THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Does PAE Cause Metabolic Syndrome? (Non-)Evidence from a Mouse Model

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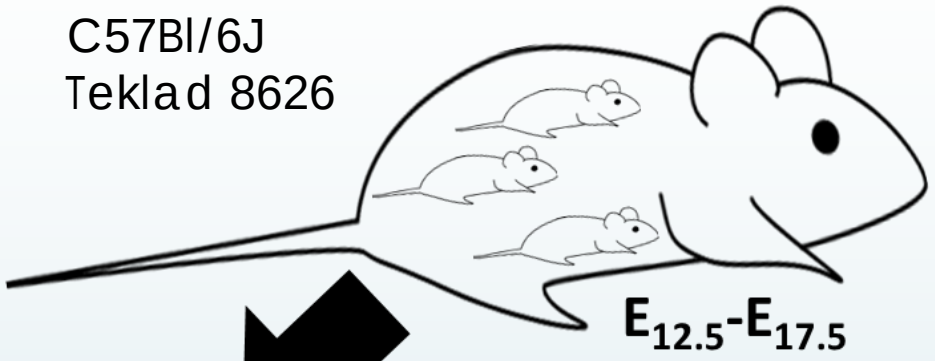
Mouse Model of PAE



- H_2O
- 3 g/kg ETOH
- Isocaloric MD
- Isocaloric MCT

Exposed Litter 17 weeks old (P_{119}, 3M/3F)

Dissection and Tissue Collection

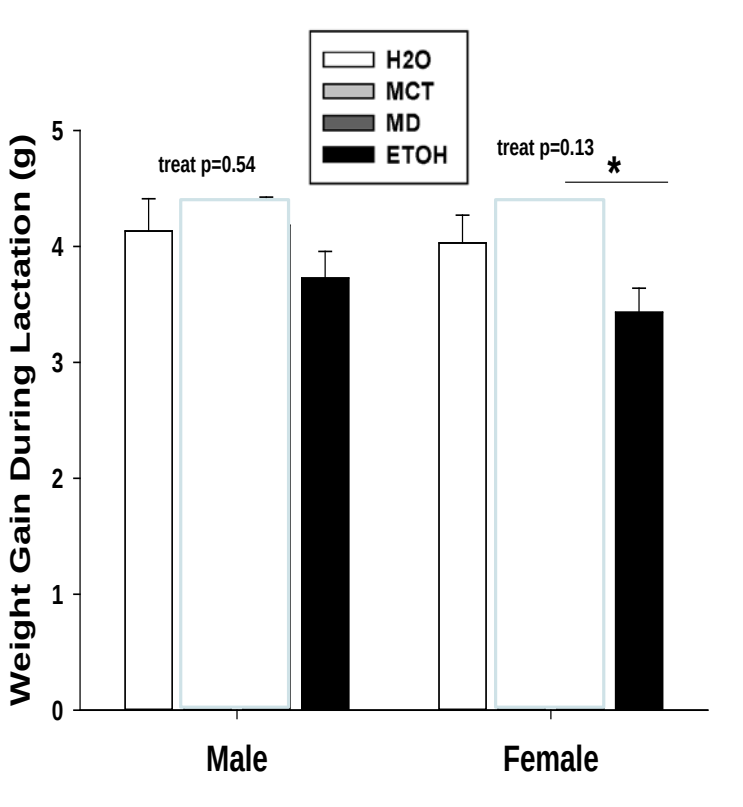
Metabolic Cage Assessment & Body Composition → Ten Days → High Fat Diet Challenge & Body Composition → Thirty Days → Oral Glucose Tolerance

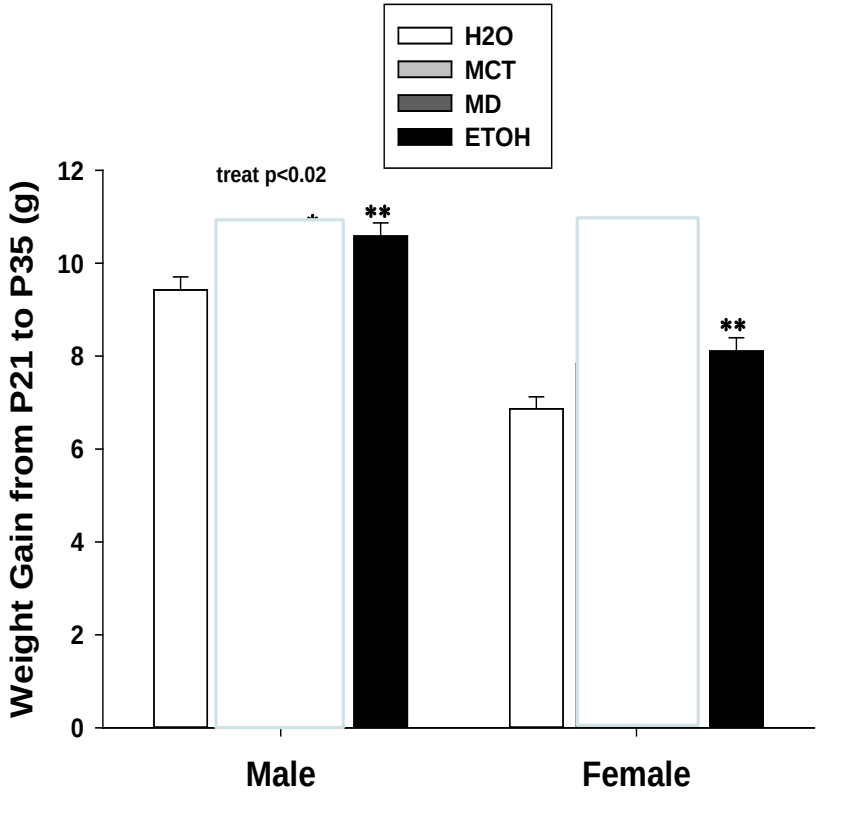
Oral Glucose Tolerance → Seven Days → Intraperitoneal Glucose Tolerance → Seven Days → Blood Pressure Assessment

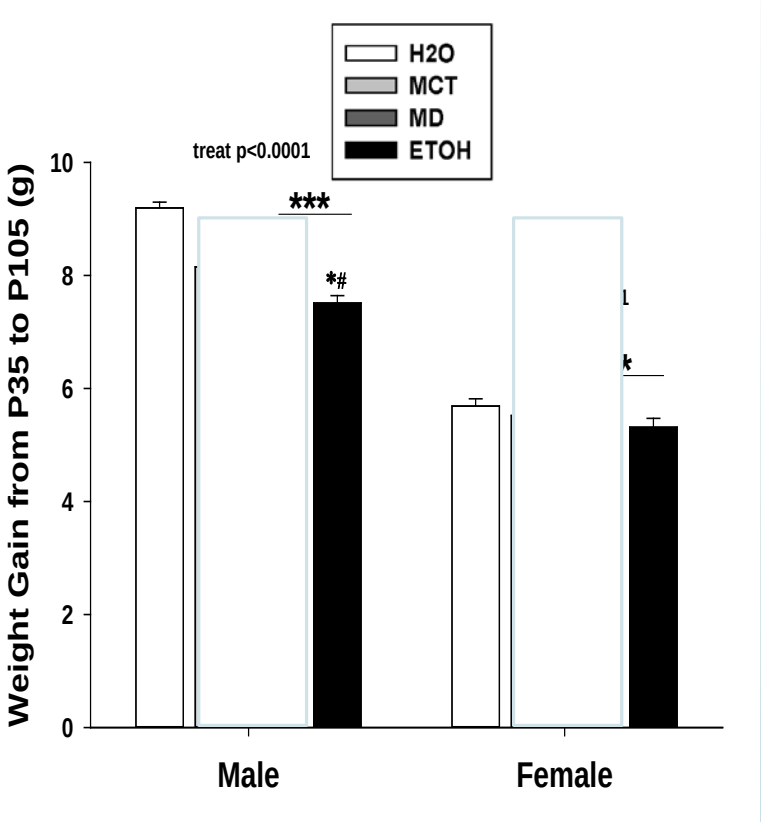
Our Controls

- Water gavage – to control for stress
- Maltodextrose – isocaloric with Alcohol
  - But elicits an insulin response
- Medium-Chain Triglycerides – isocaloric with Alcohol
  - C8-C10 (60:40)
  - Metabolized rapidly by liver, does not elicit insulin

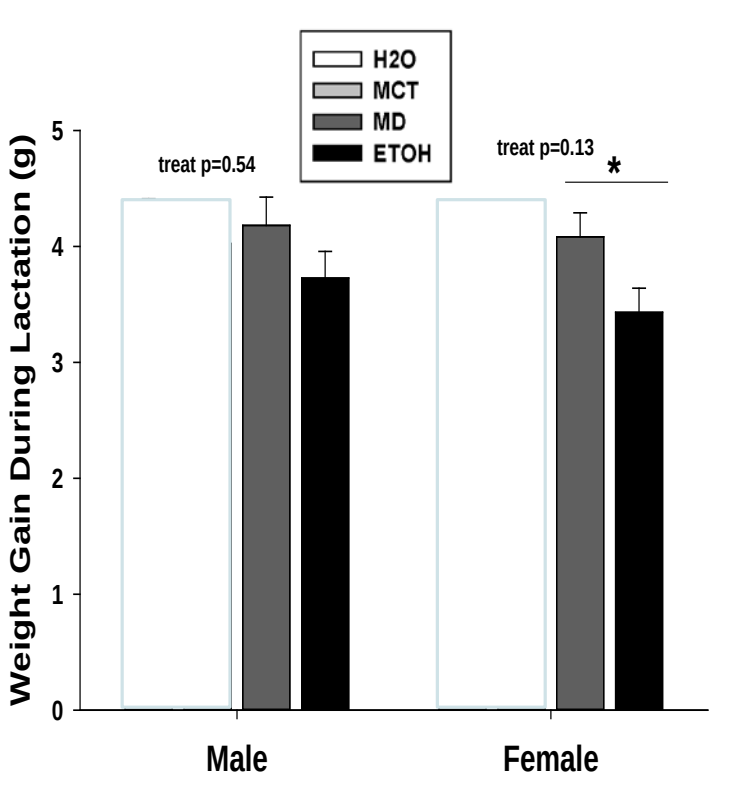
Offspring Growth
Alcohol vs. Water Gavage
PAE reduces early growth, then catch-up

