

Clinical Evidence for the Influence of Uric Acid on Hypertension, Cardiovascular Disease, and Kidney Disease: A Statistical Modeling Perspective

Robert A. Short and Katherine R. Tuttle

This article critically evaluates the clinical evidence regarding the influence of uric acid on hypertension, cardiovascular disease, and kidney disease. Data on these relationships are largely observational and exceedingly complex. The complexity is owing to indirect and direct relations, and bidirectional influences, simultaneously operating on multiple outcomes. Limitations of previous analyses include inadequate statistical methods using only bivariate correlations or poorly specified multiple regression models. As a result, great controversy developed as to whether uric acid is an independent predictor of important outcomes. An example of such analytic limitations is including hypertension as an independent variable, together with uric acid, in a multivariate model for predicting cardiovascular disease. Hypertension may predict significant variance in cardiovascular disease, but the contribution of uric acid may not be recognized if uric acid exerts its influence indirectly through hypertension. Path analysis, which can model direct and indirect influences on outcomes simultaneously, would address this substantive question. Studies of uric acid in relation to hypertension, cardiovascular disease, and kidney disease using a path-analytic approach would help specify such conditions as well as optimize design of clinical trials to determine if decreasing uric acid levels improves outcomes.

Semin Nephrol 25:25-31 © 2005 Elsevier Inc. All rights reserved.

The objective of this article is to critically evaluate clinical evidence concerned with the influence of uric acid on hypertension, cardiovascular disease, and kidney disease. Inclusion of evidence in the article will involve a consideration of the relative contribution of articles based on statistical properties of the studies. The properties include the number of patients and, hence, the power of the study; the study design; the sampling of patients and variables; and the extent to which the study was focused analytically on the topic area. A discussion highlights how such properties aid in the interpretation of the literature as a whole. Another objective is to present a statistical/mathematic model that is used as a framework to classify evidence and determine whether the data support or negate the model in terms of the associations between the variables of interest, namely whether uric acid influences hypertension, cardiovascular disease, and kidney

disease. In large part, this portion of the article emerges from controversy surrounding whether uric acid is an independent risk factor for hypertension, cardiovascular disease, and/or kidney disease. The article is not intended to be exhaustive but, rather, to bring together a representative sample of the available data. The overall objective is to present a framework for interpreting the findings while underscoring the importance of the mathematic/statistical model as it drives measurement and interpretation.

Clinical Evidence for the Influence of Uric Acid on Hypertension, Cardiovascular Disease, and Kidney Disease

Serum concentrations of uric acid influence, as well as reflect, multiple intertwining functions. The available evidence comes from many different sources that vary in quality and focus. Large studies with multivariate analysis form the basis for most of the key interpretations. Evidence for the role of uric acid in hypertension, cardiovascular disease, and kidney disease are presented and summarized in [Table 1](#). It is im-

From the Research Department, The Heart Institute of Spokane, Spokane, WA.

Supported by The Heart Institute of Spokane and Sacred Heart Medical Center.

Address reprint requests to Robert A. Short, PhD, The Heart Institute of Spokane, 122 W. 7th Ave, Suite 230, Spokane, WA 99204-2340.

Table 1 Relationships Between Uric Acid, Risk Factors, and Major Clinical Outcomes

Risk Factors and Outcome Variables	References
Correlations between risk factors and uric acid	
Nonmodifiable	
Older age	1–4
Male sex	1–4
African American race	1,16
Lifestyle	
Alcohol	11–14
Smoking	1,16
Metabolic syndrome	
Hyperinsulinemia/ hyperglycemia	1,4,13,16,27
Obesity	2,4,8,13,16,27–30
Dyslipidemia	2,11–14,16,27
Uric acid as a predictor of clinical outcomes	
All-cause mortality	1,2,12,15,28,36,38,47
Hypertension	29,30,37,38,40,41
Cardiovascular disease	
Mortality	1,4,11,47
Myocardial infarction	1,11,38
Atherosclerosis/coronary heart disease	12–14,28–30,34,35
Congestive heart failure	35,60,62
Kidney disease	
Microalbuminuria	42,64,67
Increased serum creatinine level	8,14,27,38,63,73
Loss of glomerular filtration rate	63,68,73

portant to note that risk factors influence uric acid levels, often in conjunction with effects on the outcomes of hypertension, cardiovascular disease, and kidney disease. Moreover, the data largely are observational and, because of inherent limitations of the currently tested statistical models, the information generates hypotheses but does not establish causality.

