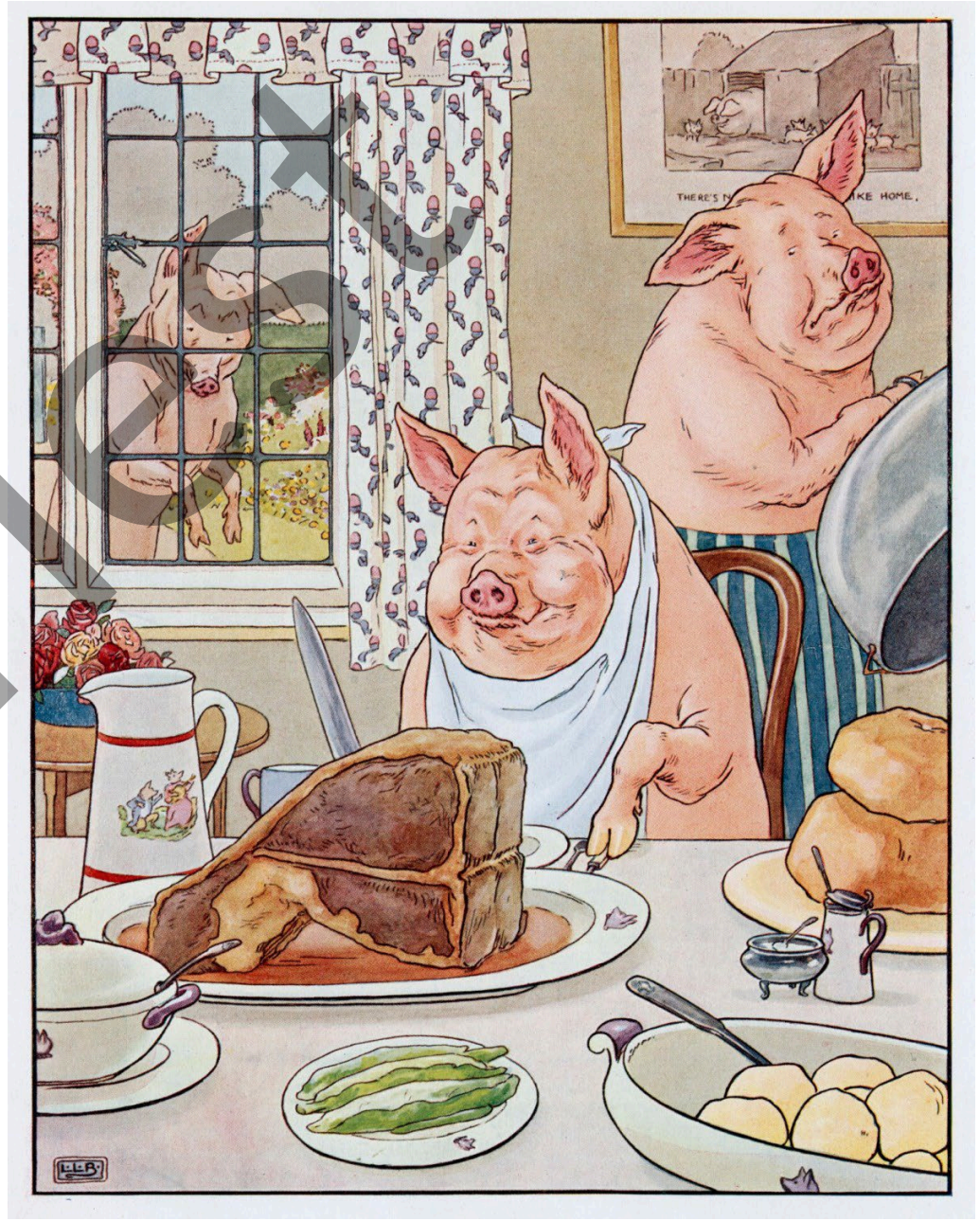
# This Little Piggy Had None

## Effects of maternal protein restriction in microswine offspring

Elizabeth DuPriest, PhD

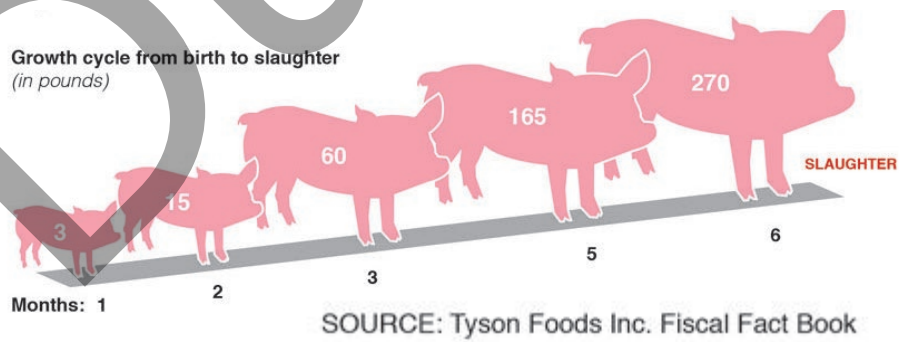
Susan Bagby, MD



https://www.royalacademy.org.uk/art-artists/work-of-art/this-little-pig-had-roast-beef

Adult blood pressure, body composition, and metabolic health are influenced by early life events that affect prenatal and postnatal growth.

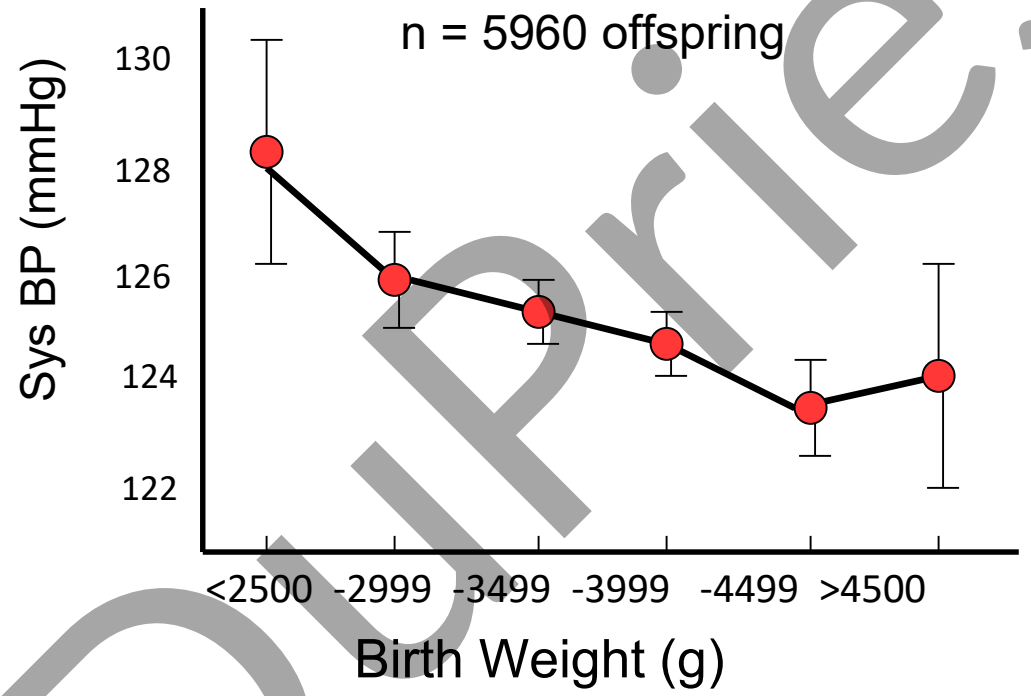
Is growth rate itself part of the programming mechanism?



