

GEROSCIENCE EDUCATION & TRAINING

Energy and Metabolism: Preclinical Models and Methods for Studying Metabolic Flux



Brought to you



GEROSCIENCE EDUCATION & TRAINING

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Preclinical models and methods for studying metabolic flux

- The limits of snapshots when trying to understand a moving picture.



Learning Objectives

- Understand how mice and rats differ regarding aging and metabolism
- Understand how strain impacts outcomes of aging and metabolism
- Understanding of how sex interacts with species and strain

Krogh Principle



"for ... a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied."

To understand how mice
and rats differ regarding
aging and metabolism

Objective 1

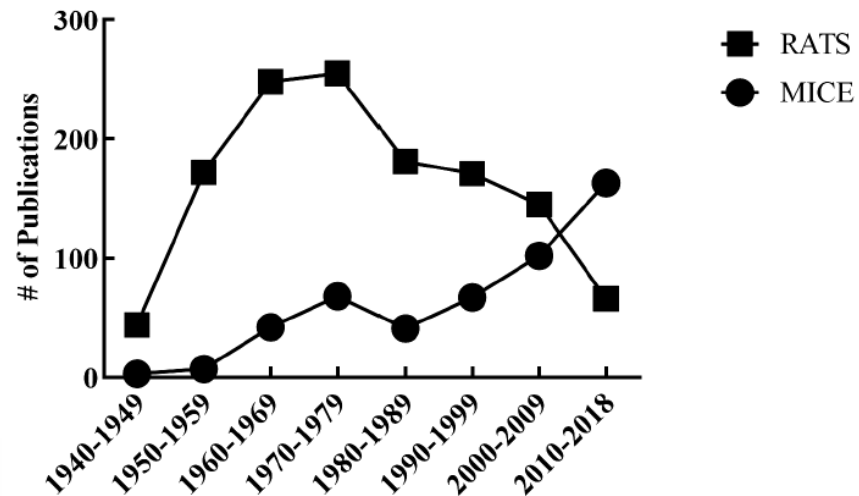
Rodent models in aging

Rats

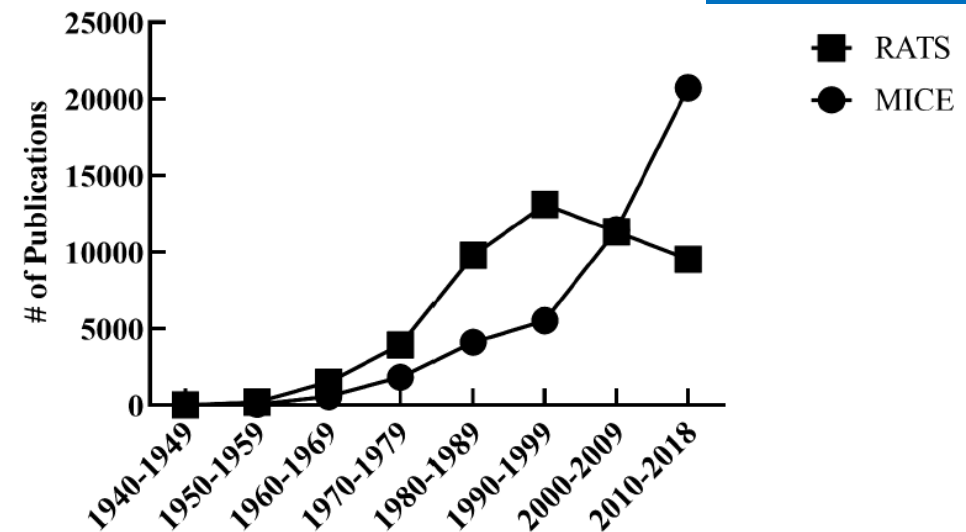
- Quantity of tissue
- Easier to handle



Journal of Gerontology (1940-1995)
and
Journals of Gerontology Series A (1995-present)



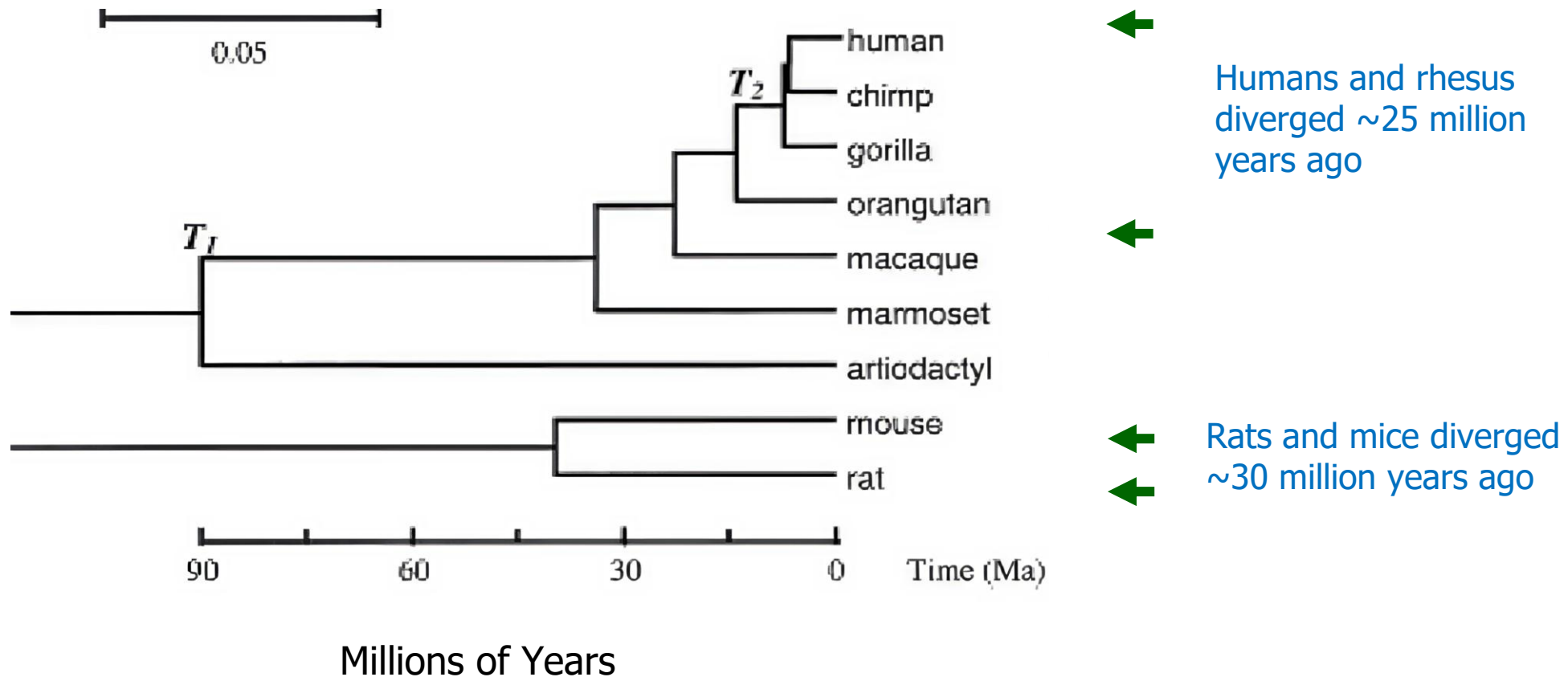
PubMed (1940-2018)



