nonhuman primate model of maternal undernutrition would allow determination of whether the variance in developmental outcomes could be explained by prenatal nutrition. In fact, the many confounding variables in a nonhuman species produced data that could not be translated into the human experience. Ultimately, this study would have been much better conducted in carefully conceived human studies.

Neither of the authors had a conflict of interest.

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REFERENCES


Reply to KN Litwak and S Levin

Dear Sir:

In their letter regarding our article entitled “Poor nutrition during pregnancy negatively impacts neurodevelopment of the offspring: evidence from a translational primate model,” Litwak and Levin claim that study flaws and multiple confounding variables negatively affected the impact of our study. Furthermore, they questioned whether hypothesis testing with regard to the impact of poor nutrition on neurodevelopmental outcomes in nonhuman primates is sufficiently translatable to humans. In terms of the concerns about study design and interpretation, Litwak and Levin have misunderstood the structure and study aims.

The study goals were to compare the development of offspring of control and maternal nutrient restriction (MNR) mothers fed 70% of the controls—a 30% caloric reduction throughout pregnancy and lactation. As stated in our previous article (1), to which they refer, in a comparable period of gestation (before 50% of gestation) control mothers ate 64.3 kcal⋅kg⁻¹⋅d⁻¹, whereas MNR mothers were fed 45.7 kcal⋅kg⁻¹⋅d⁻¹. Thus, MNR reduction in intake was 29%, exactly on target, and not 41% as stated in their letter, which is actually the reduction from the prepregnancy feeding. Our nutrition reduction model provides very precise control with a 5% CV for MNR group food intake.

The authors question whether this amount of reduction “represents undernutrition.” We have published several articles showing that this regimen produces fetal undernutrition. First, as stated in the previous methods article (1) to which Litwak and Levin refer, ad libitum–fed mothers always leave food in the cage, whereas MNR mothers always eat all food provided. Furthermore, we have shown clear changes in the MNR mother, placenta, and/or fetus. For example, whereas circulating maternal amino acids are unchanged, key fetal amino acids are somewhat paradoxically increased in MNR fetal blood, potentially reflecting a lowering of fetal amino acid metabolism to adjust for the decreased nutrient availability (2). MNR produces decreased activity in the maternal (1), placental (1), and fetal insulin-like growth factor systems (3). In our article published in the Proceedings of the National Academy of Sciences (4) we describe considerable delay in fetal frontal cortex neurogenesis, again with signs of compensatory changes such as increased cell division in an attempt to compensate for increased apoptosis. Perhaps the strongest proof that the fetus is undernourished in this paradigm is evidence we provided, for the first time in a primate, showing that the fetus responds to this moderate nutrient deficiency by decreasing methylation of the phosphoenolpyruvate carboxykinase gene in the liver, an epigenetic modification leading to an increase in this key enzyme in the gluconeogenesis pathway (5). These findings of nutrient reduction–induced changes in the developing fetus were the basis of our current work to determine whether persistent postnatal effects in behavior could be observed.

The last question posed by Litwak and Levin regarding the effectiveness of our nutrition restriction model was whether nutrition could be deficient in the absence of group differences in fetal weight. There are multiple reports in the literature of only minor decreases in birth weight in the face of decreased fetal nutrition in animal models (6), an important indication that weight is a poor measure for body composition. Matthew Gilman, a leader of many studies of developmental programming in human epidemiologic cohorts stated, “We must retire weight as an indication of outcomes in response challenges in utero. It is body composition that matters” (PW Nathanielsz, personal communication, 2011).

In raising the issue of multiple confounding variables, Litwak and Levin actually do a good job of making the case for the important translational value of testing the impact of poor nutrition on neurodevelopmental outcomes in nonhuman primates. We agree with them that maternal social status, other environmental maternal stressors, and postnatal factors moderate effects of developmental programming. In human studies, these environmental and social factors are highly confounded with prenatal nutrition, and even a “well-conceived study” in pregnancy could not be ethically conducted to parse the variance in outcomes due to such effects. In our model, nonpregnant females were allocated at random to the control and MNR groups. Food consumption between the 2 groups before study onset did not differ. All offspring were housed in their home cage until weaning and socially housed in peer groups up until they were transferred to a separate facility for behavioral testing. The movement of juvenile offspring to individual cages was only for the behavioral testing and all animal movements were the same for both groups. Housing and all other resources were the same for both groups. Data from studies using these types of experimental controls build on patterns of associations shown in epidemiologic studies by providing evidence for a causal mechanism. We, and others, would argue that this is the safest and most direct and efficient route toward developing and testing preventive interventions in humans and improving the human condition. Such interventions may be among the most cost-effective approaches to reducing the risk of common childhood physical and mental health disorders, but evidence for the causal relation between deficient prenatal nutrition and health outcomes needs to be established.
As the NIH has now recognized by the many funding mechanisms it has initiated to obtain carefully controlled scientific data such as those we report, developmental programming is a major contributor to disease susceptibility. Leading researchers in the field have stated that “The interaction of the clinical, epidemiological, and basic science communities is essential in evaluation of study outcomes and in defining future directions and needs. New mechanisms and models developed at the bench will inform clinicians as to potential markers and targets to be examined at the bedside, with novel clinical observations then characterized for underlying mechanisms in animal models” (7). Our study is a part of this essential collaborative effort, and we are extremely pleased to be able to disseminate and further clarify our findings in the Journal.

The authors reported no conflicts of interests.

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REFERENCES


Belief beyond the evidence: using the proposed effect of breakfast on obesity to show 2 practices that distort scientific evidence

Dear Sir:

Recently, Brown et al (1) highlighted 2 practices that distorted scientific evidence: “research lacking probative value” and “biased research reporting.” They conducted a cumulative meta-analysis on the “proposition that skipping breakfast causes weight gain” and concluded that J) this “proposed effect of breakfast on obesity” is presumed true despite the conflicting evidence. 2) observational studies have shown a clear direct association since 1998 that should have prevented further “gratuitous observational studies” from being conducted, and 3) there was evidence of reporting bias in one’s own research and others’ research. Whereas there may be some validity to these conclusions, a more useful meta-analysis would not just have examined the overall association without conducting any tests for heterogeneity, subgroup analyses, sensitivity analyses, and assessment of quality of included studies as per the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist (2) for observational studies and per the Quality of Reporting of Meta-analyses (QUOROM) statement (3) for randomized controlled trials.

Undeniably, there are myriad settings in which observational data can be useful, not just to get an overall estimate but also to examine various factors such as the following:

1) Consistency of evidence in diverse populations and settings, which constitutes one of the firmest criterions for causality outside of randomization.
2) Methodologic issues to discern whether the association is robust after controlling for confounding variables.
3) Sources of heterogeneity or interaction—eg, by sex, age, overall dietary pattern, overall diet quality, types of food consumed at breakfast, physical activity habits, smoking habits, and baseline BMI.
4) Duration relation (in many settings), because most, if not all, of the randomized trials conducted on this topic were of short duration; thus, it becomes crucial to evaluate this association over longer periods of follow-up (years instead of months) through observational studies and to scrutinize whether the frequency and duration of skipping breakfast is linked to weight gain.
5) Consistency of association over time as well as time sequence to show the exposure (breakfast consumption pattern) happened before the outcome (weight gain). Notably, the authors mentioned that 86% of the studies were cross-sectional; this justifies the necessity of conducting longitudinal studies, which take a long time to conduct and publish. The authors, however, generalized their statement about studies being conducted “gratuitously” to all observational studies without discerning between the different types.
6) Precision for magnitude of association, which could be mainly detected if studies were replicated over time and in different settings.