



**FACULTY: To receive CME credit
please scan this QR Code and use
your WUSTL Key to sign in**

**LGM Grand Rounds
August 17, 2023**



Credit Available For This Activity

In support of improving patient care, Washington University School of Medicine in St. Louis is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

American Medical Association (AMA) Washington University School of Medicine in St. Louis designates this live activity for a maximum of 1 AMA PRA Category 1 Credits™.

All disclosures are valid for one year from the Last Confirmed date. If older than one year from the date of the talk, the disclosure must be updated.

Any relationship shown below in italics has been divested within the last 24 months and is therefore considered mitigated. All relevant financial relationships have been mitigated.

Disclosures: None

Course Chair: **Neil Anderson, MD:** Speakers Bureau/Honoraria: Alere, Biomerieux; Consulting/Advisory Committee: Diasorin Molecular

Planning Committee: **Rachel Bosselman, PhD:** Nothing to disclose

Session Speaker: **Christopher Snyder, MD, PhD**

On Preclinical Variation and TSH Interpretation

Christopher Snyder, MD, PhD

Division of Laboratory and Genomic Medicine
Department of Pathology & Immunology

August 17, 2023



Washington University in St. Louis
SCHOOL OF MEDICINE

Disclosures

I have no relevant or financial disclosures.

Learning Objectives

By the end of this session, the learner should be able to:

1. Describe the biology, measurement, and interpretation of TSH.
2. Evaluate literature on sources of healthy TSH variation.
3. Study reference interval constructions and limitations.
4. Cover feasibility of a “big data” approach.

A wide-angle photograph of a paved road curving through a rural landscape under a dramatic, cloudy sky. In the distance, a row of wind turbines stands on a hill. The road has white dashed lines and ends at a large, stylized, semi-transparent watermark.

READY

Dr. El-Khoury



Clinical Chemistry 69:5
537–538 (2023)

**Seasonal Variation and
Thyroid Function Testing:
Source of Misdiagnosis
and Levothyroxine
Over-Prescription**

To the Editor:

"War on Error" Talk
Clin Chem Letter
Seasonal TSH

**"Seasonal Variation may lead to...
false diagnosis of subclinical hypothyroidism
and unnecessary prescriptions."**

Dr. El-Khoury



Clinical Chemistry 69:5
537–538 (2023)

Seasonal Variation and Thyroid Function Testing: Source of Misdiagnosis and Levothyroxine Over-Prescription

To the Editor:

"War on Error" Talk
Clin Chem Letter
Seasonal TSH

"Seasonal Variation may lead to...
false diagnosis of subclinical hypothyroidism
and unnecessary prescriptions."

Therapeutic intervals

- Outcome-based cutoffs
- Better answers the question for which a physician orders the labs
- Answers the question, "Should I treat?"

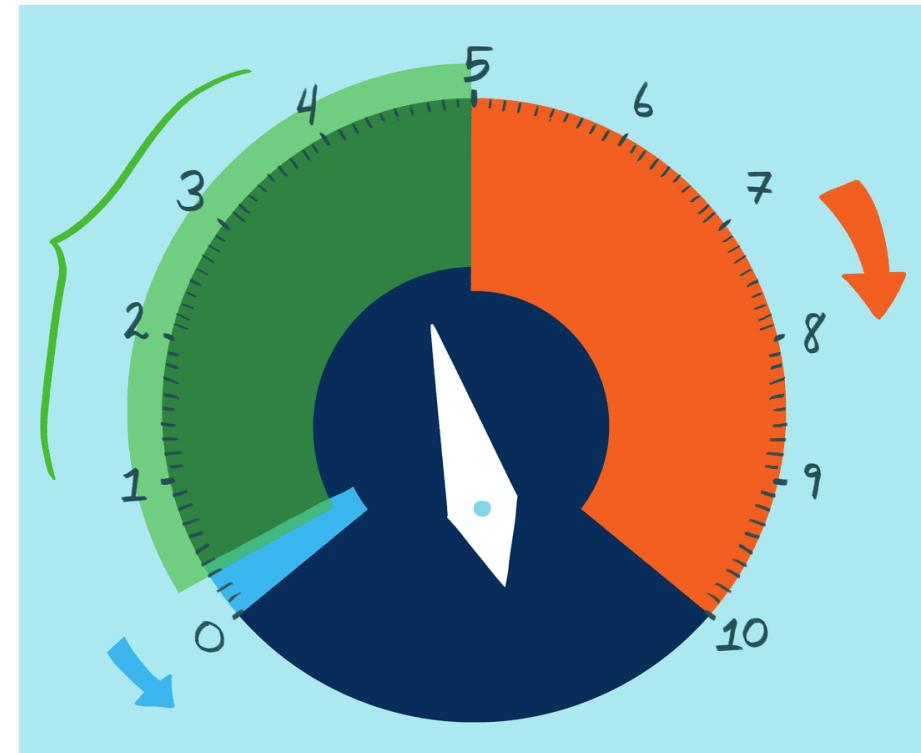
Subclinical Hypothyroidism (briefly)

Defined by

1. Slightly elevated TSH concentration
2. Normal T4

Treated with

1. T4 replacement



Cartoon of TSH. Normal Range (Green)

The Decision Limits for Treatment

- Agreement on Extremes
 - Clear guidance only for $\text{TSH} > 10 \text{ mIU/L}$, ¹
 - No treatment within "normal" ($0.3 - 4.2 \text{ mIU/L}$)
- Controversy in Between
 - "No benefit" of treatment unless TSH exceeds $7 - 10 \text{ mIU/L}$, ²
 - Controversial recommendation to lower the upper limit to 2.5 mIU/L , ³
 - Reference range adjusts over time with assay sensitivity

¹ AACE and ATA Guidelines; 2012

² Ross, "Treating Hypothyroidism Is Not Always Easy".

³ NACB Laboratory Medicine Practice Guidelines (LMPG) - *Laboratory Support of the Diagnosis and Monitoring of Thyroid Disease: PDF Documents*, NACB, 2002.

Are We Overtreating?

- 30% increase in Synthroid prescriptions over the past decade.⁴
- TSH level for initiation steadily decreasing: "between TSH values of 5 – 9^{mIU/L} for 61% of new Synthroid prescriptions.⁵"
- "the vast majority of patients initiated on Synthroid had only mild TSH elevations. . . and resulted in no improvement in health-related quality of life over time"⁴

⁴Rodriguez-Gutierrez et al., "Levothyroxine Overuse", (OptimLabs, systematic review).

⁵Ross, "Treating Hypothyroidism Is Not Always Easy".

How Big is the Impact?

Volume

- Treatment – Synthroid is one of the Top 3 prescriptions in the USA.
- 5%-10% disease prevalence by USA epidemiology studies.
- Testing – \$60,000 annually at BJC.

Responsibility

- Clinician relies on Pathologist for establishing significance.

Gravity

- Wrong choices increase mortality.
- Pan–organ morbidity.

An Endocrinologist's Perspective

- **Dr. Reik:**

- Thinks at BJH that most use high threshold for treatment
- This would avoid the risk of seasonal over-prescription

**our climate has not been studied*

**there are risks of under-prescription*

- **She also mentioned:**

- The more egregious misapplication of the reference interval is to assess thyroid function in a sick inpatient



**NACB, 2003: context dependent reference intervals:
twice the upper cut-off for inpatients*



Proposal:

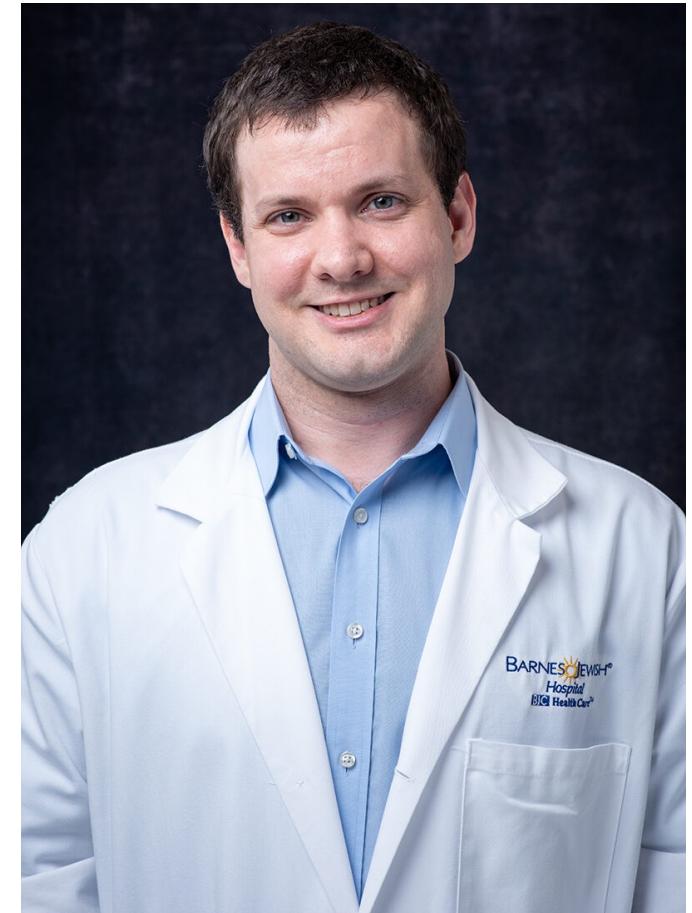
Seasonal intervals that ...

model “context-dependent significance”

correctly predict lab values 95% of the time

are called “Null Intervals”

do not replace reference intervals



TSH Biology

Afferent signals project to the  from higher brain centers.

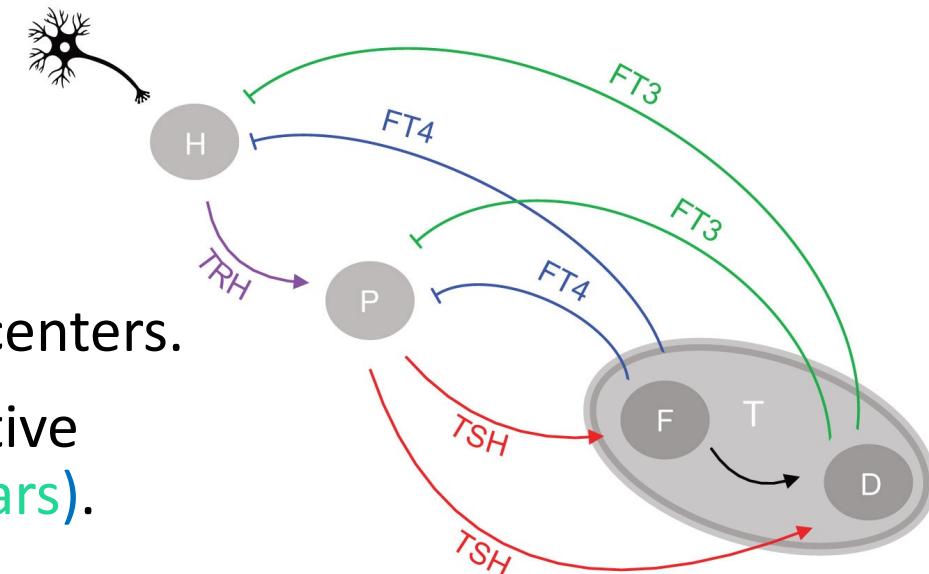
Communicate through an interactive network of positive feedforward (**arrows**) and negative feedback loops (**bars**).

Involving as signals the respective hormones produced and released by each gland into the circulation,

namely **TRH** by the  ,

TSH by the  ,

T4 and **T3** by the  .



Hoermann, R. Principles of Endocrine Regulation (2022).

TSH Measurement

Sandwich Assay

1. TSH-specific monoclonal antibody (mAB)

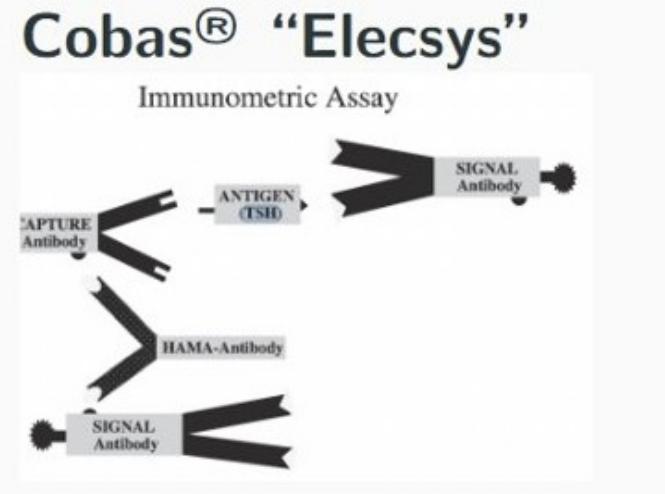
- Biotinylated
- Ruthenium Labeled

2. Magnetic Capture

- Streptavidin-coated microparticles

3. Voltage induced chemiluminescent

- Antibodies labeled with ruthenium



Caveats?

- No HAMA (chimeric AB)
- No hook
- No HIL
- Yes: macro-TSH due to auto-AB
 - (unexpectedly *high* result)

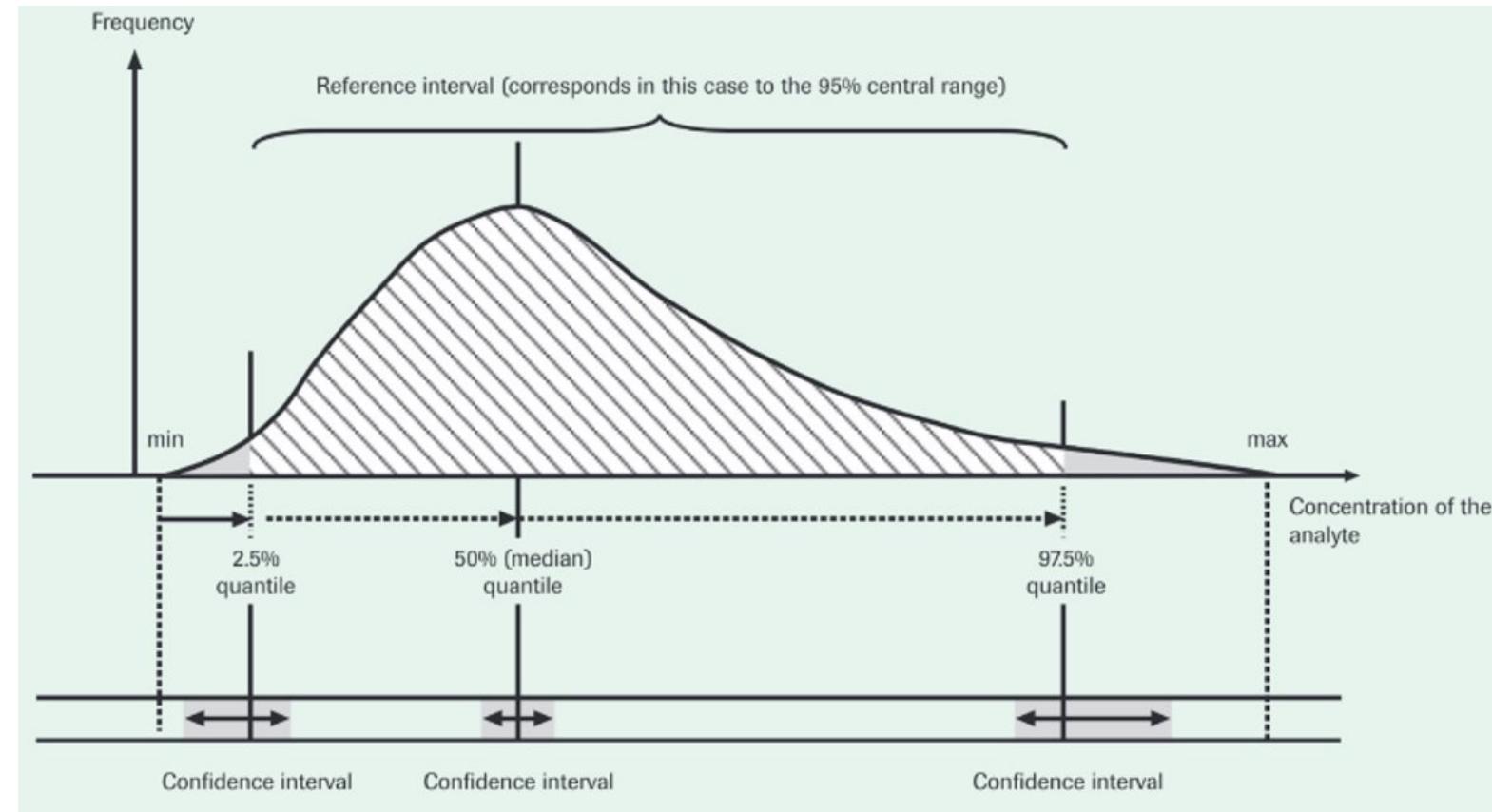
The Reference Range

Reference Population ("Healthy Controls")

Random sample from population of healthy individuals

Reference Range (Reference Interval)

Quantiles estimated from samples



Establishing Reference Intervals

Use healthy volunteers for "normal" (direct method).

