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Multigenerational cardiometabolic risk as a predictor of birth outcomes: The Bogalusa Heart Study

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Abstract

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 three-generation linkage including 177 generation 1 (grandmothers), 210 generation 2 (mothers), and 424 generation 3 children. Pre-pregnancy cardiometabolic risk factors (BMI, lipids, glucose) for generation 1 (mean age 16.2) and 2 (mean age 11.1) 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 LDL (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.

Keywords

birthweight; gestational age; blood glucose; body mass index; lipids

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The Developmental Origins of Health and Disease (DOHaD) 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 one generation may have effects on multiple generations to come. If prenatal malnutrition or over-nutrition 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, 89]

Very few human studies have examined multigenerational effects. In one study, generation 1 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, two generations later. The grandmother's risk factors could also predict a shorter gestational age.[12, 13] However, shorter gestational age may also be an indicator of suboptimal intrauterine environment,[14] and prematurity may induce developmental programming.[15] 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 [16]. Participants were initially recruited from schools in Bogalusa, LA, at ages 3–18. Over time, additional waves of data collection were performed, adding 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 two years, and in adulthood, approximately every five years. Currently, participants are largely in their 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. 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 1982–2009, including a deterministic record linkage based on maternal social security number (SSN), and probabilistic linkage when SSN was unavailable. 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 6,000 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 or higher. Situations in which the participant's name was similar to the reported maternal name (i.e. 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 – 15 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 (i.e. participant was not in the 1994 census). For the remaining 90 questionable matches, 74 (82.2%) were confirmed using census data, and two 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 Bogalusa study census data from 1994. Of these, two 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 one birth (433 individual live-births). After excluding multiple births, the three-generation linkage included 424 three-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.[17–19])

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 until analysis. Cholesterol, triglycerides and glucose were measured by enzymatic procedures (Olympus AU400e analyzer). Insulin was measured by radioimmunoassay (Millipore). Plasma glucose was measured with enzymatic methods (Beckman Coulter). Measurements were made by laboratory technicians blinded to participants' risk factors. The Bogalusa Heart Study Chemistry Laboratory adheres to rigorous quality control procedures and has participated in the CDC-NHLBI 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 pre-pregnancy 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 for generation 1 and 11.1 for generation 2

Age was calculated from participant's age at 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.[20] 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, chi-square, t-tests, and ANOVAs 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.

For the main analysis, first, two-generation relationships with birth outcomes were examined. Generation 1's cardiometabolic factors at the visit prior to pregnancy were examined as predictors of generation 2's birth outcomes, and generation 2's cardiometabolic factors were examined as predictors of generation 3's birth outcomes. Birthweight and gestational age were examined as continuous outcomes to maximize study power. Multiple linear regression models were used for continuous outcomes and logistic models for dichotomous outcomes. Three models were used to examine the relationships: the first model was unadjusted, the second adjusted for maternal BMI, and the third also adjusted for known risk factors for birth outcomes (for generation 2-generation 3, age, smoking, race, marital status, education, parity, weight gain during pregnancy, and time between the BHS visit and pregnancy; for generation 1- generation 2, age, smoking, race, parity, and time between the BHS visit and pregnancy [less information was available for this analysis because generation 2's birth outcomes were taken from the first linkage, and no data was abstracted from the birth certificate beyond birthweight and gestational age]). Multiple imputation was used to account for missing data in covariates.[21] Models were generalized

estimating equations (GEE) with an exchangeable working correlation matrix to allow for correlation within family (generation 1).

Analysis 2 examined generation 1 characteristics as a predictor of generation 3's birthweight and gestational age. Generation 1 measurements at the visit prior in to the pregnancy with generation 2's were examined as predictors, with adjustment for maternal BMI (model 2), grandmaternal BMI if not the exposure, and for maternal age, race, smoking, parity, marital status, education, weight gain during pregnancy, and time between the BHS visit and the pregnancy (model 3). An additional analysis controlled for the corresponding mother's risk profile (e.g., effect of grandmaternal glucose controlling for mother's glucose levels).