Mice

- Genetic tractability
- Ease of housing
- Cost
- Availability of tools

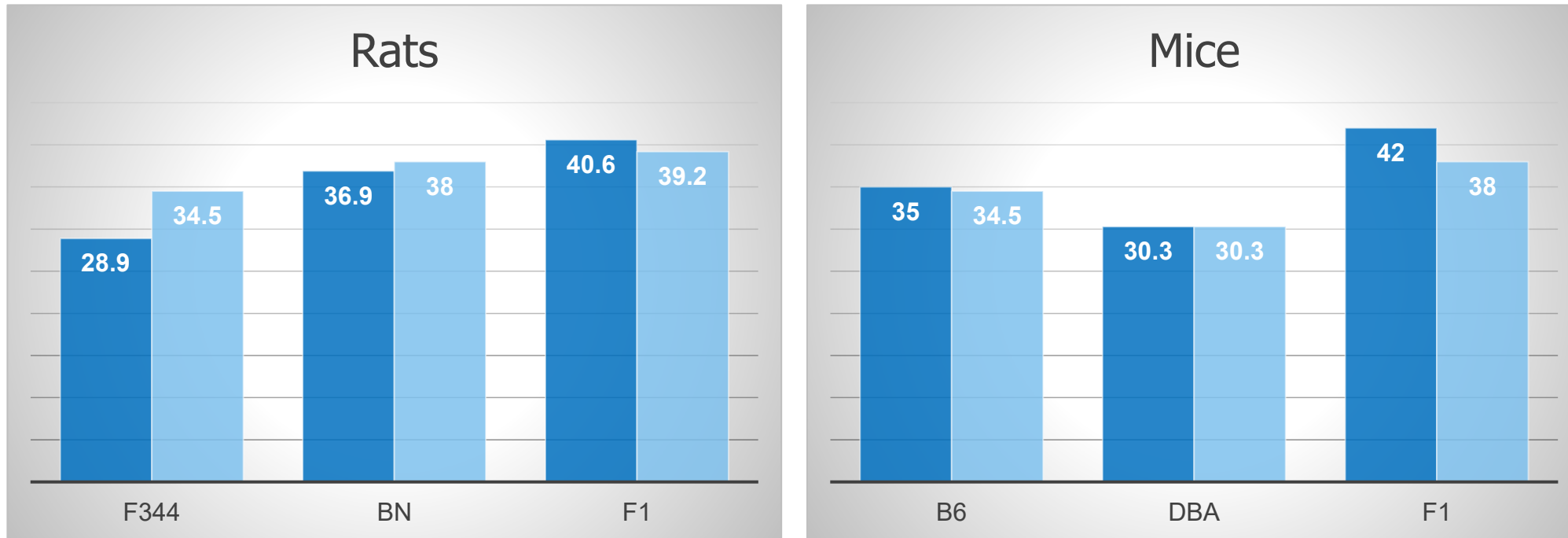
Evolutionary Relationship Between Rats and Mice



Estimation of Divergence Times for Major Lineages of Primate Species

Galina V. Glazko and Masatoshi Nei

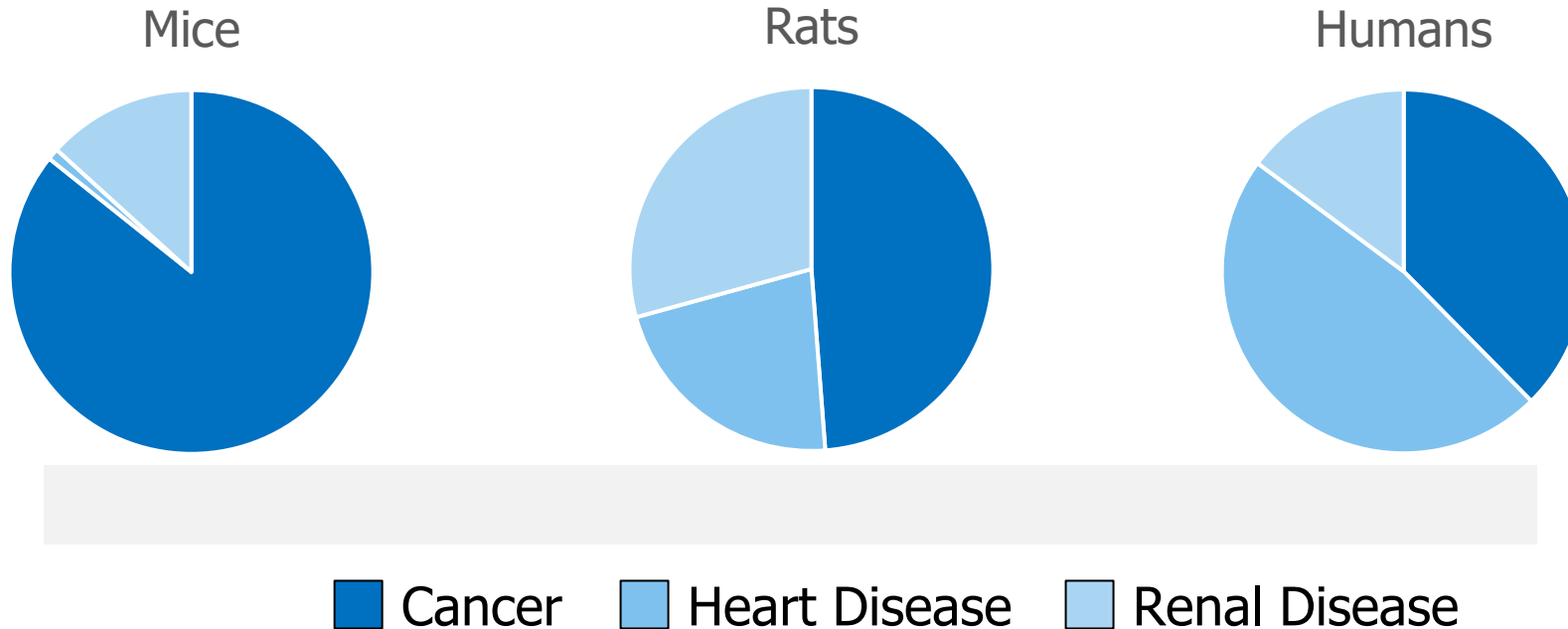
Maximum Lifespan of Common Laboratory Rats and Mice



Male
Female

Rodent versus human pathology

Incidence of Major Pathology



The regulation of glucose metabolism: implications and considerations for the assessment of glucose homeostasis in rodents

