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Arsenic and Cardiovascular Disease: New Evidence From the United States

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Mounting evidence suggests that exposure to chemicals and other environmental substances, such as ambient urban air particles, cadmium, lead, and inorganic arsenic, could have a profound effect on cardiovascular disease (CVD) risk. Inorganic arsenic, a known carcinogen, occurs naturally in groundwater, exposing millions of people in the United States and worldwide. Epidemiologic studies in villages of southwestern Taiwan with high levels of arsenic in groundwater (median, 780 μg/L) provided early evidence of a dose–response relationship of water arsenic concentrations at less than 300 μg/L, 300 to 590 μg/L, and greater than 590 μg/L with CVD mortality (1). Arsenic exposure has also been related to increased mortality from acute myocardial infarction in Chile, where arsenic concentrations in drinking water increased from 90 to 870 μg/L between 1958 and 1970 (2). Recent prospective studies from Bangladesh reported a dose–response relationship between arsenic exposure and CVD mortality at well water arsenic concentration of 10 to 300 μg/L (3, 4) or urinary creatinine–adjusted arsenic concentration of 106 to 641 μg/g creatinine (3), although estimates for lower exposure levels were less precise. In this issue, Moon and colleagues (5) report results from a U.S. study of American Indians from the Strong Heart Study. Study participants with a urinary arsenic concentration greater than 15.7 μg/g creatinine were 1.65, 1.71, and 3.03 times more likely to die of CVD, coronary heart disease, and stroke, respectively, than their counterparts with urinary arsenic levels less than 5.8 μg/g creatinine (5). The risk for incident CVD associated with urinary arsenic, although lower than that for CVD mortality, was also elevated.

As the first prospective study (to our knowledge) in a U.S. population that assessed effects of arsenic exposure on CVD risk using urinary arsenic as a biomarker measured on each participant, the study by Moon and colleagues provides critical data. To our knowledge, the Strong Heart Study is also the largest, longest longitudinal study in the United States of

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CVD in a population with a high prevalence of diabetes and has the additional strength of comprehensive and rigorous follow-up data on both fatal and nonfatal CVD and CVD risk factors. Moreover, state-ofthe-art methods were used to analyze urinary arsenic. In particular, they could measure arsenobetaine, an organic arsenical found in seafood that is not considered to be toxic. Levels were very low (median, 0.76 μg/g creatinine), which removed concerns about potential confounding by arsenobetaine. Further, although they measured urine only 1 time, temporal reproducibility, which refers to the consistency of measurements from the same person at different times, in a subset with repeated urinary arsenic measured over 10 years was 0.64. This is within the acceptable limit of the reproducibility of biomarkers with observed disease associations from significant exposure in epidemiologic studies.

The study has several noteworthy points, and the findings raise new questions. Given that urinary arsenic also captures inorganic arsenic exposure from sources other than drinking water, it is difficult to judge the extent to which the observed association was due to arsenic from drinking water versus dietary sources. Stratified analyses showed that the association between urinary arsenic and CVD risk was stronger in Arizona, where drinking water was probably the main source of arsenic exposure (5). Yet, recent data indicate that dietary staples, such as rice, can be a major source of exposure for many persons (6).

The Strong Heart Study enrolled American Indians, a population that has a high prevalence of both diabetes and obesity and, consequently, an especially high risk for CVD. Stratified analyses showed that the association between uri-nary arsenic and CVD risk was stronger in persons with diabetes at baseline, which indicated that diabetes or risk factors associated with diabetes may magnify the cardiovascular effects of arsenic exposure. Alternatively, prevalent cases of diabetes have lower levels of creatinine, which would result in differences in urinary creatinine–adjusted arsenic concentration. The authors conducted sensitivity analyses adjusting urinary arsenic using specific gravity instead and found similar results. Thus, the findings do not fully answer the question of whether the relationship between arsenic and CVD is generalizable to other U.S. populations, especially in persons without diabetes.

Another issue regarding the generalizability of the study population is that the percentage of urinary monomethylarsonic acid, a biomarker for arsenic metabolism that is in part genetically driven (7), is not related to CVD risk in the Strong Heart Study. The percentage of urinary monomethylarsonic acid has been positively related to health effects of arsenic, including cancer and CVD-related end points, in recent data from Bangladesh (8). Lack of an association in the Strong Heart Study raises questions about whether differences in arsenic metabolism influence susceptibility to arsenic-associated CVD in populations with lower exposure levels, such as in the United States.

The association with stroke risk was less clear after adjustment for potentially confounding factors, with effect estimates having wide CIs. Data from Chile (2), Taiwan (1), and Bangladesh (3) in populations with higher exposure levels showed stronger associations with coronary heart disease than stroke. With longer follow-up, the Strong Heart Study may offer insights on subtypes of CVD that may be affected by arsenic.

If the association is real, what is the mechanism? Literature has documented a positive association between greater arsenic exposure and surrogate or intermediate CVD end points, such as intima–media thickness and circulating markers of inflammation and endothelial dysfunction. Additional studies are needed on such end points of CVD in populations with exposure levels investigated in the Strong Heart Study (such as arsenic levels <100 μg/L) to understand the potential early effects and uncover the mechanism.

Finally, questions about latent effects and vulnerable windows of exposure remain. Experimental data and ecologic studies from highly exposed populations raise the possibility of cardiovascular effects from in utero or early-life arsenic exposure (2, 9). Further work indicates that, in addition to water, inorganic arsenic in rice contributes to overall arsenic burden in pregnant women (6) and children (10) in the United States. A compelling question is whether cardiovascular effects of arsenic exposure are present in these vulnerable populations and whether early-life exposure could influence risk for CVD later in life.

In summary, the Strong Heart Study alerts us to what may be a new risk factor for CVD in the United States, consistent with data from other geographic regions. It also poses new questions about the effect of arsenic exposure from not only drinking water but from foods, such as grains, and during sensitive periods that may increase lifelong risk for CVD as a result of arsenic exposure.

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