CLSI: Specific Guidelines

- 120 person recommendation
- 2.5%, 97.5% Percentiles *estimated*
 - “non-parametrically” (usually empirically)

TSH: Reference Values (BJH Catalog)

Age	Reference Interval
0 minutes - 4 days	1.00 - 25.00 mU/L
4 days - 30 days	0.50 - 10.00 mU/L
30 days - 150 years	0.30 - 4.20 mU/L

Many choose to verify manufacturer interval

Seasonal Variation in Thyroid Function in Over 7,000 Healthy Subjects in an Iodine-sufficient Area and Literature Review

Sayaka Yamada,^{1, ID} Kazuhiko Horiguchi,¹ Masako Akuzawa,² Koji Sakamaki,² Yohnosuke Shimomura,² Isao Kobayashi,² Yoshitaka Andou,² and Masanobu Yamada^{1, ID}

Background

- Existing literature suggests seasonality but is conflicting
- Previous studies lacked stringent, healthy controls

Study Design

- Cross-sectional, annual check-up
- Gunma Prefecture, Japan
- 12 month period

Dr. El-Khoury referenced paper on TSH Seasonality



Yamada, S. et al. *J Endocr Soc.* 2022 PMID: 35528829

Study Design

Exclusion Criteria (Questionnaire)

- Overt or historical thyroid disease
- Liver cirrhosis
- Renal failure
- Relevant medications, illness, steroid hormones

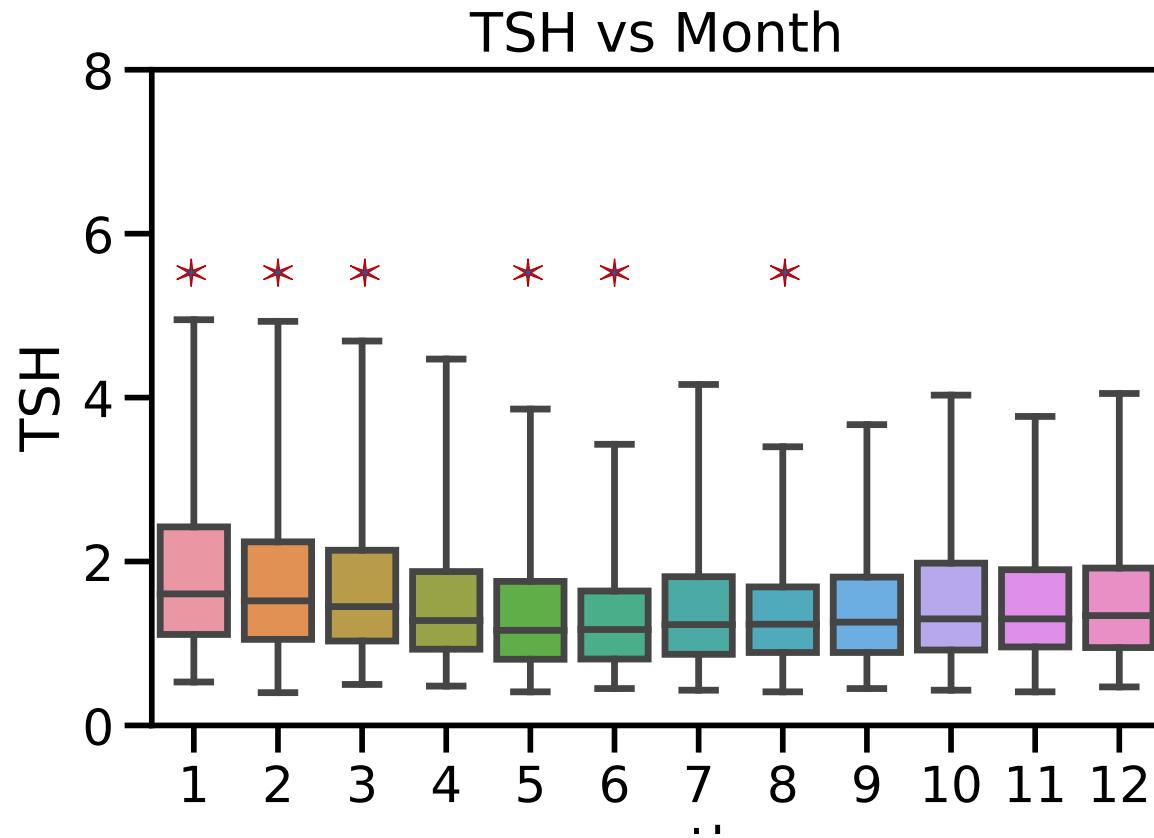
Methodology

- Collect TSH, FT3, FT4
- Blood samples collected 8:00 to 9:00 am (to exclude diurnal variation)
- All subjects had fasted 11 hours

Population

- 6,343 (3,667 men) age 53.8 ± 11 years

Yamada et al, Data



Yamada et all. 2022. Figure 1. Replotted.

Month	Positive by RI n(%)
January	17 (2.71)
February	17 (2.61)
March	12 (2.17)
April	5 (1.31)
May	3 (1.21)
June	4 (1.08)
July	7 (1.55)
August	6 (1.02)
September	3 (0.54)
October	4 (0.66)
November	7 (1.22)
December	5 (0.68)
All	90 (1.42)

Table 2. Replotted.

Findings

Implications

- Demonstrated TSH: High in winter and Low in summer.
- Linked seasonality to subclinical diagnoses (by manufacturer limit)
- Identified source of TSH variation not captured by our reference intervals
- May lead to false diagnoses & unnecessary prescriptions

Limitations

- Scope limited to single year
- (Is the effect Stationary year-to-year?)
- Controlled for many relevant effect modulating variables
- Generalizability – more next slide

Limits on Direct Comparison

- Demographic was 95% Japanese
 - Diet, Cultural (AC?), certain enzyme polymorphisms
- Effect in each geographic region unique
 - Sunlight, humidity, temperature, pO₂
 - The "Rainy Season"
 - Spring to summer transition
 - Excessive rain, less sunshine
 - Decouples sunlight and temperature correlation

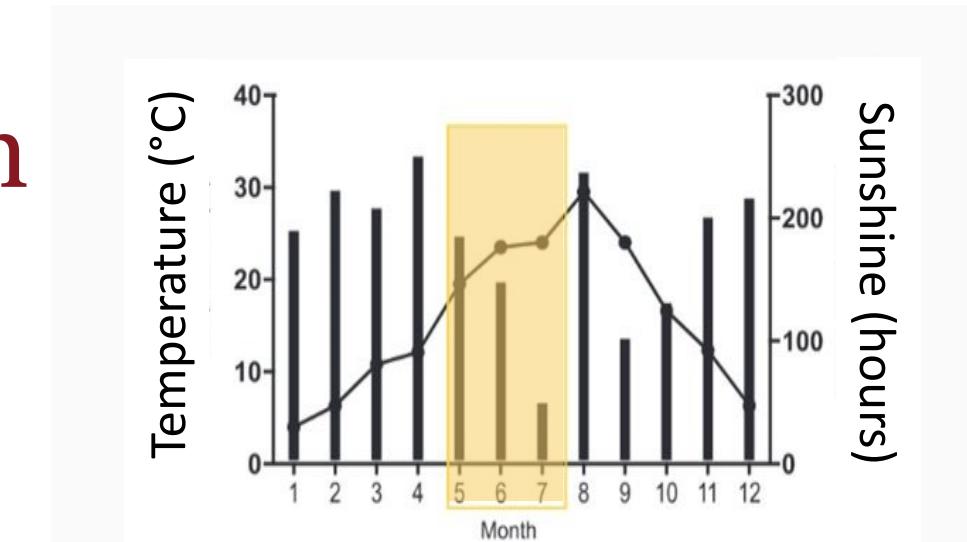
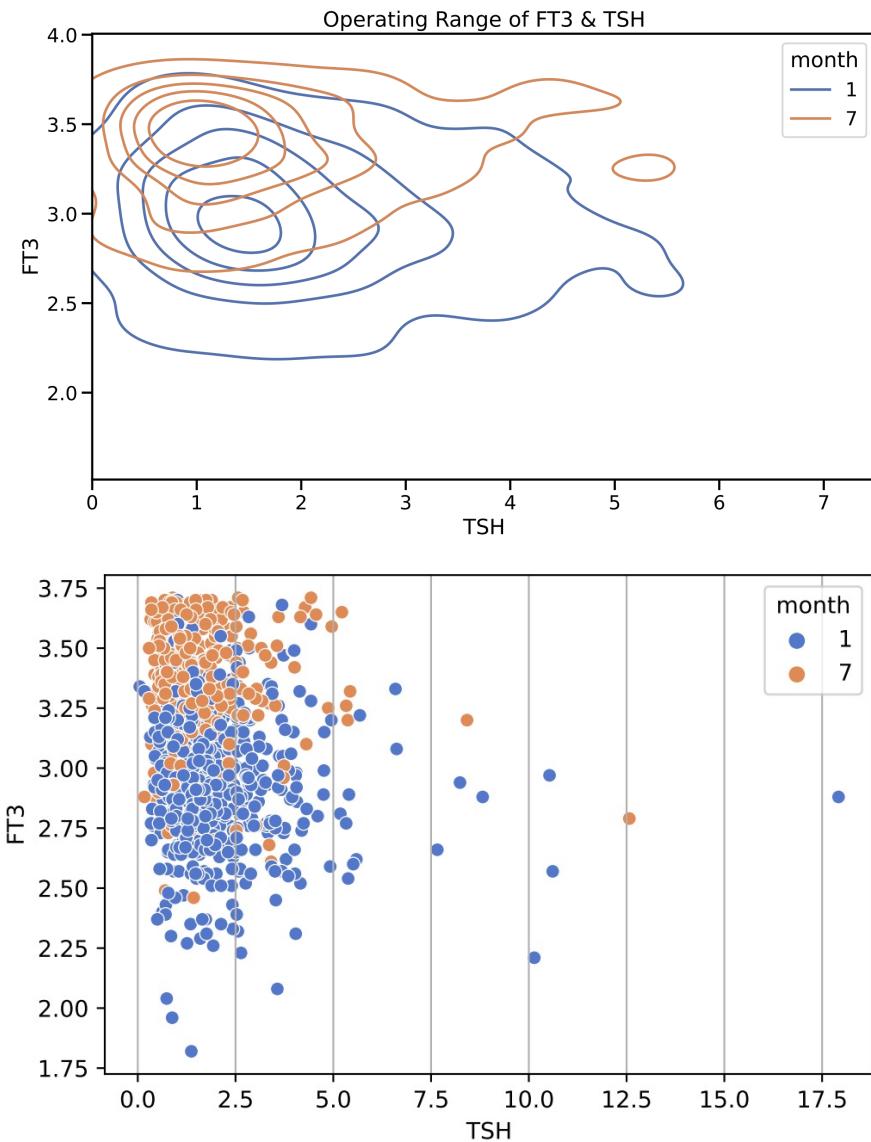
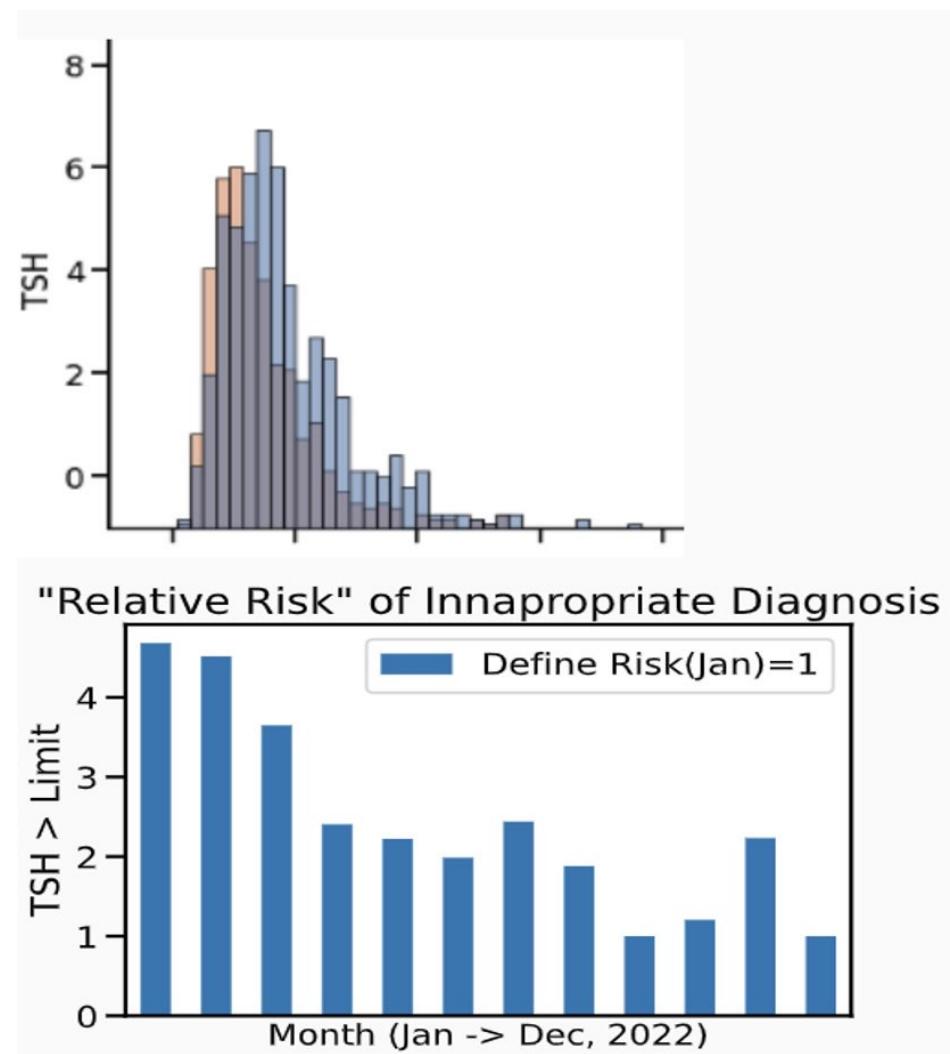


Figure 3: Yellow Rectangle encloses the Temperature vs Sunlight correlation

Temperature was negatively correlated with the serum TSH throughout the year except for July.^a

^aYamada, S. et al. *J Endocr Soc.* 2022 PMID: 35528829

Yamada et al: A Closer Look at the Data



Roche, 2003: TSH (Adult) R.I.

Who?

- 870 Adults, aged 20-69

Where?

- Leipzig, Germany

When?

- 4 month period
(May to August 2003)

TSH: Reference Values (BJH Catalog)

Age	Reference Interval
0 minutes - 4 days	1.00 - 25.00 mIU/mL
4 days - 30 days	0.50 - 10.00 mIU/mL
30 days - 150 years	0.30 - 4.20 mIU/mL

Seasonal variations in levels of human thyroid-stimulating hormone and thyroid hormones: a meta-analysis

N. V. Kuzmenko ^{a,b}, V. A. Tsyrlin ^a, M. G. Pliss ^{a,b}, and M. M. Galagudza ^a

^aDepartment for Experimental Physiology and Pharmacology, Almazov National Medical Research Centre, St. Petersburg, Russia; ^bLaboratory of Byophysics of Blood Circulation, First Pavlov State Medical University of St. Petersburg, St. Petersburg, Russia

Aims:

- To investigate the seasonal dynamics of circulating TSH
- in the published reports

Study Design:

- Meta-analysis: studies (as of 2020) w/ euthyroid adults
- Excluded extreme climates, time-of-day not recorded
- 1051 → n=20 studies (primarily cross-sectional)
- Meteorological data

Kuzmenko, N.V. et al. *Chron Int.* 2021. PMID: 33535823

Table 2. Characteristics of studies.

