Motor function and activity in Rett syndrome

Nordic Rett Syndrome Conference

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Jenny Downs

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"Clinical peculiarities and biological mysteries" *Hagberg 1995*

- Associated with a mutation on the *MECP2* gene
- Period of regression followed by stabilisation
- 4 main criteria
  - Loss of hand skills/communication skills
  - Hand stereotypies
  - Gait abnormalities
- Supportive criteria
  - Altered breathing
  - Bruxism
  - Scoliosis/kyphosis
  - Poor growth
  - Small cold hands and feet
  - Diminished response to pain
  - Intense eye communication
  - Sleep dysfunction

Neul 2010

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Overview

- Early learning of gross motor skills
  - Environmental enrichment
- Gross motor skills over the life span
- Sedentary time and activity
- Future directions

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Early learning of gross motor skills

Regression

- Sudden or gradually
- Average age of loss of hand and/or communication skills - 19.3 months (n=654)
- Developmental profiling
  - In a sample of 14 young girls, social withdrawal lasted approx. 5 months and inconsolable crying approx. 25 months

"… she was able to grab toys, and feed herself and then she started to regress … So right now, she can't self feed …"

"… the worst of it was between 9 and 12 months … her babbling ceased altogether … she would look through us and just cried …"

" … there was nothing I could do to appease her …. the hair pulling, the screaming fits, the lack of sleep. Those three things all happened around the spring of 2009"

Data collected by Joanne Lee, Masters of Clinical Psychology student

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Regression and gross motor skills

- Gross motor skills declined during regression with *loss of balance* in 8/14
  - 5 of 6 who could walk
  - 1 of 2 who could walk with assistance
  - 1 of 3 who could stand with support
  - 1 of 3 who could sit independently
- Consistent with development of truncal ataxia and impaired gait

- Loss of gross motor skills was subtle, *developing slowly over time*
- *Median age – 36 months* (range 18 to 42 months)

