Developmental milestones in early life are associated with both short- and long-term health consequences (ref). Early gestational age at birth increases the risk for short-term complications, including respiratory conditions and cardiovascular complications [1, 2]. For example, early gestational age at birth of infants predicts the two largest causes of death in premature infants: underdevelopment of mature organs and bronchopulmonary dysplasia, a chronic lung disease that damages alveolar tissue. [2]. Low birthweights are also associated with long-term familial stress and incidence of developmental and behavioral problems [3-5]. Specifically, infants of lower birthweight were found to have significantly lower IQ scores and display more anxiety, attention problems, and internalizing behavior [4]. Gaining a better understanding of the factors that contribute to early life developmental trajectories and fetal outcomes is an important medical concern.

Older chronological maternal age is correlated with increased rates of adverse birth outcomes, including decreased birth weight, length, head circumference, and body fat [6-10]. Pregnancy-related complications such as preeclampsia and placental disorders such as placental abruption are more likely to occur in older mothers [9, 10]. These two conditions increase the risk of adverse fetal outcomes, suggesting that the maternal aging process may influence fetal outcomes, thus influencing life-long health and subsequent generational mortality risks [6, 8].

Chronological aging provides an important measure of the aging process in mothers. Nonetheless, age-associated deterioration and mortality risks vary between individuals of the same chronological age. For example, some individuals living in their 80’s (in terms of chronological age) may require assistance in daily activities while others with the same chronological age may continue functioning independently. This variation, also known as biological age, combines both environmental and genetic factors and may better elucidate the effect of the maternal aging process on fetal outcomes than chronological age alone [11-13]. In fact, several studies suggest that maternal biological age may impact the early developmental outcomes of offspring [14-16]. Prenatal maternal telomere length, a marker of cellular age, has been found to be associated with an increased likelihood of adverse birth outcomes [14, 16]. Nonetheless, the role of biological aging on fetal outcomes has yet to be widely explored.

Recently, epigenomic changes have emerged as accurate indicators of biological age. These measures, also known as epigenetic clocks, utilize changes in the epigenome – particularly DNA methylation (DNAm), the methylation of cytosine-phosphate-guanine (CpG) sites on DNA. These changes are more commonly known as epigenetic age and utilize epigenetic clocks that appear to serve as good proxies for biological aging across multiple physiological and functional systems.

A number of epigenetic clocks have been generated, and each appears to capture different aspects of biological age. For example, the acceleration of the Levine-DNAmPhenoAge clock (PhenoAge) is highly predictive of cardiovascular disease, poorer likelihood of being free of disease, and presentation of coexisting morbidities. [17] The acceleration of the Lu-DNAmGrimAge clock (GrimAge) predicts specific cardiovascular conditions, such as hypertension, Type II diabetes, and overall poorer physical functioning. [18, 19] The acceleration of both the Hannum-Extrinsic Epigenetic Age Acceleration (Hannum-EEAA) and the Horvath-Intrinsic Epigenetic Age Acceleration (Horvath-IEAA) clocks has predicted all-cause mortality. [20-22] Furthermore, accelerated placental aging measured by the Horvath-IEAA clock has also been associated with lower birthweight. [23] As a result, these epigenetic clocks may serve as powerful tools to study the intergenerational effects of biological aging in mothers above and beyond chronological age.

One small study (n = 77) among Californian women demonstrated that advanced epigenetic age is associated with early gestational age at birth and low birthweight, suggesting that epigenetic age may be predictive of adverse fetal outcomes [24]. There is, however, minimal study in a large, socioeconomically diverse population with greater rates of adverse fetal outcomes that tests the relationship between maternal epigenetic age and fetal outcomes. The purpose of this paper is to conduct an analysis of maternal epigenetic age measured during pregnancies and birth outcomes in collaboration with the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a cohort following a large, diverse sample of women and their offspring in Cebu, Philippines for over 35 years [25]. In particular, the analysis was conducted on the pregnancies of 330 expecting female young adults and their newborn children between 2009 and 2014. To capture the maternal epigenetic age, the Hannum-EEAA, Horvath-IEAA, PhenoAge, and GrimAge clocks were utilized. It was hypothesized that advanced maternal epigenetic age would be associated with adverse fetal outcomes, including decreased birthweight, length, arm circumference, head circumference, abdominal circumference, and total skin fold thickness.