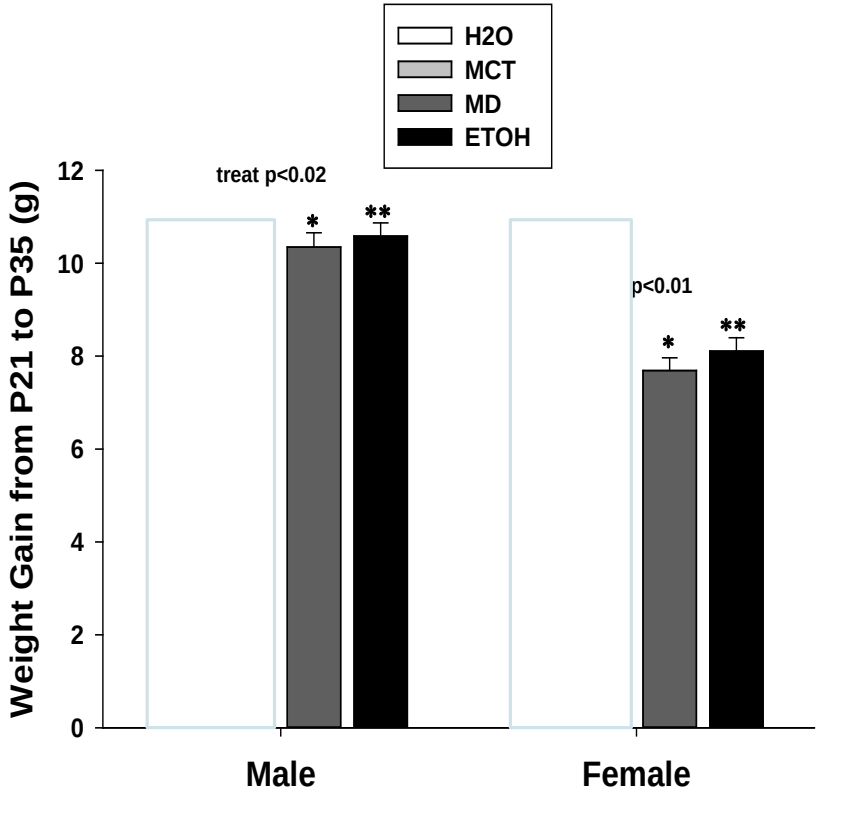


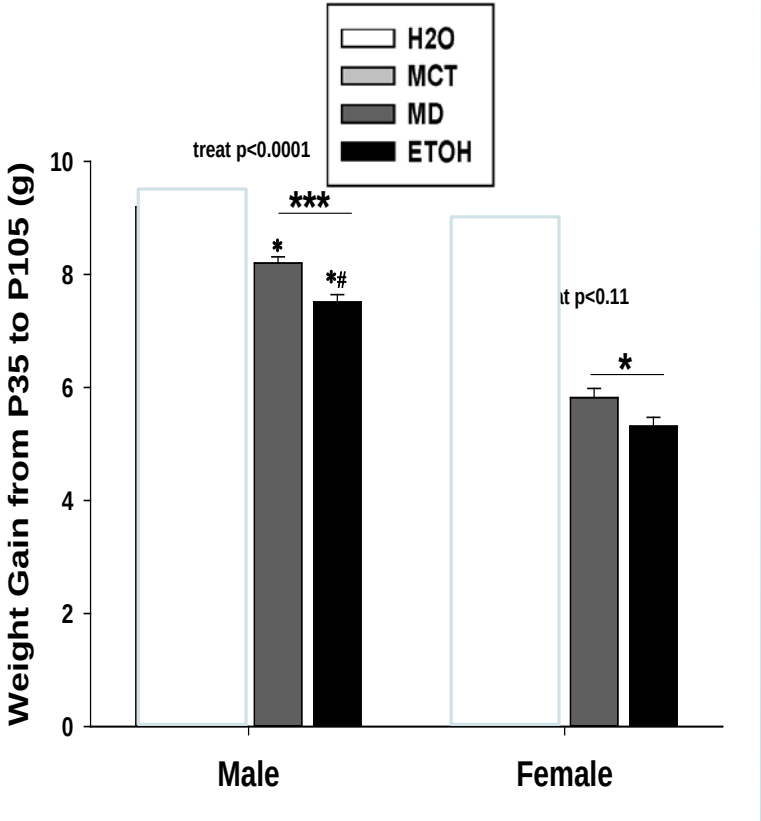




Offspring Growth
Alcohol vs. Maltodextrose
PAE reduces early growth, then catch-up



