Developmental milestones in early life are associated with both short- and long-term health consequences. Decreased gestational age at birth is associated with short-term complications, including respiratory conditions and cardiovascular complications [1, 2]. For example, bronchopulmonary dysplasia is highly associated with infants born at an early gestational age and is the second-largest cause of death in premature infants after underdevelopment of mature organs [2]. Furthermore, low birthweights were 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. 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, 12]. In fact, several studies suggest that maternal biological age may impact the early developmental outcomes of offspring [13-17]. Prenatal maternal telomere length, a marker of cellular age, has been found to be associated with an increased likelihood of adverse birth outcomes [13, 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. Specific CpG sites have been used to strongly predict biological age [12, 14, 18-21]. These changes are more commonly known as epigenetic age and may serve as powerful tools to study the intergenerational effects of biological aging in mothers above and beyond chronological age.

Studies have 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 [15, 17]. 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 clock-calculated biological age and fetal outcomes. The purpose of this paper is to conduct an analysis of maternal epigenetic clock-calculated biological 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 [22]. In particular, the analysis was conducted on the pregnancies of expecting female young adults and their newborn children between 2009 and 2014.

This is good. The other piece of this puzzle will be to outline the clocks we will look at a tiny bit. I think you might do this in the intro to epigenetic clocks section. A number of clocks have been generated, and each appears to capture different aspects of BA. For example….

Then when you come back to this in the “Here, we examined epigenetic age in 330 women…” you can say, to capture XYZ we looked at clocks A, B, and C.

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