

A STEP IN ANOTHER DIRECTION: LOOKING FOR MATERNAL GENETIC AND ENVIRONMENTAL EFFECTS ON RACIAL DIFFERENCES IN BIRTH WEIGHT*

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To advance research on birth weight differences between black and white infants, it may be useful to study maternal effects. These effects present a set of risk factors that are largely unrelated to those that are presently under investigation and fail to explain the gap in birth weight; empirical findings suggest their involvement. Although maternal effects can be environmental, as illustrated by recent findings, genetic effects could be important as well because gene frequencies are known to differ across the "racial" groups as studied by birth weight researchers, and maternal genes can exert a causal effect on birth weight.

Much research has focused on the birth weight difference between black and white babies. This research is important because of the negative association between low birth weight and health outcomes. Traditional variables provide only a partial explanation; therefore we used an approach that apportioned the difference to both genetic and environmental factors (van den Oord and Rowe 2000). Results showed no evidence for fetal genetic effects, but suggested that aspects of the fetal uterine environment that are constant across pregnancies could be important. On the basis of several arguments we speculated that maternal genes could play a role in addition to the traditional sociodemographic risk factors. We appreciate the two critiques of our article and thank the editors for offering us the opportunity to respond.

THE CONCEPT OF RACE

The critiques challenge both the idea of race as a biological concept and our use of subjects' self-identification to define their racial group. The author of one article suggested that people make these classifications merely by looking at skin color. If this were so, then dark-skinned Caucasians from the Indian subcontinent would self-classify as African. We believe that people use much more information such as their own physical appearance, including facial features and hair and eye pigmentation, as well as what they know about their familial ancestry.

We will not attempt to define race because it is not directly important for our article and because each definition is likely to be controversial. We merely note that the degree of genetic resemblance between people depends on how

many generations one must go back before there are common ancestors; thus closely related individuals such as siblings have common ancestors in the previous generation. People of the same racial or population group are much more distantly related but share ancestors because of common social and demographic history (Thompson and Neel 1997). We never claimed that racial groups were biologically discrete, nonoverlapping categories. Such a claim would be ludicrous in the case of African Americans, who obtained about 25% of their genes from European ancestors (Adams and Ward 1973; Destro Bisol et al. 1999; Reed 1969).

Birth weight researchers have classified people as African Americans and European Americans. Regardless of their exact social and demographic histories and whether or not *race* is the proper label for this classification, the crucial question is this: Do these groups possess different allele frequencies for various genetic loci? The answer must be affirmative. It is self-evidently true of the genes that influence skin color. Contrary to the suggestion made in one critique, a good deal is known about the genetics of skin pigmentation. An allele of the melanocortin 1 receptor gene (MC1R) confers black skin pigmentation and is fixed in African populations but absent in European populations (Harding et al. 2000). Cystic fibrosis and sickle cell anemia are two single-gene disorders that correlate strongly with racial self-identification. Significant differences between African Americans and European Americans have been reported for functional alleles of the dopamine beta-hydroxylase (DBH) gene, which is a candidate gene for psychiatric conditions (Cubells et al. 1997). In general, differences in allele frequency are so common that computer databases have been developed to help researchers obtain these population-specific estimates of allele frequency (Cheung et al. 2000). Thus, although we accept that "race" is a social and demographic concept, in part it is also a biological concept.

CAUSAL EFFECTS AND INTERACTIONS BETWEEN GENOTYPE AND ENVIRONMENT

We used a latent variable approach to apportion the difference in birth weight to three theoretical components without actually measuring the environmental variables and genes. We did not advance a "racial theory," and we view our model as strictly an exploratory data analysis tool. It would be equally incorrect to assume that all researchers who use ANOVAs to analyze their data think that the ANOVA model reflects their view of reality. Some basic features of our approach, however, may require further elucidation.

