

Alzheimer's Disease in People With Down syndrome

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- Consultant: Alnylam Pharmaceuticals Inc.; Ionis Pharmaceuticals Inc.
- Chair: Alzheimer's Association ISTAART Down syndrome Professional Interest Area

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Learning Objectives

1. Discuss the connection between Down syndrome and Alzheimer's disease
2. Understand how Alzheimer's disease presents in people with Down syndrome
3. Describe what is known about resiliency factors for positive aging in people with Down syndrome

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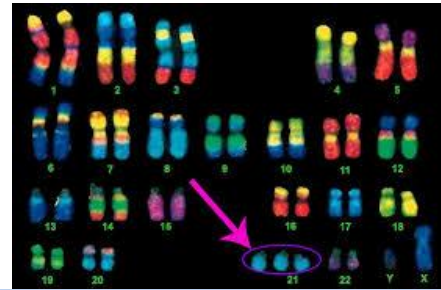
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Down Syndrome (DS)

- Full or partial trisomy 21
- Intellectual disability
- Delays and difficulties in language, motor, and cognitive skills
- Distinct physical features
- Co-occurring medical conditions
- ~1 in 700 live births in the U.S.



Physical Features

- Excess skin at the nape of the neck
- Separated joints between the bones of the skull (sutures)
- Small ears
- Small mouth
- Wide, short hands with short fingers
- White spots on the colored part of the eye (Brushfield spots)

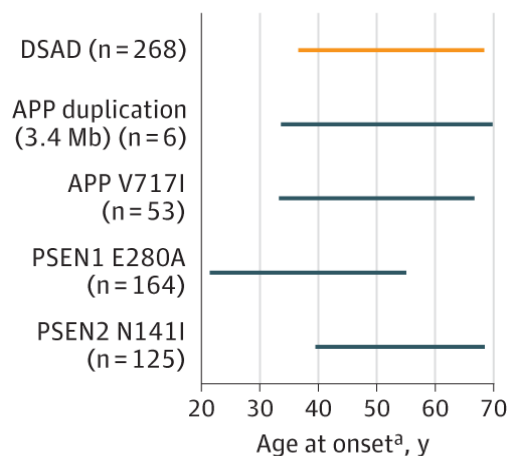


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Down syndrome associated Alzheimer's Disease (DSAD)

- **90%** lifetime prevalence for symptomatic Alzheimer's disease
- Across 44 studies from the systematic review (N = 2,695 individuals), the average age of dementia onset = **53.8 years**

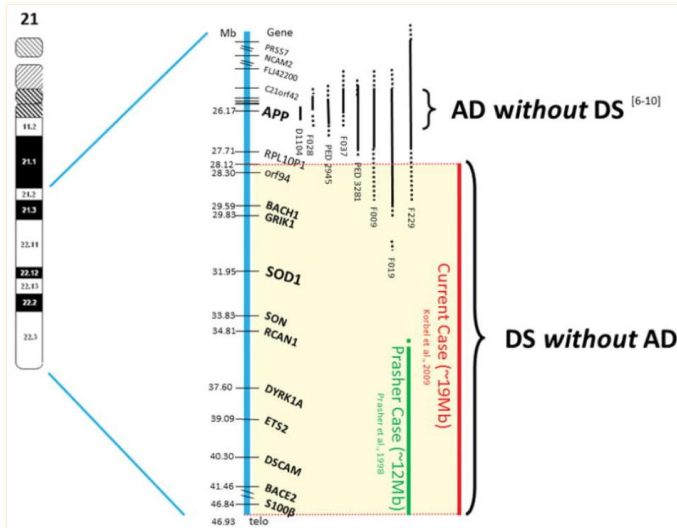
C 95% Prediction intervals



lulita et al., 2022 JAMA Network Open

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Trisomy 21 and APP Gene



Doran et al. 2017

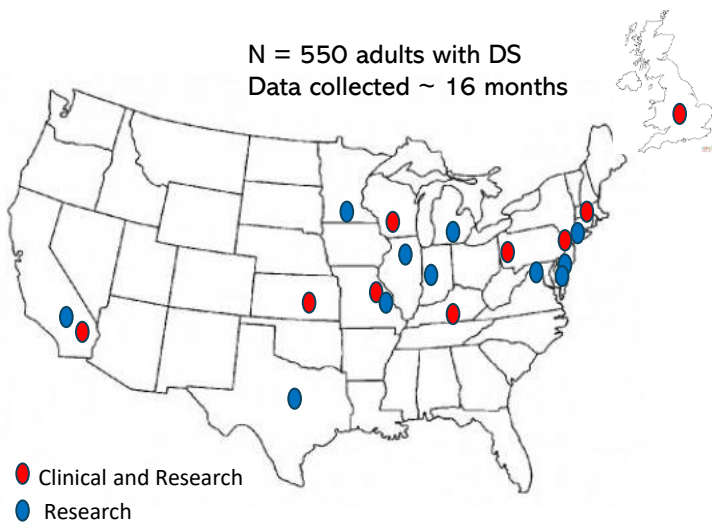
But....

