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Interaction of sex and onset site on the disease trajectory of Amyotrophic Lateral Sclerosis

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Contributions

- Juliette ORTHOLAND: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data.
- Pierre-François PRADAT: Drafting/revision of the manuscript for content, including medical writing for content;
- Sophie Tezenas du Montcel: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data.
- Stanley Durrleman: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data.

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ABSTRACT

Background: Studies showed the impact of sex and onset site (spinal or bulbar) on disease onset and survival in ALS. However, they mainly result from cross-sectional or survival analysis, and the interaction of sex and onset site on the different proxies of disease trajectory has not been fully investigated.

Methods: We selected all patients with repeated observations in the PRO-ACT database. We divided them into four groups depending on their sex and onset site. We estimated a multivariate disease progression model, named ALS Course Map, to investigate the combined temporal changes of the four sub-scores of the revised ALS Functional Rating Scale (ALSFRS_r), the forced vital capacity (FVC), and the body mass index (BMI). We then compared the progression rate, the estimated age at onset, and the relative progression of the outcomes across each group.

Results: We included 1,438 patients from the PRO-ACT database. They were 51% men with spinal onset, 12% men with bulbar onset, 26% women with spinal onset, and 11% women with bulbar onset. We showed a significant influence of both sex and onset site on the ALSFRS_r progression. The BMI decreased 8.9 months earlier (95% CI = [3.9, 13.8]) in women than men, after correction for the onset site. Among patients with bulbar onset, FVC was impaired 2.6 months earlier (95% CI = [0.6, 4.6]) in women.

Conclusion: Using a multivariable disease modelling approach, we showed that sex and onset site are important drivers of the progression of motor function, BMI, and FVC decline.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset heterogeneous neurodegenerative disease that occurs on average between 55 and 60 years. It is characterized by a degeneration of both upper and lower motor neurons¹, and the average survival time from onset to death is three to four years². The disease shows an important phenotypic variability, particularly in terms of the site of disease onset and progression³. The difference between the disease starting with dysarthria and dysphagia (bulbar onset) and the disease with limb weakness (spinal onset) is well documented. Among other, they differ in terms of incidence³; progression rate⁴⁻⁶; and survival duration⁴.

Several epidemiological studies have shown a lower incidence of ALS in women compared to men^{4,7} as well as differences in the onset site and age at onset⁸. More recently genetic⁹ and imaging¹⁰ studies have enriched the knowledge on this sexual dimorphism. However, most of these results come from cross-sectional studies^{7,8} or survival⁴ studies. By design, the first one failed to capture the longtime effect of clinical or demographic variables, such as age or sex¹¹. The second only presents half of the information on the disease progression by studying mortality, leaving aside the function in daily activities. Thus how the marked sexual dimorphism influences the progression and the presentation of each ALS form, has not been fully described.

The originality of the present study is to investigate the interaction of sex and onset site on the whole progression of the following clinical proxies: BMI¹², forced vital capacity (FVC)¹³, and sub-scores of ALS functional rating scales (ALSF_{RSr})¹⁴. To do so, we have used a recent longitudinal model designed for neurodegenerative diseases^{15,16}. This enabled us to study all the outcomes at the same time, consider the non-linearity of the progression of outcomes, and capture patients' heterogeneity better than with classic models.

MATERIALS AND METHODS

Study population

We analyzed patients from the Pooled Resource Open-Access ALS Clinical Trials Consortium (PRO-ACT) database. It is composed of an aggregation of 23 phase II and III clinical trials and one observational study. Information that could lead to any identification, such as the clinical trial, tested drug, study centres, or dates, was not included in the database. As the database is an aggregation, inclusion and exclusion criteria for patients to enter the cohort are multiple and will not be described here, more information could be found in the paper that presents the database¹⁷.

For our study, we selected patients with at least two visits for all the outcomes listed below. We collected: outcome values at all available visits; the sex of the participant; and the onset site (spinal or bulbar), a label that is available in the PRO-ACT database. We divided participants into four groups: men with bulbar onset, women with bulbar onset, men with spinal onset, and women with spinal onset.

