affect interpretation of the presented findings, we are concerned by the lack of the discussion of 2 important issues that may contribute to breast cancer in this older population: *1*) the limited role dietary iron plays in determination of body iron stores and *2*) the known remarkable increase in tissue iron stores that occurs after menopause (2).

Because there are no known excretory pathways for iron, systemic iron homeostasis is strictly controlled by regulation of gut iron uptake though the liver-derived hormone hepcidin and the enterocyte iron exporter ferroportin for both inorganic dietary iron and heme iron (3). This highly sensitive mechanism regulates iron gut absorption to compensate for iron loss, which occurs through sloughed mucosal cells and skin desquamation (1–2 mg/d). This amount of gut iron absorption represents <0.05% of the total body iron stores (4–5 g) and is largely independent of dietary iron content (4). Null results observed in many epidemiologic studies attempting to associate dietary iron with the breast cancer risk (1) and, more broadly, in all dietary iron and cancer risk studies (5) could be partly attributable to this regulatory system.

Among all known risk factors of breast cancer, estrogen status is one of the most important (6). Yet, breast cancer incidence significantly increases after menopause during the period when overall estrogen amount is decreased by 90%. As a result of cessation of menstrual blood loss, body iron stores are increased 2–3-fold during menopausal transition (2). This significant iron increase, along with estrogen locally produced in the breast tissue by aromatase cytochrome P450, the product of CYP19A1, could increase risk of breast cancer development in older women (7). Putting estrogen and iron in this context, it would be difficult to detect the significance of iron by comparing the iron overload in patients such as hemochromatosis mutation carriers with normal controls because of the low amounts of estrogen due to hypogonadism in the iron overload patients (8, 9).

To further delineate the potential role of iron in the pathophysiology of breast cancer in postmenopausal women, additional studies with direct measurement of serum ferritin or, better yet, breast tissue concentrations of ferritin and ferroportin are needed. To this extent, stronger association can be found (10), and the role of iron in breast cancer of postmenopausal women may be unarguably shown.

Neither of the authors had a conflict of interest to disclose.

Xi Huang
Stuart Katz

Department of Medicine
New York University School of Medicine
New York, NY 10016
E-mail: xi.huang@nyumc.org

REFERENCES

1. Kabat GC, Cross AJ, Park Y, et al. Intakes of dietary iron and heme-iron and risk of postmenopausal breast cancer in the National Institutes of Health–AARP Diet and Health Study. Am J Clin Nutr 2010;92:1478–83.
2. Jian J, Pelle E, Huang X. Iron and menopause: does increased iron affect the health of postmenopausal women? Antioxid Redox Signal 2009;11:2939–43.
3. Hentze MW, Muckenthaler MU, Galy B, Camaschella C. Two to tango: regulation of Mammalian iron metabolism. Cell 2010;142:24–38.
4. Andrews NC. Disorders of iron metabolism. N Engl J Med 1999;341:1986–95.
5. Huang X. Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal. Mutat Res 2003;533:153–71.
6. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276–85.
7. Huang X. Does iron have a role in breast cancer? Lancet Oncol 2008;9:803–7.
8. Abraham BK, Justenhoven C, Pesch B, et al. Investigation of genetic variants of genes of the hemochromatosis pathway and their role in breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1102–7.
9. Kallianpur AR, Hall LD, Yadav M, et al. Increased prevalence of the HFE C282Y hemochromatosis allele in women with breast cancer. Cancer Epidemiol Biomarkers Prev 2004;13:205–12.
10. Pinnix ZK, Miller LD, Wang W, et al. Ferroportin and iron regulation in breast cancer progression and prognosis. Sci Transl Med 2010;2(43):43ra56.

doi: 10.3945/ajcn.111.017947.