SOURCE: Tyson Foods Inc. Fiscal Fact Book

# Birth Weight Predicts Blood Pressure at Age 31

1966 Northern Finland Birth Cohort






Järvelin M et al. *Hypertension* 2004

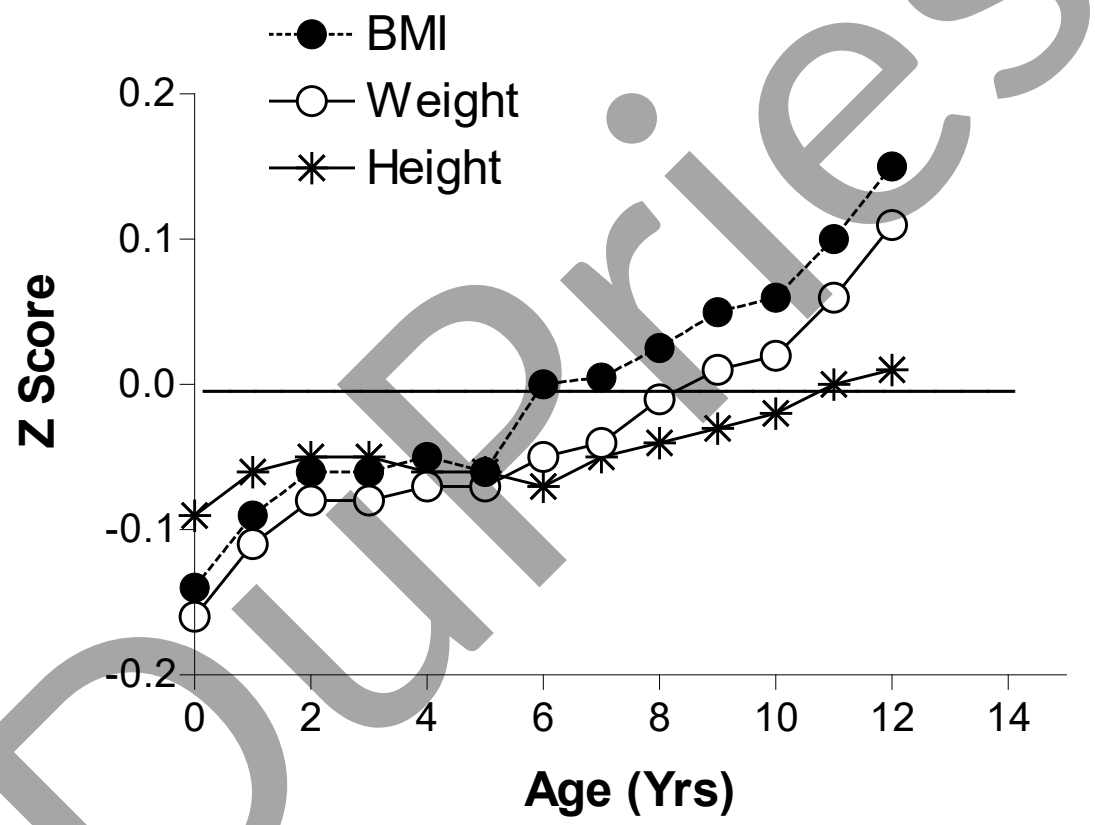
# Exposure to famine in early gestation programs obesity, especially in women

1944-45 Dutch Famine

| Sex | Body characteristic | 3rd trimester exposure | 2nd trimester exposure | 1st trimester exposure |
|---|---|---|---|---|
| Men | | | | |
| | Weight (kg) | 0.8 (-3.1, 4.7) | -2.3 (-6.6, 1.9) | 1.5 (-3.5, 6.6) |
| | BMI (% of control) | 0.4 (-3.5, 4.5) | -1.2 (-5.5, 3.3) | 0.5 (-4.6, 6.0) |
| | Waist circumference (cm) | 1.8 (-1.4, 4.9) | -1.0 (-4.5, 2.5) | 1.8 (-2.4, 6.0) |
| | Waist-to-hip ratio (x 100) | 1.3 (-0.5, 3.1) | -0.4 (-2.4, 1.6) | 1.5 (-0.9, 3.9) |
| | | | | |
| Women | | | | |
| | Weight (kg) | -1.8 (-6.1, 2.5) | -1.5 (-5.7, 2.8) | 7.9 (2.5, 13.2) |
| | BMI (% of control) | -2.1 (-7.0, 3.1) | -1.3 (-6.3, 3.9) | 7.4 (0.7, 14.5) |
| | Waist circumference (cm) | -0.7 (-4.4, 3.0) | 0.4 (-3.2, 4.1) | 5.7 (1.1, 10.3) |
| | Waist-to-hip ratio (x 100) | 0.8 (-1.2, 2.8) | 0.9 (-1.1, 2.9) | 2.2 (-0.3, 4.7) |
| | | | | |

Ravelli et al. *Am J Clin Nutr* 1999

## Growth Patterns in 1404 Children who later developed Hypertension

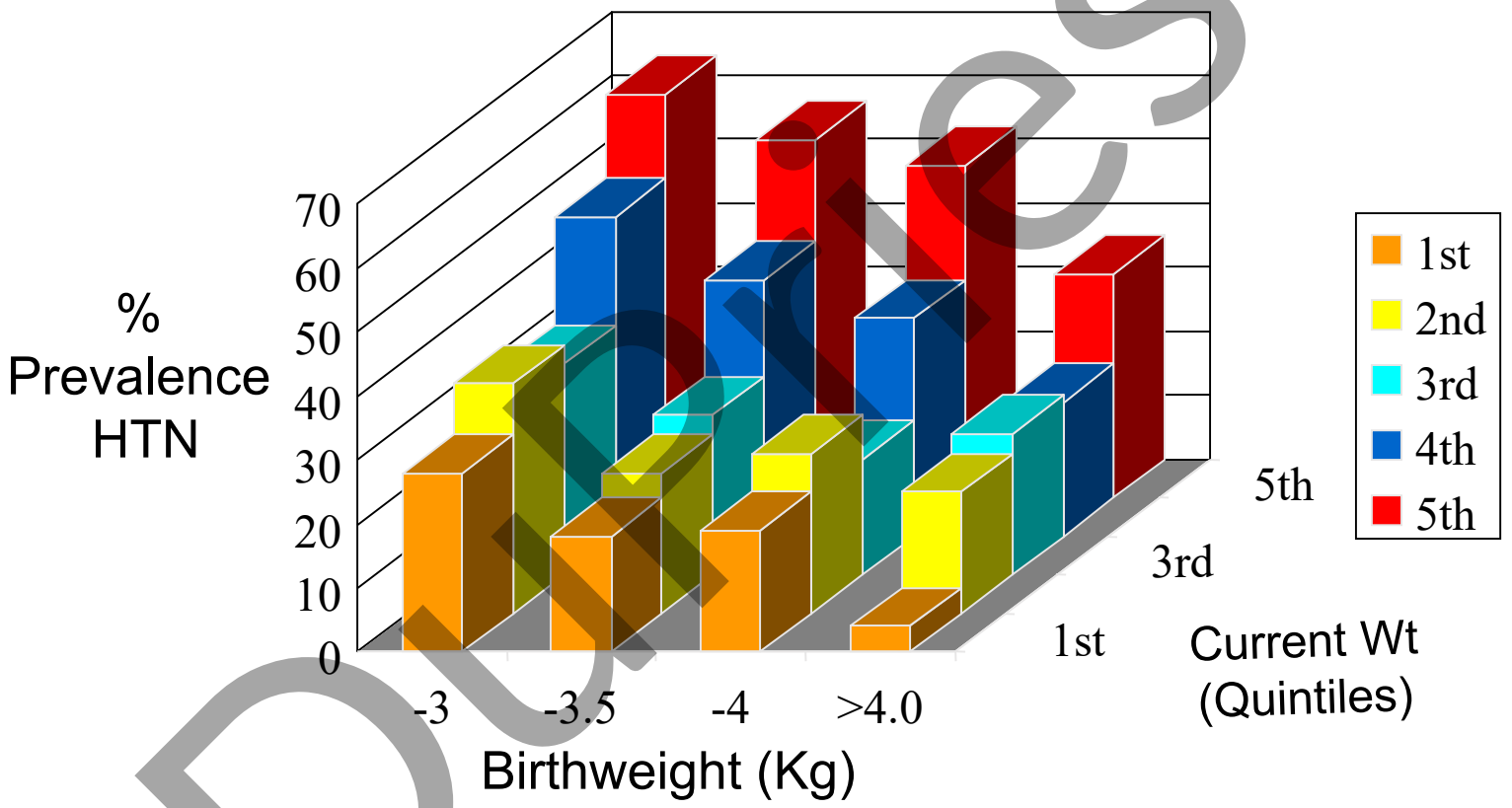



1934-44 Finland Birth Cohort:
8760 total individuals

Barker et al. *J HTN* 2002

# Birth Weight Interacts with Current BMI to Amplify Risk of Hypertension

Avg Age 62 yrs
n = 2003




Eriksson et al. *Hypertension* 2007

# Potential mechanisms for programming of hypertension include:

- Altered organ structure leading to altered function
  - Low nephron number shifts pressure-natriuresis curve
- Altered homeostatic setpoints
  - “Thrifty phenotype” – increased metabolic efficiency leading to insulin resistance
- Mismatch between functional load and capacity
  - High body weight but low nephron number

- Question: How do fetal and childhood growth contribute to risk of hypertension and metabolic disease?

# Development of a new programming model: maternal protein restriction in microswine

- Similarities to humans:
  - Size
  - Longevity
  - Gestation length
  - Major systems, including:
    - Cardiovascular
    - Renal
    - Nutritional/metabolic
    - Immunologic

