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# GENDER AND SPINAL/BULBAR ONSET INTERACTION ON ALS PROGRESSION

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## Background & Objectives

Amyotrophic Lateral Sclerosis (ALS) is a heterogeneous disease which makes the influence of covariates on disease progression an important topic. Among them spinal and bulbar onset have been well studied, yet gender and its interaction with the site of onset has not been fully covered. Most of the studies have used cross-sectional or survival methods. Several disease modelling methods have been developed but few enable to estimate several non-linear continuous outcomes at the same time.

We measure the influence of **gender and site onset interaction** on ALS progression using a **non-linear Bayesian mixed-effect model**.

## Methods

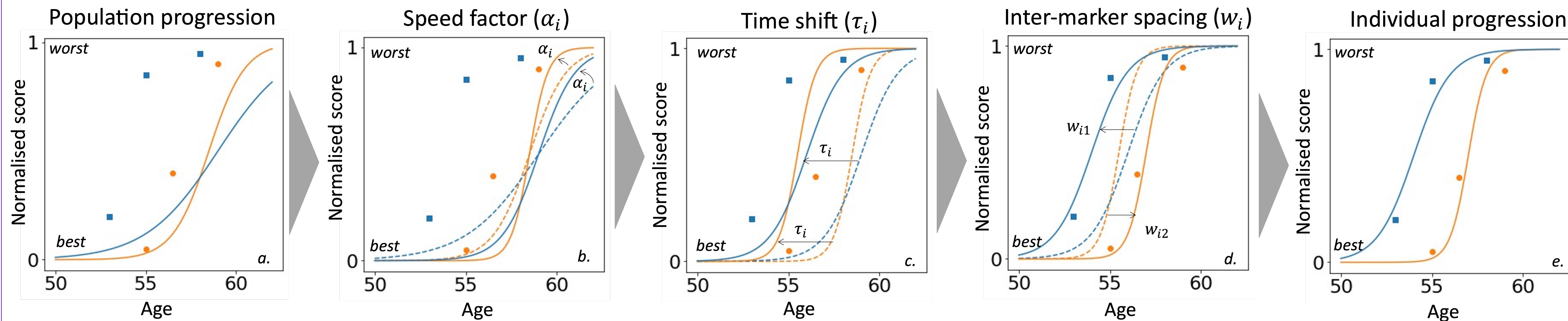
### Population

We selected patients from PRO-ACT database with:

- Gender information,
- A bulbar or spinal site of onset,
- At least two visits for all selected outcomes for study dataset and the rest for the test dataset.

We end up with four groups of patients man/woman\*spinal/bulbar.

### Statistical Methods



From ALS course map to individual trajectory: individual parameters adapted from (Koval, Scientific Reports 2021)

We used a **non-linear Bayesian mixed-effect model** (Schiratti, The Journal of Machine Learning Research 2017). It captures the **temporal multivariate progression of continuous outcomes** and is **robust to missing data** (Couronne, IEE 2019). The model starts with an idealized set of **logistics curves** that serves as a reference pattern of outcomes development. As in other mixed effect models two types of parameters are computed: **fixed effects**, referred after as **population parameters**, and **random effects**, referred after as **individual parameters** (speed factor, time shift and inter-marker spacing). We first determined the shape and position of the logistic curves (population parameters) so that the mean value of all individual parameters is 0. To do so, we iteratively performed joint estimations of these population parameters with the individual ones, to minimize errors between the idealized curves and the individual visits. **Convergence check**: rank normalized R-hat diagnostic tests below 1.2.

### Clinical Outcomes

- ALSFRSr Respiratory [/12]
- ALSFRSr Fine Motor [/12]
- ALSFRSr Bulbar [/12]
- BMI
- ALSFRSr Gross Motor [/12]
- Forced Vital Capacity (FVC) [%] (Brändli, Thorax 1996)