genes on chr21 involved in autoimmune, oxidative stress, inflammation, and metabolic pathways

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Alzheimer Biomarker Consortium- Down Syndrome (ABC-DS)

N = 550 adults with DS
Data collected ~ 16 months



Clinical and Research

- University of Pittsburgh (Handen & Cohen)
- University of Cambridge (Zaman)
- Washington University- St. Louis (Ance)
- University of WI-Madison (Christian & Hartley)
- University of California Irvine (Head & Maptone)
- Massachusetts General Hospital (Lai & Rosas)
- University of Kentucky (Schmitt)
- Columbia University/New York Institute for Basic Research (Lee & Krinsky-McHale)
- Kansas University (Ptomey & Burns)

Research

- Georgetown University; University of North Texas; University of Michigan; Mayo Clinic; Washington University- St. Louis CSF Lab; NCRAD; ATRI & LONI; Johns Hopkins

NIH Partners

- Laurie Ryan, Erika Tarver, Linda Garcia, Melissa Paris, Nina Silverberg, Sujata Bardhan

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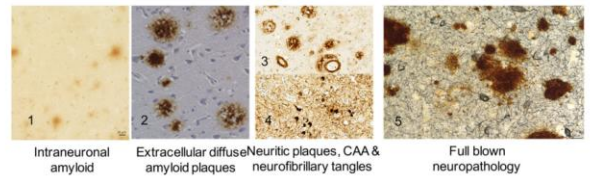
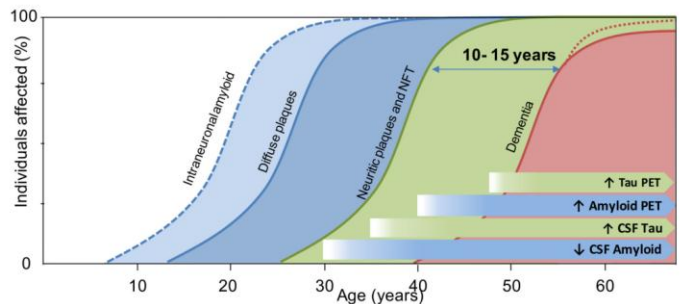
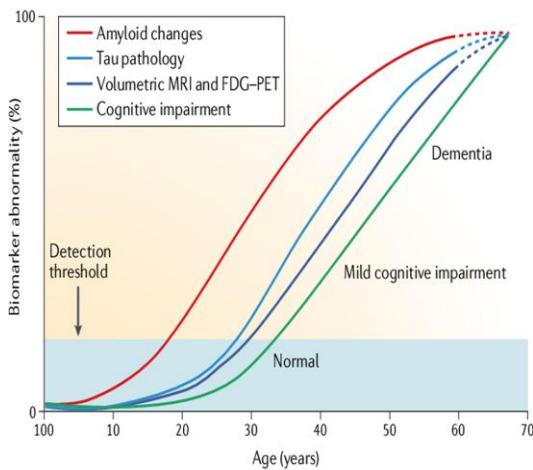
ABC-DS Objectives



- Establish an organizational infrastructure to follow and comprehensively characterize a large clinical cohort of adults with DS
- Examine biomarkers of DS-AD in the AT(N) framework, and determine if risk is modified by selected factors
- Examine genetic factors that modify DS-AD risk
- Develop precision medicine ready biomarkers for DS-AD clinical trials
- Disseminate data and biospecimens to researchers outside the ABC-DS

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DSAD Pathology



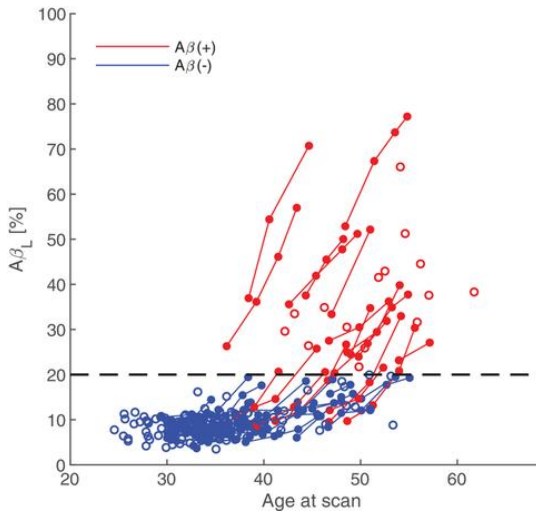
A = amyloid
T = tau
(N) = neurodegeneration

Figures: Fortea et al., 2022; Lott & Head, 2019

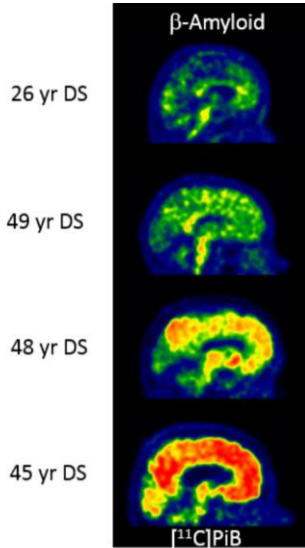
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Biomarkers of DSAD Pathology

