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

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Abstract

Background: Due to the triplication of chromosome 21 and resultant extra copy of the amyloid precursor protein gene, most adults with Down syndrome (DS) develop Alzheimer disease (AD)-like pathology and dementia. Using positron emission tomography (PET) imaging of amyloid, we compared DS with another genetic form of AD, autosomal-dominant AD (ADAD).

Methods: Participants with DS (n=192), ADAD mutation-carriers (MC) (n=265), and familial controls (n=202) with amyloid PET imaging from the Alzheimer's Biomarker Consortium-Down Syndrome and the Dominantly Inherited Alzheimer Network were included. Global and regional amyloid burdens were compared by cognitive status, *APOE ε4* status, sex, age, and estimated years to symptom onset (EYO). Finally, we evaluated the relationship between amyloid PET and CSF Aβ42/40 in a subset of participants.

Findings: PET and CSF amyloid were inversely correlated in DS and MC participants (ρ = −0·801 and −0.565 respectively; both p-values < 0·001). There were no significant differences in global amyloid burden between MC and DS when grouped by cognitive status. We also did not observe a significant effect of *APOE ε4*-positivity or sex in either group. Amyloid accumulation occurred slightly later in participants with DS (EYO −17·5) compared to MC (EYO −23·0) (p-value < 0·001). This difference was mainly driven by PSEN1 MCs. Early amyloid increases were seen in striatal and cortical regions in both MC and DS individuals. While widespread amyloid accumulation was seen in MC, occipital regions were spared in individuals with DS.

Interpretation: This study demonstrates that, despite minor differences between DS and ADAD, the overall pathophysiology is similar between these two genetic forms of AD.

INTRODUCTION

Down syndrome (DS), caused by full or partial triplication of chromosome 21, is the most common genetic disorder, with approximately 1 in 700 children born in the United States each year[1]. Due to this triplication, individuals with DS have an extra copy of the amyloid precursor protein (*APP*) gene on chromosome 21 and overproduce amyloid beta (Aβ). Consequently, almost all adults with DS develop amyloid plaques and tau neurofibrillary tangles, hallmarks of Alzheimer disease (AD)[2]. Given this fact and the dramatic rise of life expectancy, there is a growing population of adults with DS developing AD[1,3].

Previous studies have utilized cognition, fluid biomarker, and imaging measures to understand the presentation and progression of AD in individuals with DS. Cognitive symptoms of AD develop at approximately 50–55 years, with cerebrospinal fluid (CSF) markers changing years prior to these symptoms[3–5]. Positron emission tomography (PET) imaging studies also identify amyloid accumulation in cortical and subcortical brain regions years before clinical symptoms[6]. However, questions remain regarding amyloid deposition

in individuals with DS compared to other forms of AD, especially autosomal dominant AD (ADAD).

ADAD, another genetic form of AD, is caused by presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or *APP* gene mutations that lead to altered amyloid levels. Similar to DS, carriers of ADAD mutations develop AD at an earlier age (30–60 years old) than individuals with late-onset AD (LOAD) (65 years old)[7]. Studies assessing biomarker changes in DS and ADAD separately suggest similarities between these two genetic forms of AD[2]. To date, only two studies have directly compared DS and ADAD but in a limited number of individuals[8,9]. One study comparing amyloid PET found no differences between ADAD and DS but only included amyloid-positive, asymptomatic participants. The other study, which evaluated CSF biomarkers, reported greater CSF $A\beta_{40}$ and $A\beta_{42}$ levels in both asymptomatic and symptomatic DS individuals compared to ADAD counterparts. These studies suggest that, while AD pathology may be similar for DS and ADAD, differences may exist.

Here we evaluate amyloid deposition in two large cohorts of genetic causes of AD by comparing DS to ADAD. Amyloid PET was analyzed in relation to CSF amyloid levels to study the relationship between amyloid clearance and deposition. We then assessed global and regional amyloid PET as a function of cognitive performance and age for DS and ADAD individuals.

Given recent evidence of heterogeneity in amyloid accumulation between different ADAD mutations, we also compared amyloid PET measures between DS and ADAD mutation types[10]. These comparisons enhance our understanding of genetic forms of AD and may have important implications for more common forms of AD including LOAD. Given the development of novel therapeutics designed to reduce amyloid, this knowledge will be vital for providing these treatments to individuals with genetic forms of AD.

METHODS

Study Design and Participants

The Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS) enrolls adults with DS (25 years old) and sibling-controls in a multi-site study that collects longitudinal clinical, cognitive, imaging, and fluid biomarker data. For this analysis, only participants from the first data release (January 2020) who had a magnetic resonance imaging (MRI) and amyloid PET scan were included (DS, n=192; sibling-controls, n=33).

The Dominantly Inherited Alzheimer Network (DIAN) Observational Study is a multi-site longitudinal study that enrolls individuals from families with an ADAD genetic mutation. Data from DIAN data freeze 15 (December 2020) containing mutation-carriers (MC; n=265) and non-carrier familial controls (NC; n=168) with MRI and amyloid PET imaging within a similar age range as ABC-DS participants (25–73 years old) were included.

Informed consent or assent, when appropriate, was obtained from all participants and from their legally authorized representative when necessary. Study protocols were approved by the local Institutional Review Boards of all ABC-DS and DIAN sites.

Procedures

Participants with DS are given a clinical dementia diagnosis by a committee with clinical training or extensive experience in evaluating dementia in individuals with DS. This committee considers several variables (Supplemental materials) to derive a consensus diagnosis of "cognitively stable", "mild cognitive impairment" (MCI), or "dementia due to AD". If no consensus is reached, a diagnosis of "no consensus" is given. For this analysis, individuals with a consensus diagnosis of cognitively stable were categorized as asymptomatic (aDS). Those with a consensus diagnosis of MCI or dementia due to AD were categorized as symptomatic (sDS). Individuals with a consensus diagnosis of "no consensus" were excluded from the comparisons by cognitive status.

