Understanding dynamics of ALS disease progression through free-living monitoring of gait using wearable accelerometers

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Background

- Gait impairments are prevalent in individuals with amyotrophic lateral sclerosis (ALS) and contribute to increased fall risk, functional decline, and reduced quality of life.
- Traditional gait assessments often lack sensitivity to subtle changes and are limited to in-person evaluations.
- Digital health technologies (DHTs) might serve as a tool for quantifying gait changes in a free-living, naturalistic setting during daily activities.

Purpose

The aim of this project is to clinically validate a gait quantification algorithm in individuals with ALS throughout various stages of disease progression and determine whether gait-related digital measures are indicative of changing ability to walk.

Methods

Population, Devices, Data

- Data were collected as part of a longitudinal observational study, ALS Research Collaborative (ARC), led by ALS TDI.
- We analyzed data from 305 people with ALS (**Table 1**) who contributed 13,191 days of data (mean (SD) follow-up 72.8 (78.0) weeks) collected between 2016 and 2023.
- Participants were asked to wear ankle-worn accelerometer, ActiGraph GT 3X+ (Ametris, Pensacola, FL) continuously for seven days every 4-6 weeks. Participants also completed a self-reported ALS Functional Rating Scale-Revised (ALSFRS-RSE).

Gait quantification algorithm

- We have recently developed and validated a gait recognition and quantification algorithm based on distinct periodic features extracted using continuous wavelet transform (**Figure 1**).

Statistical analysis

- Valid accelerometer measurements considered days with at least 16 hours of detected wear-time.
- We computed daily step counts, top 1 minute cadence (steps per minute) and number of minutes with at least 10 s of walking. Daily measures were averaged on a weekly level.
- Baseline measures (first week) were compared between groups stratified by responses to Q8 ("Ability to walk") using a one-way analysis of variance and Tukey–Kramer post-hoc comparisons between adjacent response levels.
- Longitudinal trends (52-week window) were estimated using linear mixed-effect models with random slopes and intercepts and a group interaction.

