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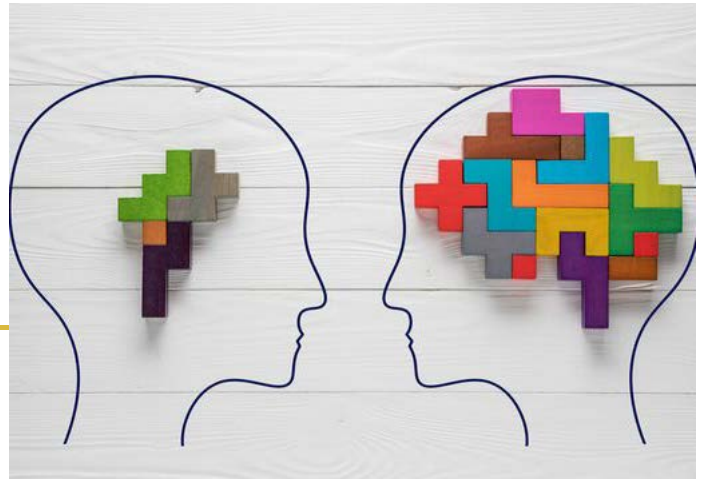
Exercise and diet effects on chemical-induced toxicity



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IN AN EXPOSED POPULATION OF HUMANS, VERY FEW GET **SICK**.
HOW CAN WE PREDICT WHO WILL? AND PROTECT THEM?

Factors that determine response to chemical exposures

IMPACTS TO UPTAKE/DISTRIBUTION, TOXICODYNAMICS, EXCRETION, AND METABOLISM.

ENVIRONMENT

LIFESTYLE

GENETICS

Muscular and systemic exercise adaptations

Within Muscle

- MITOCHONDRIAL CONTENT
- MITOCHONDRIAL PROTEIN SYNTHESIS
- FATTY ACID/KETONE METABOLISM
- PYRUVATE METABOLISM
- NADH IMPORT INTO MITOCHONDRIA

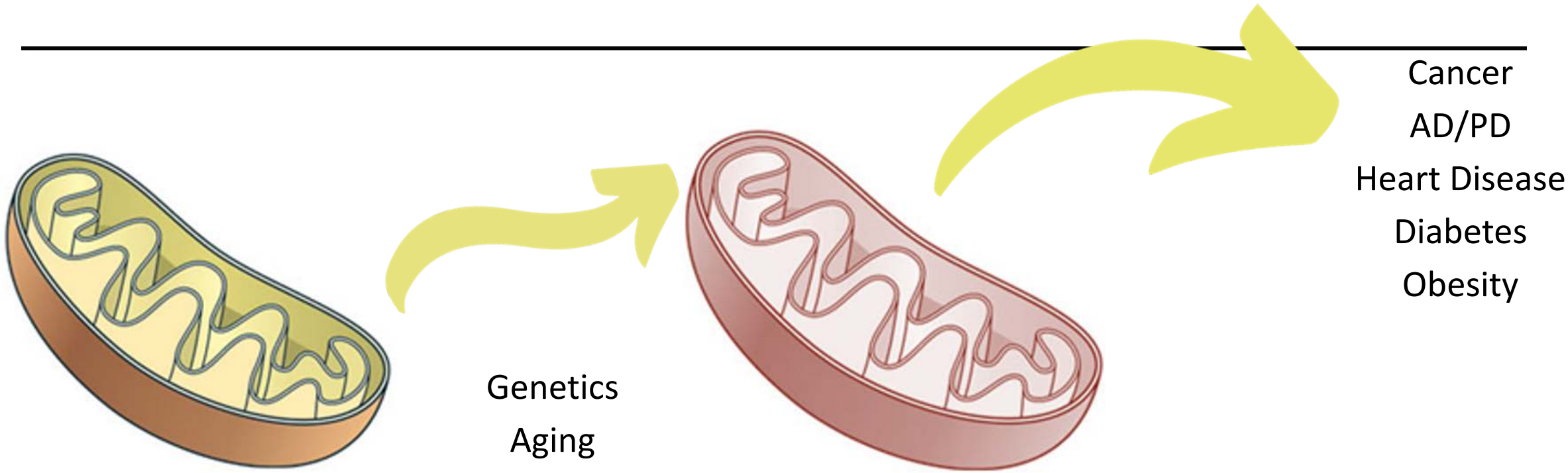
Systemically

- INCREASED MITOCHONDRIA IN NON-EXERCISED TISSUES
- CARDIOMETABOLIC IMPROVEMENTS
- PROTECTION FROM NEUROLOGICAL DISEASE, CANCER, OTHERS

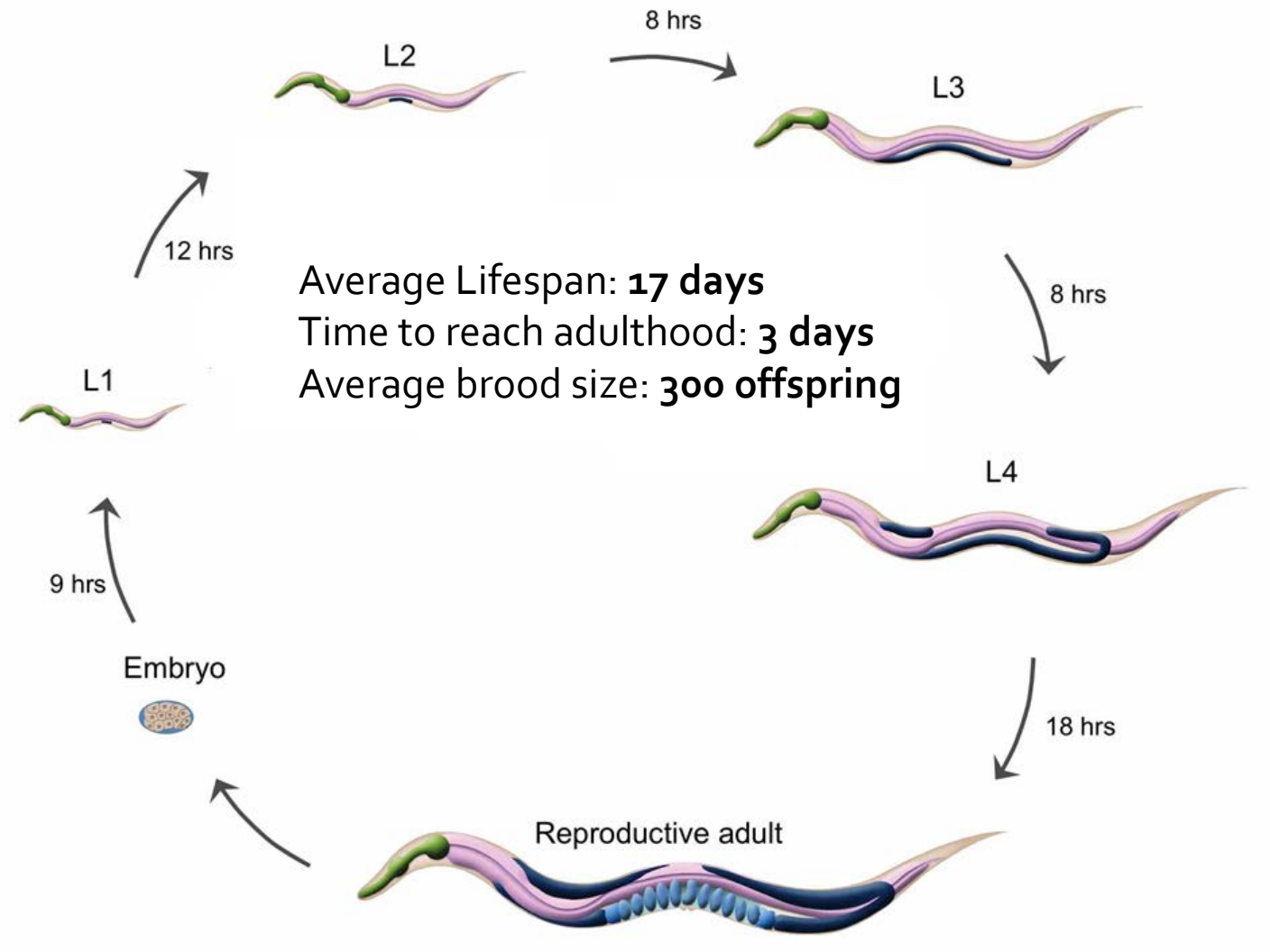
Holloszy J 1967 *J Biol Chem* 242(9):2278-2292.; Gudson AM et al 2017 *Exp Gerentol* 90:1-13. Taghizadeh et al 2016 *Free Rad Biol Med* 99:11-19. Bernardo TC et al 2017 *Brain Pathol* 26(5) 648-663. Neufer PD et al 2015 *Cell Metab* 22(1):4-11.