Publication	IF	Design	Sex, male (%)	Age	Blood sampling		Number of persons in group			
					Time	Fasting	Winter	Spring	Summer	Autumn
Arjumand et al. (2016)	0.2	P	27*	19–73**	-	+	115	-	115	-
Barchetta et al. (2015)	2.4	CS	42	18–65	Morning	+	76	71	71	76
Behall et al. (1984)	7	P	45	20–53	Morning	+	29	29	29	29
Gullo et al. (2017) (1)	3.2	P	17	37–61	Morning	+	159	-	159	-
Gullo et al. (2017) (2)	3.2	CS	17	37–61	Morning	+	3819	-	3703	-
Hassi et al. (2001)	4.8	P	100	26–40	Morning	+	20	20	20	20
Jang et al. (2008)	2	CS	57*	18–65	Morning	+	347	335	610	299
Kim et al. 2013	6	CS	58.6	18–90	Morning	+	6834	6526	7219	7517
Koono (1980) (1)	2.2	P	100	30–49	Morning	+	15	-	15	-
Koono (1980) (2)	2.2	CS	100	30–49	Morning	+	49	-	58	-
Leonard et al. (2014)	1.5	P	37*	18–81**	Morning	+	88	-	88	-
Maes et al. (1997)	3.2	P	50*	33–45	Morning	+	26	26	26	26
Mahwi and Abdulateef (2019)	2.5	P	24.3	22–46	Morning	+	152	-	152	-
Nagata et al. (1976)	5.5	P	100	20–44	Morning	+	94	-	103	-
Pasquali et al. (1984)	5	P	58	24–48	Morning	+	24	24	24	24
Pham et al. (2020)	6	CS	44*	20–69	Morning	+	169	330	148	220
Plasqui et al. (2003)	4.2	P	40*	20–30	Morning	+	25	25	25	25
Rastogi and Sawhney (1976)	6	P	100	25–37	Morning	+	8	8	8	8
Smals et al. (1977)	5.5	P	100	24–45	Morning	+	13	13	13	13
Wang et al. (2019)	3.5	CS	50	≥65	Morning	+	1275	1435	2525	1289

Kuzmenko et al, Findings (1)

Circulating TSH levels were higher in winter than in the other seasons

Significant increases in TSH levels during winter in women, but not in men

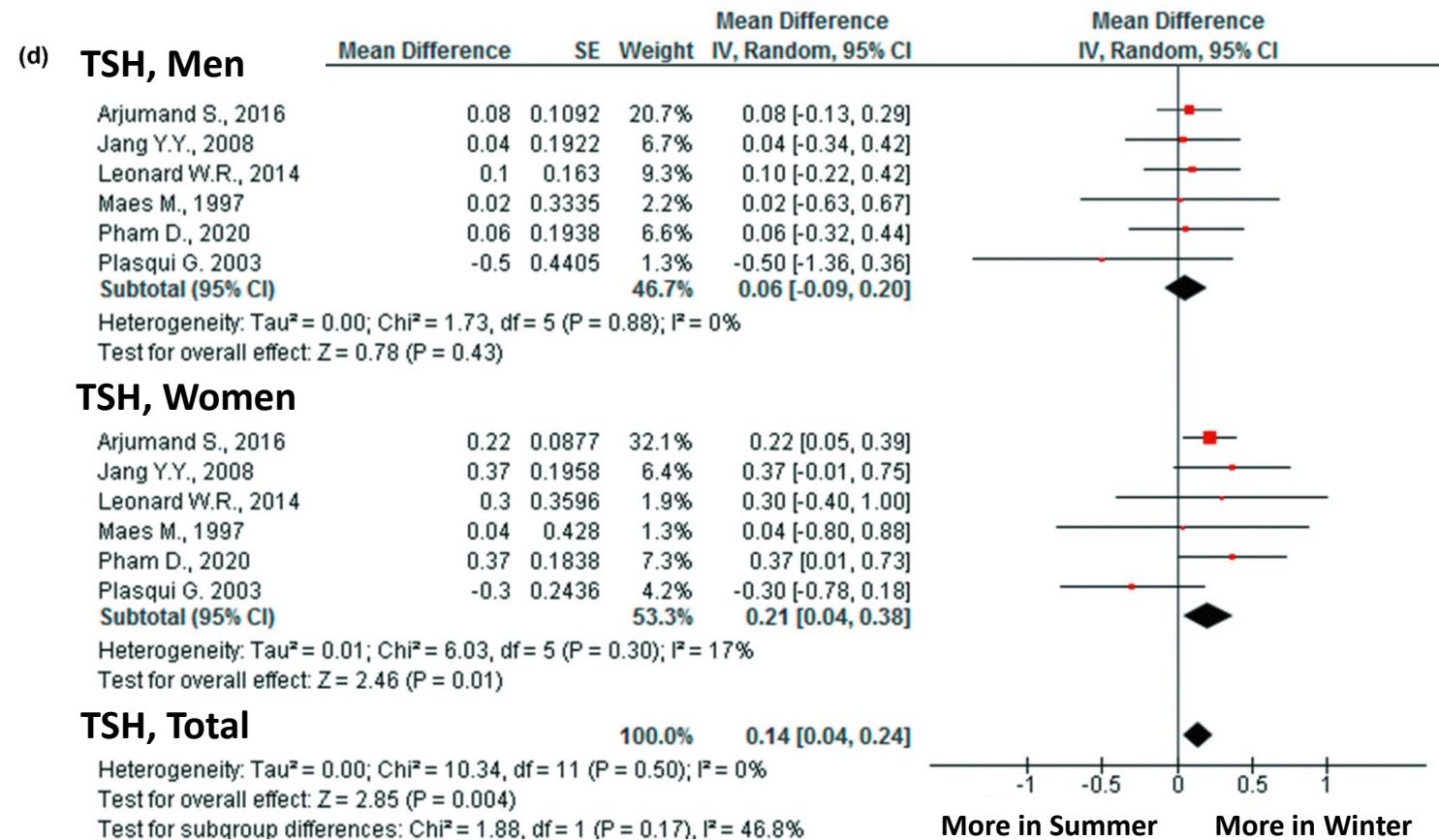


Figure 2. (c) Forest plots of circannual dynamics of FT4 (winter versus summer) depending on gender. (d) Forest plots of circannual dynamics of TSH (winter versus summer) depending on gender.

Kuzmenko, N.V. et al. *Chron Int.* 2021. PMID: 33535823

Kuzmenko et al, Findings (2)

No temperature effect size:
No dependence of TSH on amplitude of seasonal fluctuation in air temperatures

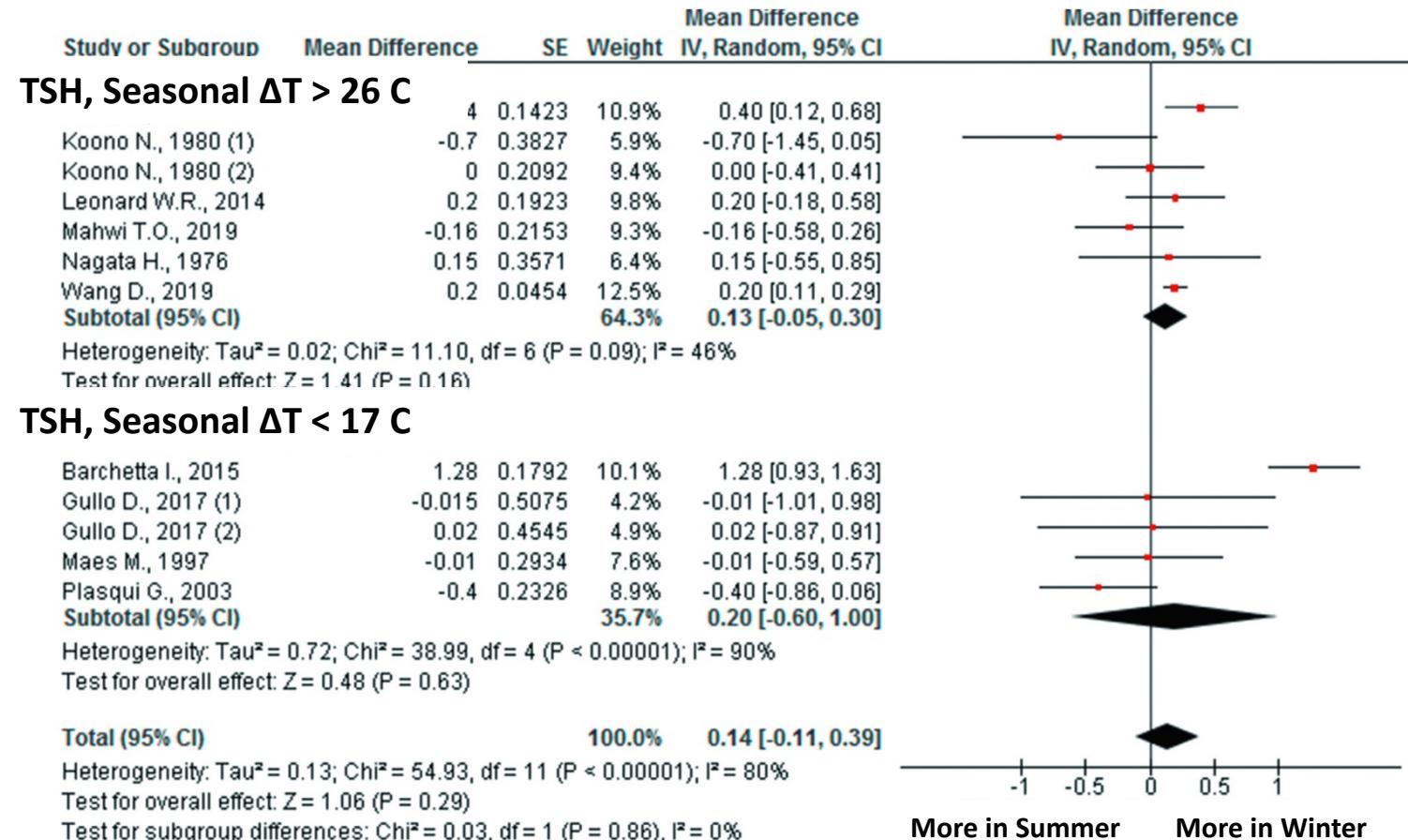


Figure 5. Forest plots of circannual dynamics of TSH (winter versus summer) depending on seasonal fluctuations in air temperature

Kuzmenko, N.V. et al. *Chron Int.* 2021. PMID: 33535823

Kuzmenko et al, Findings (3)

TSH seasonal effect magnitude correlates better with seasonal variation in mean monthly atmospheric pressure and pO₂

“seasonal dynamics of TSH is expressed in a climate in which relative humidity is higher in summer than in winter”

(Kuzmenko et al., 2021, p. 310) ([pdf](#))

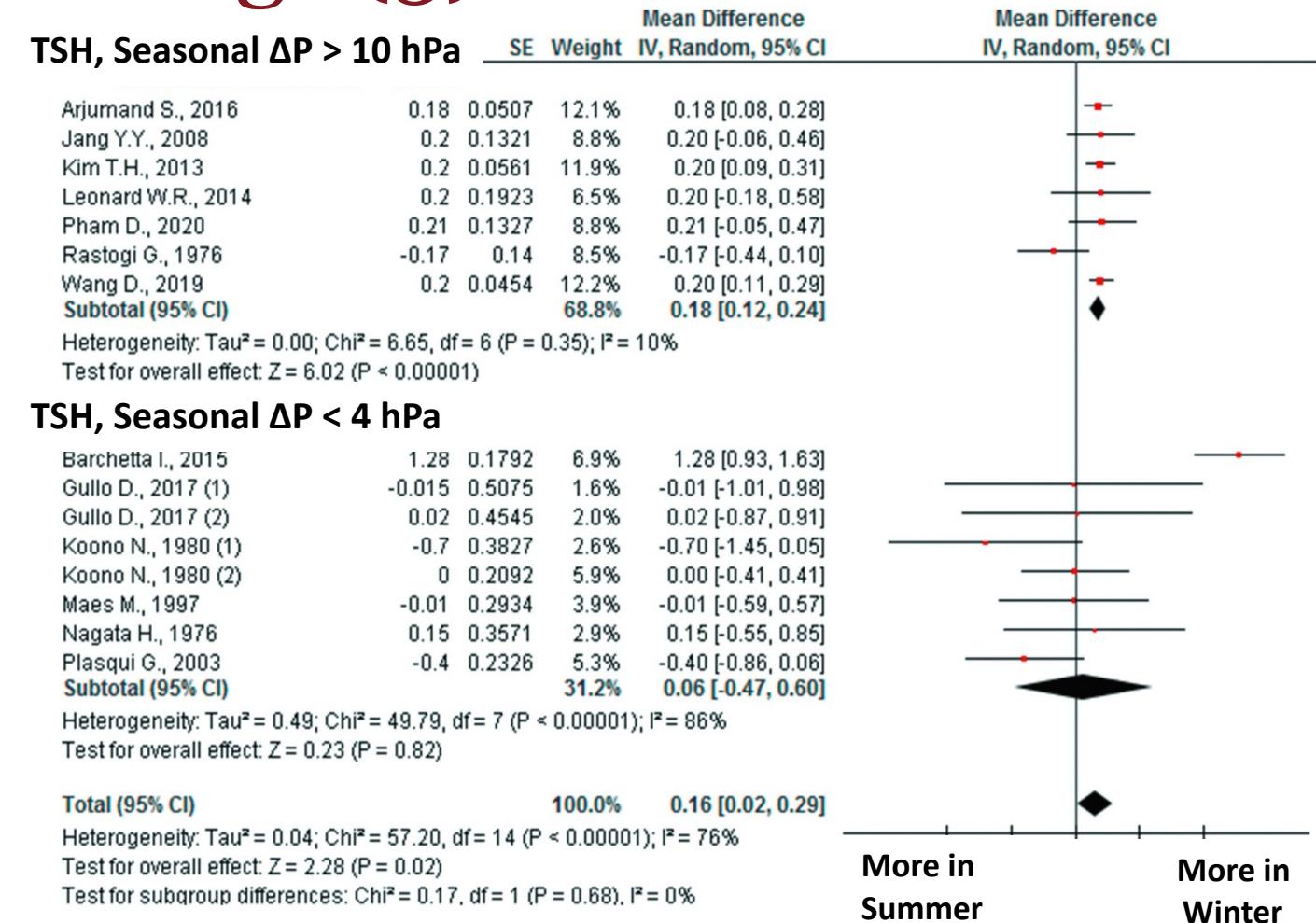


Figure 6. Forest plots of circannual dynamics of TSH (winter versus summer) depending on seasonal fluctuations of value of atmospheric pressure

Kuzmenko, N.V. et al. *Chron Int.* 2021. PMID: 33535823

Kuzmenko et al

Findings

- TSH levels higher in winter overall, statistical sig. for women
- TSH seasonality higher with...
 - Increased fluctuation of monthly pO₂ and atm pressure
 - Areas with higher humidity in summer than in winter

Kuzmenko et al

Limitations

- Underpowered to detect age effect (only 2 of 20 studies)
- Meta-analysis restricted to those published in English
- Could not trend individuals
 - (cross-sectional)
- Majority of studies not controlled for caloric intake (and iodine)
 - diet is likely also seasonal and needs further study as a causative factor
- Many unclear confounders
 - all metrological variables influence each other

The reference intervals for thyroid hormones: A four year investigation in Chinese population

[Tiancheng Xie](#),^{1, †} [Mingchuan Su](#),^{1, †} [Jie Feng](#),¹ [Xiaoying Pan](#),¹ [Chuan Wang](#),^{1, 2} and [Tian Tang](#)^{✉ 1, 2, *}

Background

- Discrepant thyroid (assoc.) disease prevalence USA (12%^[1]) vs China(40%).
 - Primarily subclinical hypothyroidism
- Authors concerned for false elevation.
- Manufacturer intervals are widely adopted but based on few samples.

Aims

- Determine dynamic trends of serum TSH, T3, FT3, T4 and FT4.
- Re-evaluate Manufacturer reference interval validity.
- Explore possible roles of age and sex on the levels of biomarkers.