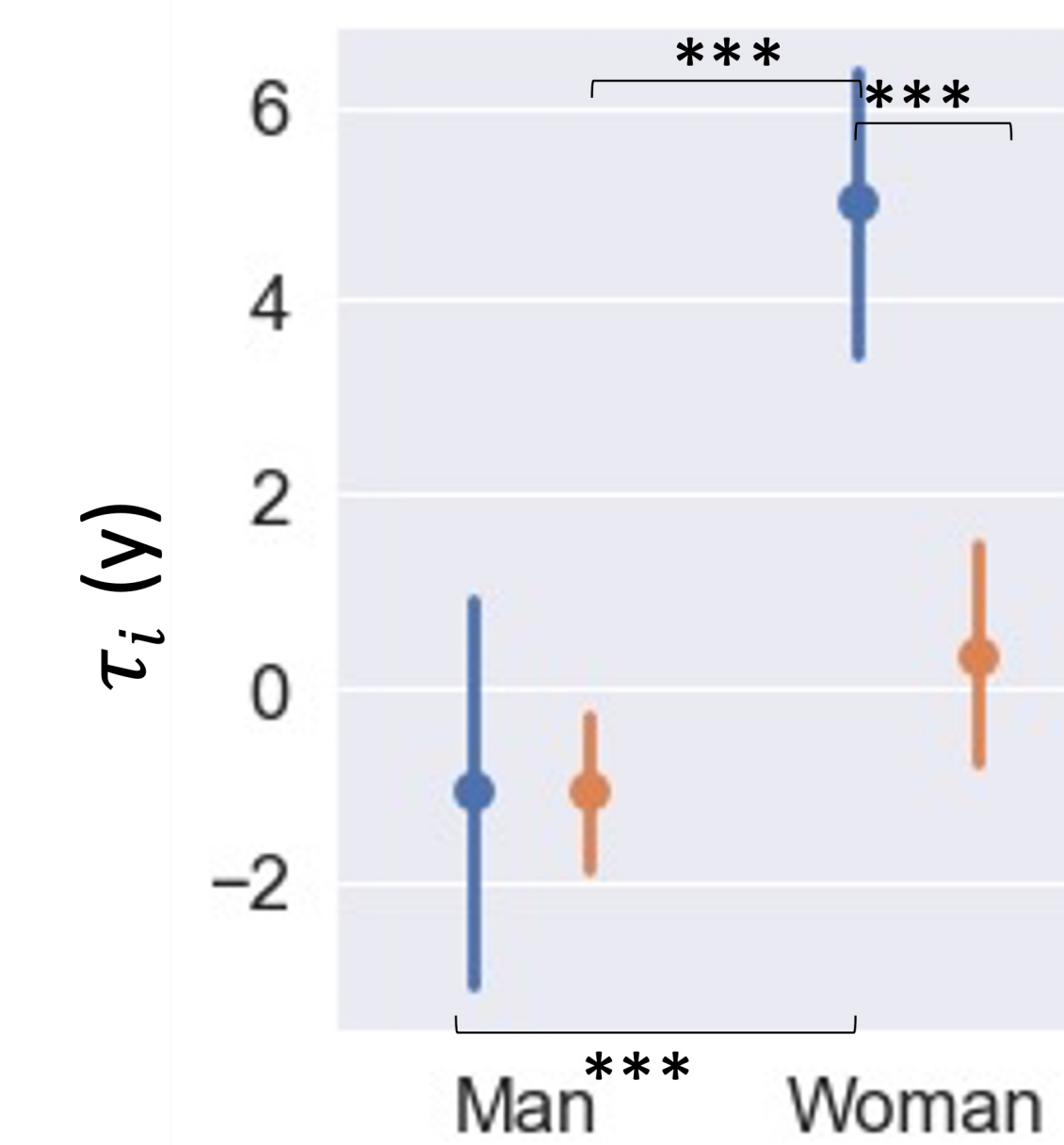
### Normalization:

- ALSFRSr scores: min-max scaling using scales,
- BMI/FVC: a box-cox transformation followed by [-3,3] min-max scaling.

