

ETHNIC DIFFERENCES IN BIRTH WEIGHT: MATERNAL EFFECTS EMERGE FROM AN ANALYSIS INVOLVING MIXED-RACE US COUPLES

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Ethnic differences in birth weight, a predictor of developmental outcomes and health, have remained largely unexplained. Using data collected by the US National Center of Health Statistics, we first cross-tabulate birth weight according to whether the mother or father was African American, European American, Native American, or Mexican American. Results confirm findings from other studies indicating the importance of maternal effects. Furthermore, traditional health and socioeconomic variables account for only a modest part of the group differences, and mothers who presumably lived in the most advantageous environments did not give birth to the heaviest babies. Next, we discuss the possible nature of the relevant maternal factors. Specific candidates include cultural differences in lifestyle that are traditionally not measured in large-scale surveys. Multiple lines of evidence in the literature also suggest that maternal genes are involved. (*Ethn Dis.* 2006;16:706–711)

Key Words: Birth Weight, Ethnicity, Maternal Effects, Genetics

INTRODUCTION

Considerable differences exist among ethnic groups in the average birth weight and the prevalence of low birth weight (<2,500 g). Black newborns, for instance, have approximately double the risk of low birth weight compared to White newborns.¹ Birth weight is associated with infant illness and death,¹ developmental outcomes in childhood,^{2,3} and medical conditions such as coronary artery disease and type 2 diabetes later in life.⁴ A tremendous research effort has therefore been devoted to discovering the determinants of ethnic differences in birth weight.

Economic disparities may explain part of the ethnic differences in birth weight. Cramer,⁵ for instance, studied African American and European American babies. He found that in this sample, birth weight was related to a group of causally “distant” variables such as income, years of education, and receipt of public aid. He also examined some “immediate” variables including smoking cigarettes, drug use, perinatal care, and the mother’s weight-for-height. Combining “distant” and “immediate” variables in a regression model could account for ≈10% of the within-ethnic-group variation. Despite the predictive power of his regression model, the birth weight gap remained substantial. One reason was that, although their greater poverty explained part of the Black-White gap for birth weight, Blacks had more favorable statuses on some of the immediate variables (eg, they smoked less), which acted in the opposite direction.

Differences among other ethnic groups may be smaller and easier to

account for in terms of traditional risk factors. Hessol and Fuentes-Afflick⁶ compared the birth weights of infants of Mexican-origin women to infants born to non-Hispanic White women. After adjusting for maternal, paternal, and infant factors, they could account for the higher unadjusted risk of low birth weight infants and actually found some evidence of a perinatal advantage for Mexican women. Questions remain, however, concerning whether these factors fully explain the birth weight differences. One issue involves the validity of correcting birth weights for gestational age, which may be an indicator for health risks at birth.⁷ Another issue involves the finding that adjustment birth weights seemed more favorable in Mexican women. This may not be a chance finding and seems to provide some evidence for what has become known as the low birth weight paradox; the observation that relatively few low-weight births occur among Mexican Americans despite their socioeconomic disadvantages.⁸

As socioeconomic variables measured in traditional large-scale surveys seem to explain only part of the ethnic differences in birth weight, attention may be directed toward other possible explanations. We can easily generate a long list of omitted variables that might add to the explanation of birth weight, such as sexually transmitted diseases, social support from family members, support from the child’s biological father, nutrition, physical illnesses, exposure to discrimination, and so on. However, the large domain of possible influences, and the difficulty of measuring them in large surveys, makes a resolution of the causes underlying ethnic differences in birth weight difficult.

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MATERNAL EFFECTS

Instead of trying to measure a long list of omitted variables, we can also apportion ethnic differences in birth weight to general components to obtain a picture of the most relevant factors. In a previous paper, we used a genetically informative sibling design that decomposed the difference in birth weights between African American and European American babies into contributions of fetal genetic and environmental factors.⁷ Results suggested that aspects of the fetal uterine environment that are constant across pregnancies, such as the physical or physiologic characteristics of the mother, could be important. Because of the specific design, we could further narrow down the relevant maternal effects to those that are stable across pregnancies, thereby excluding diseases or other environmental hazards that vary across pregnancies.

Here we took a different approach to examine whether we could replicate the importance of maternal effects for ethnic differences in birth weight. The data consisted of the birth weights of infants from mixed-race couples, which presents a powerful alternative design for studying ethnic differences in maternal effects.⁹ In this article, the terms ethnicity and race are interchangeable and refer to groups in the population as they are often distinguished in large-scale studies. The aim of the first analysis was to determine whether maternal or paternal race is a more

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important determinant of ethnic differences in birth weight. For this purpose, we cross-tabulated birth weight according to whether the mother or father was African American (AA), European American (EA), Native American (NA), or Mexican American (MA). If maternal race were the most important factor, the birth weights of the biracial infants would mainly depend on the mother, and paternal race would make little difference. If paternal race were most important, the opposite pattern would be expected. In the second analysis, we regressed out the effects of several traditional health and socioeconomic variables. We then inspected the adjusted birth weights to examine the extent to which differences for these background variables could explain the ethnic differences in birth weight.

