Alzheimer's disease in Down syndrome

LonDowns consortium & Horizon21 Consortium

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LonDownS

Dementia in older adults with Down syndrome

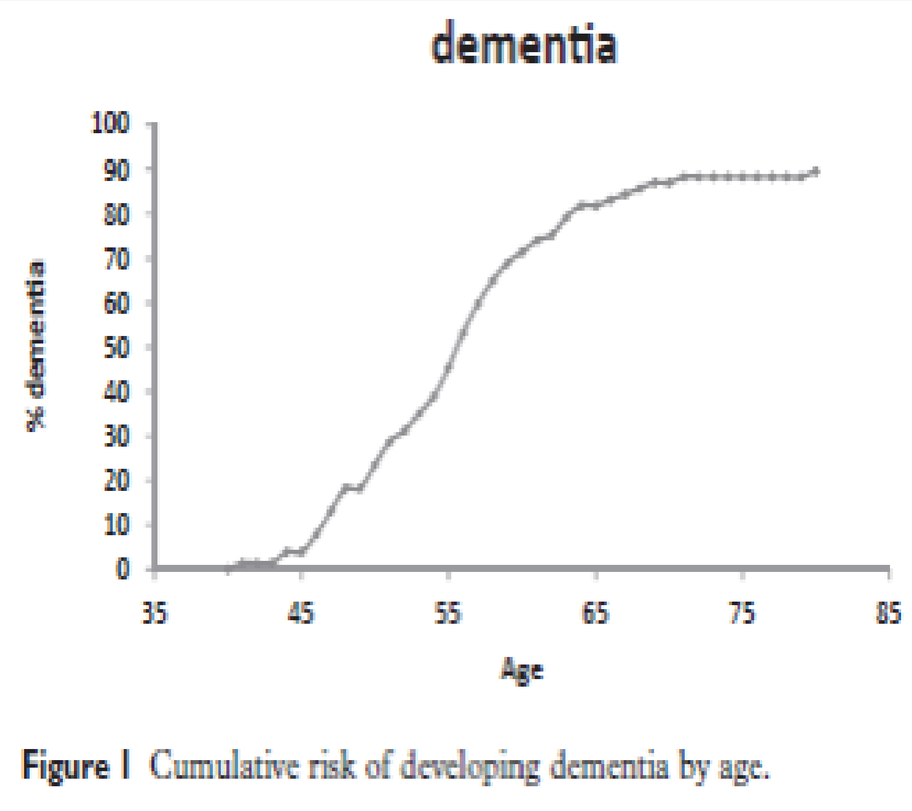
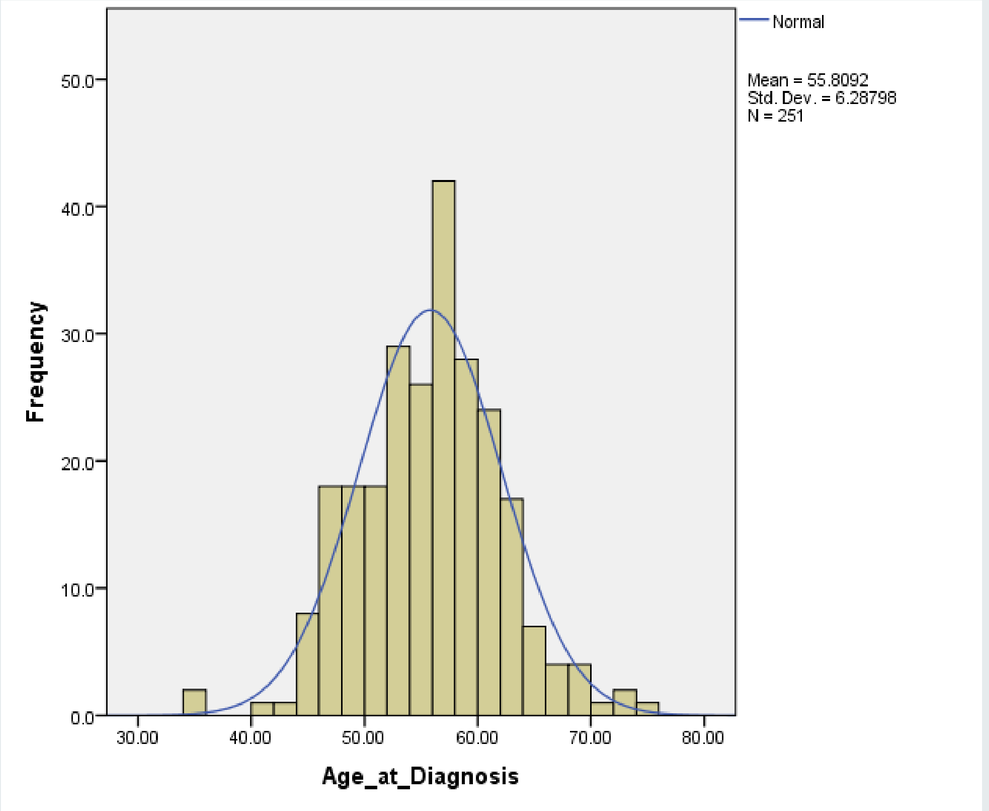


Figure 1 Cumulative risk of developing dementia by age.

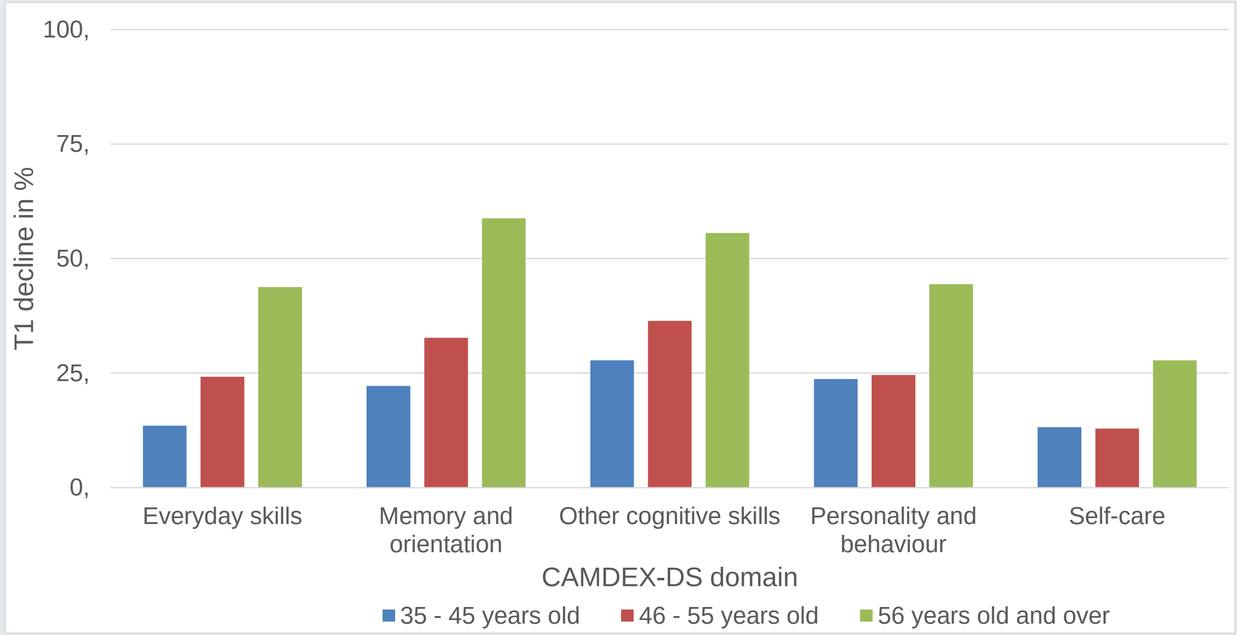


Dementia may affect more than 90% of older adults with Down syndrome
Develops 2-3 decades earlier compared to other people with Alzheimer's

McCarron, M., McCallion, P., Reilly, E., & Mulryan, N. (2014). A prospective 14-year longitudinal follow-up of dementia in persons with Down syndrome. Journal of Intellectual Disability Research, 58(1), 61-70.

Sinai, A., Mokrysz, C., Bernal, J., Bohnen, I., Bonell, S., Courtenay, K., ... & McBrien, J. Strydom, A. (2018). Predictors of age of diagnosis and survival of Alzheimer's disease in down syndrome. *Journal of Alzheimer's Disease*, (2017).

Development of dementia symptoms



- **Incidence of any new dementia symptoms in individuals aged 36 and older:**

- 25 per 100 person-years (95% CI = 16.18 – 36.90)

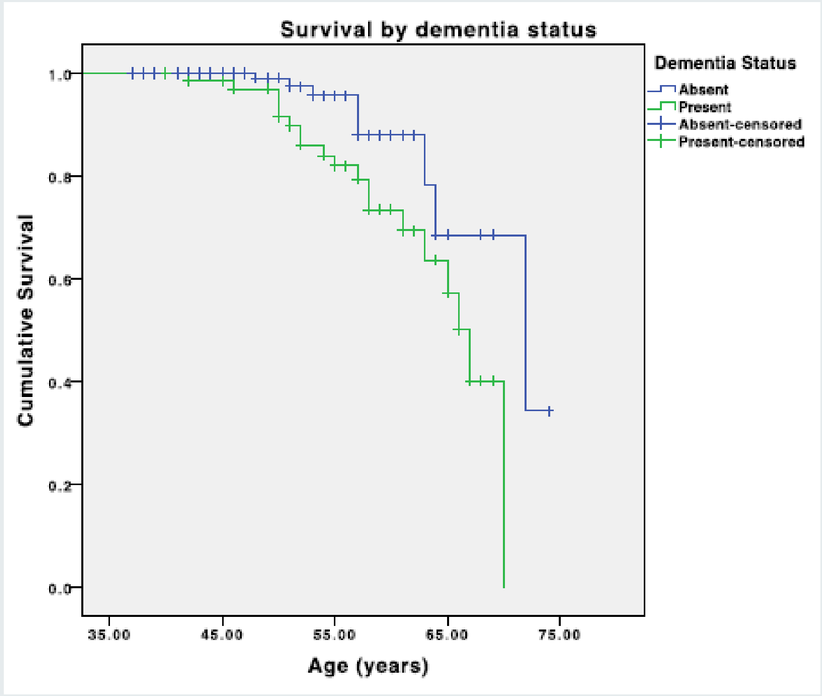
Mortality in older adults with Down syndrome

In our LonDowns study, older adults (age 36 and older; n = 211)

27 died during 2 years of follow up

- 70% had a clinical diagnosis of dementia before they died
- Most of the rest showed signs of dementia (seizures) before they died

