Next Generation Health Technology Assessment

A *two-stage* prediction model for heterogeneous effects for many treatment options

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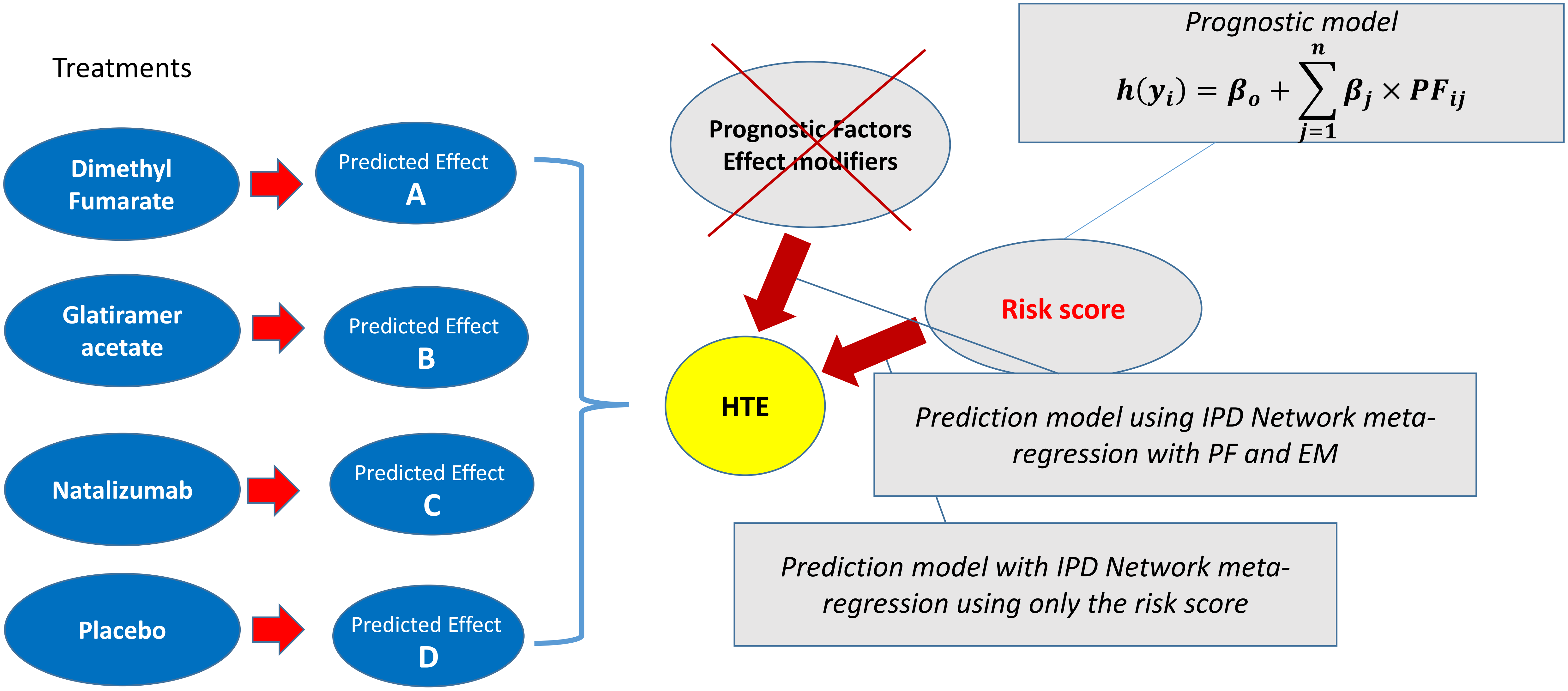
Motivation: Effectiveness of drugs in Relapsing-Remitting Multiple Sclerosis (MS)

