**Introduction**

Infants who are born small for gestational age, or who experience early growth faltering have the opportunity for catch-up growth should environmental conditions improve (Boersma and Wit 1997; Singhal 2017; Wells 2018; Metcalfe and Monaghan 2001). Catch-up growth is marked by rapid weight or height gain following a period of restricted development (Boersma and Wit 1997; Hornick et al. 2000). During a catch-up phase, elevated growth rates allow a child to either approach or reach their genetically predetermined, “normal” growth curve (Boersma and Wit 1997). However, there is evidence that such accelerated growth may carry deleterious long-term health effects, suggesting a physiological cost of growth (Singhal 2017; Metcalfe and Monaghan 2001; Wells 2018). In this paper we investigate how these costs may present in terms of epigenetic age during adulthood

The idea that growth carries a biological cost is supported by life history theory, which treats energy as a finite resource that must be partitioned to fitness components. Organisms differentially allocate energy between growth, survival, or reproduction (Jones 2011). The optimal allocation strategy is under selection to maximize fitness. During a period of catch-up growth, it is expected that energy would be diverted away from cell maintenance. Such a process favors immediate survival and early reproduction over future survival, thus decreasing long-term life expectancy (Wells 2018; Metcalfe and Monaghan 2001).

To measure a possible cost of growth, we will look at adult epigenetic age and determine if individuals who experienced childhood catch-up growth appear biologically older than expected. Epigenetic age, or DNAm age, is measured by the proportion of methylated CpG sites within the DNA of a given sample (Ryan 2021; Horvath and Raj 2018). DNA methylation occurs at predictable rates, allowing for an accurate estimate of chronological age, and a proxy for predicting life-cycle changes (Ryan 2021) Bocklandt et al 2011). Deviations from chronological age, however, do occur. An individual who appears epigenetically older than anticipated displays positive age acceleration-- a phenomenon which predicts mortality risk among adults (Horvath and Raj 2018; Ryan 2021; Simpkin et al. 2016; ).

Epigenetic age increases more rapidly during periods of growth, and is associated with certain childhood developmental changes (Horvath and Raj 2018; Simpkin et al. 2016; 2017). Childhood and adolescent accelerated epigenetic age can persist into adulthood, where it predicts elevated mortality (Horvath and Raj 2018). There is also evidence to suggest that early catch-up growth is indicative of non communicable disease risk and a shorter lifespan (Metcalfe and Monaghan 2001; Singhal 2017; Wells 2018). It has been acknowledged, however, that the relationship between catch-up growth and life expectancy is difficult to measure because of both confounding variables and ethical concerns (Lee, Monaghan, and Metcalfe 2013; Boersma and Wit 1997). Our study aims to answer this question by relating catch-up growth to positive age acceleration with data from the Cebu Longitudinal Health and Nutrition Survey. We predict a positive relationship between early growth rate and epigenetic age in adulthood. This association would indicate a biological cost of growth, and a life-history tradeoff between cell maintenance and development.

This is a very good start!

All the pieces are there – I might restructure a bit to make sure we have the background, and are not backtracking. Something like the following:

* P1. Evolutionary life history posits tradeoffs between biological functions, including growth, reproduction, and maintenance. Investment in one, such as growth, may come at the expense of another, such as maintenance (so your second paragraph, reframed a bit to lead with life history theory more generally).
* P2. Individuals who are born small have the opportunity to catch-up in their growth, but this may detract from maintenance when… However, this may detract from health of the individual…(so basically your first paragraph). For example, in birds…or something. Flesh this out a bit.
* P3. Catch up growth in humans does occur. Examples of apparent health ‘costs’ of catch up growth. However, it is still unclear how catch-up growth affects the aging process, and how early the costs of catch-up growth can be detected.
* P4. Studying the impacts of catch-up growth on aging often relies on long-term studies, which are expensive and logistically challenging. What is needed are measures of biological aging that can be used to measure the pace of aging and providing an index of health and longevity long before health consequences are known. A recent biomarker of aging called epigenetic clocks may provide such a measure. Epigenetic clocks are are based on DNAm. DNAm is this.
* P5. Here, we used epigenetic clocks in 500 young adults, to study the impact of catch up growth on rate of aging.

Goal: to study the potential life-history costs of accelerated aging. To observe the effect of post-natal and childhood compensatory growth on adult epigenetic age.

Question: Is there a cost to accelerated growth rate during infancy and or childhood, and are these increased growth rates associated with higher levels of DNA methylation in adulthood?

Hypothesis: Early compensatory growth is predicted to be associated with accelerated epigenetic age in adulthood.

Connect to epigenetic age which is a strong predictor of non communicable disease risk and mortality.

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