4-step longitudinal analysis of latent traits derived from measurement scales in chronic diseases: quality-of-life in multiple system atrophy

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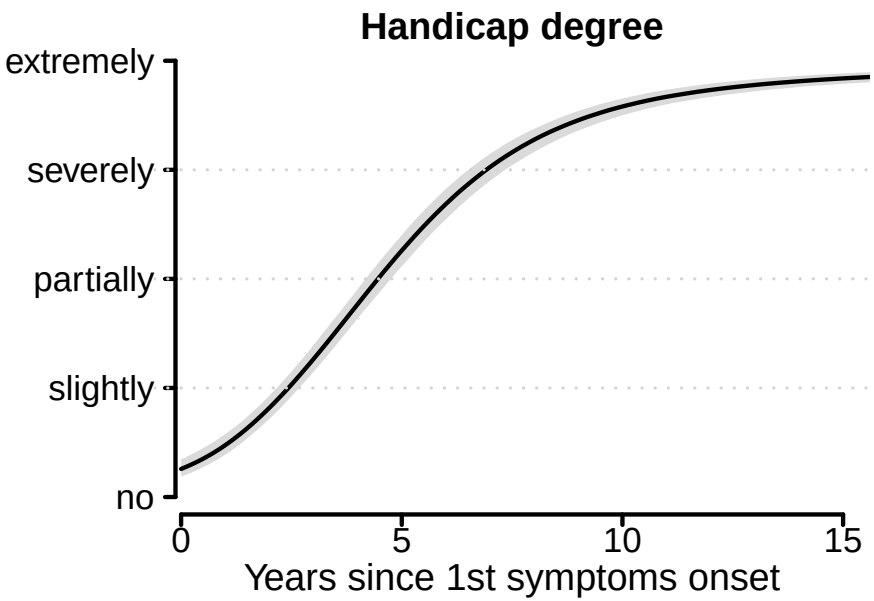
Multiple-System Atrophy (MSA)

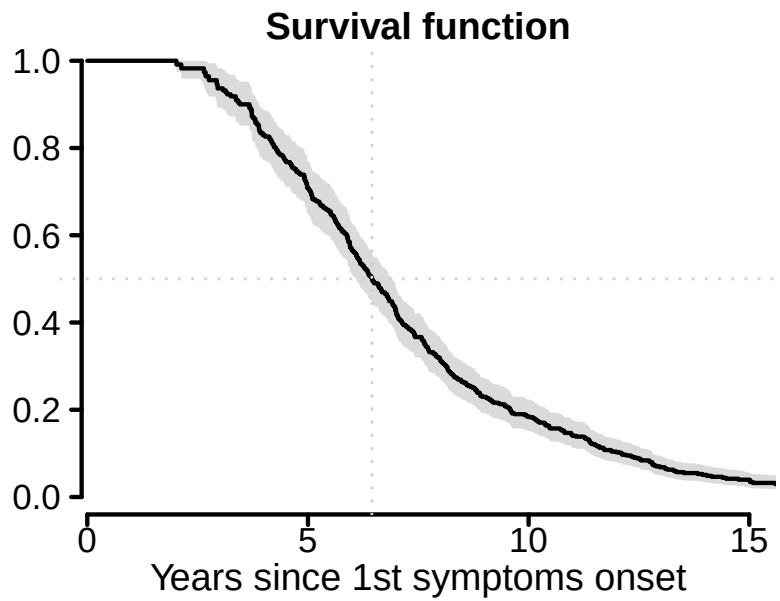
- neurodegenerative and rare disease

  prevalence around 5,000 cases in France
- Parkinsonian syndrome, cerebellar syndrome, dysautonomic disorders
- fast progression, fatal prognostic, no cure treatment
- potential accelerated model of Parkinson's disease

French MSA cohort

- Bordeaux and Toulouse hospitals = national reference MSA centre
- open cohort, created in 2007
- $>$ 700 patients
- complete annual follow-ups with clinical assessment





Quality-of-Life (QoL)

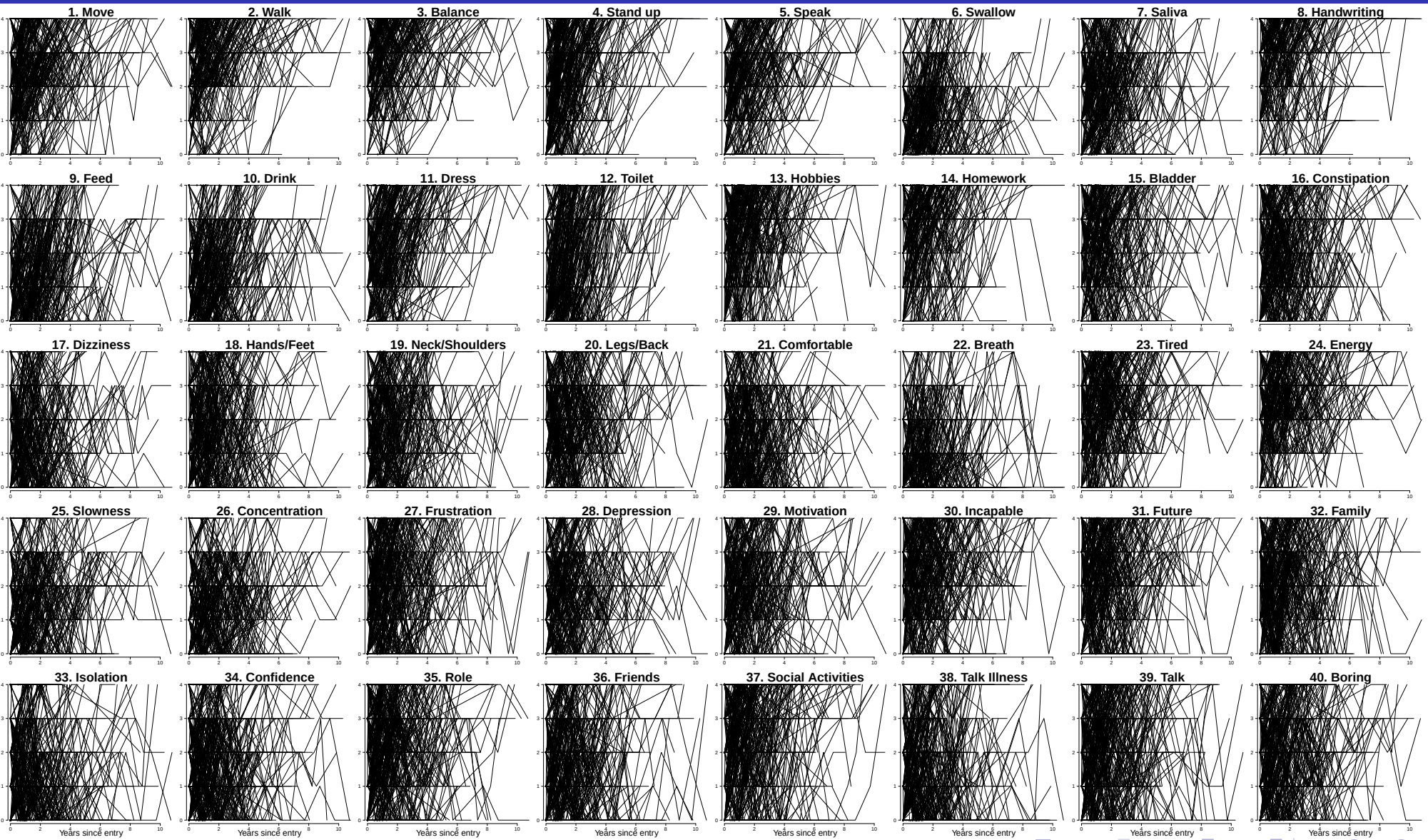
- reflects patients' perception about their health condition
- focus on patients' feelings
  - $\rightarrow$ crucial information to deliver better support
  - $\rightarrow$ FDA requirement: new treatments must improve QoL

MSA-QoL scale

In the last 4 weeks have you ...	No	Slight	Moderate	Marked	Extreme
1. Had difficulty moving?					
2. Had difficulty walking?					
3. Had problems with your balance?					
4. Had difficulty standing up without support?					
5. Had difficulty speaking?					
6. Had difficulty swallowing food?					
7. Had too much saliva or drooling?					
8. Had difficulty with handwriting?					
9. Had difficulty feeding yourself?					
10. Had difficulty drinking fluids?					
11. Had difficulty dressing yourself?					
12. Needed help to go to the toilet?					
13. Had to stop doing things that you liked to do, e.g. your hobbies?					
14. Had difficulty doing things around the house, e.g. housework?					
15. Experienced bladder problems?					
16. Experienced problems with constipation?					
17. Experienced dizziness when standing up?					
18. Suffered from cold hands or feet?					
19. Experienced pain in your neck or shoulders?					
20. Experienced pain elsewhere, e.g. in your legs or your back?					
21. Had difficulty getting comfortable during the night?					
22. Had difficulty breathing during the night?					
23. Been feeling tired very quickly (without exerting yourself)?					
24. Experienced lack of energy?					
25. Experienced slowness of thinking?					
26. Had difficulty with your concentration, e.g. reading or watching TV?					
27. Felt frustrated?					
28. Felt depressed?					
29. Experienced a loss of motivation?					
30. Been feeling incapable?					
31. Worried about the future?					
32. Worried about your family?					
33. Felt on your own or isolated?					
34. Experienced loss of confidence when interacting with others?					
35. Felt that your role in your family or among friends has changed?					
36. Experienced difficulty seeing your friends?					
37. Had to give up social activities, e.g. going out for a meal, participating in events?					
38. Had difficulty talking to friends about your illness?					
39. Been embarrassed to talk to people?					
40. Felt that life has become boring?					

- specific to MSA
- developed in 2008, by A. SCHRAG team
- 40 ordinal items
- 5 levels :
  0. no problem,
  1. slight,
  2. moderate,
  3. marked,
  4. extreme

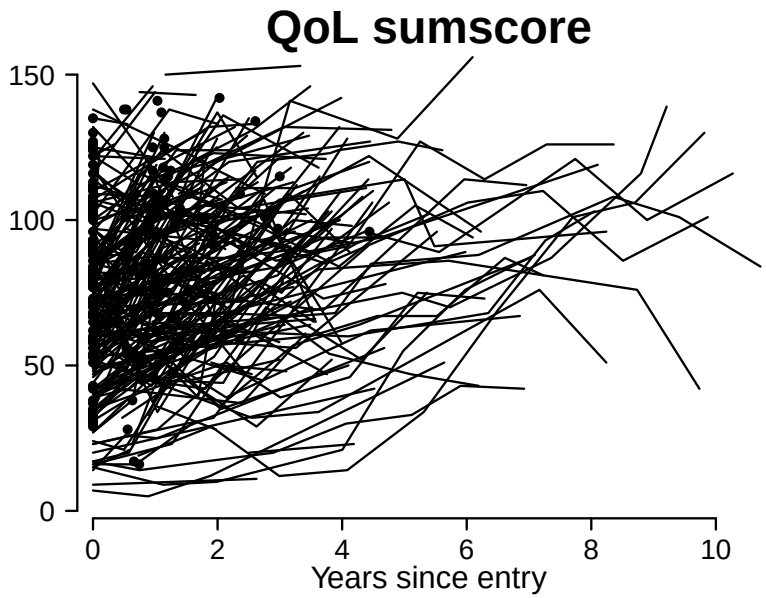
MSA-QoL data


1. Move
2. Walk
3. Balance
4. Stand up
5. Speak
6. Swallow
7. Saliva
8. Handwriting
9. Feed
10. Drink
11. Dress
12. Toilet
13. Hobbies
14. Homework
15. Bladder
16. Constipation
17. Dizziness
18. Hands/Feet
19. Neck/Shoulders
20. Legs/Back
21. Comfortable
22. Breath
23. Tired
24. Energy
25. Slowness
26. Concentration
27. Frustration
28. Depression
29. Motivation
30. Incapable
31. Future
32. Family
33. Isolation
34. Confidence
35. Role
36. Friends
37. Social Activities
38. Talk Illness
39. Talk
40. Boring
Years since entry

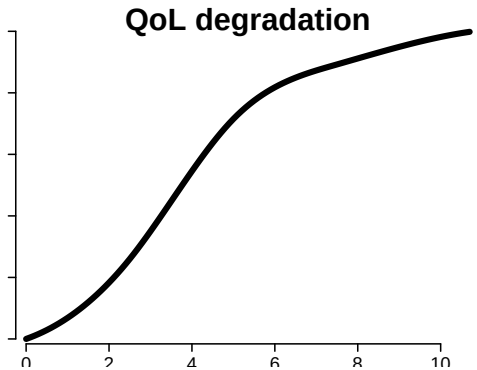
Summarize multivariate data : Sumscore

Sumscore

- loss of information
- no distinction between items
- missing item not allowed
- ...

