Dietary Protein and Amino Acid Composition in the Regulation of Healthy Aging

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We are all familiar with CR…

THE EFFECT OF RETARDED GROWTH UPON THE LENGTH OF LIFE SPAN AND UPON THE ULTIMATE BODY SIZE [1]

C. M. McCAY, MARY F. CROWELL AND L. A. MAYNARD
Animal Nutrition Laboratory, Cornell University, Ithaca

ONE FIGURE

(Received for publication January 18, 1935)

In a preliminary report, the literature concerning the effect of retarded growth upon the life span was reviewed (McCay and Crowell, '34). In this report was also included a summary in the nature of a progress report dealing with a study

but 6 years earlier (1929) McCay showed that protein restriction (PR) led to decreased mortality of trout!

Why was PR forgotten?

Many studies gave inconsistent results, that in retrospect were probably due to:

- Dietary protein is essential;
- There is not a linear response – there is a "threshold effect";
- Dietary protein sources vary in AA composition;
- May be less efficacious in females, certain genetic backgrounds, or in older mice.

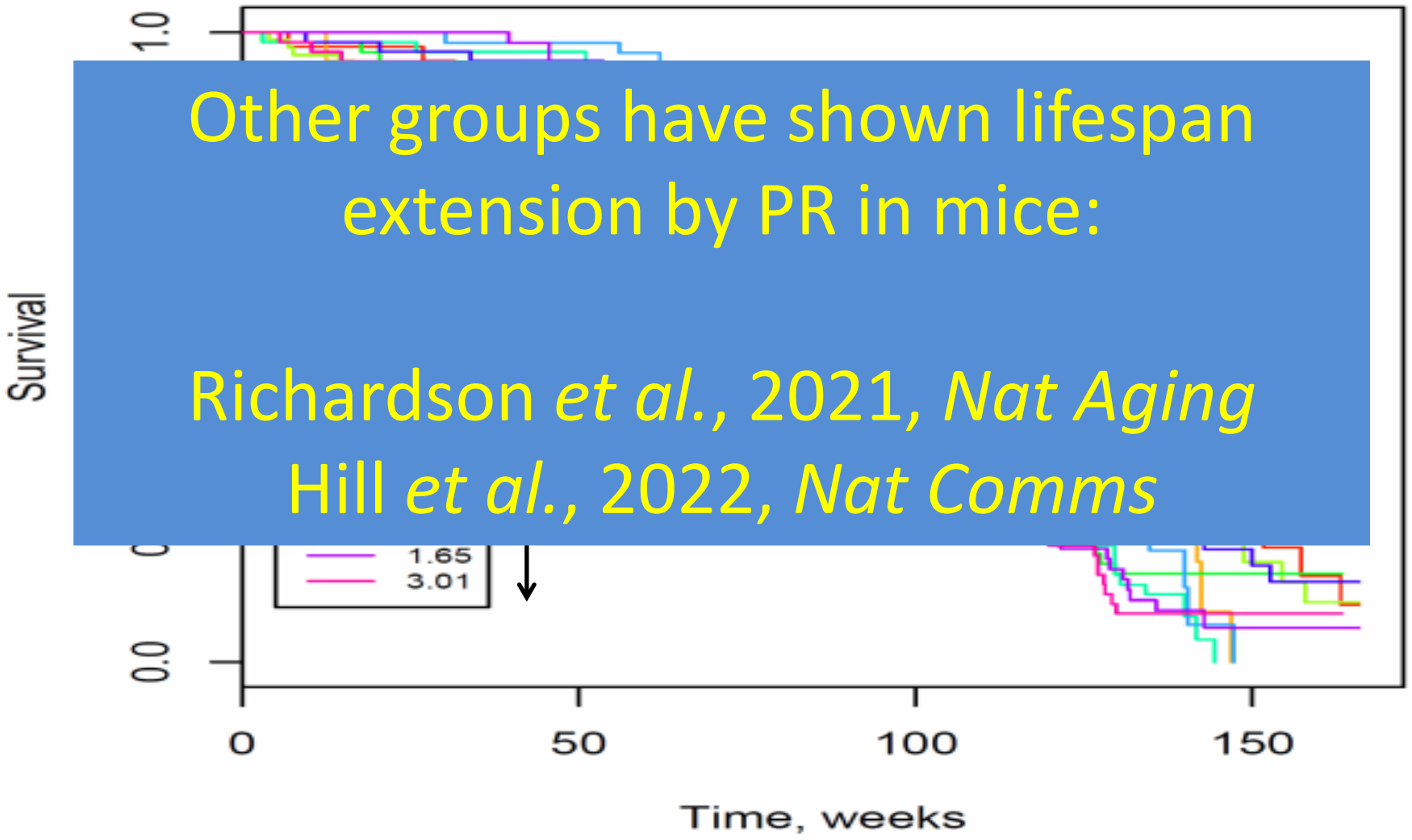
AND… lots of people think protein is good

- Protein helps build skeletal muscle, which should promote robustness and insulin sensitivity
  - Protein supplements are taken by athletes who are in excellent shape
  - High protein diets are prescribed to older adults to fight sarcopenia
- Protein promotes satiety
  - Basis of various fad diets

Over the past 20 years, it has become clear that dietary protein is a key regulator of healthy aging

- Mair and Partridge (2005) – PR extends fly lifespan
- Levine and Longo (2014) – Protein intake in humans is correlated with cancer, diabetes, and mortality
- Solon-Biet and Simpson (2014) – Nutritional geometry approach shows mice live the longest on low protein diets