1. Escobar, G.J., R.H. Clark, and J.D. Greene, *Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions.* Semin Perinatol, 2006. **30**(1): p. 28-33.

2. Patel, R.M., *Short- and Long-Term Outcomes for Extremely Preterm Infants.* Am J Perinatol, 2016. **33**(3): p. 318-28.

3. Hack, M., N.K. Klein, and H.G. Taylor, *Long-term developmental outcomes of low birth weight infants.* Future Child, 1995. **5**(1): p. 176-96.

4. Hollanders, J.J., et al., *Long-Term Neurodevelopmental and Functional Outcomes of Infants Born Very Preterm and/or with a Very Low Birth Weight.* Neonatology, 2019. **115**(4): p. 310-319.

5. Taylor, H.G., et al., *Long-term family outcomes for children with very low birth weights.* Arch Pediatr Adolesc Med, 2001. **155**(2): p. 155-61.

6. Eichelberger, K.Y., *On odds, age, and preterm birth.* BJOG, 2017. **124**(8): p. 1245.

7. Fuchs, F., et al., *Effect of maternal age on the risk of preterm birth: A large cohort study.* PLoS One, 2018. **13**(1): p. e0191002.

8. Joseph, K.S., et al., *The perinatal effects of delayed childbearing.* Obstet Gynecol, 2005. **105**(6): p. 1410-8.

9. Kenny, L.C., et al., *Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort.* PLoS One, 2013. **8**(2): p. e56583.

10. Scime, N.V., et al., *Pregnancy complications and risk of preterm birth according to maternal age: A population-based study of delivery hospitalizations in Alberta.* Acta Obstet Gynecol Scand, 2020. **99**(4): p. 459-468.

11. Jylhava, J., N.L. Pedersen, and S. Hagg, *Biological Age Predictors.* EBioMedicine, 2017. **21**: p. 29-36.

12. Ryan, C.P., *"Epigenetic clocks": Theory and applications in human biology.* Am J Hum Biol, 2021. **33**(3): p. e23488.

13. Levine, M.E., *Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age?* J Gerontol A Biol Sci Med Sci, 2013. **68**(6): p. 667-74.

14. Akkad, A., et al., *Telomere length in small-for-gestational-age babies.* BJOG, 2006. **113**(3): p. 318-23.

15. Bell, J.T., et al., *Epigenome-wide scans identify differentially methylated regions for age and age-related phenotypes in a healthy ageing population.* PLoS Genet, 2012. **8**(4): p. e1002629.

16. Hanna, C.W., et al., *Telomere length and reproductive aging.* Hum Reprod, 2009. **24**(5): p. 1206-11.

17. Levine, M.E., et al., *An epigenetic biomarker of aging for lifespan and healthspan.* Aging (Albany NY), 2018. **10**(4): p. 573-591.

18. Hillary, R.F., et al., *Epigenetic measures of ageing predict the prevalence and incidence of leading causes of death and disease burden.* Clin Epigenetics, 2020. **12**(1): p. 115.

19. Lu, A.T., et al., *DNA methylation GrimAge strongly predicts lifespan and healthspan.* Aging (Albany NY), 2019. **11**(2): p. 303-327.

20. Chen, B.H., et al., *DNA methylation-based measures of biological age: meta-analysis predicting time to death.* Aging (Albany NY), 2016. **8**(9): p. 1844-1865.

21. Breitling, L.P., et al., *Frailty is associated with the epigenetic clock but not with telomere length in a German cohort.* Clin Epigenetics, 2016. **8**: p. 21.

22. Marioni, R.E., et al., *DNA methylation age of blood predicts all-cause mortality in later life.* Genome Biol, 2015. **16**: p. 25.

23. Tekola-Ayele, F., et al., *Sex differences in the associations of placental epigenetic aging with fetal growth.* Aging (Albany NY), 2019. **11**(15): p. 5412-5432.

24. Ross, K.M., et al., *Epigenetic age and pregnancy outcomes: GrimAge acceleration is associated with shorter gestational length and lower birthweight.* Clin Epigenetics, 2020. **12**(1): p. 120.

25. Adair, L.S., et al., *Cohort profile: the Cebu longitudinal health and nutrition survey.* Int J Epidemiol, 2011. **40**(3): p. 619-25.