Received: 8 June 2020 | Revised: 21 September 2020 | Accepted: 6 October 2020

DOI: 10.1002/alz.12222

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Optimal age and outcome measures for Alzheimer's disease prevention trials in people with Down syndrome

Rosalyn Hithersay[1,2,3] | **R. Asaad Baksh**[1,2] | **Carla M. Startin**[1,2,3,4] | **Peter Wijeratne**[5] | **Sarah Hamburg**[1,2,3] | **Ben Carter**[6] | **The LonDownS Consortium**[1] | **Andre Strydom**[1,2,3]

[1] Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[2] The LonDownS Consortium, London, UK

[3] Division of Psychiatry, University College London, London, UK

[4] Department of Psychology, University of York, UK

[5] Department of Computer Science, University College London, London, UK

[6] Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Correspondence
Dr. Rosalyn Hithersay, Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.
Email: rosalyn.hithersay@kcl.ac.uk

Funding information: This work was funded by a Wellcome Trust (grant number: 098330/Z/12/Z) conferred upon The London Down Syndrome (LonDownS) Consortium. Further support was provided by the Medical Research Council (grant number: MRC S011277/1, MR/T027770/1, MR/R024901/1, MR/S005145/1). National Institute for Health Research (grant number: NIHR-INF-0655). The study funders and sponsors had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Abstract

Introduction: People with Down syndrome (DS) typically develop Alzheimer's disease (AD) neuropathology before age 40, but a lack of outcome measures and longitudinal data have impeded their inclusion in randomized controlled trials (RCTs).

Methods: Cohort study. Event-based and dose-response E_{max} models were fitted to longitudinal cognitive data, to stage AD and determine the earliest ages of decline. Results informed sample size estimations for hypothetical RCTs of disease-modifying treatments that reduced decline by 35% or 75%.

Results: Seventy-five percent of participants progressed or remained stable in the AD staging model; effect sizes varied by age group and tests. Varied treatment effects could be detected with 50-200 people per arm when using sensitive cognitive outcome measures and targeting recruitment to ages 36 to 45 years.

Discussion: Efficient RCTs of AD preventative treatments can be conducted in the DS population using sensitive outcome measures to monitor early decline. Dose-response models could help tailor future RCTs.

KEYWORDS
Alzheimer's disease, clinical trial design, cognitive decline, Down syndrome

1 | BACKGROUND

Trisomy 21 ("Down syndrome"; DS) is the most common genetic driver of early-onset Alzheimer's disease (AD),[1] present in approximately 40,000 people in the UK,[2] and between 3.3 and 12.8 live births per 10,000 worldwide.[3] Chromosome 21 contains the amyloid precursor protein (*APP*) gene,[4] which when over-expressed or in certain mutated forms plays a key role in determining the deposition of amyloid plaques

in the brain as people age. Such plaques, alongside neurofibrillary tangles of tau protein, form the characteristic neuropathology of AD, which develops nearly universally in adults with DS before the age of 40 years.[5,6] Dementia is most frequently diagnosed between 50 and 55 years, and 90% of adults with DS are expected to develop dementia in their lifetime.[7–9]

The predictable onset of AD neuropathology and symptoms in DS opens opportunities for early intervention that are unfeasible in sporadic AD. Yet despite advances in understanding the development of AD in DS, people with DS have historically been, and continue to be, excluded from randomized controlled trials (RCTs).[10] Aside from being a missed scientific opportunity, this exclusion limits access to health care that is appropriate and targeted to this population's needs.

A lack of data detailing the subtle cognitive changes that occur during the preclinical to prodromal (ie, symptomatic) stages of AD in DS has likely contributed to adults with DS being overlooked for inclusion in AD prevention trials. Impact on clinical outcomes remains a prerequisite for approvals of drugs targeting these early stages of AD (that is, progression from stage 1 to 3 in the FDA classification).[11] Fluid and neuroimaging biomarker studies are underway in people with DS,[12–14] and will undoubtedly help with future targeted trial recruitment. However, given difficulties in obtaining such data in this population, detailed examination of early cognitive signs may offer a complementary approach for monitoring disease progression.

A further limitation of current RCT design in AD is the absence of considering the earliest age at which decline in cognitive abilities can be detected. Identifying the inflection point in transition from preclinical to prodromal stage AD could help determine the ideal window to intervene with pharmacological treatments, such as amyloid-targeting drugs, that could slow or prevent further neuropathological progression.

With the advent of large, longitudinal DS cohort studies, data are now becoming available that can help address these concerns.[15–17] Such data can help accelerate progress in this high-dementia risk population, offering important insights into AD development, prevention, and treatment that could eventually improve AD outcomes for those both with and without DS.

1.1 | Objectives

In keeping with the European Medicines Agency guidance highlighting the need to identify subscales and items that are sensitive during early stages of symptomatic AD,[11] we aimed to use longitudinal data from a DS cohort study to:

1. Validate a dementia staging model with new data in order to identify the earliest stages of AD-related cognitive decline and cognitive tests associated with these changes
2. Identify the trajectory of cognitive decline in preclinical and prodromal stages of AD for each outcome measure, in order to guide optimal recruitment periods for clinical trials
3. Estimate likely effect sizes and sample sizes for future RCTs

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using the Scopus database. The genetic risk for Alzheimer's disease (AD) in Down syndrome (DS) is well documented, and several studies have examined early stage clinical symptoms. However, there remains a lack of data and approaches for determining expected trajectories of cognitive decline at the earliest stages of AD.
2. Interpretation: This study shows that existing cognitive tools can be used to detect early cognitive decline in adults with DS, and provides approaches for determining optimal age bands and outcome measures for clinical trials.
3. Future directions: These findings will help facilitate the inclusion of people with DS in AD clinical trials. Working with a large population who have a known genetic risk for AD will allow trials that are unfeasible in sporadic AD. Repurposing dose-response models could be a simple way to improve targeted recruitment in other clinical trial areas.

