Forum Norr Statistikernätverk

Lunchseminarium 11/3 2024

From Data to Decision: A Guide to Developing and Assessing Risk Prediction Models

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Outlines

- What is the risk prediction model?
- How and when to use it?
- How to develop a risk prediction model?
- How to evaluate?

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Predictor finding studies (risk factor or prognostic factor studies)

Aim to identify which predictors independently contribute to the prediction of a diagnostic or prognostic outcome

Prediction model studies

Aim to develop, validate or update a multivariable prediction model

Wolff RF, Moons KGM, Riley RD, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019 Jan;170(1):51–8.

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Risk prediction models

- Use predictors (covariates) to estimate the **absolute probability or risk** in an individual with a particular predictor profile

- Predictors
  - subject characteristics (eg, age and sex), examination results, imaging, electrophysiology, blood, urine, genetic markers, proteins and metabolites, etc.

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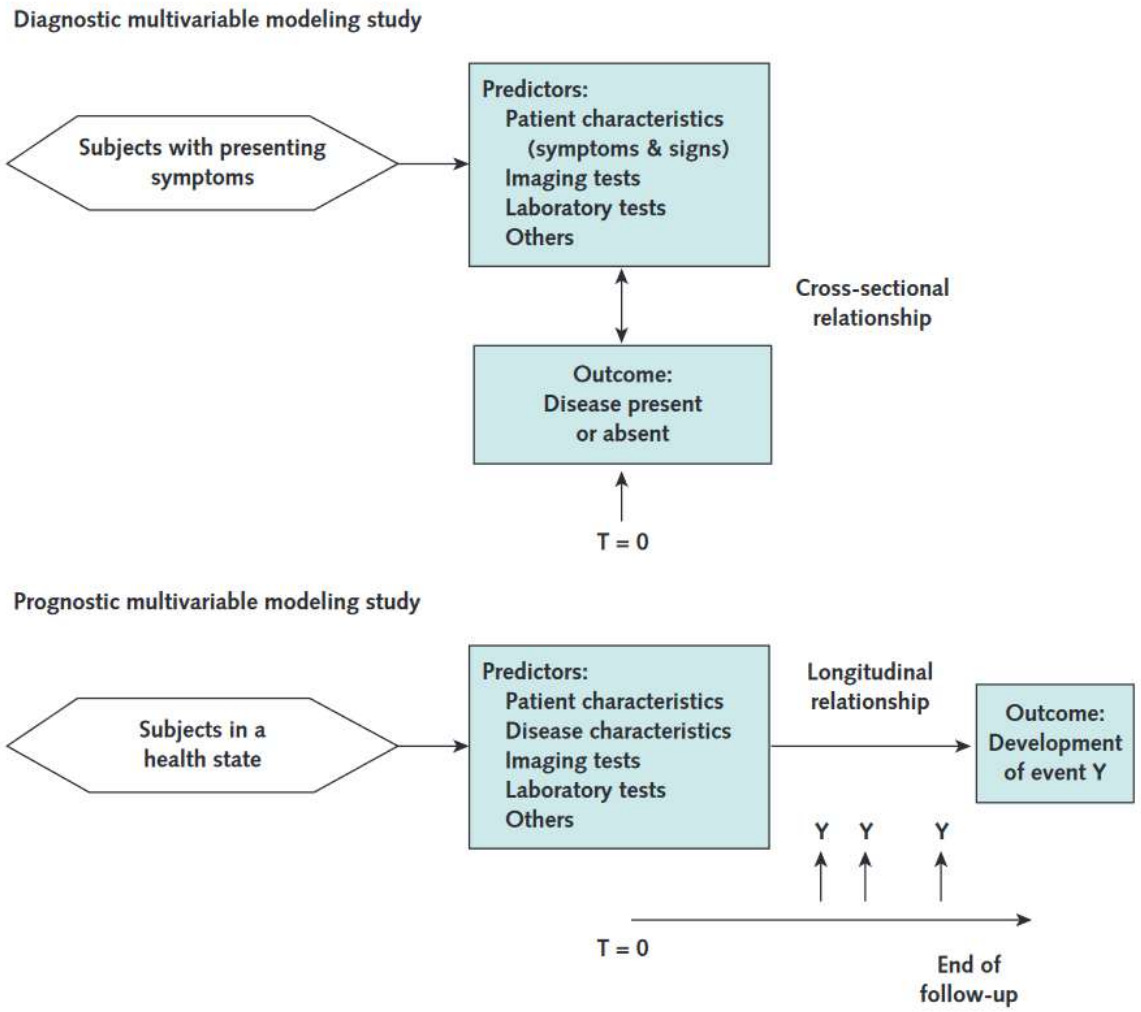
TRIPOD statement

Box A. Schematic representation of diagnostic and prognostic prediction modeling studies.



Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration. Ann Intern Med. 2015 Jan 6;162(1):W1–73.

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Purpose

- to guide healthcare professionals and individuals in their decision making
  - decide whether we need further testing by predicting the probability of the underlying disease
  - decide whether we need to start a treatment/use more intensive treatment/delay a treatment
  - decide whether we need a surgery by balancing short-term risks (e.g., 30-day mortality) and long-term risks (e.g., long-term survival risk)

- to inform individuals about their risks of having (diagnosis) or developing (prognosis) a particular disease or outcome.

