



## 2024 IMPACT CIRCLE

**Project Title:** Identifying Antagonistic Pleiotropy Mechanisms in Humans: Genetic Associations Between Childbirth Timing with Aging Outcomes

**Investigator(s) and collaborations:** Dr. Pankaj Kapahi

**Unmet Need/Primary Question:** The process of aging is often attributed to the diminishing impact of natural selection over time. Thus, genes associated with aging are likely to exert their effects earlier in life. The antagonistic pleiotropic (AP) theory posits that aging arises from genes that promote early growth and reproduction, leading to tradeoffs later in life, thus contributing to the aging process and age-related diseases. However, substantial evidence supporting AP in humans remains elusive. Here, we will investigate the relationship between important reproductive activity, age at first childbirth, and age-related outcomes, employing human cohort data from the UK Biobank (UKBB). The study aims to address a crucial gap in understanding genetic determinants of aging through the exploration of AP theory that could guide the development of gender-sensitive healthcare strategies for aging.

**Background:** The growing aging population and age-related adverse outcomes, particularly in females, underscore the urgency of understanding genetic determinants. Interestingly, the relationships between women's reproductive activities and their health impact can be partly explained by the AP hypothesis. For instance, genes promoting high fertility might also increase the risk of certain late-life age-related diseases, and individuals with higher polygenetic scores for reproduction have lower survivorship to age 76, which supports the AP theory and the tradeoff between reproduction and aging. This could be partly attributed to hormonal changes and their long-term impact, such as metabolic changes, leading to decreases in organ functions. Consequently, reproductive activities are associated with organ health and systemic aging. Published studies to date are mostly observational, and the research at the genetic level is limited. Thus, there is a strong rationale to understand how childbirth at various ages affects aging outcomes, with the aim of identifying an optimal age for childbirth. Such research could provide valuable insights into minimizing potential health risks associated with aging in women.

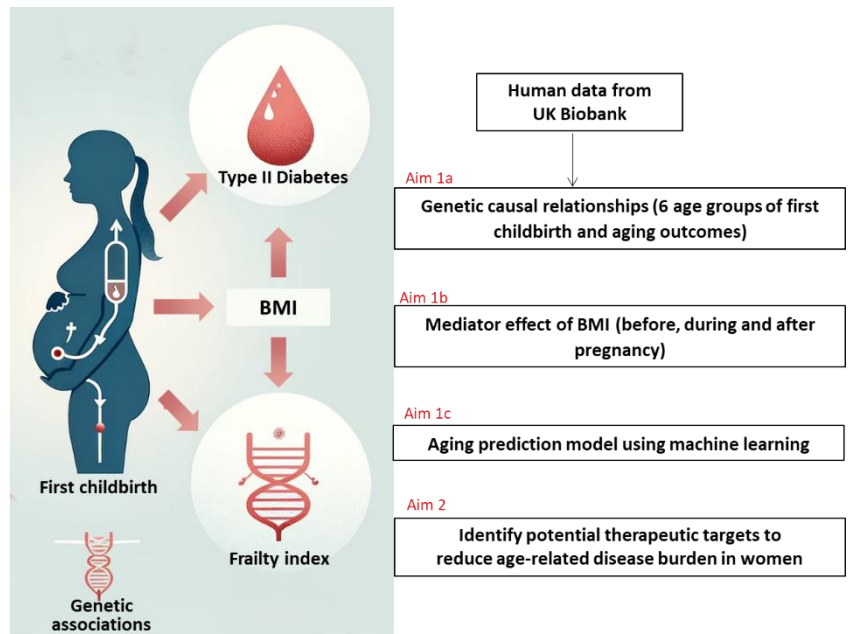
**Novel Hypothesis:** Our hypothesis builds upon the idea that AP genes, with their dual impact on both reproduction and aging, particularly in the context of early childbirth, might contribute to an elevated body mass index (BMI) and faster systemic aging. This, in turn, could potentially lead to adverse aging outcomes characterized by adverse aging outcomes, such as a heightened frailty index and an increased risk of type II diabetes (T2D).

**Project Proposal:** We will test our hypothesis through the following two specific aims:

**Aim 1: *Determine the impact of age at first childbirth on aging outcomes of different age groups with BMI as a mediator and identify AP functioning genetic loci using the Mendelian randomization (MR) approach.*** In Aim 1a we will quantify the genetic effects of first childbirth at different ages by 6 groups by

conducting MR analyses for 2 distinct aging-related outcomes: type II diabetes and frailty index. Furthermore, we will identify genetic loci for AP effects in humans, which play a key role in the genetic causal relationships. In **Aim 1b** we will use a specialized analysis technique (longitudinal mediation model) that looks at data over time, like following people from before pregnancy to after childbirth. We will focus on BMI plays a role before, during, and after pregnancy. By doing this, we hope to figure out when it's most crucial to keep BMI in check. This will help us understand if the way women age depends on their BMI during specific times in life. In **Aim 1c** we will create computer models (with machine learning methods using advanced techniques called Long Short-Term Memory networks). These models will predict how quickly someone might become frail, whether they might develop type II diabetes, and how healthy they will be as they get older. We will use information from Aim 1a and 1b as well as data before childbirth to make these predictions. **Aim 2: Identify potential therapeutic targets targeting either variant occurring in the identified candidate genetic variants or their downstream pathways to improve later-life health outcomes.** We will validate identified genetic human variants (from Aim 1) in mouse or human cellular models to test the hypothesis that increased maternal age is a contributing factor to poor metabolic health outcomes in mothers. The screen will identify promising lead compounds ready for advancement down the drug development pathway as well as new targets for future drug development efforts. Furthermore, we will identify approved drugs against some of the gene targets for their repurposed use in modulating aging outcomes.

**Description of Potential Impact:** This research could help us understand how reproductive choices can shape health trajectories in later life based on AP theory, potentially informing female childbirth guidelines. Our results could help reform gender-sensitive healthcare strategies that take into account how women's reproductive health is linked to aging through genetics. This could help create interventions to enhance women's health and lifespan. Using human genetic data-driven hypotheses to discover new drug targets makes our approach faster and more cost-effective, providing new insights into disease mechanisms and targets. Importantly, this gene-to-drugs project will be the first to use reproductive exposure-influenced genetic data as a guide for the development of gender-specific therapeutic approaches addressing women's long-term health. By doing this, we aim to develop treatments tailored to women's long-term health needs, like preventing diseases or slowing down their progression.



**Figure 1.** Left panel: A schematic showing evidence for antagonistic pleiotropy in humans from public GWAS data using Mendelian Randomization analyses. Right panel: Proposed workflow for the proposal.