Outcomes

We selected a set of outcomes that are important clinical proxies of ALS progression and are available in the PRO-ACT database. We considered the most widely used functional rating system in patients with ALS, namely the revised version of the ALS functional rating scale (ALSFRS_r)¹⁴. The scale starts at a maximum theoretical value of 48 and decreases with the severity of the disease till zero. We considered the four ALSFRS_r sub-scores assessing four distinct domains: bulbar, gross motor, fine motor, and respiratory functions. Each sub-scale has 12 points each¹⁴. In addition, we considered the FCV¹³ that we normalized using the computed normal FVC¹⁸ and the BMI¹².

We normalized the outcomes between 0 (the healthiest value) and +1 (the maximum pathological change). The four ALSFRS_r sub-scores have been normalized using their theoretical maximum and minimum values. For FVC and BMI, we first applied a box-cox transformation (estimated on the whole PRO-ACT dataset) to get a standard normal distribution^{19,20,21}. We then clipped the resulting value between -3 and 3 points and converted them to the 0 to 1 scale.

In addition to these repeated measures, we collected the following covariates when available: riluzole use, trial arm (active, placebo, observational), age at first symptom, age at diagnosis, age at baseline, Mitos²² and FT9 scores²³ at baseline. These data were not used as input for the disease progression model.

ALS Course Map

We used a disease progression model, named ALS Course Map, which is a multivariate non-linear Bayesian mixed-effects model^{15,16}. The model estimates the progression of a series of outcomes from a longitudinal dataset. It estimates a subject-specific set of curves for each outcome and summarizes them at the population, or sub-group level. The model does not require imputation as it is robust to missing data²⁴. In addition, it does not require a standardized time between visits²⁴.

ALS course map models the progression with a logistic pattern of outcomes development. As in other mixed effect models, two types of parameters are computed: fixed effect, referred to as population parameters, and random effect, referred to as individual parameters. Population parameters capture the average ALS progression from which patients deviation could be captured by three individual parameters:

The first individual parameter is the disease time shift, τ_i , expressed in years. It represents the delay between the estimated age at disease onset for patient i and the whole population. For instance, $\tau_i = -1$ means that the estimated disease onset of the patient occurs one year earlier than the average patient in the population. The estimation of the time shift takes all outcomes into account. There is a single time shift for a given subject.

The second one is the progression rate, α_i . It represents a value that multiplies the population progression rate to get the rate of the patient i . For instance, $\alpha_i = 1.2$ means that the disease progresses 1.2 times faster than the average patient in the population. The estimation of the progression rate also takes all outcomes into account. There is a single rate for a given subject.

Finally, a series of inter-marker spacings, ω_{ij} , expressed in months. One ω_{ij} changes the onset of the outcome j of the patient i while keeping other outcomes fixed. For instance, $\omega_{ij} = +2$ means that the j -th outcome changes two months earlier than for the average patient in the population, all other things being equal. Each subject has six inter-marker spacings, one per outcome in the model. Inter-marker spacings are centred (i.e. their weighted sum equals zero) so that they do not interplay with the estimation of the time shift.

We used the open-source software, Leaspy, to estimate the model parameters from a longitudinal dataset. The software is publicly available at: [https://gitlab.com/icm-institute/aramislab/leaspy/Experimental design](https://gitlab.com/icm-institute/aramislab/leaspy/Experimental%20design). This disease progression model has been applied to other neurodegenerative conditions^{25,26}.

Statistical analysis

We trained the model with the whole data set composed of four groups. We assessed the convergence with a rank normalized R-hat diagnostic test using a threshold of 1.2. To study the goodness-of-fit of the model to the actual data, we compared the estimated value of each visit with its real available value to compute the reconstruction error. We compared the reconstruction error among groups.

