Timeline to symptomatic Alzheimer's disease in people with Down syndrome as assessed by amyloid-PET and tau-PET: a longitudinal cohort study

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Summary

Background Adults with Down syndrome are at risk for Alzheimer's disease. Natural history cohort studies have characterised the progression of Alzheimer's disease biomarkers in people with Down syndrome, with a focus on amyloid β-PET and tau-PET. In this study, we aimed to leverage these well characterised imaging biomarkers in a large cohort of individuals with Down syndrome, to examine the timeline to symptomatic Alzheimer's disease based on estimated years since the detection on PET of amyloid β-positivity, referred to here as amyloid age, and in relation to tau burden as assessed by PET.

Methods In this prospective, longitudinal, observational cohort study, data were collected at four university research sites in the UK and USA as part of the Alzheimer's Biomarker Consortium–Down Syndrome (ABC–DS) study. Eligible participants were aged 25 years or older with Down syndrome, had a mental age of at least 3 years (based on a standardised intelligence quotient test), and had trisomy 21 (full, mosaic, or translocation) confirmed through karyotyping. Participants were assessed twice between 2017 and 2022, with approximately 32 months between visits. Participants had amyloid-PET and tau-PET scans, and underwent cognitive assessment with the modified Cued Recall Test (mCRT) and the Down Syndrome Mental Status Examination (DSMSE) to assess cognitive functioning. Study partners completed the National Task Group-Early Detection Screen for Dementia (NTG-EDSD). Generalised linear models were used to assess the association between amyloid age (whereby 0 years equated to 18 centiloids) and mCRT, DSMSE, NTG-EDSD, and tau PET at baseline and the 32-month follow-up. Broken stick regression was used to identify the amyloid age that corresponded to decreases in cognitive performance and increases in tau PET after the onset of amyloid β positivity.

Findings 167 adults with Down syndrome, of whom 92 had longitudinal data, were included in our analyses. Generalised linear regressions showed significant quadratic associations between amyloid age and cognitive performance and cubic associations between amyloid age and tau, both at baseline and at the 32-month follow-up. Using broken stick regression models, differences in mCRT total scores were detected beginning 2·7 years (95% credible interval [CrI] 0·2 to 5·4; equating to 29·8 centiloids) after the onset of amyloid β positivity in cross-sectional models. Based on cross-sectional data, increases in tau deposition started a mean of 2·7–6·1 years (equating to 29·8–47·9 centiloids) after the onset of amyloid β positivity. Mild cognitive impairment was observed at a mean amyloid age of 7·4 years (SD 6·6; equating to 56·8 centiloids) and dementia was observed at a mean amyloid age of 12·7 years (5·6; equating to 97·4 centiloids).

Interpretation There is a short timeline to initial cognitive decline and dementia from onset of amyloid β positivity and tau deposition in people with Down syndrome. This newly established timeline based on amyloid age (or equivalent centiloid values) is important for clinical practice and informing the design of Alzheimer's disease clinical trials, and it avoids the limitations of timelines based on chronological age.

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Introduction

Individuals with Down syndrome have a 75–90% lifetime risk of symptomatic Alzheimer's disease,[1,2] driven mainly by overexpression of the *APP* gene on chromosome 21. PET imaging with carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) has shown that the accumulation of extracellular brain amyloid β plaques in Down syndrome can begin in the third and fourth decade of life.[3] Deposition of amyloid β in adults with Down syndrome is detected at first in the striatum,[4] similar to the pattern of deposition seen in people with autosomal-dominant Alzheimer's disease involving *APP* or *PSEN1* and *PSEN2* variants. Thereafter, spatial progression of amyloid β deposition in people with Down

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Research in context

Evidence before this study

We searched PubMed from database inception to March 1, 2024, for articles published relating to the progression of amyloid β and tau deposition in adults with Down syndrome. We used the search terms "amyloid", "Down syndrome", "tau", "Alzheimer's disease", "cognitive decline", and "amyloid chronicity," without language restrictions. One previous study outlined the progression of tau in adults with Down syndrome without consideration of cognitive decline or clinical status. Other studies reported cognitive decline associated with amyloid β burden and estimated years to Alzheimer's disease symptom onset in Down syndrome. Amyloid age estimates have also been established for older neurotypical adults and compared with cognitive performance, but this has not been investigated in individuals with Down syndrome.

Added value of this study

The timeline to symptomatic Alzheimer's disease in relation to amyloid burden, expressed as duration of amyloid β positivity, and tau spread has yet to be described in adults with Down syndrome. Our longitudinal study is the first to provide a timeline of cognitive decline and transition to mild cognitive impairment and dementia in relation to amyloid β positivity and tau burden.

Implications of all the available evidence

In a cohort study of 167 adults with Down syndrome, based on cross-sectional data, cognitive decline and tau desposition began 2·7 years after reaching the threshold for amyloid β positivity (equating to 18 centiloids). Adults with Down syndrome converted to mild cognitive impairment around 7 years after reaching the threshold for amyloid β positivity and to dementia around 12–13 years after reaching the threshold. This shortened timeline reporting symptoms of Alzheimer's disease from reaching the threshold for amyloid β positivity and tau deposition in Down syndrome based on amyloid age (or corresponding centiloid values) could inform the design of clinical trials of Alzheimer's disease interventions, and they might be of use in clinical settings for counselling.

syndrome[3] mirrors the pattern seen in individuals with sporadic late-onset Alzheimer's disease.[5] Subsequent to reaching the threshold for amyloid β-positivity (equating to 18 centiloids) on PET, neurofibrillary tau deposition is observed, following the conventional Braak staging of tau pathology, and it is similar to the patterns of tau spread noted in people with sporadic late-onset Alzheimer's disease and autosomal-dominant Alzheimer's disease.[6,7]

To facilitate therapeutic Alzheimer's disease trials in people with Down syndrome, and to inform clinical decisions, the timeline to symptomatic Alzheimer's disease based on amyloid β and tau neuropathology, as assessed on PET imaging, needs to be established. Initial work has evaluated Alzheimer's disease biomarkers in relation to estimated years to symptom onset (EYO), by subtracting an individual with Down syndrome's chronological age from the population-mean age of symptomatic Alzheimer's disease onset, which is 52·5 years.[1,8] In autosomal-dominant Alzheimer's disease, EYO is measured based on parent's age of onset, providing more accurate patient-specific estimates. Thus, timelines based on EYO in Down syndrome do not account for within-population variability in the age of onset of symptomatic Alzheimer's disease, with sample mean onset ranging from 45–58 years.[1] The range in Alzheimer's disease symptom onset is related to heterogeneity in the age of individuals reaching the amyloid β positivity threshold across individuals with Down syndrome, which is shown to span from age 36 to 55 years.[4,9] This heterogeneity in age at which individuals reach the amyloid β positivity threshold limits the utility of Alzheimer's disease timelines based on EYO.

