Largest study to date finds multiple urinary metals play key role in cardiovascular disease and mortality

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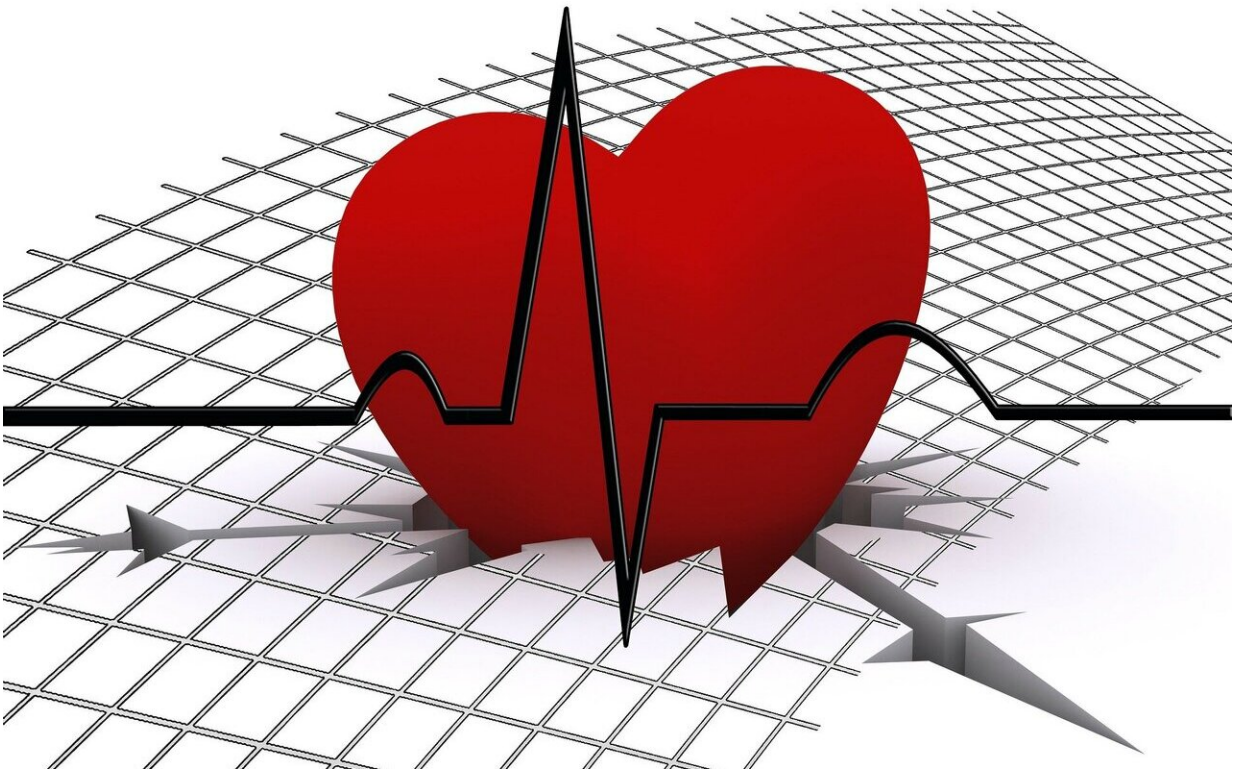

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Higher levels of urinary metals such as cadmium, tungsten, uranium, cobalt, copper and zinc are linked to increased cardiovascular disease

and mortality in a racially and ethnically diverse U.S. population, according to a new study at Columbia University Mailman School of Public Health. While it is well documented that exposure to certain metals has been associated with cardiovascular disease (CVD) and mortality, until now the evidence was limited beyond arsenic, cadmium, and lead; and for a racially diverse population. The findings are published in the journal *Circulation*.

When analyzed together, the six-metal mixture including cadmium, tungsten, uranium, copper, cobalt, and zinc was associated with a 29% increased risk of cardiovascular disease and a 66% increased risk of death over the study follow up of 18 years. Increased risk of CVD and mortality was also identified for every metal individually.

"Our study presents the results from the largest prospective study of urinary metals and cardiovascular disease to date and supports the role of urinary metals as novel risk factors for CVD and all-cause mortality risk," said Irene Martinez-Morata, MD, Ph.D., in the Department of Environmental Health Sciences at Columbia Mailman School, and lead author. "Our findings can inform risk prediction and preventive strategies to improve cardiovascular health by reducing metal exposures across diverse populations."

