Response to Comment on: Kaiyala et al. (2010) Identification of Body Fat Mass as a Major Determinant of Metabolic Rate in Mice. Diabetes;59:1657–1666

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We thank MacLean (1) for his insightful comments regarding both the need to present unadjusted energy expenditure (EE) data and the issue of model selection for EE normalization.

We agree with the recommendation to present unadjusted EE data as part of the analysis—indeed, this standard should be widely adopted in metabolic research. The question of whether to adjust EE for only the best estimate of "metabolic mass," e.g., lean body mass (LBM), is complex and raises issues of both theoretical and practical importance.

From a theoretical perspective, MacLean notes that when a genetic or other intervention influences EE by altering one or more components of the axis that couples fat mass (FM) to metabolic rate (e.g., leptin secretion rate or leptin signal transduction in target neurons), the inclusion of FM in the model could "adjust out" and thus attenuate or eliminate this source of group variation from the group EE comparison (2). We agree with this assessment but note that if variation in FM is an important regulatory-based determinant of a group difference in EE, this distinction should be made when possible.

Accordingly, as part of the overall analysis, we recommend that, when feasible, a model that adjusts for both LBM and FM should be used to determine whether a group difference that occurs when only LBM is included is attenuated or eliminated by the inclusion of FM. If so, that would constitute evidence of an independent regulatory effect involving FM on the EE phenotype and would provide an important basis for interpreting phenotypic differences. Furthermore, failure to adjust for both LBM and FM (or alternatively for total body mass [TBM]) may produce a group comparison that remains correlated with and thus confounded by variation in TBM. This is an important concern for comparisons wherein most of the variation in TBM reflects variation in FM, with more limited variation in LBM. Finally, in assessments of daily 24-h EE, including FM is justified on grounds that the component of EE that is due to activity is dependent on the total mass of the animal.

From a practical perspective, sample size is often a limiting factor in mouse genetics research, and small sample sizes limit the potential to distinguish between models that include LBM and FM versus those including LBM only. A model including only metabolic mass may be appropriate in this setting, but with the caveats alluded to above. We see a need for study designs involving large enough sample sizes to permit more robust and nuanced evaluations of mouse EE phenotypes.

We anticipate that discussion of both regression model selection and sample size considerations in EE normalization will be fruitful going forward, hopefully leading toward a consensus approach that applies across species. We thank MacLean for promoting this discussion.

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REFERENCES

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