Analysis 3 examined whether discrepancies in the BMI of the generation 1 and 2 were associated with differences in the infant's birthweight and gestational age. The BMIs were categorized as: (1) both generations 1 and 2 overweight/obese; (2) neither overweight nor obese; (3) generation 1 overweight/obese/generation 2 not; and (4) generation 2 overweight/obese/generation 1 not. These four categories were examined as predictors of generation 3's birthweight/gestational age. A similar strategy was followed for other risk factors, with top quartile as the cut-off for "high."

Analysis 4 examined discrepancies in birthweight, looking at whether the generation 1's characteristics produced a pattern whereby one or the other of the generation 2 and generation 3 had lower birthweight, but the other was not. Due to the small numbers, "lower birthweight" was defined as $<20^{th}$ percentile for this study population.

Finally, we examined the hypothesis that intrauterine undernutrition would produce low birthweight in generation 2, followed by increased risk for obesity/diabetes, leading to increased birthweight in generation 3. We compared the group with generation 1 normal/underweight, generation 2 $<20^{th}$ percentile on birthweight, generation 2 later BMI overweight/obese, to all others. Analyses were performed using SAS software version 9.3 with two-sided p-values.

Results

The generation 1 and 2 women included in this analysis were 58% African-American, 42% white, and the mean age at the BHS visit prior to pregnancy was 16.2 for generation 1 and 11.1 for generation 2 (Table I). Age of the generation 1 participants included in this analysis was older at earliest visit (14.4 vs. 9.6) as well as most recent visit (34.5 vs. 18.8), compared with women in the overall BHS sample (Table I). Included participants were much more likely to be African-American (58% of this sample, compared with 36% of the larger sample). Mean BMI and cholesterol were not different once race and age were accounted for, and blood pressure was slightly lower than women in the overall sample (systolic −1.31 mmHg, p=0.08). The included generation 1 participants were much more likely to be smokers (56% vs. 36% ever smoked), though this, too, was somewhat explained by the age difference (p=0.14 for differences in smoking, after adjustment for race and age). The included mothers had a younger age at earliest visit (mean 7.8) and latest visit (11.5) compared with the overall population of women. Mean BMI and cholesterol were not

different once race and age were accounted for, and blood pressure was slightly lower (systolic −1.64 mmHg, p<0.01). Mean birthweight in the generation 1 was 3083 g, in the generation 2 was 3187 g, and in the generation 3 was 3037 g, and birthweights were correlated across generations (generation 1-generation 2, r=0.39, p<0.01; generation 2-generation 3, r=0.24, p<0.01)

Two-generation comparison

Generation 2 (mother) higher BMI was associated with higher birthweight (28 g per 1 unit of BMI, 95% CI 16, 40) and gestational age (0.08 weeks, 95% CI 0.02,0.14) in the generation 3 (child), and generation 1 (grandmother) higher BMI was associated with higher birthweight (52 g,95% CI 34, 70) in the generation 2 (mother) (Table II). Higher glucose and triglycerides in generation 2 were associated with increased birthweight and LDL with higher gestational age in generation 3, but these were to some degree explained by confounding.

Three-generation comparison

Generation 1's glucose levels were associated with higher birthweight in generation 3 (adjusted beta=111, 95% CI 33–189), and triglycerides (−21, −43-0) and LDL (−24, −48-0) were associated with lower birthweight (Table III). HDL was weakly associated with higher gestational age (0.12, 0.00–0.24). Examination of discrepant risk factor patterns indicated associations of birth outcomes with both generation 1 and 2 (Table IV). The highest birthweight was seen in those with both generation 1 and generation 2 overweight/obese, although there was substantial overlap in the confidence intervals with the effects from a single generation being obese.

Generation 1's glucose level was more strongly associated with birthweight than generation 2's, and the negative relationship between generation 1's LDL and birthweight was mostly in those whose generation 2's LDL was not high. Generation 2's triglycerides were mostly associated with higher gestational age if the generation 1 was not in the "high" category.

Generation 1 BMI was very strongly inversely associated with the pattern of generation 2 having a lower birthweight, but generation 3 not (OR per 1 unit, 0.81, 95% CI 0.69–0.96) (Table V; available at www.jpeds.com), and higher generation 1 triglycerides were also associated with an increased likelihood of generation 3 having a lower birthweight, but generation 2 not (OR per 10 units, 1.10, 95% CI 1.00–1.20; data not shown).

