Handling frequent observations of composite scores: Application to PROs in COPD

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What this talk is about

- For the 1st time: extended **IRT modelling** with the **Markov models (MM)**
- MM needed due to frequent and therefore correlated observations
- **Exemplified** with **COPD patient data**

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COPD

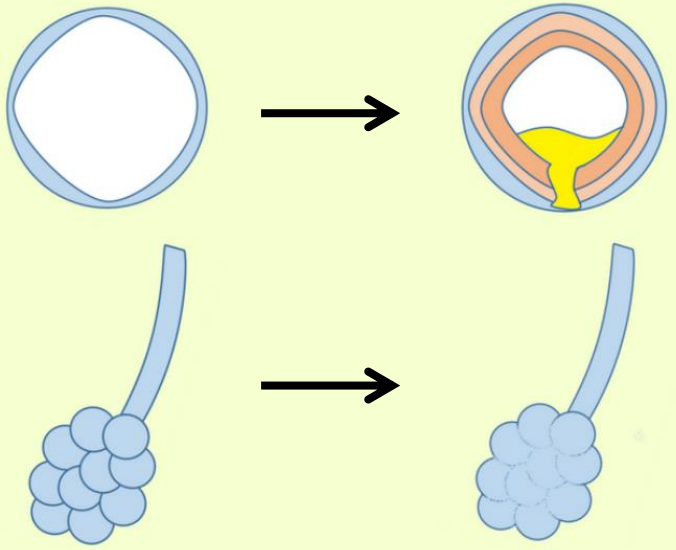
Chronic Obstructive Pulmonary Disease

TOP 5

- top 5 disease burden worldwide (1,2)
- 3 mil deaths/year (3)

WHAT?

- progressive airflow obstruction
- inflammatory disease of the lung



EXACERBATIONS

- faster decline of pulmonary function
- ↑ risk of cardiovascular events
- ↓ quality of life
- ↑ hospital admissions, morbidity & mortality

[1]Prince *et al*., Lancet, 2015. **385**: 549-62. [2]Lozano *et al*., Lancet, 2012. **380**: 2095-128. [3]Rabe *et al*., Lancet, 2017. **389**: 1931-40.

Patient reported outcomes (PRO)

- PRO data[1]
  - Patient's health status reports
  - Directly from the patient, not altered by anyone
  - Increasingly used in drug development & to inform clinical decisions
  - Collected using questionnaires, i.e. EXAcerbations of COPD Tool (EXACT) questionnaire[2]

[1]Basch, N Engl J Med, 2010. **362**(10): 865-9. [2]Leidy *et al*., Value Health, 2010. **13**(8): 965-75.

EXACT questionnaire

- Daily electronic diary
- Standardised approach for assessing the symptomatic manifestations of COPD exacerbations
- 14 items (score: 0-3/4)
- ↑ score → ↑ severe symptom

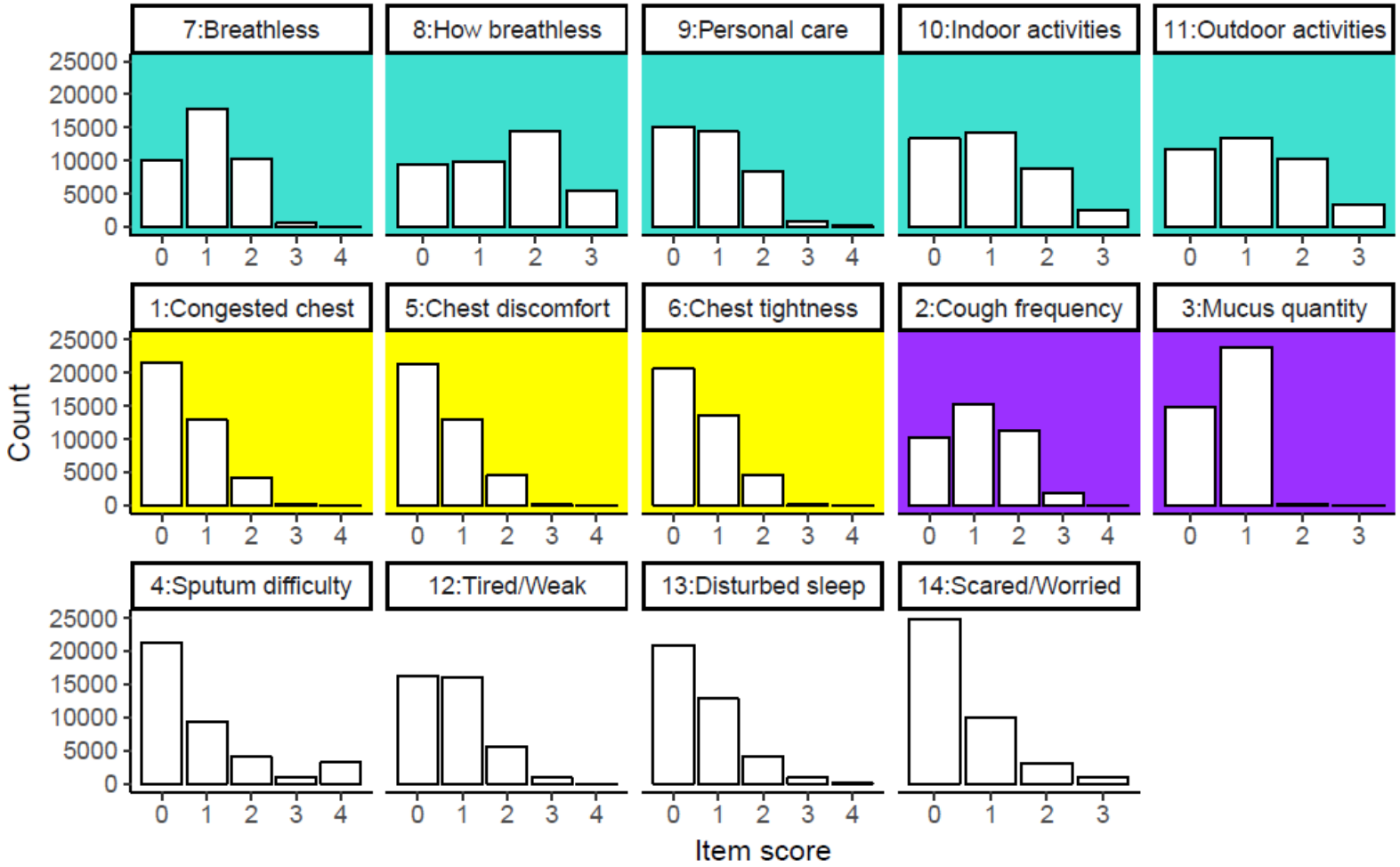
item	description	scale	domain
7	we	0-4	breathlessness
8	de	0-3	breathlessness
9	we pe	0-4	breathlessness
10	we inc	0-3	breathlessness
11	we act	0-3	breathlessness
1	did	0-4	chest symptoms
5	did	0-4	chest symptoms
6	did	0-4	chest symptoms
2	ho	0-4	cough and sputum
3	ho	day 0-3	cough and sputum
4	ho	0-4	difficulty with sputum
12	we	0-4	tired or weak
13	las	0-4	sleep disturbance
14	ho	ay 0-3	psychological state

