Comparison of amyloid burden in individuals with Down syndrome versus autosomal dominant Alzheimer's disease: a cross-sectional study

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Summary

Background Important insights into the early pathogenesis of Alzheimer's disease can be provided by studies of autosomal dominant Alzheimer's disease and Down syndrome. However, it is unclear whether the timing and spatial distribution of amyloid accumulation differs between people with autosomal dominant Alzheimer's disease and those with Down syndrome. We aimed to directly compare amyloid changes between these two groups of people.

Methods In this cross-sectional study, we included participants (aged ≥25 years) with Down syndrome and sibling controls who had MRI and amyloid PET scans in the first data release (January, 2020) of the Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) study. We also included carriers of autosomal dominant Alzheimer's disease genetic mutations and non-carrier familial controls who were within a similar age range to ABC-DS participants (25–73 years) and had MRI and amyloid PET scans at the time of a data freeze (December, 2020) of the Dominantly Inherited Alzheimer Network (DIAN) study. Controls from the two studies were combined into a single group. All DIAN study participants had genetic testing to determine *PSEN1*, *PSEN2*, or *APP* mutation status. *APOE* genotype was determined from blood samples. CSF samples were collected in a subset of ABC-DS and DIAN participants and the ratio of amyloid β42 (Aβ42) to Aβ40 (Aβ42/40) was measured to evaluate its Spearman's correlation with amyloid PET. Global PET amyloid burden was compared with regards to cognitive status, *APOE ε4* status, sex, age, and estimated years to symptom onset. We further analysed amyloid PET deposition by autosomal dominant mutation type. We also assessed regional patterns of amyloid accumulation by estimated number of years to symptom onset. Within a subset of participants the relationship between amyloid PET and CSF Aβ42/40 was evaluated.

Findings 192 individuals with Down syndrome and 33 sibling controls from the ABC-DS study and 265 carriers of autosomal dominant Alzheimer's disease mutations and 169 non-carrier familial controls from the DIAN study were included in our analyses. PET amyloid centiloid and CSF Aβ42/40 were negatively correlated in carriers of autosomal dominant Alzheimer's disease mutations (n=216; r=–0·565; p<0·0001) and in people with Down syndrome (n=32; r=–0·801; p<0·0001). There was no difference in global PET amyloid burden between asymptomatic people with Down syndrome (mean 18·80 centiloids [SD 28·33]) versus asymptomatic mutation carriers (24·61 centiloids [30·27]; p=0·11) and between symptomatic people with Down syndrome (77·25 centiloids [41·76]) versus symptomatic mutation carriers (69·15 centiloids [51·10]; p=0·34). *APOE* ε4 status and sex had no effect on global amyloid PET deposition. Amyloid deposition was elevated significantly earlier in mutation carriers than in participants with Down syndrome (estimated years to symptom onset –23·0 *vs* –17·5; p=0·0002). *PSEN1* mutations primarily drove this difference. Early amyloid accumulation occurred in striatal and cortical regions for both mutation carriers (n=265) and people with Down syndrome (n=128). Although mutation carriers had widespread amyloid accumulation in all cortical regions, the medial occipital regions were spared in people with Down syndrome.

Interpretation Despite minor differences, amyloid PET changes were similar between people with autosomal dominant Alzheimer's disease versus Down syndrome and strongly supported early amyloid dysregulation in individuals with Down syndrome. Individuals with Down syndrome aged at least 35 years might benefit from early intervention and warrant future inclusion in clinical trials, particularly given the relatively high incidence of Down syndrome.

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See Online for appendix

Introduction

Down syndrome, caused by full or partial triplication of chromosome 21, is one of the most common genetic disorders, with approximately one in 700 children born with Down syndrome in the USA each year.[1] Due to this triplication, individuals with Down syndrome have an extra copy of the *APP* gene and overproduce amyloid β (Aβ). Consequently, almost all adults with Down syndrome develop amyloid plaques and tau neurofibrillary tangles, which are the hallmarks of Alzheimer's disease.[2] Given this fact and the substantial increase in life expectancy in people with Down syndrome, there is a growing population of adults with Down syndrome developing Alzheimer's disease.[1,3]

Previous studies have used cognition, fluid biomarker, and imaging measures to understand the presentation and progression of Alzheimer's disease in individuals with Down syndrome.[3–6] The cognitive symptoms of Alzheimer's disease develop at approximately 50–55 years-of-age in people with Down syndrome, with CSF markers changing years before the onset of these symptoms.[3–5] PET imaging studies have also identified amyloid accumulation in cortical and subcortical brain regions years before the presentation of clinical symptoms.[6] However, questions remain regarding the nature of amyloid deposition in individuals with Down syndrome versus individuals with other forms of Alzheimer's disease, particularly autosomal dominant Alzheimer's disease.

Autosomal dominant Alzheimer's disease, another genetic form of Alzheimer's disease, is caused by mutations in *PSEN1*, *PSEN2*, or *APP* that lead to altered amyloid concentrations. Similar to Down syndrome, carriers of these mutations develop Alzheimer's disease at an earlier age (30–60 years) than do individuals with late-onset Alzheimer's disease (≥65 years).[7] Much of our understanding about the biomarker cascade in sporadic Alzheimer's disease comes from research of genetic forms of the disease, particularly autosomal dominant Alzheimer's disease.[8] However, although mutations causing autosomal dominant Alzheimer's disease are relatively rare, Down syndrome is the most common chromosomal abnormality and is the more common genetic form of Alzheimer's disease.

Studies assessing biomarker changes in Down syndrome and autosomal dominant Alzheimer's disease suggest similarities between these two genetic forms of Alzheimer's disease.[2] As of February, 2022, only two studies have directly compared Down syndrome with autosomal dominant Alzheimer's disease, but were done with a small number of individuals.[9,10] One study[10] comparing amyloid deposition by PET found no differences between people with autosomal dominant Alzheimer's disease mutations

Research in context

Evidence before this study

We searched PubMed for articles in English published between May 1, 2021, and Feb 27, 2022, relating to measures of cerebral amyloid in individuals with Down syndrome or autosomal dominant Alzheimer's disease. Search terms included "amyloid", "Alzheimer disease", "Alzheimer's disease", "autosomal dominant", "cerebral", "cerebrospinal fluid", "Down syndrome", "familial", and "positron emission tomography". Most previous studies examining amyloid changes in Down syndrome were limited by the absence of a comparison with autosomal dominant Alzheimer's disease. Only two studies directly compared the two cohorts but were limited in sample size and generalisability. The first study reported no differences in amyloid PET accumulation between individuals with Down syndrome and people with autosomal dominant Alzheimer's disease, but included only amyloid-positive asymptomatic individuals. The second study evaluated CSF biomarkers and found significantly higher amyloid β40 and amyloid β42 concentrations in individuals with Down syndrome versus those with autosomal dominant Alzheimer's disease.