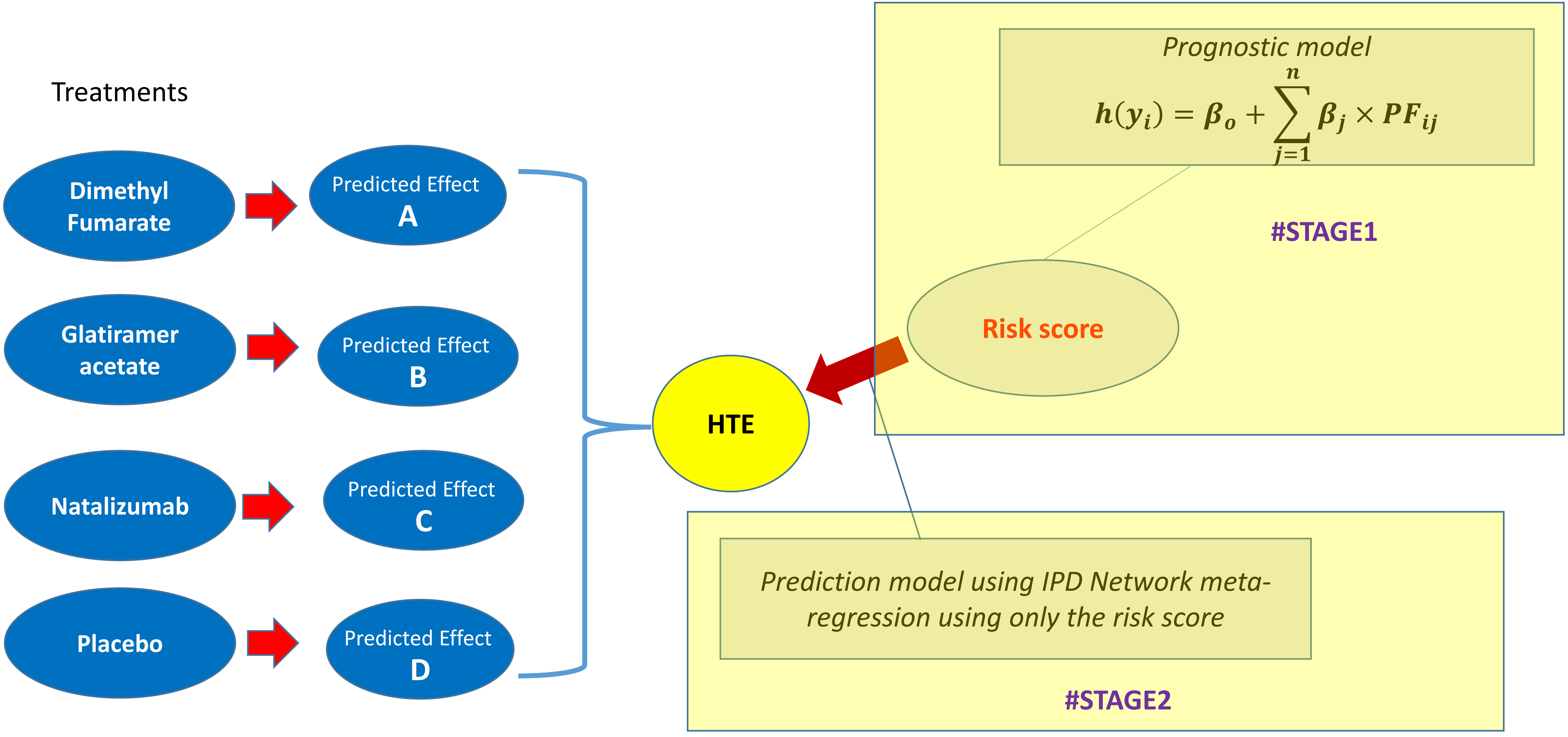
- Several drugs, compared in Network Meta-Analyses (NMA)

  - Tramacere I. et al., 2015
- We focus on ***Dimethyl fumarate***, ***Glatiramer acetate***, and ***Natalizumab***
- Outcome: ***Relapse MS in 2 years*** (Yes/No)
- We want to find the drug that minimizes the risk of relapse, subject to patient characteristics
  - Previous evidence suggests that patients at different age groups and at different stages of the disease might respond differently to the same treatment ➡ **H**eterogeneous **T**reatment **E**ffects

Aim

To develop a ***two-stage*** evidence synthesis ***prediction model*** to predict the most likely outcome under several possible treatment options while accounting for patients' characteristics using ***individual participant data network meta-regression*** with ***risk scores***


Treatments
Dimethyl Fumarate
Glatiramer acetate
Natalizumab
Placebo
Predicted Effect A
Predicted Effect B
Predicted Effect C
Predicted Effect D
~~Prognostic Factors Effect modifiers~~
HTE
Risk score
Prognostic model
$h(y_i) = \beta_o + \sum_{j=1}^{n} \beta_j \times PF_{ij}$
Prediction model using IPD Network meta-regression with PF and EM
Prediction model with IPD Network meta-regression using only the risk score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Prognostic model
$h(y_i) = \beta_o + \sum_{j=1}^{n} \beta_j \times PF_{ij}$
#STAGE1
Risk score
Prediction model using IPD Network meta-regression using only the risk score
#STAGE2

