ELSEVIER

Social Science & Medicine 66 (2008) 1670–1674

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

Functional or futile?: The (in)utility of methodological critiques of genetic research on racial disparities in health. A commentary on Kaufman's "Epidemiologic analysis of racial/ethnic disparities: Some fundamental issues and a cautionary example"

Reanne Frank*

Department of Sociology, Ohio State University, 300 Bricker Hall, 190 N. Oval Mall, Columbus, OH 43210, USA

Available online 14 January 2008

Keywords: Health disparities; Statistical inference; Causality; Etiology; Race/ethnicity

In 1994, Richard J. Herrnstein and Charles Murray published *The Bell Curve*, a book that used a range of statistical techniques to posit racial differences in intelligence (Herrnstein & Murray, 1994). According to Hammonds (2006), there have been two different types of reactions to the publication. On one hand, the book generated a host of detailed critiques that were devoted to carefully dissecting the statistical analyses and describing every methodological flaw and inconsistency in an effort to debunk the book's findings (Devlin, Fienberg, Resnick, & Roeder, 1997; Fischer et al., 1996; Heckman, 1995). The second type of reaction not only acknowledged the importance of the first, but also pointed to its futility. This camp argued that methodological critiques will fail to discredit theories on racial difference in intelligence because they ignore the fact that the research is being driven by more ideological forces (Aronowitz, 1996).

Extending Hammond's typology, Kaufman's (2008) article falls squarely into the first camp in terms of the way it responds to research that posits genetic difference as a cause of racial/ethnic disparities in health. The first part of the critique is definitional and argues that epidemiological analytic models that are used to posit genetic explanations for racial health disparities violate the statistical foundation of causal inference. The second part of the critique is more practical, focusing narrowly on the methodology behind a 2001 *New England Journal of Medicine* (*NEJM*) paper that compared the efficacy of ACE inhibitors with placebo in Black and White patients (Exner, Dries, Domanski, & Cohn, 2001).

Most of the points addressed in the critique have been raised by Kaufman himself in earlier work. In a series of articles written over the last 10 years, Kaufman and his co-author Richard S. Cooper have argued the same points that are repeated here regarding the problems inherent in using counterfactual models to test hypotheses of innate differences (Cooper & Kaufman, 1998; Kaufman & Cooper, 1999; Kaufman & Cooper, 2001; Kaufman, Cooper, & McGee, 1997). As echoed in the present article, they have stated that while counterfactual models are appropriate for testing theories of discrimination (i.e. the causal factor is external to the individual), they are not acceptable models when the

* Tel.: +1 614 247 4679; fax: +1 614 292 6687.
E-mail address: frank.219@osu.edu

0277-9536/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.socscimed.2007.11.047

causal factor driving racial disparities is hypothesized to be intrinsic to the individual. The more basic claim that an innate factor cannot be considered a causal factor goes back even farther to the mid-1980s when Paul W. Holland addressed the fundamental question of what logically constitutes a cause in statistical modeling (Holland, 1986). He concluded that, "for causal inference, it is critical that each unit be *potentially exposable* to any one of the causes. As an example, the schooling a student receives can be a cause, in our sense, of the student's performance on a test, whereas the student's race or gender cannot" (Holland, 1986; 946). This argument has not been without its critics. One such argument has questioned the appropriateness of delimiting what can or cannot be a cause in statistical inference. For example, Glymour (1986) argues that if counterparts are conceivable, e.g. if there was a male counterpart to my female self who was otherwise identical to me at the moment of conception, then counterfactuals and causal relations are appropriate, even if the exposed and unexposed counterparts cannot meaningfully be described as the same individual. Despite these considerations, practical applications of counterfactual models often allow for some violation of their logical premises. As a result, many of the debates are relegated to a philosophical domain that is often outside of the purview of current practitioners of standard epidemiological analyses (for more debate see Kaufman & Cooper, 1999; Muntaner, 1999).