Alzheimer's disease is now the main cause of death in adults with Down syndrome



Hithersay R, Startin CM, Hamburg S, et al. Association of Dementia With Mortality Among Adults With Down Syndrome Older Than 35 Years. JAMA Neurol. Published online November 19, 2018. doi:10.1001/jamaneurol.2018.3616

Age at diagnosis and survival

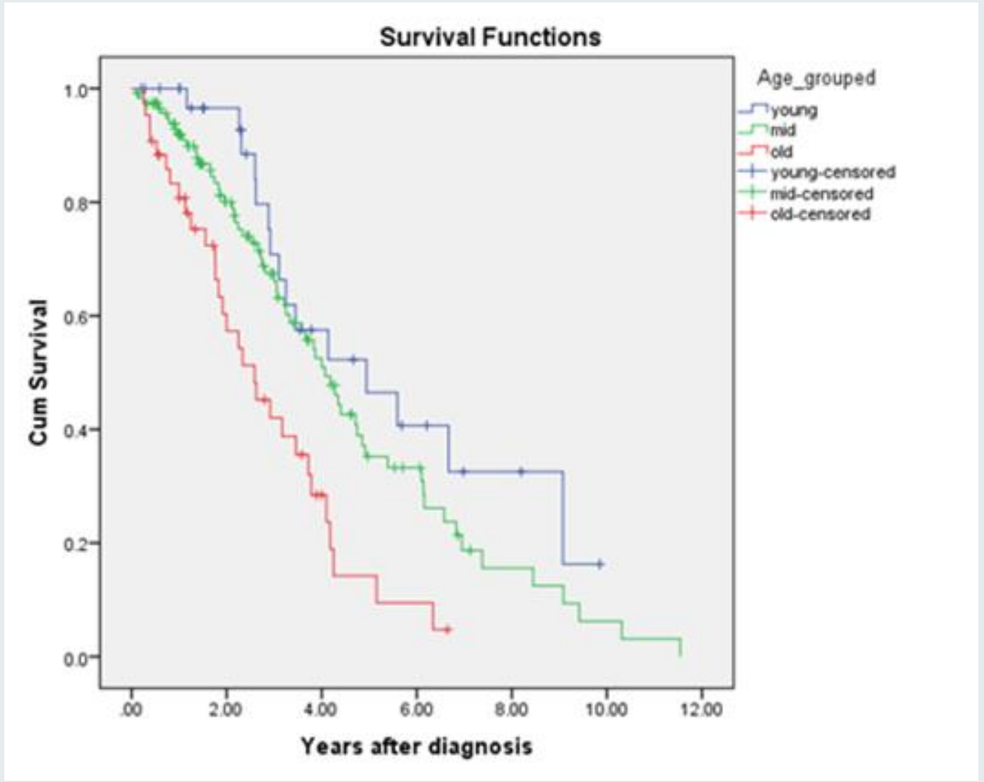
Mean survival after diagnosis of dementia

4.44 years (mean age at death of 59.98 years, SD 5.98, range 46.9 – 75.0 years)

If diagnosed before age 50 - median survival 4.94 years (95% CI 2.22 - 7.66)

Between 50-60 - median survival of 4.06 years (95% CI 3.36 – 4.75)

After 60 - median survival of 2.56 years (95% CI 1.56 – 3.58)

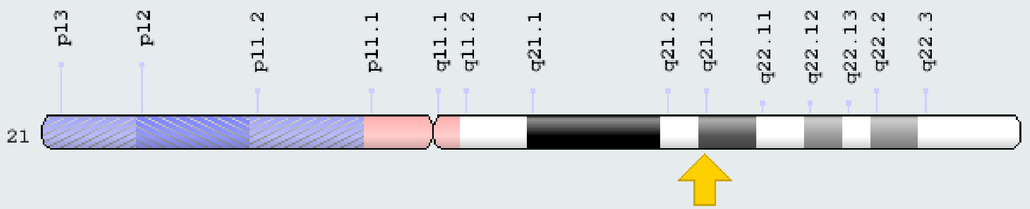


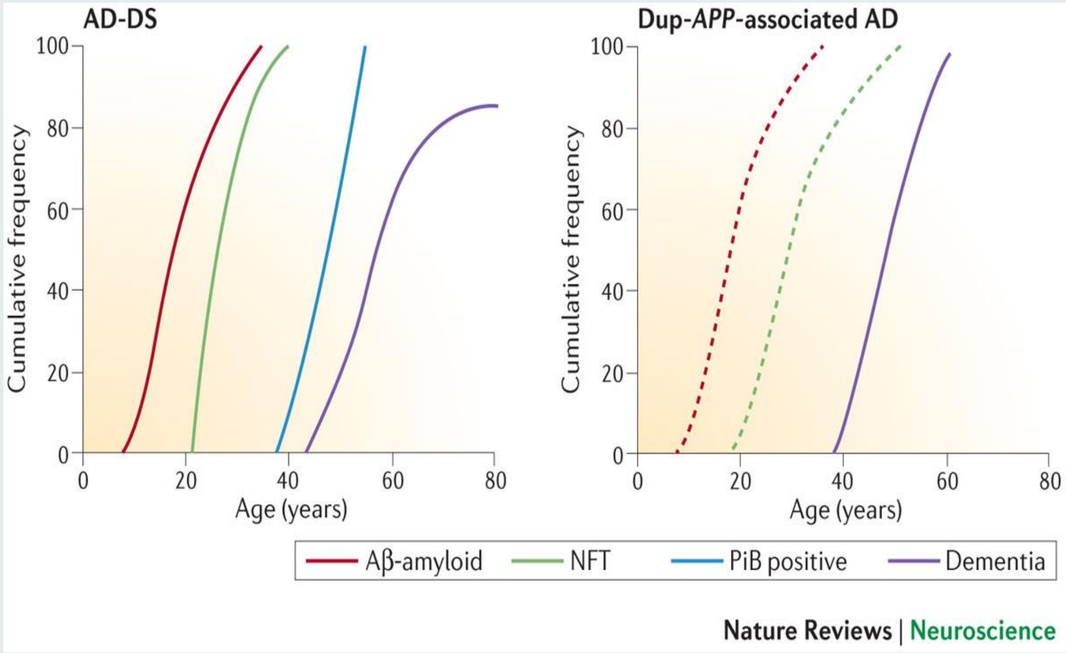
Sinai, A., Mokrysz, C., Bernal, J., Bohnen, I., Bonell, S., Courtenay, K., ... & McBrien, J. Strydom, A. (2018). Predictors of age of diagnosis and survival of Alzheimer's disease in Down syndrome. *Journal of Alzheimer's Disease*.

Alzheimer's in Down syndrome is a genetic condition

- DS is due to having 3 copies of chromosome 21, with 3 copies instead of two) of Chr21 genes
- Some of these genes are dosage-sensitive
- Amyloid precursor protein (APP) gene is on chr21; all DS individuals with full trisomy 21 have 3 x APP

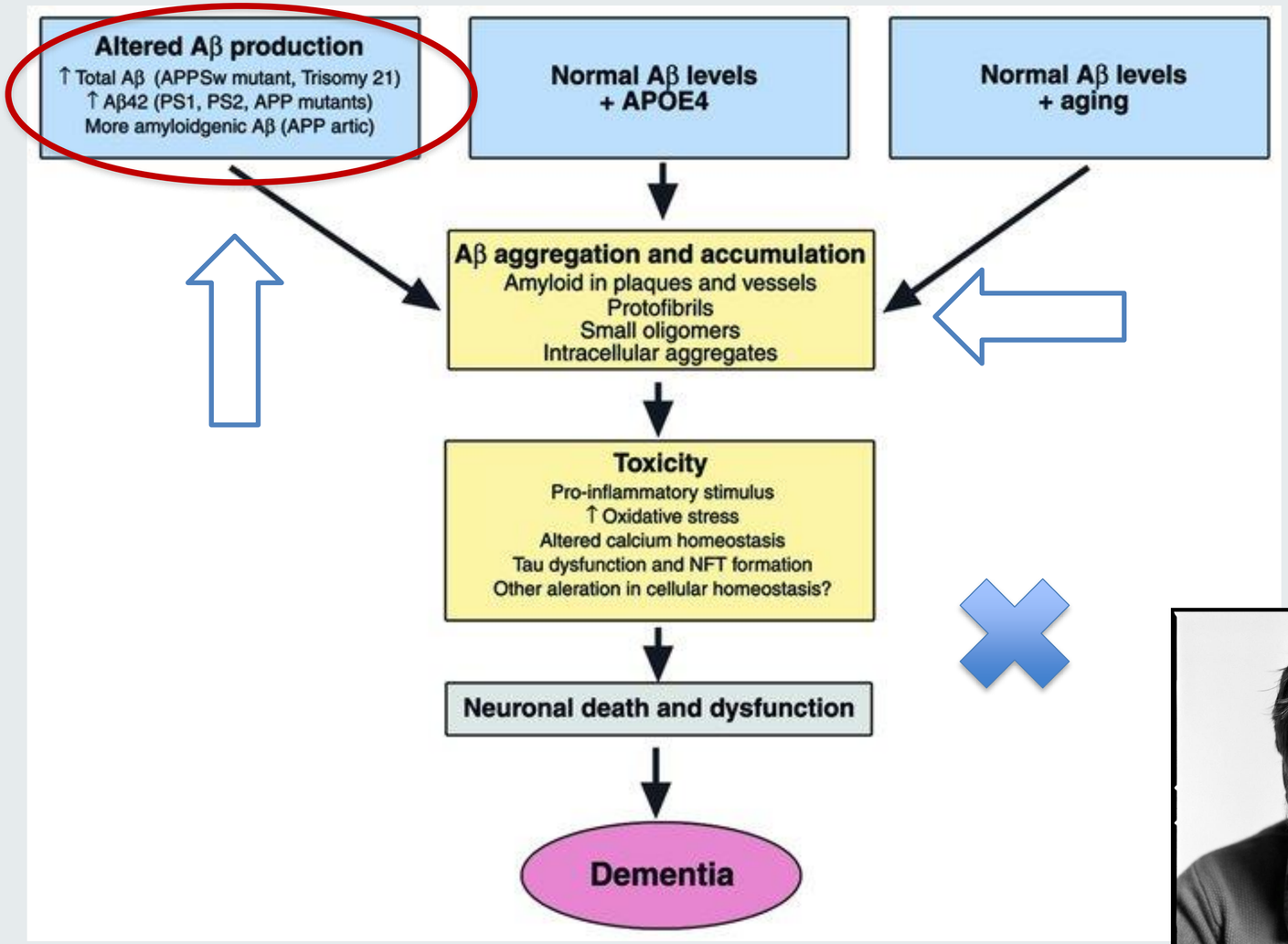
- Rare individuals with DS without an extra APP do not develop AD
- Rare individuals with Duplication APP (without DS) all present with AD





Wiseman, F. K., Al-Janabi, T., Hardy, J., Karmiloff-Smith, A., Nizetic, D., Tybulewicz, V. L., ... & Strydom, A. (2015). A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nature Reviews Neuroscience.

