Protein restriction improves metabolic health but not lifespan in aged mice
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Introduction
- Low protein (LP) dietary intervention has been shown to improve metabolic health, decrease frailty, and improve lifespan when used as a lifelong dietary pattern.
- High protein (HP) diets are often recommended to aging individuals to combat age-related muscle loss (sarcopenia) and retain adequate muscular function.
- Typical dietary protein content lies around 21% of calories from protein (MP).
- The effects of late-life dietary protein restriction or supplementation on lifespan remain unclear.

Methods
- 80 mice (21 months old C57BL/6j) were used, with 20 mice per group (LP, MP, HP). Mice were randomized to initial frailty diets at 22-24 weeks on diet.
- Male C57BL/6j mice were obtained from the NIA aging colony and separated into weight-matched diet groups at 21 months of age.
- Body weights were tracked weekly while frailty, MRI, and food consumption measurements were obtained approximately every 8 weeks.
- No tissue collections were performed, as this was a lifespan study.

Results (continued)

A

B

C

D

E

F

Protein restriction improves body composition
Longitudinal body composition data from aged male mice in which LP fed mice display reduced body weight (A), fat mass (B), lean mass (C), and overall adiposity (D). LP fed mice ate more food per body weight (E), while all dietary groups consumed distinct amounts of protein (F). (Max n=26-28 animals per group).

LP fed mice have increased metabolic activity
Metabolic chamber data where LP fed mice display increased energy expenditure per body weight in both light and dark phases (A), a difference which is not attributable to differences in body weight by ANCOVA analysis (B). LP fed mice also display elevated respiratory exchange ratio in both phases (C), though without differences in food consumption over the same period (D). MP fed mice display higher activity levels in the dark phase (E). Data are represented as mean ± SEM (n=15-18 animals/group). Two-way ANOVA followed by Tukey’s *=p<.05, **=p<.01, ***=p<.001, ****=p<.0001.

LP and HP fed mice have reduced lifespan
Average rotarod (A) and inverted cling test (C) performance with ANCOVA against body weight (B, D). Lifespan survival % after diet start at approximately 640 days of life (E) and accumulated frailty burden over lifespan (F). Data are represented as mean ± SEM. One-way ANOVA followed by Tukey’s *=p<.05, **=p<.01, ***=p<.001, ****=p<.0001.

Conclusions
- Late life LP diet recapitulates effects of lifelong LP diet including reduced body weight and adiposity despite increased food consumption, while providing improved glucose and insulin tolerance.
- Late life LP diet results in elevated energy expenditure and RER.
- Late life HP diet increases frailty burden and does not improve metabolic health, nor does it offer benefits to muscular function.
- LP and HP diets reduce lifespan when introduced as late life dietary interventions.