PMID:32175364

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Examples

Journal of
Clinical Medicine

MDPI

Article

Loss of Smell and Taste Can Accurately Predict COVID-19 Infection: A Machine-Learning Approach

$$x = -1.76 + 0.88 \times ((1 \text{ if VAS for loss of smell} \geq 21) \text{ or } (0 \text{ if VAS for loss of smell} < 21)) + 1.83 \times ((1 \text{ if VAS for loss of taste} \geq 44) \text{ or } (0 \text{ if VAS for loss of taste} < 44)) + 0.79 \times ((1 \text{ if VAS for dyspnea} \geq 28) \text{ or } (0 \text{ if VAS for dyspnea} < 28)) + 0.61 \times ((1 \text{ if fever}) \text{ or } (0 \text{ if no fever})) + 0.70 \times ((1 \text{ if diarrhea}) \text{ or } (0 \text{ if no diarrhea})) - 1.13 \times ((1 \text{ if female}) \text{ or } (0 \text{ if male}))$$

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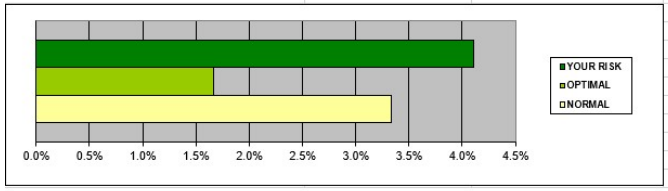
Examples

- Framingham risk score

From The Framingham Heart Study — **Enter Values Here**

General CVD Risk Prediction

Risk Factor	Units	(Type Over Placeholder Values in Each Cell)	Notes
Sex	male (m) or female (f)	f	
Age	years	45	
Systolic Blood Pressure	mmHg	135.0	
Treatment for Hypertension	yes (y) or no (n)	n	
Smoking	yes (y) or no (n)	n	
Diabetes	yes (y) or no (n)	n	
HDL	mg/dL	45	
Total Cholesterol	mg/dL	180	
Your 10-Year Risk (The risk score shown is derived on the basis of an equation. Other print products, use a point-based system to calculate a risk score that approximates the equation-based one.)		4.1%	*If value is < the minimum for the field, enter the minimum value. If value is > the maximum for the field, enter the maximum value.*
Your Heart/Vascular Age		49	



Calculator prepared by R.B. D'Agostino and M.J. Pencina based on a publication by D'Agostino et al. in Circulation

https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/

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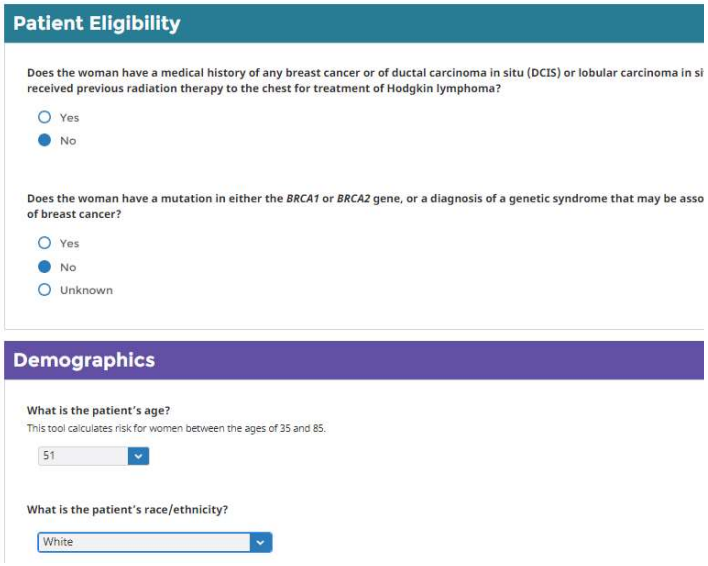
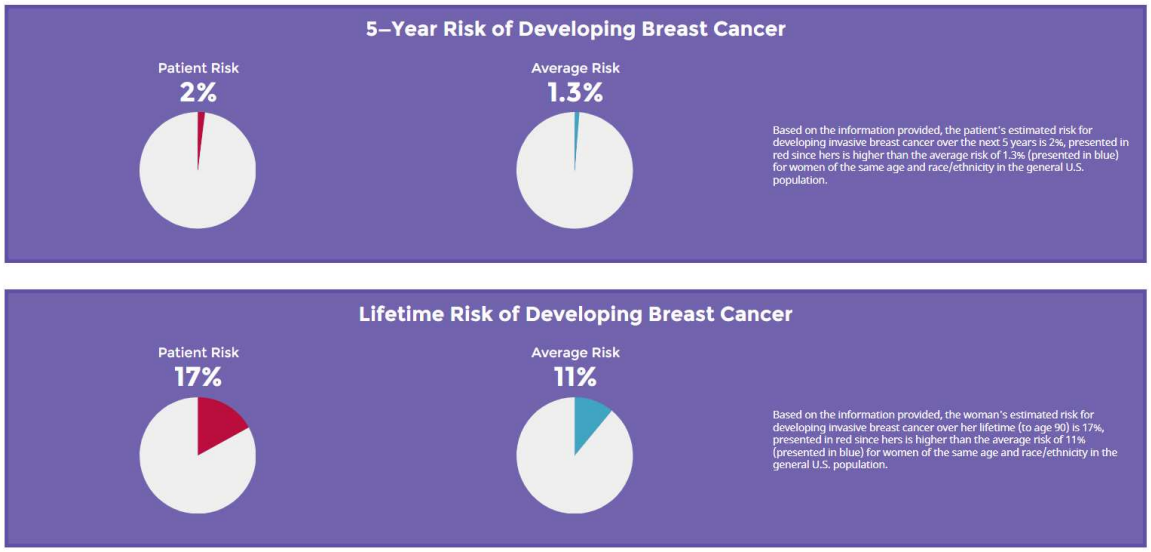
Examples