Analysis of PRO data

- Two main approaches:
  - Standard approach: total-score based approach
    - Sub-scores ignored → potential information loss
  - Alternative approach: item response theory (IRT) models
    - All sub-score data used

Data

- Acute Exacerbation and Respiratory InfectionS in COPD (AERIS) study[1,2]
- Single centre
- Standard-of-care
- M/F 40-85 years
- ≥ moderate COPD
- N=127 IDs
- 14 items: 4/5 categories
- ~ 40,000 observations per item
- ~ 4,000-5,000 observations per subject



[1]Bourne *et al.*, BMJ Open, 2014. **4**(3): e004546.
[2]Wilkinson *et al.*, Thorax, 2017. doi:10.1136/thoraxjnl-2016-209023

Problem

- Information from several individual elements
- Daily observations → dependence between consecutive observations

- → **Aim**: Develop a model to describe and learn from these type of (PRO) data

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Outline

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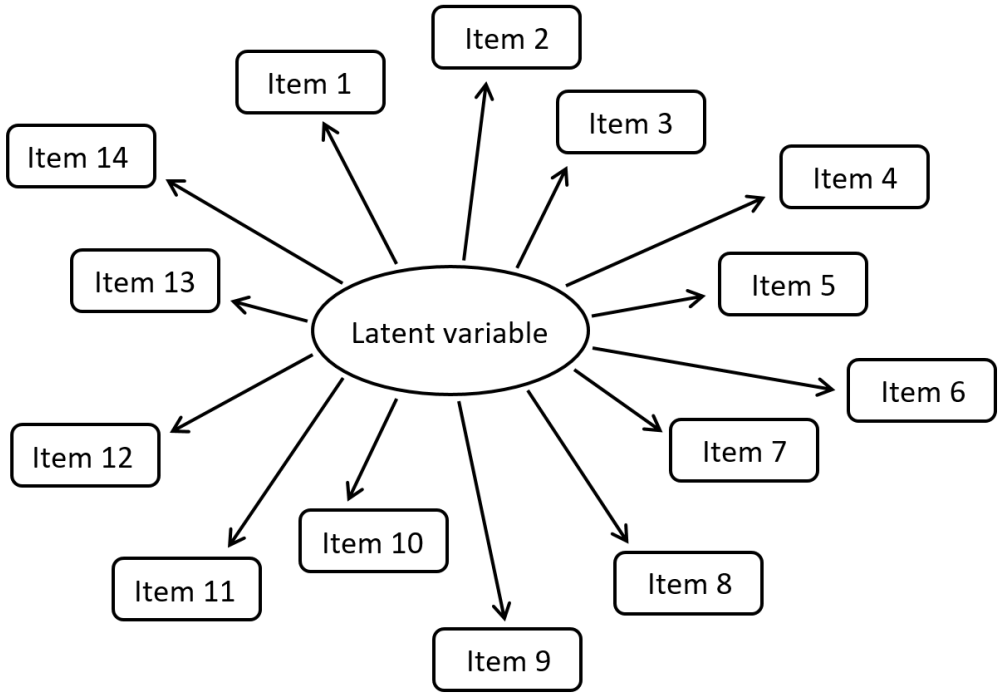
Item response theory

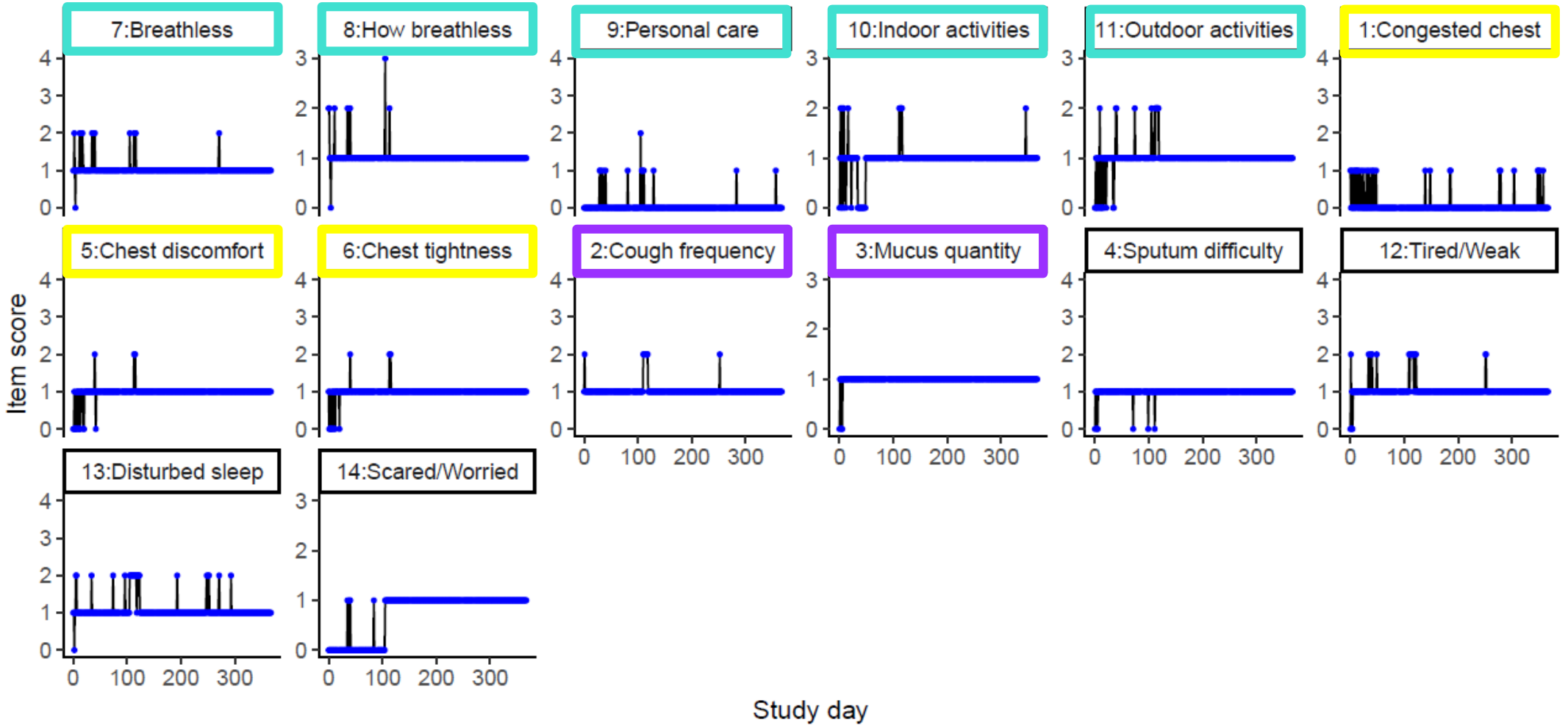
- Probabilities of an observation modelled
- Probability of a response to an item related to a latent variable[1] (e.g. COPD disease severity)
- This methodology was used in different disease areas, e.g. Alzheimer's disease[1], schizophrenia[2], multiple sclerosis[3]; however, no MM