To address these limitations, Alzheimer's disease timelines based on amyloid β positivity, or so-called amyloid age, have been created for older neurotypical adults with a family history of Alzheimer's disease[10,11] and individuals with Down syndrome.[12] These estimates of amyloid age were produced from longitudinal PET data and based on trajectory modelling that predicts the number of years that an individual has been positive for amyloid β deposition (≥18 centiloids), with the timeline centred at zero years (equating to 18 centiloids).[10,12] In our previous research, amyloid age had robust associations with the timing of PET tau deposition in people with Down syndrome,[12] and increases in tau were identified during the first 2·5–5·0 years after the detection of amyloid β positivity. The timing of Alzheimer's disease symptom onset in relation to amyloid age, and relative to tau, remains unknown in Down syndrome.

Previous studies in individuals with Down syndrome have shown associations between amyloid β-PET and Alzheimer's disease-related cognitive impairment.[13–15] Across 3 years, increases in amyloid β-PET predicted declines in memory, executive functioning, and motor processing speed before onset of dementia in Down syndrome.[16] Adults with Down syndrome who were amyloid β-positive (≥18 centiloids) had greater memory decline relative to those who had minimal amyloid β deposition or who became amyloid β-positive during the study.[13] Among individuals with Down syndrome who were amyloid β-positive, cognitive declines were only evident with elevated tau, suggesting a short time lag between tau deposition and Alzheimer's disease symptom onset.[17]

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In the present study, we aimed to establish the timeline to symptomatic Alzheimer's disease in relation to amyloid age and relative to tau deposition in Down syndrome. The main hypothesis was that after the onset of amyloid β positivity, cognitive decline would be closely linked to tau deposition, with the transition to mild cognitive impairment and dementia observed shortly after. This work is timely, considering the publication of updated Alzheimer's Association workgroup guidelines that base diagnosis and initial Alzheimer's disease staging on amyloid positivity.[18]

Methods

Study design and participants

For this prospective, longitudinal, observational cohort study, we analysed data that had been collected at four university research sites in the UK and USA (University of Cambridge [Cambridge, UK], University of Wisconsin-Madison [Madison, WI, USA], University of Pittsburgh [Pittsburgh, PA, USA], and Washington University in St Louis [St Louis, MO, USA]) as part of the Alzheimer Biomarker Consortium–Down Syndrome (ABC–DS) study.[19] Participants who provided data for our study were recruited to the ABC–DS cohort, and study visits were completed between 2017 and 2022. Participants were eligible for inclusion in ABC–DS if they were aged 25 years or older, had a mental age of at least 3 years (based on standardised intelligence quotient tests), and had trisomy 21 (full, mosaic, or translocation) confirmed through karyotyping. Exclusion criteria included an untreated or unstable medical or psychiatric condition that impaired cognition or a condition that was a contraindication for MRI (eg, metallic implants). The ABC–DS study protocol was approved by a central institutional review board (Advarra Pro00044843) and written informed consent was obtained from all participants or their legal representatives.

Procedures

As part of ABC–DS, participants underwent PET and MRI imaging and completed a series of cognitive tests at baseline and at 32 months. A study partner reported the participant's age, biological sex, race, ethnicity, participant's functioning, behaviour, and medical history. *APOE* ε4 status (present or absent) was determined through genetic testing. Premorbid intellectual disability level (ie, intellectual disability level before the manifestation of any dementia symptoms) was estimated using the Stanford-Binet Intelligence Scale, fifth edition,[20] whereby intelligence quotient was coded as mild, moderate, or severe or profound.

To assess cognitive functioning, three tests from the ABC–DS protocol were used: the Down Syndrome Mental Status Examination (DSMSE);[21] the modified Cued Recall Test (mCRT);[22] and the National Task Group-Early Detection Screen for Dementia (NTG-EDSD).[23] These three tests were selected because they have been shown to be sensitive to detecting early Alzheimer's disease-related decline in people with Down Syndrome. The DSMSE has clinical utility for distinguishing adults with Down syndrome with Alzheimer's disease dementia from those without.[24] Scores on the DSMSE range from 0 to 87, with higher scores indicating better cognitive performance. The mCRT measures episodic memory and is sensitive to Alzheimer's disease dementia in Down syndrome.[25] Total scores on the mCRT range from 0 to 36, with higher scores indicating better memory; the mCRT intrusion score specifies the number of incorrect items (ie, memory errors). The NTG-EDSD is an informant report that assesses functional and behavioural dementia-related changes. The six-domain total score ranges from 0 to 51, with higher values indicating more dementia symptoms. The NTG-EDSD is an accurate screen for mild cognitive impairment (area under the curve [AUC] 0·76) and dementia (AUC 0·94) in individuals with Down syndrome.[26]

Clinical status (categorised as cognitively stable, mild cognitive impairment, or dementia) was determined from a consensus process independent of imaging results.[19] Cognitive test results were reviewed, alongside a participant's medical and psychiatric history, by study clinicians and staff.[19] If cognitive or functional declines were observed, but medical or psychiatric conditions or life changes could not be ruled out as the cause, a status of unable to determine was assigned.

T1-weighted MRI scans were completed on a Signa 750 machine (GE Healthcare, Chicago, IL, USA) at the University of Wisconsin-Madison; on a MAGNETOM Trio or Prisma machine (Siemens, Erlangen, Germany) at the University of Pittsburgh and Washington University-St Louis; and on a Signa PET/MR machine (GE Healthcare) at the University of Cambridge; all MRIs were processed using FreeSurfer (version 5.3.0). PET scans were performed on a ECAT HR+ scanner (Siemens) at the University of Wisconsin-Madison and University of Pittsburgh; on a four-ring Biograph mCT machine (Siemens) at the University of Wisconsin-Madison, University of Pittsburgh, and the Washington University-St Louis; and on a Signa PET/MR machine (GE Healthcare) at the University of Cambridge.[11] To assess amyloid β deposition, 15 mCi ^{11}C-PiB was injected intravenously, and PET scans were acquired after 50–70 min. Standardised uptake value ratio images were generated using grey matter cerebellum as the reference. Following the ^{11}C-PiB scan, 10 mCi ^{18}F-AV-1451 was injected intravenously to assess tau spread, and measurements were acquired after 80–100 min.

Amyloid was initially quantified using the amyloid load metric and equivalent centiloids. In a previous study,[12] we established a population-based trajectory of amyloid β increase in Down syndrome using a sampled iterative local approximation algorithm, which is publicly available. Briefly, longitudinal amyloid β PET trajectories with respect to chronological age were

For more on the **local approximation algorithm** see https://github.com/Betthauser-Neuro-Lab/SILA-AD-Biomarker

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modelled using the Euler method to generate a population-averaged curve of amyloid β centiloids with respect to time, denoted as amyloid age. Amyloid age of 0 years represents the onset of PET amyloid β positivity, defined as 18 centiloids for this population (chronological age approximately 42 years).[9] Then, individual amyloid β centiloid values were aligned to this curve to determine amyloid age. Amyloid age was subtracted from the participant's chronological age to determine the estimated years to or from amyloid β positivity.