**6-Mo Adult Microswine**

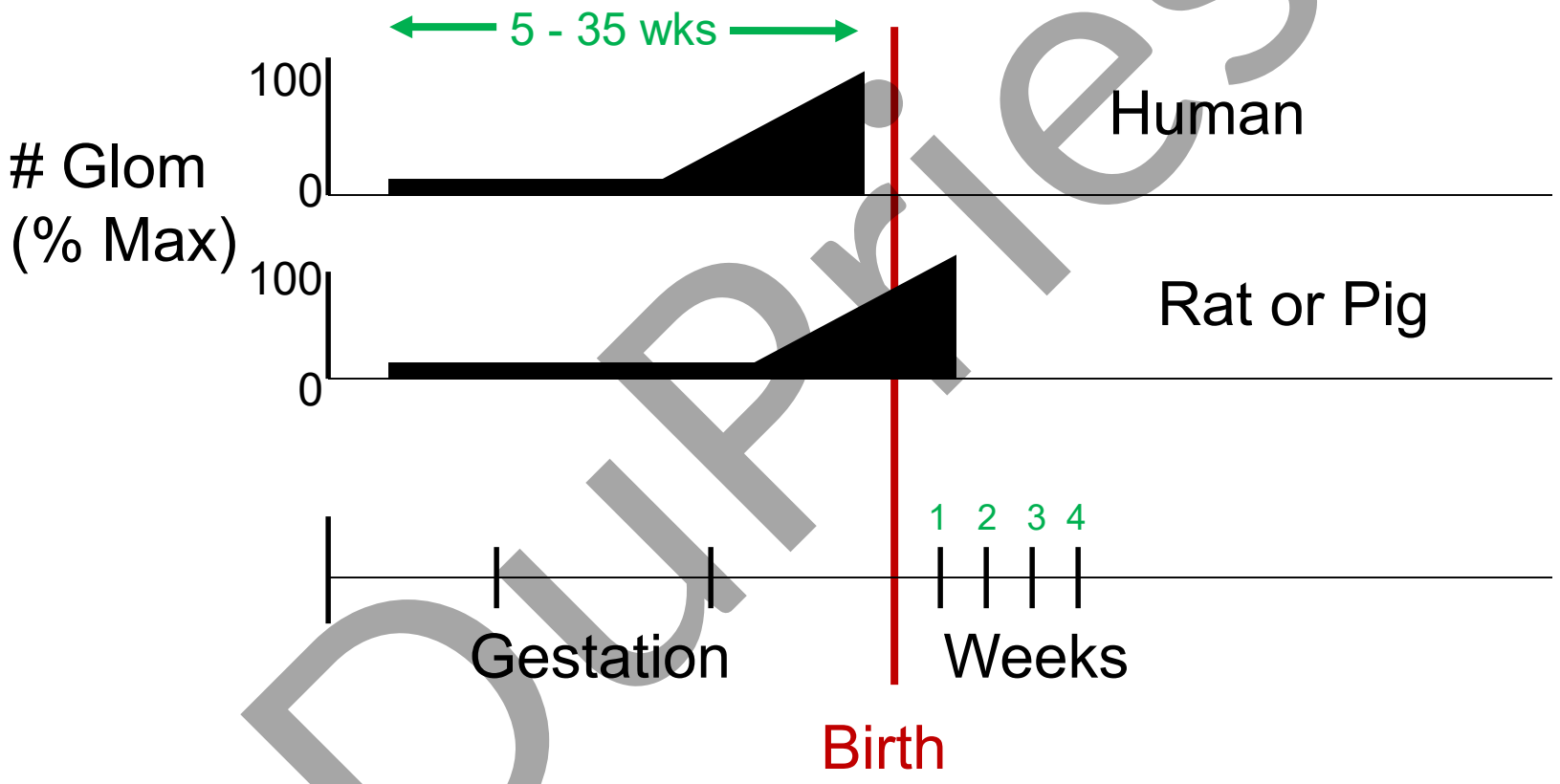
# Maternal Protein Restriction yields IUGR

- Microswine MPR was used to generate intrauterine growth restriction (IUGR) rather than to model a specific human condition
  - Kwashiorkor – severe protein malnutrition – wasting with edema – common in children in developing countries but rare in the US
  - IUGR can arise due to myriad reasons at any location

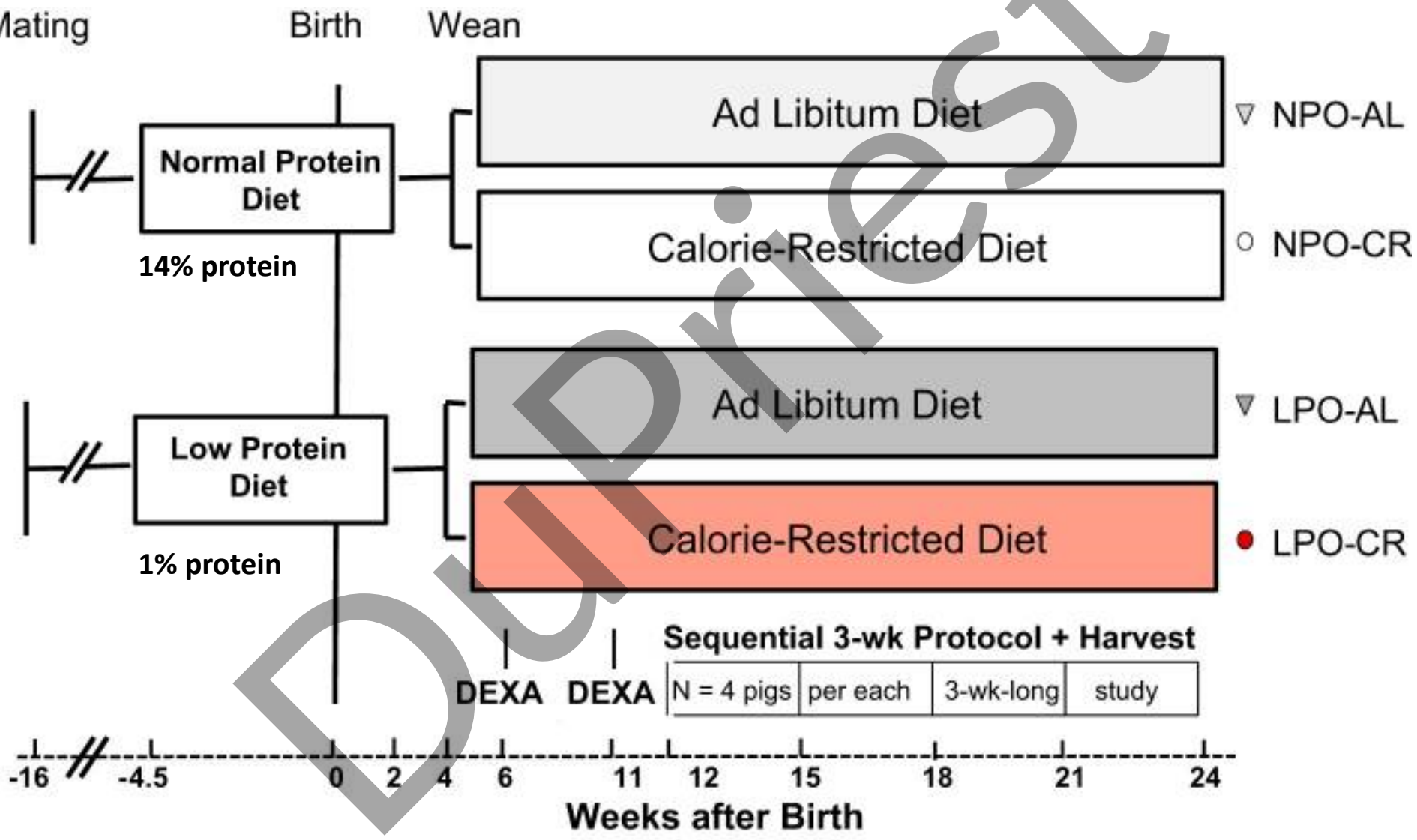
# Protein/Amino Acid needs during pregnancy

- Protein Recommended Daily Allowance (meets needs of 98% of people):
  - Non-pregnant adults: 0.8 g/kg body weight/day
  - Pregnant: 1.1 g/kg /day
  - Newer data: 1.2 g/kg/day in early gestation (16 wks), 1.52 g/kg/d in late gestation (36 wks) (Elango and Ball, 2016)
  - Don't overdo protein intake in pregnancy – too much can reduce birth length and childhood linear growth (Switkowski, 2016)
- Amino acid needs increase too, but in differing amounts by A.A.
  - No human data published yet
  - Swine data (Elango and Ball, 2016) show increases in late vs. early gestation of:
    - 55% for Thr
    - 45% for Lys
    - 63% for Ile
    - 35% for Trp