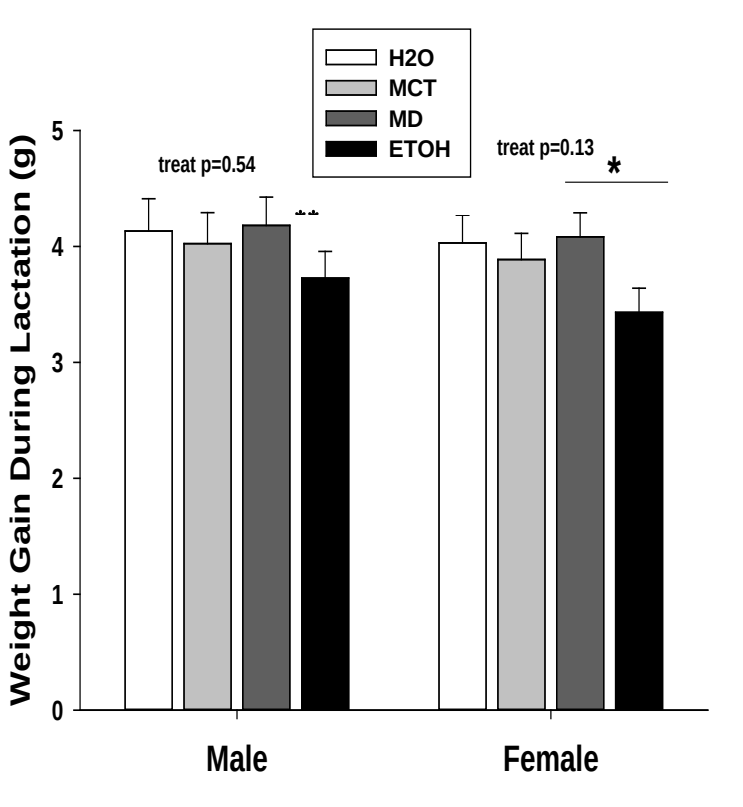


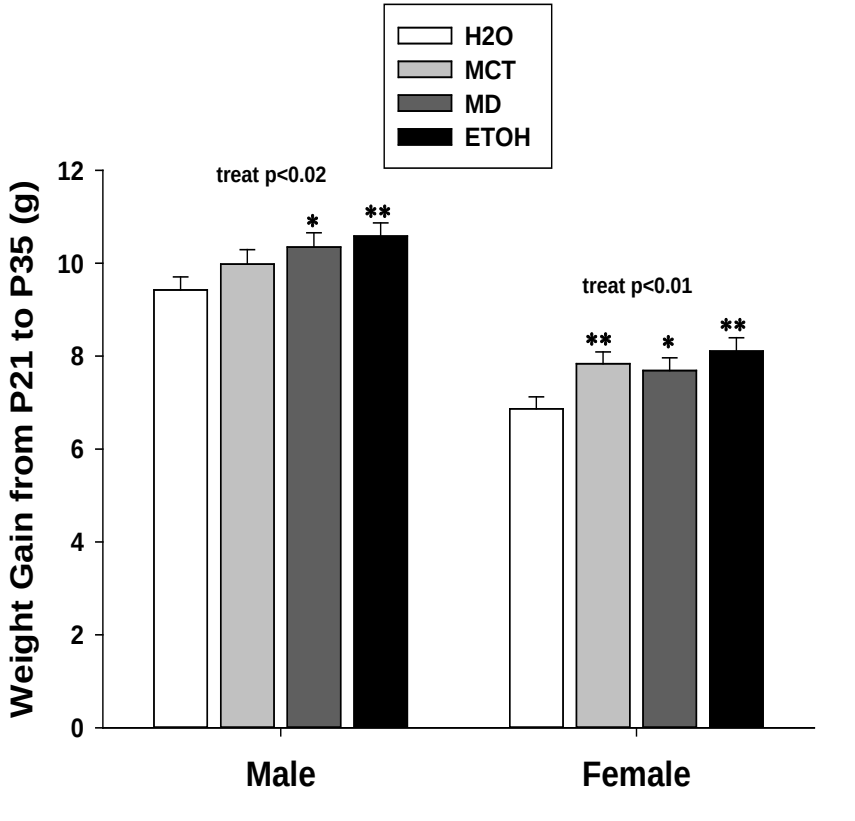


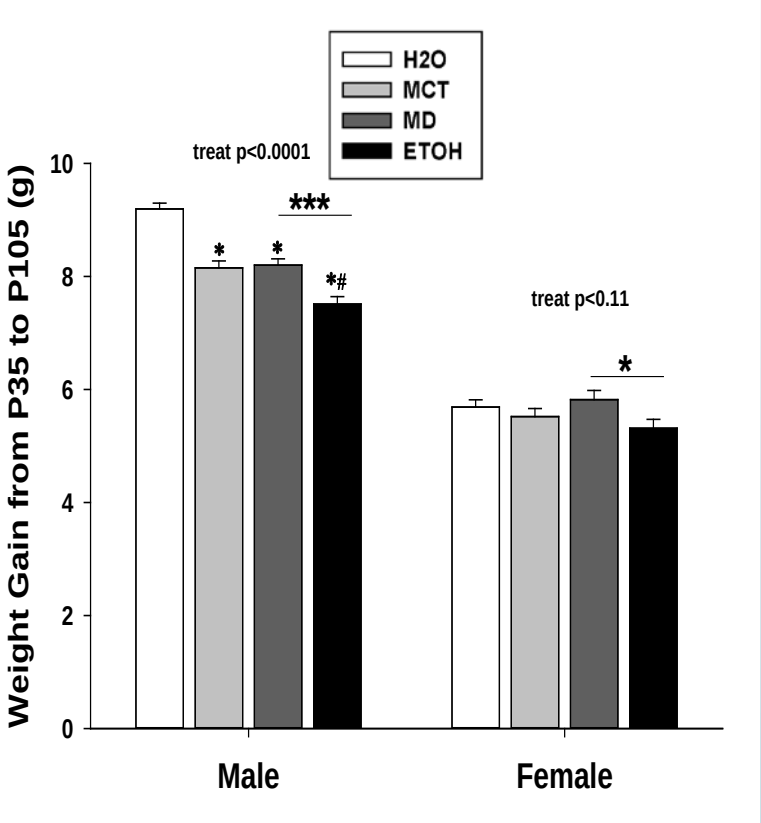
Offspring Growth

Alcohol vs. All Controls

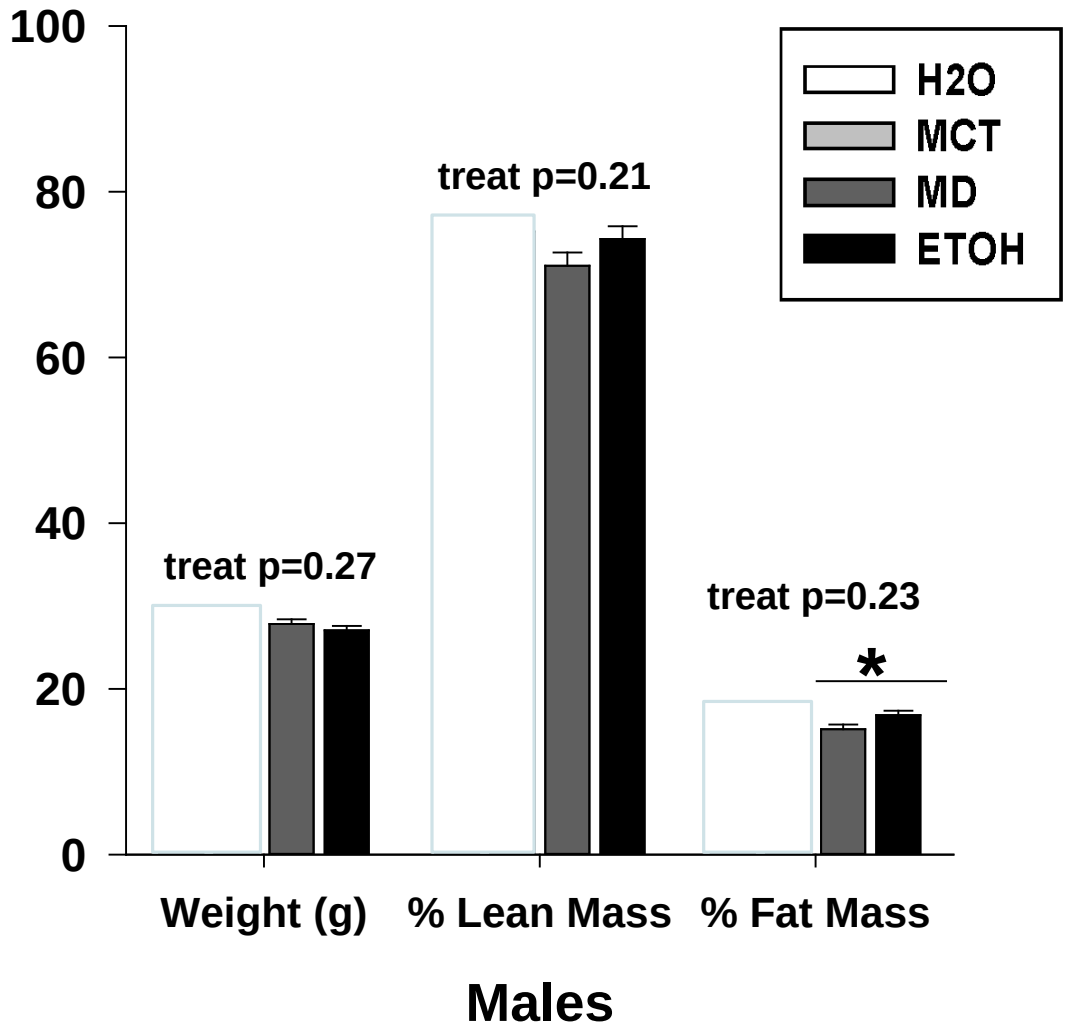
Calories incr juvenile growth & decr later growth

