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.

Maternal chronological age contributes to 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 also increase the risk of adverse fetal outcomes, suggesting that the maternal aging process may influence fetal outcomes, and by extension life-long health and inter-generational mortality risks [6, 8].

Chronological age provides an important measure of the aging process, but heterogeneity in frailty, disease prevalence, and all-cause mortality vary even between individuals sharing the same chronological age (refs).This variation, often referred to as biological age, may better reflect the fundamental balance between deterioration and resiliency thought to underlie aging, and may help to explain the relationship between maternal chronological age and fetal outcomes [11-13]. For example, prenatal maternal telomere length, a marker of cellular age, is associated with an increased likelihood of adverse birth outcomes, including X, Y, and Z [14, 16]. Nonetheless, the relationship between telomere length and many clinical measures of aging is modest, and the role of biological aging on fetal outcomes using othe proxies has yet to be widely explored.

Recently, epigenomic changes have emerged as exceptionally accurate indicators of biological age. These measures, also known as epigenetic clocks, utilize changes in the epigenome – particularly DNA methylation (DNAm) – to predict chronological age (ref), physiological aging (ref), and mortality (ref). Epigenetic clocks have been found serve as good proxies for biological aging across multiple physiological and functional systems, making them powerful markers for studying the effect of maternal biological age on offspring health and developmental outcomes. 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 study (n = 77) among a subset of American women found 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 to adequately test the relationship between maternal epigenetic age and fetal outcomes.

Here, we examine the relationship between maternal epigenetic age measured during pregnancy and birth outcomes among young Filipino women (n = 330 or so). These women are long-term participants in the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a 3-generation, 30+ year study in Cebu Metropolitan Area[25]. This analysis focuses on pregnancies of 330 expecting young women and their newborn children between 2009 and 2014. Epigenome-wide DNAm was measured using the Illumina EPIC array. Maternal biological age was measured using the Hannum-EEAA, Horvath-IEAA, PhenoAge, and GrimAge clocks. We 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.

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