Added value of this study

To our knowledge, this study is the largest to date looking at amyloid changes in people with genetic forms of Alzheimer's disease. Our study compared amyloid burden on PET between individuals with Down syndrome and people carrying autosomal dominant Alzheimer's disease mutations to assess global and regional amyloid deposition as a function of cognitive performance and age. We also investigated a subset of participants with CSF measures of amyloid to analyse amyloid PET in relation to CSF amyloid concentrations to study the relationship between amyloid clearance and deposition.

Implications of all the available evidence

In our study, amyloid accumulation occurred significantly earlier before symptom onset in carriers of autosomal dominant Alzheimer's disease mutations (–23·0 years) than in people with Down syndrome (–17·5 years), implying the presence of a potential protective factor delaying amyloid accumulation in individuals with Down syndrome. These findings build on previous evidence that amyloid changes measured by CSF occur before cerebral accumulation measured by PET in two different genetic causes of Alzheimer's disease. Despite the relatively higher incidence of Down syndrome compared with autosomal dominant Alzheimer's disease, previous clinical trials in genetic forms of Alzheimer's disease have mainly focused on autosomal dominant Alzheimer's disease. Clinical trials in individuals with Down syndrome could help to examine how amyloid-directed interventions might slow, prevent, or treat Alzheimer's disease. The timing and spatial distribution of amyloid accumulation is important to consider when designing and recruiting participants for clinical trials of amyloid-targeting therapies. The similarities we have found in the pattern of amyloid changes suggest the presence of potential overlap for Alzheimer's disease therapies within genetic forms of Alzheimer's disease.

and people with Down syndrome, but included only amyloid-positive asymptomatic participants. Another study,[9] which evaluated CSF biomarkers, reported greater CSF Aβ40 and Aβ42 concentrations in people with Down syndrome, whether asymptomatic or symptomatic for Alzheimer's disease, than in people with autosomal dominant Alzheimer's disease. These studies suggest that, although Alzheimer's disease pathology might be similar for people with Down syndrome versus autosomal dominant Alzheimer's disease, subtle differences might exist and might influence our understanding of genetic forms of Alzheimer's disease.

We aimed to evaluate amyloid deposition in two large cohorts of people with genetic causes of Alzheimer's disease (Down syndrome *vs* autosomal dominant). We analysed amyloid PET in relation to CSF amyloid concentrations to study the relationship between amyloid clearance and deposition. We also assessed global and regional amyloid PET as a function of cognitive performance and age for individuals with Down syndrome and autosomal dominant Alzheimer's disease. Due to evidence of heterogeneity in amyloid accumulation between patients with autosomal dominant Alzheimer's disease caused by different mutations, we also aimed to compare amyloid PET measures by mutation type.[11] These comparisons will enhance our understanding of genetic forms of Alzheimer's disease and might have important implications for more common forms of Alzheimer's disease, including late-onset Alzheimer's disease. Given the development of novel therapeutics designed to reduce amyloid deposition, our results will have relevance to the use of potential anti-amyloid therapies in individuals with genetic forms of Alzheimer's disease, particularly because clinical trials are now being considered for adults with Down syndrome.[12]

Methods

Study design and participants

In this cross-sectional study, we sourced data from the Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) study, which enrols adults (aged ≥25 years) with Down syndrome and sibling controls from nine sites in the USA and the UK and collects longitudinal clinical, cognitive, imaging, and fluid biomarker data. For this analysis, we only included participants from the first data release (January, 2020) who had MRI and amyloid PET scans. We also sourced data from the observational, longitudinal Dominantly Inherited Alzheimer Network (DIAN) study, which enrols individuals (aged ≥18 years) from families with an autosomal dominant Alzheimer's disease genetic mutation, from 20 sites in ten countries worldwide. For this analysis, we included carriers of autosomal dominant Alzheimer's disease mutations and non-carrier familial controls within DIAN at data freeze 15 (December, 2020) who were within a similar age range to ABC-DS participants (25–73 years) and who had MRI and amyloid PET scans. Informed consent or assent was obtained from all participants, and from their legally authorised representative when necessary. Study protocols were approved by the local institutional review boards of all ABC-DS and DIAN sites.

Procedures

In the ABC-DS study, participants with Down syndrome are given a clinical dementia diagnosis by a committee with clinical training or extensive experience in evaluating dementia in individuals with Down syndrome. This committee considers several variables (appendix p 1) to derive a consensus diagnosis of either cognitively stable, mild cognitive impairment, or dementia due to Alzheimer's disease. If no consensus is reached, a diagnosis of no consensus is given. For some analyses, individuals with a consensus diagnosis of cognitively stable were categorised as asymptomatic and those with a consensus diagnosis of mild cognitive impairment or dementia due to Alzheimer's disease were categorised as symptomatic.

Cognitive status for DIAN participants was determined by use of the Clinical Dementia Rating (CDR) scale, on which a score of 0 indicates normal cognitive function, a score of 0·5 represents very mild dementia, a score of 1 represents mild dementia, a score of 2 represents moderate dementia, and a score of 3 represents severe dementia. Only non-carrier control participants with a CDR of 0 were included. For some analyses, participants with autosomal dominant mutations were categorised as asymptomatic (CDR 0) or symptomatic (CDR >0) or as having mild cognitive impairment (CDR 0·5–1) or Alzheimer's disease (CDR>1).

For participants with Down syndrome, karyotype was obtained from medical records or genetic testing. All DIAN study participants had genetic testing to determine *PSEN1, PSEN2,* or *APP* mutation status. For the analyses considering autosomal dominant Alzheimer's disease mutation type, mutation carriers were categorised into four groups: mutation in *PSEN1* before codon 200; mutation in *PSEN1* after codon 200; *PSEN2* mutation; or *APP* mutation. Individuals carrying the *APP* Glu693Gln mutation were excluded from these analyses due to evidence of inconsistent PET tracer uptake.[13]

CSF samples were collected in a subset of ABC-DS and DIAN participants who agreed to have a lumbar puncture, and were processed centrally (Washington University in St Louis, St Louis, MO, USA). Concentrations of Aβ40 and Aβ42 were measured by use of the Lumipulse G1200 platform (Fujirebio; Malvern, PA, USA; appendix p 1). *APOE* genotype was determined from blood samples by use of KASP genotyping assays (LGC Genomics; Beverly, MA, USA) for ABC-DS participants and a TaqMan assay (Applied Biosystems; Waltham, MA, USA) for DIAN participants. Individuals were categorised as *APOE* ε4-positive if they had at least one ε*4* allele.

