Birth outcomes like birth weight, length and gestational timing are strong predictors of both short- and long-term health. For example, early gestational age at birth 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 [1, 2]. In addition, the field of the Developmental Origins of Health and Disease (DOHaD) has established that being born small also predicts elevated long-term risk for developing respiratory conditions like idiopathic lung disease and chronic metabolic diseases like hypertension, diabetes, and other cardiovascular diseases [2-6]. Experimental work with animal models shows that restricting prenatal nutrition, or imposing acute stress during pregnancy, replicates many of these long-term outcomes in offspring, showing that gestational conditions can have lasting effects on health in the next generation [7, 8].

While nutrition has received broadest attention for its role in fetal growth, there is growing evidence that the mother’s physiology and metabolism, including systems like stress physiology and inflammation, can impact fetal growth and development operating through effects on gestational conditions like nutrient delivery, oxidative stress or exposure to metabolic or other hormones [9]. As a result, disturbances in the normal levels and amounts of exposure of these biological effectors may produce altered structure, function, and adverse outcomes [10]. As a common example, dysregulation of the hypothalamic-pituitary axis (HPA) during pregnancy is associated with increased levels of maternal cortisol, which elevates risks for premature delivery and low birth weight and can cross the placenta to have direct “programming” effects on fetal metabolism and physiology [11, 12]. Hypertension has been shown to lead to lower birth weights, likely operating through factors like altered blood flow, along with the common co-occurrence of elevated inflammatory cytokines that can suppress growth [13, 14]. Conversely, dysregulated glucose homeostasis, as reflected in uncontrolled diabetes during pregnancy, increases delivery of glucose across the placenta, and can lead to larger than expected newborns with elevated risk of developing obesity and diabetes in as adults [15, 16].

A newly-described set of tools called epigenetic clocks have recently been shown to reflect various domains of maternal physiology and metabolism, and thus could be useful for gauging the intergenerational impacts of chronic maternal physiologic and metabolic dysregulation. Epigenetic clocks are calculated using predictable age-related changes in the epigenome – particularly DNA methylation (DNAm), the methylation of cytosine-phosphate-guanine (CpG) sites on DNA. Although commonly-used epigenetic clocks are notable for their ability to predict one’s chronological age, individuals who appear older epigenetically than their chronological age, a state known as epigenetic age acceleration (EAA), tend to have increased risk for future mortality and to have shorter expectancies. Other clocks have been trained on suites of clinical markers and have been shown to be particularly powerful predictors of life expectancy and the pace of biological aging.

Since epigenetic clocks can be trained on effectively any set of metabolic/physiological processes or states, they are a powerful tool to characterize these states by providing integrative, summary information on a mother’s metabolic and physiological state and measuring the associated “wear-and-tear” on the next generation. One small study (n = 77) among Californian women demonstrated that advanced maternal epigenetic age is associated with early gestational age at birth and low birthweight in offspring, suggesting that epigenetic age may be predictive of adverse fetal outcomes [17]. To date, little is known about the potential for these measures to predict outcomes in a socioeconomically diverse population with greater rates of adverse fetal outcomes.

In this paper, we analyze several prominently used epigenetic clocks, obtained during pregnancies, in relation to longitudinally collected birth outcomes in the offspring of those pregnancies. Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a cohort study that has followed a large, diverse sample of women and their offspring in metropolitan Cebu City, Philippines for nearly four decades [18]. The present analyses focus on pregnancies of 330 expecting female young adults and their newborns born between 2009 and 2014. We used four published epigenetic clocks to provide complementary information on the mother’s chronic biological dysregulation, as reflected in the degree of accelerated biological aging. EAA using the Levine-DNAmPhenoAge clock (PhenoAge) has been shown to be highly predictive of cardiovascular disease, a poorer likelihood of being free of disease, and to be afflicted with additional morbidities [19]. Acceleration of the Lu-DNAmGrimAge clock (GrimAge) similarly predicts specific cardiovascular conditions, such as hypertension, Type II diabetes, and overall poorer physical functioning [20, 21]. EAA using both the Hannum-Extrinsic Epigenetic Age Acceleration (Hannum-EEAA) and the Horvath-Intrinsic Epigenetic Age Acceleration (Horvath-IEAA) clocks have predicted all-cause mortality [22-25]. We hypothesized that advanced maternal EAA based upon such indices would predict adverse fetal outcomes, including decreased gestational age and measured weight. We further anticipated a gradient of impact, with skinfolds being most labile and sensitive, followed by weight, length and finally, the most canalized outcome of head circumference.

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