented here are in agreement with those of previously published studies performed in older subjects. Data from the Rotterdam Study (15) showed that the age- and gender-adjusted hazard ratio for diabetes was greatest among persons in the highest quartile of serum urate level and the population attributable risk of hyperuricemia for diabetes was 24%. Herman and Goldbourt (31) demonstrated that serum urate levels were higher in prediabetic subjects than in nondiabetics. In contrast, the present study assessed the association between serum urate level and both the incidence of type 2 diabetes and prediabetes endpoints and suggested that hyperuricemia can be a useful predictor of diabetes mellitus.

Pathophysiologic links between hyperuricemia, insulin resistance, and prediabetes have not been clearly established and are under investigation. Hyperuricemia is often the result of the underexcretion of urate, and renal clearance of urate has been shown to be inversely related to the degree of insulin resistance (32). In addition, insulin resistance is associated with reduced levels of nitric oxide, and increased serum urate concentration has been shown to reduce nitric oxide levels (33). Increases in the

concentration of insulin may also affect renal tubular function and subsequent clearance of urate (32–35). This raises the possibility that hyperuricemia may merely be a marker for the renal effect of hyperinsulinemia. Our analyses showed a negligible relation between plasma insulin and serum urate levels at baseline, suggesting that hyperuricemia precedes insulin resistance, not vice versa.

Beyond this, there is some suggestion that the link between hyperuricemia and diabetes lies with the *SCL2A9* gene and perhaps other genes not yet identified. *SCL2A9* was first recognized to encode for the glucose/fructose transporter, GLUT9, which is expressed in 2 different isoforms in the liver, kidney, intestine, leukocytes, and chondrocytes. *SCL2A9*/GLUT9 was later identified in genome-wide studies as a major transporter of urate in the renal proximal tubule (33). Certain *SCL2A9* alleles have been shown to be strongly associated with an increased risk of hyperuricemia and gout in different populations (33). When Brandstätter et al. (36) analyzed 4 such alleles, 3 were shown to be significantly influenced by increasing body mass index. However, although the authors observed significant correlations between serum urate and the components of metabolic syndrome, no association between the 4 alleles and prevalent or incident metabolic syndrome could be established. Additional studies will be needed to determine whether the underlying genetic risks for hyperuricemia are also those for diabetes.

One possible limitation of this study is the type of population enrolled. It may be that persons who agree to participate in long-term studies such as the CARDIA Study are not representative of the general US population. As such, the "effect size" of the hyperuricemia-diabetes link in this cohort may not necessarily be generalizable to other populations. Future modeling studies can help establish the incremental value of adding serum urate level to the existing risk scoring methods. Another methodological limitation is that the pathway from normoglycemia through insulin resistance and prediabetes to diabetes could not be adequately modeled using our data. The main strengths of this study included the large number of participants, the long-term follow-up, and the young age of this biracial cohort. However, being an epidemiologic study, it did not address the pathophysiologic and mechanistic links underpinning our observations.

In summary, this study supports the use of serum urate concentration as an inexpensive marker for assessing the risk of future incident type 2 diabetes and diabetes-related outcomes in nonobese individuals. Serum urate level could be utilized either singly or as an integrated part of a risk score so that appropriate, targeted interventions could be formulated for at-risk patients.

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