2 | METHODS

2.1 | Study design

This was a longitudinal cohort study.

2.2 | Setting

The study was conducted in a community setting in England. Baseline assessments were completed between October 2013 and September 2015, with follow-up assessments 2 years later. Assessments took place at participants' homes, day-care centers or university testing centers, according to participant preference.

2.3 | Ethics

Ethical approval was obtained from the North West Wales Research Ethics Committee (13/WA/0194). Written informed consent was obtained from individuals who had capacity to consent. Where individuals did not have capacity to consent, a consultee was asked to approve the individual's inclusion based on their knowledge of the individual and their wishes, in accordance with the UK Mental Capacity Act 2005.

2.4 | Participants

Adults with DS were recruited from the LonDownS cohort.[16] Participants aged 36 years or older at baseline were eligible (n = 173). By this

age, AD neuropathology is universally expected;[5,18] thus participants can be considered to be in at least a preclinical stage of AD. DS was confirmed genetically for 163 participants (details in supplementary material).

2.5 | Cognitive outcome measures

Outcomes used in the current analyses include performance in measures of **general verbal and non-verbal abilities** (Kaufmann Brief Intelligence Test [KBIT-2], **orientation, memory** CANTAB paired associates learning [PAL], immediate and delayed object memory, observer memory questionnaire revised version [OMQ-R]), **executive functioning** (Tower of London, semantic verbal fluency, CANTAB intra-extra dimensional shift task [IED], Behavior Rating Inventory of Executive Function [BRIEF]), **attention** (CANTAB simple reaction time [SRT] task), and **hand-eye co-ordination** (finger-nose task, NEPSY car and motorbike task) from the LonDownS cognitive battery.[16] Full details are given in the supplementary material.

2.6 | Demographic variables

The demographic data were sex, age, level of intellectual disability (ID; carer reported, based on ICD-10 descriptions).

2.7 | Clinical variables

To ensure dementia diagnoses were independent of neuropsychological assessments undertaken for this analysis, we used diagnoses based on clinical assessments by each individual's psychiatrist. The CAMDEX-DS (Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities)[19] was additionally used to identify symptoms of decline in cognition, adaptive functioning, or behavior indicative of early dementia-related change.

2.8 | Eligibility criteria

Participants required data for at least one outcome measure at baseline and follow-up, complete CAMDEX data, and sufficient hearing and vision to comfortably engage with the cognitive tests (see supplementary material).

For the trajectory modeling of the outcomes using an E_{max} model, individuals with a dementia diagnosis or performance at floor-level on a given outcome measure at baseline were excluded, in order to focus on decline in the preclinical and prodromal stages of AD only.

2.9 | Statistical analysis

2.9.1 | Event-based modeling

We used event-based models (EBMs)[20] to estimate the sequence in which cognitive markers become measurably abnormal, and to stage patients along this sequence. In brief, the EBM is a probabilistic model of observed data generated by an unknown sequence of events, where an event is defined as the transition of a marker from a normal to an abnormal state. The model learns distributions of normality and abnormality for each marker separately and enables estimation of the most likely sequence of abnormality over the whole population. The EBM has been applied extensively to progressive neurological diseases, including AD[21] and Huntington's disease.[22]

We recently developed an EBM for AD in DS using baseline data from the LonDownS adult cohort.[17] Here, we used this model to test the sequence of events estimated in the original work,[17] by refitting the model using baseline data from participants with both baseline and follow-up data. We then examined the progression in stage between time points. Non-parametric mixture models[23] were fit to the distributions of cognitively normal participants (CN; as assessed by the CAMDEX-DS) and participants with clinical dementia diagnoses for each marker (ie, outcome) in the cognitive battery. All cognitive markers were adjusted for ID severity in the CN cohort at baseline. Following Firth et al.,[23] the mixture models were used to calculate the likelihoods of normality and abnormality for each marker across the whole cohort, and the maximum likelihood sequence of abnormal events was estimated from the posterior with a uniform prior on the initial stage. Uncertainty in the maximum likelihood sequence was estimated using Markov Chain Monte Carlo sampling of the posterior. Participants were then staged at baseline and follow-up according to their maximum likelihood position in the baseline sequence.

2.9.2 | Trajectory modeling of cognitive decline using E_{max} models

To determine the earliest age-bands of change for each outcome measure, we examined dose-response relationships between performance change over 2 years, and increasing "doses" of age. We assumed a sigmoidal (ie, "S-shaped") relationship between performance decline and age in years. This constrained a baseline level of cognitive stability, followed by a period of decline that eventually plateaus.

To allow exploration of changes on a yearly basis, mean proportional change in performance between time points was calculated across participants in 5-year smooth moving-average baseline age bands, starting at age 36 and subsequently incrementing by 1 year. Age bands with fewer than four observations and individual change score outliers (>1.5 times the interquartile range of the static 5-year age band or due to clinical anomalies, such as substantial improvement in performance in an older adult) were excluded from the analysis.

A sigmoid E_{max} model[24,25] was fitted to these change scores, using the "DoseFinding" package for R (version 0.9-16). In the context of our data, the model estimates the following: the baseline group performance in the absence of aging-related decline (E_0); the maximum effect of age on performance (E_{Max}); the age at which half of the effect of the E_{max} is observed (EC_{50}); and an h parameter, the steepness of the curve at the EC_{50} value. Jackknife resampling was performed on each model to estimate bias.