Data collected by Joanne Lee, Masters of Clinical Psychology student

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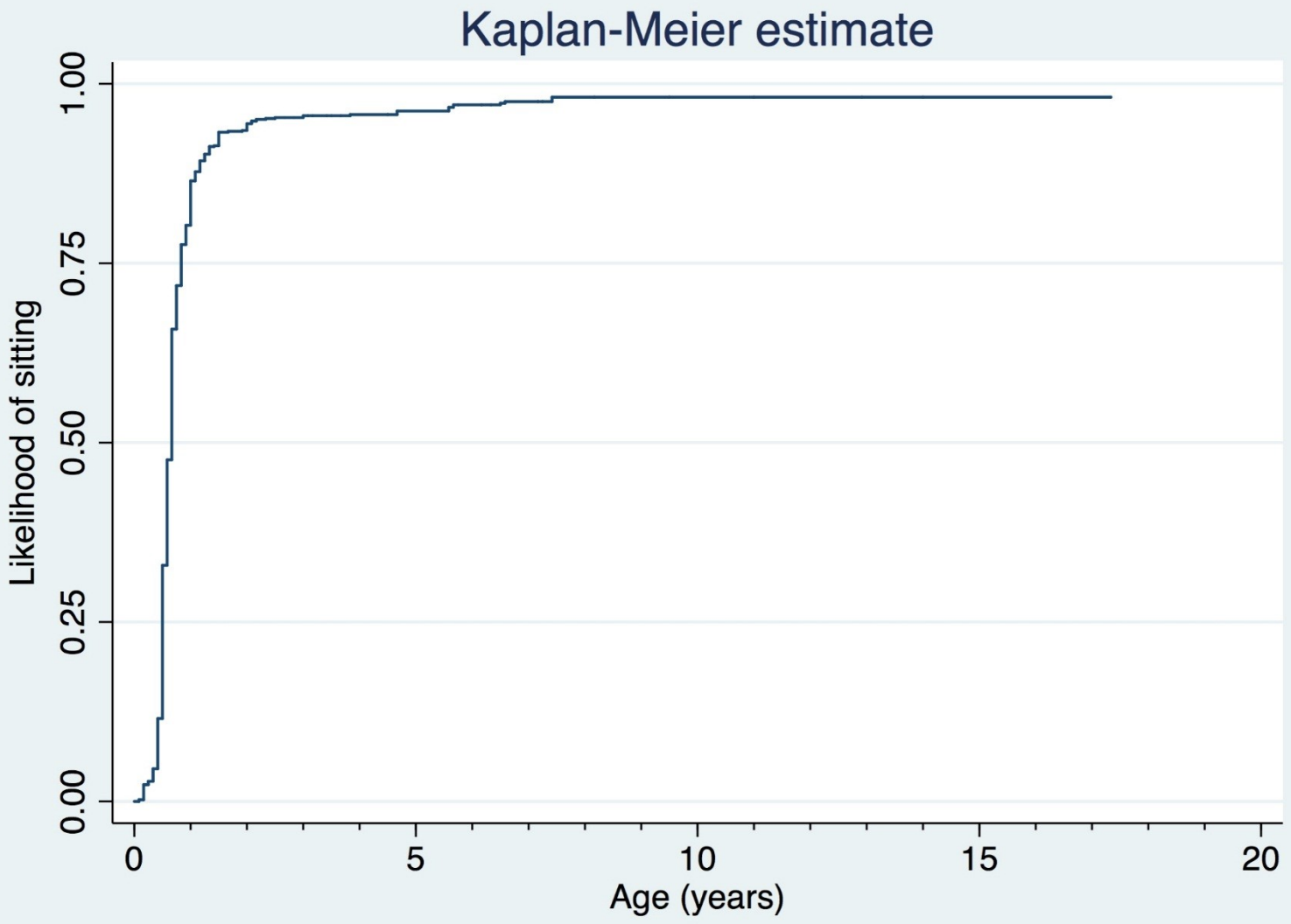
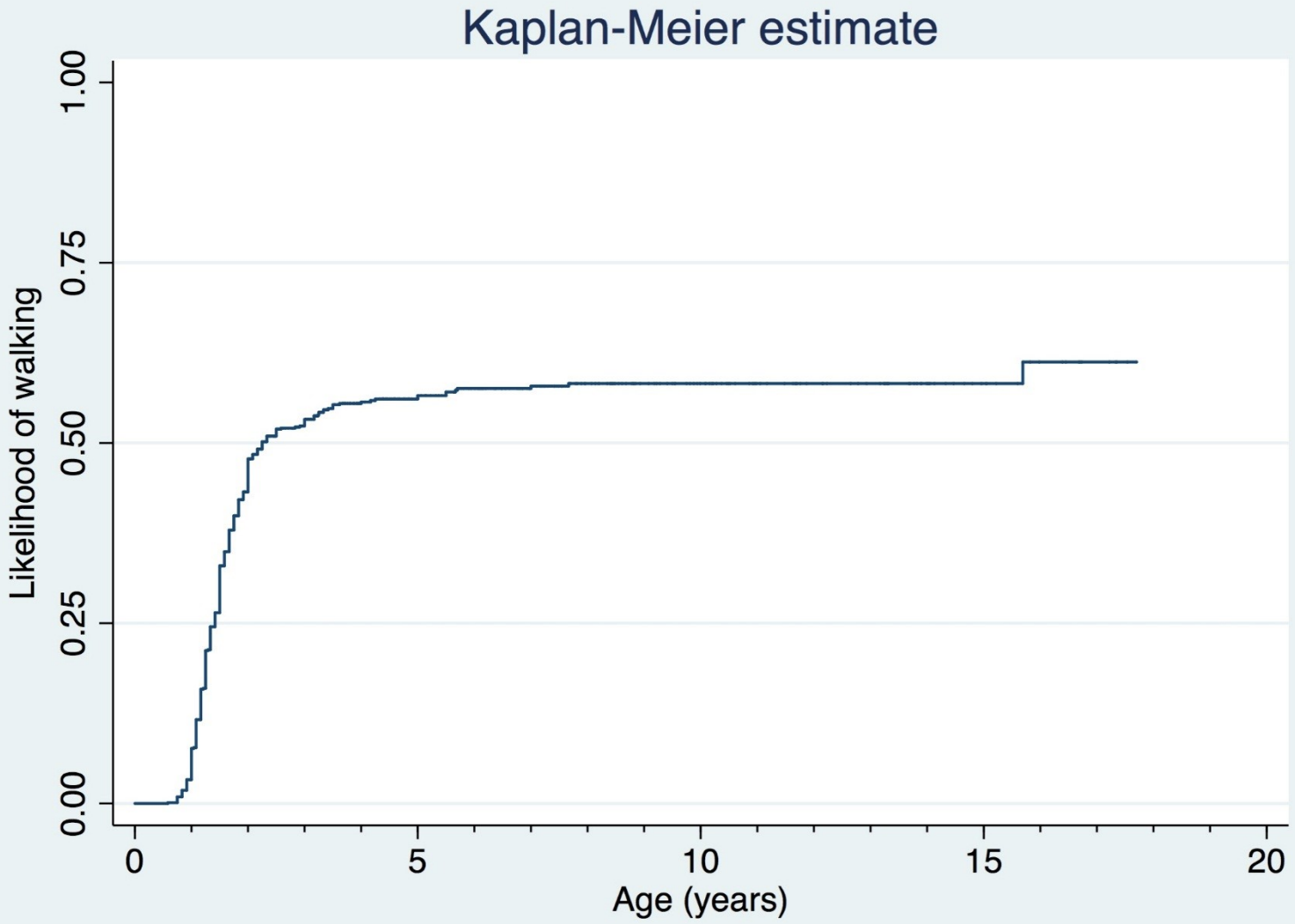
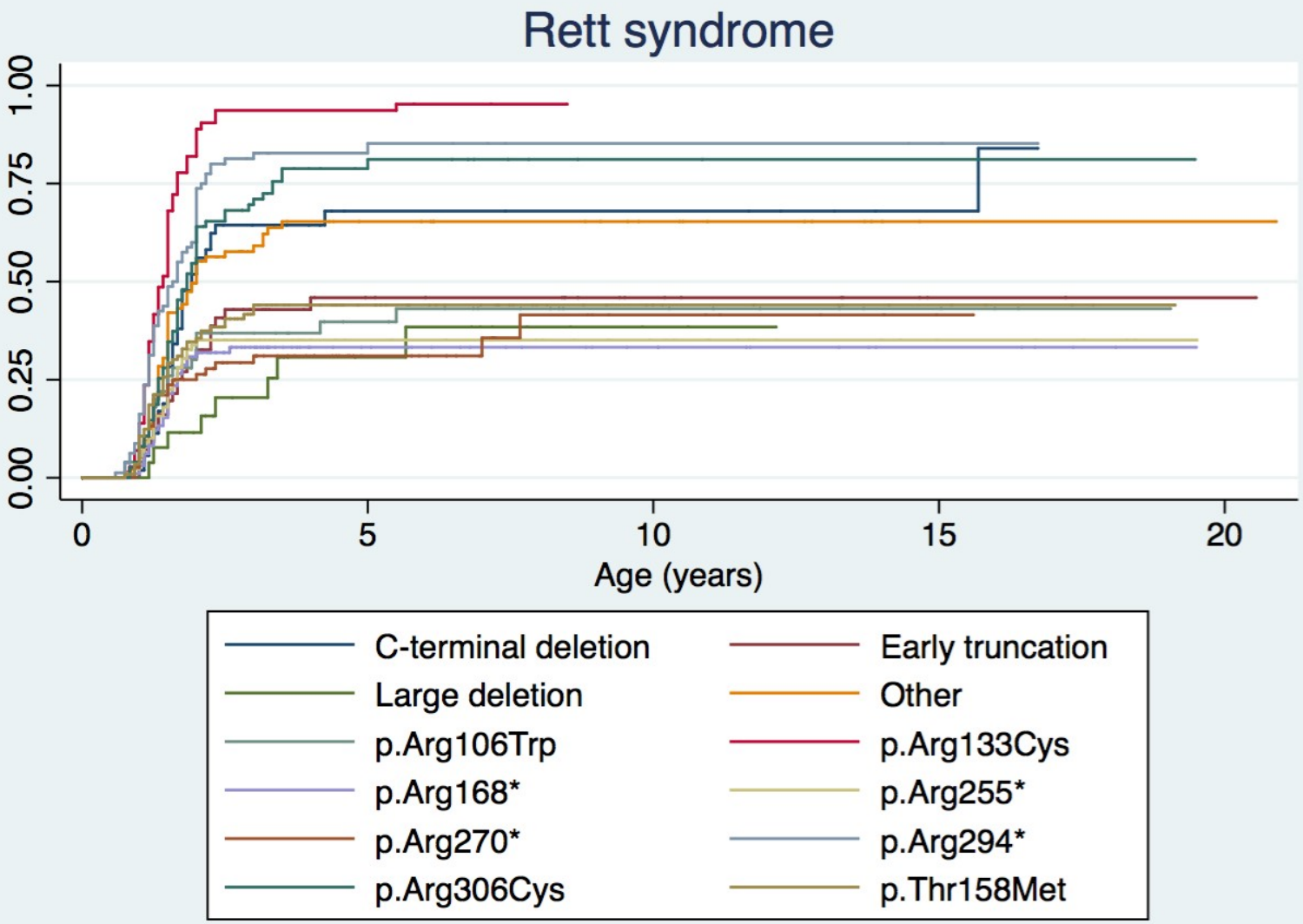
Acquisition of sitting (n=829)



