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A comparison of direct and indirect methods for the estimation of health utilities from clinical outcomes

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Introduction

- Mapping (or 'cross-walking') is used to estimate a utility score/index from a different outcome measure
  - clinical trials without a preference based measure
  - Within PROMS agenda as performance indicators
  - Essential element of VBP
- Mapping involves:
  - Estimating a relationship using a statistical model
  - Predicting using the estimated model
- **THIS IS ESSENTIALLY A STATISTICAL ISSUE!**

EQ-5D-3L UK-tariff

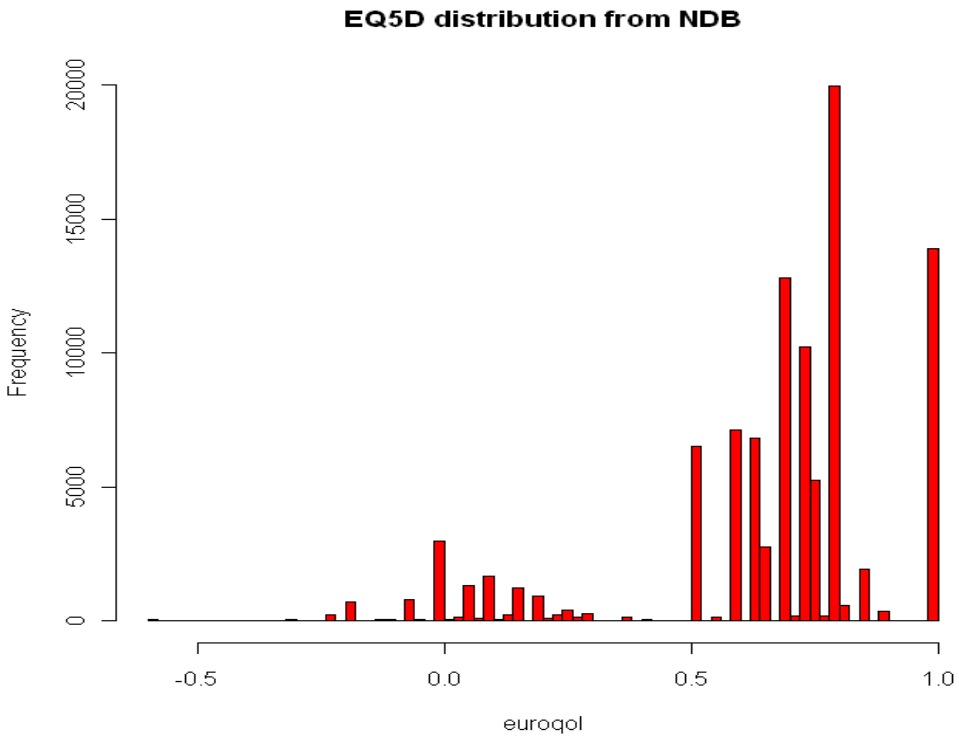
- Descriptive system 11111, 21123
  - 5 dimensions - mobility, self care, usual activities, pain, anxiety and depression
  - 3 levels in each dimension- no problems, some problems, extreme problems
  - 243 combinations
- Valuation (Dolan *et al* 1995) – utility scores
  - Analysis of preference data: 3000 individuals

Two general methods

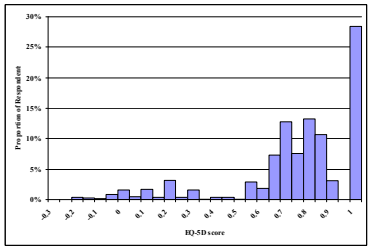
- Direct: dependent variable – utility/index scores
  - 11213 -> 0.378
- Indirect: dependent variables – levels of descriptive system.
  - Expected index score is calculated as a second step
  - “Response mapping”

AIM: Estimate EQ-5D as a function of HAQ, Pain and other covariates – direct & indirect methods

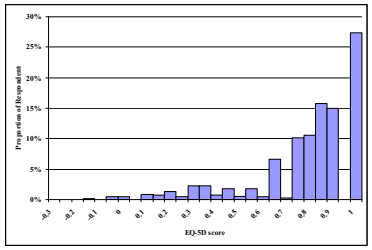
- US not-for-profit database
- N=100,398 (16k patients)
- Adults with RA diagnosis
- Classic EQ-5D (UK tariff) distribution
- Multimodal
- Peak at 1
- Bounded top and bottom
- Gap between 1 and 0.883



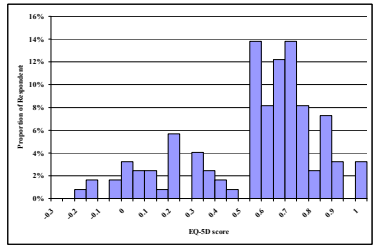
Asthma (n=2,935)



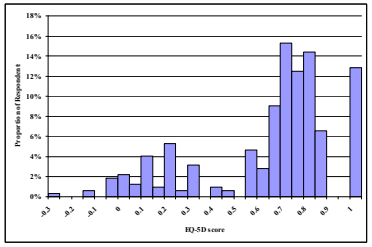
Chest pain (n=679)



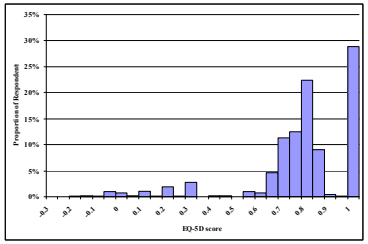
Cronic obstructive pulmonary disease (n=185)



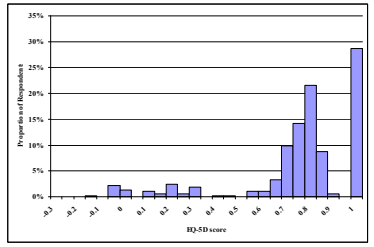
Clodronate (n=320)



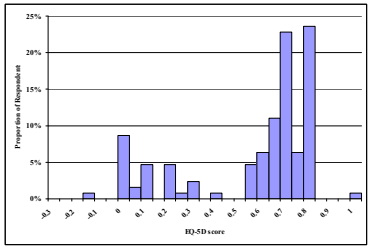
Hormone replacement therapy (n=755)



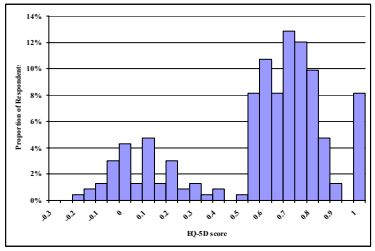
Irritable bowel syndrome (n=374)