Exposure to metals is widespread. The sources and routes of exposure vary, and can be exacerbated by climate change, leading to the contamination of air, soil and water, and ultimately the food chain. Higher burden of metal exposures has been documented across population groups such as non-Hispanic Black, Hispanic/Latino, Chinese, and American Indians, and among communities with lower socioeconomic status, revealing that sociopolitical, historical and structural factors, contribute to disparities beyond individual-level factors such as smoking, occupation and diet.

"Interventions to reduce metal exposure can particularly benefit these population groups who also suffer a higher burden of CVD mortality," adds Martinez-Morata.

The American Heart Association recently recognized the toxic metals arsenic, cadmium, and lead as associated with some incidence of CVD. However, until now, studies assessing the effects of less studied metals, including biometals such as copper and zinc, and metal mixtures, more likely to mimic real life exposures, have been limited.

Using the Multi-Ethnic Study of Atherosclerosis (MESA), the researchers assessed the association of six urinary metals with CVD events and mortality from six urban and suburban U.S. communities: Baltimore City and Baltimore County, Maryland; Chicago; Forsyth County, North Carolina; Los Angeles County; Northern Manhattan and the Bronx, NYC; and St. Paul, Minnesota, in July 2000–August 2002. Urine samples were analyzed at the Trace Metals Core Laboratory at Columbia University. To assess the joint effect of urinary metals as a mixture, the researchers conducted additional analyses using a machine learning approach recently developed at the Department of Biostatistics at Columbia University.

Of the population analyzed, 39% were non-Hispanic white, 27% non-Hispanic Black, 22% Hispanic/Latino, and 12% of Chinese descent. Over the study follow-up period, 1,162 participants developed CVD and 1,844 participants died.

After accounting for established risk factors of CVD like smoking, hypertension or diabetes, the study identified that higher levels of the mixture of cadmium, tungsten, uranium, cobalt, copper, and zinc in the urine were associated with a 29% and a 66% increased risk of CVD and mortality, respectively, over the study follow-up. For individual metals, higher levels of cadmium were associated with up to 25% and 68%

higher risk of CVD and mortality, respectively. Similar associations were identified for all the other metals.

"Exposure to less studied metals such as tungsten and uranium is common in the U.S. and can occur through drinking water, food, air pollution, and indoor dust," observed Martinez-Morata. While some metals known as biometals, like copper and zinc, are needed in small amounts by our bodies, high levels of these metals in the urine can be harmful.

"While this is an ongoing field of study, high levels of essential metals in the urine can indicate an excess in exposure or loss of body reserves of these nutrients, which can occur when the metabolism is starting to malfunction, as it occurs in early stages of cardiovascular disease.

"Implementing policies and regulations for air pollution, drinking water and food contamination, and consumer products at the federal level, in addition to addressing community and household vulnerability factors, and individual behavioral changes can reduce exposure to metals, and we note that further analyses will help inform prevention strategies and interventions, including those directed at less studied and unregulated metals such as tungsten or cobalt," noted Martinez-Morata.

"And while federal regulations for lowering maximum contaminant levels for drinking water and banning leaded gasoline, for example, have successfully reduced exposure to toxic metals such as arsenic, cadmium, and lead in water and air, much more study is needed to understand the contributions of such metals as tungsten and cobalt."

"A strength of our study is how we assessed the association of urine metals as a mixture," said Ana Navas-Acien, MD, Ph.D., professor and chair of Columbia Mailman School Department of Environmental Health Sciences. "In addition to sampling a large population size and a

racially and diverse participant base, we used state-of-the-art laboratory methods—led by our Trace Metals Core Laboratory, and we analyzed outcomes over a long follow-up. However, future studies using repeated measures of urine metal levels can provide even more advanced information about exposure over time."

"The findings underscore the importance of reducing environmental exposure to these metals, which have disproportionately affected minority and poorer communities," says Cashell Jaquish, Ph.D., a genetic epidemiologist at the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), and a program officer with the MESA study. "The results could lead to efforts to reduce metal exposure in our communities and thereby reduce health disparities in heart disease, the leading cause of death in this country."

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More information: The association of urinary metals with cardiovascular disease incidence and all-cause mortality in the Multi-Ethnic Study of Atherosclerosis (MESA), *Circulation* (2024).

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