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In one article we were faulted for ascribing causality to latent variables. Yet there is no sharp distinction between our latent variables and the observed variables that typically are used in demography. Social class is often indexed by years of parental education, but few scholars would take a correlation as literally meaning that parents' "seat time" in school somehow affects the fetus' growth or its gestation time. Educational attainment indexes a latent variable that represents a process that presumably links education to birth weight. Thus, although our model explicitly uses latent variables, conceptually regression analyses can involve latent variables as well.

A second criticism is that we used race as a causal variable and that it is impossible to ascribe causality to variables that cannot be manipulated. First, not race but the latent genetic and environmental factors are the causal variables. In our approach we basically estimate the mean genetic and environmental effect in each group, and then use the regression coefficients within groups to estimate the impact of these latent means on the observed group means. Although we use measured variables, this procedure is identical to that of other studies of racial differences in birth weight. That is, correlates of low birth weight such as poverty typically are incorporated in a regression analysis to examine how extensively group differences in poverty can explain the race gap. We fully agree that causal inferences from correlational data can be problematic. The same criticism, however, applies to the great majority of birth weight studies as well as to many studies from other scientific disciplines. These inference problems cannot be an argument for refraining from nonexperimental studies. Experimental designs often may not be possible for practical or ethical reasons, and studying phenomena in isolation may fail to capture the complexity of the reality.

In addition, causal hypotheses can be meaningful even if controlled experiments are not possible. Thus the astronomers' statement that the sun shines because it burns hydrogen fuel in nuclear fusion is not trivial simply because it cannot be confirmed scientifically by direct manipulation of the sun.

There are no fundamental problems in assigning a causal role to genes. Associations between measured genes and other variables even must be causal effects of the gene (except in the presence of "population stratification," but approaches exist to control for this; e.g., Thomson 1995). The reason is that phenotypes and environmental factors cannot cause allelic variation in the measured genotypes (Allison et al. 1999). Genetic effects also can be manipulated. In mice, researchers "knock out" or insert genes to study their functional significance and to create animal models for diseases (Cvetkovic et al. 2000). In gene therapy, genes are added to somatic tissue to correct for particular genetic deficiencies (Somari et al. 2000). Therefore the conceptual status of genes as causal variables is as strong as that of most environmental variables.

Interactions between genotype and environment may be involved in the origin of racial differences in birth weight. In our study we did not test for interactions. One reason is that we lack a hypothesis about how fetal genes could interact

with environmental effects; thus we began by testing for main effects. Another reason is that interactions between genotype and environment seem difficult to detect (McCall 1991; Wahlsten 1990): among the possible explanations are methodological limitations that apply to our study design as well. Finally, it may be important to define precisely what is meant by "interaction"; the presence of an interaction does not necessarily mean that our conclusions about the main effects are invalid. Thus studies demonstrating changes in physiologic pathways as a response to environmental influences may not imply that our latent fetal genetic and environmental variables should interact in the *statistical* "analysis of variance" sense of the word. Even if they did so, one could argue that although the size of this effect depends on fetal genes, there is still a main maternal effect. Nonetheless, the subject is important, and we share an interest in studying the interplay of genetic and environmental factors (Rowe, Jacobson, and van den Oord 1999; van den Oord 1999).

MATERNAL GENES

In both articles the authors suggested that we cited genetic influences in our conclusion because we failed to find them in our analyses. Yet when traditional variables explain birth weight differences only partially (Cramer 1995; Hulse, Abner, and Alexander 1991), it makes sense to speculate about risk factors that are largely unrelated to those presently under investigation on the basis of the results from one's own study and what is known from the literature. Neither article described our reasoning in detail. We want to draw attention not to the fact that we speculated about maternal genetic effects but to the substance of our arguments.

Our analysis suggested that a fetal environment that is constant across pregnancies is important for the difference in birth weight. Because uterus-specific factors are included in this environmental component, we argued that maternal effects could be an additional factor. This idea is supported by the many studies showing that the birth weights of maternal siblings, who share the same uterine environment, are much more alike than those of paternal siblings, who may share the same family environment but not the same "maternal" environment. Furthermore, the uterine environment is likely to be affected by the mother's physical and physiological characteristics, it makes evolutionary sense for maternal biology to exert control over birth weight, and the determinants of maternal effects should be stable across pregnancies. Therefore we speculated further that maternal genes could affect birth weight via the uterine environment.