Risk Factors Associated With Increased Uric Acid Levels

Nonmodifiable and Lifestyle Risk Factors

Considering the nonmodifiable risk factors, evidence is sufficient to conclude that age, sex, and race influence uric acid levels. Specifically, uric acid increases with age, particularly in women,^{1–4} is higher in men than in women,^{1–4} and is higher in African Americans than in Caucasians.¹ Worthy of note is that investigators often accept evidence for these associations with uric acid level based solely on bivariate correlations, as opposed to requiring a statistically independent contribution in a multivariate model. In addition to the influence on uric acid, these nonmodifiable risk factors (age, sex, and race) also directly influence hypertension,^{5,6} cardiovascular disease,^{2,7,8} and kidney disease.^{9,10}

Among the lifestyle factors that can be modified, alcohol consumption has a potent impact to increase uric acid levels.^{11–14} Smoking has been found to have a minor affect on uric acid levels.^{8,11–15} In some studies, smoking was associated with a decreased uric acid level,^{1,16} which may reflect consumption of antioxidants (see later). Lifestyle variables also directly influence the metabolic syndrome, hypertension, cardiovascular disease, and kidney disease. Although an in-depth discussion of these relations is beyond the scope of this article, the epidemic of obesity and dietary excess is driving this spectrum of diseases associated with hyperuricemia.^{6,17}

Metabolic Syndrome

The metabolic syndrome is defined by the constellation of abdominal obesity, hyperinsulinemia, insulin resistance, hyperglycemia, dyslipidemia (hypertriglyceridemia and low high-density lipoprotein cholesterol), and hypertension.^{18,19} The metabolic syndrome has been implicated as a major contributor to cardiovascular disease, and likely to kidney disease, in the developed world.^{20–23} In addition to the traditional criteria, uric acid has been linked to the metabolic syndrome.^{24,25} By inducing endothelial dysfunction, uric acid may cause resistance to insulin action²⁶ and, consequently, hyperinsulinemia.^{16,27} Uric acid was correlated strongly with body weight,^{4,8,27–29} was found to predict obesity,³⁰ and was correlated with serum insulin level.^{31,32} In preliminary studies, we have found that higher uric acid levels predict subsequent development of increased insulin levels in patients who have had a myocardial infarction (Short and Tuttle, unpublished data). In at least one study, uric acid level was found to be associated with insulin resistance independently of obesity.³³ Although uric acid is associated with other components of the metabolic syndrome,² these relationships do not exclude the possibility that uric acid also directly causes complications,³² cardiovascular disease, in particular.^{31,34}

Uric acid and the metabolic syndrome involve a clustering of multiple risk factors. Only a few studies conceptualize their analysis in terms of examining such clustering and present correlation matrices or results of factor analysis.^{35,36} Rather, investigators often simply report bivariate correlations with uric acid. Correlations have been noted with lipids, glucose, insulin, obesity, and glucose tolerance.^{4,13,14,24,27,29,35,36} However, the relative contributions of the various components to the important clinical consequences of metabolic syndrome remain unresolved.

Effects of Uric Acid on Clinical Outcomes

Hypertension

The role of uric acid in hypertension recently was reviewed in-depth.³⁷ Uric acid has strong correlations with blood pressure and the use of diuretic therapy in the hypertensive population.^{2,8,38,39} Diuretics are well known to reversibly increase serum uric acid levels. Thus, diuretic use typically correlates with an increase in serum uric acid level and confounds the bivariate relationship between uric acid and hypertension. Nevertheless, uric acid level has been shown to be an independent risk factor for prediction of hypertension.^{29,40,41} In

survival studies, uric acid predicted 5-year all-cause mortality, regardless of whether the patients were on medications (including diuretics) for hypertension.³⁶ Increases in uric acid level for hypertensive patients with microalbuminuria have been noted, but may have been owing to more obesity in these patients.⁴² The relationship between uric acid level and hypertension seems to be stronger in African Americans.²⁸ In a recent study of untreated adolescents, the correlation of uric acid level and blood pressure was strong (correlation coefficient, .8; $P < .001$) and independent of kidney function.⁴³ Despite such evidence, some investigators dispute that uric acid level is an independent risk for hypertension or its complications on the basis of other observational data.^{44,45} Again, interpretation of these studies is clouded based on their observational nature; the complexity of relationships between uric acid, other risk factors, and clinical outcomes; and statistical models that do not account adequately for this complexity.