Data

DEFINE → 1234 observations

CONFIRM → 1417 observations

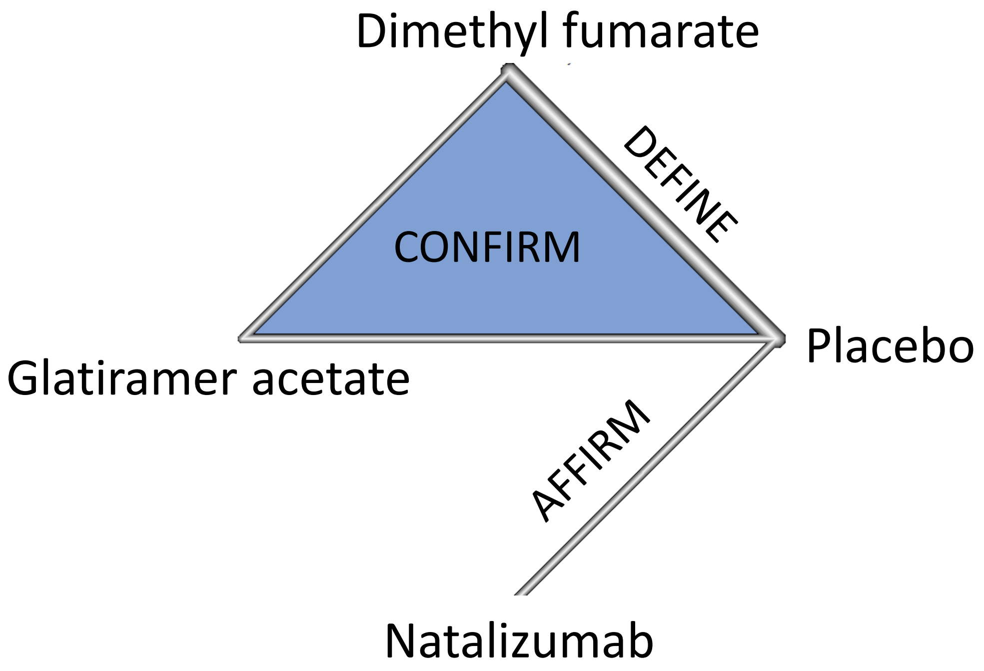
AFFIRM → 939 observations

Total: 2990 observations

70 potential prognostic factors

- previous treatment,
- years since onset of symptoms,
- etc.

Data Cleaning



33 potential prognostic factors

Two-stage model

1. Build the ***prognostic score model***
2. Use the risk score in the ***Individual Participant Data Network meta-regression***

Step 1: Build the prognostic score model (in R using packages glmnet, pentrace)

Build the prognostic score model–
Fit various models

Selection of factors included in the model

Model 1 → LASSO variable selection technique through the **whole dataset** **–** 10-fold cross validation to choose the optimal λ that minimizes the Binomial deviance of the model

Model 2 → Exactly the same variables as in Model 1 & restricted cubic splines for non-linearity

Model 3 → Exactly the same variables as in Model 1 & LASSO selection technique for all possible interactions

Model 4 →
1. Creation of 100 randomly half-datasets
2. LASSO technique for variable selections to each one of them
3. We selected the variables that were included in the model more than 40 times (40%)

Model 5 → The variables indicated as prognostic factors in the literature (Fabio Pellegrini et al., 2019).

Build the prognostic score model

Fit various models using 2 shrinkage approaches

Shrinkage of coefficients

Uniform shrinkage → Uses a heuristic shrinkage factor s

$\boldsymbol{s = (model\chi^2 - df)/model\chi^2}$,

$model\chi^2$: the likelihood of the fitted model and

df: the degrees of freedom of the model

Penalized shrinkage → Maximizes a penalized version of the log-likelihood in which a penalty factor is used. The optimal value of penalty λ is the one that maximizes a modified Akaike's Information Criterion (AIC)

Build the prognostic score model

Results: Model selection

Select the best model with response to predictive ability and calibration ***(500 bootstraps & correction for optimism)***

Model & Shrinkage method	c-index	Calibration slope
Model1 uniform shrinkage	0.6458	0.888
Model1 penalized shrinkage	0.6480	1.004
Model2 uniform shrinkage	0.6485	0.887
Model2 penalized shrinkage	0.6497	1.004
Model3 uniform shrinkage	0.6397	0.758
Model3 penalized shrinkage	0.6425	0.912
Model4 uniform shrinkage	0.6277	0.935
Model4 penalized shrinkage	0.6281	1.004
Model5 uniform shrinkage	0.6254	0.882
Model5 penalized shrinkage	0.6263	0.988