Statistical analysis

Analyses were based on all available data from the relevant ABC–DS data collection sites and was a convenience sample of adults with Down Syndrome who volunteered to be part of a research study. Distributions for amyloid age, tau PET, and cognitive variables were examined for skewness and outliers. Generalised linear models examined the association between amyloid age (considering up to cubic polynomials) and mCRT, DSMSE, and NTG-EDSD at baseline, controlling for sex, premorbid intellectual disability, and *APOE* ε4. For participants with longitudinal data, cognitive change scores were created (32-month follow-up minus baseline scores). Generalised linear models evaluated the association between amyloid age and cognitive change scores with the same covariates (sex, premorbid intellectual disability, and *APOE* ε4). Next, generalised linear models examined the association between amyloid age and tau PET in Braak neurofibrillary tangle stages I–II, III–IV, and V–VI,[12] controlling for sex, premorbid intellectual disability, and *APOE* ε4 for baseline and longitudinal data. The striatum was excluded from the neurofibrillary tangles regions due to off-target ^{18}F-AV-1451 binding. Cross-sectional comparisons between amyloid age and tau PET have been previously reported,[12] and were included in the current study to compare cognitive performance and Alzheimer's disease clinical status. The mcp package in R identified, using broken stick regression, the amyloid age that corresponded to decreases in cognitive performance and increases in tau PET

	Total (n=167)	Cognitively stable (n=141)	Mild cognitive impairment (n=8)	Alzheimer's disease (n=7)	Unable to determine (n=11)
Age, years	38·91 (8·47)	37·16 (7·41)	48·88 (5·08)	52·00 (3·83)	45·73 (10·13)
Amyloid-β positivity	56 (34%)	36 (26%)	7 (88%)	7 (100%)	6 (55%)
Amyloid age, years	–2·05 (7·06)	–3·70 (5·64)	7·40 (6·58)	12·72 (5·61)	2·89 (6·66)
Neurofibrillary tangle stage					
I–II	1·19 (0·21)	1·14 (0·14)	1·56 (0·28)	1·52 (0·30)	1·35 (0·34)
III–IV	1·14 (0·21)	1·09 (0·09)	1·51 (0·32)	1·64 (0·45)	1·26 (0·27)
V–VI	1·10 (0·22)	1·05 (0·08)	1·44 (0·40)	1·66 (0·60)	1·17 (0·18)
Sex					
Male	85 (51%)	69 (49%)	6 (75%)	4 (57%)	6 (55%)
Female	82 (49%)	72 (51%)	2 (25%)	3 (43%)	5 (45%)
Premorbid intellectual disability					
Mild	92 (55%)	78 (55%)	5 (63%)	4 (57%)	5 (45%)
Moderate	53 (32%)	42 (30%)	3 (37%)	3 (43%)	5 (45%)
Severe or profound	22 (13%)	21 (15%)	..	..	1 (10%)
Karyotype					
Trisomy 21	148 (88%)	123 (87%)	7 (88%)	7 (100%)	11 (100%)
Mosaicism	5 (3%)	4 (3%)	1 (12%)	..	..
Translocation	13 (8%)	13 (9%)	..	..	..
Not available	1 (1%)	1 (1%)	..	..	..
Ethnicity					
Not Hispanic or Latino	164 (98%)	138 (98%)	8 (100%)	7 (100%)	11 (100%)
Hispanic Latino	3 (2%)	3 (2%)	..	..	..
mCRT total score (n=158*)	31·58 (6·72)	33·21 (4·13)	22·25 (9·29)	18·71 (9·46)	23·57 (12·71)
mCRT Intrusion score (n=158*)	4·56 (5·53)	3·36 (3·60)	10·38 (5·85)	15·71 (9·76)	10·00 (10·75)
DSMSE (n=160†)	64·30 (12·53)	66·25 (11·18)	59·50 (9·79)	46·50 (12·04)	49·14 (17·12)
NTG-EDSD 6-domain score (n=166‡)	3·38 (6·10)	1·40 (2·33)	8·38 (5·01)	19·00 (8·69)	16·55 (8·41)

Data are mean (SD) or n (%). Descriptive statistics at baseline. mCRT=Modified Cued Recall Test. DSMSE=Down Syndrome Mental Status Examination. NTG-EDSD=National Task Group-Early Detection Screen for Dementia. *Data were missing for five participants in the congitively stable group and four participants from the unable to determine group. †Data were missing for three participants in the congitively stable group and four participants in the unable to determine group. ‡Data were missing for one participant in the Alzheimer's disease group.

Table 1: **Participant characteristics**

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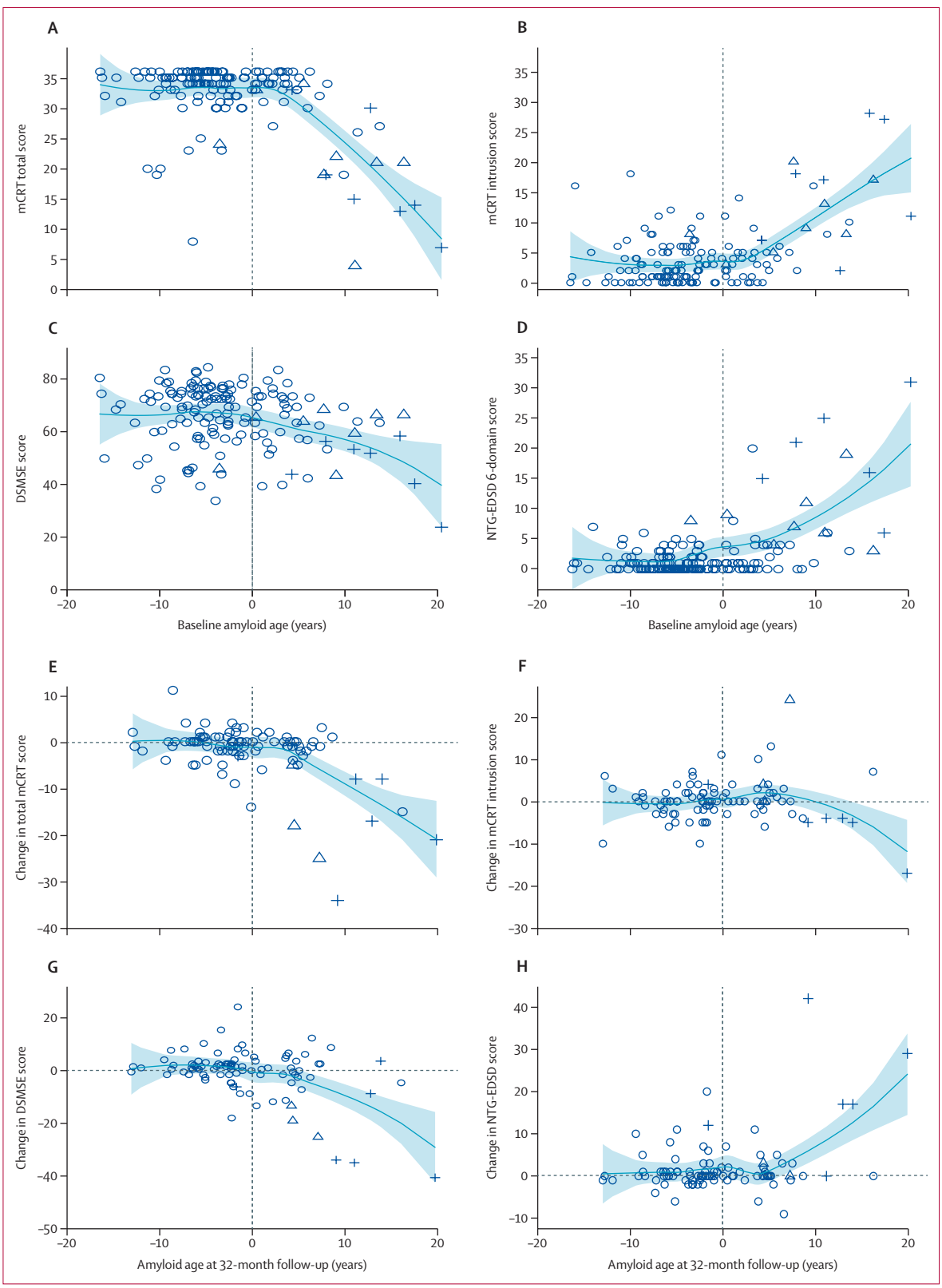

