

Supplementary information

Data collection and Training

Training was conducted by investigator meetings quarter to yearly over the course of the study and videotapes of prototype exams. New sites were typically initiated by visits to the primary site (Children's Hospital of Philadelphia) to observe a typical study visit. AOO is assessed at FRDA diagnosis (typically at the baseline visit), and GAA repeat lengths were assessed in commercial laboratories (without standardization).

Statistical Methodology and Analysis

- Study site showed no notable influence on the overall results (amount of progression) when included as fixed effect and was omitted from the final models
- Mixed model assumptions were checked using residual- and Q-Q-plots, and sensitivity to outliers was investigated using Cooks D analysis.
- E.g., for the mFARS outcome (ambulatory phase), exclusion of the 30 most influential observations (determined by their Cooks D distance) resulted in all progression estimates changing by less than 0.10 points per year. Similar results were obtained for FARS E, and none of the changes impacted the conclusions.

eTable 1: Centers participating in the FACOMS study

University	Location	Participants in this study	Age Range
Emory University	Atlanta	72	7.9 - 65.2
University of Auckland	Auckland, New Zealand	11	29.3 - 68.5
University of Chicago	Chicago	20	10.4 - 54.4
Ohio State University	Columbus	12	8.7 - 57
University of Colorado	Denver	2	46.7 - 65.7
University of Florida	Gainesville	29	8.3 - 72
University of Iowa	Iowa City	28	9.2 - 46.2
University of California Los Angeles	Los Angeles	204	6.1 - 61
Murdoch Children's Research Institute	Melbourne, Australia	185	4.9 - 81.5
University of Minnesota	Minneapolis	17	13.7 - 45.3
Centre Hospitalier de l'Université de Montréal	Montreal, Canada	15	14.5 - 56.5
Children's Hospital of Philadelphia	Philadelphia	454	4.1 - 78.1
University of Rochester	Rochester	2	32.9 - 47.1
University of South Florida	Tampa	43	9.9 - 69.8
Sick Kids Hospital	Toronto, Canada	21	3.7 - 20.3
Emory University	Atlanta	72	7.9 - 65.2