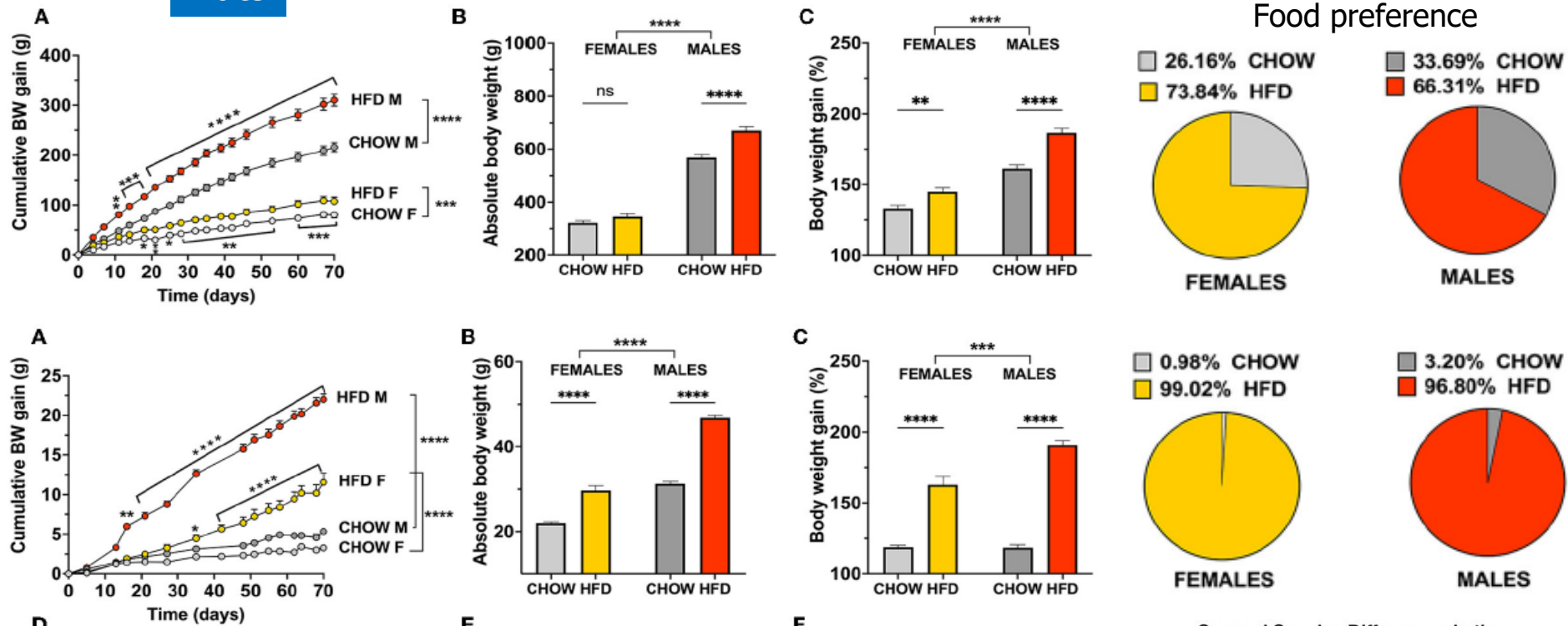
Greg M. Kowalski and Clinton R. Bruce

Table 1. Comparison of metabolic parameters between humans, rats, and mice

	Human	Rat	Mouse (C57Bl/6)
Body mass, kg	50–100	0.20–0.30	0.02–0.03
Blood glucose, mmol/l	4–6	4–7	7–9
Plasma FFA, mmol/l	0.2–0.6	0.4–0.7	0.5–1.5
Plasma triglyceride, mmol/l	1.0–1.5	1.0–1.5	1.0–1.5
Plasma insulin, pmol/l	40–70	200–300	100–200
Plasma glucagon, ng/l	60–150	45–100	40–150
Liver glycogen, $\mu\text{mol/g}$ wet wt	250–300	150–250	100–200
Muscle glycogen, $\mu\text{mol/g}$ wet wt	55–85	25–40	10–20
Basal EGP, $\text{mg kg}^{-1} \text{ min}^{-1}$	1.5–2.5	8–15	20–30
Gluconeogenesis, %contribution to EGP	40–50	50	80
Glycogenolysis, %contribution to EGP	50–60	50	20

Rodent versus human metabolism

Rats



Mice

Sex and Species Differences in the Development of Diet-Induced Obesity and Metabolic Disturbances in Rodents

Ivana Maric^{1,2,3}, Jean-Philippe Krieger^{1,2}, Pauline van der Valken^{1,2}, Stina Borchers^{1,2}, Mohammed Askar^{1,2}, Milica Vujic¹, Ingrid Wernstedt Asterholm¹ and Karolina P. Skibicka^{1,2,3*}

Muscle Differences

	Change in force (%)	Change in mass (%)	Change in myofiber # (%)	Change in myofiber CSA	Change in specific tension (%)	Change in moto-neuron (%)
Men	40	35	25	I 5% II 35%	20	10-25
Male C57Bl6	20	15	20		10	
Male F344BN	45	25	20	I 10% IIA 10% IIB 30%	30	20
Male F344	20	15	10	I 0-10% IIA 0-15% IIB 10-25%	10	10
Male Wistar	10	10	5	I 5-10% IIA 15-20%	0	

Review

Aging related changes in determinants of muscle force generating capacity: A comparison of muscle aging in men and male rodents

Sam B. Ballak^{a,b,*}, Hans Degens^a, Arnold de Haan^{a,b}, Richard T. Jaspers^b

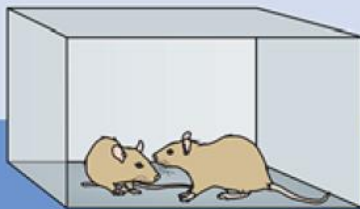
Brain Differences

5. Social behaviour

As illustrated below, the open-field test can be used to investigate degrees of social interaction. Pairs of animals of the same gender are placed in the open-field apparatus and behaviours such as aggression and anxiety monitored. The conditioned place preference (CPP) model can also be used for social interaction tests (see main text; not shown here).

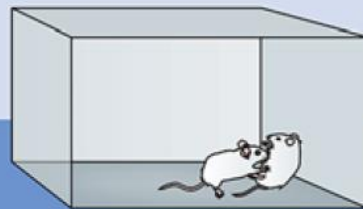
Rats

- Show more affiliative social behaviour.
- Spend more time in close proximity to each other.
- Most rats find social behaviour rewarding and prefer areas where they had previous contact with other rats.



Mice

- Show more aggressive social behaviour.
- Most mice avoid areas where they previously encountered other mice.

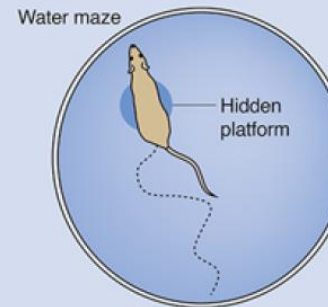


8. Cognitive behaviour

In the Morris water navigation maze assay, animals are released from different points in a large swimming pool and have to find the location of a platform hidden below the water surface. The test is used to study spatial learning and memory.

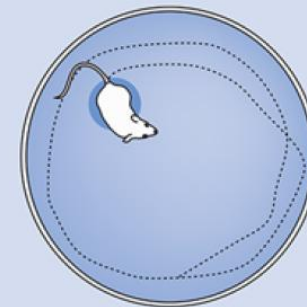
Rats

- Are more adapted to water and show less stress in water mazes.
- Show a more clear-cut spatial strategy in maze-learning.



Mice

- Are much more stressed in a water maze.
- Show a less efficient strategy in maze-learning, preferring to take a circular path.
- Often require substantially more training to reach criterion.



Rodent models in neuroscience research: is it a rat race?