Mouse longevity is greatest on low protein:high carbohydrate diets

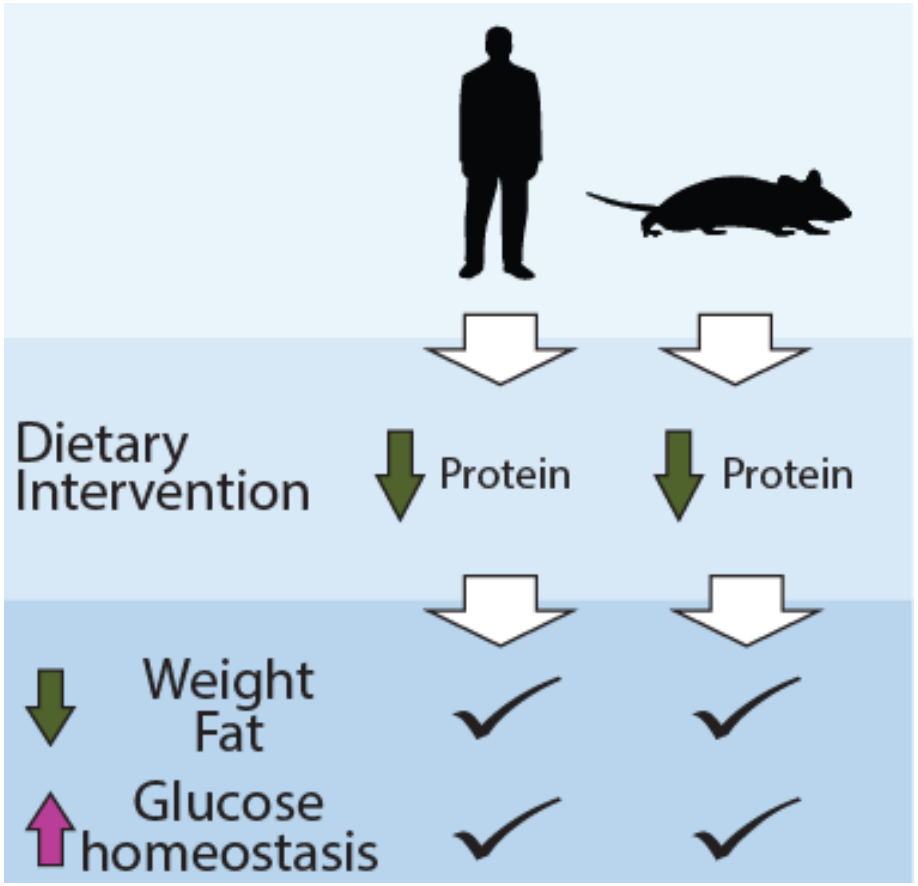


Other groups have shown lifespan extension by PR in mice:

Richardson *et al.*, 2021, *Nat Aging*

Hill *et al.*, 2022, *Nat Comms*

PR improves metabolic health



Levine *et al.*, 2014, *Cell Metab*
Solon-Biet *et al.*, 2014, *Cell Metab*

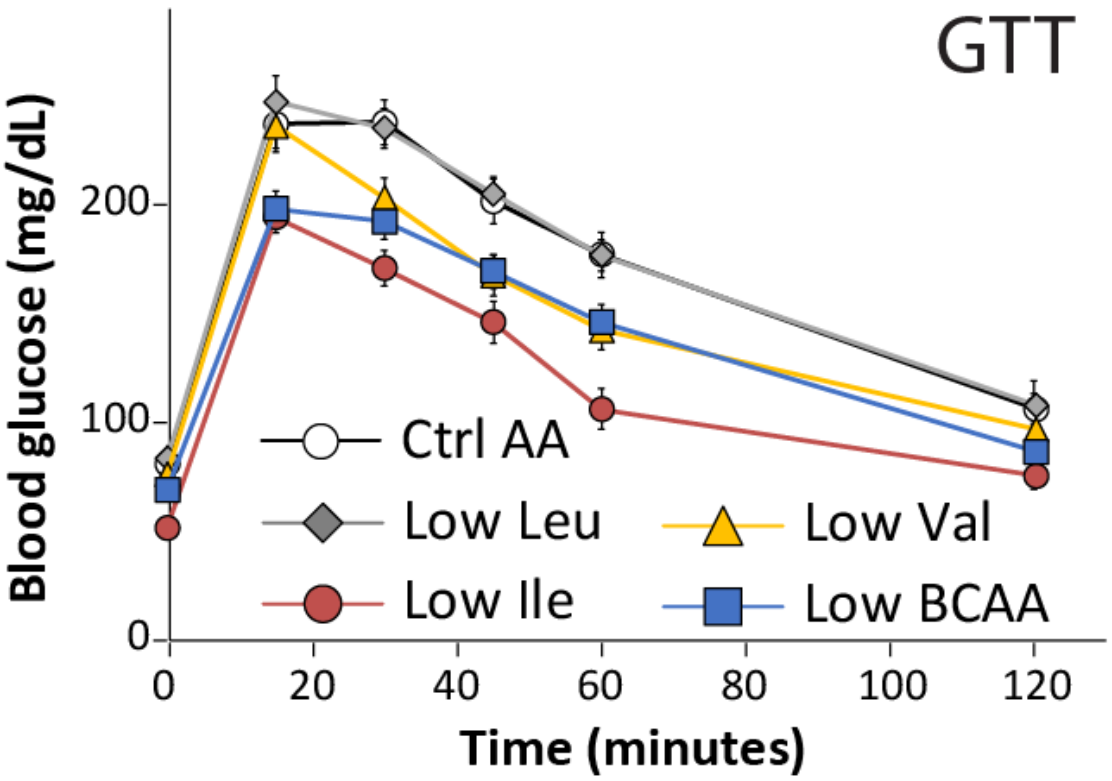
Fontana *et al.*, 2016, *Cell Rep*
Maida *et al.*, 2016, *JCI*
Cummings *et al.*, 2018, *J Physiol*

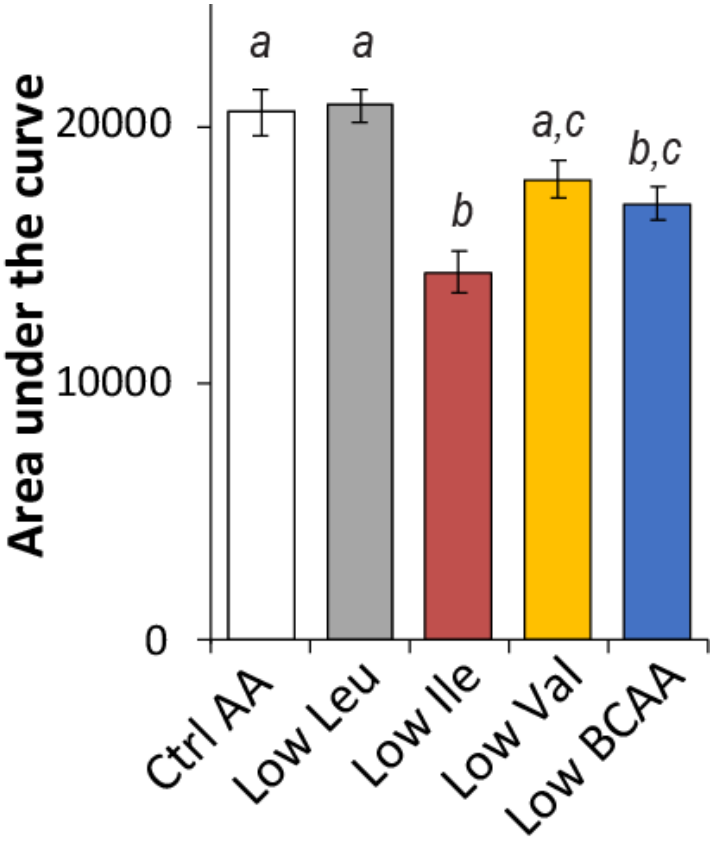
Green *et al.*, 2022, *Cell Metab*
Ferraz-Bannitz *et al.*, 2022, *Nutrients*

What is altered during protein restriction that promotes metabolic health?