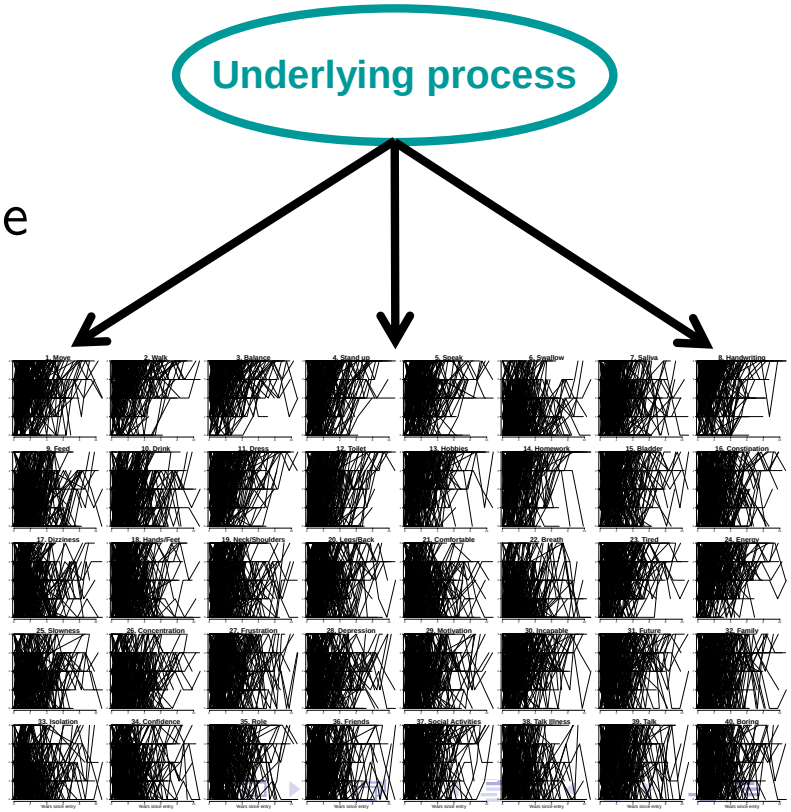


Summarize multivariate data : Underlying process

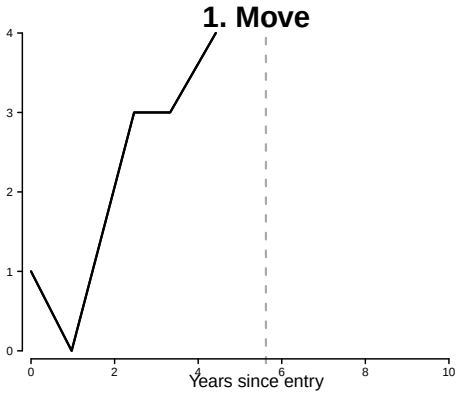


Underlying process

- creation of a *latent variable*
- not directly measurable or observable



Other statistical challenges



...

Challenges

- follow-up / repeated measures
- ordinal outcomes
- death occurence $\rightarrow$ [informative] dropout
- multi-dimensionality : not only one quantity of interest

$\rightarrow$ **4-step strategy of analysis**

Cohort description (N = 536)

Characteristics at inclusion	N (%)	mean ± sd
Sex female (vs male)	268 (50.0%)	
Subtype MSA-P (vs MSA-C)	363 (67.7%)	
Certainty Probable (vs Possible)	400 (74.6%)	
Age at study inclusion		65.1 ± 8.0
Care delay		4.5 ± 2.4
Orthostatic hypotension yes (vs no)	361 (67.4%)	
Urinary disorder yes (vs no)	365 (68.1%)	
Handicap degree		
Completely independent (stage I)	111 (20.7%)	
Not completely independent (stage II)	239 (44.6%)	
More dependent (stage III)	105 (19.6%)	
Very dependent (stage IV)	63 (11.8%)	
Totally dependent (stage V)	2 (3.0%)	
Characteristics during follow up		
Visits	1501	
Visits per patient		2.8 ± 1.9
Years of follow-up		2.5 ± 2.4
Dropouts	87 (16.2%)	
Deaths	338 (63.1%)	

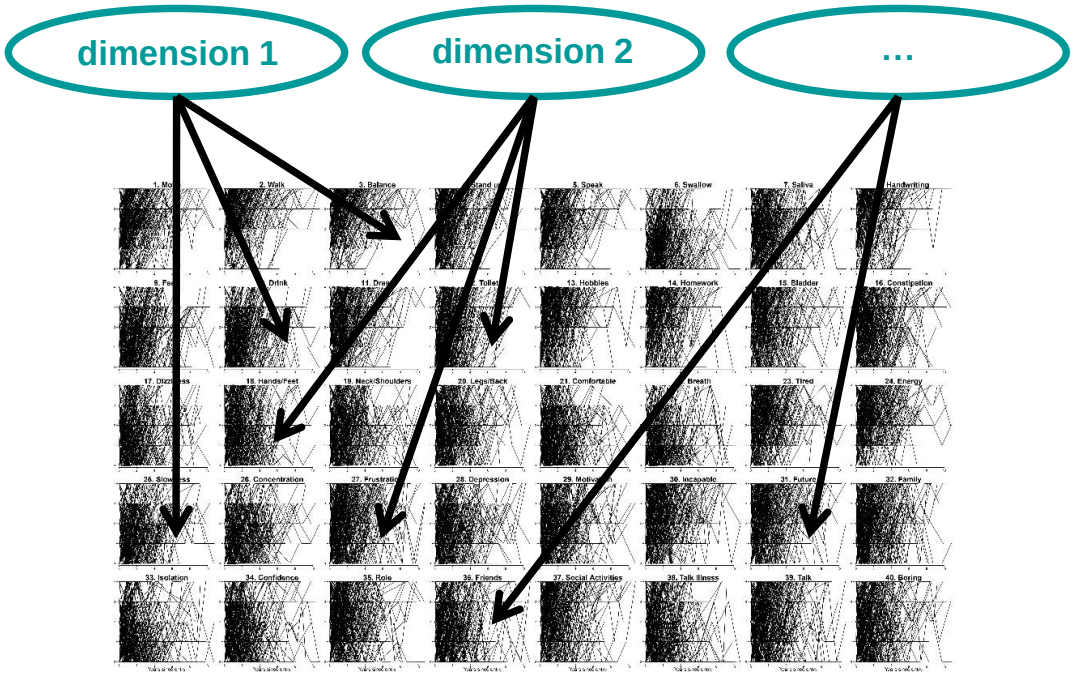
Step 1 : Identify scale sub-dimensions

PROMIS method

(B.B. REEVE et al., 2007)

3 hypotheses of scale calibration

- **Unidimensionality**
  items from a same sub-dimension measure the same phenomenon
  → *factorial analyses*
- Conditional independance
- Increasing monotonicity



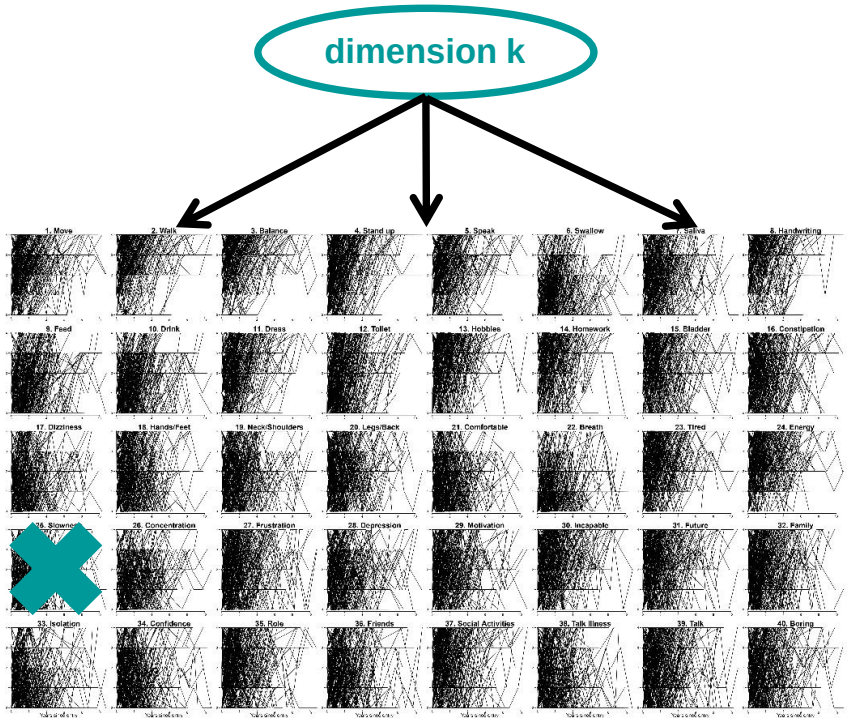
Step 1 : Identify scale sub-dimensions

PROMIS method

(B.B. REEVE et al., 2007)

3 hypotheses of scale calibration

- Unidimensionality
- **Conditional independance**
  no redundant information
  between items from
  a same sub-dimension
  → *residual correlations*
- Increasing monotonicity



Step 1 : Identify scale sub-dimensions

PROMIS method

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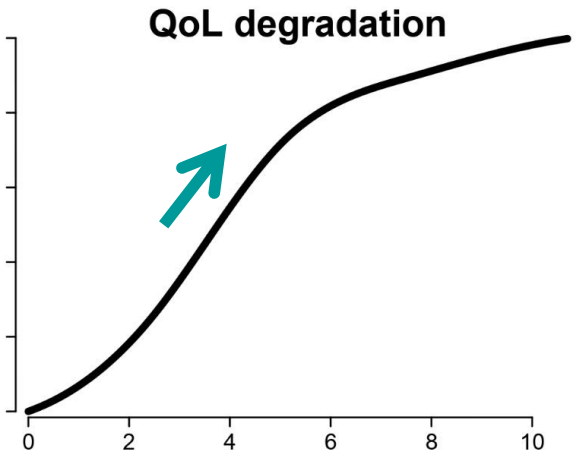
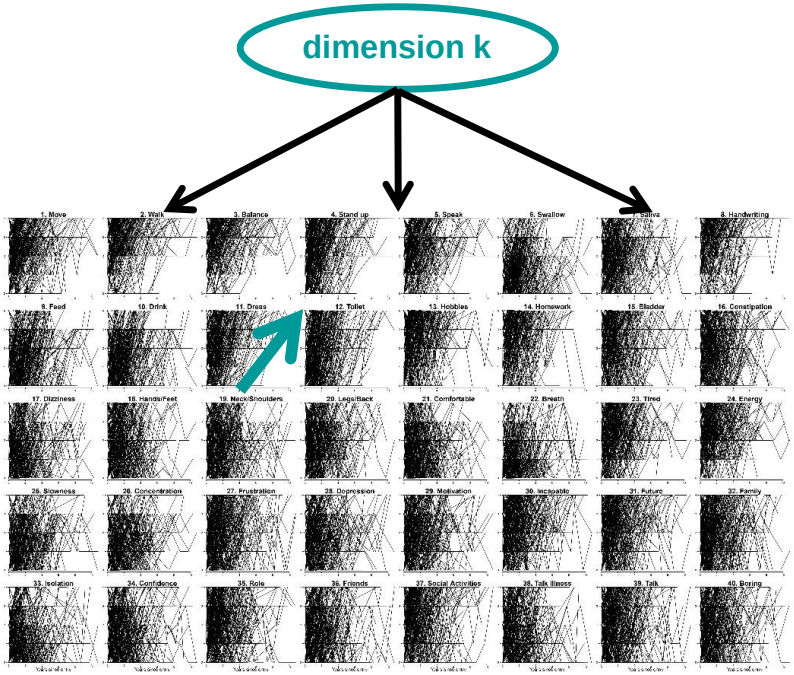


3 hypotheses of scale calibration

- Unidimensionality
- Conditional independance
- **Increasing monotonicity**
  the higher the item level,
  the higher the degradation level
  → *endorsement probabilities*