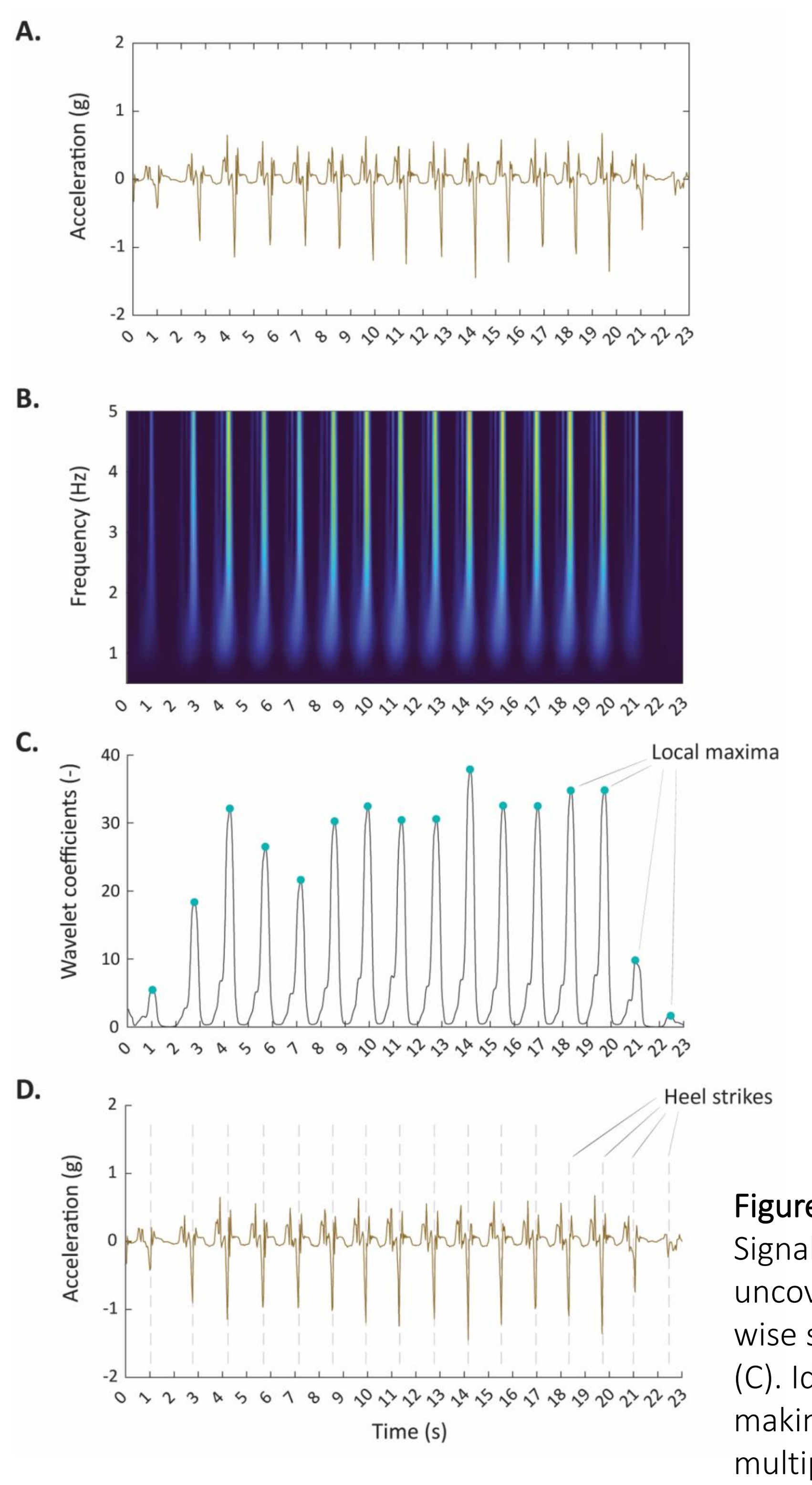

Figure 1. Framework for detecting heel strikes using ankle-worn accelerometers. Signal from vertical axis (A) is decomposed using a continuous wavelet transform which uncovers sharp spikes corresponding to individual heel strikes (B). Local peaks in frequency-wise summation of wavelet coefficients help identify heel strikes locations within the signals (C). Identified locations correspond to heel strikes from one foot (D); assuming another foot making the same number of steps, total step counts are calculated as number of heel strikes multiplied by 2.

Table 1. Selected baseline demographics and descriptive statistics for ALSFRS-RSE and wearable sensor data in the analytic sample. Data were summarized as mean (SD), when possible.

N	305
Sex, females	103
Age, years	55.1 (10.6)
Height, cm	173.6 (9.9)
Weight, kg	79.1 (15.8)
BMI, kg/m2	26.2 (4.5)
Disease characteristics	
ALSFRS-RSE Q1—Q12	40.2 (5.6)
ALSFRS-RSE Q8	3.0 (0.9)
Outcome and accelerometer data	
ALSFRS-RSE	
Number of surveys, count	14.7 (13.8)
Time between surveys, weeks	3.1 (1.9)
Accelerometer data	
Follow-up, weeks	72.8 (78.0)
Valid accelerometer bouts, weeks	11.5 (13.1)
Time between bouts, weeks	6.9 (9.1)

Results

At baseline, gait-related digital measures are significantly lower for participants reporting impaired walking.

