



## 2026 IMPACT CIRCLE

**Project Title:** The Missing Model of Aging: Menopause

**Investigator(s) and collaborations:** Annalise Schweickart, PhD, and Nathan Price, PhD

**Unmet Need/Primary Question:**

Menopause is one of the most significant biological transitions in adult life, yet it remains largely excluded from preclinical models of aging. However, human studies show that the menopausal transition is associated with accelerated biological aging and increased risk of chronic disease, suggesting it represents a concentrated period of system-wide, age-related change. Menopause simultaneously alters metabolic, cardiovascular, immune, and neuroendocrine function through a shared underlying cause: the loss of cyclic hormonal regulation. This makes menopause a uniquely powerful setting to study how multiple physiological systems destabilize and reorganize together, much like aging itself.

One way to approach this type of coordinated, multi-system change is to borrow the framework of resilience from the dynamical systems modeling field. This framework is explicitly designed to detect early warning signals of system transition, including increased instability, slower recovery, and breakdown of coordination across sub-systems. We therefore propose to use a dynamical systems framework of resilience to quantify changes in stability, recovery, and coordination across physiological systems during menopause.

This project asks: Can we model the coordinated biological changes associated with the menopausal transition through dynamic, system-level measures of physiological resilience? Further, does this provide a quantitative framework for studying system-wide reduction in resilience in humans?

**Novel Hypothesis:**

We hypothesize that system-level measures of physiological resilience, including estimates of stability, recovery after perturbation, and altered correlation of molecular pathways, will be associated with menopausal status in women. We further hypothesize that models developed in menopausal cohorts will generalize to broader aging populations.

**Project Proposal:**

In the Arivale cohort (~3,000 women enrolled in a scientific wellness program), we will quantify system-level measures of physiological resilience across menopausal status. Recovery dynamics will be estimated using longitudinal wearable-derived physiology by identifying real-world perturbations (e.g., deviations in sleep or activity) and quantifying time to return to baseline. Stability metrics will be derived from both longitudinal wearable data and repeated clinical

chemistry measurements, capturing within-individual variability over time. Coordination across biological subsystems will be assessed using network models constructed from multi-omics data, including microbiome, metabolomics, and proteomics, with separate networks estimated for pre- and post-menopausal women.

We will test whether stability and recovery metrics are reduced following menopause, consistent with loss of physiological resilience, and evaluate how connectivity between functional modules changes across menopausal status. Together, these analyses will determine whether dynamic, system-level measures capture coordinated biological changes associated with menopause.

To evaluate generalizability, we will test whether resilience metrics and models developed in the Arivale cohort extend to independent population-scale datasets, including All of Us and UK Biobank. We will then assess whether these measures show similar associations with age and health-related outcomes in broader populations, and whether model parameters learned in the menopausal cohort generalize to mixed-sex, population-level data.

**Description of Potential Impact:**

This project addresses a major blind spot in aging research by treating menopause as a biologically meaningful window into system-wide aging. By applying dynamical systems models to deep phenotyping data across menopausal status, this work will help reveal how multiple physiological systems shift, destabilize, and reorganize during one of the most significant transitions in adult life.

Scientifically, it will test whether methods developed to study system transitions in engineering can capture coordinated biological change in humans. Clinically, it may identify measurable signatures of instability and altered recovery that help explain why disease risk rises after menopause. More broadly, this work reframes menopause as a model for studying complex age-related change rather than an exception to it.