A framework for developing, implementing and evaluating clinical prediction models across multiple studies with binary outcomes

Thomas Debray

Moons KGM, Ahmed I, Koffijberg H, Riley RD

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University Medical Center
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for Health Sciences and Primary Care

Prediction modeling and IPD meta-analysis

- Opportunities
  - Increase effective sample size
  - Improve generalizability
- Challenges
  - **Heterogeneity** of IPD populations (e.g. baseline risk)
  - **Validation** of aggregated model
  - **Implementation** of aggregated model in new individuals
- Assumptions
  - Logistic regression models
  - Homogeneity of predictor-outcome associations
- Illustrative example
  - Diagnosis of Deep Venous Thrombosis
  - IPD from 12 studies ($N = 153 - 1768$)

Step 1: Estimation of predictor-outcome associations

What β terms will be used in the final model?

- Stacking

$$y_i \sim \text{Bernoulli}\left(\pi_i\right)$$
$$\text{logit}\left(\pi_i\right) = \alpha + \boldsymbol{\beta}'\mathbf{X}_i$$

- Random effects modeling of the intercept

$$\text{logit}\left(\pi_{ij}\right) = \alpha_j + \boldsymbol{\beta}'\mathbf{X}_{ij} \quad \text{with} \quad \alpha_j \sim \mathcal{N}\left(\alpha, \tau_\alpha^2\right)$$

- Stratified estimation of the intercept

$$\text{logit}\left(\pi_{ij}\right) = \sum_{m=1}^{M}\left(\alpha_m I_{m=j}\right) + \boldsymbol{\beta}'\mathbf{X}_{ij}$$

Step 2: Choosing an appropriate model intercept

What α term will be used in the final model?

- Average intercept
  - Stacking
  - Random effects
- Intercept from an included study
  - Random effects
  - Stratified estimation
  - Select intercept by similarity in outcome frequency
- New intercept
  - Estimate from outcome prevalence
    (requires mean-centering of predictor variables)
  - Estimate from new IPD