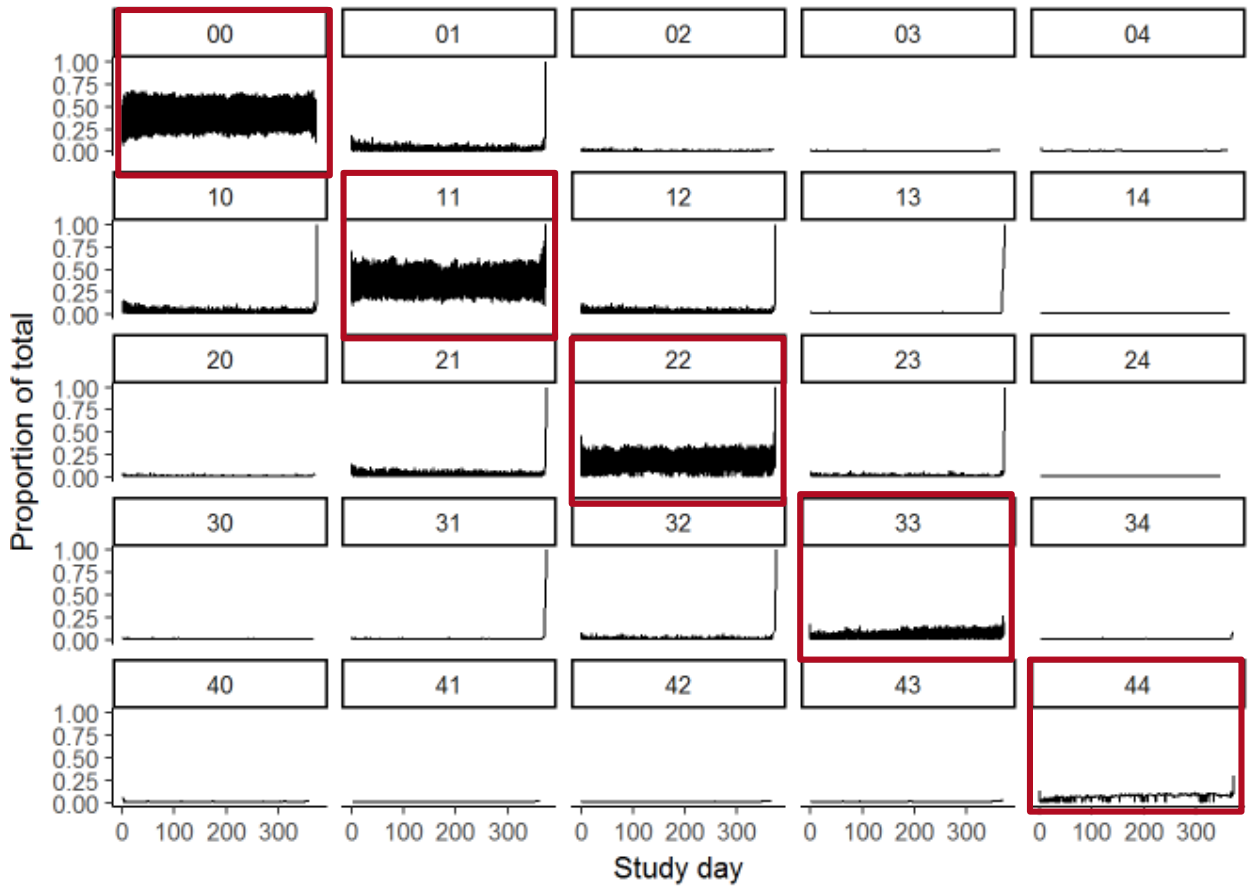
$$logit\ P\left(Y_{ij} \geq k\right) = a_j \cdot (D_i - b_j)$$

[1]Ueckert *et al*., Pharm Res, 2014. **31**(8): 2152-65
[2]Krekels *et al*, CPT PSP, 2017; doi: 10.1002/psp4.12207
[3]Novakovic *et al*, AAPS J. 2017;19(1):172-179