Bart Ellenbroek* and Jiun Youn

Lifespan extension differences

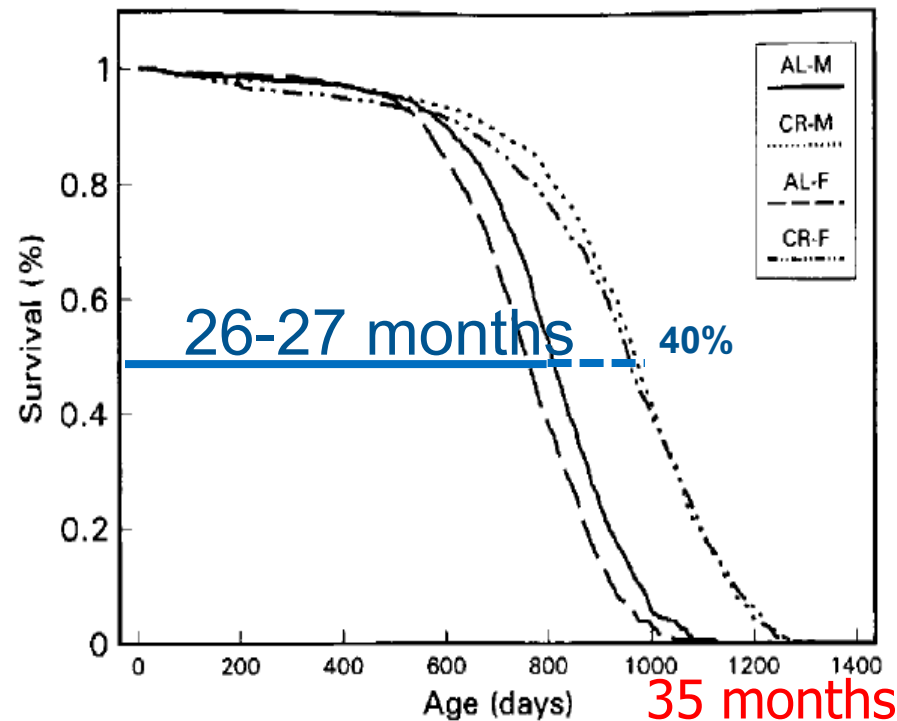


Figure 13. Survival and age in B6-NIH mice—Total. Survival of ad libitum

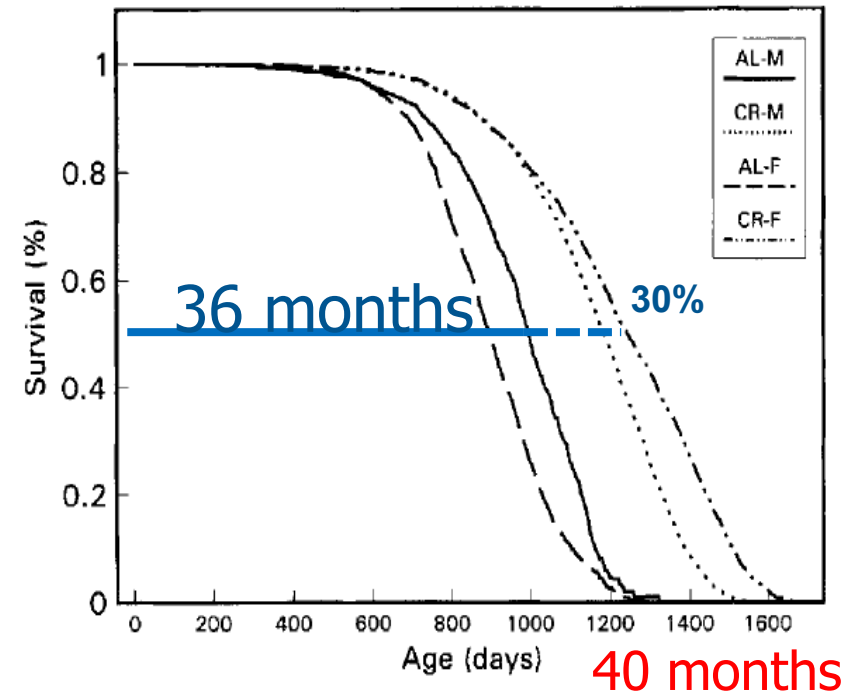
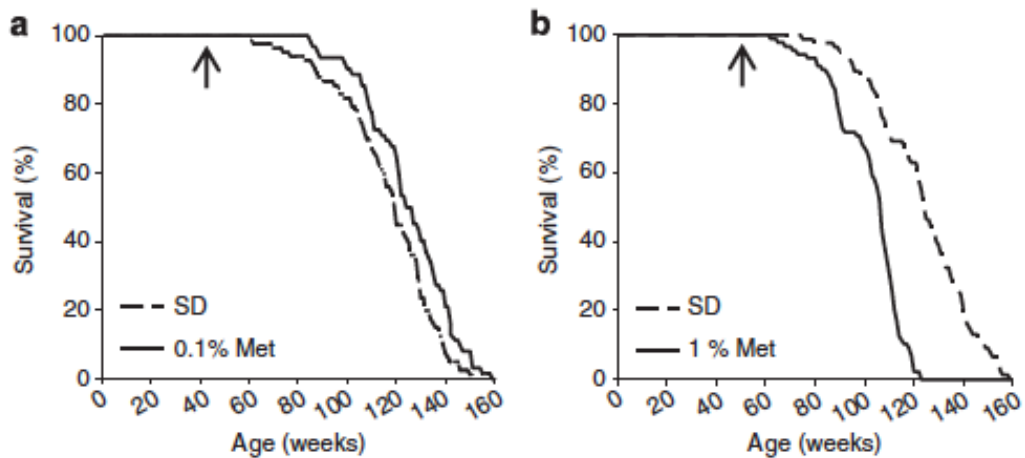


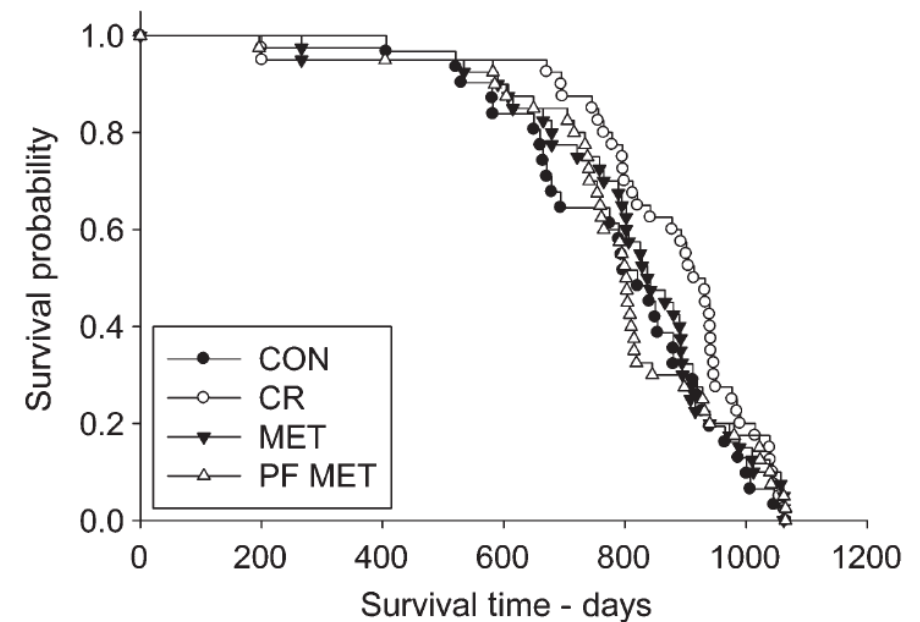
Figure 16. Survival and age in F344 x BN F1 rats—Total. Survival of ad libitum

Lifespan extension differences



Metformin improves healthspan and lifespan in mice

Alejandro Martin-Montalvo^{1,*}, Evi M. Mercken^{1,*}, Sarah J. Mitchell^{1,2,3}, Hector H. Palacios¹, Patricia L. Mote⁴, Morten Scheibye-Knudsen⁵, Ana P. Gomes⁶, Theresa M. Ward¹, Robin K. Minor¹, Marie-José Blouin⁷, Matthias Schwab⁸, Michael Pollak⁷, Yongqing Zhang⁹, Yinbing Yu¹⁰, Kevin G. Becker⁹, Vilhelm A. Bohr⁵, Donald K. Ingram¹¹, David A. Sinclair⁶, Norman S. Wolf¹², Stephen R. Spindler⁴, Michel Bernier¹ & Rafael de Cabo¹



Metformin Supplementation and Life Span in Fischer-344 Rats

Daniel L. Smith Jr,^{1,2} Calvin F. Elam Jr,³ Julie A. Mattison,⁴ Mark A. Lane,⁵ George S. Roth,⁶ Donald K. Ingram,⁷ and David B. Allison^{1,2,3}