T1-weighted MRI scans were collected for ABC-DS and DIAN participants on 3-T MRI scanners and segmented

For the **ABC-DS study** see https://www.nia.nih.gov/research/abc-ds

For the **DIAN study** see https://dian.wustl.edu/our-research/observational-study/

For more on **FreeSurfer** see https://surfer.nmr.mgh.harvard.edu/

For the **PET Unified Pipeline** see https://github.com/ysu001/PUP

into regions of interest by use of FreeSurfer 5.3-HCP, with identical quality control procedures in each study. ABC-DS participants had amyloid PET with [^{11}C]-Pittsburgh compound B ([^{11}C]-PiB) or [^{18}F]-AV45 (florbetapir; appendix p 1) lasting 20 min (four 5-min frames) at 50–70 min after bolus injection. DIAN participants had amyloid PET with [^{11}C]-PiB (appendix p 1), which either started at the time of injection and lasted for 70 min or was run between 40 min and 70 min after injection. All PET images were processed and aligned to FreeSurfer MRI segmentation by use of an established processing pipeline (the PET Unified Pipeline). Regional standard uptake value ratios were calculated by use of the cerebellar cortex as the reference region. Because the ABC-DS study used different tracers, standard uptake value ratios were transformed to the centiloid scale (appendix p 1).[14] [^{11}C]-PiB standard uptake value ratios were calculated from the 50–70 min post-injection time window for both studies and underwent partial volume correction.

	Controls (n=202)	Down syndrome (n=192)	Autosomal dominant Alzheimer's disease (n=265)	p value
Age, years	40 (33 to 49)	41 (35 to 49)	39 (33 to 48)	0·14
Sex	..	..	..	0·0029
Female	123 (61%)	84 (44%)*	140 (53%)	..
Male	79 (39%)	108 (56%)	125 (47%)	..
Race	..	..	..	0·027
White	186 (92%)	184 (96%)†	232 (88%)	..
Black or African American	<3 (1%)‡	2 (1%)	<3 (1%)‡	..
Unknown	3 (1%)	0	<3 (1%)‡	..
Other	12 (6%)	6 (3%)	29 (11%)	..
APOE ε4-positive	57 (28%)	38 (20%)	78 (29%)	0·059
Cognitive status	..	..	..	<0·0001
Asymptomatic	202 (100%)	155 (81%)*†	164 (62%)*	..
Symptomatic	0	28 (15%)	101 (38%)	..
No consensus	NA	9 (5%)	NA	..
Down syndrome type§	..	..	..	..
Full trisomy 21	NA	168 (88%)	NA	..
Translocation	NA	12 (6%)	NA	..
Mosaicism	NA	6 (3%)	NA	..
Autosomal dominant mutation	NA	NA	..	..
PSEN1	NA	NA	202 (76%)	..
PSEN2	NA	NA	22 (8%)	..
APP	NA	NA	41 (15%)	..
Centiloid score	–2·93 (–5·66 to –0·07)	8·45 (1·32 to 49·78)*†	31·72 (4·58 to 67·19)*	<0·0001

Data are median (IQR) or n (%). p values refer to comparisons among all three groups. NA=not applicable. *Significantly different from control group (p<0·05 after Benjamini–Hochberg correction for multiple comparisons). †Significantly different from mutation carriers (p<0·05 after Benjamini–Hochberg correction for multiple comparisons). ‡Due to unblinding concerns, it is the policy of DIAN to not include exact values when demographic numbers are <5. §Karyotype information was not available in six individuals with Down syndrome; however, in these individuals, the diagnosis of Down syndrome was confirmed by medical records.

Table: **Participant characteristics**

Statistical analysis

We combined controls from the ABC-DS and DIAN studies into a single group. We evaluated differences in demographic characteristics between controls, autosomal dominant Alzheimer's disease mutation carriers, and people with Down syndrome using χ^2 tests for categorical variables and Kruskal–Wallis rank sum tests for continuous variables after determining a non-normal distribution using the Kolmogorov–Smirnoff test. If differences were significant, post-hoc two-sample tests were done (χ^2 test for categorical variables and Mann-Whitney U test for continuous variables).

We assessed the correlation between CSF measures of amyloid concentration and amyloid PET uptake using Spearman's correlation test. We plotted global amyloid PET deposition (in centiloids) as a function of CSF Aβ42 to Aβ40 ratio (Aβ42/40), Aβ42, and Aβ40, and analysed the correlation between these measures for carriers of autosomal dominant Alzheimer's disease mutations and people with Down syndrome categorised by cognitive status.

We used Mann–Whitney U tests to examine differences in amyloid accumulation between groups categorised by cognitive status (controls, asymptomatic people with Down syndrome, symptomatic people with Down syndrome, asymptomatic carriers of autosomal dominant Alzheimer's disease mutations, and symptomatic carriers of autosomal dominant Alzheimer's disease mutations) and within these five groups by *APOE* ε4 status and sex, as previous studies of late-onset disease have reported an effect on amyloid for these variables.[15–20] Individuals with no committee consensus were excluded from comparisons by cognitive status. We further delineated the symptomatic groups into mild cognitive impairment versus Alzheimer's disease to analyse differences in amyloid accumulation. The Benjamini–Hochberg procedure was used to correct for multiple comparisons.

Using a bootstrapping approach and a generalised additive model with a cubic regression spline (appendix p 2), we assessed amyloid PET deposition between controls, carriers of autosomal dominant Alzheimer's disease mutations, and people with Down syndrome as a function of age and estimated years to symptom onset, as Alzheimer's disease progression is typically evaluated in people with autosomal dominant disease as a function of estimated years to symptom onset. The median estimated number of years to symptom onset or the median age at which amyloid accumulation for mutation carriers or people with Down syndrome became significantly elevated versus controls were calculated and compared to identify whether accumulation began significantly later in either group. For DIAN participants, the number of years to symptom onset was estimated by subtracting an individual's current age from the age at which their parent began to have symptoms.[7] Because a method to calculate the number of years to symptom onset in individuals with Down syndrome has not been established, we estimated

the number of years to symptom onset for ABC-DS participants by separately subtracting their current age from three average ages of symptom onset observed in previous studies (50·0 years, 52·5 years, and 55·0 years), focusing on the average age of 52·5 years for comparisons with carriers of autosomal dominant Alzheimer's disease mutations.[3,4,21–26] We further analysed amyloid PET deposition by mutation type as a function of age and estimated years to symptom onset (average age of symptom onset 52·5 years for people with Down syndrome). Additionally, we evaluated whether *APOE* ε4 status or sex caused a temporal shift in amyloid PET deposition. We also assessed regional patterns of amyloid accumulation in participants with Down syndrome or autosomal dominant Alzheimer's disease mutations by estimated number of years to symptom onset (appendix p 2). For the regional analysis, we compared only the ABC-DS and DIAN participants with a [^{11}C]-PiB PET scan. We examined standard uptake value ratios in 34 cortical and seven subcortical regions. Using a bootstrapping approach, the estimated number of years to symptom onset at which amyloid deposition in each region became significantly elevated compared with controls was determined with 10 000 iterations. The median estimated number of years to symptom onset for each region was calculated to assess the spatial pattern of amyloid accumulation. All analyses used R (version 4.1.2) and the packages mgcv, tidymv, ggplot, and ggseg. A p-value threshold of <0·05 was used to determine statistical significance (except in the bootstrapping regional analysis, which used a stricter significance threshold of p<0·01).

