

You are what your mother ate?^{1,2}

Christopher W Kuzawa

First brought to scientific attention several decades ago by the report of a dose-response, inverse relation between birth weight and adult risk of cardiometabolic diseases (1), evidence that early nutrition, stress, and other similar environmental exposures can have lingering impacts on later health outcomes has now been widely documented in human populations and in experimental animal model work (2). A central problem in this field is identifying the mechanisms that underlie the biological “memory” of early nutrition and other exposures. Early proposals focused on growth alterations or changes in the function of organs such as the kidneys or liver, which it was speculated would be short-changed under conditions of fetal nutritional stress. Although this likely helps to explain some of the human findings (3), more recent work has consolidated around identifying epigenetic changes induced by prenatal or maternal experiences, which provide particularly attractive candidates (4, 5). Epigenetic modifications typically involve chemical changes to the chromatin that influence which genes can be expressed, silencing or amplifying gene production in a targeted fashion. DNA methylation refers to the addition of a methyl group to cytosine nucleotides in the vicinity of a gene promoter, which impedes gene transcription. It is among the best studied of epigenetic processes and one that is chemically stable enough to potentially account for late-life effects of early nutrition.

A long-running study in Keneba, Gambia, provides an unusual opportunity to probe the effect of maternal diet as an inducer of epigenetic change in offspring in a quasi-experimental fashion. Longitudinal studies of nutrition, growth, and health have been conducted in this region for more than 60 y (6). An important feature of the local ecology is a strong seasonal change in nutritional stress that is secondary to the annual harvest cycle and compounded by seasonal changes in workload in the fields and infectious disease. During the rainy season, workloads are high and crop stores are generally running thin, and, as a result, adults typically lose weight during this season (7). Not surprisingly, rainy-season birth weights also tend to be smaller.

A recent study of children in Keneba by Waterland et al (8) showed that methylation at putative “metastable epialleles”—regions where gene promoter methylation is stochastically rather than genetically based and environmentally sensitive during early development—was contingent on season of birth (8). The goal of the study was to evaluate whether a climatically driven seasonal change in nutritional stress experienced around the time of conception would predict differences in methylation in adulthood. This would help to establish that methylation at those loci was not simply genetically based while also demon-

strating the stability of the induced changes. The authors did find differences in epigenetic marking by season of birth but were somewhat surprised to find that methylation was increased during the nutritionally stressful rainy season, when food supplies dwindle. This finding ran counter to their expectations because it suggested that methylation was in fact enhanced at times when one might expect the diet to be most deficient in methyl donors and related cofactors that are required of methylation. The authors speculated that seasonal changes in dietary availability of essential nutrients, rather than gross changes in calories or macronutrients, might account for the apparent increased methyl transfer capacity during times of dietary dearth.

A new study in this issue of the Journal by the same group (9) takes an important step toward evaluating this idea by measuring seasonal changes in dietary intake of methyl donors and related cofactors and at the same time by evaluating their circulating concentrations. The authors weighed household food intake and analyzed the concentrations of choline, betaine, folate, methionine, riboflavin, and vitamins B-6 and B-12 in 98 locally common foods to estimate intake of these nutrients. To evaluate whether dietary intake predicted circulating concentrations, the authors also collected monthly blood samples and measured blood levels of the same nutrients, along with several metabolites involved in methyl transfer. Their findings were a bit mixed, but they did find seasonal changes in intake of these essential nutrients and also changes in circulating biomarkers. In some instances, but not all, these changes were correlated. The authors also found evidence for seasonal shifts in the body’s reliance on different methyl donor pathways. Of importance, the changes in circulating biomarkers were generally in agreement with the finding of an increased capacity for methylation during the difficult rainy season.

Where does this new study leave us? To the extent that seasonal changes in dietary intake have remained relatively constant across a generation or so, the authors’ findings bolster the case that dietary methyl donors, rather than energy or macronutrient intake, help to explain season-of-birth-related variation in epigenetic state in the adult population. This is important and suggests

¹ From the Department of Anthropology and Cells to Society (C2S): The Center on Social Disparities and Health at the Institute for Policy Research, Northwestern University, Evanston, IL.

² Address correspondence to C Kuzawa, Northwestern University, Department of Anthropology, 1810 Hinman Avenue, Evanston, IL 60208. E-mail: kuzawa@northwestern.edu.

First published online May 8, 2013; doi: 10.3945/ajcn.113.063347.

that this population provides a natural experiment for probing the dietary determinants of long-term epigenetic programming in humans with greater specificity, and with an unusually strong basis for causal inference owing to the fact that dietary changes are driven primarily by climate and season rather than by more inherently confounded factors like socioeconomic status. Because methyl donor intake is elevated when energy and macronutrient intakes are most compromised, there is also greater assurance that the relations truly reflect an effect specific to these essential nutrients rather than being secondary to greater energy or macronutrient intake generally.

Although these factors are apparently important locally, it is not yet clear how important dietary intake of methyl donors and related cofactors are likely to be as influences on health in populations with diverse diets and ecologies. It seems unlikely, for instance, that the finding that helped launch this field—a dose-response relation between birth weight and cardiovascular disease risk across the entire birth-weight distribution, even in well-nourished, high-income populations—will be explained by gradients of dietary methyl donor intake. Indeed, earlier work in this population failed to find evidence that early-life nutritional stress or growth faltering predicted measures of diabetes and cardiometabolic disease as expected (10), raising questions about how this population might differ from others in which these relations have been found. Perhaps the fact that dietary methyl donor intake peaks during what is otherwise a season of nutritional stress will ultimately help to shed light on this negative finding.

The author declares no conflict of interest.

REFERENCES

1. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;298:564–7.
2. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. *Am J Clin Nutr* 2011; 94(suppl):1754S–8S.
3. Luyckx VA, Brenner BM. Low birth weight, nephron number, and kidney disease. *Kidney Int Suppl* 2005; Aug (97):S68–77.
4. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr* 2007;27:363–88.
5. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med* 2009;27:358–68.
6. Rayco-Solon P, Moore SE, Fulford AJ, Prentice AM. Fifty-year mortality trends in three rural African villages. *Trop Med Int Health* 2004;9: 1151–60.
7. Roberts SB, Paul AA, Cole TJ, Whitehead RG. Seasonal changes in activity, birth weight and lactational performance in rural Gambian women. *Trans R Soc Trop Med Hyg* 1982;76:668–78.
8. Waterland RA, Kellermayer R, Laritsky E, Rayco-Solon P, Harris RA, Travisano M, Zhang W, Torskaya MS, Zhang J, Shen L, et al. Season of conception in rural gambia affects DNA methylation at putative human metastable epialleles. *PLoS Genet* 2010;6:e1001252; DOI: 10.1371/journal.pgen.1001252.
9. Dominguez-Salas P, Moore SE, Cole D, da Costa K-A, Cox SE, Dyer RA, Fulford AJC, Innis SM, Waterland RA, Zeisel SH, et al. DNA methylation potential: dietary intake and blood concentrations of one-carbon metabolites and cofactors in rural African women. *Am J Clin Nutr* 2013;97:1217–27.
10. Moore SE, Halsall I, Howarth D, Poskitt EM, Prentice AM. Glucose, insulin and lipid metabolism in rural Gambians exposed to early malnutrition. *Diabet Med* 2001;18:646–53.

