Title: URINARY CREATININE: THE GRAND ENIGMA - IMPLICATIONS OF ITS USE AS A URINE DILUTION ADJUSTMENT FACTOR IN EPIDEMIOLOGIC STUDIES

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Urinary biomarkers of exposures and outcomes are often measured in epidemiologic studies focused on the health effects of environmental contaminants. These biomarker concentrations, often measured using spot urine samples, need to be corrected for urine dilution. One commonly employed approach is to adjust the biomarker concentration for the concentration of urinary creatinine (uCr), which is excreted at a relatively constant rate. Because most creatinine originates in muscle, uCr concentrations are correlated with muscle mass and differ by age, sex, and ethnicity. Two different adjustment approaches are regularly employed: 1) dividing the concentration of the urinary biomarker by the concentration of uCr and 2) including uCr as a covariate in regression models. The first approach is problematic as it may result in observed associations between the urinary biomarker and the outcome that are solely due to associations between the outcome and confounding variables that are associated with uCr. There are also problems with the second approach. For example, in regression models that are stratified by sex and include uCr as a covariate, one may observe apparent sex-specific associations between a urinary biomarker and outcome variable that are explained by differences in uCr by sex, rather than true sex differences in the association of interest. An additional layer of complexity exists for researchers who study As; both the methylation of As and the biosynthesis of creatine, the precursor of creatinine, occur via one-carbon metabolism. Our group and others have shown that uCr is a predictor of the relative distribution of As metabolites in urine for reasons that remain unclear. Numerous illustrations of these issues will be presented using data from our ongoing studies of As in Bangladesh. Alternative approaches to adjust for urine dilution should continue to be explored; measurements of specific gravity by refractometer appear to be a promising alternative.