Mitochondrial dysfunction and disease

A POTENTIAL ROLE FOR ENVIRONMENTAL EXPOSURES



Caenorhabditis elegans is an attractive model organism for toxicology/biochemistry

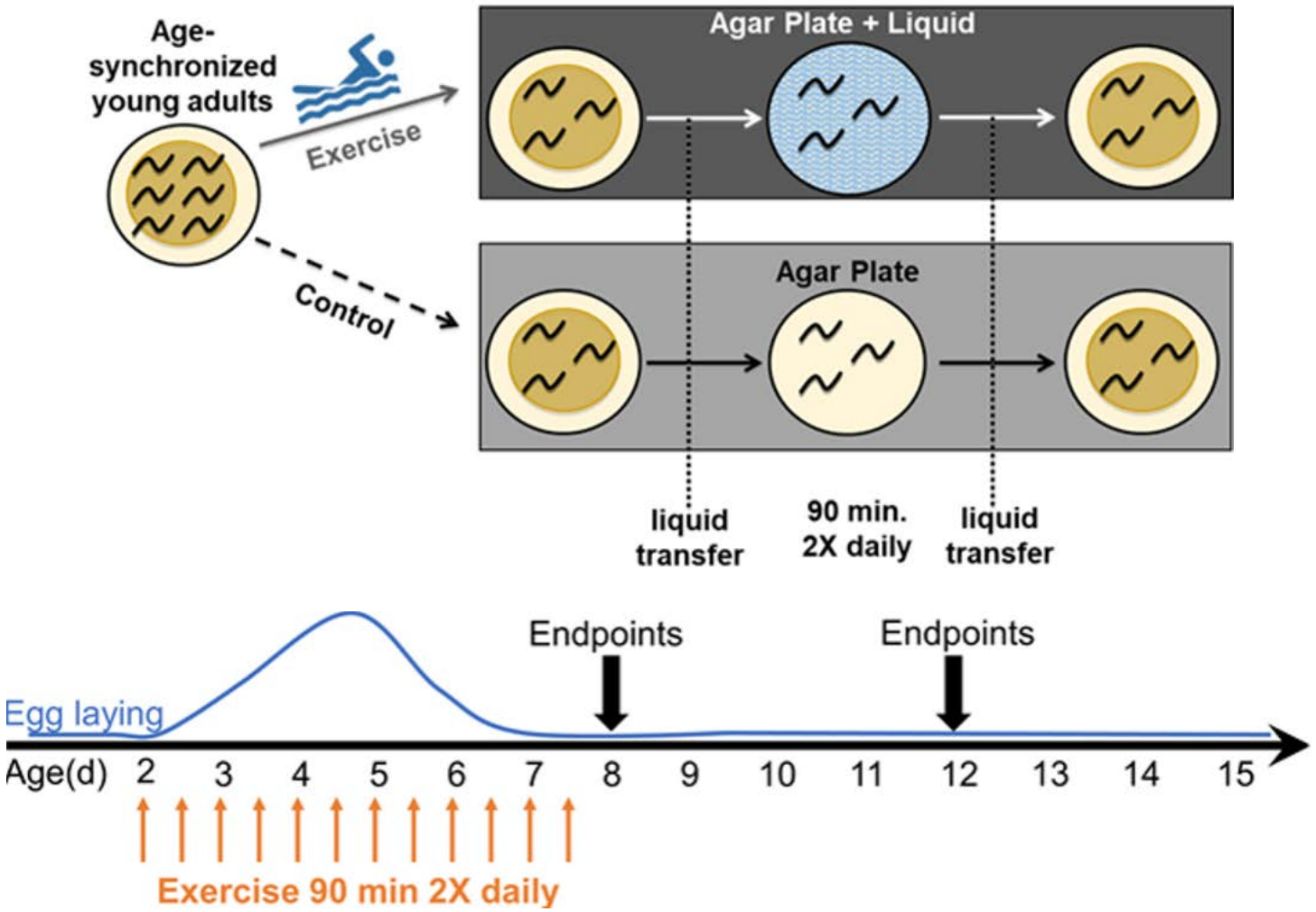


Average Lifespan: **17 days**
Time to reach adulthood: **3 days**
Average brood size: **300 offspring**

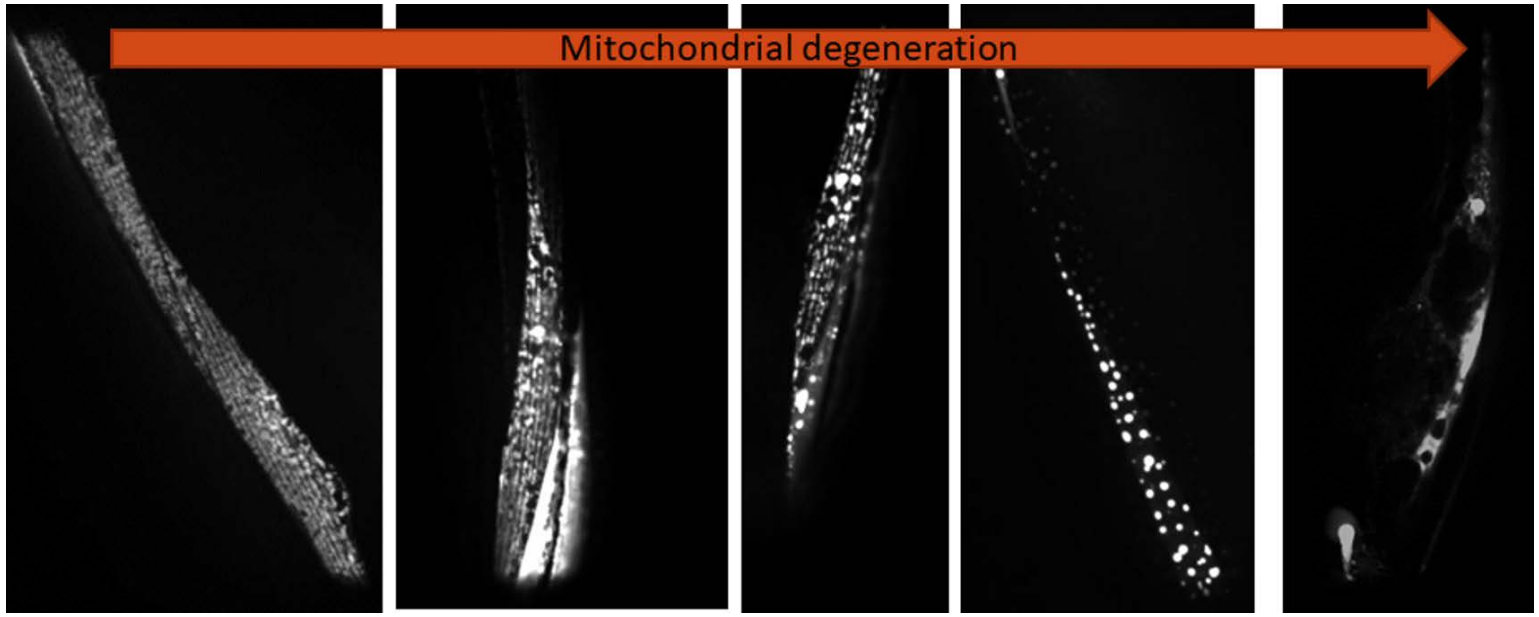
“So how do you exercise a worm?”

