**Introduction**

Birth outcomes like birth weight, length and gestational age predict 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 early and small for gestational age 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 (Levine et al. 2018, Lu et al. 2019; Belsky et al. 2020).

Since epigenetic clocks can be trained on effectively any set of metabolic/physiological processes or states, they are powerful tools for characterizing these states by providing integrative, summary information on a mother’s metabolic and physiological state and for measuring the potential impact of maternal “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]. A more recent study of American women found a link between epigenetic age and gestational age at birth, but in the opposite direction, and only among a subset of women (Lancaster et al.). To date, little is known about the potential for these measures to predict outcomes in more socioecologically diverse populations with more varied reproductive histories and greater rates of adverse fetal outcomes.

In this paper, we analyze 13 prominently used epigenetic clocks, obtained during pregnancy, 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 examined 13 published epigenetic clocks to provide complementary information on the mother’s chronic biological dysregulation, and to attempt to replicate previous analyses using smaller, less diverse samples. Clocks included two first generation epigenetic clocks trained on chronological age (Horvath 2013, Hannum 2013), two second generation clocks trained on mortality risk (Levine et al. 2018; Lu et al) and 9 clocks trained on clinical biomarkers that are themselves linked with morbidity and mortality (Lu et al. 2019; Lu et al. 2019). 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.

**Methods**

*Study sample and design*

Data originate from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a longitudinal survey of 3,080 infants and their mothers who were recruited during their pregnancies between 1983-1984 in Metropolitan Cebu, Philippines. Out of the 1447 original female cohort infants, 823 were interviewed in a later 2009 survey (at ages 25-26). This additional survey tracked new pregnancies among these women between 2009-14. There were 383 who reported pregnancies (28% with 2-3 pregnancies) within the tracking period, yielding 507 pregnancies. Women were visited in-home during pregnancy for anthropometric and questionnaire assessments, along with collection of a dried blood spot (DBS)—capillary whole blood collected on filter paper—for DNAm measurement. A second visit was arranged soon after delivery to obtain additional information from the mothers and to obtain phenotypic measures of their newborns. Newborn anthropometric outcomes included weight, length, head circumference, arm circumference, abdominal circumference, and five skinfold thicknesses (triceps, subscapular, suprailiac, bicep and calf), which were measured in-home by trained interviewers using standardized procedures [reference later] as soon after birth as possible. All research was conducted under conditions of written informed consent, and with approval of the Institutional Review Boards of Northwestern University (Evanston, Illinois), and the Office of Population Studies Foundation (Cebu, Philippines).

*Variable construction*

A composite score of socioeconomic status was measured as a combination of income, education, and assets. Participants reported their annual income from all sources, including in-kind services, and the sale of livestock or other products by household members during the prior year, which were summed to determine total household income. Incomes were log-transformed. Maternal education (in years) was also reported. Participants also reported on ten assets (coded 0, 1) that were selected to capture population-relevant aspects of social class, including electricity, refrigerators, air conditioners, color televisions, cable tv, tape recorders, electric fans, jeepneys, cars, trucks, and owning their residence. In addition, house construction type (i.e., light, mixed, permanent structure) was coded as 1, 2, or 3, respectively. Thus, asset scores ranged from 0 to 13. A principal components analysis was run on log income and assets, along with maternal education, at sample collection. The first component of 70% of the variation, and individual scores for the top component of variation were used as our measure of SES.

Because women were enrolled in the birth outcome sub-study after they were pregnant, we used height and weight measurements collected during prior surveys to estimate pre-pregnancy BMI. We used 2009 BMI when available, and then used 2007 and 2005 data as necessary. Under the assumption that women will tend to maintain a stable position within the population BMI distribution even as the population mean increases with age, we converted all BMIs to age-specific within-sample Z-scores before pooling into a single pre-pregnancy BMI variable. Supporting the validity of this approach, the correlation between Z-scores for BMI measured in 2005 and 2009 was very high (r=0.84). Offspring gestation age was calculated using the time between the last reported menstrual period and infant birth date. Days pregnant at maternal blood sampling was determined by subtracting the time between the blood sample and infant birth date from gestation age. Descriptive statistics of anthropometric measurements and other covariates are provided in Table 1.