Cognitive status for DIAN participants was determined using the Clinical Dementia Rating® (CDR®) scale. CDR = 0 indicates normal cognitive function, CDR = 0·5 very mild dementia, CDR = 1 mild dementia, CDR = 2 moderate dementia, and CDR = 3 severe dementia. Only NC control participants with CDR = 0 were included. MC participants were categorized as asymptomatic (CDR=0; aMC) or symptomatic (CDR>0; sMC).

For participants with DS, karyotype was obtained from medical records or genetic testing. All DIAN study participants underwent genetic testing to determine *PSEN1*, *PSEN2*, or *APP* mutation status. For the analyses considering ADAD mutation type, mutation-carriers were categorized by location of mutation on PSEN1 before codon 200, PSEN1 after codon 200, PSEN2, or APP (Supplemental Material). Individuals carrying the *APP* Glu693Gln (Dutch) mutation were excluded due to evidence of inconsistent PET tracer uptake.

CSF samples were collected in a subset of ABC-DS and DIAN participants and processed at Washington University using a Lumipulse platform (Supplemental material). *APOE* genotype was determined from blood samples using KASP genotyping assays (LGC Genomics, Beverly, MA) for ABC-DS participants and a TaqMan assay (Applied Biosystems, Waltham, MA) for DIAN participants. Individuals were categorized as *APOE4*-positive if they had at least one ε*4* allele.

T1-weighted MRI scans were collected for ABC-DS and DIAN participants on 3-Tesla MR scanners and segmented into regions of interest using FreeSurfer 5.3-HCP with identical quality control procedures. ABC-DS participants underwent amyloid PET imaging using [^{11}C]-Pittsburgh Compound B (PiB) or [^{18}F]-AV45 (Florbetapir) (Supplemental material). DIAN participants received PiB (Supplemental material). All PET images were processed and aligned to the FreeSurfer MR segmentation using an established processing pipeline (PET Unified Pipeline; https://github.com/ysu001/PUP). Regional standard uptake value ratios (SUVRs) were calculated using the cerebellar cortex as the reference region.

As ABC-DS used different tracers, SUVRs were transformed to the Centiloid scale[11] (Supplemental material). For the regional analysis, we compared only the ABC-DS and

DIAN participants with a PiB PET scan. PiB SUVR values were calculated from the 50–70 minute post-injection time window and underwent partial volume correction.

Statistical analysis

We evaluated differences in demographic characteristics between controls, MC, and DS 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 performed. We used the Mann-Whitney U test to examine differences in amyloid accumulation between groups categorized by cognitive status: controls, aDS, sDS, aMC, and sMC. We also compared amyloid accumulation in these five groups with regards to *APOE4* status and sex using the Mann-Whitney U test. The Benjamini-Hochberg procedure was used to correct for multiple comparisons.

We assessed the correlation between CSF measures of amyloid and amyloid PET levels using the Spearman Correlation test. Amyloid PET levels were assessed as a function of age. Since AD progression is typically evaluated in ADAD as a function of estimated years to symptom onset (EYO), we also compared amyloid levels over EYO. For DIAN participants, EYO was estimated by subtracting an individual's current age from the age at which their parent began experiencing symptoms[7]. Since a method to calculate EYO in individuals with DS has not been established, we estimated EYO for ABC-DS participants by subtracting their age from an average age of symptom onset (AAO). Based the range of average age of AD symptom onset observed in prior studies, we calculated EYO in participants with DS using AAOs of 50, 52.5, and 55 years but focused on an AAO of 52.5 years for comparisons to MCs using EYO[3,4,12–17]. Amyloid was evaluated by age and EYO in controls, MC, and DS using a bootstrapping approach and generalized additive model (GAM) with a cubic regression spline (Supplemental Materials). We also assessed the regional pattern of amyloid accumulation in DS and MC participants (Supplemental Materials). All analyses used R (version 4.1.2) and the packages mgcv, tidymv, ggplot, and ggseg.

Role of the funding source

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

RESULTS

Participant demographics

A total of 192 individuals with DS and 33 sibling controls from ABC-DS and 265 MC and 169 NC familial controls from DIAN were included. Controls from ABC-DS and DIAN were combined into a single group.

Control, DS, and MC groups did not differ by age or *APOE e4*-positivity status ($p > 0.05$) (Table 1). There were fewer females in the DS group (44%) compared to control (61%) and MC groups (53%) ($p = 0.003$). A smaller percentage of individuals with DS identified as non-white compared to MCs ($p = 0.027$), although a large majority of all groups (>85%) identified

as white. A higher percentage of MCs (38%) compared to DS (15%) were categorized as symptomatic ($p<0.001$). Of the 101 symptomatic MCs, 57 (56%) were very mildly impaired (CDR=0.5), 27 (27%) were mildly impaired (CDR=1), and 17 (17%) were moderately or severely impaired (CDR>1). Of the 28 symptomatic participants with DS, 16 (57%) had MCI, and 12 (43%) had dementia due to AD.

Comparison of PET and CSF amyloid

The subset of participants with DS with CSF data (n=32) was older (mean 49.8 years [SD 5.75 years]) than the MC group (n=216) (mean 39.8 years [SD 9.74 years]) but similar with regards to *APOE4* status, sex, and race (Supplemental Table 2).