Exercise Protocol

TWELVE 90 MINUTE SWIM SESSIONS OVER 6 DAYS



Exercise improves mitochondrial ***morphology*** and ***function***



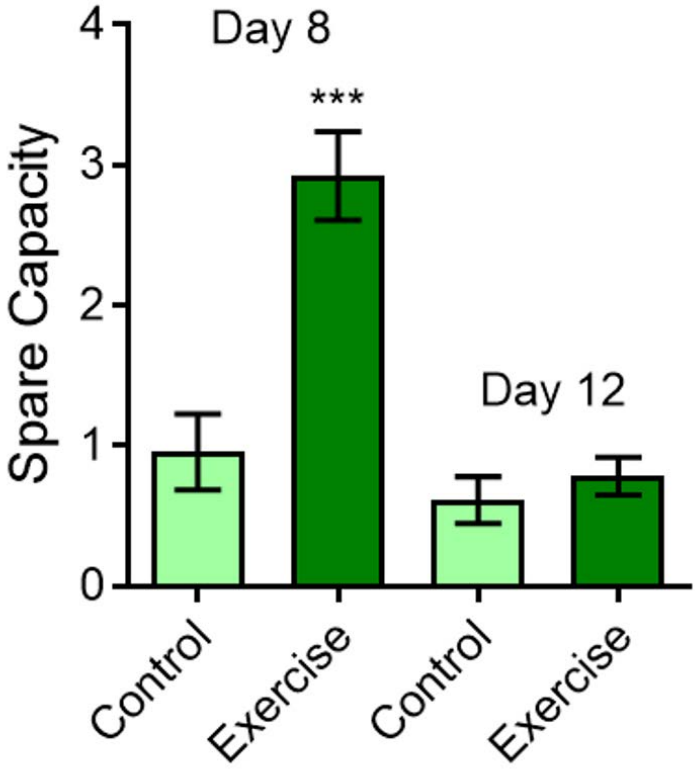
1 day after exercise…

exercised worms

50% 25% 15% 7% 3%

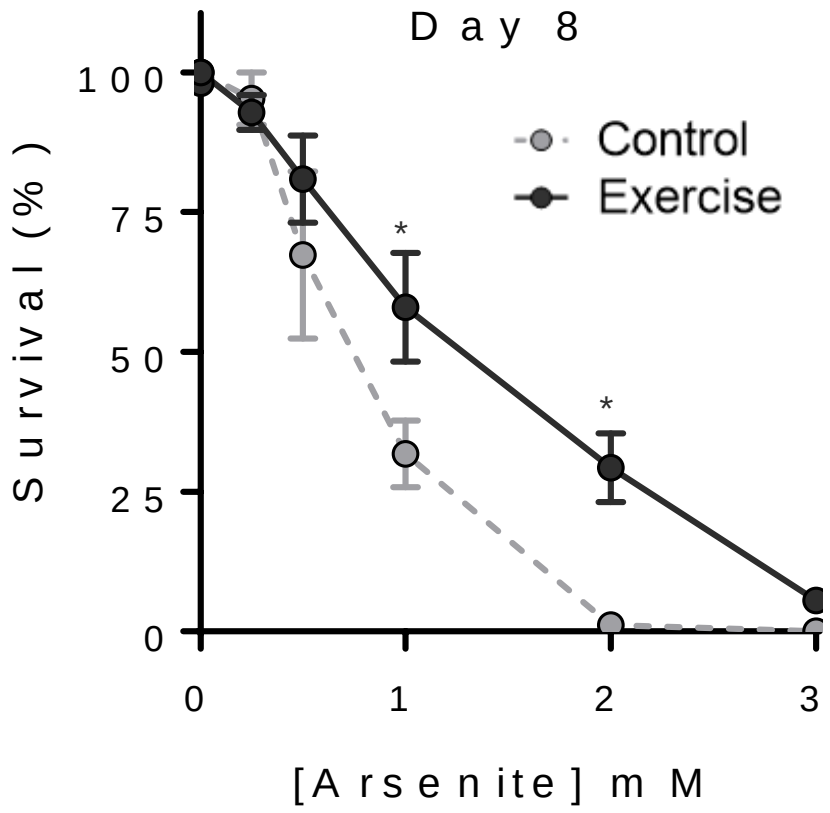
non-exercised worms

25% 25% 25% 20% 5%



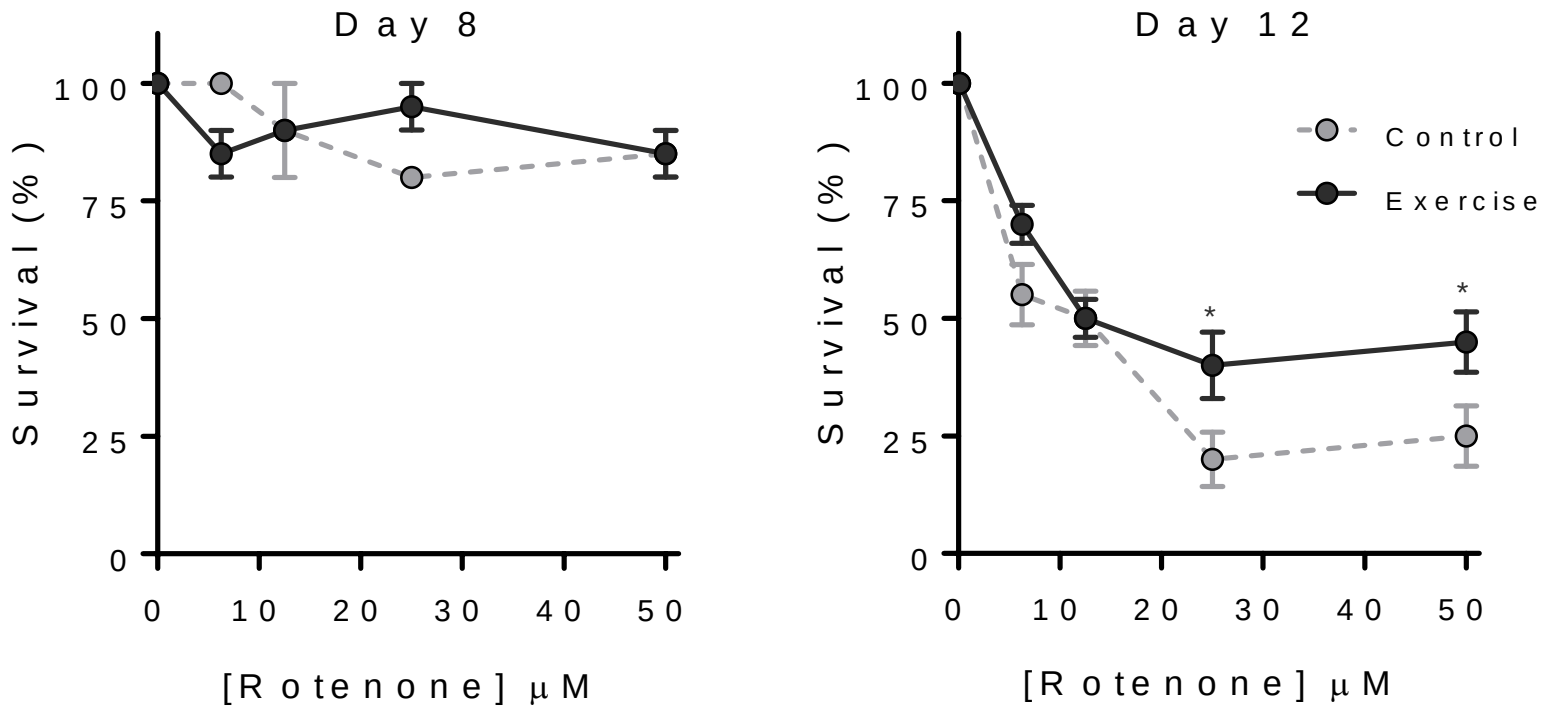
Hartman JH *et al* (2018) *Scientific Reports*, 8(1): 8359.