- To understand how strain impacts outcomes of aging and metabolism

Objective 2

Strain Considerations

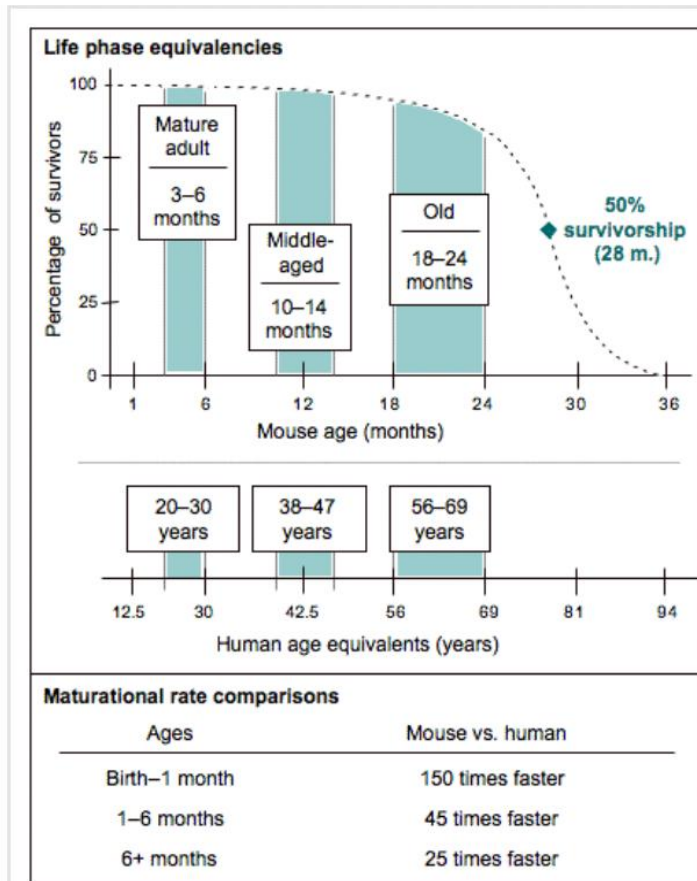
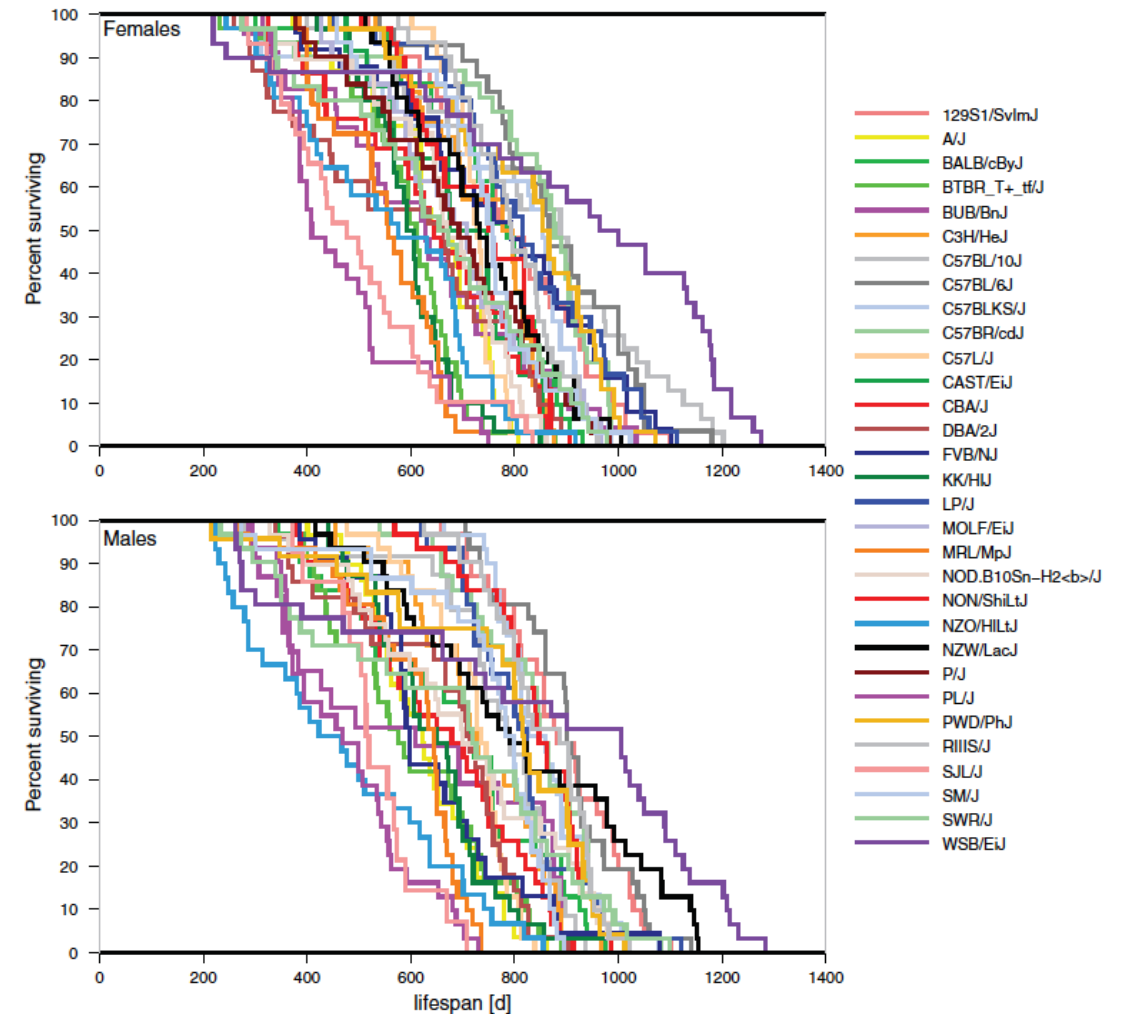


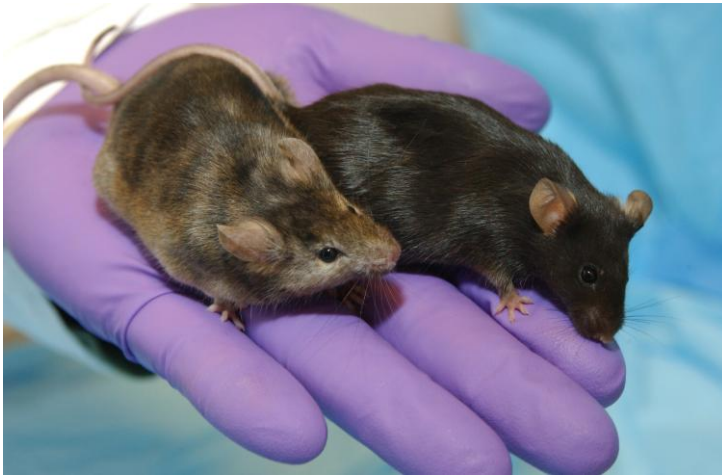
Figure V.3. Representative age ranges for mature life history stages in C57BL/6J mice; comparison to human beings. (Adapted from Figure 20-3: Flurkey K, Currer JM, Harrison DE. 2007. *The Mouse in Aging Research*. In *The Mouse in Biomedical Research 2nd Edition*. Fox JG, et al, editors. American College Laboratory Animal Medicine (Elsevier), Burlington, MA. pp. 637-672.)



