NIA Interventions Testing Program (ITP)

https://www.nia.nih.gov/research/dab/interventions-testing-program-itp

nadonn@nia.nih.gov

Goal of the ITP:

- To test compounds/diets purported to benefit healthy aging, using a genetically heterogeneous rodent model, with lifespan as the primary read-out and health span measurements as secondary read-outs

Community approach

3 Testing sites:

- U. Michigan – Richard Miller
- UTSAHSC – Randy Strong
- The Jackson Laboratory – David Harrison

Two advisory committees

Sponsors – research community proposes compounds for study, partners in study design

Test platform

-Genetically heterogeneous mice - 4-way cross (BALB, B6, C3H, DBA/2)

-Sample size chosen for 80% power to detect 10% change for each sex, even if one site lost

-Control group doubled to add statistical power

-Control diet and test diets are made in bulk and shared amongst the 3 sites

-SOPs standardize husbandry to extent possible

-Pilot studies

To date, 6 compounds have shown significant extension of median lifespan:

- Aspirin – males only
- Rapamycin – males and females (M>F)
- 17αEstradiol – males only
- Acarbose – males and females (M>>>F)
- NDGA (nordihydroguaiaretic acid) – males only
- Protandim® - males only (unpublished)

NIA ITP

The NIA ITP can be the poster child for the importance of addressing sex as a biological variable!

Some key points about the sex differences for rapamycin, Acarbose, and NDGA

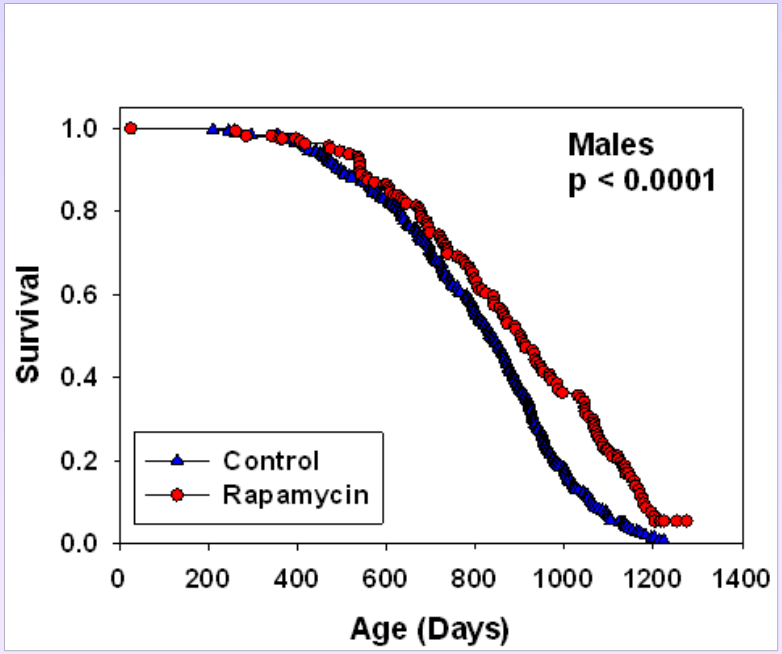
NIH

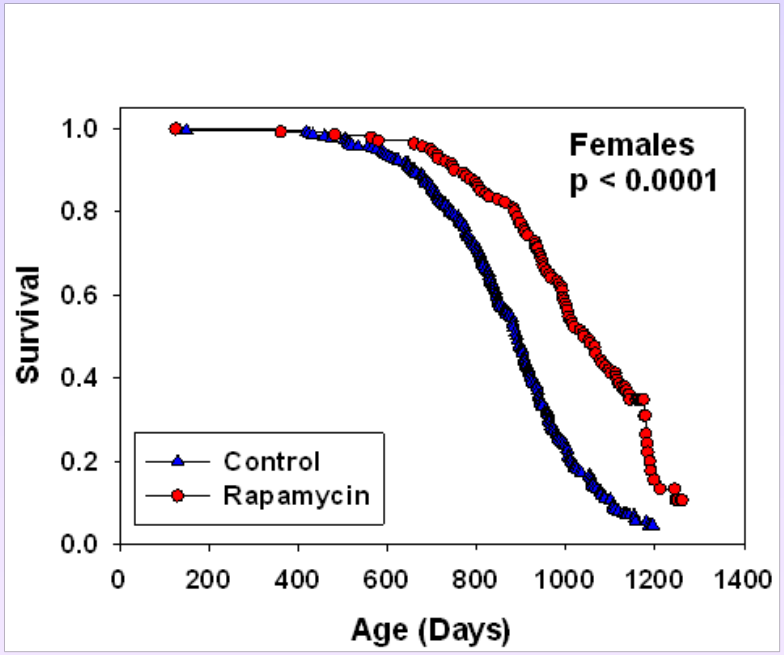
NIA ITP

Rapamycin – antimicrobial, immunosuppressive activity

At 14 ppm, starting at 9 mo.:

- Males – 10% increase in median LS
- Females – 18% increase in median LS



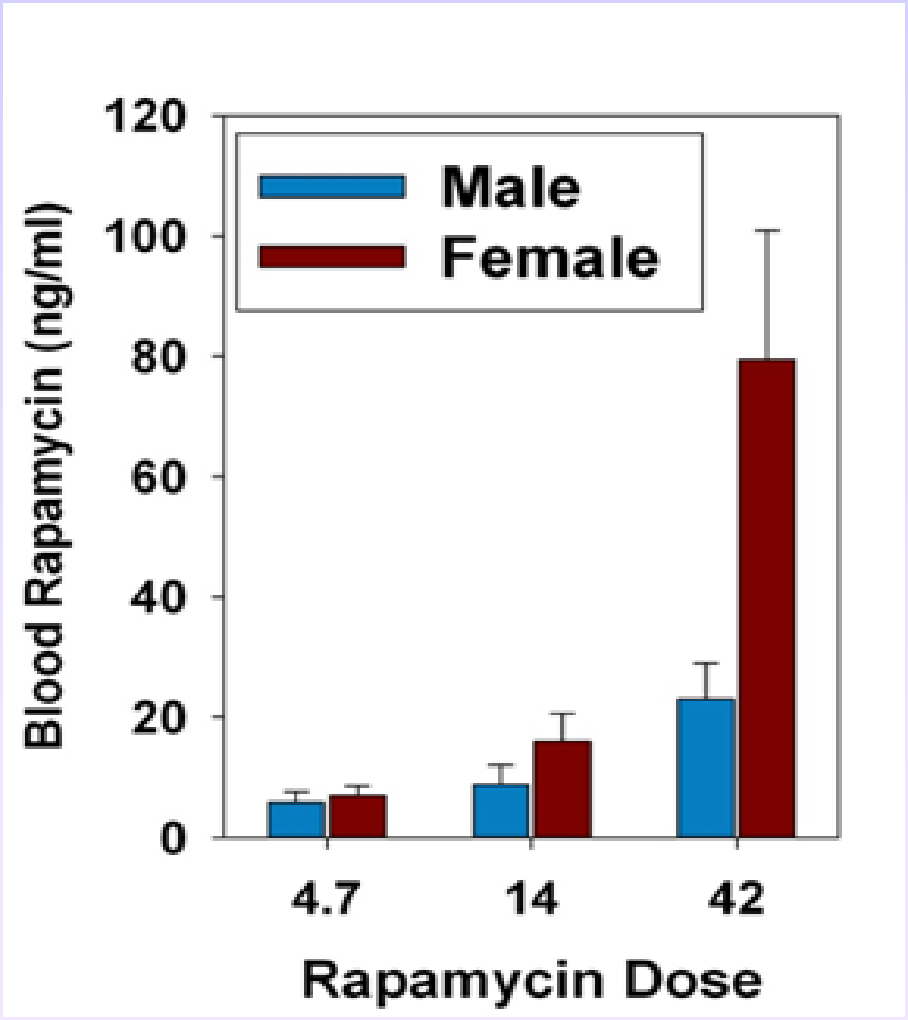


NIH

Rapamycin extended LS when initiated at 9 months or 20 months of age

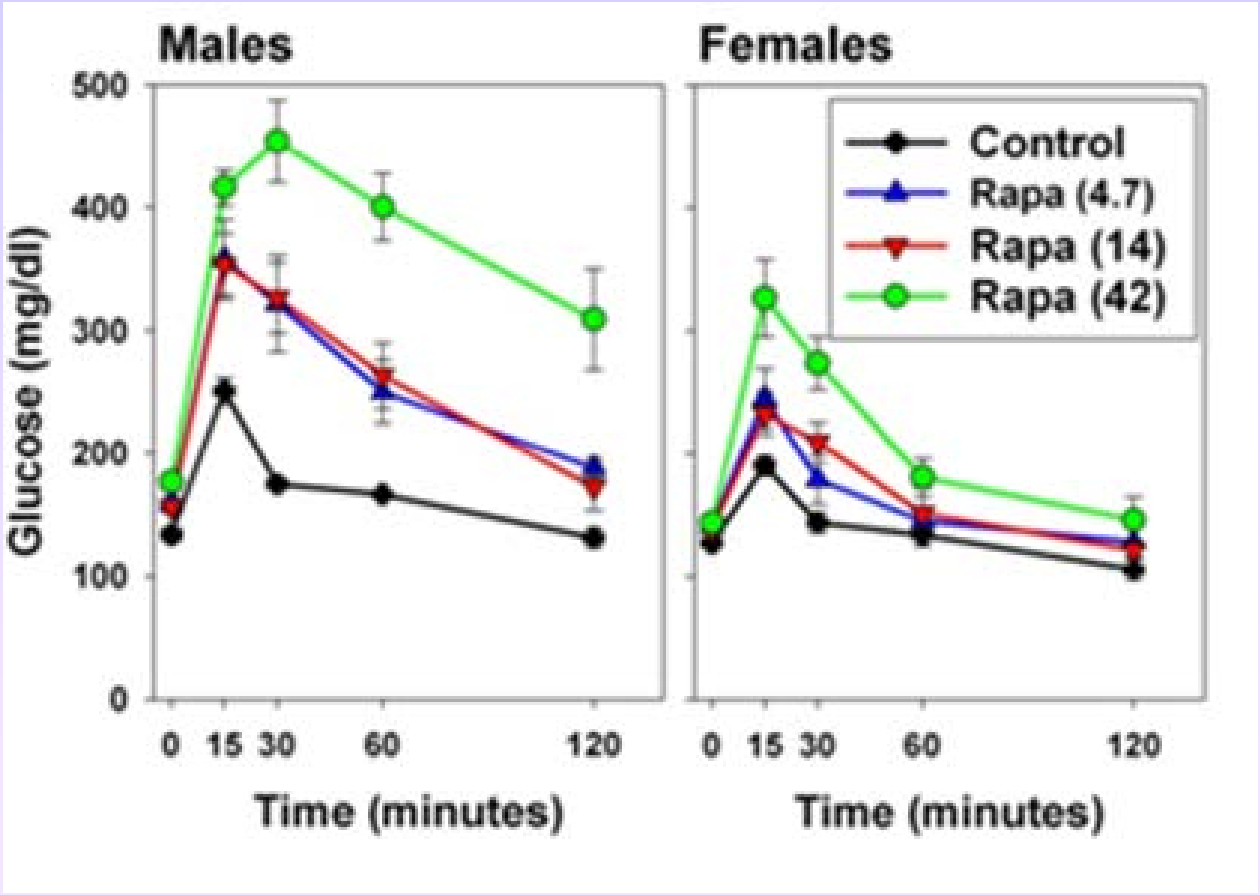
Rapamycin Initiation Age	Cohort, Dose	% Median LS ↑ Males - Females
20 mo.	C2005, 14 ppm	9% - 13%
9 mo.	C2006, 14 ppm	10% - 18%