	Protein restricted	within-group *P*	**Control**	within-group *P*	Among-group *P*
Leucine (µmol/L)					
Baseline	132 .02 ± 13.62		132.42 ± 20.89		
Follow-up	116.21 ± 21.87		136.41 ± 27.26		
Δ Leucine	**-15.81 ± 21.03**	**0.004**		0.37	**0.004**
Isoleucine (µmol/L)					
Baseline	66.43 ± 10.01		64.97 ± 11.28		
Follow-up	60.29 ± 13.57		70.06 ± 15.07		
Δ Isoleucine	**-6.14 ± 13.22**	0.06	**2.08 ± 11.01**	0.42	**0.04**
Valine (µmol/L)					
Baseline	237.82 ± 29.50		244.37 ± 42.29		
Follow-up	193.18 ± 40.36		244.58 ± 47.90		
Δ Valine	**-44.64 ± 42.72**	**< 0.0001**	**0.21 ± 31.24**	0.98	**0.001**
Methionine (µmol/L)					
Baseline	24.01 ± 3.91		24.97 ± 4.13		
Follow-up	24.04 ± 4.24		25.54 ± 3.56		
Δ Methionine	**0.03 ± 3.68**	0.98	**0.57 ± 3.45**	0.48	0.64

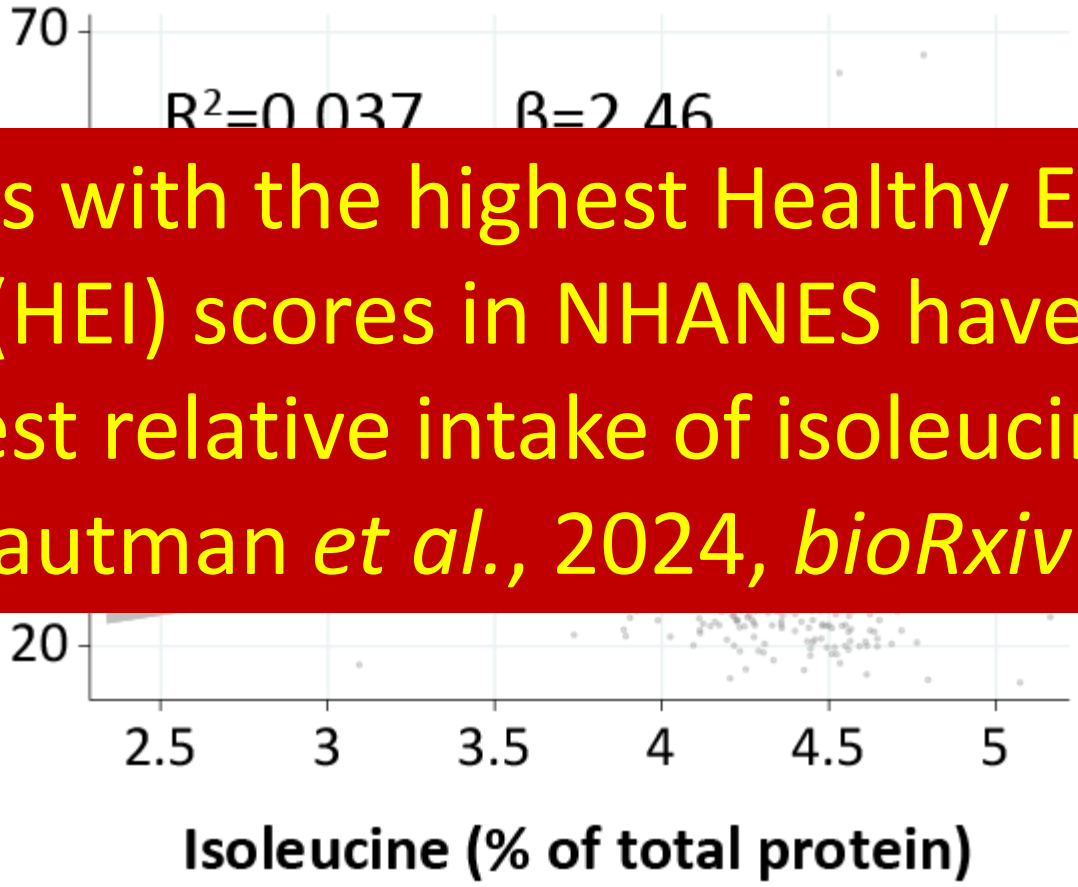
Dietary isoleucine and valine are potent regulators of glucose tolerance





"Low" = 67% restriction, from the level found in a 21% protein diet to the level found in a 7% diet

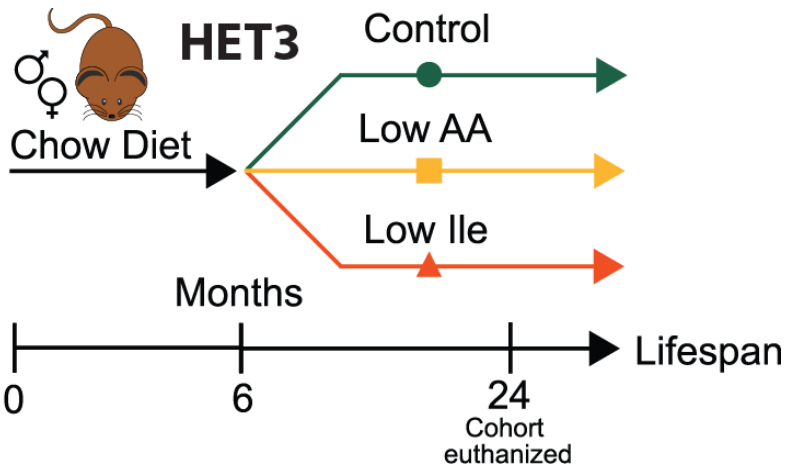
Increased dietary isoleucine levels are associated with higher BMI in Wisconsin residents