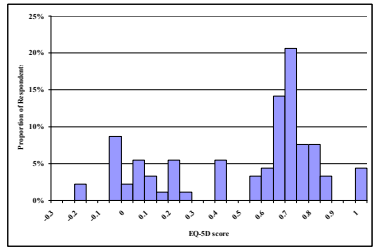
Lower back pain (n=500)



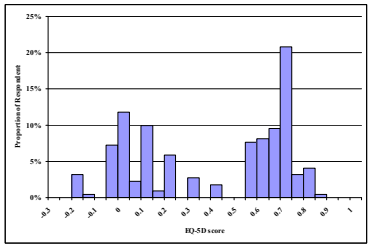
Leg Ulcers (n=233)



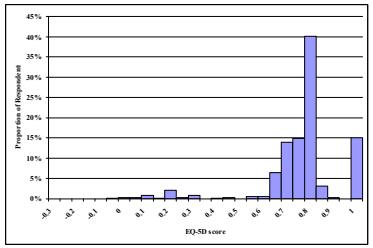
Leg reconstruction (n=92)



Osteoporosis (n=221)



Varicose veins (n=887)



Existing evidence

- Direct methods:
  - Linear regression
  - Tobit (often incorrectly applied!)
  - CLAD
  - Two-part models

Poor fit
Underestimate at top
Overestimate at bottom

Biased estimates of treatment effect

Methods and models

- Direct methods:
  - Adjusted Limited Dependent Variable Mixture Model

    (development of Hernández Alava *et al* 2012)
  - RE linear regression
- Indirect method:
  - Set of Generalised Ordered Probits

    (development of "Response Mapping" Gray *et al* 2006)

Direct method: Finite Mixture Modelling

- Useful where simple models don't fit complex data
- Model data as a finite mixture of component models (usually of the same type)
- Often used where interest is in identifying clusters of groups
- But here we are interested in approach because of flexibility
- **Any** continuous distribution can be approximated by a mixture of normals

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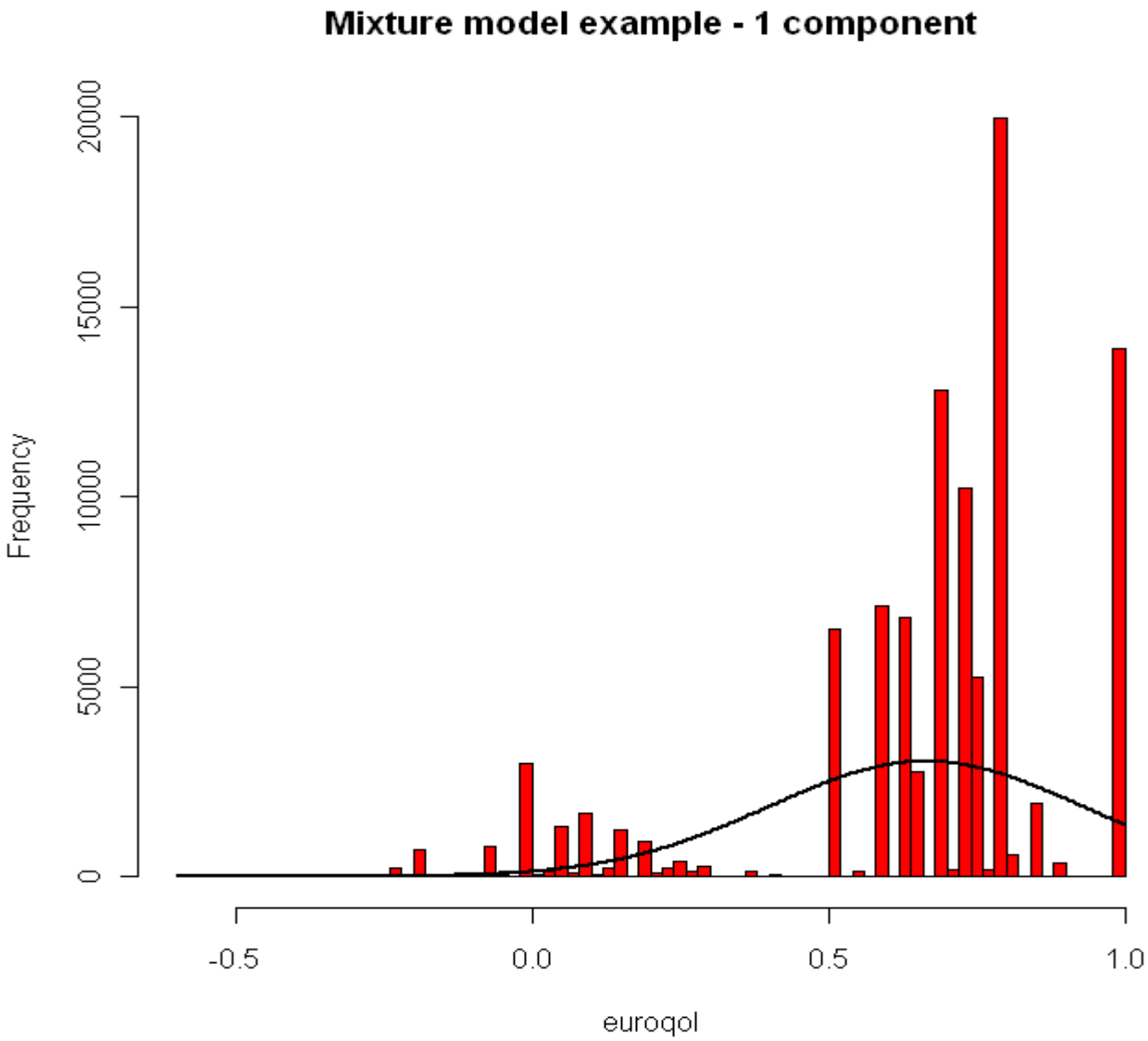