Acquisition of walking (n=908)



Learning to walk by mutation group



What is the effect of environmental enrichment for young girls with Rett syndrome?

Rettsyndrome.org
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Modified randomised stepped wedge trial design

Baseline_ Group	Obs 1 - mid Jan	Obs 2 - mid Feb	Obs 3 - mid Mar	Obs 4 - mid April	Obs 5 - mid May	Obs 5 - mid June	Obs 6 - mid July	Obs 7 - mid Aug	Obs 8 - mid Sept	Obs 9 - mid Oct	Obs 10 - mid Nov	Obs 11 - mid Dec	Obs 12 - mid Jan
1	A1	A2			A3			A4			A5		KEY
1	A1	A2			A3			A4			A5		Blood sample
1	A1	A2			A3			A4			A5		Baseline period
1	A1	A2			A3			A4			A5		Treatment period
2	A1		A2			A3			A4			A5	
2	A1		A2			A3			A4			A5	
2	A1		A2			A3			A4			A6	
2	A1		A2			A3			A4			A5	
3	A1			A2			A3			A4			A5
3	A1			A2			A3			A4			A5
3	A1			A2			A3			A4			A5
3	A1			A2			A3			A4			A5

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Outcomes

- Gross motor skills
  - Rett Syndrome Gross Motor Scale
  - Blinded assessment of video footage
- Blood levels of BDNF
  - Samples taken mid-afternoon
  - RayBiotech ELISA kits
  - Tested in triplicate and mean values analysed
- Growth
  - Height, weight and BMI
- Sleep quality
  - Disorders of Initiating and Maintaining Sleep subscale of the Sleep Disturbance Scale for Children
- Mood
  - Mood subscale of the Rett Syndrome Behaviour Questionnaire

