

Normal Values

and their Pitfalls

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disclosures

institutional

contribution to studies (Actelion, Medtronic, Edwards, Occlutech, Novartis, Lilly, Bayer, Bristol-Myers Squibb)

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consulting reimbursement (Actelion, Bayer, Ethypharm, GlaxoSmithKline)

shareholder (Pfizer)

Normal Value

(~6000 years ago)

Random group of healthy subjects

→ measurements

→ mean



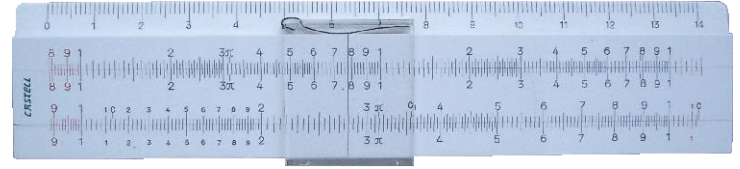
Patient

What is the range ?

$$x / \bar{x} * 100\%$$

Normal Range

(two centuries ago)



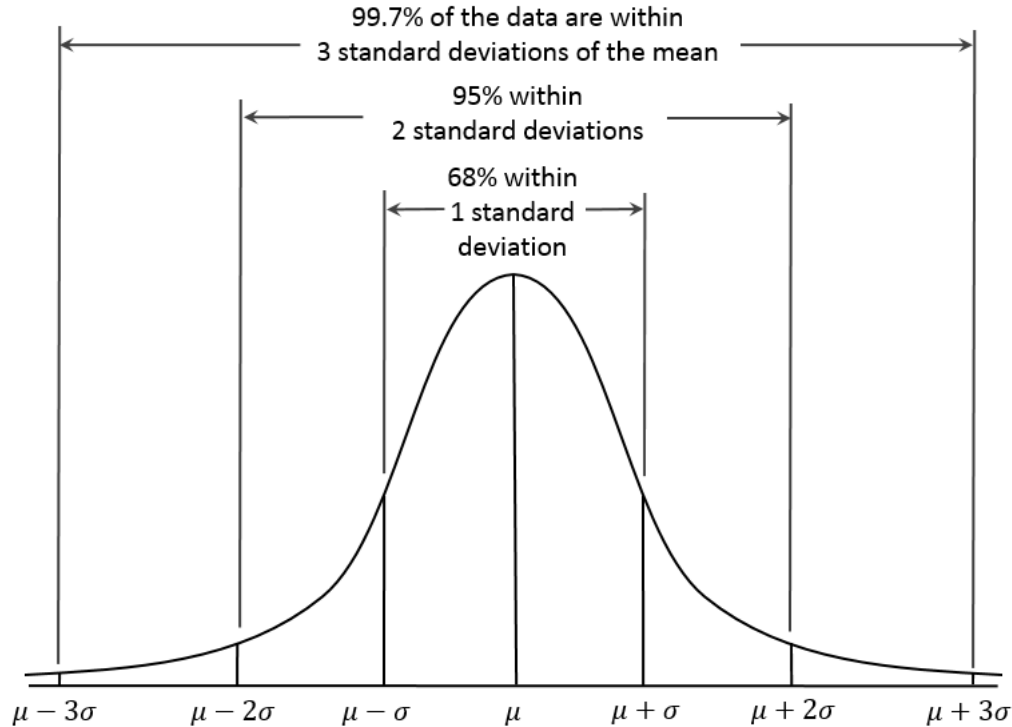
Random group of healthy subjects
→ measurements
→ mean $\pm$ s.d.