*Sample inclusion criteria*

Women for the present study were selected based on reproductive history and sample availability for DNAm measurement. DNAm was measured for a total of 334 women and only women with complete information for all variables were included. For each woman, the last pregnancy during the 2009-2014 tracking period was used unless inadequate DBS sample remained, in which case a blood sample from an earlier pregnancy was used. Fifteen women were missing pre-pregnancy BMI, 2 women were missing data on offspring developmental outcomes, and DNAm for one woman did not pass quality control, and these women were excluded. Analyses were further limited to women with newborns with gestational ages between 32 and 44 weeks, which excluded 5 very premature births, and 10 late deliveries between 45-53 weeks. To minimize impacts of the infant’s environment and growth after birth, analyses of infants were also limited to those measured within 2 weeks of birth and models adjusted for age at measurement ( 4 individuals measured more than 2 weeks after birth were excluded). After all exclusions, the final sample with all necessary biological and questionnaire data included 297 women singleton births with complete information.

*DNA methylation sample processing and epigenetic clock calculation*

DNA was extracted from dried blood spots (DBS) using a standard protocol. 750ng of genomic DNA was treated with sodium bisulfite (Zymo EZDNA, Zymo Research, Irvine, CA, USA), and 160ng of converted DNA was applied to the Illumina Infinium MethylationEPIC BeadChip under standard conditions (Illumina Inc., San Diego, CA). Technicians were blind to any information regarding participant characteristics, and samples were randomly assigned to plate, chip, and row. Background subtraction and color correction were performed using Illumina Genome Studio with default parameters. Data were then exported into R for further analysis. Quality control involved first confirming participant sex and replicate status. This was followed by quantile normalization using lumi on all probes including SNP-associated and XY multiple binding probes. To maximize the number of sites available for the epigenetic age calculator, probes with detection p-values above 0.01 were called NA for poor performing samples only, and were otherwise retained. DNAmAge for all clocks were calculated using an online calculator (http://labs.genetics.ucla.edu/horvath/dnamage/), designed to be generally robust to cell-type differ- ences associated with age. Background-corrected beta values were processed further using the calculator’s internal normalization algorithms.In all cases, maternal epigenetic age acceleration (EAA), which is the residual of epigenetic age on chronological age, was used.

*Statistical analysis*

We ran a sequence of multivariate linear regression models designed to assess relationships between maternal epigenetic age acceleration and two fetal outcomes (gestational age and measured weight after birth). We also ran a set of secondary analyses on a set of alternative measures of infant growth and development: infant length, arm circumference, abdominal circumference, head circumference, and the sum of skin fold thickness (Supplementary materials). Models predicting postnatal outcomes were adjusted for days after birth of anthropometry measurement, gestational age at birth, offspring gender, composite socioeconomic status score. Because birth outcomes are potentially impacted by the mother’s adiposity, we also adjusted for the mother’s pre-pregnancy body mass index (BMI) z-scores. All statistical analyses were conducted using R.

**Results**

* Sample characteristics table?

Yes. Make a table with mean, sd, median, range (min and max) for maternal age at blood draw, weeks pregnant at blood draw, maternal pre-pregnancy BMI, maternal education in years (if we have it), smoking behavior (y/n). Also, have a slightly different section below with the same metrics for gestational age, infant weight, sex makeup (proportion of males), average age measured.

* Regression Models Summary table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | Predictor | b | SE | β | p |
| Gestational Age | IEAA | 0.17 | 0.23 | 0.04 | 0.47 |
|  | EEAA | -0.16 | 0.29 | -0.03 | 0.58 |
|  | PEAA | -0.03 | 0.19 | -0.01 | 0.87 |
|  | GrimAgeAccel | -0.43 | 0.36 | -0.07 | 0.24 |
|  | DNAm ADM | -0.14 | 0.06 | -0.12 | **0.03** |
|  | DNAm B2M | 0.00 | 0.00 | -0.05 | 0.38 |
|  | DNAm Cystatin C | 0.00 | 0.00 | -0.06 | 0.31 |
|  | DNAm GDF | 0.00 | 0.01 | 0.01 | 0.88 |
|  | DNAm Leptin | 0.00 | 0.00 | -0.17 | **0.004** |
|  | DNAm Smoking Pack Years | -0.04 | 0.18 | -0.01 | 0.81 |
|  | DNAm PAI-1 | 0.00 | 0.00 | -0.01 | 0.85 |
|  | DNAm TIMP1 | 0.00 | 0.00 | -0.03 | 0.60 |
|  | DNAm TL | -9.43 | 7.52 | -0.07 | 0.21 |
| Measured Weight | IEAA | 0.00 | 0.01 | 0.04 | 0.51 |
|  | EEAA | -0.01 | 0.01 | -0.08 | 0.15 |
|  | PEAA | 0.00 | 0.01 | -0.03 | 0.58 |
|  | GrimAgeAccel | 0.02 | 0.01 | 0.09 | 0.10 |
|  | DNAm ADM | 0.00 | 0.00 | 0.08 | 0.14 |
|  | DNAm B2M | 0.00 | 0.00 | 0.00 | 0.95 |
|  | DNAm Cystatin C | 0.00 | 0.00 | 0.02 | 0.67 |
|  | DNAm GDF | 0.00 | 0.00 | 0.01 | 0.86 |
|  | DNAm Leptin | 0.00 | 0.00 | 0.01 | 0.79 |
|  | DNAm Smoking Pack Years | 0.01 | 0.01 | 0.08 | 0.12 |
|  | DNAm PAI-1 | 0.00 | 0.00 | 0.01 | 0.82 |
|  | DNAm TIMP1 | 0.00 | 0.00 | 0.05 | 0.37 |
|  | DNAm TL | 0.21 | 0.22 | 0.05 | 0.34 |