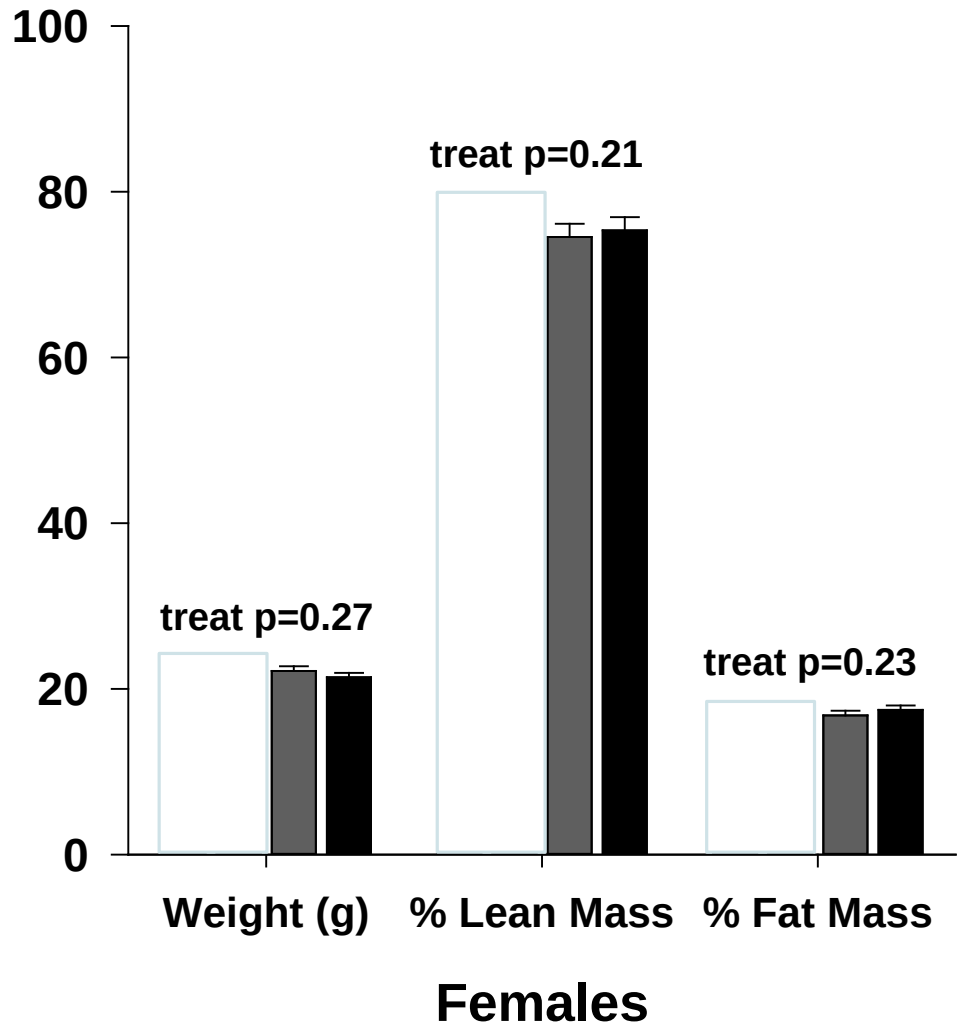




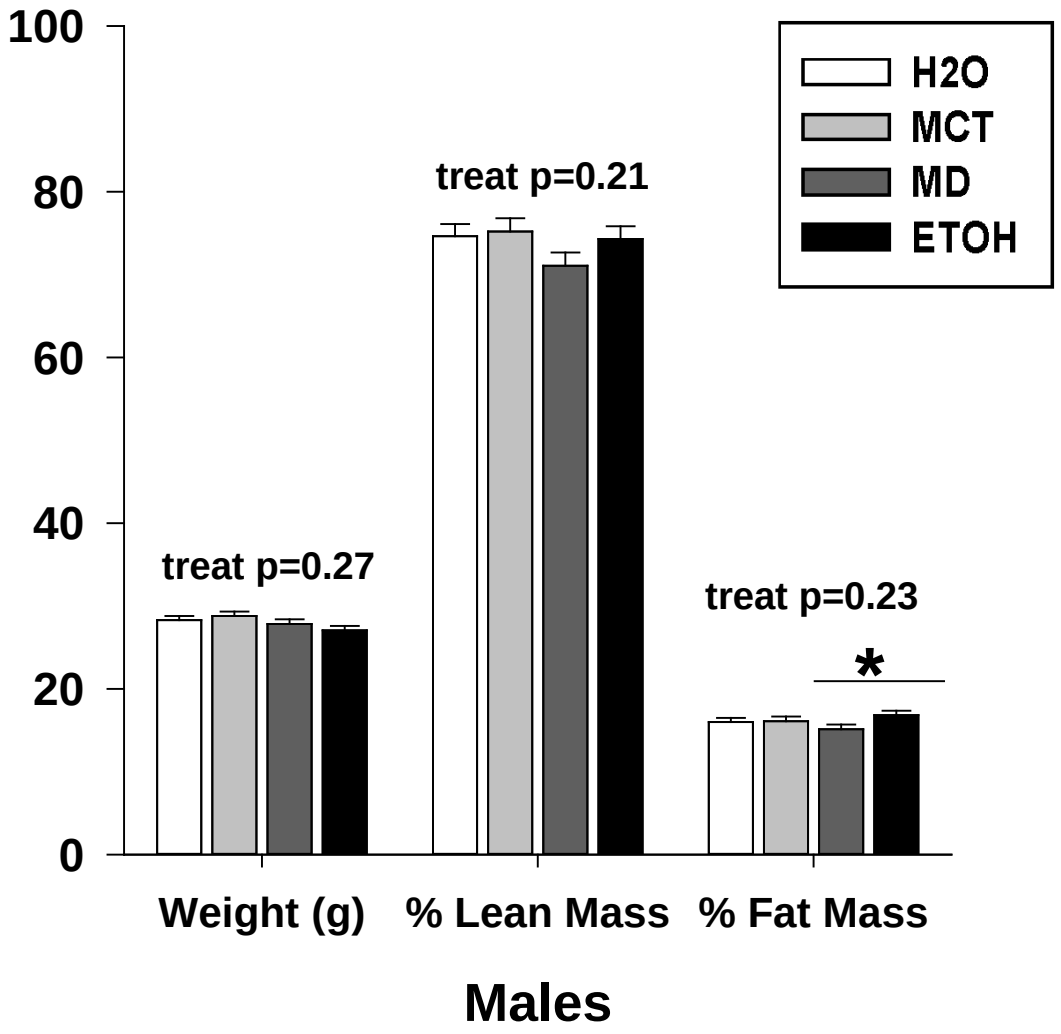


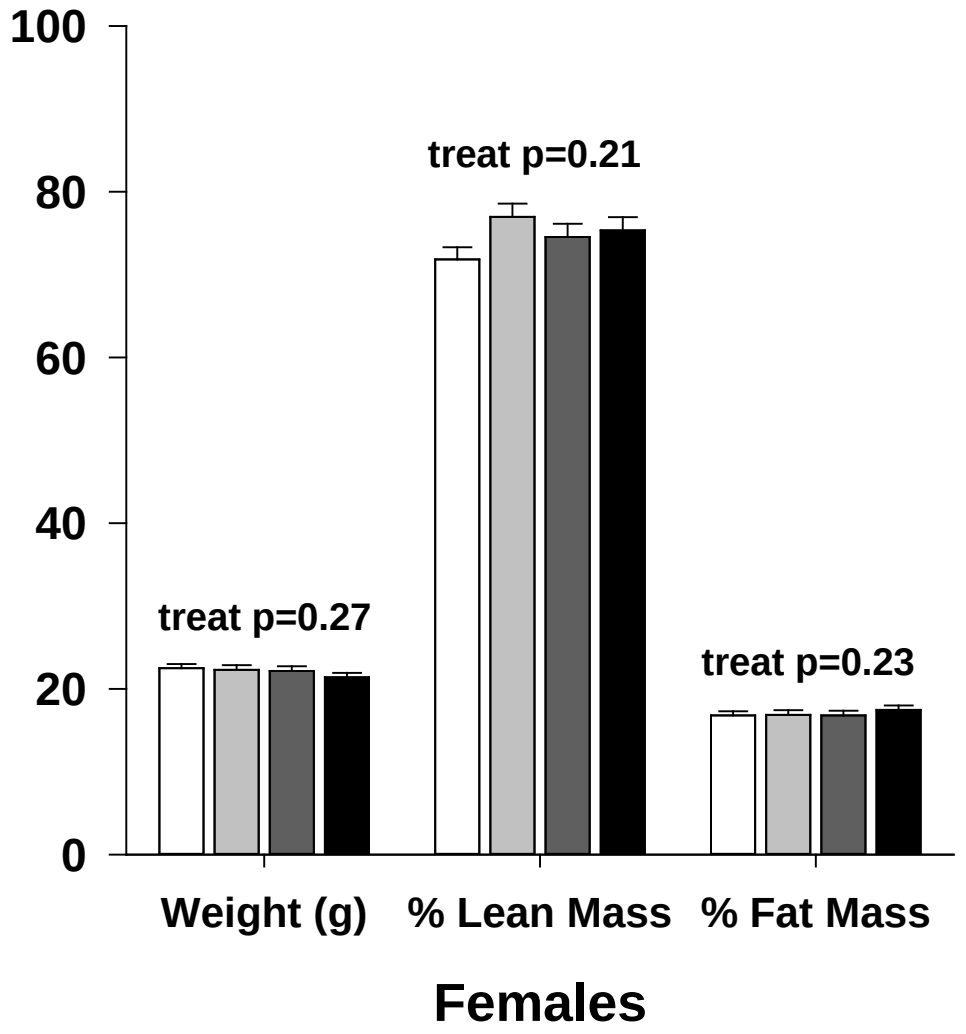
PAE doesn't increase adiposity vs. MD



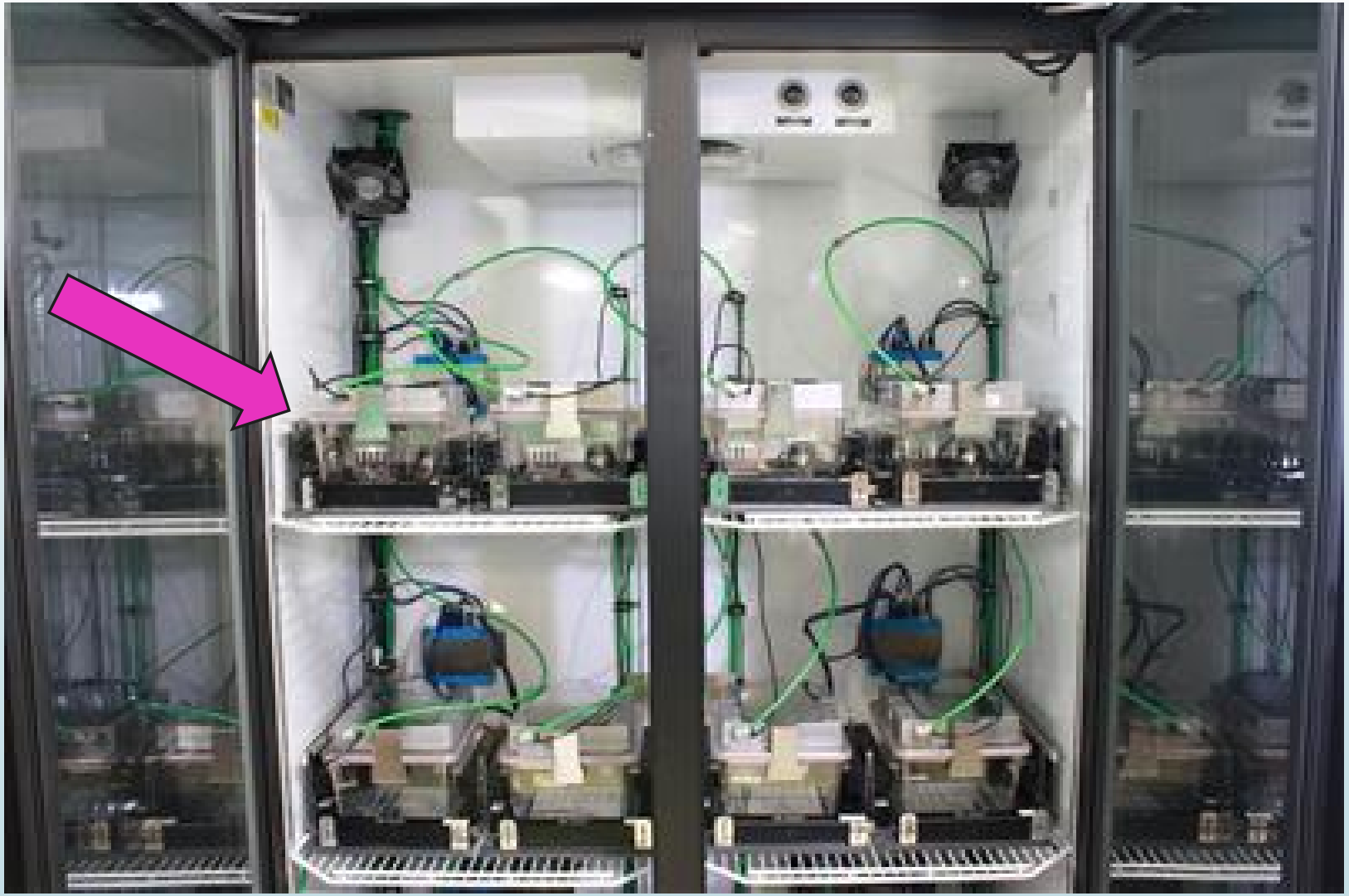


PAE doesn't increase adiposity as compared with all controls





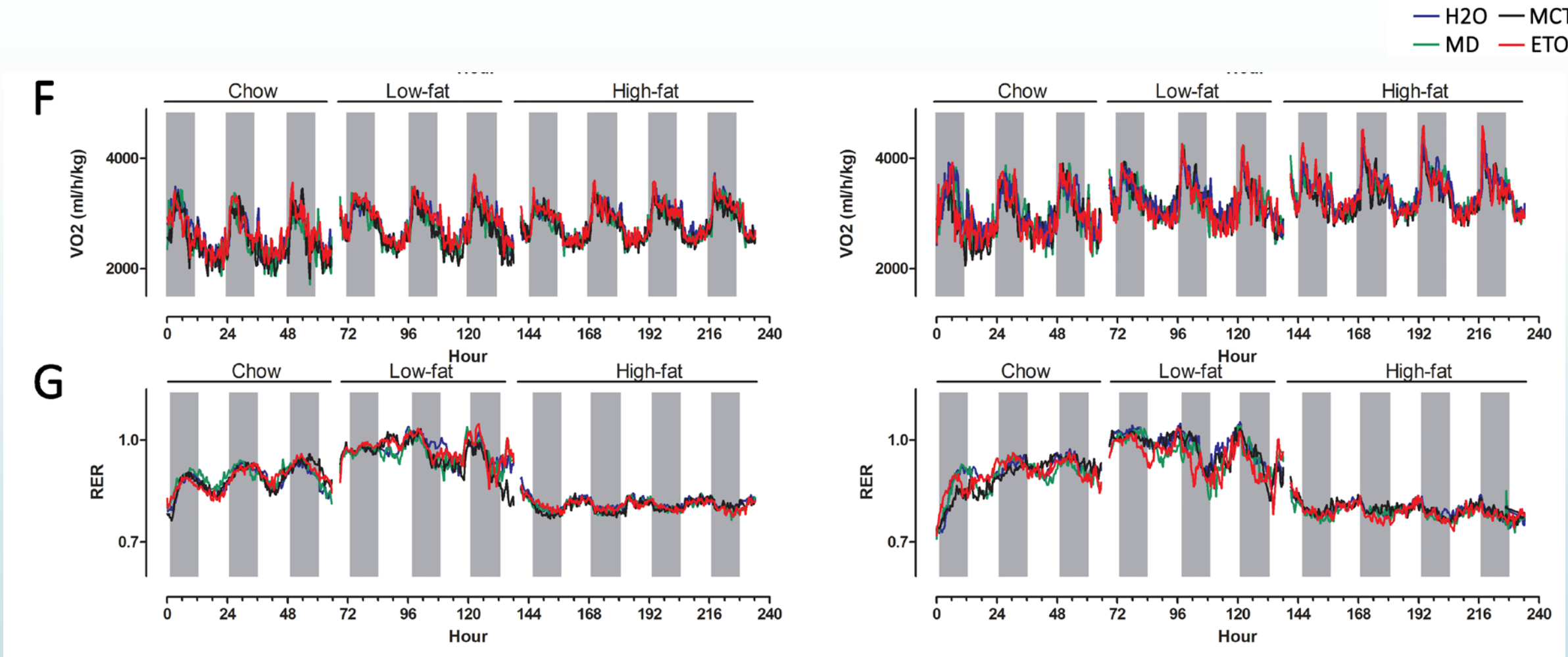