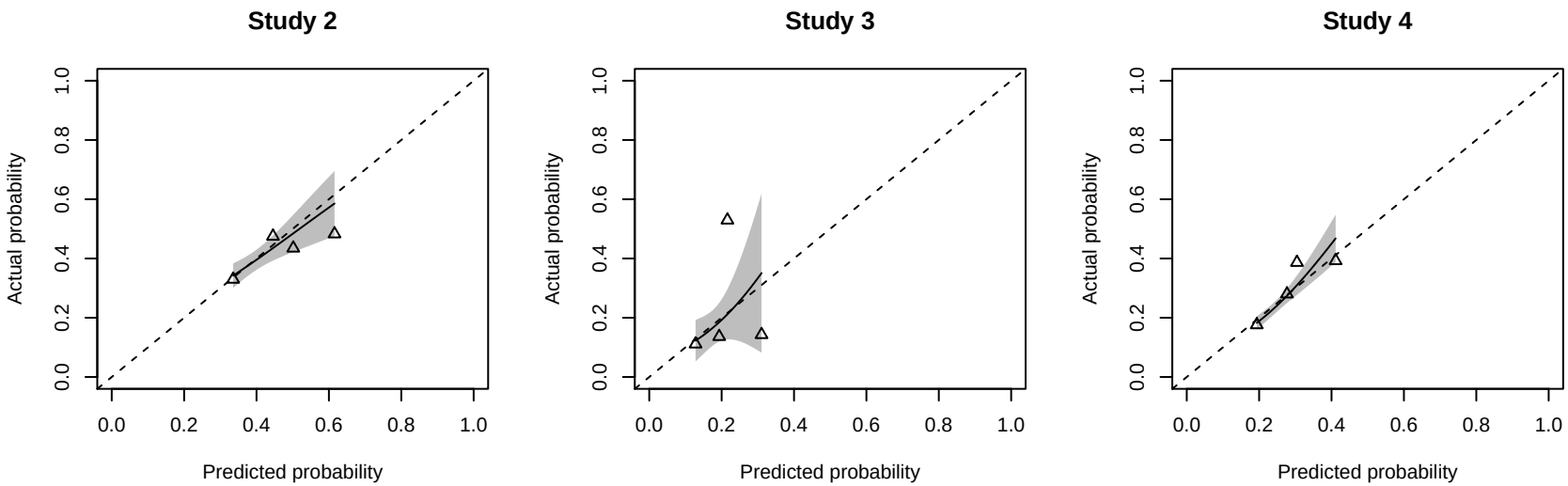
Step 3: Model evaluation

Evaluate entire strategy of **model development** and **intercept choice**

- Internal-external cross-validation (IECV, by Royston *et al.*)
- Iteratively use M-1 studies for derivation and the remaining study for validation
- Distinguish between **discrimination** and **calibration**
- Interpret model performance across M validation rotations
- Develop final model

Illustrative example: DVT (stratified estimation)

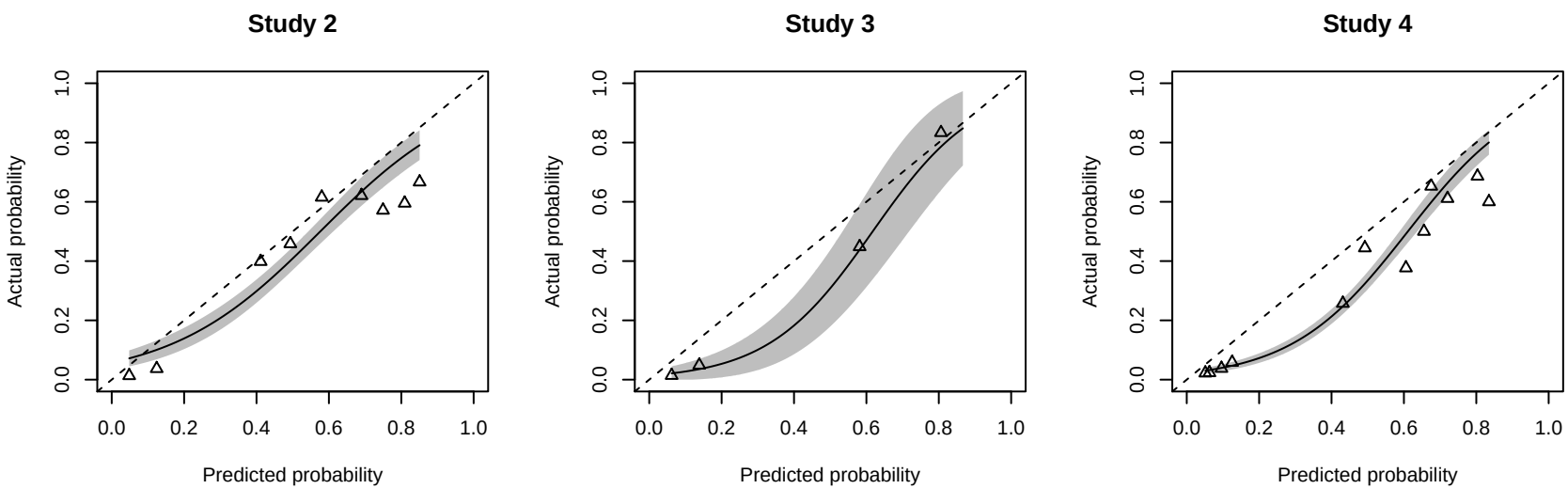
- (Nearly) homogeneous predictor-outcome associations
  - $\hat{\alpha} = -1.80$ ($\hat{\tau} = 0.47$)
  - $\hat{\beta}_{\text{sex}} = 0.47$ ($\hat{\tau} = 0.03$)
  - $\hat{\beta}_{\text{surg}} = 0.67$ ($\hat{\tau} = 0.05$)
- AUC between **0.55** and **0.65** in the IECV



Results for stratified estimation of the intercept (mean-centering of predictor variables). The intercept is estimated from the outcome frequency in the validation population.

