# Epigenetic ageing biomarkers are associated with predicted cardiovascular risk in women with prior hypertensive disorders of pregnancy

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## Background

Women with a history of hypertensive disorders of pregnancy (HDP) have an increased long-term risk of cardiovascular disease (CVD). DNA methylation-derived epigenetic ageing biomarkers may capture biological processes underlying this increased risk beyond conventional cardiovascular risk factors. This study evaluated the association between multiple epigenetic ageing biomarkers and predicted cardiovascular risk in women with prior HDP.

## Methods

Women with prior HDP from the 1994/1995 Busselton Health Study with available DNA methylation, phenotype, and linked health outcome data were included. Women aged ≥45 years with complete data required to calculate an adapted 5-year PREDICT cardiovascular risk score comprised the final analysis cohort (n = 193). Six DNA methylation-derived ageing biomarkers (GrimAge2, Horvath, AltumAge, PCGrimAge, Hannum, and DunedinPACE) were evaluated. Associations with predicted cardiovascular risk were assessed using Pearson correlation and linear regression. Participants were categorised into low (<5%), intermediate (5–10%), and high (≥10%) predicted cardiovascular risk groups. Group differences were assessed using one-way ANOVA with Tukey post-hoc testing, and BMI-adjusted linear regression.

## Results

Among the six epigenetic ageing biomarkers evaluated, DunedinPACE was the only biomarker significantly associated with predicted cardiovascular risk. DunedinPACE was positively associated with predicted 5-year CVD risk ($r = 0.276$, $p < 0.001$), remained significant after BMI adjustment ($\beta = 0.0057$, $p < 0.001$), and differed across predicted cardiovascular risk groups (ANOVA $p = 0.001$), with higher values in the high-risk group than the low-risk group (Tukey-adjusted $p = 0.0013$). GrimAge2, Horvath, AltumAge, PCGrimAge, and Hannum age acceleration were not significantly associated with predicted cardiovascular risk, although weak non-significant trends were observed for PCGrimAge.

## Conclusions

Among the six epigenetic ageing biomarkers evaluated, DunedinPACE was the only biomarker significantly associated with predicted cardiovascular risk in women with prior HDP. These findings suggest that pace-of-ageing measures may capture cardiovascular risk-related biological processes more effectively than first- and second-generation epigenetic age

acceleration measures in this population and support further investigation of DNA methylation-derived biomarkers for cardiovascular risk stratification following HDP.