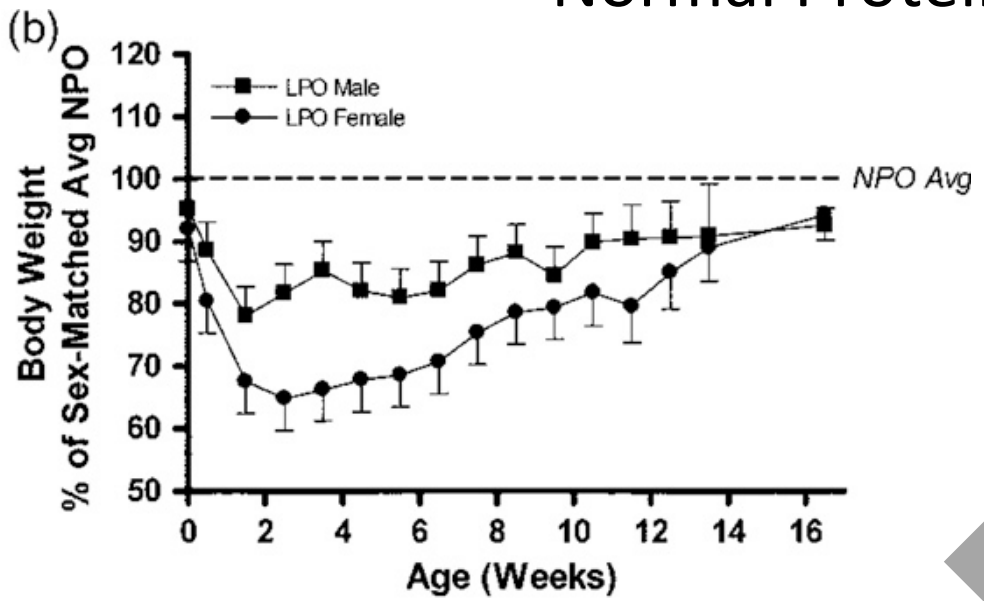
# Time Course of Renal Development

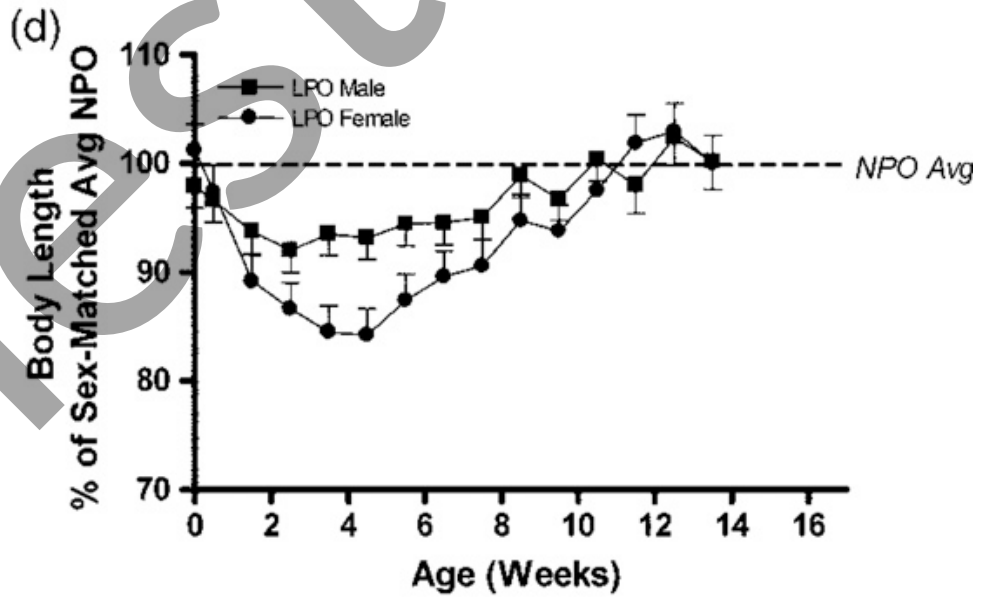


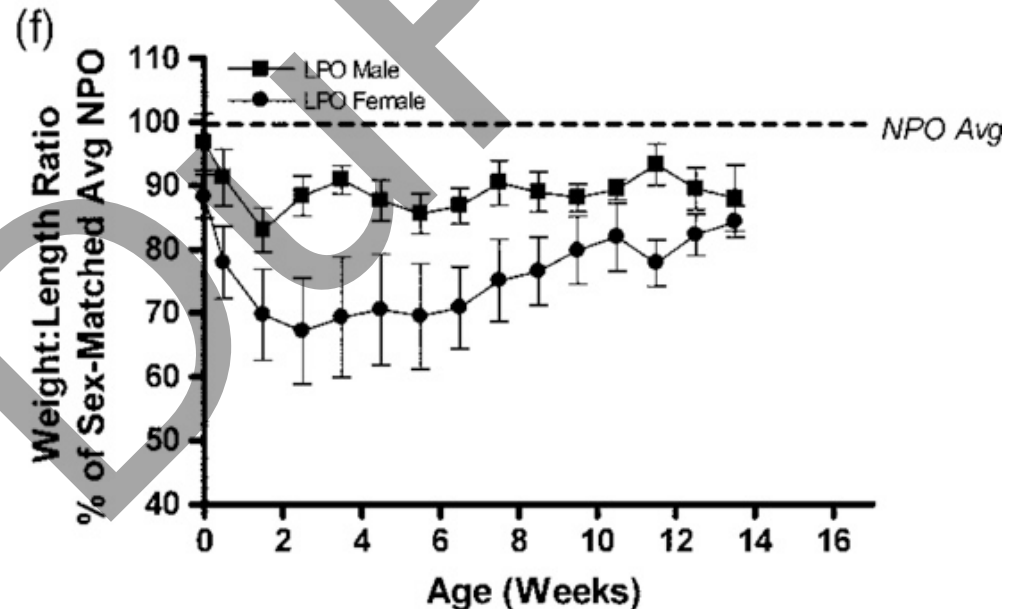
# Experimental Protocol



# Low Protein Offspring are born smaller than Normal Protein Offspring but grow rapidly



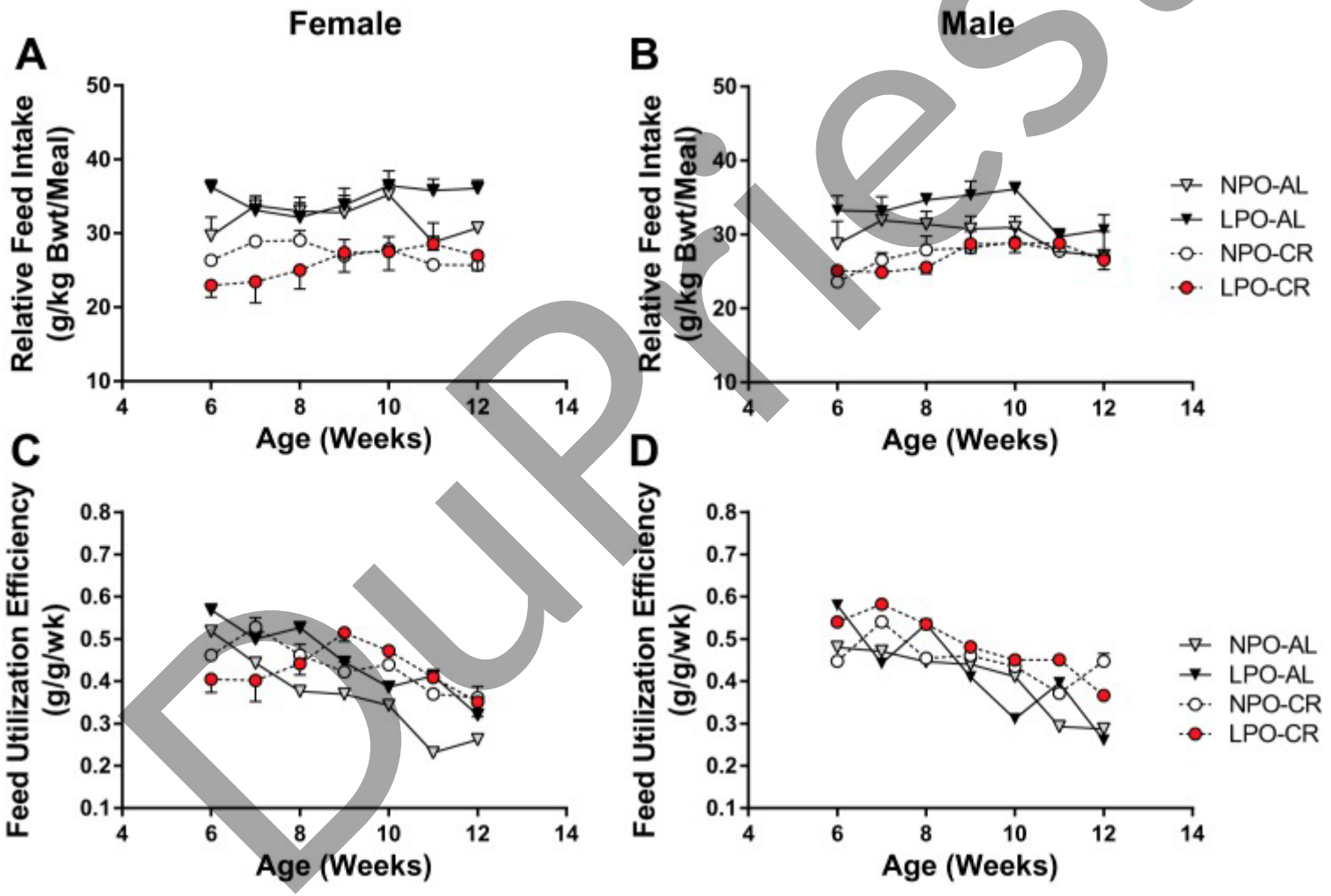






DuPriest et al. *J DOHaD* 2012