Role of the funding source

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

Results

192 individuals with Down syndrome and 33 sibling controls from the ABC-DS study and 265 carriers of autosomal dominant Alzheimer's disease mutations and 169 non-carrier familial controls from the DIAN study were included in our analyses. Controls from the two studies were combined into a single group. For the autosomal dominant mutation types present in people included in our study, see appendix (pp 8–9). Participant characteristics for each group are shown in the table. Groups did not differ by age or *APOE* ε4-positivity status. There were fewer women in the Down syndrome group (44%) compared with the control (61%) and mutation carrier (53%) groups. Compared with carriers of autosomal dominant Alzheimer's disease mutations, a smaller proportion of individuals with Down syndrome identified as non-White (p=0·031), although most people in our analysis identified as White. A higher proportion of mutation carriers (38%) than people with Down syndrome (15%) were categorised as symptomatic (p<0·0001). Of the 101 symptomatic mutation carriers, 57 (56%) had very mild dementia (CDR 0·5), 27 (27%) had mild dementia (CDR 1), and 17 (17%) had moderate or severe dementia (CDR 2–3). Of the 28 symptomatic participants with Down syndrome, 16 (57%) had mild cognitive impairment and 12 (43%) had dementia due to Alzheimer's disease.

In the subset of participants with both CSF and amyloid PET data, people with Down syndrome (n=32) were older (mean age 49·78 years [SD 5·75]) than people with autosomal dominant Alzheimer's disease mutations (n=216; 39·75 years [9·74]), but similar with regard to *APOE* ε4 status, sex, cognitive status, and race (appendix p 9). We plotted global amyloid deposition on PET (in centiloids) as a function of CSF Aβ42/40, Aβ42, and Aβ40 for carriers of autosomal dominant Alzheimer's disease mutations and people with Down syndrome categorised by cognitive status (figure 1;

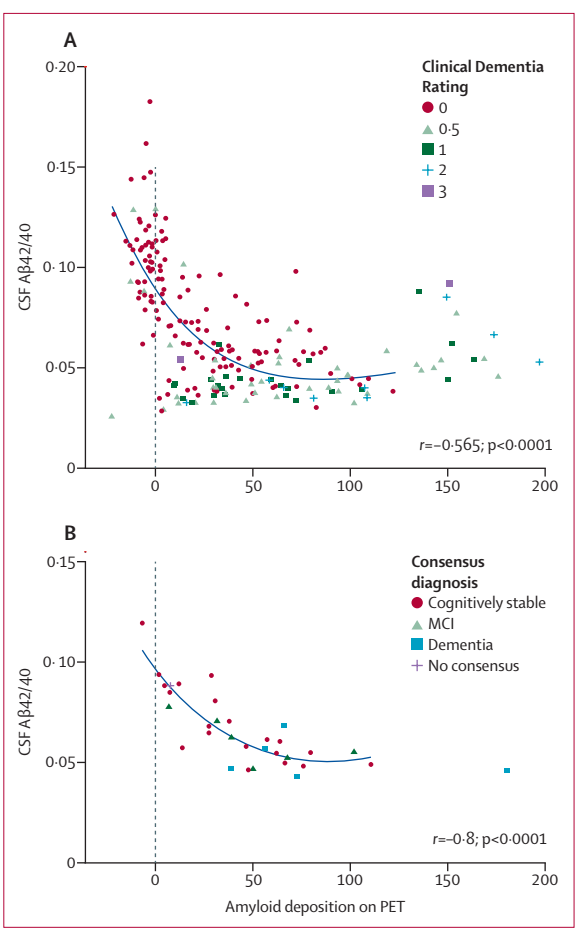

Figure 1: **Global amyloid deposition on PET versus CSF amyloid**
Global amyloid PET deposition in centiloids plotted against the Aβ42/40 in CSF in autosomal dominant Alzheimer's disease mutation carriers (n=216; A) and participants with Down syndrome (n=32; B). Plotted data points were categorised by participants' cognitive status, as measured by the Clinical Dementia Rating in mutation carriers and by consensus diagnosis in people with Down syndrome. A locally weighted estimated scatterplot smoothing curve was added to visualise the relation between CSF amyloid and amyloid PET. MCI=mild cognitive impairment. Aβ42/40=amyloid β42 to amyloid β40 ratio.

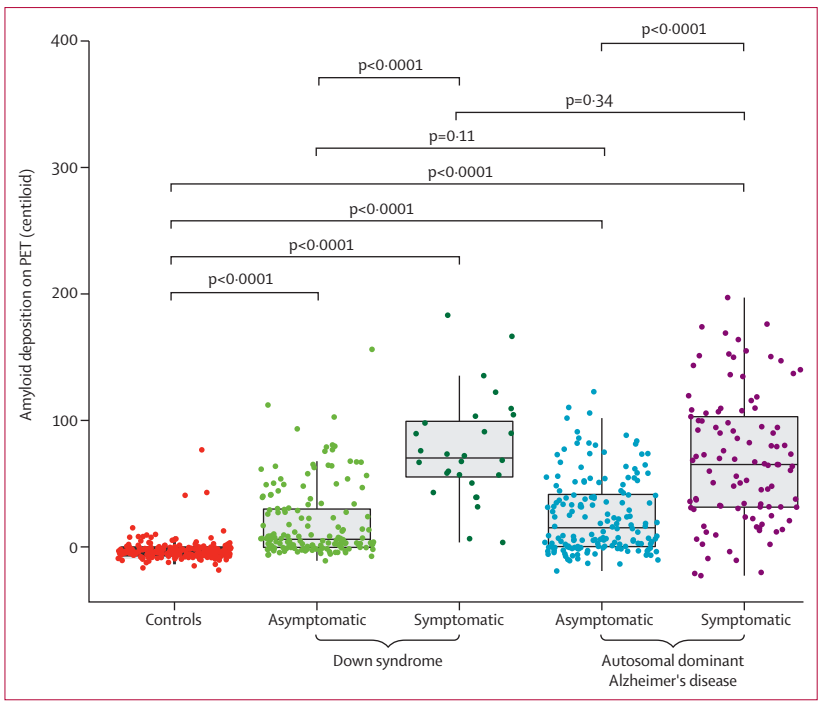

Figure 2: **Global amyloid deposition on PET by cognitive status**
Controls, n=202; asymptomatic Down syndrome, n=155; symptomatic Down syndrome, n=28; asymptomatic autosomal dominant Alzheimer's disease, n=164; symptomatic autosomal dominant Alzheimer's disease, n=101.

appendix p 4). In mutation carriers, we measured a negative correlation between CSF Aβ42/40 and amyloid PET deposition (r=–0·565; p<0·0001). The CSF Aβ42/40 was diminished and amyloid PET centiloids were elevated in symptomatic (CDR>0) versus asymptomatic (CDR=0) carriers (figure 1A). We observed a similar relationship between CSF Aβ42/40 and amyloid PET centiloids when we grouped carriers by mutation type (appendix p 3). We also found that the CSF Aβ42/40 was negatively correlated with amyloid PET centiloids in people with Down syndrome (r=–0·801; p<0·0001), with participants with a consensus diagnosis of dementia having increased amyloid PET centiloids and reduced CSF amyloid ratios versus cognitively stable (asymptomatic) participants (figure 1B). Similar significant negative correlations were observed when amyloid PET was plotted as a function of CSF Aβ42 concentrations in both carriers of autosomal dominant Alzheimer's disease mutations (r=–0·53) and people with Down syndrome (r=–0·61), but no significant correlation was measured between CSF Aβ40 concentrations and amyloid PET in either group (appendix p 4).