Mediation considerations: serum potassium and the racial disparity in diabetes risk

Dear Sir:

We read with interest the article by Chatterjee et al (1) on whether low serum potassium accounts for a portion of the elevated risk of incident diabetes among African Americans compared with whites. The authors conducted a mediation analysis by assessing whether the association between race and diabetes risk was attenuated on introduction of a potential mediator in a Cox proportional hazards regression model. With this method, the authors effectively sought to decompose the effect of race on the risk of incident diabetes into direct (ie, the effect of race on diabetes risk not due to serum potassium concentrations) and indirect (ie, the effect of race on diabetes risk that occurs via serum potassium) components.

This approach was formalized by Baron and Kenny (2) in the mid-1980s. Since then, there has been a growing literature on how such an approach to estimate direct and indirect effects requires strong assumptions that may often be violated in practice (3). There are at least 3 issues that present difficulties in many research settings: the presence of unit-level exposure-mediator interactions, noncollapsibility of the association measure, and confounding of the mediator-outcome association. Each of these issues can lead to substantial bias in the estimates of direct and indirect effects.

First, to make viable inferences using the technique the authors used requires the absence of unit-level interactions between the intermediate and the exposure under study (4). That is, in the context of the present study, there must be no individuals for whom race and serum potassium concentrations interact to influence the risk of incident diabetes. Without this condition, it may be impossible to define a single direct effect of interest, because there are separate direct effects for each level of the intermediate. Although this condition is impossible to verify with data, establishing that the association between race and incident diabetes is constant across strata of serum potassium might be used to argue that this assumption is plausible. The use of a nonlinear (ie, Cox proportional hazards) model to assess this homogeneity makes it difficult to causally interpret their direct and indirect effect estimates (5); yet, Chatterjee et al (1) do provide an indication of the potential viability of this assumption in the legend of their Figure 2.

Second, the authors compared unadjusted hazard ratios to hazard ratios adjusted for a covariate thought to be a potential mediator of the race-diabetes association. Mediators were identified as those variables that, on adjustment, *1*) sufficiently attenuated the hazard ratio for race when added to the model and *2*) that were statistically associated with the risk of incident diabetes. However, the hazard ratio is a noncollapsible measure of association (6). Because of noncollapsibility, an unadjusted hazard ratio can be different than a covariate-adjusted hazard ratio for reasons that have nothing to do with an actual causal process. Therefore, using the change in the hazard ratio upon covariate adjustment can be a misleading tool for identifying mediators. This issue is often overlooked when conducting mediation analyses using nonlinear models, and it is most problematic when the outcome of interest is common (eg, >15%). In the study conducted by Chatterjee et al (1), because only 12% of the sample were patients with incident diabetes, noncollapsibility was unlikely to have posed any serious problems.

Third, identifying and adjusting for any potential confounders of the mediator-outcome association is an important and often neglected step in estimating direct and indirect effects (7), one that the authors do not fail to consider. For example, they note that body mass index (BMI) may be a common cause of both serum potassium (K^+) and incident diabetes (D), and therefore a confounder of the mediator-outcome association, as shown in **Figure 1**. Accordingly, the authors adjust for BMI in their proportional hazards model. However, BMI—and many other potential confounders of the mediator-outcome association that the authors adjust for, such as leisure-time physical activity, hypertension, income, and education—are or may be affected by race. By adjusting for covariates that *1*) may be affected by race, *2*) may influence the risk of incident diabetes, and *3*) may also affect serum potassium concentrations, the authors have adjusted for confounders of the mediator-outcome association that are intermediates on the causal path between race and the risk of incident diabetes. Consequently, the 18% reported by the authors may not be the excess risk of incident diabetes in African Americans explained by serum potassium. Rather, it would be more appropriately interpreted as the percentage of the excess risk that does not occur through measured causal intermediates such as BMI that confound the mediator-outcome association explained by serum potassium. Therefore, this "proportion explained" estimate may not be meaningful from a policy or intervention standpoint.