A = amyloid



Zammit et al., 2020



Lao et al., 2018

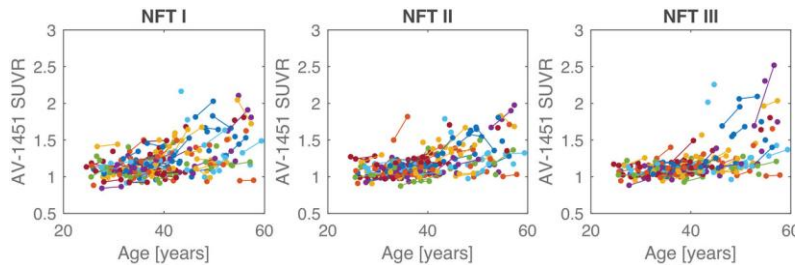


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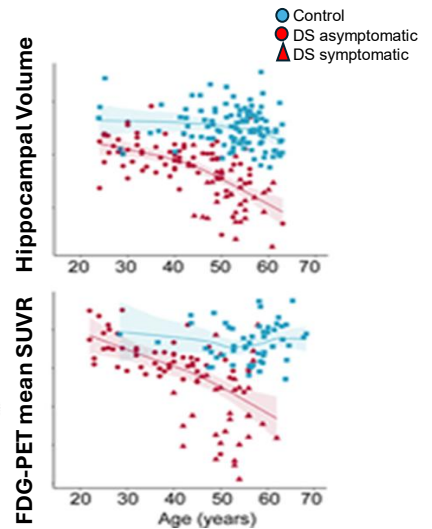
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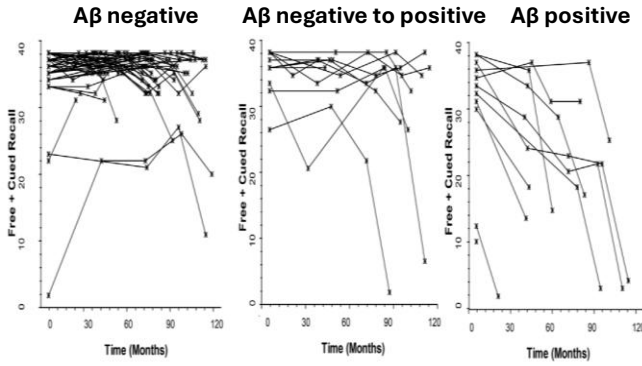
Zammit et al., 2024



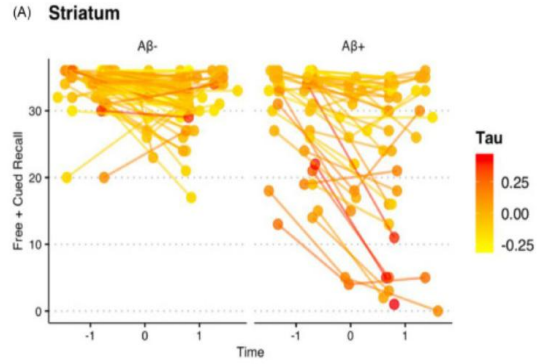
Fortea et al., 2024

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DSAD Symptomology



Hartley et al., 2020

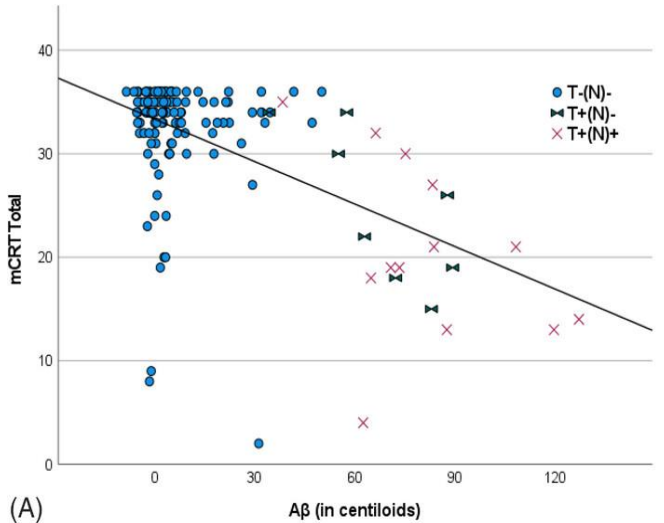
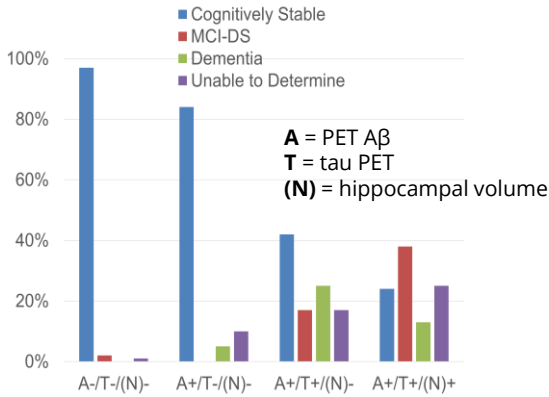