Build the prognostic score model

Results: Model selection

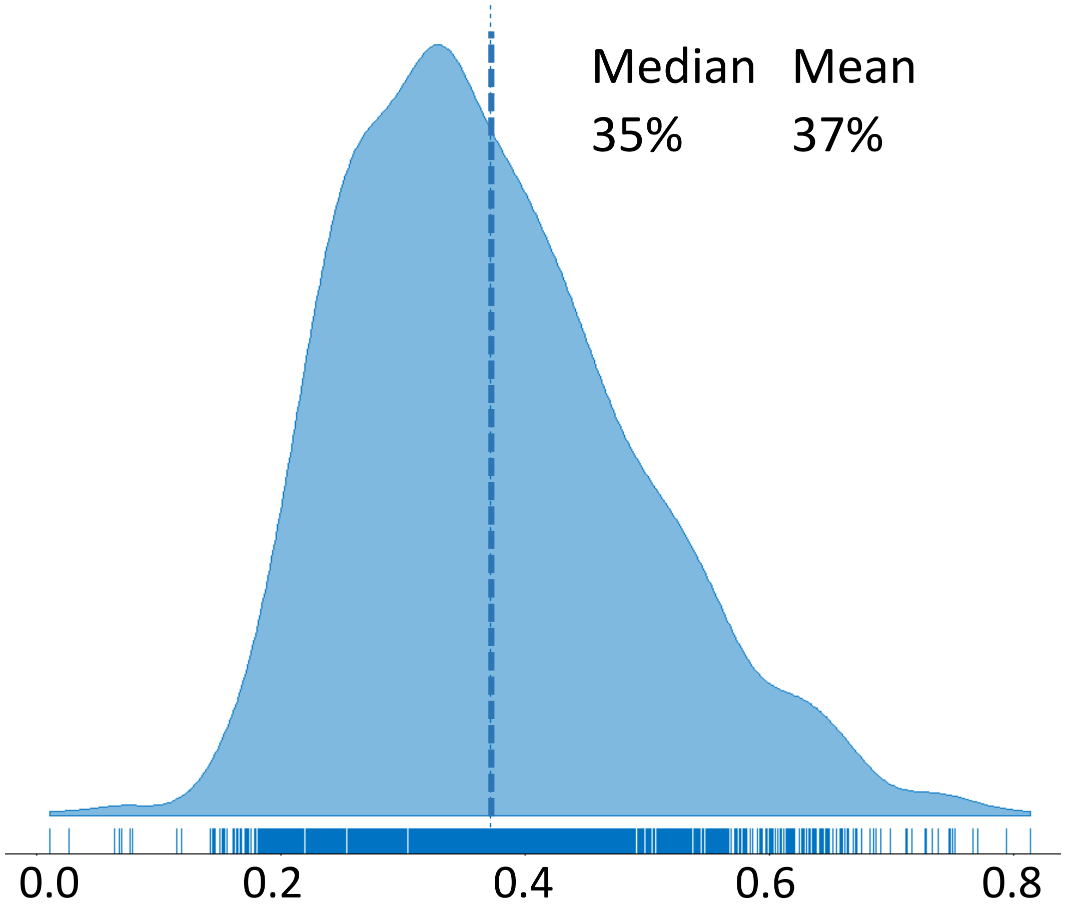
Age	Weight	Expanded disability status scale	Splines(No. of relapses 3 years prior to study)
Months since recent Pre-Study relapse	Prior MS treatment group	Region	Baseline 9 Hole Peg Test Average score
Baseline Gadolinium Lesions	Baseline Short Form (SF) 36 Health Survey Physical Component Summary (PCS)	Baseline Sensory Functional Systems Scores (FSS)	Baseline Actual Distance Walked

