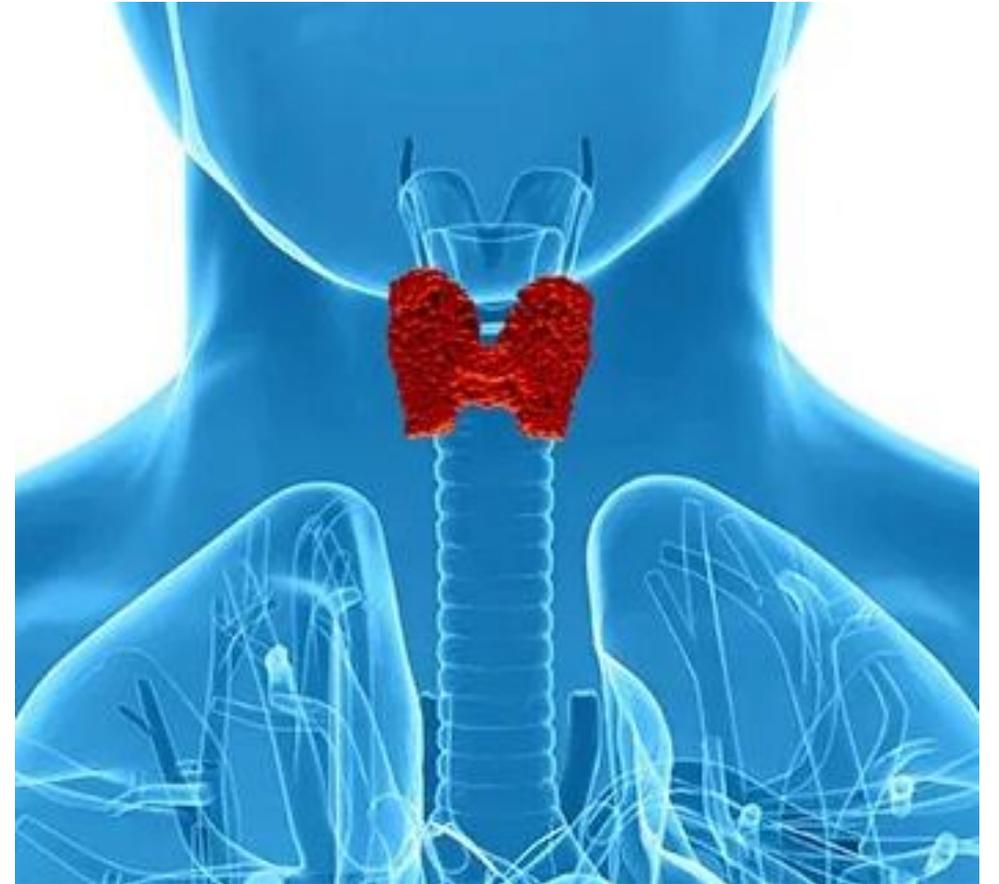# Re-Examining Population Biomarkers of Thyroid Function
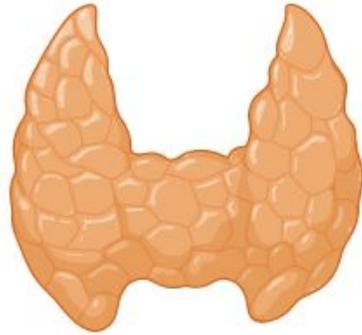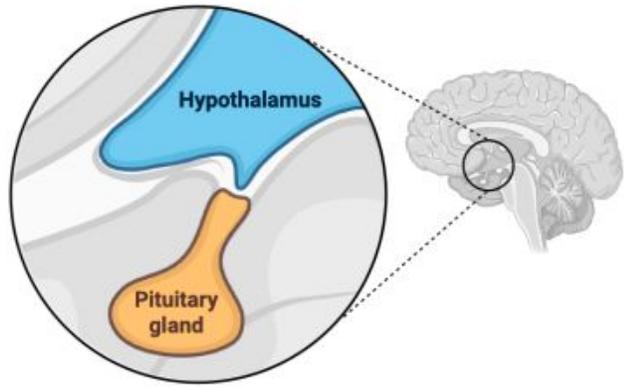
Ralph Lawton, Bernardo Sabatini & Daniel Hochbaum

Biomarker Network Meeting 2023

# Hypothalamic-Pituitary-Thyroid (HPT) axis

- Central regulation of energy expenditure and metabolism.