Grigороva et al., 2021

mCRT = modified Cued Recall Test

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DSAD Symptomology

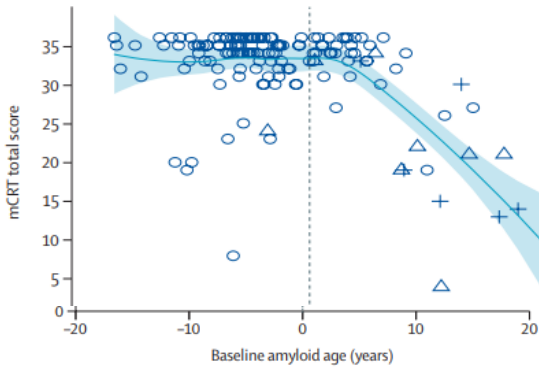


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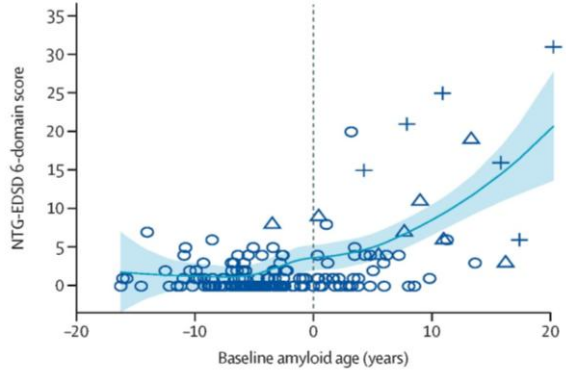
Hartley et al., 2023

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Amyloid Clock and DSAD



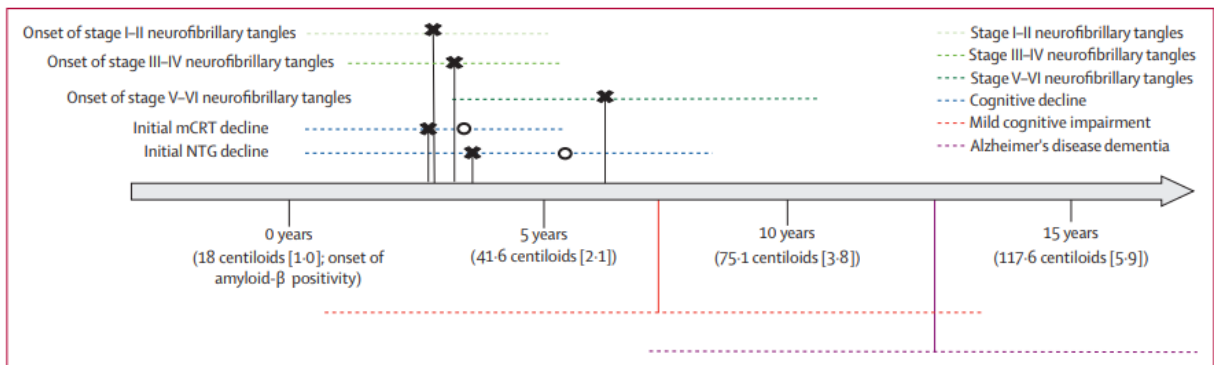
Schworer,
Zammit et al.,
2024



CL = 18

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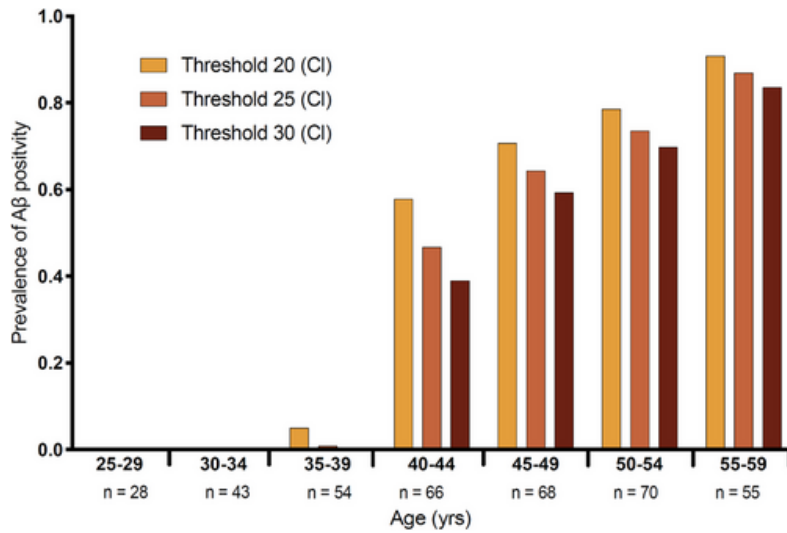
Amyloid Clock and DSAD



