

Reproductive Hormones and Aging

in humans and animal models

the need for more and bigger datasets

James F. Nelson, PhD
Barshop Institute for Longevity and Aging Studies
Cellular and Integrative Physiology
UT Health San Antonio



Outline

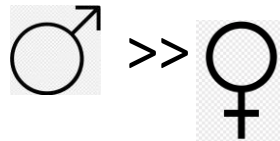
- Reproductive Hormones: a primer
- How they affect the body (emphasis on aging)
- How they change with age
- Recent hormone-dependent findings relevant to Geroscience
- Knowledge gaps

Key natural^{*} sex steroids:

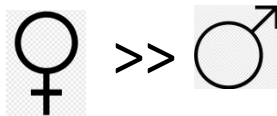
Progestins -- 21 carbon



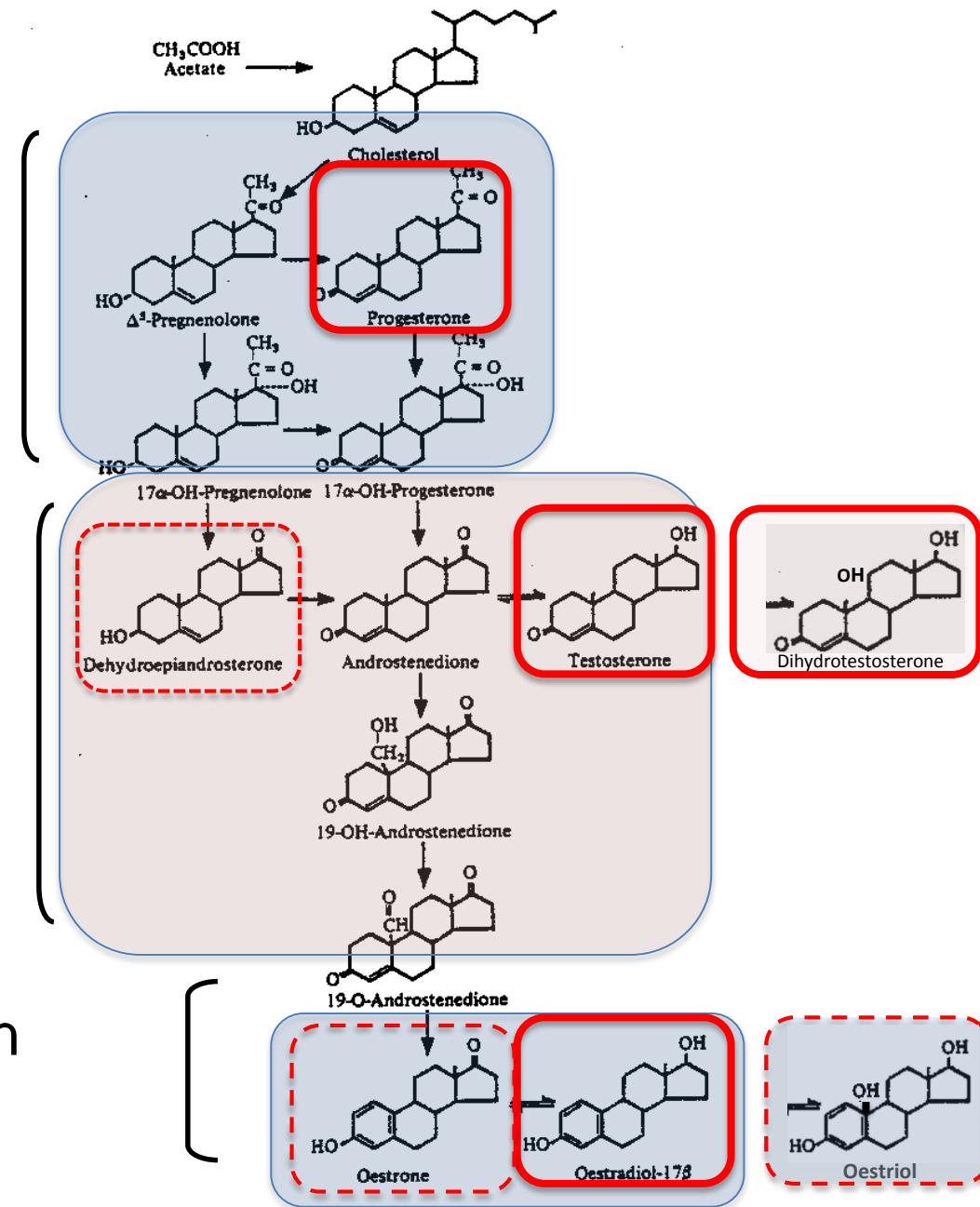
Androgens -- 19 carbon



Estrogens -- 18 carbon



^{*}countless pharmacologic derivatives

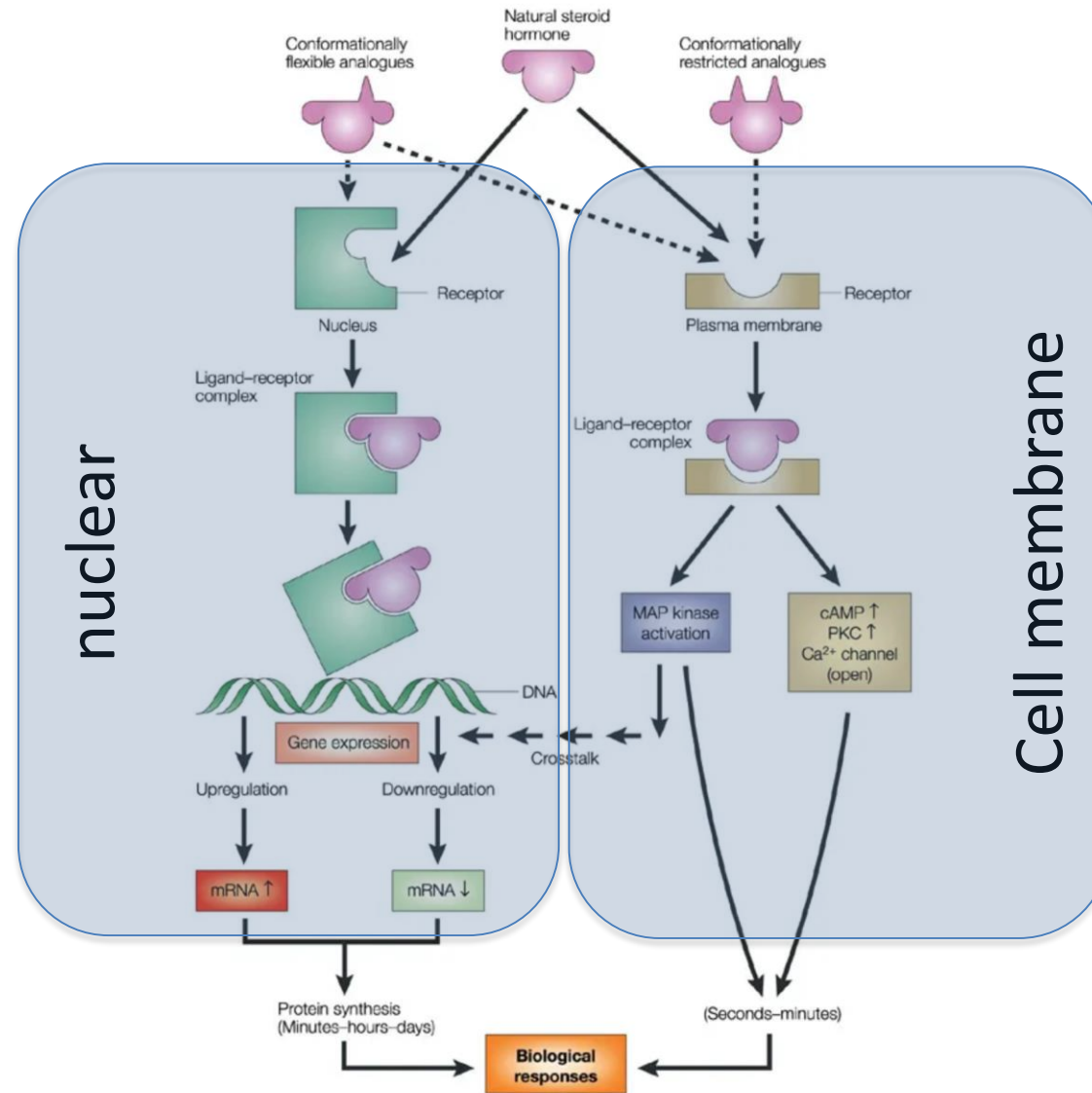


Steroid Receptors

Estrogens: ER α & ER β

Androgens: AR

Progestins: PR, GR1, GR2

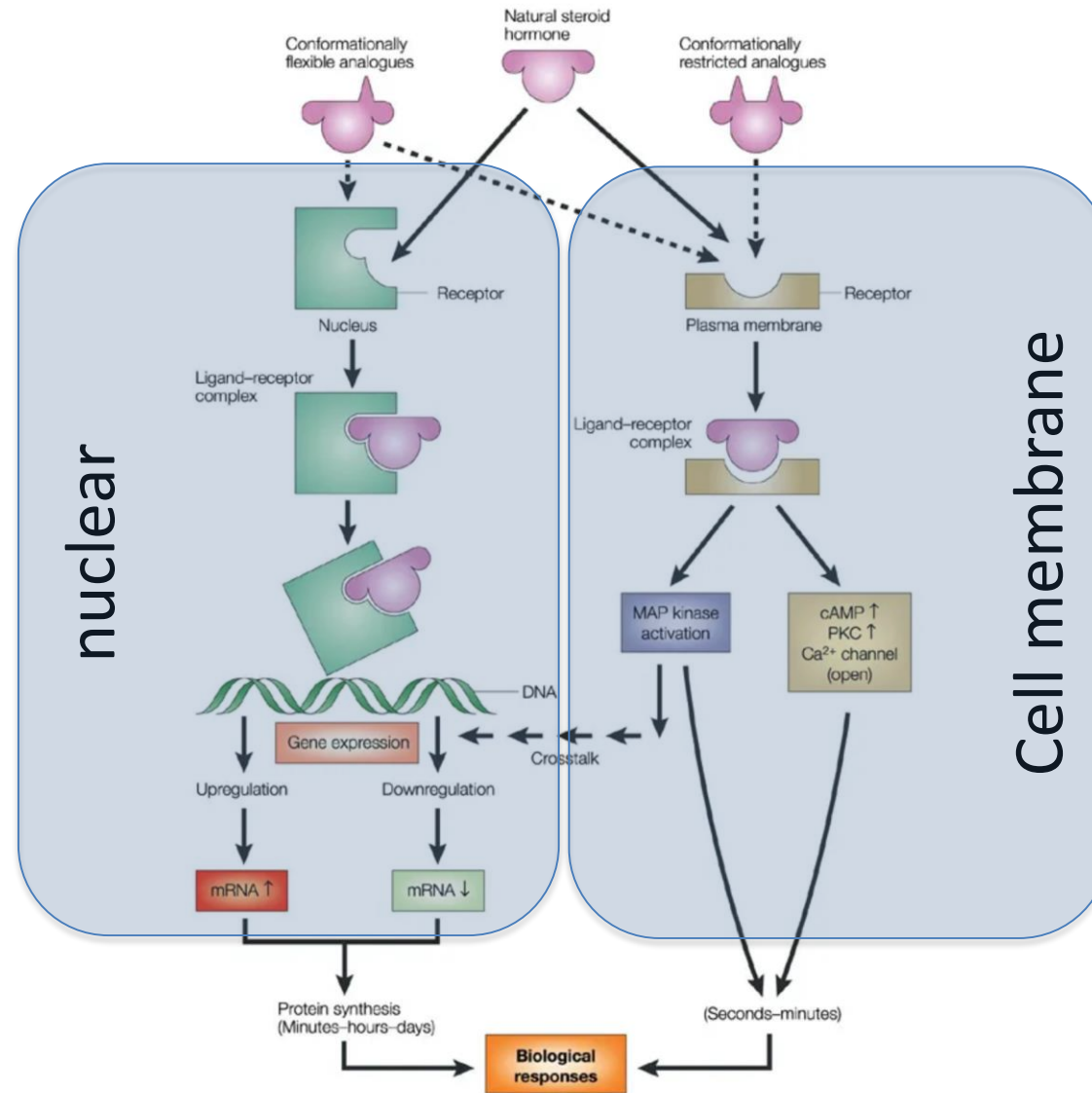


Nature Reviews | Drug Discovery

Steroid Receptors

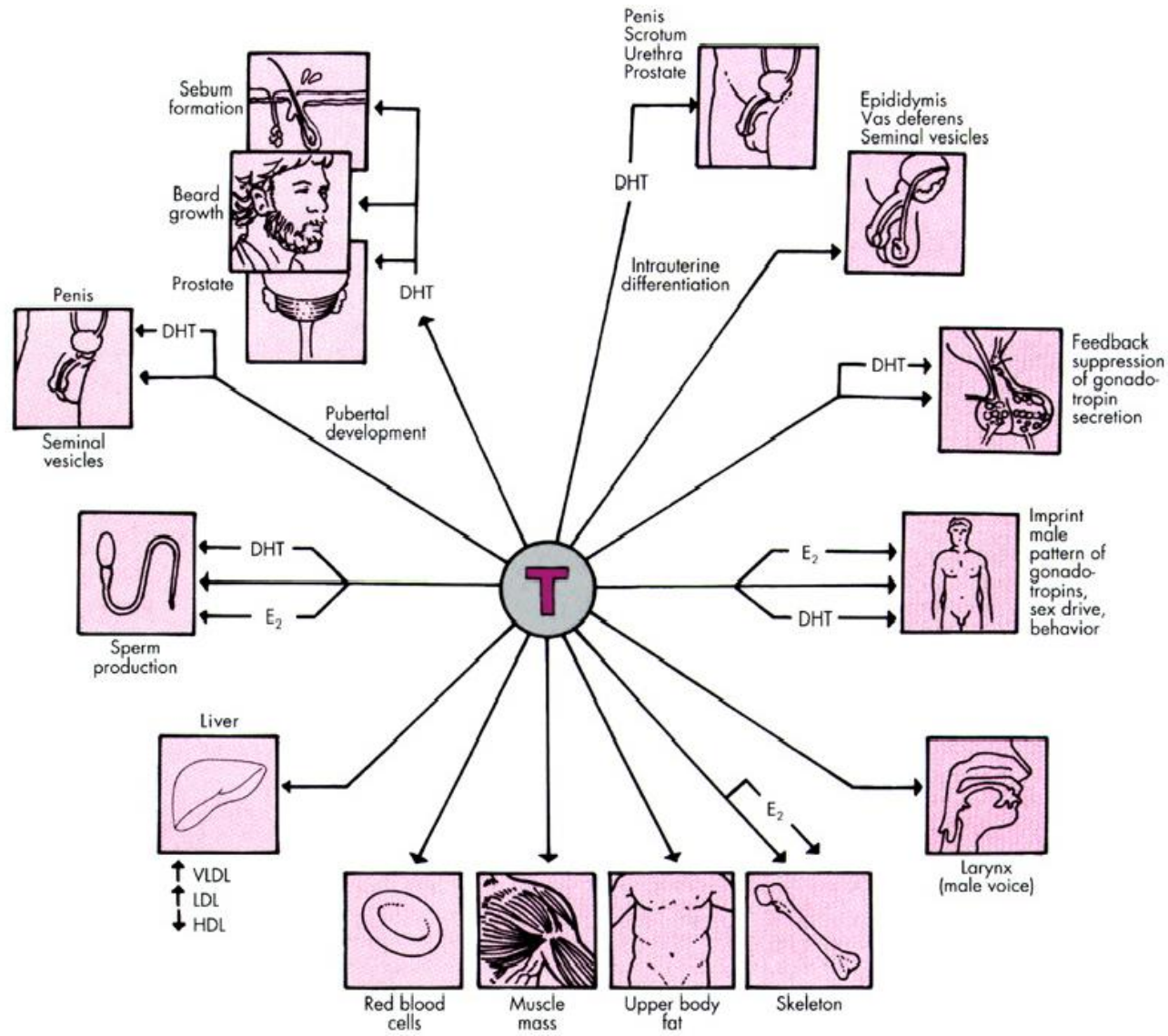
Knowledge gap:

Post 70's, absence of characterization of effect of aging on detailed advances in hormone receptor signaling pathways