^[1] American Thyroid Association

Xie T et al. *Frontiers in Endocrinology*. 2023. PMID 36686466

The reference intervals for thyroid hormones: A four year investigation in Chinese population

[Tiancheng Xie](#), ^{1, †} [Mingchuan Su](#), ^{1, †} [Jie Feng](#), ¹ [Xiaoying Pan](#), ¹ [Chuan Wang](#), ^{1, 2} and [Tian Tang](#) ^{✉ 1, 2, *}

Study Design

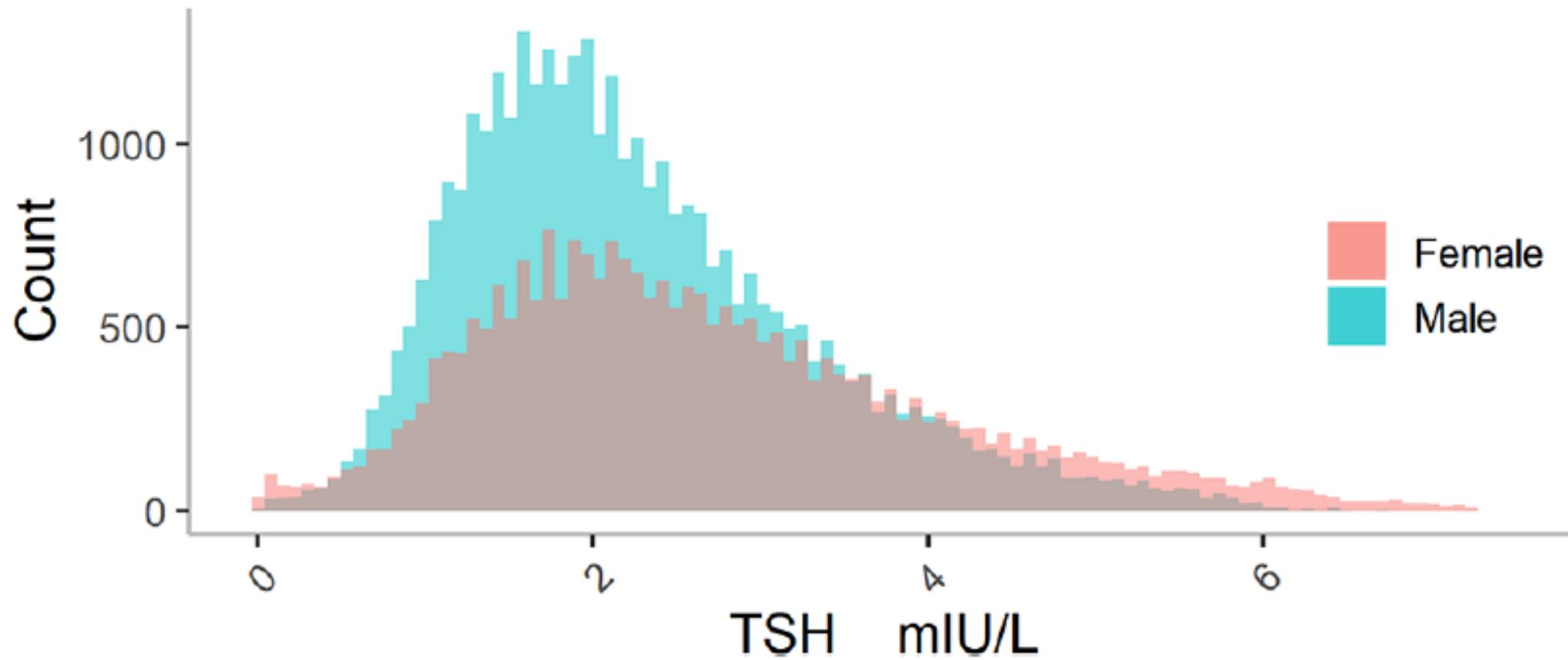
- Cross Sectional Study
- Healthy Adults ages 22 - 70 years, 8/2019 - 9/2020
- > 66,000 individuals met inclusion criteria

Methodology; Exclusion Criteria

- Pregnancy, past of family endocrine history, medications affecting thyroid function
- Required patients to fast for 8 hours
- TSH measured on Roche Cobas E 601

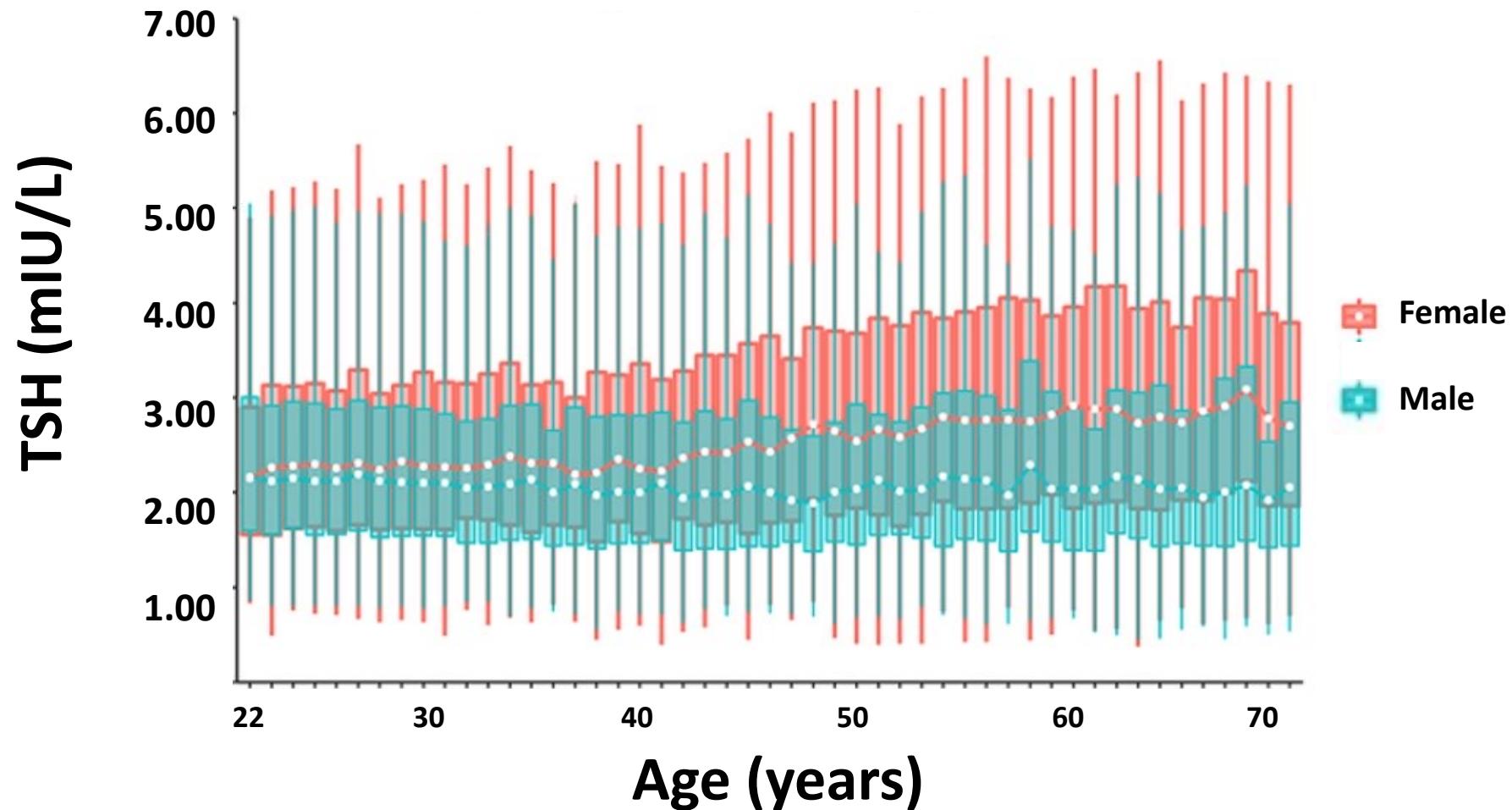
Xie T et al. *Frontiers in Endocrinology*. 2023. PMID 36686466

Distribution of TSH



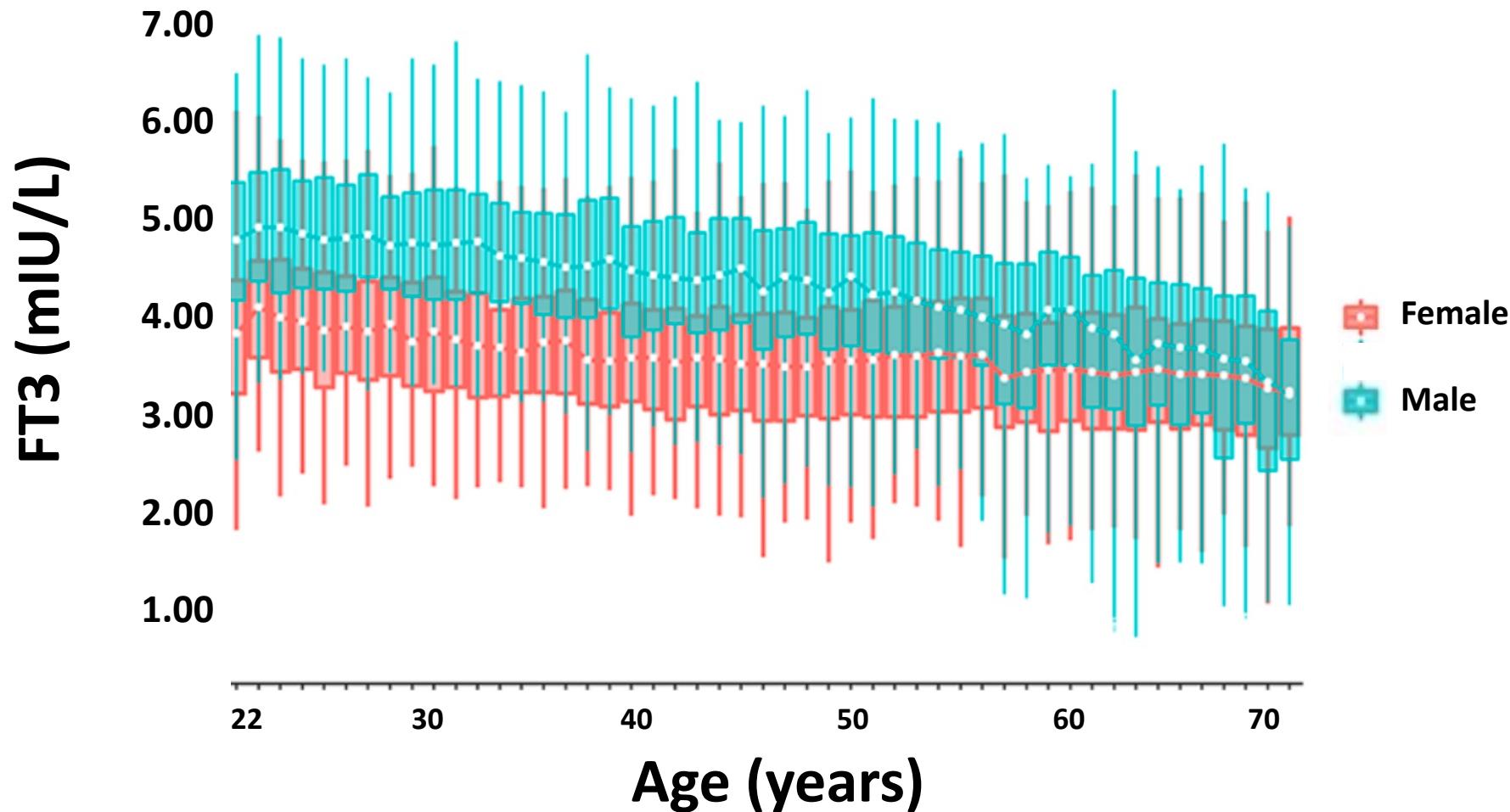
Xie T et al. *Frontiers in Endocrinology*. 2023. PMID 36686466

The Change of TSH over Age and Sex



Xie T et al. *Frontiers in Endocrinology*. 2023. PMID 36686466

The Change of FT3 over Age and Sex



Xie T et al. *Frontiers in Endocrinology*. 2023. PMID 36686466

Conclusion from Measuring Local Ref. Interval *(same assay and manufacturer we use)*

manufacturer 0.270 - 4.20 miU/L

proposed by Xie et al. 0.683 - 5.45 miU/L

Package Insert: Thyrotropin TSH. Roche Corporation 04/2021.

Conclusion from Measuring Local Ref. Interval *(same assay and manufacturer we use)*

TABLE 3 RI_s provided by the manufacturer versus the RI_s we proposed.

Analytes	Gender	RI _s provided by the manufacturer	RI _s we proposed
T3	male	(1.3-3.1) nM	(1.20-2.70) nM
	female		(1.06-2.49) nM
T4	unisex	(66-181) nM	(65.90-147.5) nM
FT3	male	(3.1-6.8) pM	(3.54-6.63) pM
	female		(3.24-5.93) pM
FT4	unisex	(12-22) pM	(12.11-22.82) pM
TSH	unisex	(0.270~4.20) mIU/L	(0.683-5.45) mIU/L

Package Insert: Thyrotropin TSH. Roche Corporation 04/2021.

Xie et al

Implications

- Large difference between manufacturer and own RI.
- Established significant age- and sex- effects on TSH.
- Function indicators, based on CLSI EP28-A3c guidelines.

Xie et al

Implications

- Established age- and sex-stratified RIs for thyroid function indicators, based on CLSI EP28-A3c guidelines.

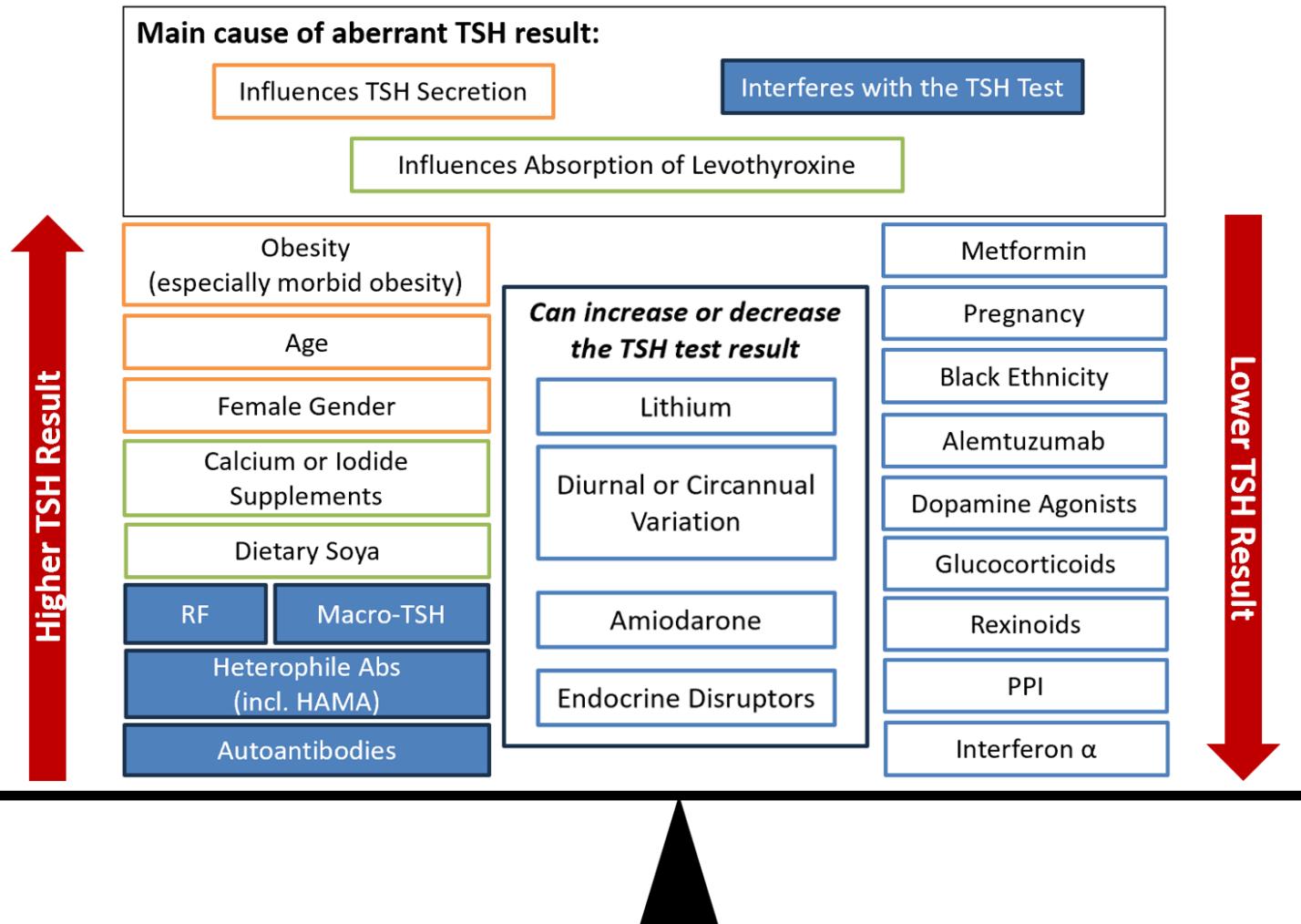
Limitations

- Inclusion/exclusion criteria offset by large data sample
- Does not account for cofactors
 - e.g. iodine intake, ethnicity, climate, seasonal changes
- Did not specify time of day samples were taken