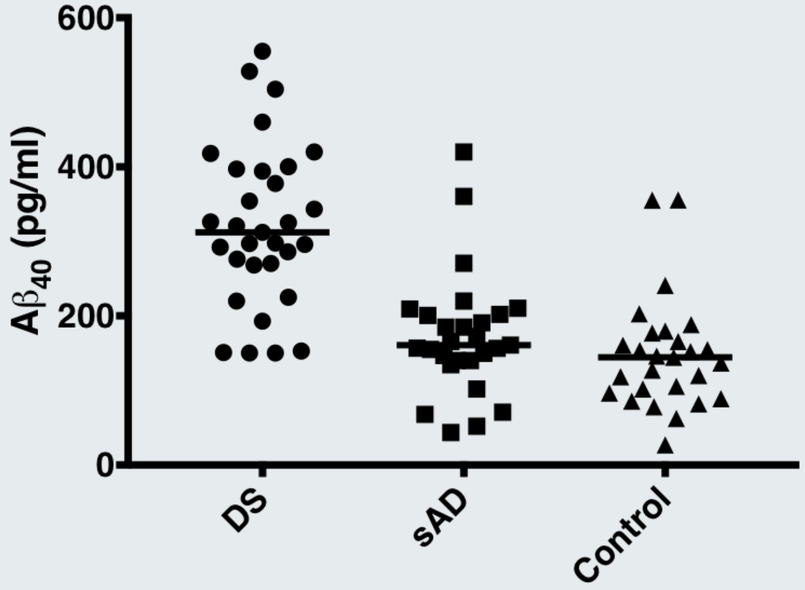
Amyloid cascade and preventing Alzheimer's

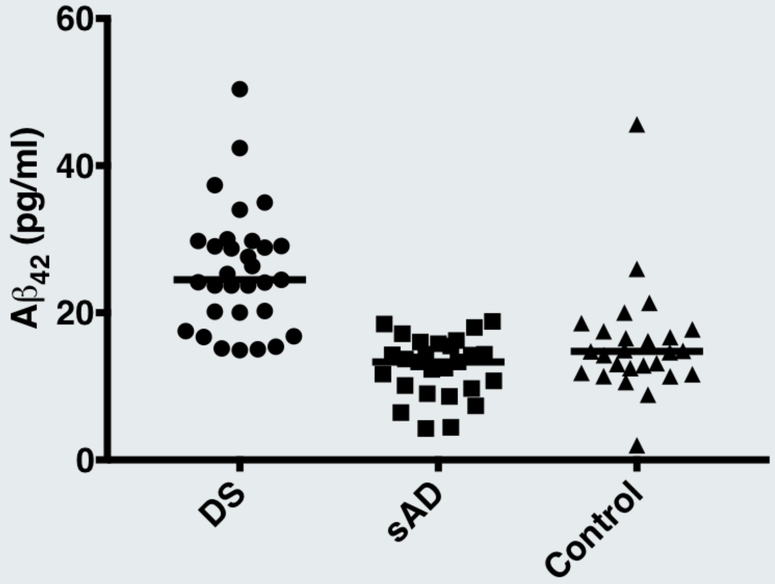


Amyloid β is increased in Down syndrome

SIMOA - single molecule immunoassays allows single molecules to be counted, with 1000-fold increase in sensitivity

Age matched DS, controls and AD cases





Startin *et al. Alzheimer's Research & Therapy* (2019) 11:26
https://doi.org/10.1186/s13195-019-0477-0

Alzheimer's Research & Therapy

RESEARCH Open Access

Plasma biomarkers for amyloid, tau, and cytokines in Down syndrome and sporadic Alzheimer's disease

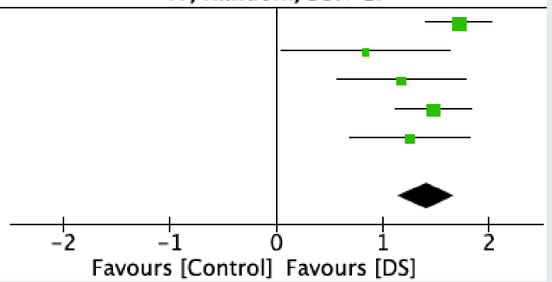
Carla M. Startin[1,2,3*], Nicholas J. Ashton[4,5,6,7], Sarah Hamburg[1,2,3], Rosalyn Hithersay[1,2,3], Frances K. Wiseman[3,8], Kin Y. Mok[3,9,10], John Hardy[3,9,11], Alberto Lleó[12], Simon Lovestone[13], Lucilla Parnetti[14], Henrik Zetterberg[6,8,15,16], Abdul Hye[4,5], LonDownS Consortium and André Strydom[1,2,3]

Amyloid biomarkers in blood vs. Controls (meta analysis)

- AB 42 – DS vs controls

	DS			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Fortea et al. 2018	14.22	3.12	194	9.41	1.51	67	31.9%	1.71 [1.40, 2.03]
Head et al. 2011	32.882883	18.57255	17	19.81982	6.7228881	11	9.3%	0.84 [0.04, 1.63]
Iulita et al. 2016	16.62	7.79037868	21	9.14	5.01098793	31	14.5%	1.17 [0.57, 1.78]
Schupf et al. 2001	22.4	6.1	97	14.2	4.5	64	28.4%	1.48 [1.12, 1.83]
Startin et al. 2019	25.79355	8.291008	31	15.72185	7.43029	27	15.8%	1.26 [0.69, 1.83]
Total (95% CI)			**360**			**200**	**100.0%**	**1.41 [1.15, 1.68]**

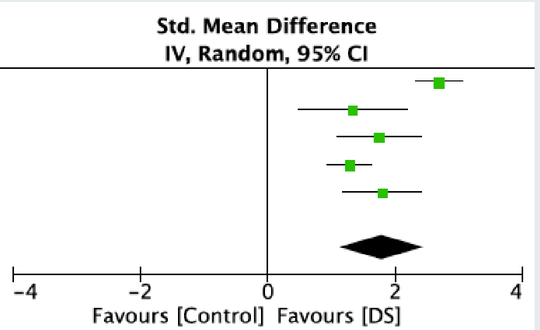
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.20$, df = 4 (P = 0.18); $I^2 = 36\%$
Test for overall effect: Z = 10.46 (P < 0.00001)



- AB 40 - DS vs. Controls

	DS			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Fortea et al. 2018	341.52	60.19	194	196.77	26.58	67	22.1%	2.69 [2.33, 3.05]
Head et al. 2011	327.705628	117.80302	17	196.969697	40.201513	11	16.9%	1.33 [0.48, 2.17]
Iulita et al. 2016	228.4	109.06530154	21	90.17	46.76922065	31	19.1%	1.75 [1.09, 2.40]
Schupf et al. 2001	132	44.4	97	84.7	19.6	64	22.2%	1.28 [0.94, 1.63]
Startin et al. 2019	321.29968	108.691489	31	148.38889	75.74618	27	19.6%	1.80 [1.18, 2.42]
Total (95% CI)			**360**			**200**	**100.0%**	**1.79 [1.14, 2.44]**

Heterogeneity: $Tau^2 = 0.46$; $Chi^2 = 32.42$, df = 4 (P < 0.00001); $I^2 = 88\%$
Test for overall effect: Z = 5.40 (P < 0.00001)

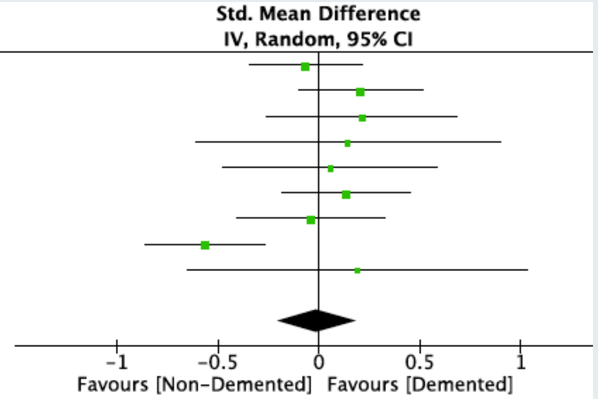


Amyloid biomarkers (blood) in DS-dementia vs. No dementia

- AB 42

Study or Subgroup	Demented DS Mean	SD	Total	Non demented DS Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Coppus et al. 2012	50	17.5	62	51	14.8	264	15.6%	−0.07 [−0.34, 0.21]
Fortea et al. 2018	14.79	3.42	49	14.12	3.18	233	14.5%	0.21 [−0.10, 0.52]
Head et al. 2011	23.783784	17.2157	52	20.585586	8.26868	26	9.8%	0.21 [−0.26, 0.68]
Iulita et al. 2016	17.75	7.27323862	10	16.62	7.79037868	21	5.2%	0.14 [−0.61, 0.90]
Jones et al. 2009	27.85	16.63474977	21	27.07	11.42834634	39	8.5%	0.06 [−0.47, 0.59]
Mastouka et al. 2009	1,887.39	2,972.97	52	1,527.027	2,599.0991	148	14.3%	0.13 [−0.18, 0.45]
Prasher et al. 2010	33.2	15.9	44	33.8	15	83	12.7%	−0.04 [−0.40, 0.33]
Schupf et al. 2010	25.8	21.77062241	61	33.4	8.59127464	164	14.9%	−0.56 [−0.86, −0.26]
Startin et al. 2019	27.06857	8.193582	7	25.42167	8.456324	24	4.4%	0.19 [−0.65, 1.03]
Total (95% CI)			**358**			**1002**	**100.0%**	**−0.01 [−0.20, 0.19]**

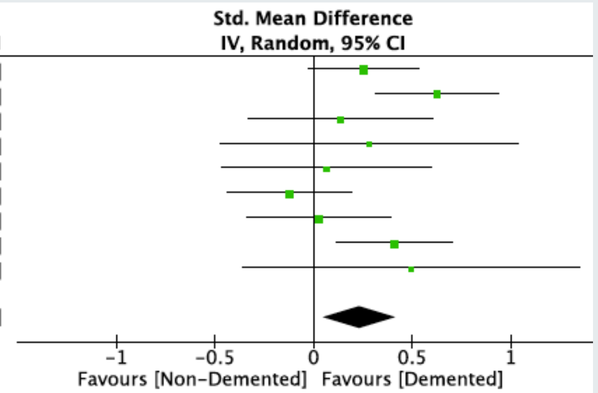
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 17.15$, df = 8 (P = 0.03); $I^2 = 53\%$
Test for overall effect: Z = 0.08 (P = 0.94)