Finally, comparing the group with generation 1 normal/underweight, generation 2 <20th percentile on birthweight, generation 2 later BMI overweight/obese, to all others, birthweight in generation 3 was an average of 251 g (p=0.13) higher, reduced after adjustment for confounding (adjusted beta 163 g, p=0.35).

Discussion

The results of this study are consistent with a previous study in Malta that linked clinical databases for 182 mothers and daughters, who then gave birth to 233 infants, [22] in that maternal BMI was one of the strongest drivers of birthweight. Unlike this previous study,

however, we did find some generation 1- generation 3 relationships with cardiometabolic factors. The Maltese study, however, was limited to what was recorded in a clinical database, and so had much less detailed measures of the pre-pregnancy cardiometabolic risk factors.

Our results suggest the possibility of multigenerational developmental programming of birth outcomes, although mechanisms (whether biological or environmental) are undetermined. Also, although DOHaD research has linked low birthweight with both adult cardiovascular and metabolic health,[23] these effects may need to be distinguished for perinatal outcomes – it has long been known that maternal glucose is associated with higher birthweight,[24] and higher lipids have been associated with lower gestational age.[25] Animal work indicates the possibility of transgenerational or multigenerational influences on health, although the research is still in its early stages: maternal diet in generation 1 has been found to predict adiposity in mice through generation 3 and sometimes 4.[26, 27] Biological mechanisms that could account for effects on three-generational effects could include epigenetic changes [26, 27] including changes in the oocytes or in tissues or altered gene expression.[28] It is also possible that nutritional or metabolic dysfunction in generation 1 could induce developmental programming of metabolism or hormone levels in generation 2 that was especially prominent under conditions of stress, such as being pregnant, thus amplifying or leading to additional programming of generation 3.[29]

Our study considers only maternally-mediated associations. Some studies indicate a stronger paternal effects, or stronger effects working through the male offspring's line rather than the female; this was the case for the Overkälix study.[10] It is possible that our results would have been stronger, or different, if grandfathers or fathers could have been considered

There were limitations to the study. Included participants were different from other BHS participants. Except for the race difference, these differences largely reflect the form of the study, which includes several cross-sectional studies for which there was little follow-up, and a core group that has been followed up multiple times; as well as the fact that allowing three generations generally requires that the earliest generation have entered the study at an older age. The sample for this analysis is limited to those who could be contacted and/or linked, which makes them different from the overall sample in the ways demonstrated in Table I; there is no reason to believe, however, that biological mechanisms would operate differently in this group.

Other limitations are related to the available data. Pre-pregnancy cardiometabolic health is represented with a single measurement, closest in time to pregnancy. Some women do have multiple pre-pregnancy measures, but the number is too small for analysis (n=26). Even using a single measure, the sample is small. A second limitation is the non-standardized measurement timing, either at the same age or before pregnancy, which in some cases led to long gaps between the cardiovascular measurement and the pregnancy outcome. All of these factors limit our ability to detect anything beyond very large effects, and our ability to distinguish transgenerational from genetic and environmental effects.

Future studies should examine larger sample sizes; explore possible epigenetic and programming mechanisms of effect; include male generation 1 and 2 participants; and assess metabolic health in the third generation.

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Abbreviations

BMI	body mass index
DOHaD	developmental origins of health and disease
BHS	Bogalusa Heart Study