We used data from the 1991 birth cohort as collected by the US National Center of Health Statistics. Two variables from this dataset were used to determine parental ethnicity. The first

variable subdivided the subjects into EA, AA, and NA groups, the second variable pertained to Hispanic ancestry. Parents categorized as EA, AA, and NA in this study were classified EA, AA, or NA category on the first variable and were non-Hispanic according to the second variable. Parents categorized as Mexican American (MA) in this study were those for whom the second variable indicated that they were from Mexico and had Hispanic ancestors. We also considered including parents from Asia (Chinese and/or Japanese). However, except for Asian-EA couples, sample sizes were very small. For example, the number of Chinese/non-EA couples ranged from only 12 to 114.

The first block of Table 1 shows the sample sizes that ranged from 2.2 million babies from EA-EA couples to 326 babies from AA-NA couples. The second block reports the (unadjusted) birth weight expressed as deviations from the unweighted grand mean of 3339 g. Results suggest that maternal race is a more important determinant for birth weight than paternal race. For instance, regardless of paternal race, having a EA or NA mother always increases the birth weight and having an AA mother always decreases it. To obtain a quantitative measure of the importance of maternal versus paternal race, we first computed the "main" effects of paternal race. This main effect was an unweighted mean indicating how much a parent of a certain race added to the birth weight of his or her

Table 1. Birth weight in infants from mixed-race couples

Mother (SD*=99)	Father (SD*=35)								
	Sample Size				Birth Weight				
	EA	AA	NA	MA	EA	AA	NA	MA	Mean
European American (EA)	2.2 × 10 ⁶	28,364	8878	39,759	81	13	37	24	39
African American (AA)	6965	357,600	326	1659	-81	-201	-134	-167	-146
Native American (NA)	7743	801	14,021	1534	106	28	70	106	77
Mexican American (MA)	30,253	4286	694	320,443	69	-6	30	23	29
Mean					44	-41	1	-3	

* SD is the standard deviation of the reported means for the mother (last column) and father (last row). Cells report the deviation of the mean birth weight from the unweighted grand mean of 3339 g.

Table 2. Adjusted* birth weight in infants from mixed-race couples

Mother (SD†=23)	Father (SD†= 95)								Mean
	Sample Size				Birth Weight				
	EA	AA	NA	MA	EA	AA	NA	MA	
European American (EA)	1.6 × 10 ⁶	16,706	5805	18,256	37	41	47	-13	28
African American (AA)	3876	221,162	178	564	-83	-185	-78	-156	-125
Native American (NA)	5213	459	10,269	678	107	66	84	153	102
Mexican American (MA)	14,064	1437	293	106,246	-1	-31	40	-29	-5
Mean					15	-27	23	-11	

* Birth weight adjusted for maternal age, education, and marital status; the child's sex and birth order; paternal education; adequacy of prenatal care; and the number of cigarettes the mother smoked during pregnancy.

† SD is the standard deviation of the reported means for the mother (last row) and father (last column).

Cells report the deviation of the mean birth weight from the unweighted grand mean of 3339 g.

children, regardless of the race of the other parent. For instance, for EA mothers this was $(81 + 13 + 37 + 24)/4 = 39$ g. Next, we computed the standard deviation (SD) of these main effects to obtain a measure for the importance of maternal versus paternal race. An SD of zero would mean that parental race is not important for birth weight, and a non-zero SD would indicate differences between the different ethnic categories with respect to their impact on birth weight.

Table 1 shows that the SD for the main effect of maternal race (99) was considerably larger than the SD (35) for the main effect of paternal race. The first conclusion is, therefore, that maternal race was much more important than paternal race. This replicates findings from other studies of biracial infants.¹⁰ Despite the fact that a completely different approach was used, this study also seemed to replicate the main conclusion from our previous study.