To test for the interaction of sex and onset site on the ALS course map individual parameters we used ANOVAs. We compared the individual parameters estimated by the ALS Course Map between sex and onset site interaction using ANOVAs. For significant results, we computed an independent pairwise Tukey-Kramer test²⁷. Otherwise, we computed an ANOVA without interaction to test the influence of each covariate adjusted for the other. All the results are presented with a 95% confidence interval computed with pairwise Tukey-Kramer or ANOVA without interaction, depending on the interaction significance. We used the same comparison process to describe the cohort and compare the groups at baseline. For the cohort description, results are associated with the corrected sample standard deviation. Statistical tests were performed at a conventional 2-tailed type I error of 0.05. Data were analyzed using python software 3.8, using packages statsmodel²⁸ and bioinfokit²⁹.

Standard Protocol Approvals, Registrations, and Patient Consents

Data used in this study came from the PRO-ACT database which is institutional review board–approved. Patients originally consented to participate in clinical trials that have been aggregated in the database. Every patient has been de-identified. We accessed the data following the access procedure detailed here: <https://ncr1.partners.org/ProACT/Account/Register>.

Data availability

Access to the database PRO-ACT could be asked for through the procedure above. Further information for replication of the study is available in supplementary material in eReproducibility.

RESULTS

Population

Among the 8,571 patients (78,824 visits) in the PRO-ACT database, we dropped 220 values of BMI and 45 values of FVC that were out of the normalization range. We then selected the 1,463 patients with at least two visits for all the outcomes selected. Finally, we selected the 1,438 patients with information about the onset site. Note that sex was available for all patients. Their characteristics are presented in Table 1. The cohort was composed of 51% men with spinal onset, 12% men with bulbar onset, 26% women with spinal onset, and 11% women with bulbar onset. There were no significant differences in follow-up duration (1.00 ± 0.59 years); the number of visits per patient (11.6 ± 7.2 visits); and time between visits (34.5 ± 28.5 days) over the four groups. Nevertheless, we observed significant differences among groups for ages, time durations, and scores at baseline.

ALS Course Map

We can first extract qualitative results from the four groups' trajectories. Figure 1 represents the progression of ALSFRS_r subscores for each subgroup. Overall, curves are shifted on the right for patients with bulbar onset (Figure 1 B and D) compared to patients with spinal onset (Figure 1 A and C). Curves are also shifted on the right for women (Figure 1 A and B) compared to men (Figure 1 C and D), illustrating later onset for women compared to men.

The model also exhibited differences in the timing of outcomes. For instance, it confirmed the progression order of ALSFRS_r bulbar curve (orange) and ALSFRS_r motor curves (red and green): they are switched between patients with spinal onset (Figure 1 A and C) and patients with bulbar onset (Figure 1 B and D).

Finally, we can note differences in speed. Patients with spinal onset (Figure 1 A and C and Figure 2 purple and grey) seem to have steeper curves than patients with bulbar onset (Figure 1 B and D and Figure 2 cyan and pink). All these results are confirmed below by quantitative statistical tests.

Estimated age at disease onset

We found an interaction between the onset site and sex for the estimated disease onset ($p = 0.0020$) (in supplementary materials eFigure 1). For patients with bulbar onset, the disease onset for men occurs 6.0 years earlier (95% CI = [2.6, 9.5]) than for women while for a woman with spinal onset, it occurs 4.7 years earlier (95% CI = [1.9, 7.4]) than for women with bulbar onset.

Rate of progression

We did not find any significant interaction between the onset site and sex for the rate of progression ($p=0.14$) (in supplementary materials eFigure 2). Patients with bulbar onset were found to progress 1.4 times faster (95% CI = [1.2, 1.6]) than patients with spinal onset independently of sex.