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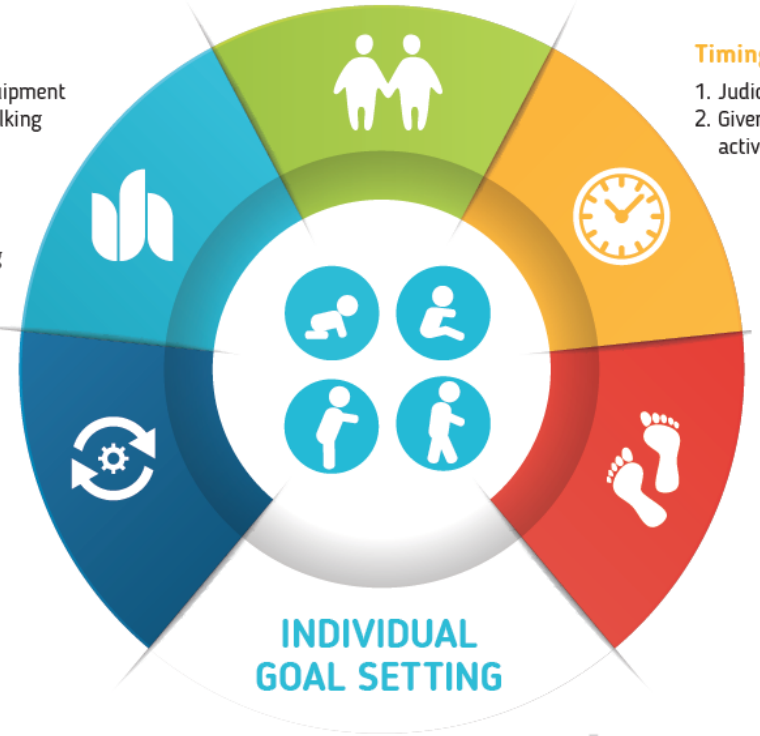
Intervention



Social stimulation

Engagement with

1. Other children
2. Other therapists
3. Parent involvement

Sensory stimulation

1. Visual – colourful room/equipment
2. Textural – standing and walking on different surfaces
3. Vestibular – activities with rhythm and balance shift
4. Taste using snacks of food
5. Welcome and goodbye song

Timing of activities

1. Judicious use of rest periods
2. Given time to start and complete activities to take account of dyspraxia

Cognitive engagement

1. Eye contact and establishing rapport
2. Choices of activities
3. Activities with purpose and ageappropriate
4. Praise for effort and achievements

Gross motor movements practice and exercise

1. Balance
2. Mobility
3. Transition

Characterised by

1. Repetition
2. Challenge
3. Building of endurance

INCREASE IN GROWTH-RELATED PROTEIN: BDNF

BEHAVIOUR CHANGE Functional improvement

Analysis

- Sample size calculation
  - Based on previous data, we estimated a sample size of 12 girls will give us 80% power to identify improvement in RSGMS scores of at least 4 points for each subject and using a 5% two-tailed test
- ICCs calculated to assess stability with different durations of baseline
- Linear mixed-effects regression model with random intercepts was used to investigate the effects of treatment on the outcome variables
  - Adjusted for child age, age of regression

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Baseline characteristics

MECP2 mutation	N (%)
C-terminal deletion	1 (8.3)
Early truncating	1 (8.3)
Large deletion	1 (8.3)
p.Arg168*	1 (8.3)
p.Arg255*	2 (16.7)
p.Arg270*	3 (25.0)
p.Arg294*	1 (8.3)
p.Thr158Met	2 (16.7)

	Mean (SD) Range
Age at recruitment (y)	3.0 (1.1) 1.5 to 5.2
Age at regression (y)	1.5 (0.4) 1 to 2.3
RSGMS score (/45)	22.4 (10.4) 0 to 33

		N (%)
Walking 10 steps	Independently	5 (41.7)
	Assisted	4 (33.3)
	Unable	3 (25.0)
Epilepsy (pretest)	Yes	2 (16.7)

Baseline stability

Baseline (months)	RSGMS		Blood BDNF (ng/ml)	
	Mean difference	ICC (95%CI)	Mean difference (ng/ml)	ICC (95%CI)
1	<1	0.977 (0.751, 0.998)	27.7	0.615 (-0.31, 0.968)
2	<1	0.987 (0.813, 0.999)	40.6	0.223 (-0.957, 0.969)
3	1	0.976 (0.772, 0.998)	9.9	0.309 (-1.042, 0.939)