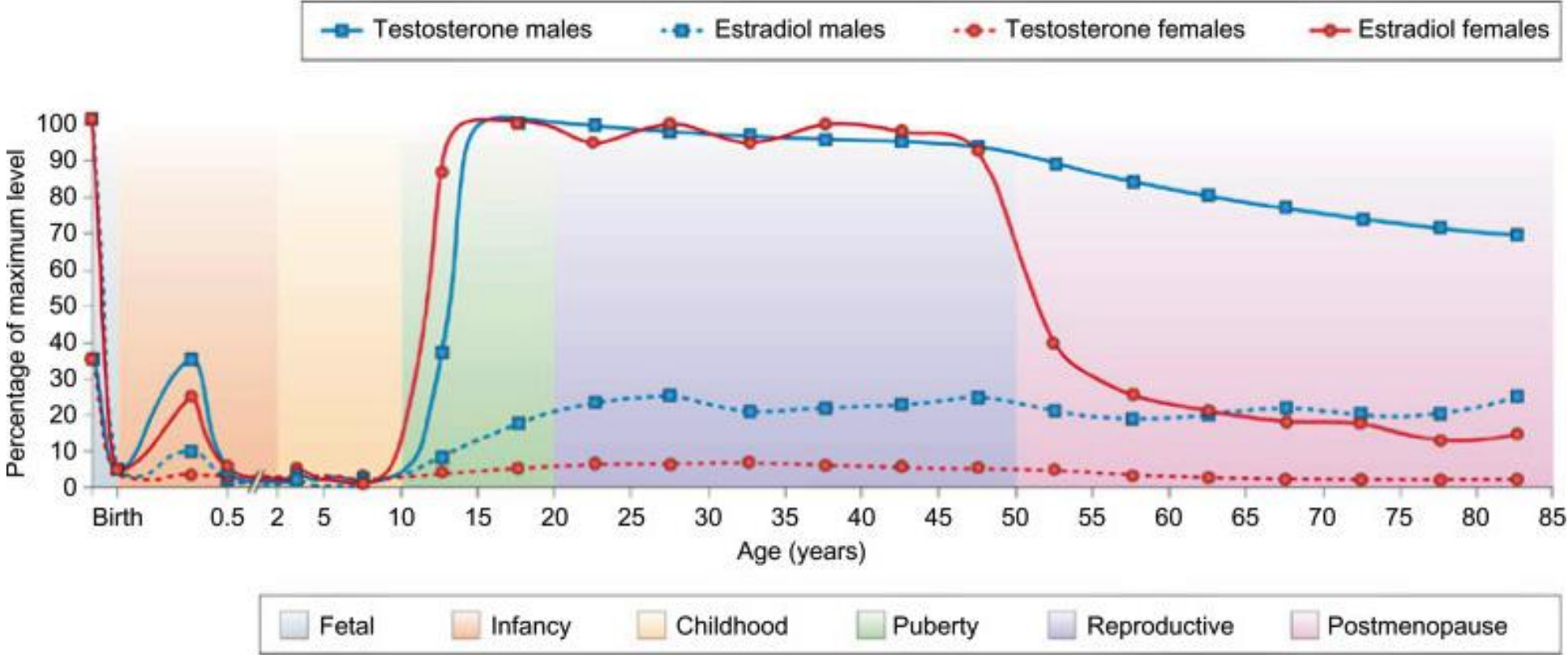


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Sex Hormones Don't Just act on Reproductive Targets (i.e., receptors are everywhere)

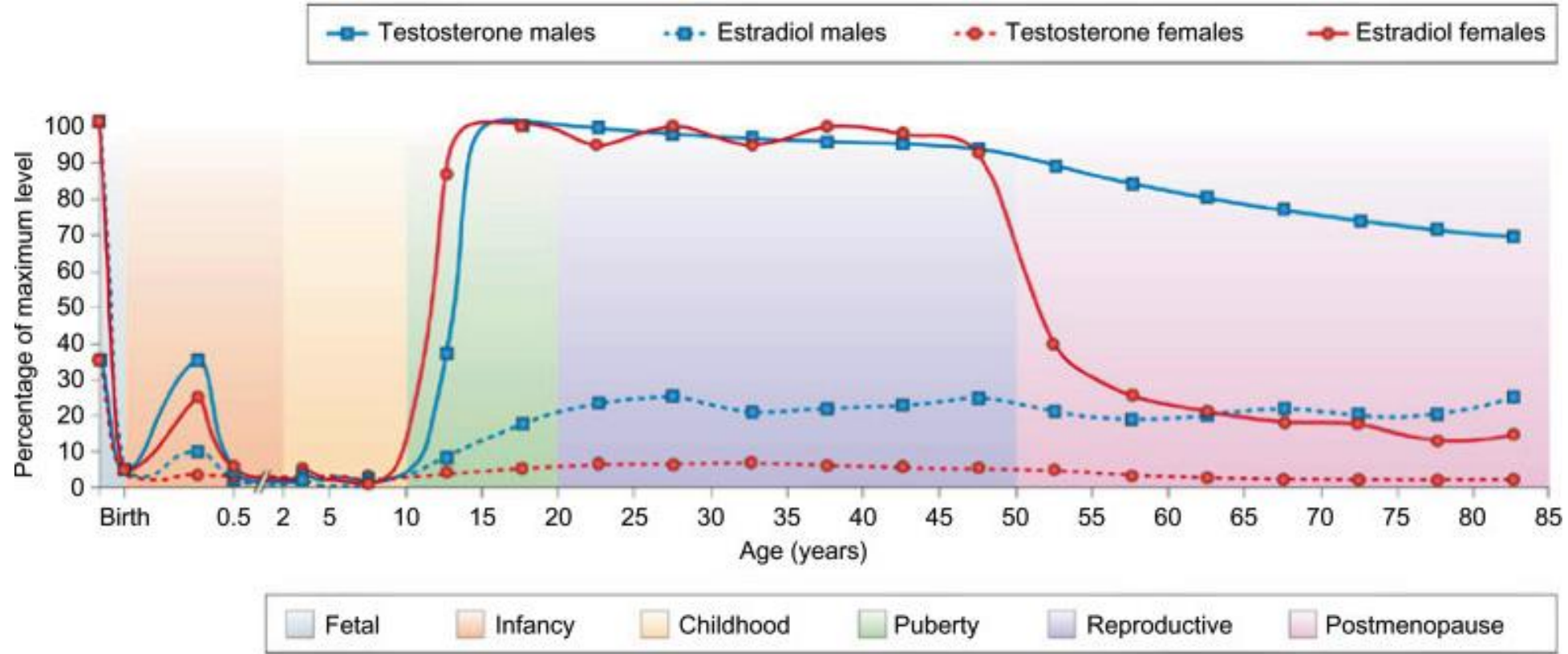


Estradiol and Testosterone Across the Lifespan



Nature Reviews | **Genetics**

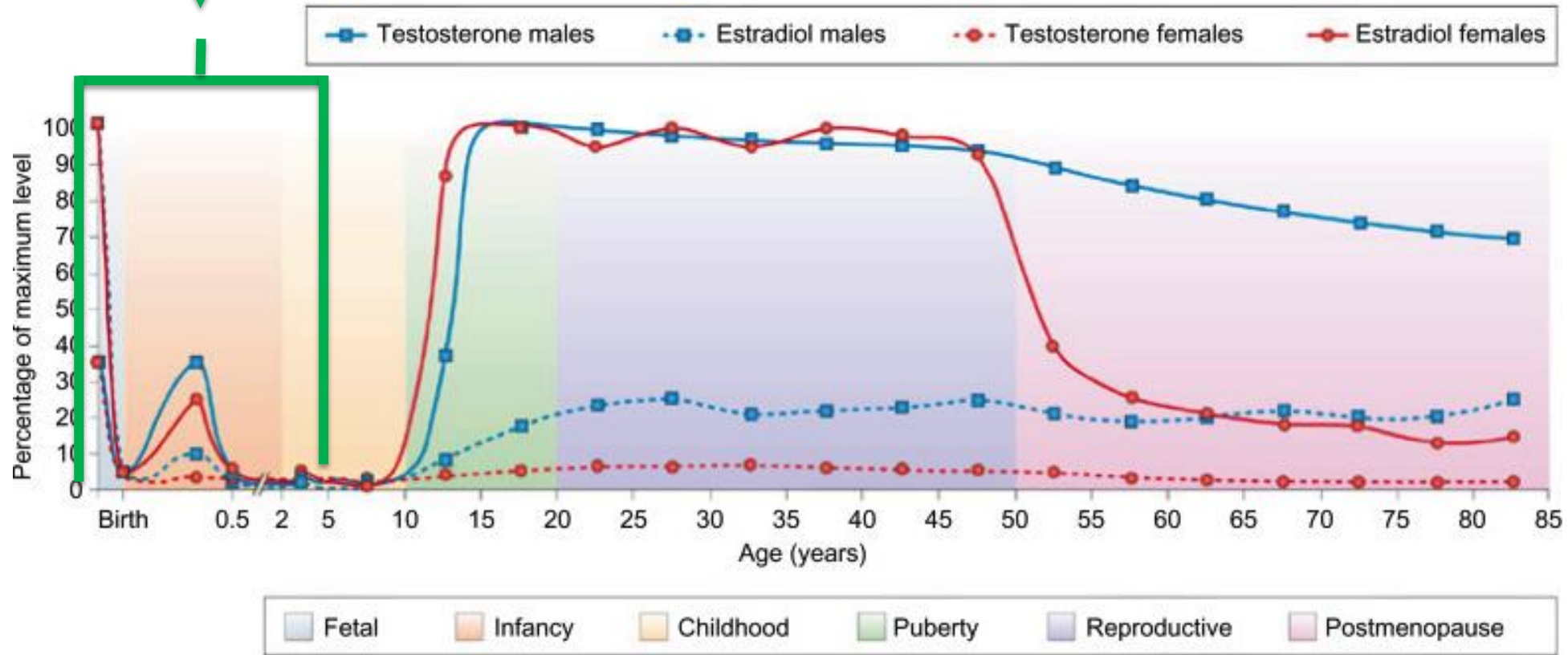
Knowledge gaps: estrone?, estriol?, progesterone?, dihydrotestosterone?



