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A Potential Contribution of Acrylonitrile to Accelerated Epigenetic Aging of the Lungs of Smokers

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Cigarette smoke contains large amounts of volatile organic compounds (VOCs) that are attributed to age-related respiratory diseases. We and others reported a significant association of smoking with accelerated biological age determined by DNA methylation. However, little is known about the relationship between specific VOCs, lung aging, and inflammation among smokers. This study assessed the well-studied DNA methylation-age estimates (mAge) that are linked to mortality (Grim-mAge and Pheno-mAge).

Epigenetic age estimates were assessed in the lung epithelium of 31 never-smokers (NS) and 13 smokers (SM) with no pulmonary diseases. We examined the differences in mAge between SM and NS using regression models after adjusting for potential confounders, including chronological age, sex, and race. In smokers, we investigated the relationship between ten smoking-related VOCs (cotinine-adjusted), the mAge-acceleration (-mAA), and lung inflammatory cytokines after adjusting for the covariates.

While there was no statistical difference in the chronological age between SM and NS (25.3 and 26.2, $p=0.4$), SM had significantly older GrimAge ($p=0.0002$) and Pheno-mAge ($p=0.03$) compared to NS. SM had up to 30-fold higher levels of VOCs compared to NS. In SM, of metabolites measured, a higher level of 2-cyanoethyl mercapturic acid (CEMA, a metabolite of acrylonitrile) was associated with faster Pheno-mAA ($r=0.85$, $p=0.002$), while a borderline significance was found for Grim-mAA ($r=0.63$, $p=0.05$). A borderline significant positive association was found between Pheno-mAA and IL-1β ($p=0.05$).

Our data suggest a potential contribution of acrylonitrile to premature lung aging among smokers, which supports a future larger study of its contribution to pulmonary diseases.