We compared amyloid accumulation between groups categorised by cognitive status (figure 2). As expected, amyloid PET centiloids in controls clustered near zero (mean –1·77 centiloids [SD 8·77]) and were lower than those in asymptomatic people with Down syndrome (18·80 centiloids [28·33]), symptomatic people with Down syndrome (77·25 centiloids [41·76]), asymptomatic carriers of autosomal dominant Alzheimer's disease mutations (24·61 centiloids [30·27]), and symptomatic mutation carriers (69·15 centiloids [51·10]; table; figure 2). The symptomatic groups had higher levels of amyloid PET deposition than did their respective asymptomatic group (figure 2). Similar results were seen when the symptomatic groups were further delineated into mild cognitive impairment and Alzheimer's disease (data not shown). There was no difference in amyloid PET deposition between asymptomatic people with Down syndrome versus asymptomatic mutation carriers and between symptomatic people with Down syndrome versus symptomatic mutation carriers (figure 2). For individuals with Down syndrome and autosomal dominant Alzheimer's disease, no differences in amyloid PET deposition were observed between *APOE* ε4-positive and *APOE* ε4-negative individuals (appendix p 5) or between men and women (appendix p 6).

We evaluated trajectories of amyloid accumulation as a function of estimated years to symptom onset using an average age of onset of 52·5 years for participants with Down syndrome (figure 3). Amyloid PET deposition was elevated in carriers of autosomal dominant Alzheimer's disease mutations at a significantly earlier timepoint before symptom onset than in participants with Down syndrome (–23·0 years *vs* –17·5 years; p=0·0002; figure 3A). We found similar results when using an average age of symptom onset of 50·0 years (p<0·0001) and 55·0 years (p=0·056) for participants with Down syndrome (appendix p 6). When we compared people with Down syndrome with people with different autosomal dominant mutation types, amyloid accumulation in participants with Down syndrome was elevated significantly later than in people with *PSEN1* mutations after codon 200 (figure 3D) but not in people with *PSEN1* mutations before codon 200 (figure 3C). There were no significant differences in the time of amyloid PET elevation between people with Down syndrome versus people with *PSEN2* or *APP* mutations (figure 3). Amyloid PET deposition was elevated at a significantly earlier age in carriers of autosomal dominant Alzheimer's disease mutations than in participants with Down syndrome (25·4 years *vs* 34·0 years; p<0·0001; appendix p 7). People with *PSEN1* mutations had elevated amyloid PET at a significantly earlier age than participants with Down syndrome (appendix p 7). Amyloid accumulation in participants with Down syndrome occurred at a similar age as in participants with *PSEN2* and *APP* mutations (appendix p 7). When plotting amyloid PET accumulation by estimated years to symptom onset or age range, we observed no temporal shift by *APOE* ε4 status in people with Down syndrome or autosomal dominant mutations (appendix p 5). A similar analysis examining sex did not show a temporal shift in amyloid PET accumulation between men and women for either people with Down syndrome or people with autosomal dominant mutations (appendix p 6).

We examined standard uptake value ratios in 34 cortical and seven subcortical regions in people with Down

