Multigenerational Cardiometabolic Risk as a Predictor of Birth Outcomes: The Bogalusa Heart Study

Emily W. Harville, PhD[1], Marni B. Jacobs, PhD[2], Lu Qi, MD[1], Wei Chen, MD[1], and Lydia A. Bazzano, MD[1]

Objective To examine the relationship between generation 1 (grandmaternal) cardiometabolic risk factors and generation 3 (grandchild's) birthweight and gestational age.

Study Design Mother-daughter pairs in the Bogalusa Heart Study (1973-present) were linked to their children's birth certificates; women were also interviewed about their reproductive histories, creating a 3-generation linkage including 177 generation 1 (grandmothers), 210 generation 2 (mothers), and 424 generation 3 (children). Prepregnancy cardiometabolic risk factors (body mass index [BMI], lipids, glucose) or generation 1 (mean age 16.2 years) and 2 (mean age 11.1 years) were examined as predictors of generation 3 birthweight and gestational age using linear and logistic regression with adjustment for age, race, parity, and other confounders.

Results Generation 2 higher BMI was associated with higher birthweight (28 g per 1 unit, 95% CI 12-44) and gestational age (0.08 weeks, 95% CI 0.02-0.14) in generation 3, and generation 1 higher BMI was associated with higher birthweight (52 g, 95% CI 34-70) in the generation 2. Generation 1's higher glucose levels were associated with higher birthweight in generation 3 (adjusted beta 111 g, 95% CI 33-189), and triglycerides (adjusted beta –21, 95% CI –43-0) and low-density lipoprotein (adjusted beta –24, 95% CI –48-0) were associated with lower birthweight.

Conclusions These results suggest the possibility of multigenerational developmental programming of birth outcomes, although mechanisms (whether biological or environmental) are undetermined. *(J Pediatr 2017;181:154-62).*

The Developmental Origins of Health and Disease hypothesis posits that in utero exposures have lifelong effects on health[1]: perhaps the most well-known example is the relationship between low birthweight and adult cardiometabolic disease.[2] This work has spurred increased interest in the determinants of birthweight as well as how prenatal exposures may affect later-life health. It also leads to the hypothesis that exposures in 1 generation may have effects on multiple generations to come. If prenatal malnutrition or overnutrition in the first generation leads to changes in birthweight in second generation, the second generation's adult metabolic health would be altered, which would lead to effects on birth outcomes in the third generation. Alternately, nutrition in the first generation could have direct effects on the oocytes of the third generation,[3] change the microbiome,[4] or have epigenetic consequences,[5,6] meaning that effects on the third generation could be as strong or stronger, and even affect subsequent generations.

Animal studies indicate the possibility of multigenerational inheritance related to nutrition and metabolism.[7-9] Very few human studies have examined multigenerational effects. In 1 study, generation 1 body mass index (BMI) was directly linked to generation 2 birthweight and BMI, but not third generation BMI, nor did metabolic syndrome in the first generation produce any changes in the birthweight of generations 2 or 3.

If the hypothesis of multigenerational transmission of metabolism is true, we would expect the metabolic or nutritional status of the grandmother to predict a baby's birthweight, 2 generations later. The grandmother's risk factors could also predict a shorter gestational age,[10,11] which may also be an indicator of suboptimal intrauterine environment,[12] and prematurity may induce developmental programming.[13] We hypothesized that generation 1 (grandmother)'s risk factors would predict baby's birthweight and gestational age, and intrauterine undernutrition would produce low birthweight in generation 2, followed by increased risk for obesity/diabetes, leading to increased birthweight in generation 3.

Methods

The Bogalusa Heart Study (BHS) is a long-running study of childhood, adolescent, and now adult cardiovascular health, founded by Dr Gerald Berenson in 1973.[14] Participants were initially recruited from schools in Bogalusa, Louisiana, at ages 3-18 years. Over time, additional waves of data collection were performed, adding

BMI	Body mass index
BHS	Bogalusa Heart Study
LDL	Low-density lipoprotein

From the [1]Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, LA; and [2]Children's National Health System, Division of Biostatistics and Study Methodology, Washington, DC

The Bogalusa Heart Study is supported by the National Institutes of Health (R01HL02942, HL15103, HD069587, HD32194, and AG16592). The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.10.031

additional participants up to adulthood. Female participants have between 1 and 15 study visits, with a median of 2. In childhood, data collection occurred approximately every 2 years, and in adulthood, approximately every 5 years. Currently, participant ages are largely in the 40s through 60s, and follow-up for cardiovascular and early aging measures continues. The data linkages were approved by the Institutional Review Board of Tulane University under a waiver of informed consent. Parents and participants provided informed consent for original data collection and interviews.