**Discussion**

Adverse birth outcomes, such as early gestational age and low birth weight can have lasting effects on morbidity and mortality, even into adulthood. Being able to predict birth outcomes and the factors that contribute to them early on is therefore an important goal in clinical medicine and public health. Epigenetic clocks, which have emerged as powerful tools for quantifying biological aging and physiological dysregulation, hold great promise for studying the relationship between maternal and infant health, and in predicting birth outcomes. Nevertheless, evidence that maternal epigenetic age can predict birth outcomes remains scarce, and has been largely confined to women in affluent societies with relatively low rates of adverse birth outcomes. We sought to replicate and expand on previous studies by studying the relationship between maternal epigenetic clocks and birth outcomes in a large and socioeconomically diverse sample of women in the Philippines.

We found little evidence that maternal epigenetic age during pregnancy predicts offspring birth weight, or most other measures of infant body size or composition. Maternal DNAm TL – a proxy of telomere length and replicative senescence – was positively associated with infant length shortly after birth, but no other measures of offspring size. There was some evidence for a positive correlation between maternal DNAm GrimAge and infant weight and length, but these findings did not pass the threshold for statistical significance after correcting for pre-pregnancy BMI, and were in the opposite direction as those reported by Ross et al. (2020).

Of the DNAm clocks previously associated with gestational age, DNAm ADM showed the greatest evidence for an association with birth outcomes. DNAm ADM was significantly associated with body length shortly after birth, and marginally but non-significantly associated with gestation age and body weight shortly after birth. DNAm ADM is trained on adrenomedullin, a peptide hormone involved in angiogenesis, vasodilation, and tolerance to oxidative stress and hypoxia (REF). ADM levels are higher among pregnant women compared to non-pregnant women, increase throughout pregnancy, and are higher in multiple pregnancies (i.e. in twins and triplets compared to singletons) (Shinozaki et al.). Both maternal and fetal tissues express ADM, and there is some evidence that ADM levels are lower among pre-eclamptic relative to normotensive pregnancies (Li et al. 2003). This implies that ADM levels plays a role in fetal hemodynamics in both normal and pathological pregnancies, possibly helping to explain our findings related to gestational age (Albrecht and Pepe 2015). ADM is released in response to hypoxia, which could arise through insufficient remodeling of the maternal uteroplacental spiral arteries by the trophoblast (Marinoni et al. 2011), a trait that can in turn can lead to fetal growth restriction and preterm birth. Thus, both high or low ADM levels during pregnancy may reflect dysregulated fetal-maternal hemodynamics and a risk for preterm birth (REF). Although the relationship between DNAm ADM and gestational age (or infant weight) did not pass the threshold for statistical significance in our study, the direction and phenotype are consistent with findings previously reported by Ross et al. (2020), supporting the possibility that adrenomedullin or its surrogate DNAm clock could provide an early prognostic marker of gestational age.