9 mo.	C2009, 4.7 ppm	3% - 16%
9 mo.	C2009, 14 ppm	13% - 21%
9 mo.	C2009, 42 ppm	23% - 26%

Difference in blood levels might explain the sex difference in lifespan extension



Miller et al., 2014

Rapamycin-induced loss of glucose tolerance was more pronounced in males



Miller et al., 2014

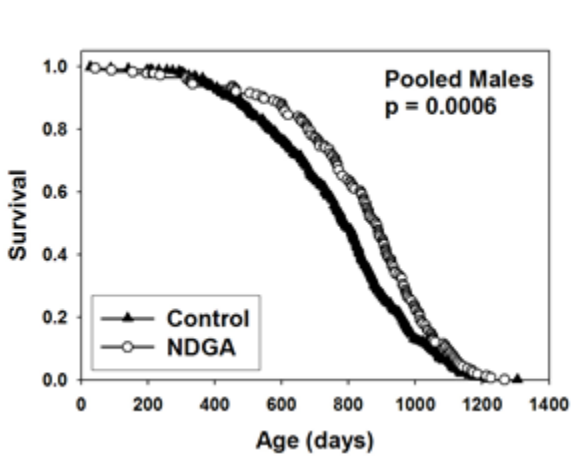
Metformin benefit was also preferentially seen in males