Exercise protects from arsenic lethality



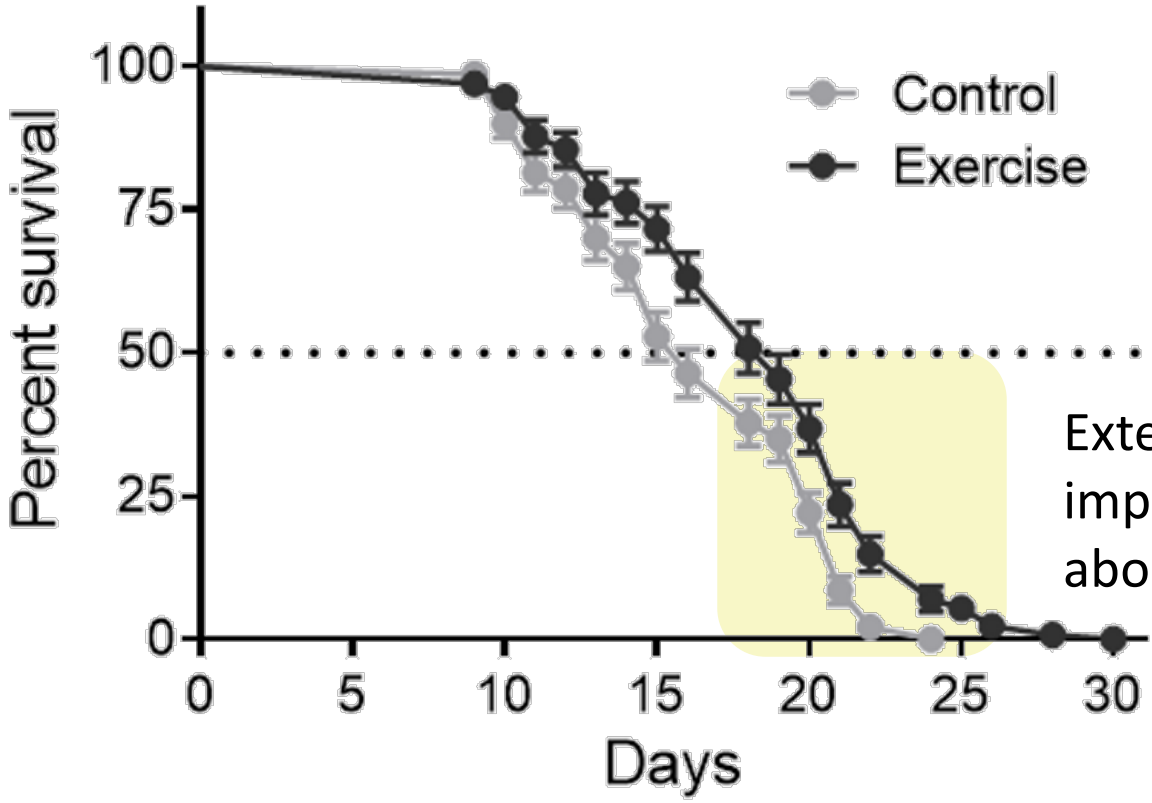
Hartman JH *et al* (2018) *Scientific Reports*, 8(1): 8359.

Exercise-conditioned worms are less sensitive to rotenone exposures



Hartman JH *et al* (2018) *Scientific Reports*, 8(1): 8359.

Lifespan is extended by exercise intervention



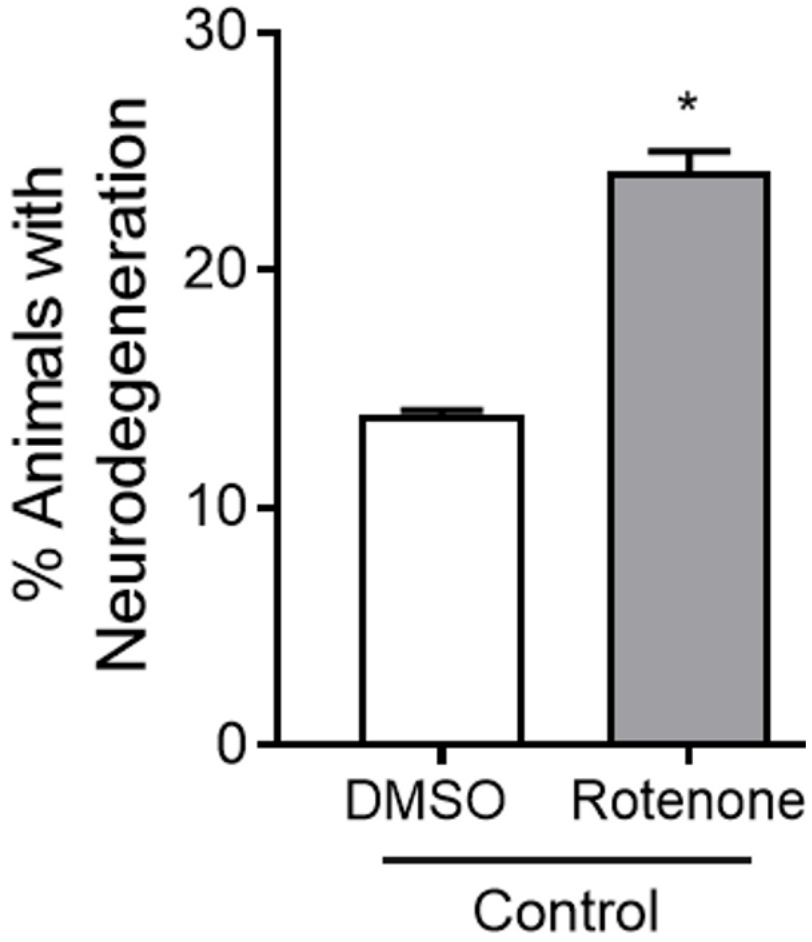
Extending lifespan is important, but what about healthspan?