- Breast cancer risk assessment model (The Gail Model)





https://bcrisktool.cancer.gov/calculator.html

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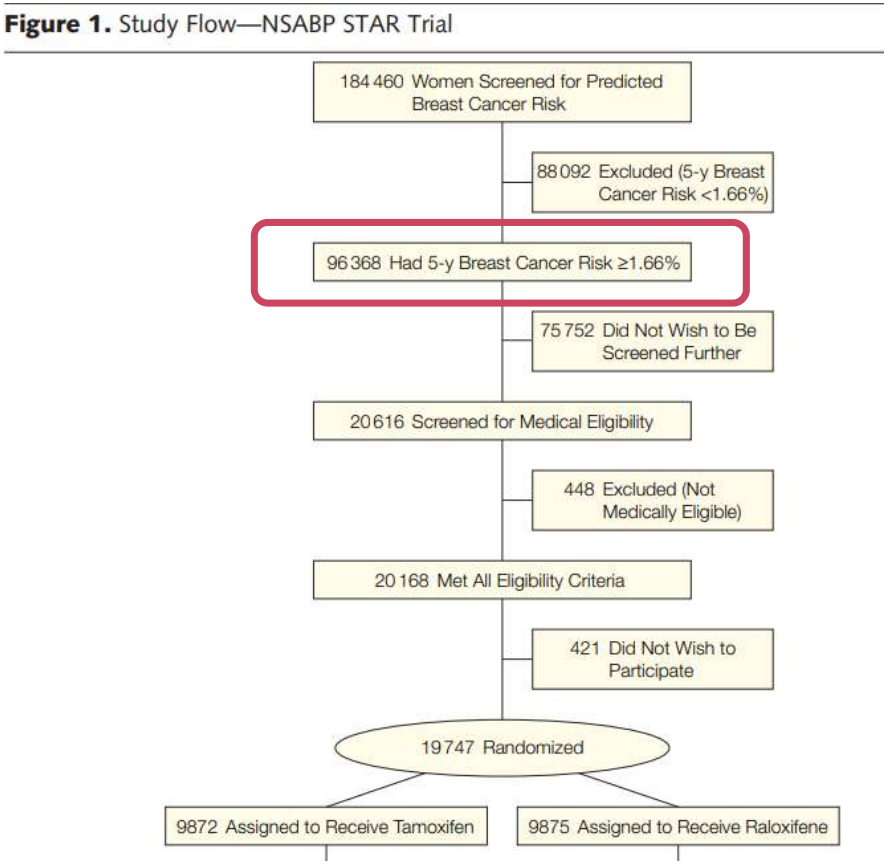
Applications

- Select appropriate participants for randomized controlled trials



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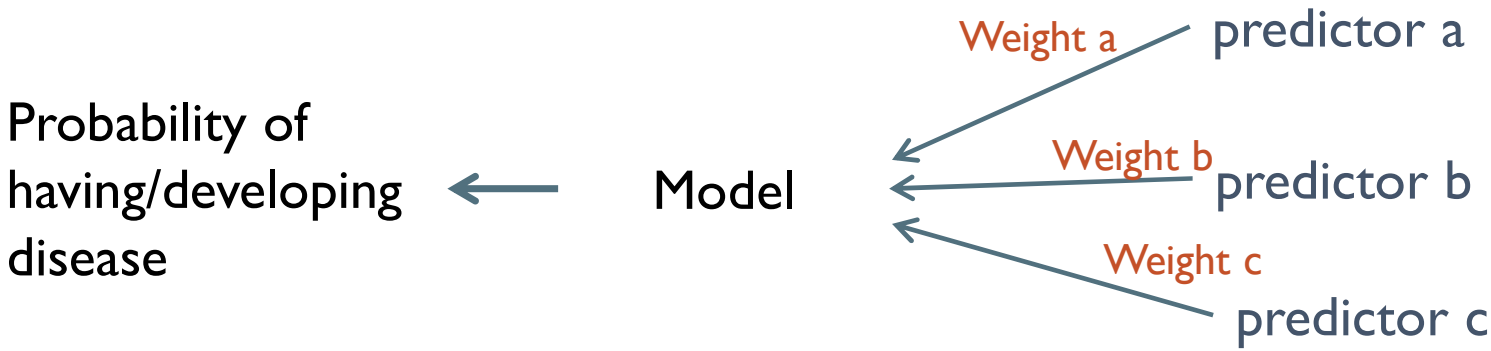
Risk prediction model



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Developing a risk prediction model

- Identification of the important predictors (out of a set of preselected candidate predictors)
- Assigning the relative weights for each predictor in a combined risk score
- Estimating the model's predictive performance
  - Including its calibration, discrimination and reclassification properties
- Assessing its potential for optimism using so-called internal validation techniques
- Adjusting the model for over fitting if necessary

Moons KGM, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012 May 1;98(9):683–90.