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Table 1

Female participants in the Bogalusa Heart Study and three-generational linkage

	Overall BHS population (women, n=5914)	Generation 1(grandmother) (n=177)		Generation 2 (mother) (n=210)	
Race	**N(%)**	**N(%)**	**p-value[b]**	**N(%)**	**p-value[b]**
African-American	2143 (36.2)	102(57.6)	<0.01	123 (58.6)	<0.01
white	3771 (63.8)	75(42.4)		87 (41.4)	
Age at first birth[a]					
<20	975(26.9)	87(20.0)	0.01	37(18.6)	<0.01
20–<25	1308(36.1)	75(43.1)		113(56.8)	
25–<30	804(22.2)	12(6.9)		43(21.6)	
>=30	534(14.8)	0(0.0)		6(3.0)	
Smoking					
Ever smoked, yes	1588(36.1)	98(56.0)	<0.01	8(4.4)	<0.01
Smoked prior to pregnancy	429(18.8)	57(42.2)		5(3.6)	
BMI at visit prior to pregnancy					
<20	1758(49.5)	58(36.7)	<0.01	126(63.3)	<0.01
20–<25	1138(32.0)	69(43.7)		46(23.1)	
25–<30	413(11.6)	21(13.3)		23(11.6)	
30+	245(6.9)	10(6.3)		4(2.0)	
BMI (kg/m^2)	Mean (SD)	Mean (SD)		Mean (SD)	
child (<13)	17.3(3.2)	17.8(3.7)	0.73	17.4(3.4)	0.40
adolescent (13–17)	21.5(4.6)	21.0(4.0)	0.15	21.9(5.2)	0.36
adult (18+)	26.6(7.1)	27.2(7.2)	0.33	25.4(7.5)	0.52
Cholesterol (mg/dL)					
child (<13)	167.8(27.3)	166.6(28.2)	0.38	171.3(27.1)	0.06
adolescent (13–17)	161.3(27.5)	160.5(24.6)	0.96	165.9(30.0)	0.14
adult (18+)	180.2(34.0)	183.0(37.1)	0.41	151.9(26.2)	<0.01
Glucose (mg/dL)					
child (<13)	81.4(9.7)	82.6(6.0)	0.69	79.2(7.9)	<0.01
adolescent (13–17)	83.4(8.9)	84.6(10.6)	0.38	79.9(8.1)	<0.01
adult (18+)	83.7(18.5)	89.0(31.7)	0.28	81.0(6.3)	0.25

	Overall BHS population (women, n=5914)		Generation 1(grandmother) (n=177)			Generation 2 (mother) (n=210)		
Race	**N(%)**		**N(%)**	**p-value[b]**		**N(%)**	**p-value[b]**	
	mean (SD)	range	mean(SD)	range	p-value	mean(SD)	range	p-value
Age at first visit [c]	9.6(5.1)	3–62	14.4(9.8)	4–57	<0.01	7.8(2.0)	4–18	<0.01
Age at last visit [c]	18.8(11.6)	4–62	34.5(11.0)	12–57	<0.01	11.5(5.4)	4–43	<0.01
Time since last visit [c]	25.4 (9.15)	6–43	19.3(10.0)	6–42	<0.01	22.5(3.3)	8–29	
Age at visit prior to pregnancy [c]	14.9(5.8)	4–39	16.2(2.9)	7–24	<0.01	11.1(4.3)	4–33	<0.01
Time between visit and estimated LMP for pregnancy [c]	8.5(5.6)	1–32	3.9(2.4	0.8–10.5	<0.01	11.8(4.0)	0.8–20.8	<0.01

[a] among women with information on at least one birth, n=3621

[b] bivariate comparison, included women vs. all other women in BHS sample

[c] in years

Table 2

Associations between maternal pre-pregnancy cardiovascular risk factors and birth outcomes, the Bogalusa Heart Study