We also identified a significant negative relationship between gestational age and DNAm leptin, a finding that has not been previously reported. Leptin – a peptide hormone secreted from white adipocytes but also fetal and placental tissues – is a key regulator of food intake and energetic expenditure (Albrecht and Pepe 2015). Leptin is important in placentation and maternal metabolic homeostasis during pregnancy (Tessier et al. 2013). Late pregnancy is associated with leptin resistance and elevated leptin levels, necessary to meet the energetic requirements of the rapidly growing late-stage fetus. To the extent that DNAm leptin is a proxy of circulating leptin levels (Lu et al. 2019), and higher leptin during pregnancy is a result of leptin resistance, a negative relationship between DNAm leptin and gestation age could indicate a compensatory response of the fetus to insufficient nutrient availability. Inadequate placentation due to deficient invasion of the spiral arteries is a major cause of such nutritional stress as well as preterm birth, and would be consistent with our findings and those of Ross et al. for DNAm ADM. Although we controlled for pre-pregnancy body mass index, higher leptin predicting gestation age might be expected to be particularly common in cases of maternal obesity, where pre-pregnancy leptin resistance can elevate baseline leptin levels and exacerbate pregnancy-induced leptin resistance.

To our knowledge, ours is the largest study of commonly-used epigenetic clocks and birth outcomes to date, and the only one outside of affluent, Western settings where fertility tends to be low and adverse birth outcomes relatively uncommon (REF). For example, contrasting with prior work where primiparous women made up 61% of the sample (Ross et al.), only 14% of women in our study were primiparous. Furthermore, our sample exhibited a great deal of variability in fertility, with over 15% having been pregnant 5 or more times and more than half having been pregnant 3 or more times. Variation in fertility and study context are important because placentation and corresponding birth outcomes are affected by birth order, and because epigenetic age varies across socioecological contexts (Horvath, Gurven et al).

Our study is not without limitations. We were unable to acquire reliable measures of birth weight, length, or size immediately after birth due to the diversity of the sample, birth contexts, and geographic spread across the Cebu Metropolitan area. Thus, our measures of weight and length taken in infants are only proxies for outcomes measured at the time of birth. We minimized the potential for this to affect our results by including on infants measured within 2-weeks of birth, and our approach has the benefit of all measurements being taken in triplicate by experienced staff using the same protocols. Another limitation was that our blood samples were not taken at the same time during pregnancy for each woman. This may be important because prior work has demonstrated that DNAm in general and epigenetic age specifically and their relationship with birth outcomes can change during pregnancy (Ryan et al.; Ryan et al. EMPH; Lancaster). Nevertheless, our blood sampling fell within a relatively narrow range of 23-41 weeks.

One study of 77 Californian women found a relationship between four epigenetic clocks and gestational age and birthweight (Ross et al.). However, no effect was found for the other nine clocks examined, and no correction for multiple comparisons was used, making the robustness of these findings unclear. A more recent study among American women examined the relationship between maternal epigenetic age using Horvath’s clock and infant gestational age. A positive relationship between maternal epigenetic age and gestational age – opposite that predicted – was found, and appeared to be confined to a subset of women who identified as African American (Lancaster et al. 2021).

Our study is the largest to date

But this could also be an artifact. Because we sought to replicate previous work, and with the understanding that multiple clocks pointing in the same direction would be consistent with accelerated cellular aging in mom affecting offspring development, we did not correct for multiple testing. Our finding with leptin is not enough to support that, and the biological pathways to help explain how leptin would lead to offspring outcomes are not obvious.

I can help with this. We’re going to start with a quick overview of the background (like 1-2 sentences that summarizes the intro. Why did we do this?). Then we quickly mention Ross et al. “a paper among 75 women found x” or something. Mention the Lancaster paper. We sought to test for the effect of maternal biological age on offspring development and replicate previous research expanded this analysis in a larger, more diverse sample of women in the Philippines. We found nothing for any of the major epigenetic clocks, suggesting that maternal cellular aging is not associated with offspring developmental outcomes.

We can start by highlighting some of the strengths of our study. Yet we found nada for most clocks. There were two exceptions. ADM and leptin clocks. Break down the ADM finding. We will need to go into the biology of ADM – what does it mean and how might it be related to pregnancy/birth outcomes. We will then talk about leptin clock. We can think about some potential biological reasons for the relationship between leptin and gestation. But this could also be an artifact. Because we sought to replicate previous work, and with the understanding that multiple clocks pointing in the same direction would be consistent with accelerated cellular aging in mom affecting offspring development, we did not correct for multiple testing. Our finding with leptin is not enough to support that, and the biological pathways to help explain how leptin would lead to offspring outcomes are not obvious.

**Conclusions**

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