Moreover, given that the authors adjust for causal intermediates, their direct and indirect effect estimates may be subject to selection bias (8). This can occur if, as shown in Figure 1, the association between the causal intermediate (BMI) and the risk of incident diabetes is itself confounded by some unmeasured covariate U or if unmeasured confounders of the serum potassium-diabetes association exist (not shown). Marginal structural models fit using inverse probability weights are an alternative to standard regression that can be used to control for confounders and mediators while avoiding selection biases due to conditioning on casual intermediates (9). Explanations of how marginal structural models can be used to assess direct and indirect effects have recently been published (10).

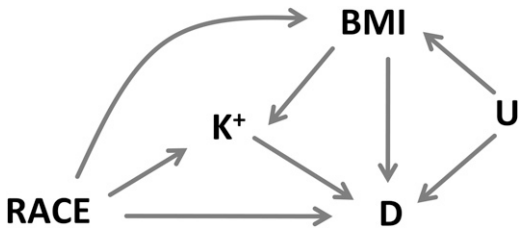

FIGURE 1. Simplified causal diagram representing the relations between race, diabetes (D), serum potassium (K^+), BMI, and an unmeasured confounder (U) of the association between BMI and D.

The authors sought to better understand the pathways by which race affects health. Such research is timely and, we believe, should be prioritized in the biomedical literature. Chatterjee et al (1) should be commended for identifying some often neglected prerequisites needed to make traditional mediation analysis viable. We hope that future research will apply methods that can more closely approximate the causal effects of interest in the context of such relevant research questions.

None of the authors had personal or financial conflicts of interest.

Ashley I Naimi

Department of Epidemiology
University of North Carolina at Chapel Hill
McGavran-Greenberg Hall CB#7435
Chapel Hill, NC 27599
E-mail: ashley.naimi@unc.edu

Jay S Kaufman

Department of Epidemiology, Biostatistics, and Occupational Health
McGill University
1020 Pine Avenue West
Montreal, PQ, H3A 1A2
Canada

Chanelle J Howe
Whitney R Robinson

Department of Epidemiology
University of North Carolina at Chapel Hill
McGavran-Greenberg Hall CB#7435
Chapel Hill, NC 27599

REFERENCES

1. Chatterjee R, Yeh H-C, Shafi T, et al. Serum potassium and the racial disparity in diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2011;93:1087–91.
2. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173–82.
3. Hafeman DM, Schwartz S. Opening the Black Box: a motivation for the assessment of mediation. Int J Epidemiol 2009;38:838–45.
4. Kaufman JS, MacLehose R, Kaufman S. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. Epidemiol Perspect Innov 2004;1:4.
5. Hafeman DM. "Proportion explained": a causal interpretation for standard measures of indirect effect? Am J Epidemiol 2009;170:1443–8.
6. Greenland S. Absence of confounding does not correspond to collapsibility of the rate ratio or rate difference. Epidemiology 1996;7:498–501.
7. Cole SR, Hernán MA. Fallibility in estimating direct effects. Int J Epidemiol 2002;31:163–5.

8. Hernán MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615–25.
9. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.
10. VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. Epidemiology 2009;20:18–26.

doi: 10.3945/ajcn.111.018176.

Thiamine deficiency in ill children

Dear Sir:

Thiamine deficiency is increasingly recognized in varied parts of the world. In many areas of rural Southeast Asia, thiamine deficiency (seemingly related to rice preparation practices) is the accepted cause of wet beriberi, which presents with respiratory distress and heart failure and rapidly improves after thiamine administration (1). Lima et al (2) have provided important data showing that low thiamine concentrations were common in critically ill children at their center in Brazil. These data add a compelling global dimension to pediatric thiamine deficiency and prompt further questions.