To explore this hypothesis regarding maternal-genetic determinants of the racial difference in birth weight, we suggested the use of genetically informative samples of mothers: for example, a sample of monozygotic twins and a sample dizygotic twins. Other possibilities exist, however. Some studies examined birth weights of infants with parents of different races (Collins and David 1993; Migone et al. 1991). With controls for sociodemographic and reproductive variables, birth weights of infants born to white mothers and black fathers were higher than those of infants with

black mothers and white fathers and similar to those of infants born to white couples. This finding supports the first part of our hypothesis, which assumes that maternal effects are important for racial differences in birth weight but are not informative about whether these effects are environmental or genetic.

Collins and David (1993) support environmental effects and reject the genetic explanation on the basis of the argument that (X-linked) inheritance exclusively through the mother is unlikely. Indeed it seems possible that environmental variables that usually are not measured in birth weight studies, such as the stress experienced by pregnant black women as a result of institutional and individual racism, influence birth weight and are different for white-black couples than for black-white couples. A genetic explanation is equally plausible, however. A gene governing blood pressure may be irrelevant when present in the father but important if present in the mother because it could affect the blood circulation in the placenta. This example also shows that the relevant genes need not be X-linked.

Further research strategies are suggested by molecular genetics. The decrease in the cost of genotyping should make it feasible to measure the degree of racial admixture with European-heritage kin in mothers from African American families (Destro Bisol et al. 1999; Shriver et al. 1997). The genetic hypothesis would be supported if a higher level of racial admixture decreases birth weight, even with controls for various environmental covariates. This design is attractive because it does not require measuring maternal genes for birth weight. The use of known maternal genes would make it possible to evaluate directly their contribution to the race gap. In this way a recent study found that the maternal C825T allele of the GNB3 gene lowered the children's birth weight (Hoche et al. 2000). This gene is particularly interesting because its high-risk C825T allele is much more frequent in Africans and African Americans (up to 80%) than in Caucasians (about 30%; Siffert et al. 1999). On the assumption that the effect of the maternal C825T allele on birth weight can be replicated (Feldman and Hegele 2000), the implication is that it will contribute to the race gap.

CONCLUSIONS

Our reply perhaps may be summarized best with a concrete example. Assume that the findings for GNB3 can be replicated and that its C825T allele is a risk factor for low birth weight. In theory it is possible to manipulate the effect of this allele; because birth weight cannot cause allelic variation in the maternal GNB3 gene, there is no reason to deny it causal status. Regardless of their exact social and demographic histories and whether or not *race* is the proper label for this classification, the frequency of the C825T allele appears to be considerably higher in African Americans than in European Americans. This fact implies a maternal genetic contribution to lower birth weight among black infants.

At present little is known about such specific genes; therefore we used a latent variable approach that enabled us to apportion the differences in birth weight to genetic and

environmental effects without actually specifying and measuring all the specific variables. This approach was not meant as a remedy for all problems but as an attempt to consider a set of risk factors that are largely unrelated to those which are presently under investigation and fail to explain the gap in birth weight. As is true for many other nonexperimental studies of complex phenotypes studied in real life, we acknowledge that there are limits to the extent to which causal conclusions can be drawn and to the complexity of the models that can be fitted.

In our opinion, a promising way to advance research on birth weight differences between black and white infants is to test competing genetic and environmental models of this maternal effect. We need astute research strategies that incorporate these competing hypotheses on the racial difference and that allow for possible interactions and correlations between genotype and environment. Racial self-classification remains interesting because of racial disparities in the frequency of babies with low birth weight. Just as demographers did nothing wrong in making the original racial classification, we see nothing wrong with using this classification to explore the possible origin of the differences in birth weight, whether this origin is genetic, environmental, or both.

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