To Recap

- It's complicated
- A range of promising steps

Non-Seasonal Modifiers of TSH



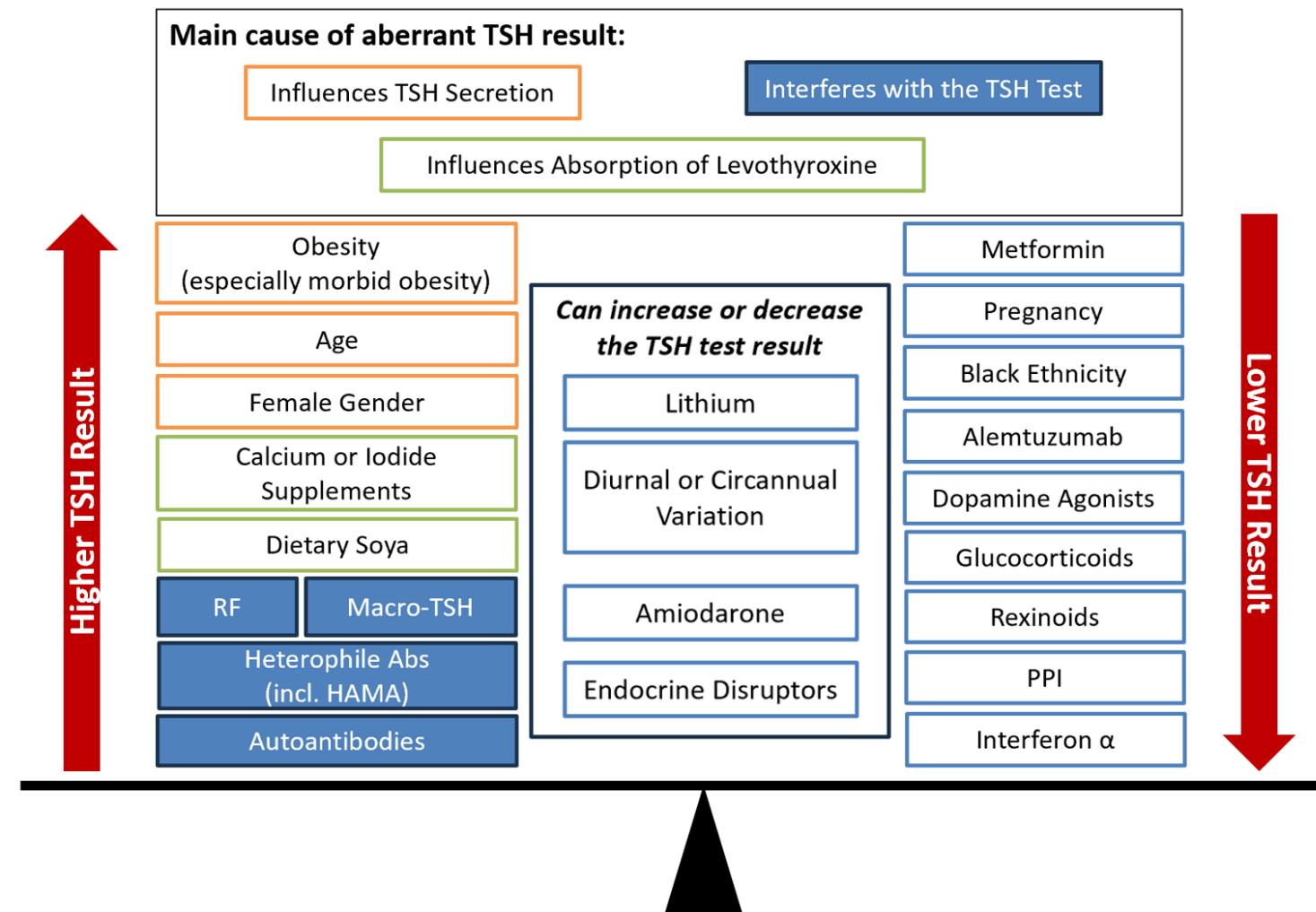
To Recap

- It's complicated
- A range of promising steps

I see value in :

1. Doing an informatic sanity check of Roche RI
2. A Null Interval that knows about 1 to N factors

Non-Seasonal Modifiers of TSH



To Recap

- It's complicated
- A range of promising steps

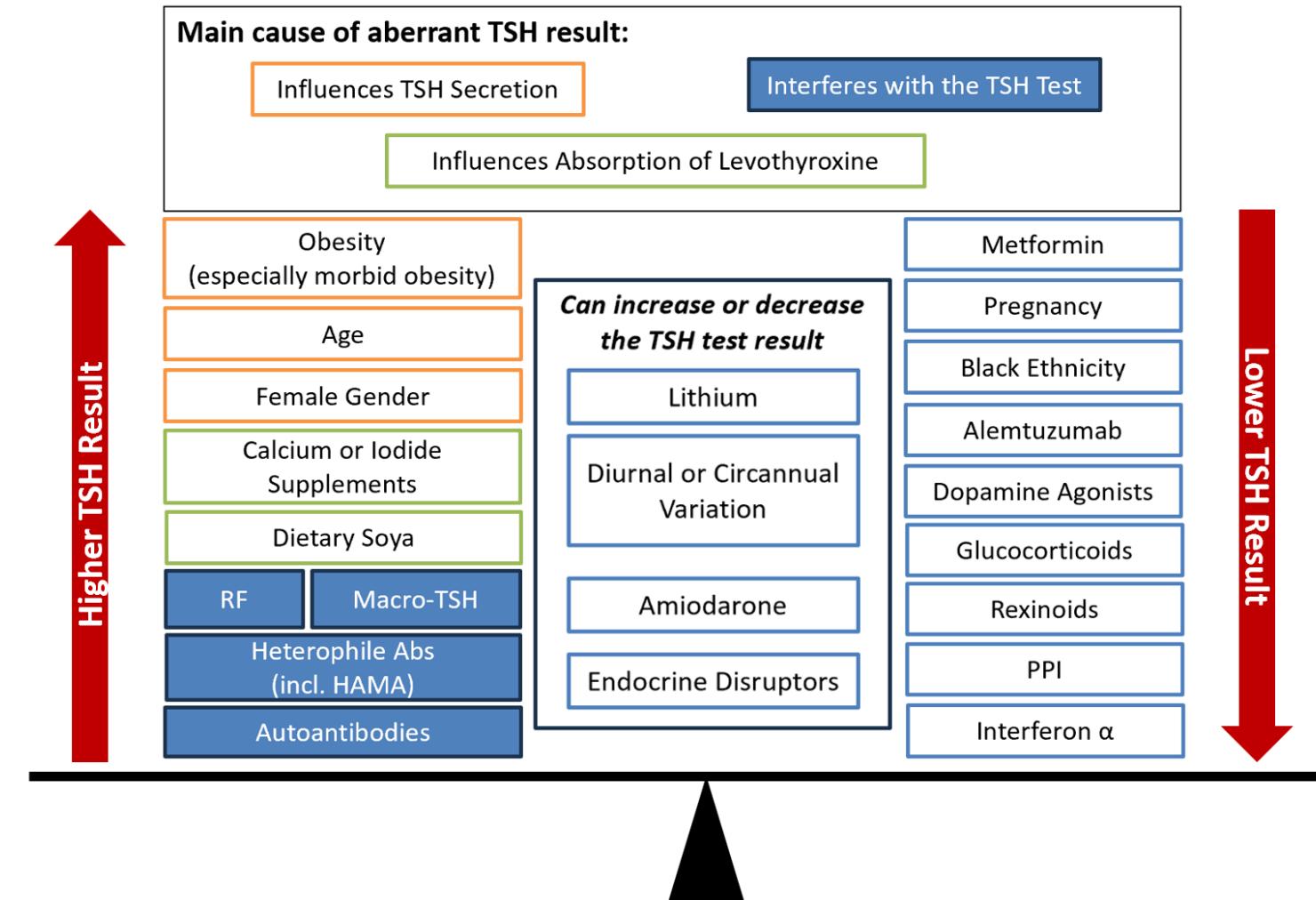
I see value in :

1. Doing an informatic sanity check of Roche RI
2. A Null Interval that knows about 1 to N factors

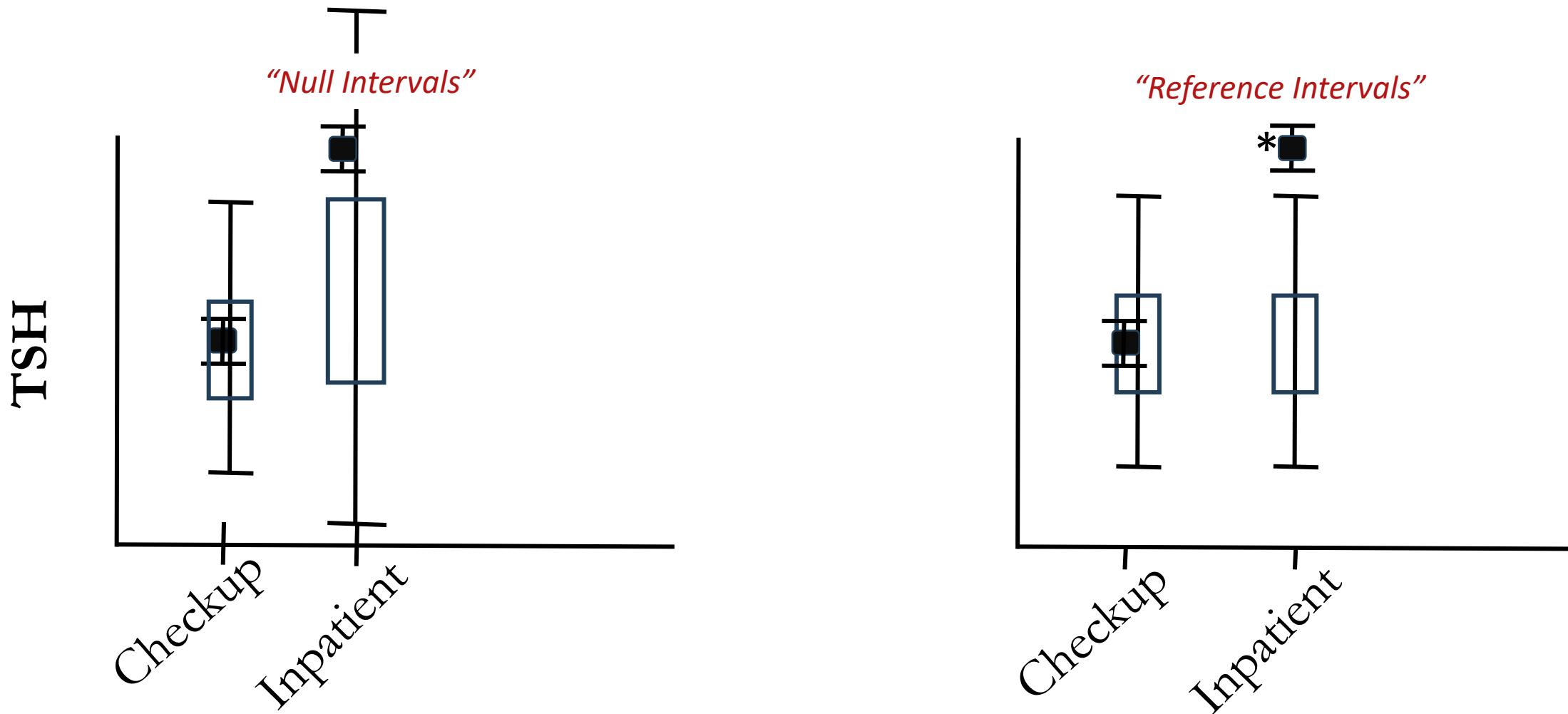
One worries about:

Whether is it even possible
to make so many corrections

Non-Seasonal Modifiers of TSH

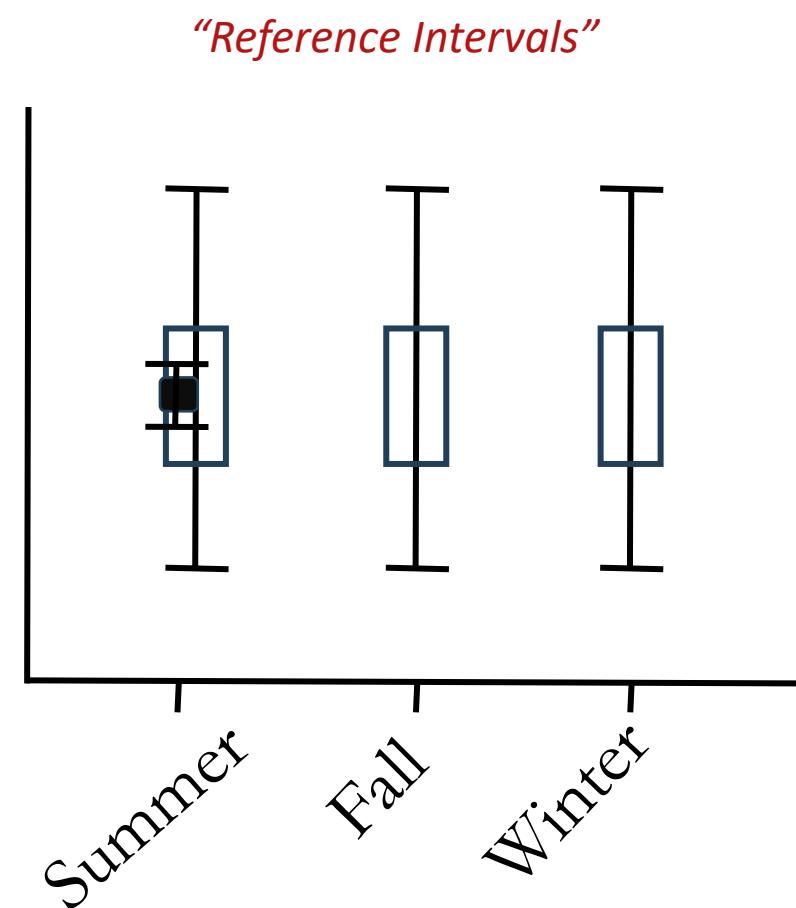
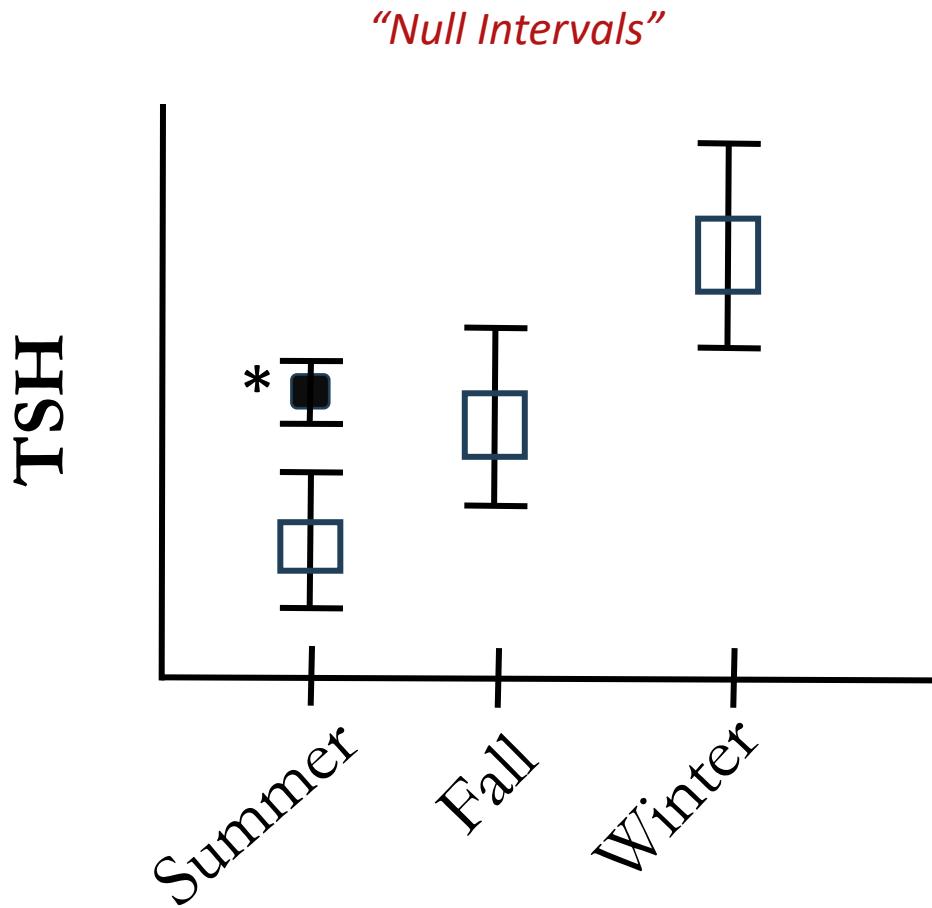