Amyloid PET (Centiloids) was plotted as a function of CSF Aβ42/40, Aβ42, and Aβ40 for MC and DS categorized by cognitive measure (CDR for MC, consensus diagnosis for DS) (Figure 1, Supplemental Figure 1). In MC participants, we measured a negative correlation between CSF Aβ42/40 and amyloid PET levels ($\rho = -0.565$, p-value < 0.001). CSF Aβ42/40 levels were diminished and Centiloids were elevated in symptomatic (CDR>0) compared to asymptomatic (CDR=0) MC participants (Figure 1A). We observed a similar relationship between CSF Aβ42/40 and Centiloids when we grouped MC participants by mutation type (Supplemental Figure 1). Similar results were also seen in participants with DS (Figure 1B). CSF Aβ42/40 levels were also negatively correlated with Centiloid levels ($\rho = -0.801$, p-value < 0.001). We also observed that "cognitively stable" participants have elevated Centiloids and reduced CSF Aβ42/40 versus participants with a consensus diagnosis of "dementia". Similar results were observed when amyloid PET was plotted as a function of CSF Aβ42 in both MC and DS ($\rho = -0.53$ and -0.61, both p-values < 0.001) (Supplemental Figure 2A and 2B), but no significant correlation was measured between CSF Aβ40 and amyloid PET in either group (Supplemental Figure 2C and 2D).

Amyloid PET as function of cognitive status, APOE4 status, and sex

We compared amyloid levels in the control, DS, and MC groups categorized by cognitive status (control, asymptomatic DS [aDS], symptomatic DS [sDS], asymptomatic MC [aMC], and symptomatic MC [sMC]). As expected, Centiloids in controls clustered near zero (mean −1.77 [SD 8.77]) and were lower compared to aDS, sDS, aMC, and sMC (*p*-values<0.001) (Figure 2). The sDS and sMC groups had higher levels compared to their respective asymptomatic groups (*p*-values<0.001). Similar results were seen when sDS and sMC were further delineated into MCI and AD (CDR 0.5–1 and CDR > 1 for MC, respectively) (data not shown). aDS and aMC were not different (*p*>0.05) nor were sDS and sMC (*p*>0.05).

Since previous studies of LOAD have reported an effect of *APOE4* status and sex on amyloid levels, we evaluated these variables in DS and MC individuals. No differences in amyloid PET were observed between *APOE4*-positive and *APOE4*-negative individuals or between males and females for all groups (aDS, sDS, aMC, or sMC) (*p*-values>0.05) (Supplemental Figures 3A and 5A).

Amyloid PET as a function of EYO and age

We evaluated trajectories of amyloid accumulation for controls, DS, and MC groups as measured by EYO using an average age of onset of 52.5 years for participants with DS (Figure 3). Centiloids were elevated in MCs at an earlier EYO compared to participants with DS (−23·0 and −17·5 years old, respectively; p-value < 0·001). This result was similar when using an AAO of 50 and 55 years for participants with DS (p-value < 0·001 and p-value = 0·056, respectively; Supplemental Figure 6). When we compared DS to different ADAD mutation types using an AAO of 52.5 years of age, amyloid accumulation in participants with DS was elevated significantly later than PSEN1 mutations after codon 200 (p-value = 0·0032; Figure 3D) and trended later than PSEN1 mutations before codon 200 (p-value = 0·1074; Figure 3C). There were no significant difference between DS and PSEN2 or APP MCs (both p-values > 0·05) (Figure 3E&F).

When we repeated the comparison to MC participants using age, Centiloids were elevated in MCs at an earlier age compared to participants with DS (25.4 and 34.8 years old, respectively; p-value < 0·001) (Supplemental Figure 7A). When we compared DS to different ADAD mutations, PSEN1 mutations before or after codon 200 were elevated earlier than participants with DS (both p-values < 0·001; Supplemental Figure 7C & D). Amyloid accumulation in participants with DS occurred at a similar age for PSEN2 and APP MCs (both p-values > 0·05; Supplemental Figure 7E & F).

We evaluated if *APOE4*-positivity led to earlier changes in amyloid PET (left shift) in DS and MC individuals. When plotting Centiloids by EYO, we observed no temporal shift in *APOE4*-positive DS (Supplemental Figure 3B) or MC individuals (Supplemental Figure 3C). We also did not observe a significant difference between amyloid-positive and negative individuals when assessed by age range (Supplemental Figure 4). A similar analysis examining sex did not show a temporal shift in Centiloids between males and females for either DS (Supplemental Figure 5B) or MC individuals (Supplemental Figure 5C).

Regional amyloid PET group comparison

We were interested in the spatial pattern of amyloid distribution by EYO for DS compared to MC individuals. We examined SUVR values in 34 cortical and seven subcortical regions in the subset of DS (n=128), MC (n=265), and control (n=202) participants with a PiB PET scan. Within this subset, participants with DS were younger (*p*=0·015) and a majority were asymptomatic (88%) (Supplemental Table 3). Fewer participants with DS were *APOE4*-positive (18%) compared to MC (29%) and controls (28%) (*p*=0.048).

Earliest amyloid accumulation in MC occurred in the occipito-parietal cortices and was closely followed by the frontal lobe and striatum (Figure 4A, Figure 5, Video 1, Supplemental Figure 8, Supplemental Table 4). Early regional amyloid accumulation in participants with DS occurred in the frontal and striatum followed by regions in the parietal and temporal lobes (Figure 4B, Figure 5, Video 1). While we measured amyloid accumulation throughout all cortical regions in MC, amyloid SUVRs were not elevated in DS within the medial occipital regions (cuneus, pericalcarine, and lingual cortices).