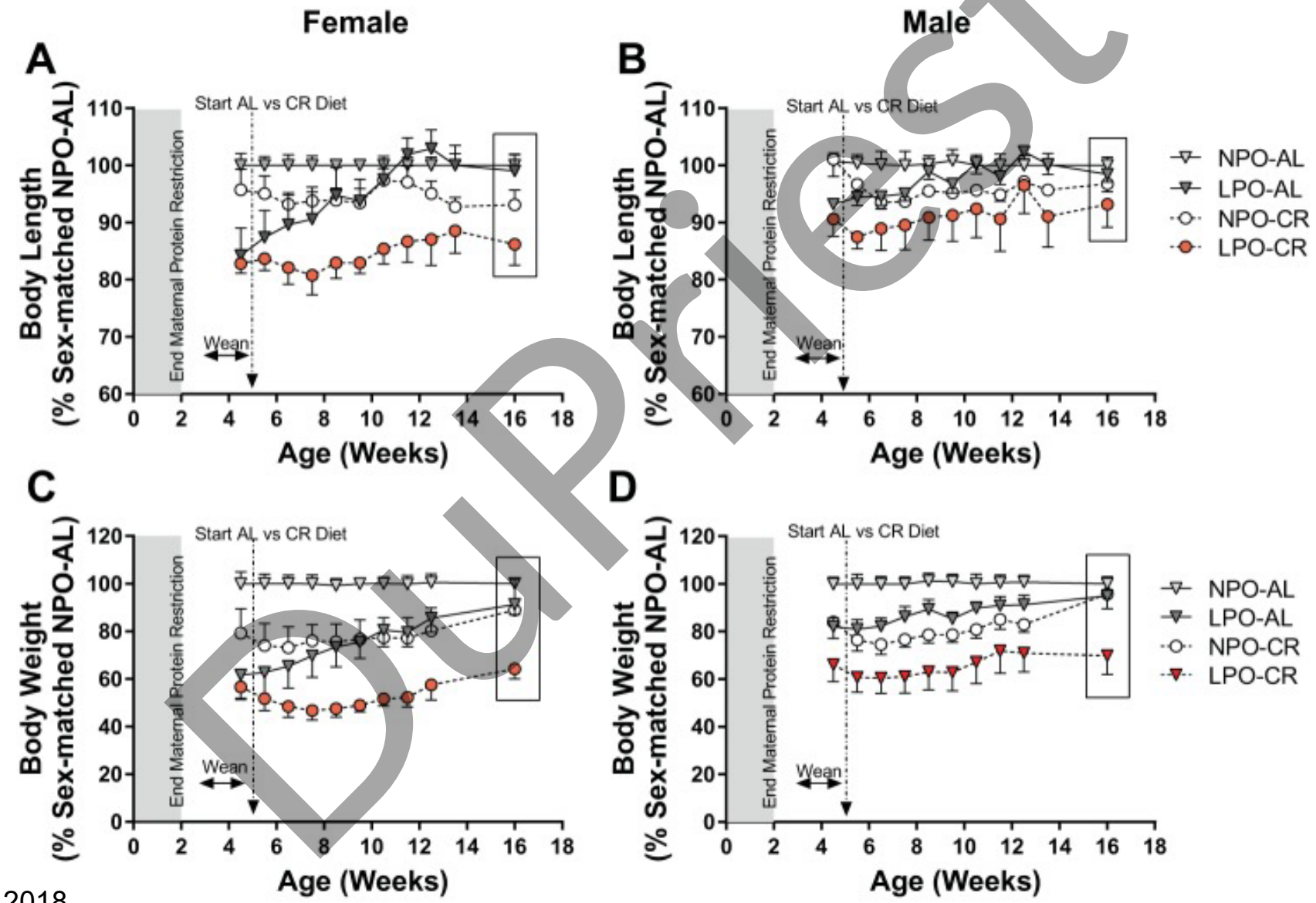
# LPO have increased food intake and feed utilization efficiency






DuPriest et al. *J DOHaD* 2018

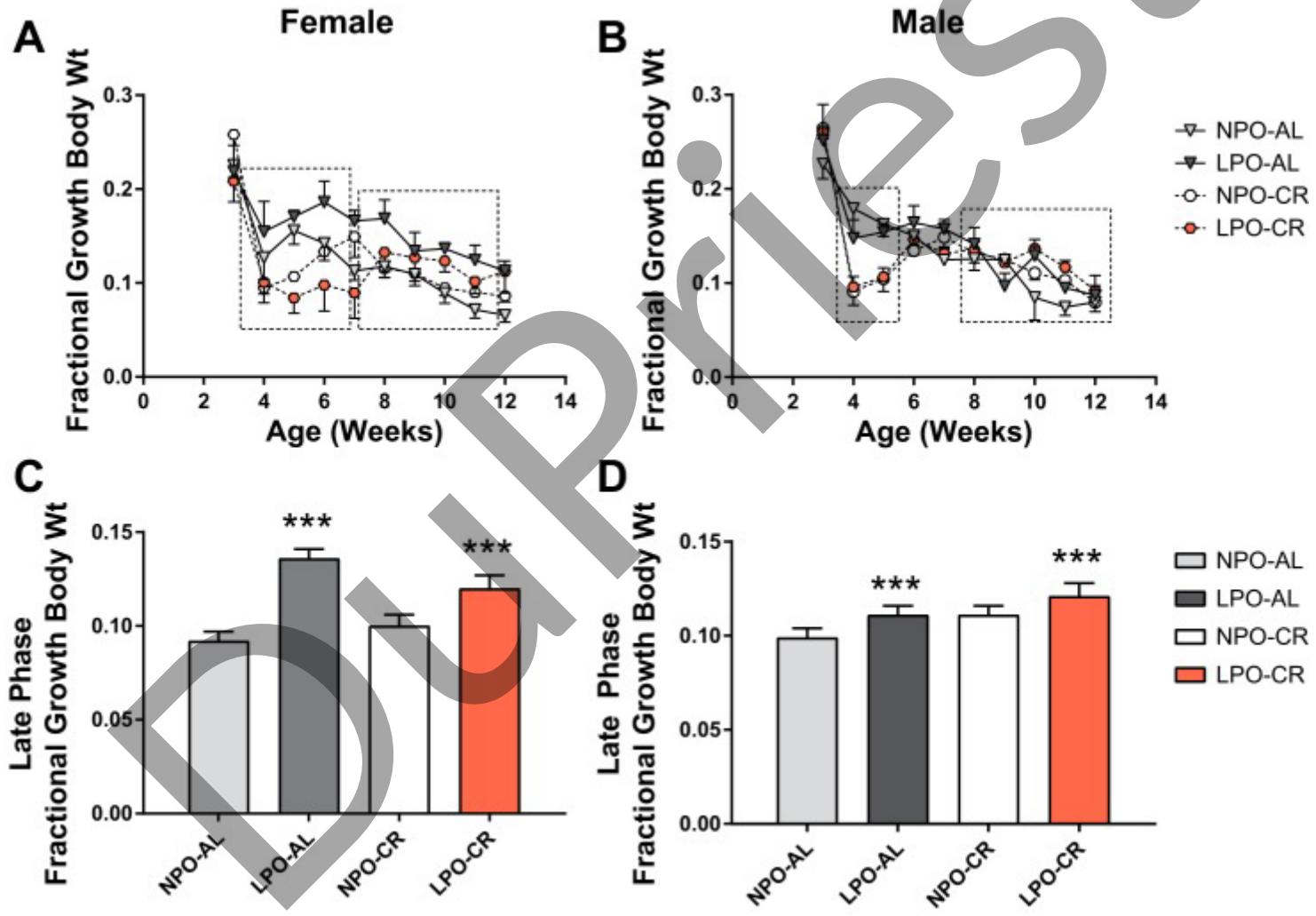
# Caloric Restriction after weaning prevents catch-up growth






DuPriest et al. *J DOHaD* 2018

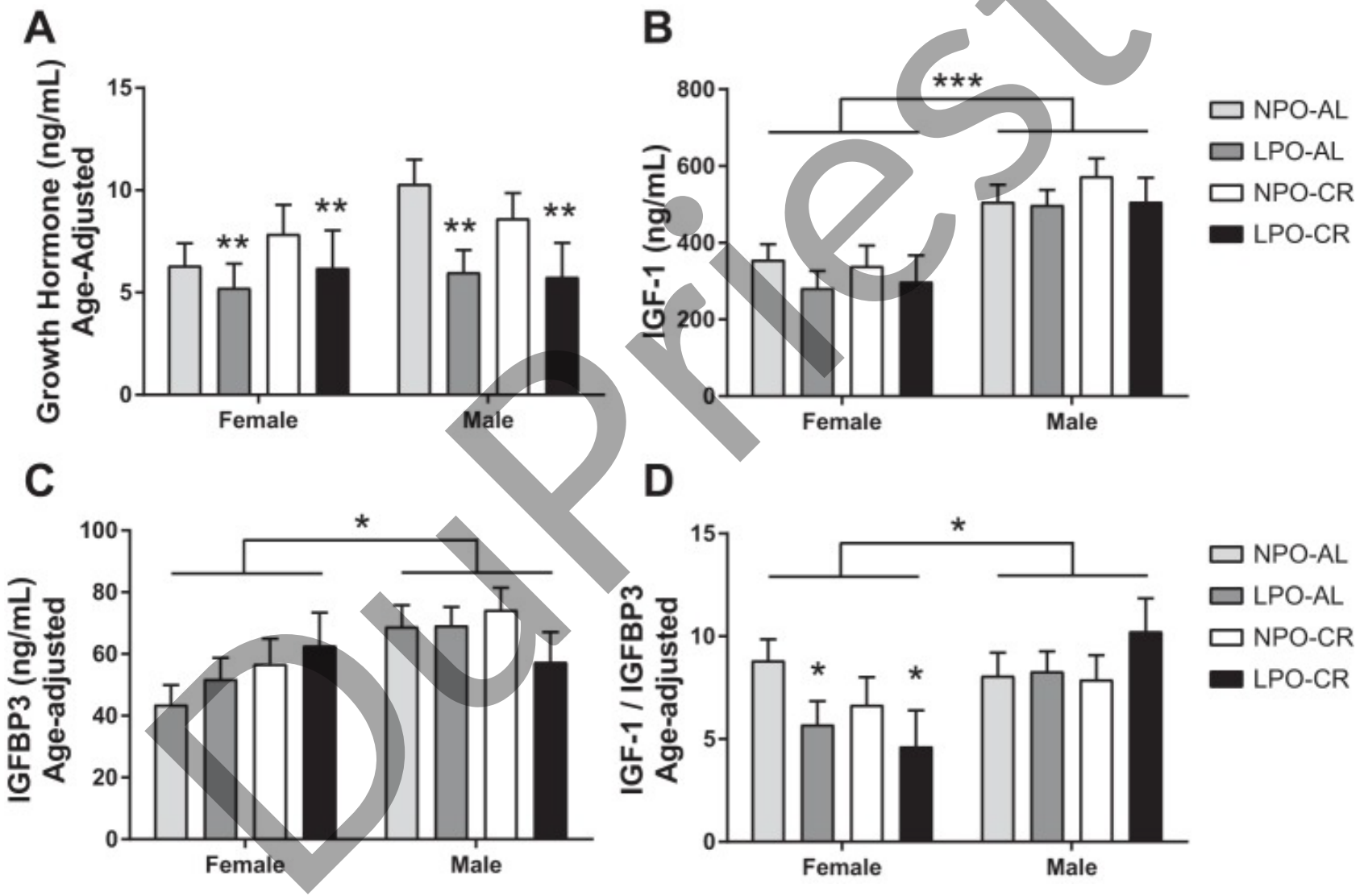
# LPO gain more weight, pound for pound – not changed by CR