Events per variable = 39

Build the prognostic score model

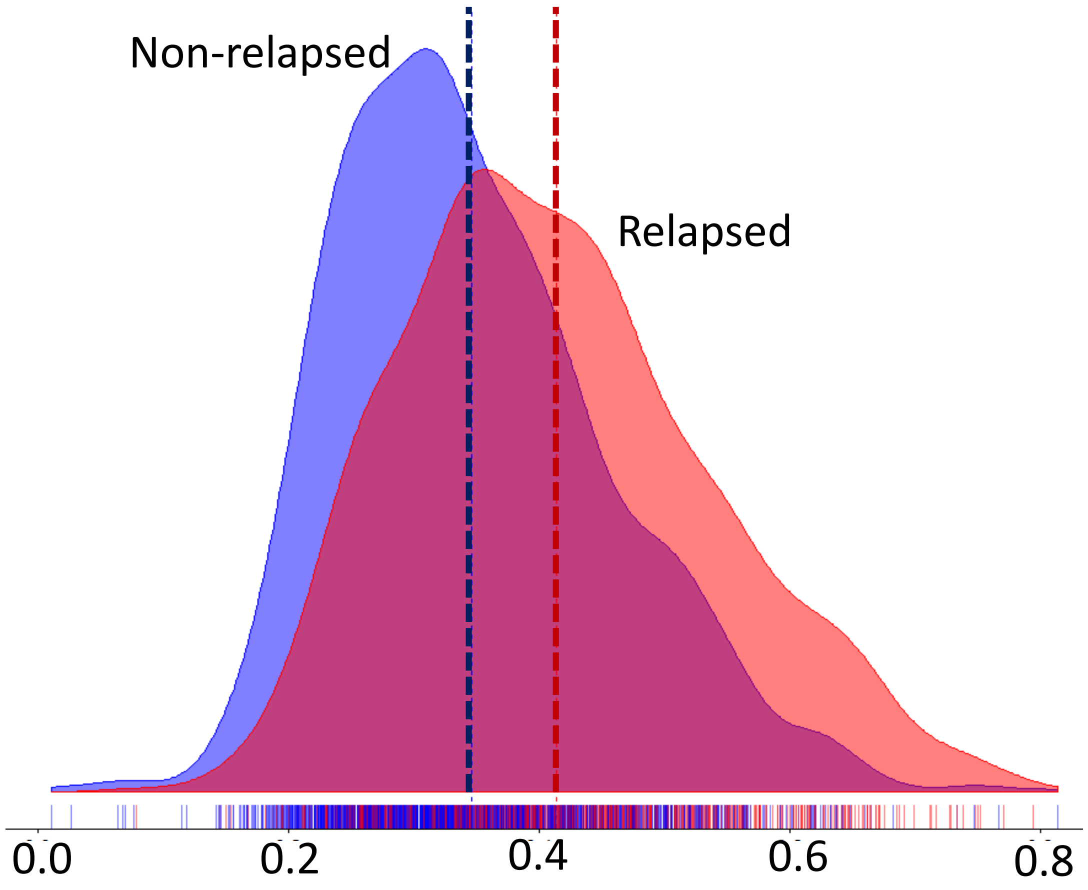
Results: Distribution of Risk

The distribution of the Risk in the whole dataset



C-index=0.65

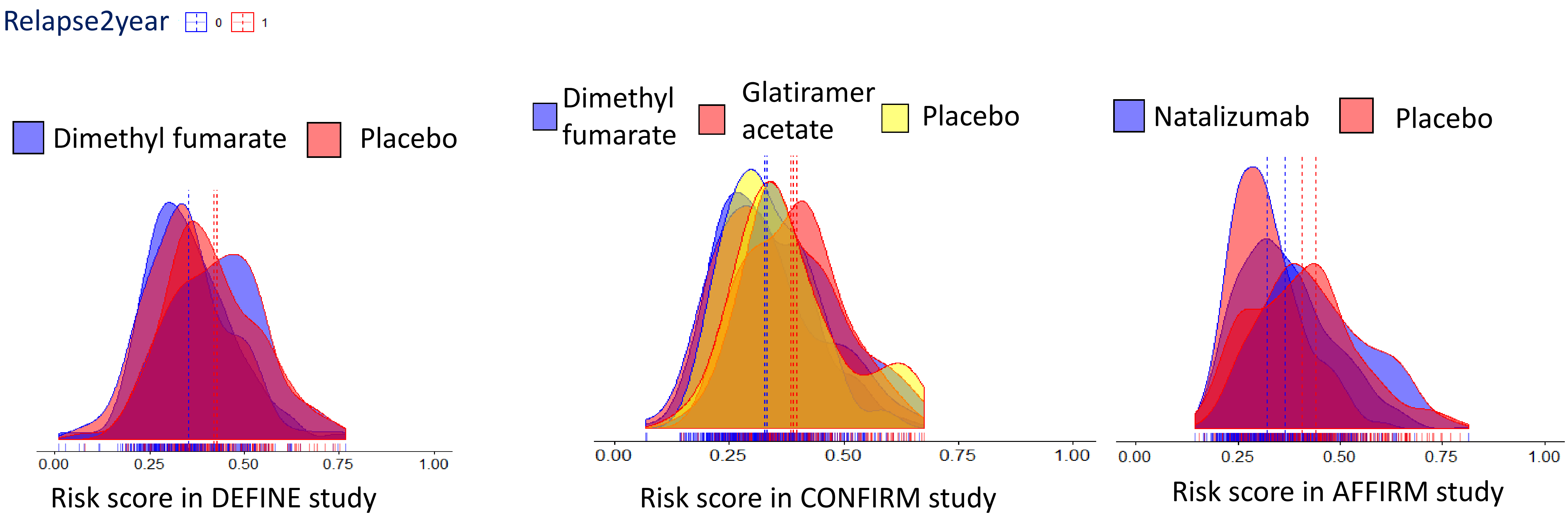
Risk per relapse or non-relapse (Risk as a prognostic factor)