Cardiovascular Disease

Evidence for the involvement of uric acid in cardiovascular disease is extensive, and so is the controversy surrounding the interpretation of the data. Several large studies have yielded conflicting results regarding the influence of uric acid level on cardiovascular disease. In the Framingham Heart Study,^{2,12,38,46} baseline uric acid levels were found to predict cardiovascular and all-cause mortality over 20 years. Similar results were reported in a Finnish sample in which higher uric acid levels predicted all-cause mortality. Furthermore, in women, a higher cardiovascular mortality was shown.⁴ Results reported from the National Health and Nutrition Examination Survey (NHANES) study and the Chicago Heart Study also suggested that serum uric acid levels were associated with increased risk for mortality from ischemic heart disease and all causes, primarily in women.^{1,28} Most studies have found such relationships to be greatest in women;^{15,29} yet at least one study found a stronger association in men.⁴⁷ A more recent report from the NHANES data indicated that the relationship between uric acid level and ischemic heart disease was apparent in both men and women.¹¹ The relationship between uric acid and cardiovascular disease also was apparent in the elderly population.^{14,48,49} In the Systolic Hypertension in the Elderly Program trial,¹⁴ in which diuretics were shown to decrease cardiovascular mortality in the elderly, the protection from cardiovascular disease was lost in those patients whose uric acid levels increased. Overall, a number of other large studies also support uric acid level as a risk factor in cardiovascular disease,^{8,13,14,29,31,47,50,51,52} with significant relationships after adjustment for other risk factors and potential confounders. However, other studies claim that uric acid level predicts cardiovascular disease, but, after adjusting for other risk factors, the association becomes nonsignificant.^{24,28,53,54} For example, in the general population, uric acid level did not predict electrocardiographic indications of heart disease.²⁸ The Atherosclerosis Risk in Communities study found little association between uric acid level and coronary heart disease events after adjusting for a variety of risk factors.⁵⁵ Nevertheless, it is impor-

tant to emphasize that if uric acid causes cardiovascular disease as a consequence of causing hypertension or renal disease, then it may not consistently be independent of these factors in a typical multivariate analysis with cardiovascular events as the dependent or outcome variable.⁵⁶

In studies in which increased risk for cardiovascular disease was shown, the idea of a J-shaped risk profile has been suggested. The lowest levels of uric acid yield an increased risk relative to levels in the range of approximately 5.2 to 5.5 mg/dL, which yield the lowest risk, and levels greater than 6 mg/dL yield the highest risk.^{52,57} Because uric acid is the by-product of purine metabolism in which a free radical is formed, uric acid level may be a marker of oxidative stress.⁵⁸ An important yet opposing influence of uric acid level is its antioxidant properties.^{58,59} The increase in serum uric acid level in patients with cardiovascular disease may reflect a compensatory mechanism to counter the oxidative stress that occurs with tissue hypoxia.³⁵ Thus, the higher levels of uric acid corresponding to high risk may reflect response to tissue injury, whereas the higher risk at lower uric acid levels may be the result of decreased antioxidant capacity. In patients with congestive heart failure, uric acid is higher than in healthy controls⁶⁰ and strongly predicts mortality.⁶¹ Moreover, in congestive heart failure patients, higher uric acid levels reflect a lower anaerobic threshold, an indicator of illness severity.⁶² In patients with atherosclerotic heart disease, high uric acid levels were correlated with high total antioxidant capacity.⁵⁹ To the contrary, low uric acid levels have been associated with greater cardiovascular disease risk^{52,57} and smoking.¹⁶ These latter observations were interpreted to reflect even more severe disease and loss of antioxidant capacity owing to excess utilization.

Kidney Disease

Fewer studies of populations with kidney disease are available. In hypertensive patients, uric acid level has been correlated with the development of chronic renal insufficiency.^{63,64} Furthermore, in the general population, uric acid levels are higher in patients with decreased kidney function.^{27,65,66} Higher uric acid levels also are associated with microalbuminuria.^{42,67} These clinical observations do not, however, clarify whether hyperuricemia is a cause or consequence of kidney disease. Indeed, when the glomerular filtration rate decreases, uric acid may be excreted at a lower rate, thereby increasing serum uric acid levels.⁶⁸ Uric acid also may cause damage to both the vascular and tubular structures in the kidney, as extensively reviewed in other articles in this issue of *Seminars in Nephrology*. In some cases, toxicity from cadmium or lead, which causes direct tubular damage, increases serum uric acid level because of impaired tubular secretion, the syndrome of saturnine gout.⁶⁹⁻⁷¹ Higher uric acid levels appear to be associated with more rapid progression of kidney disease.^{64,72-74} Yet, as for cardiovascular disease, the data for kidney disease also are inconsistent. For example, in a large clinical study of dietary protein restriction and blood pressure control, the Modification of Diet in Renal Disease (MDRD) study, uric acid level was not found to be an independent predictor for loss of kidney

Table 2 Definitions and Examples of Variables and Analyses Used in Statistical Models

Variables and Analyses	Definitions	Examples
Variables		
Independent	Potential causal factor	Uric acid
Dependent	Outcome	Cardiovascular disease
Manifest	Measurement	Blood pressure
Latent	Construct	Hypertension
Analyses		
Univariate	Descriptive parameters	Mean \pm SD
Bivariate	Relationship between 2 variables	Correlation
Multiple Regression	Multiple variables to define independent determinants of outcome	Linear or logistic multiple regression
Path	Strategy taking into account interrelationships between 3 or more variables simultaneously	Indirect and direct effects, path coefficients, and interaction terms

function.⁷⁵ However, only a single baseline measurement of uric acid was available, which may have decreased the ability to detect an association between serum uric acid levels and progression of kidney disease.