Outcomes onset of impairment

Respiratory function

We found an interaction between sex and onset site for FVC ($p<0.001$) but not for ALSFRS_r respiratory score ($p=0.058$), once corrected for the estimated age at disease onset and rate of progression (Figure 3 E and F). Among patients with bulbar onset, FVC is impaired 2.6 months earlier (95% CI = [0.6, 4.6]) in women than in men. Among men, FVC is impaired 5.4 months earlier (95% CI = [3.8, 7.0]) in patients with bulbar onset compared to spinal onset. Among women, the difference increases to 8.3 months (95% CI = [6.7, 9.9]). ALSFRS_r respiratory scale changes 2.4 months earlier (95% CI = [0.7, 4.0]) for patients with bulbar onset compared to spinal onset independently of the sex.

Motor function

We found an interaction between sex and onset site for gross motor ($p < 0.001$) but not for fine motor scores ($p = 0.12$), once corrected for the estimated age at disease onset and rate of progression (Figure 3 A and B). Among patients with spinal onset, ALSFRS_r gross motor scale deteriorates 4.5 months later (95% CI = [3.1, 6.0]) in women than in men. But ALSFRS_r fine motor scale changes 3.5 months earlier (95% CI = [2.6, 4.4]) in women than in men, independently of the onset site. Among men, ALSFRS_r gross motor scale changes 10.6 months earlier (95% CI = [8.3, 12.8]) for patients with spinal onset compared to bulbar onset. Among women, the difference increases to 16.0 months earlier (95% CI = [13.7, 18.2]). ALSFRS_r fine motor scale changes 10.2 months earlier (95% CI = [9.0, 11.3]) for patients with spinal onset compared to bulbar onset, independently of the sex.

Bulbar function

We did not observe any interaction between sex and onset site for ALSFRS_r bulbar score ($p = 0.01$), once corrected for the estimated age at disease onset and rate of progression (Figure 3 C). Among patients with bulbar onset, ALSFRS_r bulbar scale changes 6.4 months earlier (95% CI = [1.6, 11.1]) in women than men. Among men, ALSFRS_r bulbar scale changes 27.2 months later (95% CI = [23.4, 31.0]) for patients with spinal onset compared to bulbar onset. Among women, the difference increases to 32.5 months later (95% CI = [28.7, 36.3]).

BMI

We did not observe an interaction between sex and onset site for BMI ($p = 0.17$), once corrected for the estimated age at disease onset and rate of progression (Figure 3 D). BMI decreases 8.9 months earlier (95% CI = [3.9, 13.8]) in women than men, independently of the onset site. BMI decreases 10.0

months earlier (95% CI = [3.8, 16.1]) for patients with bulbar onset compared to spinal onset, independently of the sex.

DISCUSSION

Sex and onset site interact with disease progression in ALS as demonstrated on all the clinical proxies studied, including disability, weight loss, and respiratory function. In particular, several proxies were affected earlier in women than in men.

Concerning the effect on weight, we showed that BMI starts to decrease 9 months earlier in women than men, independently of the onset site. Considering the rapid progression of ALS, with a mean survival of 3-6 years, this inter-sex difference appears clinically meaningful. Weight loss is a classical consequence of bulbar impairment leading to dysphagia. But alterations in body weight are present in ALS patients already decades before clinical manifestation of ALS³⁰ and are a negative prognostic factor associated with shorter survival³¹. Weight loss is also associated with increased energy expenditure. It is present in almost half of the patients and is associated with shorter survival³². Inter-sex differences in metabolism may also affect the disease trajectory. The role of energy and lipid metabolism abnormalities in the pathogenesis of ALS is currently a focus of many studies in animal models and ALS patients³³⁻³⁶. Inter-sex differences in the percentage of body fat may also modify disease progression. It is higher in women³⁷ and may vary with menopausal status³⁸. Studies comparing fat mass with impedancemetry or dual-energy X-ray absorptiometry are needed to better investigate the role of metabolism and the effect of sex on disease progression³⁹.

The effect of sex on the respiratory decline has not been reported so far. We showed that among patients with bulbar onset, FVC is impaired 2.6 months earlier in women than in men. This difference

is also clinically meaningful since respiratory distress is the main cause of death in ALS and the decline of FVC is the main criterion for the indication of non-invasive ventilation⁴⁰.