In the critique of the analysis of the Studies of Left Ventricular Dysfunction (SOLVD) data, Kaufman again raises a problem that he has frequently articulated in earlier work regarding the problems of attempting to statistically adjust for confounding variables, either through the addition of controls or through matching strategies, without accounting for the large number of unmeasured factors that are related to the outcome and differ between Blacks and Whites (Kaufman & Cooper, 2001; Kaufman et al., 1997). The argument follows that because racism creates imbalances on such a large number of potential covariates, no statistical adjustment with covariates that we are able to measure will ever be sufficient to allow for counterfactual contrasts. As a result, any remaining racial/ethnic differences in a given outcome could always be due to differences in unmeasured variables across the racial/ethnic groups. This is why critics are so quick to fault analyses (such as is exhibited with the SOLVD data) that attribute unexplained variation in the outcome to genetic differences between racial groups.

The repetitiveness of the critiques posited by Kaufman and the consistency with which they are ignored in current research gets back to the second type of reaction to *The Bell Curve*. This camp argues that methodological critiques are futile because they are never able to overcome the enticing logic that racial/ethnic differences are caused by innate genetic factors and not by societal inequities. Kaufman (2008) also notes this at the end of his article when he cites a "strong predilection for racial essentialism in biological thinking". These concerns raise the timely question as to whether methodological critiques of research on racial differences in biology end up being more futile than functional. If racial essentialist thinking is so ingrained in the mindsets of researchers then specific methodological critiques are unlikely to be an effective strategy in countering the research. Instead of trying to convince researchers of the methodological problems in their analyses, we may be better served by going back to the very foundations of racial essentialist thought in science.

My own answer to this concern and one that I think Kaufman would share is that these are not two completely separate endeavors. Methodological critiques have the potential to push researchers to question more fundamental assumptions of their understanding of racial differences. There is, however, the continued danger that current critiques are doomed to recycle the same ideas over and over with little impact on current research. Below, I enumerate several suggestions that may help to avoid this fate.

First, the content of future methodological critiques should be narrowly focused and include in-depth analyses. Some of the strongest points made in Kaufman's article concern detailing specific errors committed in the SOLVD analysis. One example is the observation that baseline differences in risk bias the treatment effect for the sicker population (i.e. the Black population in the SOLVD data) towards the null when a ratio measure of treatment effect is used. Kaufman also makes the key point that there were no significant differences between Blacks and Whites in the primary endpoint of mortality and that this finding was essentially ignored in the *NEJM* paper's discussion in favor of a focus on the more problematic outcome of hospitalization. An interesting follow-up to the *NEJM* article is that a paper by one of the original authors re-analyzed the SOLVD data and published findings countering the *NEJM* article's conclusion of biological racial differences (Dries, Strong, Cooper, & Drazner, 2002). This subsequent paper has been referenced to demonstrate the tenuous nature of many findings of racial biological difference in treatment effects and the role of methodological decisions in influencing conclusions of racial

difference. Specific critiques of earlier analyses are useful to the extent that they point out definable problems, giving readers concrete evidence with which to evaluate the conclusions. They also give researchers the tools with which to avoid making the same types of mistakes themselves, hopefully minimizing their occurrence and subsequent need for further critiques.

The importance of specific and in-depth critiques can be seen in a current trend in health disparities research. As the increase in genetic data and related technologies continues unabated, some disparities researchers have begun to embrace the possibility of genetic explanations for racial differences in their research (Risch, 2006; Salari et al., 2005; Sinha, Larkin, Elston, & Redline, 2006). One development concerns the importation of the concept of geographical ancestry into analyses of racial differences. Instead of discussing genetic differences by race, some researchers have instead chosen to refer to the possibility of differences by ancestral background (Bamshad, 2005). For a good deal of research, and particularly in medical practice, this will likely only become a matter of semantics, with race being switched out for the more palatable term of ancestry (Frank & Frank, 2005). The underlying logic of genetic racial differences remains untouched. Other researchers are developing statistical measures of ancestral background that are being marketed as a way to account for and/or identify genetic differences among contemporary population groups (Bamshad et al., 2003; Shriver et al., 2005; Tang et al., 2005). Yet these measures, and the ways in which they have been used in studies of health disparities, have been contested (Pfaff, Barnholtz-Sloan, Wagner, & Long, 2004; Romualdi et al., 2002; Weiss & Fullerton, 2005). As researchers who study racial differences begin to incorporate ancestral arguments into their research, it is important that they be informed of the ways in which biogeographical ancestry is estimated and the concerns with how different technologies are currently being used in genetic association studies. To make matters more complicated, many of the potential pool of new users of this technology lack a familiarity with genetic concepts that would allow them to be critical consumers of the knowledge. In such a situation, methodological critiques that specify how these estimates were created and how they do (or do not) differ from older biological conceptualizations of race will be invaluable. As ancestral estimates gain more prominence in research on racial differences in complex disease, there is a corresponding need for specific methodological critiques detailing the problems and assumptions of this type of technology.