A Statistical Approach to the Controversy—Path Analysis

For a factor to be considered potentially causal in a disease process, it should independently contribute to the disease outcomes. In the case of uric acid as a risk factor, the results have been inconsistent for the important outcomes of hypertension, cardiovascular disease, and kidney disease. The source of the controversy concerning the influence of uric acid level on these outcomes largely derives from the manner in which data were analyzed. When variables were included in an analysis without consideration of their role in the statistical model, misinterpretation of the results could have occurred. An example is the practice of including hypertension as an independent variable, together with levels of uric acid, in a multivariate regression model for predicting cardiovascular disease. Hypertension may predict significant variance in cardiovascular disease, but this variance may be the same variance that uric acid predicts. Including hypertension in the multiple regression equation as an independent variable may lead to a better regression equation in terms of the percent of predicted variance (a mathematic criterion for inclusion), but it has not helped in defining the role of uric acid in the pathogenesis of cardiovascular disease (the substantive question). Uric acid may exert its influence on cardiovascular disease indirectly through hypertension, or uric acid may have a direct influence on cardiovascular disease. These are 2 very different models, and they are not mutually exclusive. Each pathway, denoting both direct and indirect influence, has important implications.

Here we focus on concepts regarding roles of variables and types of analyses used in statistical models (Table 2). Two different categories of variables are examined: (1) manifest variables, which are defined as measured, data derived, and operationally defined sets of scores; and (2) latent variables, which describe a concept or theory and are termed *constructs*.

A latent variable, or construct, may be specified to be a source of influence for several measurement variables. Measured variables may be considered manifestations of such latent variables. Thus, systolic and diastolic blood pressures are measurement variables for the construct hypertension. Further, hypertension is a latent variable that may be theoretically useful in describing an impact on other constructs, such as heart disease or kidney disease. Roles of variables, and the relationships between them, can be presented by way of path diagrams (Fig 1). Path diagrams indicate the functional associations between variables that relate potential causes to effects. Such diagrams are useful descriptive tools and can be translated into statistical models. Creation of path diagrams, and performing the corresponding analyses, is known as path analysis. In path analysis, the relationships between several variables can be examined simultaneously and their influence on multiple outcomes can be assessed.⁷⁶⁻⁷⁸ For example, by using this approach, the relative contributions of uric acid and hypertension on cardiovascular disease can be assessed simultaneously with the influence of uric acid on hypertension. Such considerations reinforce the importance of specification of relations between variables—whether a variable has a direct or indirect influence on another variable or construct. The specified hypotheses and the model of associations between variables must be clear to optimize study design and analysis.

As for other statistical methods, in path analysis the number of patients is a strong determinant of the power to detect associations and adds to the confidence in estimated magnitudes of the relationships between variables. Studies with large numbers of patients provide a framework for interpreting the smaller and less-extensive studies in the field. Estimates of associations between variables have a certain amount of variance associated with them, and the expected variability is higher in studies with fewer patients. Further, the variability in these estimates can affect the results of statistical analyses and the subsequent interpretation of those results. For example, in conventional stepwise multiple regression procedures, uric acid may be eliminated in one study but not in another study. It could be the variability of the estimates of association between uric acid and the outcome measurement that is the cause of the differing results, rather than