- AB 40

Study or Subgroup	Demented DS Mean	SD	Total	Non-Demented DS Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Coppus et al. 2012	352.3	103.5	62	326.4	101.3	264	16.4%	0.25 [−0.02, 0.53]
Fortea et al. 2018	384.39	79.87	49	343.83	60.95	233	14.8%	0.63 [0.31, 0.94]
Head et al. 2011	289.61039	98.9575545	52	275.757576	104.62923	26	9.4%	0.14 [−0.34, 0.61]
Iulita et al. 2016	258.5	93.28719098	10	228.4	109.06530154	21	4.7%	0.28 [−0.48, 1.04]
Jones et al. 2009	125.6	84.13608976	21	121.32	50.70938747	39	8.0%	0.07 [−0.46, 0.60]
Mastouka et al. 2009	1,047.619	1,389.61039	52	1,246.7532	1,662.33766	148	14.7%	−0.12 [−0.44, 0.19]
Prasher et al. 2010	179.6	59.7	44	177.8	67.8	83	12.7%	0.03 [−0.34, 0.39]
Schupf et al. 2010	172.1	52.32867283	61	150.1	53.78624359	164	15.5%	0.41 [0.11, 0.71]
Startin et al. 2019	363.71429	116.143811	7	308.92875	105.750514	24	3.8%	0.49 [−0.36, 1.35]
Total (95% CI)			**358**			**1002**	**100.0%**	**0.23 [0.05, 0.41]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.50$, df = 8 (P = 0.07); $I^2 = 45\%$
Test for overall effect: Z = 2.54 (P = 0.01)



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REVIEW ARTICLE

WILEY

Plasma amyloid and tau as dementia biomarkers in Down syndrome: Systematic review and meta-analyses

Falah Alhajraf [1,2] | Deborah Ness [3,4] | Abdul Hye [5] | Andre Strydom [3,4]

THE LonDownS CONSORTIUM

Alzheimer's disease in Down syndrome:

- Predictive phenotypes & markers
- Causative genes & mechanisms

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Londowns Participants and clinical collaborators

Participants

- From across England / Wales
- 124 adults aged 16-35
- 190 adults aged 36+, with follow up assessments after 2 years for 133 adults

Clinicians

- Dr Mark Scheepers
- Dr T. Hussain
- Dr Vesna Jordanova
- Dr Angela Hassiotis
- Dr Saif Sharif
- Dr Sujeet Jaydeokar
- Dr Ken Courtenay
- Professor Vee Prasher
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- Dr Salim Razak
- Dr Richard Hillier
- Dr Peter Speight
- Dr Talib Abbas
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- Dr E Anand
- Dr Kelly Rayner

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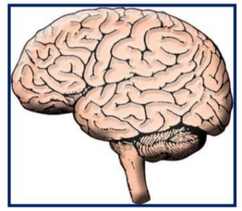
NHS
NIHR

What is our work about?

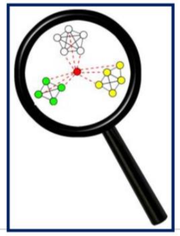
We are finding out about people with Down syndrome

.



- We want to find out how different parts of the brain work in people with Down syndrome

- We want to find out about differences between people with Down syndrome



- We want to find out if there are genetic or other reasons for this. Genes are like a recipe. They make us who we are.

Do you have to take part?

You can tell us **Yes** if you want to take part

You can tell us **No** if you do not want to take part

If you say no it will **not** change the care you get

If you decide to take part, we will ask you to sign a **consent form**

LonDowns Cohort

		Younger children (0-5·5 years)	Older children (5·5-15 years)	Younger adults (16-35 years)	Older adults (36+ years)
Number		115	35	170	282
Age		2·18 ± 1·13 (3·6 months to 5 years 1·3 months)	10·63 ± 3·05 (5 years 6·5 months to 14 years 8·5 months)	25·25 ± 5·46 (16-35 years)	50·21 ± 7·76 (36-73 years)
Sex	Male	62 (53·9%)	16 (45·7%)	83 (48·8%)	153 (54·3%)
	Female	53 (46·1%)	19 (54·3%)	87 (51·2%)	129 (45·7%)
Ethnicity	White	93 (81·6%)	25 (86·2%)	145 (85·3%)	261 (92·6%)
	Black	5 (4·4%)	0 (0·0%)	7 (4·1%)	11 (3·9%)
	Asian	6 (5·3%)	0 (0·0%)	8 (4·7%)	6 (2·1%)
	Mixed	7 (6·1%)	4 (13·8%)	8 (4·7%)	2 (0·7%)
	Other	3 (2·6%)	0 (0·0%)	2 (1·2%)	2 (0·7%)

All participants:
In-depth cognitive phenotyping
Detailed medical history
DNA samples
Cell samples
EEG/ ERP

Adults:
Plasma biomarker samples
fNIRS, longitudinal EEG

Older adults (>36):
Longitudinal cognitive/ clinical/ fluid biomarker data after 2 & 4 years

LonDownsPREVENT:

- Run-in trial cohort aged 30 – 55 (n = 120), with younger contrast group
- CSF at baseline
- Annual cognitive assessments
- Plasma
- MRI (Structural, SWI, DTI, ASL, fMRI)

Can we measure early changes due to Alzheimer’s in people with Down syndrome?

Cognitive profile in Down syndrome

Visuospatial learning is better than visual object learning due to relatively preserved maturation of the dorsal compared to ventral components of the visual system

Non-verbal abilities better than verbal abilities ; receptive language is better than expressive language

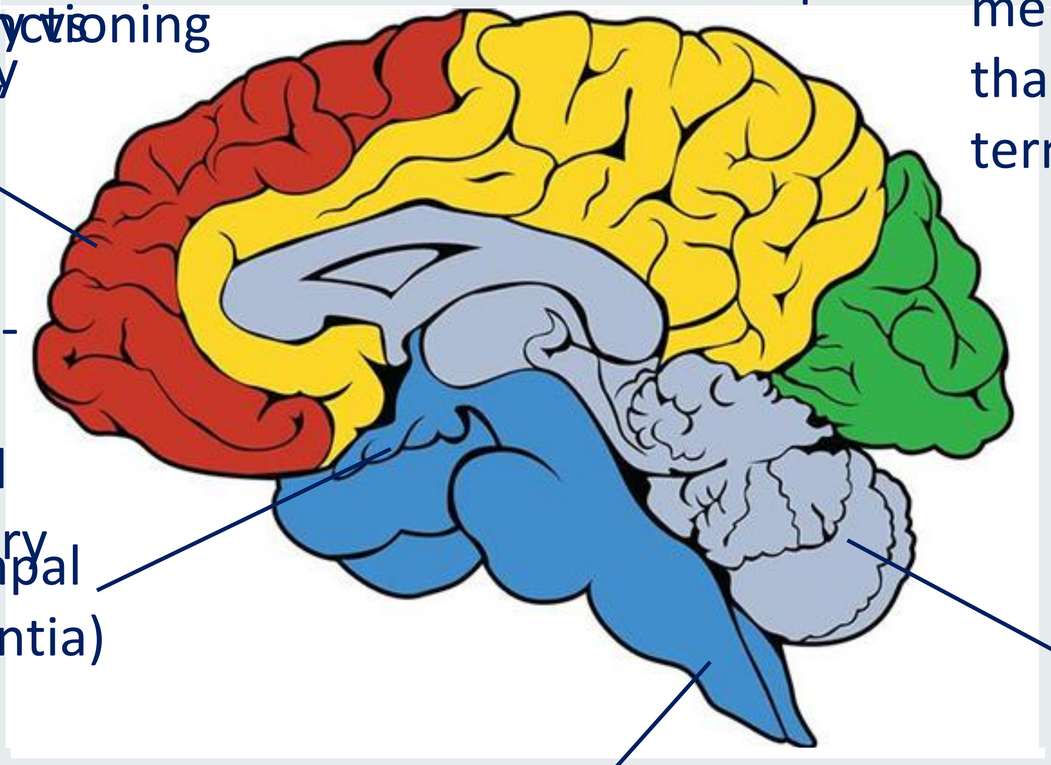
Relative weakness in short-term memory vs long-term memory

Relative weakness in executive functioning

Relative weakness in auditory short-term memory

Hypofrontality

Implicit long-term memory is better than explicit long-term memory



Visuospatial short-term memory is better than verbal short-term memory

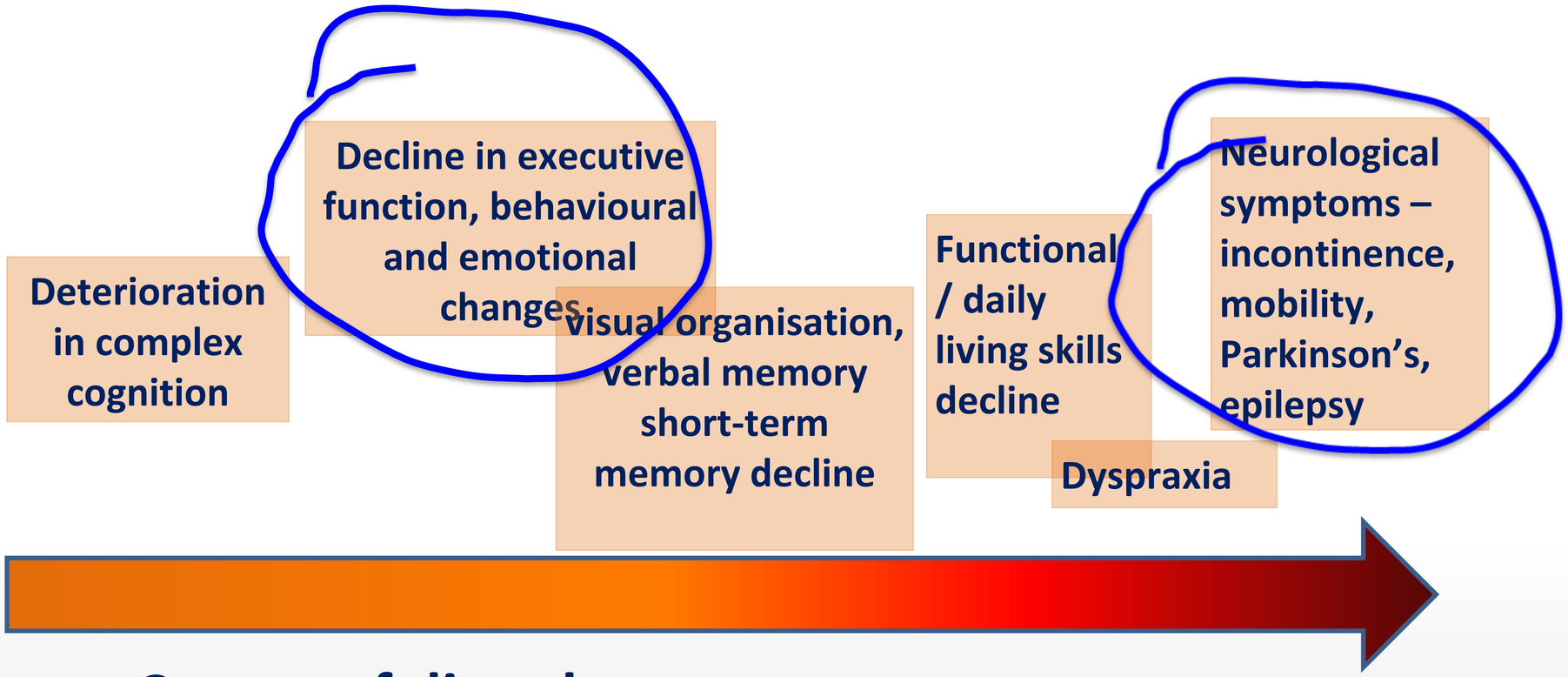
Reduced hippocampal volume (pre-dementia)