- Brain development

- Implicated in slowing metabolism with age

TSH ⟶ T4 ⟶ T3

deiodinase

- TSH is the primary clinical biomarker
- T4 to a lesser extent
- T3 is active hormone, mostly generated peripherally from T4
  - Deiodinases

- Body defends a T3 "set point"

# Consequences of HPT-dysregulation

- Clinically:
  - Hypo : weight gain, <u>lethargy</u>, depression, cog deficits
  - Hyper: weight loss, <u>agitation</u>, sleep-disruption, mania, psychosis

  - Sub-clinical hypo- : very common, poorly understood, "mismatch"

- Very little attention on normal HPT-axis variation

# Consequences of HPT-dysregulation

- Minimal (if any) population-level work on HPT axis.

- Implicated in metabolic syndrome and psychiatric disease

- Important links to brain function among adults, including dementia and risk-taking behavior


- Non-clinical hypothyroidism (mismatch in thyroid supply/demand) common but poorly surveilled. Clinical debate on tx.
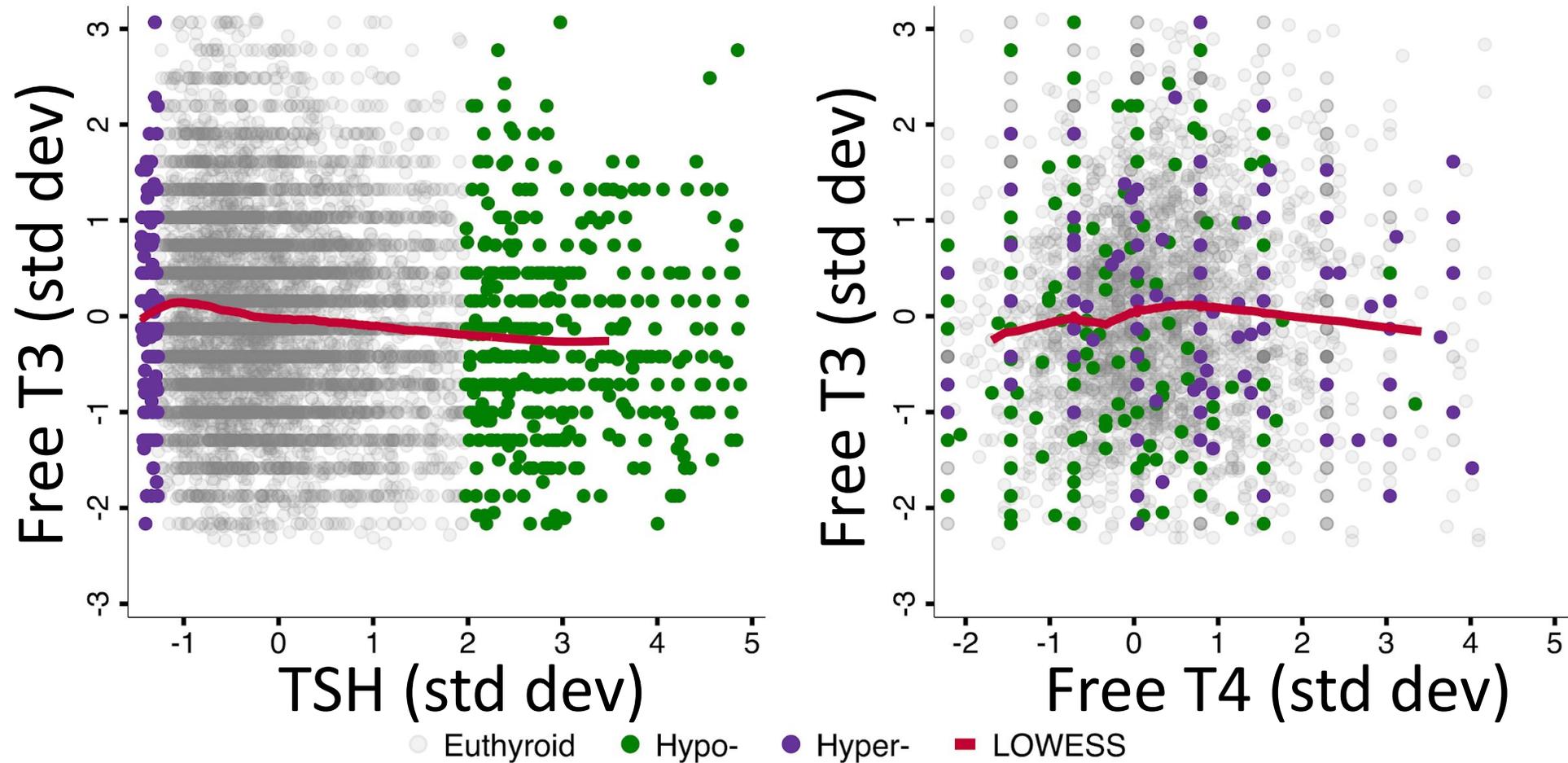
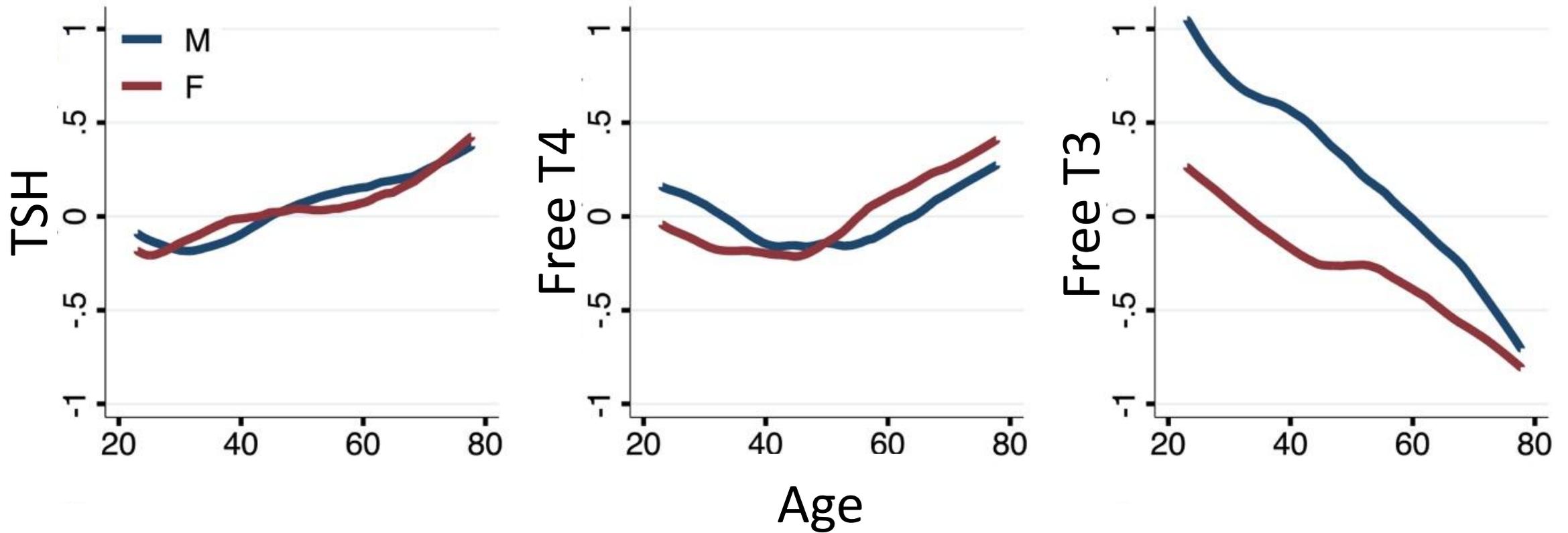# Data    National Health and Nutrition Examination Survey

- NHANES – 2007-2012
- ~8,000 adults 20+.
- Drop top + bottom 1% of T3/T4/TSH

- Results robust to controls for demographics, health behavior, diet, iodine, med use.