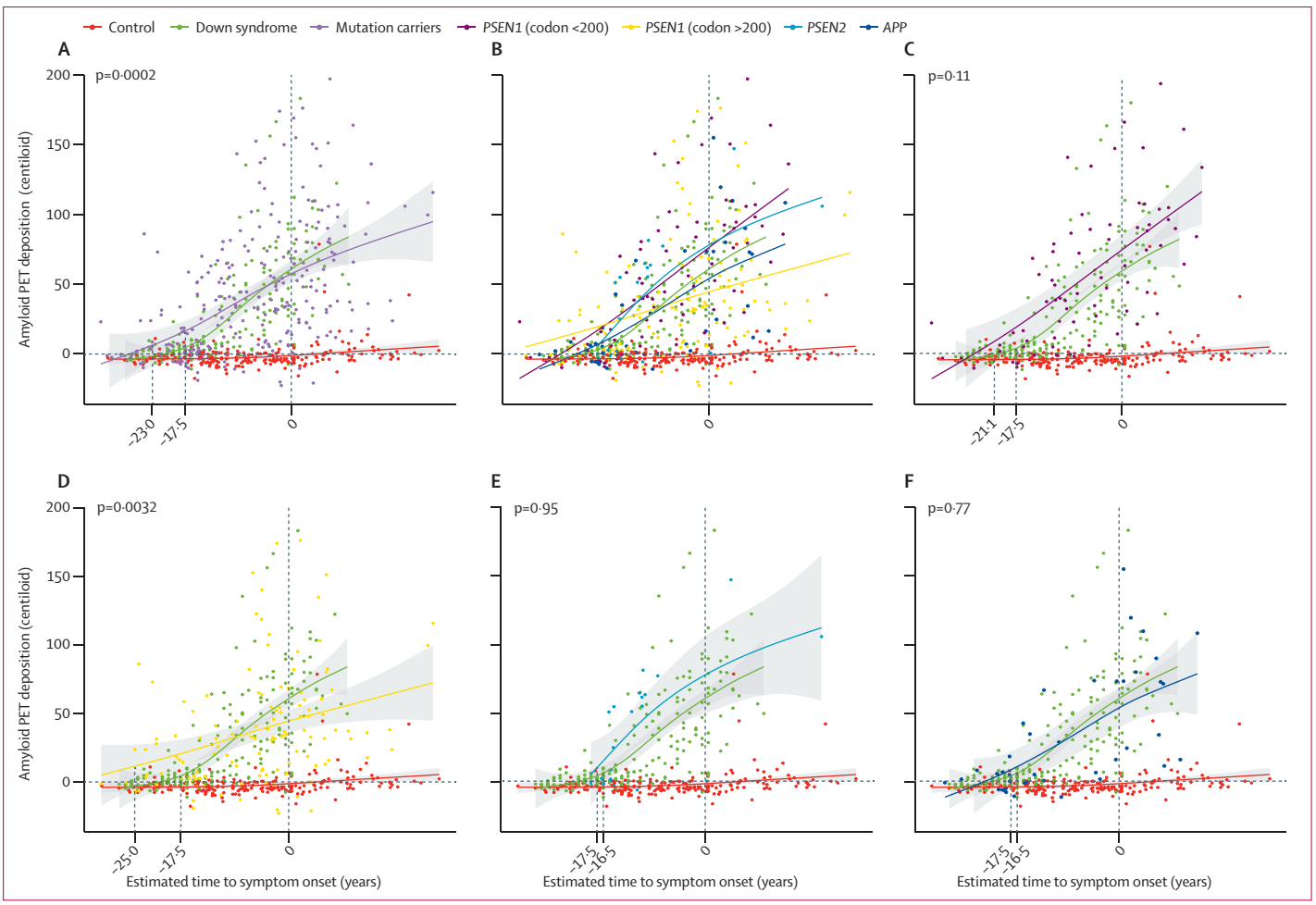

Figure 3: **Global amyloid deposition on PET as a function of estimated years to symptom onset**
Global amyloid PET deposition as a function of estimated years to symptom onset in controls (n=202) versus people with Down syndrome (n=92) versus all carriers of autosomal dominant Alzheimer's disease mutations (n=265; A), mutation carriers stratified by mutation type (B), mutation carriers with *PSEN1* mutations before codon 200 (n=74; C), mutation carriers with *PSEN1* mutations after codon 200 (n=128; D), mutation carriers with *PSEN2* mutations (n=22; E), and mutation carriers with *APP* mutations (n=41; F).

syndrome (n=128) or autosomal dominant mutations (n=265) and control participants (n=202) with [^{11}C]-PiB PET scans. Within this subset, most participants with Down syndrome were asymptomatic (88%) and significantly fewer participants with Down syndrome were *APOE* ε4-positive (18%) compared with carriers of autosomal dominant Alzheimer's disease mutations (29%) and controls (28%; appendix p 9). Amyloid accumulation in mutation carriers occurred earliest in the occipito-parietal cortices, closely followed by the frontal lobe and striatum (figures 4A, 5; video; appendix pp 7, 10). Early amyloid accumulation in participants with Down syndrome occurred in the frontal lobe and striatum, followed by regions in the parietal and temporal lobes (figures 4B, 5; video; appendix p 10). Although we found amyloid accumulation in all cortical regions in carriers of autosomal dominant Alzheimer's disease mutations, amyloid standard uptake value ratios were not elevated within the medial occipital regions (cuneus, pericalcarine, and lingual cortices) of people with Down syndrome (figures 4, 5; video; appendix p 10).

Discussion

In this cross-sectional study including participants with two different genetic forms of Alzheimer's disease, we compared amyloid deposition within a large cohort of individuals with Down syndrome and carriers of autosomal dominant Alzheimer's disease mutations. Overall, we observed many similarities between these groups. To our knowledge, this study is the first to assess the relation between PET amyloid deposition and CSF amyloid concentrations in people with Down syndrome. Our results showed an inverse relation between these two amyloid measures, suggesting that amyloid concentrations decrease in the CSF before accumulating in the brain in people with Down syndrome, similar to the pattern seen in people with late-onset Alzheimer's disease and autosomal dominant Alzheimer's disease.[27,28] When

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we assessed amyloid deposition by PET, it was similar between individuals with Down syndrome and people with autosomal dominant Alzheimer's disease mutations when grouped by cognitive status. For both groups, asymptomatic participants (ie, individuals with Down syndrome diagnosed as cognitively stable or people with autosomal dominant Alzheimer's disease and a CDR of 0) had higher global amyloid PET deposition than controls and symptomatic individuals had even higher amyloid deposition than their asymptomatic counterparts. These results are supported by our finding that amyloid accumulation began approximately two decades before symptom onset in people with Down syndrome and in people with autosomal dominant Alzheimer's disease. Our results suggest that amyloid accumulation begins in the early preclinical stages in individuals with Down syndrome and continues to increase as cognitive impairment progresses, similar to what is observed in people with late-onset Alzheimer's disease and autosomal dominant Alzheimer's disease.[27,28]

Although our findings suggest that amyloid begins accumulating at the early stages of Alzheimer's disease progression in both groups, we also observed subtle but significant differences between people with Down syndrome and carriers with autosomal dominant Alzheimer's disease in the timing of initial amyloid accumulation. In particular, amyloid accumulation began earlier in carriers of autosomal dominant Alzheimer's disease mutations than in people with Down syndrome but approached similar concentrations at the estimated symptom onset. After differentiating mutation carriers by autosomal dominant mutation type, we found that this difference in timing was mainly driven by *PSEN1* mutations. This result is consistent with previous work by Chhatwal and colleagues,[11] in which the magnitude of amyloid PET changes was different for *PSEN1* mutation carriers than for carriers of other mutations. The time of initial amyloid accumulation in participants with Down syndrome was similar to that of people with *APP* mutations. One hypothesised explanation for the delay in amyloid accumulation in people with Down syndrome versus autosomal dominant Alzheimer's disease is that other triplicated genes on chromosome 21—eg, *BACE2*, which encodes β-secretase 2—could be protective. The θ-secretase activity of β-secretase 2 could cleave amyloid into smaller, non-amyloidogenic Aβ isomers instead of amyloidogenic Aβ42.[29] However, one study measured significantly higher concentrations of CSF Aβ42 in asymptomatic individuals with Down syndrome compared with asymptomatic carriers of autosomal dominant Alzheimer's disease mutations, suggesting that amyloidogenic Aβ42 is still highly produced in individuals with Down syndrome despite *BACE2* triplication.[9] Another possible explanation for delayed amyloid accumulation in individuals with Down syndrome is that they might clear amyloid more

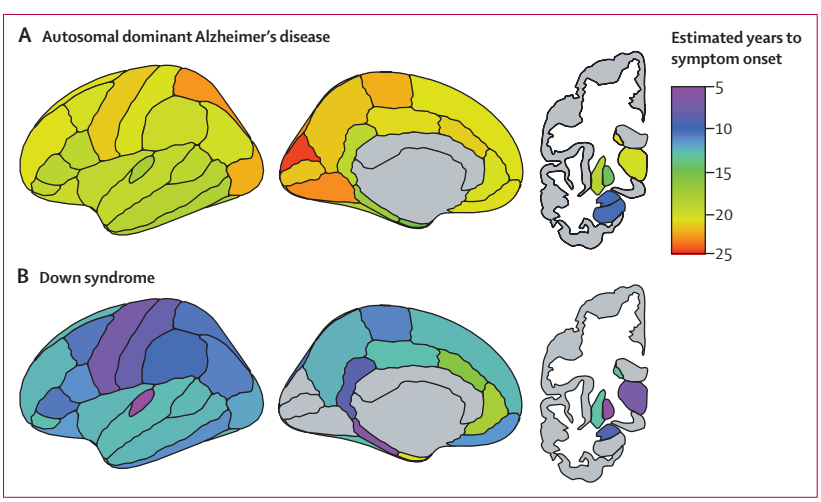

Figure 4: **Regional amyloid accumulation by estimated years to symptom onset**
Estimated years to symptom onset at which regional amyloid accumulation in autosomal dominant Alzheimer's disease mutation carriers (A) and individuals with Down syndrome (B) was significantly greater than in controls.