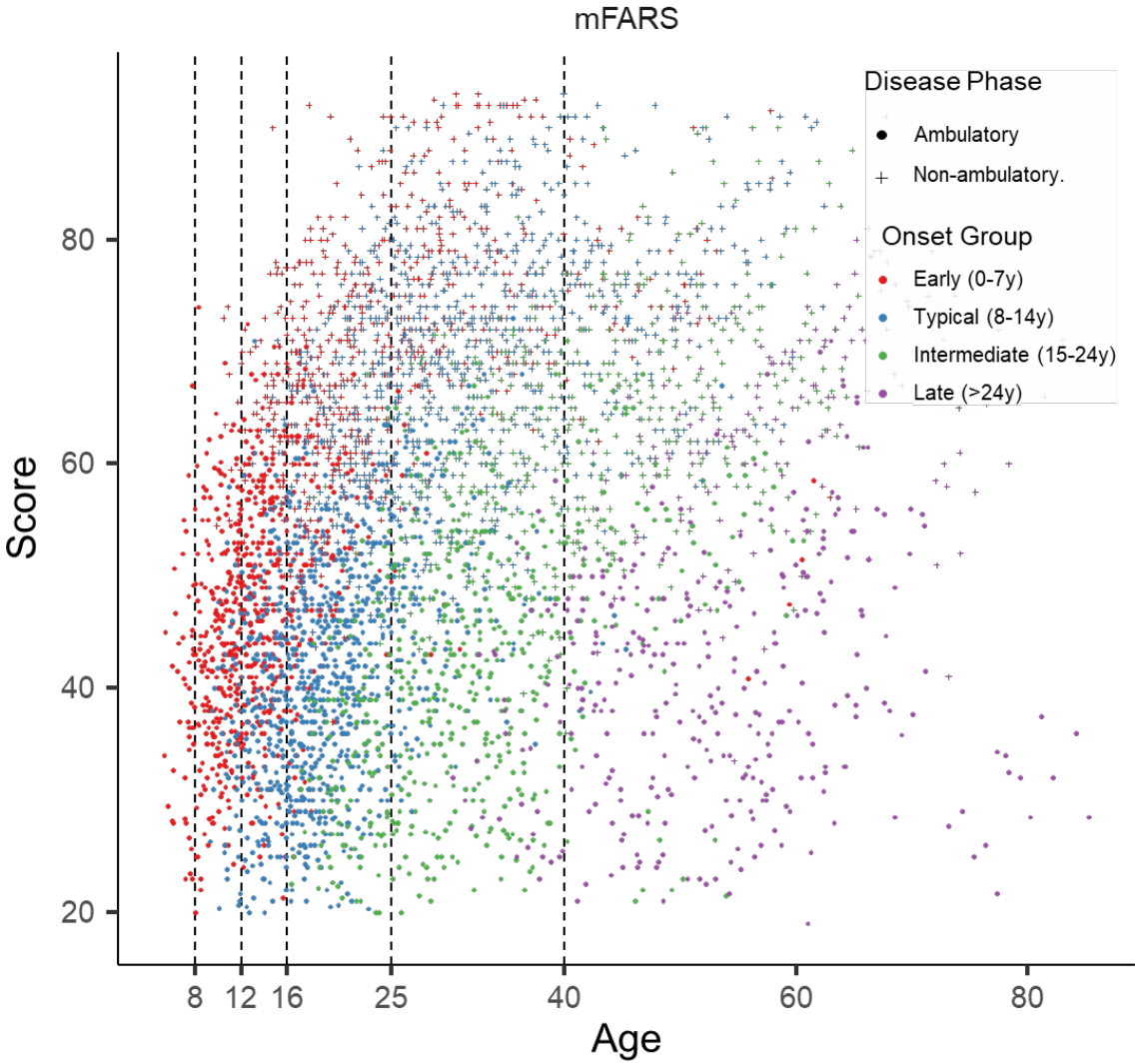
eTable 2: Follow-Up Times by Ambulation Status

Onset Group	<8y (early)	8-14y (typical)	15-24y (intermediate)	>24y (late)	Overall
N	324	438	234	119	1115
(% of overall)	(29)	(39)	(21)	(11)	
Follow-Up (ambulatory)	178	226	126	63	593
N	3.5	3.9	5.1	5.6	4.0
[y]	[1.6, 5.6]	[1.9, 6.2]	[2.1, 7.6]	[2.4, 9.3]	[2.0, 6.7]
Follow-Up (non-ambulatory)	126	163	74	28	391
N	4.6	4.6	5.2	5.1	4.8
[y]	[2.1, 8.1]	[2.6, 8.2]	[2.3, 8.8]	[2.0, 8.0]	[2.4, 8.2]
Patients without follow-up (%)	20	22	24	29	23

Data are % or median [IQR];

!Excluding point mutations (n=57) and participants with missing repeat length information (n=58).

eFigure 1: mFARS scores used in longitudinal analyses (N=4661)



eTable 3: Features of the ambulatory FRDA population in FACOMS. Proportion of patients by genetic severity and by age group. Individuals can contribute data to more than one age-interval.

% Of patients enrolled (% of visits) by Age- and Onset Group		Age Group					
		Children			Adults		
		<8y	8-11y	12-15y	16-24y	25-40y	>40y
		(n = 39)	(n = 159)	(n = 266)	(n = 441)	(n = 369)	(n = 236)
Age of Onset	0-7y (Early Onset)	100 (100)	73 (83)	37 (58)	21 (30)	12 (16)	3 (5)
	8-14y (Typical Onset)		27 (17)	62 (41)	56 (58)	40 (44)	17 (19)
	15-24y (Intermediate Onset)			1 (0)	23 (11)	41 (38)	27 (31)
	>24y (Late Onset)					7 (3)	53 (45)

eTable 4: Disease progression from slope models. All outcome measures including mFARS subscores, by ambulation status and FRDA severity group. The typical onset group was used as reference for onset group comparisons. P-values are in bold/grey by significance level. SE = Standard Error, CI = Confidence Interval