A second recommendation for how methodological critiques can be made to be more effective involves their scope. While the content of methodological critiques should be specific and narrow, their scope should be broad. Racial essentialist thinking is pervasive in research on racial/ethnic differences across a wide range of health and behavioral outcomes. The present article focused on the majority of epidemiological studies that use observational data to test for racial differences using the logic of counterfactual causal models. Exempt from this critique would be all randomized controlled trials that theoretically account for imbalances in both observed and unobserved differences in covariate distributions. Yet the long arm of a biological conceptualization of race has touched even this gold standard of epidemiological analyses. In 2005, the US Food and Drug Administration (FDA) approved BiDil, the first drug in the United States to be based on a patent formulated in terms of its benefit to a specific racial or ethnic group. BiDil, a combination of hydralazine and isosorbide dinitrate, was approved to treat heart failure in African-Americans exclusively, potentially ushering in a new era of race-based medicine and medical care. The FDA's approval of BiDil was based on the results of a randomized control trial (A-Heft) that was so successful it was halted early due to higher mortality in the placebo group compared to the group receiving BiDil (Taylor, Cohn, & Worcel, 2005).

The methodological flaws in the A-Heft trial, if there are any, are likely minor. It was a well-run and costly randomized controlled trial. Nonetheless, it merits one of the most stringent of methodological critiques. The logic behind the A-HeFT trial was that BiDil would work differently in African-Americans because they are biologically different than other racial groups, in this case possibly due to lower levels of nitric oxide in their blood (Taylor et al., 2005). But instead of making lower levels of nitric oxide the determining factor for admission into the trial, admission depended on whether or not the participants self-identified as Black. As detailed elsewhere by Kahn (2004), the decision to include only Blacks in the A-Heft trial was motivated largely by commercial interests. Because BiDil combined two generic drugs, the only way to obtain a new drug approval was through a race-specific patent. The end result has been that BiDil biologized race by suggesting that African-Americans benefit from a drug in ways that Whites do not because of unspecified characteristics inherent to being Black. To date, the response of Whites or other groups with heart failure receiving current standard therapy to BiDil remains unknown.

The point of detailing the story of BiDil is to highlight the need for methodological critiques that are broad in scope. If future critiques are limited to those that demonstrate flawed statistical reasoning or poor methodology we will end up missing a good deal of influential research that biologizes racial differences and is worthy of critique.

A third recommendation for future methodological critiques is that researchers broaden their thinking about what constitutes social influences versus biological or genetic with regard to health. Causal processes that are located outside the body (i.e. racism) have physiological effects (i.e. inside the body). It is important to remember that there are innumerable physiological processes that are influenced by the environment and whose effects are not pre-programmed in an individual's DNA (Krieger, 2005). Findings of racial differences inside the body (e.g. racial differences in nitric oxide levels) do not necessarily point to racial differences in genotype. Rather, different social environments could impinge on physiological processes to influence nitric oxide levels. This is an important point because it acknowledges the key role of gene/environment interactions in influencing phenotype. The current push in research on racial health disparities towards documenting the role of racial differences in genotype is overstepping the potentially much more important role of gene/environment interaction in contributing to differential risk. Researchers of racial differences in complex disease should engage in more concerted interdisciplinary collaborations to explore the possibility of gene and environment interactions and their role in contributing to disparities. While an understanding of more complex interactions is perhaps a long way off, the initiation of collaborations now will help to pave the way for more detailed work in the future (Cooper, 2003).