Metabolic Phenotyping of Mice using Environmental Chambers



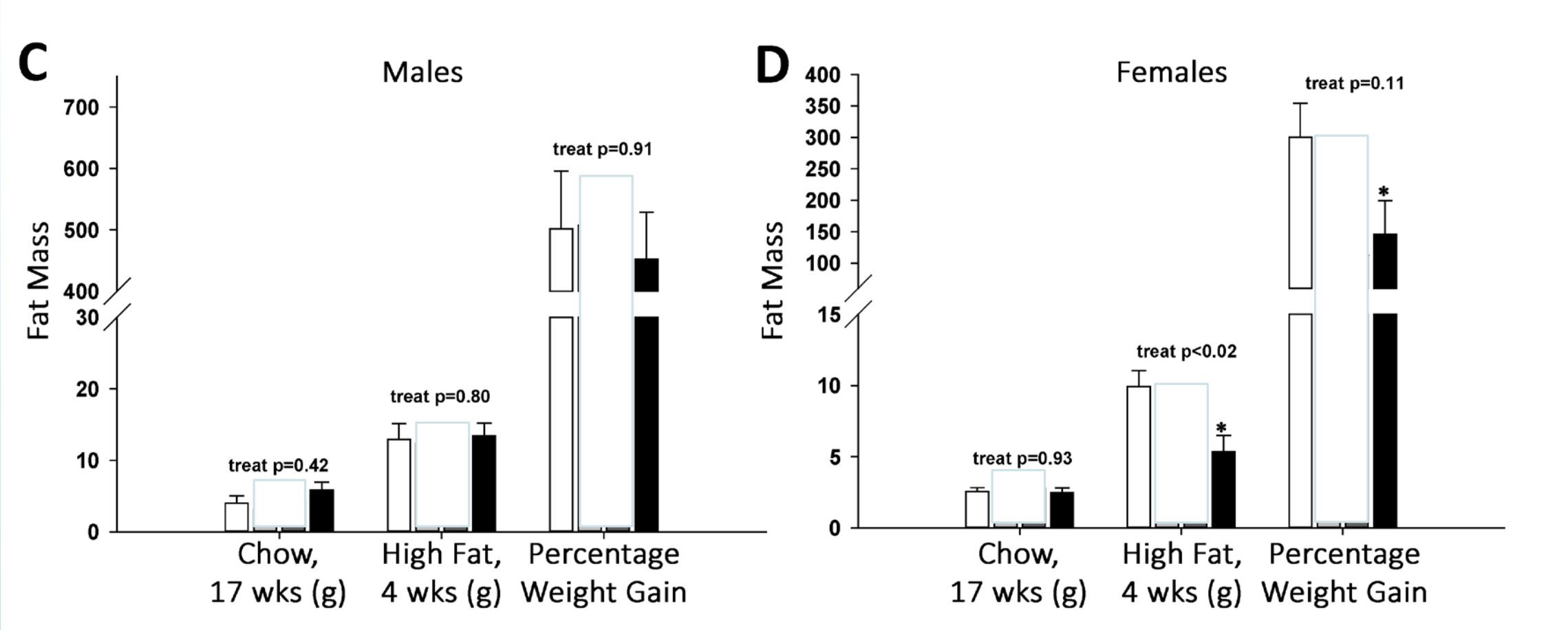
- 3 days chow
- 3 days low-fat diet (10% kcals)
- 3 days high-fat diet (60% kcals)

- Measure body temp, food & water intake
- Measure CO2 exhaled & O2 consumed
- Calculate energy expenditure