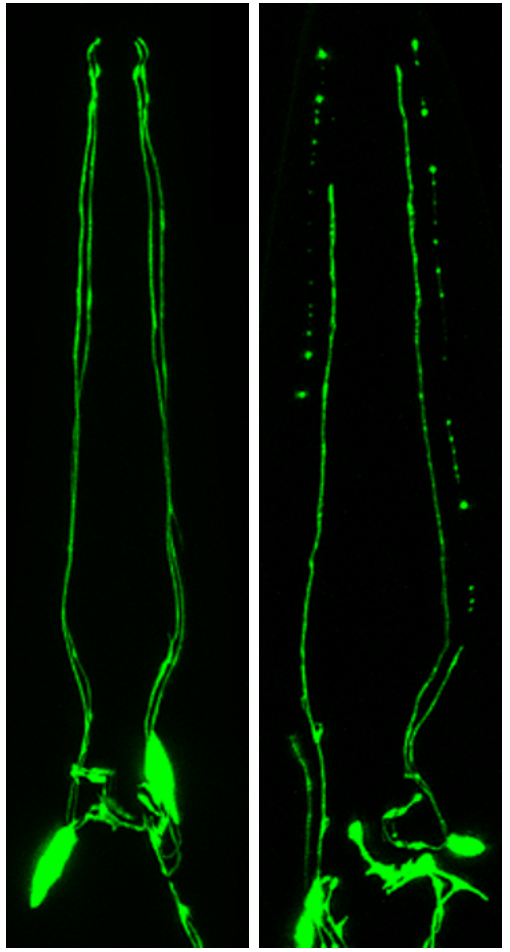
Hartman JH *et al* (2018) *Scientific Reports*, 8(1): 8359.

Currently no drugs that modify or slow the progression of Parkinson's Disease

Physical exercise improves patient symptoms through unknown mechanisms.

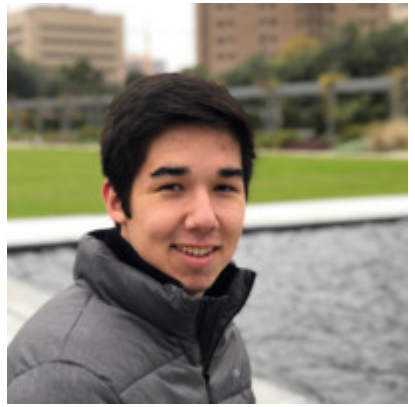
Exercise protects from age- and toxicant-induced neurodegeneration





If we think about our exercise results as an effect of positive energy balance, what about negative metabolic effects (i.e. from diet)?

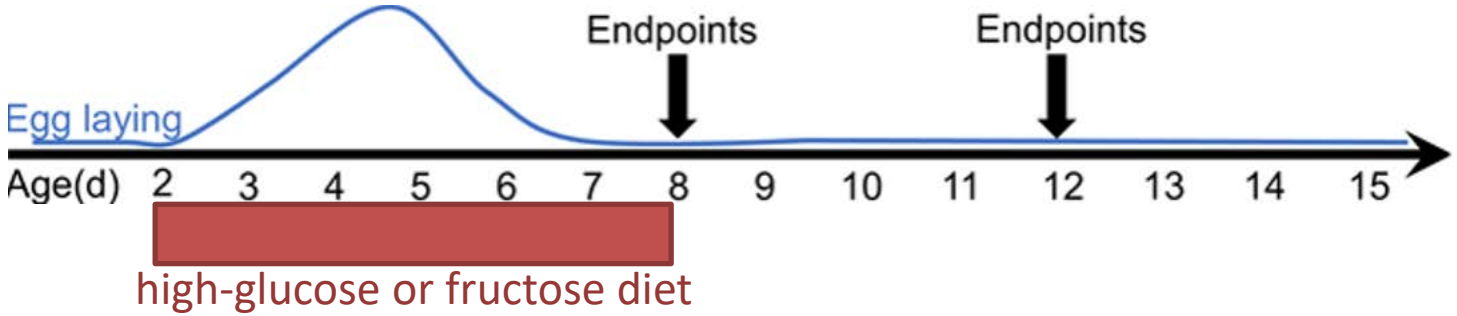
Kate Morton
Ph.D. student,
Meyer lab



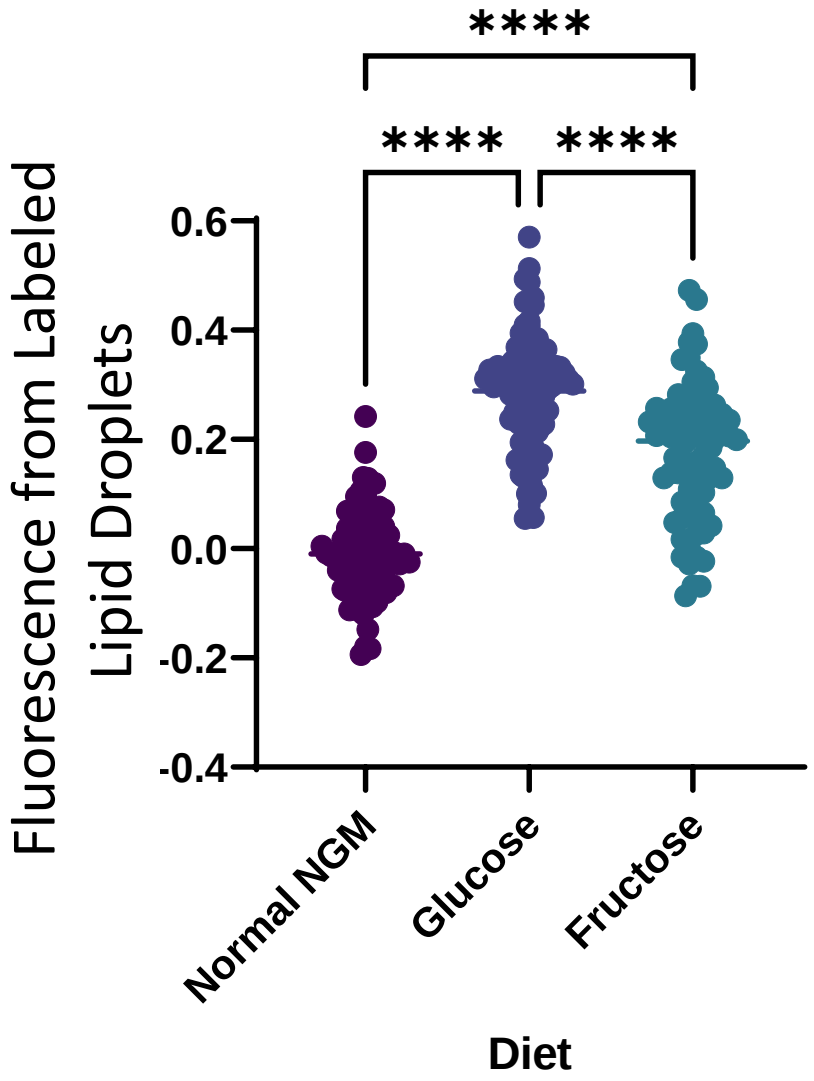
Nathan Heffernan
Undergraduate,
Meyer lab