Parameter	Disease Phase	Onset Group	Rate of Decline			Difference vs Typical Onset		
			Estimate (SE)	95%CI	p	Estimate	95%CI	p
mFARS	ambulatory	0-7y	2.62 (0.14)	2.35, 2.90	<0.001	0.79	0.43, 1.15	<0.001
		8-14y	1.83 (0.12)	1.60, 2.06	<0.001			
		15-24y	1.24 (0.15)	0.95, 1.53	<0.001	-0.59	-0.96, -0.22	0.002
		>24y	1.18 (0.20)	0.79, 1.56	<0.001	-0.66	-1.10, -0.21	0.005
	non-ambulatory	0-7y	1.21 (0.12)	0.98, 1.45	<0.001	0.31	0.00, 0.62	0.047
		8-14y	0.90 (0.10)	0.71, 1.10	<0.001			
		15-24y	0.75 (0.15)	0.46, 1.05	<0.001	-0.15	-0.50, 0.20	0.404
		>24y	0.53 (0.25)	0.05, 1.02	0.032	-0.37	-0.90, 0.15	0.162
Bulbar Function (FARS A)	ambulatory	0-7y	0.05 (0.01)	0.03, 0.07	<0.001	0.04	0.02, 0.07	<0.001
		8-14y	0.01 (0.01)	-0.01, 0.02	0.321			
		15-24y	0.02 (0.01)	-0.00, 0.04	0.092	0.01	-0.02, 0.03	0.487
		>24y	0.03 (0.01)	0.00, 0.05	0.032	0.02	-0.01, 0.05	0.192
	non-ambulatory	0-7y	0.09 (0.01)	0.06, 0.11	<0.001	0.03	-0.00, 0.06	0.094
		8-14y	0.06 (0.01)	0.04, 0.08	<0.001			
		15-24y	0.02 (0.02)	-0.01, 0.06	0.135	-0.03	-0.07, 0.01	0.088
		>24y	-0.03 (0.03)	-0.08, 0.03	0.341	-0.08	-0.14, -0.03	0.005
Upper Limb Function (FARS B)	ambulatory	0-7y	0.30 (0.08)	0.15, 0.45	<0.001	0.31	0.12, 0.50	0.002
		8-14y	-0.01 (0.06)	-0.14, 0.11	0.819			
		15-24y	0.01 (0.08)	-0.15, 0.16	0.904	0.02	-0.17, 0.22	0.812
		>24y	0.20 (0.10)	-0.01, 0.40	0.058	0.21	-0.03, 0.45	0.081
	non-ambulatory	0-7y	0.57 (0.09)	0.39, 0.74	<0.001	0.15	-0.08, 0.38	0.211
		8-14y	0.42 (0.08)	0.27, 0.57	<0.001			
		15-24y	0.24 (0.11)	0.01, 0.46	0.038	-0.18	-0.45, 0.08	0.180
		>24y	0.08 (0.19)	-0.29, 0.44	0.687	-0.34	-0.74, 0.05	0.090