DISCUSSION

In this study, we compared amyloid deposition within a large cohort of individuals with DS and MC for ADAD. Overall, we observed many similarities between individuals with DS and MC. This study is the first to assess the relationship between PET and CSF amyloid levels in DS. Our results showed an inverse relationship between the two and suggest amyloid levels decrease in the CSF prior to accumulation in the brain as measured by PET, similar to LOAD and ADAD[18,19]. When we assessed amyloid PET, Centiloid levels were similar between individuals with DS and MC when grouped by cognitive status. However, when we assessed amyloid levels by EYO and performed regional analyses, we noted slight differences between MC and individuals with DS. In particular, amyloid accumulation began earlier in MC compared to DS but approached similar levels by EYO 0. Our results suggest that this difference is driven primarily by PSEN1 mutations. The timing of initial amyloid accumulation in participants with DS was similar to APP MCs. We also observed early striatal and cortical amyloid increases in both MC and DS, but while significant amyloid accumulation was measured throughout the brain in MC, accumulation was spared in certain occipital regions for DS. Our findings suggest that, despite a few subtle differences, overall, cerebral amyloid deposition is similar between ADAD and DS.

When we assessed the relation to cognitive impairment, we observed similar results for DS and MC individuals. In both groups, asymptomatic participants had higher global amyloid levels compared to controls; symptomatic individuals with DS and ADAD had even higher amyloid deposition compared to their asymptomatic counterparts. This is supported by our results showing amyloid accumulation begins approximately two decades prior to symptom onset in both DS and ADAD. These results suggest amyloid accumulation begins in the early pre-clinical stages in individuals with DS and continues to increase as cognitive impairment progresses, similar to what is observed in LOAD and ADAD[18,19].

While our results suggest amyloid begins accumulating at similar early stages of AD progression, we also observed subtle but significant differences between DS and MC in the timing of initial amyloid accumulation. Our results suggest amyloid accumulation begins slightly later in individuals with DS compared to MC. Upon differentiating MCs by ADAD mutation type, we saw that these changes were primarily driven by PSEN1 mutations. No significant differences were observed between individuals with DS and AAP MCs. One possible explanation for this temporal delay for DS is that other triplicated genes on chromosome 21, such as the gene for β-site APP cleaving enzyme 2 (BACE2), could be protective. Studies have suggested the θ-secretase activity of BACE2 cleaves amyloid into smaller non-amyloidogenic Aβ isomers instead of amyloidogenic Aβ$_{42}$[20]. However, a study measured significantly higher levels of CSF Aβ$_{42}$ in asymptomatic individuals with DS compared to asymptomatic MC, suggesting production of amyloidogenic Aβ42 in individuals with DS despite BACE2 triplication[8]. Another possible explanation for the delayed amyloid accumulation in individuals with DS is that they may clear amyloid more efficiently. A study of the DS critical region 1 (DSCR1) on chromosome 21 demonstrated improved amyloid clearance in mice with upregulated DSCR1[21]. Future studies are needed to elucidate potential protective factors in individuals with DS as they could serve as a target for potential therapies.

With regards to spatial pattern of amyloid distribution, our results support previous work showing early amyloid accumulation in MC in the striatal, occipito-parietal, and frontal regions and was relatively consistent across mutation types[9,22]. Similar to previous studies, we measured early striatal amyloid accumulation in DS, in addition to early changes in the anterior cingulate and frontal cortex[23]. This early amyloid accumulation in the striatum in MC and DS supports previous studies and is a key deviation from LOAD[9]. However, while our results showed relatively early amyloid deposition in the medial occipital lobe in MC, we did not observe significant amyloid accumulation in this region for individuals with DS. Our work supports a previous amyloid PET study showing the occipital lobe is one of the last regions to develop amyloid in individuals with DS, a pattern more closely resembling LOAD[23,24]. These regional differences of amyloid deposition between DS, ADAD, and LOAD are important to consider for future clinical trials. Different regions may need to be included when determining amyloid-positivity for these groups as well as when evaluating the efficacy of anti-amyloid therapies.

The presence of at least one *APOE ε4* allele is associated with earlier amyloid changes in LOAD[25]. However, both our work and prior ADAD studies did not observe an effect of *APOE4* on the timing of amyloid accumulation in MC participants[7,26,27]. In DS, several studies have observed a significant effect of *APOE4* on cognitive outcomes. With regards to the effect of APOE4 on amyloid PET measures in DS, mixed results have been observed[14,28,29]. Several studies reported no effect, but a recent study by Bejanin et al. observed higher amyloid PET deposition in subset of APOE4-positive participants aged 41–54 years[30]. In the present study of 192 participants with DS, amyloid PET was not elevated in *APOE4*-positive individuals, and amyloid accumulation did not occur earlier compared to *APOE4*-negative individuals. When we replicated the Bejanin et al. comparison by age range, we did not observe differences between amyloid-positive and negative participants with DS. Overall, our results suggest the presence of the *APOE ε4* allele does not affect the magnitude or timing of amyloid accumulation in genetic forms of AD. These results suggest that genetic mutations in DS and MC individuals overshadow the effects of *APOE* genotype on amyloid. Observed changes in cognition seen with APOE ε4 positive with DS may be mediated by tau, but additional longitudinal studies of multiple biomarkers are needed.

Previous studies also identify a potential role of sex on the trajectory and development of LOAD[31]. Whether sex has an effect in individuals with DS is unclear. Some studies found no effect of sex on the prevalence or timing of dementia diagnosis in adults with DS. Other studies reported males with DS are more likely to develop dementia but at a later age than females[14,28,32,33]. We found no differences in the magnitude or timing of amyloid PET between males and females with DS. These results are supported by previous studies that also did not observe any effect of sex on amyloid PET[23,34–37]. These findings suggest that, while sex may affect cognitive presentation of AD, it does not affect amyloid deposition in adults with DS.

This large cohort of participants with DS and MC presents a notable strength of this study, but limitations should also be acknowledged. Although these two populations are genetically predisposed to develop AD, most ADAD mutations alter the processing of the APP protein by affecting γ-secretase activity. The closest direct comparison to DS would

be individuals with a rare *APP* duplication. Only eight MC participants in our sample 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 AD progression. Information on which ABC-DS participants with DS 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 understand how amyloid accumulation for these two genetic forms of AD. Additionally, this study calculated EYO for individuals with DS using an average age of symptom onset based on the results of several prior studies of individuals with DS. However, using a fixed average age of onset in DS does not account for individual differences. Future analyses are necessary to improve our ability to predict symptom onset and calculate EYO for an individual with DS.