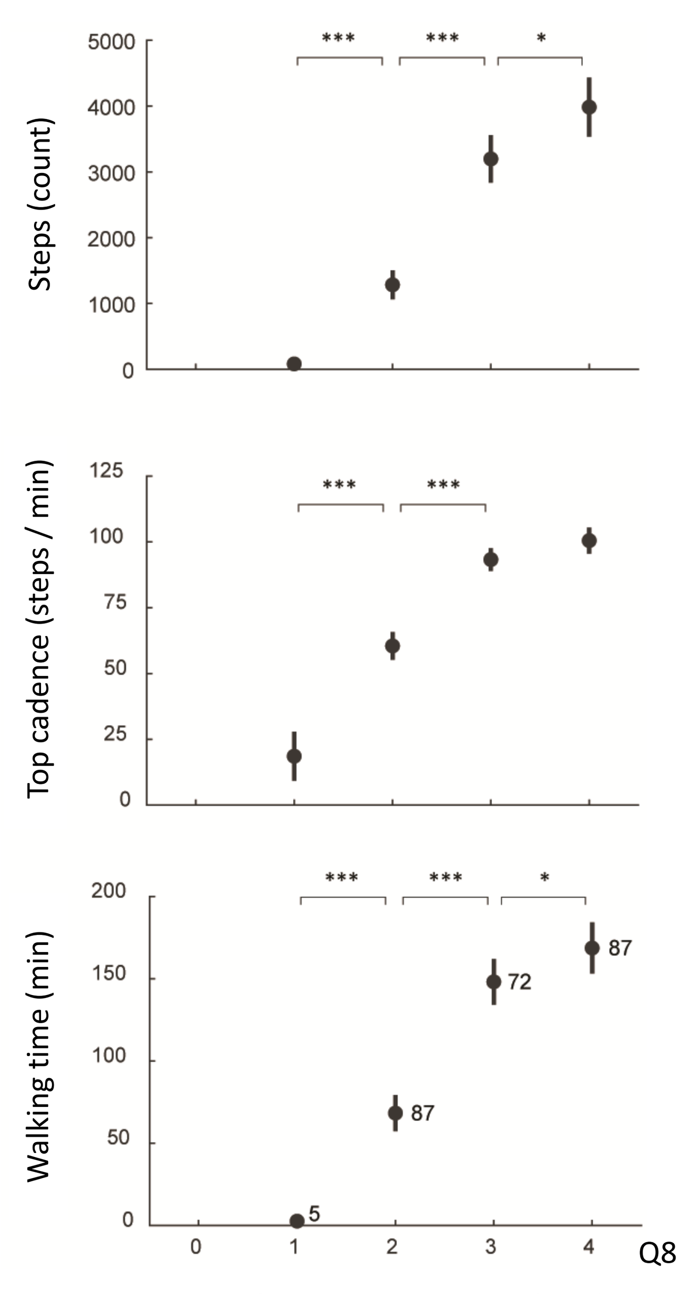

Figure 2. Mean and 95% CI of step counts stratified by responses to ALSFRS-RSE Q8. Values displayed next to the mean step counts indicate group size reporting a given functional status. Asterisks indicate significant differences between adjacent groups '*' indicates p-value < 0.05, '***' p-value < 0.001

Gait-related digital measures reveal faster relative decline for participants with worse self-reported functioning.

Table 2. Population-level weekly change (95 % CI) of gait-related digital measures estimated within groups with stable responses to Q8 in ALSFRS-RSE.

Digital measure	Q8	Intercept	Slope	p-val.	R-sq.	Rel. change (%)
Step counts	4	4188 [3701, 4675]	-17.4 [-28.1, -6.7]	0.001	0.81	**-0.42**
	3	3306 [2956, 3656]	-16.5 [-25.9, -7.1]	0.001	0.86	**-0.50**
	2	1583 [1360, 1805]	-21.9 [-27.1, -15.9]	<0.001	0.87	**-1.36**
Top cadence	4	102.4 [98.9, 105.8]	-0.17 [-0.27, -0.08]	<0.001	0.60	**-0.17**
	3	94.5 [91.2, 97.8]	-0.20 [-0.29, -0.11]	<0.001	0.85	**-0.21**
	2	68.6 [64.5, 72.7]	-0.47 [-0.61, -0.34]	<0.001	0.86	**-0.69**
Walking time	4	174.9 [159.3, 190.6]	-0.53 [-0.90, -0.15]	0.006	0.72	**-0.30**
	3	146.4 [135, 157.9]	-0.63 [-0.94, -0.32]	<0.001	0.87	**-0.43**
	2	81.5 [71.6, 91.4]	-1.18 [-1.46, -0.89]	<0.001	0.86	**-1.44**

Note: Relative weekly change was calculated as a ratio between population-level slope and intercept; p-val. ~ p-value, R-sq. ~ R-squared, Rel. ~ relative change.

Responses to Q8:
4 – "Normal", 3 – "Early ambulation difficulty", 2 – "Walks with assistance", 1 – "Non-ambulatory functional movement", 0 – "No purposeful leg movement" (<u>not reported in this dataset</u>)

Gait-related digital measures decline faster for participants reporting gait changes in Q8 from baseline. Differences in group-level slopes were statistically significant for participants reporting 3 or 2 on Q8 at baseline.

