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Biological Age Acceleration in the Norfolk Island Health Study with Independent Replication in the UK Biobank

Background: Chronological age (CA) often does not reflect the true physiological state of an individual. Biological age (BA), which estimates the functional integrity of cells, tissues, and organ systems, can deviate from CA due to genetic, environmental, and lifestyle factors. When BA exceeds CA, this is referred to as biological age acceleration (BAA), a phenomenon associated with increased risk of morbidity, mortality, and age-related diseases. As the global population continues to age, understanding the determinants and consequences of BAA and age-related disease has become a critical focus in aging research. BAA is increasingly recognized as a complex, multifactorial phenotype that cannot be captured by a single biomarker or mechanism. Specifically, understanding the cause and affect of BAA and age-related diseases can guide interventions to increase health span. BAA is heritable yet thus far little of the genetic architecture has been captured and many aging calculators are limited to small datasets resulting in a lack of population scale research.

Methods: The Norfolk Island Health Study (NIHS) was used as the primary discovery cohort. NIHS has three collections spanning 20 years full of rich omic data and is well characterised through in-depth genealogical records. Due to the population's isolation, lower genetic variability can amplify genetic affects, and lower environmental variability can reduce confounding affects. These benefits were leveraged within the study. The UK Biobank was used as a replication cohort and for population comparisons.

BAA calculation was performed with an R tool, BioAge, which uses predefined clinical biomarkers to train an algorithm on healthy adult data from the CALORIE study in the US which is then projected into the study data. The tool was used to calculate multiple biological age measures: Klemera-Doubal method (KDM), phenotypic age (PhenoAge), and homeostatic dysregulation (HD). Considerable batch testing was conducted with batch correction between collections to ensure the entire core pedigree cause be analysed. Correlation and association testing was performed between BAA, clinical biomarkers and health metrics. GWAS was conducted using GCTA due to the tools ability to handle relatedness. Replication of results was conducted with the UK Biobank.

Results: Batch effect was negated through ML methods. Phenotypic analyses in NI revealed that males had greater biological aging compared to females across all BAA measures. Correlations with biomarkers associated with chronic diseases were identified highlighting which age-related diseases are associated with BAA. Accelerated aging outliers' health records were found to support these biomarker association findings. Initial GWAS findings have revealed a novel locus for PhenoAge on chromosome 10 ($p=2.56e-08$).

Conclusions: This BAA calculation method is very close to disease making it good for health span focused prediction models but also extending into large scale datasets and biobank-scale cohorts enhancing aging research.