An individual example

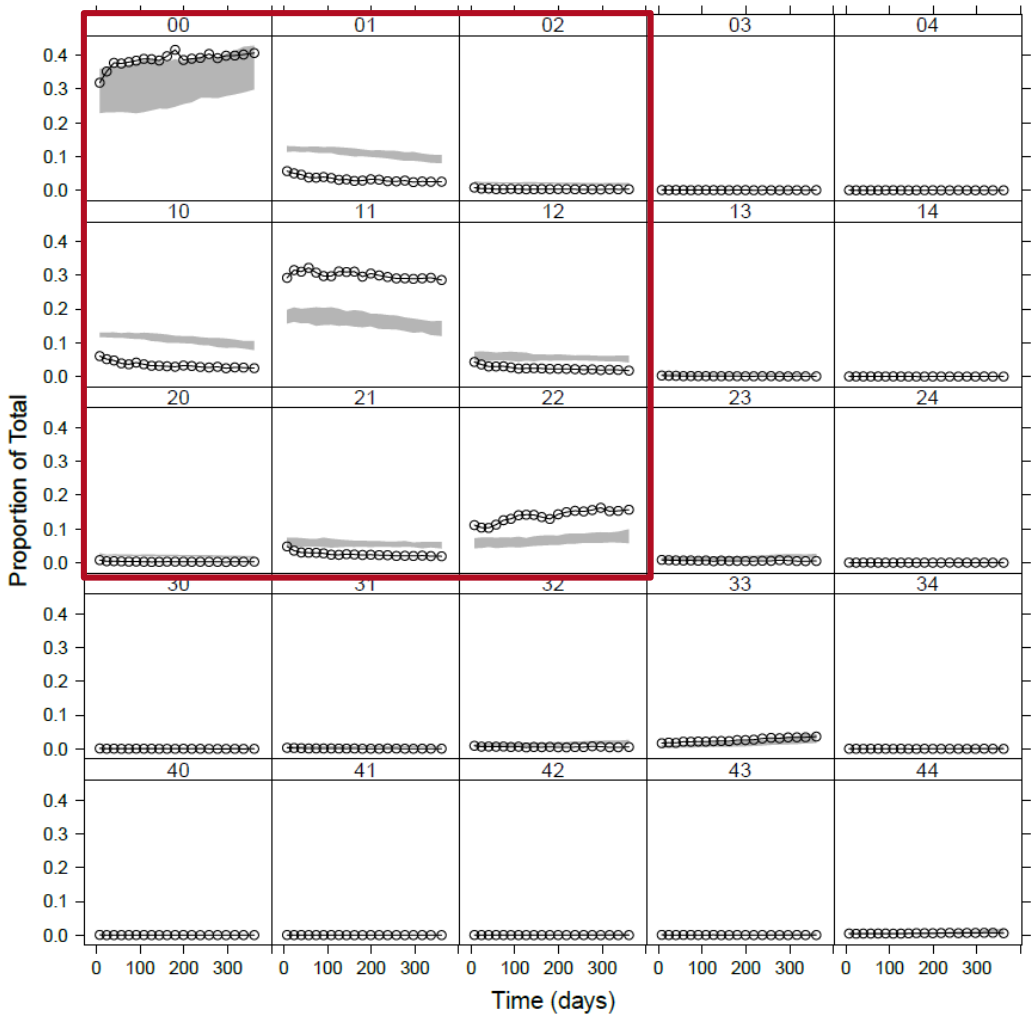


Data: transitions



No Markov elements

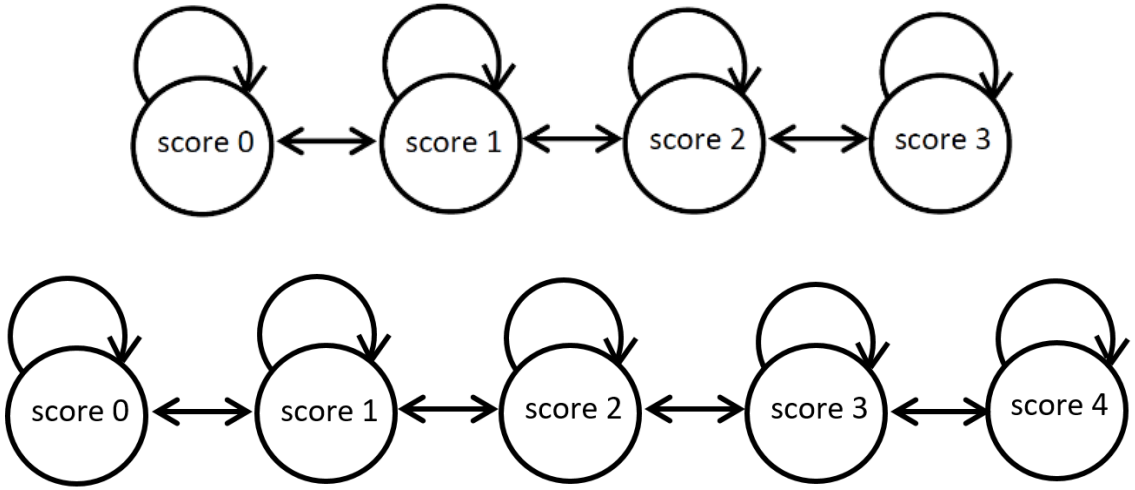
- No-MM: misspecification
- → MM needed



MM=Markov model

Markov models

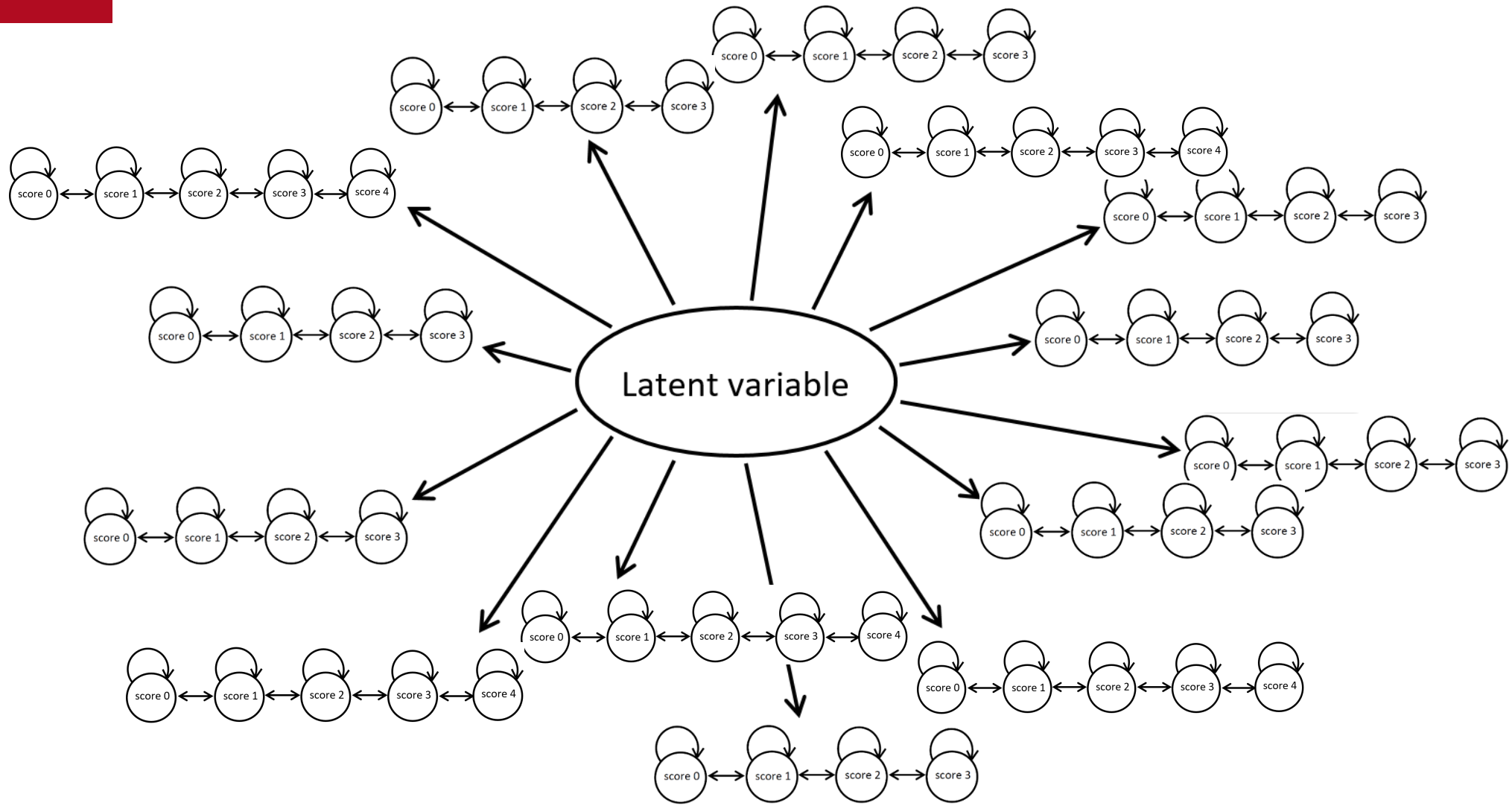
- Observation depends on the previous observation (i.e. state)
- Based on compartment or transition probabilities
- Minimal Markov models used[1]:
  - Transitions between neighbouring scores
  - Mean equilibrium time (MET) assumed the same between different states