Schworer, Zammit et al., 2024

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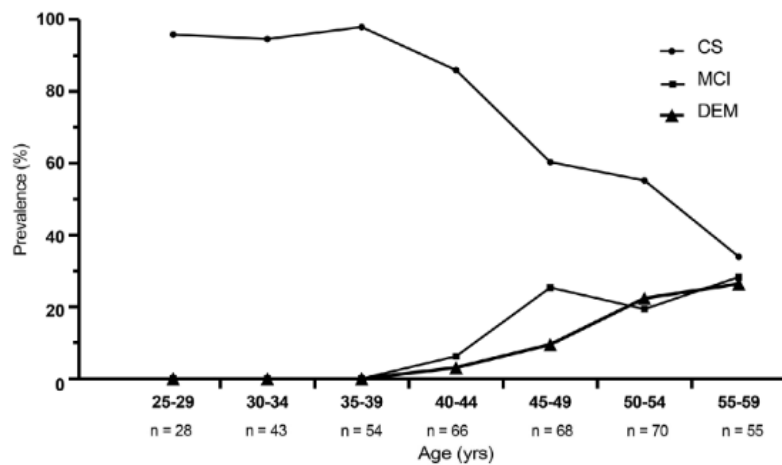
Age of amyloid positivity



Krasny, Yan, Hartley et al., 2024

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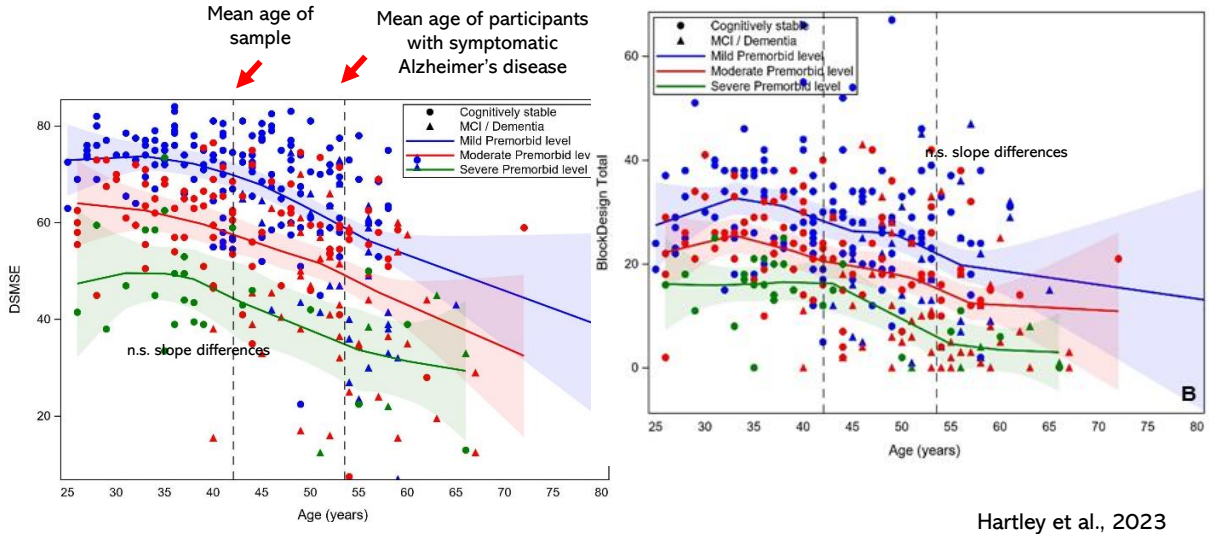
Age of MCI and Dementia



Krasny, Yan, Hartley et al., 2024

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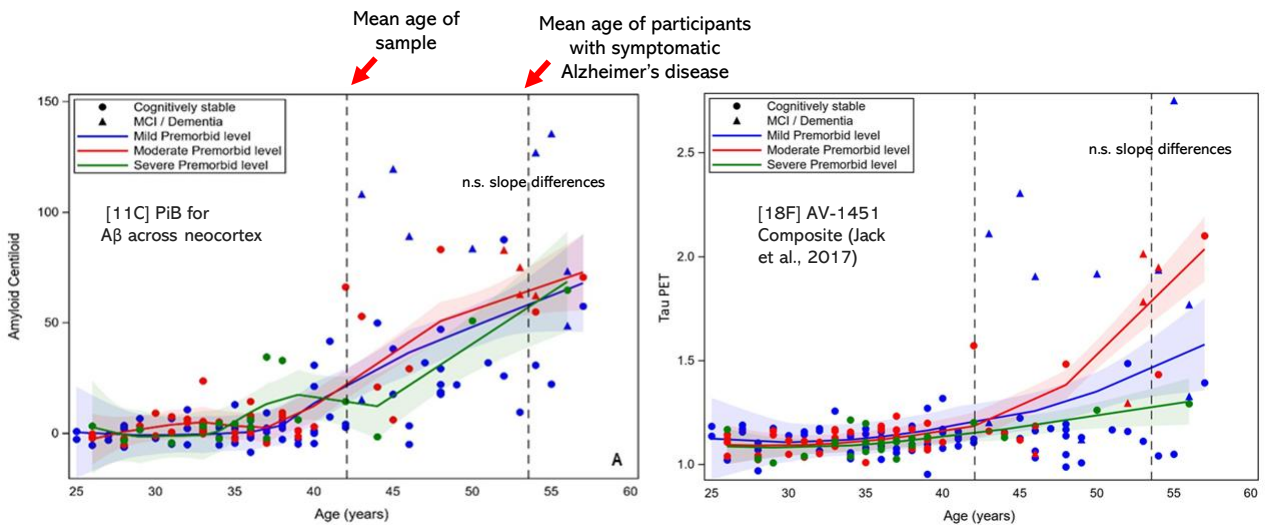
Lifetime Intellectual Disability Level