An unexpected result was that the ALSFRSr fine motor scale changes earlier in women, regardless of the onset site, but that the ALSFRSr gross motor scale changes later in women among patients with spinal onset. Further studies are needed to investigate whether these differences might be related to sexual dimorphism in the anatomic pattern of abnormalities, both in terms of susceptibility to neurodegeneration and compensatory mechanisms. The advances in neuroimaging enable an increasing number of research studies investigating cortical and subcortical structure in both health and disease conditions^{41,42}. Note that a dimorphism of regions linked to fine motors has been shown in healthy participants⁴³. In addition, significant sex differences in the anatomical patterns of cortical and subcortical pathology have been shown in ALS⁴¹. Finally, these sex differences might be a bias in the self-evaluation of motor abilities using ALSFRSr.

On the one hand, from a biological perspective, the mechanisms of sexual dimorphism in ALS have been shown at an anatomical level in specific brain regions, in vivo, thanks to imaging¹⁰ and related to sex-specific microglial regulation⁴⁴, sex hormones⁴⁵, or susceptibility to oxidative stress⁴⁶. A study, performed on a large number of ALS women with natural menopause and well-defined oral contraceptive usage, has demonstrated that longer exposure to female hormones has neuroprotective effects on motoneurons in ALS (positive association between a longer reproductive condition, the susceptibility to ALS, and the survival of ALS patients)⁴⁵. On the other hand, the overall heritability of ALS is estimated to be of approximately 21% using genome-wide association studies (GWAS) datasets⁹. The effect of sex was found to be different according to the type of mutation C9orf72 or SOD1 on ALS progression⁹. Recent studies on presymptomatic ALS phase support the emerging hypothesis of a

general disorder in development, both in animal⁴⁷ and humans at cognitive⁴⁸ and structural level⁴⁹. From a developmental origin of health and disease perspective⁵⁰, the well-known sexual dimorphism in physiological development could also play a role.

A strength of our study is that our model was based on a large, multicentric, and longitudinal cohort. We used a mixed effect model following neurological research recommendation⁵¹. The model used is robust to missing data and does not require a standardized time between visits²⁴. Logistic curves were used to overcome common limitations on score analysis: curvilinearity, and potential floor or ceiling effects⁵². The reconstruction error of the model was of the same range as the one of the Alzheimer's disease study²⁵, for which the model has been originally developed (eFigure 3 and eFigure 4 in supplementary materials).

Our study has several limitations. PRO-ACT may not be representative of the real-life ALS patient population. Since the database aggregates clinical trial data, there is an overrepresentation of men, young subjects, patients with spinal onset, and slow progressors. Nevertheless, these results could help better understand the progression of placebo arms and design strategies for patient stratification in clinical trials. Due to the high level of death censoring in PRO-ACT, we were not able to analyse the survival in addition to the disease progression. The outcomes selected has also their own limits. BMI does not capture the distinction between fat, muscle, or bone mass. We have also used the sub-scores of ALSFRS_r separately as recommended¹⁴, but as lower motor neurons often dominate in the overall clinical presentation⁵, the score might be ill-suited for other sub-form of the disease. A population-based study showed the existence of plateaus in ALSFRS_r mainly shorter than 6 months, with only 10% of patients with wider plateaus⁵³. Thus, modeling the progression of ALSFRS_r subscores by logistic curves could be debated. Nevertheless, plateaus appear in high scores and are unlikely to change the

results since our patients' average length of follow-up is one year. The absence of information on genetic mutation³; neuropsychological symptoms³, exposure to metals or agricultural factor⁵⁴ and lifestyle^{55,56} also limits the interpretation of the results.

To summarize, we showed that sex and onset site interaction is an important driver of ALS progression considering many clinical proxies such as disability, weight loss, and respiratory function. Pathophysiological mechanisms underlying these differences are elusive and may account for an interplay of biological, lifestyle, and environmental factors. Further studies in animal models and patients are needed to better understand their respective contributions.