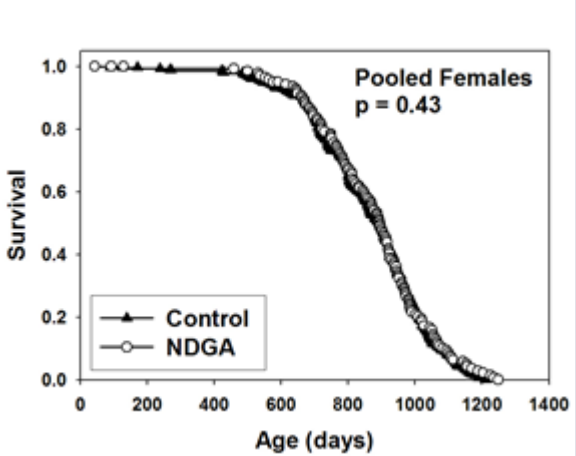
	Males	Females
Treatment	**% Change**	**% Change**
Metformin	8	0
Rapa plus Metformin	24	23
Rapa [C2006]	10	18
Rapa [C2009]	13	21

Strong et al. submitted

NDGA (Nordihydroguaiaretic acid):

- Anti-inflammatory agent with anti-oxidant properties
- Median LS increased in male mice but not females
- Body weight reduced in NDGA-treated females but not males