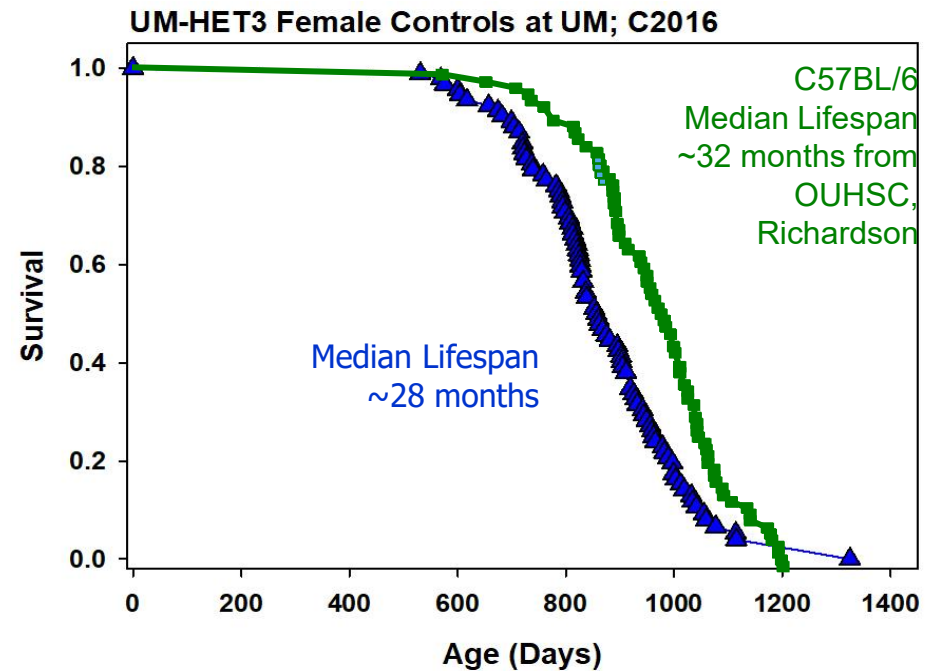
Accessing Data Resources in the Mouse Phenome Database for Genetic Analysis of Murine Life Span and Health Span

Molly A. Bogue,¹ Luanne L. Peters,¹ Beverly Paigen,¹ Ron Korstanje,¹ Rong Yuan,² Cheryl Ackert-Bicknell,¹ Stephen C. Grubb,¹ Gary A. Churchill,¹ and Elissa J. Chesler¹

Strain Considerations

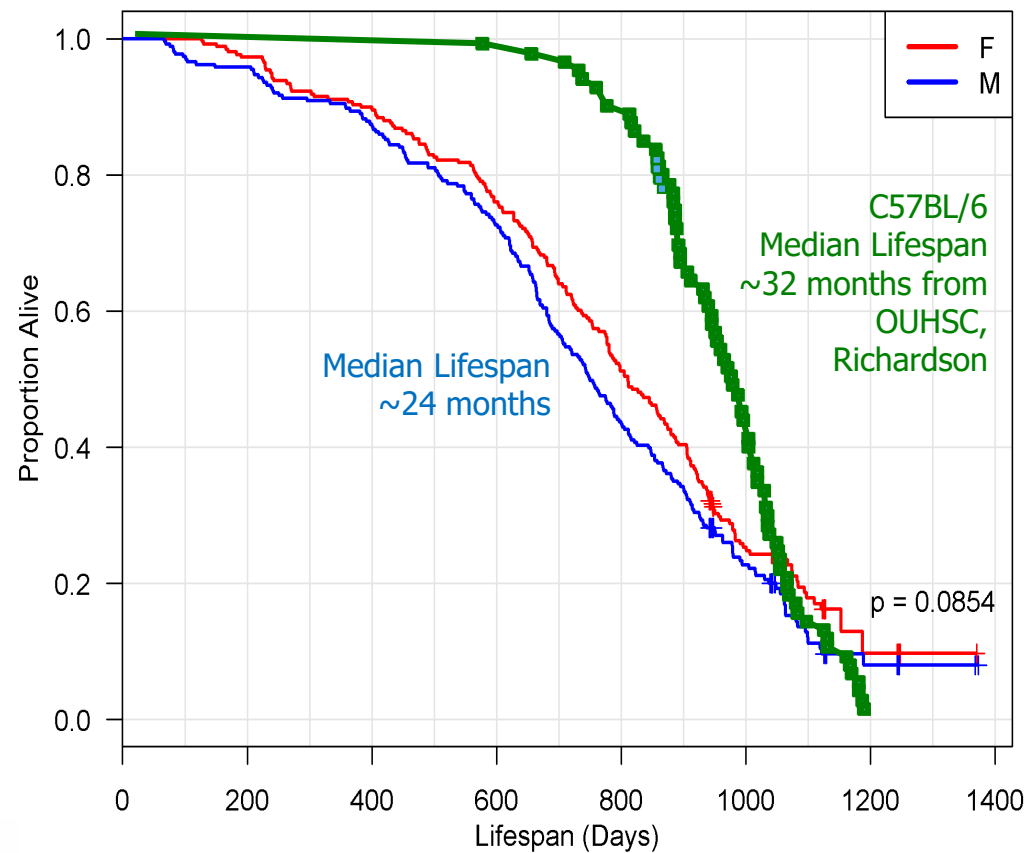


UM-HET3 Mice (F2): CB6F₁ females (BALB/cJ and C57BL/6J) crossed to C3D2F₁ males (C3H/HeJ X DBA/2J)



UM-HET3 lifespan data from Rich Miller

Strain Considerations



Diversity Outcross (DO): Derived from 8-way cross using 5 inbred strains (A/J, C57BL/6J, 129S1/ SvImJ, NOD/LtJ, and NZO/HILtJ) and 3 wild-derived strains (CAST/ EiJ, PWK/PhJ, and WSB/EiJ)

Lifespan for DO mice from Gary Churchill at JAX

To understanding of
how sex interacts with
species and strain

Objective 3

Sex Differences

Growth Curves and Survival Characteristics of the Animals Used in the Biomarkers of Aging Program

Angelo Turturro,¹ William W. Witt,² Sherry Lewis,³ Bruce S. Hass,² Ruth D. Lipman,⁵ and Ronald W. Hart⁴

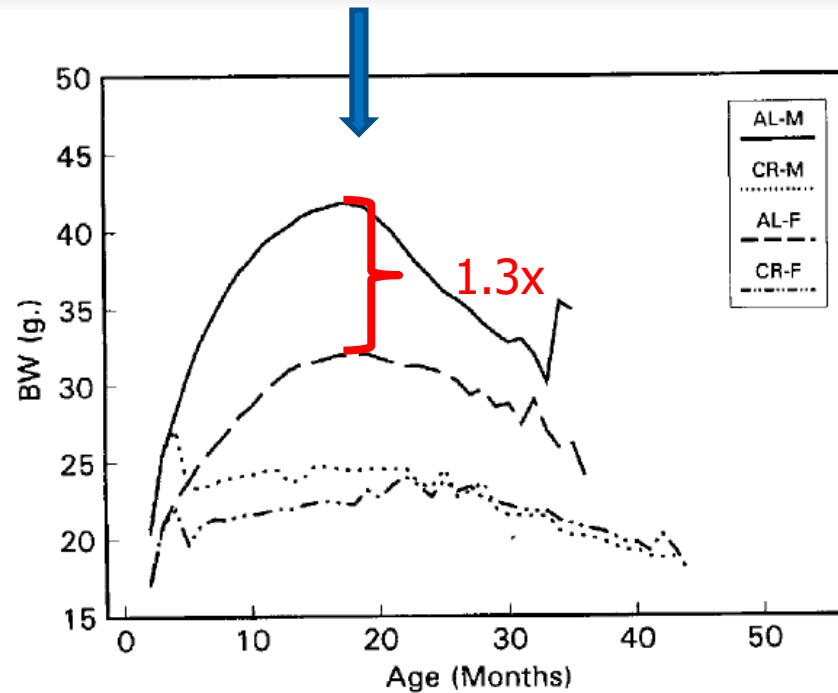


Figure 4. Body weight and age in B6-NIH mice—Shipping Group. Average body weight (BW) for ad libitum (AL) and calorically restricted (CR) male AL (AL-M), female AL (AL-F), male CR (CR-M), and female CR (CR-F) mice at different ages (in months). Data early in the life span from over 2,400 (male) and 1,100 (female) animals.