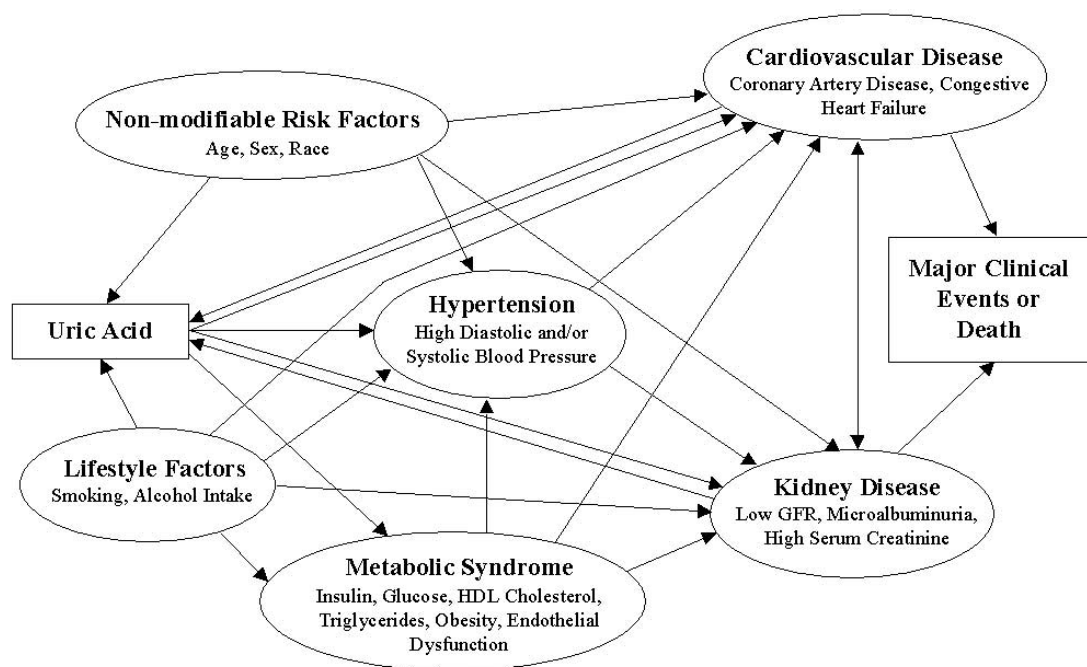


Figure 1 Path diagram for relations between uric acid, hypertension, cardiovascular disease, and kidney disease.

how the variables are associated with one another in reality. Consideration of the population studied is also of statistical importance. Variance may be restricted by inclusion or exclusion criteria and, in turn, restrict the apparent magnitude of the association between variables. In other words, the interpretation of significant and nonsignificant relations between the independent and dependent variables may change, depending on the types of patients in the sample.

The use of path analysis, including the path diagram, allows the incorporation of a myriad of complex relationships between uric acid, hypertension, cardiovascular disease, and kidney disease (Fig 1). Specification of this model was guided by the clinical evidence reviewed and by a number of excellent review articles in the area.^{25,37,39,46,79,80} Each construct in the path diagram (hypertension, cardiovascular disease, and kidney disease) is defined by several measured variables that are considered manifestations of the constructs. For example, hypertension is represented by diastolic and systolic blood pressure. Kidney disease is manifest by impaired glomerular filtration rate, a high serum creatinine level, and/or a high urinary albumin-to-creatinine ratio. Cardiovascular disease is manifest by evidence for coronary artery disease or congestive heart failure (which may, in turn, be defined by positive angiographic findings, occurrence of angina, structural abnormalities of the heart, and/or evidence of a myocardial infarction). Uric acid level is shown to influence hypertension, which, in turn, influences cardiovascular disease and kidney disease. Uric acid level is affected by nonmodifiable risk factors such as age, sex, and race; by lifestyle variables, most notably smoking and alcohol intake; and by development of the metabolic syndrome. All of these risk factors, both the modifiable and nonmodifiable, also affect hypertension, cardiovascular disease, and kidney disease.

To complicate matters further, uric acid is influenced by the development of cardiovascular disease and kidney disease. Although uric acid may promote hypertension, cardiovascular disease, and kidney disease directly, reciprocally, cardiovascular disease (congestive heart failure, in particular³⁵), and kidney disease (decreased glomerular filtration rate) act to increase uric acid levels further. The extent to which such feedback loops operate indirectly through other variables currently is unclear and requires further investigation. Cardiovascular disease and kidney disease are interrelated closely: either condition makes the other worse. Once kidney disease and cardiovascular disease are present, they often lead to major clinical events (eg, death, myocardial infarction, renal failure). These events are the culmination of multiple positive feedback cycles that increase uric acid level, from a variety of risk factors to target organ diseases. The statistical models required to define these relationships are complex and, if not specified correctly, can generate conflicting conclusions.

Perspectives

The clinical data on uric acid, hypertension, cardiovascular disease, and kidney disease are exceedingly complex. These complexities include both indirect and direct relations, feedback loops, bidirectional influences, and multiple manifest variables and constructs. Limitations of previous analyses include inadequate statistical methods using only bivariate correlations, or poorly specified multiple regression or Cox survival models. Controversy seemingly stems from trying to fit the substantive problem into a conventional statistical analysis, rather than designing an analysis that fits the substantive problem. As an example, in general, the multiple

regression analysis approach is used to examine only direct effects of a manifest variable on an outcome, and does not take into account potential indirect effects or interactions among variables. Such indirect effects and interactions between variables provide important insights and frequently are ignored. The result can be gross model misspecification, with resulting bias in the model parameters. Path-analytic techniques, including latent variable or construct modeling, have been shown to be useful in other disciplines and should be applied to the statistics of studies in this field as well.