Outcomes	Study cohort	Test cohort	T-test
Patients	1438	5415	-
Person years	1492	4992	-
Visits	17253	48425	-
Man	883 (61%)	3352 (62%)	-
Spinal onset	1162 (81%)	4153 (77%)	-
Visits per patient	12.0 ± 9.3	8.9 ± 4.4	***
Years of follow up	1.0 ± 0.7	0.9 ± 0.5	***
Days betw. two visits	34.5 ± 28.5	42.4 ± 29.7	***
Age at baseline	55.4 ± 11.1	56.2 ± 11.8	*
ALSFRSr Respiratory <sup>†</sup>	11.2 ± 1.3 (61%)	11.3 ± 1.1 (17%)	***
ALSFRSr Bulbar <sup>†</sup>	9.9 ± 2.3 (61%)	10.0 ± 2.4 (62%)	***
ALSFRSr Fine motor <sup>†</sup>	8.1 ± 2.8 (61%)	8.0 ± 3.1 (62%)	***
ALSFRSr Gross motor <sup>†</sup>	7.6 ± 2.7 (61%)	7.7 ± 3.0 (62%)	***
BMI <sup>†</sup>	26.7 ± 4.5 (98%)	25.5 ± 4.7 (68%)	***
FVC <sup>†</sup>	74.3 ± 14.5 (97%)	67.7 ± 22.4 (54%)	0.26

Legend: <sup>†</sup>: Distribution on all visits with the percentage of observed data  
\*: <0.05, \*\*: <0.01, \*\*\*: <0.001

### Time-shift (p-value 0.0020)

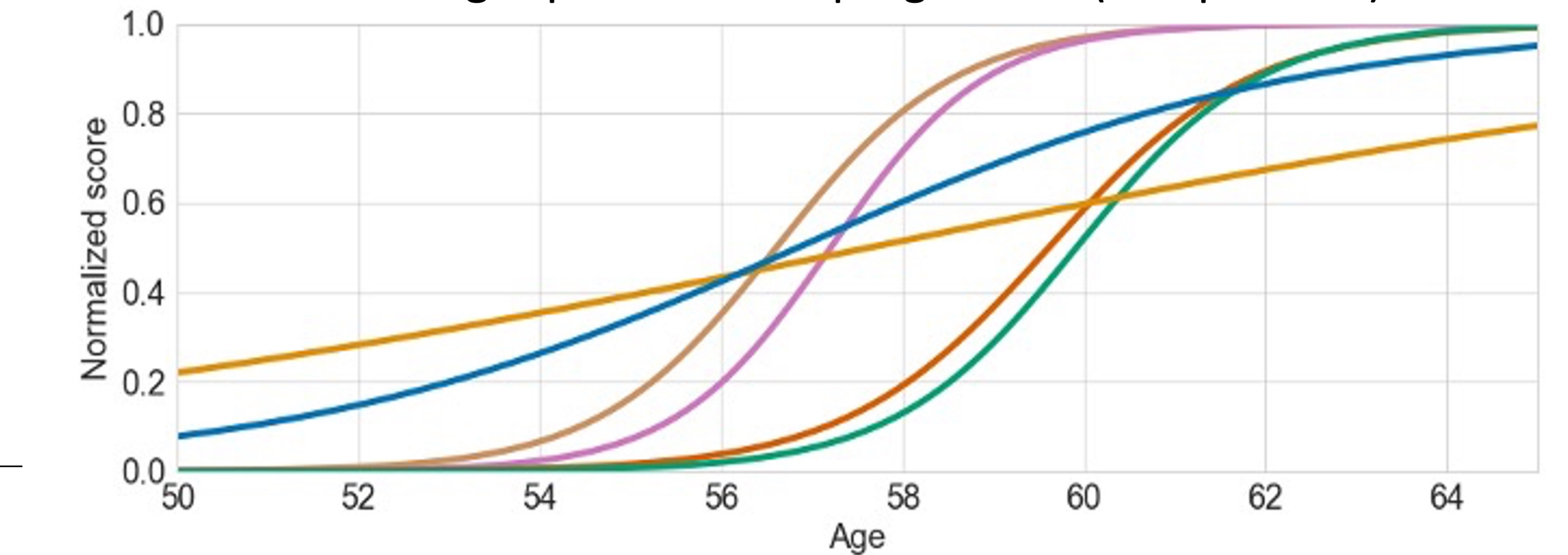


Legend: (blue): Bulbar onset, (orange): Spinal onset, \*: <0.05, \*\*: <0.01, \*\*\*: <0.001, p-value: ANOVA interaction p-value