Cerebellar hypoplasia

Relative sparing of trunk and posterior cortical structures

Previous research

Course of dementia in Down syndrome



Crayton *et al.* 1998
Devenny *et al.* 2000, 2002
Krinsky-McHale *et al.* 2002
Visser et al, 1997
Ball et al, 2008

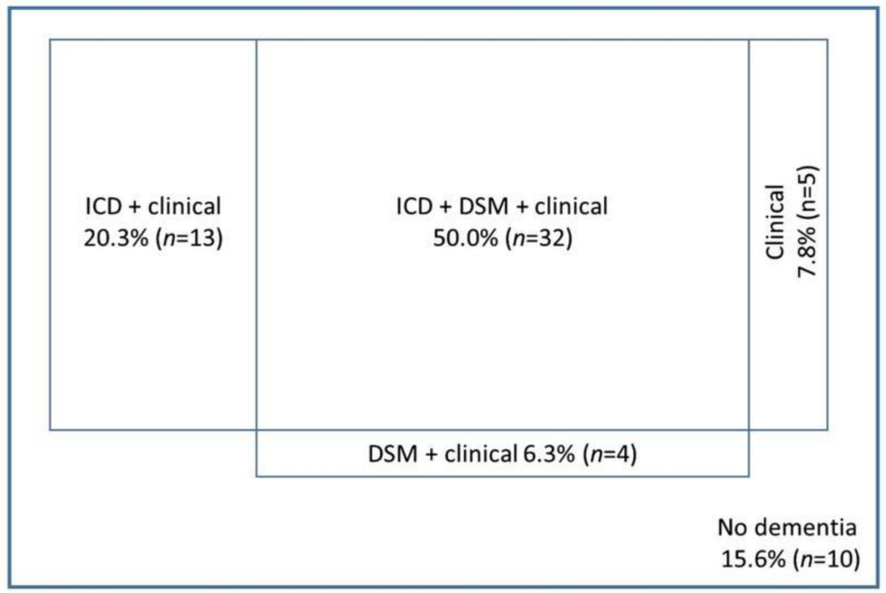
Dementia diagnosis and cognitive outcome measures in adults with Down syndrome

Dementia diagnosis

More difficult in people with learning disabilities

But reliable

- Change from an individual baseline
- Exclude other causes of decline



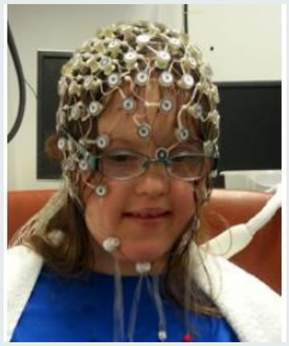
Int J Geriatr Psychiatry. 2015 August ; 30(8): 857–863. doi:10.1002/gps.4228.

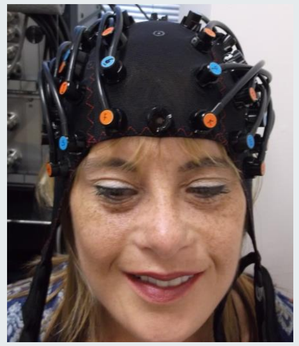
Dementia diagnostic criteria in Down syndrome

Rory Sheehan[1,6], Amanda Sinai[1], Nick Bass[1], Pippa Blatchford[2], Ingrid Bohnen[3], Simon Bonell[4], Ken Courtenay[1,5], Angela Hassiotis[1,6], Therese Markar[7], Jane McCarthy[8], Kamalika Mukherji[7], Asim Naeem[9], Dimitrios Paschos[10], Natalia Perez-Achiaga[2], Vijaya Sharma[11], David Thomas[12], Zuzana Walker[1], and Andre Strydom[1,10,13]

LonDownS research assessment battery

Cognitive assessment: general abilities, memory, executive function, attention, motor coordination
Informant questionnaires: demographics, medical history, dementia symptoms, everyday adaptive abilities, memory, executive function
Physical examination
Biological samples: saliva (genetic analysis), hair (cellular development via induced pluripotent stem cells), blood (blood biomarkers), CSF
EEG assessment: resting state EEG, ERP memory paradigms
fNIRS assessment: executive functioning paradigms





LonDowns cognitive test battery

Cognitive test issues:

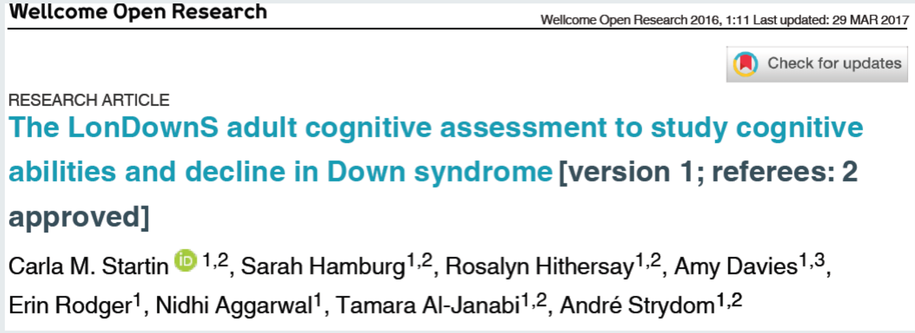
- Cannot use usual tests and threshold
- Baseline variable
- Floor effects

Measure earliest changes

- Range of cognitive abilities

Suitable for most people with Down syndrome

- Use both individual tests and carer-ratings
- Adapt scoring
- and difficulty levels where necessary



Wellcome Open Research

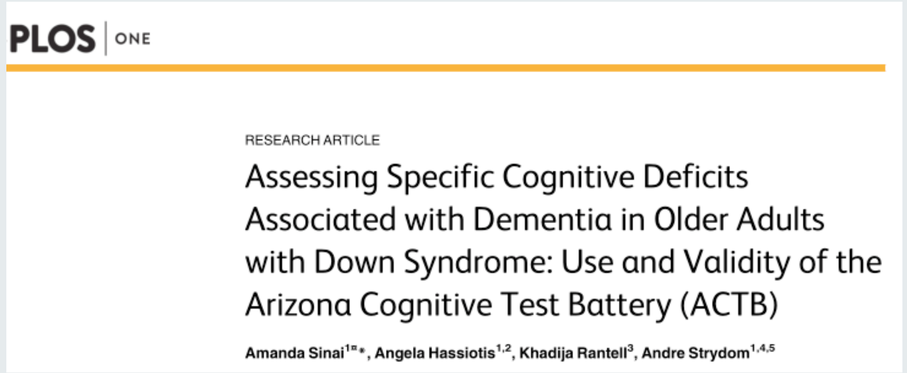
Wellcome Open Research 2016, 1:11 Last updated: 29 MAR 2017

Check for updates

RESEARCH ARTICLE

The LonDownS adult cognitive assessment to study cognitive abilities and decline in Down syndrome [version 1; referees: 2 approved]

Carla M. Startin [1,2], Sarah Hamburg[1,2], Rosalyn Hithersay[1,2], Amy Davies[1,3], Erin Rodger[1], Nidhi Aggarwal[1], Tamara Al-Janabi[1,2], André Strydom[1,2]



PLOS ONE

RESEARCH ARTICLE

Assessing Specific Cognitive Deficits Associated with Dementia in Older Adults with Down Syndrome: Use and Validity of the Arizona Cognitive Test Battery (ACTB)

Amanda Sinai[1¤*], Angela Hassiotis[1,2], Khadija Rantell[3], Andre Strydom[1,4,5]

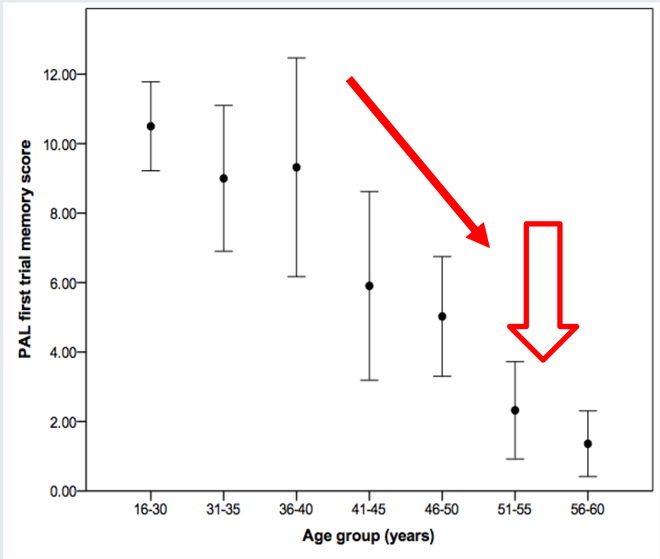
Cognitive decline in DS

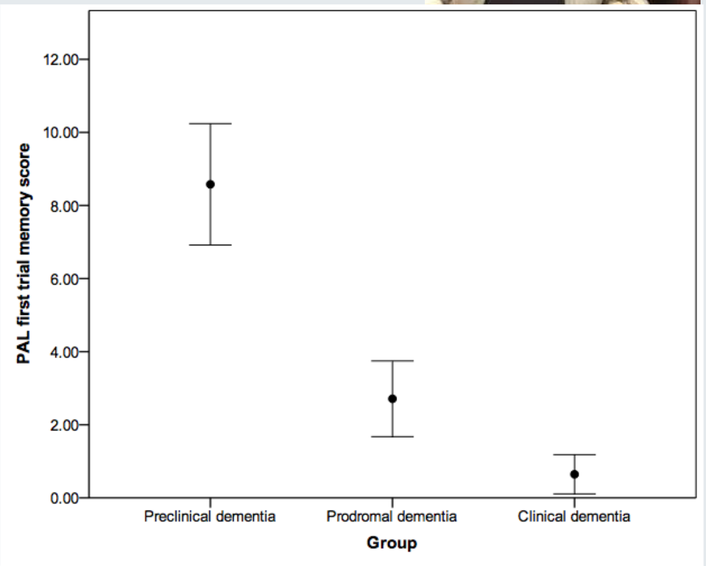
Earliest changes seen for memory and attention measures, with poorer performance starting from early 40s