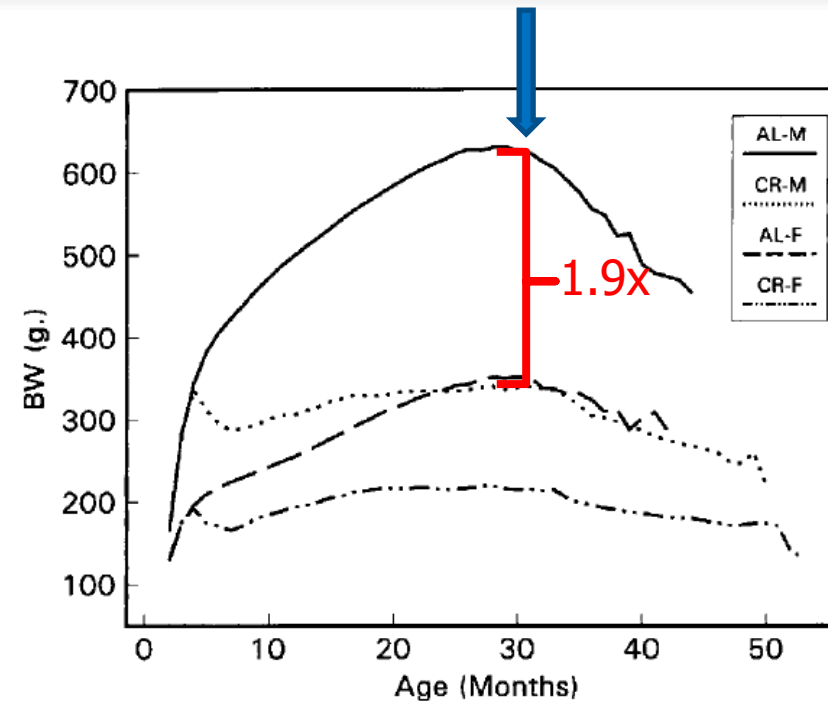
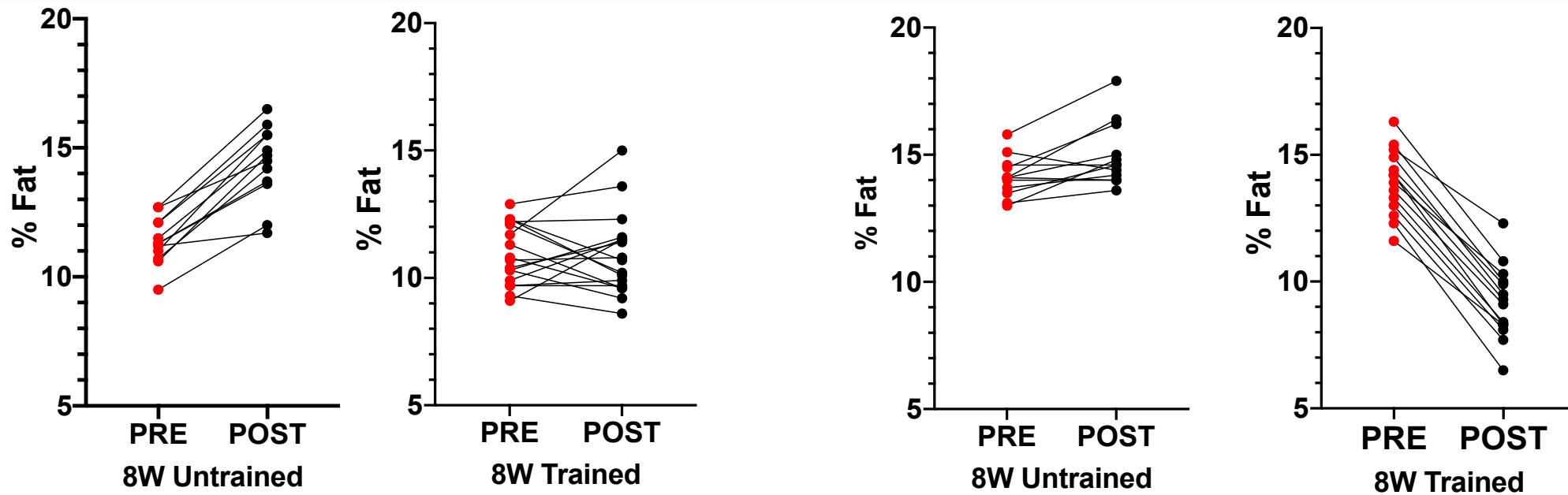


Figure 7. Body weight and age in F344 × BN F1 rats—Shipping Group. Average body weight (BW) for ad libitum (AL) and calorically restricted (CR) male AL (AL-M), female AL (AL-F), male CR (CR-M), and female CR (CR-F) rats at different ages (in months). Data early in the life span from over 2,000 (male) and 1,500 (female) animals. Note the difference in scale from Figure 6.

Sex Differences



Female

Male

MoTrPAC

8 weeks aerobic exercise training at 6 months of age

Sex Differences

Compound	Amount in Food	Age at treatment initiation	Females (Median; at 90% mortality)	Males (Median; at 90% mortality)	Source
Aspirin	20 ppm	4 months	0; 0	Increased 8%; 0	(Strong et al., 2008a)
NFP	200 ppm	4 months	0; 0	0; 0	(Strong et al., 2008a)
NDGA	2500 ppm	9 months	0; 0	Increased 12%; 0	(Strong et al., 2008a)
4-OH-PBN	315 ppm	4 months	0; 0	0; 0	(Strong et al., 2008a)
CAPE	30 ppm	4 months	0; 0	0; 0	(Harrison et al., 2009)
CAPE	300 ppm	4 months	0; 0	0; 0	(Harrison et al., 2009)
Enalapril Maleate	120 ppm	4 months	0; 0	0; 0	(Harrison et al., 2009)
Rapamycin	14 ppm	20 months	Increased 13(38)%*	Increased 9(28)%*	(Harrison et al., 2009)
Rapamycin	14 ppm	9 months	Increased 18%; Increased 13%;	Increased 10%; Increased 16%;	(Miller et al., 2011)
Simvastatin	12 ppm	10 months	0; 0	0; 0	(Miller et al., 2011)
Simvastatin	120 ppm	10 months	0; 0	0; 0	(Miller et al., 2011)
Resveratrol	300 ppm	12 months	0; 0	0; 0	(Miller et al., 2011)
Resveratrol	1200 ppm	12 months	0; 0	0; 0	(Miller et al., 2011)
Resveratrol	300 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Oxaloacetic acid	2200 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Green tea extract	2000 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Curcumin	2000 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
Medium chain triglyceride oil	60000 ppm	4 months	0; 0	0; 0	(Strong et al., 2013)
17 α -Estradiol	4.8 ppm	10 months	0; 0	Increased 12%; 0	(Harrison et al., 2014)
Methylene Blue	28 ppm	4 months	0; 0	0; 0	(Harrison et al., 2014)
Acarbose	1000 ppm	4 months	Increased 5%; Increased 9%	Increased 22%; Increased 11%	(Harrison et al., 2014)
Rapamycin_LoP hase II	4.7 ppm	9 months	Increased 16%; Increased 5%	3%; 0	(Miller et al., 2014)

Compound	Amount in Food	Age at treatment initiation	Females (Median; at 90% mortality)	Males (Median; at 90% mortality)	Source
Rapamycin_Mid Phase II	14 ppm	9 months	Increased 21%; Increased 11%	Increased 13%; Increased 8%	(Miller et al., 2014)
Rapamycin_HiP hase II	42 ppm	9 months	Increased 26%; Increased 11%	Increased 23%; Increased 8%	(Miller et al., 2014)
NDGA Lo_Phase II	800 ppm	6 months	--**	Increased 8% (median)**	(Harrison et al., 2014)
NDGA Med_Phase II	2500 ppm	6 months	--**	Increased 10% (median)**	(Harrison et al., 2014)
NDGA Hi_Phase II	5000 ppm	6 months	0; --**	Increased 9% (median)**	(Harrison et al., 2014)