DuPriest et al. *J DOHaD* 2018

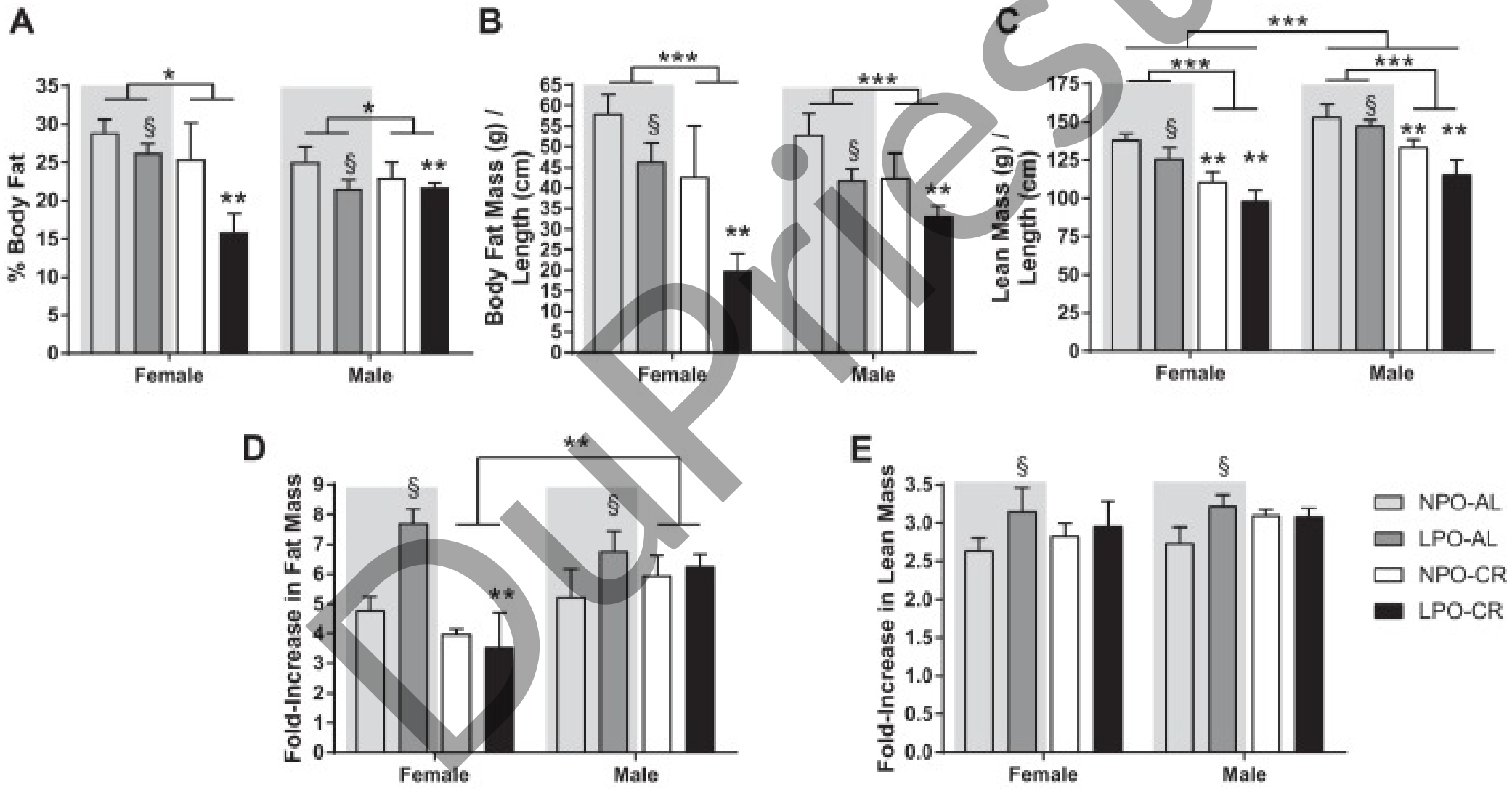
# Growth Hormone is paradoxically reduced in LPO






DuPriest et al. *J DOHaD* 2018

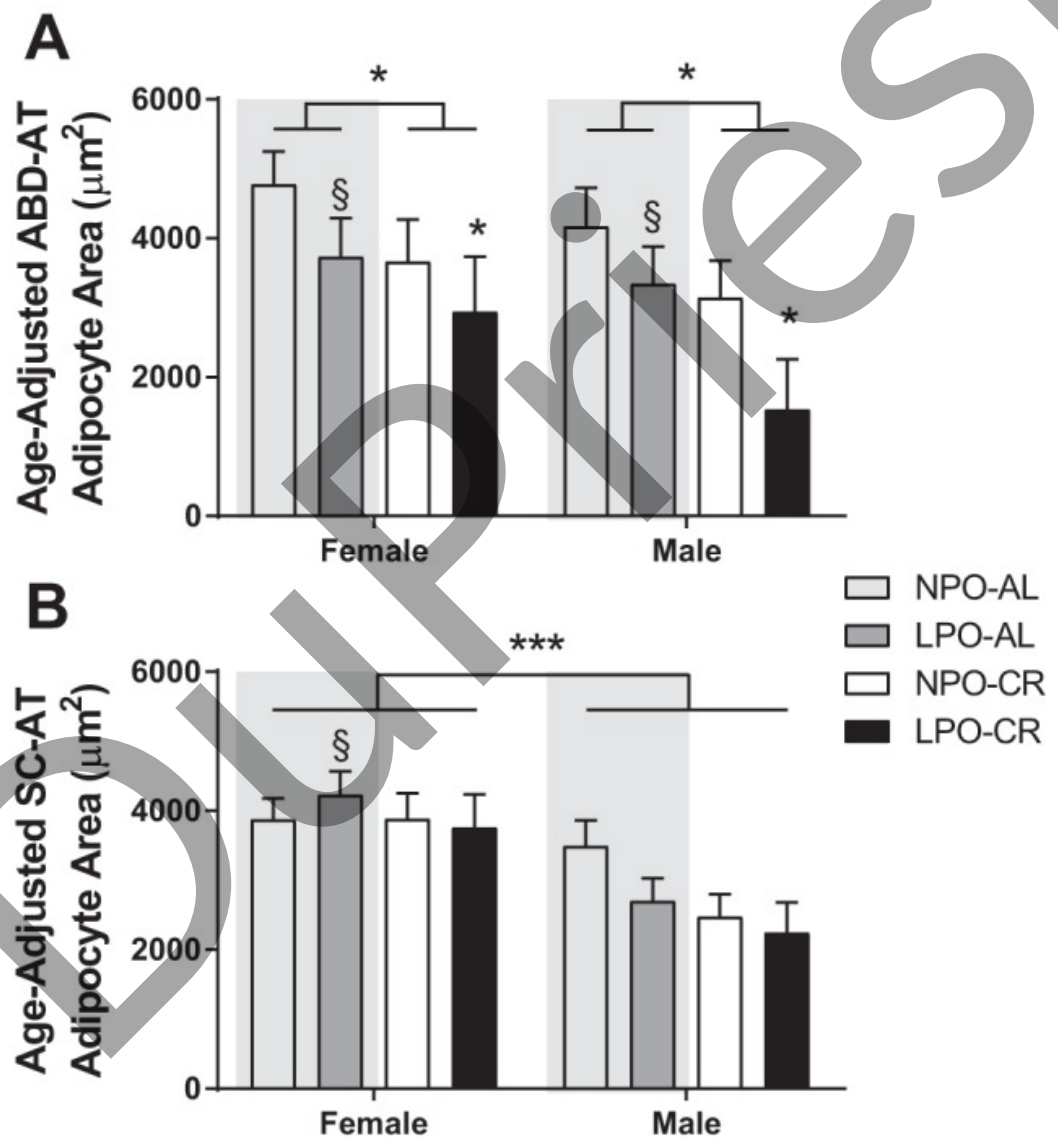
# LPO are “skinny”, and CR reduces their fat and lean tissue accrual