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Source of data

- Cohort, (nested case-control, case-cohort)
- Registry data
- RCT

- Case-control study (only for diagnostic multivariable model)

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Candidate predictors

- Theoretically, all variables suspected of being associated with the outcome of interest could be considered as candidate predictors, but this association does not need to be causal.
- Existing knowledge of previously established predictors
- Clearly defined and measured in a standardized and reproducible way
  - Lower measurement error or inter-observer variability (reliability, consistency)
- More pragmatic (applicability, availability and cost)
  - Develop a model that is applicable in daily practice→ use predictors that are in line with daily practice
  - Quite readily available, not too costly to obtain, and can be measured with reasonable precision

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Analysis

- Missing data:
  - Imputation of missing values often yields less biased results
- Continuous predictors
  - Should not be turned into dichotomies and linearity should not be assumed
- Model

Spline

Type of response variable	Model
Continuous	Linear regression
Binary	Logistic regression
Time to event	Cox PHs regression

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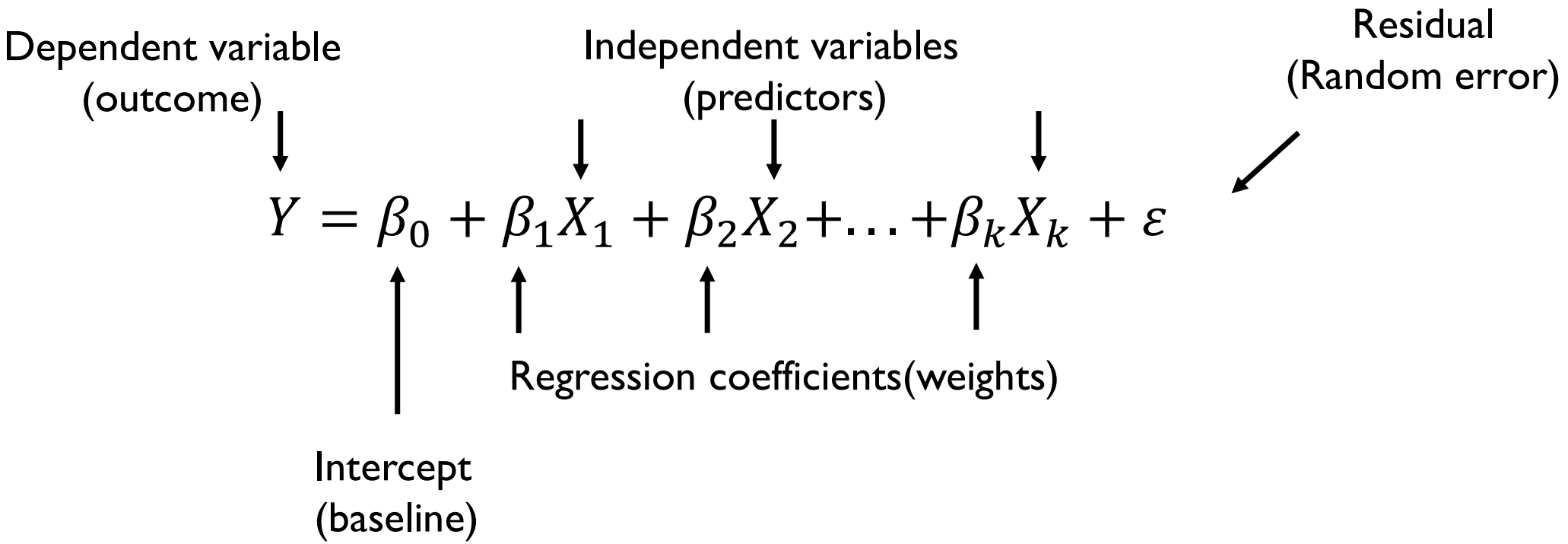
Linear regression



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Logistic regression

Dependent variable (outcome)

Independent variables (predictors)

$$log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$$

Regression coefficients (weights)

Intercept (baseline)

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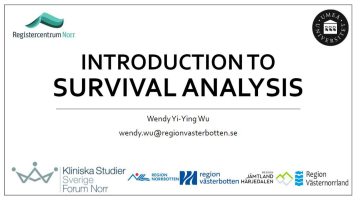
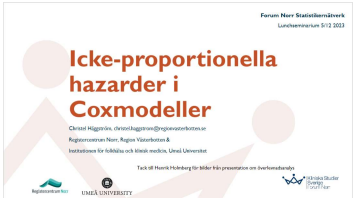
Cox proportional hazards regression





Dependent variable (outcome)

Independent variables (predictors)

$$h(t) = h_0(t) \times \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k)$$

baseline hazard

Regression coefficients (weights)

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Analysis

- Too many predictors but too little data (p>>n)
  - Problems?
    - False positive findings
    - Poor validation
  - Solution:
    - Sample size calculation
    - EPV (event per variable): 1 to 10 (20) rule of thumb is often applied.
    - Data reduction: variable clustering
      - Combined similar predictors to a single one: all different types of CVD history
      - Principle component analysis/ hierarchical clustering

Type of response variable	Model	Number of predictors
Continuous	Linear regression	Total sample size / 15
Binary	Logistic regression	$\text{Min}(n_1,n_2)$ /15
Time to event	Cox PHs regression	Number of failures / 15

Harrell, F. E., Jr. (2016). *Regression modeling strategies*. Springer International Publishing.