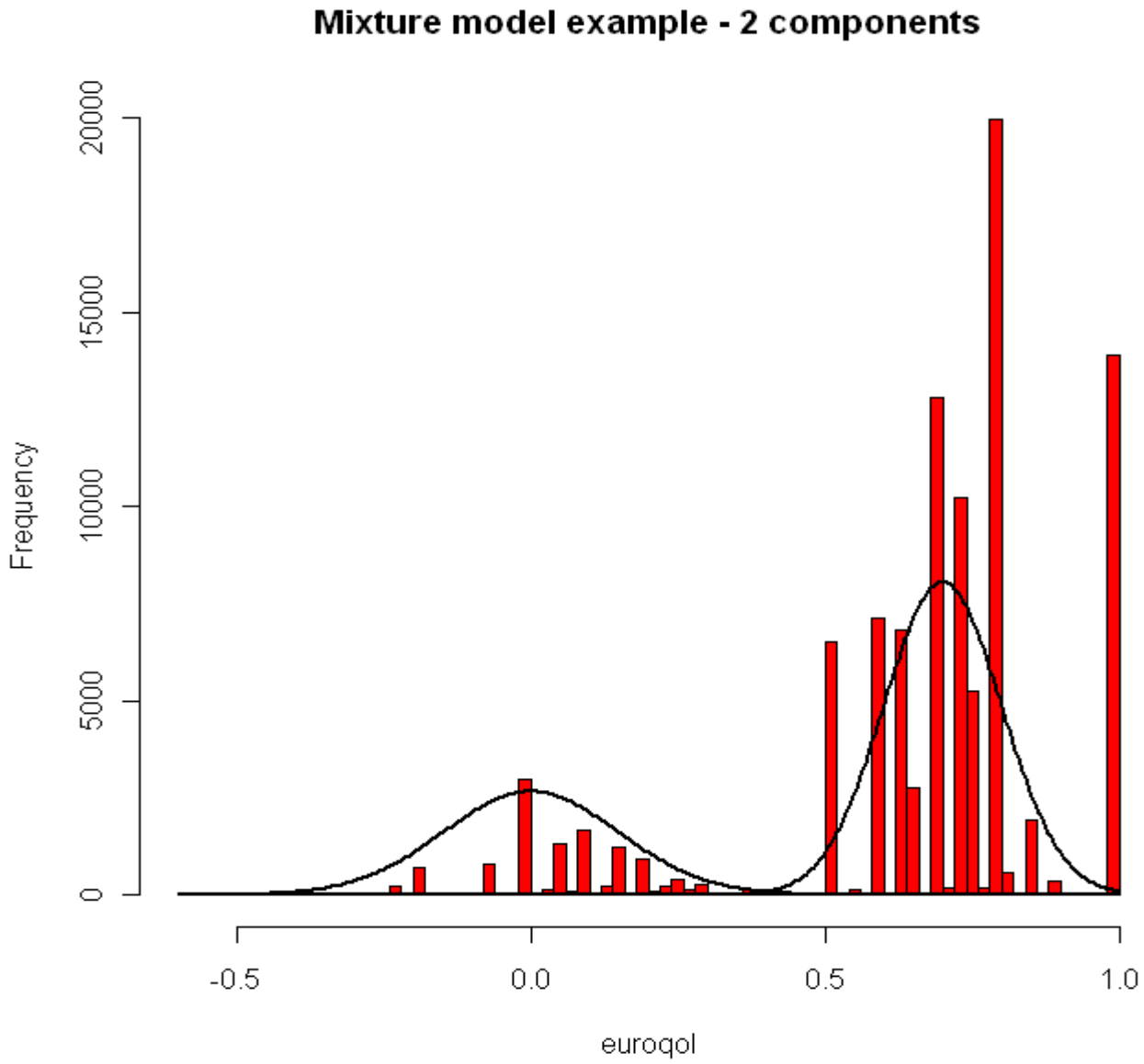
Mixture model example - 2 components
Frequency
0
5000
10000
15000
20000
-0.5
0.0
0.5
1.0
euroqol

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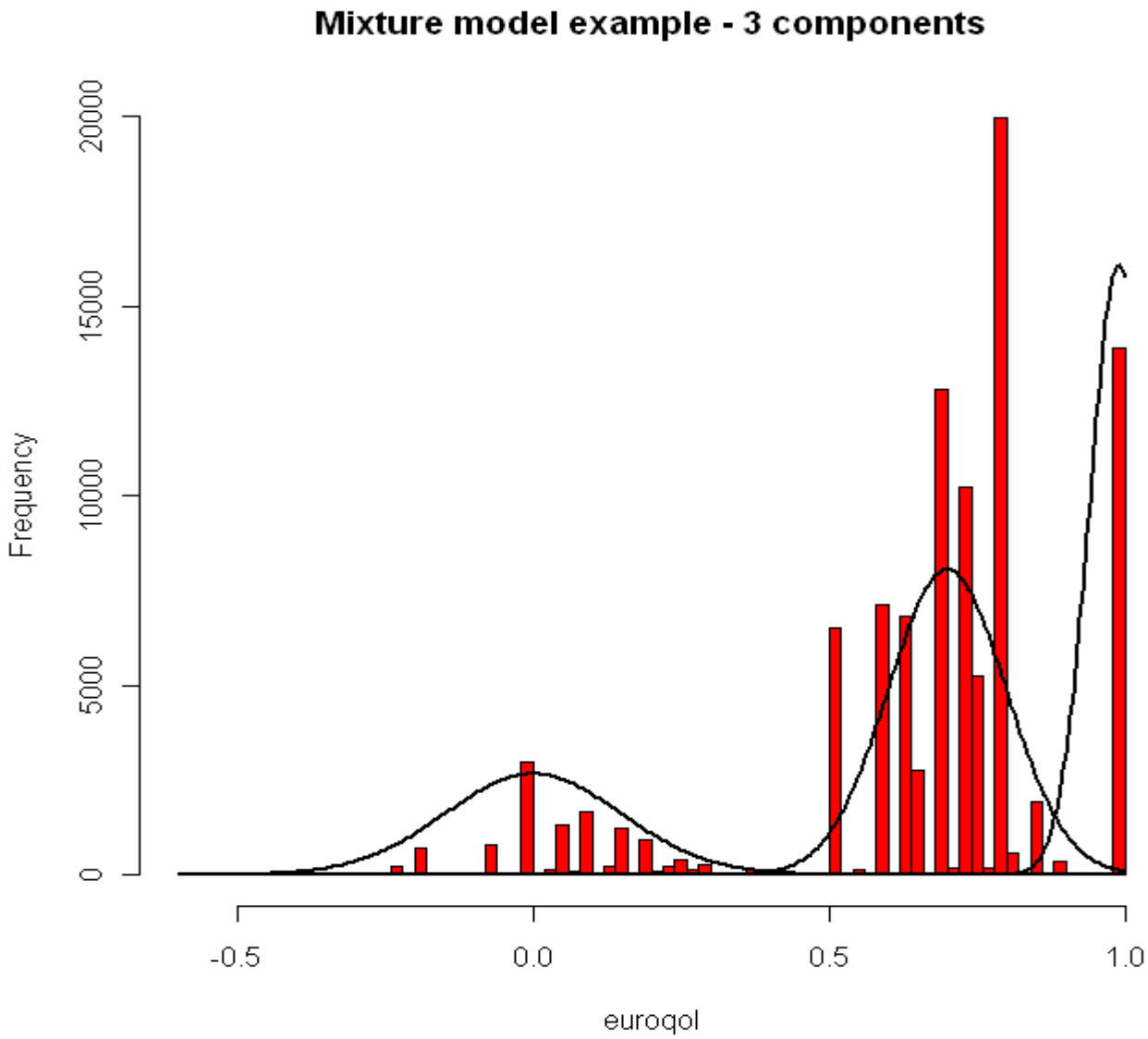