EC_1 values were calculated from the model results using a freely available online calculator (https://tinyurl.com/emaxcalc). These values give the age bands in which we can expect to see 1% of the maximum effect of age on performance and were used here as the earliest ages of decline. For reference, EC_5 and EC_{10} values are also given in the supplementary pages.

2.9.3 | Indicative effect size and sample size estimation

Raw performance changes in the age band at EC_1 for each outcome measure were used to estimate required sample sizes to compare groups in hypothesized RCTs where pharmacological treatments would reduce aging-related decline by 35% or 75% compared to placebo, over a 2-year period. Cohen's *d* was used to show the effect sizes of these hypothetical group differences.

Sample size calculations were performed in GPower 3.1, using independent samples *t*-tests ($\alpha = 0.05$), and 80% power.

TABLE 1 Participant demographics

	All participants (n = 132)
Age, y (SD)	48.73 (7.18)
Sex	
Male	73 (55.3)
Female	59 (44.7)
APOEε4 carrier[a]	29 (24.0)
Dementia diagnosis at baseline	28 (21.2)
Number converting to dementia at follow-up	11 (8.3)
Level of intellectual disability	
Mild	50 (37.9)
Moderate	53 (40.2)
Severe	29 (21.9)
Ethnicity	
White	117 (88.6)
Not white	15 (11.4)
Medication[b]	
Acetylcholinesterase inhibitors	19 (14.7)
Psychotropic medications	34 (26.4)

Data are total number (%) or mean (SD).
[a] *APOE genotype data were not available for seven participants, another four participants had APOE genotype ε2:ε4 and so were excluded from APOE descriptive statistics.*
[b] *Medication data were missing for three participants.*
Abbreviations: APOE, Apolipoprotein E; SD, standard deviation.

3 | RESULTS

3.1 | Participants

A total of 132 participants (76.3% of invitees) completed a follow-up assessment, as 17 (9.8%) of the original invitees were deceased and 24 (13.9%) refused or could not attend. In the follow-up, 28/132 (21.2%) had a clinical diagnosis of dementia at baseline and 11 (8.3%) converted to clinical dementia between the two assessments. Table 1 shows participant demographics.

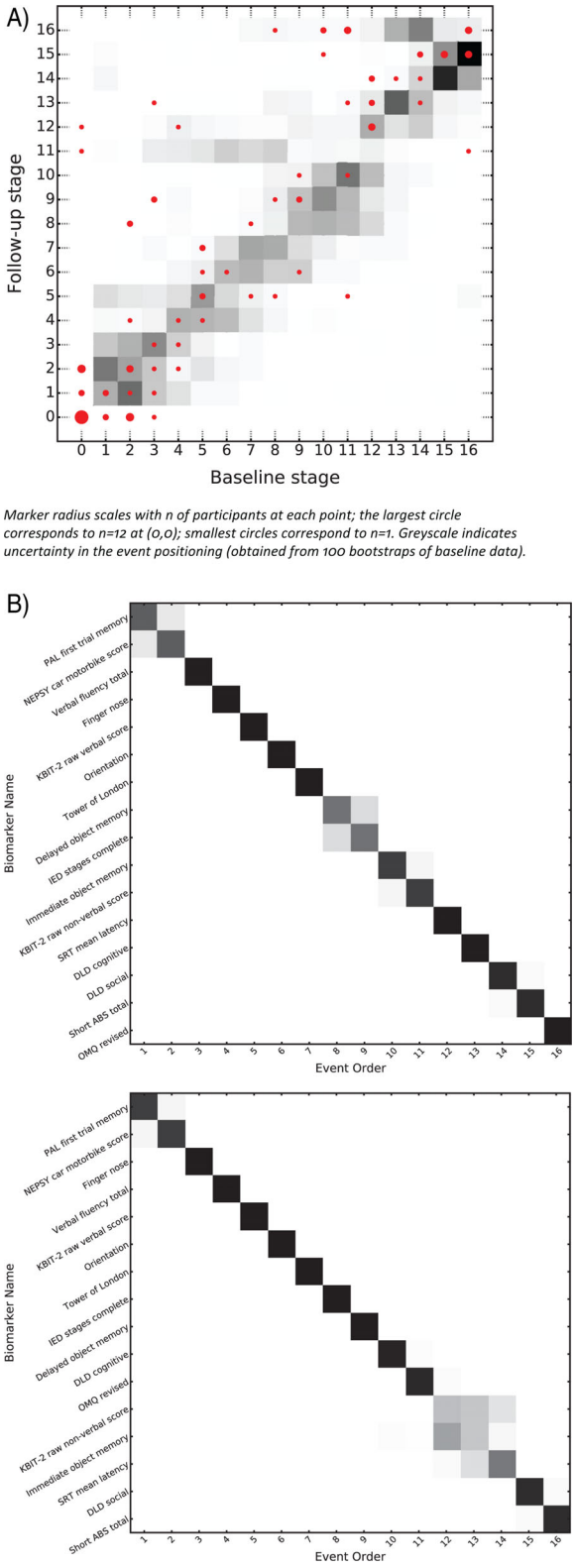
Follow-up assessments occurred after a mean of 23.69 months (standard deviation 0.81 months, range 22–28 months, all but four were completed after 23–25 months).

3.2 | EBM sequence and staging analysis

Figure 1A shows the predicted individual EBM stage at baseline versus follow-up. To permit longitudinal staging and reduce staging uncertainty due to missing data, we required participants to have measurements at both baseline and follow-up and less than 50% missing data; these criteria removed 30 participants (Figure 2). To give an estimate of the uncertainty in the staging due to the sequence, the uncertainty in the sequence ordering estimated by 100 bootstraps of the data is also shown in the supplementary material (Supplementary Figure I). We observed a general increase of EBM stage with time: 74.5% of the participants (76/102) either increased in stage (n = 39) or were stable (n = 37). Two participants regressed more than three stages due to improvements in cognitive test scores between baseline and follow-up; likely due to missing some assessments at baseline which they then completed at follow-up. We also observed general consistency between the sequences estimated separately using participants at baseline and follow-up (Figure 1B), with the earliest changes in the PAL (visuo-spatial memory) and NEPSY car motorbike (sustained attention/ praxis) markers.