Developing the final model

- There is no consensus about the best method of arriving at the final model.
  - Full model
    - all candidate predictors are included in the final prediction model
  - Predictor selection strategy
    - Backward elimination better than forward selection

Risk scores

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k + \varepsilon$$

$$log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$$

$$h(t) = h_0(t) \times \exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k)$$

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Model performance

Discrimination

- How well the model differentiates individuals who experienced the outcome from those who remained event free

Calibration

- Agreement between prediction probability and observed outcome frequencies

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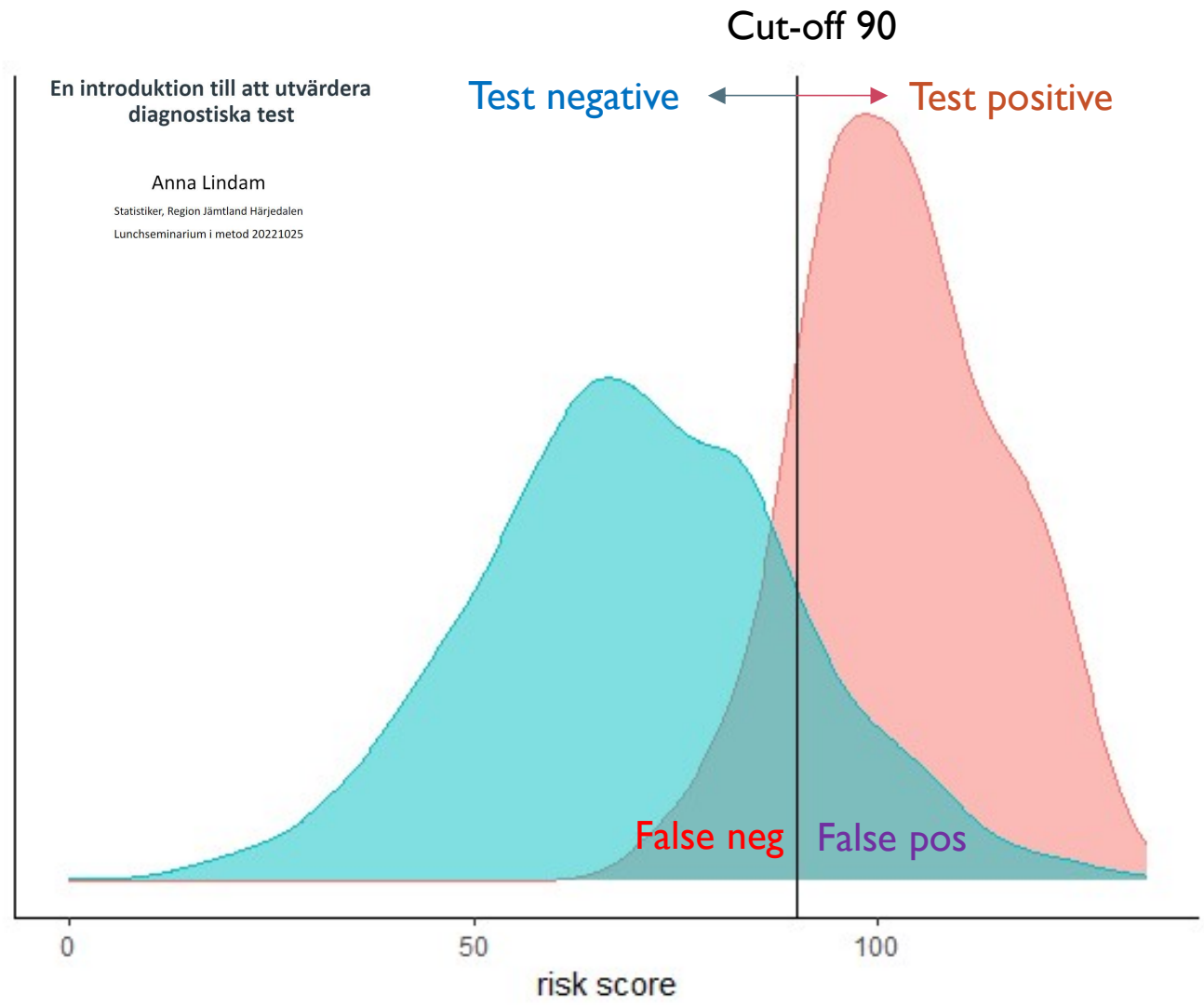
Discrimination



	Disease status	
Test (90)	Yes	No
Positive	a	c
Negative	b	d

Sensitivity: a/(a+b)
Specificity: d/(c+d)

case

	Disease status	
Test (80)	Yes	No
Positive	a+x	c+y
Negative	b-x	d-y

Sensitivity: (a+x)/(a+b)
Specificity: (d-y)/(c+d)