Conclusions

To confirm a causal role for uric acid level in hypertension, cardiovascular disease, and kidney disease will require longitudinal controlled studies of decreasing uric acid level in patients at risk. Given the available data from clinical studies and the experimental models reviewed in this issue of *Seminars in Nephrology*, the therapeutic rationale for decreasing uric acid level is strong. In the meantime, further prospective, population-based studies of uric acid level in relation to hypertension, cardiovascular disease, and kidney disease using a robust path-analytic approach should be applied to define these conditions further, their relationships, and opportunities for intervention.

Acknowledgment

The authors are grateful to Marcia J. Hauger for graphics and word processing.

References

- Freedman DS, Williamson DF, Gunter EW, et al: Relation of serum uric acid to mortality and ischemic heart disease: The NHANES I epidemiologic follow-up study. *Am J Epidemiol* 141:637-644, 1995
- Kannel WB: Metabolic risk factors for coronary heart disease in women: Perspective from the Framingham Study. *Am Heart J* 114:413-418, 1987
- Levine W, Dyer AR, Shekelle RB, et al: Serum uric acid and 11.5-year mortality of middle-aged women: Findings of the Chicago Heart Association Detection Project in Industry. *J Clin Epidemiol* 42:257-267, 1989
- Reunanen A, Takkunen H, Knekt P, et al: Hyperuricemia as a risk factor for cardiovascular mortality. *Acta Med Scand* 668:S49-S59, 1982
- Gillum RF, Mussolino ME, Madans JH: Fish consumption and hypertension incidence in African Americans and whites: The NHANES I epidemiologic follow-up study. *J Natl Med Assoc* 93:124-128, 2001
- Paeratakul S, Lovejoy JC, Ryan DH, et al: The relation of gender, race and socioeconomic status to obesity and obesity comorbidities in a sample of US adults. *Int J Obes Relat Metab Disord* 26:1205-1210, 2002
- Gillum RF, Mussolino ME, Madans JH: Coronary heart disease incidence and survival in African-American women and men. The NHANES I epidemiologic follow-up study. *Ann Intern Med* 127:111-118, 1997
- Alderman MH, Cohen H, Madhavan S, et al: Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 34:144-150, 1999
- Stengel B, Tarver-Carr ME, Powe NR, et al: Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology* 14:479-487, 2003
- Klag MJ, Whelton PK, Randall BL, et al: End-stage renal disease in African-American and white men. 16-year MRFIT findings. *JAMA* 277:1293-1298, 1997
- Fang J, Alderman MH: Serum uric acid and cardiovascular mortality: The NHANES I epidemiologic follow-up study, 1971-1992. *JAMA* 283:2404-2410, 2000
- Abbott RD, Brand FN, Kannel WB, et al: Gout and coronary heart disease: The Framingham study. *J Clin Epidemiol* 41:237-242, 1988
- Iribarren C, Sharp DS, Curb JD, et al: High uric acid: A metabolic marker of coronary heart disease among alcohol abstainers? *J Clin Epidemiol* 49:673-678, 1996
- Fransse VF, Pahor M, Di Bari M, et al: Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 18:1149-1154, 2000
- Bengtsson C, Lapidus L, Stendahl C, et al: Hyperuricaemia and risk of cardiovascular disease and overall death. *Acta Med Scand* 224:549-555, 1988
- Nakanishi N, Tatara K, Nakamura K, et al: Risk factors for the incidence of hyperuricaemia: A 6-year longitudinal study of middle-aged Japanese men. *Int J Epidemiol* 28:888-893, 1999
- Choi HK, Atkinson K, Karlson EW, et al: Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 350:1093-1103, 2004
- 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). National Cholesterol Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation* 106:3143-3421, 2002
- Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539-553, 1998
- DeFronzo RA, Ferrannini E: Insulin resistance. A multifaceted syndrome responsible for NIDDM obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173-194, 1991
- Lakka HM, Laaksonen DE, Lakka TA, et al: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709-2716, 2002
- Sattar N, Gaw A, Scherbakova O, et al: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414-419, 2003
- Chen J, Muntner P, Hamm L, et al: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 140:167-174, 2004
- Wannamethee SG, Shaper AG, Whincup PH: Serum urate and the risk of major coronary heart disease events. *Heart* 78:147-153, 1997
- Wannamethee SG: Is serum uric acid a risk factor for coronary heart disease. *J Hum Hypertens* 13:153-156, 1999
- Zavaroni I, Mazza S, Fantuzzi M, et al: Changes in insulin and lipid metabolism in males with asymptomatic hyperuricaemia. *J Intern Med* 234:25-30, 1993
- Staessen J, for Members of the European Working Party on High Blood Pressure in the Elderly: The determinants and prognostic significance of serum uric acid in elderly patients of the European Working Party on High Blood Pressure in the Elderly Trial. *Am J Med* 90:50S-54S, 1991
- Persky VW, Dyer AR, Idris-Soven E, et al: Uric acid: A risk factor for coronary heart disease? *Circulation* 59:969-977, 1979
- Rathmann W, Hauner H, Dannehl K, et al: Association of elevated serum uric acid with coronary heart disease in diabetes mellitus. *Diabetes Metab* 9:159-166, 1993
- Masuo K, Kawaguchi H, Mikami H, et al: Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* 42:474-480, 2003
- Tuttle KR, Short RA, Johnson RJ: Sex differences in uric acid and risk factors for coronary artery disease. *Am J Cardiol* 87:1411-1414, 2001
- Short RA, Johnson RJ, Tuttle KR: Uric acid predicts cardiovascular disease in the absence of hypertension and independent of diuretic therapy, renal function, and microalbuminuria. *J Am Soc Nephrol* 14:676A, 2003
- Tuomilehto J, Zimmet P, Wolf E, et al: Plasma uric acid level and its