3.3 | E_{max} analysis

In order to focus on the earliest signs of decline, for these analyses we excluded participants with dementia, or possible confounding conditions (n = 48). Figure 2 provides further details. For the cognitive test outcome measures only, a further 14 were excluded for failing to meet hearing/vision thresholds. E_{max} model results are shown in Table 2, with related plots in Figure 3. Jackknife resampling confirmed that bias was not substantially greater than the standard error for model parameters of interest in any of the tasks (see supplementary material).



Marker radius scales with n of participants at each point; the largest circle corresponds to n=12 at (0,0); smallest circles correspond to n=1. Greyscale indicates uncertainty in the event positioning (obtained from 100 bootstraps of baseline data).

FIGURE 1 Predicted EBM stage at (A) baseline and follow-up, with (B) associated staging at each baseline (left) and follow-up (right). Abbreviations: DLD, dementia questionnaire for people with learning disabilities; IED, intra-extra dimensional shift task; KBIT-2, Kaufman brief intelligence test – second edition; NEPSY, a developmental NEuroPSYchological assessment; OMQ, observer memory questionnaire; PAL, paired associates learning task; S-ABS, short adaptive behavior scale; SRT, simple reaction time task.

3.4 | Sample size calculations

EC_1 values and required sample sizes varied across the test battery (Table 3), offering helpful insight into which outcome measures show change earliest, and are thus most suitable for potential preventive RCTs.

Measures of *memory* (PAL) and *executive functioning* (verbal fluency and Tower of London) show the earliest EC_1 values in our dataset, with the PAL first trial memory score and Tower of London each showing decline from ages 35 to 39 years. At 80% power, using the PAL task, 102 people would be required to detect a difference between control and treatment arms with a treatment capable of reducing expected decline by 75%, and 462 people with one at 35% efficacy. For the Tower of London, a 35% effective treatment would require 324 people, and 72 if the treatment were 75% effective. Decline in the verbal fluency task has a smaller effect size in this age band, requiring a sample of more than 600 for a 75% effective treatment. By EC_{10} (age 44-48 years; see supplementary material), however, just 74 people would be required for the 75% effective treatment, or 332 for a 35% effective treatment. The verbal fluency task is therefore still useful for monitoring change in age groups where most individuals are in the preclinical or prodromal stages of AD.

Sustained attention and *hand-eye co-ordination* tasks also show very early EC_1 values, with both finger-nose and the NEPSY car and motorbike scores showing decline at ages 36 to 40 years. Required sample sizes, however, are at least 4 times greater for these tasks than for the PAL or Tower of London, even when extending to later EC values (see supplementary material), suggesting that they may not be optimal for monitoring early decline.

The mean latency of the SRT could, however, be a good measure of early sustained attention decline. Although the EC_1 value for the SRT is later than for other measures, effect sizes are medium to large even in the earliest age bands. Less than 100 participants would be required for a hypothetical RCT of a 75% effective treatment, and less than 350 for a 35% effective treatment if targeting recruitment at any of the age bands starting below 40 (data in supplementary material).

The IED, immediate and delayed object memory, and the informant questionnaires (the OMQ-R for memory and the BRIEF for executive functioning) are likely unsuitable for monitoring early decline, given their later EC_1 values and greater sample size requirements. Orientation is also insufficiently sensitive at the earliest point of decline, however by EC_5 (age 45-49 years) 100 people would be required to see group differences with a 75% effective treatment, and 450 at 35% efficacy.

In sum, a small battery of cognitive tests including the CANTAB PAL (first trial memory score), SRT (mean latency) and the Tower of London would allow subtle early changes to be detected over a 2-year trial in individuals aged 35 to 40 years at baseline. Sample size requirements vary from less than 50 people per arm, to around 200 people per arm depending on the efficacy of the treatment, which given existing cohorts, would be feasible for an international RCT. This battery would take 20-30 minutes to administer, depending on each individual's performance. Changes in orientation and verbal fluency can be seen with