		Rate of Decline				Difference vs Typical Onset		
Parameter	Disease Phase	Onset Group	Estimate (SE)	95%CI	p	Estimate	95%CI	p
Lower Limb Function (FARS C)	ambulatory	0-7y	0.51 (0.05)	0.41, 0.62	<0.001	0.27	0.13, 0.40	<0.001
		8-14y	0.25 (0.04)	0.16, 0.33	<0.001			
		15-24y	0.16 (0.06)	0.05, 0.27	0.005	-0.09	-0.23, 0.05	0.221
		>24y	0.03 (0.07)	-0.12, 0.17	0.694	-0.22	-0.39, -0.05	0.012
	non-ambulatory	0-7y	0.40 (0.06)	0.29, 0.52	<0.001	0.11	-0.03, 0.26	0.129
		8-14y	0.29 (0.05)	0.20, 0.39	<0.001			
		15-24y	0.37 (0.07)	0.23, 0.51	<0.001	0.07	-0.09, 0.24	0.384
		>24y	0.38 (0.12)	0.15, 0.61	0.001	0.09	-0.16, 0.34	0.478
	ambulatory	0-7y	1.78 (0.08)	1.61, 1.94	<0.001	0.21	-0.00, 0.43	0.055
		8-14y	1.57 (0.07)	1.43, 1.71	<0.001			
		15-24y	1.06 (0.09)	0.88, 1.24	<0.001	-0.51	-0.73, -0.29	<0.001
		>24y	0.90 (0.12)	0.67, 1.13	<0.001	-0.67	-0.94, -0.40	<0.001
ADL	ambulatory	0-7y	1.06 (0.08)	0.90, 1.21	<0.001	0.01	-0.19, 0.21	0.913
		8-14y	1.05 (0.07)	0.92, 1.18	<0.001			
		15-24y	0.74 (0.08)	0.58, 0.90	<0.001	-0.31	-0.52, -0.10	0.004
		>24y	0.48 (0.11)	0.27, 0.70	<0.001	-0.56	-0.82, -0.31	<0.001
	non-ambulatory	0-7y	0.65 (0.06)	0.53, 0.78	<0.001	0.19	0.03, 0.35	0.023
		8-14y	0.47 (0.05)	0.36, 0.57	<0.001			
		15-24y	0.40 (0.08)	0.25, 0.55	<0.001	-0.07	-0.25, 0.11	0.449
		>24y	0.46 (0.13)	0.21, 0.72	<0.001	-0.01	-0.28, 0.27	0.966
	ambulatory	0-7y	-0.09 (0.00)	-0.15, -0.12	<0.001	-0.01	-0.03, 0.02	0.658
		8-14y	-0.07 (0.00)	-0.15, -0.12	<0.001			
		15-24y	-0.05 (0.00)	-0.10, -0.06	<0.001	0.05	0.03, 0.07	<0.001
		>24y	-0.04 (0.01)	-0.09, -0.04	<0.001	0.06	0.04, 0.09	<0.001
9-Hole Peg Test [1/min]	non-ambulatory	0-7y	-0.07 (0.01)	-0.10, -0.08	<0.001	-0.02	-0.03, -0.01	<0.001
		8-14y	-0.05 (0.00)	-0.07, -0.06	<0.001			
		15-24y	-0.03 (0.01)	-0.06, -0.04	<0.001	0.02	0.01, 0.03	0.002
		>24y	-0.04 (0.01)	-0.06, -0.03	<0.001	0.02	0.01, 0.04	<0.001
Timed 25 Feet Walk [m/s]	non-ambulatory	0-7y	-0.14 (0.01)	-0.08, -0.06	<0.001	-0.02	-0.03, -0.01	<0.001

Parameter	Disease Phase	Onset Group	Rate of Decline			Difference vs Typical Onset		
			Estimate (SE)	95%CI	p	Estimate	95%CI	p
		8-14y	-0.13 (0.01)	-0.06, -0.04	<0.001			
		15-24y	-0.08 (0.01)	-0.04, -0.02	<0.001	0.02	0.01, 0.03	0.003
		>24y	-0.07 (0.01)	-0.06, -0.02	<0.001	0.01	-0.01, 0.03	0.248

eTable 5: Ambulatory Phase: mean changes and outcome sensitivity, as well as influence of the baseline/AOO covariates from mixed models. P-values are in bold/grey by significance level.