- association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. *Am J Epidemiol* 127:321-336, 1988
34. Weitzman S, Maislos M, Bodner-Fishman B, et al: Association of diabetic retinopathy, ischemic heart disease, and albuminuria with diabetic treatment in type 2 diabetic patients. *Acta Diabetol* 34:275-279, 1997
 35. Leyva F, Anker S, Swan JW, et al: Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. *Eur Heart J* 18:858-865, 1997
 36. The Hypertension Detection and Follow-up Program Cooperative Research Group. Mortality findings for stepped-care and referred-care participants in the Hypertension Detection and Follow-up Program, stratified by other risk factors. *Prev Med* 14:312-335, 1985
 37. Johnson RJ, Kang DH, Feig D, et al: Is there a pathogenic role for uric acid in hypertension, cardiovascular and renal disease? *Hypertension* 41:1183-1190, 2003
 38. Brand FN, McGee DL, Kannel WB, et al: Hyperuricemia as a risk factor of coronary heart disease: The Framingham study. *Am J Epidemiol* 121:11-18, 1985
 39. Puig JG, Ruilope LM: Uric acid as a cardiovascular risk factor in arterial hypertension. *J Hypertens* 17:869-872, 1999
 40. Selby JV, Friedman GD, Quesenberry CP: Precursors of essential hypertension: Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol* 131:1017-1027, 1990
 41. Jossa F, Farinara E, Panico S, et al: Serum uric acid and hypertension: The Olivetti heart study. *J Hum Hypertens* 8:677-681, 1994
 42. Torres RJ, Martinez MA, Sancho T, et al: Serum uric acid levels and microalbuminuria in mild hypertensive patients. *Adv Exp Med Biol* 486:135-137, 2000
 43. Feig DI, Johnson RJ: Hyperuricemia in childhood primary hypertension. *Hypertension* 42:247-252, 2003
 44. Bulpitt CJ, Beevers DG, Butlier A, et al: The survival of treated hypertensive patients and their causes of death: A report from the DHSS Hypertensive Care Computing Project (DHCCP). *J Hypertens* 4:93-99, 1986
 45. Culleton BF, Larson MG, Kannel WB, et al: Serum uric acid and risk for cardiovascular disease and death: The Framingham Heart Study. *Ann Intern Med* 131:7-13, 1999
 46. Culleton BF: Uric acid and cardiovascular disease: A renal-cardiac relationship? *Curr Opin Nephrol Hypertens* 10:371-375, 2001
 47. Liese AD, Hense HW, Löwel H, et al: Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg Cohort. *Epidemiology* 10:391-397, 1999
 48. Casiglia E, Spolaore P, Ginocchio G, et al: Predictors of mortality in very old subjects aged 80 years or over. *Eur J Epidemiol* 9:577-586, 1993
 49. Wang JG, Staessen JA, Fagard RH, et al: Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. *Hypertension* 37:1069-1074, 2001
 50. Bickel C, Rupperecht HJ, Blankenberg S, et al: Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. *Am J Cardiol* 89:12-17, 2002
 51. Goldberg RJ, Burchfiel CM, Benfante R, et al: Lifestyle and biologic factors associated with atherosclerotic disease in middle-aged men. *Arch Intern Med* 155:686-694, 1995
 52. Verdecchia P, Schillaci G, Reboldi G, et al: Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: The PIUMA Study. *Hypertension* 36:1072-1078, 2000
 53. The Coronary Drug Project Research Group: Serum uric acid: Its association with other risk factors and with mortality in coronary heart disease. *J Chron Dis* 29:557-569, 1976
 54. De Leeuw PW, Thijs L, Birkenhäger WH, et al: Prognostic significance of renal function in elderly patients with isolated systolic hypertension: Results from the Syst-Eur Trial. *J Am Soc Nephrol* 13:2213-2222, 2002