Despite these limitations, we used PET imaging to observe important similarities between two genetic forms of AD. Our results showed that levels of amyloid are similar between individuals with DS and ADAD. In both individuals with DS and ADAD, amyloid accumulation begins at the earliest stages of AD progression, around 20 years prior to the onset of cognitive symptoms. Our results still suggest subtle differences with amyloid accumulation beginning a few years later in individuals with DS and not occurring in all regions of the brain. The safety and efficacy of potential amyloid-lowering AD therapies has yet to be evaluated in individuals with DS. Based on our results, studying individuals with DS at least age 35 years or older would be ideal for potential anti-amyloid therapies. In conclusion, this study demonstrates that, while there are subtle differences between DS and ADAD, the overall pathophysiology is similar between these two genetic forms of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DECLARATION OF INTERESTS

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RESEARCH IN CONTEXT

Evidence before this study:

Between May 2021 and February 2022, we searched PubMed for articles relating to measures of cerebral amyloid in individuals with Down syndrome or autosomal dominant Alzheimer disease. Search terms included: "amyloid", "Alzheimer disease", "Alzheimer's disease", "autosomal dominant", "cerebral", "cerebrospinal fluid", "Down syndrome", "familial", and "positron emission tomography". While many studies have assessed amyloid biomarkers in individuals with Down syndrome (DS) and autosomal dominant Alzheimer disease (ADAD), we found only two that have directly compared these two genetic forms of Alzheimer disease and within a limited sample size. The first study comparing amyloid PET measures reported no differences between individuals with DS and ADAD but included only amyloid-positive, asymptomatic individuals. The other study compared only CSF biomarkers and measured significantly higher amyloid-β_{40} ($A\beta_{40}$) and $A\beta_{42}$ in individuals with DS.

Added value of this study:

To our knowledge, this is the first study to assess the relationship between CSF and PET amyloid measures in individuals with DS. It is also the largest study to date comparing amyloid accumulation as measured by PET imaging, processed in a similar manner, between individuals with DS and ADAD. We observed an inverse relationship between CSF and PET measures of amyloid in individuals with DS, which is similar to the relationship previously seen for ADAD and late-onset AD. Overall levels of amyloid accumulation were also similar between individuals with DS and ADAD with regard to degree of cognitive impairment. Amyloid accumulation began earlier in ADAD than in DS with regards to EYO, but this difference was primarily driven by carriers of PSEN1 mutations. Our analysis supported previous evidence of early striatal amyloid accumulation for both ADAD and DS. However, while amyloid accumulation occurred throughout the cerebral cortex in ADAD, we observed no accumulation in certain occipital regions in individuals with DS.

Implications of all the available evidence:

Our results support prior evidence suggesting similar levels of global amyloid accumulation in individuals with DS and ADAD. These findings also build on prior evidence that amyloid changes may occur in the CSF prior to cerebral accumulation measured by PET. Our findings suggest a potential protective factor delaying amyloid accumulation in individuals with DS, which may offer alternative targets for AD therapies. This timing and spatial distribution of amyloid accumulation are important to consider when designing and recruiting participants for clinical trials of amyloid-targeting therapies in DS and ADAD. The overwhelming similarities in the pattern of amyloid changes suggest potential overlap in the use of AD therapies for individuals with DS and ADAD.
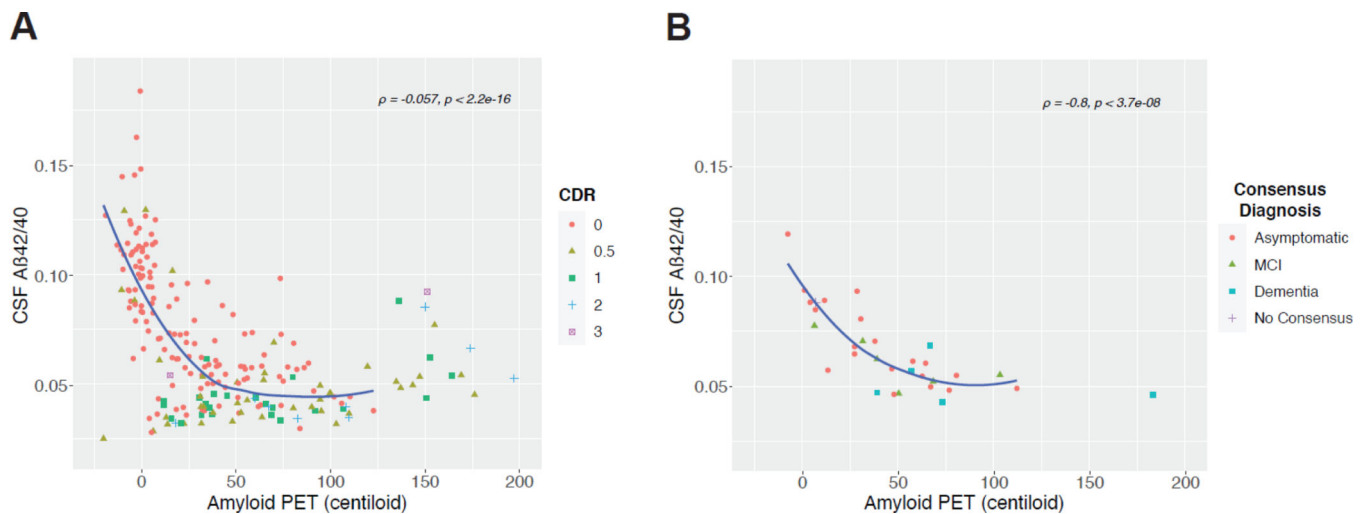
Figure 1:

Global amyloid deposition in Centiloids plotted against CSF levels of Aβ42/Aβ40 in **A)** ADAD MCs (n = 219) and **B)** participants with DS (n = 32). Plotted data points were categorized by participants' cognitive status as measured by CDR in MCs and consensus diagnosis in DS. Correlation analysis between CSF Aβ42/Aβ40 and Centiloids was performed using Spearman's rank correlation test. <u>Abbreviations</u>: Aβ = amyloid-beta; CDR = clinical diagnosis rating; CSF = cerebrospinal fluid; DS = Down syndrome; MC = mutation-carrier; MCI = mild cognitive impairment; PET = positron emission tomography
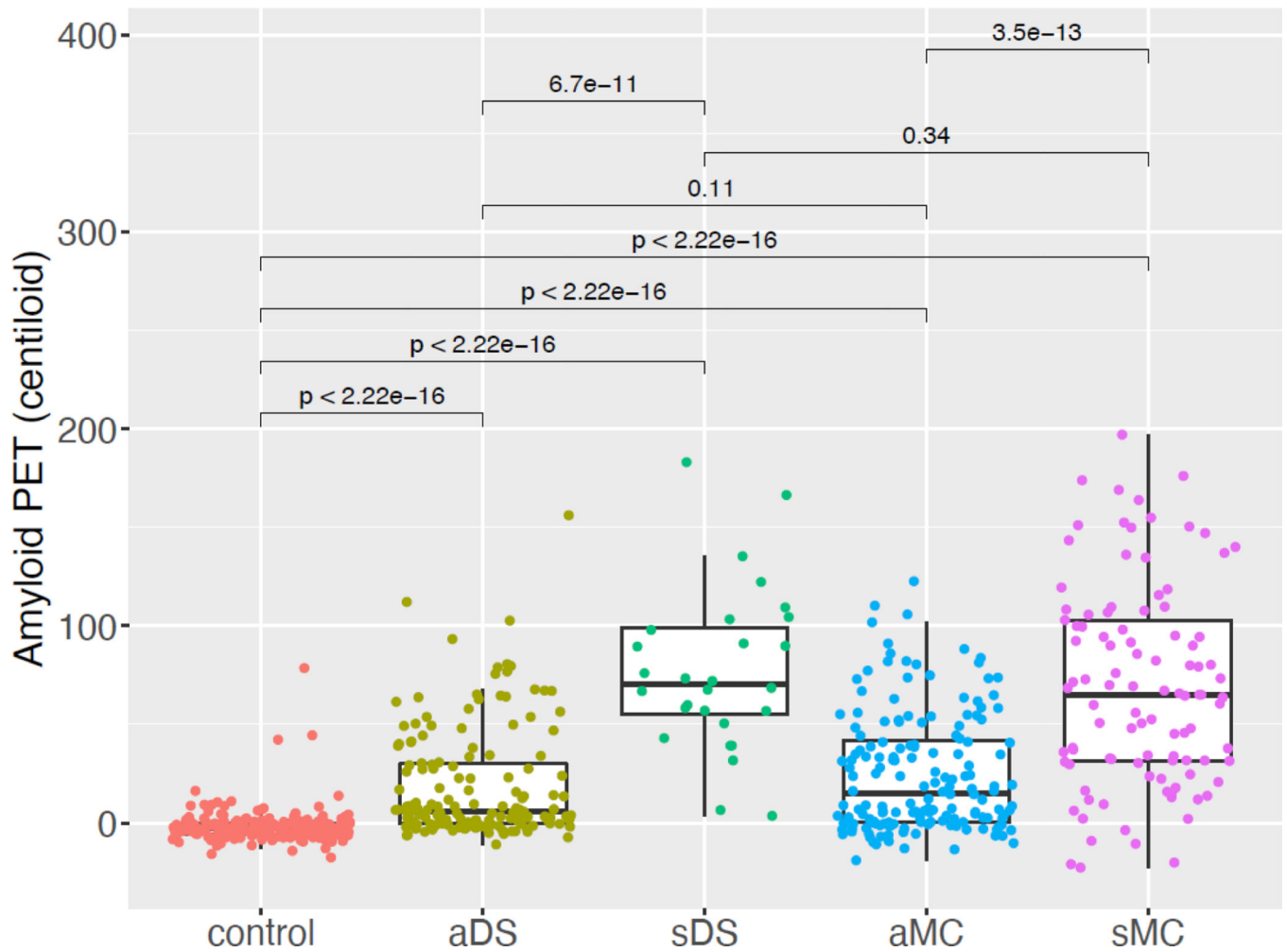
Figure 2:
Global amyloid deposition for control, DS, and MC participants were grouped by cognitive status. P-values were calculated using the Mann-Whitney U test and adjusted for multiple comparisons using the Benjamini-Hochberg method. <u>Abbreviations</u>: aDS = asymptomatic DS; aMC = asymptomatic MC; sDS = symptomatic DS; sMC = symptomatic MC; DS = participants with Down syndrome; MC = autosomal dominant mutation carriers; PET = positron emission tomography
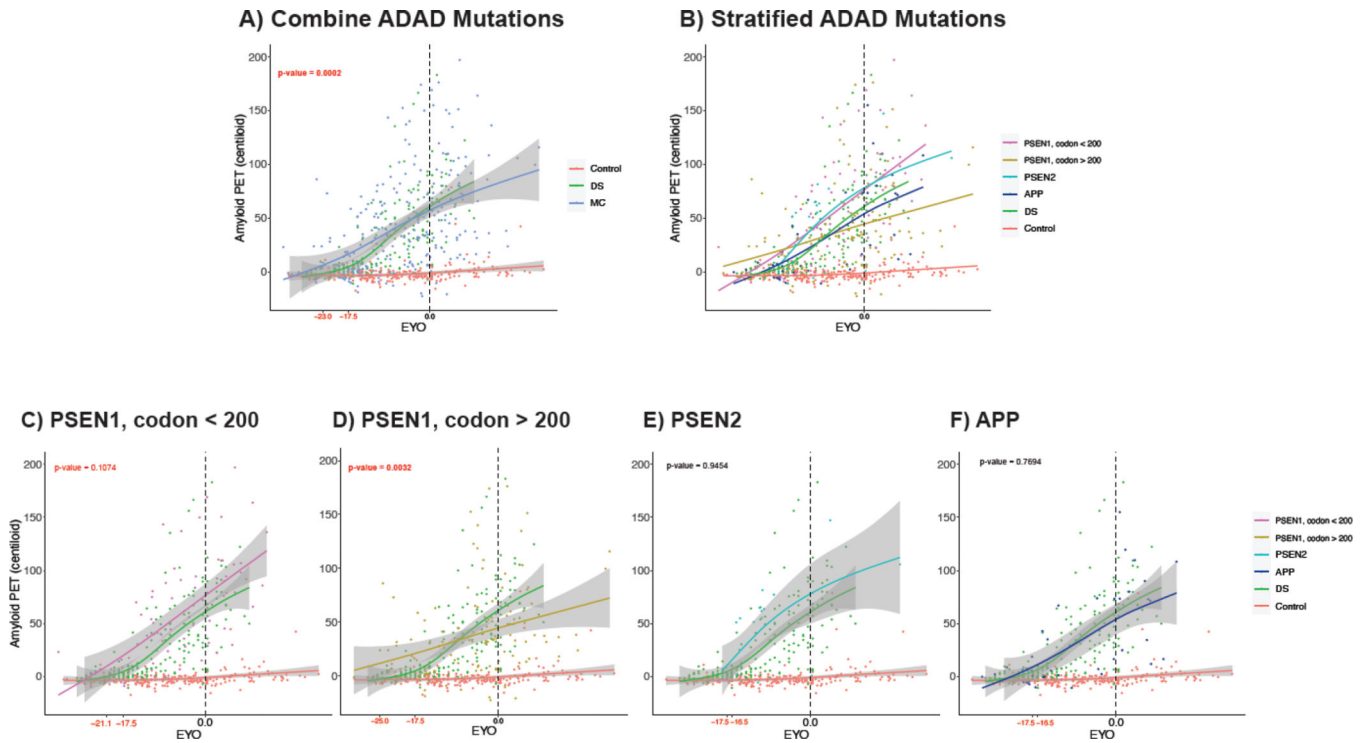
Figure 3:

