Polygenic Risk and Age-Related Health Decline:
Evidence from a 4-Decade Longitudinal Study

The traditional approach to understanding health decline in aging begins with diseases arising within specific bodily systems that in turn contribute to impaired functioning and ultimately death. An alternative approach begins with aging as a root cause of disease – as a pattern of coordinated decline in physiological integrity across multiple bodily systems. A challenge in human research pursuing this alternative approach is that the phenotypic manifestations of aging-related health decline and their molecular drivers are difficult to observe prior to the onset of age-related disease. Here, we seek address this challenge by (1) devising measures of the aging process that can be taken prior to the onset of age-related disease; and (2) testing whether genetic risks discovered for diseases of specific bodily systems predispose to a more general process of accelerated health decline in aging.

Data come from the Dunedin Longitudinal Study, a 1972-1973 birth cohort of 1,037 individuals (91% of eligible births; 52% male) followed prospectively through their fourth decade of life with almost no loss to follow-up; 95% of surviving cohort members completed the age-38 assessment in 2012.

We develop 2 phenotypic measures of aging. The first measure follows the method described by Levine (2014) to compare cohort members at age 38 years to a mixed-age reference panel and assign each individual a "biological age"—how old they look based on a biomarker profile. The second measure tracks change over time in a panel of aging-related biomarkers to calculate each individual's "pace of aging." We show that these aging phenotypes are predictive of physical and cognitive functioning in individuals who have not yet developed age-related disease.

We then construct measures of polygenic risk for a panel of age-related diseases. We calculate polygenic risk for each disease as the sum of risk alleles across loci identified in genome-wide association studies of the disease—a genetic risk score. We then test associations between the genetic risk scores and the aging phenotypes. We further test the extent to which pleiotropic genetic influences on multi-system aging phenotypes operate independently of genetic influences on specific bodily systems affected by the diseases for which they were discovered.

Levine ME. Modeling the rate of senescence: Can estimated biological age predict mortality more accurately than chronological age? *J Geron A: Biol Sci*, 68(6):667-674, 2014.