Step 1 : MSA-QoL sub-dimensions

ORIGINAL MSA-QoL SCALE	MOTOR	1. Had difficulty moving?
		2. Had difficulty walking?
		3. Had problems with your balance?
		4. Had difficulty standing up without support?
		5. Had difficulty speaking?
		6. Had difficulty swallowing food?
		7. Had too much saliva or drooling?
		8. Had difficulty with handwriting?
		9. Had difficulty feeding yourself?
		10. Had difficulty drinking fluids?
		11. Had difficulty dressing yourself?
		12. Needed help to go to the toilet?
		13. Had to stop doing things that you liked to do, e.g. your hobbies?
		14. Had difficulty doing things around the house, e.g. housework?
	NON-MOTOR	15. Experienced bladder problems?
		16. Experienced problems with constipation?
		17. Experienced dizziness when standing up?
		18. Suffered from cold hands or feet?
		19. Experienced pain in your neck or shoulders?
		20. Experienced pain elsewhere, e.g. in your legs or your back?
		21. Had difficulty getting comfortable during the night?
		22. Had difficulty breathing during the night?
		23. Been feeling tired very quickly (without exerting yourself)?
		24. Experienced lack of energy?
		25. Experienced slowness of thinking?
		26. Had difficulty with your concentration, e.g. reading or watching TV?
	EMOTIONAL / SOCIAL	27. Felt frustrated?
		28. Felt depressed?
		29. Experienced a loss of motivation?
		30. Been feeling incapable?
		31. Worried about the future?
		32. Worried about your family?
		33. Felt on your own or isolated?
		34. Experienced loss of confidence when interacting with others?
		35. Felt that your role in your family or among friends has changed?
		36. Experienced difficulty seeing your friends?
		37. Had to give up social activities, e.g. going out for a meal, participating in events?
		38. Had difficulty talking to friends about your illness?
		39. Been embarrassed to talk to people?
		40. Felt that life has become boring?

Step 1 : MSA-QoL sub-dimensions

ORIGINAL MSA-QoL SCALE			REVISED MSA-QoL SCALE
MOTOR	1. Had difficulty moving?	MOTOR	
	2. Had difficulty walking?		
	3. Had problems with your balance?		
	4. Had difficulty standing up without support?		
	5. Had difficulty speaking?		
	6. Had difficulty swallowing food?	FOOD INTAKE	
	7. Had too much saliva or drooling?		
	8. Had difficulty with handwriting?	MOTOR	
	9. Had difficulty feeding yourself?	FOOD INTAKE	
	10. Had difficulty drinking fluids?		
	11. Had difficulty dressing yourself?	MOTOR	
	12. Needed help to go to the toilet?		
	13. Had to stop doing things that you liked to do, e.g. your hobbies?		
	14. Had difficulty doing things around the house, e.g. housework?		
NON-MOTOR	15. Experienced bladder problems?	MOTOR	
	16. Experienced problems with constipation?	NON-MOTOR	
	17. Experienced dizziness when standing up?		
	18. Suffered from cold hands or feet?		
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	20. Experienced pain elsewhere, e.g. in your legs or your back?		
	21. Had difficulty getting comfortable during the night?		
	22. Had difficulty breathing during the night?		
	23. Been feeling tired very quickly (without exerting yourself)?		
	24. Experienced lack of energy?		
	25. Experienced slowness of thinking?	X	
	26. Had difficulty with your concentration, e.g. reading or watching TV?	NON-MOTOR	
EMOTIONAL / SOCIAL	27. Felt frustrated?	EMOTIONAL / SOCIAL	
	28. Felt depressed?		
	29. Experienced a loss of motivation?		
	30. Been feeling incapable?		
	31. Worried about the future?		
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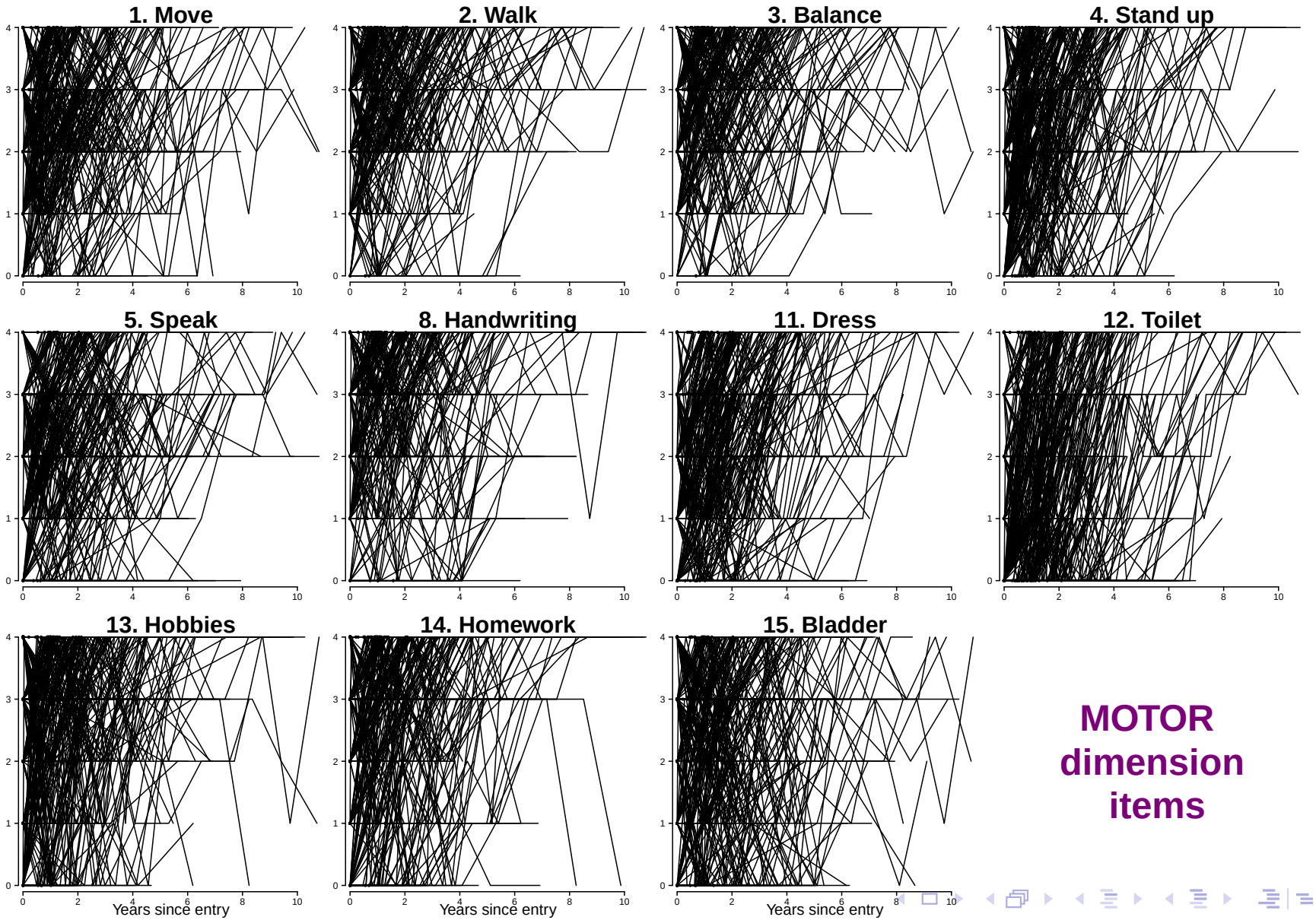
	39. Been embarrassed to talk to people?		
	40. Felt that life has become boring?		

Hypotheses :

- **Unidimensionnality**
  - 4 sub-dimensions (instead of 3)
  - similarity with the original scale
- **Conditional independance**
  - item 25 redundant with item 26
- **Increasing monotonicity**
  - checked ✓

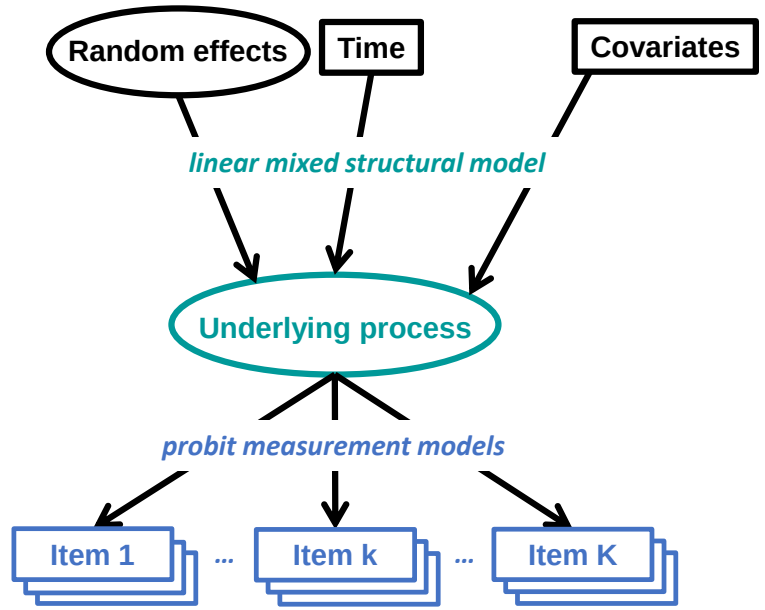
Step 2 : Model each sub-dimension evolution