$$\lambda_{(k-1,k)} = \left(MET \cdot \left(1 + \frac{P\left(Y_{ij} = k-1\right)}{P\left(Y_{ij} = k\right)} \right) \right)^{-1}$$

[1]Schindler *et al*., PAGE, 2017. Abstr 6077

IRT + Markov models



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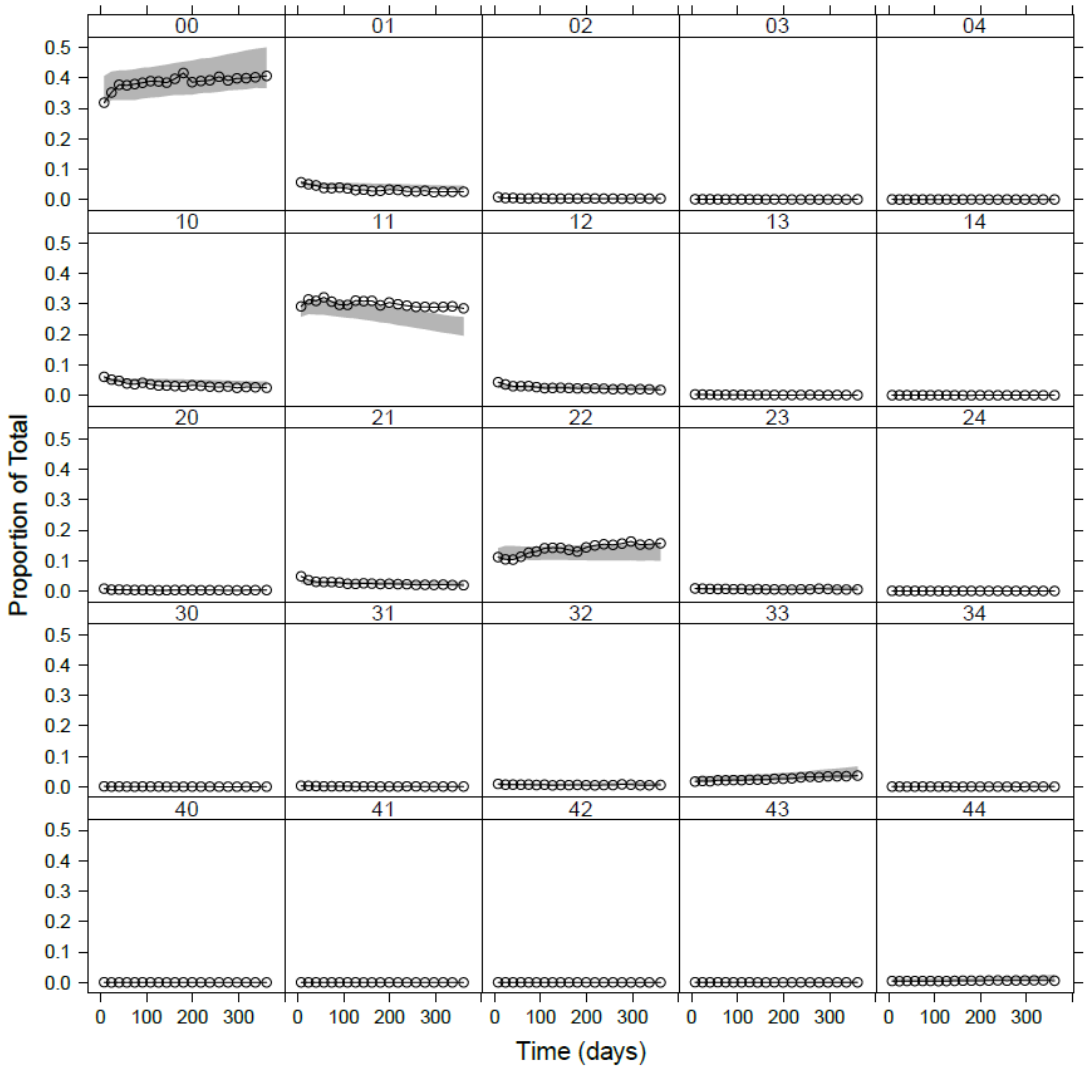
Transition VPC (all items)



0

1

2

3

4

Mean (standard error)
MET: 2.7 (0.2) day;
0.72* (0.097) IIV

MET=mean equilibrium time
IIV= inter-individual variability
*on the variance scale