Patient → single measurement → calculate „SDS“ (= „z-score“)

$$z = (x - \bar{x}) / \text{s.d.} = (x/\bar{x} - 1) / (\text{s.d.} / \bar{x})$$

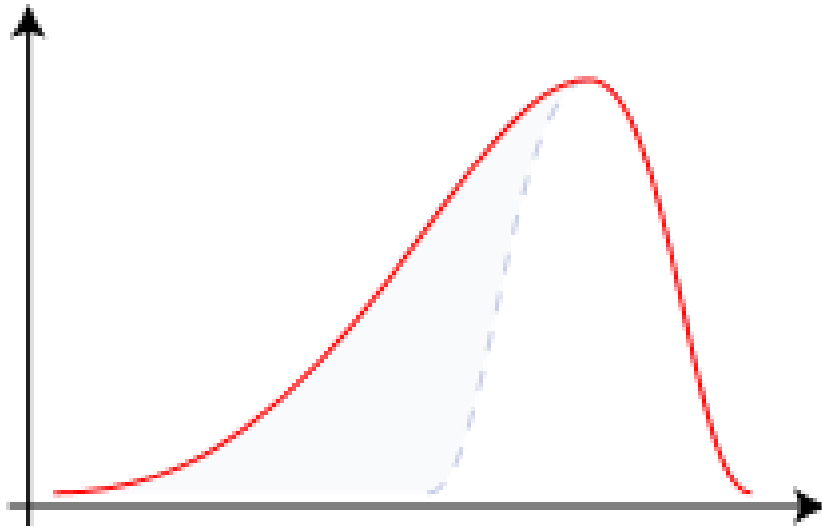
Coefficient of variation

Normal Distribution



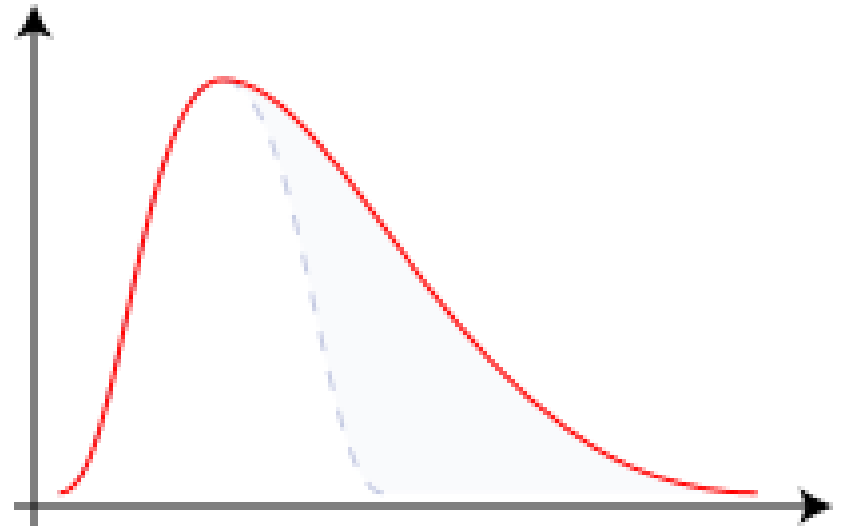
Skewed Data

SpO₂



Negative Skew

BNP, AST, ALT, GGT



Positive Skew

LMS System

(since 1964)

Random group of healthy subjects

→ measurements

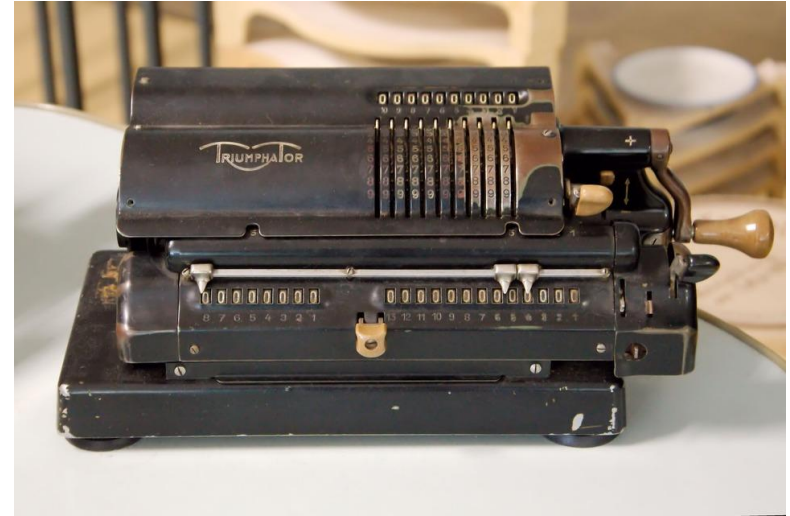
→ $M = (\text{arithmetic mean} + \text{geometric mean} + \text{harmonic mean}) / 3$

