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Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study

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ABSTRACT

BACKGROUND Although epidemiological studies have reported positive associations between circulating urate levels and cardiometabolic diseases, causality remains uncertain.

OBJECTIVES Through a Mendelian randomization approach, we assessed whether serum urate levels are causally relevant in type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), ischemic stroke, and heart failure (HF).

METHODS This study investigated 28 single nucleotide polymorphisms known to regulate serum urate levels in association with various vascular and nonvascular risk factors to assess pleiotropy. To limit genetic confounding, 14 single nucleotide polymorphisms exclusively associated with serum urate levels were used in a genetic risk score to assess associations with the following cardiometabolic diseases (cases/controls): T2DM (26,488/83,964), CHD (54,501/68,275), ischemic stroke (14,779/67,312), and HF (4,526/18,400). As a positive control, this study also investigated our genetic instrument in 3,151 gout cases and 68,350 controls.

RESULTS Serum urate levels, increased by 1 SD due to the genetic score, were not associated with T2DM, CHD, ischemic stroke, or HF. These results were in contrast with previous prospective studies that did observe increased risks of these 4 cardiometabolic diseases for an equivalent increase in circulating urate levels. However, a 1 SD increase in serum urate levels due to the genetic score was associated with increased risk of gout (odds ratio: 5.84; 95% confidence interval: 4.56 to 7.49), which was directionally consistent with previous observations.

CONCLUSIONS Evidence from this study does not support a causal role of circulating serum urate levels in T2DM, CHD, ischemic stroke, or HF. Decreasing serum urate levels may not translate into risk reductions for cardiometabolic conditions. (J Am Coll Cardiol 2016;67:407–16) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

GRS = genetic risk score

HF = heart failure

MR = Mendelian randomization

SNP = single nucleotide polymorphism

T2DM = type 2 diabetes mellitus

Uric acid is the end product of purine metabolism and circulates in the blood as the anion urate. Blood levels of uric acid are causally associated with gout, as implicated by evidence from randomized clinical trials using urate-lowering therapies (1). In 1923, Kylin initially described a constellation of metabolic disturbances that included hypertension, hyperglycemia, and elevated uric acid levels. Since then, circulating levels of serum uric acid have been reported to be positively correlated with several vascular risk factors including blood pressure, lipids, kidney function, and other metabolic traits (2). A number of prospective epidemiological studies have associated increased serum uric acid levels and elevated risk for type 2 diabetes mellitus (T2DM) (3), coronary heart disease (CHD) (4–7), ischemic stroke (8,9), and heart failure (HF) (10,11).

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No large-scale intervention studies, however, have evaluated urate-lowering therapies for metabolic and

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