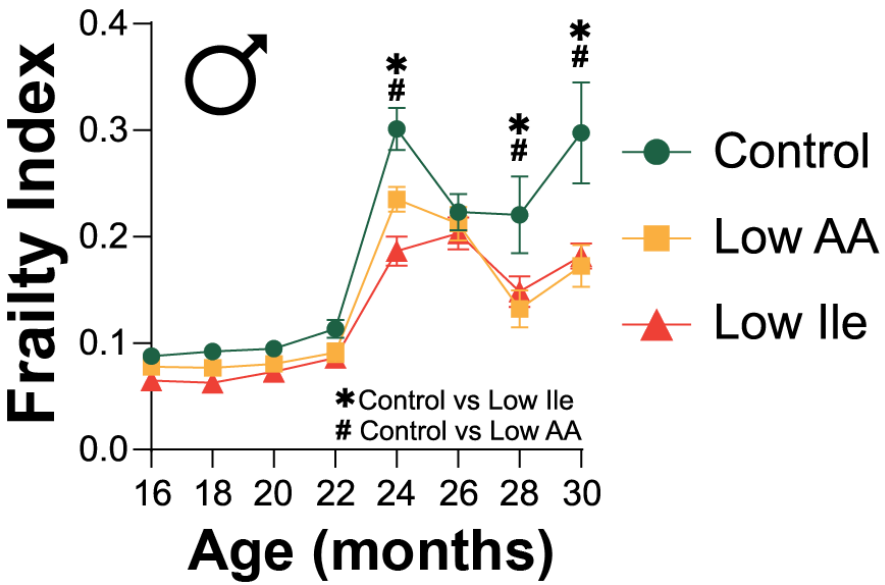


Humans with the highest Healthy Eating Index (HEI) scores in NHANES have the lowest relative intake of isoleucine
Trautman *et al.*, 2024, *bioRxiv*