MOTOR dimension items

Step 2 : Longitudinal submodel structure

Item Response Theory (IRT) model
Graded Response model framework



Dimension process

linear mixed model

$$\Delta_i(t) = X_i^\top(t)\beta + Z_i^\top(t)b_i$$

with $b_i \sim \mathcal{N}(0, B)$

Items

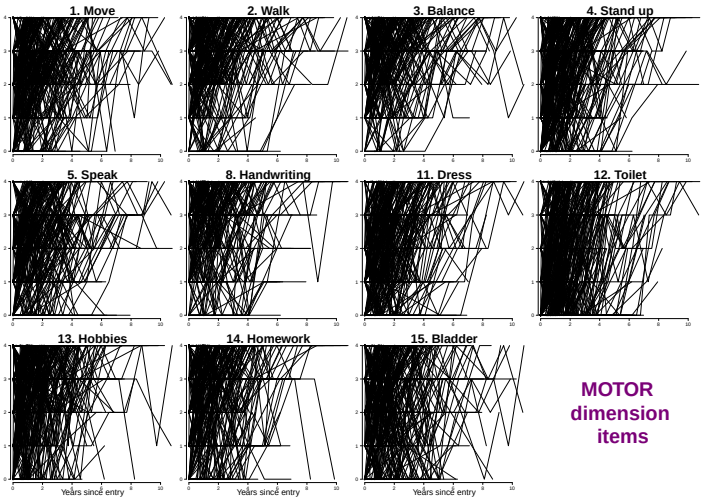
cumulative probit models

$$Y_{ik}(t) = m$$

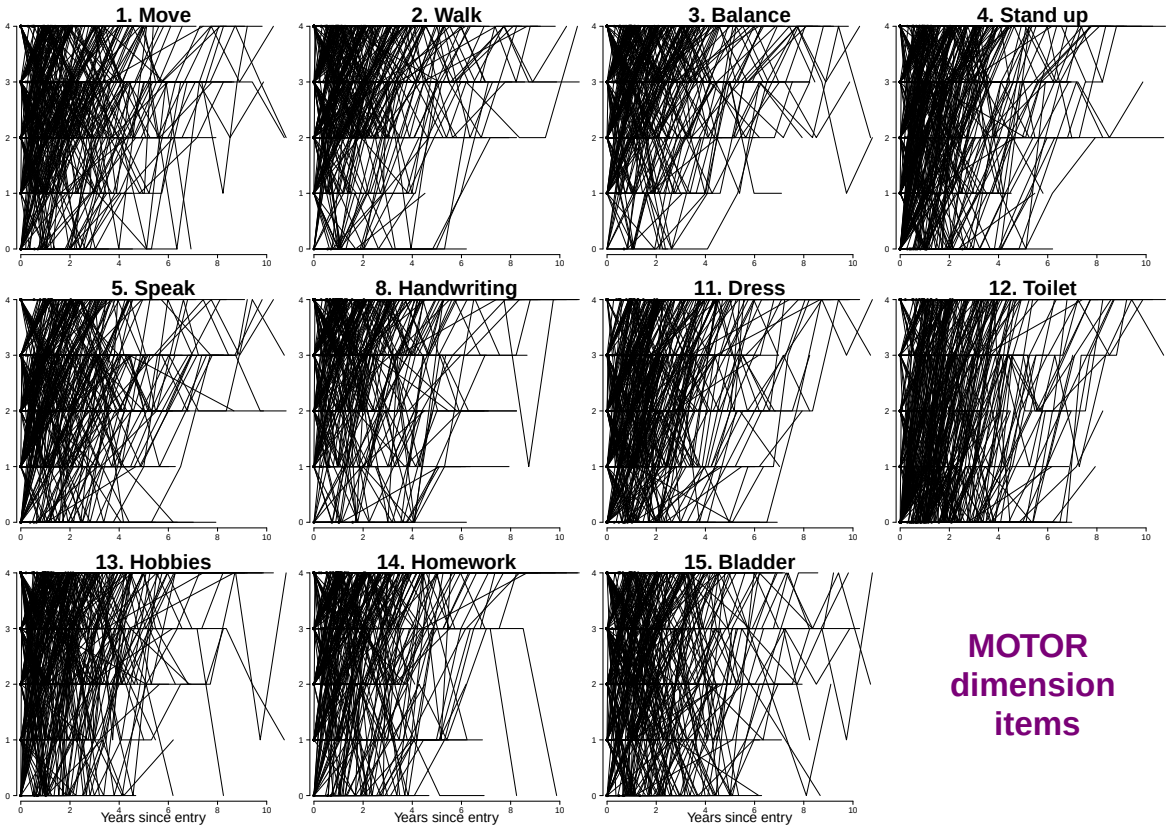
$$\Leftrightarrow \quad \eta_{k,m} < \Delta_i(t) + \epsilon_{ik}(t) \leq \eta_{k,m+1}$$

with $\epsilon_{ik} \sim \mathcal{N}(0, \sigma_k^2)$; $m \in \{1, ..., M_k\}$;

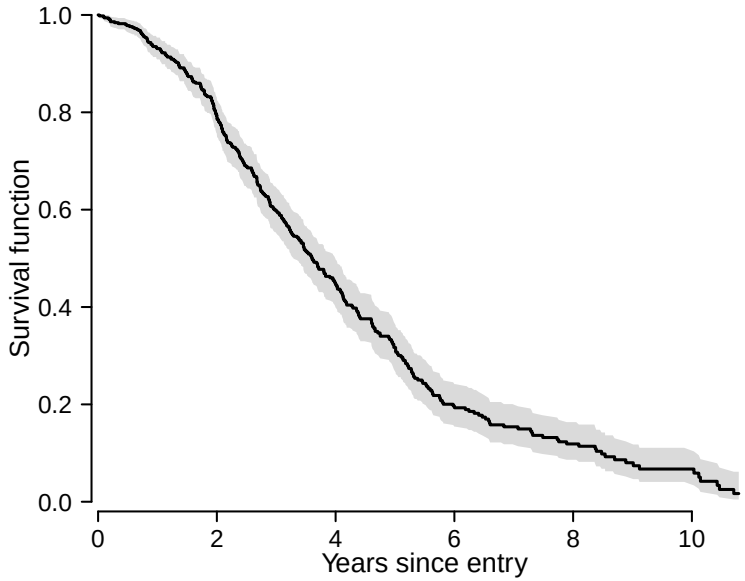
$$-\infty = \eta_{k,1} \leq ... \leq \eta_{k,m} \leq ... \leq \eta_{k,M_k+1} = +\infty$$



Step 2 : Informative dropout



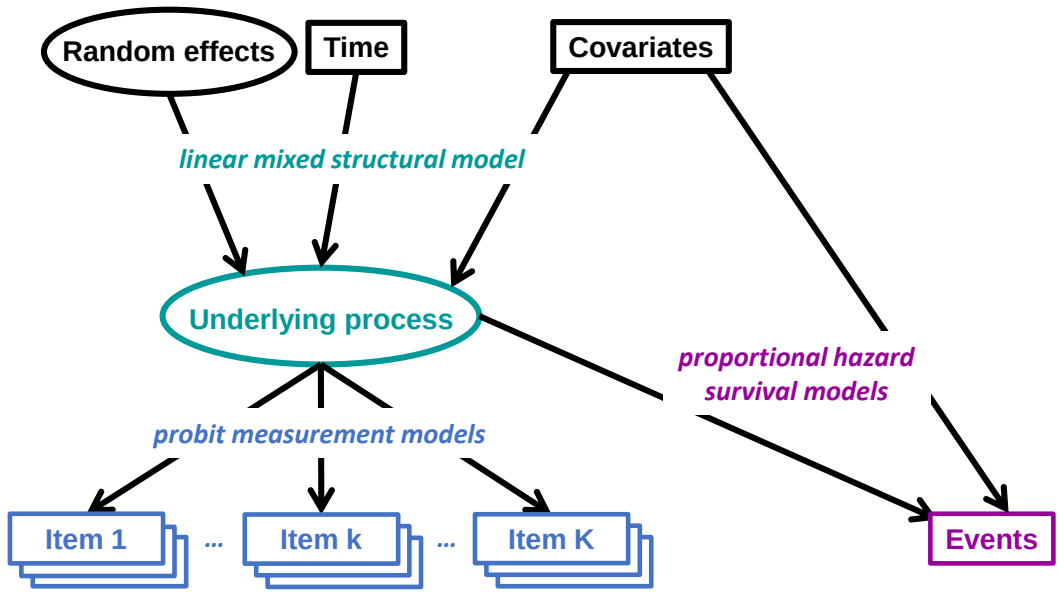
MOTOR dimension items



Step 2 : Survival submodel structure

IRT model

in the **Joint framework**

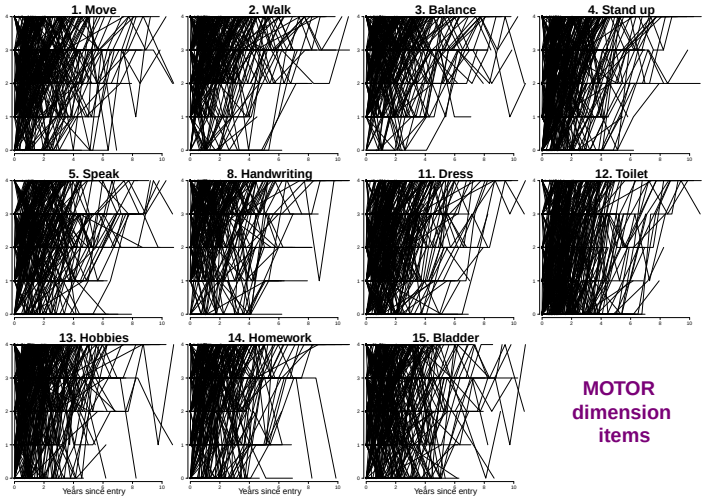


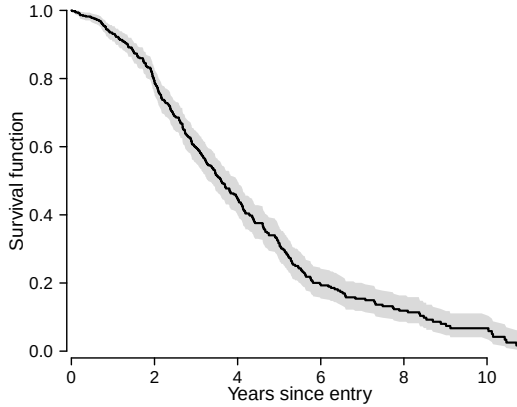
Survival part

proportional hazard model(s),

cause p

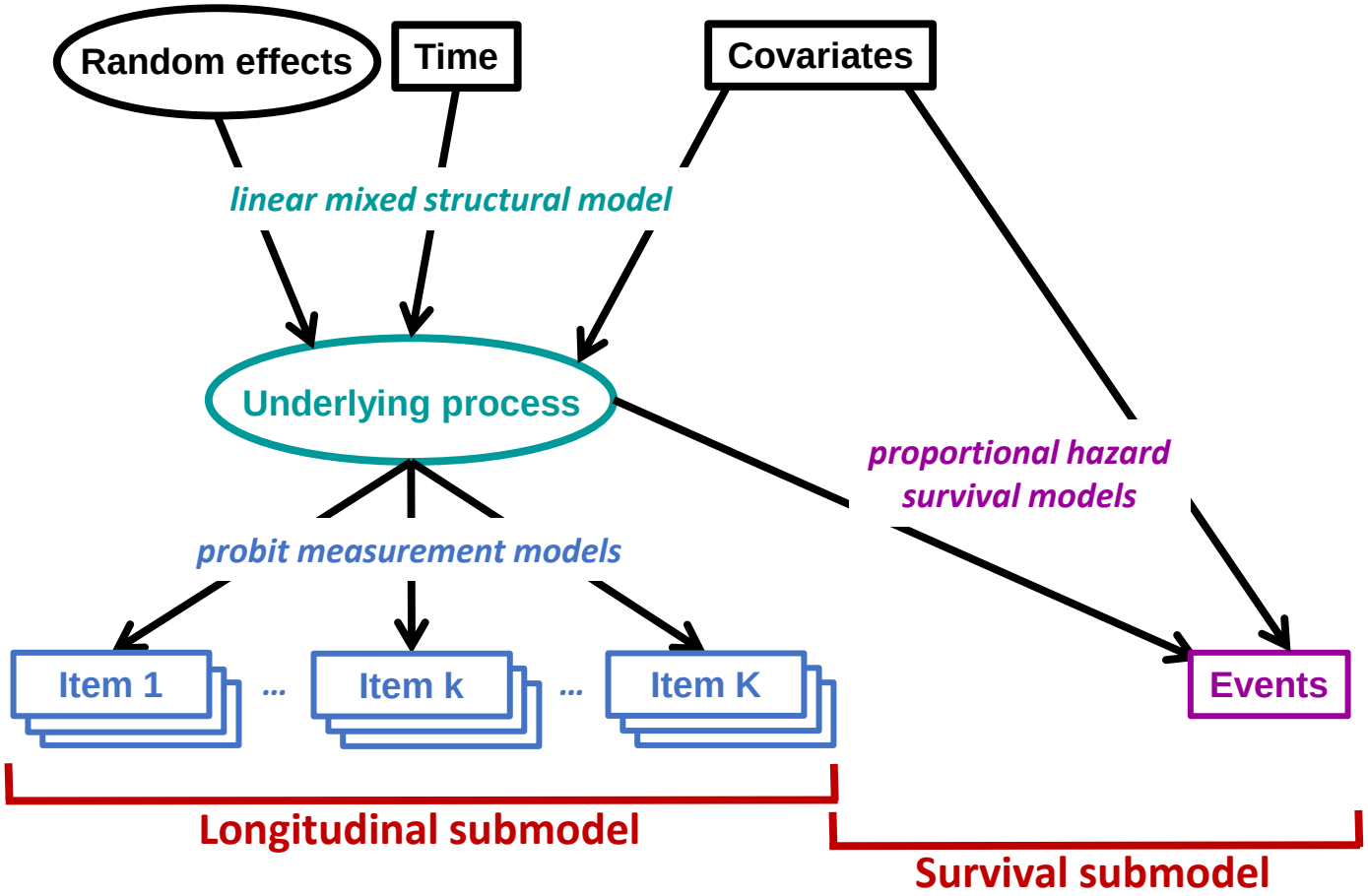
$$\lambda_{ip}(t) = \lambda_{0p}(t;\psi_p)\, exp(X_{pi}^{\top}\gamma_p) \times exp(\Delta_i(t)\alpha_p)$$





Step 2 : Joint latent process model (JLPM)