First, is thiamine deficiency a cause, an effect, or an incidental finding unrelated to the illness that prompted admission to an intensive care unit? Thiamine deficiency might have been the major cause of illness in some of Lima's patients, but only about a third were <1 y of age, the age at which wet beriberi is most commonly seen in Asian children. We recently studied Cambodian infants with a clinical diagnosis of wet beriberi and found that thiamine concentrations were low not only in clinical cases but also in most seemingly healthy matched control infants from the same district (K Shelton-Dodge, personal communication, 2010). Similarly, a recent report from Laos suggests that sick children without clinical signs of beriberi often have biochemical evidence of thiamine deficiency (4). Hence, low thiamine concentrations do not in themselves prove that an acute illness is beriberi. In some sick children with low thiamine blood concentrations, thiamine deficiency may be unrelated or may be an important cofactor that, together with another factor (eg, intercurrent infection), precipitates or worsens clinical illness. It is currently unclear how beriberi is best distinguished from thiamine deficiency accompanying another acute cardiorespiratory illness in infants. Criteria that might be useful include the presence of dysphonia (a distinctive and perhaps fairly specific sign of infantile beriberi), absence of findings of infection, and rapid resolution of symptoms after thiamine administration. Lima et al did not report these clinical features in their patients.

Second, how frequently is thiamine deficiency implicated in severe childhood disease and death? Lima et al (2) observed thiamine deficiency in 28% of their severely sick children but did not show a statistically significant association between thiamine concentrations and mortality. In Laos, however, thiamine deficiency conferred a 9-fold risk of illness-related mortality in sick children (4). In Mesang District, Prey Veng province of Cambodia, where clinical beriberi is frequently diagnosed, we recently conducted a verbal autopsy survey and identified 51 deaths during the first year of life (48 of the 51 during the first 6 mo of life) among 910 live births from January 2005 through 15 April 2008. Thirty-seven (73%) of the children who died were reported to have had tachypnea or dyspnea during the illness leading to death, and 25 (49%) of the children who died had dysphonia [21 of 33 (64%) who died after 7 d of age had dysphonia]. Heart failure with tachypnea is typical of but not specific for beriberi. Using a conservative case definition of beriberi as dysphonia with $\geq$2 of 4 other typical findings (respiratory distress, irritability, vomiting, wheezing), 23 of the 51 (45%) dying babies had beriberi. Of course, some of these children could have died of pneumonia (with a hoarse voice due to irritability and crying) unrelated to beriberi or thiamine deficiency. But, because not all patients with beriberi have dysphonia, it is also possible that more than half of infant deaths were due to beriberi; thiamine deficiency could be a major contributor to childhood mortality in Cambodia where 6% of children die before their fifth birthday (5).

We are grateful to Lima et al (2) for providing new data about the high frequency of thiamine deficiency in sick Brazilian children. Their data raise important questions about the role of thiamine in acute illnesses other than wet beriberi (isolated thiamine deficiency). Although thiamine deficiency appears to be a major cause of infant mortality in Southeast Asian populations, it remains unclear whether it is a significant contributor to mortality in sick children from other parts of the world.

None of the authors had any financial, ethical, or other conflicts of interest in regard to this article.

Greta Kauffman
Debra Coats

Eastern Mennonite Missions
Prey Vang Province
Cambodia

Somonn Seab

Svai Chrum Health Center
Mesang District
Prey Vang Province
Cambodia

Mark D Topazian
Philip R Fischer

Mayo Clinic
200 First Street SW
Rochester, MN 55905
E-mail: fischer.phil@mayo.edu

REFERENCES

1. Soukaloun D, Kounnavong S, Pengdy B, et al. Dietary and socio-economic factors associated with beriberi in breastfed Lao infants. Ann Trop Paediatr 2003;23:181–6.
2. Lima LF, Leite HP, Taddei JA. Low blood thiamine concentrations in children upon admission to the intensive care unit: risk factors and prognostic significance. Am J Clin Nutr 2011;93:57–61.
3. Khounnorath S, Chamberlain K, Taylor AM, et al. Clinically unapparent infantile thiamin deficiency in Vientiane, Laos. PLoS Negl Trop Dis 2011; 5:e969.