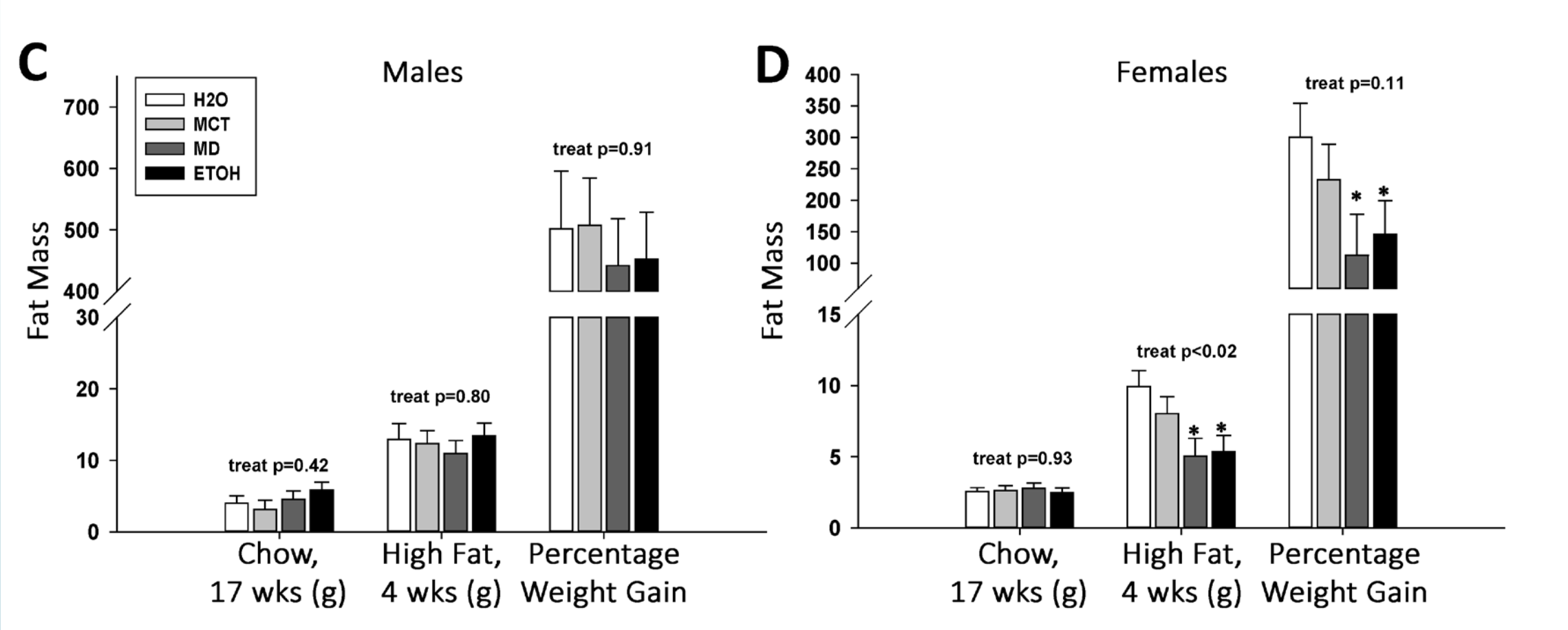
PAE does not affect metabolic rate



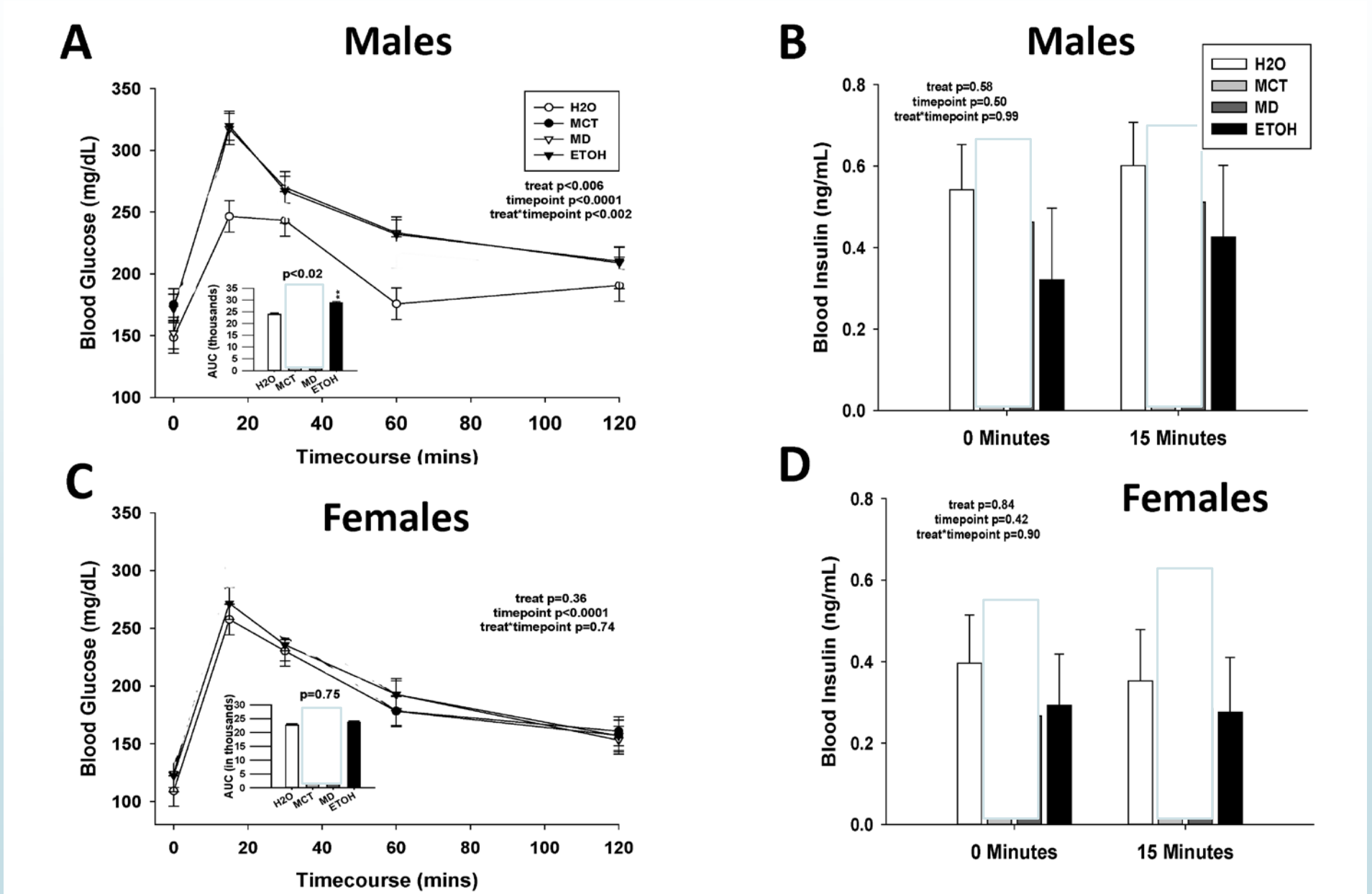
PAE reduces adiposity vs. water controls in response to high-fat diet