A fourth goal for future methodological critiques is that they become self-generating. Researchers who cite articles that have received critiques should also reference the critique in addition to the original findings. In the case of the *NEJM* piece, Kaufman notes that it has been cited repeatedly in support of the possibility that genetic factors may be responsible for disparate treatment effects across racial groups. All of these references were published *after* two articles had questioned the results of the *NEJM* analysis, one using the same data and finding no difference in treatment effects and another using a meta-analysis to demonstrate no significant racial differences in the effects of beta-blockers or ACE inhibitors (Dries et al., 2002; Shekelle et al., 2003). A more recent trial that purposively included large enough numbers of Blacks and Whites to conduct stable sub-group analyses found no significant differences in the treatment effects of antihypertensive treatment regimes in the development of cardiovascular disease (Wright et al., 2005). The only way for methodological critiques to gain any traction is for researchers themselves to take on the responsibility of reporting these types of contradictory findings when they exist.

A final point is that methodological critiques of research on racial disparities in health should try to avoid setting up "us" against "them" dichotomies. In describing the limits of methodological critiques, Hammonds (2006) points out that many times such exercises end up "pejoriatively" labeling scientists who are committed to uncovering the causes of racial disparities in health as racists or antiquated relics from a previous era. In an effort to avoid this fate, critics of more genetically oriented health disparities research would do well to remember that most of the researchers who study health disparities are committed to identifying the causes of disparities and eliminating them. This means that one way to increase the effectiveness of such critiques is to appeal to specific scientific evidence or to critique the lack thereof. If critiques are formulated in such a way that they are detailed, accessible, and consistent then I believe that there is hope that they will begin to make a visible impact on the quality and quantity of research that alleges genetic differences as a cause of racial health disparities.

References

Aronowitz, S. (1996). Interview with Stanley Aronowitz. In J. L. Kincheloe, S. R. Steinberg, & A. D. Gresson III (Eds.), *Measured lies: The Bell Curve examined* (pp. 411–418). St. Martin's Press.

Bamshad, M. (2005). Genetic influences on health: does race matter? *The Journal of the American Medical Association, 294*(8), 937–946.

Bamshad, M. J., Wooding, S., Watkins, W. S., Ostler, C. T., Batzer, M. A., & Jorde, L. B. (2003). Human population genetic structure and inference of group membership. *American Journal of Human Genetics, 72*(3), 578.

Cooper, R. S. (2003). Gene-environment interactions and the etiology of common complex disease. *Annals of Internal Medicine, 139*(5), 437–440.

Cooper, R. S., & Kaufman, J. S. (1998). Race and hypertension: science and nescience. *Hypertension, 32*, 813–816.

Devlin, B., Fienberg, S. E., Resnick, D. P., & Roeder, K. (1997). *Intelligence, genes and success: Scientists respond to the Bell Curve*. Springer.

Dries, D. L., Strong, M. H., Cooper, R. S., & Drazner, M. H. (2002). Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *Journal of the American College of Cardiology, 40*(2), 311–317.

Exner, D. V., Dries, D. L., Domanski, M. J., & Cohn, J. N. (2001). Lesser response to angiotensin-converting-enzyme inhibitor

therapy in black as compared with white patients with left ventricular dysfunction. *New England Journal of Medicine, 344*(18), 1351–1357.

Fischer, C. S., Hout, M., Jankowski, M. S., Lucas, S. R., Swidler, A., & Voss, K. (1996). *Inequality by design: Cracking the Bell Curve Myth*. Princeton University Press.

Frank, R., & Frank, D. (2005). Race and genetic influences on health-letter. *The Journal of the American Medical Association, 295*, 384–385.

Glymour, C. (1986). Comment: statistics and metaphysics. *Journal of the American Statistical Association, 81*(396), 964–966.