	birthweight								
	unadjusted			adjusted for maternal BMI			adjusted for age, race, BMI, smoking, parity, marital status, education, pregnancy weight gain, time between visit and pregnancy		
	mean difference[a]	SE	p	mean difference	SE	p	mean difference	SE	p
Generation 2(mother's) characteristics predict generation 3 birth outcomes									
BMI (n=197 gen 2/n=405 gen 3)	28	6.	<0.01				28.	8	<0.01
cholesterol (n=189 gen 2/n=386 gen 3)	18	13	0.20	13	12	0.26	12	12	0.30
glucose (n=188 gen 2/n=385 gen 3)	82	33	0.01	56	31	0.07	49	31	0.11
triglycerides (n=189 gen 2/n=386 gen 3)	19	8	0.01	8	7	0.23	5	7	0.44
HDL (n=189 gen 2/n=386 gen 3)	−25	29	0.39	−2	28	0.95	8	30	0.79
LDL (n=189 gen 2/n=386 gen 3)	21	16	0.19	19	15	0.23	16	15	0.28
insulin (n=165 gen 1/n=341 gen 3)	66	52	0.21	−4	60	0.94	−4	55	0.94
Generation 1 characteristics (grandmother) predict generation 2 (mother) birth outcomes	unadjusted			adjusted for generation 1 BMI			adjusted for age, race, parity, BMI, smoking, time between visit and pregnancy		
BMI (n=119 gen 1/n=144 gen 2)	46	9	<0.01				52	9	<0.01
glucose (n=98 gen 1/n=113 gen 2)	30	46	0.51	22	49	0.65	−33	46	0.47
triglycerides (n=119 gen 1/n=144 gen 2)	16	13	0.23	10	13	0.42	89	65	0.17
cholesterol (n=119 gen 1/144 gen 2)	−1	19	0.97	−2	17	0.93	−23	24	0.34
HDL (n=119 gen 1/144 gen 2)	−35	21	0.10	−22	19	0.24	−62	79	0.43
LDL (n=119 gen 1/144 gen 2)	15	18	0.41	8	17	0.63	−28	69	0.68

	gestational age								
	unadjusted			adjusted for maternal BMI			adjusted for age, race, BMI, smoking, parity, marital status, education, pregnancy weight gain, time between visit and pregnancy		
	mean difference[a]	SE	p	mean difference	SE	p	mean difference	SE	p
Mother's (generation 2) characteristics predict child's birth outcomes (generation 3)									
BMI (n=197 gen 2/n=405 gen 3)	0.09	0.03	<0.01				0.08	0.03	0.01
cholesterol (n=189 gen 2/n=386 gen 3)	0.12	0.05	0.01	0.11	0.05	0.02	0.12	0.05	0.01
glucose (n=188 gen 2/n=385 gen 3)	0.29	0.16	0.06	0.20	0.15	0.19	0.21	0.16	0.20
TG (n=189 gen 2/n=386 gen 3)	0.06	0.03	0.02	0.02	0.02	0.30	0.02	0.03	0.54
HDL (n=189 gen 2/n=386 gen 3)	0.06	0.12	0.60	0.15	0.12	0.22	0.20	0.13	0.13

	unadjusted			adjusted for maternal BMI			adjusted for age, race, BMI, smoking, parity, marital status, education, pregnancy weight gain, time between visit and pregnancy		
	mean difference[a]	**SE**	**p**	**mean difference**	**SE**	**p**	**mean difference**	**SE**	**p**
LDL (n=189 gen 2/n=386 gen 3)	0.13	0.07	0.05	0.12	0.06	0.06	0.13	0.07	0.06
insulin (n=165 gen 1/n=341 gen 3)	0.22	0.14	0.10	0.02	0.16	0.88	−0.01	0.18	0.94
Generation 1 characteristics (grandmother) predict generation 2 (mother) birth outcomes									
	unadjusted			adjusted for generation 1 BMI			adjusted for age, race, BMI, smoking, parity, time between visit and pregnancy		
BMI (n=119 gen 1/n=144 gen 2)	0.01	0.01	0.58				0.05	.11	0.67
glucose (n=98 gen 1/n=113 gen 2)	0.14	0.37	0.70	0.39	0.46	0.39	0.39	0.26	0.13
triglycerides (n=119 gen 1/n=144 gen 2)	−0.04	0.08	0.62	−0.04	0.08	0.60	−0.12	0.08	0.14
cholesterol (n=119 gen 1/144 gen 2)	0.03	0.11	0.80	0.04	0.11	0.73	0.07	0.12	0.55
HDL (n=119 gen 1/144 gen 2)	−0.16	0.18	0.38	−0.14	0.18	0.41	0.00	0.20	0.99
LDL (n=119 gen 1/144 gen 2)	0.15	0.12	0.20	0.15	0.12	0.19	0.11	0.11	0.32