Figure 1: **Associations between amyloid age and cognitive performance**
Scatterplots and Loess visualisations of the association between amyloid age and mCRT total score (A), mCRT intrusion score (B), DSMSE score (C), and NTG-EDSD score (D) at baseline (n=167), and change in mCRT total score (E), mCRT intrusion score (F), DSMSE score (G), and NTG-EDSD score (H) at 32-month follow-up (n=92). The solid lines shows the loess regression curves and the shaded areas show the 95% CIs. Circles represent participants who were cognitively stable at baseline. Triangles represent individuals with mild cognitive impairment at baseline. Crosses represent participants with Alzheimer's disease at baseline. An amyloid age of −10 years is equal to −0·3 centiloids, 0 years to 18 centiloids, 10 years to 75·1 centiloids, and 20 years to 160·3 centiloids; an amyloid age of 0 years indicates amyloid β positivity. mCRT=Modified Cued Recall Test. DSMSE=Down Syndrome Mental Status Examination. NTG-EDSD=National Task Group-Early Detection Screen for Dementia.

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following amyloid β positivity. This approach assumes the slope before the change point is zero (plateau), and uses a Bayesian approach to identify change points and model the regression function flexibly. A non-zero after-change point slope is considered if its 95% credible interval does not cross zero. Finally, amyloid age and tau PET were compared between participants by Alzheimer's disease clinical status using one-way ANOVA with Tukey's honestly significant difference test.

Role of the funding source

The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

167 adults with Down syndrome, of whom 92 had longitudinal data, were included in our analyses. Participant demographics are shown in table 1 (appendix p 2). No significant differences were identified between participants for whom only baseline data were available and those for whom longitudinal data were available (p=0·13 to p=0·49), with regard to the distribution by sex (χ^2=0·5), race (χ^2=2·5), ethnicity (χ^2=0·6), *APOE* ε4 (χ^2=0·4), Down syndrome type (χ^2=1·5), or premorbid intellectual disability (χ^2=4·1). However, participants with longitudinal data were a mean of 3 years younger than were those with only baseline data available (*t*=2·65; p=0·0089). The mean duration between visits was 37 months (SD 6·3). During the study, three (3%) of 167 participants converted from cognitively stable to mild cognitive impairment, one (1%) from cognitively stable to dementia, and five (5%) from mild cognitive impairment to dementia. Amyloid age and DSMSE scores were normally distributed. There was slight skewness for the mCRT total score (skew –2·3), mCRT intrusion score (skew 2·1), NTG-EDSD score (skew 2·8), and tau PET (skew 1·7–4·2), which was expected considering that most participants were cognitively stable. Log transformations were computed for cognitive and tau variables, and generalised linear models were re-run, and

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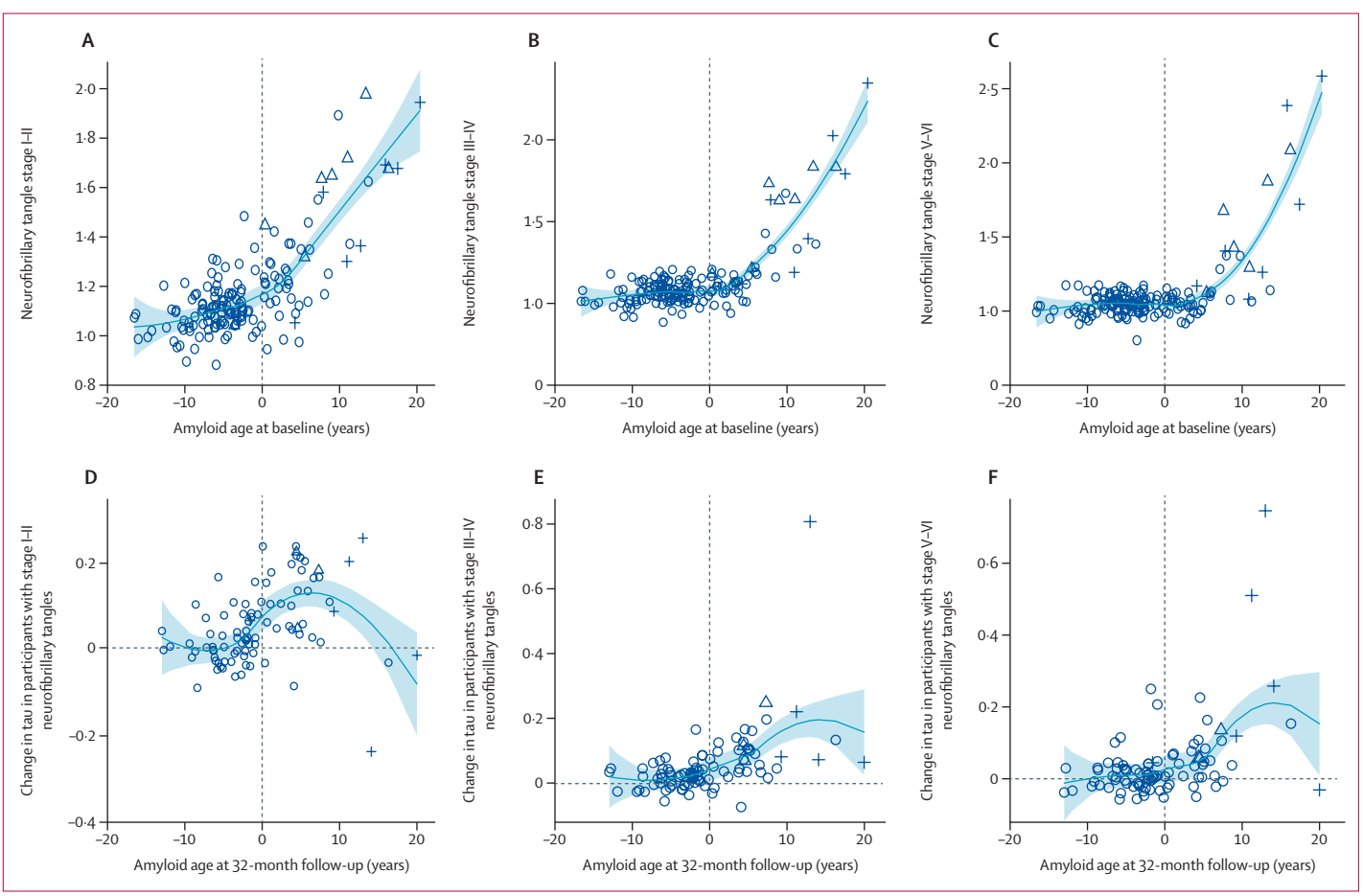