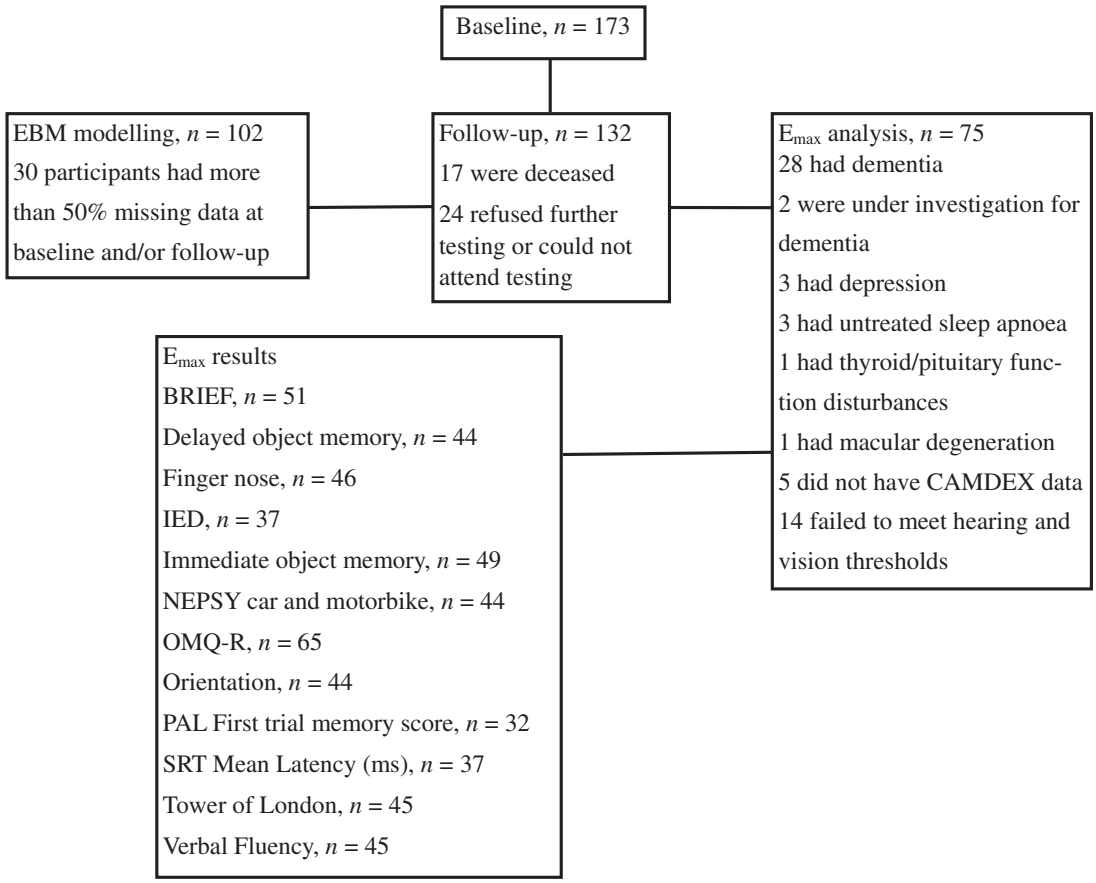


FIGURE 2 Participant exclusion flow chart

TABLE 2 E_{max} results

Outcome	n	E_0	E_{max}	EC_{50}	h
BRIEF	51	−2.19	183.14	70.52	10
Delayed object memory	44	8.87	−3339.67	82.50	10
Finger nose	46	0.03	−151.39	58.04	10
IED	37	−3.95	430.39	69.64	10
Immediate object memory	49	16.21	−711.82	66.30	10
NEPSY car and motorbike	44	−4.19	−201.28	58.04	10
OMQ-R	65	−0.28	1807.71	82.50	10
Orientation	44	3.47	−247.57	61.11	10
PAL first trial memory score	32	−1.66	−245.84	56.49	10
SRT mean latency (ms)	37	7.44	4704.46	82.50	10
Tower of London	45	−8.64	−102.23	57.20	10
Verbal fluency	45	0.91	−134.89	55.64	10

Outcomes: E_0 = baseline group performance in the absence of aging-related decline; E_{max} = the maximum effect of age on performance; EC_{50} = the age at which half of the effect of the E_{max} is observed; h = the steepness of the curve at the EC_{50} value.

Abbreviations: BRIEF, behavior rating inventory of executive function; IED, intra-extra dimensional shift task; ms, millisecond; NEPSY, a developmental NEuroPSYchological assessment; OMQ-R, revised observer memory questionnaire; PAL, paired associates learning task; SRT, simple reaction time task.

similarly sized samples from age 44, thus these tasks may also be useful for monitoring early decline, given that the average age of dementia diagnosis in DS is around 55.

4 | DISCUSSION

Due to their known genetic risk for AD, people with DS are increasingly being considered for early AD intervention RCTs. However, progress has been impeded by a lack of data characterizing the trajectory of AD-related change in these adults, as well as concerns regarding response to treatments such as anti-amyloid antibodies given immune system differences associated with DS.[26]

Using longitudinal cognitive data from a DS cohort, we combined EBM with E_{max} modeling approaches to determine optimal cognitive outcome measures and age bands for tracking the earliest signs of cognitive decline in this population. We demonstrated that the EBM model may be useful for tracking stages of cognitive decline in DS.

Considering a sub-sample that would be eligible for preventive RCTs, we found that cognitive decline could be observed over 2-years in participants 20 years younger than the average age of dementia diagnosis (around 55 years in those with DS).[9]

The cognitive outcome measures showing greatest sensitivity at these early stages, with highest feasibility for use in RCTs, were the