Hartley et al., 2023

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Lifetime Intellectual Disability Level



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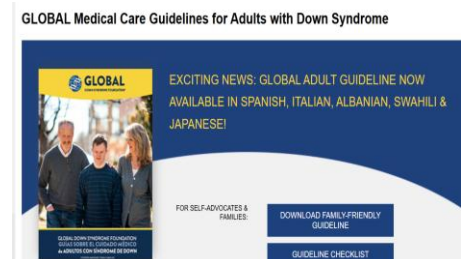
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Screening and Diagnostic Considerations

- Consider age
- Multiple sources of information and overall pattern of findings
- Consider the individual's lifetime intellectual disability level
- Focus on change in cognitive or functional ability
- Rule out medical and psychiatric conditions and significant life events
- When possible, consider biomarkers of Alzheimer's disease pathology (e.g., amyloid plaques or neurofibrillary tangles of tau)



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Assessment Batteries

Baseline Component

Intellectual disability level (IQ)
Functional/adaptive abilities
Language/communication abilities
Memory
Attention/executive function
Visuospatial ability
Psychiatric or behavioral Changes
Sensory status (vision, hearing)
Gait
Weight

Baseline ~ age 30 yrs

Common Valid Cognitive Test

Modified Cued Recall Test
CAMDEX-DS-II
DSMSE
NTG-EDSD
DLD



THE NIA ALZHEIMER'S DISEASE RESEARCH CENTERS PROGRAM
National Alzheimer's Coordinating Center

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Early Signs of DSAD

- Social withdrawal
- Change in ability to complete tasks of daily living
- Deterioration in short term memory e.g. forgetting what they have said, losing their belongings, asking the same question repeatedly
- Loss of interest in previously enjoyed activities
- Anxious or asking for reassurance
- Difficulties learning new things
- Less talkative, not able to express thoughts to same extent
- Difficulty in finding the correct word
- New or increased confusion and/or disorientation
- Changes in sleep pattern
- Difficulties with walking – shuffling, unsteady
- Difficulties with steps, stairs - depth perception problems
- Increased walking about without a clear reason
- Unintentional weight loss

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Things to rule out

- Depression or other psychiatric problems
- Lack of sleep or untreated sleep apnea
- Medical conditions – e.g., urinary tract infection, thyroid disorders, diabetes, seizures, stroke, constipation, dehydration
- Adverse effects of medication or recent major illnesses
- Untreated pain (e.g. dental pain)
- Hearing/Visual impairment
- Stressful life events

[Dementia and people with intellectual disabilities: Guidance on the assessment, diagnosis, interventions and support of people with intellectual disabilities who develop dementia | BPS - British Psychological Society](#)

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Examples of Cognitive Tests

- Video

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Clinical Trials and DSAD

ABATE

Sponsor: AC Immune
Therapy: AC1-24.060; Vaccine immunotherapy
Route: intramuscular injection
Phase: 1b/2

HERO

Sponsor: Ionis Pharmaceuticals
Therapy: ION269; Antisense Oligonucleotide
Route: lumbar puncture
Phase: 1b

ALADDIN Study

Sponsor: Alzheimer's Clinical Trials Consortium –
Down syndrome (ACTC-DS)
Therapy: Donanemab; Antibody immunotherapy
Route: intravenous infusion
Phase: 4

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ACTC-DS Affiliated Clinical Trials



- ABATE Trial www.abate-study.com
- Participants 35-50 years old with DS
- The study is specifically designed for people with DS and is testing a potential treatment for Alzheimer's disease
- We have 2 goals:
 - To learn more about the study treatment's safety
 - To see if it slows down memory loss and thinking problems