Figure 2: **Associations between amyloid age and tau**

Scatterplots and Loess visualisations of the association between amyloid age and tau stage I–II (A), stage III–IV (B), and stage V–VI (C) neurofibrillary tangles at baseline, and change in tau stage I–II (D), stage III–IV (E), and stage V–VI (F) neurofibrillary tangles at 32-months' follow-up. The solid lines show the loess regression curves and the shaded areas show the 95% CIs. Circles represent participants who were cognitively stable at baseline. Triangles represent individuals with mild cognitive impairment at baseline. Crosses represent participants with Alzheimer's disease at baseline. An amyloid age of –10 years is equal to –0·3 centiloids, 0 years to 18 centiloids, 10 years to 75·1 centiloids, and 20 years to 160·3 centiloids; an amyloid age of 0 years indicates amyloid β positivity.

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the same pattern of significant effects was observed for the transformed and non-transformed variables. For the sake of interpretability, the non-transformed models are presented here, because they are meaningful in a clinical context. Of the 167 participants, 56 (34%) were amyloid β-positive at baseline. Key variables were examined by site, and no meaningful differences were detected.

Generalised linear models examined the effect of baseline amyloid age on baseline cognitive performance, controlling for covariates. No covariate met criteria for collinearity (p=0·27 to p=0·91). A significant association was identified between premorbid intellectual disability and mCRT and DSMSE scores. Participants with mild intellectual disability had higher mCRT total scores and DSMSE scores than did those with moderate or severe intellectual disability (appendix p 3). There was also a significant association between sex and baseline DSMSE scores; DSME scores were a mean of 3·3 points higher in females than males (mean score 62·73 [SD 12·82] for males *vs* 65·99 [12·07] for females). *APOE* ε4 was not a significant predictor in models and nor was it associated with amyloid age when controlling for chronological age (*r*=0·09; p=0·20). A quadradic association was identified between amyloid age and mCRT total score (R^2=0·48; p<0·0001), mCRT intrusion score (R^2=0·44; p<0·0001), DSMSE score (R^2=0·52; p<0·0001), and NTG-EDSD score (R^2=0·25; p<0·0001). Models predicting longitudinal cognitive change showed a significant quadratic effect of amyloid age for all outcomes except mCRT intrusion score (figure 1; appendix p 3).

Generalised linear models assessed the effect of baseline amyloid age on baseline tau PET in neurofibrillary tangle stages I–II, III–IV, and V–VI, controlling for covariates. A quadradic association was identified between amyloid age and neurofibrillary tangles stages I–II (R^2=0·64; p<0·0001) and cubic associations between amyloid age and neurofibrillary tangle stages III–IV (R^2=0·77; p<0·0001) and neurofibrillary tangle stages V–VI (R^2=0·75; p<0·0001). Models predicting tau change showed cubic associations between amyloid age and all neurofibrillary tangle stages (figure 2; appendix p 4).

Broken stick regressions identified change points after amyloid β positivity for cognitive measures (tables 2 and 3). These estimates provide the mean time between reaching the threshold for amyloid β positivity and cognitive decline or an increase in dementia symptoms would be expected. In models predicting baseline performance, after detection of amyloid β positivity, there was a mean change point of 2·7 years for the mCRT total score, 2·8 years for mCRT intrusions, and 3·8 years for the NTG-EDSD score. After these change points, mCRT total score decreased by 1·3 points per year, mCRT intrusions increased by 1·0 point, and NTG-EDSD score increased by 0·8 points per year. Change points after amyloid β positivity were also identified for tau deposition relative to amyloid age. There was a mean change point of 2·7 years for neurofibrillary tangle stages I–II, 3·4 years for neurofibrillary tangle stages III–IV, and 6·1 years for neurofibrillary tangle stages V–VI (table 2). After these change points, tau PET increased by 0·04–0·08 units per year.

In models predicting change in cognitive measures from baseline to 32-month follow-up, there was a change point of 3·6 years for the mCRT total score. After this change point, the mCRT total score decreased by 1·0 point per year. A significant change point was identified for the NTG-EDSD score at 5·4 years, with scores increasing by 1·0 point per year thereafter (table 2). No significant change slopes were identified after the detection of amyloid β positivity in neurofibrillary tangle stages I–VI from baseline to 32-month follow-up.

Alzheimer's disease clinical status at baseline was significantly associated with amyloid age (p<0·0001).

	Cognitive functioning *vs* amyloid age (baseline)			Slope after change point		
	Change point (years)	Lower	Upper	Mean	Lower	Upper
mCRT total score	2·68*	0·21	5·40	−1·33	−1·83	−0·88
mCRT intrusion score	2·76*	0·21	5·40	0·99	0·60	1·40
DSMSE score	8·51	0·22	17·70	−1·12	−3·55	0·88
NTG-EDSD 6-domain score	3·80*	0·21	8·31	0·80	0·28	1·34
Change in tau in people with stage I–II NFTs	2·71*	0·24	4·99	0·04	0·03	0·05
Change in tau in people with stage III–IV NFTs	3·38*	1·44	5·14	0·06	0·05	0·07
Change in tau in people with stage V–VI NFTs	6·11*	3·18	10·50	0·08	0·05	0·14

mCRT=modified Cued Recall Test. DSMSE=Down Syndrome Mental Status Examination. NTG-EDSD=National Task Group-Early Detection Screen for Dementia. *Significant non-zero slope based on 95% credible interval after the change point.