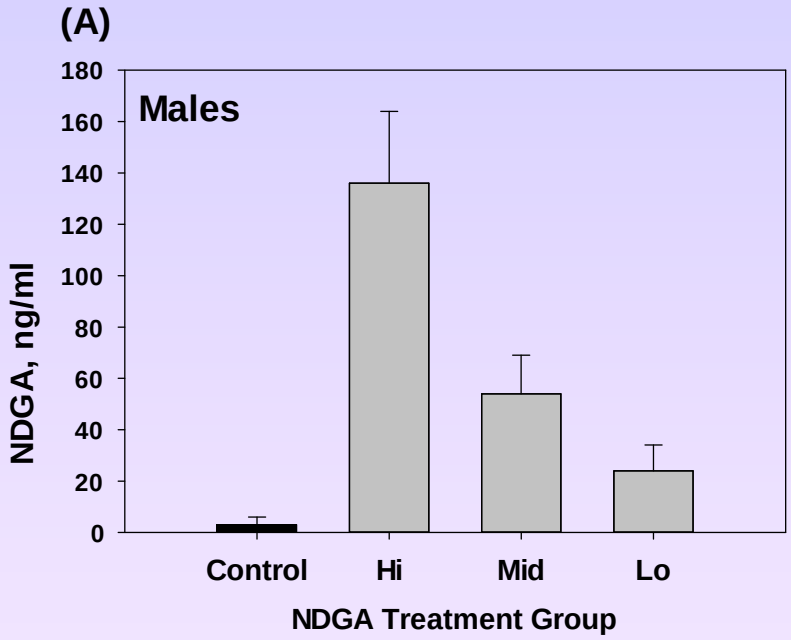


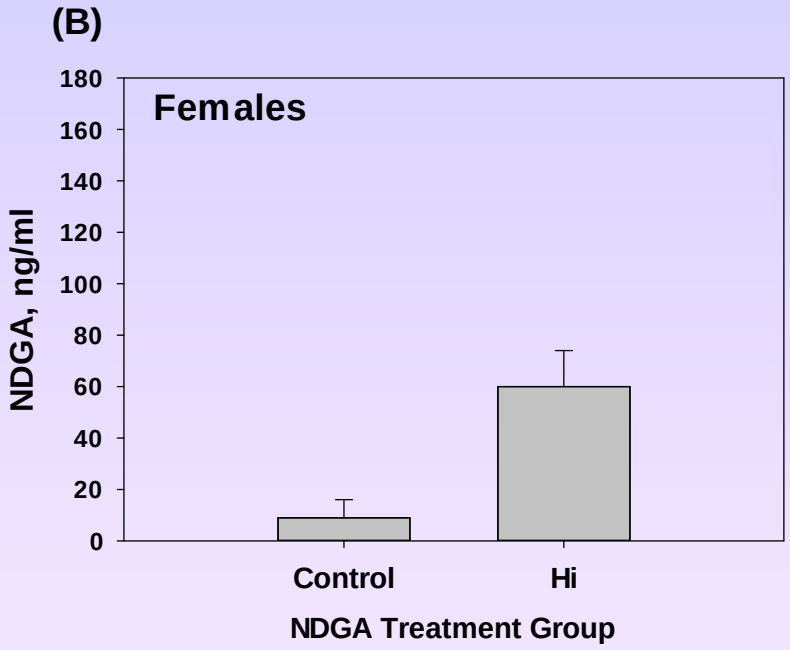


Strong et al., 2008

NIA ITP

Blood NDGA levels were different in males and females

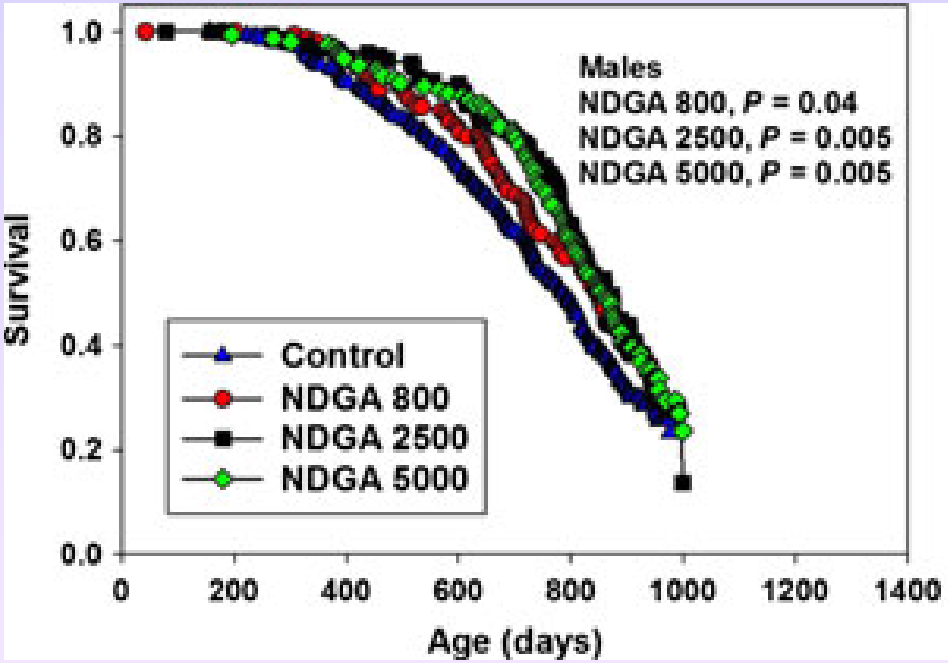


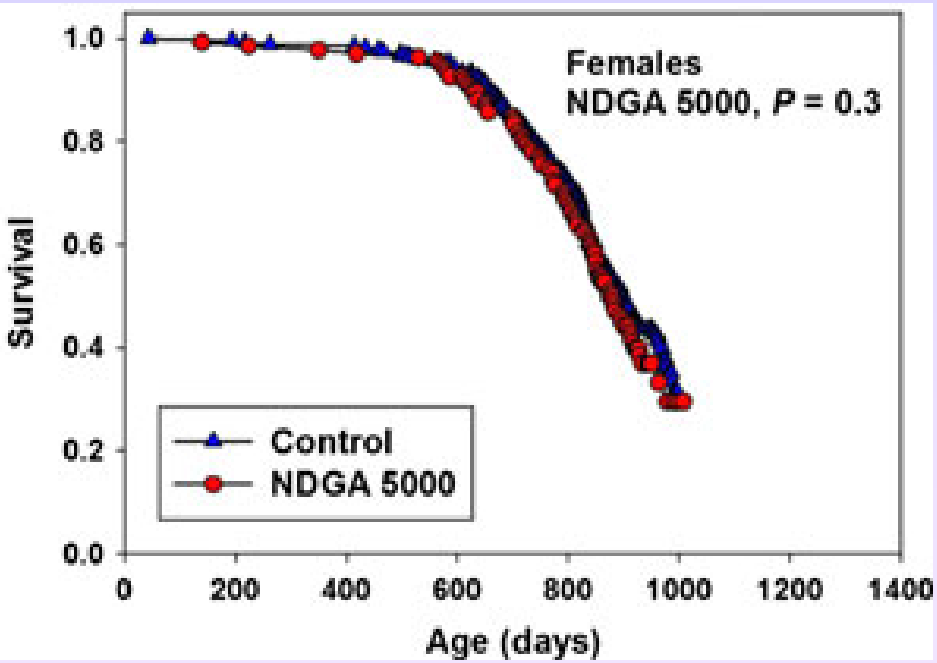


Harrison et al., 2013

NIH

Even at a dose where NDGA blood levels in females matched effective dose in males, there was no LS increase