Nature Reviews | Genetics

Sex Hormone Actions Relevant to Aging

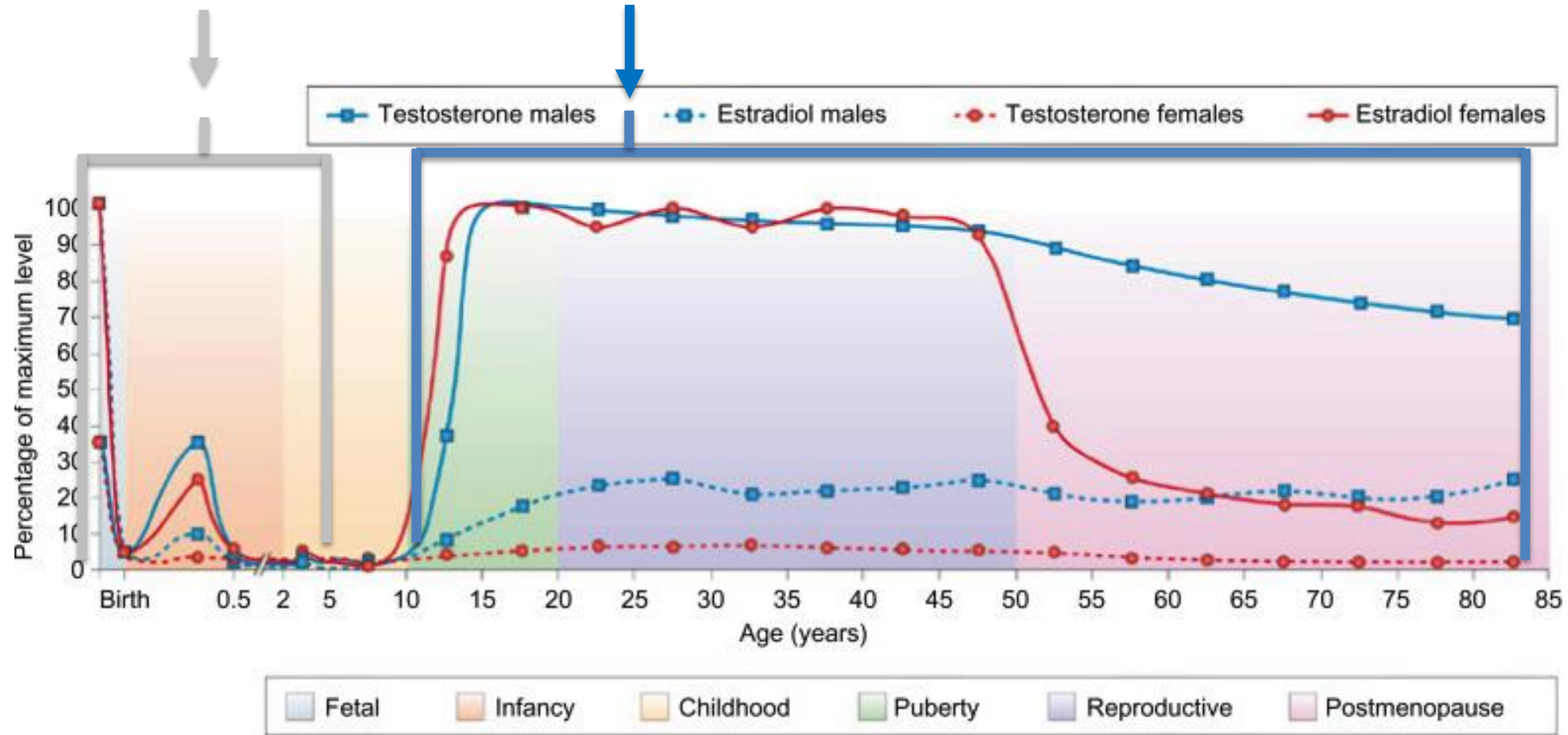
Organizational (e.g. neuronal)



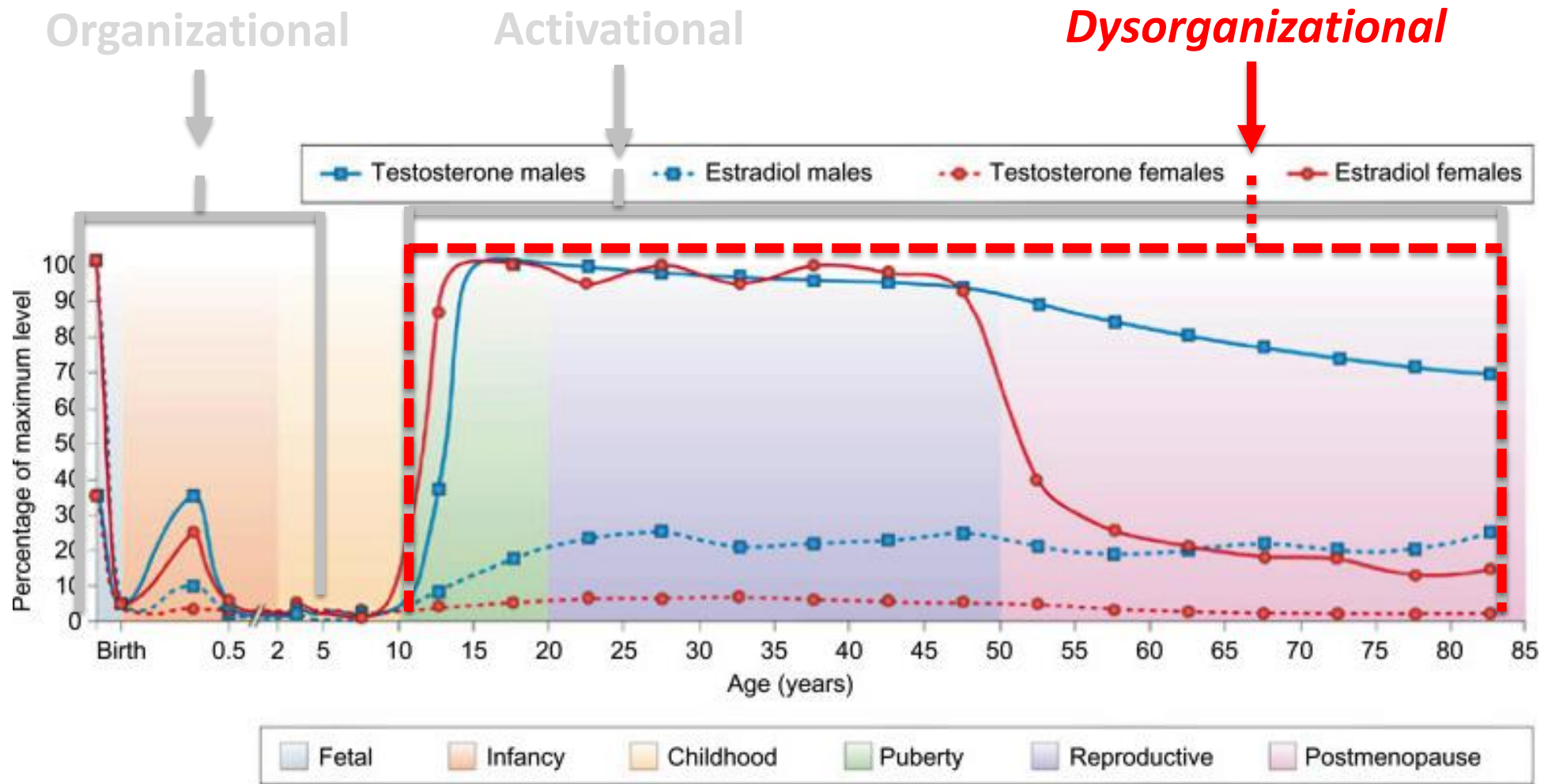
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Organizational