→ $S = \text{s.d.} / M$

→ $L = \text{Box-Cox-Power}$ ($L=1$ normal distribution, $L=0$ log. distribution)

Patient → single measurement → calculate „z-value“

$$\left\{ \begin{array}{l} z = ((x/M)^L - 1) / S / L \\ \text{if } L=0: \quad z = \ln(x/M) / S \end{array} \right.$$



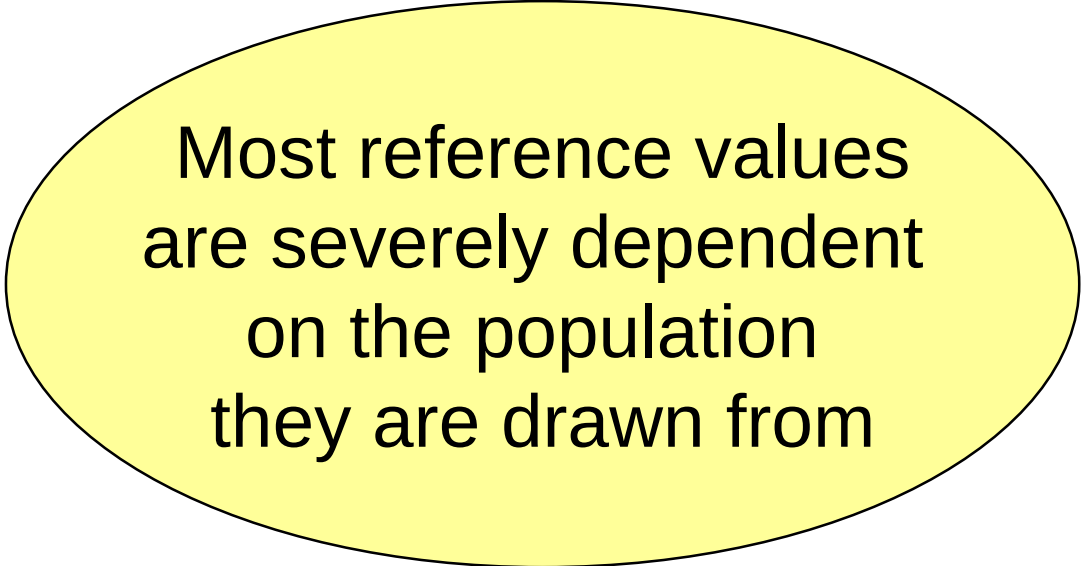
One reference for all subjects?

„YES“ for plasma sodium

„NO“ for almost everything else

Which variables to account for?

- Age
- Sex
- Body mass
- Body height
- Race
- Economic status
- Smoking status
- Medication
- Disease
- ...



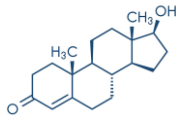
Most reference values
are severely dependent
on the population
they are drawn from

Sex



Sex

Gender



SRY-Gen

Phenotype

Role
(Gender role)

(Gender identity)



X0, XXX, ...
XX

Deletion
SRY -

Estradiol
(Testosterone)



Trans-woman
Woman



Mosaicism
XX/XY, X0/XY

Translocation
Deletion
Mutations

Adrenogenital
syndrome (AGS)

Intersex

Non-binary

We all



XY
XXY, XYY, ...