Build the prognostic score model

Results: Distribution of Risk

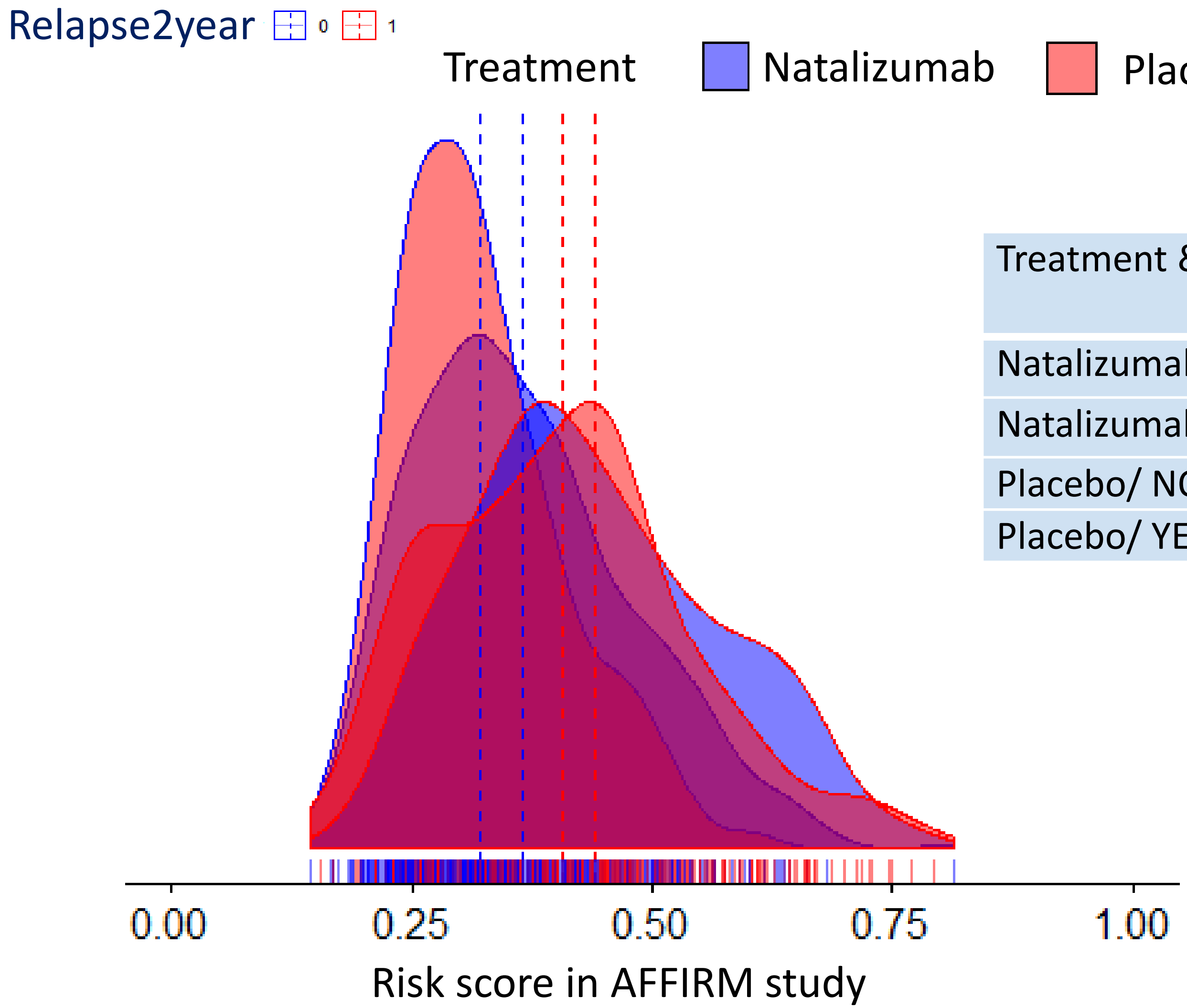
The Risk per arm and relapse non-relapse (risk as effect modifier)



Build the prognostic score model

Results: Distribution of Risk

The Risk per arm and relapse non-relapse (risk as effect modifier)



Treatment & Outcome	Median pre-treatment Risk	95% CI of mean
Natalizumab/ NO relapse	35%	(35% , 38%)
Natalizumab/ YES relapse	42%	(42% , 46%)
Placebo/ NO relapse	31%	(30% , 33%)
Placebo/ YES relapse	40%	(39% , 43%)

Step 2: Use the risk score in the IPD Network meta-regression
(In JAGS using self-programmed routines)

IPD Network meta-regression

Notation

i: Individuals

j: study

k: treatment

b_j: baseline treatment in study j

Likelihood

$Y_{ijk} \sim Bernoulli(p_{ijk})$

B: Individual level covariate regression term for Risk / the impact of Risk as prognostic factor

D_{b_jk}: the treatment effect of treatment k versus placebo / ***fixed effect***

G_{b_jk}: The interaction of treatment and risk. Different for each treatment vs study's control / the impact of Risk as effect modifier

$$logit(p_{ijk}) = \begin{cases} u_j + B \times (logitR_{ij} - \overline{logitR_j}) if \;\; k = b_j \\ u_j + D_{b_jk} + B \times (logitR_{ij} - \overline{logitR_j}) + G_{b_jk} \times (logitR_{ij} - \overline{logitR_j}), if \; k \neq b_j \end{cases}$$