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Table 1: Patient characteristics Legend: data are expressed as mean± standard deviation (percentage of available data) or frequency (percentage), p-value: ANOVA interaction p-value, BM:

Outcomes		Spinal Man	Bulbar Man	Spinal Woman	Bulbar Woman	p-value	Subgroup relations	
Numbers	Patients	757	126	405	150			
	Visits	9236	1447	4771	1799			
	Visits per patient	12.2 ± 10.0	11.5 ± 7.4	11.8 ± 9.0	12.0 ± 7.7	0.46	-	
Riluzole use	Took at least once	533 (70%)	82 (65%)	286 (71%)	96 (64%)			
	Never took	126 (17%)	31 (25%)	72 (18%)	29 (19%)			
	No information on use	98 (13%)	13 (10%)	47 (12%)	25 (17%)			
Trial arm	Active	378 (50%)	66 (52%)	204 (50%)	65 (43%)			
	Placebo	210 (28%)	35 (28%)	115 (28%)	40 (27%)			
	Observational	169 (22%)	25 (20%)	86 (21%)	45 (30%)			
Age	First symptoms	52.3 ± 11.1 (100%)	53.1 ± 11.6 (100%)	54.1 ± 10.9 (100%)	59.5 ± 9.5 (100%)	0.0021	(SM,BM,SW)<BW	
	Diagnosis	53.0 ± 11.1 (87%)	53.7 ± 11.7 (89%)	54.7 ± 10.6 (85%)	60.5 ± 9.5 (90%)	0.0012	(SM,BM,SW)<BW	
	Baseline	54.1 ± 11.1 (100%)	54.6 ± 11.7 (100%)	56.0 ± 10.8 (100%)	61.1 ± 9.4 (100%)	0.0018	(SM,BM,SW)<BW	
Time duration	Patient time of follow-up (y)	1.0 ± 0.7 (100%)	1.0 ± 0.6 (100%)	1.0 ± 0.8 (100%)	1.0 ± 0.6 (100%)	0.58	-	
	Time between visits (d)	34 ± 28 (100 %)	35 ± 28 (100 %)	35 ± 30 (100 %)	34 ± 29 (100 %)	0.33	-	
	Disease duration (y)	1.8 ± 1.0 (100%)	1.4 ± 0.9 (100%)	1.9 ± 1.1 (100%)	1.6 ± 0.9 (100%)	0.61	B<S***	
Outcomes at baseline	Mitos	0.2 ± 0.5 (59%)	0.2 ± 0.5 (59%)	0.3 ± 0.5 (61%)	0.2 ± 0.5 (71%)	0.70	-	
	FT9	1.8 ± 0.9 (59%)	1.9 ± 1.0 (59%)	1.9 ± 0.9 (61%)	1.9 ± 1.0 (71%)	0.52	-	
	ALSFRS _r score	Total	37.2 ± 5.4 (59%)	37.4 ± 5.8 (59%)	35.9 ± 5.5 (61%)	37.3 ± 5.3 (71%)	0.19	W<M***
		Respiratory	11.3 ± 1.3 (59%)	11.1 ± 1.3 (59%)	11.2 ± 1.3 (61%)	11.1 ± 1.2 (71%)	0.73	-
		Bulbar	10.8 ± 1.5 (59%)	7.6 ± 2.1 (59%)	10.5 ± 1.7 (61%)	6.7 ± 2.3 (71%)	0.025	BW<BM<(SW,SM)
		Fine motor	7.6 ± 2.8 (59%)	9.2 ± 2.6 (59%)	8.0 ± 2.7 (61%)	10.0 ± 2.1 (71%)	0.39	M<W**;B<S***
	Gross motor	7.6 ± 2.5 (59%)	9.5 ± 2.5 (59%)	6.2 ± 2.4 (61%)	9.5 ± 2.3 (71%)	0.0012	SW<SM<(BW,BM)	
	Forced vital capacity	75.9 ± 14.4 (97%)	70.3 ± 13.6 (96%)	74.6 ± 14.4 (96%)	68.7 ± 13.8 (97%)	0.83	B<S***	
	BMI	27.1 ± 4.2 (98%)	26.8 ± 4.3 (97%)	26.4 ± 5.0 (98%)	25.6 ± 4.9 (98%)	0.46	W<M***	

bulbar men, BW: bulbar women, SM: spinal men, SW: spinal women, *: <0.05, **: <0.01, *: <0.001**