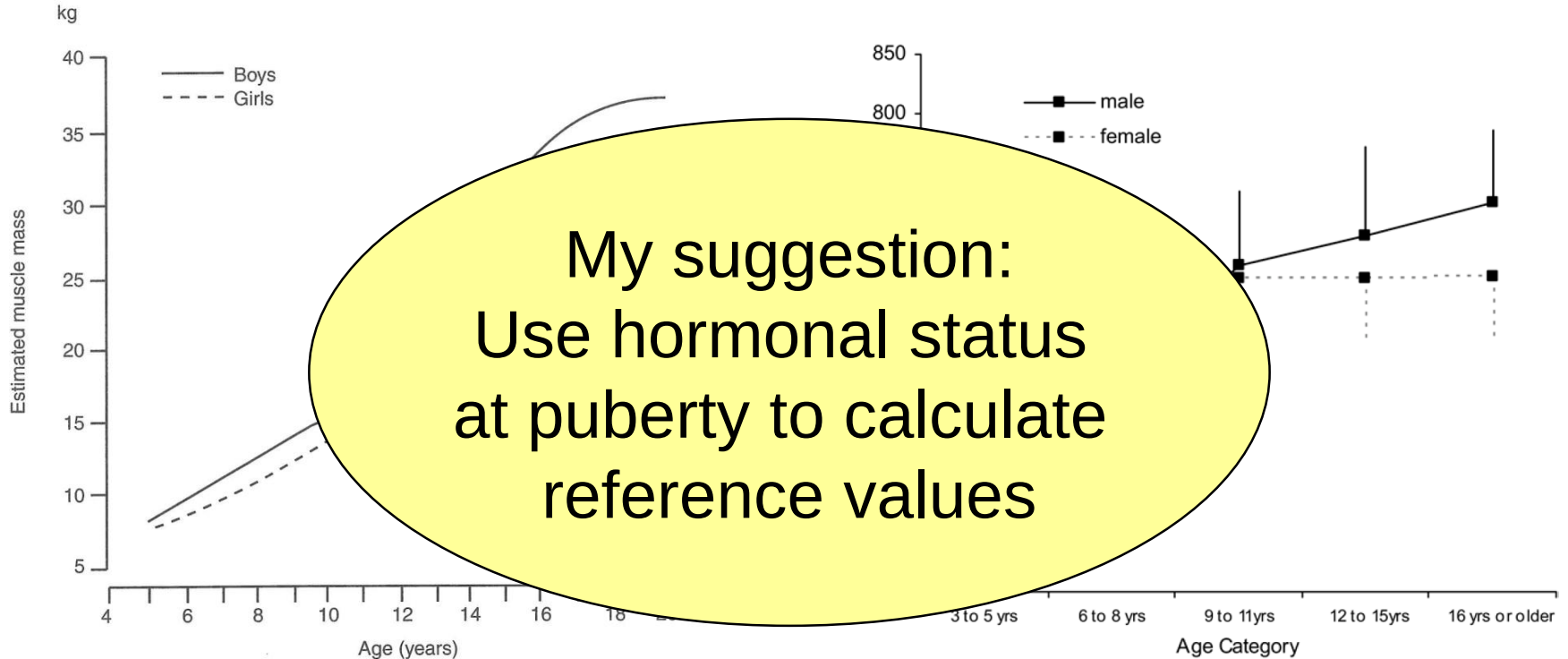
SRY +
Translocation