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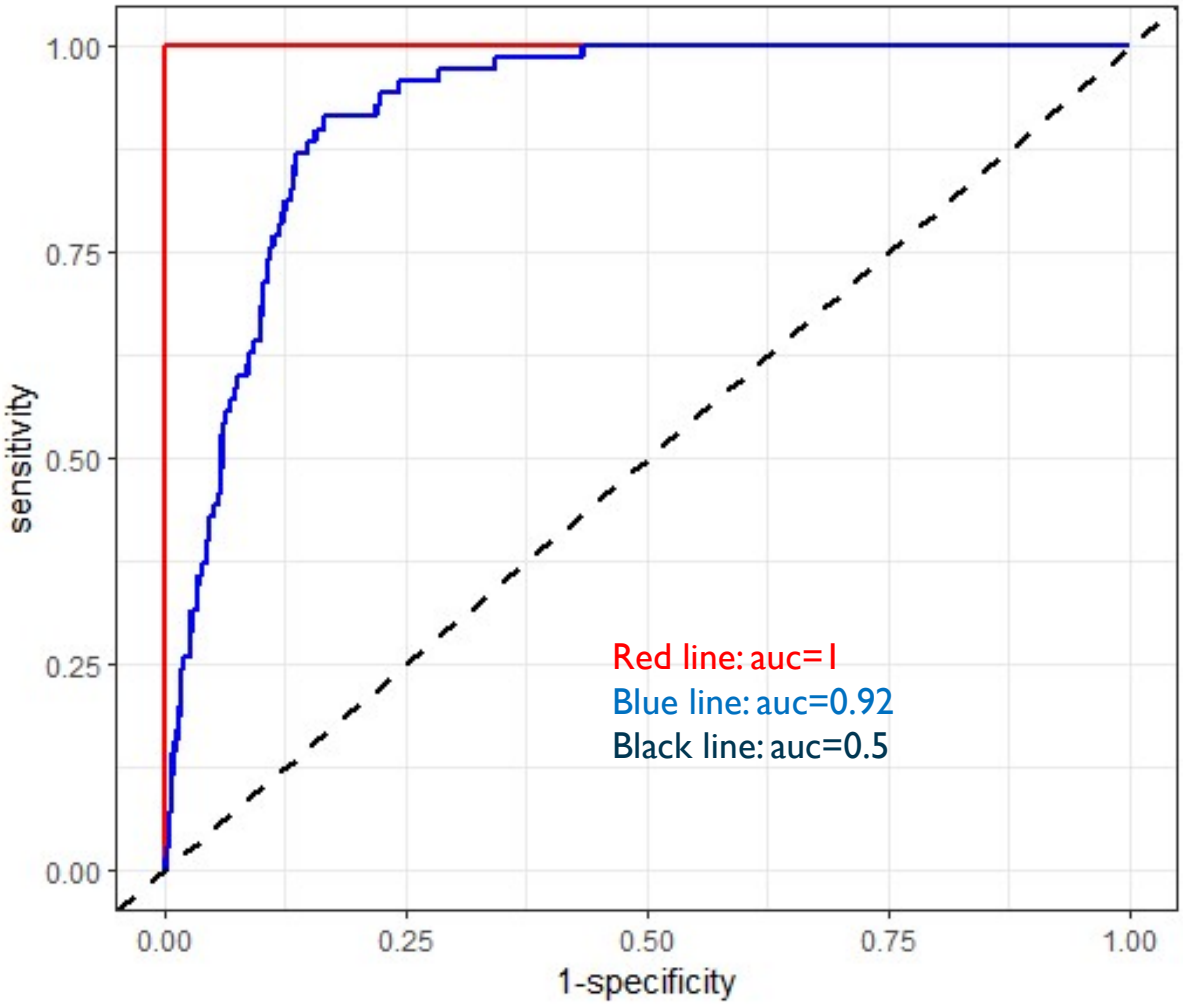
Discrimination

Receiver operating characteristic (ROC)



Area under curve (c-statistics):

- the chance that given two individuals, one who will develop the event of interest and one who will remain event free, the prediction model will assign a higher probability of an event to the former.

- C statistics
  - <0.6 poor discrimination
  - 0.6-0.75, possibly helpful discrimination
  - >0.75 clearly helpful discrimination

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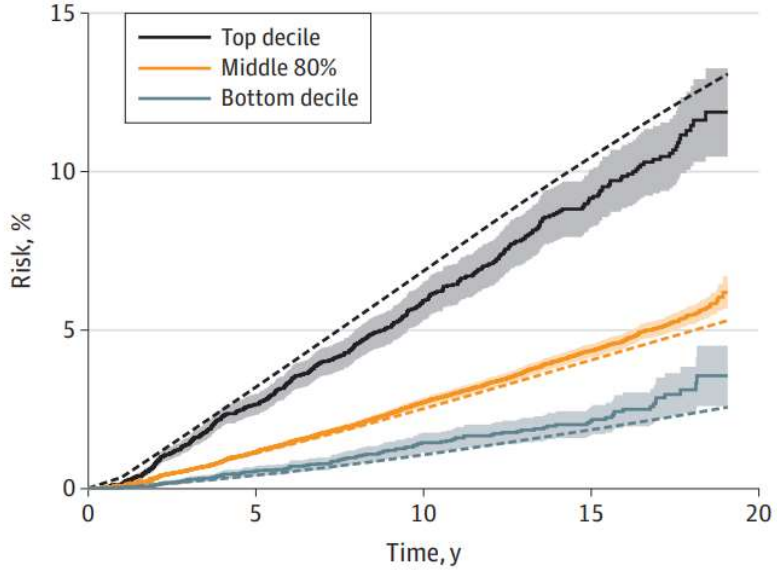
Calibration