# The HPT-axis hormones are not tightly related



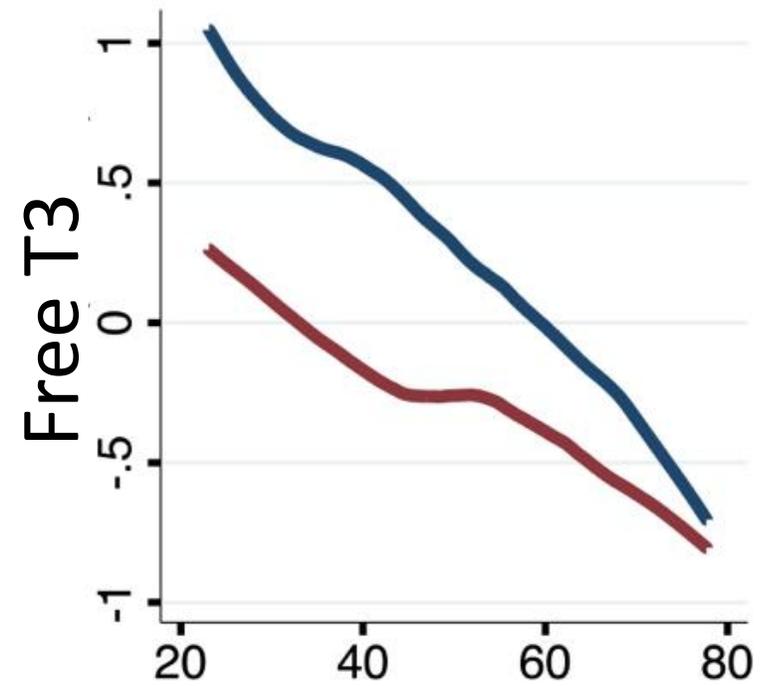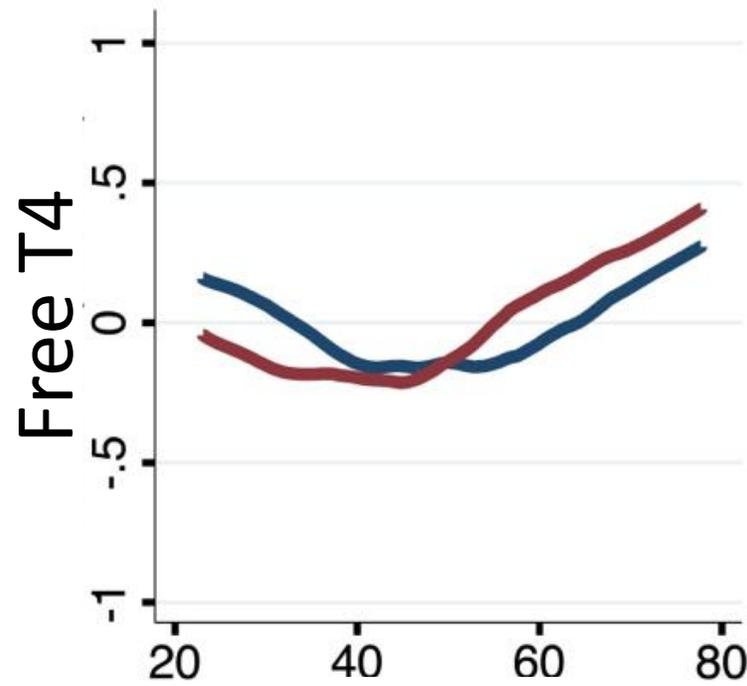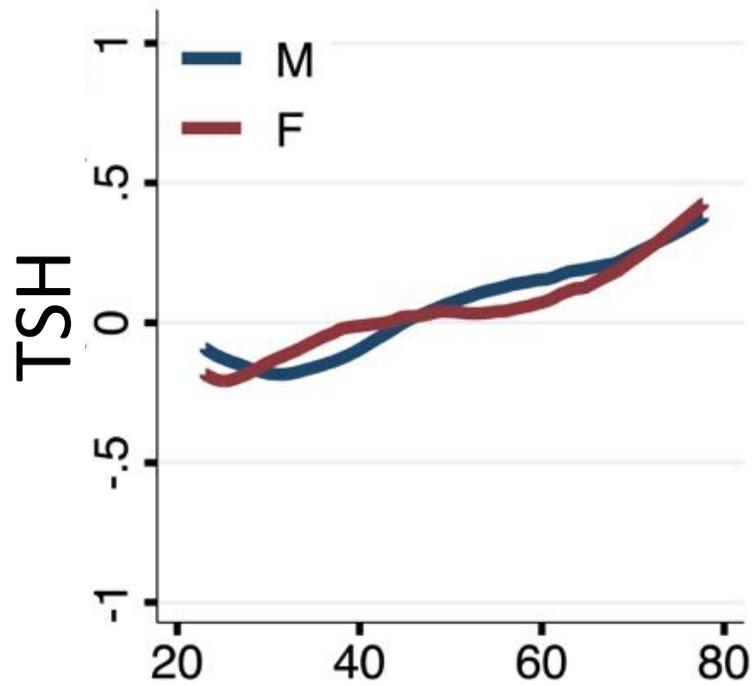Euthyroid   Hypo-   Hyper-   LOWESS