Figure 1 Average progression of ALSFRSr subscores depending on sex and onset site: Respiratory(blue), Bulbar (orange), Fine Motor (red), Gross Motor (green)

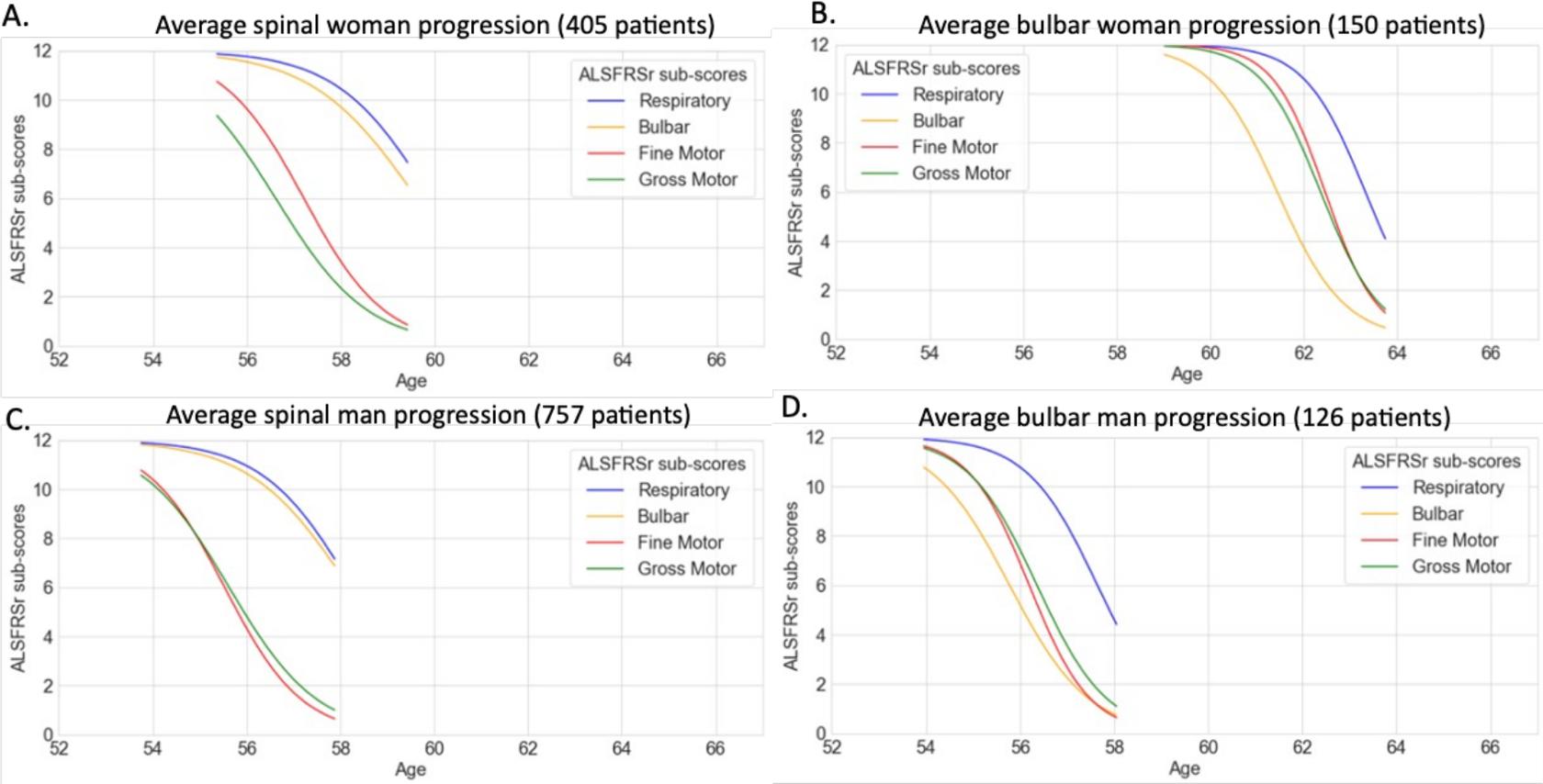
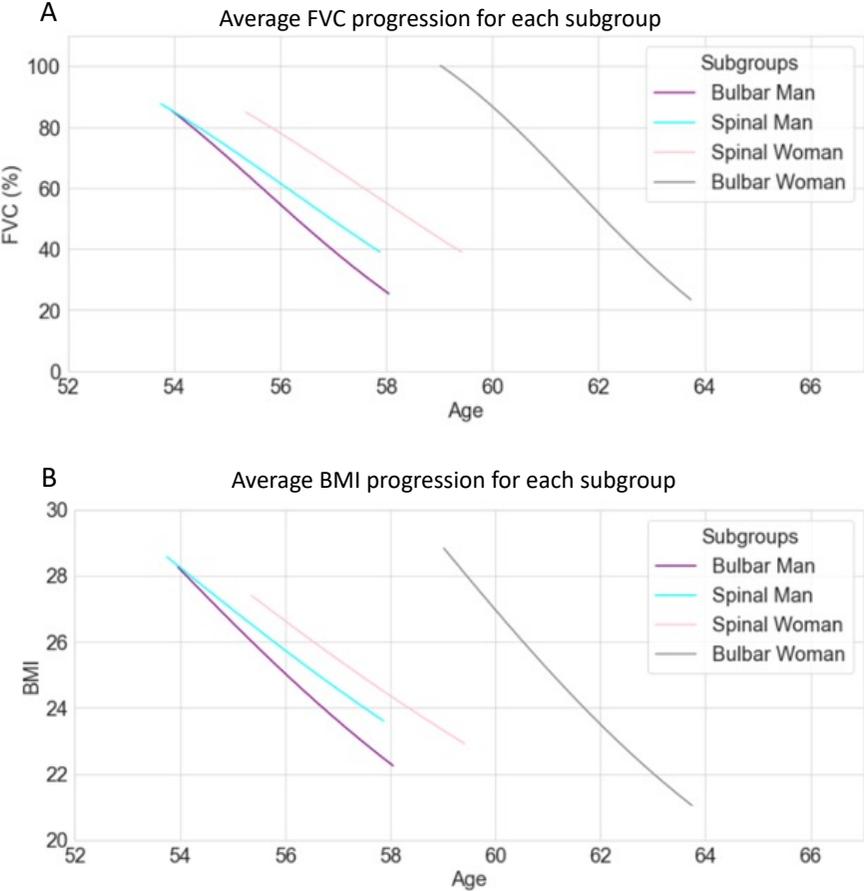


Figure 2: Average subgroup progressions of FVC and BMI for each subgroup



Legend: FVC: Forced vital capacity, BMI: Body mass index

Figure 3: Onset of impairment depending on sex and onset site

The vertical axis presents the delay of outcome impairment onset in month compared to the mean onset of the whole population. The horizontal axis is for sex with estimation for the bulbar patients in blue and the spinal patients in orange. The graph displays the mean of this delay with its confidence interval. Results are corrected for the group rate of progression and estimated age at onset. ANOVA interaction p-value is below 0.001 for ALSFRSr gross motor, ALSFRSr bulbar, and FVC and equal to 0.058 for ALSFRSr respiratory, 0.12 for ALSFRSr fine motor, and 0.17 for BMI. FVC: Forced Vital Capacity (%), **: p-value for pairwise comparison <0.01, ***: p-value for pairwise comparison <0.001