		1y-Intervals				2y-Intervals			
	Age Group	Subjects (Observations)	Mean Change (SD)	Sensitivity (SRM)	P (baseline)	P (AOO)	Subjects (Observations)	Mean Change (SD)	Sensitivity (SRM)
mFARS	<8y	25 (33)	3.97 (9.65)	0.41	0.067	0.502	21 (29)	8.79 (9.04)	0.97
	8-11y	116 (227)	3.14 (6.56)	0.48	0.002	0.290	89 (178)	4.98 (6.59)	0.76
	12-15y	159 (288)	1.93 (5.45)	0.35	<0.001	0.036	124 (210)	4.06 (5.96)	0.68
	16-24y	176 (475)	1.87 (5.33)	0.35	<0.001	<0.001	150 (390)	3.92 (6.15)	0.64
	25-40y	108 (300)	1.14 (4.82)	0.24	<0.001	0.006	86 (241)	3.02 (5.93)	0.51
	>40y	60 (243)	0.83 (5.20)	0.16	0.021	0.450	55 (206)	1.64 (6.25)	0.26
Bulbar Function (FARS A)	<8y	25 (33)	0.08 (0.50)	0.15	0.002	0.505	21 (29)	0.22 (0.49)	0.46
	8-11y	116 (227)	0.13 (0.47)	0.27	<0.001	0.900	89 (178)	0.12 (0.47)	0.26
	12-15y	159 (288)	0.02 (0.50)	0.03	<0.001	0.020	124 (210)	0.09 (0.58)	0.15
	16-24y	176 (475)	0.01 (0.50)	0.02	<0.001	0.017	150 (390)	0.04 (0.51)	0.09
	25-40y	108 (300)	-0.04 (0.56)	0.06	<0.001	0.197	86 (241)	0.00 (0.54)	0.00
	>40y	60 (243)	0.04 (0.52)	0.08	<0.001	0.109	55 (206)	0.01 (0.62)	0.02
Upper Limb Function (FARS B)	<8y	25 (33)	2.17 (4.20)	0.52	0.002	0.609	21 (29)	2.84 (5.40)	0.53
	8-11y	116 (227)	0.65 (3.78)	0.17	<0.001	0.741	89 (178)	0.71 (3.74)	0.19
	12-15y	159 (288)	-0.14 (3.13)	0.04	<0.001	0.185	124 (210)	-0.20 (3.15)	0.06
	16-24y	176 (475)	0.08 (3.16)	0.02	<0.001	0.009	150 (390)	0.22 (3.32)	0.07
	25-40y	108 (300)	0.06 (3.25)	0.02	<0.001	0.126	86 (241)	0.32 (3.29)	0.10
	>40y	60 (243)	0.05 (3.21)	0.01	<0.001	0.603	55 (206)	0.10 (3.86)	0.03
Lower Limb Function (FARS C)	<8y	25 (33)	0.76 (2.87)	0.26	<0.001	0.121	21 (29)	1.76 (2.80)	0.63
	8-11y	116 (227)	0.51 (2.18)	0.23	<0.001	0.294	89 (178)	0.72 (2.37)	0.31
	12-15y	159 (288)	0.33 (2.29)	0.14	<0.001	0.052	124 (210)	0.63 (2.77)	0.23
	16-24y	176 (475)	0.39 (2.34)	0.17	<0.001	<0.001	150 (390)	0.68 (2.52)	0.27
	25-40y	108 (300)	0.20 (2.20)	0.09	<0.001	<0.001	86 (241)	0.50 (2.47)	0.20
	>40y	60 (243)	0.13 (2.29)	0.06	<0.001	0.139	55 (206)	0.12 (2.51)	0.05
Upright Stability (FARS E)	<8y	25 (33)	0.97 (5.72)	0.17	0.024	0.530	21 (29)	3.97 (4.96)	0.80
	8-11y	116 (227)	1.85 (3.78)	0.49	<0.001	0.080	89 (178)	3.42 (4.00)	0.86
	12-15y	159 (288)	1.73 (3.22)	0.54	<0.001	0.005	124 (210)	3.54 (3.58)	0.99
	16-24y	176 (475)	1.39 (2.78)	0.50	<0.001	<0.001	150 (390)	2.98 (3.47)	0.86
	25-40y	108 (300)	0.91 (2.53)	0.36	<0.001	0.022	86 (241)	2.20 (3.28)	0.67
	>40y	60 (243)	0.61 (2.88)	0.21	0.008	0.177	55 (206)	1.41 (3.57)	0.39
ADL	<8y	16 (23)	0.58 (3.34)	0.18			18 (23)	0.22 (5.27)	0.04
	8-11y	109 (203)	1.03 (4.00)	0.26	<0.001	0.007	88 (165)	2.60 (4.51)	0.58
	12-15y	162 (290)	0.95 (3.25)	0.29	<0.001	0.008	124 (206)	2.10 (3.68)	0.57
	16-24y	175 (451)	1.20 (2.95)	0.41	<0.001	0.023	145 (365)	2.19 (3.30)	0.67