p<0.05 p<0.01 p<0.001

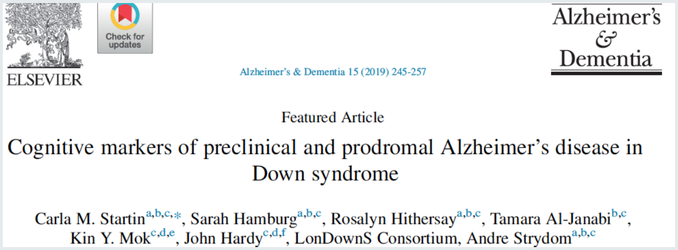
		41-45 years	46-50 years	51-55 years	56-60 years
IQ	KBIT-2 verbal raw score				
	KBIT-2 non-verbal raw score				
Memory	PAL first trial memory score				
	PAL stages completed				
	Orientation				
	Object memory immediate trials				
	Object memory delayed trial				
	DLD cognitive score				
	OMQ total score				
Executive function	IED stage 1 errors				
	IED stages completed				
	Verbal fluency				
	Tower of London				
	BRIEF-A total score				
	BRIEF-A behavioural regulation index				
	BRIEF-A metacognition index				
Attention	SRT total correct				
	SRT mean latency				
	SRT latency standard deviation				
Motor	Finger-nose pointing				
	NEPSY-II train and car				
	NEPSY-II car and motorbike				
Adaptive	Short ABS total score				
	Short ABS personal self-sufficiency				
	Short ABS community self-sufficiency				
	Short ABS personal-social responsibility				
	DLD social score				

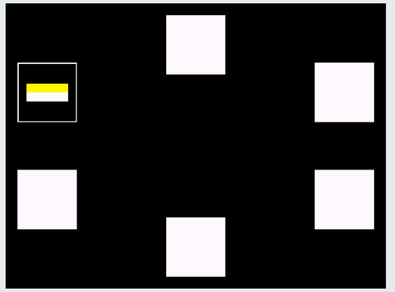
Memory changes with aging





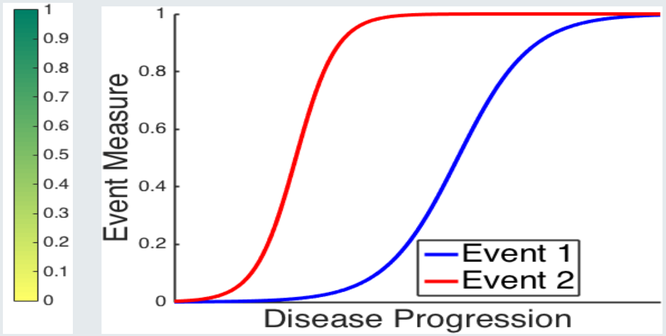
Memory loss years before dementia diagnosis

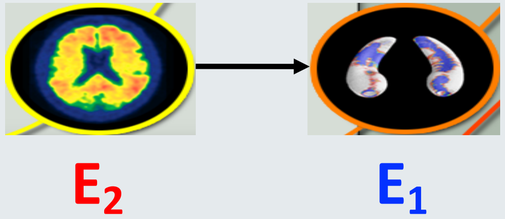


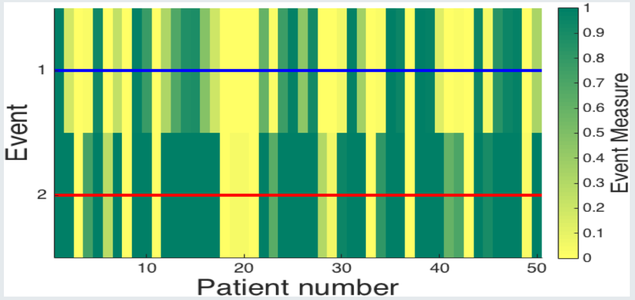


Event-based model (EBM) to identify stages of decline

EBM estimates ordering of **binary events** from data – normal or abnormal
Data can be cross-sectional and any combination of types (imaging, clinical, genetic…)

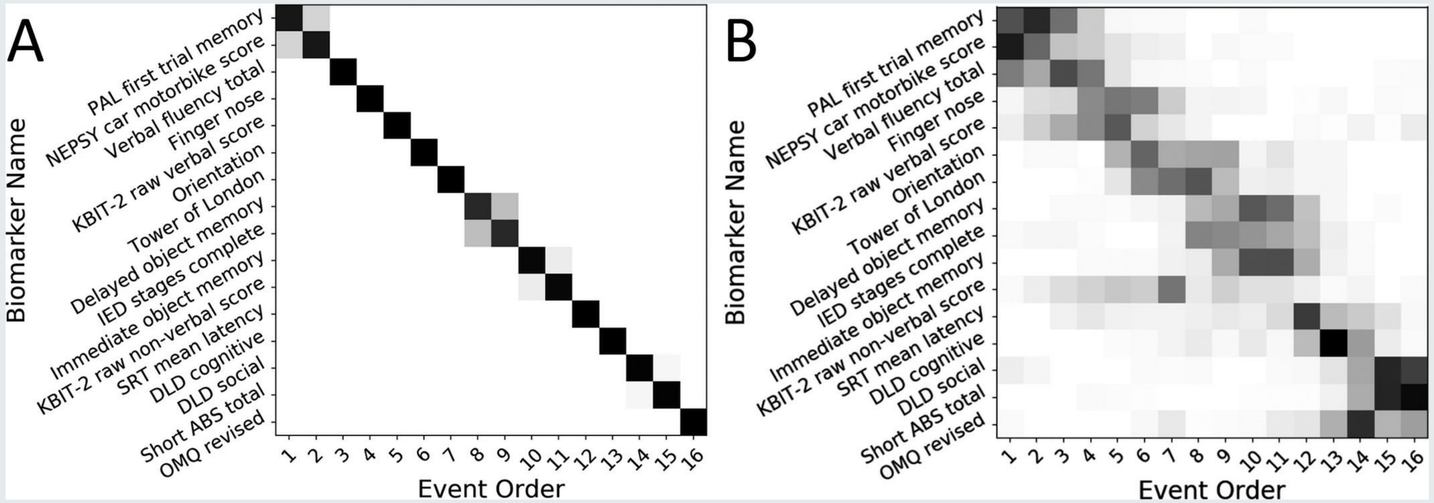






<u>Simple example: 2 event measures</u>
More patients have greater abnormality in Event 2 than Event 1 at particular assessment
→Event2 **measurably abnormal** before Event1

Stages of decline in DS before dementia diagnosis using Event based modelling



Early stages of decline defined by memory and sustained attention tests

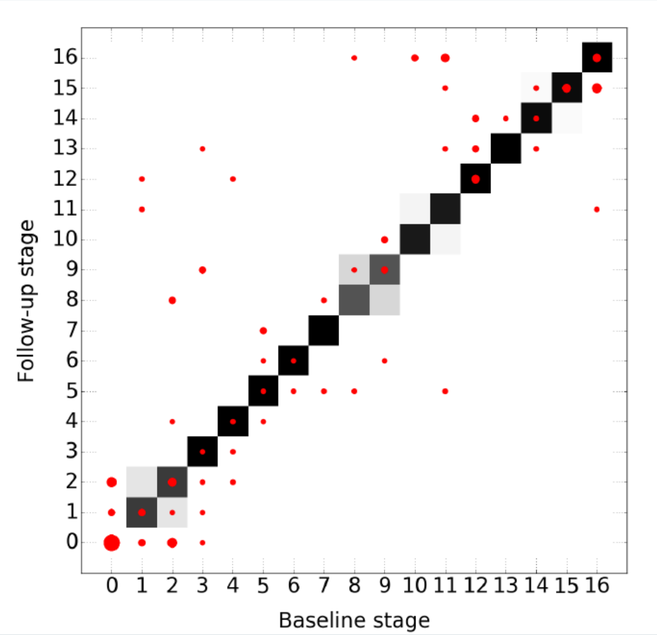
Later stages defined by informant ratings of function (dementia diagnosis)

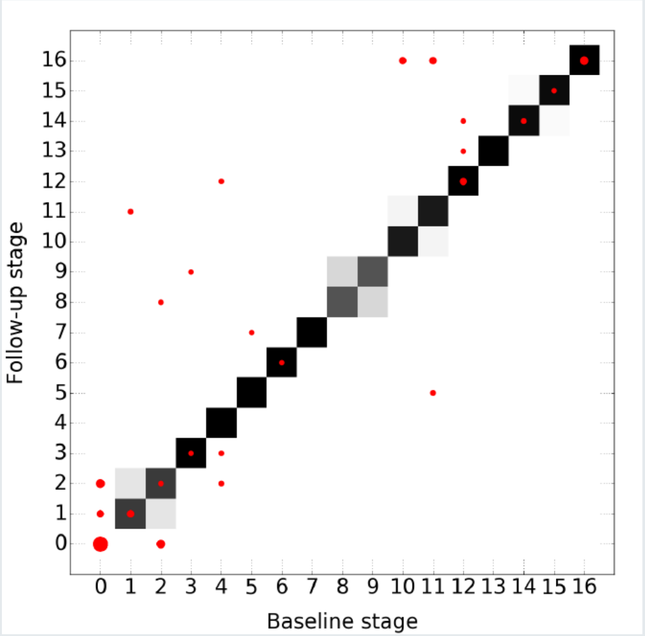
Firth, N. C., Startin, C. M., Hithersay, R., Hamburg, S., Wijeratne, P. A., Mok, K. Y., ... & Strydom, A. (2018). Aging related cognitive changes associated with Alzheimer's disease in Down syndrome. Annals of Clinical and Translational Neurology.