Joint latent process model (JLPM)
based on **Graded Response models** from **Item Response Theory** (IRT),
and extended to the **Joint framework**



implementation
R-package **JLPM**
available on CRAN

publication
Saulnier T. et al.,
(2022) Methods

Step 2 : Maximum likelihood estimation

vector of all parameters

$$\Theta = (\underbrace{\beta, B}_{\text{structural model}} , \underbrace{(\eta_{k,m})_{k,m}, (\epsilon_k)_k}_{\text{measurement models}}, \underbrace{(\psi_p)_p, (\gamma_p)_p, (\alpha_p)_p}_{\text{survival model(s)}})^\top$$

log-likelihood

$$\mathcal{L}(\Theta) = \sum_{i=1}^{N} logL_i(\Theta)$$

with **individual contribution**

$$\begin{aligned} L_i(\Theta) &= f_{Y_i,(T_i,\delta_i)}(Y_i,(T_i,\delta_i);\Theta) \\ &= \int_{\mathbb{R}^q} \prod_{k=1}^{K} \{f_{Y_{ik}|b_i}(Y_{ik}|b;\Theta)\} f_{(T_i,\delta_i)|b_i}((T_i,\delta_i)|b;\Theta) f_{b_i}(b;\Theta) db \end{aligned}$$

Step 2 : JLPM algorithms

- **optimisation** algorithm : Marquardt-Levenberg (MLA)

- **integral approximation** algorithms :
  - Quasi-Monte-Carlo (QMC)

$$L_i(\Theta) = \int_{\mathbb{R}^q} \prod_{k=1}^{K} \{f_{Y_{ik}|b_i}(Y_{ik}|b;\Theta)\} f_{(T_i,\delta_i)|b_i}((T_i,\delta_i)|b;\Theta) f_{b_i}(b;\Theta) db$$

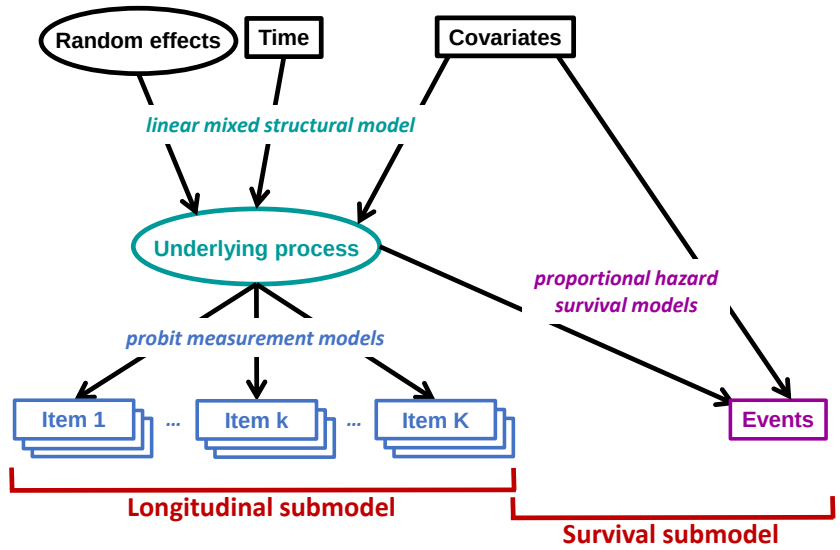
  - Gauss-Kronrod Gaussian quadrature with 15 points

$$S_i(t|b;\Theta) = \prod_{p=1}^{P} exp(-\int_0^t \lambda_{ip}(s|b;\Theta) ds)$$

Step 2 : Specification of MSA-QoL dimensions' models

Dimension process *linear mixed model*

$$\Delta_i(t) = t \cdot \beta_1 + X_{i,sex}\beta_2 + X_{i,diagnosis}\beta_3 + X_{i,certainty}\beta_4 + X_{i,age.0}\beta_5 + X_{i,orth.hypo.0}\beta_6 + X_{i,urin.dis.0}\beta_7 + X_{i,care.delay}\beta_8 + X_{i,ttt}(t)\beta_9 + b_{0i} + t \cdot b_{1i} \quad \text{with } b_i = (b_{0i}, b_{1i})^\top \sim \mathcal{N}(0, B)$$



Items *cumulative probit models*

$$Y_{ik}(t) = m \quad \Leftrightarrow \quad \eta_{k,m} < \Delta_i(t) + \epsilon_{ik}(t) \leq \eta_{k,m+1} \qquad \forall \text{ item } k, \text{ level } m$$

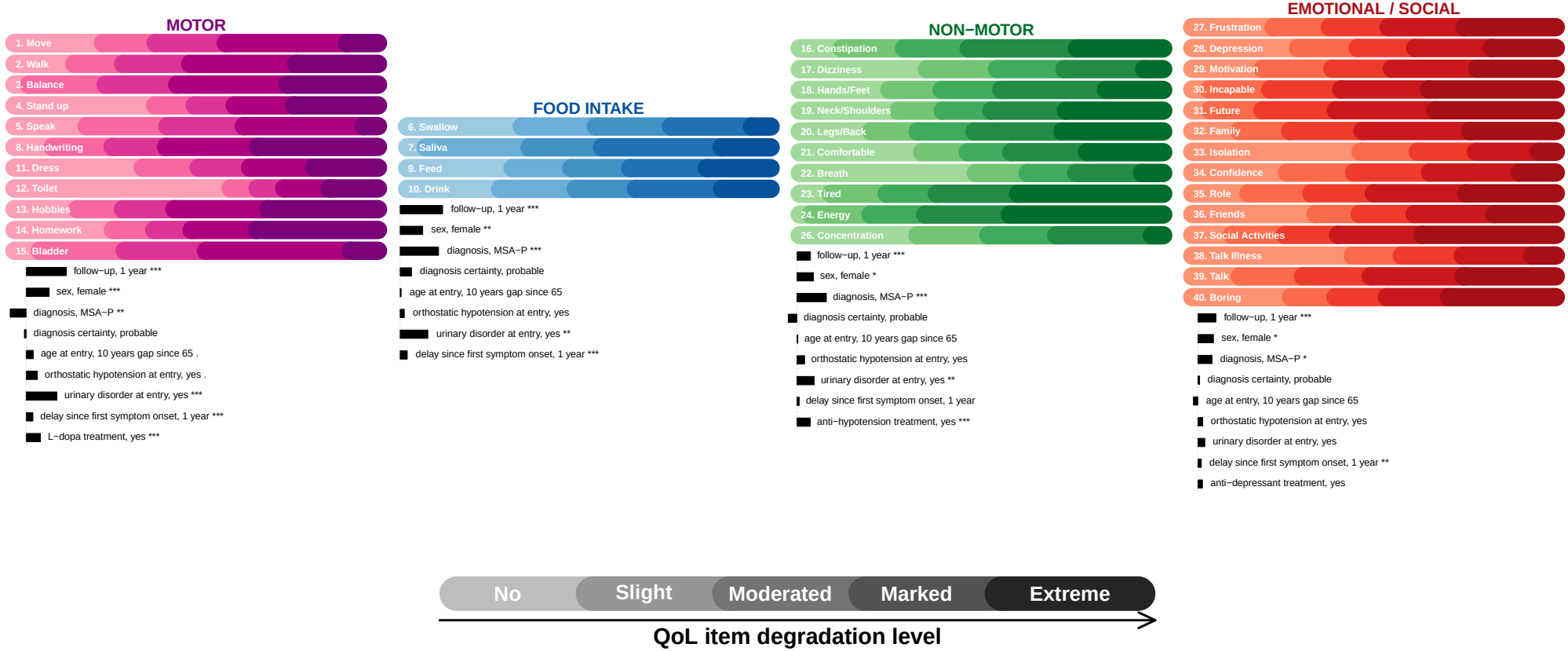
with $\epsilon_{ik} \sim \mathcal{N}(0, \sigma_k^2)$; $m \in \{1, ..., M_k\}$

Survival part *proportional hazard model*, death cause

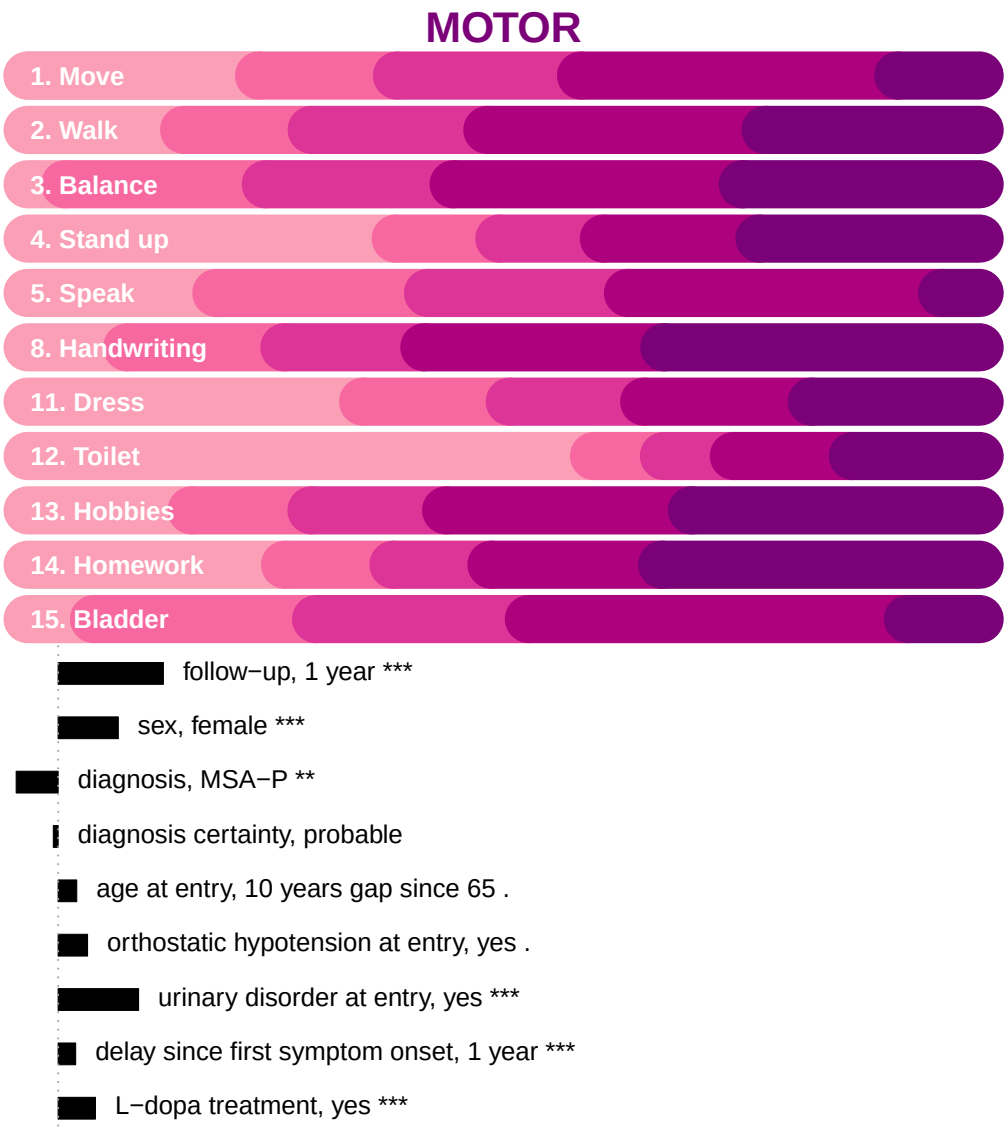
$$\lambda_i(t) = \lambda_0(t; \Psi)\ exp(\Delta_i(t)\alpha)$$

with $\lambda_0(.)$ Weibull function

Step 2 : MSA-QoL sub-dimensions evolution



Step 2 : ZOOM on MOTOR sub-dimension evolution



← **Items**

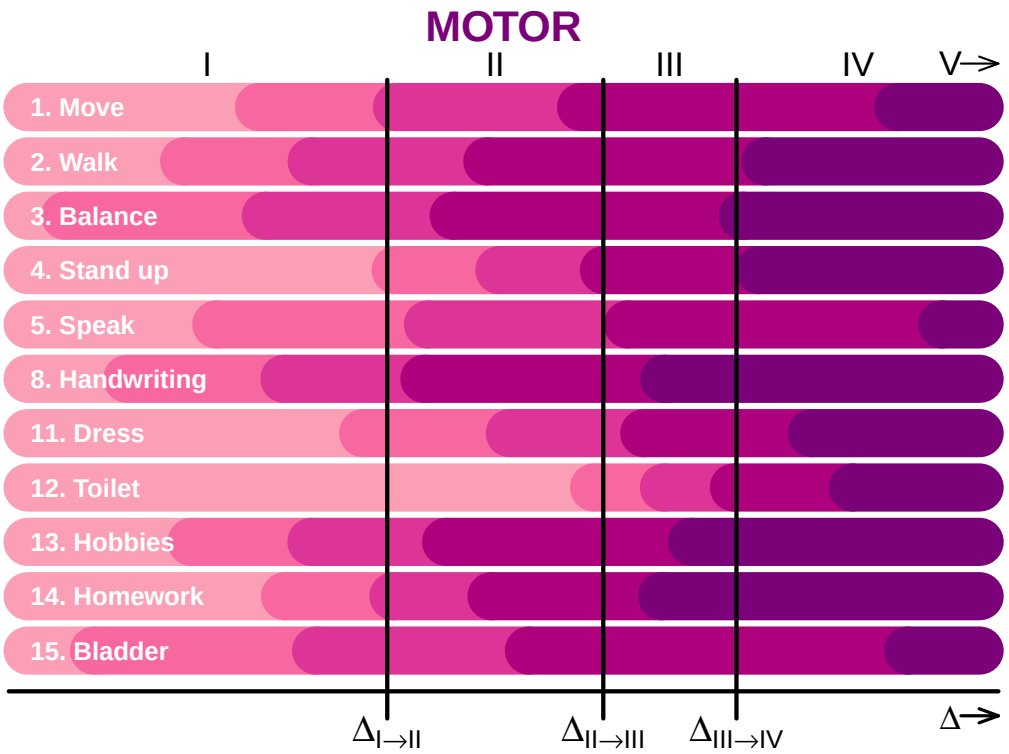
$$Y_{ik}(t) = m$$

$$\Leftrightarrow \eta_{k,m} < \Delta_i(t) + \epsilon_{ik}(t) \leq \eta_{k,m+1}$$

