Background and Aims: Arsenic (As) exposure has been linked to epigenetic modifications such as DNA methylation in vitro and animal studies. This association has also been explored in highly exposed human populations, but studies among populations environmentally exposed to low As levels are lacking. We aimed to evaluate the association between As exposure and DNA methylation changes in a population of community-dwelling elderly men. We also explored the possibility of effect modification by plasma folate, cobalamine (B12), and pyridoxine (B6).

Methods: We measured toenail As levels by inductively coupled plasma spectrometry and DNA methylation in Alu and Long Interspersed Nucleotide Element-1 (LINE-1) repetitive elements by quantitative polymerase chain reaction-pyrosequencing of blood leukocytes. The study population was 581 participants from the Normative Aging Study in Boston, USA, with 434, 140, and 7 of them having 1, 2 and 3 visits, respectively, between 1999-2002 and 2006-2007. We used mixed effects models and included interaction terms to assess potential effect modification by plasma folate, B12, and B6.

Results: There was a trend of increasing Alu and decreasing LINE-1 DNA methylation as arsenic exposure increased. In subjects with plasma folate below the median (less than 14.1 ng/ml), As was positively associated with Alu DNA methylation (beta=0.08; 95%CI, 0.03 to 0.13 for one interquartile range [0.06 mcg/g] increase in As) while a negative association was observed in subjects with plasma folate above the median (beta=-0.08; 95%CI, -0.17 to 0.01).

Conclusions: In our study, the association between As exposure and DNA methylation in Alu repetitive elements varied by folate level, a factor that participates in one-carbon metabolism. This suggests a potential role for nutritional factors in As toxicity.