Misdefined energy flux and increased fatness

Dear Editor:

The recent article by Hume et al. (1) investigates energy metabolism in adolescence and early adulthood and how differences therein may predict subsequent excess fat gain. Unfortunately, there were errors in the definition of terms and flaws in the statistical approach that resulted in fatally flawed conclusions.

The authors incorrectly refer to the term "energy intake" as habitual energy intake. Habitual energy intake is defined as the energy consumed to maintain stable body energy stores or, in the case of children, normal growth of those stores. What they calculated was the short-term energy intake for the 2-wk period of doubly labeled water measurement. The result was a faulty conclusion that long-term habitual energy surfeit predicts future fat gain, when, in fact, it was the 2-wk energy surfeit that was tested.

The authors also misdefined energy flux as the sum of energy intake and energy expenditure. This definition is wrong. Flux is the magnitude and direction of flow through a system. Energy intake is the influx of energy into the body, and energy expenditure is the efflux of energy from the body. The 2 are equal at energy balance, and the difference between the 2 is energy imbalance. Summing ignores directionality of the flow, and the sum has no numerical or physiologic definition. Only influx and efflux, or their difference, have physiologic meaning.

Contrary to the statements of the authors, the misdefined "high flux" values they reported could still have resulted from high short-term energy intake or a high total energy expenditure (TEE), either of which could have been traced to a high resting metabolic rate (RMR), a high physical activity expenditure, or a large body size. The exclusion of those with a difference of $>33\%$ is arbitrary and does not solve the problem of having the same "flux" but for different reasons. Moreover, as indicated in the authors' Figure 3, 70% of the increase in the "high flux" group was actually due to high 2-wk calculated energy intake and was not traced to high physical activity. Thus, they should have concluded that the best predictor of a lower percentage of body fat was a 2-wk period of 700 kcal excessive energy intake/d. This conclusion is counterintuitive, suggesting there are other flaws in the analysis, but it is what their data analysis actually implies. It is interesting to note that some of these authors previously used another statistical model for the analysis of excess weight gain, and the authors reported that excessive weight gain during the first 2 y of follow-up in these studies was due to high energy intake (2). That model also did not include any adjustment for differences in body size; thus, those conflicting findings were also flawed.

In this current analysis, the authors do attempt an adjustment for metabolic body size, but that adjustment introduces bias. They expressed the energy terms (either "energy flux" or RMR) per kilogram of fat-free mass (FFM). Although both TEE and RMR are linearly related to FFM, the regression lines do not have a zero intercept and thus the use of the ratio is contraindicated (3). The use of the ratio introduces artifacts that create apparent deficiencies in energy expenditure among those subjects who are larger than the cohort average. The appropriate adjustment for FFM is to use FFM as a covariant for energy expenditure (3).

The authors' Figure 1 indicates that these correlations, flawed as they are, are also highly influenced by a few data points at the extremes. This is particularly true for study 2, for which a single data point at the right-most extreme has an excessive influence on the correlation.

The authors failed to account for the complexity of normal weight and fatness changes during adolescence. It is not clear why this was not done because some of the authors did include such considerations in a previous analysis of this data (4).

The correlation between the authors' "energy flux" and RMR is a trivial association. RMR is the largest component of TEE and TEE is the largest component of "energy flux." Thus, correlation is expected because of interdependence of the variables. To test the hypothesis that RMR is influenced by either energy intake imbalance of high levels of physical activity, either TEE − energy intake or TEE − RMR should be used as the dependent variable.

The calculated energy balances as presented in this article are, as indicated above, the short-term energy balance during the 2-wk doubly labeled water period and not the inferred long-term energy balances and would not be sustained without large changes in weight. It is likely that the absolute imbalances have been overestimated because of the limiting precision of the body-composition measurement. Air-displacement plethysmography has a lower reproducibility than many other methods. Precisions are on the order of 1% fat, or up to 1.4% for the difference between serial measures as used in this article (5). This uncertainty for the change in percentage of fat over 2 wk in a 60-kg individual introduces a 1-SD random error of $\leq$570 kcal/d on energy intake. Thus, many of their conclusions were based on small effect sizes.

The conclusions drawn by Hume et al. in their recent article (1) are flawed. This is due to their incorrect and inconsistent use of the term "energy flux," which, at points in the article, is defined as the energy sum of the components of energy expenditure, to the sum of intake and expenditure, to an absolute level of energy balance, and to levels of physical activity. They further compound this lack of consistency by erroneously stating that their estimate of 2-wk energy intake is a measure of habitual energy intake and by using an adjustment for body size that is known to bias the resulting relations. It is not clear why they selected these flawed approaches instead of appropriately adjusted, correctly defined flux measures that are available to them.

I have been a co-investigator on several of Dr. Stice's studies and received funding for the analyses of total energy expenditure reported herein.