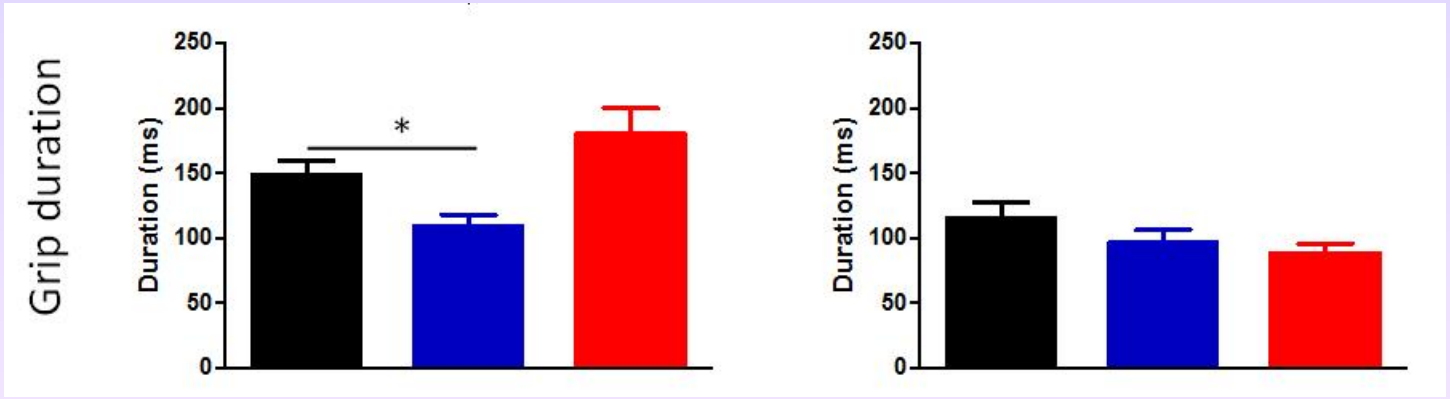
Harrison et al., 2013

NIA ITP

At equivalent blood levels of NDGA, males showed improved grip duration, females did not show benefit