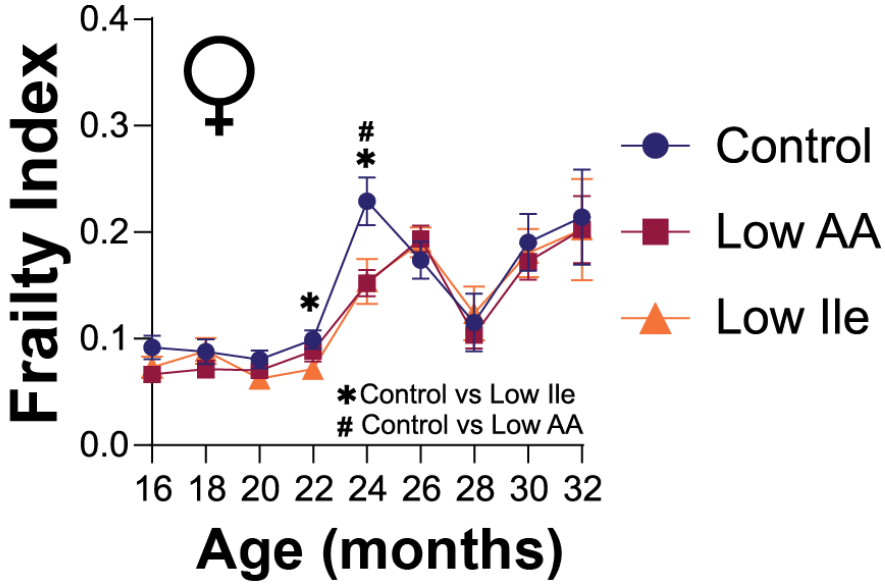
Richardson *et al.*, 2021, *Cell Metab*

Reducing dietary isoleucine reduces frailty in HET3 mice





Diet: p<0.0001 Age: p<0.0001
Diet * Age: p<0.0001



Diet: p=0.3158 Age: p<0.0001
Diet * Age: p=0.0561

A Low Ile diet extends the lifespan of HET3 mice

Increased BCAAs shortens mouse lifespan

Solon-Biet *et al.*, 2019, *Nature Metab*

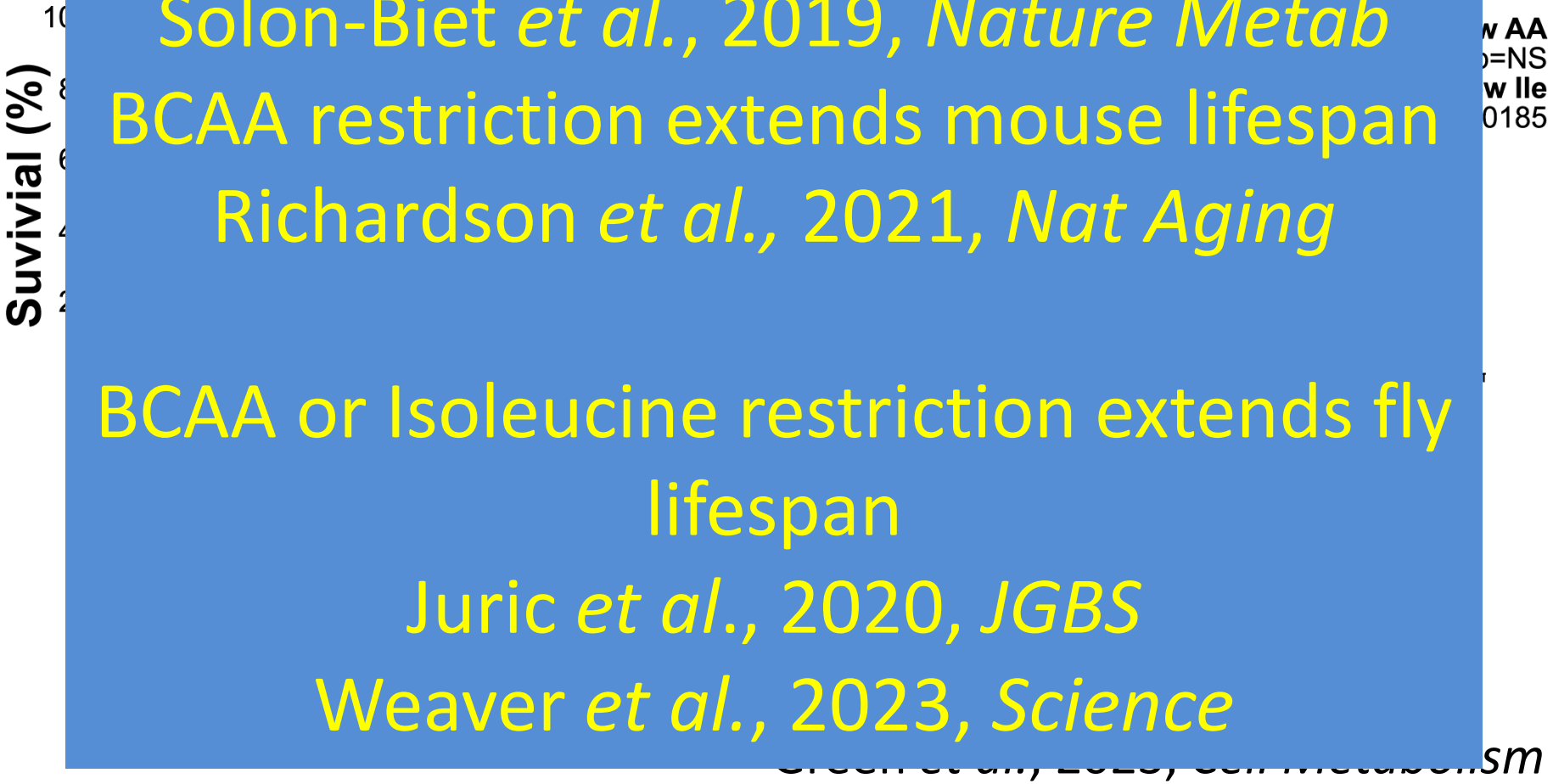
BCAA restriction extends mouse lifespan

Richardson *et al.*, 2021, *Nat Aging*

BCAA or Isoleucine restriction extends fly lifespan

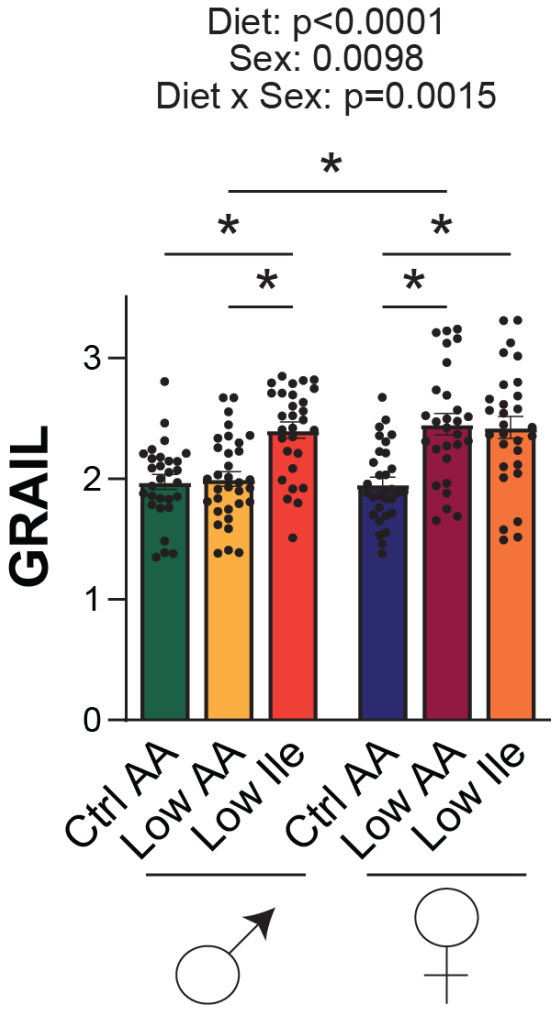
Juric *et al.*, 2020, *JGBS*

Weaver *et al.*, 2023, *Science*



Green *et al.*, 2023, *Cell Metabolism*

Low Ile diet – and in females, a Low AA diet - quantitatively extends healthspan

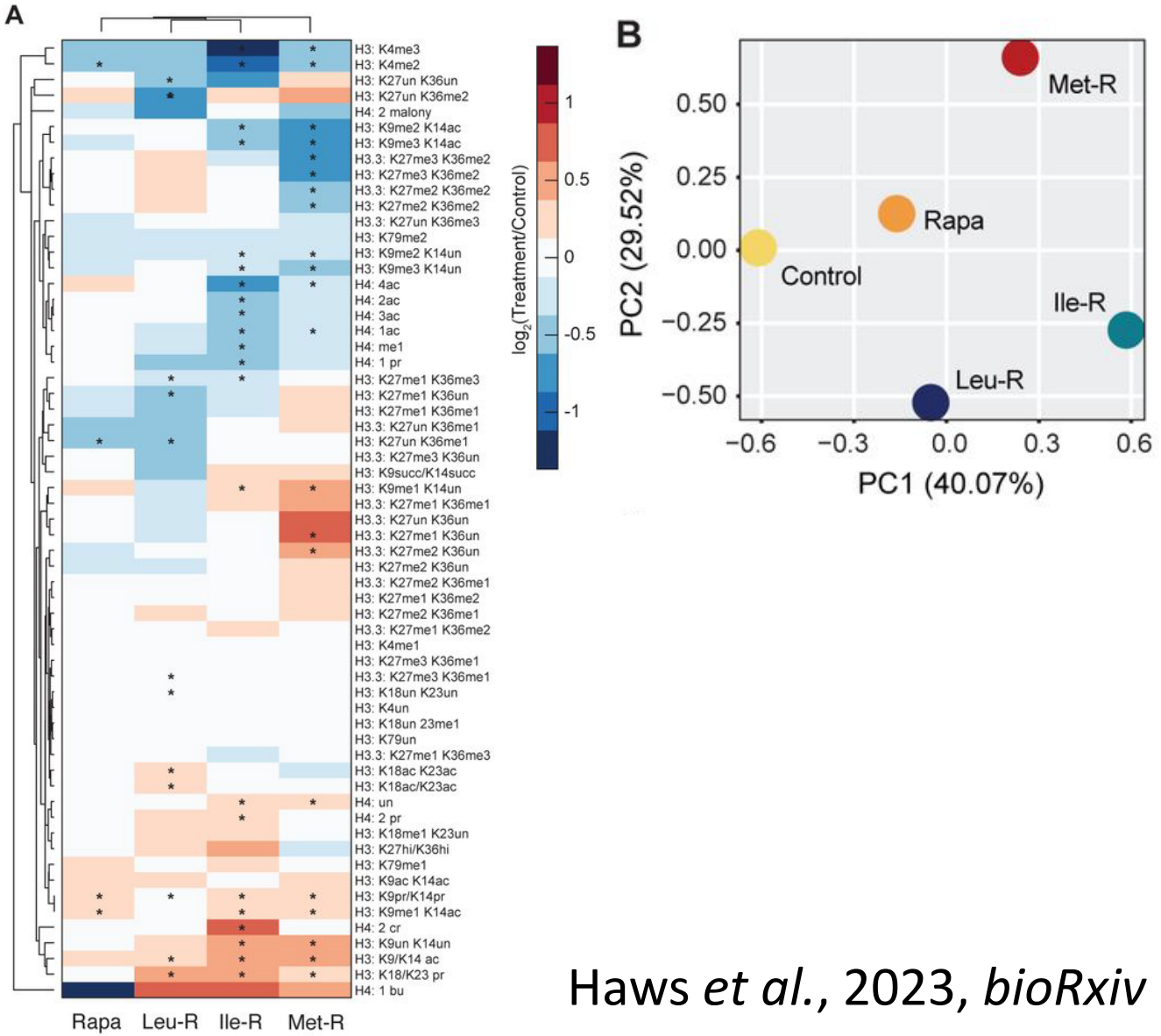


GRAIL (Gauging Robust Aging when Increasing Lifespan: GRAIL) integrates frailty over the course of the lifespan with healthspan assays and the hallmarks of aging