the accuracy of absolute risk estimates

A Tyrer-Cuzick model



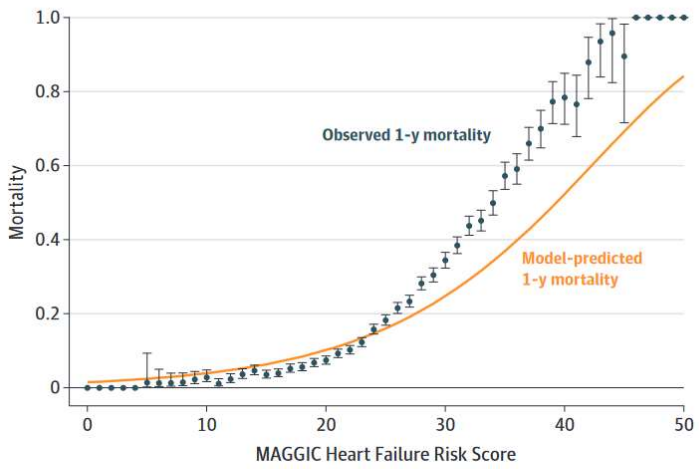
No. at risk

Top decile	13214	6331	3234	1545
Middle 80%	105712	55209	30492	16232
Bottom decile	13213	6616	3504	1766

Solid lines indicate observed risk;
broken lines indicate expected risk

PMID: 29621362

Figure 2. Observed and Predicted 1-Year Mortality



The graph represents the relationship between observed (the data markers represent the mean and the error bars represent the 95% CI) and predicted 1-year mortality using the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (orange line). The model underestimated mortality in patients with a predicted mortality greater than 30%. Adapted from Sartipy et al.[29]

PMID: 29049590

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Internal Validation

- The model was designed to optimally fit the development samples and it becomes less accurate when tested in new but similar individuals (overfitting)
  → Models might yield optimistic apparent performance
  - Optimism in model performance increases when the number of predictors increases and the number of events decreases
- Internal validation
  - to estimate the potential for overfitting and optimism in model performance
  - to calculate a developed prediction model's reproducibility for the derivative sample and protects current data from being misinterpreted.

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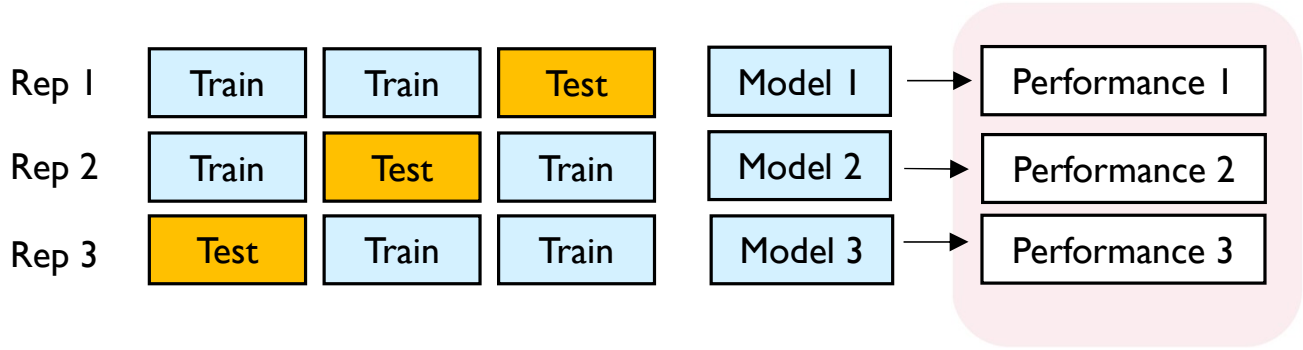
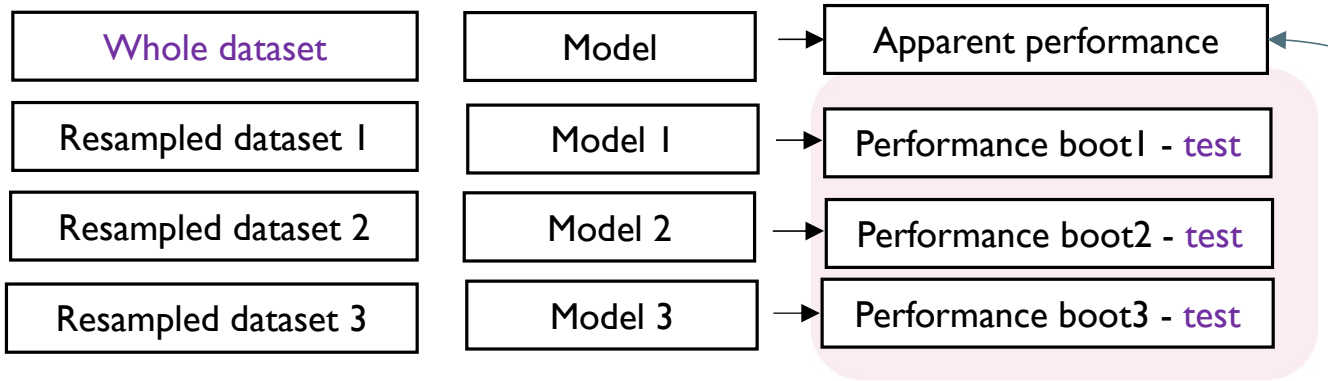
Internal Validation

- Split-sample
  - 2/3 trained dataset and 1/3 validation
- Cross-validation

Statistically inefficient because not all data are used to produce the prediction model



