


We thank Drs. Knowles and Reaven for their insightful letter (1), which meaningfully adds to the debate regarding uric acid as a biomarker of risk of or causal factor for cardiovascular disease. Here are a few additional observations to add to this discussion.

The existing body of scientific literature suggests that uric acid is not causal in the pathogenesis of diabetes. This is evident not only in Mendelian randomization studies (2) but also in how uric acid is generated in the body. Uric acid is a product of glucose metabolism via the pentose phosphate shunt pathway. As a result, factors that contribute to the pathogenesis of diabetes also contribute to elevations in uric acid, such as excess intracellular glucose (3) or dietary choices that increase glycolysis (4). Despite this, the epidemiologic literature has shown uric acid to be a strong marker of the risk of diabetes. Uric acid concentration is typically elevated before diabetes is diagnosed, sometimes even before elevations in serum glucose levels are observed (5–7). Our study further demonstrated that despite being elevated before a diabetes diagnosis, uric acid concentrations decline in persons with diabetes over time independently of serum measures of kidney function, insulin, or glucose (8).

The role of uric acid as a causal factor in the pathogenesis of cardiovascular disease is more controversial. As pointed out by Knowles and Reaven, Mendelian randomization studies provide evidence that uric acid is not a cause of elevated blood pressure, elevated fasting glucose levels, chronic kidney disease, or coronary heart disease (9). However, there is substantial evidence from animal models that hyperuricemia may increase blood pressure (10) and contribute to chronic kidney disease in the form of crystal deposition (11), renin-angiotensin interference (12), or glomerular injury (13). Furthermore, several randomized, controlled trials of urate-lowering therapy demonstrated that reductions in uric acid may lower blood pressure (14–16) and even improve kidney function (16–19). Given these contradictory data, whether uric acid reduction has direct effects on cardiovascular risk remains unknown.

Our study highlights the challenge of studying individual components of complex metabolic states with constituents that evolve and interact over time. Unlike environmental or infectious agents, which may be individually sufficient and necessary to cause disease (20), biomarkers are rarely aberrant without influencing multiple other biomarkers and organs. With better understanding of these interactions, future studies will be able to account for the complex relationship of diabetes and uric acid in analytic models and/or in the selection of their study populations.

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Joshua W. Knowles and Gerald Reaven (e-mail: knowlej@stanford.edu)
Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA

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We read with interest the paper by Huang et al. (1) suggesting that neonatal jaundice is associated with childhood asthma. Using data from the Collaborative Perinatal Project (CPP), Huang et al. examined whether the associations between neonatal jaundice and childhood asthma could be due to phototherapy (which was unavailable at the time of the CPP) or a high bilirubin level itself, but the accompanying commentary (2) raised the issue of a potential common cause (CPP) or a high bilirubin level itself, but the accompanying commentary (2) raised the issue of a potential common cause due to phototherapy (which was unavailable at the time of the CPP) or a high bilirubin level itself, but the accompanying commentary (2) raised the issue of a potential common cause. These relationships are bound to be complex, and careful attention is needed to properly model the potential confounders and mediators of maternal-infant-childhood associations (5). In this case, Huang et al. adjusted their results for maternal allergic conditions (1), but this is a poor proxy for maternal asthma, since about half of current asthma is nonallergic and perhaps 30% of nonasthmatics have a common allergy response. On the other hand, we recognize that the differences between asthma diagnosis and treatment in the 1960s and in the present day add further complexity to the interpretation of these findings. This is an intriguing area of research.

REFERENCES


Stephen P. Juraschek and Elizabeth Selvin
(e-mail: lselvin@jhsph.edu)
Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

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