DuPriest et al. *J DOHaD* 2018

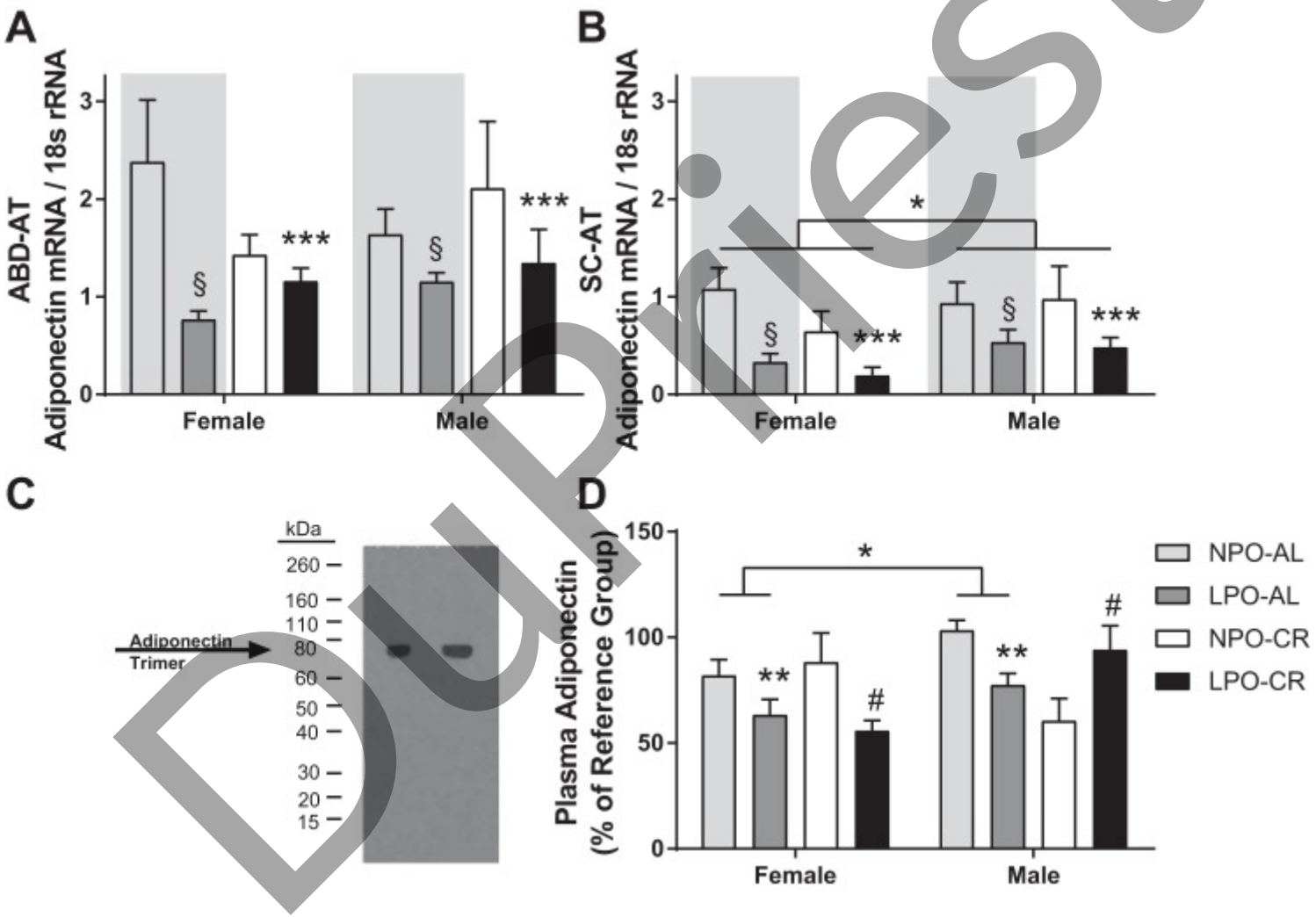
# LPO have small intra-abdominal adipocytes; CR makes them even smaller






DuPriest et al. *J DOHaD* 2018

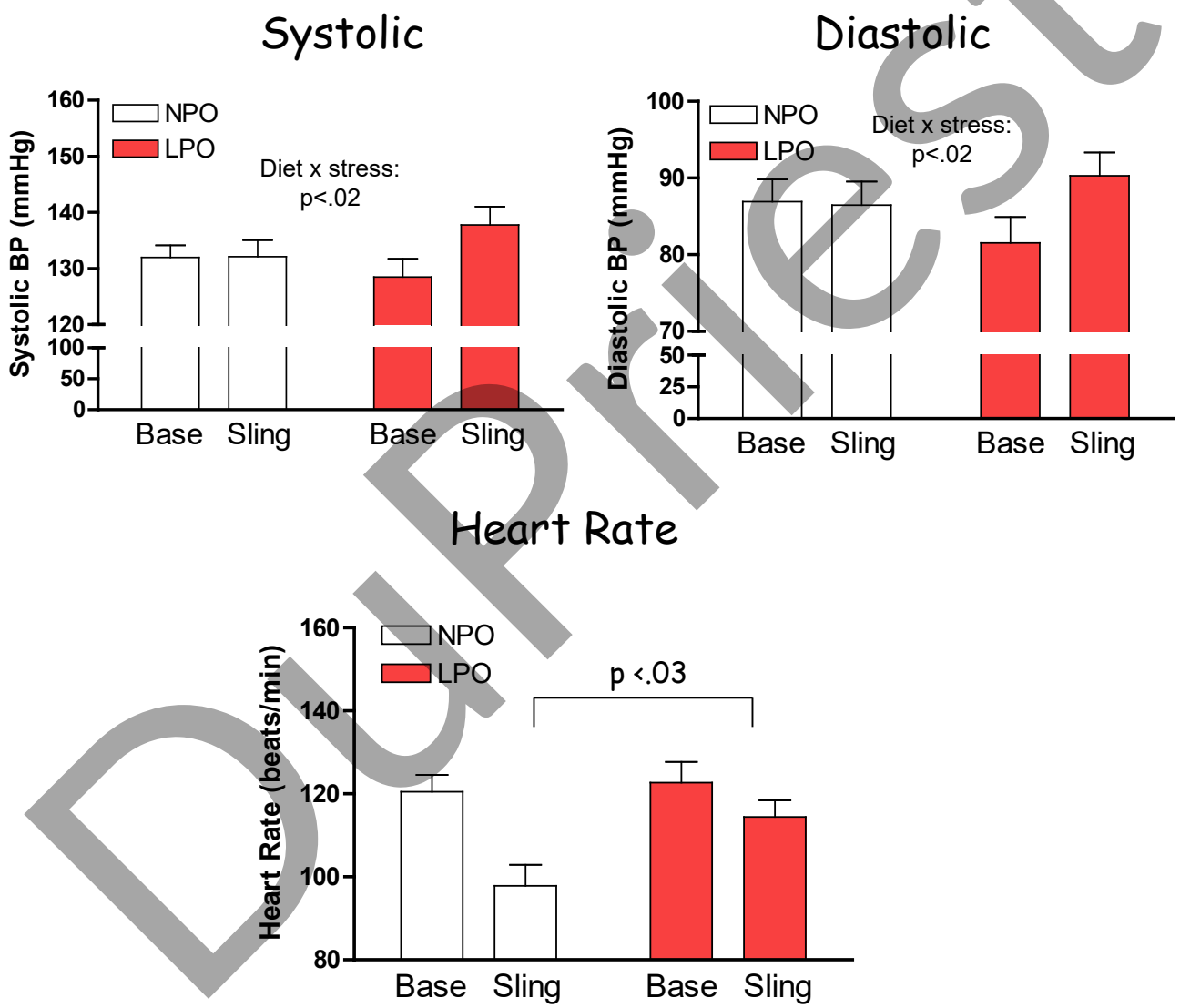
# LPO have low adiponectin mRNA and circulating protein; CR does not ameliorate this