[a] per 1 unit BMI and 10 units of other predictors

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Table 3

Grandmother's pre-pregnancy cardiovascular risk as predictor of grandchild's birthweight

	birthweight											
	unadjusted			adjusted for maternal BMI			+ age at pregnancy, race, grandmaternal BMI, smoking, parity, marital status, education, time between visit and pregnancy			+ maternal factor[a]		
	mean difference[b]	SE	p	mean difference	SE	p	mean difference	SE	p			
BMI (n=156 gen 1/n=369 gen 3)	8	0.8	0.31	−12	8	0.15	−12	10	0.23			
glucose (n=116 gen 1/n=261 gen 3)	56	62	0.37	31	57	0.59	111	40	0.01	111	41	0.01
triglycerides (n=155 gen 1/n=367 gen 3)	−11	14	0.43	−21	11	0.06	−21	11	0.05	−24	10	0.02
cholesterol (n=155 gen 1/n=367 gen 3)	−5	13	0.70	−11	13	0.36	−10	12	0.41	−13	12	0.30
HDL (n=155 gen 1/n=367 gen 3)	15	18	0.41	13	17	0.44	22	17	0.21	23	18	0.20
LDL (n=155 gen 1/367 gen 3)	−18	12	0.14	−21	13	0.09	−24	12	0.05	−29	12	0.02

	gestational age											
	unadjusted			adjusted for maternal BMI			+ age, race, grandmaternal BMI, smoking, parity, marital status, education, time between visit and pregnancy			+ maternal factor		
	mean difference	SE	p	mean difference	SE	p	mean difference	SE	p			
BMI (n=156 gen 1/n=369 gen 3)	0.10	0.03	0.85	−0.05	0.04	0.19	−0.07	0.04	0.11			
glucose (n=116 gen 1/n=261 gen 3)	−0.18	0.17	0.29	−0.25	0.16	0.12	−0.04	0.16	0.82	−0.06	0.16	0.71
triglycerides (n=155 gen 1/n=367 gen 3)	0.02	0.04	0.58	−0.05	0.04	0.19	−0.05	0.04	0.19	−0.05	0.04	0.16
cholesterol (n=155 gen 1/n=367 gen 3)	0.03	0.05	0.53	0.01	0.05	0.90	0.02	0.05	0.73	−0.02	0.05	0.76
HDL (n=155 gen 1/n=367 gen 3)	0.10	0.06	0.09	0.08	0.06	0.15	0.12	0.06	0.05	0.10	0.06	0.10
LDL (n=155 gen 1/367 gen 3)	−0.03	0.05	0.51	−0.04	0.04	0.34	−0.05	0.04	0.26	−0.08	0.04	0.08

[a] effect of grandmother's glucose level adjusted for mother's glucose level, etc.

[b] per 1 unit BMI and 10 units of other predictors

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Table 4

Discrepant risk factor patterns as predictors of grandchild's birth outcomes

	birthweight					
	unadjusted			adjusted for maternal age, race, parity, maternal and grandmaternal BMI, smoking, marital status, education, and time between visit and pregnancy		
	mean difference	SE	p	mean difference	SE	p
BMI (146 gen 1/353 gen 3)						
Neither obese/ovtwt	ref			ref		
G obese/ovtwt, M not	122	119	0.30	170	125	0.17
G not, M obese/ovtwt	324	139	0.02	245	140	0.08
Both obese/ovtwt	364	138	0.01	347	136	0.01
glucose (103 gen 1/234 gen 3)						
Neither high	ref			ref		
G high, M not	158	136	0.25	247	122	0.04
G not, M high	152	134	0.36	87	121	0.47
Both high	287	133	0.03	222	121	0.07
triglycerides (138 gen 1/333 gen 3)						
Neither high	ref			ref		
G high, M not	32	111	0.77	21	108	0.85
G not, M high	227	117	0.05	165	110	0.13
Both high	71	116	0.54	−57	113	0.62
cholesterol (138 gen 1/333 gen 3)						
Neither high	ref			ref		
G high, M not	−6	135	0.97	−5	131	0.97
G not, M high	230	130	0.08	195	133	0.14
Both high	59	116	0.61	22	114	0.84
HDL (138 gen 1/333 gen 3)						
Neither high	ref			ref		
G high, M not	168	127	0.19	161	113	0.15
G not, M high	−35	132	0.79	15	128	0.91
Both high	19	123	0.87	45	116	0.70
LDL (138 gen 1/333 gen 3)						

