Racial differences in susceptibility to obesity

Dear Sir:

We disagree with the conclusions about the uncoupling protein 3 gene (UCP3) as a genetic determinant of susceptibility to obesity in blacks and whites that were put forward by Kimm et al in their report in a recent issue of the Journal (1) and in the accompanying editorial (2). A serious problem exists in genetic epidemiology in relation to multiple statistical testing. Kimm et al studied 8 single-nucleotide polymorphisms (SNPs) and reported that, when one of them (UCP3 exon 5) was used to create a stratum, a significant difference existed for resting metabolic rate (RMR) between blacks and whites (P < 0.02 for the race interaction). However, at least 8 tests would need to have been conducted for that analysis alone, even without consideration of the other possible phenotypes (eg, obesity and RMR). A standard multiple testing correction would require a much smaller P value than was reported, because this was not an a priori hypothesis. It also appears that the significant comparison involving the CC genotype was based on 6 blacks and 15 whites, which does not seem like a very large sample on which to base an inference that genetic susceptibility varies between 2 entire populations. It should further be noted that this SNP had no relation to RMR in whites, which suggests that the finding in blacks is a Type 1 error.

Aside from the deficiencies in the statistical analysis, we are concerned about the inference of causality that is being made. Whereas it is true that many studies have shown that RMR is lower in blacks than in whites and that a nominally significant difference exists by genotype between the racial groups in this study that ignores multiple comparisons, no evidence is presented by Kimm et al that RMR is related to obesity. In fact, of all studies from the literature, only one shows a causal connection between lower RMR and susceptibility to obesity, even though that is an obvious hypothesis. It is not at all clear to us, therefore, why the authors and the editorialists would conclude that the UCP genotype is a cause of differential racial susceptibility to obesity when there is little evidence it is related to obesity.

On the other hand, it seems to us that there are other, much more plausible explanations for the differences in obesity among the various ethnic or racial groups in the United States. The large social class effect suggests a crucial role for lifestyle. Many groups, notably Native Americans and Hispanics, suffer from epidemic obesity to the same or a greater degree and are not particularly similar to blacks in terms of genetic affinity. Likewise, temporal trends show that, in the 1960s, blacks were not more obese in general than were whites, and in other countries blacks do not have high rates of obesity (3).

A tendency exists in epidemiologic research to conclude that genetic factors are important in racial differences, and a substantial number of reports make this assertion in other areas, such as hypertension (4–7). That literature, however, has been very unreliable, postulating effects that can never be replicated. In fact, it is very difficult to identify a report of causal genetic differences between blacks and whites in which the findings have stood the test of time as reliable or useful. In the case addressed here, it seems to us that much more would be accomplished by attempting to define the underlying causes of obesity before postulating genetic causes of differences. Kimm et al have prospective data on RMR and weight change, for example. It would have been more instructive to know whether a relation exists between RMR and obesity before concluding that a causal connection exists between an SNP in UCP and the differences between blacks and whites in susceptibility to obesity.

In our opinion, race has been overused in epidemiologic research as the basis for causal hypotheses (6, 7). This practice has been a serious distraction and has wasted considerable resources (8). Without a clear-cut demonstration of a relation between the putative at-risk genotype and the phenotype of interest in both groups, causal inferences are not justified.

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Reply to R Cooper and A Luke

Dear Sir:

We appreciate the comments of Cooper and Luke in response to our recently published report (1). Although we welcome a lively debate in the interest of scientific inquiry, we are concerned that Cooper and Luke attribute to us conclusions that we did not actually draw. We agree that multiple hypothesis testing can be problematic. For this reason, we presented the estimated P value for all of our tests so that readers may draw their own conclusions from the data. Certainly, our sample size was small, and that is the reason all of our conclusions were expressed only as tantalizing clues. We stated, “This observation of racial differences in the UCP3 exon 5 gene effect is made more complex by the overall small sample size in the present study . . . .” We also acknowledged that further study with a larger sample size is necessary.
As for the writers’ concern about the nature of the causal inference made, we noted in our report that the polymorphism in question is not a functional change and therefore cannot be causal. Our primary analysis considered only resting energy expenditure, not obesity. Our secondary (ie, exploratory) analysis examined adiposity, not obesity. Hence, we refute the assertion that we made a “causal inference” regarding obesity. Nowhere do we “conclude” that the UCP3 genotype is a “cause” of differential racial susceptibility to obesity. Any connection made with racial differences in obesity appears only in our speculative discussion at the end of a report in which no conclusions were drawn.

