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Supplemental Material

Arsenic Exposure and Epigenetic Aging: The Association with Cardiovascular Disease and All-Cause Mortality in the Strong Heart Study

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Table S5. Number of incident cardiovascular disease (CVD), fatal CVD, or all-cause death cases per 100,000 person-years attributable to a doubling in urinary arsenic levels through (indirect effect) and not through (direct effect) changes in epigenetic age acceleration for each epigenetic aging measure (Hannum age acceleration, and Horvath age acceleration), using mediation analysis by the product of coefficients approach as adapted by Lange and Hansen, in the Strong Heart Study (N=2323).

Table S6. Results of further adjustment of mediation models in Table S5 for CVD risk factors; number of incident cardiovascular disease (CVD), fatal CVD, or all-cause death cases per 100,000 person-years attributable to a doubling in urinary arsenic levels through (indirect effect) and not through (direct effect) changes in epigenetic age acceleration for each epigenetic aging measure (Hannum age acceleration, and Horvath age acceleration), using mediation analysis by the product of coefficients approach as adapted by Lange and Hansen, in the Strong Heart Study (N=2323).

Table S7. Hazard ratios (95% CI) for CVD incidence, CVD mortality, and all-cause mortality comparing the interquartile ranges of epigenetic aging measures (PhenoAge age acceleration, GrimAge age acceleration, and DunedinPACE), using Cox proportional-hazards models in the Strong Heart Study (N=2323, missing=0).

Table S8. Hazard ratios (95% CI) for CVD incidence, CVD mortality, and all-cause mortality comparing the interquartile ranges of epigenetic aging measures (Hannum age acceleration and Horvath age acceleration), using Cox proportional-hazards models in the Strong Heart Study (N=2323, missing=0).

Table S9. Subdistribution hazard ratios obtained from the Fine Gray model for the competing risks by death analysis for CVD incidence and mortality.

Figure S1. Forest plot of epigenetic age distributions (Hannun, Horvath, and PhenoAge) and pace of aging (DunedinPACE, years of biological aging/chronological years), by participants' baseline characteristics. (N=2323, missing=0). Corresponding data is in Excel Table S3.

Figure S2. Simplified directed acyclic graph depicting the relationships between arsenic exposure, epigenetic age acceleration, cardiovascular disease, and other mediating variables. For simplicity, we are not showing the arrow between CVD risk factors and DNA-methylation based metrics of biological aging but it is well-established that CVD risk factors can also accelerate biological aging. Also for simplicity we are not showing the arrows between age, sex, and study center and other variables, including cardiovascular disease, and other covariates.

Additional Files- Excel Document and mediation_analysis_code.R