Lamming, 2024, *GeroScience*

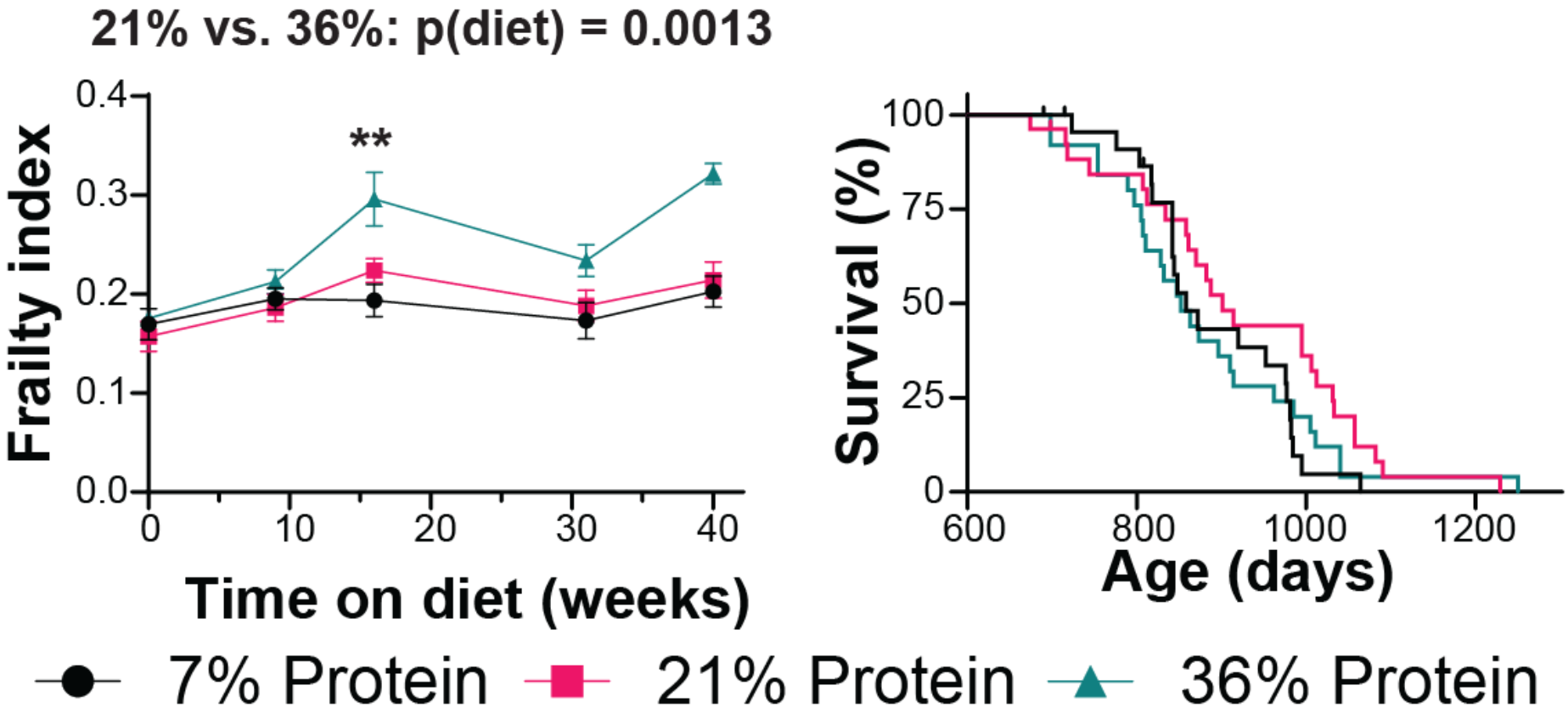
Major gaps in the field

How do PR/IleR and other AA-restricted diets reprogram metabolism and promote healthy aging?