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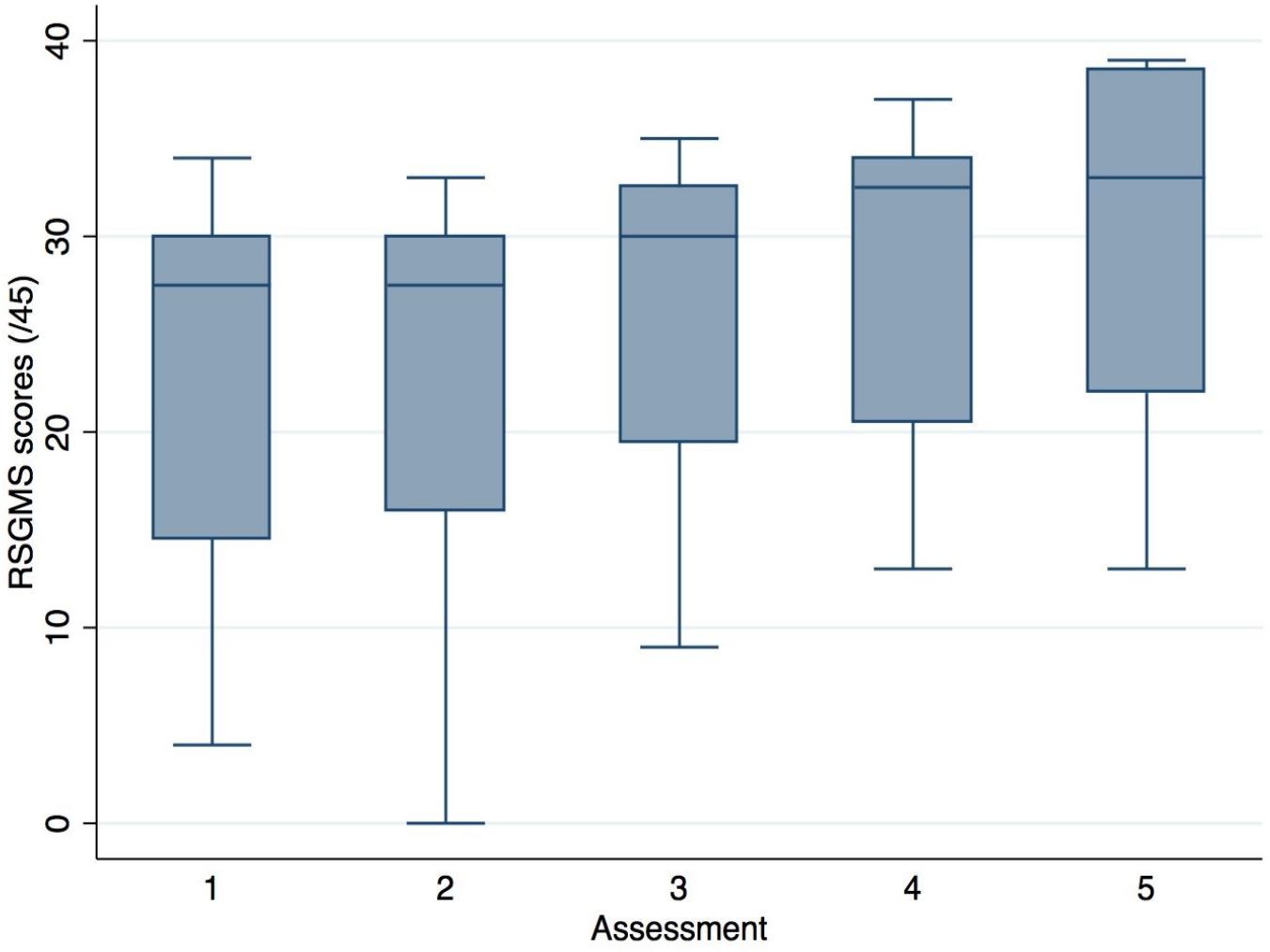
Gross motor scores



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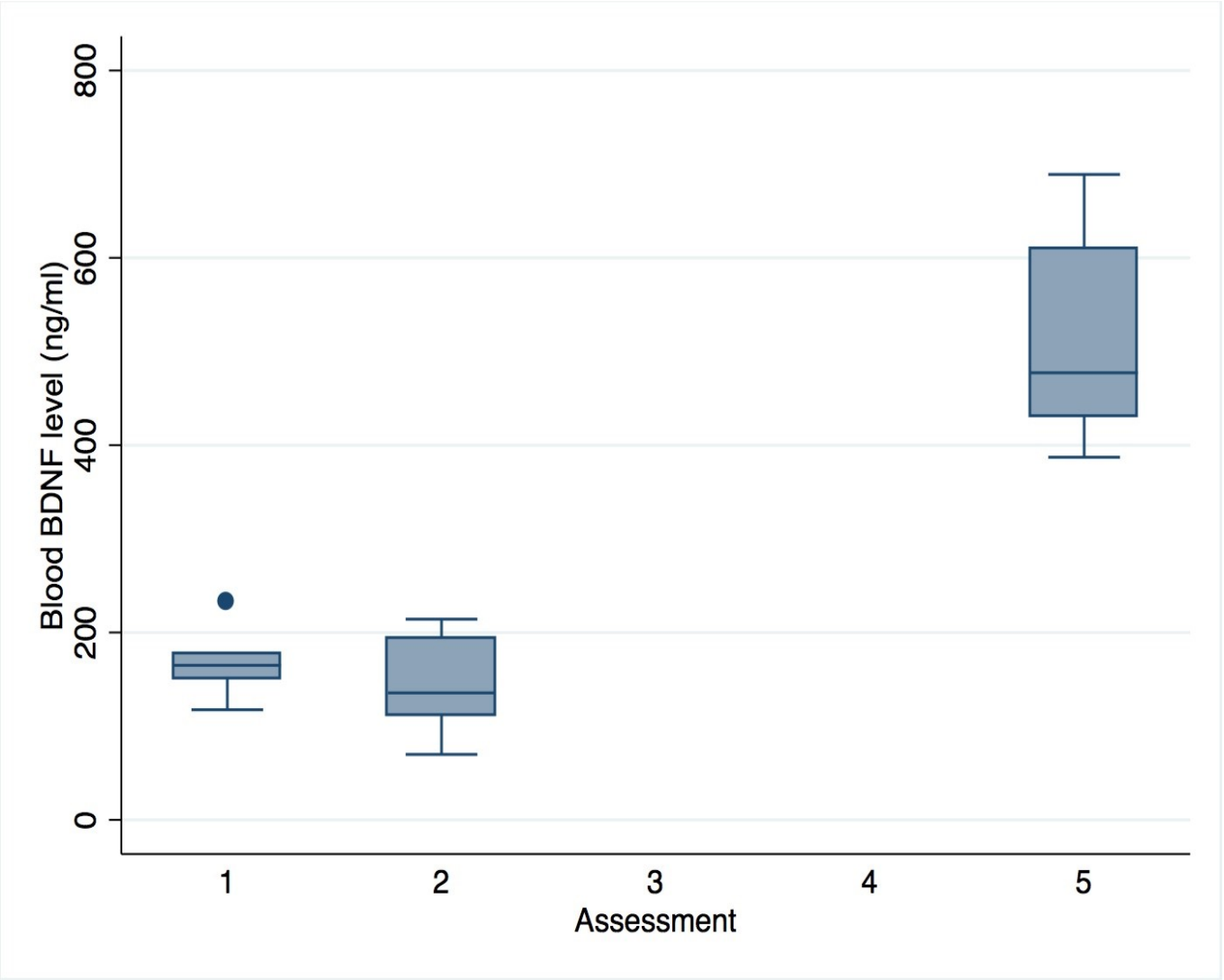
BDNF levels