Table 2: **Broken stick regression identifying change point in cognitive performance and tau in relation to amyloid age for individuals with amyloid age values of ≥0 at baseline**

	Cognitive change score *vs* amyloid age (32-month follow-up)			Slope after the change point		
	Change point (years)	Lower	Upper	Mean	Lower	Upper
Change in mCRT total score	3·56*	0·03	8·97	−0·98	−1·73	−0·24
Change in mCRT intrusions	8·63	0·05	18·00	−0·46	−1·34	0·39
Change in DSMSE score	6·54	0·04	16·40	−1·05	−2·50	0·45
Change in NTG-EDSD 6-domain score	5·43*	0·03	12·80	1·03	0·01	2·08
Change in tau in people with stage I–II NFTs	9·04	0·52	18·80	−0·01	−0·02	0·01
Change in tau in people with stage III–IV NFTs	7·57	0·03	18·30	0·01	−0·01	0·02
Change in tau in people with stage V–VI NFTs	5·69	0·03	17·20	0·01	−0·01	0·02

mCRT=modified Cued Recall Test. DSMSE=Down Syndrome Mental Status Examination. NTG-EDSD=National Task Group-Early Detection Screen for Dementia. *Significant non-zero slope based on 95% credible interval after the change point.

Table 3: **Broken stick regression identifying change point in cognitive performance and tau in relation to amyloid age for individuals with amyloid age values of ≥0 at the 32-month follow-up**

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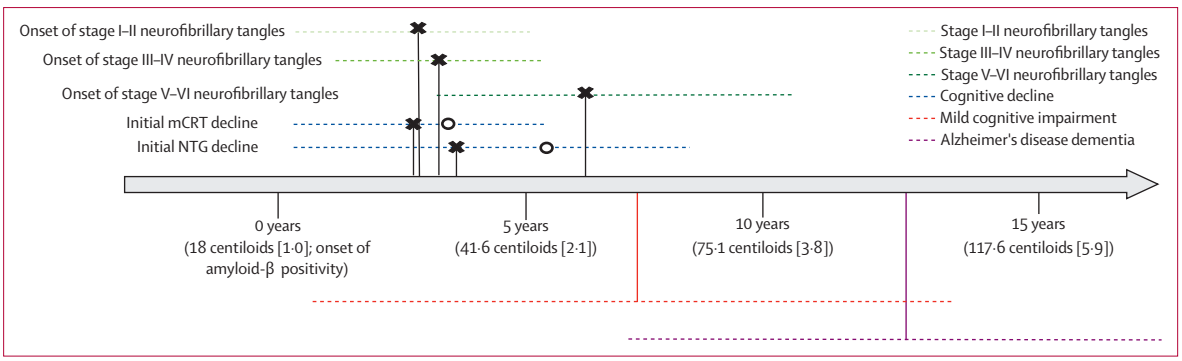

***Figure 3*: Timeline to symptomatic Alzheimer's disease in Down syndrome**

Crosses show mean change points for cross-sectional cognitive decline (mCRT and NTG-EDSD) and tau (stage I–VI Braak neurofibrillary tangles) and circles show mean change points for longitudinal cognitive decline. Blue and green dotted lines indicate cognitive decline and tau upper and lower ranges. Red lines show average mean amyloid age for mild cognitive impairment and purple lines show Alzheimer's disease dementia. Dotted red and purple lines show SDs. Mean centiloids (SD) are provided in 5-year increments. mCRT=Modified Cued Recall Test. NTG=National Task Group-Early Detection Screen for Dementia.

Participants who were cognitively stable at baseline had a mean amyloid age of –3·7 years (SD 5·6), which was lower than for participants with mild cognitive impairment (7·4 years [6·6]) or dementia (12·7 years [5·6]; p<0·0001; appendix p 2). Alzheimer's disease clinical status at baseline was significantly associated with neurofibrillary tangle tau PET stage I–II (p<0·0001), neurofibrillary tangle stage III–IV (p<0·0001), and neurofibrillary tangle stage V–VI (p<0·0001; appendix p 6). Across all neurofibrillary tangle regions, cognitively stable participants had lower tau PET than did those with mild cognitive impairment or dementia (p<0·0001). Figure 3 shows the timeline of tau spread, cognitive decline, mild cognitive impairment, and dementia, based on amyloid age.

Discussion

The present study describes the timeline of symptomatic Alzheimer's disease relative to duration of amyloid β positivity (amyloid age) in people with Down syndrome. Amyloid age can be directly related to centiloid magnitude, and thus this timeline is of high clinical utility for Alzheimer's disease intervention trials and clinical practice. Our findings indicate that cognitive performance remains stable for the first 2–3 years after detection of amyloid β positivity before declining. After this stable period (2·7 years based on baseline and 3·6 years based on change scores), mCRT total and intrusion scores decreased by 1·3 and 1·0 points per year, respectively. For mCRT intrusions, a change point was identified at 2·8 years after detection of amyloid β positivity, with an increase of 1·0 intrusions per year thereafter. Changes in the NTG-ESDS score did not begin until 3·8 years (baseline) or 5·4 years (32-month follow-up) after onset of amyloid β positivity. The 2–3 year lag in change on the NTG-EDSD score (baseline change point 6·1 years and 5·4 years for change scores), relative to mCRT (baseline change point 2·7 years and 3·6 years for change scores), is consistent with previous reports that episodic memory is affected early in Alzheimer's disease in people with Down syndrome[27] and direct measures are more sensitive to early declines than are informant reports.[26]

Longitudinal change point estimates and slopes were more conservative than were the cross-sectional findings, which could be due to differences in sample sizes or the slightly younger age of the longitudinal cohort. Alternatively, some individuals with Down syndrome predicted to show declines might not have due to resiliency factors. Change points from the within-person longitudinal analyses, which are generally viewed as more robust than cross-sectional estimates, can guide longitudinal clinical Alzheimer's disease intervention design. Efficacious interventions involving the mCRT total score as an outcome would be expected to demonstrate delayed onset of decline after detection of amyloid β positivity (>3·6 years) or slowed rate of decline (<1·3 points per year) relative to this natural history cohort. This study also offers meaningful information for entering individuals with Down syndrome into clinical trials of Alzheimer's disease interventions. Intervention effects might be optimised for individuals with Down syndrome who have not yet reached amyloid β positivity or within the first 3 years of being amyloid β positive, since cognitive decline has not yet begun.