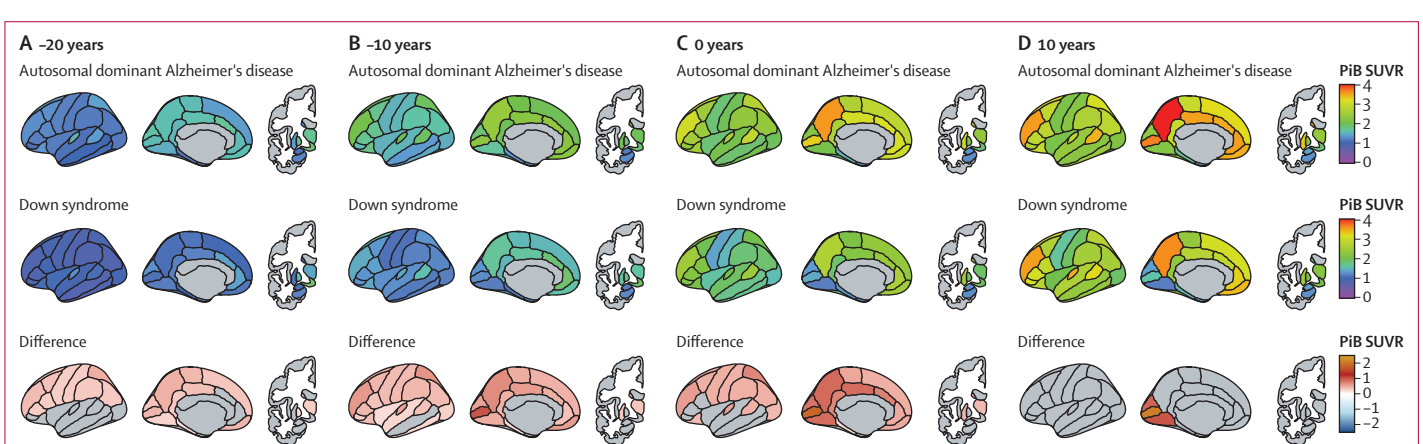

Figure 5: **PiB SUVR by estimated years to symptom onset group**
(A) Estimated 20 years before symptom onset. (B) Estimated 10 years before symptom onset. (C) Estimated at symptom onset. (D) Estimated 10 years after symptom onset. We used 99% CIs to adjust for multiple comparisons. PiB SUVR=[^{11}C]-Pittsburgh compound B standard uptake value ratio.

efficiently compared with people with autosomal dominant Alzheimer's disease. One study found improved amyloid clearance in mice with upregulated *DSCR1* (also known as *RCAN1*), a gene on chromosome 21.[30] Future studies are needed to elucidate hypothesised protective factors in individuals with Down syndrome.

The spatial pattern of amyloid distribution was fairly similar between people with autosomal dominant Alzheimer's disease and people with Down syndrome. Our results support previous work showing early amyloid accumulation in carriers of autosomal dominant Alzheimer's disease mutations in the striatal, occipitoparietal, and frontal regions.[10,31] Amyloid accumulation was relatively consistent across mutation types. Similar to previous work, we measured early amyloid accumulation in the striatum in people with Down syndrome, in addition to early changes in the anterior cingulate and frontal cortex.[32] This finding of early amyloid accumulation in the striatum in both carriers of autosomal dominant Alzheimer's disease mutations and people with Down syndrome aligns with the results of previous studies and is a key deviation from late-onset Alzheimer's disease.[10,32,33] However, although we found amyloid accumulation in the medial occipital lobe in carriers of autosomal dominant Alzheimer's disease mutations, we did not observe significant amyloid accumulation in this region in individuals with Down syndrome. This finding is consistent with the results of a previous amyloid PET study,[32] which showed that the occipital lobe was one of the last regions to accumulate amyloid in individuals with Down syndrome, a temporal pattern closely resembling late-onset Alzheimer's disease.[34] Despite being subtle, these regional differences in amyloid deposition between people with Down syndrome, autosomal dominant Alzheimer's disease, and late-onset Alzheimer's disease are important to consider for future clinical trials. Different brain regions might need to be evaluated when determining amyloid-positivity and the efficacy of anti-amyloid therapies for these groups.

The presence of at least one *APOE* ε4 allele is associated with earlier amyloid changes in people with late-onset Alzheimer's disease.[18] However, similar to previous work, we did not observe an effect of *APOE* ε4 on the timing of amyloid accumulation in carriers of autosomal dominant Alzheimer's disease mutations.[7,35,36] In people with Down syndrome, several studies have observed a significant effect of *APOE* ε4 on cognitive outcomes,[23,37,38] but results have been mixed for amyloid PET measures.[39–41] Despite several studies reporting no effect,[39,40] the study by Bejanin and colleagues[41] found more amyloid PET deposition in *APOE* ε4-positive participants with Down syndrome aged 41–54 years compared with *APOE* ε4-negative participants with Down syndrome. In our study, we found no differences between *APOE* ε4-positive and *APOE* ε4-negative participants with Down syndrome in amyloid PET deposition or the timing of amyloid accumulation. When we replicated the comparison by age range from the study by Bejanin and colleagues,[41] we did not observe differences in amyloid PET deposition between *APOE* ε4-positive and negative participants with Down syndrome. Overall, our results suggest that the presence of the *APOE* ε4 allele does not affect the amount or timing of amyloid accumulation in genetic forms of Alzheimer's disease. Genetic mutations in Down syndrome and autosomal dominant Alzheimer's disease might overshadow the effects of *APOE* genotype on amyloid. Previously observed changes in cognition with *APOE* ε4 positivity in people with Down syndrome could be mediated by tau, but additional longitudinal studies of multiple biomarkers are needed.

Previous studies have also identified a potential role for sex on the trajectory and development of late-onset Alzheimer's disease.[15–17] Whether sex influences the presentation of Alzheimer's disease in individuals with Down syndrome is unclear. Some studies have found no effect for sex on the prevalence or timing of dementia diagnosis in adults with Down syndrome.[37,42] Other studies have reported an effect of sex in individuals with Down syndrome on the risk of developing dementia or on the age of dementia onset.[23,43] We found no differences in the amount or timing of amyloid PET deposition between men and women with Down syndrome, consistent with previous studies that also did not observe any effect of sex on amyloid PET.[32,39,44–46] These findings suggest that, although sex might affect the cognitive presentation of Alzheimer's disease, it does not affect amyloid deposition in adults with Down syndrome.