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Discussion

- Improved motor skills, on average by 8 points
  - Change greater than within subject error
  - Improvement irrespective of baseline motor skills
- Increased BDNF more than twofold
  - Increased age associated with more BDNF production
  - Baseline levels a little lower than general population (1 study) - relatively high in other neurodevelopmental disorders
  - Improvements reflect those seen in animal models and other disorders

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Strengths and limitations

- Strategies to reduce bias
  - Individuals were randomised to duration of baseline
  - Within subject comparison
  - Met our sample size requirement
  - Blinded assessment of videos
  - Standardised time for blood draw
- Available sample and funding precluded a RCT

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Gross motor skills over the lifespan

Walking trajectories

- Up to six observation points per person used to examine walking trajectory
- AussieRett (n = 394)

Independent	131 (33%)
Assisted walking	50 (13%)
Decreased ability	55 (14%)
Unable to walk	127 (32%)

Downs 2016

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Rett Syndrome Gross Motor Scale

Sitting	Transfers	Standing	Locomotor	
Floor	Sit to stand	3 seconds	Walking 10 steps	Slope
Chair with back	Floor to stand	10 seconds	Turning 180	Stepping over obstacle
Stool	Bending down, returning to stand	20 seconds	Side-stepping	Running

Based on the GMFM

Downs 2008

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Mobility skills (n=255)

Factor loadings for individual scale items onto each of the three factors (n=255) *Downs 2016*

Item	N	'Sitting' (Factor 3)	'Standing and walking' (Factor 1)	'Challenge' (Factor 2)
Sitting on the floor	233	**0.694**	0.245	0.350
Sitting on a chair	250	**0.747**	0.493	0.077
Sitting on a stool	238	**0.844**	0.336	0.109
Sit to stand	240	0.305	**0.727**	0.157
Standing 3 s	252	0.361	**0.878**	0.183
Standing 10 s	249	0.356	**0.857**	0.452
Standing 20 s	241	0.326	**0.830**	0.197
Walks 10 steps	249	0.303	**0.891**	0.218
Side steps	234	0.272	**0.747**	0.405
Turns	242	0.279	**0.870**	0.293
Walking on a slope	220	0.213	**0.819**	0.353
Steps over an obstacle	226	0.185	**0.623**	0.515
Stands up from floor	228	0.285	0.359	**0.734**
Bends to touch the floor	233	0.123	0.194	**0.867**
Runs	243	0.069	0.195	**0.847**

Relationship between gross motor skills and mutation, adjusted for age (n=255)

Downs 2016

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Relationship between total score, standing and walking score and *age*, adjusted for mutation (n=255)

Downs 2016

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Collaboration with Denmark to evaluate reliability

N = 38
Median (IQR) age - 16.9 (6.8, 34.7) years
Assessments a median (IQR) of seven (7, 7) days apart

	ICC (95%CI)	Standard error of measurement (repeated measures ANOVA)	Minimal detectable difference
Total score (/45)	0.988 (0.978, 0.934)	1.5	**4**
Sitting subscale (/9)	0.920 (0.851, 0.957)	0.7	2
Standing/Walking subscale (/27)	0.983 (0.968, 0.991)	1.4	4
Challenge subscale (/9)	0.983 (0.969, 0.991)	0.3	1

Lead by Michelle Stahlhut, Denmark

(MDD =SEM x 1.96 x √2)

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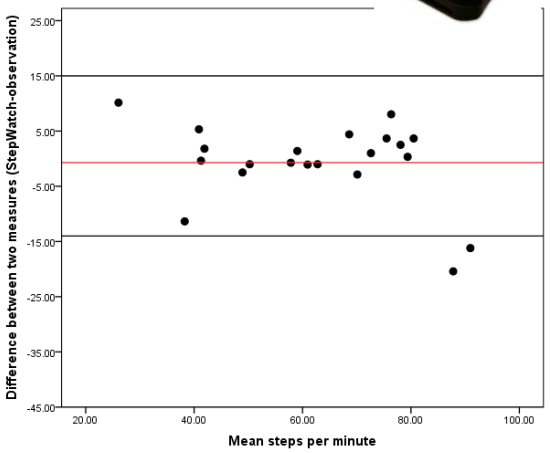
Change in gross motor skills over 3 to 4 years (n=70)