Activational



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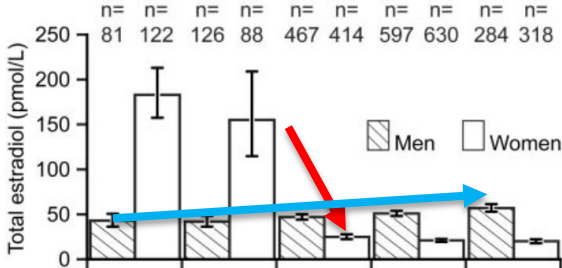
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Examples of the data we need

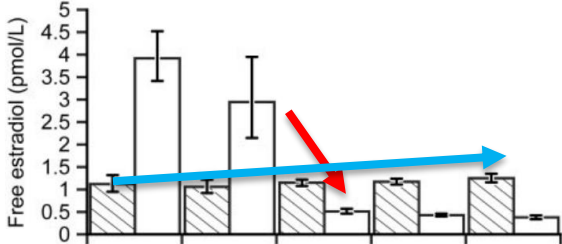
Plasma estradiol declines profoundly in **women** and increases in **men** (at least in Tromso, Norway)

♀ n=1952

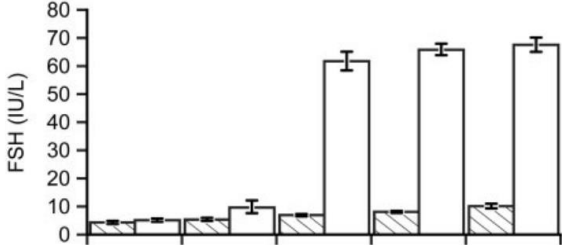
♂ n=1555



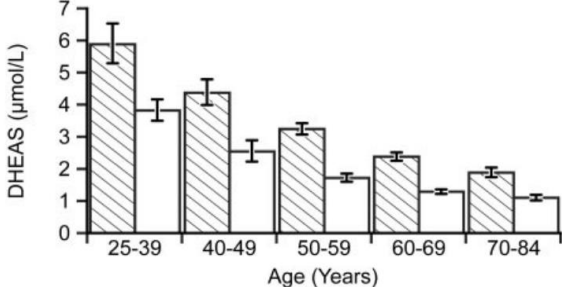
Total Estradiol



Free Estradiol



FSH



DHEAS

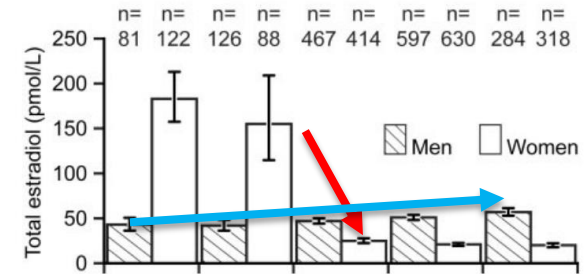
Plasma estradiol declines profoundly in women and increases in men (*at least in Tromso, Norway*)

Knowledge gap:

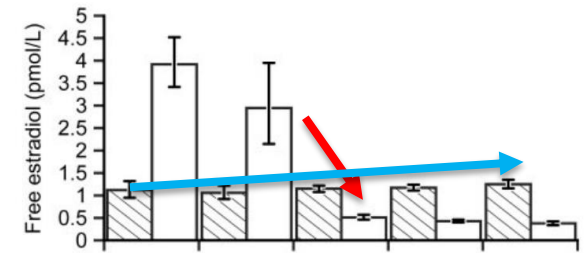
Effects of genetics, race, ethnicity, socioeconomic status?

♀ n=1952

♂ n=1555



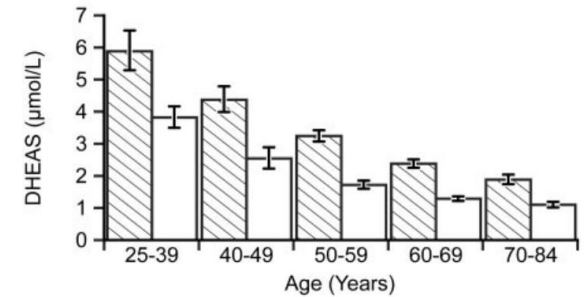
Total Estradiol



Free Estradiol

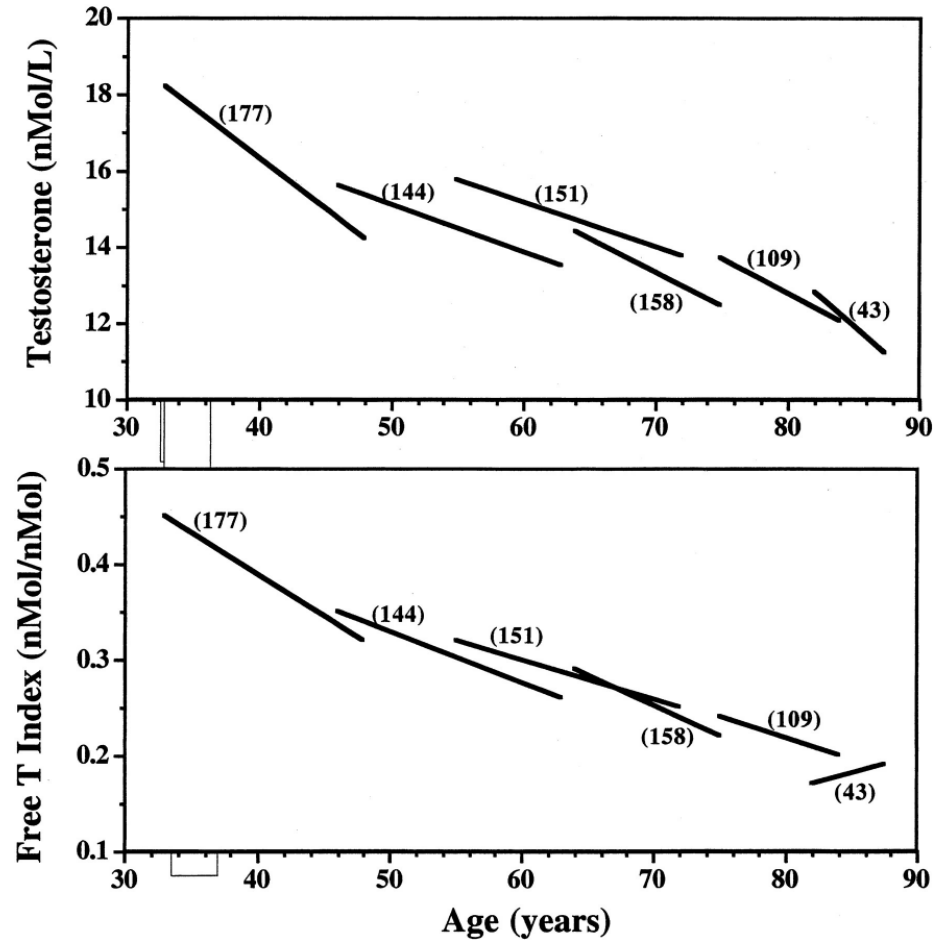


FSH



DHEAS

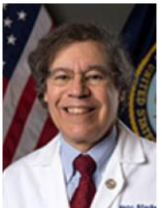
Plasma Testosterone declines progressively with age in largely Caucasian, socioeconomically advantaged males