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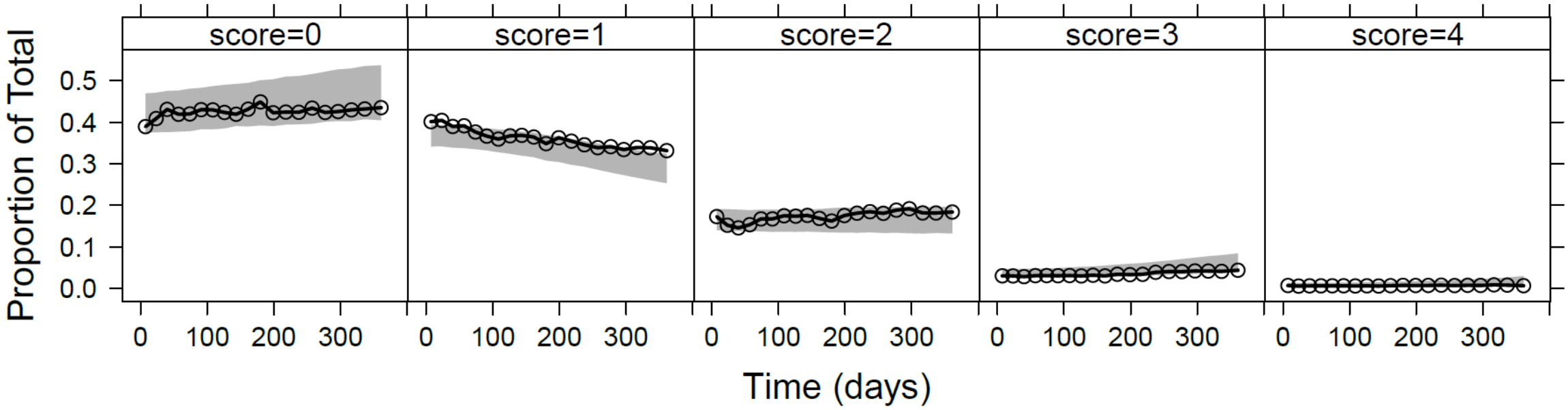
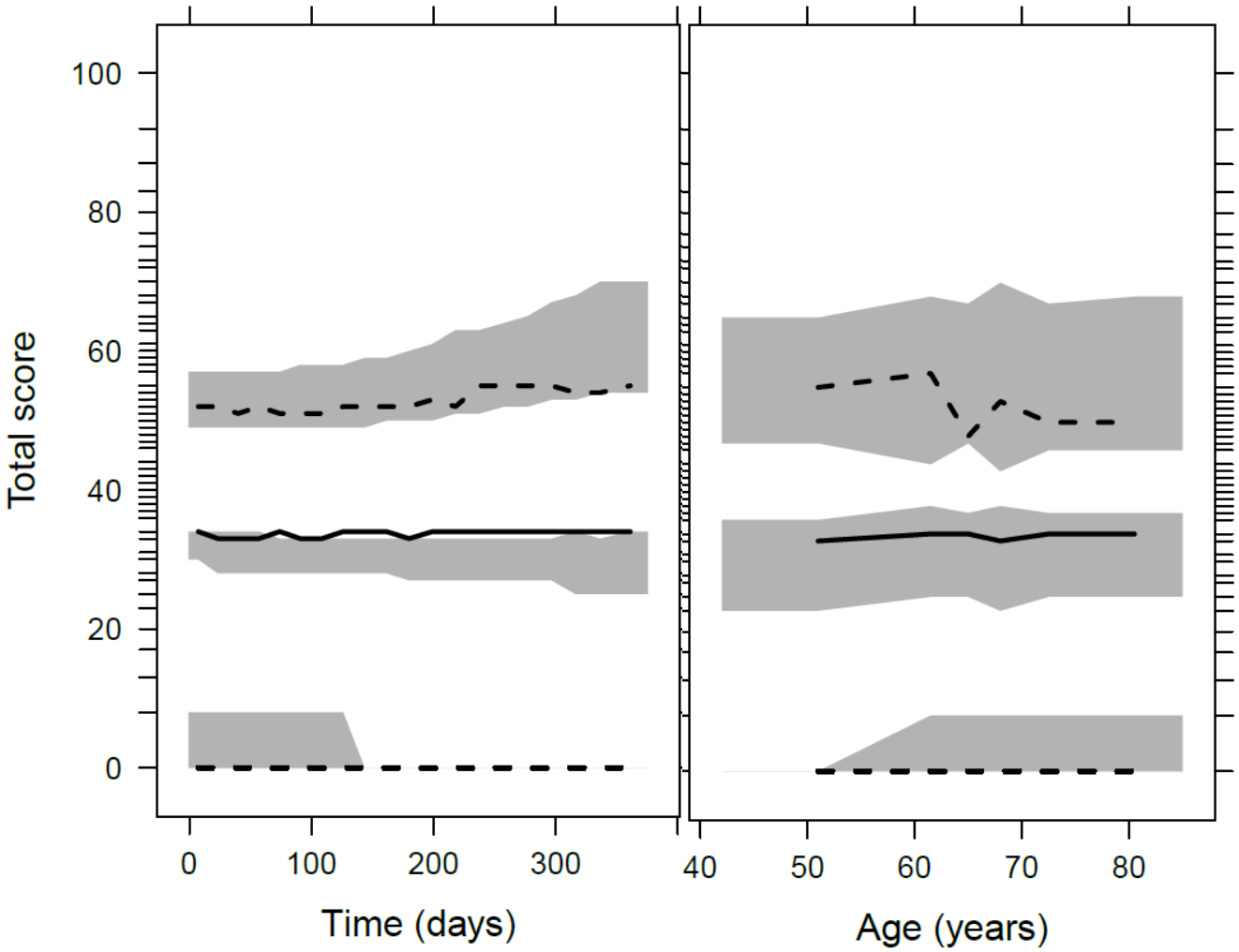
Sub-score VPC (all items)



Total score VPC



Mean (standard error) slope*: -0.18 (0.13) year^{-1}; 1.85** (0.60) IIV

*on the latent variable scale
**on the variance scale
IIV= inter-individual variability

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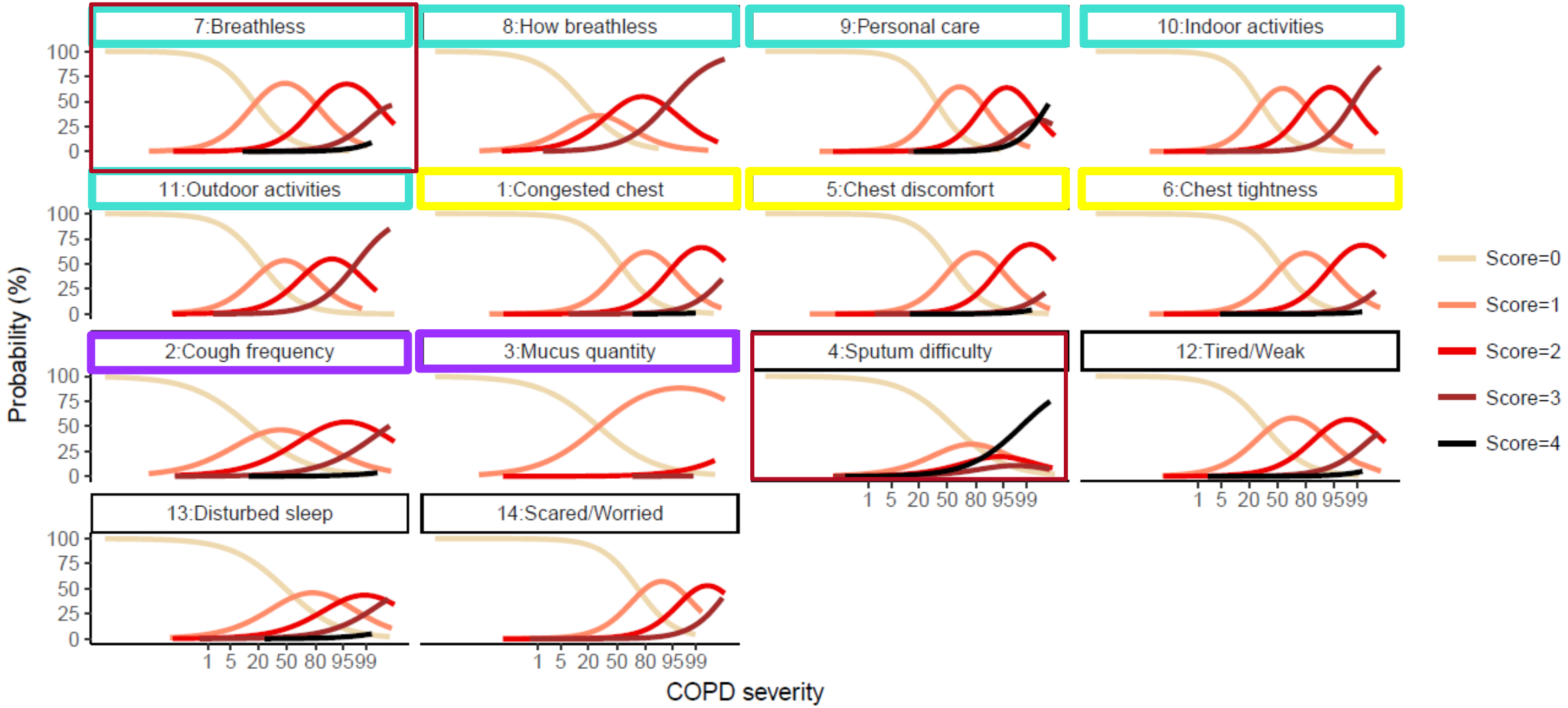
Item characteristic curves