The large size of the cohort of participants with Down syndrome and autosomal dominant Alzheimer's disease in this study represents a notable strength, but limitations should also be acknowledged. Although these two populations are genetically predisposed to develop Alzheimer's disease, most autosomal dominant Alzheimer's disease mutations alter the processing of the APP protein by affecting γ-secretase activity. The closest direct comparison to Down syndrome would therefore be individuals with a rare *APP* duplication. Only fewer than ten carriers of autosomal dominant Alzheimer's disease mutations in our study had an *APP* duplication. A future study with a larger sample of *APP* duplication carriers would be useful in assessing other genes on chromosome 21 and their effects on Alzheimer's disease progression. Information on which ABC-DS participants with Down syndrome and sibling controls were related was unavailable, preventing us from adjusting for potential correlations between related participants. The cross-sectional nature of this study is another important limitation. Future longitudinal studies are necessary to better our understanding of how amyloid accumulates in people with these two genetic forms of Alzheimer's disease. Additionally, we estimated the number of years to symptom onset for individuals with Down syndrome using a set of three average ages of symptom onset from several previous studies. However, using a fixed average age of onset does not account for

individual differences. Future analyses are necessary to improve our ability to predict the number of years to symptom onset for an individual with Down syndrome.

Despite these limitations, we used PET to observe important similarities between two genetic forms of Alzheimer's disease. We found similar amounts of amyloid deposition on PET between individuals with Down syndrome and people with autosomal dominant Alzheimer's disease mutations, with amyloid beginning to accumulate at the earliest stages of the Alzheimer's disease cascade, around 20 years before the onset of cognitive symptoms. The safety and efficacy of potential amyloid-lowering Alzheimer's disease therapies have yet to be evaluated in individuals with Down syndrome. On the basis of our results, potential anti-amyloid therapies would be better evaluated in people with Down syndrome aged at least 35 years. In conclusion, this study shows that, although there are subtle differences, Alzheimer's disease pathophysiology is similar among people with Down syndrome and people with autosomal dominant Alzheimer's disease.

Contributors

AHB, BMA, and BAG conceptualised and designed the study and had access to raw data. AMF, BLH, BTC, EH, MM, SO'B, HDR, FL, JHL, WS, AMB, JPC, CC, RJP, CX, JH, EMD, RJB, and BMA contributed to data collection. AHB, WS, BAG, SF, RLH, OHB, NMK, and CDC contributed to data analysis. AHB, BAG, JW, SF, OHB, NMK, CDC, and BMA contributed to data interpretation. AHB and BMA were responsible for writing the manuscript. BTC, EH, BLH, MM, CX, and RJB verified the data. All authors contributed to the critical review of the manuscript, had full access to all the data in the study, and have seen and approved the final version. BMA had final responsibility for the decision to submit for publication.

Declaration of interests

TLSB has received funding from the National Institutes of Health and Siemens; has a licensing agreement from Sora Neuroscience but receives no financial compensation; has received honoraria for lectures, presentations, speakers bureaus, or educational events from Biogen and Eisai Genetech; has served on a scientific advisory board for Biogen; holds a leadership role in other board, society, committee, or advocacy groups for the American Society for Neuroradiology (unpaid) and Quantitative Imaging Biomarkers Alliance (unpaid); and has participated in radiopharmaceuticals and technology transfers with Avid Radiopharmaceuticals, Cerveau, and LMI. EMD received support from the National Institute on Aging, an anonymous organisation, the GHR Foundation, the DIAN-TU Pharma Consortium, Eli Lilly, and F Hoffmann La-Roche; has received speaking fees from Eisai and Eli Lilly; and is on the data safety and monitoring board and advisory boards of Eli Lilly, Alector, and Alzamend. WS has received research funding from the National Institute on Aging and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. JPC serves as the chair of the American Neurological Association Dementia and Aging Special Interest Group and is on the medical advisory board of Humana Healthcare. CC has received consulting fees from GSK and Alector. AMF reports personal fees from Roche Diagnostics, Araclon/Grifols, and Diadem Research and grants from Biogen, outside the submitted work. BLH has received research funding from Roche and Autism Speaks; receives royalties from Oxford University Press for book publications; and is the chair of the data safety and monitoring board for the Department of Defense-funded study, "Comparative Effectiveness of EIBI and MABA". BTC receives research funding from the National Institutes of Health. EH receives research funding from the National Institutes of Health and the BrightFocus Foundation. FL is supported by grants from the National Institute on Aging. HDR has received funding from the National Institutes of Health and is on the scientific advisory committee for the Hereditary Disease Foundation. JHL has received research funding from the National Institutes of Health and the National Institute on Aging. RJP receives research funding from the National Institutes of Health and the National Institute on Aging. RJB is Director of DIAN-TU and Principal Investigator of DIAN-TU001; receives research support from the National Institute on Aging of the National Institutes of Health, DIAN-TU trial pharmaceutical partners (Eli Lilly, F Hoffmann-La Roche, Janssen, Eisai, Biogen, and Avid Radiopharmaceuticals), the Alzheimer's Association, the GHR Foundation, an anonymous organisation, the DIAN-TU Pharma Consortium (active members Biogen, Eisai, Eli Lilly, Janssen, and F Hoffmann-La Roche/Genentech; previous members AbbVie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi, and United Neuroscience), the NfL Consortium (F Hoffmann-La Roche, Biogen, AbbVie, and Bristol Myers Squibb), and the Tau SILK Consortium (Eli Lilly, Biogen, and AbbVie); has been an invited speaker and consultant for AC Immune, F Hoffmann-La Roche, the Korean Dementia Association, the American Neurological Association, and Janssen; has been a consultant for Amgen, F Hoffmann-La Roche, and Eisai; and has submitted the US non-provisional patent application named "Methods for Measuring the Metabolism of CNS Derived Biomolecules In Vivo" and a provisional patent application named "Plasma Based Methods for Detecting CNS Amyloid Deposition". BMA receives research funding from the National Institutes of Health and has a patent pending ("Markers of Neurotoxicity in CAR T patients"). MSR has received consulting fees from AC Immune, Embic, and Keystone Bio and has received research support from the National Institutes of Health, Avid, Baxter, Eisai, Elan, Genentech, Janssen, Lilly, Merck, and Roche. All other authors declare no competing interests.

Data sharing

The data used in this analysis are available on request to the respective studies (ABC-DS and DIAN), provided data request applications are approved by the studies' committees. The data request application is available for ABC-DS at https://pitt.co1.qualtrics.com/jfe/form/SV_cu0pNCZZlrdSxUN and for DIAN at https://dian.wustl.edu/our-research/for-investigators/dian-observational-study-investigator-resources/data-request-form/.

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