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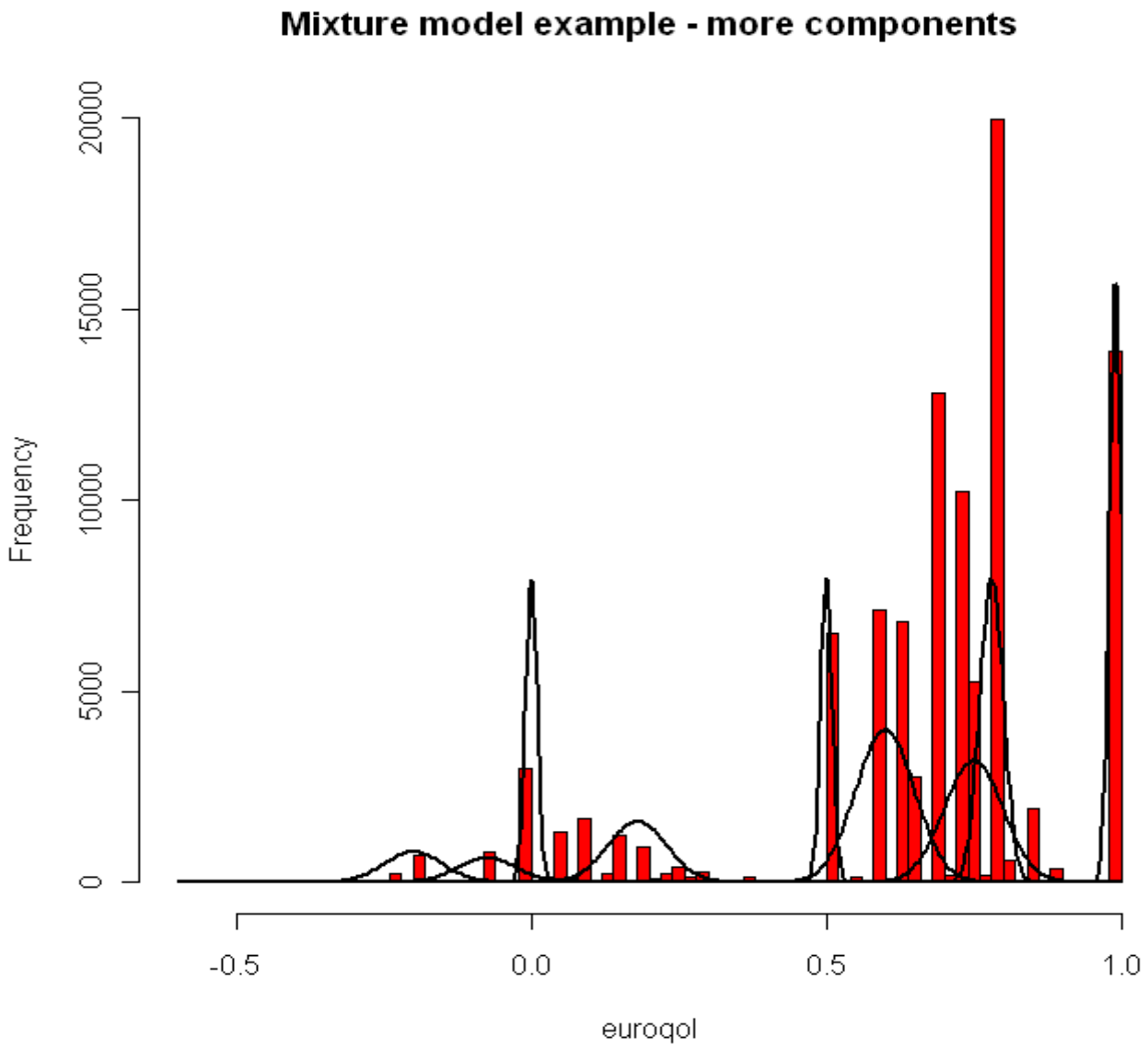
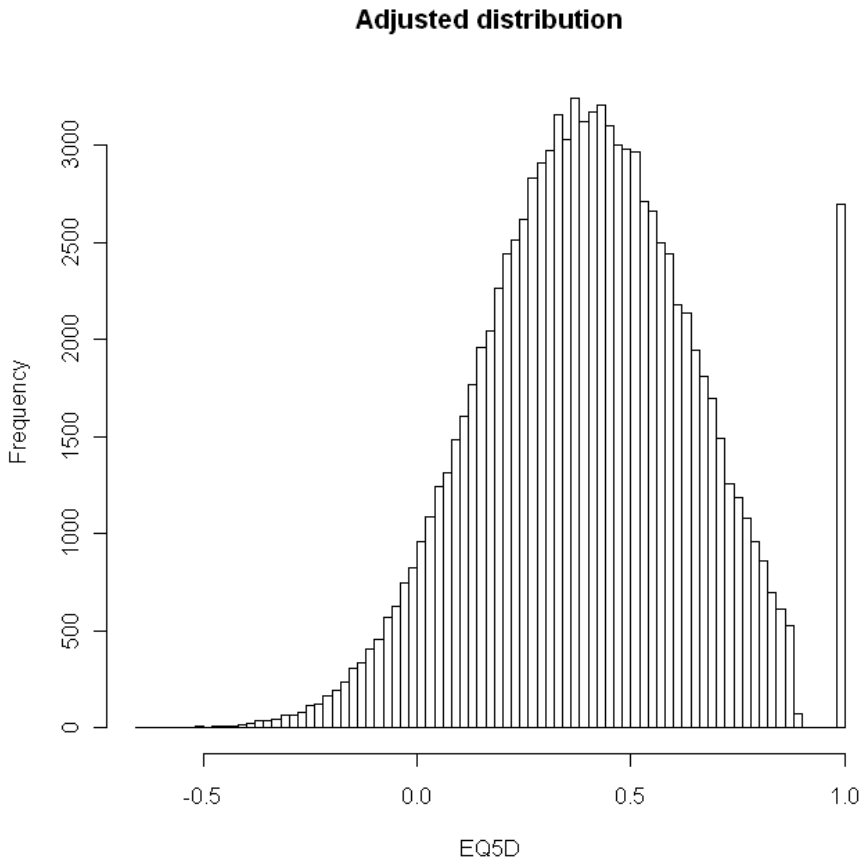


- Don’t need to use normal distributions
- More appropriate bespoke distribution
- Each component reflects EQ-5D properties
- Overcomes need for a class of “1”’s
- Combination of:

  a) Adjusted dist

  AND

  b) Mixture framework



More formally...