PAE does not worsen adiposity in response to high-fat diet

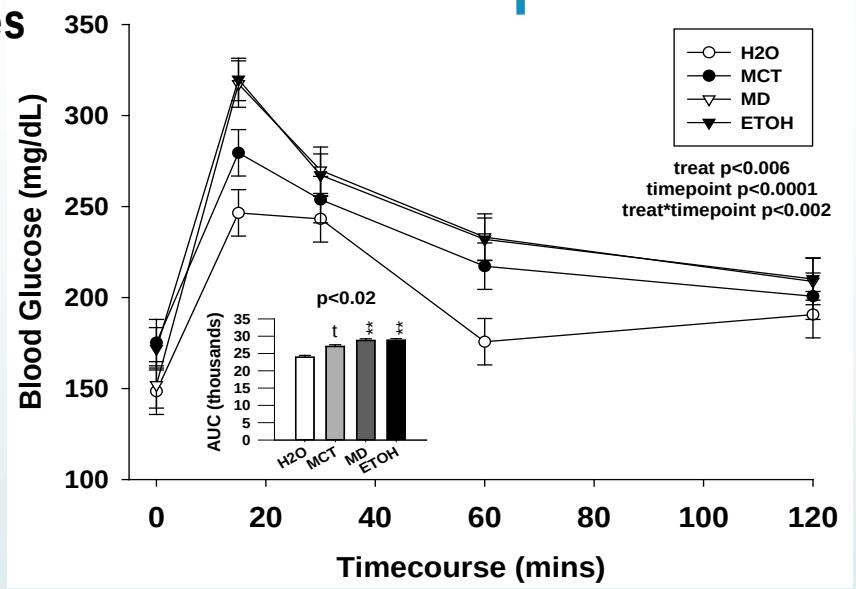


PAE worsens Glucose Tolerance vs. Water-gavage

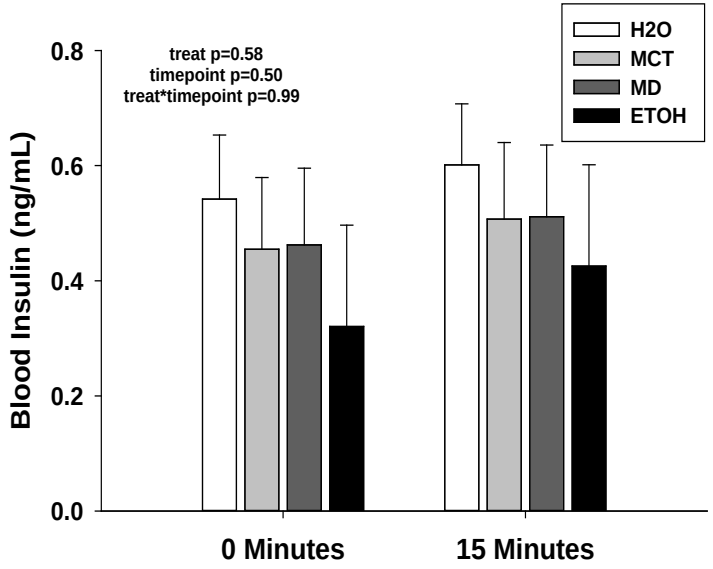


PAE does not affect Glucose Tolerance when compared with caloric controls

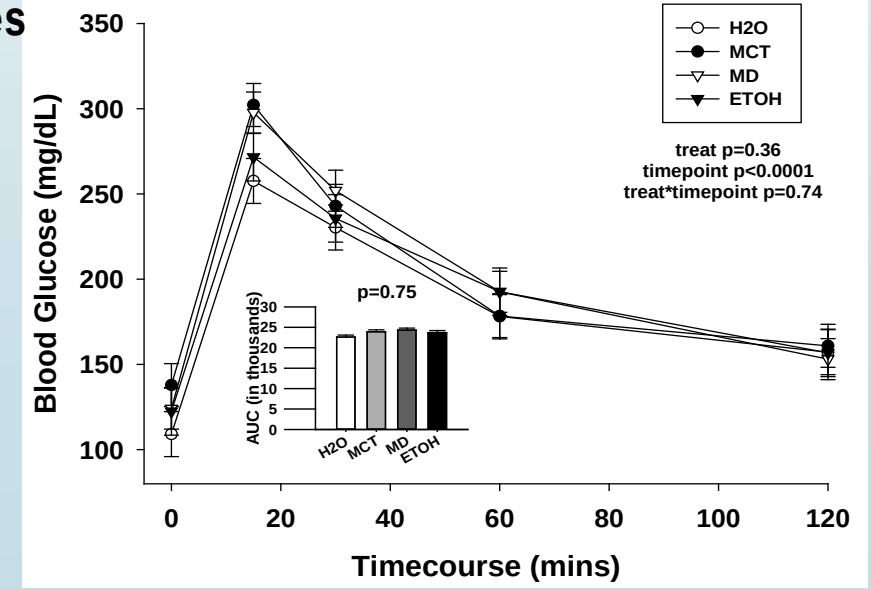
Males



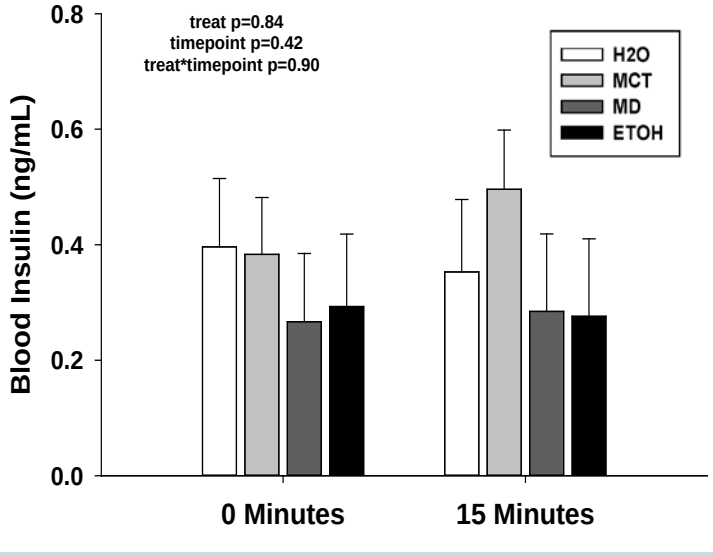
Males



Females

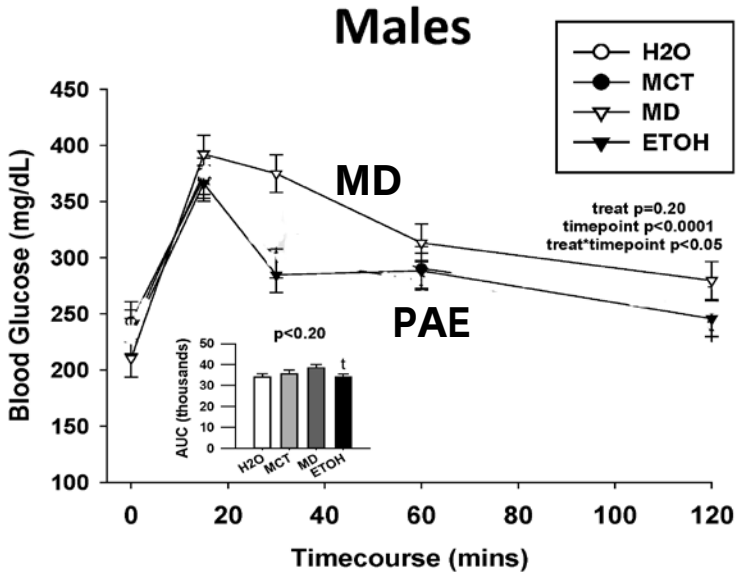


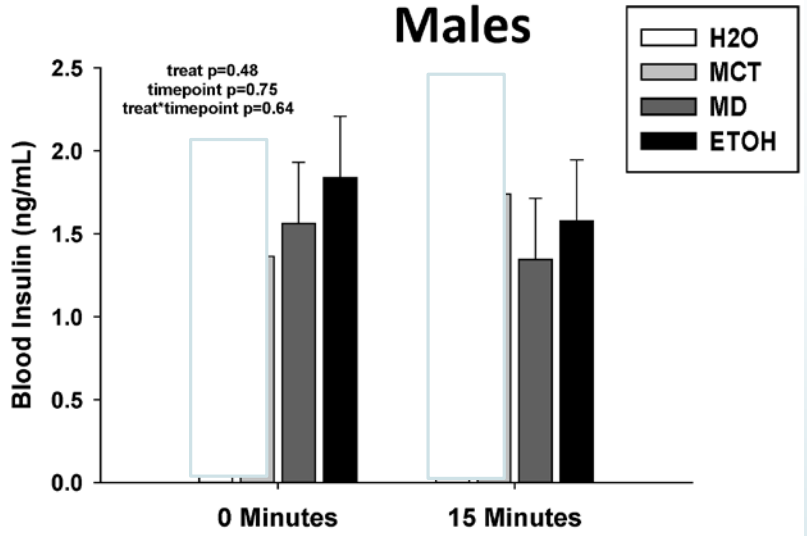
Females

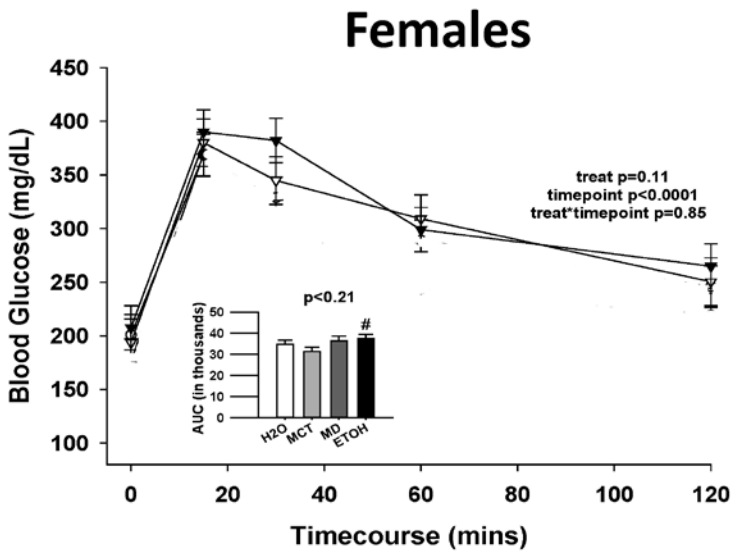


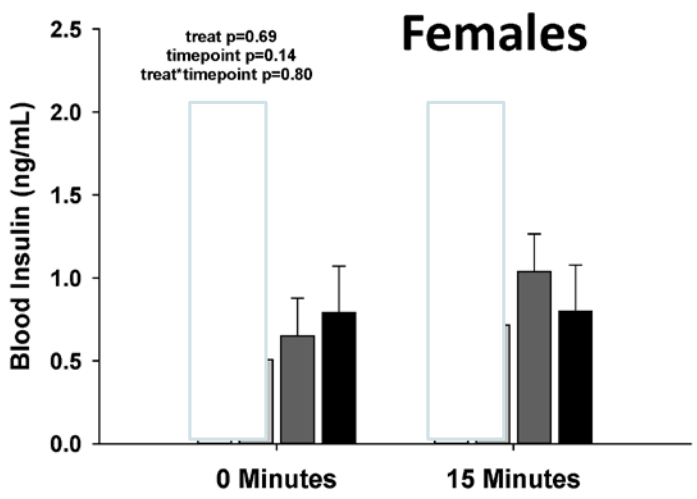
Oral Glucose Tolerance Test

High-Fat Diet worsens Glucose Intolerance: More in Maltodextrin Males; More in PAE Females