$R^2 < 0.01$

# Age relationships vary dramatically by hormone of choice



Clinical Hypo: High TSH, Low T4
Clinical Hyper: Low TSH

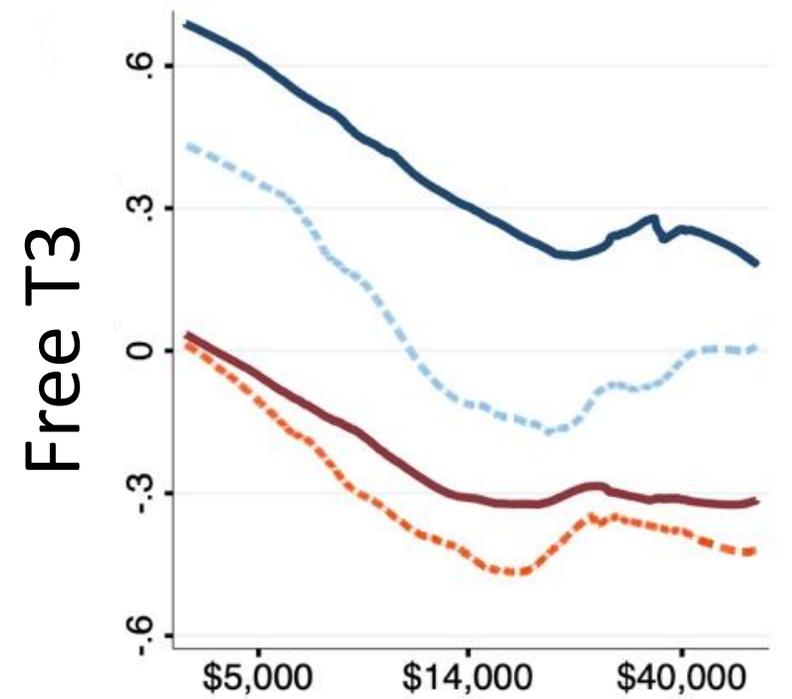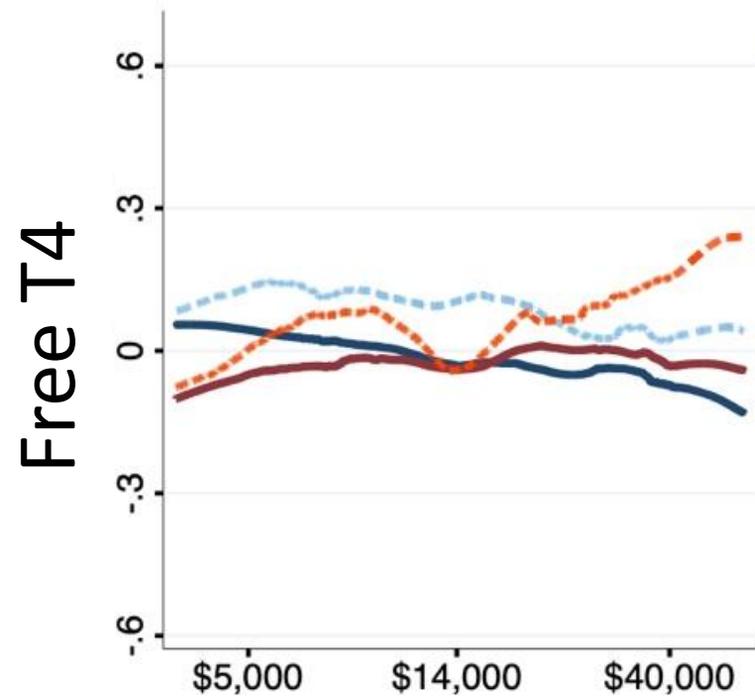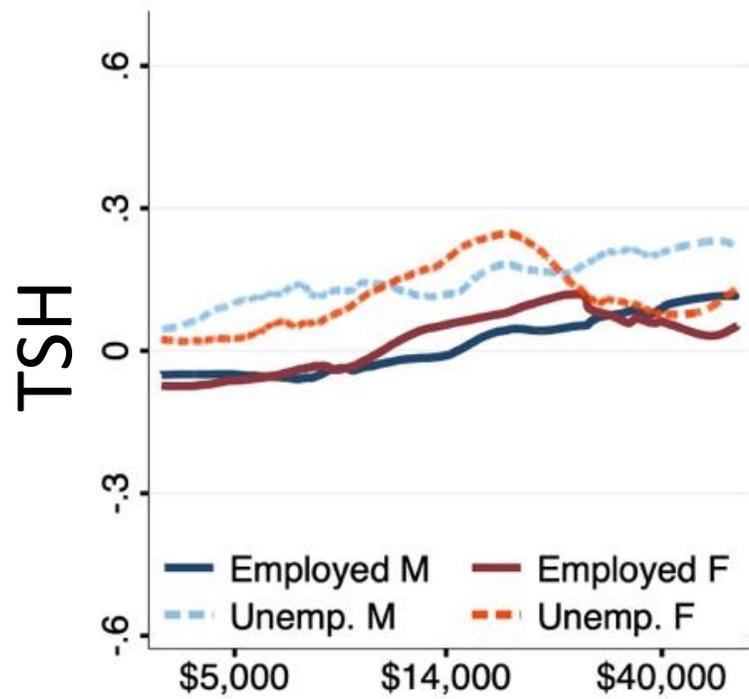# Much tighter relationships between T3 and demographics.