Limited at top, with a gap, and bottom

$$y_{it}|c = \begin{cases} 1 & if\ y_{it}^{*}|c > 0.883 \\ max\{y_{it}^{*}|c, -0.594\} & otherwise \end{cases}$$

$$y_{it}^{*}|c = x_{it}'\beta_c + \varepsilon_{it}^{c}$$

Within component (HAQ, HAQ^2, Pain, Age, Age$^{2)}$

$$\beta_{0c} = z_i'\alpha_c + u_i$$

Random effect (gender)

$$P(C_{it} = c|w_{it}) = \frac{\exp(w_{it}'\partial_c)}{\sum_{s=1}^{P}\exp(w_{it}'\partial_s)}$$

Component membership (HAQ, Pain, Pain^2)

Indirect method: Random Effects Generalised Ordered Probit

- 3 point ordered discrete dependent variable for each of the five dimensions of EQ-5D
- (RE) Ordered Probit – implicit parallel regression assumption too restrictive
- Multinomial logit model BUT ignores ordinality of the dependent variable

Indirect method: Random Effects Generalised Ordered Probits

- q_{it}^{s} discrete dependent variables for s={mobility, self care, usual activities, pain, anxiety and depression}

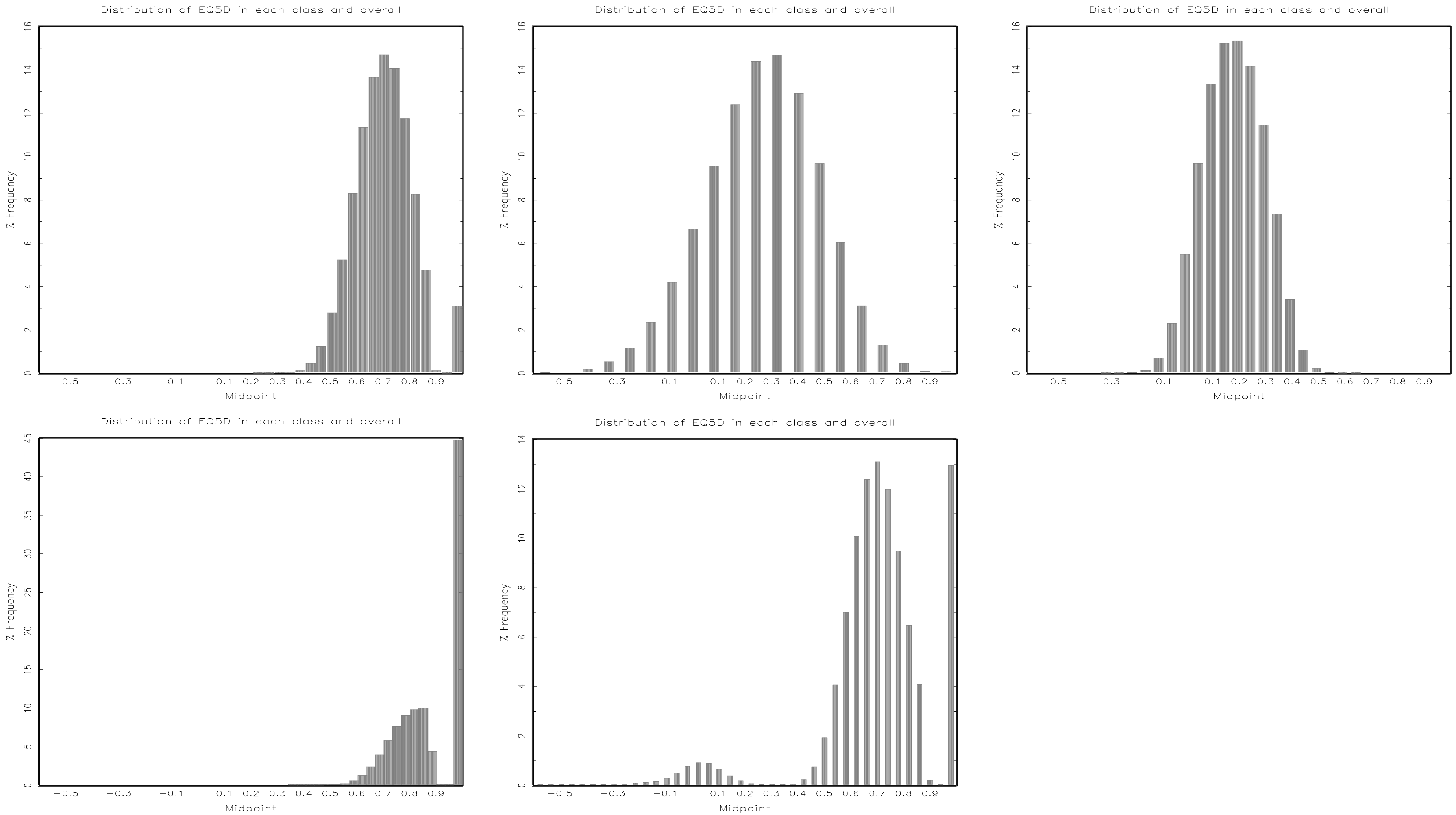
$$P(q_{it}^{s} = 1|x_{it}, u_i^{s}) = 1 - \Phi(x_{it}\beta_1^{s} + u_i^{s})$$
$$P(q_{it}^{s} = 2|x_{it}, u_i^{s}) = \Phi(x_{it}\beta_1^{s} + u_i^{s}) - \Phi(x_{it}\beta_2^{s} + u_i^{s})$$
$$P(q_{it}^{s} = 3|x_{it}, u_i^{s}) = \Phi(x_{it}\beta_2^{s} + u_i^{s})$$