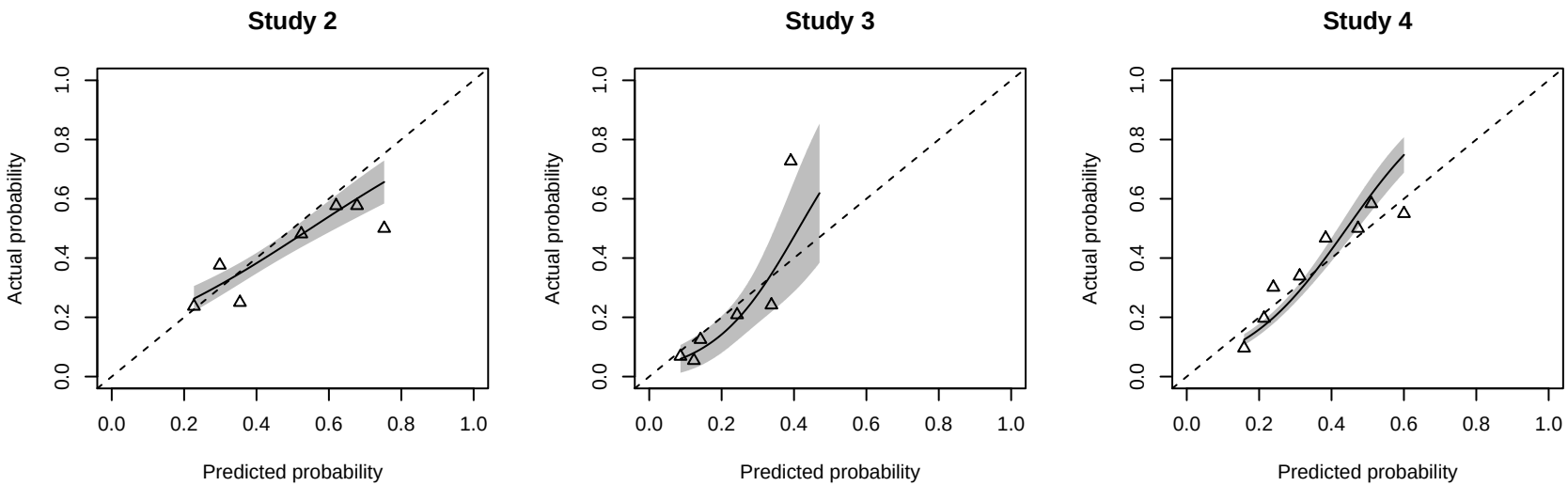
Illustrative example: DVT (stratified estimation)

- Heterogeneous predictor-outcome associations
  - $\hat{\alpha} = -3.98$ ($\hat{\tau} = 0.31$)
  - $\hat{\beta}_{\text{malign}} = 0.38$ ($\hat{\tau} = 0.35$)
  - $\hat{\beta}_{\text{calfdif3}} = 1.05$ ($\hat{\tau} = 0.16$)
  - $\hat{\beta}_{\text{surg}} = 0.25$ ($\hat{\tau} = 0.09$)
  - $\hat{\beta}_{\text{ddimdich}} = 2.76$ ($\hat{\tau} = 0.41$)
- AUC between **0.73** and **0.92** in the IECV



Illustrative example: DVT (stratified estimation)

- Weakly heterogeneous predictor-outcome associations
  - $\hat{\alpha} = -2.25$ ($\hat{\tau} = 0.47$)
  - $\hat{\beta}_{\text{sex}} = 0.37$ ($\hat{\tau} = 0.06$)
  - $\hat{\beta}_{\text{surg}} = 0.56$ ($\hat{\tau} = 0.15$)
  - $\hat{\beta}_{\text{calfdif3}} = 1.28$ ($\hat{\tau} = 0.19$)
- AUC between **0.64** and **0.76** in the IECV



Discussion

- Stratified estimation helps to improve generalizability
  - Final intercept estimated from outcome frequency
  - Final intercept selected based on outcome frequency
  - Average final intercept
  - Requires reporting of estimated intercepts!
- Internal-external cross-validation
  - Appraise model fit and its predictive ability
  - Identify heterogeneous populations
  - Ascertain the best strategy for choosing an intercept
- Avoid heterogeneity
  - Focus on (nearly) homogeneous predictor-outcome associations
  - Investigate non-linear or interaction terms
  - Discard heterogeneous studies from the meta-analysis