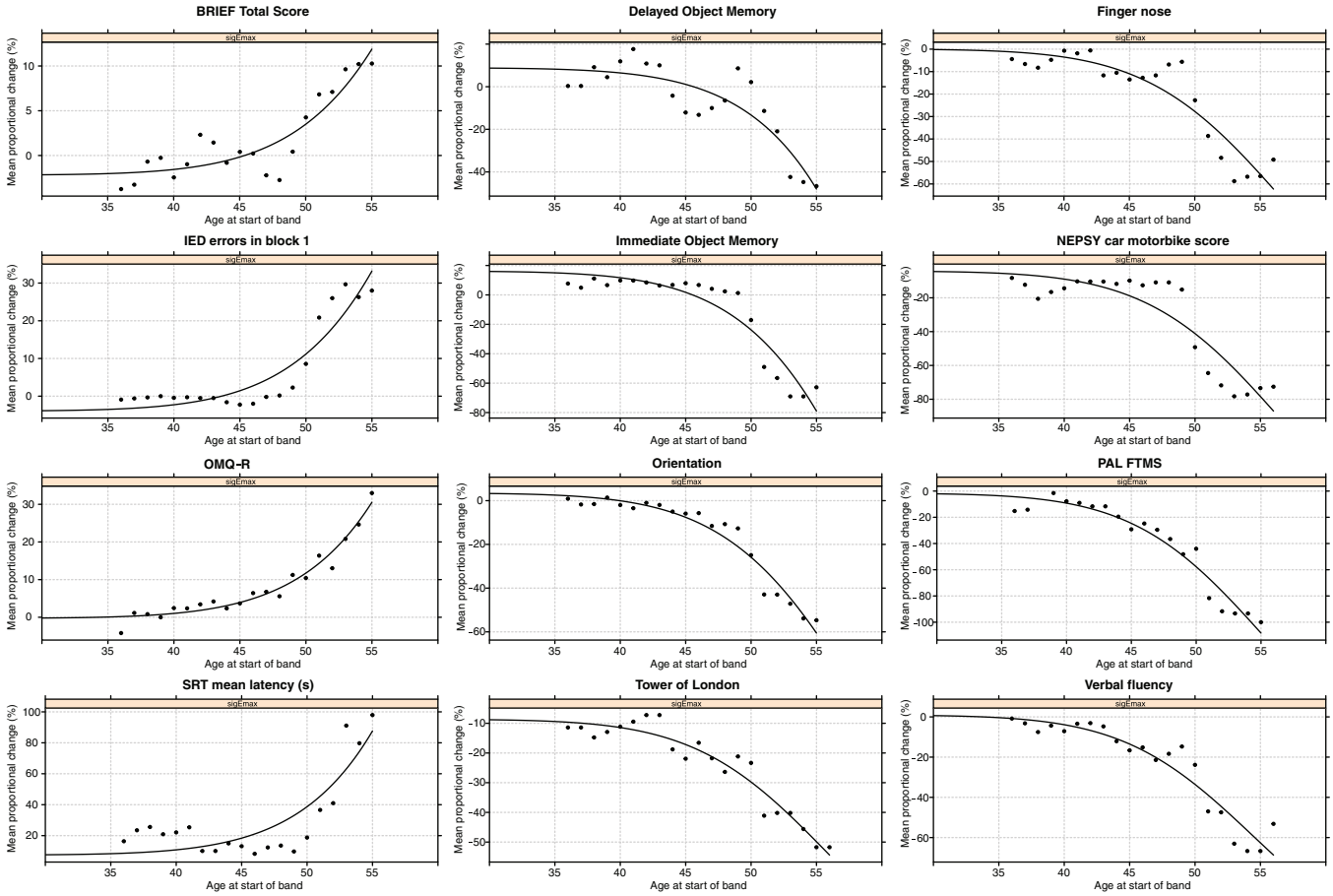


FIGURE 3 E_{max} model plots for each outcome measure. BRIEF, behavior rating inventory of executive function; IED, intra-extra dimensional shift task; NEPSY, a developmental NEuroPSYchological assessment; OMQ-R, revised observer memory questionnaire; PAL FTMS, paired associates learning task, first trial memory score; SRT, simple reaction time task.

CANTAB PAL, SRT, and the Tower of London. In a hypothetical treatment trial where a treatment was able to prevent cognitive decline by 75% compared to our observed changes, these tasks would require samples of approximately 50 people per arm to detect group differences when targeting recruitment at ages 35 to 41 years. For a treatment at 35% efficacy, sample sizes would be closer to 200 per arm, which would be feasible in an international RCT. Orientation and a semantic verbal fluency task may be useful additions for monitoring change in participants in their 40s. At this age range, 90% of adults with DS would still be expected to be in preclinical or prodromal stages of AD,[8] and required sample sizes are in line with the other three tasks.

This combination of using E_{max} modeling results alongside sample size calculations is important for determining suitable outcome measures. While the E_{max} results show that changes in verbal fluency performance can be detected from very early age bands (35-39), more than 600 people would be required for a trial even if the treatment were 75% effective, limiting feasibility in this population at this age range. However, by ages 44 to 48 years, this task can detect change in samples of less than 100. Similarly, the E_{max} model did not fit well for the SRT, leading to a very late EC_1 value. However, sample size calculations confirmed that performance changes could be observed at ages below 40 years with less than 150 trial participants per arm for a 35% effective treatment, suggesting measures of attention may also be useful for monitoring early decline. Extending our approach to include a wider age range of participants may improve model fit in future studies.

Between 2002 and 2012, 413 compounds were assessed in RCTs for AD, showing an overall failure rate of 99.6%.[27] There has been little improvement in the years since,[28] highlighting the urgent need to apply innovative approaches in designing RCTs. Primary challenges in designing disease-modifying therapies arise from the substantial delay between the onset of AD neuropathology and dementia symptomology.

Working with populations who have a genetically driven form of AD can allow potential disease-modifying therapies to be trialed at an earlier stage. This current work offers novel data and statistical approaches to improve trial and recruitment design in a large genetic population who have been largely excluded from clinical studies. Further improvements can potentially be made by incorporation of fluid and/or neuroimaging biomarkers to increase power or shorten duration of prevention RCTs.