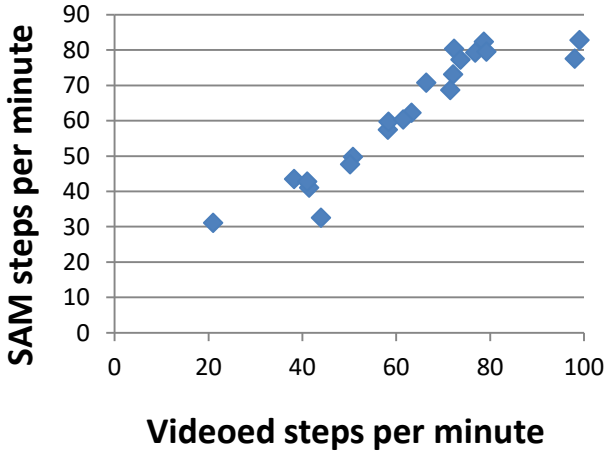
		% Increased	% Maintained	% Decreased
Sitting	Floor	2	74	27
	Chair	11	83	6
	Stool	8	69	23
Standing	3s	14	71	15
	10s	14	66	20
	20s	8	74	18
Transitions	Sit to stand	8	63	28
Walking	Walking 10 steps	2	86	12
	Side stepping	4	87	7
	Turning	6	83	11
	Obstacle	8	78	14
	Walking on a slope	6	83	11