Saramago et al., 2012

IPD Network meta-regression

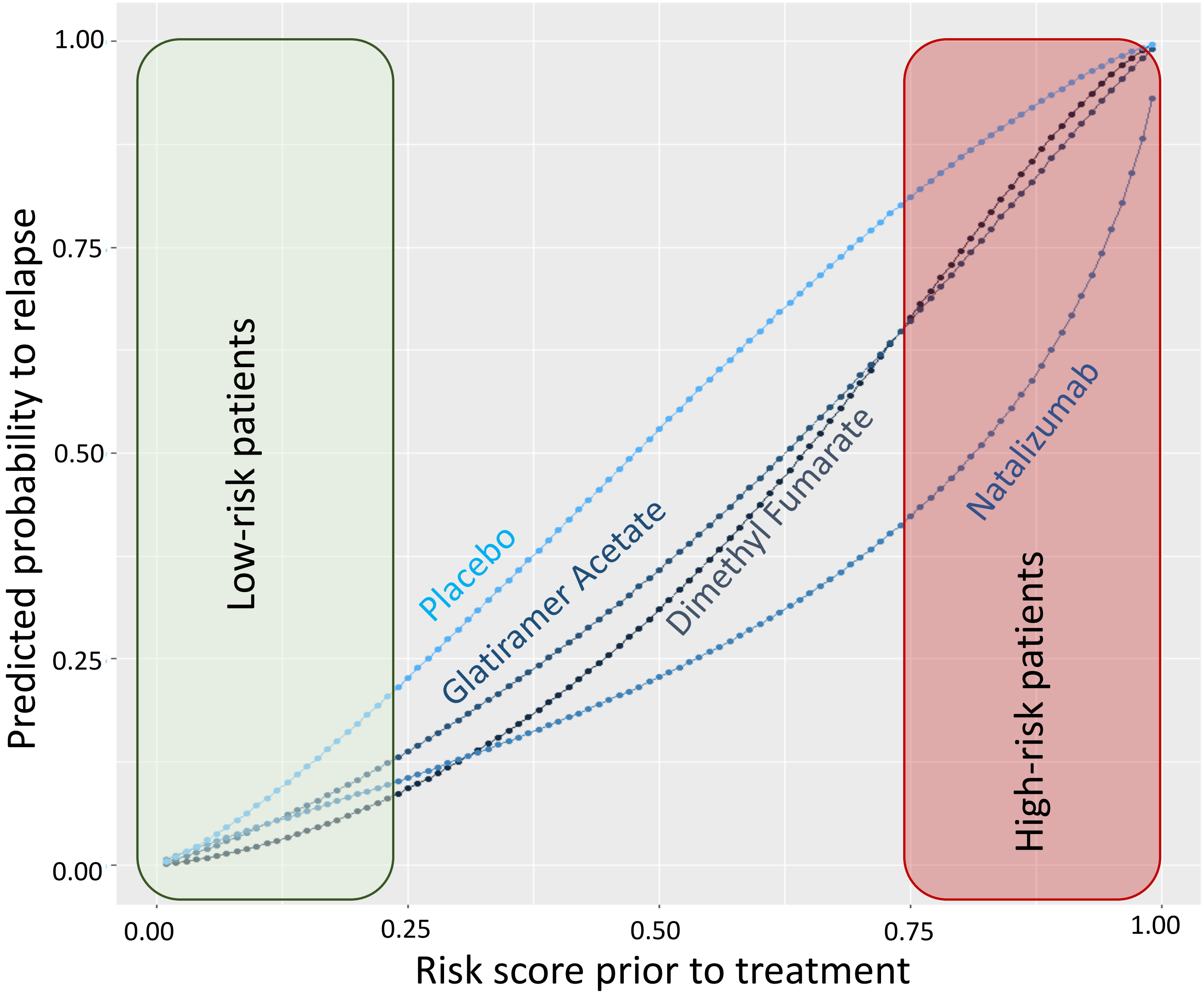
Results: Estimation of model parameters

OR for relapse for one unit increase in logit-risk in untreated patients (placebo) - **(exp(B))** = 3.38

	OR for relapse versus placebo at the study mean risk **(exp(D))**	OR versus placebo for one unit of increase in the logit risk (**exp(G)**)
Natalizumab	0.27	0.68
Glatiramer Acetate	0.50	0.92
Dimethyl Fumarate	0.40	1.14

$$logit(p_{ijk}) = \begin{cases} u_j + B \times (logitR_{ij} - \overline{logitR_j}) if \;\; k = b_j \\ u_j + D_{b_jk} + B \times (logitR_{ij} - \overline{logitR_j}) + G_{b_jk} \times (logitR_{ij} - \overline{logitR_j}), if \; k \neq b_j \end{cases}$$