Change points in tau deposition were identified in models using baseline data. Increases in tau deposition occurred between 2·7–6·1 years after reaching the threshold for amyloid β positivity. The timing of tau deposition in people with stage I–II neurofibrillary tangles is closely aligned with initial cognitive decline in Down syndrome. Cognitive declines in people with stage V–VI neurofibrillary tangles lag by an estimated 3 years from initial medial temporal tau deposition, consistent with our previous findings.[12] When evaluating change in neurofibrillary tangles, an initial rapid increase in tau was observed after amyloid β positivity before reaching a plateau or, in the case of stage I–II neurofibrillary tangles, decrease at high amyloid age (≥15 years; 117·6 centiloids).

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In Down syndrome, ventricle enlargement occurs with ageing and Alzheimer's disease, which erodes the stage I–II neurofibrillary tangle regions of interest and introduces partial volume effects. The change observed in people with stage III–IV neurofibrillary tangles has greater uncertainty at high amyloid ages due to the small sample size in this range. Trajectories at high amyloid ages (or centiloid values) should be modelled as ABC–DS progresses.

Similar to previous findings,[12,16] we did not observe effects of sex or *APOE* ε4 on imaging or mCRT and NTG-EDSD outcomes. This finding distinguishes people with Down syndrome from those with sporadic late-onset Alzheimer's disease, because individuals with *APOE* ε4 and women have a higher risk of sporadic Alzheimer's disease.[28] Other Down syndrome studies have identified effects of *APOE* ε4 on Alzheimer's disease biomarker onset,[29] in which dementia occurs around 2 years earlier in people with Down syndrome and *APOE* ε4 versus people with Down syndrome who are *APOE* ε4 carriers.[30] Considering the young age of our cohort, and low incidence of mild cognitive impairment and dementia, we might be evaluating biomarker changes too early to capture the effects of APOE status.

The current study is the first to report the timing of mild cognitive impairment and dementia relative to amyloid age and in relation to tau burden in Down syndrome. Mean amyloid age for individuals with Down syndrome with mild cognitive impairment was 7·4 years (SD 6·6) and 12·7 years (5·6) years for those with dementia, corresponding to 62·1 and 99·3 centiloids, respectively. This suggests a potentially accelerated timeline to Alzheimer's disease symptomology in Down syndrome relative to sporadic late-onset Alzheimer's disease, where progression to mild cognitive impairment occurs 15·5 years after amyloid β positivity.[11] This accelerated timeline in Down syndrome mirrors that of autosomal-dominant Alzheimer's disease.[8] Individuals with Down syndrome with a clinical status classified as unable to determine had a mean amyloid age of 2·9 years. Many of these individuals were likely to have initial Alzheimer's disease-related symptoms, matching their biomarker profile.

A limitation of the current study is that we included a low proportion of individuals with mild cognitive impairment or dementia, which means that the amyloid age of individuals in these groups (as opposed to amyloid age at initial transition to these clinical statuses) was evaluated. Thus, the amyloid age values associated with mild cognitive impairment or dementia might be overestimated. Additionally, negative amyloid age estimates (ie, amyloid age <0 years) have poor predictive power in determining amyloid β positivity directly due to the native signal detection limits of PET scanners. This limitation was mitigated by focusing on inflection points after reaching the threshold for amyloid β positivity (amyloid age 0 years, 18 centiloids). Future work should also include comparisons between amyloid age and CSF and plasma Alzheimer's disease biomarkers. Another limitation is that longitudinal models were based on two data collection cycles spanning 32 months; however, longer time frames should be evaluated in future studies. Analyses included a zero slope before the change point in broken stick regressions, which was consistent with data visualisation and consistent with previous research showing stable cognitive performance early during the fifth decade of life (ie, age ≥40 years).[14] Future research with larger sample sizes could afford even greater sensitivity to account for any subtle fluctuations in cognitive performance prior to Alzheimer's disease-related decline. Additionally, models were controlled for sex, premorbid intellectual disability, and *APOE* ε4. Future research should examine the role of these variables and other lifestyle variables (eg, physical activity and cognitive stimulation) and health variables (eg, cardiovascular conditions) as potential resiliency effects that alter the timeline from amyloid β positivity to Alzheimer's disease symptomology in Down syndrome. The study sample represents the adult population of people with Down syndrome in terms of sex and premorbid intellectual disability level, but includes a greater proportion of participants who were White and non-Hispanic than the broader population with Down syndrome. Efforts are needed to increase participation from under-represented groups in Down syndrome Alzheimer's disease research. Although DSMSE declines were associated with amyloid age, significant inflection points of change were not detected potentially due to higher between and within-person variability in DSMSE scores. The DSMSE also assesses a wide range of cognitive skills and might better capture advanced stages in Alzheimer's disease progression.

This study documents the timeline to Alzheimer's disease symptomology in relation to amyloid age and tau in Down syndrome. Findings indicate a short time relative to sporadic late-onset Alzheimer's disease from amyloid β positivity to initial cognitive decline (3 years) in Down syndrome, with declines closely associated with tau in neurofibrillary tangle stage I–II and III–IV.[31] Tau in stage V–VI neurofibrillary tangles was estimated to increase 6 years after detection of amyloid β positivity. On average, individuals with Down syndrome transition to mild cognitive impairment after around 7 years of amyloid β positivity and dementia after around 12–13 years of amyloid β positivity. Our Alzheimer's disease symptom timeline based on amyloid age can be directly related to centiloid magnitude[12] and thus has utility for Alzheimer's disease clinical trials and practice. For example, an adult with Down syndrome with PET centiloid of 31, which equates to an amyloid age of 3 years, has an estimated 4 years to mild cognitive impairment and 9 years to Alzheimer's disease dementia. Timelines based on amyloid age offer improvements over timelines based on EYO, which do not account for

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within-population variability in age at which amyloid β positivity is detected in Down syndrome. The amyloid age estimates used in this study are publicly available[12] and provide the timeline to Alzheimer's disease symptomology without intervention, information that is needed for clinical trials of Alzheimer's disease interventions in Down syndrome.

Contributors

EKS, MDZ, and SLH wrote the original draft of the manuscript with support from BTC and BLH. BTC and SLH conceptualised the paper. BLH, BTC, and SLH verified underlying data. Formal analysis and data visualizations were carried out by JW, EKS, and MDZ. All authors reviewed the final manuscript, had access to raw data, and had final responsibility for the decision to submit for publication. Funding was acquired by BLH, BTC, SLH, and the Alzheimer's Biomarker Consortium–Down Syndrome (ABC–DS; https://www.nia.nih.gov/research/abc-ds#data).

