The strategy of adjusting racial differentials for measures of social status to separate the “biologic” and “nonbiologic” pathways that produce these disparities has elicited significant criticism. The problems are numerous: Causal parameters for race effects of interest are not well defined (1). Deficiencies in the specification or measurement of causal intermediates can lead to spurious apparent race effects (2). Measured intermediates are inherently inadequate because of incommensurability of social measures between racial groups (3). Adjustment is made for factors that are causally subsequent to exposure (4). Finally, even if race were considered a meaningful “exposure” and assumed (however absurdly) to be essentially randomized to individuals, this assumption would be sufficient only to identify total effects of race; effects transmitted through direct or indirect pathways still would not be separately identifiable without additional, unrealistic assumptions about factors affecting both measured intermediates and disease outcome (5, 6).

Despite these and other criticisms, the inferential strategy of positing biologic race effects by adjusting for social factors is unfortunately still quite commonly used. The paper by Robbins et al. in a recent issue of the Journal (7) seems to be distinguished from others in this category by the authors’ many stated caveats and reservations, some of which appear self-contradictory. The authors agreed that there were serious problems with the analytical approach they pursued, but they nonetheless concluded that their results were “…consistent with the hypothesis that racial differences in rates of death from prostate cancer are due to biologic factors” (7, p. 414). The authors focused on their finding that the adjusted death rate ratio comparing Blacks with Whites was “larger” among younger men than among older men, even though the estimate for the older men (relative risk = 1.20) fell within the 95 percent confidence interval for the younger men (95 percent confidence interval: 1.15, 1.72) (7, table 2). In addition, since the death rate rises with age, a greater rate ratio may mean a smaller rate difference among the younger men (6). The authors further stated that differences in ecologic socioeconomic status measures “accounted” for 100 percent of the racial difference in rates of death from causes other than prostate cancer among older men (ages ≥65 years) (7, p. 413). The reader is left to speculate as to whether taking older Black men from the poorest 15 percent of the census tracts and simply relocating them to the wealthiest 15 percent of the census tracts would really give these men survival probabilities equal to those of Whites for all causes of death other than prostate cancer.

Robbins et al. provided an extensive discussion of the weaknesses inherent in their methodological approach; nonetheless, they felt justified in speculating that Black men of all ages have some biologic (genetic?) abnormality, manifested as “more virulent tumors” of the prostate, which “explains” the observed survival disparity in prostate cancer mortality. Making an informal Bayes-like calculation in reverse, we can surmise only that the posterior emphasis on “biologic” differences between racial groups in this study, given methods so admittedly weak that they should not be very influential in transforming one’s beliefs, implies that the authors began with a strong prior preference for “biologic” explanations. The pattern of higher incidence and shorter survival among Blacks compared with Whites, especially at younger ages, is not restricted to prostate cancer but is seen for many other common conditions, including hypertension, diabetes mellitus, coronary heart disease, stroke, breast cancer, and lung cancer, to name but a few. Although attributing the racial differentials for each of these conditions to “biologic factors” may sound plausible if the conditions are considered one at a time, the overall pattern is most compatible with Black exposure to a higher-risk social and physical environment. Robbins et al. ignore this obvious prior constraint on their etiologic conclusions.

REFERENCES
THE AUTHORS REPLY

Some lay people and scientists believe that social and environmental factors can completely explain racial and ethnic differences in rates of disease and death. This appears to be the case in the letter by Kaufman et al. (1), which pointedly repeats the limitations to causal inferences discussed at length in our paper (2). Without presenting any supporting data, Kaufman et al. give a list of conditions for which they assert that the higher incidence and mortality of African Americans is “most compatible with Black exposure to a higher-risk social and physical environment” (1). It is noteworthy that their list excludes sickle cell anemia. Also noteworthy is the absence of conditions such as cutaneous malignant melanoma and epithelial ovarian cancer, for which the death rates in African Americans are lower than those in Whites, and for which the racial differences cannot be explained by known environmental risk factors (3). As a factual point, it must be noted that the words “genetic” and “abnormality,” which the authors suggest we would invoke as a speculative explanation for the higher prostate cancer mortality in Blacks, do not appear in our paper.