Table 2 reports the birth weights adjusted for ethnic differences in maternal age, education, and marital status; the child's sex and birth order; paternal education; adequacy of prenatal care; and the number of cigarettes the mother smoked during pregnancy. Multiple regression was used to adjust for the effect of all these variables simultaneously. The somewhat smaller sample size can be explained by missing values on the predictor variables. The birth weights are again expressed as deviations

from the unweighted grand mean. The SD of the main effect for paternal race was reduced more (from 35 to 23) than the SD for the effect of maternal race (from 99 to 95). The main conclusion seems to be, however, that the racial differences in birth weight remained largely unexplained by these covariates. This finding replicates results from other studies¹¹ indicating that traditional sociodemographic and health variables merely explain a modest part of the ethnic differences. In this context of explaining birth weight differences on the basis of traditional socioeconomic variables, we should also note that mothers who presumably live in the most advantageous environments, the EA group, do not give birth to the heaviest babies. Babies of NA mothers have birth weights significantly higher than those of EA or any other mothers. Finally, birth weight differences do not correlate perfectly with weight differences in adults. Although obesity rates have are higher in NA,¹² AA who have the lowest birth weights may have a heavier body composition, for a variety of reasons.¹³⁻¹⁵ Thus, rather than being a general feature, the differences reported in the table may, to some extent, be caused by factors specific to birth weights.

Tables 1 and 2 only use the birth weights of infants if race is known for both parents. However, paternal race was missing for 15.6% of the infants. The impact of these missing values on

the between-group variation (as measured by the SDs) accounted for by maternal race can be studied. We can compute the birth weights of infants born to: 1) mothers for whom we know the race of their partner; and 2) mothers for whom we do not know the race of their partner. When we computed the between-group differences including both groups of mothers we observed that the SD increased from the 99 reported in Table 1 to 146. The explanation is that the percentage of missing observations for paternal race varied: 9.1% in EA, 43.5% in AA, 32.0% in NA, and 10.6% in MA groups. In addition we observed that the average birth weight was 159, 107, 82, and 127 g lower in EA, AA, NA, and MA mothers for whom their partner's race was missing. The explanation for the increase in SD therefore seems to be that the birth weights reported in Tables 1 and 2 are overestimated in different extents for the different ethnic groups. For example, in EA mothers, the overestimation is relatively modest because only 9.1% of the observations are missing. In AA mothers, the overestimation is more severe because 43.5% of babies with birth weights that are on average 107 g lower are not included in Table 1 and 2. A similar phenomenon may have underestimated the variance explained by paternal race. However, because we do not have similar information, we cannot estimate this as we did for the maternal

contribution to the between-group differences. The conclusion seems warranted, however, that missing paternal race cannot explain the maternal effects found in Tables 1 and 2.

IDENTIFICATION OF SPECIFIC MATERNAL FACTORS

Our results are consistent with other research findings suggesting that health and socioeconomic variables as measured in traditional large-scale studies account for only a modest part of the ethnic differences in birth weight. The current studies may be flawed, and further improving our methods and measures may eventually allow us to explain all ethnic differences in birth weight. An alternative strategy would be to shift the focus to risk factors that are largely unrelated to those presently under investigation. Studies of general classes of explanatory factors provide some clues about the possible nature of these alternative risk factors. First, maternal effects seem to be the most important component contributing to ethnic differences in birth weight. Other important characteristics of the relevant maternal factors are that they seem uncorrelated with the traditional socioeconomic and health behaviors, may not reflect specific differences between EA and AA groups, and are stable across pregnancies.⁷ One possibility is environmental variables that are traditionally not measured in large-scale surveys. Indeed, Collins and colleagues¹⁶ reported that racial discrimination affected birth weight differences between EA and AA groups. This finding could be due to the psychophysiological effect of stress or a result of a reduced quality in prenatal care. Other examples of environmental variables that are traditionally not measured include cultural differences in lifestyle.

Another risk factor that fits the above general description is maternal

genes. From a theoretical perspective, physical and physiologic characteristics of the mother are likely to affect the uterine environment, which is a determinant of birth weight. For maternal biology to exert control over birth weight also makes evolutionary sense.¹⁷ That is, in parents discordant for body size, the maternal control of fetal growth removes what might otherwise constitute an obstetric risk. Furthermore, empiric studies have shown that maternal factors influence the implantation of the conceptus, recognition of pregnancy, and formation of the placenta and cardiovascular system.¹⁸ Although genes are involved,¹⁹⁻²² the relative contributions of fetal versus maternal genes are often not distinguished. This distinction can be made using so-called reciprocal embryo transfer procedures where embryos from one strain of animals are transferred to the uteri of pseudopregnant recipients from a genetically different strain of the same animal. These studies show that, at least in mice, large maternal genetic effects may influence body weight at birth.^{23,24}

A maternal gene that affects birth weight can only explain ethnic differences if its allele frequencies vary among ethnic groups. Allele frequencies are a function of the social, demographic, and evolutionary history as well as random factors.²⁵ An obvious example is skin color, but these differences are not likely confined to physical appearance. In fact, allele frequency differences are so common that computer databases have been developed to help researchers obtain all the population-specific allele frequency estimates.²⁶