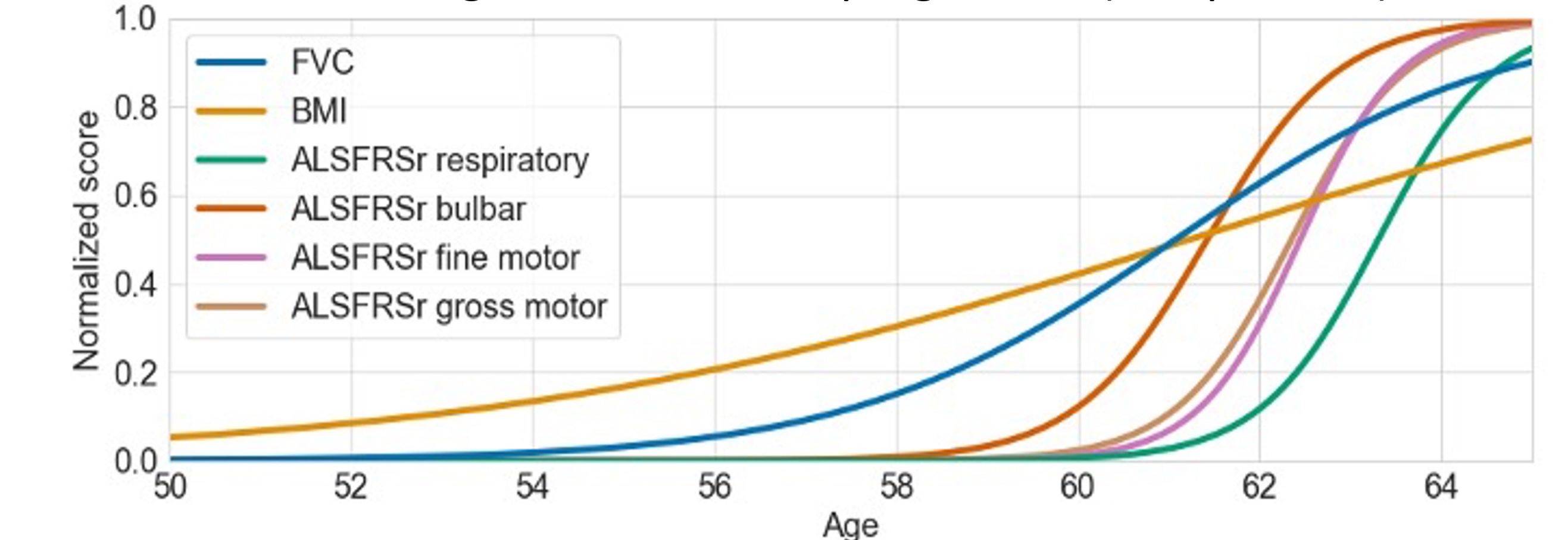
## Results

**Absolute reconstruction errors** go from  $2.8 \pm 2.9\%$  for BMI to  $7.5 \pm 7.6\%$  for ALSFRSr respiratory, with a **maximum variation of median between groups** of 2.18 for FVC, 0.05 for BMI, 0.19 respiratory, 0.31 bulbar, 0.08 fine motor and 0.07 gross motor. On the test cohort, **absolute errors of prediction** (using 2 visits to predict one in  $2 \pm 1$  months) go from  $4.1 \pm 6.3\%$  for BMI to  $13.7 \pm 19.8\%$  for ALSFRSr respiratory.

### Average spinal woman progression (405 patients)



### Average bulbar woman progression (150 patients)



We can observe **differences on the estimated age at onset**: curves are shifted on the right for patients with bulbar onset compared to patients with spinal onset. **Differences in progression order of outcomes** can also be observed: progression order of ALSFRSr bulbar (red) and ALSFRSr motors (pink and brown) is switched between patients with spinal onset and patients with bulbar onset.

## Discussion

- + Large, multicentric cohort representative of clinical trial placebo arm
- + Encouraging prediction results
- + Same range of reconstruction error as (Koval, Scientific Reports 2021)
- Logistic progression: existence of plateaux for some patients in ALSFRSr (Vasta, European Journal of Neurology 2020)
- Persistent differences between reconstruction error medians

Using a multivariable disease modelling approach, we found a **significant interaction effect of gender and onset site**.

This study may lead to further consideration on **clinical trial stratifications** and this methodology can pave the way to **discriminate fast and slow progressor**.