- Bootstrapping



Things to consider

Don't do this

- Predictors: what I have in hand
- Analysis: excluding the participants with missing values
- Analysis: categorised a continuous variable
- Validation: randomly splitting a single data set into model development and model validation data sets

Do this

- Predictors: formulating good hypotheses that lead to specification of relevant candidate predictors and possible interactions.
- Analysis: imputing the missing values if possible.
- Analysis: using a continuous variable and allow nonlinearity
- Validation: using entire sample for model development and bootstrapping for internal validation

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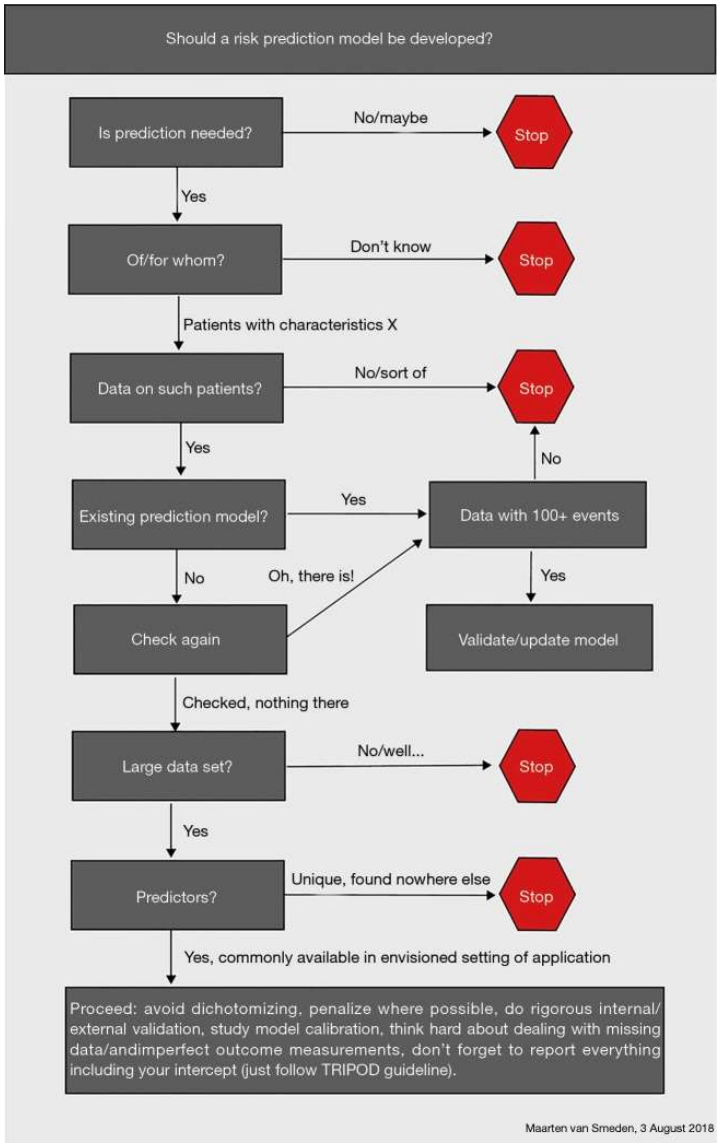

Should a risk prediction model be developed?

https://twitter.com/MaartenvSmeden/status/1025315100796899328

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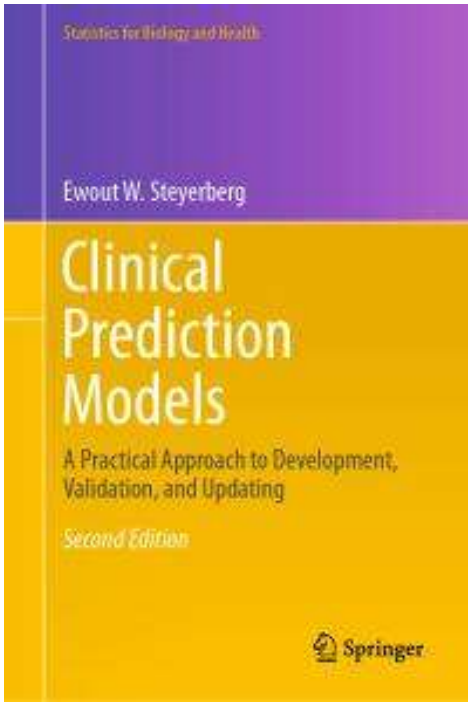
Suggested references



- Moons KGM, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012 May 1;98(9):683–90.
- Moons KGM, Kengne AP, Grobbee DE, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012 May 1;98(9):691–8.
- Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration. Ann Intern Med. 2015 Jan 6;162(1):W1–73.
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Coming Seminars

- Canvas page: https://www.canvas.umu.se/courses/2600
- **10/4 kl 12-13 Rensning och samkörning av forskningsdata**

  Christel Häggström, Region Västerbotten/ Institutionen för folkhälsa och klinisk medicin, Umeå universitet
- **7/5 kl 12-13 Metoder för upprepade mätningar**

  Staffan Betnér, Region Västerbotten/ Institutionen för folkhälsa och klinisk medicin, Umeå universitet
- **30/5 kl 12-13 Korstabeller och andra jämförelse över andelar**

  Anna Lindam, Region Jämtland Härjedalen / Institutionen för folkhälsa och klinisk medicin, Umeå universitet

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