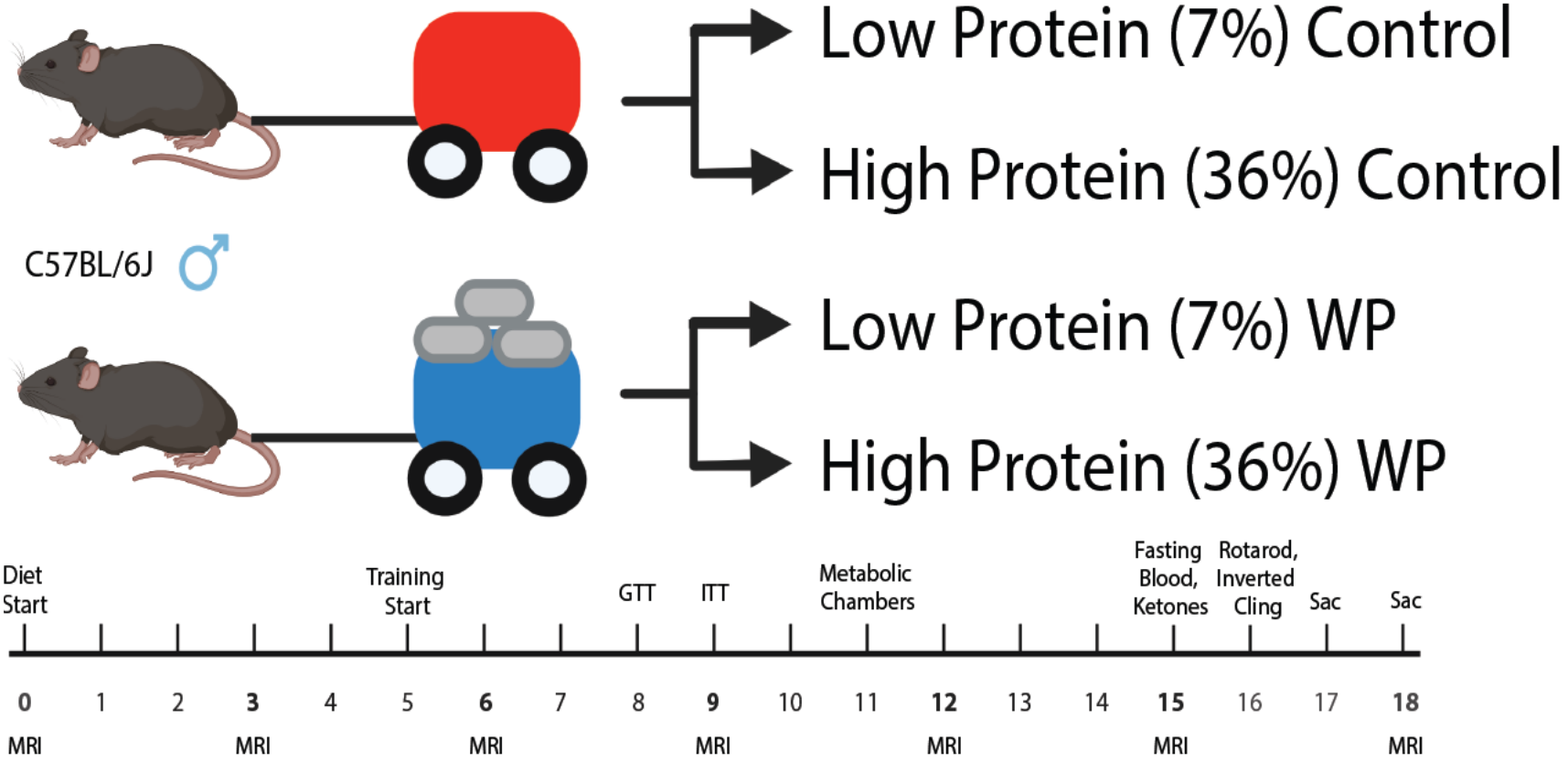
Haws *et al.*, 2023, *bioRxiv*

What is the optimal diet at each life stage?



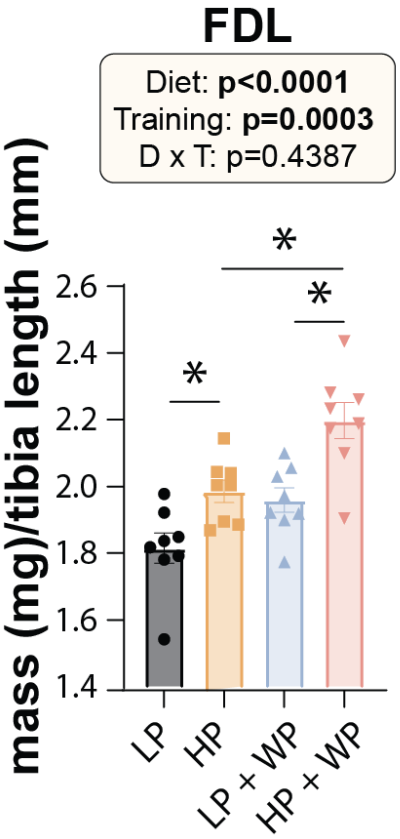
How does exercise interact with dietary protein?

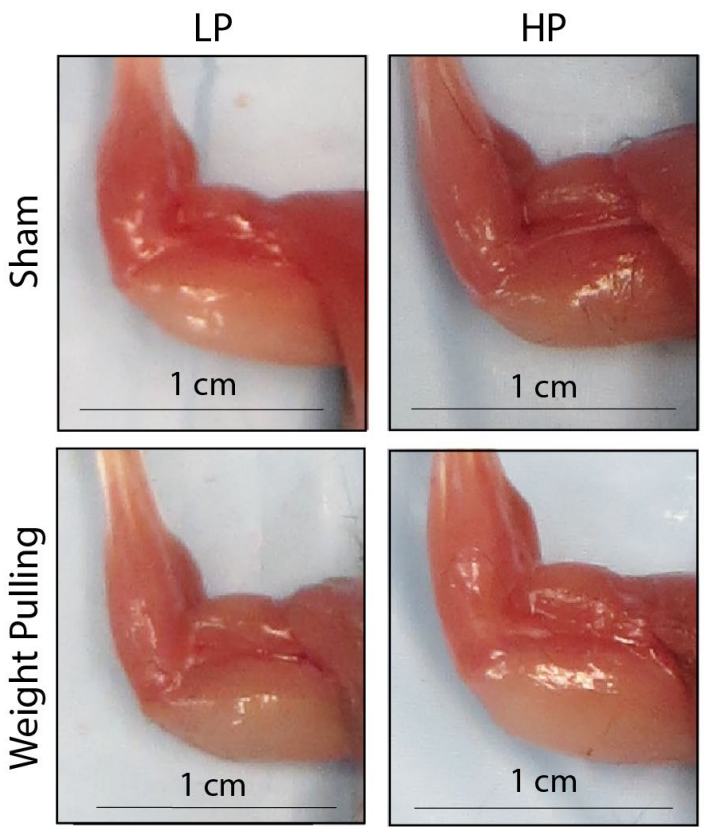
- Despite the overwhelming evidence that higher dietary protein consumption in sedentary rodents and humans is detrimental…
- Human athletes taking protein and/or AA supplements are some of the most metabolically healthy people.

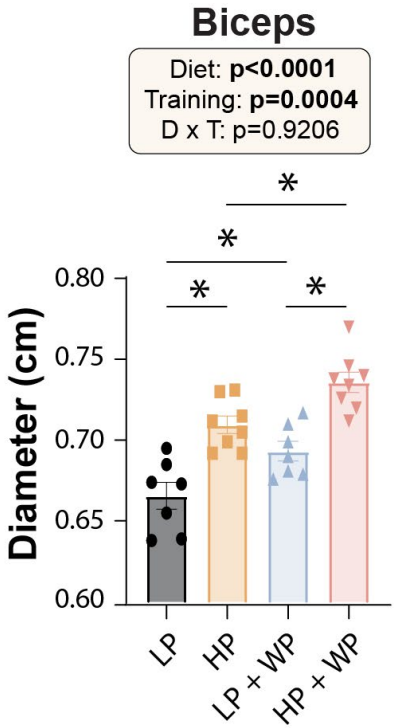


Trautman *et al.*, 2023, *eLife*

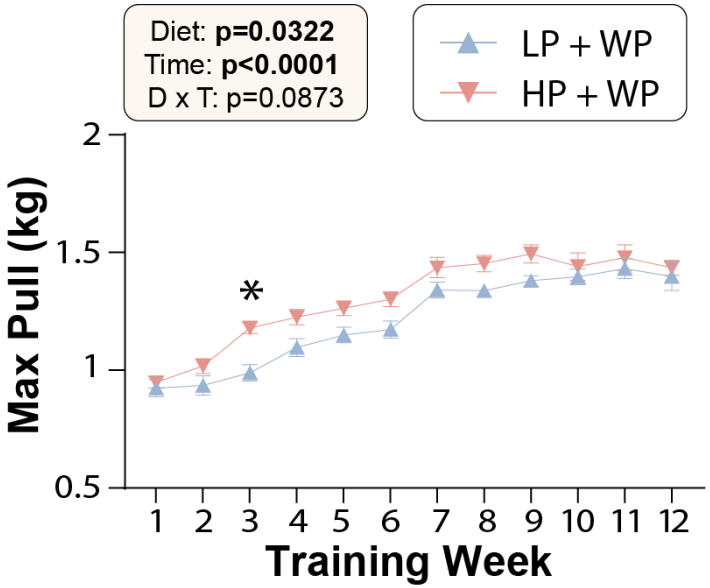
HP and weight pulling promote muscle hypertrophy