		1y-Intervals				2y-Intervals			
	Age Group	Subjects (Observations)	Mean Change (SD)	Sensitivity (SRM)	P (baseline)	P (AOO)	Subjects (Observations)	Mean Change (SD)	Sensitivity (SRM)
Timed 25 Feet Walk [m/s]	25-40y	109 (291)	0.77 (2.49)	0.31	<0.001	0.462	84 (233)	1.30 (2.73)	0.47
	>40y	61 (241)	0.34 (3.00)	0.11	<0.001	0.003	54 (204)	0.87 (2.97)	0.29
	<8y	25 (33)	-0.04 (0.45)	0.10	<0.001	0.947	18 (24)	-0.19 (0.47)	0.40
	8-11y	112 (213)	-0.11 (0.36)	0.31	<0.001	0.093	80 (159)	-0.26 (0.36)	0.73
	12-15y	136 (242)	-0.15 (0.29)	0.52	<0.001	0.076	107 (175)	-0.30 (0.35)	0.86
	16-24y	149 (357)	-0.13 (0.24)	0.57	<0.001	0.202	117 (272)	-0.26 (0.27)	0.97
	25-40y	80 (191)	-0.08 (0.21)	0.40	<0.001	0.058	61 (150)	-0.18 (0.28)	0.64
	>40y	54 (185)	-0.05 (0.18)	0.27	<0.001	0.051	46 (147)	-0.12 (0.22)	0.53
	<8y	19 (25)	-0.09 (0.22)	0.43			18 (24)	-0.14 (0.25)	0.58
	8-11y	110 (214)	-0.08 (0.17)	0.48	0.103	0.327	84 (168)	-0.20 (0.19)	1.05
	12-15y	148 (273)	-0.09 (0.16)	0.54	0.011	0.274	119 (202)	-0.18 (0.16)	1.11
	16-24y	170 (459)	-0.07 (0.13)	0.55	<0.001	0.514	144 (372)	-0.15 (0.15)	1.03
	25-40y	105 (289)	-0.04 (0.15)	0.30	<0.001	0.021	82 (232)	-0.09 (0.15)	0.59
	>40y	58 (229)	-0.04 (0.18)	0.22	<0.001	0.385	54 (198)	-0.10 (0.22)	0.43

9-Hole Peg Test [1/min]

eTable 6: Non-ambulatory phase: mean changes and outcome sensitivity, as well as influence of the baseline/AOO covariates (from MMRM models). P-values are in bold/grey by significance level.