We observed a sharp difference in the effect of adjustment for socioeconomic status (SES) on Black-White death rate ratios—a very large effect of SES adjustment for causes of death other than prostate cancer versus little effect of SES adjustment for death from prostate cancer. It was this observation, and not “a strong prior preference” as asserted by Kaufman et al., that led to the conclusions in our paper. On the contrary, we would have actually preferred to find that SES-associated differences entirely explained the elevated Black-White death rate ratios for death from prostate cancer as well as for death from other causes. The path toward a potential solution would have been clearer, since there are a number of potentially modifiable factors associated with SES, such as diet, physical activity, medical care, and level of social support.

Our data are consistent with the hypothesis that race-related biologic differences contribute to higher prostate cancer mortality in Blacks. We hope that our presenting these data will lead to further investigation resulting in a better understanding of the biology of prostate cancer, and ultimately a reduction in mortality for both Black and White men. To not allow for the possibility of a biologic basis for these results would be scientifically unwarranted.

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RE: “IMPLICATIONS OF A NEW DIETARY MEASUREMENT ERROR MODEL FOR ESTIMATION OF RELATIVE RISK: APPLICATION TO FOUR CALIBRATION STUDIES”

We read with interest the recent contribution by Kipnis et al. (1) suggesting a new model for the correction of measurement error in the assessment of dietary intake. The authors questioned the adequacy of standard methods of correcting relative risks for measurement error and concluded that failure to detect an association in diet research may well be due to residual attenuation of the risk estimate. They suggested that available methods do not adequately account for the correlation between person-specific biases in a food frequency questionnaire (FFQ) and a reference instrument. Claiming to be unaware of any data that would allow them to estimate the correlation of person-specific biases, the authors supported their assumptions with sensitivity analyses using data from four calibration studies.

However, one of the references Kipnis et al. cited—a two-part paper by Plummer and Clayton (2, 3)—provides relevant data with which to estimate the correlation in question. Plummer and Clayton employed data on nitrogen intake from a pilot project of the European Prospective Investigation of Cancer and Nutrition (EPIC) Norfolk (Cambridge, United Kingdom) that were collected using four diet assessment methods (4-day weighed records, 7-day dietaries assessed for FFQ, and a 24-hour recall) and 24-hour urine samples. The urinary values can be assumed to have had errors that were uncorrelated with the errors of the other assessment methods, thus allowing quantification of the error correlations of the dietary assessment methods. From table 2 in the second part of Plummer and Clayton’s paper (3), we can calculate the average error correlation for repeated administrations of FFQ (corr(ε′, ε′) = 0.38) and 7-day diet records (corr(µ, µ′) = 0.53) and the error correlation between the FFQ and the diet record (corr(ε′, µ′) = 0.21). With this information and using the formulae and assumptions made by Kipnis et al. (1), we can calculate the correlation between person-specific biases for nitrogen intake from the FFQ and the diet record as a reference instrument, as follows.

Following Kipnis et al., the covariance of the person-specific biases from the FFQ (r) and the reference instrument (s) is

\[\text{cov}(r,s) = \text{corr}(r,s) \times \sqrt{\text{var}(r) \times \text{var}(s)}.\]

Plummer and Clayton define this covariance in terms of the total error (person-specific plus random error) for the FFQ (ε′) and the diet record (µ′) as

\[\text{cov}(r,s) = \text{corr}(\epsilon', \mu').\]

\[\times \sqrt{\text{var}(r) + \text{var}(\epsilon')} \times \sqrt{\text{var}(s) + \text{var}(\mu')}.\]

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We can solve these two equations for \( \text{corr}(r,s) \):
\[
\text{corr}(r,s) = \frac{\epsilon_i}{\sqrt{1 - \text{corr}(\epsilon_i, \mu_j) \times \text{corr}(\mu_i, \mu_j)}}
\]
\[
= 0.21 \times \sqrt{1 - 0.38 \times 0.53}
\]
\[
= 0.47.
\]

In view of the values in Kipnis et al.'s Table 2, a correlation between person-specific biases of 0.47 translates to a substantial attenuation factor. Therefore, the deattenuated relative risk would be substantially larger than the one observed. This result is consistent with larger validation studies carried out in EPIC Norfolk that are currently being analyzed.