Male

Female



Young Control
Old Control
Old NDGA

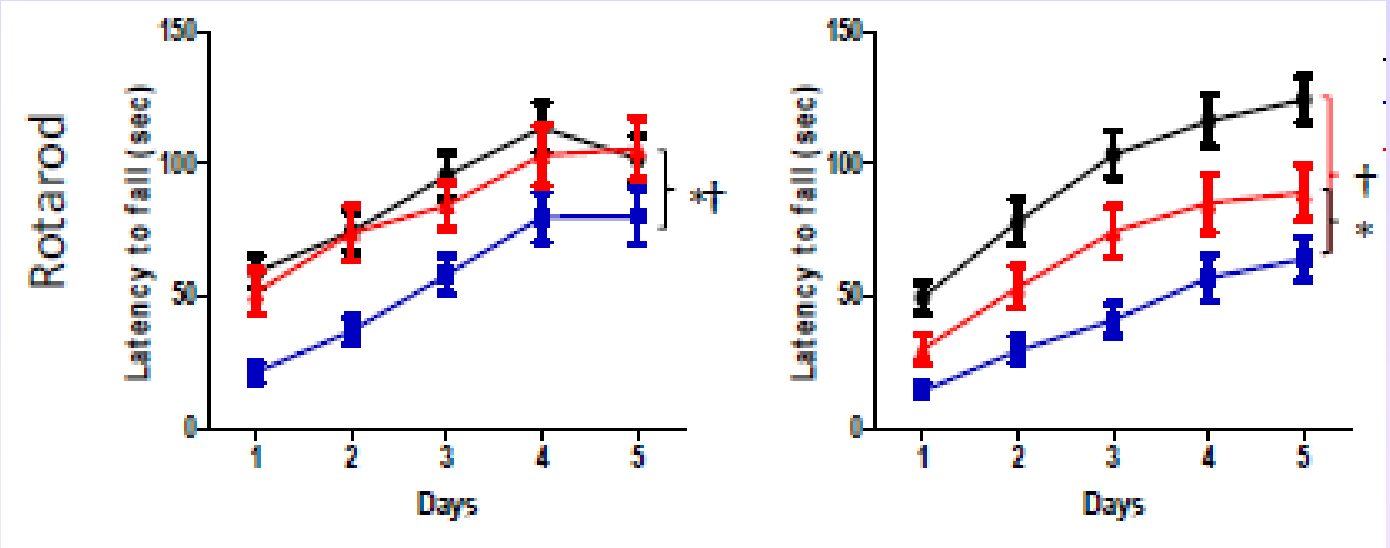
Strong et al., submitted

NIH

Females did show some benefit of NDGA on rotarod performance

Male

Female



Young Control
Old Control
Old NDGA

Strong et al., submitted

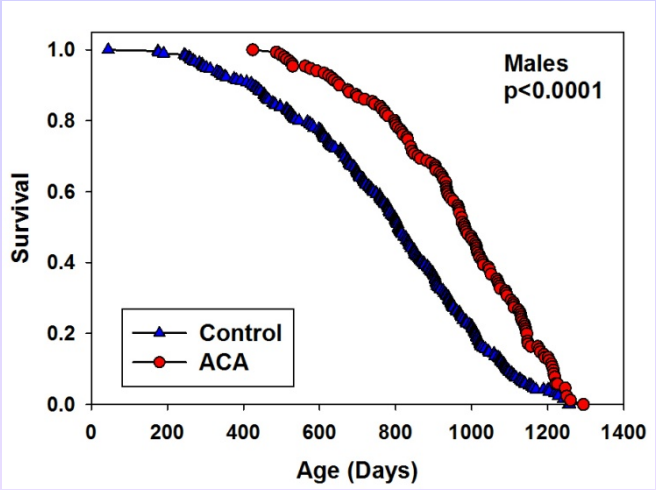
Acarbose – inhibits digestion of complex carbohydrates, blunting post-prandial surges in blood glucose levels

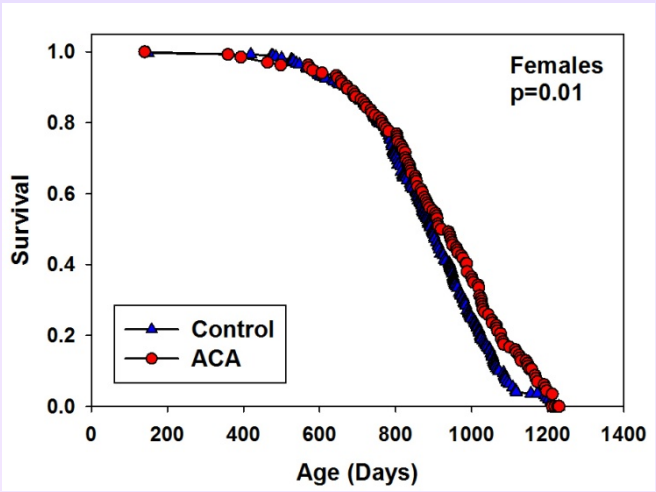
- Median LS increase – Males >>> Females

  (22% vs 5%)

- Maximal (90%) LS increase about the same

  (11% vs 9%)