Null Intervals vs Reference Intervals:



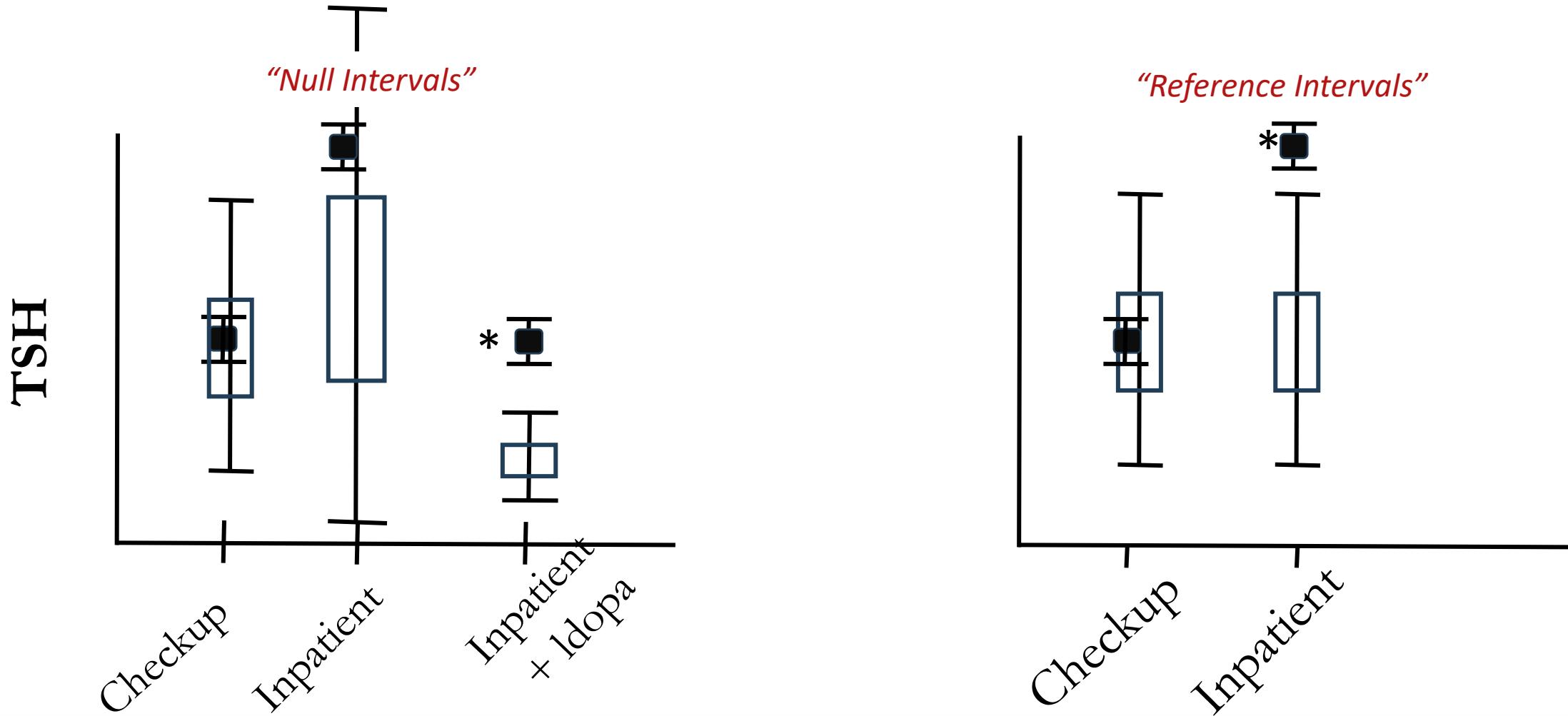
Null Intervals vs Reference Intervals:

The Difference in TSH Interpretation (illustrative data)



Null Intervals vs Reference Intervals:

The length of the 95% interval is Variable!



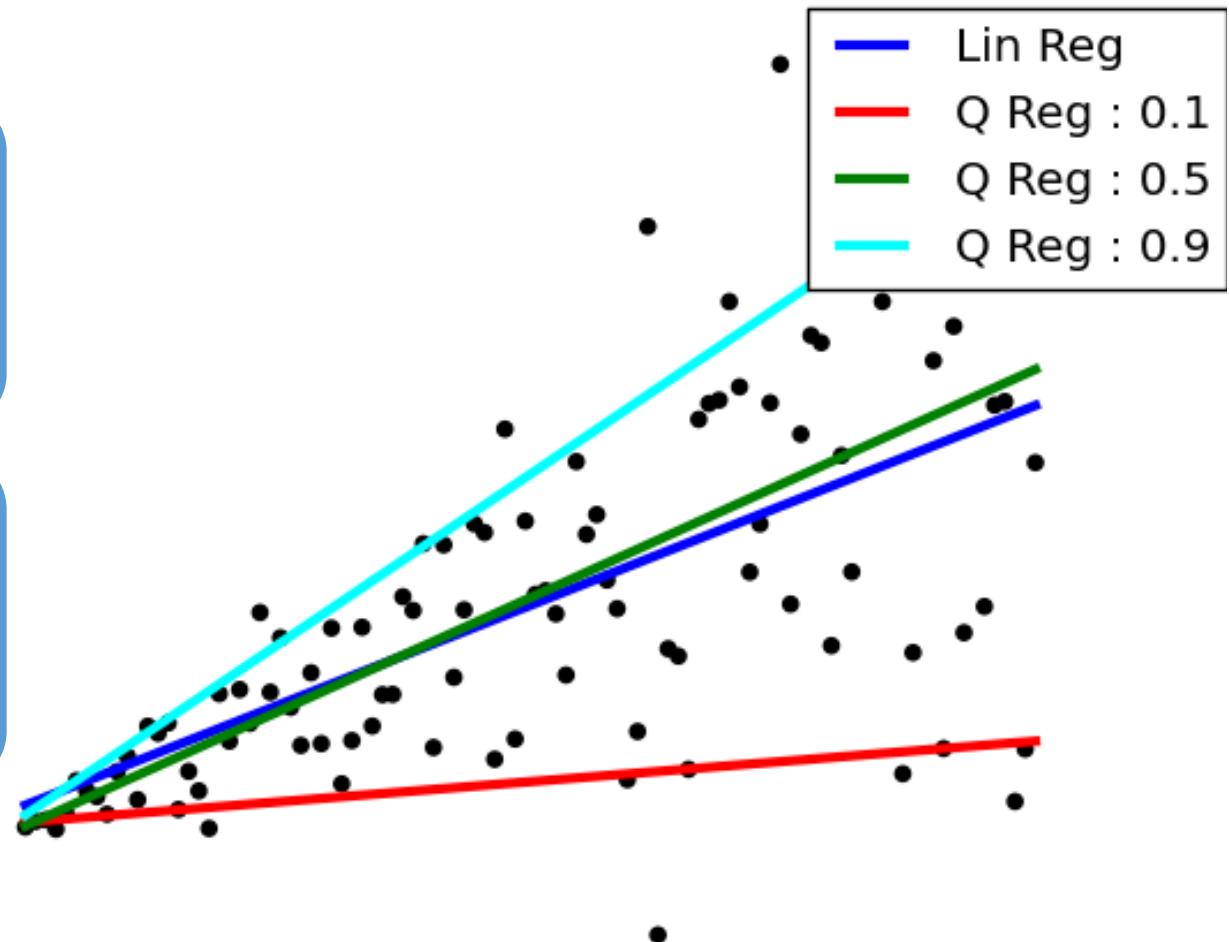
M-A-T-H



Quantile Regression:

“1 Simple Trick”

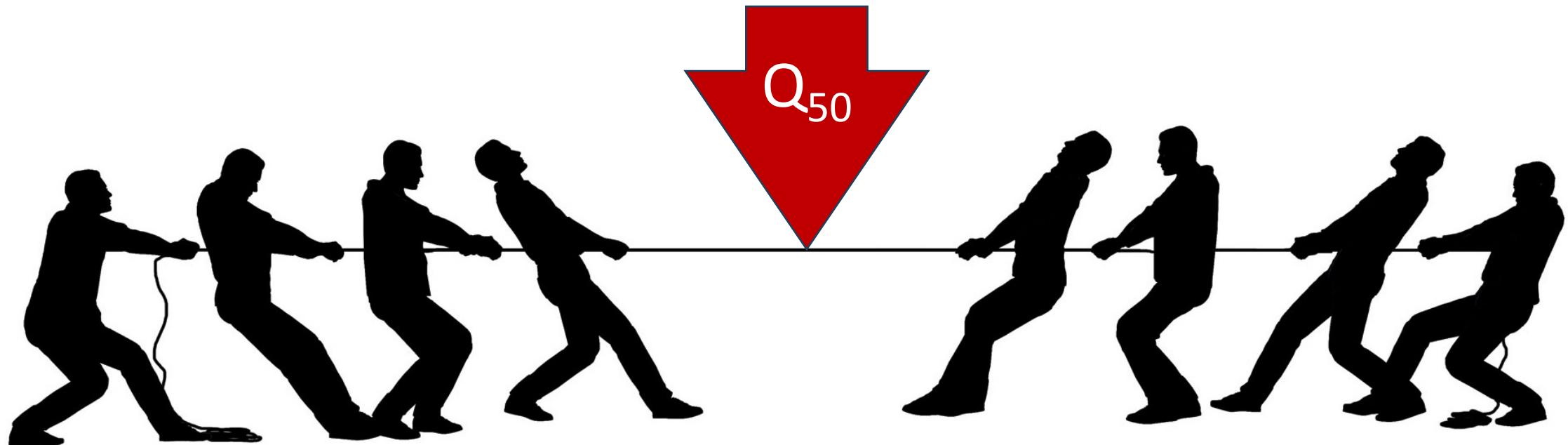
Curve fitting adapted
to percentiles!



Bates. A Gentle Introduction to Conformal Prediction and Distribution-Free Uncertainty Quantification. 2022

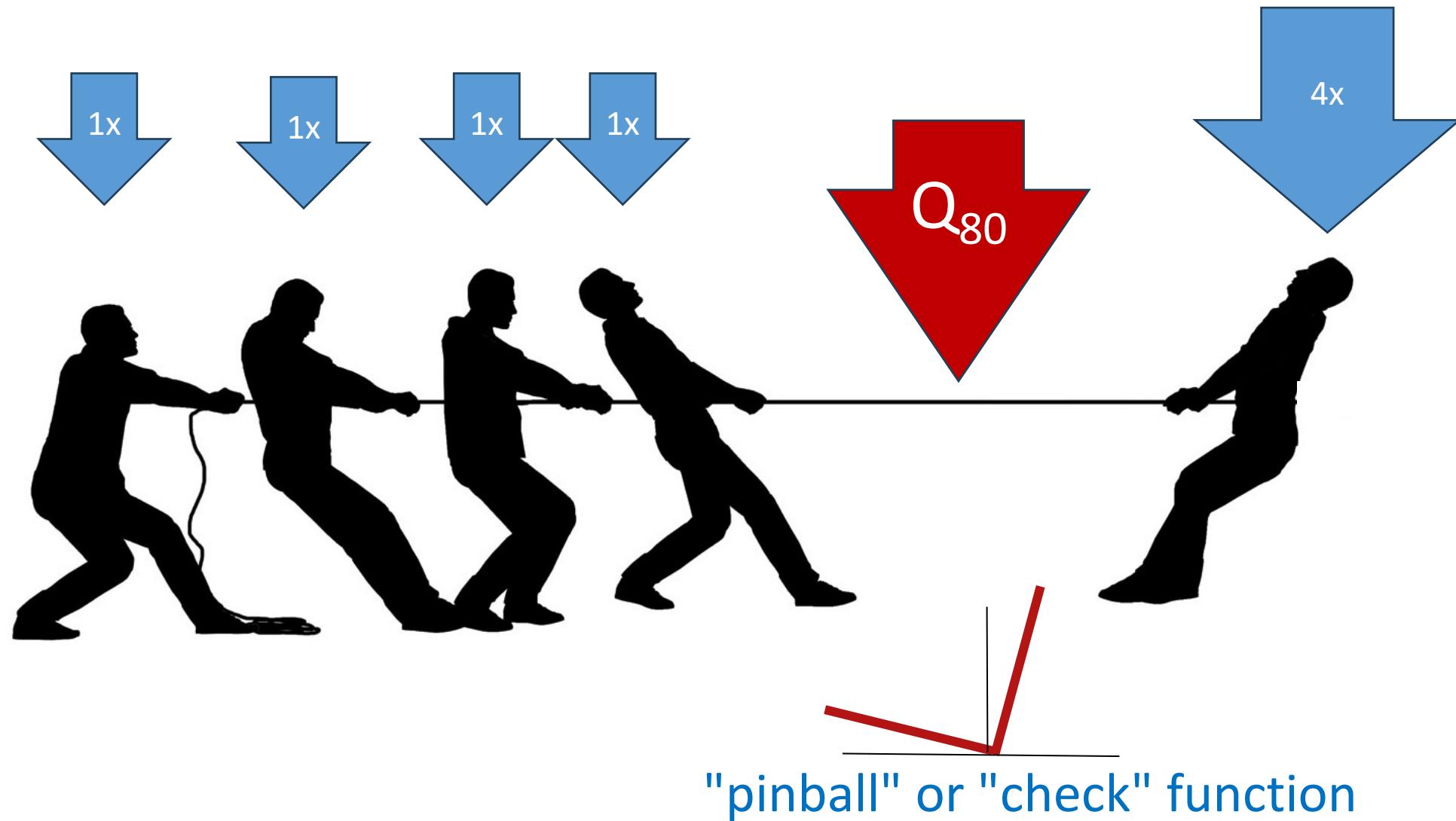
Quantile Regression:

- What is a median
(0.50 Quantile)

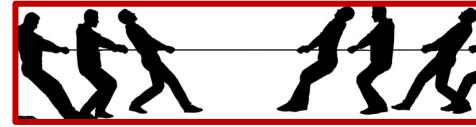


Bates. A Gentle Introduction to Conformal Prediction and Distribution-Free Uncertainty Quantification. 2022

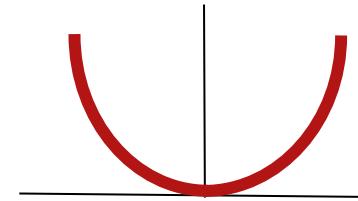
Quantile Regression:



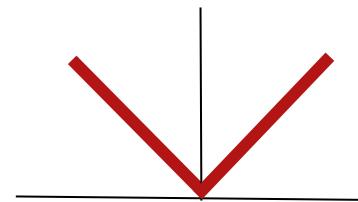
Quantile Regression *in context*



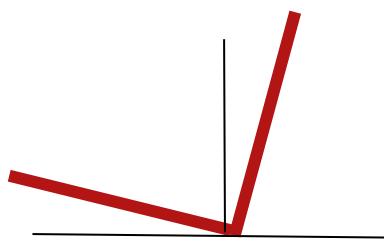
Mean



Median



Quantile

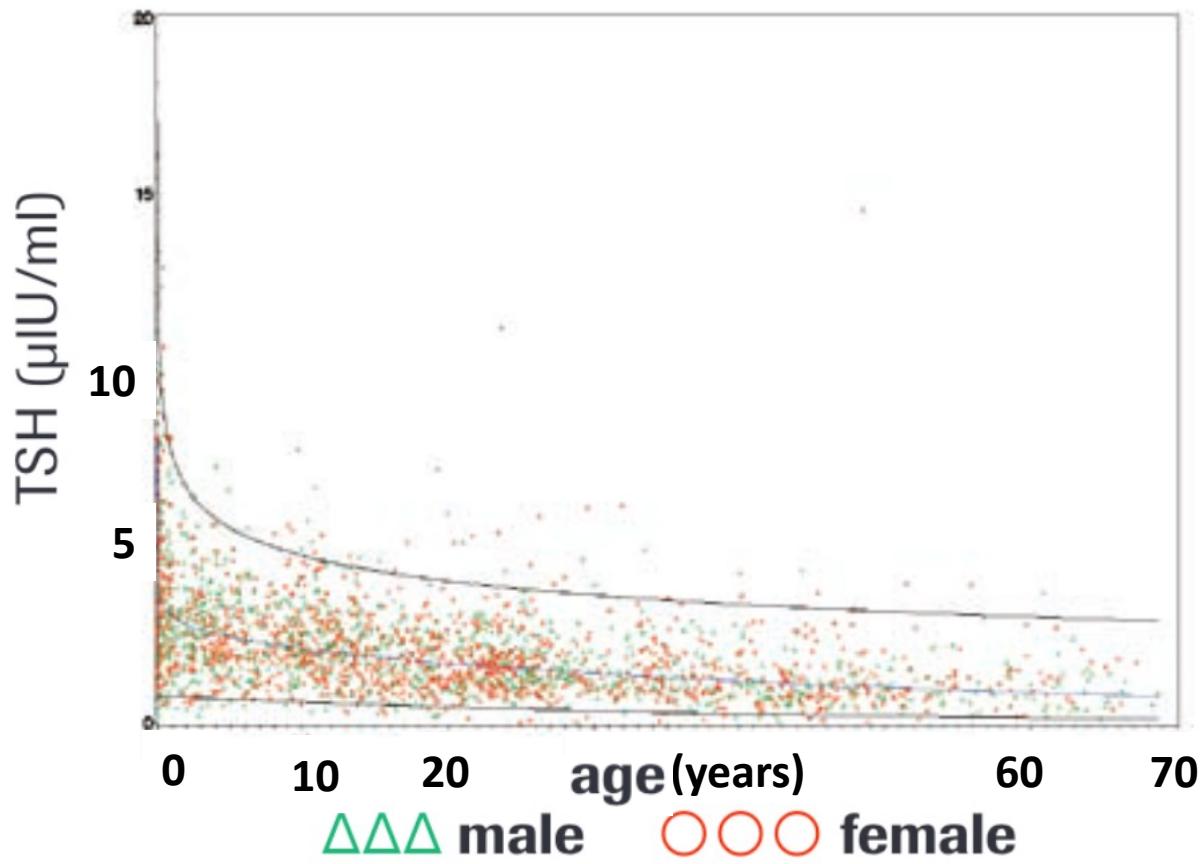


Quantile Regression

Reference Intervals
for Children and Adults



Elecsys and **cobas e** analyzers
Elecsys Thyroid Tests



- Roche used this technique in 2009 to model 97.5%-tile of TSH
- Age-Dependent Estimates
- No binning needed
- What can go wrong?

Roche, 2009. Reference Intervals for Children and Adults.

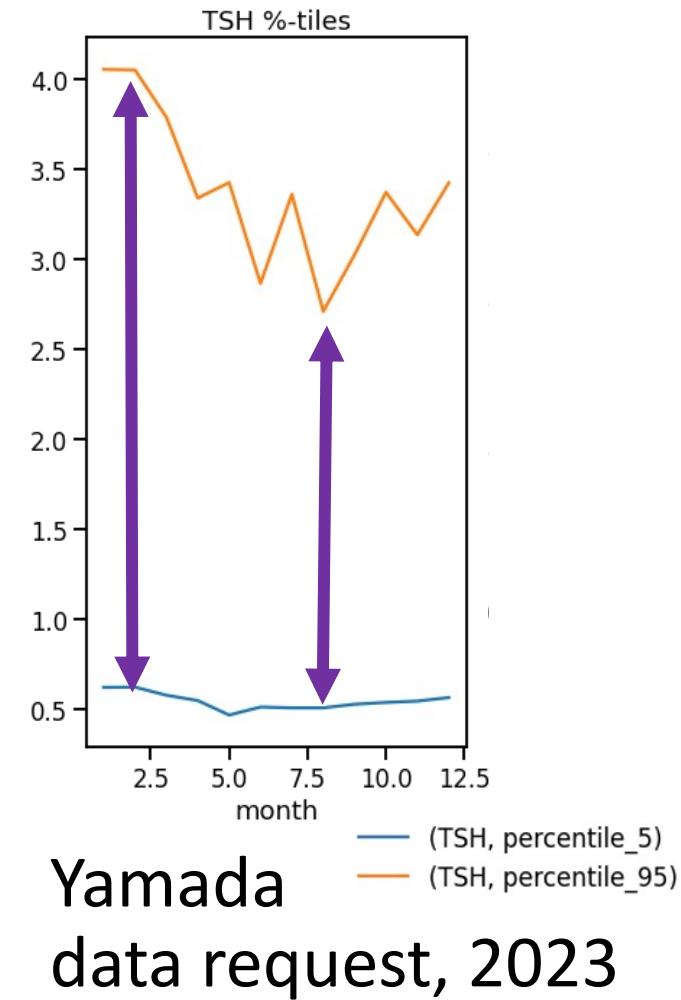
Model Criteria: *Accommodate Heteroskedasticity*

Not

"Most likely[Y|X] plus noise"

$$Y \in q_{50}(X) \pm \sigma$$

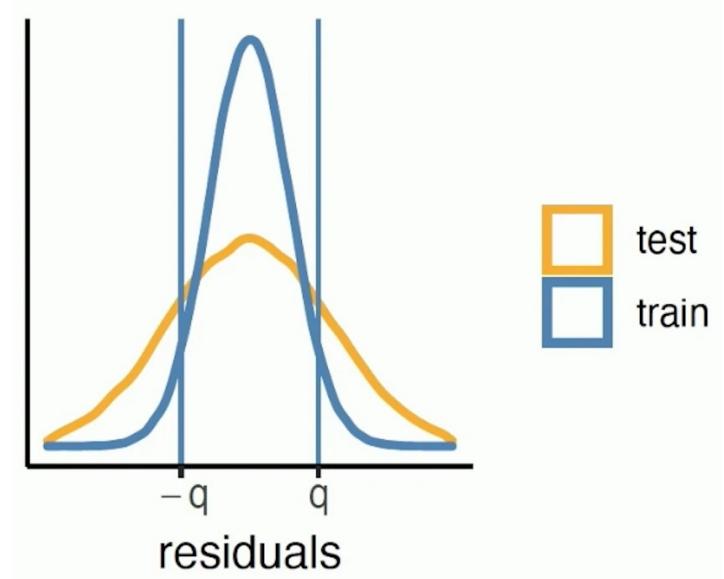
σ needs dependence on X too!



Quantile Regression

Limitations

- “Overfitting”
- “Over-Confident” models produce intervals that are too short!
- Neural networks especially prone to this

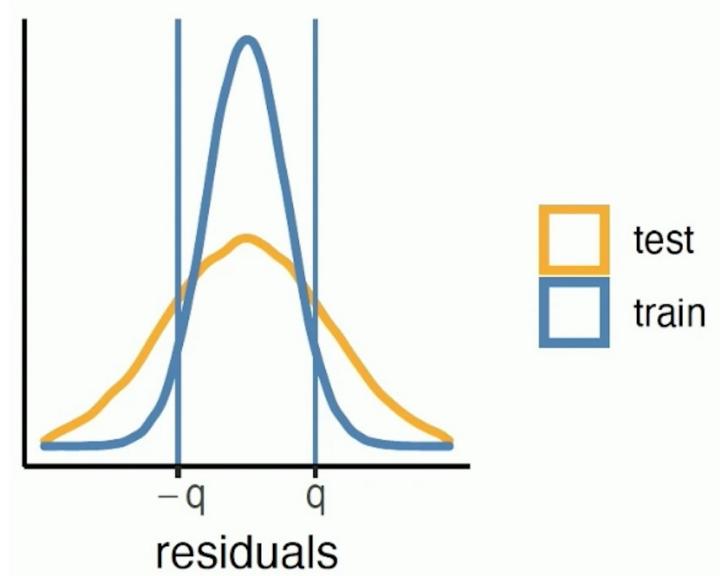


Doesn't work! training residuals much smaller than test residuals (extreme for neural nets)

Quantile Regression

Limitations

- “Overfitting”
- “Over-Confident” models produce intervals that are too short!
- Neural networks especially prone to this



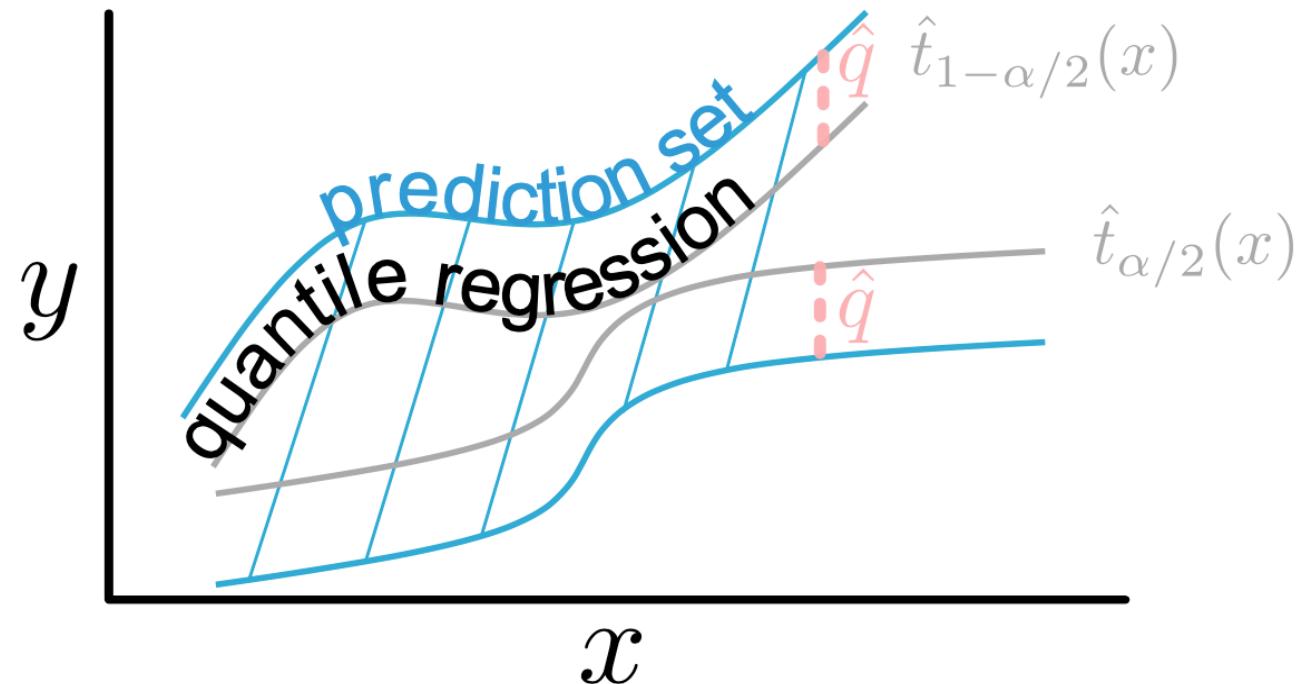
Doesn't work! training residuals much smaller than test residuals (extreme for neural nets)

Want: $\mathbb{P}\{Y_{n+1} \in C(X_{n+1})\} \geq 1 - \alpha$

Conformal Prediction:

*>1000 citations/year since
2019*

"user-friendly paradigm for
creating statistically rigorous
uncertainty sets"



Bates. A Gentle Introduction to Conformal Prediction and Distribution-Free Uncertainty Quantification. 2022

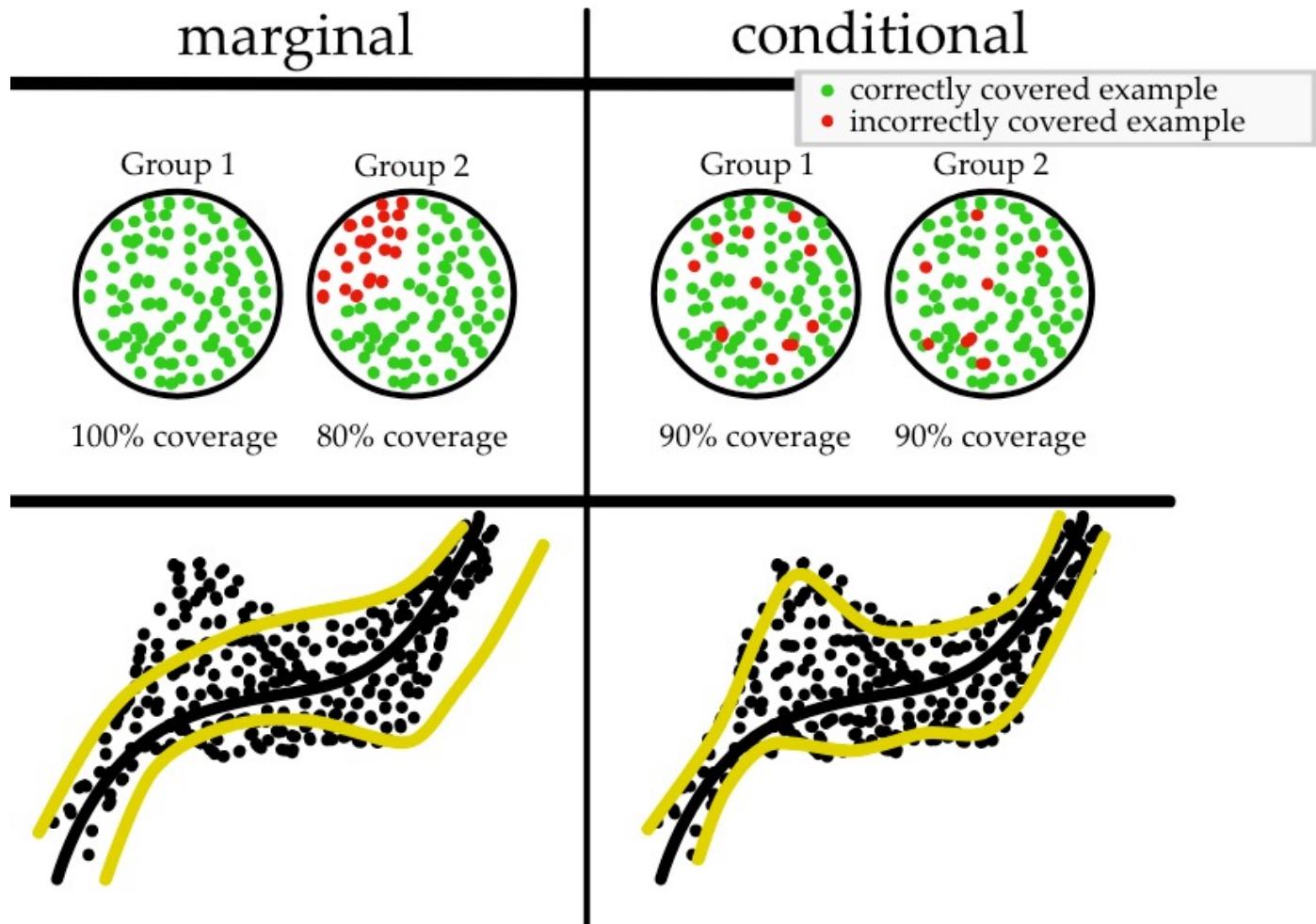
Conformal Prediction:

Limitations

- All models will satisfy 95% criteria
- Not all models are equal

Many useful extensions:

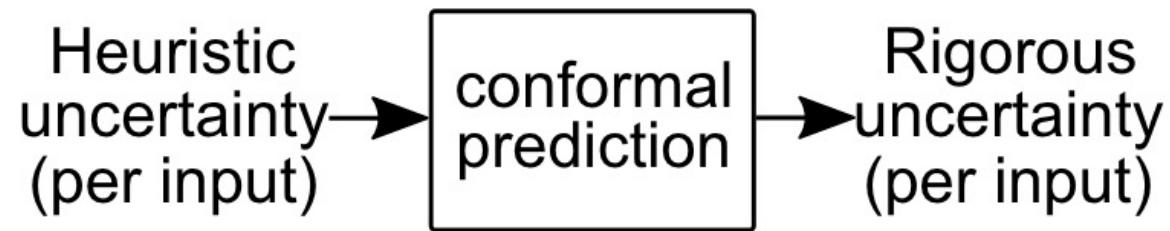
- Can limit false discovery rate
- Can adapt to climate drift



A Gentle Introduction to Conformal Prediction and Distribution-Free Uncertainty Quantification. 2018

Conformal Prediction

A method for taking any heuristic notion of uncertainty from any model and converting it to a rigorous one.