Hammonds, E. M. (2006). ''Straw men and their followers: the return of biological race.'' Is race real? [A Web Forum organized by the Social Science Research Council (SSRC)] Available from. <http://raceandgenomics.ssrc.org/>.

Heckman, J. J. (1995). Lessons from the Bell Curve. *Journal of Political Economy, 103*(5), 1091–1120.

Herrnstein, R. J., & Murray, C. (1994). *The Bell Curve: Intelligence and class structure in American life*. Free Press.

Holland, P. W. (1986). Statistics and causal inference. *Journal of the American Statistical Association, 81*(396), 945–960.

Kahn, J. (2004). How a drug becomes ''Ethnic'': law, commerce, and the production of racial categories in medicine. *Journal of Health Policy, Law, and Ethics, IV*(1), 1–46.

Kaufman, J. S. (2008). Epidemiologic analysis of racial/ethnic disparities: Some fundamental issues and a cautionary example. *Social Science & Medicine, 66*(8), 1659–1669.

Kaufman, J. S., & Cooper, R. S. (1999). Seeking causal explanations in social epidemiology. *American Journal of Epidemiology, 150*(2), 113–120.

Kaufman, J. S., & Cooper, R. S. (2001). Commentary: considerations for use of racial/ethnic classification in etiologic research. *American Journal of Epidemiology, 154*(4), 291–298.

Kaufman, J. S., Cooper, R. S., & McGee, D. L. (1997). Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. *Epidemiology, 8*(6), 621–628.

Krieger, N. (2005). Embodiment: a conceptual glossary for epidemiology. *Journal of Epidemiology and Community Health, 59*, 350–355.

Muntaner, C. (1999). Invited commentary: social mechanisms, race, and social epidemiology. *American Journal of Epidemiology, 150*(2), 121.

Pfaff, C. L., Barnholtz-Sloan, J., Wagner, J. K., & Long, J. C. (2004). Information on ancestry from genetic markers. *Genetic Epidemiology, 26*(4), 305–315.

Risch, N. (2006). Dissecting racial and ethnic differences. *New England Journal of Medicine*.

Romualdi, C., Balding, D., Nasidze, I. S., Risch, G., Robichaux, M., & Sherry, S. T., et al. (2002). Patterns of human diversity, within and among continents, inferred from biallelic DNA polymorphisms. *Genome Research, 12*(4), 602–612.

Salari, K., Choudhry, S., Tang, H., Naqvi, M., Lind, D., & Avila, P. C., et al. (2005). Genetic admixture and asthma-related phenotypes in Mexican American and Puerto Rican asthmatics. *Genetic Epidemiology, 29*(1), 76–86.

Shekelle, P. G., Rich, M. W., Morton, S. C., Atkinson, C. S. W., Tu, W., & Maglione, M., et al. (2003). Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *Journal of the American College of Cardiology, 41*(9), 1529–1538.

Shriver, M., Mei, R., Parra, E. J., Sonpar, V., Halder, I., & Tishkoff, S. A., et al. (2005). Large-scale SNP analysis reveals clustered and continuous patterns of human genetic variation. *Human Genomics, 2*(2), 81–89.

Sinha, M., Larkin, E., Elston, R. C., & Redline, S. (2006). Self-reported race and genetic admixture. *New England Journal of Medicine, 354*(4), 421.

Tang, H., Quertermous, T., Rodriguez, B., Kardia, S. L. R., Zhu, X. F., & Brown, A., et al. (2005). Genetic structure, self-identified race/ethnicity, and confounding in case–control association studies. *American Journal of Human Genetics, 76*(2), 268–275.

Taylor, A. L., Cohn, J., & Worcel, M. (2005). Isosorbide dinitrate and hydralazine in Blacks with heart failure. *New England Journal of Medicine, 352*, 1043.

Weiss, K. M., & Fullerton, S. M. (2005). Racing around, getting nowhere. *Evolutionary Anthropology, 14*, 165–169.

Wright Jr., J. T., Dunn, J. K., Cutler, J. A., Davis, B. R., Cushman, W. C., & Ford, C. E., et al. (2005). Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *The Journal of the American Medical Association, 293*(13), 1595–1608.