♂ n=890



S Mitchell Harman, MD, PhD



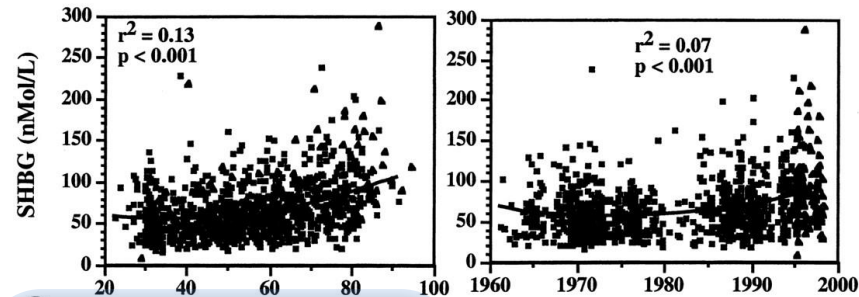
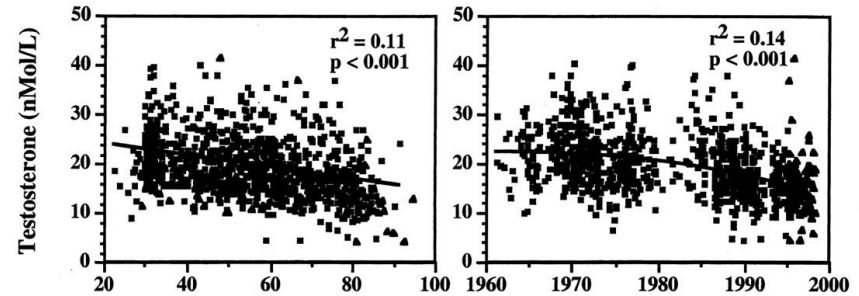
Marc Blackman, MD

Harman, Blackman et al. The Journal of Clinical Endocrinology & Metabolism, Volume 86, Issue 2, 1 February 2001, Pages 724–731, <https://doi.org/10.1210/jcem.86.2.7219>

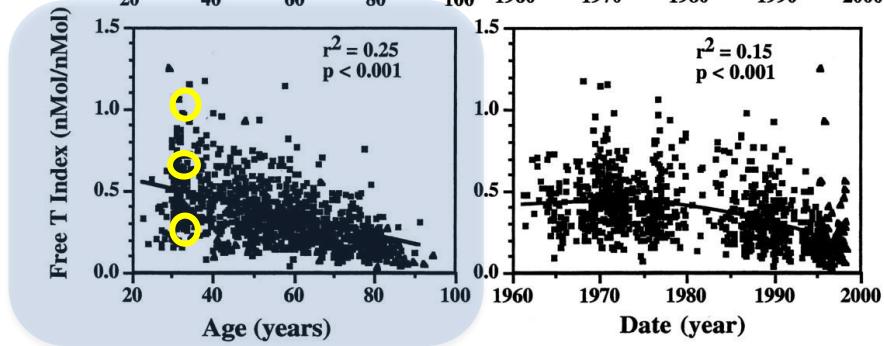
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Profound Individual Variation

Total Testosterone



Free Testosterone



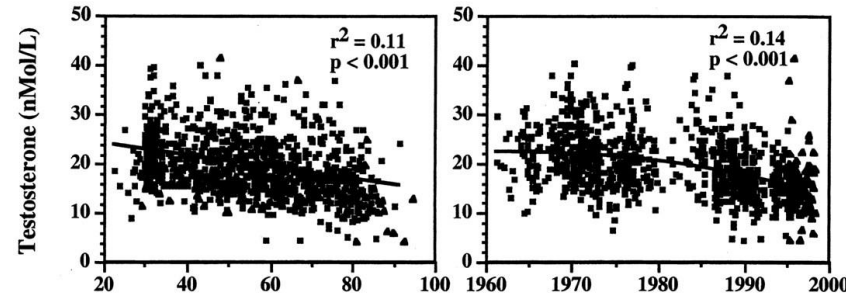
♂ n=890

Harman, Blackman et al. The Journal of Clinical Endocrinology & Metabolism, Volume 86, Issue 2, 1 February 2001, Pages 724–731, <https://doi.org/10.1210/jcem.86.2.7219>

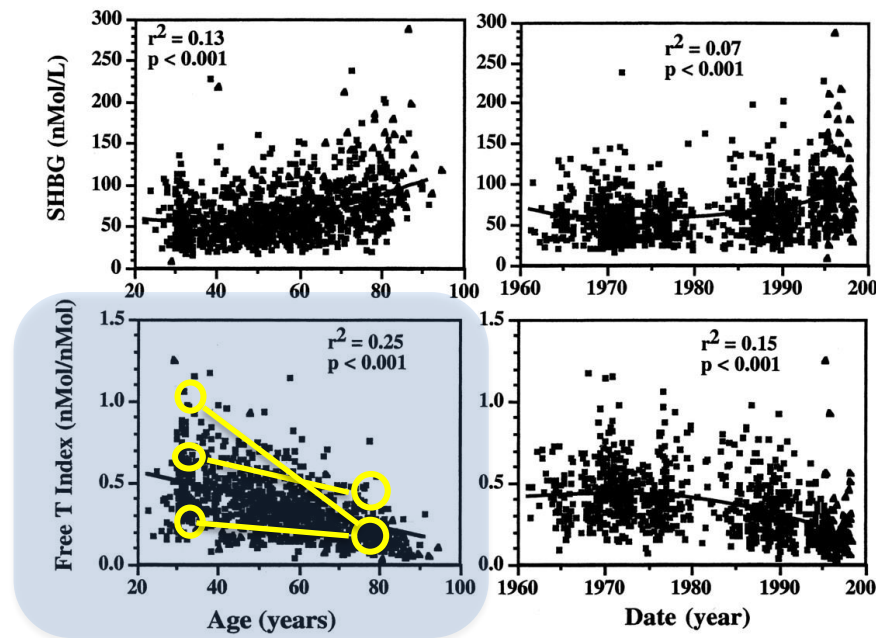
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Profound Individual Variation

Total Testosterone



Free Testosterone



Knowledge Gap:

The basis for and significance of this variation to healthspan and lifespan of this variation.

♂ n=890

Finding a Mouse Model

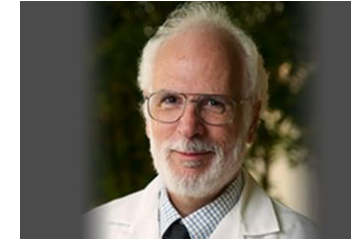
(to probe the role of sex hormones in aging)

Criteria

- genetically heterogeneous
- models human aging demographics
- models reproductive hormonal changes
- statistically powered to probe variation and its implications.

UM-HET3 – genetically heterogeneous 4-way cross

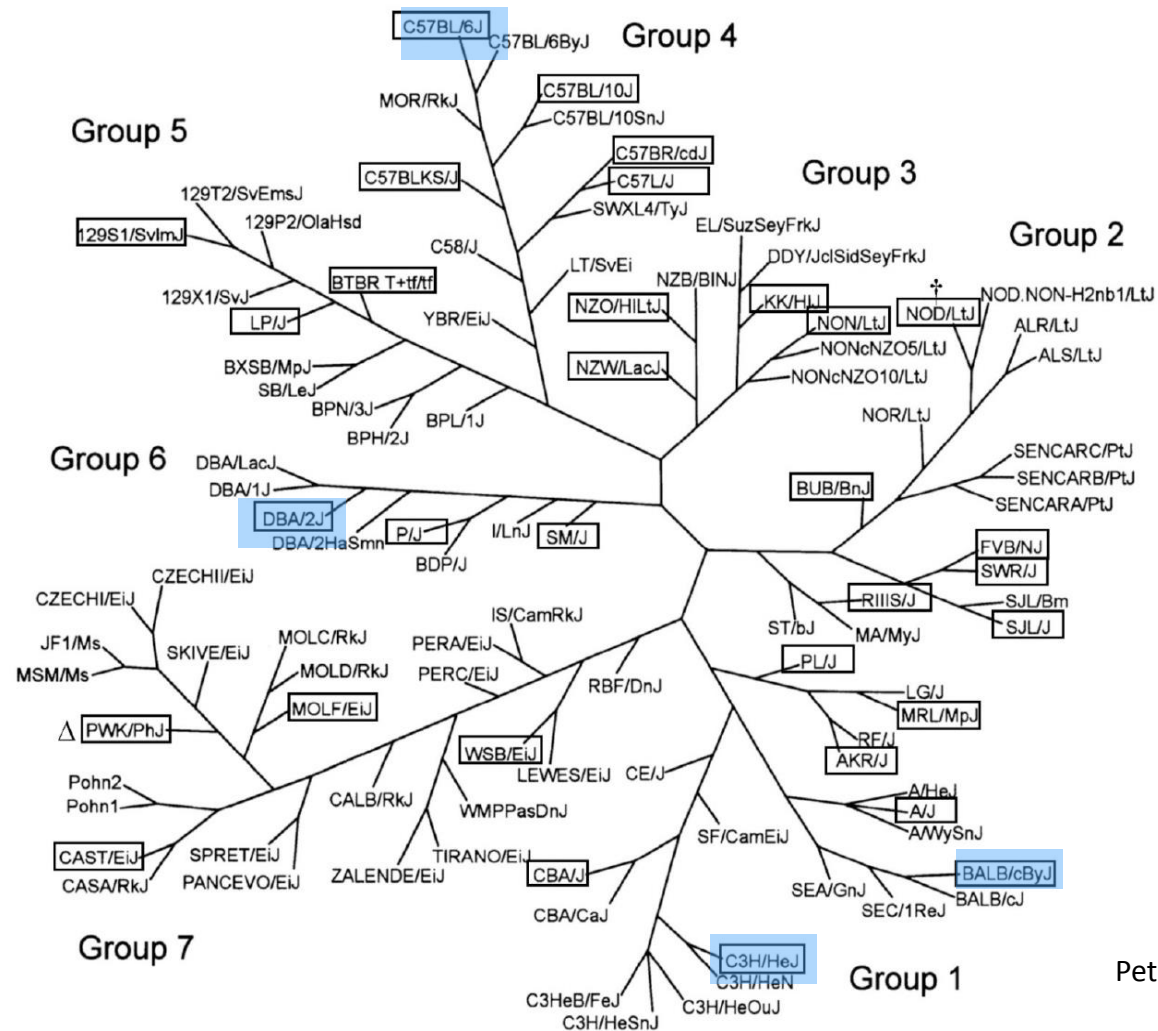
[BALB/cByJ X C57BL/6J] X [C3H/HeJ X DBA/2J]