	birthweight					
	unadjusted			adjusted for maternal age, race, parity, maternal and grandmaternal BMI, smoking, marital status, education, and time between visit and pregnancy		
	mean difference	SE	p	mean difference	SE	p
Neither high	ref			ref		
G high, M not	−288	129	0.03	−307	128	0.02
G not, M high	64	136	0.64	53	127	0.68
Both high	−18	116	0.88	−48	113	0.67

	gestational age					
	unadjusted			adjusted for maternal age, race, parity, maternal and grandmaternal BMI, smoking, marital status, education, and time between visit and pregnancy		
	mean difference	SE	p	mean difference	SE	p
BMI (146 gen 1/353 gen 3)						
Neither obese/ovtwt	ref			ref		
G obese/ovtwt, M not	0.36	0.46	0.44	0.46	0.45	0.31
G not, M obese/ovtwt	1.20	0.49	0.01	0.92	0.59	0.12
Both obese/ovtwt	0.85	0.51	0.10	0.87	0.49	0.08
glucose (103 gen 1/234 gen 3)						
Neither high	ref			ref		
G high, M not	0.21	0.52	0.68	0.43	0.52	0.40
G not, M high	0.42	0.49	0.39	0.17	0.50	0.73
Both high	0.19	0.56	0.73	0.05	0.54	0.92
triglycerides (138 gen 1/333 gen 3)						
Neither high	ref			ref		
G high, M not	0.43	0.52	0.40	0.45	0.47	0.34
G not, M high	1.05	0.46	0.02	1.02	0.43	0.02
Both high	0.56	0.48	0.24	0.16	0.47	0.73
cholesterol (138 gen 1/333 gen 3)						
Neither high	ref			ref		
G high, M not	0.69	0.55	0.21	0.57	0.50	0.25
G not, M high	0.97	0.47	0.04	0.90	0.48	0.06
Both high	0.63	0.47	0.18	0.41	0.46	0.38
HDL (138 gen 1/333 gen 3)						

	gestational age					
	unadjusted			adjusted for maternal age, race, parity, maternal and grandmaternal BMI, smoking, marital status, education, and time between visit and pregnancy		
	mean difference	SE	p	mean difference	SE	p
Neither high	ref			ref		
G high, M not	0.97	0.47	0.04	0.97	0.45	0.03
G not, M high	0.45	0.42	0.28	0.60	0.44	0.17
Both high	0.55	0.48	0.26	0.63	0.45	0.16
LDL (138 gen 1/333 gen 3)						
Neither high	ref			ref		
G high, M not	−0.66	0.56	0.23	−0.79	0.59	0.18
G not, M high	0.26	0.52	0.62	0.33	0.50	0.51
Both high	0.18	0.41	0.67	0.00	0.42	0.99

G, grandmother; M, mother; ovtwt, overweight; high=top quartile

Table 5

Grandmother's cardiometabolic risk factors as predictors of cross-generational discrepancy in birthweight (mother <20th percentile for birthweight, child not)

	unadjusted		adjusted for maternal BMI, age, race, parity, weight gain during pregnancy, smoking, prenatal care, marital status, education	
	OR[a]	95% CI	OR	95% CI
BMI (118 gen 1/289 gen 3)	0.80	0.68, 0.93	0.81	0.69, 0.96
glucose (97 gen 1/217 gen 3)	0.96	0.63, 1.48	0.99	0.58, 1.71
triglycerides (118 gen 1/289 gen 3)	0.92	0.79, 1.06	0.94	0.80, 1.10
cholesterol (118 gen 1/289 gen 3)	1.06	0.88, 1.28	1.08	0.89, 1.32
HDL (118 gen 1/289 gen 3)	1.17	0.95, 1.45	1.19	0.92, 1.53
LDL (118 gen 1/289 gen 3)	0.97	0.80, 1.19	1.00	0.81, 1.24

[a] per 1 unit BMI and 10 units of other predictors