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THE AUTHORS REPLY

We thank Drs. Michels and Day (1) for their comments on our paper (2), in which we suggested a new dietary measurement error model and evaluated its implications for estimation of diet-disease associations. In particular, our model indicates that failure of the standard correction for measurement error to account for correlated person-specific biases in food frequency questionnaires (FFQs) and reference instruments, such as 24-hour recalls or multiple-day food records, can lead to underestimated relative risks. This "residual attenuation" becomes substantial if the correlation between person-specific biases in an FFQ and a reference instrument exceeds 0.3. Without access to data on unbiased biomarker measurements, our results were based on a sensitivity analysis of four conventional calibration studies. Michels and Day (1) note that Plummer and Clayton (3, 4) provided relevant data for estimation of the correlation in question. According to their calculations, the correlation between person-specific biases in the FFQ and 7-day diet records is 0.47. Tempting as it may be to admit our oversight and use this result as a confirmation of the assumptions behind our model and its implications, we add the following notes of caution.

Firstly, the results of Plummer and Clayton were based on a much more general model (4, model II(c)) that includes ours as a special case. Without introducing person-specific biases, their model specifies only that within-person errors in urinary values be independent of errors in urinary and dietary assessment measurements taken in different seasons. All other parameters, including group-specific biases ("scaling biases" in the terminology of Plummer and Clayton) and within-person error variances and covariances, are allowed to vary both in repeat administrations of the same instrument and across instruments. In contrast, in our model these parameters are assumed to be constant in repeat administrations of the same instrument, with the error variance-covariance matrix being fully specified by person-specific biases and within-person random errors (2). To overcome the difference between the two models, Michels and Day suggest averaging over error correlations for repeat instrument administrations provided in the second paper by Plummer and Clayton (4, table 2). Plummer and Clayton fitted their model to the data set with many missing values using the method of maximum likelihood. As a result, averaging error correlations estimated by a much more general model, with the number of parameters exceeding the number of observations, may produce results different from the estimated correlations obtained by fitting our model directly to the same data.

Secondly, Michels and Day seem to ignore the fact that the 7-day dietary record was modified in season 4, and, perhaps more importantly, a different FFQ was used in season 3 (3, 4). Both the two different modifications of the 7-day diary and, especially, the two different FFQs seem to have quite different error structures (5). Averaging error correlations in this situation may produce rather confusing results.

In summary, the calculations suggested by Michels and Day are indeed important to stimulate an interest in the problem of correlated person-specific biases in dietary assessment instruments. However, in our view, they should only be taken as indications and probably should not be used in place of the results obtained by fitting the new model to the original data.

REFERENCES


Zhang et al. (1) reported that paternal age, but not maternal age, is significantly and positively associated with the risk of prostatic cancer. These authors suggested that this effect may operate through increased germ cell mutation or by “mechanisms not yet defined” (1, p. 1208). I should like to suggest such a possible mechanism.

Both prostatic cancer and coital rates are reportedly associated with androgen levels. In particular, the androgen most closely related to coital rates is dihydrotestosterone (DHT) (2), which is also strongly suspected of being causally related to prostatic cancer. This suspicion is based on the findings that the well-established racial variation in the incidence of prostatic cancer is paralleled by racial variation in rates of activity of 5-alpha-reductase (which metabolizes testosterone to DHT) (3–5).

If it were correct that DHT is causally implicated in prostatic cancer, one might suggest that the association with elderly fathers is mediated by coital rate and hence fecundability (6) and hence fertility; even (perhaps especially) at advanced parental ages, many pregnancies are unplanned. In other words, men who sire children at advanced ages do not constitute a random sample of fathers. Instead, one would expect them to be self-selected for high levels of androgens. High androgen levels are associated with the psychological trait of sensation seeking—and, in particular, varied sexual experience and risk taking (7). Ex hypothesi, elderly fathers have higher DHT levels (when age is controlled) than other fathers do. Moreover, testosterone, at any level, shows substantial heritability (8). Thus, if I am correct, the finding of a paternal age effect in prostatic cancer can be reconciled with the hypothesis that the disease is caused by androgens.

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Editor’s note: In accordance with Journal policy, Dr. Zhang and colleagues were asked whether they wanted to respond to this letter but chose not to do so.