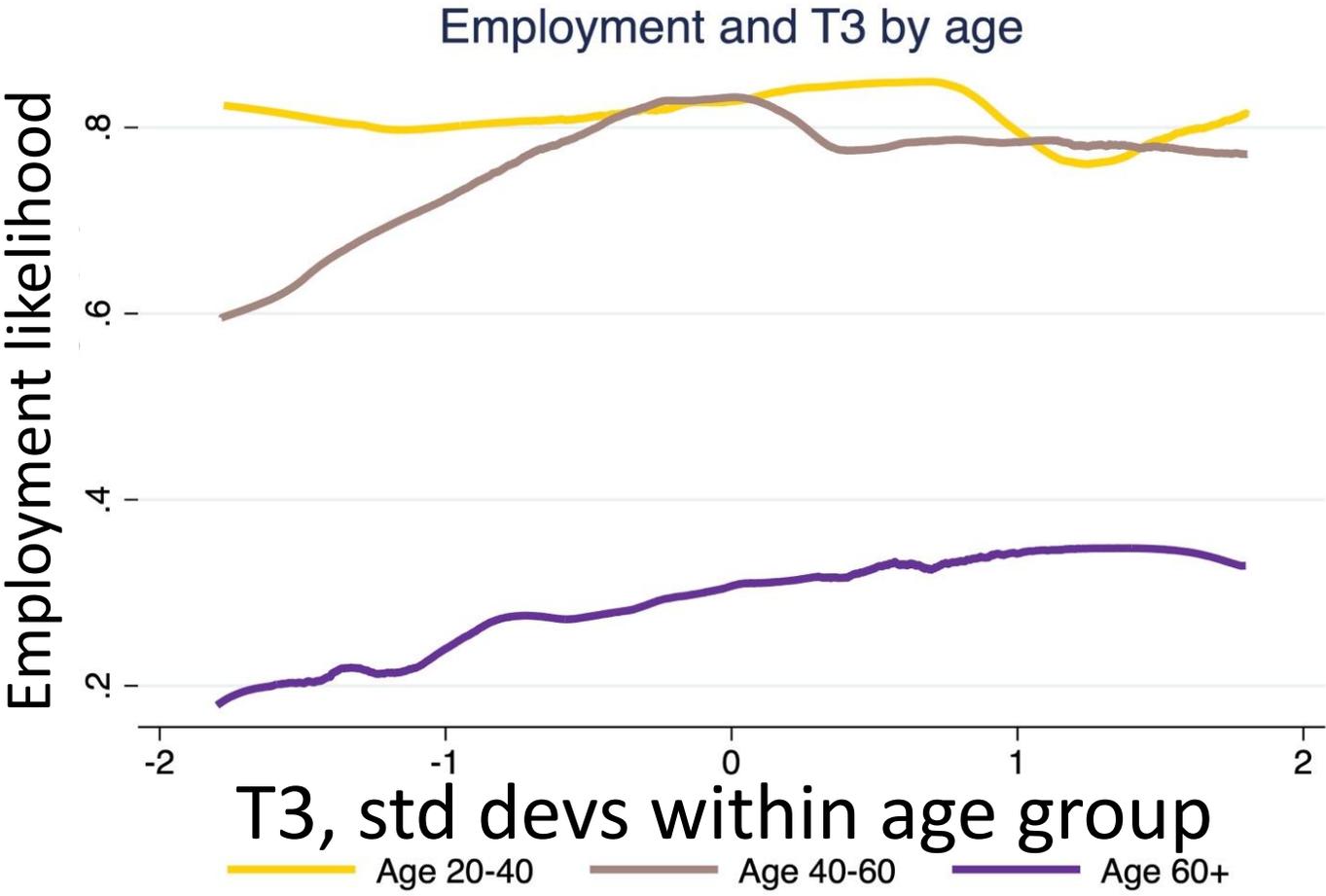| R²: | 0.058 | 0.045 | <u>0.241</u> |

Gender + Seasonality only observed in T3

# Household resources only linked to T3



Kink at $22k/year

# T3 predicts labor force participation in mid/older ages



Employment and T3 by age

# Mortality stratified sharpest (and inverse) by T3/T4
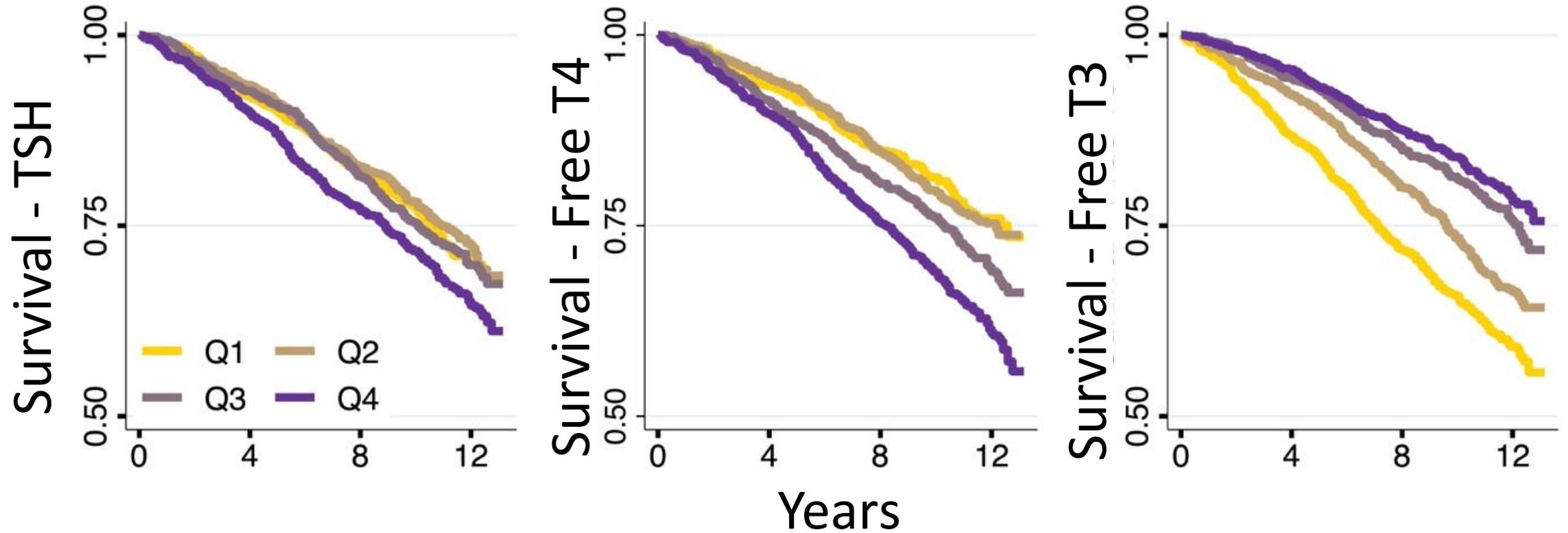


- Coefs similar in magnitude to cardiovascular biomarkers and A1C
- Reconciles conflicting mortality RCT results

# Conclusions

- In general pop, thyroid biomarkers not tightly linked.

- Strongest links between classic (and less classic) HPT-domains and T3.

- First evidence of socioeconomic relationships with HPT-axis.

- Deiodinases strongly implicated.