Predictive validity of EBM staging model

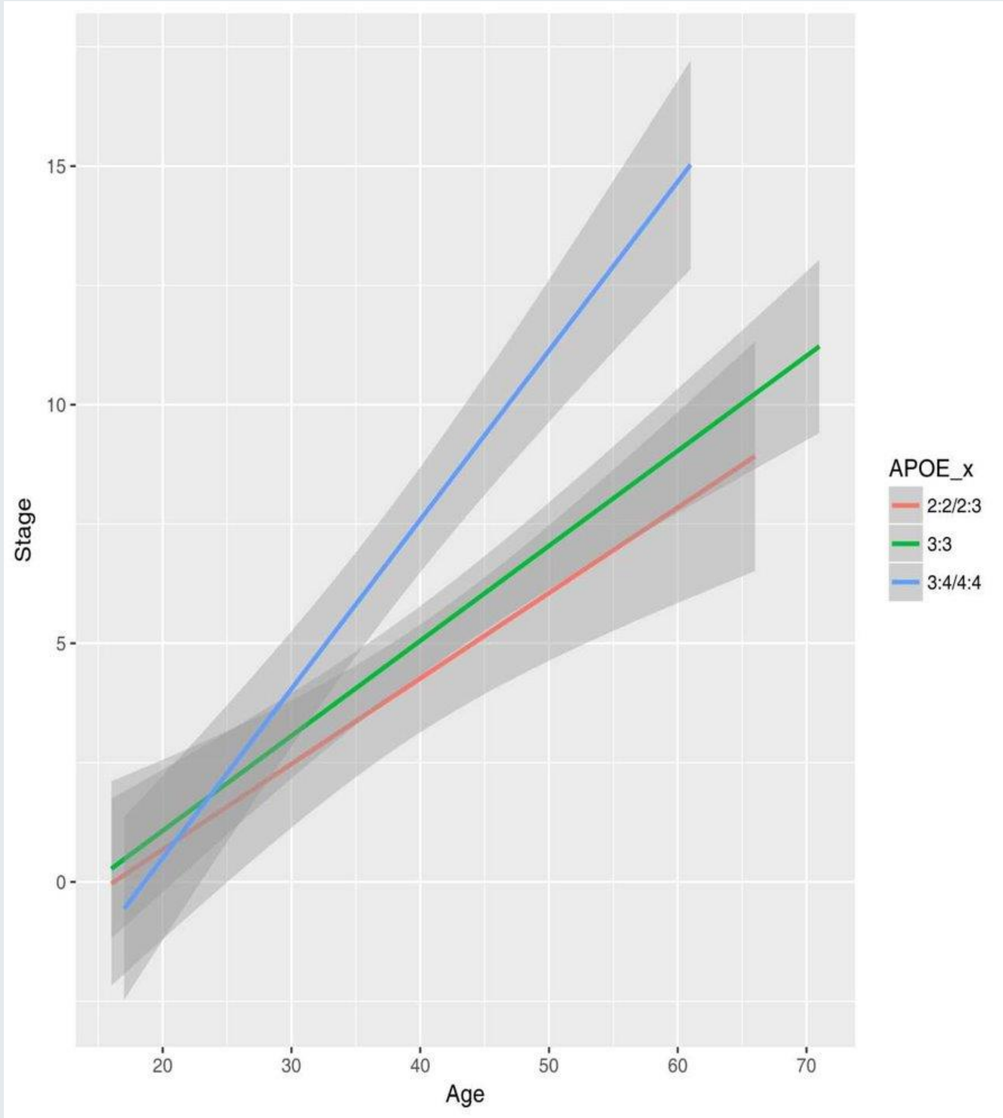
Follow up of older participants (> age 35) after 2 years

- General increase in EBM stage - >80% of participants either increase in stage, or remain the same
- Missing data may explain outliers





Staging by APOE status



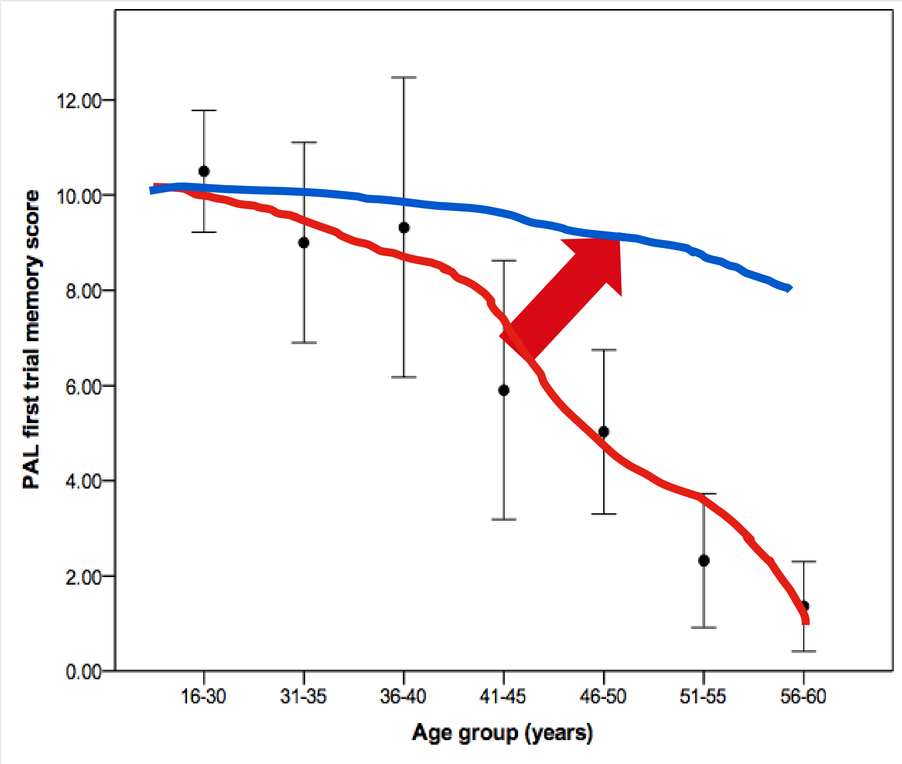
Getting ready for prevention trials in Down syndrome

How many people need to take part in a trial to show an effect?

Longitudinal results - PAL first trial memory score as outcome

For those with preclinical dementia (i.e. no noticeable signs of cognitive decline) and not at floor at baseline:

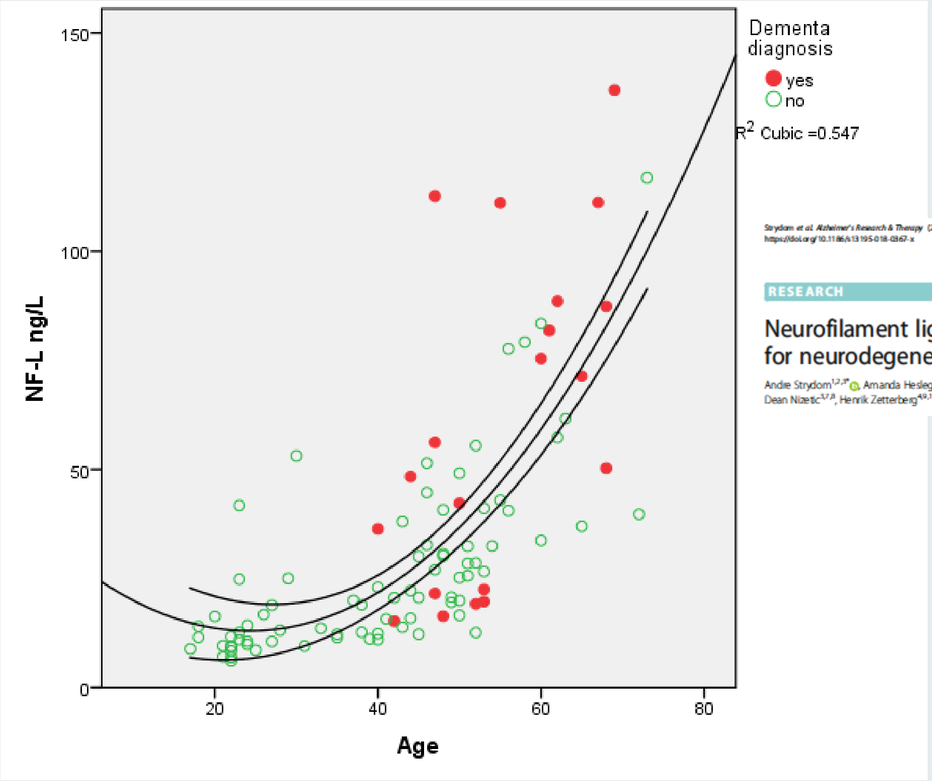
- 2 year trial n ~ 400 participants (90% power, $p<0.05$)



Biomarkers for Alzheimer's in Down syndrome

Good biomarkers can speed up clinical trials if shown to be linked with clinical outcomes

Neurofilament light: A neuronal structural protein associated with cell death, measured with SIMOA assays in serum



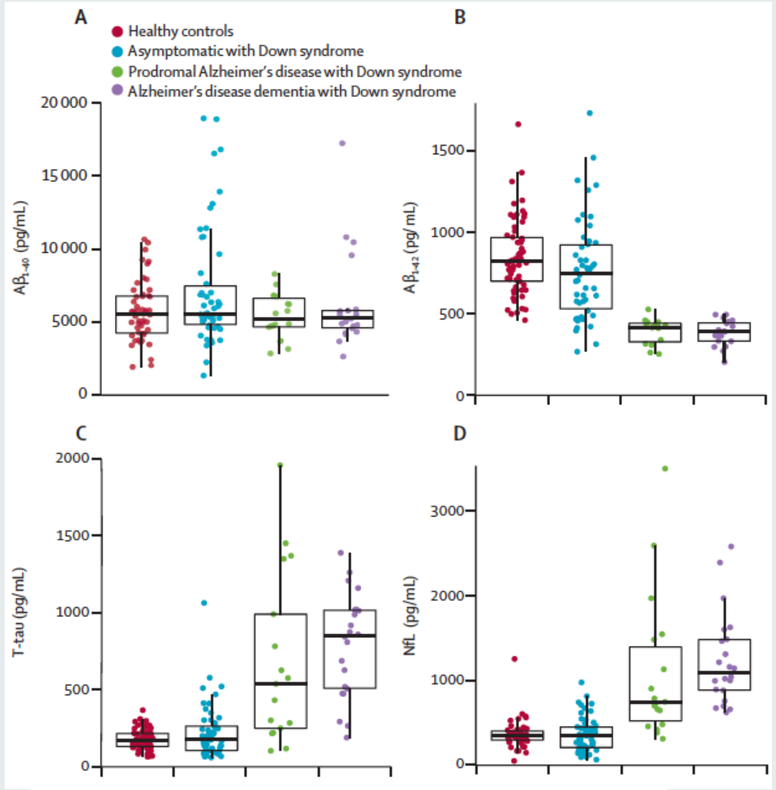
Strydom et al. Alzheimer's Research & Therapy (2018) 10:39
https://doi.org/10.1186/s13195-018-0367-x