Two linkages with reproductive outcomes have been performed. The first, performed in the early 90s, linked participants with their own birth certificates. The linkage was performed manually based on name and birthdate. A total of 6928 participants were linked to data on birthweight and gestational age. The second linkage was performed in 2012-2015. Female participants were linked to their children's birth certificates for Louisiana, Mississippi, and Texas births from 1982 to 2009, including a deterministic record linkage based on maternal social security number, and probabilistic linkage when social security number was unavailable. Furthermore, 1591 women also had been interviewed about their reproductive history during 2012-2016, including data on birthweight and gestational age of each pregnancy and birth.

Two Generation Linkage

First and last name of the mother had been recorded at some time point for 10 292 of the 12 138 study participants. A manual record review was conducted comparing maternal name with the names of the nearly 6000 female study participants. (An attempt to link to paternal participants proved impracticable.) A match was considered likely when the recorded maternal name was identical to the female participant's name, and the participant's age at the time of the child's birth was 16 years or higher. Situations in which the participant's name was similar to the reported maternal name (ie, common alternative spellings or possible misspellings, nicknames, or typos), or the name was identical but the participant would have been between the ages of 12 and 15 years at the time of the birth or the participant's birthdate was missing, were flagged as questionable matches. Using this method, 702 possible mother/child pairs were identified, including 114 questionable matches. Questionable matches were checked against reported addresses, when available, for further verification. Of the questionable matches, 24 were not verifiable (ie, participant was not in the 1994 census). For the remaining 90 questionable matches, 74 (82.2%) were confirmed using census data, and 2 of the incorrect matches were corrected using census data. Thus, of the 114 questionable matches, 100 were considered true matches based on the high verification rate (24 unchecked + 74 verified + 2 corrected). A random sample of 50 likely matches was also checked against BHS census data from 1994. Of these, 2 were not verifiable, and all of the remaining 48 verifiable matches were confirmed; thus, all 588 likely matches were considered true matches. In total, this process led to 688 mother/child pairs (688 children [generation 2] to 437 women [generation 1]).

Three-Generation Linkage

Of the 688 children (generation 2) matched during the mother/child BHS match, 345 (50.2%) were female. Of these, 211 had been linked to at least 1 birth (433 individual live-births). After excluding multiple births, the 3-generation linkage included 424 3-generational triads: 177 generation 1 (grandmothers), 210 generation 2 (mothers), and 424 generation 3 (children). Data for both the first and second generation women was drawn from BHS visits, and data for the third generation was obtained from vital statistics (n = 383) and interviews (n = 41).

Exposure and Outcome Measures

Birthweight and gestational age (obstetric estimate) were taken from the vital statistics data, or, if this was not available, mother's report (mother's report of her infants' birth outcomes is generally valid[15-17]).

All participants were measured and weighed in duplicate in light clothing with shoes off; the average of the measures was used. Fasting blood samples were drawn by venipuncture and stored at −80°C until analysis. Cholesterol, triglycerides, and glucose were measured by enzymatic procedures (Olympus AU400e analyzer, Center Valley, Pennsylvania). Insulin was measured by radioimmunoassay Phadebas Insulin Kit (Pharmacia Diagnostics AB, Uppsala, Sweden). Plasma glucose was measured with enzymatic methods (Beckman Coulter, Indianapolis, Indiana). Measurements were made by laboratory technicians blinded to participants' risk factors. The BHS chemistry laboratory adheres to rigorous quality control procedures and has participated in the Centers for Disease Control and Prevention-National Heart, Lung, and Blood Institute Lipid Standardization Program since 1981. The intraclass correlation coefficient, a reliability measure of interindividual variability, for human blind duplicate samples ranged from 0.92 for glucose to 0.99 for total cholesterol. If multiple prepregnancy measures were available, the one closest in time to the pregnancy was used. Mean age at the BHS visit prior to pregnancy was 16.2 years for generation 1 and 11.1 years for generation 2.

Age was calculated from participant's date of birth. Race was recorded at the initial BHS visit. Smoking was based on reporting of current smoking at any visit. Parity was taken from number of reported pregnancies or birth certificate data; marital status and education (highest grade completed) were taken on self-report or as recorded on the birth certificate. Pregnancy weight gain was taken from vital statistics data or maternal self-report, which is moderately if not perfectly associated with recorded data.[18] The reproductive history interview contained information on tobacco use, marital status at birth, parity, highest grade completed, and weight gain during pregnancy.

Statistical Analyses

To compare the included sample with the overall BHS sample, χ^2, t tests, and ANOVA were used for bivariate comparisons. Linear and logistic models were also used to determine whether differences remained after adjusting for age at first and last visit and race. The generation 1 women and the generation 2 women were compared with the overall sample in separate analyses.