Declaration of interests

MZ received honoraria from LuMind International Down Syndrome Community and a travel award from the Trisomy21 Research Society. BH receives royalties from two co-authored books; is paid consulting fees from Patient-Centered Outcomes Research Institute grant; received honoraria from the University of North Carolina; and served on a data monitoring board for a Department of Defense funded grant. TB has received honoraria from National Institutes of Health and Intermountain Healthcare; and travel support from University College London, the Alzheimer's Association, and National Institutes of Health. DLT participated in the REMBRAND study advisory board. SZ reports grants from Cambridgeshire and Peterborough Foundation National Health Service Trust and serves on committees for the Trisomy21 Research Society. MM receives royalties from University of Rochester; and consulting fees from NovoGlia and Ireneo Health; has US patents (numbers 7 645 140, 10 578 629, #10 718 021, 10 890 589, 10 900 977, and 10 900 980); serves on the scientific advisory board for Brain Neurotherapy Bio, Davis Phinney Foundation for Parkinson's, and Alzheon; is the chair of data and safety monitoring board for the Aerobic Exercise and Cognitive Training Trial; and owns stock in Ireneo Health. EH reports grants from Brightfocus and the Alzheimer's Association. ES, JW AC, BA, CL, BC, and SH declare no competing interests.

Data sharing

The data that support the findings of this study are openly available in the ABC-DS database (https://ida.loni.usc.edu/login.jsp?project=ABCDS).

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References

1 Iulita MF, Garzón Chavez D, Klitgaard Christensen M, et al. Association of Alzheimer Disease with life expectancy in people with Down Syndrome. *JAMA Netw Open* 2022; **5:** e2212910.
2 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:** 843–52.
3 Lao PJ, Betthauser TJ, Hillmer AT, et al. The effects of normal aging on amyloid-β deposition in nondemented adults with Down syndrome as imaged by carbon 11-labeled Pittsburgh compound B. *Alzheimers Dement* 2016; **12:** 380–90.
4 Zammit MD, Laymon CM, Betthauser TJ, et al. Amyloid accumulation in Down syndrome measured with amyloid load. *Alzheimers Dement (Amst)* 2020; **12:** e12020.
5 Collij LE, Salvadó G, Wottschel V, et al. Spatial-temporal patterns of β-amyloid accumulation: a subtype and stage inference model analysis. *Neurology* 2022; **98:** e1692–703.
6 Sanchez JS, Becker JA, Jacobs HIL, et al. The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. *Sci Transl Med* 2021; **13:** eabc0655.
7 Therriault J, Pascoal TA, Lussier FZ, et al. Biomarker modeling of Alzheimer's disease using PET-based Braak staging. *Nat Aging* 2022; **2:** 526–35.
8 Boerwinkle AH, Gordon BA, Wisch J, et al. Comparison of amyloid burden in individuals with Down syndrome versus autosomal dominant Alzheimer's disease: a cross-sectional study. *Lancet Neurol* 2023; **22:** 55–65.
9 Zammit MD, Tudorascu DL, Laymon CM, et al. PET measurement of longitudinal amyloid load identifies the earliest stages of amyloid-beta accumulation during Alzheimer's disease progression in Down syndrome. *Neuroimage* 2021; **228:** 117728.
10 Betthauser TJ, Bilgel M, Koscik RL, et al. Multi-method investigation of factors influencing amyloid onset and impairment in three cohorts. *Brain* 2022; **145:** 4065–79.
11 Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. *Alzheimers Dement (Amst)* 2020; **12:** e12007.
12 Zammit MD, Betthauser TJ, McVea AK, et al. Characterizing the emergence of amyloid and tau burden in Down syndrome. *Alzheimers Dement* 2023; **20:** 388–98.
13 Hartley SL, Handen BL, Devenny DA, et al. Cognitive functioning in relation to brain amyloid-β in healthy adults with Down syndrome. *Brain* 2014; **137:** 2556–63.
14 Fortea J, Vilaplana E, Carmona-Iragui M, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. *Lancet* 2020; **395:** 1988–97.
15 Krasny S, Yan C, Hartley SL, et al. Assessing amyloid PET positivity and cognitive function in Down syndrome to guide clinical trials targeting amyloid. *Alzheimers Dement* 2024; **20:** 5570–77.
16 Hartley SL, Handen BL, Devenny D, et al. Cognitive decline and brain amyloid-β accumulation across 3 years in adults with Down syndrome. *Neurobiol Aging* 2017; **58:** 68–76.
17 Hartley SL, Handen B, Tudorascu D, et al. AT(N) biomarker profiles and Alzheimer's disease symptomology in Down syndrome. *Alzheimers Dement* 2023; **19:** e062613.
18 Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement* 2024; **20:** 5143–69.

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19 Handen BL, Lott IT, Christian BT, et al. The Alzheimer's Biomarker Consortium-Down Syndrome: rationale and methodology. *Alzheimers Dement* 2020; **12:** e12065.

20 Roid G. Stanford-Binet Intelligence Scale, Fifth Edition. Riverside Publishing: Itasca, IL, 2003.

21 Haxby JV. Neuropsychological evaluation of adults with Down's syndrome: patterns of selective impairment in non-demented old adults. *J Ment Defic Res* 1989; **33:** 193–210.

22 Devenny DA, Zimmerli EJ, Kittler P, Krinsky-McHale SJ. Cued recall in early-stage dementia in adults with Down's syndrome. *J Intellect Disabil Res* 2002; **46:** 472–83.

23 Esralew L, Janicki MP, Keller SM. Neuropsychological Assessments of Dementia in Down Syndrome and Intellectual Disabilities. In: Prasher VP, ed. National Task Group Early Detection Screen for Dementia (NTG-EDSD). Cham: Springer International Publishing, 2018: 197–213.

24 Krinsky-McHale SJ, Zigman WB, Lee JH, et al. Promising outcome measures of early Alzheimer's dementia in adults with Down syndrome. *Alzheimers Dement (Amst)* 2020; **12:** e12044.

25 Krinsky-McHale SJ, Hartley S, Hom C, et al. A modified cued recall test for detecting prodromal AD in adults with Down syndrome. *Alzheimers Dement* 2022; **14:** e12361.

26 Silverman W, Krinsky-McHale SJ, Lai F, et al. Evaluation of the National Task Group-Early Detection Screen for Dementia: sensitivity to 'mild cognitive impairment' in adults with Down syndrome. *J Appl Res Intellect Disabil* 2021; **34:** 905–15.

27 Benejam B, Aranha MR, Videla L, et al. Neural correlates of episodic memory in adults with Down syndrome and Alzheimer's disease. *Alzheimers Res Ther* 2022; **14:** 123.

28 Pike CJ. Sex and the development of Alzheimer's disease. *J Neurosci Res* 2017; **95:** 671–80.

29 Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol* 2021; **20:** 930–42.

30 Prasher V, Sajith S, Rees S, et al. Significant effect of APOE epsilon 4 genotype on the risk of dementia in Alzheimer's disease and mortality in persons with Down syndrome. *Int J Geriatr Psychiatry* 2008; **23:** 1134–40.

31 Birdsill AC, Koscik RL, Cody KA, et al. Trajectory of clinical symptoms in relation to amyloid chronicity. *Alzheimers Dement* 2022; **14:** e12360.

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