← **Dimension process**

$$\Delta_i(t) = X_i^\top(t)\beta + Z_i^\top(t)b_i$$

Step 3 : MOTOR sub-dimension linked to disease stages

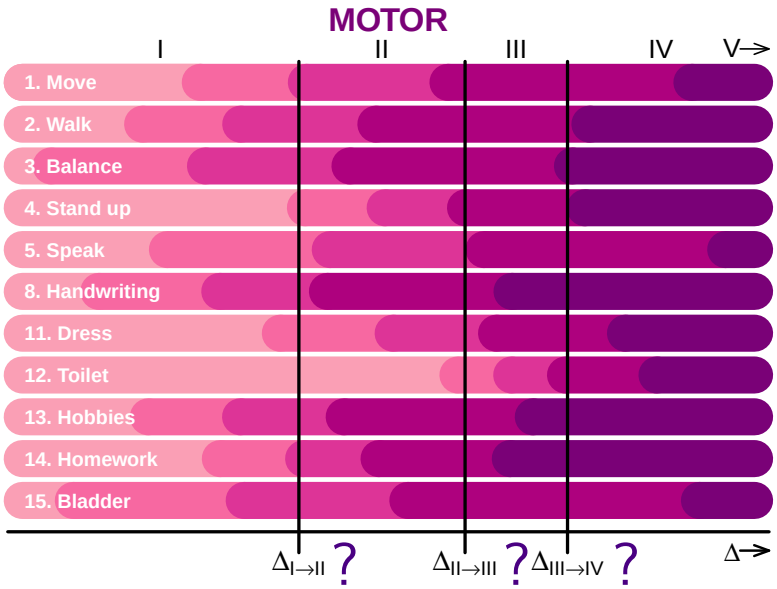


Projection of disease stages
on QoL sub-dimensions' evolution

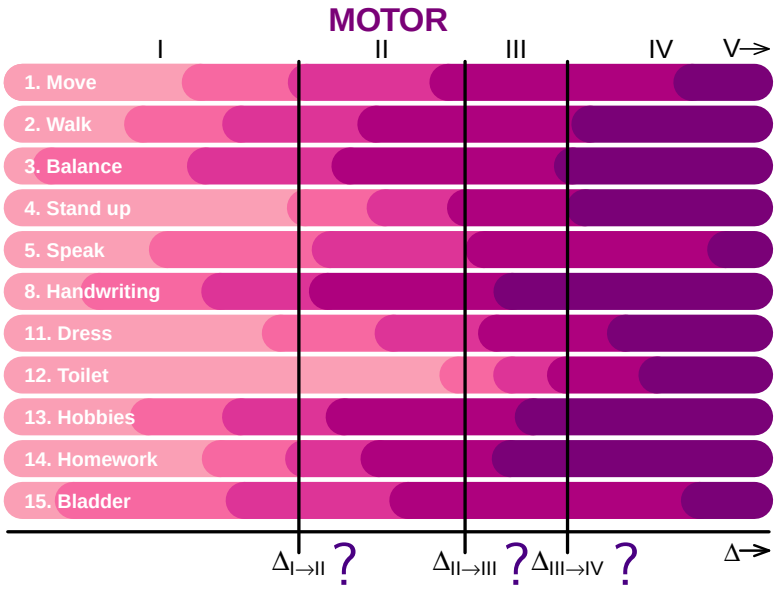
MSA stages

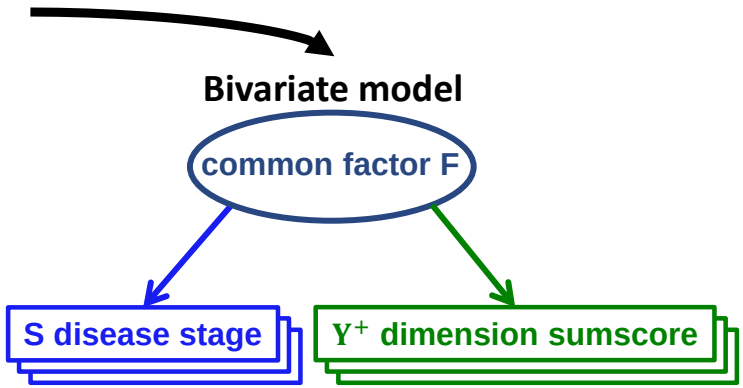
- **I** completely independent
- **II** not completely independent
- **III** more dependent
- **IV** very dependent
- **V** totally dependent, helpless

Step 3 : Projecting disease stages



Step 3 : Projecting disease stages





with R-package **JLPM**

disease stage S

ordinal outcome with 5 levels

cumulative probit model

$S_i(t) = s$

$\Leftrightarrow \eta_s < F_i(t) + \epsilon_i(t) \leq \eta_{s+1}$

dimension sumscore Y^+

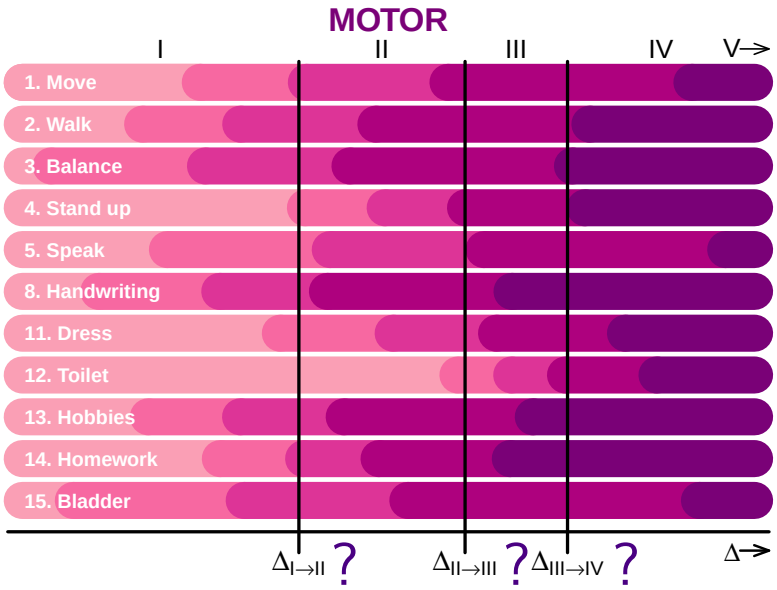
continuous (non-Gaussian) outcome

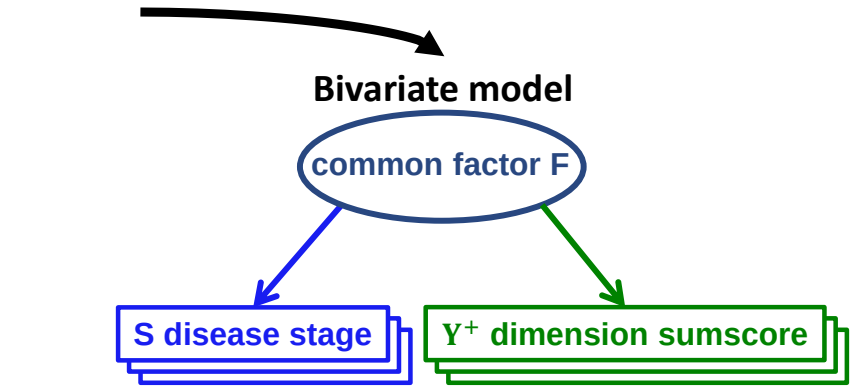
curvilinear model

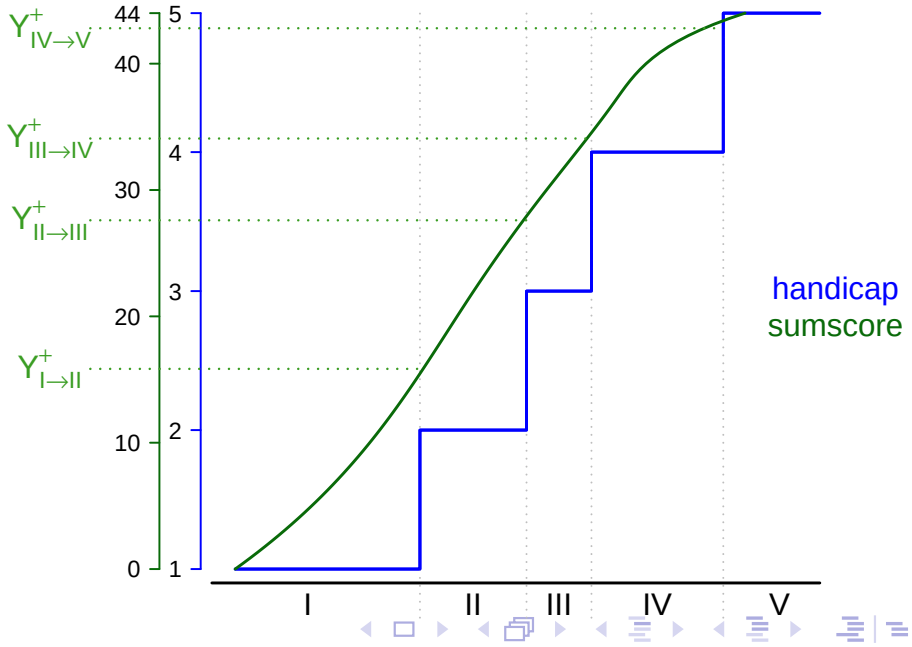
$$H(Y_i^+(t);\eta) = F_i(t) + \epsilon_i'(t)$$