Sedentary time and activity

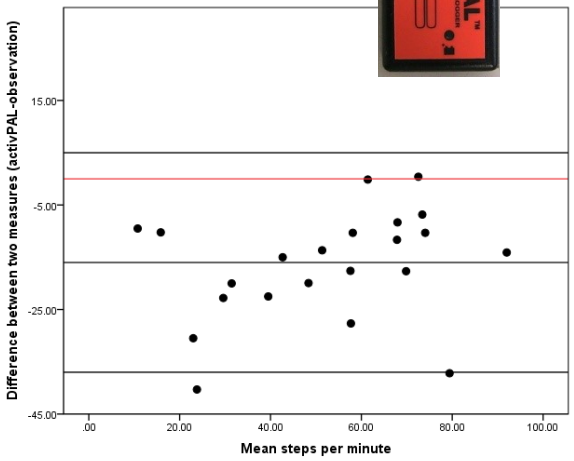
Bland Altman plots vs correlations

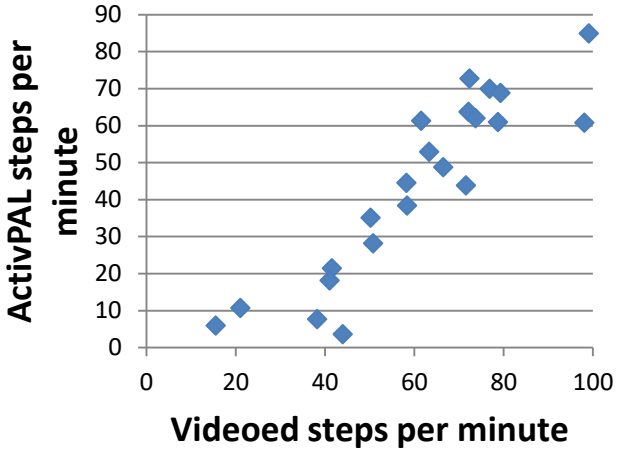
StepWatch



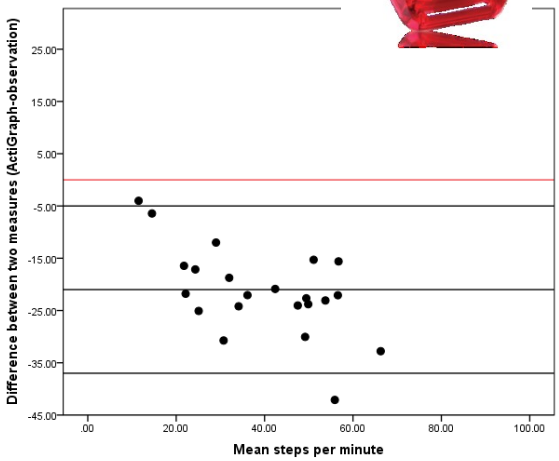


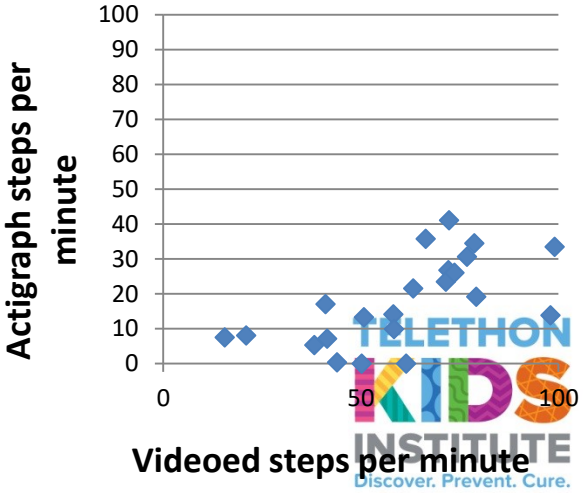
ActivPAL





Actigraph





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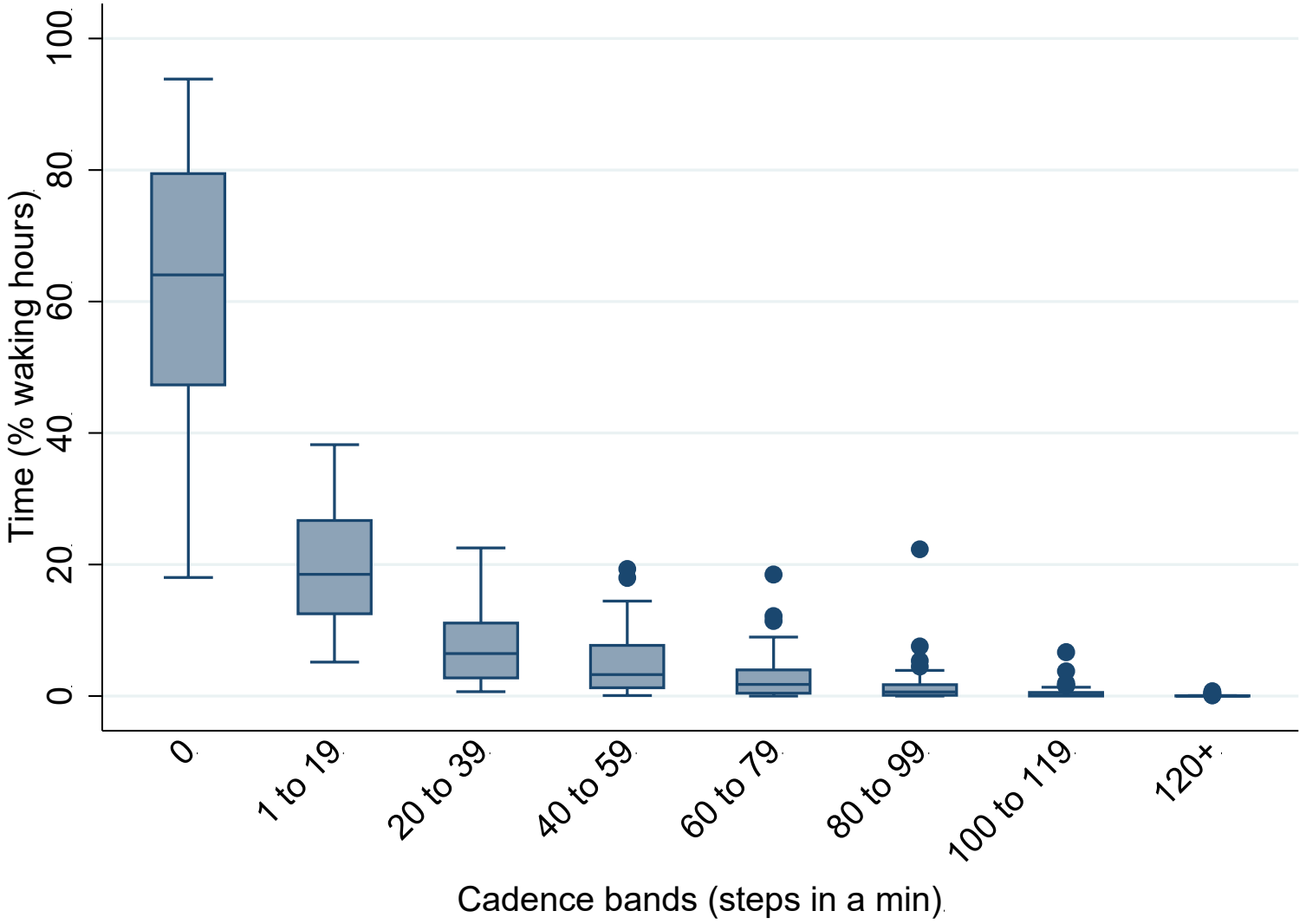
Whole day activity (n=64)



Step counts		Median (IQR)	Coefficient (95% CI)	P value
Age group	< 13	9,489 (5,850-12,840)	-	-
	13 to 18	8,017 (2001-10,594)	0.692 (0.413, 1.159)	0.158
	>= 19	3,250 (1,486-4,809)	0.408 (0.273, 0.610)	<0.001
Sedentary time		**Mean (SD)**	**Coefficient (95% CI)**	**P value**
	< 13	49.0 (13.9)	-	-
	13 to 18	64.3 (22.2)	13.3 (2.4, 24.2)	0.018
	>= 19	74.4 (12.6)	21.2 (12.6, 29.8)	<0.001

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Respiratory health and walking status (n=388)

Walking status	Relative risk ratio	95% CI	P value
Risk of hospital admissions for LRTI in previous 5 years, adjusting for age, perceived impact of hyperventilation, perceived impact of breath holding			
Learned to walk and currently independently walking	REF	-	-
Learned to walk and currently assisted walking	3.04	1.28, 7.20	0.01
Never learned to walk and currently assisted walking	3.66	1.65, 8.12	<0.01
Learned to walk but currently unable to walk	5.16	2.04, 13.01	<0.01
Never learned to walk and currently unable	6.73	3.42, 13.45	<0.01

Proposition 1 - Active ageing and wellness

Goals along the physical activity continuum

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2 - The joys of activity with others and in the natural environment

Future directions

- Early learning of new gross motor skills
  - How can new skills be maintained and will they be associated with better health trajectories?
  - How can we adapt the enriched environment model to different settings?
- Sedentary time and activity across the life span
  - How can we better measure and build balance?
  - How can we better structure daily routines to reduce sedentary time and enhance quality of life?
  - How can be best advocate to promote physical activity in Rett syndrome?

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Acknowledgements

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  - Denmark – Michelle Stahlhut

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