	1y-Intervals					2y-Intervals			
	Age Group	Subjects (Observations)	Mean Change (SD)	Sensitivity (SRM)	P (baseline)	P (AOO)	Subjects (Observations)	Mean Change (SD)	Sensitivity (SRM)
mFARS	8-11y	3 (5)	1.80 (2.66)	0.68			3 (5)	2.10 (4.20)	0.50
	12-15y	29 (52)	2.79 (5.19)	0.54	0.169	0.995	30 (47)	5.11 (5.97)	0.86
	16-24y	116 (282)	1.39 (4.72)	0.30	<0.001	0.421	104 (233)	2.73 (4.72)	0.58
	25-40y	148 (507)	0.75 (4.58)	0.16	<0.001	<0.001	132 (401)	1.71 (4.89)	0.35
	>40y	96 (389)	0.41 (4.47)	0.09	<0.001	0.063	85 (326)	1.37 (4.97)	0.28
Bulbar Function (FARS A)	8-11y	3 (5)	0.30 (0.57)	0.53			3 (5)	0.80 (0.57)	1.40
	12-15y	29 (52)	0.04 (0.67)	0.06	<0.001	0.438	30 (47)	0.28 (0.86)	0.32
	16-24y	116 (282)	0.08 (0.73)	0.11	<0.001	0.205	104 (233)	0.17 (0.73)	0.23
	25-40y	148 (507)	0.02 (0.70)	0.03	<0.001	<0.001	132 (401)	0.05 (0.76)	0.07
	>40y	96 (389)	0.02 (0.69)	0.03	<0.001	0.004	85 (326)	0.08 (0.65)	0.13
Upper Limb Function (FARS B)	8-11y	3 (5)	-0.80 (3.62)	0.22			3 (5)	-1.30 (4.37)	0.30
	12-15y	29 (52)	1.26 (4.71)	0.27	<0.001	0.849	30 (47)	1.70 (4.11)	0.41
	16-24y	116 (282)	0.44 (3.78)	0.12	<0.001	0.462	104 (233)	1.12 (4.08)	0.27
	25-40y	148 (507)	0.36 (4.02)	0.09	<0.001	<0.001	132 (401)	0.98 (4.29)	0.23
	>40y	96 (389)	0.07 (3.71)	0.02	<0.001	0.132	85 (326)	0.58 (3.91)	0.15
Lower Limb Function (FARS C)	8-11y	3 (5)	1.50 (3.57)	0.42			3 (5)	1.60 (2.63)	0.61
	12-15y	29 (52)	1.16 (2.48)	0.47	0.011	0.953	30 (47)	2.49 (3.46)	0.72
	16-24y	116 (282)	0.70 (2.21)	0.32	<0.001	0.158	104 (233)	1.15 (2.22)	0.52
	25-40y	148 (507)	0.28 (1.55)	0.18	<0.001	<0.001	132 (401)	0.48 (1.82)	0.26
	>40y	96 (389)	0.24 (1.57)	0.15	<0.001	0.008	85 (326)	0.52 (1.91)	0.27
ADL	8-11y	2 (3)	0.50 (2.18)	0.23			3 (4)	2.75 (3.52)	0.78
	12-15y	28 (48)	1.12 (2.33)	0.48	<0.001	0.333	28 (45)	1.90 (3.28)	0.58
	16-24y	111 (256)	0.77 (3.00)	0.26	<0.001	0.139	94 (201)	1.56 (3.28)	0.48
	25-40y	138 (436)	0.43 (3.01)	0.14	<0.001	<0.001	123 (354)	0.81 (2.93)	0.28
	>40y	91 (345)	0.29 (2.85)	0.10	<0.001	0.081	81 (285)	0.80 (2.89)	0.28
9-Hole Peg Test [l/min]	8-11y	3 (5)	-0.10 (0.20)	0.51			3 (5)	-0.16 (0.13)	1.16
	12-15y	23 (33)	-0.09 (0.12)	0.73	0.578	0.456	16 (22)	-0.20 (0.13)	1.50
	16-24y	89 (196)	-0.08 (0.12)	0.65	<0.001	0.006	78 (147)	-0.17 (0.14)	1.21
	25-40y	96 (255)	-0.04 (0.11)	0.41	<0.001	0.041	82 (190)	-0.09 (0.11)	0.77
	>40y	62 (222)	-0.04 (0.12)	0.33	0.018	0.653	55 (182)	-0.08 (0.12)	0.66