TABLE 3 Sample size estimations

Outcome	Age-band at EC_1	Mean expected change in control group	Pooledsd	Treatment at 35% efficacy			Treatment at 75% efficacy		
				Mean expected change in treatment group	*Effect size (d)*	Total required sample size	Mean expected change in treatment group	*Effect size (d)*	Total required sample size
BRIEF	44-48	−2.05	26.94	−1.33	−0.03	34876	−0.51	−0.06	7596
Delayed object memory	52-56	−0.86	2.04	−0.56	−0.15	1140	−0.21	−0.30	250
Finger nose	36-40	−1.18	3.63	−0.77	−0.11	1906	−0.29	−0.24	416
IED	43-47	−0.25	1.58	−0.16	−0.06	8078	−0.06	−0.12	1760
Immediate object memory	41-45	0.82	1.72	0.53	0.17	896	0.20	0.34	198
NEPSY car and motorbike	36-40	−2.10	8.20	−1.37	−0.09	3080	−0.53	−0.19	672
OMQ-R	52-56	6.55	12.56	4.25	0.18	746	1.64	0.39	164
Orientation	38-42	−0.14	0.90	−0.09	−0.06	8010	−0.04	−0.12	1746
PAL First trial memory score	35-39[a]	−2.38	3.58	−1.54	−0.23	462	−0.59	−0.50	102
SRT mean latency (ms)	52-56	486.14	281.54	315.99	0.60	70	121.54	1.30	18
Tower of London	36-40	−1.09	1.38	−0.71	−0.28	324	−0.27	−0.59	72
Verbal fluency	35-39[a]	−0.70	2.63	−0.46	−0.09	2846	−0.18	−0.20	622

[a]Data in our sample starts at age 36, so using band 36-40 for sample size estimation. *Mean expected change based on observed raw score changes over a 2-year follow-up period, with hypothetical treatments that reduce expected decline by 35% or 75%. Effect size is Cohen's d, calculated with the standard deviation from observed changes. Required sample sizes estimated with 80% power.*

Abbreviations: BRIEF, behavior rating inventory of executive function; IED, Intra-extra dimensional shift task; ms, milliseconds; NEPSY, a developmental NEuroPSYchological assessment; OMQ-R, revised observer memory questionnaire; PAL, paired associates learning task; SRT, simple reaction time task.

Prevention trials in people with DS may ultimately benefit trial design in other populations with AD and provide proof of concept for trials in sporadic AD, which are urgently needed.[29]

4.1 | Limitations

The E_{max} modeling had relatively small sample sizes in each age band. We minimized this limitation by using moving average age bands. Replication using larger, geographically diverse samples, ideally with longer follow-up periods, would help to confirm the utility of this approach for identifying key time windows in which to intervene. Individual assessment location was not available. Future work would be valuable to ascertain whether assessment performance differs when people are tested at their home or other locations.

Dementia diagnoses were primarily based on assessments by the participants' own clinicians. This ensured diagnoses were made independently of the neuropsychological test scores, but may have introduced variability in diagnostic thresholds. However, individuals with DS in the UK are typically assessed in specialist intellectual disability clinics that have experience in dementia assessments in this population, and such diagnoses have been shown to be reliable and valid.[30]

Data handling in older adults presents a further challenge. For the E_{max} models, we excluded individuals who had dementia at baseline in order to focus on early changes in cognition. Past age 55 years, most people with DS show cognitive decline. Those without dementia in these later ages are likely showing some unique protection against AD neuropathology, and thus performing very differently to the rest of the population. However, a lack of participants at older age ranges will also have an impact on the model fit. Again, further applications of this approach using other datasets would be welcomed. Finally, the clinically meaningful difference associated with the changes in cognitive scores we report requires further exploration.

4.2 | Conclusion

The cognitive stages of AD in DS can be identified using an EBM staging model, and may have potential to track AD-related change over time. In addition, using a novel application of dose-response models, we determined optimal recruitment age bands and outcome measures for RCTs of drugs targeting the earliest stages of disease in a population at exceptionally high risk of developing AD.

Our results have allowed us to determine a short cognitive battery, taking less than 30 minutes to administer, that is capable of detecting cognitive decline in adults with DS up to 20 years before their average age of dementia diagnosis, to improve prospects for RCTs in individuals with DS.

ACKNOWLEDGMENTS

The London Down Syndrome (LonDownS) Consortium principal investigators are Andre Strydom (chief investigator), PhD, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, England, and Division of Psychiatry, University College London, London, England; Elizabeth Fisher, PhD, Department of Neurodegenerative Disease, University College London Institute of Neurology, London, England; Dean Nizetic, PhD, Blizard Institute, Barts and the London School of Medicine, Queen Mary University of London, London, England, and Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; John Hardy, PhD, Reta Lila Weston Institute, Institute of Neurology, University College London, London, England, and UK Dementia Research Institute at University College London, London, England; Victor Tybulewicz, PhD, Francis Crick Institute, London, England, and Department of Medicine, Imperial College London, London, England; and Annette Karmiloff-Smith, PhD, Birkbeck University of London, London, England (deceased). Students who all helped with data collection, entry, or checking during a placement with LonDownS were Nidhi Aggarwal, Amy Davies, Lucy Fodor-Wynne, Bryony Lowe, and Erin Rodger and Kate Thurlow, BSc. They received travel expenses for work conducted during the study. Tamara Al-Janabi, PhD, managed the LonDownS project as a whole. No compensation was received from a funding sponsor for such contributions.

CONFLICT OF INTEREST

This work was funded by a Wellcome Trust (grant number: 098330/Z/12/Z) conferred upon The London Down Syndrome (LonDownS) Consortium. Further support was provided by the Medical Research Council (grant number: MRC S011277/1, MR/T027770/1, MR/R024901/1, MR/S005145/1). National Institute for Health Research (grant number: NIHR-INF-0655). The study funders and sponsors had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

AUTHOR CONTRIBUTIONS

Rosalyn Hithersay: recruitment, data collection, data analysis design, and data analysis for E_{max} modeling, interpretation, primary draft of the article

Asaad Baksh: design and data analysis for E_{max} modeling (equally shared with RH), interpretation

Carla Startin: recruitment, data collection

Sarah Hamburg: recruitment, data collection

Peter Wijeratne: data analysis (event-based modeling), interpretation

Ben Carter: analysis design, statistical advice

Andre Strydom: study design, interpretation

All co-authors contributed to the final article.