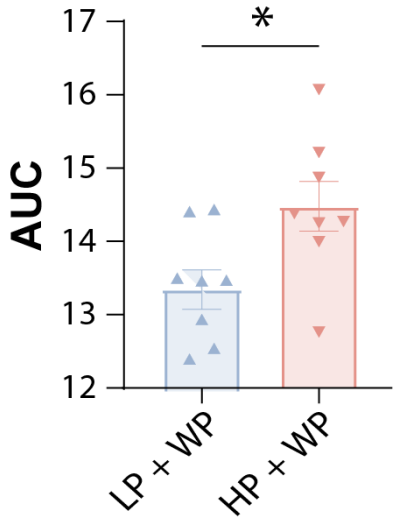


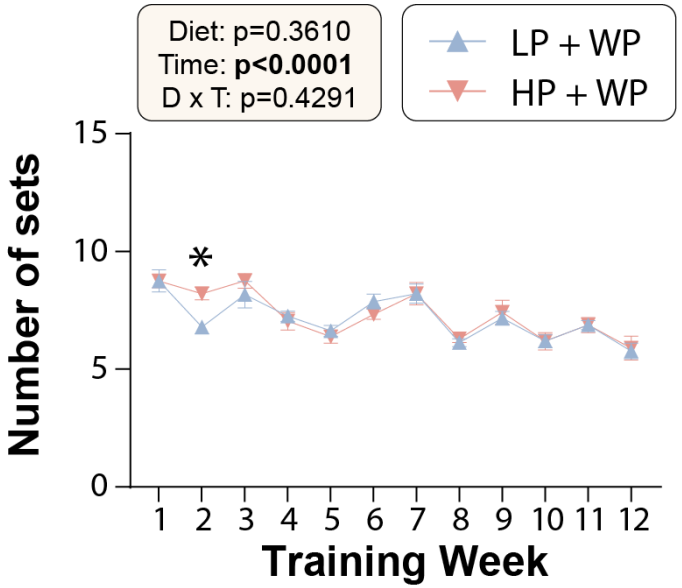




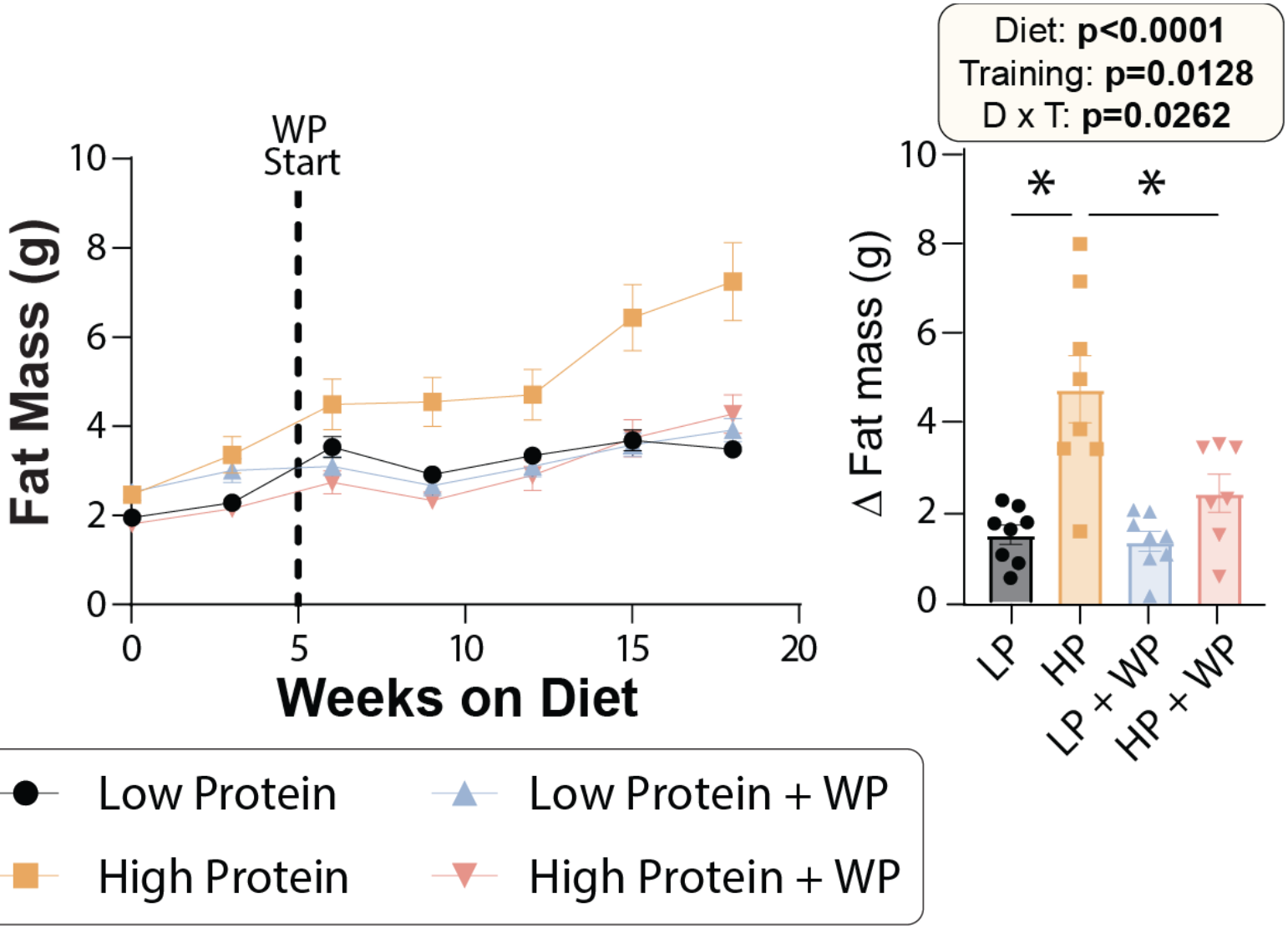
Resistance training benefits strength similarly in LP-fed and HP-fed mice







Sedentary HP-fed mice accrete excess fat mass



Summary

- Restriction of protein or specific amino acids like isoleucine promotes healthy aging in mice
- …and is associated with metabolic health and healthy aging in humans.
- Many questions regarding the molecular mechanisms by which PR/IleR regulate metabolism and promote health.
- Use of these interventions may need to be personalized – age, exercise, genetic background, and sex.

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Hevolution

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