Modeling negative metabolic effects in worms

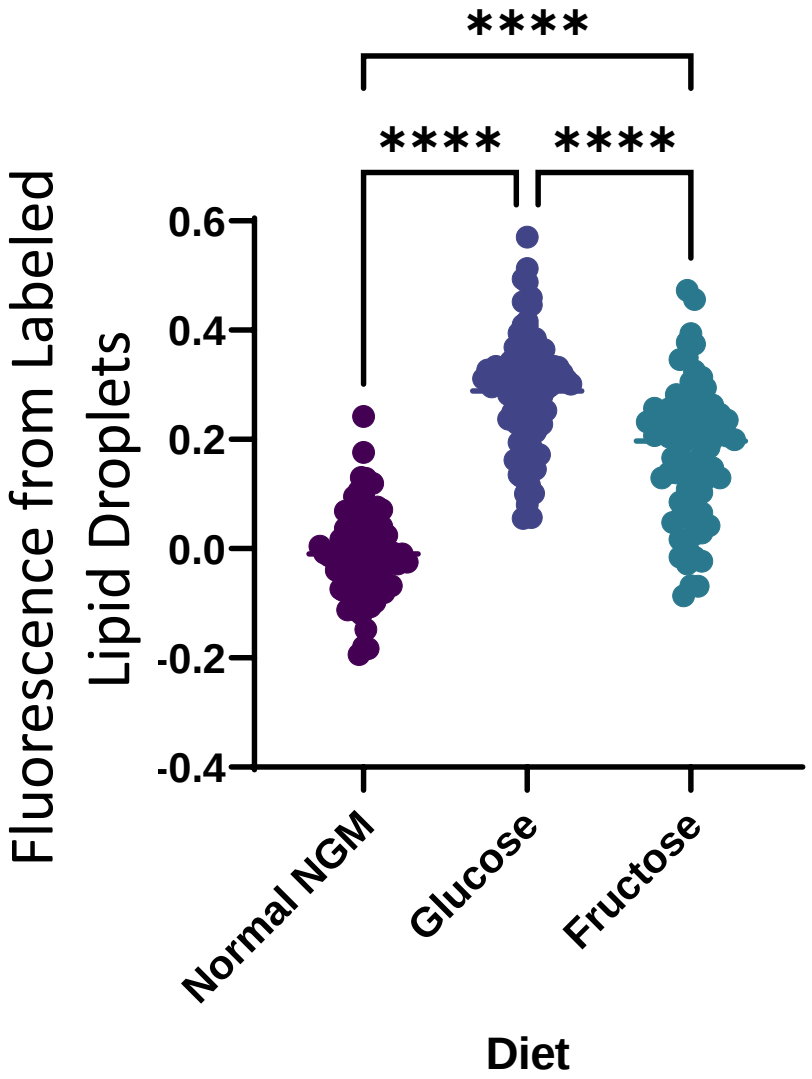
- Increasing metabolic dysfunction worldwide
- We modeled increased fat storage and metabolic disruptions by feeding the worms a high-sugar diet