Predicted relapse rate by baseline risk score

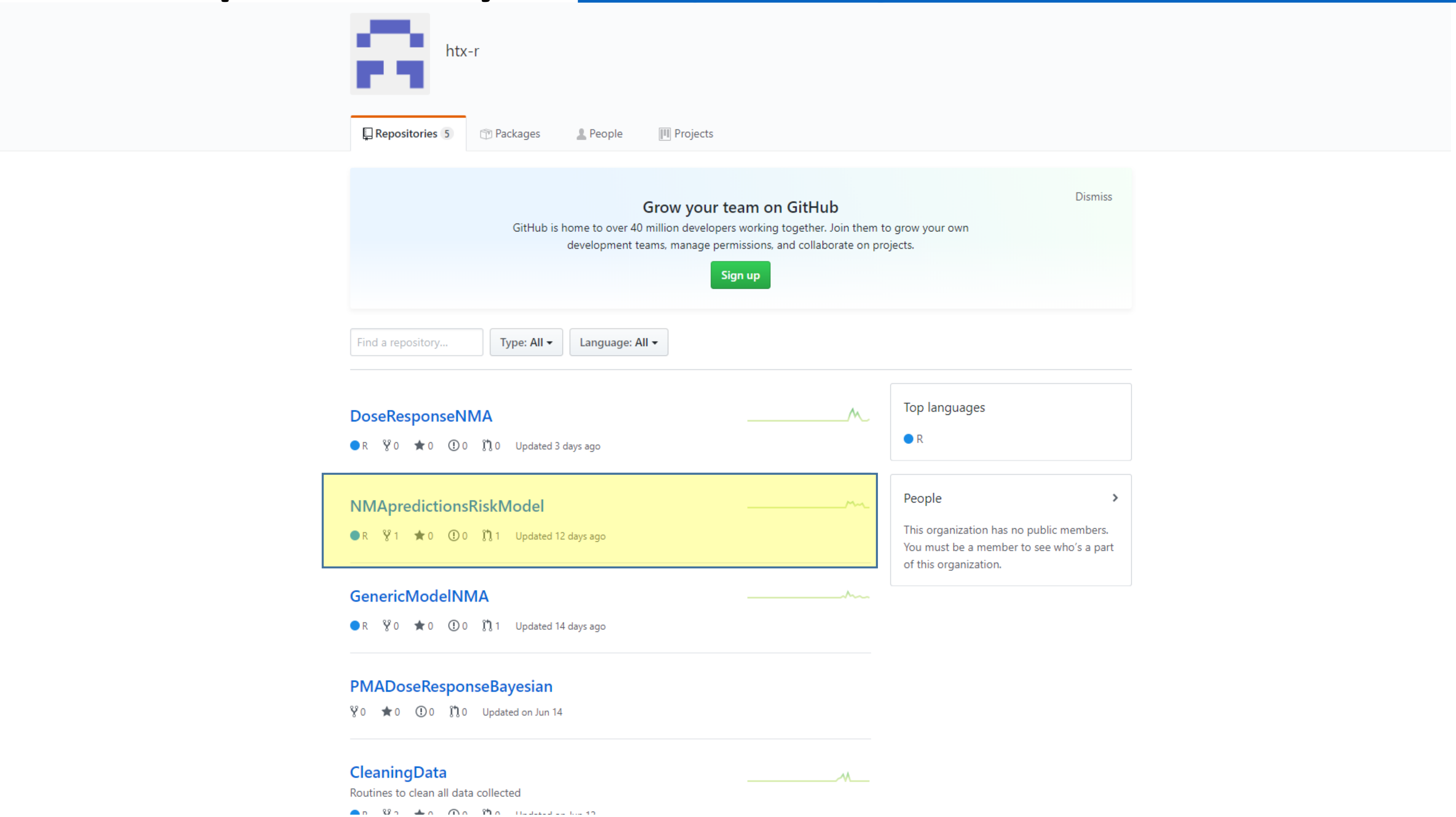


Treatment	**Mean**	Less than 25% Risk	More than 75%
Natalizumab	29%	12%	48%
Glatiramer Acetate	41%	10%	60%
Dimethyl Fumarate	39%	9%	62%

Best treatment **Dimethyl fumarate - 3% Absolute benefit** compared to Natalizumab

Best treatment **Natalizumab- 14% Absolute benefit** compared to Dimethyl Fumarate

Github repository - https://github.com/htx-r



Conclusions and further research

Future research

- Comparison with effect modification method
- Use of Swiss MS cohort to build the risk score
- External validation of prediction model
- R-shiny app

Conclusions

- This is the first prediction model that uses ***risk score*** from a nested prognostic model ***within a IPD Network meta-regression*** framework
- The risk of relapse at baseline is important for the **optimal treatment choice** and **moderates** the **absolute benefit**
  - **Dimethyl fumarate** seems to be the optimal choice for low-risk patients, whereas **Natalizumab** seems to be the optimal choice for high-risk patients