DATA SHARING

Deidentified cognitive data collected by the LonDownS consortium will be made available to researchers upon request and following approval of a protocol and a signed data access agreement. A data dictionary with variable descriptions will be made available with each request. Data requests should be made to Professor Andre Strydom at King's College London: andre.strydom@kcl.ac.uk .

REFERENCES

1. Wiseman FK, Al-Janabi T, Hardy J, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. *Nat Rev Neurosci*. 2015;16:564-574.
2. Wu J, Morris JK. The population prevalence of Down's syndrome in England and Wales in 2011. *Eur J Hum Genet*. 2013;21:1016-1019.
3. Antonarakis SE, Skotko BG, Rafii MS, et al. Down syndrome. *Nat Rev Dis Primers*. 2020;6:9.
4. Patterson D, Gardiner K, Kao FT, Tanzi R, Watkins P, Gusella JF. Mapping of the gene encoding the beta-amyloid precursor protein and its relationship to the Down syndrome region of chromosome 21. *Proc Natl Acad Sci U S A*. 1988;85:8266-8270.
5. Mann DMA, Esiri MM. The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome. *J Neurol Sci*. 1989;89:169-179.
6. Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol*. 1985;17:278-282.
7. Hithersay R, Startin CM, Hamburg S, et al. Association of Dementia With Mortality Among Adults With Down Syndrome Older Than 35 Years. *JAMA Neurol*. 2019;76(2):152-160.
8. McCarron M, McCallion P, Reilly E, Dunne P, Carroll R, Mulryan N. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *J Intellect Disabil Res*. 2017;61:843-852.
9. Sinai A, Mokrysz C, Bernal J, et al. Predictors of Age of Diagnosis and Survival of Alzheimer's Disease in Down Syndrome. *J Alzheimers Dis*. 2018;61:717-728.
10. Strydom A, Coppus A, Blesa R, et al. Alzheimer's disease in Down syndrome: an overlooked population for prevention trials. *Alzheimers Dement (N Y)*. 2018;4:703-713.
11. Committee for Medicinal Products for Human Use. *Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease*. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicines-treatment-alzheimers-disease-revision-2_en.pdf (2020).
12. Startin CM, Ashton NJ, Hamburg S, et al. Plasma biomarkers for amyloid, tau, and cytokines in Down syndrome and sporadic Alzheimer's disease. *Alzheimers Res Ther*. 2019;11:26.
13. Fortea J, Benejam B, Alcolea D, et al. P4-267: Core Alzheimer's disease csf biomarkers in Down syndrome. *Alzheimer's and Dementia*. 2014;10:P882.
14. Annus T, Wilson LR, Acosta-Cabronero J, et al. The Down syndrome brain in the presence and absence of fibrillar β-amyloidosis. *Neurobiol Aging*. 2017;53:11-19.
15. Startin CM, Hamburg S, Hithersay R, et al. Cognitive markers of preclinical and prodromal Alzheimer's disease in Down syndrome. *Alzheimers Dement*. 2019;15:245-257.
16. Startin CM, Hamburg S, Hithersay R, et al. The LonDownS adult cognitive assessment to study cognitive abilities and decline in Down syndrome. *Wellcome Open Res*. 2016;1:11.
17. Firth NC, Startin CM, Hithersay R, et al. Aging related cognitive changes associated with Alzheimer's disease in Down syndrome. *Ann Clin Transl Neurol*. 2018;5:741-751.
18. Mann DMA, Davidson YS, Robinson AC, et al. Patterns and severity of vascular amyloid in Alzheimer's disease associated with duplications and missense mutations in APP gene, Down syndrome and sporadic Alzheimer's disease. *Acta Neuropathol*. 2018;136(4):569-587.
19. Ball S, Holland AJ, Huppert FA, et al. *CAMDEX-DS: The Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and*

Others with Intellectual Disabilities. Cambridge: Cambridge University Press; 2006. 2006.
20. Fonteijn HM, Modat M, Clarkson MJ, et al. An event-based model for disease progression and its application in familial Alzheimer's disease and Huntington's disease. *Neuroimage*. 2012;60:1880-1889.
21. Young AL, Oxtoby NP, Daga P, et al. A data-driven model of biomarker changes in sporadic Alzheimer's disease. *Brain*. 2014;137:2564-2577.
22. Wijeratne PA, Young AL, Oxtoby NP, et al. An image-based model of brain volume biomarker changes in Huntington's disease. *Ann Clin Transl Neurol*. 2018;5:570-582.
23. Firth NC, Oxtoby NP, Primativo S, et al. Non-parametric mixture modelling and its application to disease progression modelling. *bioRxiv*. 2018:297978.
24. MacDougall J. Analysis of Dose–Response Studies—E max Model. In: N Ting, ed. *Dose Finding in Drug Development*. New York, NY: Springer; 2006:127-145.
25. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. *J Pharmacokinet Biopharm*. 1993;21:457-478.
26. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. *Clin Exp Immunol*. 2011;164:9-16.
27. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther*. 2014;6:37.
28. Mehta D, Jackson R, Paul G, Shi J, Sabbagh M. Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. *Expert Opin Investig Drugs*. 2017;26:735-739.
29. Hithersay R, Hamburg S, Knight B, Strydom A. Cognitive decline and dementia in Down syndrome. *Curr Opin Psychiatry*. 2017;30:102-107.
30. Sheehan R, Sinai A, Bass N, et al. Dementia diagnostic criteria in Down syndrome. *Int J Geriatr Psychiatry*. 2015;30:857-863.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Hithersay R, Baksh RA, Startin CM, et al. Optimal age and outcome measures for Alzheimer's disease prevention trials in people with Down syndrome. *Alzheimer's Dement*. 2021;17:595–604.
https://doi.org/10.1002/alz.12222