 55. Moriarty JT, Folsom AR, Iribarren C, et al: Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 10:136-143, 2003
 56. Johnson RJ, Tuttle KR: Much ado about nothing, or much to do about something? The continuing controversy over the role of uric acid in cardiovascular disease. *Hypertension* 35:E10, 2000
 57. Kagan A, Gordon T, Rhoads GG, et al: Some factors related to coronary heart disease incidence in Honolulu Japanese Men: The Honolulu Heart Study. *Int J Epidemiol* 4:271-279, 1975
 58. Ward HJ: Uric acid as an independent risk factor in the treatment of hypertension. *Lancet* 352:670-671, 1998
 59. Nieto FJ, Iribarren C, Gross MD, et al: Uric acid and serum antioxidant capacity: A reaction to atherosclerosis? *Atherosclerosis* 148:131-139, 2000
 60. Leyva F, Anker SD, Godsland IF, et al: Uric acid in chronic heart failure: A marker of chronic inflammation. *Eur Heart J* 19:1814-1822, 1998
 61. Anker SD, Doehner W, Rauchhaus M, et al: Uric acid and survival in chronic heart failure: Validation and application in metabolic, functional, and hemodynamic staging. *Circulation* 107:1991-1997, 2003
 62. Leyva F, Chua TP, Anker SD, et al: Uric acid in chronic heart failure: A measure of the anaerobic threshold. *Metabolism* 47:1156-1159, 1998
 63. Segura J, Campo C, Ruilope LM: How relevant and frequent is the presence of mild renal insufficiency in essential hypertension? *J Clin Hypertens* 4:332-336, 2002
 64. Leoncini G, Viazzi F, Parodi D, et al: Mild renal dysfunction and subclinical cardiovascular damage in primary hypertension. *Hypertension* 42:14-18, 2003
 65. Iseki K, Oshiro S, Tozawa M, et al: Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res* 24:691-697, 2001
 66. Tomita M, Mizuno S, Yamanaka H, et al: Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. *J Epidemiol* 10:403-409, 2000
 67. Bigazzi R, Bianchi S, Baldari D, et al: Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 16:1325-1333, 1998
 68. Ruilope LM, Garcia-Puig J: Hyperuricemia and renal function. *Curr Hypertens Rep* 3:197-202, 2001
 69. Geiger H, Bahner U, Heidland A: Does cadmium contribute to the development of renal parenchymal hypertension. *Int J Artif Organs* 12:733-737, 1989
 70. Geiger H, Bahner U, Anderes S, et al: Cadmium and renal hypertension. *J Hum Hypertens* 3:23-27, 1989
 71. Miranda-Carus E, Mateos FA, Sanz AG, et al: Purine metabolism in patients with gout: The role of lead. *Nephron* 75:327-335, 1997
 72. Gerhardt U, Grosse HM, Hohage H: Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant recipients. *Clin Transplant* 13:375-379, 1999
 73. Ohno I, Hosoya T, Gomi H, et al: Serum uric acid and renal prognosis in patients with IgA nephropathy. *Nephron* 87:333-339, 2001
 74. Syrjänen J, Mustonen J, Pasternack A: Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. *Nephrol Dial Transplant* 15:34-42, 2000
 75. Hunsicker LG, Adler S, Caggiula A, et al: Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 51:1908-1919, 1997
 76. James LR, Mulaik SA, Brett JM: *Causal Analysis: Assumptions, Models, and Data*. Beverly Hills, CA, Sage Publications, Inc., 1982
 77. Joezlin JC: *Latent Variable Models: An Introduction to Factor, Path, and Structural Analysis*. Hillsdale, NJ, Lawrence Erlbaum Associates, 1987
 78. Hayduk LA: *Structural Equation Modeling with LISREL: Essentials and Advances*. Baltimore, The Johns Hopkins University Press, 1987
 79. Breckridge A: Hypertension and hyperuricaemia. *Lancet* 1:15-18, 1966
 80. Johnson RJ, Kivlighn SD, Kim YG, et al: Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. *Am J Kidney Dis* 33:225-234, 1999