Richard Miller, MD, PhD



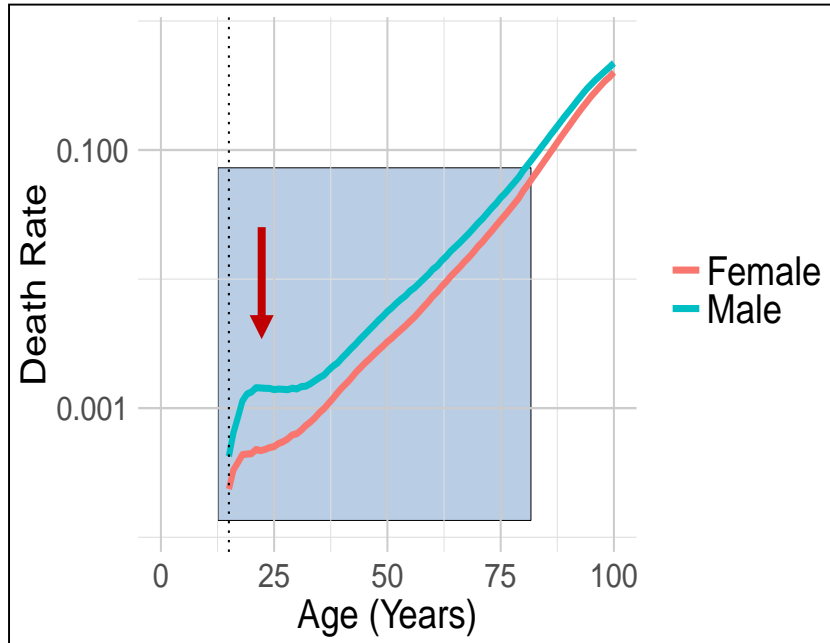
Courtesy R. de Cabo



Petrov et al. 2004

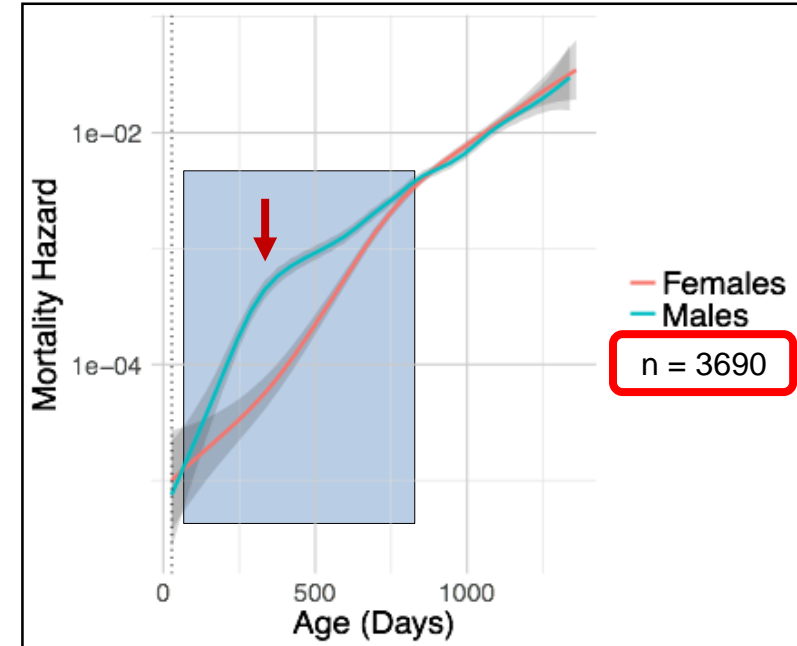
UM-HET3 mice exhibit similar early/midlife male-specific mortality increase as humans

Humans



(HumanMortality Database)

Mice



Cheng, Gelfond, Diaz, Strong, Nelson,
Aging Cell (2019)



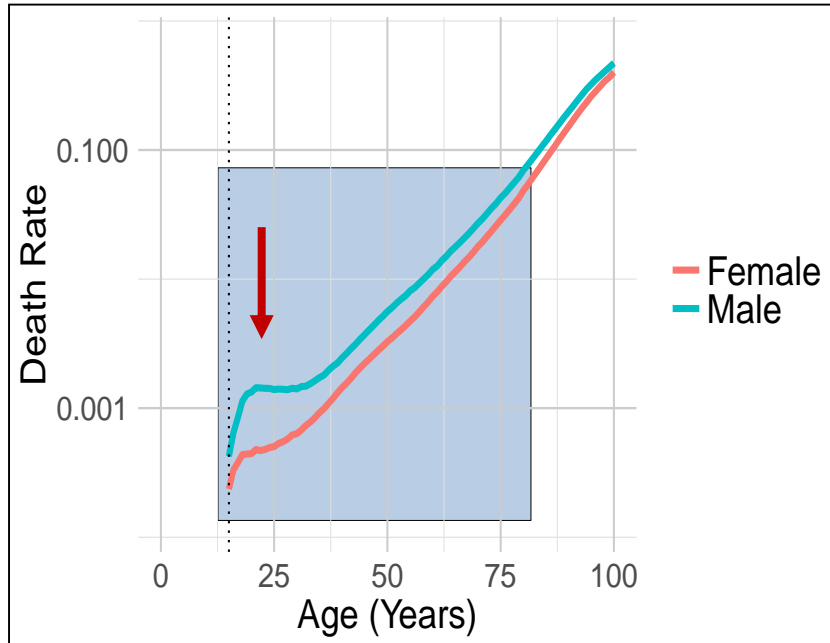
Catherine
Cheng PhD



Jonathan
Gelfond, MD
PhD

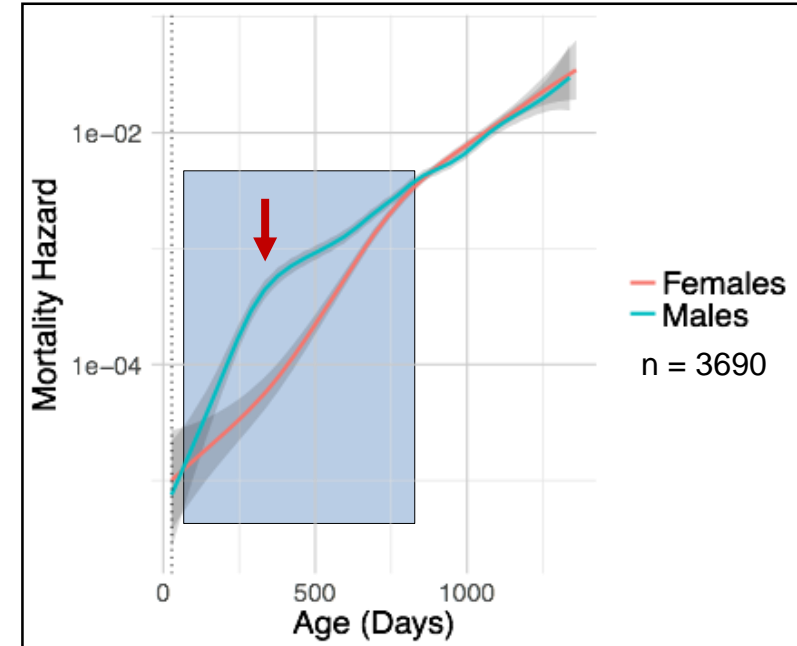
What underlies the increased male mortality hazard in early/mid adulthood?