Global amyloid deposition in Centiloids as a function of EYO for healthy controls, participants with DS, and A) all ADAD mutation type MCs B) MCs stratified by ADAD mutation type, C) PSEN1 before codon 200 MCs (n = 74), D) PSEN1 after codon 200 MCs (n = 128), E) PSEN2 MCs (n = 22), and F) APP MCs (n = 41). EYO was determined by parental AAO for MC and by AAO of 52.5 years for DS. Curves were generated using a generalized additive model and cubic regression spline. Using a bootstrapping approach, the median EYOs in red at which MC and DS Centiloids became significantly elevated compared to controls were calculated and compared to determine whether accumulation began significantly later in participants with DS compared to MCs. Abbreviations: AAO = age at onset; ADAD = autosomal dominant Alzheimer disease; APP = amyloid precursor protein; DS = Down syndrome; MC = mutation-carrier; PET = positron emission tomography; PSEN = presenilin

Figure 4:
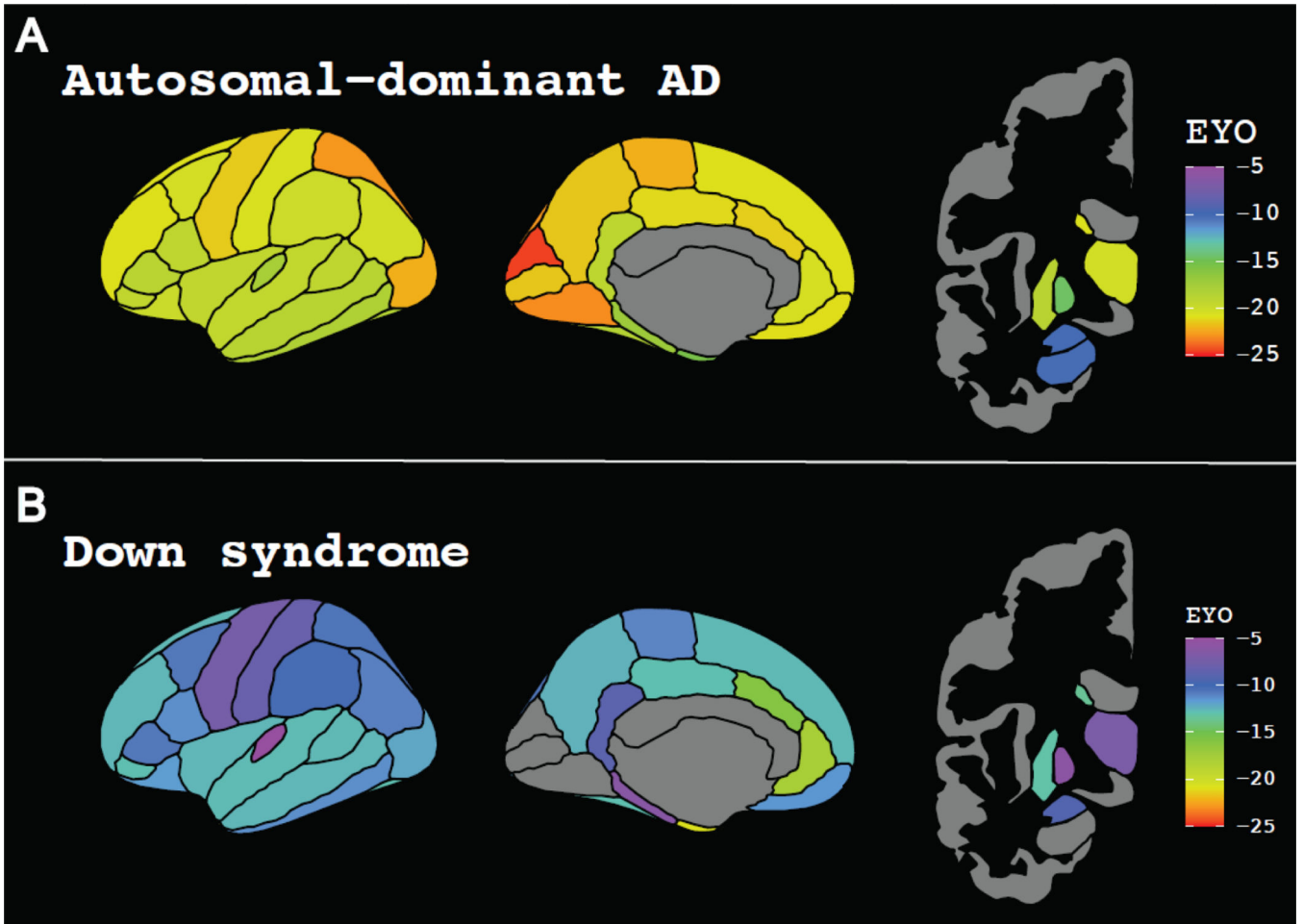EYO at which regional amyloid accumulation in **A)** ADAD mutation-carriers and **B)** individuals with DS was significantly greater than controls. Using a bootstrapping approach, the EYO at which each region became significantly elevated was determined over 10,000 iterations. The median EYO for each region was calculated to assess the spatial pattern of amyloid accumulation. Abbreviations: ADAD = autosomal dominant Alzheimer disease; EYO = estimated years to symptom onset; DS = Down syndrome