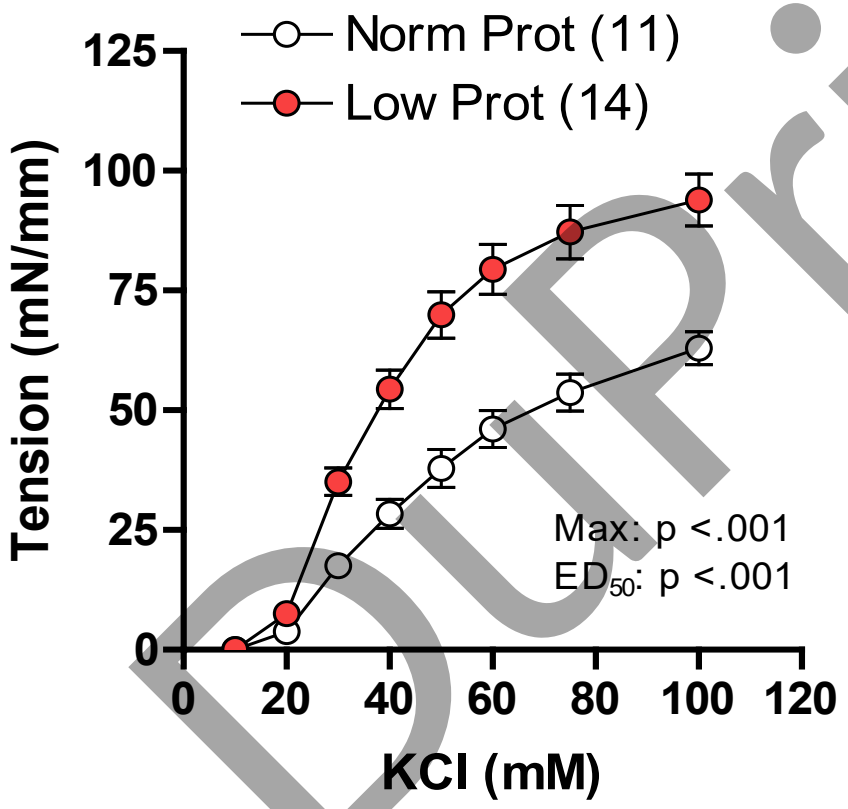


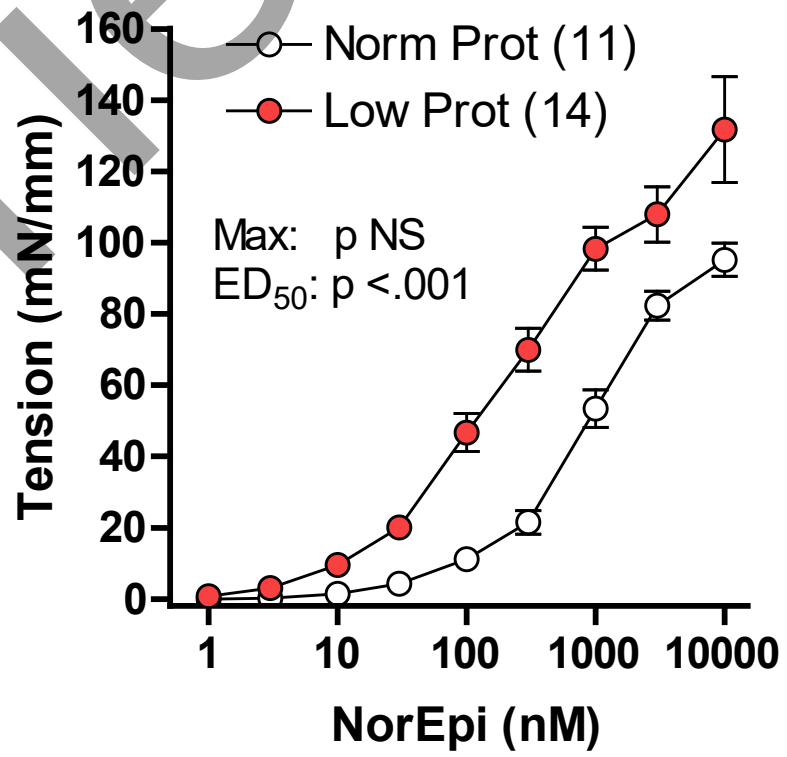

DuPriest et al. *J DOHaD* 2018

# Hemodynamic Responses to Restraint in Juvenile Offspring

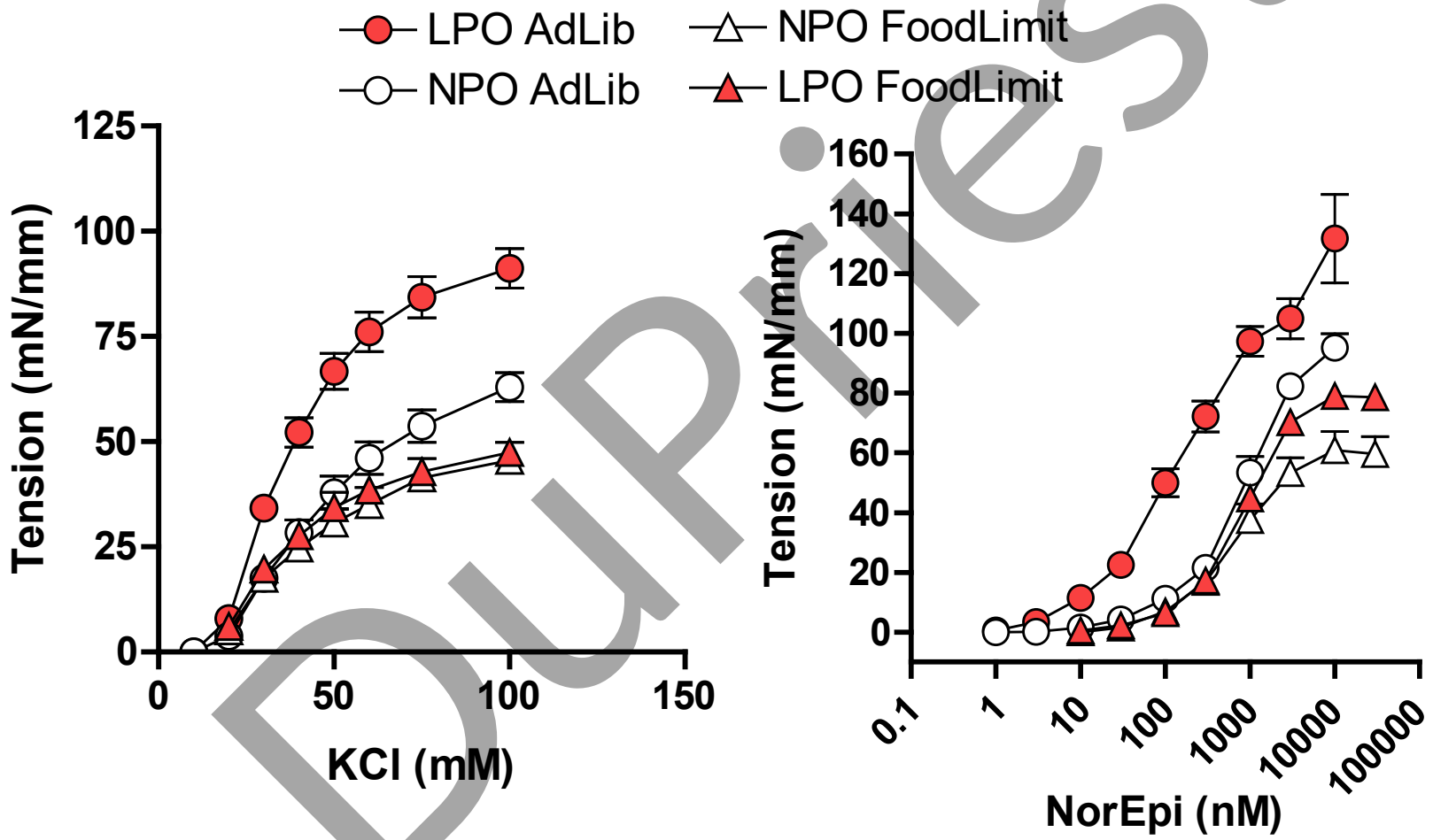


# LPO have vascular hypersensitivity to pressors



# CR restores normal vascular sensitivity to pressors



# Effects of MPR in microswine:

- Generates IUGR with postweaning catch-up growth without increased adiposity
  - Rapid growth occurs despite low plasma GH and low-normal IGF-1
- Alters adipose tissue structure and function and influences circulating metabolic factors, especially adiponectin
- Causes stress-dependent increases in BP with increased vascular sensitivity to pressors

# Effects of postweaning caloric restriction in juvenile microswine:

- Prevents catch-up growth in absolute terms (by design) but not in relative (fractional) terms
- Increases feed utilization efficiency, at least temporarily
- Reduces fat mass >>> lean mass, and lowers intra-abdominal adipocyte size
- Restores normal vascular reactivity to pressors

# Summaries and conclusions

- Some things are determined by prenatal exposure only
  - Adiponectin levels
  - Feed utilization efficiency

- Some things are determined by prenatal exposure but can be modified by postweaning caloric restriction
  - Vascular hyper-reactivity to pressors
  - Insulin sensitivity

# Additional thoughts

- It is critical to examine the sexes separately – there are different responses even during the juvenile period prior to exposure to high levels of sex hormones

- DOHaD models likely do not program individual outcomes (e.g., HTN, insulin resistance, obesity, etc.). They change entire interconnected systems

# Where do we go from here?

- What is behind the increased feed utilization efficiency, and does it persist into adulthood? Is it reflective of the human condition?
- What is behind the increased sensitivity to GH, IGF-1, pressors?
- What is causing the reduction in adiponectin, and what are the long-term metabolic consequences of this reduction?
- Does sustained hypertension develop late in life in DOHaD settings, and if so, what is the mechanism?

# Thank you!

- Susan Bagby, MD & Lab
  - Baoyu Lin
  - Amruta Bhusari
  - Linda LeBard
  - Philipp Kupfer
  - Martha Choate
  - Kaiu Sekiguchi
  - Jonathan McNeil
  - Eden Paster
- Jonathan Purnell, MD
- Terry Morgan, MD, PhD
- Funding
  - NIH/NICHD
  - Eagle Foundation
  - Tartar Trust
  - American Heart Assoc.


That's all Folks!
kalilak