Humans



(HumanMortality Database)

Mice



Cheng, Gelfond, Diaz, Strong, Nelson,
Aging Cell (2019)

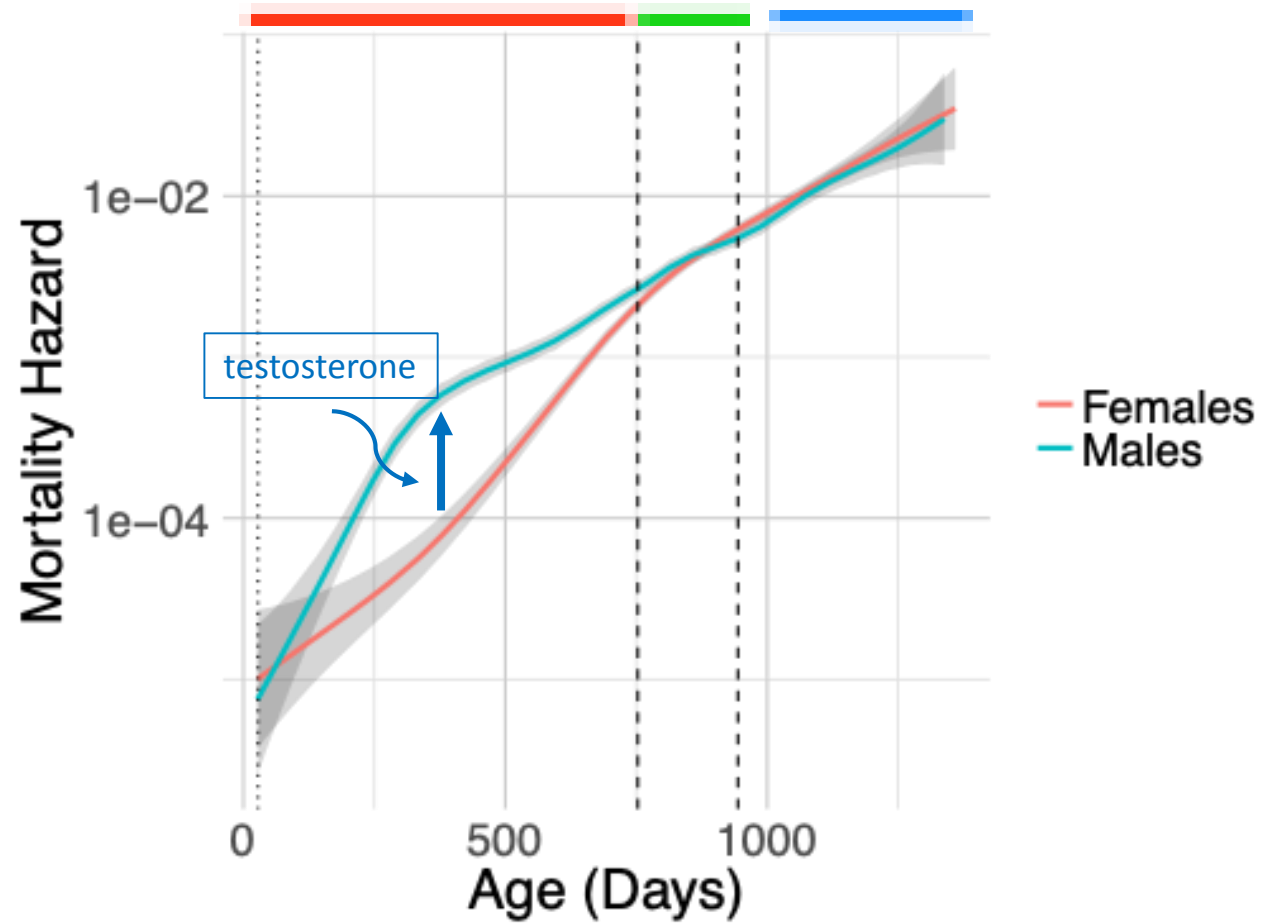


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Cheng PhD



Jonathan
Gelfond, MD
PhD

Hypothesis: Post-pubertal testicular steroids increase male mortality



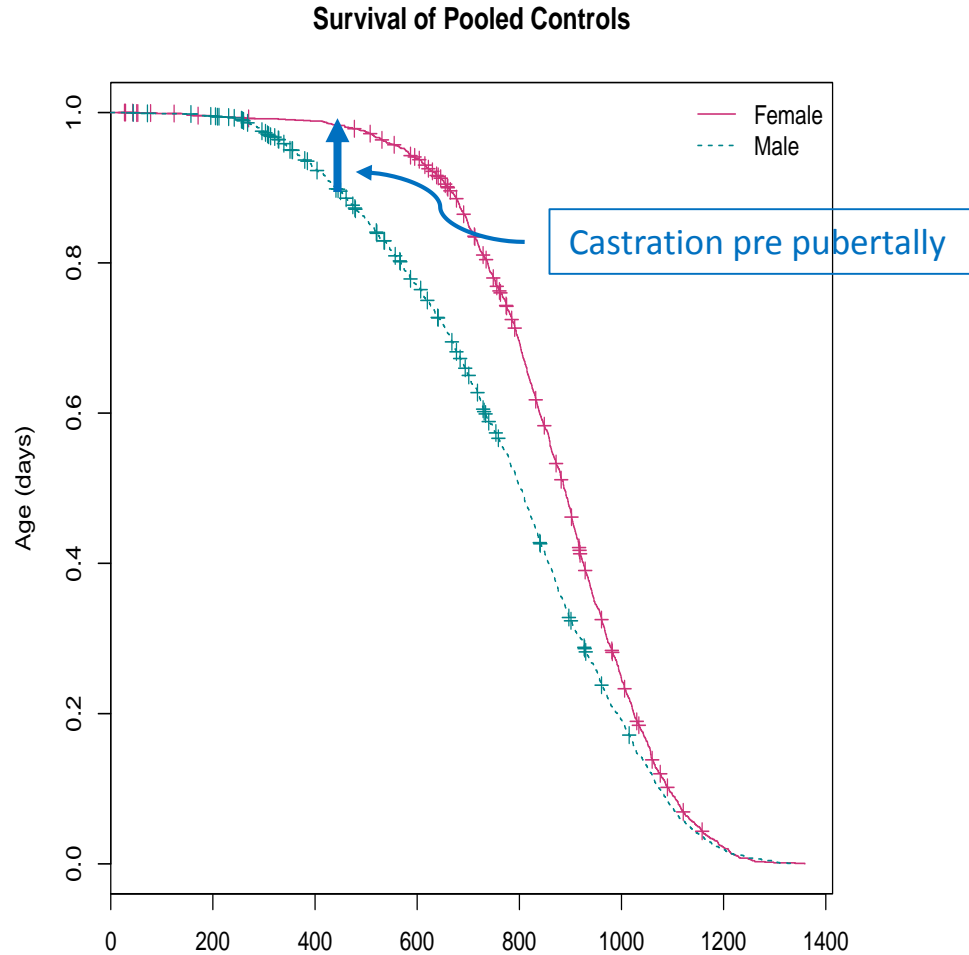
Catherine
Cheng



Jonathan
Gelfond, MD
PhD

Cheng, Nelson, Strong, Gelfond,
(unpublished)

Hypothesis: Pre-pubertal castration will increase male survival



Catherine
Cheng



Jonathan
Gelfond, MD
PhD

Cheng, Nelson, Strong, Gelfond,
(unpublished)

A few, among many, important unanswered questions

1. Mechanisms and tissue targets of androgen-induced excess male mortality.
2. Roles of androgens in age-specific mortality and declining healthspan in late life.
3. Roles of androgens/estrogens during the organizational phase on healthspan and longevity
4. Roles of estrogens (estradiol/estrone/estriol) on healthspan and longevity
5. Genetic, ethnic, racial variation on age-related changes of reproductive hormones
6. Effects of aging on hormone receptor / signaling cascades and target tissue sensitivity to reproductive hormones.
7. Mechanisms of sex differences in the response to life and healthspan lengthening drugs.

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