Acarbose+Rapa
Metformin+Rapa

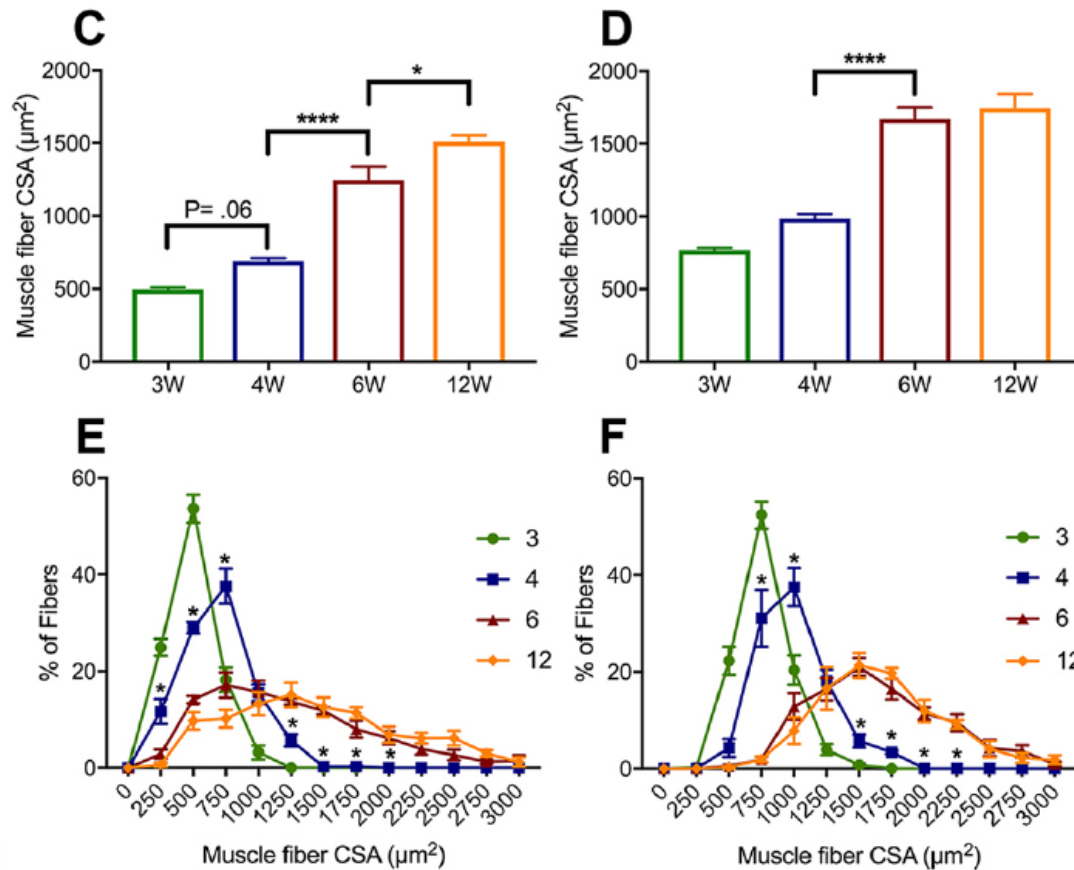
Sex Differences in Lifespan

Steven N. Austad^{1,*} and Kathleen E. Fischer¹

Other important reminders

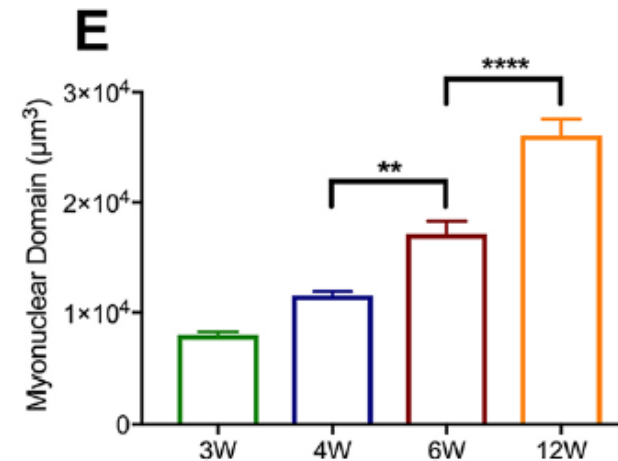
Objective 4

Age (the control)

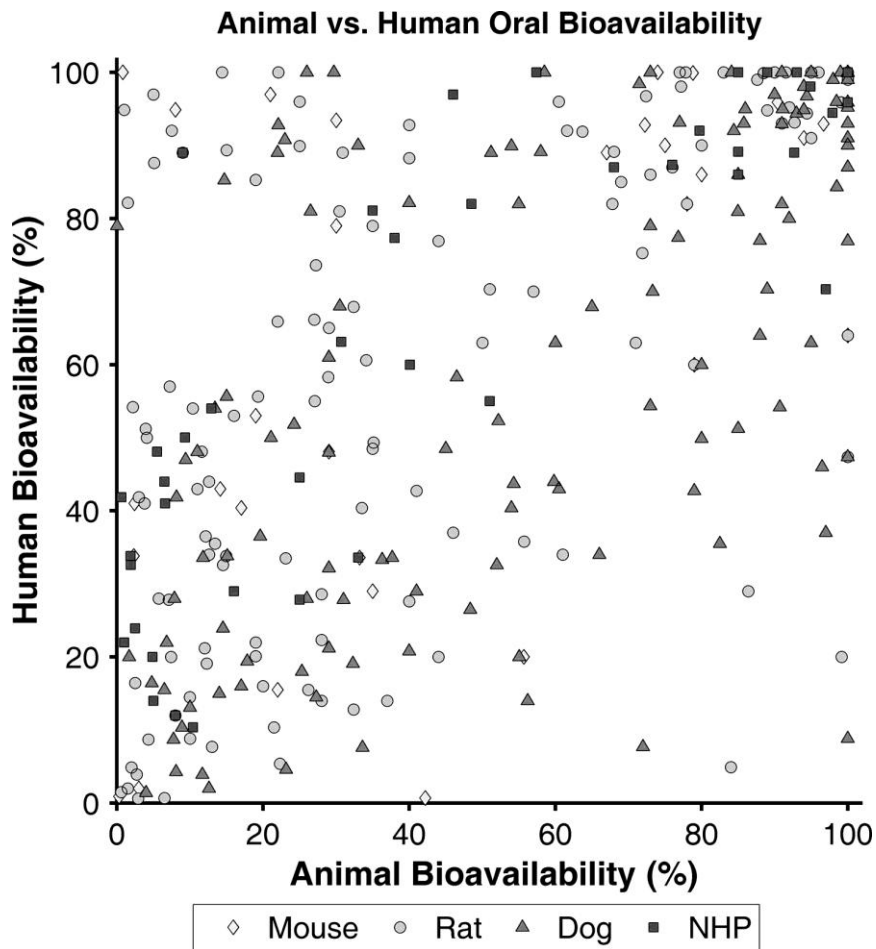


Prepubertal skeletal muscle growth requires Pax7-expressing satellite cell-derived myonuclear contribution

John F. Bachman^{1,2}, Alanna Klose², Wenxuan Liu^{2,3,*}, Nicole D. Paris², Roméo S. Blanc², Melissa Schmalz², Emma Knapp⁴ and Joe V. Chakkalakal^{2,5,‡}



Bioavailability



Animal versus human oral drug bioavailability: Do they correlate?



Helen Musther^a, Andrés Olivares-Morales^b, Oliver J.D. Hatley^b, Bo Liu^a, Amin Rostami Hodjegan^{a,b,*}

What is your goal?

- Mechanism
 - Genetic tractability – Mice
- Translation
 - Some organ systems and the trajectory of aging – Rats
- Adopt model based on experimental goals

Learning Objectives (revisted)

- Described how mice and rats differ regarding aging and metabolism
- Described how strain impacts outcomes of aging and metabolism
- Described of how sex interacts with species and strain

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