with H(.) splines function

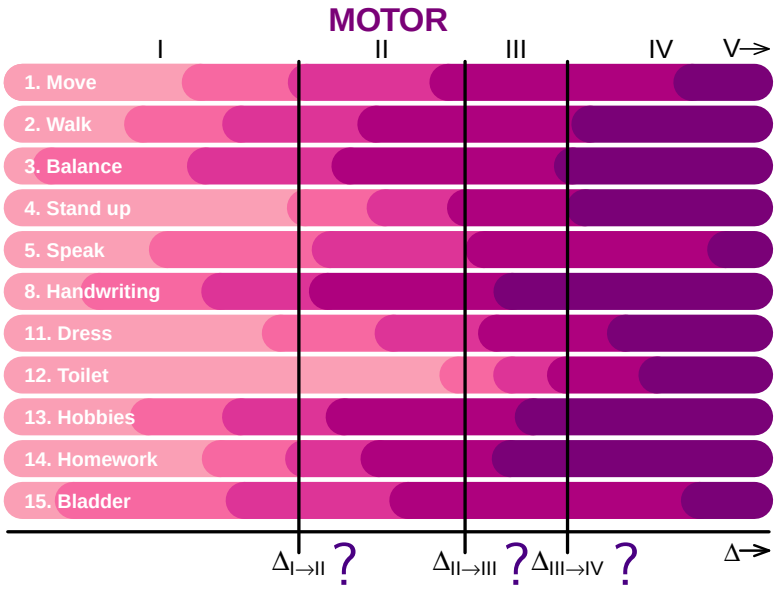
Step 3 : Projecting disease stages





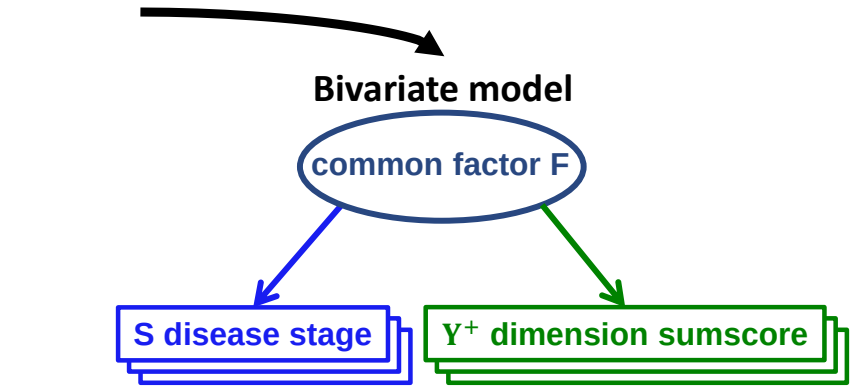


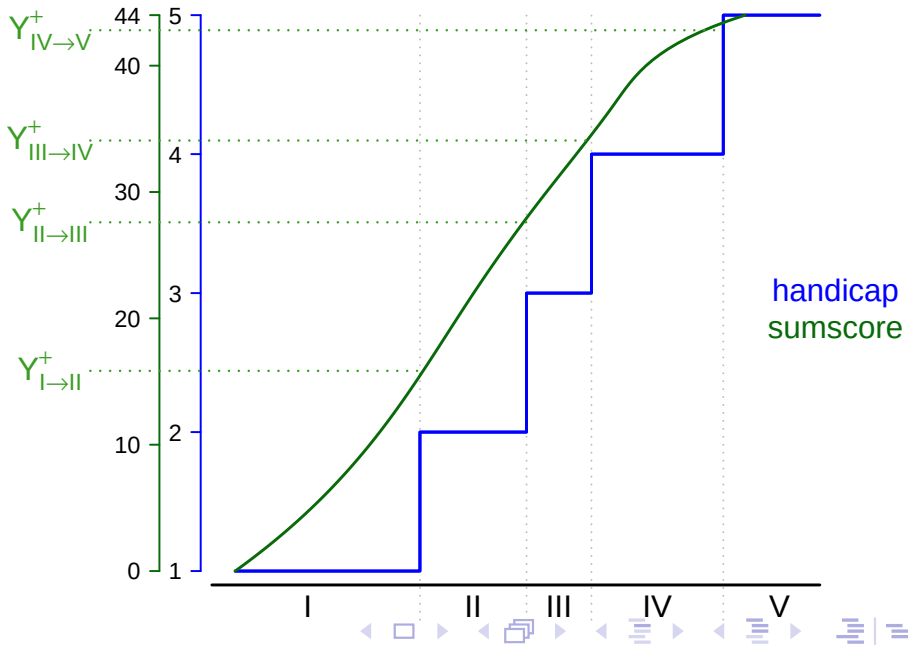
Step 3 : Projecting disease stages



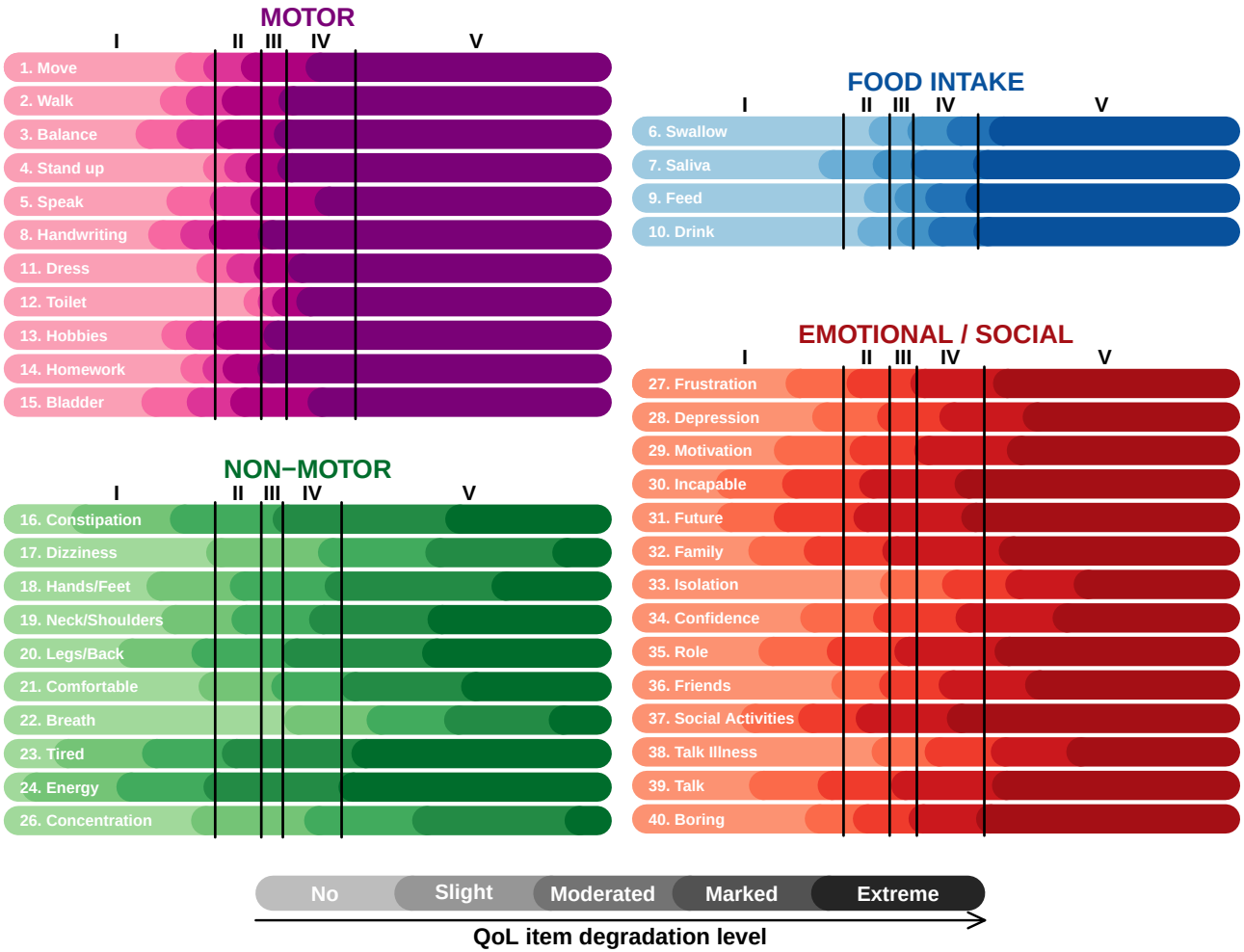
Search Δ as

$$\mathbb{E}\left[\sum_{k=1}^{K} Y_k|\Delta\right] = Y^{+}{}_{s\to s+1}$$





Step 3 : MSA-QoL evolution according to disease stages



Projection of disease stages as temporal benchmarks

MSA stages

I completely independent

II not completely independent

III more dependent

IV very dependent

V totally dependent, helpless

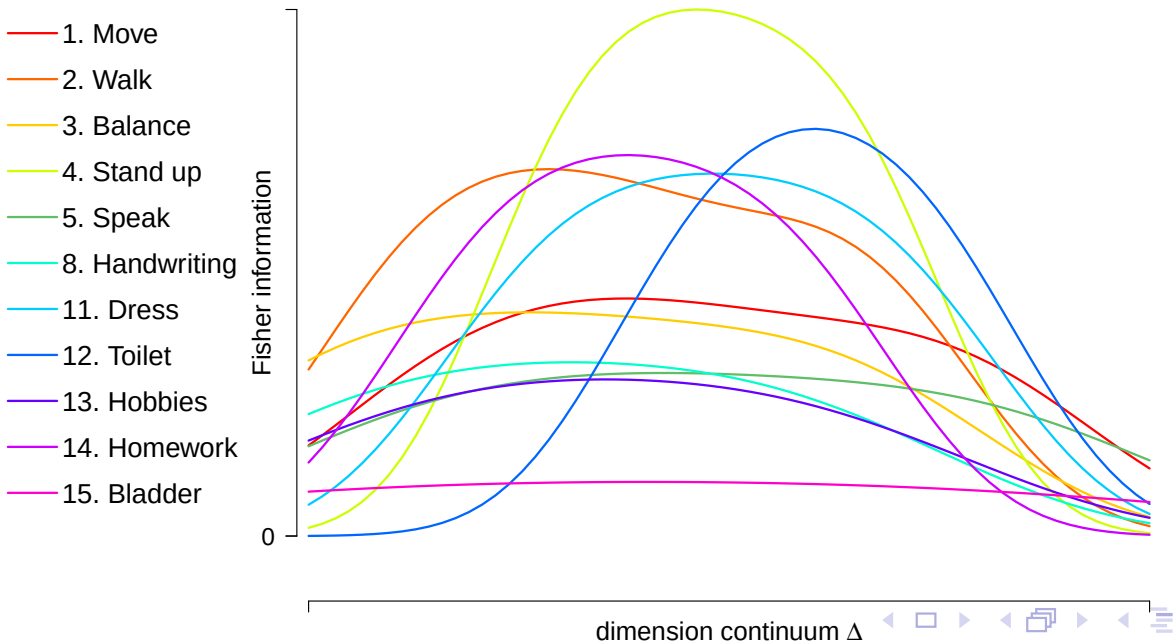
Step 4 : Information carried by items, Fisher information

Fisher information function of item k for a given degradation level Δ

$$I_k(\Delta) = -\mathbb{E}[\frac{\partial^2}{\partial \Delta^2} log\mathbb{P}(Y_k|\Delta)]$$

$$= -\sum_{m=0}^{M_k}[\mathbb{P}(Y_k = m|\Delta)\frac{\partial^2}{\partial \Delta^2}\mathbb{P}(Y_k = m|\Delta)]$$

MOTOR

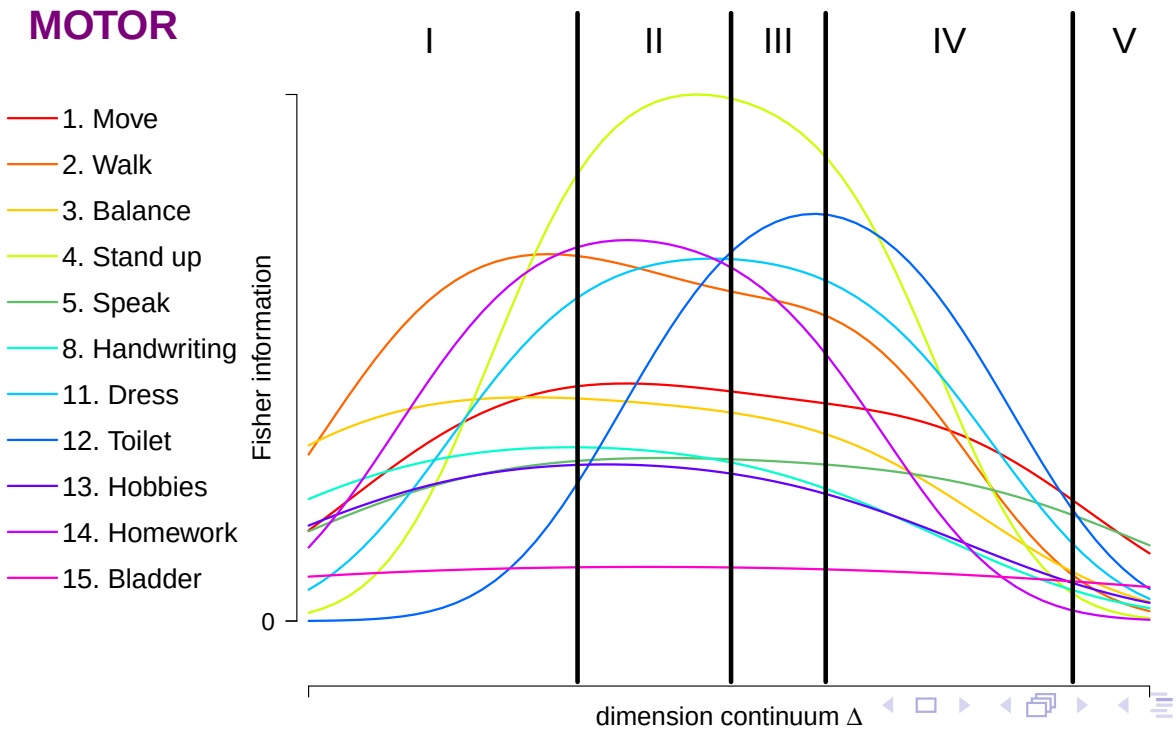


Step 4 : Information carried by items, Fisher information

Fisher information function of item k for a given degradation level Δ

$$I_k(\Delta) = -\mathbb{E}[\frac{\partial^2}{\partial \Delta^2} log\mathbb{P}(Y_k|\Delta)]$$

$$= -\sum_{m=0}^{M_k}[\mathbb{P}(Y_k = m|\Delta)\frac{\partial^2}{\partial \Delta^2}\mathbb{P}(Y_k = m|\Delta)]$$