Slides: Michael
Rafii

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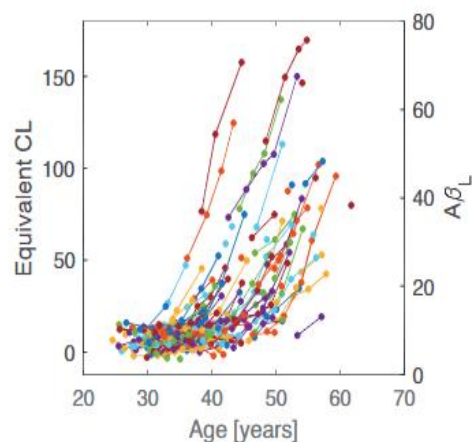
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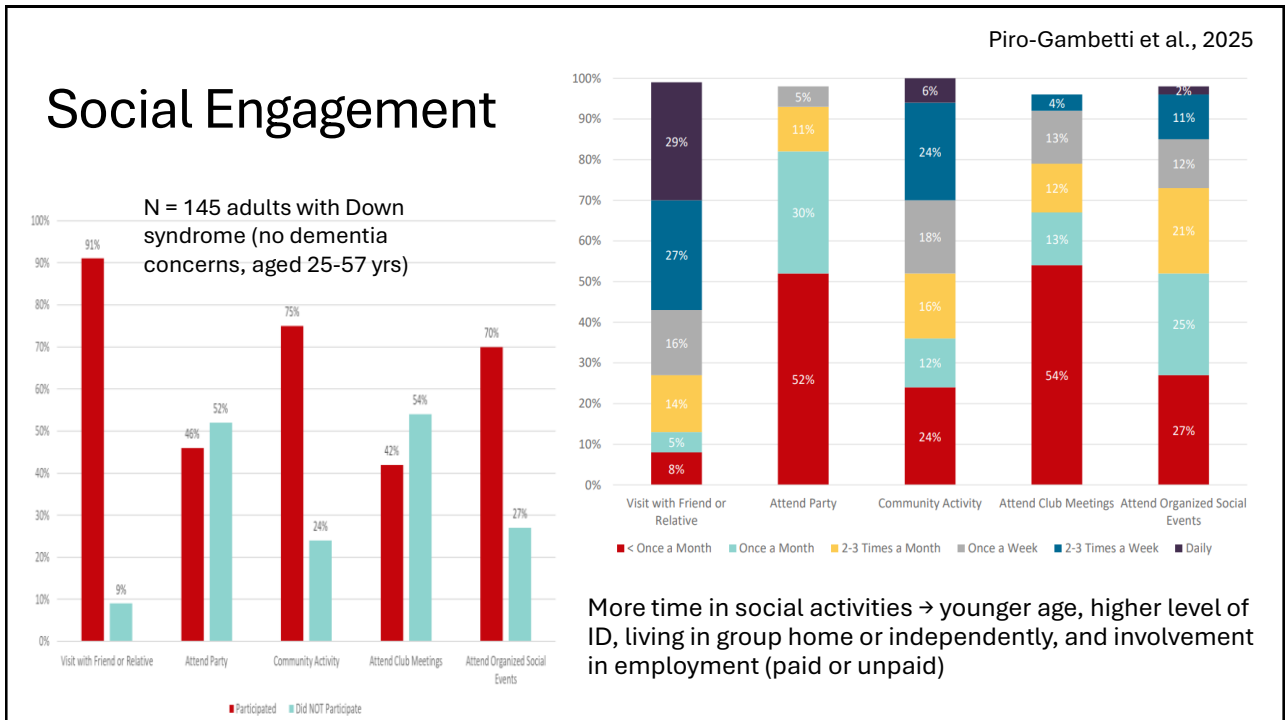
Evidence of Resistance and Resilience in DSAD

- Within studies, age of dementia onset spans ~22 years, on average (Iulita et al., 2022)
- Post-mortem brain autopsy studies - 13% of adults with Down syndrome had significant Alzheimer's disease neuropathology but no clinical manifestations of dementia (Flores et al., 2025)



Zammit et al., 2023

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Benefits of Social Engagement

- **Greater variety** of social activities → higher QoL (World Health Organization Quality of Life-Disabilities module)
- **More time** in social activities → lower depression (Glasgow Depression Scale for people with a Learning Disability)
- **Take away:** Engaging in *social activity (even if with few partners and limited activities)* may help prevent depression. *Involvement in a variety of social activities (with different social partners)* may increase QoL.

Piro-Gambetti et al., 2025

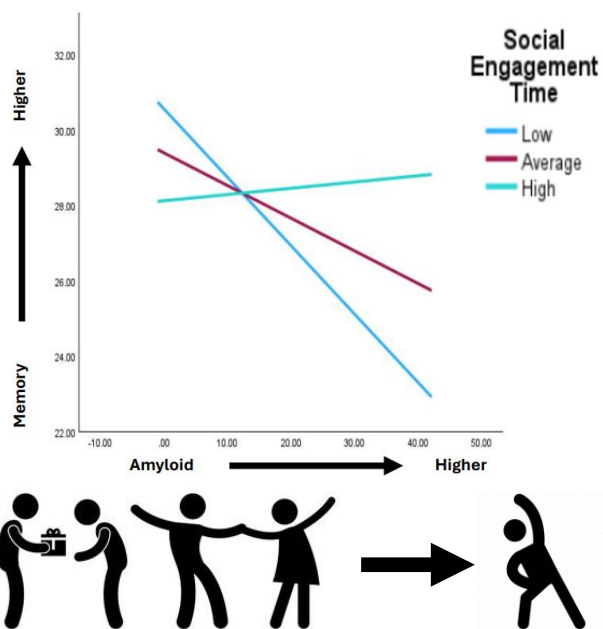
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Benefits of Social Engagement