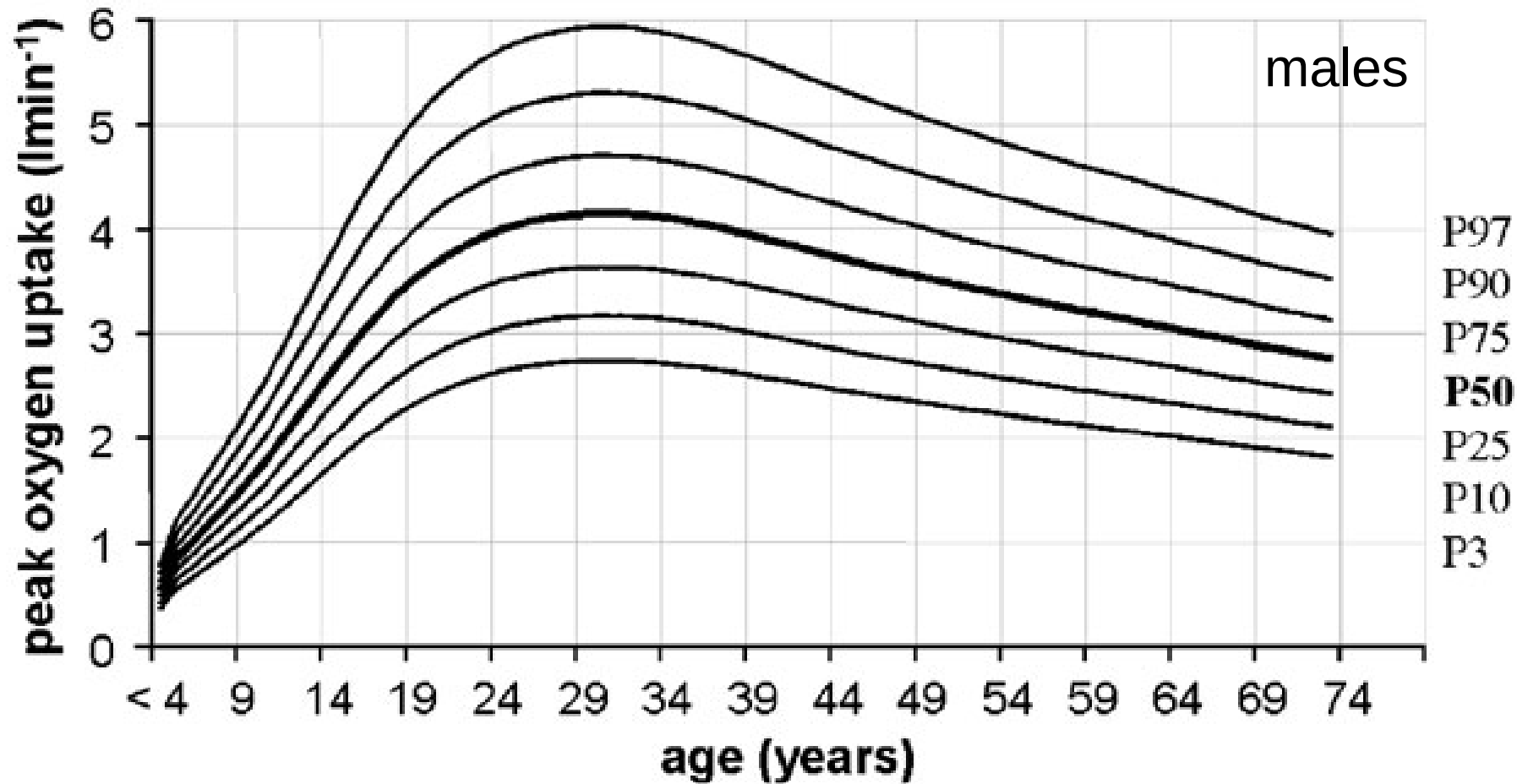
Testosterone
(Estrogens)