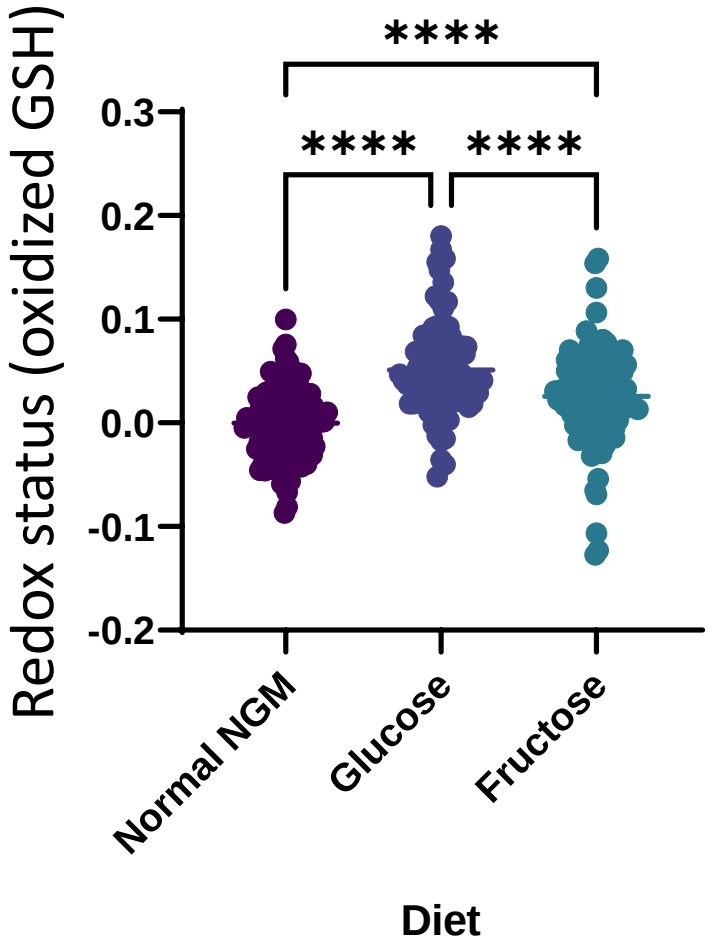


A high sugar diet (glucose or fructose supplementation) increases lipid storage

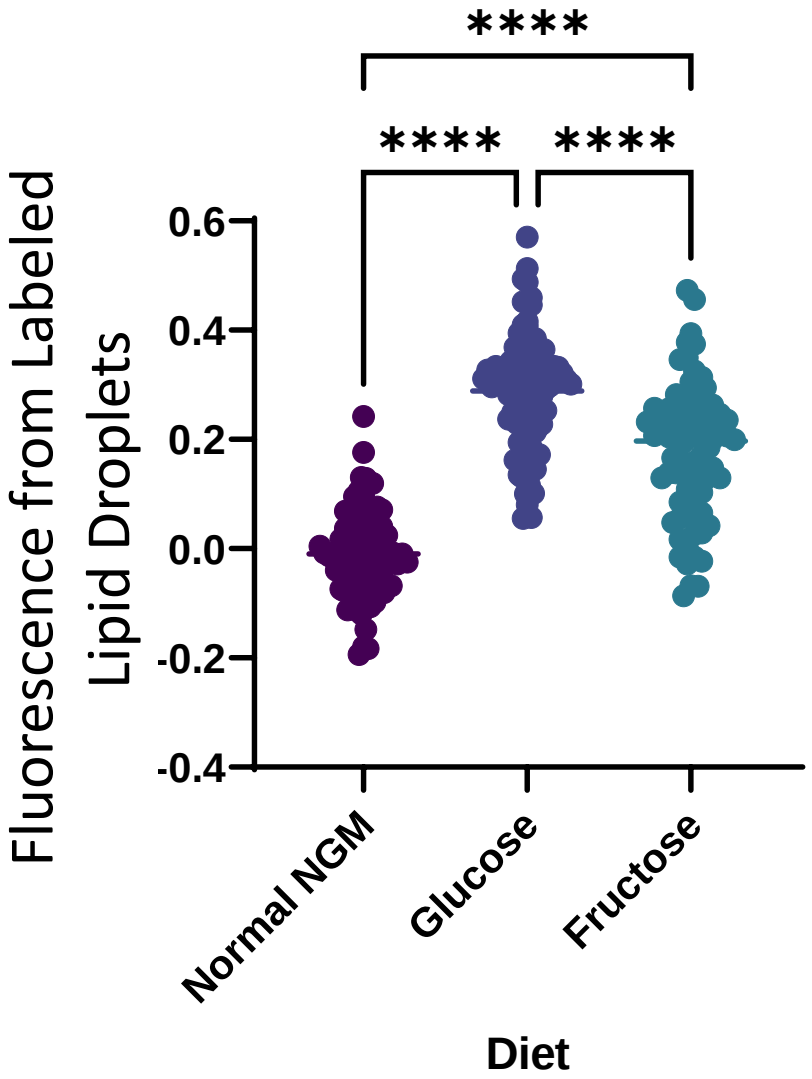


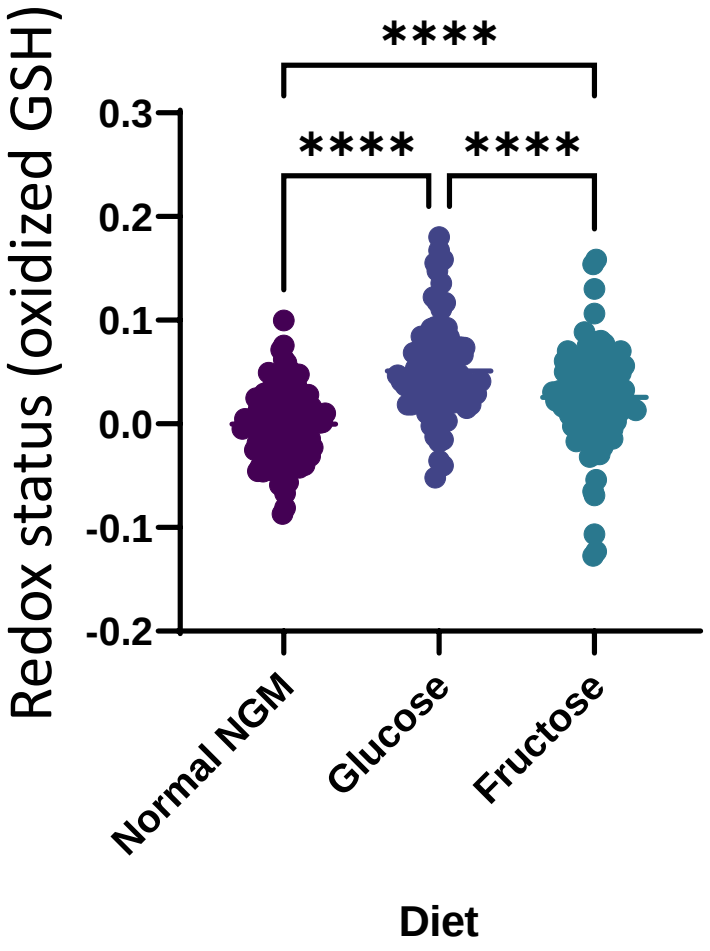
…and increases oxidation of glutathione

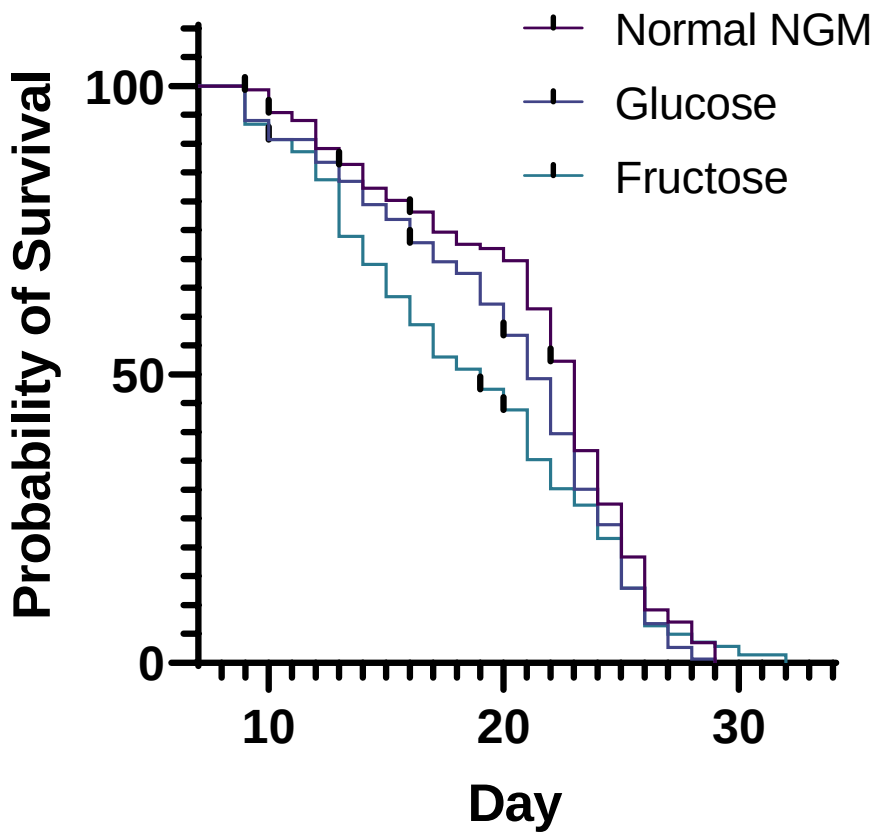




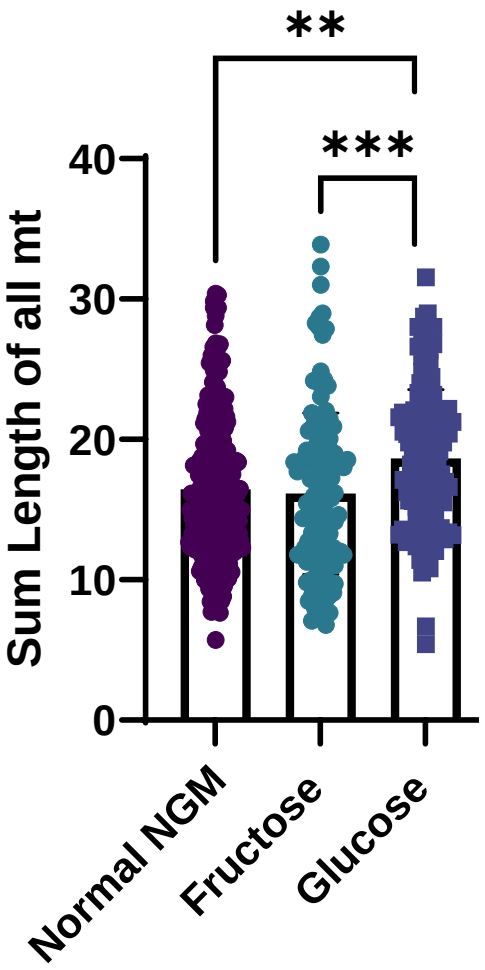
…and shortens lifespan

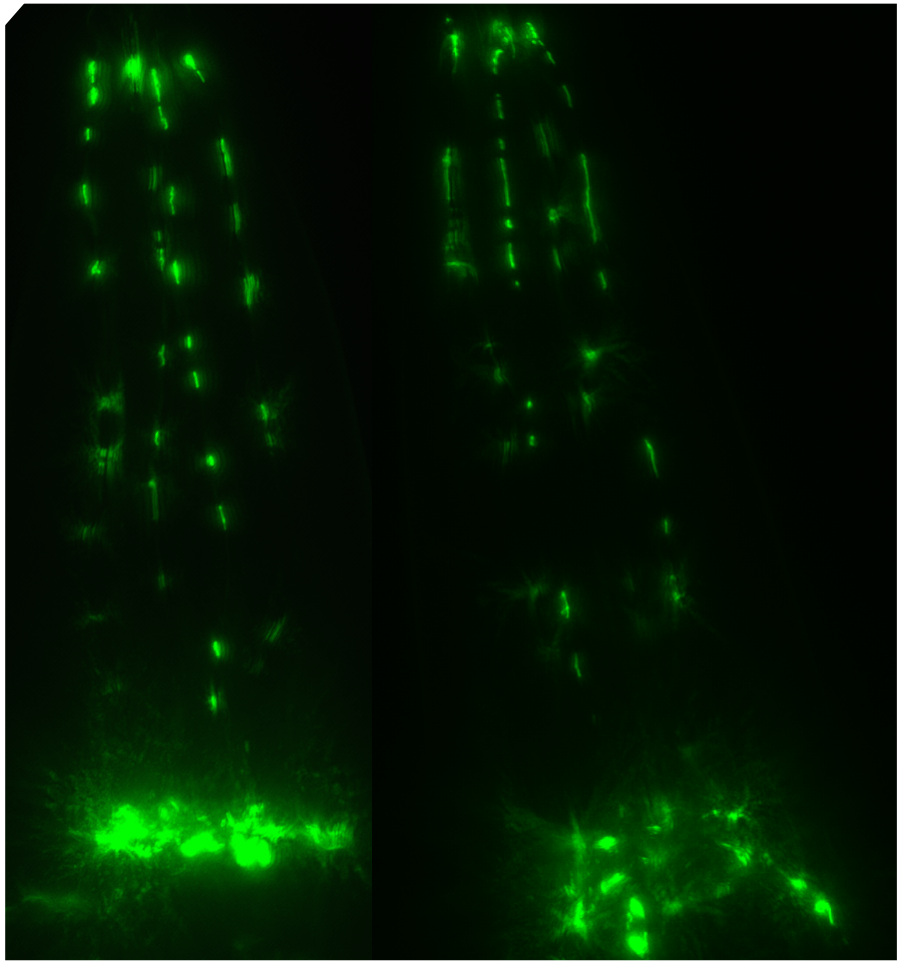




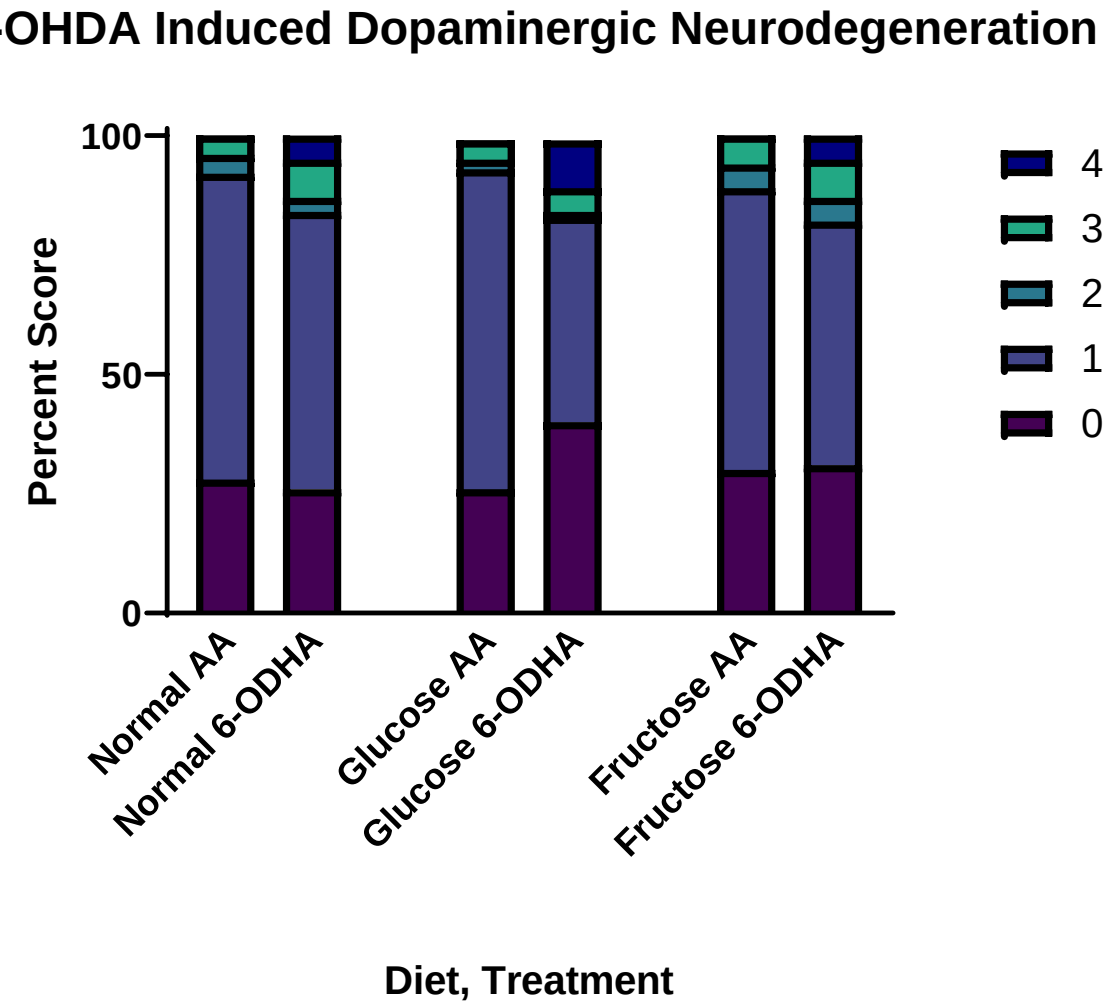


Mitochondria are more fused in dopamine neurons after high-glucose diet





Despite mitochondrial changes, no impact on neurotoxicity from 6-hydroxydopamine



Major Conclusions (so far)

AS IN HUMANS, EXERCISE IMPROVES WORM MITOCHONDRIA

morphology and function

EXERCISE PROTECTS AGAINST CHEMICAL EXPOSURES

aging and toxicant exposures

EXERCISE ALSO PROTECTS DOPAMINERGIC NEURONS

aging and neurotoxicant exposures

SURPRISINGLY, DIET- AND GENETIC-INDUCED FAT STORAGE ALSO IS PROTECTIVE

metabolic alterations from increased sugar intake may have complex effects

ACKNOWLEDGEMENTS

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