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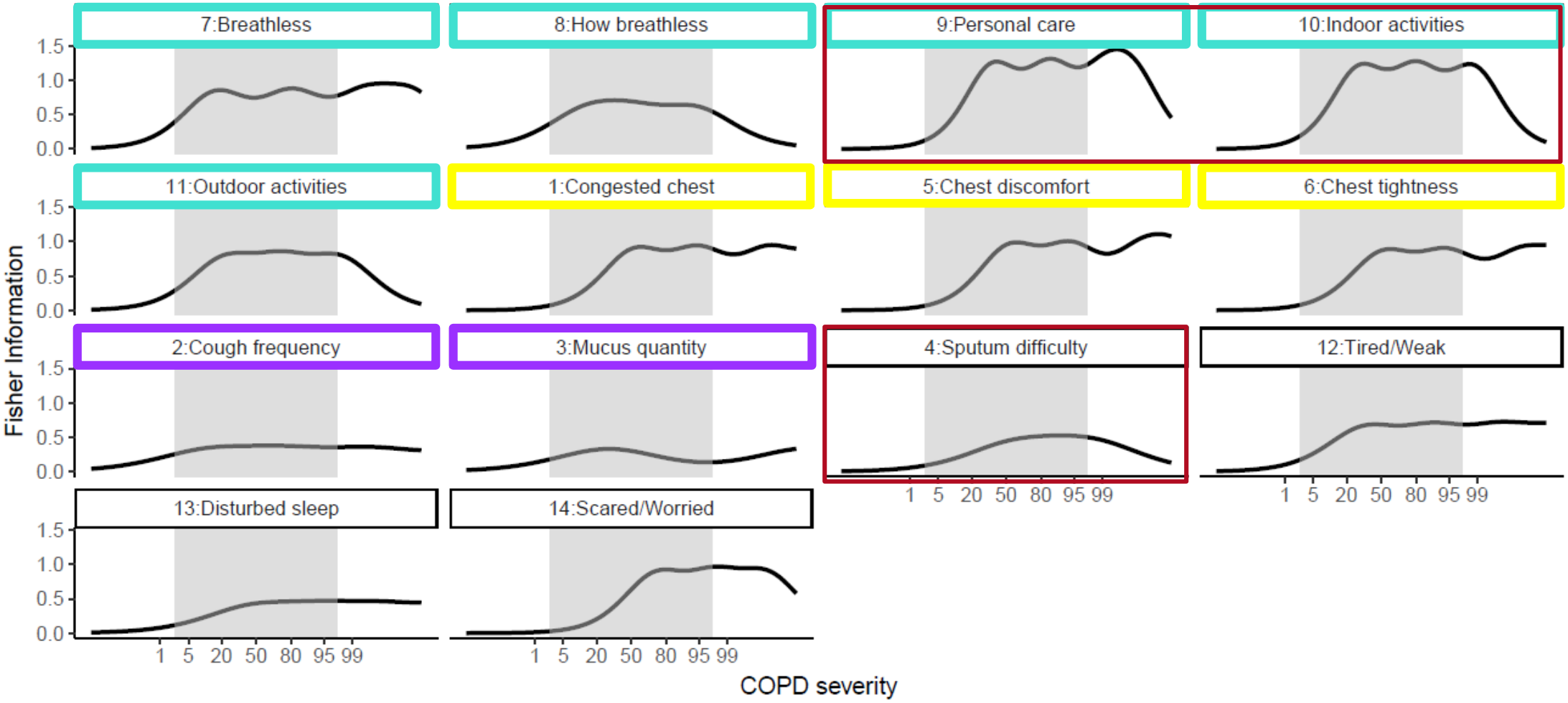
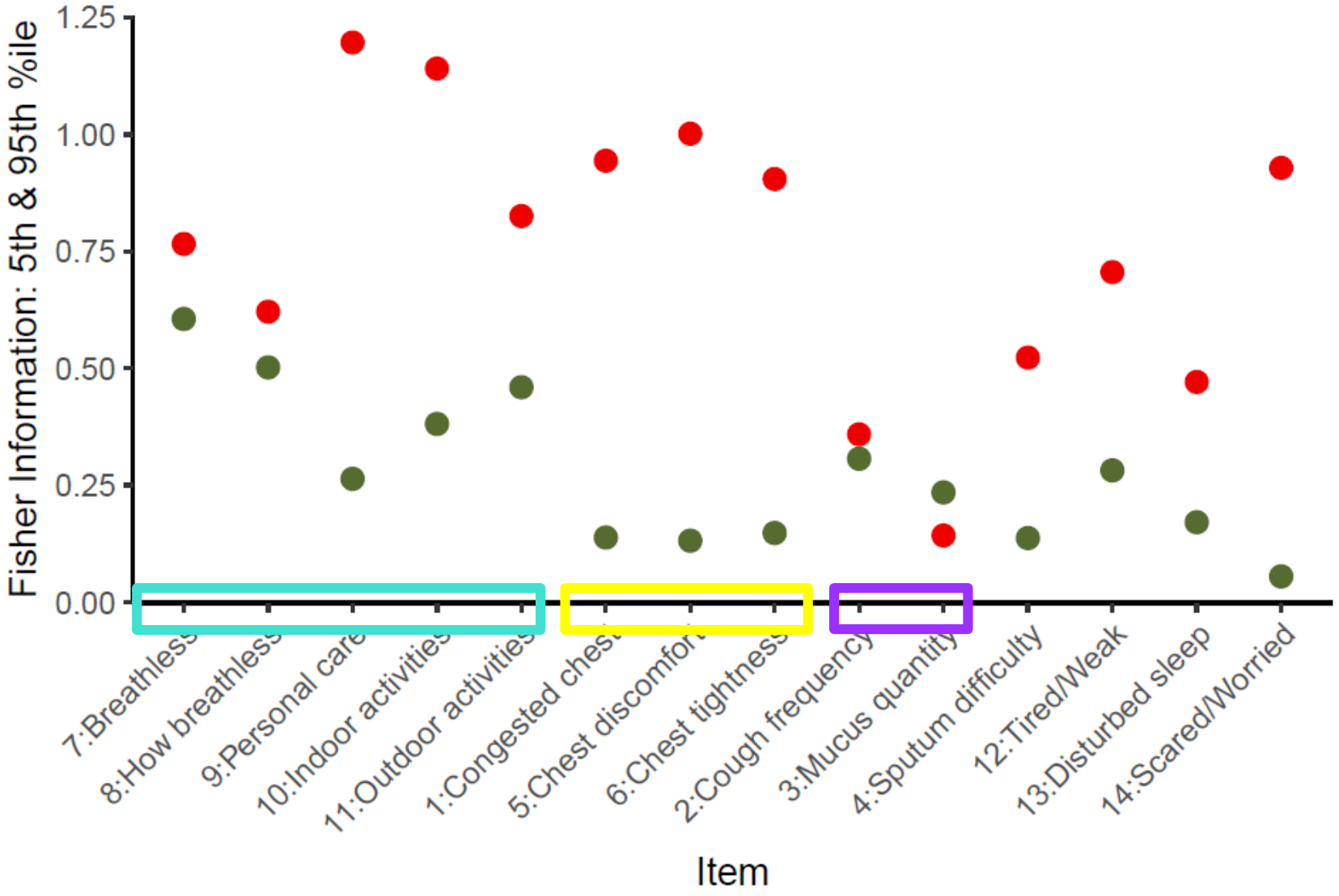
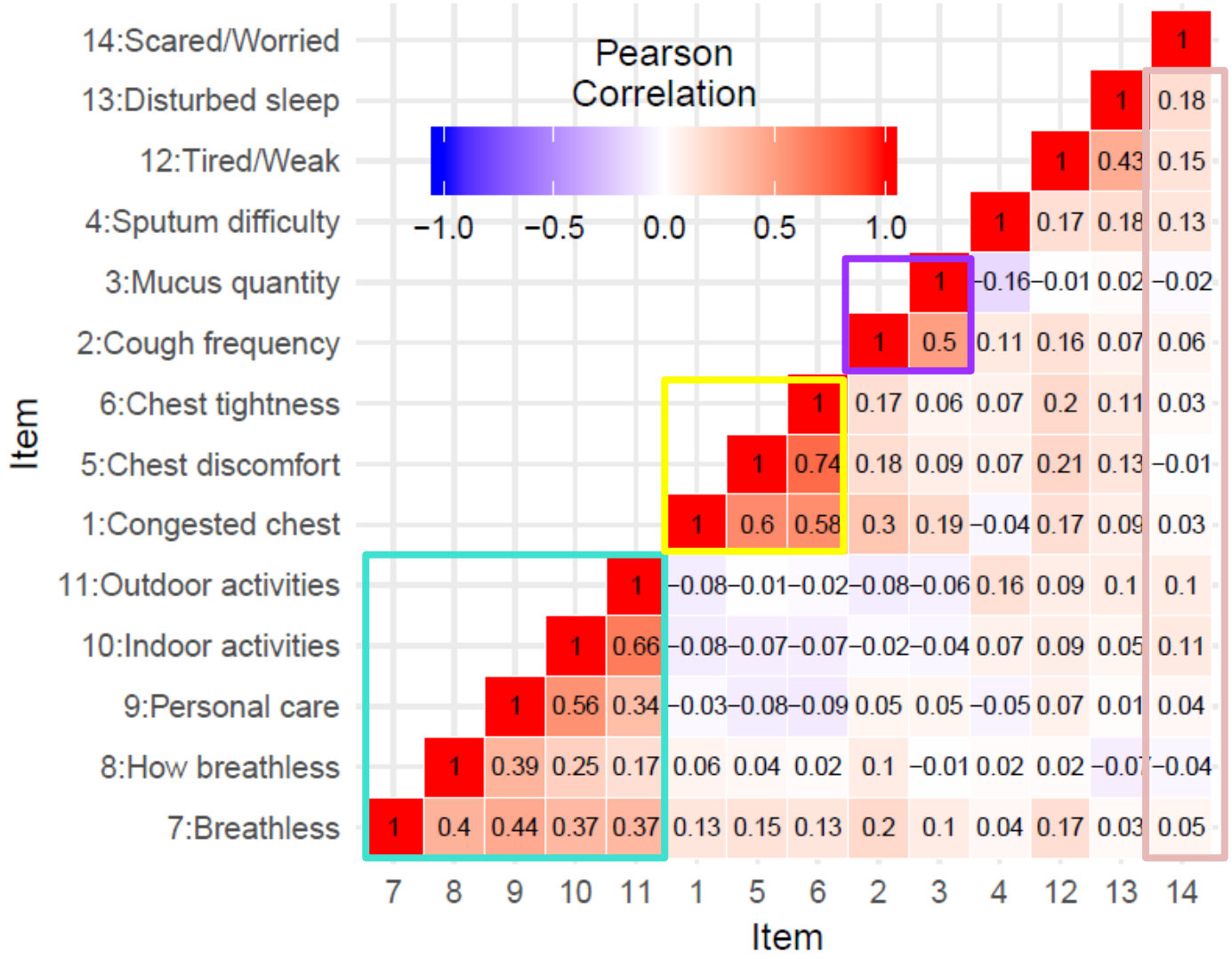
Item information



Item information: 5th and 95th percentiles



Item residual correlation plot



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Conclusion

- First mixed-effects IRT model with longitudinal Markov elements was developed
- The model was able to handle both composite scores & frequent observations – as shown on the example of COPD sub-score data from the EXACT questionnaire

- An addition of Markov models to an IRT model is expected to be needed with similar types of data

Acknowledgements

Thank you for your attention!

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I have no conflicts of interest