Alzheimer's Research & Therapy

RESEARCH Open Access

Neurofilament light as a blood biomarker for neurodegeneration in Down syndrome

Andre Strydom[1,2,3*], Amanda Heslegrave[4], Carla M. Startin[1,2,3], Kin Y. Mok[3,4,5], John Hardy[3,4,6], Jurgen Groet[3,7], Dean Nizetic[3,7,8], Henrik Zetterberg[4,9,10] and The LonDownS Consortium



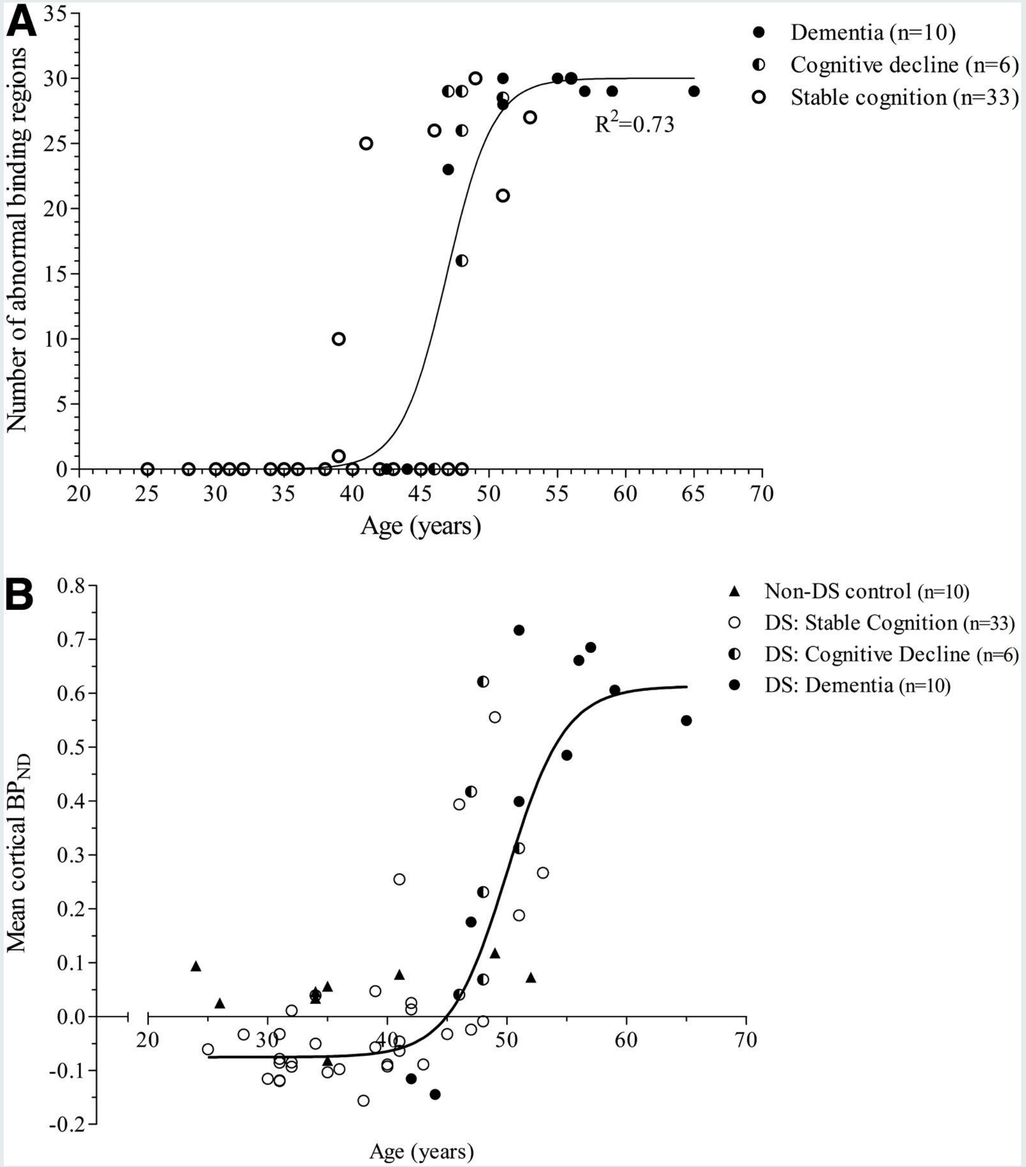
Plasma and CSF biomarkers for the diagnosis of Alzheimer's disease in adults with Down syndrome: a cross-sectional study

Juan Fortea, María Carmona-Iragui, Bessy Benejam, Susana Fernández, Laura Videla, Isabel Barroeta, Daniel Alcolea, Jordi Pegueroles, Laia Muñoz, Olivia Belbin, Mony J de Leon, Aleksandra Maceski, Christophe Hirtz, Jordi Clarimón, Sebastián Videla, Constance Delaby, Sylvain Lehmann, Rafael Blesa*, Alberto Lleó*

Summary
Background Diagnosis of Alzheimer's disease in Down syndrome is challenging because of the absence of validated

Lancet Neurol 2018

Amyloid PET brain scans



The pattern of amyloid accumulation in the brains of adults with Down syndrome Tiina Annus, Liam R. Wilson, Young T. Hong, Julio Acosta–Cabronero, Tim D. Fryer, Arturo Cardenas–Blanco, Robert Smith, Istvan Boros, Jonathan P. Coles, Franklin I. Aigbirhio, David K. Menon, Shahid H. Zaman, Peter J. Nestor, Anthony J. Holland, Alzheimer's & Dementia, Volume 12, Issue 5, Pages 538-545 (May 2016)

What next?

We can measure cognitive change before onset of Dementia in Down syndrome

- But need better cognitive outcome measures

Promising biomarkers associated with development of Alzheimer's disease

- But need to establish how it relates to cognitive changes and symptom onset over time

Clinical trials based upon rational drug targets is within grasp

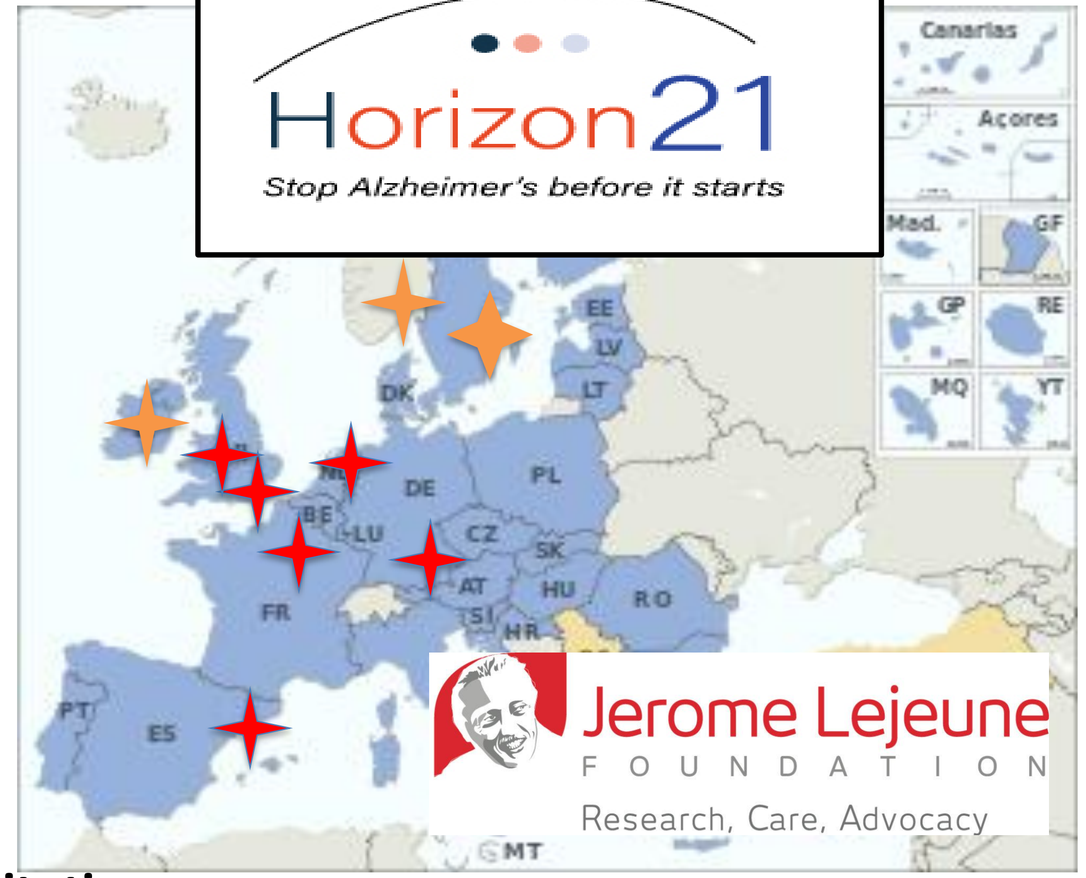
- But need to develop clinical trial networks
- Understand underlying biology to select optimal treatments

Cambridge U.

LonDowns

Horizon21

Stop Alzheimer's before it starts



Jerome Lejeune

FOUNDATION

Research, Care, Advocacy

<u>Institutions</u>:

- Institut Jérôme Lejeune, Paris. PI: A.S. Rebillat
- University of Cambridge. PI: S. Zaman
- Kings College London PI: A. Strydom.
- Dichterbij, Center for ID, Gennep. PI: A. Coppus.
- LMU Munich. PI: J. Levin.
- Hospital of Saint Pau: J. Fortea
- Trinity College, Dublin; Norway

Horizon21

Stop Alzheimer's before it starts

DS 1000
Europeant trial ready cohort & registry (N=1000)

Horizon 21 Genomics Consortium
Leader: Tonnie Coppus, Cornelia van Duijn

Main goals:

- Prepare a large trial-ready cohort and registry
- Develop clinical & cognitive outcome measures
- Validate biomarkers
- Design clinical trials to ensure feasibility

New CAMCOG-DS
Leader: Shahid Zaman

Multicenter NfL study
Leader: Juan Fortea

New NPS tools
Leader: André Strydom

Sleep study (PSG)
Leaders:
Sandra Gimenez
Anne-Sophie Rebillat

Funders & support

The Baily Thomas
Charitable Fund

Maudsley
Biomedical Research Centre