Man
Trans-man

Sex





Dubowy, treadmill, reference data

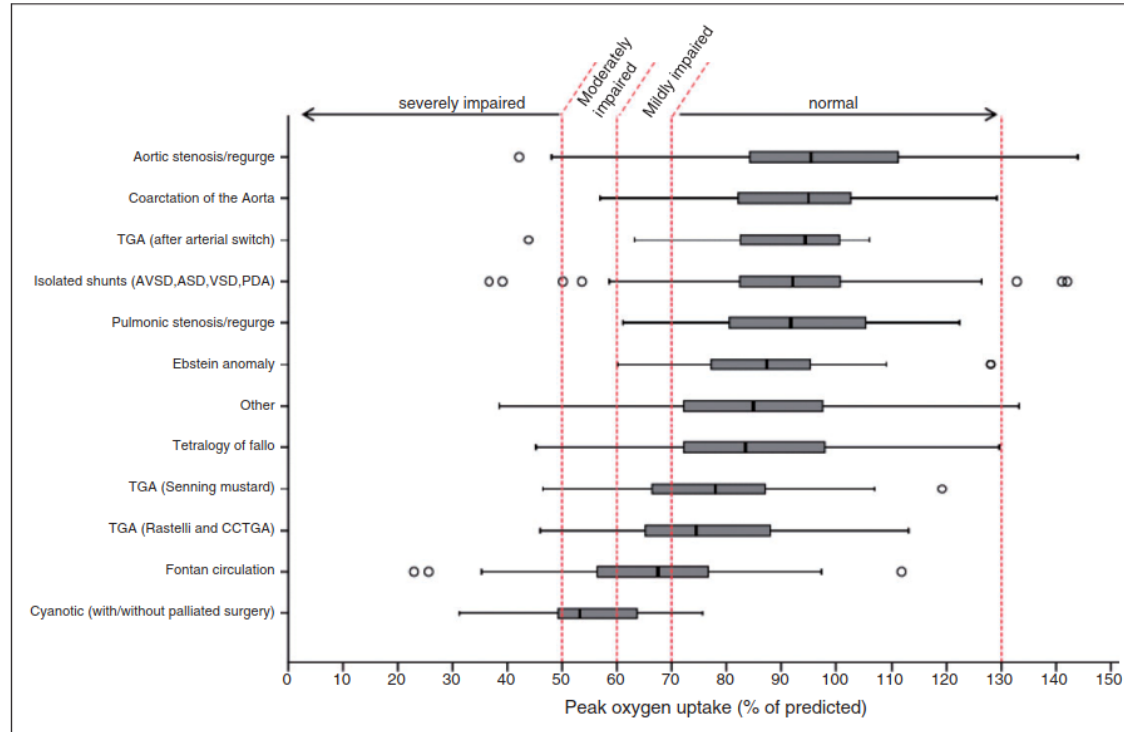
Is it useful to update?

- Current reference data represent the current normal population
- Useful for body mass?
- Useful for blood pressure?
- Useful for exercise capacity?

Disease-specific References

- 1. Peterman JE, Arena R, Myers J, Marzolini S, Ades PA, Savage PD, et al. Reference Standards for Cardiorespiratory Fitness by Cardiovascular Disease Category and Testing Modality: Data From FRIEND. Journal of the American Heart Association. 2021;10(22):e022336.

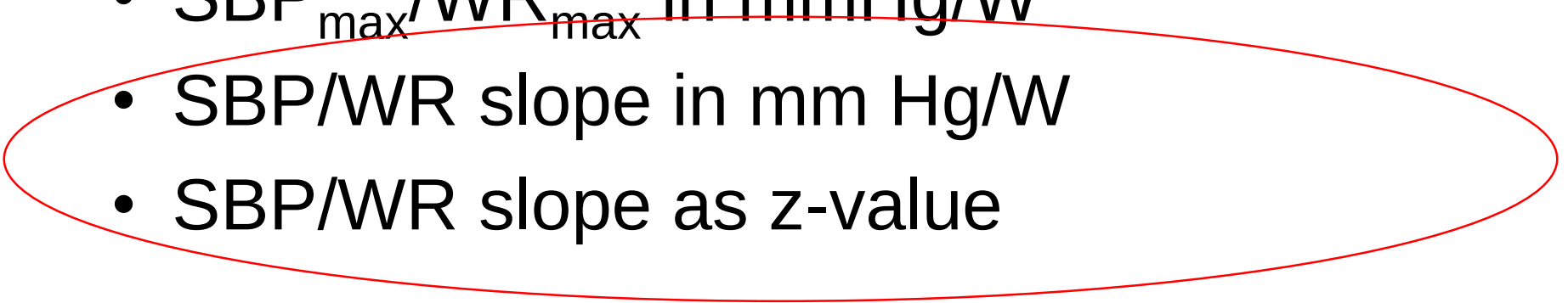
Disease Specific References



Which values?