A concrete example comes from a study by Hocher and colleagues²⁷ who reported that the maternal C825T allele of the GNB3 gene lowered the birth weight of a mother's children; the frequency of the C825T allele is known to vary across ethnic groups.²⁸ Together these findings suggest that this gene may affect ethnic differences in birth weight. For instance, because the frequency of

its high-risk allele is $\approx 80\%$ in Black Africans versus 30% in Caucasians, the maternal GNB3 gene could explain part of the lower birth weights in AA babies. Another study could not replicate the association of the maternal C825T allele with birth weight.²⁹ The authors did find a relation with reduced head circumference and speculated that the maternal C825T allele could influence the fetal metabolic environment. Non-replication is common in genetics, and it does not necessarily imply that the original finding was a false positive.^{30,31} Other examples could be added, such as a study by Wang et al³² who found that women with specific variants in the CYP1A1 and GSTT1 genes had babies weighing significantly less. Allele frequencies of these genes also vary across populations.³³

Although more replication studies are required, these concrete examples demonstrate the general mechanism through which maternal genes could account for ethnic differences in birth weight. Furthermore, they address two misunderstandings. First, although assuming the existence of genetically homogeneous distinct "races" is ludicrous, ethnic groups as studied in large-scale studies may show genetic differences in the form of variations in allele frequencies. Second, some authors have suggested that the involvement of maternal genes may be unlikely because it would imply X-linked inheritance.¹⁰ However, we should not discard genetic explanations on the basis of the argument that they imply X-linked inheritance. Genes do not have to be on the X chromosome to affect birth weight through the mother but not through the fathers. The GNB3 gene, which is not on the X chromosome, is a candidate for hypertension. It possibly only has an effect when present in the mother because it could then, for instance, affect the blood circulation in the placenta. Similarly, CYP1A1 and GSTT1 are candidates for nicotine dependence, and one can see why

nicotine dependence in the mother is more important than nicotine dependence in the father.

Several strategies could be used to study the possible role of maternal genetic effects. A first approach would be to use genetically informative samples such as twins. The magnitude of the maternal genetic effects could then be estimated by comparing the similarity of the birth weights of infants from monozygotic twins versus the similarity of the birth weights of infants from dizygotic twins. The second approach would be to try to identify the relevant genetic variation. The full arsenal of genetic techniques can, in principle, be used. Many interesting genes are candidates, such as maternal genes for the insulin-like growth factor I that seem to influence fetal growth.^{34,35} Insulin secreted by the fetal pancreas in response to maternal glucose concentrations may be a key growth factor.⁴ Genes such as calpain-10 that seem to affect maternal blood glucose levels³⁶ and show differences in allele frequencies across ethnic groups³⁷ are therefore also potentially relevant. Finally, many candidates can be found in the literature on placenta development (eg, blood vessel formation), partly because similar processes are relevant to medical conditions such as cancer and chronic inflammation. Although scanning whole genomes with linkage studies has proved more difficult than originally had been envisioned,³⁸ large scale association studies may become possible in the future. Finally, microarray studies could be done to detect genes that are expressed in maternal placentas. A third approach is to measure the extent mothers belong to a certain ethnic genetic background.^{39,40} This measurement can be done by using a panel of markers that are selected for having alleles with high frequencies in one population but low frequencies in other populations. By typing these markers, a quantitative measure can be obtained that expresses how (a)typical a mother is for a certain

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ethnic group. This measure can then be correlated with birth weight. The hypothesis that maternal genes account for ethnic differences would be supported if this correlation were significant. For instance, if genes contribute to the low birth weight in AA babies, one would expect that mothers with a more typical AA background would give birth to babies with relatively lower weights. Furthermore, this genetic measure of ethnic background could be analyzed in combination with environmental risk factors to elucidate the possible role of gene-environment interactions.

A good way to advance research on ethnic differences in birth weight may be to search for the determinants of maternal effects. The study of environmental factors such as discrimination and cultural differences in lifestyle is important in this respect. Although some exceptions exist,⁴¹ clear theoretical and empiric indications show that maternal genes are involved. Therefore, these factors deserve to be considered too. Searching for genetic effects may sound controversial. However, certain ethnic groups may be at higher risk for diseases because of genetic reasons. Howard University, for instance, has started to gather blood samples or cheek swabs from 25,000 people to study specific health risks in AA. Birth weight is a predictor of health outcomes. Also, from a public health perspective, we should consider all potential risk factors. In vitro studies have shown that the maternal contribution to the quality of the uterine environment can in principle be improved.⁴² Knowledge of the relevant maternal genes and their func-

tion therefore has the potential to reduce the prevalence of low birth weight in ethnic groups that are at a particularly high risk.

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