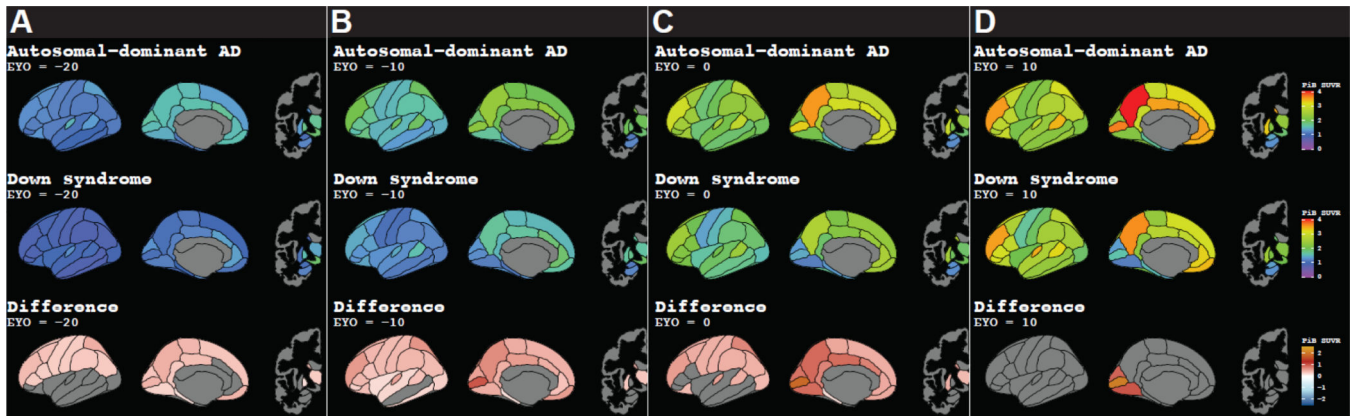
Figure 5:
Regional PiB SUVRs at **A)** EYO = −20, **B)** EYO = −10, **C)** EYO = 0, and **D)** EYO = 10 in autosomal dominant AD MCs, participants with DS, and the significant difference between MC and DS SUVRs using a 99% confidence interval to adjust for multiple comparisons.
<u>Abbreviations</u>: AD = Alzheimer's disease; EYO = estimated years to symptom onset; DS = Down syndrome; MC = autosomal dominant AD mutation carrier; SUVR = standard uptake value ratio

Table 1.

Participant demographics

	Controls (n = 202)	Down syndrome (DS) (n = 192)	Mutation-carrier (MC) (n=265)	p-value
Age, years (median [IQR])	40 [33, 49]	41 [35, 49]	39 [33, 48]	0·137
Female	123 (61%)	84 (44%) [*]	140 (53%)	**0·003**
Race				**0·027**
White	186 (92%)	184 (96%) [†]	232 (87%)	
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				**< 0·001**
Asymptomatic	202 (100%)	155 (81%) [*†]	164 (62%) [*]	
Symptomatic	0	28 (15%)	101 (38%)	
No consensus	NA	9 (4%)	NA	
Down syndrome type				---
Full trisomy 21	--	168 (87·5%)	--	
Translocation	--	12 (6%)	--	
Mosaicism	--	6 (3%)	--	
ADAD mutation type				---
PSEN1	--	--	202 (76%)	
PSEN2	--	--	22 (8%)	
APP	--	--	41 (15%)	
Centiloid (median [IQR])	-2·93 [−5·7, −0·07]	8·45 [1·3, 49·8] [*†]	31·72 [4·6, 67·2] [*]	**<0·0001**

Abbreviations: ADAD = autosomal dominant Alzheimer disease; APP = amyloid precursor protein; IQR = interquartile range; PSEN = presenilin; SD = standard deviation

[*] 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)