How is it possible to construct a statistically valid prediction set even if the heuristic notion of uncertainty of the underlying model is arbitrarily bad?

Summary of Recommendations

- Better quantification of population TSH values is a high-impact area with low hanging fruit.
- It has been >20 years since the Roche RI study.
- It's clear that there is *some* real exogenous effect on TSH, but the driving factors are not crystal clear.
- It's well worth looking into seasonal variation, but it will be difficult to know what to look for.
- An AI model serves as a good positive control for finding nebulous signal.
- Recent advances in AI allow true null hypothesis modeling—clinically relevant.

Made Possible by



Dr. Farnsworth, PhD

Dr. Gronowski, PhD

Dr. Zayzman MD, PhD



Dr. El-Khoury, PhD (left)

Dr. Amy Riek, MD (right)



Thank you!

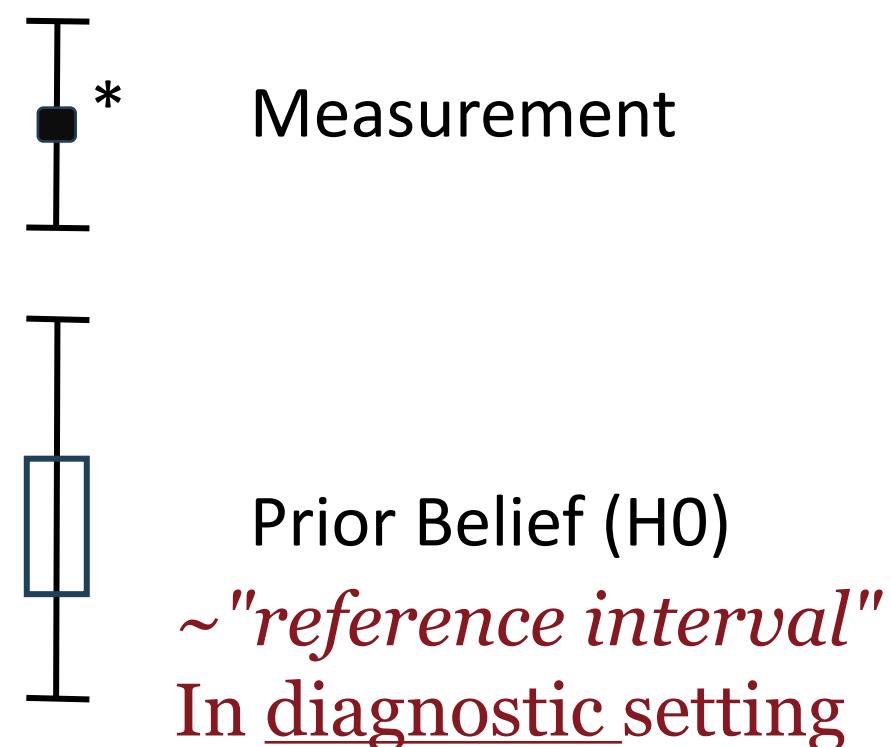


Washington University in St. Louis
SCHOOL OF MEDICINE

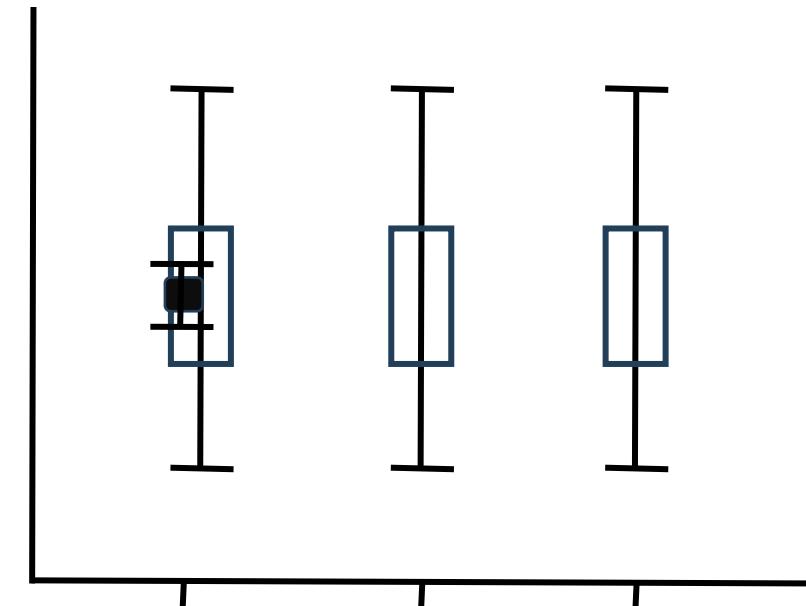
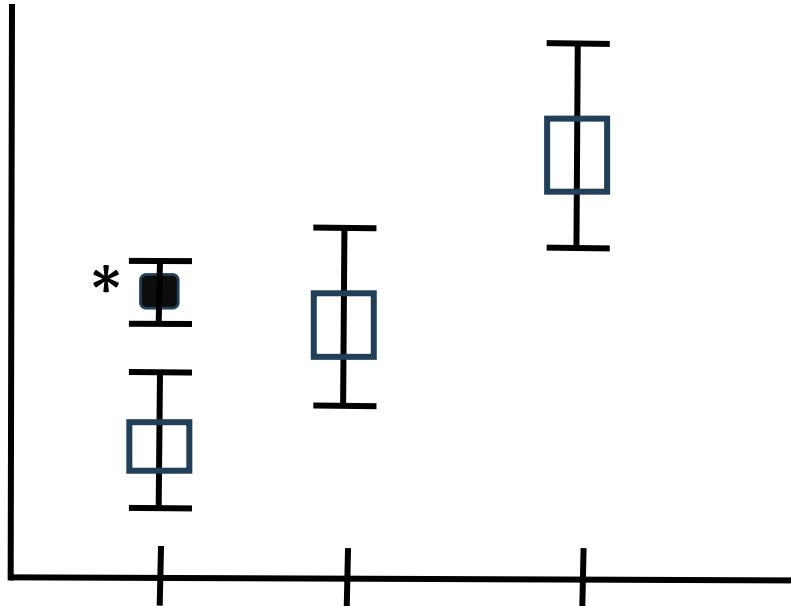
What Makes a Lab Value Informative?

Uncertainty Quantification.

- Significance is *relative* to a prior (H_0) model
- H_0 depends on what you know!
- NACB calls for reference range of 0.2 – 10.0 for inpatients



Analogy with “Instrument Diagnosis”



- Samples with *known* concentrations are measured ■
- Which is the more appropriate interval for comparison? □

“Pre-Clinical”

- affects measurement
- presumed clinically uninformative
- known at time of measurement

Sources of Laboratory Variation

"Laboratory Error" Degrades Clinical Predictive Value

*Pre-Analytical**

*patient preparation
specimen collection*

Analytical

*interference
malfunction*

Approach: Process Control and Measurement Calibration

Sources of Laboratory Variation

"Laboratory Error" Degrades Clinical Predictive Value

*Pre-Analytical**

*patient preparation
specimen collection*

Analytical

*interference
malfunction*

Approach: Process Control and Measurement Calibration

Are there uncontrollable sources of variation?

"Pre-Clinical"

- **Preclinical Variation:** *Unavoidable*, measurement variation caused by benign circumstances of measurement and benign patient characteristics.
 - *Timing* of measurement (of year)
 - Gender/Age of patient
 - Seasonality
 - Diet

"Pre-Clinical"

- **Preclinical Variation:** *Uncontrollable* influence on measurement or sample of patient *timing* or *trait* consistent with healthy variation
 - Gender
 - Seasonality
 - "*Normal Variation*" within a Reference Population
- Approach: Uncertainty Control Characterization

Causes of Error

Observable

Hidden

Modifiable

Standardization
Calibration

—

Intrinsic

? X ?

Reference
Intervals

Setup:

TSH measurement Y

Side Information X

p variables time of day, season of year, age, Rx, admitted?...

Setup:

Learn from n previous from the same population...

$$(X_1, Y_1), \dots, (X_n, Y_n)$$

TSH measurement Y

Side Information X

p variables time of day, season of year, age, Rx, admitted?...

Criteria for Model:

A. Answer

"is Y_{n+1} consistent with X_{n+1} ?"

B. Provably Correct

"at least 95% of the time"

Model Assumptions:

For each encounter measuring TSH

encounters measuring TSH := (X_{n+1}, Y_{n+1})

A.

"is Y_{n+1} consistent with X_{n+1} ?"

$\Leftarrow X_{n+1}$ predicts Y_{n+1} *(no new information)*

B.

"at least 95% of the time"

Y_{n+1} is in prediction set $C(X_{n+1})$ except for at most 5% of the time

$$\boxed{\mathbb{P}\{Y_{n+1} \in C(X_{n+1})\} \geq 1 - \alpha}$$

Model Criteria:

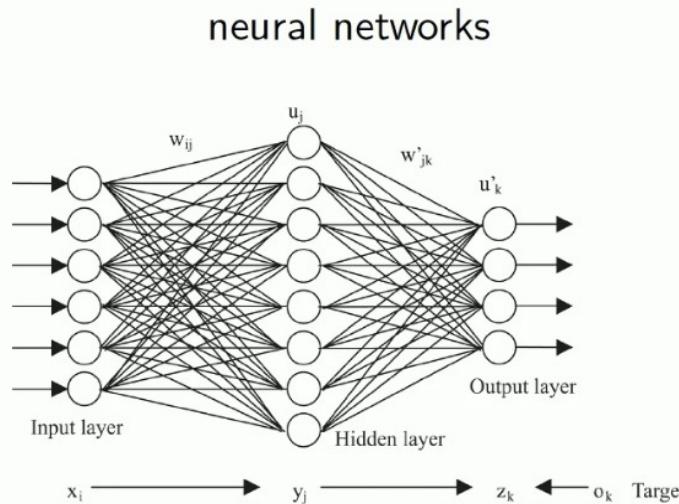
Make no Assumptions

Beware Dimensionality

- No assumptions about dependence of TSH (Y) on features (X)
- Avoid "Curse of Dimensionality"
 - Fit $q(Y|X)$ instead of $q(X,Y)$ (Favor prediction>inference)

Use:

$p \gg n$



Model Criteria: *Output = Interval*

- Not a straight forward prediction problem
- Model Interval using *two* models

$$q_\alpha(x) := \inf\{y \in \mathbb{R} : F(y \mid X = x) \geq \alpha\}$$

$$[\hat{q}_{\alpha_{lo}}(X_{n+1}), \hat{q}_{\alpha_{hi}}(X_{n+1})]$$

$$\hat{q}_{\alpha_{lo}}(X_i) \leq Y_i \leq \hat{q}_{\alpha_{hi}}(X_i)$$

- TSH *Conditional Percentile* $q_\alpha(X)$
 $q_\alpha(X) \sim \text{NeuralNet}_\alpha(X, \text{parameters})$

Model Criteria: *Output = Interval*

- Not a straight forward prediction problem

- Model Interval using *two* models

$$q_\alpha(x) := \inf\{y \in \mathbb{R} : F(y | X = x) \geq \alpha\}$$

$$[\hat{q}_{\alpha_{\text{lo}}}(X_{n+1}), \hat{q}_{\alpha_{\text{hi}}}(X_{n+1})]$$

$$\hat{q}_{\alpha_{\text{lo}}}(X_i) \leq Y_i \leq \hat{q}_{\alpha_{\text{hi}}}(X_i)$$

- TSH *Conditional Percentile* $q_\alpha(X)$

$$q_\alpha(X) \sim \text{Net}_\alpha(X, \text{parameters})$$

"Coverage Interval" $C(X)$

- Set $\alpha = 0.05$ $\alpha_{\text{low}} = \alpha/2$, $\alpha_{\text{high}} = 1 - \alpha/2$
- $C(X) = [q_{\alpha_{\text{low}}}(X), q_{\alpha_{\text{high}}}(X)]$

Interval $C(X)$ is "Valid" if

$$\mathbb{P}\{Y_{n+1} \in C(X_{n+1})\} \geq 1 - \alpha$$

Feedback - still fundamental

Content

- Was the topic clinically relevant?
- Did you take a clear stand?
- Did you critically review literature?
- Did you discuss lab testing details?
- Was it relevant to local practices?

The speaker presented an important and controversial topic in laboratory and genomic medicine.	<input type="radio"/>				
The speaker took a clear stand on an issue and defended it effectively.	<input type="radio"/>				
There was evidence of critical evaluation of data rather than just "reporting".	<input type="radio"/>				
The speaker demonstrated expert knowledge of the subject matter.	<input type="radio"/>				
The speaker discussed relevant laboratory testing/procedures in appropriate detail.	<input type="radio"/>				
The speaker included an analysis of impact on WUSM/BJC practices.	<input type="radio"/>				

Feedback - still fundamental

Delivery

- Speaker
- Scope
- Slides

	Strongly disagree	Disagree	Agree	Strongly agree	Exceeds expectations
The speaker spoke clearly and effectively, with no distracting verbal tics or body language.	<input type="radio"/>				
The scope of material was appropriate for a one-hour presentation, with a reasonable amount of time spent on background and on each paper presented.	<input type="radio"/>				
The PowerPoint presentation was effective and avoided confusing charts or "wall of text".	<input type="radio"/>				



Feedback - still fundamental

Overall

- Benchmarking
- Feedback

The trainee presentation was high quality, effectively demonstrating speaker and presentation skills outlined above



Please add any specific comments you have for the speaker below, especially any improvement (or not) compared with previous presentations.

Was this presentation free of commercial bias? Yes/No?

The Conditions for Diagnosis

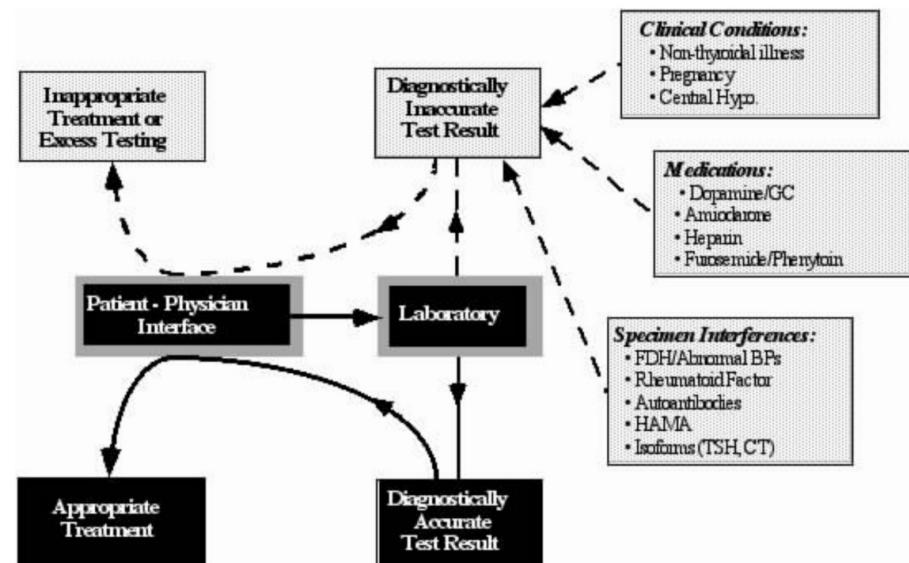


Fig 11. Consequences of Diagnostically Inaccurate Thyroid Tests

a

^a "Section 4. The Importance of the Laboratory-Physician Interface", NACB.

- Re-measurement of specimens with discordant results by an alternative method
- myriad effects: NTI, medications, autoantibodies
- high TSH ⇒ repeat TSH + FT4