In any genetic study, the definition of phenotype is critical. In our analysis, the phenotype was resting energy expenditure, not obesity or body mass index. Cooper and Luke seem to suggest that this is not the “phenotype of interest.” We strongly disagree, because we believe that attempts to understand differences in resting energy expenditure will lead to a better understanding of the metabolic aspect of the energy balance equation.

We agree with Cooper and Luke on the crucial role that lifestyle plays. In fact, our concluding statement is, “...the high prevalence of obesity in African American women in the United States today may be the result of their contemporary lifestyle of relatively high energy intake and physical inactivity in the presence of an underlying genetic propensity for efficient energy conservation.”

Finally, Cooper and Luke are mistaken in their assertion that we have longitudinal data on resting energy expenditure and weight change. We have data on resting energy expenditure at only one time point, when the study subjects were aged 18–21 y. We hope that this response fully addresses and helps clarify some of the issues raised by Cooper and Luke.

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Furthermore, we believe that these statistical limitations can be mostly discounted because the association between uncoupling protein 3 (UCP3) and UCP2 alleles and metabolic rate has already been replicated in at least 2 other studies (2, 3). Although differences between studies preclude conclusions about the roles of specific polymorphisms in racial differences, other investigators have reported differences in allelic frequencies and association between African Americans and whites for alleles for UCP2 and UCP3 (4). We have numerous other differences of opinion with Cooper and Luke on topics not reviewed by Kimm et al (1) or Schonfeld-Warden and Warden (5).

Before discussing these specific issues, we would like to point out that neither Kimm et al nor the accompanying editorial (5) suggested that a G→T single-nucleotide polymorphism (SNP) in exon 5 of UCP3 caused metabolic and obesity effects. Rather, both publications suggest that this SNP might be linked with other alleles that do have such effects. This suggestion is consistent with recent reports of differences between African Americans and whites in the sizes and numbers of haplotype blocks. Haplotype blocks are sizable genomic regions for which there is little evidence for historical recombination and within which only a few common haplotypes (linked SNPs on the same chromosome) are observed (6). The authors of a recent study stated, “We estimate that half of the human genome exists in blocks of 22 kb or larger in African and African-American samples and in blocks of 44 kb or larger in European and Asian samples. Within each block, a very small number of common haplotypes (3 to 5) typically capture 90% of all chromosomes in each population. Both the boundaries of blocks and the specific haplotypes observed are shared to a remarkable extent across populations. The main variation is a subset of alleles (haplotypes and recombinant forms) that are observed only in samples with more recent African ancestry” (6). Thus, it is possible (likely) that the SNP genotyped by Kimm et al in exon 5 of UCP3 is a member of a smaller or different haplotype block in African Americans than in whites. The immediate implication is that the UCP3 exon 5 SNP may be providing different information about adjacent SNPs and adjacent genes, such as UCP2, in African Americans than in whites.

Our first specific difference of opinion with Cooper and Luke concerns the roles of UCP3 and UCP2 in causing obesity. In their first sentence, they stated, “We disagree with the conclusions about the uncoupling protein 3 gene (UCP3) as a genetic determinant of susceptibility to obesity in blacks and whites that were put forward by Kimm et al in their report in a recent issue of the Journal … and in the accompanying editorial ….” A recent review of the literature (7) identified multiple independent studies with significant associations between UCP2 and UCP3 alleles with obesity. Many of these studies reported such low P values for the association of UCP2 or UCP3 alleles with obesity phenotypes that the P values remain highly significant even after correction for multiple testing. Several (but not all) alleles in both UCP2 and UCP3 have been associated with obesity (usually body mass index but sometimes also fat mass) in several different ethnic groups, including Europeans, Indians, Asians, and African Americans (7). Thus, although no monogenic obesity disorders have been attributed to mutations of UCP3 or UCP2, current evidence is strongly consistent with the hypothesis that one or both influence the development of human obesity.

Our second disagreement with statements made by Cooper and Luke concerns the relation of energy expenditure to obesity. We agree that a