Fitness and energy trade-offs after early-life microbiome disruption differ by sex and antibiotic dose

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Background & Objectives

- Exposure to Early-Life Antibiotics (ELA) promotes adult obesity across diverse species

Part 1: Variation in antibiotic dosage [1]

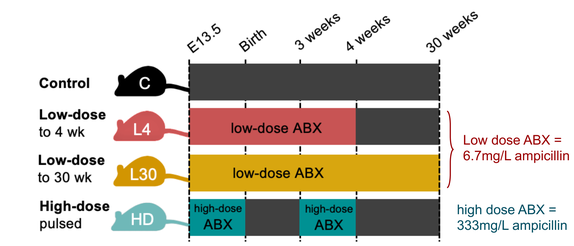
- Humans are typically exposed to pulsed, therapeutic (high-dose) ELA, while most mouse studies use chronic sub-therapeutic (low-dose) exposures
- **Q:** How do high- and low-dose ELA compare in their short- and long-term impact on energy metabolism?

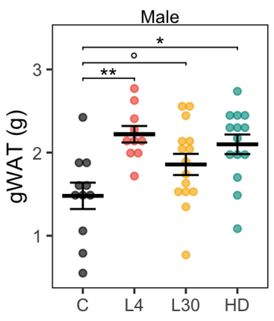
Part 2: Fitness trade-offs of ELA

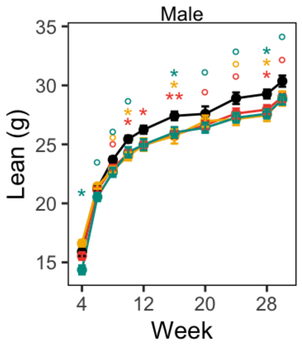
- ELA-induced obesity is predominant in males
- **Q:** Could the traits that predispose ELA males to obesity when food is plentiful be adaptive to food scarcity?
- **Q:** Could female resistance to ELA-induced obesity come at the cost of other aspects of health?

[1] LD Schell & RN Carmody (2025). An energetic framework for gut microbiome-mediated obesity induced by earl-life exposure to antibiotics. *Cell Host & Microbe 33*(4)

Part 1.1: Both high-dose and low-dose ELA promote adiposity in adult males





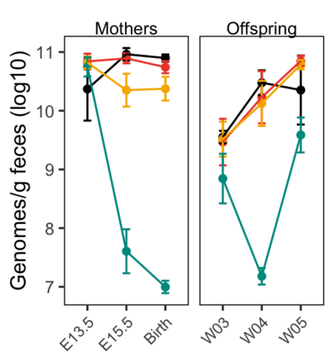


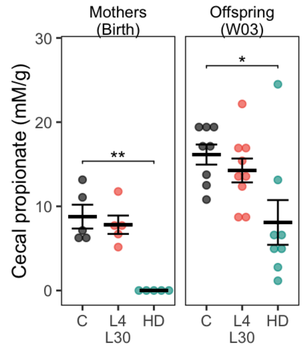
↑ visceral fat deposits

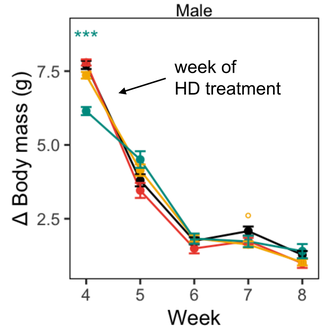
↓ lean mass
(also ↓ energy expenditure)

Females body composition is largely unaffected (data not shown)

Part 1.2: High-dose antibiotics disrupt gut microbial contributions to host energy availability







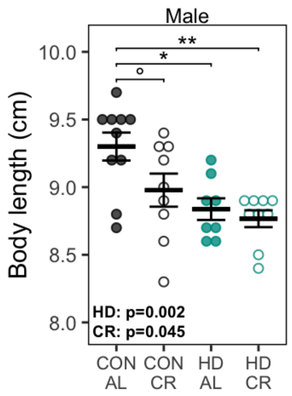
↓ gut microbial density

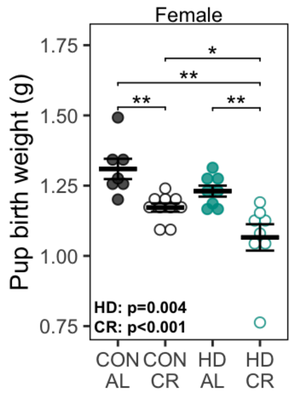
↓ SCFAs

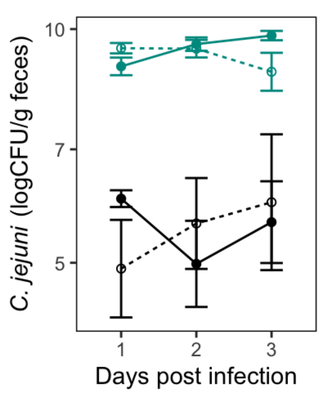
growth restriction

Recovery following cessation of treatment

Part 2.1: Growth, reproduction, and immune outcomes after high-dose ELA







♂ stunted growth

Also: ↓ in lean mass in HD males

Female adult body size unaffected

♀ dysregulated gestation

Also: ↓ blood glucose but ↑ food intake in pregnant HD females

Male sperm counts unaffected

♂ ↑ susceptibility to infection ♀

Also: minimal immune activation in HD mice, and ↑ weight loss in HD-CR vs AL-CR

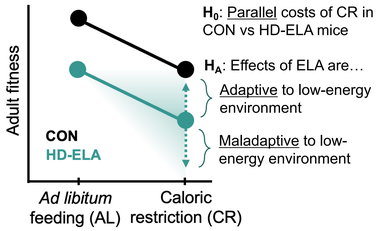
Part 2.2 Fitness trade-offs

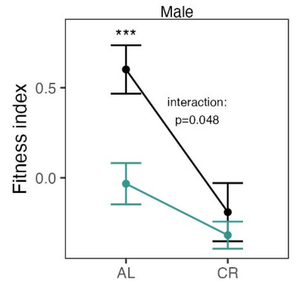
Fitness index

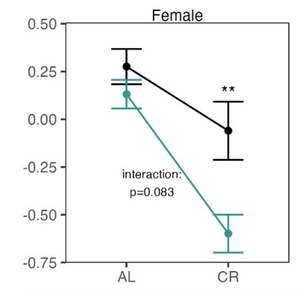
Mean Z-scores for:

- Visceral fat
- Body length
- Lean mass
- Live *C. jejuni* in feces
- Weight loss after *C. jejuni* infection
- Sperm counts (males)
- Testes size (males)
- Pup birth weight (females)
- Total pup count (females)

Potential outcomes







♂ better than expected under CR

♀ worse than expected under CR

Conclusions

Part 1: Energetics of antibiotics across dosages

- Both high- and low-dose ELA promote male obesity via reductions in lean body mass and energy expenditure (i.e., "thrifty" metabolism)
- High-dose antibiotics uniquely impair short-term gut microbial contributions to the host energy availability

Part 2: Fitness outcomes

- Males: Development of "thrifty" metabolism after ELA is adaptive to an energy-poor environment
- Females: Resistance to ELA-induced obesity and "thrifty metabolism" is beneficial under standard conditions, but exacerbates fitness reduction in an energy-poor environment

Novel implications for human health

- Thrifty metabolism in ELA males may hinder attempts at weight loss
- Dysregulated pregnancy in ELA females, especially when combined with food restriction, may increase risk of metabolic disease in next generation

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