- Expected value calculated mathematically – average of all 243 utility values weighted by their estimated probabilities

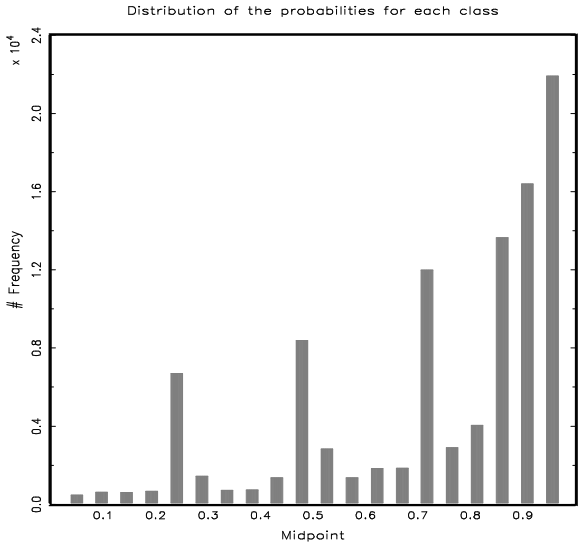
Model selection and comparisons

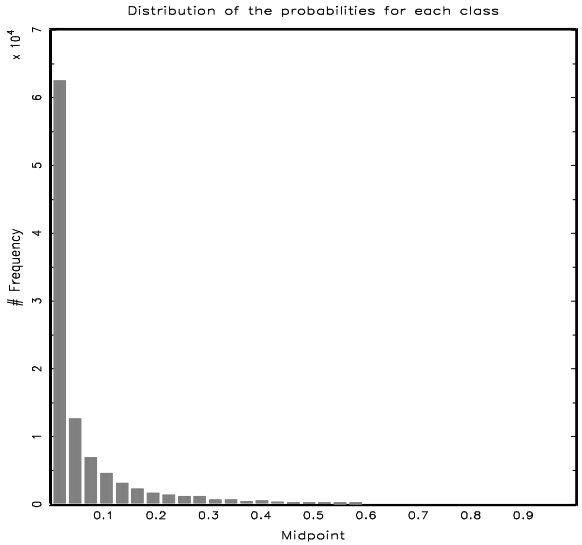
- Explanatory variables: HAQ, HAQ^2, pain, gender, age and age^2
- BIC to choose number of mixture components – 4
- MAE & RMSE (insensitive but widely used)
- Monte Carlo simulation to generate data from models and compare to observed data

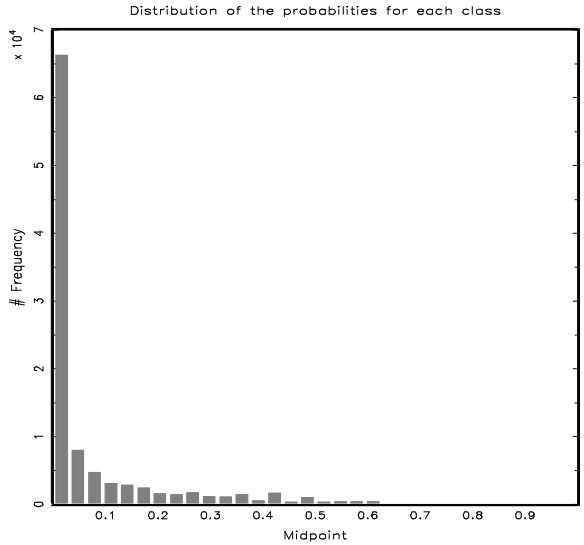
EQ-5D distribution in each class and overall