- peakVO₂ in ml/min/kg
- peakVO₂ in ml/min/kg as %predicted
- peakVO₂ in ml/min
- peakVO₂ in ml/min as %predicted
- peakVO₂/peakWR in ml/min/W
- VO₂/WR slope in ml/min/W
- delta VO₂/WR slope („double-slope“)?

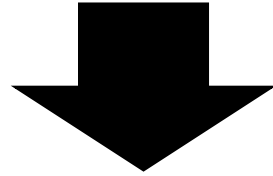
Which values?

- Systolic Blood Pressure in mmHg
 - SBP as % predicted
 - SBP_{max}/WR_{max} in mmHg/W
 - SBP/WR slope in mm Hg/W
 - SBP/WR slope as z-value
- 

Out-of-Range Subjects

- Are they diseased?
 - body mass -> obesity (yes)
 - body height -> Marfan? (maybe)
 - genetic polymorphisms (no)
- Do they need treatment?

Reference Ranges



Disease Specific Thresholds

Thresholds

Usually derived from ROC analysis
and optimized for sensitivity and specificity
by the

Yes

Screening test: sensitivity more important
Confirmation test: specificity more important

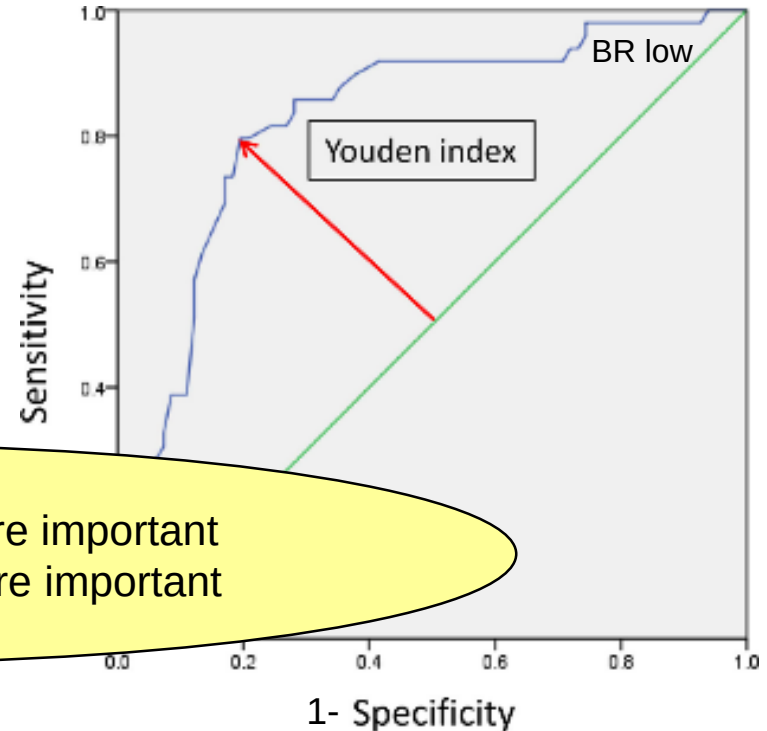
Specificity -1

Youden index

breathing reserve
@ peak exercise
represents
pulmonary disease

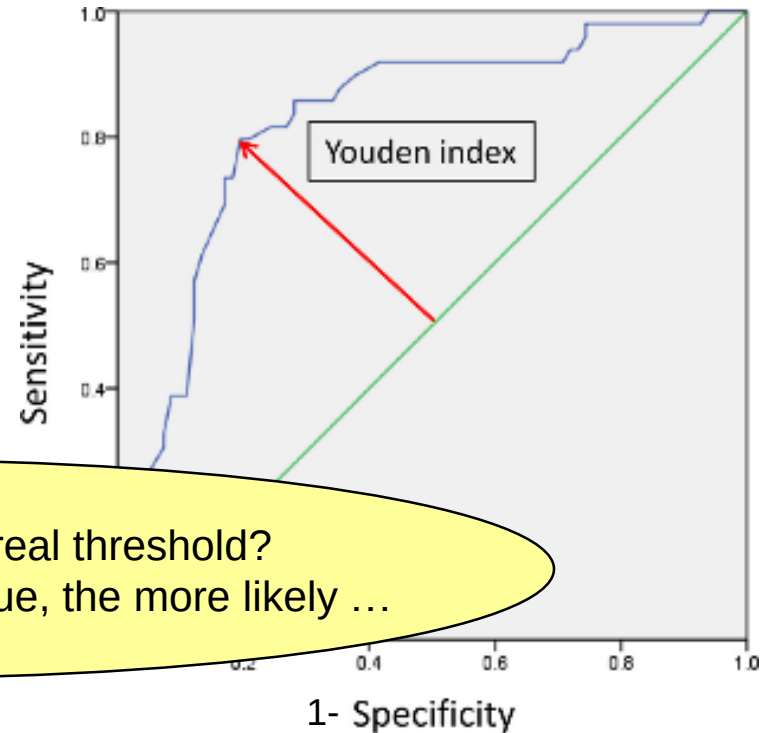
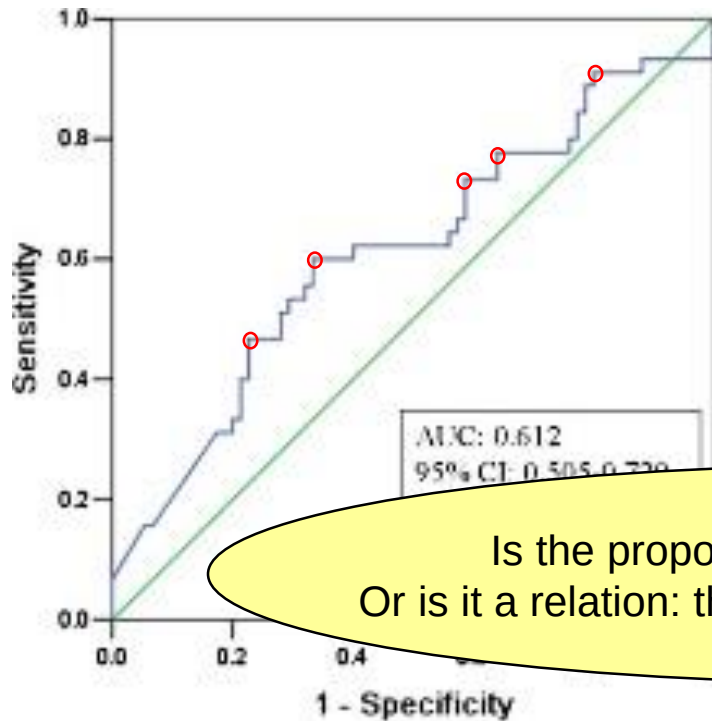
Low value = high sensitivity

High values = high



Screening test: sensitivity more important
Confirmation test: specificity more important

Youden index



Is the proposed threshold a real threshold?
Or is it a relation: the higher the value, the more likely ...

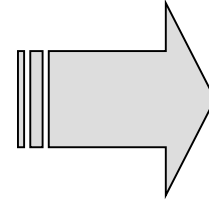
BR Thresholds

- In athletes (and active children) breathing reserve is depleted at the end of exercise
- A higher cadence rate leads to less work rate, higher V_E , and **less BR**, with similar VO_{2peak} (Knox-Brown 2025)
- In healthy subjects BR is rarely below 10%, which indicates ventilatory disease (Wasserman)
- In heart failure patients BR is rarely below 33%, which indicates COPD (Barron 2016)

- M
- Mos

All proposed thresholds
are severely dependent on the population
they are derived from

Take-Home Message



Reference values from healthy populations

can be used when no disease specific data is available.

They should be analyzed with care (*treating patients not values*).

Thresholds from disease specific studies

are much more relevant for diagnostic purposes or disease specific risk assessment. However, they depend severely on the inclusion criteria of the population they are derived from

(*pretest conditions or pretest probability*).

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