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Reply to DA Schoeller

Dear Editor:

We respect that our former collaborator Dr. Schoeller prefers different definitions of some of the terms we used and defined in our energy flux article (1), favors the use of different covariates than we selected and were asked by reviewers to use, and has reservations about using air-displacement plethysmography to estimate total body fat percentage. These differences in opinion play a vital role in scientific progress and we are grateful that he decided to share his perspectives. We had originally invited him to collaborate on this article, but the differences in opinion precluded a successful collaboration.

Although we respect Schoeller's opinions, the objective of our study was to investigate how best to combine the gold-standard estimates of habitual total energy intake and energy expenditure, on the basis of doubly labeled water, to predict future body fat change. Most researchers and clinicians believe that excessive weight gain results from consuming more calories than are expended, but we discovered that no prospective studies had tested whether estimated habitual energy intake minus estimated habitual energy expenditure predicts future body fat accumulation. We therefore provided what appeared to be the first prospective studies to test the energy balance model of excess body fat gain. In that context, we also tested an alternative theory proposed >20 y ago (2, 3), following the original definition of the construct of energy flux.

To our surprise, we found that energy intake minus energy expenditure did not predict body fat gain in 2 prospective studies, controlling for baseline body fat or body mass. More importantly, we also found that energy intake plus energy expenditure did predict future body fat gain in both studies, again controlling for initial body fat or body mass. For the latter analyses, we excluded participants who were markedly out of energy balance, because the original definition of energy flux outlines that energy intake and energy output must be roughly similar because individuals could have the same total energy flux for completely opposite reasons for those who are markedly out of energy balance. Our operationalization of energy balance did not predict future increases in body fat (mean $r = -0.07$), whereas our operationalization of energy flux did (mean $r = -0.26$).

Given that our primary objective was to identify the best way to combine estimates of habitual energy intake and expenditure to predict future body fat gain, we were happy to "let the data speak" with regard to which method of combining these 2 terms had greater predictive validity. After all, the only difference between the 2 predictors is that one is calculated by subtracting the gold-standard estimates of habitual energy intake and energy expenditure and the other by summing these 2 variables. Because it has been difficult to identify biological factors that reliably predict body fat gain, which we feel has limited the efficacy of prevention programs and treatments for obesity, the second leading cause of death worldwide, we were willing to think laterally and investigate the predictive effects of a unique way of combining energy intake and expenditure data. An important cornerstone of science is to try innovative approaches when accepted convention has not worked. We hope others appreciate this perspective.

Unconventional approaches have proven to be critical for addressing several public health problems, such as the initially controversial use of vaccines to eradicate small pox and polio, which saved millions of lives. The results of our study have very clear and testable implications for the prevention and treatment of obesity. Rather than instructing individuals to reduce caloric intake to reduce body fat, which has not produced lasting fat loss in hundreds of randomized trials because caloric restriction produces a range of energy-conserving changes that result in attenuated fat loss, the findings from the energy flux analyses have a different implication. Specifically, the results suggest that it might be more effective for people to increase their physical activity and not reduce caloric intake, because this may allow the natural processes that govern satiety and hunger to function properly. We plan to test the thesis that individuals who maintain high energy flux are more likely to eat healthier foods. This might add to the idea that long-term weight-loss maintenance is more achievable via upregulations in energy intake and expenditure rather than by reducing caloric intake alone.

Because another critical cornerstone to science is transparency and independent replication, we offer Schoeller the opportunity to model these data as he sees fit to determine whether his approach has greater predictive validity for forecasting future body fat gain. We are more interested in identifying reliable predictors of body fat change than in reifying accepted perspectives in the literature. We have already shared these data with him and hope he will communicate the results of the approach he feels is superior. Our expectation is that covarying for factors that naturally correlate with estimated habitual energy intake and expenditure, such as fat-free mass, will only reduce the amount of variance in future body fat change explained and not produce testable hypotheses about how better to prevent and treat obesity. But this is an empirical question, and one that is worth addressing given the pressing need to develop more effective weight-control interventions.

Because we were unable to assess the temporal stability of energy flux, future studies should assess energy intake and energy expenditure repeatedly over time with doubly labeled water to determine whether the estimates based on 2-wk observation periods show temporal reliability. It would also be useful to test whether energy flux, which is estimated over a longer observational period, shows stronger relations to future body fat gain. Perhaps more importantly, given that it is always possible that prospective effects identified in longitudinal analyses are driven by an omitted third variable, we think it would be important to use randomized trials to test whether increasing physical activity is more effective in producing long-term weight loss or preventing excessive body fat gain than is reducing caloric intake. This is a perfectly falsifiable hypothesis and one that we hope multiple independent teams will address in the future.

The authors declared no conflicts of interest.

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