Distribution of probabilities in each class







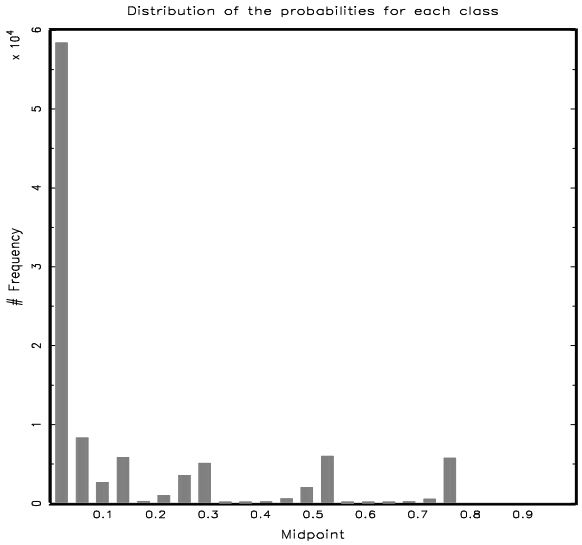
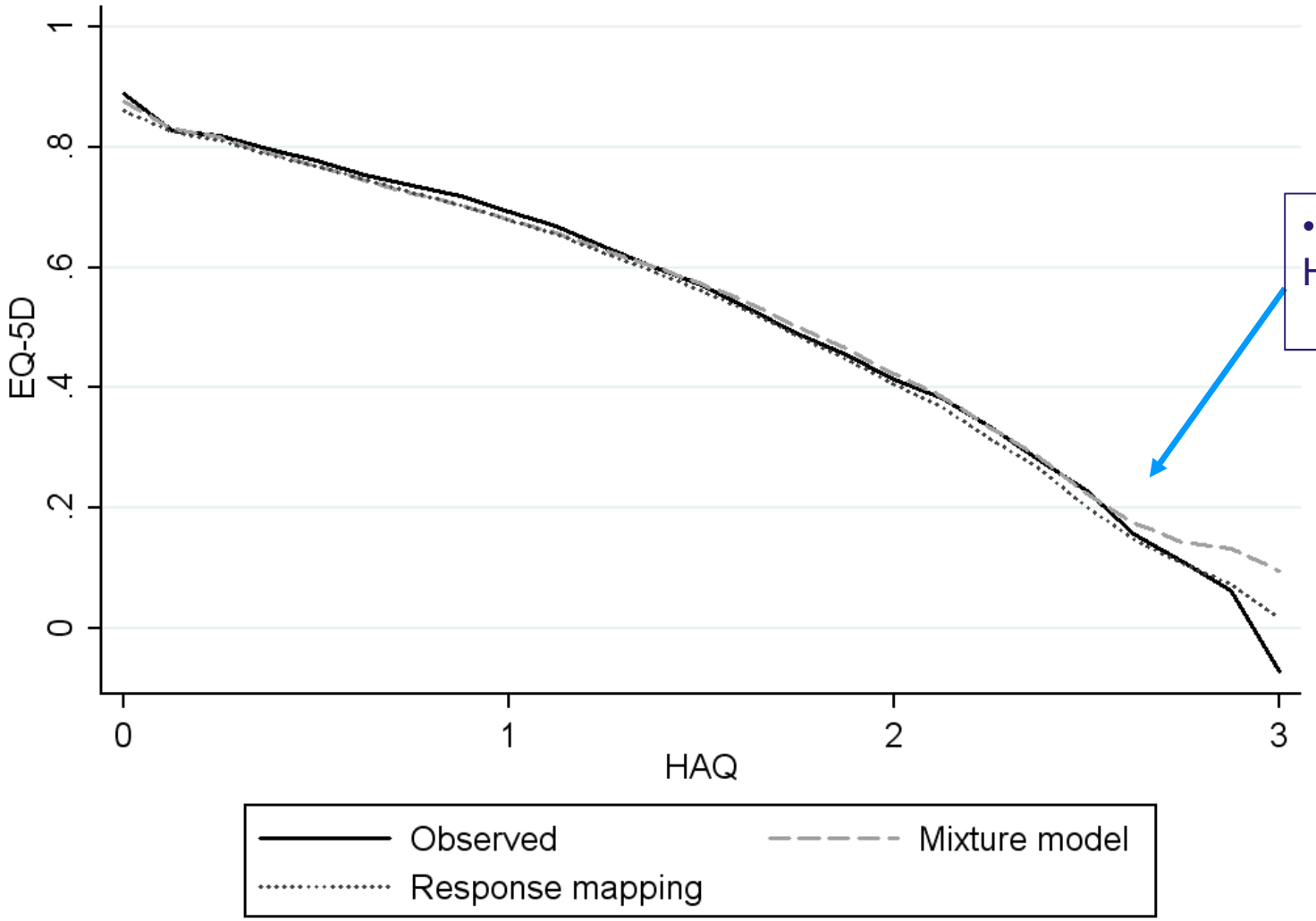
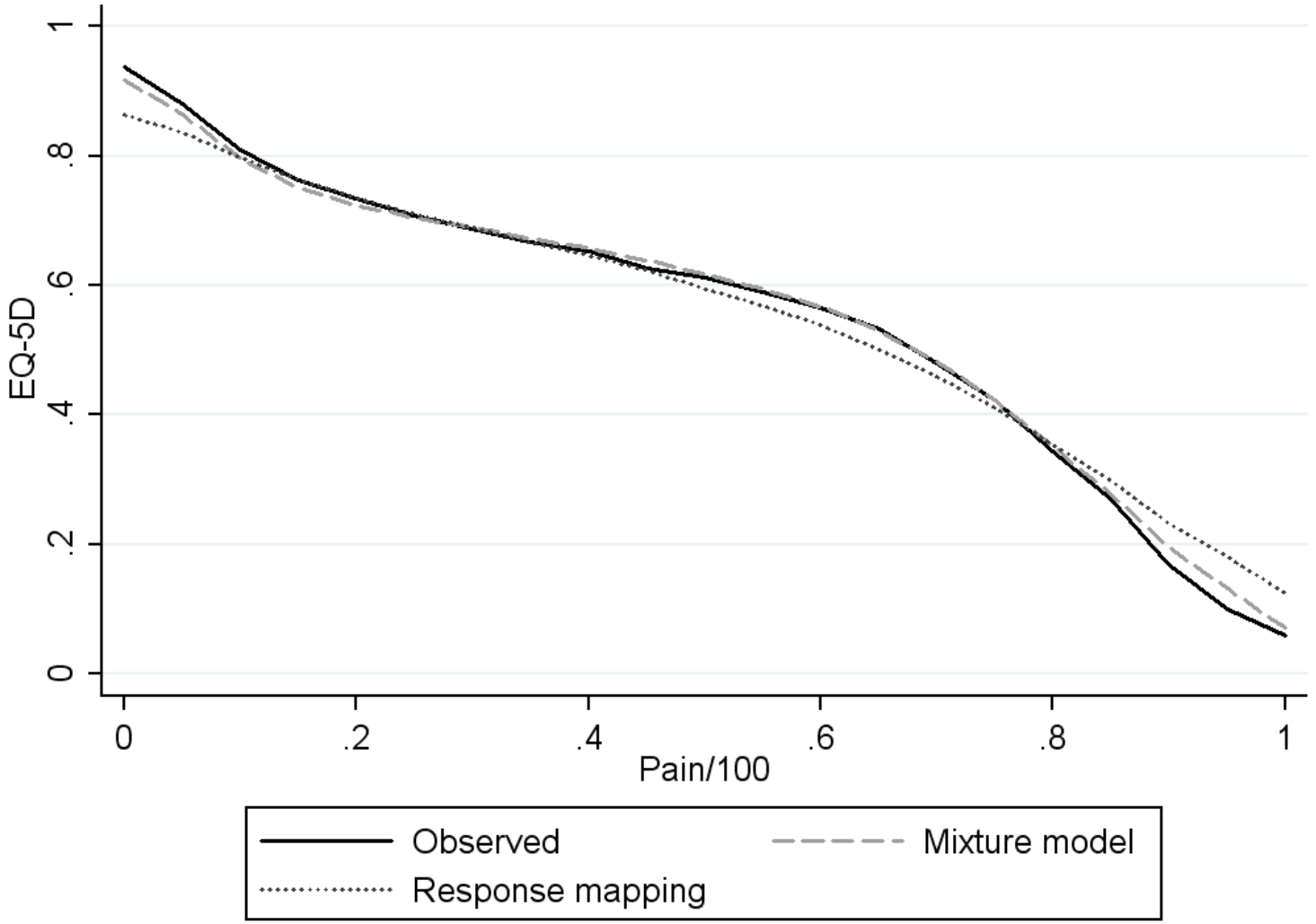