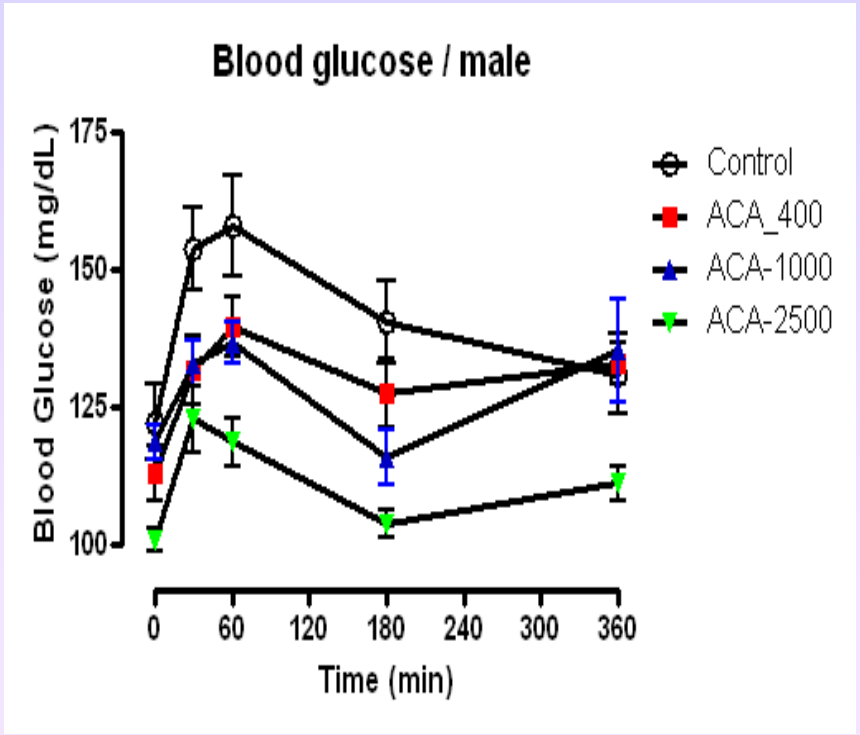


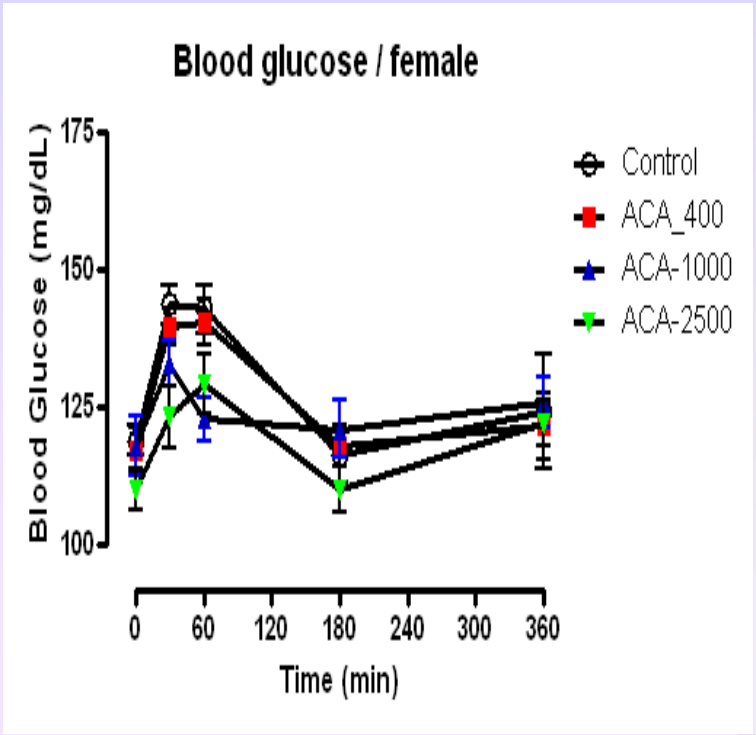


Harrison et al., 2013

NIA ITP

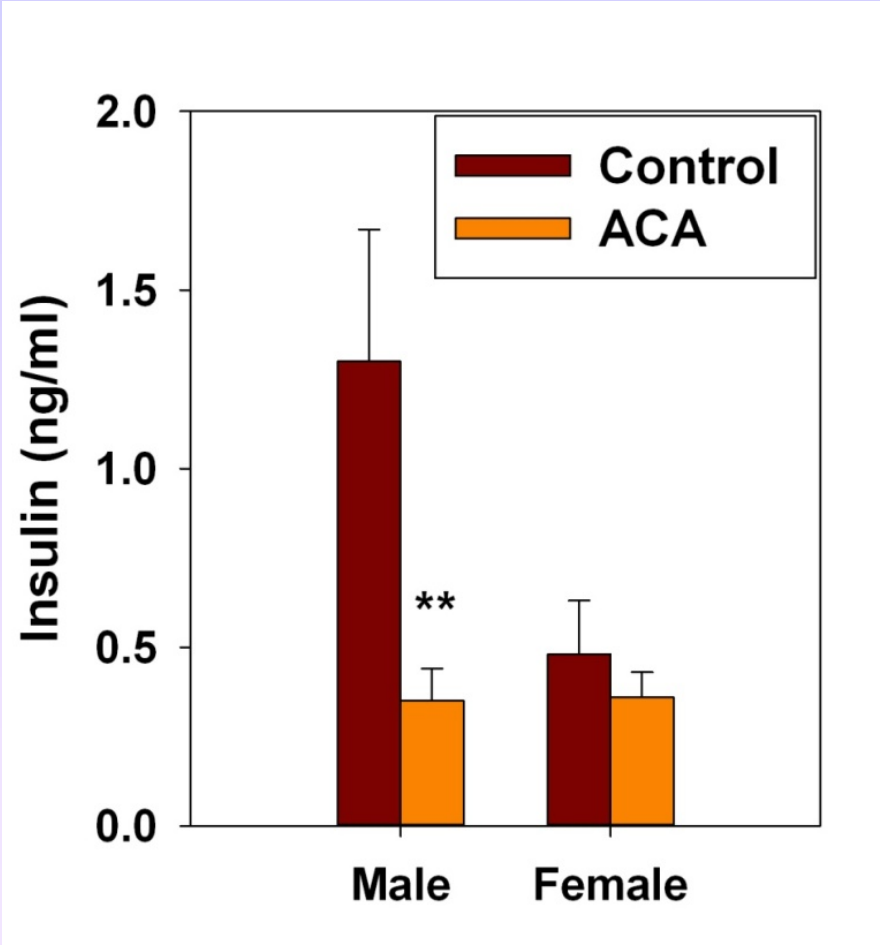
Effect of Acarbose on post-prandial glucose was greater in males than females





NIH

Acarbose impacts insulin pathway



Fasting insulin was much higher in control males than in control females, but similar in Acarbose-treated males and females

Harrison et al., 2013

Summary

Sex differences in the effects of pharmacological and dietary interventions appear widespread and very complex – achieving equivalent blood levels is not always a magic bullet.

Mechanistic studies to understand them are needed, and translational studies should always address sex as a biological variable.