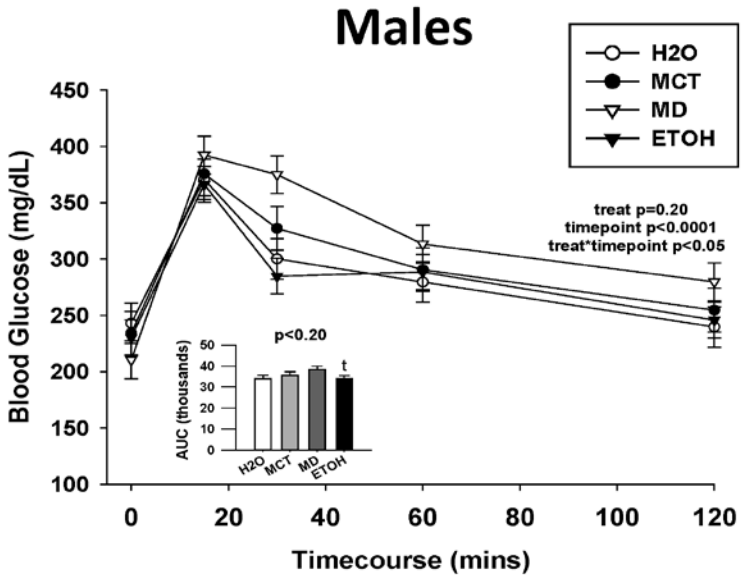


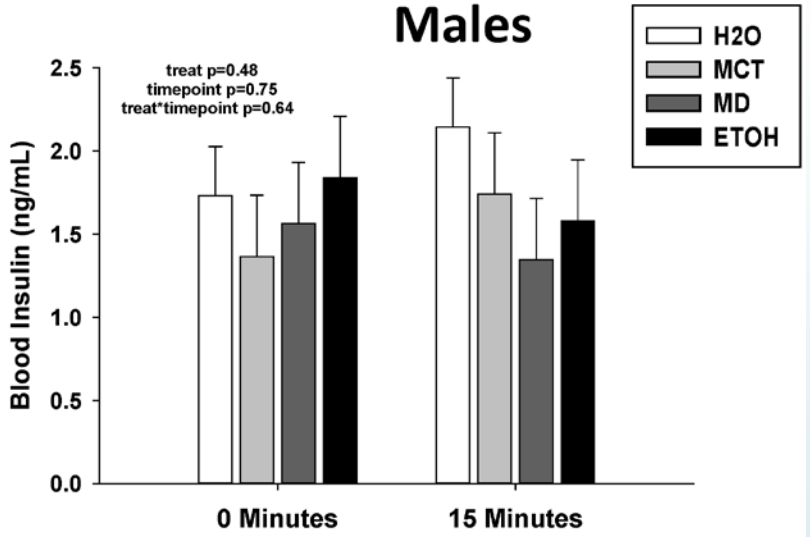


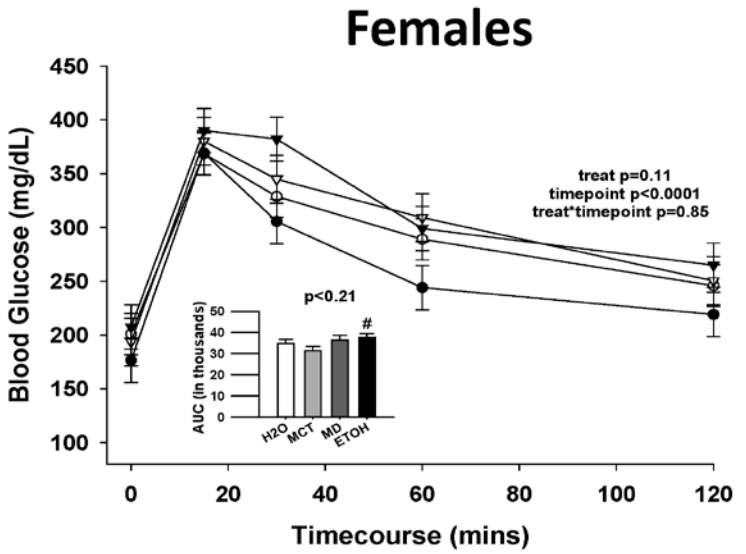


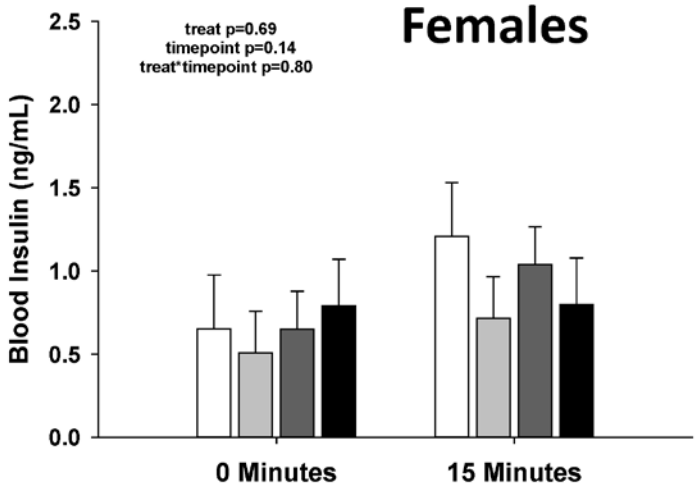


High-Fat Diet doesn't Unmask Glucose Intolerance in PAE



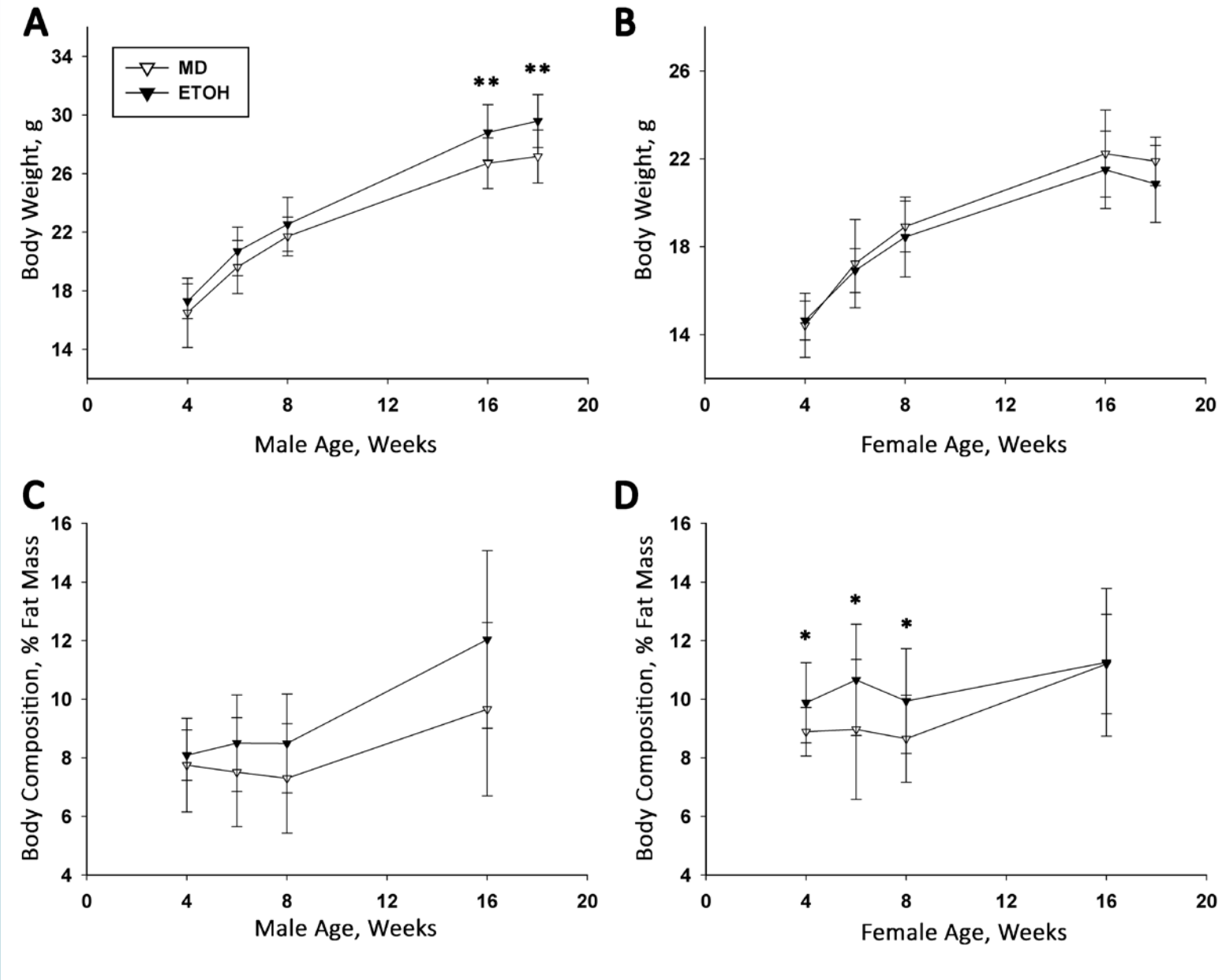






High-Dose PAE doesn't Cause Adiposity in PAE

- 4.5 g/kg
- GD 12.5 – GD 17.5
- PAE vs. Maltodextrin



CAVEATS

- Did we study the wrong exposure window? GD12.5 – GD17.5
  - No – Chen & Nyomba 2004; Gardebjer et al. 2017; Kaminen-Ahola et al. 2010; Yao et al 2006; Yao et al. 2013)
- Was the dose too low? ~110 mg/dl
  - 30 mg/dl cause metabolic change in offspring (Probyn et al. 2013)
- Did we study the wrong mouse strain?
  - C57Bl/6J is commonly used to study obesity and diabetes & PAE
- Were the mice too young?
  - No hint of a problem in RER studies, nor in diet challenge study (Chen et al. 2004)
- Is fetal growth restriction necessary?
  - No, moderate doses alter glucose homeostasis (Gardebjer et al. 2017; Probyn et al. 2013; Yao et al. 2007 & 2013)

SUMMARY

- If we compare PAE & Water, we see some differences
- If we compare PAE and MD, we see some differences

But…

- Neither 3g/kg or 4.5 g/kg caused a unique adiposity
- 3g/kg did not cause glucose intolerance
- High-fat diet didn't unmask a phenotype
- PAE didn't affect metabolic rate
- Extra Calories caused glucose intolerance & adiposity (versus water)
- PAE resembles Caloric Intervention
- Alcohol is metabolized more like MCT, than carbohydrate or water

So…*Does* PAE Increase Obesity Risk in Later Life?

Yes…But the cause is not metabolic dysregulation or imprinting

- Influence of medications?
- Challenges in purchasing & preparing healthy food
- Challenges in sensing appetite signals?
- Influence of executive function?

Recommendations

- Assessment by Registered Dietitian to guide food choices
- Assessment by Physician to review medications & BMI concerns

Acknowledgements

- University of North Carolina at Chapel Hill
  - **Robyn M. Amos-Kroohs, Ph.D.**
- University of Wisconsin-Madison
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Pregnancy Parameters
PAE did not affect newborn weight