

Rhianna C. Laker,<sup>1,2</sup> Jessica J. Connelly,<sup>1,3</sup> and Zhen Yan<sup>1,2,3,4</sup>



RESPONSE TO COMMENT ON LAKER ET AL.

# Exercise Prevents Maternal High-Fat Diet–Induced Hypermethylation of the *Pgc-1 $\alpha$* Gene and Age-Dependent Metabolic Dysfunction in the Offspring. *Diabetes* 2014;63:1605–1611

*Diabetes* 2014;63:e6–e7 | DOI: 10.2337/db14-0135

The letter by Cedernaes and Benedict (1) commenting on our article in this issue of *Diabetes* (2) raised some very interesting points and valuable insights that, in future studies, will further our understanding of parent-offspring transmission of disease and effective intervention strategies. We would like to address the points raised and provide additional discussion.

We agree that the timing of exercise could be extremely important. In our study, we started diet and exercise interventions prior to pregnancy for technical reasons, which limited our interpretations. We postulate that the epigenetic modification occurs during fetal development likely around midgestation when myogenesis is initiated since hypermethylation of the *Pgc-1 $\alpha$*  promoter observed at birth was apparent in the skeletal muscle but not the liver. Other studies have reported positive impacts on offspring metabolic outcomes with maternal exercise started prior to pregnancy (3–5). Carefully designed timing studies will be of great value to human situations where pregnancy may not be noticed or diagnosed for some weeks or months after conception.

Cedernaes and Benedict discussed a very interesting study showing paternal obesity causing an early onset of  $\beta$ -cell dysfunction in the offspring (6). Ascertaining whether exercise is effective in preventing this or other types of negative impacts of paternal obesity to the

offspring is clearly very important. The findings will be pertinent to the timing question as well.

Finally, based on findings by Barrès et al. (7), the authors raised the possibility of intergenerational impact of a single bout of exercise during pregnancy. Considering the following, we speculate that this is unlikely. First, we showed that under normal chow conditions, in the absence of maternal obesity, maternal exercise did not cause *Pgc-1 $\alpha$*  hypomethylation or impact later metabolic function in the offspring. Second, our findings were in the offspring muscle, and it was the mothers that performed the exercise. Third, we measured basal level *Pgc-1 $\alpha$*  methylation while Barrès et al. (7) detected transiently induced methylation possibly through the action of a different epigenetic machinery. In sum, we suspect that the epigenetic effect of maternal exercise we observed is not a direct response to muscle contraction, but likely to an improved uterine milieu in the mother.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

## References

1. Cedernaes J, Benedict C. Comment on Laker et al. Exercise prevents maternal high-fat diet–induced hypermethylation of the *Pgc-1 $\alpha$*  gene and age-dependent

<sup>1</sup>Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA

<sup>2</sup>Center for Skeletal Muscle Research at Robert M. Berne Cardiovascular Research Center, University of Virginia School of Medicine, Charlottesville, VA

<sup>3</sup>Department of Molecular Physiology and Biological Physics, University of Virginia School of Medicine, Charlottesville, VA

<sup>4</sup>Department of Pharmacology, University of Virginia School of Medicine, Charlottesville, VA

Corresponding authors: Jessica J. Connelly, [jessica.connelly@virginia.edu](mailto:jessica.connelly@virginia.edu), and Zhen Yan, [zhen.yan@virginia.edu](mailto:zhen.yan@virginia.edu).

© 2014 by the American Diabetes Association. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

- metabolic dysfunction in the offspring. *Diabetes* 2014;63:1605–1611 (Letter). *Diabetes* 2014;63:e5. DOI: 10.2337/db14-0086
2. Laker RC, Lillard TS, Okutsu M, et al. Exercise prevents maternal high-fat diet–induced hypermethylation of the *Pgc-1 $\alpha$*  gene and age-dependent metabolic dysfunction in the offspring. *Diabetes* 2014;63:1605–1611
  3. Carter LG, Lewis KN, Wilkerson DC, et al. Perinatal exercise improves glucose homeostasis in adult offspring. *Am J Physiol Endocrinol Metab* 2012;303:E1061–E1068
  4. Carter LG, Qi NR, De Cabo R, Pearson KJ. Maternal exercise improves insulin sensitivity in mature rat offspring. *Med Sci Sports Exerc* 2013;45:832–840
  5. Vega CC, Reyes-Castro LA, Bautista CJ, Larrea F, Nathanielsz PW, Zambrano E. Exercise in obese female rats has beneficial effects on maternal and male and female offspring metabolism. *Int J Obes (Lond)*. 16 August 2013 [Epub ahead of print]
  6. Ng SF, Lin RC, Laybutt DR, Barrès R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs  $\beta$ -cell dysfunction in female rat offspring. *Nature* 2010; 467:963–966
  7. Barrès R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab* 2012;15:405–411