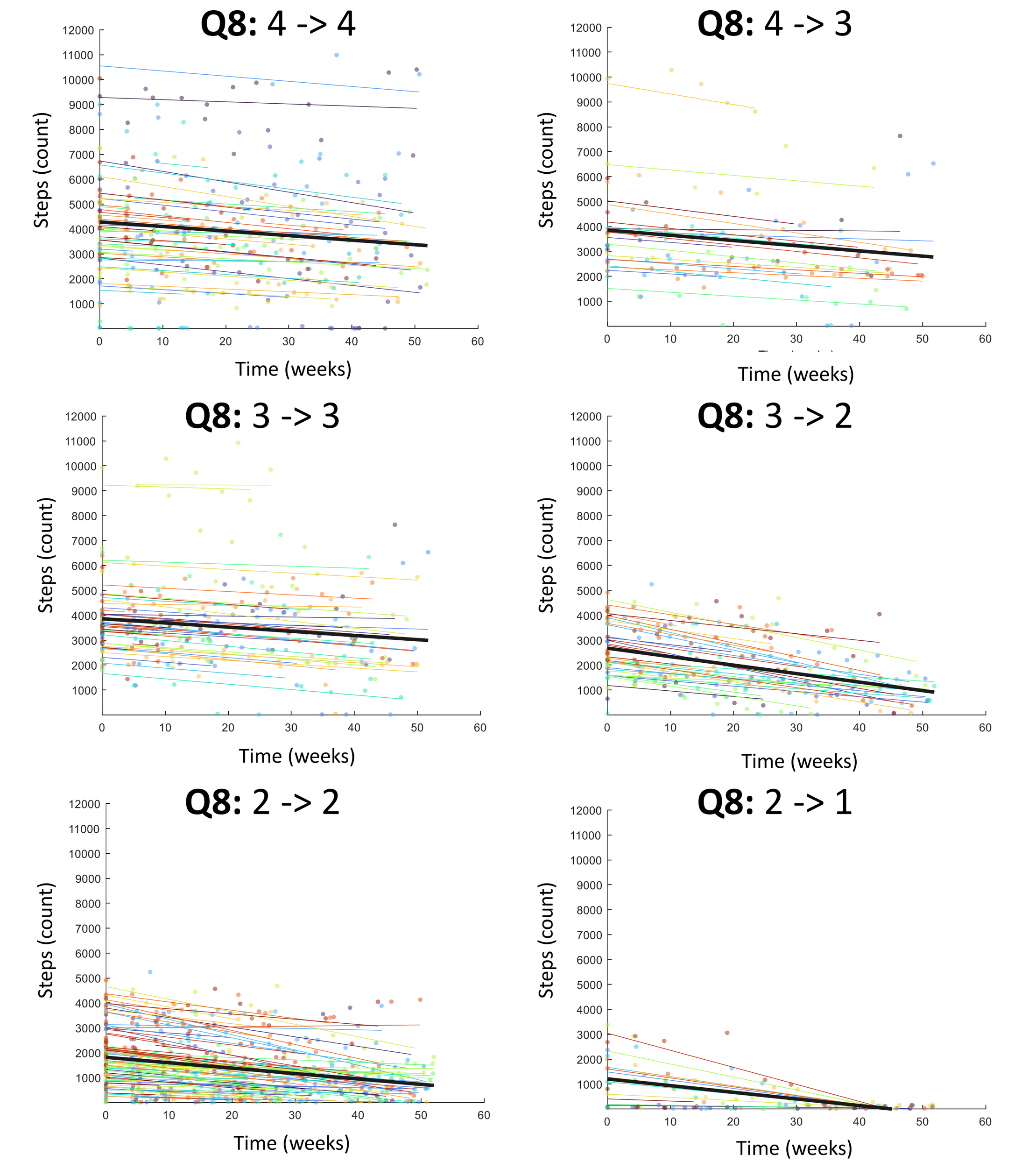

Figure 3. Association between time and daily-level step counts estimated with linear mixed-effects models (LMMs). In each plot, points represent observed values, lines represent participants' conditional means, and both points and lines have been color-coded by participant (the colors are fixed across the panels). Black lines represent population means.

Discussion and Conclusion

- The proposed approach allows for gait monitoring throughout disease progression, from the normal gait patterns to impaired gait where the individual may be moving more slowly or with an assistive device.
- Free-living gait-related digital measures are sensitive indicators of disease progression and may be predictive of status change in gross motor functioning.
- Our findings support the use of DHTs in longitudinal monitoring of ALS disease progression.
- Future work should advance analytical and clinical validation of gait measures to meet regulatory guidelines for implementation in clinical studies.

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