Step 4 : Information carried by items, Fisher information

Fisher information function of item k for a given degradation level Δ

$$\begin{aligned} I_k(\Delta) &= -\mathbb{E}[\frac{\partial^2}{\partial \Delta^2} log\mathbb{P}(Y_k|\Delta)] \\ &= -\sum_{m=0}^{M_k}[\mathbb{P}(Y_k = m|\Delta)\frac{\partial^2}{\partial \Delta^2}\mathbb{P}(Y_k = m|\Delta)] \end{aligned}$$

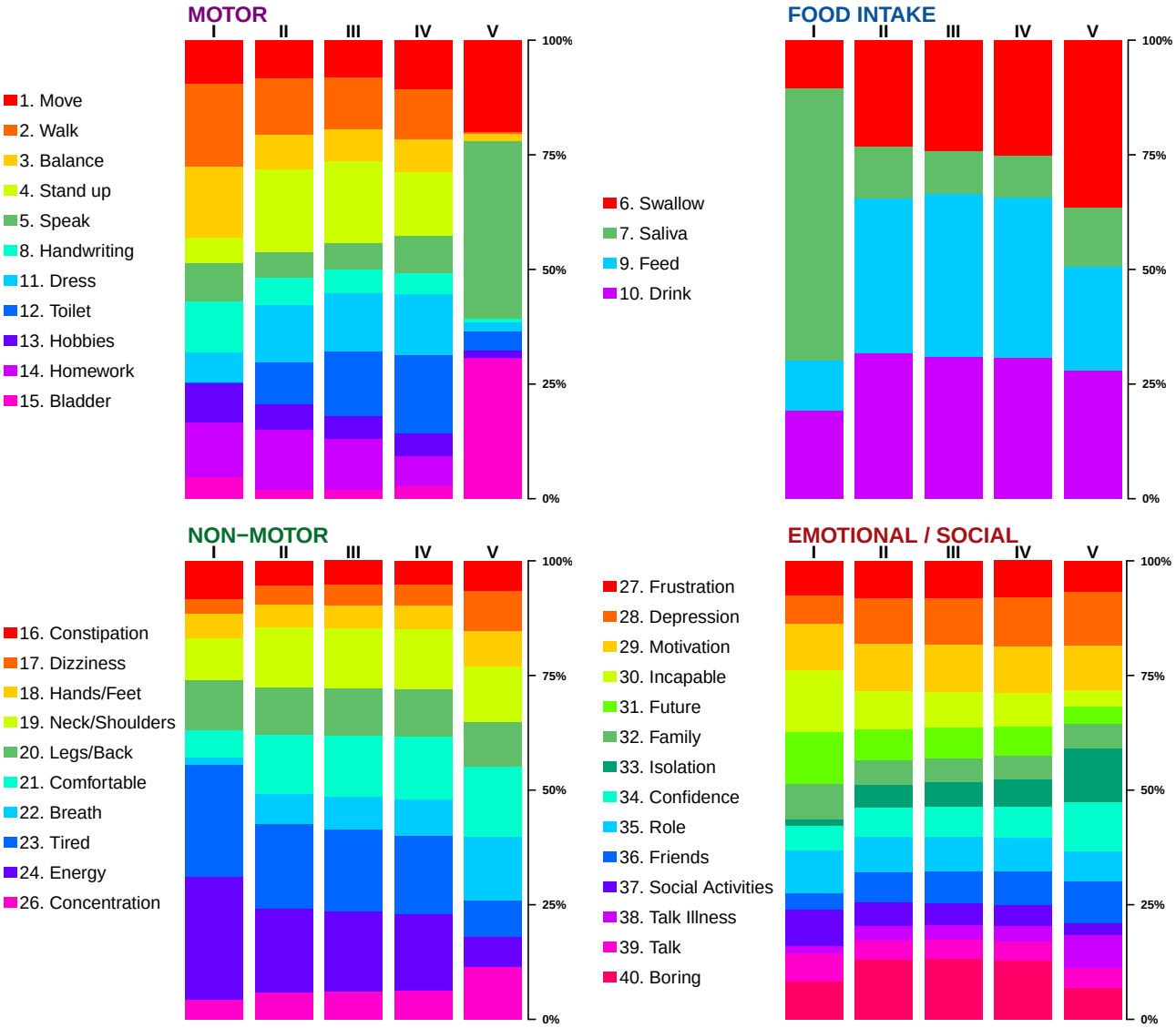
Fisher information carried by item k during stage s

$$I_{k,s} = \int_{\Delta_{s-1\rightarrow s}}^{\Delta_{s\rightarrow s+1}} I_k(\Delta)d\Delta$$

Percentage of Fisher information carried by item k during stage s

$$I_{k,s}^{\%} = \frac{I_{k,s}}{\sum_{j=1}^{K} I_{j,s}}$$

Step 4 : MSA-QoL informative items



MSA stages

I completely independent

II not completely independent

III more dependent

IV very dependent

V totally dependent, helpless

Discussion

Conclusion

Complete strategy to analyze data from measurement scales
Model implemented in a R-package JLPM, available to all
Could also be useful to other pathologies and scales' studies

References

- Saulnier, T., Philipps, V., Meissner, W. G., Rascol, O., Pavy-Le Traon, A., Foubert-Samier, A., Proust-Lima, C. (2022). Joint models for the longitudinal analysis of measurement scales in the presence of informative dropout. Methods, vol. 203, p. 142-151.

- Meissner, W. G., Foubert-Samier, A., Dupouy, S., Debs, R., Gerdelat-Mas, A., De Cock, V. C., ... Pavy-Le Traon, A. (2013). Validation of the French version of the MSA health-related Quality of Life scale (MSA-QoL). Revue neurologique, 169(1), 53-58.

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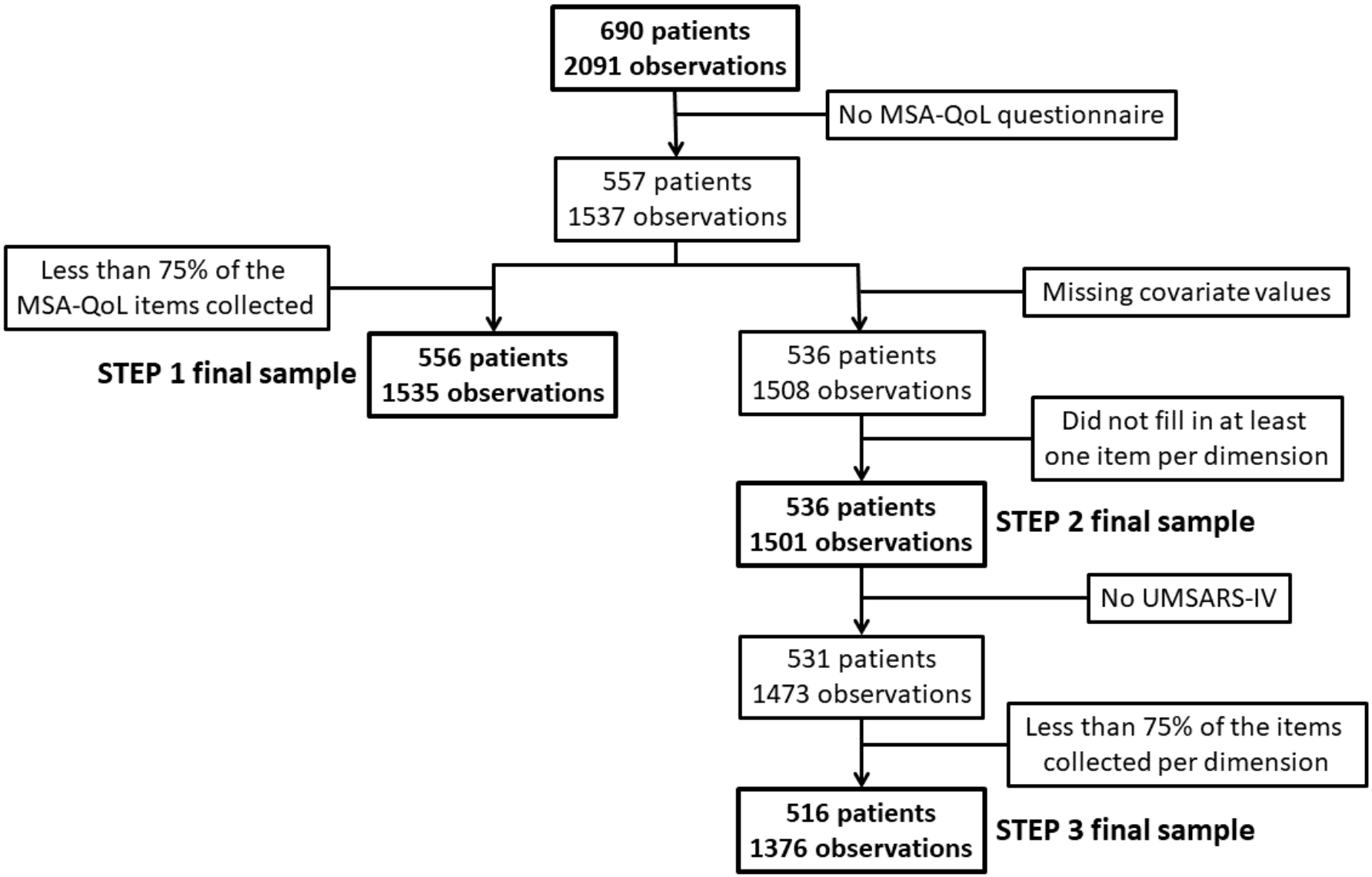
CHU BDX CENTRE HOSPITALIER UNIVERSITAIRE BORDEAUX

Thank you for your attention

APPENDIX 1 : Sample selection - *flowchart*



APPENDIX 2 : Sample description

Characteristics at inclusion	N (%)	mean ± sd
Patients	536	
Sex female (vs male)	268 (50.0%)	
Centre Bordeaux (vs Toulouse)	308 (57.5%)	
Subtype MSA-P (vs MSA-C)	363 (67.7%)	
Certainty Probable (vs Possible)	400 (74.6%)	
Age at study inclusion		65.1 ± 8.0
Age at symptom onset		60.6 ± 8.1
Care delay		4.5 ± 2.4
Orthostatic hypotension yes (vs no)	361 (67.4%)	
Urinary disorder yes (vs no)	365 (68.1%)	
Treatment		
Ldopa	366 (68.3%)	
antihypotension	161 (30.0%)	
antidepressant	111 (20.7%)	
Original MSA-QoL scale		
MOTOR dimension sumscore (/56)		27.1 ± 11.9
NON-MOTOR dimension sumscore (/48)		20.1 ± 8.9
EMOTIONAL-SOCIAL dimension sumscore (/56)		25.9 ± 13.2
Handicap degree		
Completely independent (stage I)	111 (20.7%)	
Not completely independent (stage II)	239 (44.6%)	
More dependent (stage III)	105 (19.6%)	
Very dependent (stage IV)	63 (11.8%)	
Totally dependent (stage V)	2 (3.0%)	
Characteristics during follow up		
Visits	1501	
Visits per patient		2.8 ± 1.9
Years of follow-up		2.5 ± 2.4
Dropouts	87 (16.2%)	
Deaths	338 (63.1%)	