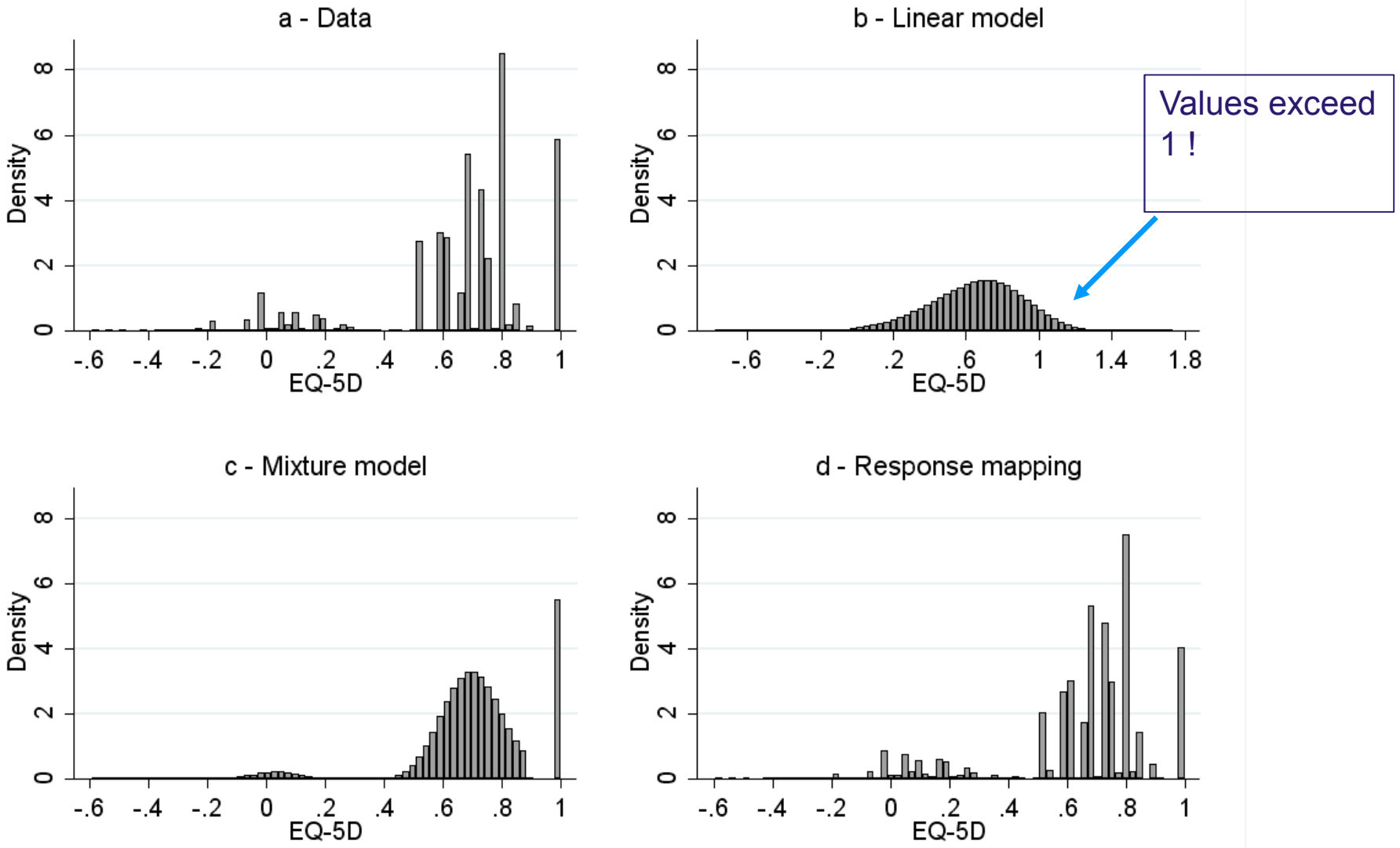
Table 4: Comparison of Models 1, 2 and 3

	N		RE linear regression	ALDVMM	*% diff 2 vs 1*	RE GOProbit	*% diff 3 vs 1*	*% diff 2 vs 3*
HAQ 0-1	54,086	MAE	0.0968	0.0854	*11.77%*	0.0906	*6.46%*	*5.68%*
		RMSE	0.1292	0.1215	*5.96%*	0.1250	*3.22%*	*2.83%*
HAQ 1-2	38,307	MAE	0.1571	0.1458	*7.17%*	0.1515	*3.53%*	*3.77%*
		RMSE	0.2061	0.2025	*1.75%*	0.2033	*1.39%*	*0.37%*
HAQ 2-3	8,005	MAE	0.2309	0.2052	*11.11%*	0.2130	*7.77%*	*3.63%*
		RMSE	0.2626	0.2520	*4.01%*	0.2543	*3.16%*	*0.88%*
Overall	100,398	MAE	0.1305	0.1180	*9.56%*	0.1236	*5.30%*	*4.50%*
		RMSE	0.1752	0.1693	*3.37%*	0.1713	*2.24%*	*1.16%*



- Only 1% with HAQ>2.5


EQ-5D
0
.2
.4
.6
.8
1
0
.2
.4
.6
.8
1
Pain/100
Observed
Mixture model
Response mapping


a - Data
b - Linear model
c - Mixture model
d - Response mapping
Density
EQ-5D
0
2
4
6
8
-.6
-.4
-.2
0
.2
.4
.6
.8
1
1.4
1.8
Values exceed 1 !

Does it matter?

- Example CE model: Rituximab for MTX intolerant patients with RA (Sharma et al. 2009)

	Inc Costs	Inc QALYs	ICER	%diff base lin	%diff base response
Linear model	£ 1,952	0.166	£11,754		
Response	£ 1,952	0.190	£10,315	12.2%	
Mixture	£ 1,952	0.158	£12,372	-5.3%	-19.9%

Does it matter?

- Tentative results only
- Assume less severe patients

	Inc Costs	Inc QALYs	ICER	%diff base lin	%diff base response
Linear model	£ 2,223	0.058	£ 38,441		
Response	£ 2,222	0.062	£ 35,903	6.6%	
Mixture	£ 2,225	0.066	£ 33,535	-12.8%	-6.6%

Conclusion/Discussion

- Linear models are not appropriate for mapping
  - Response mapping and mixture model approaches substantially better in all regards
  - …and it matters!
- Generalized ordered probit can be used for response mapping
  - Respects ordered nature of data

Conclusion/Discussion

- Bespoke mixture model performs best overall in this example
- Further work
  - Develop response mapping (correlations, more flexible functional forms)
  - Compare methods in other datasets/simulation/outcomes
  - How will it work with EQ-5D-5L?
    - Depends how valuations are modelled

References

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- Sharma T., Tosh J., Longworth L., Wailoo A., Akehurst R. (2009) Use Of Rituximab In Patients With Rheumatoid Arthritis With Concomitant Dmards, Or As Monotherapy, For Patients Who Are Intolerant To Methotrexate. Yorkshire and the Humber Specialised Commissioning Group, iEDM Report 5/09

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