- More time in social activities → better memory (Modified Cued Recall Test) and fewer dementia symptoms (National Task Group – Early Detection Screen for Dementia) with amyloid plaques

Take away: Social activities may build cognitive flexibility to help compensate for early AD pathology and foster brain health by reducing stress and promoting physical activity

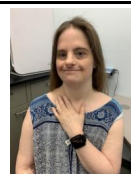
Piro-Gambetti et al., 2025



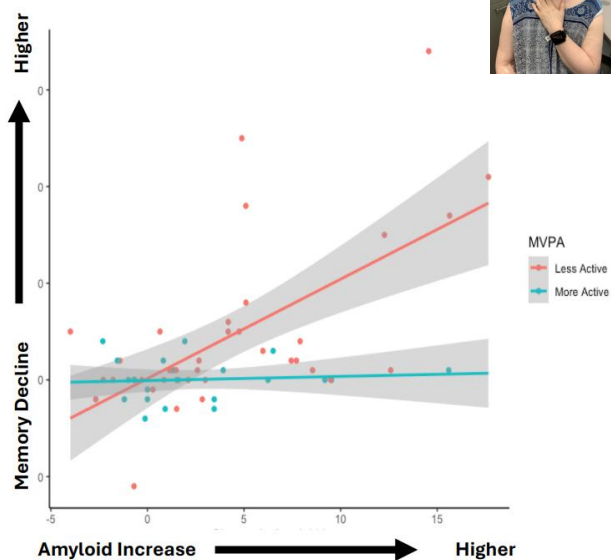
Jenkins et al., 2025

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Physical Activity Benefits



- Examined physical activity during a typical week
- Physical activity (% time in MVPA) was not related to baseline amyloid ($\beta = -0.005$, $p = 0.710$) or change in amyloid ($\beta = 0.003$, $p = 0.670$)
- Higher physical activity (% time in MVPA) was predicted less decline in memory with increasing amyloid

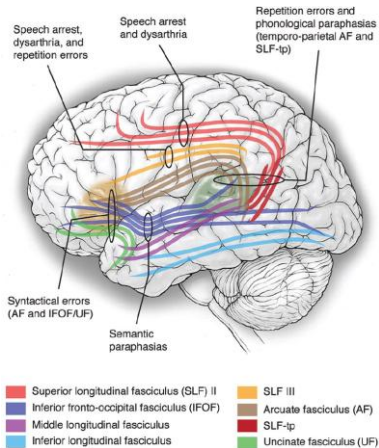


Fleming et al., 2025

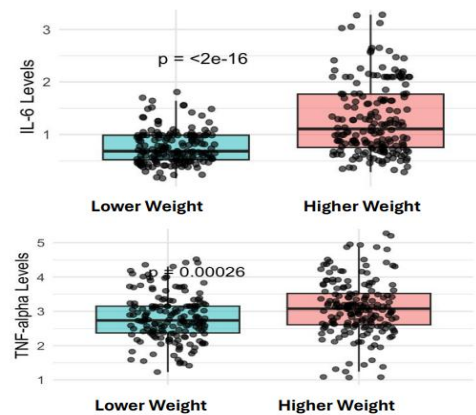
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Physical Activity Benefits

- Improves brain white matter



- Reduces inflammation



Fleming et al., 2022; 2025

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Physical Activity Benefits

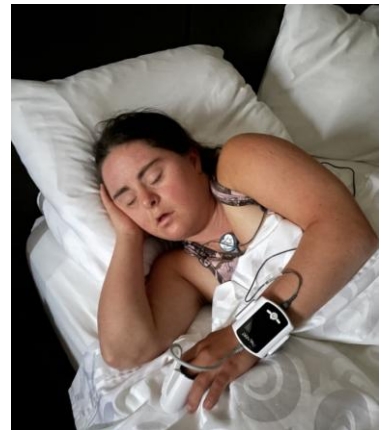
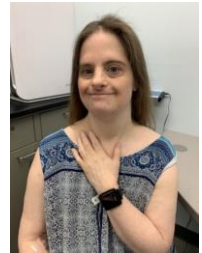
- When we compared the effect of different lifestyle factors for preserving memory in the face of amyloid plaques
 - Physical had stronger effect social activity, leisure, and employment activities (Schworer et al., 2025)
- Take home:** Physical activity may be an especially important lifestyle factor for healthy brain functioning and protecting memory as adults with Down syndrome age



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Sleep and DSAD

- Adults with Down syndrome have high risk of obstructive sleep apnea
- Higher levels of sleep disruptions are connected to cognitive impairments and PET amyloid and tau cross-sectionally in people with Down syndrome (Cody et al., 2019; Yoon et al., 2025)
- Sleep screenings are important across adulthood



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Summary

- People with Down syndrome have a high prevalence of Alzheimer's disease and an early onset of the disease
- DSAD has a similar presentation of pathology as what is seen in autosomal dominant Alzheimer's disease, BUT faster progression
- Screening for DSAD is needed, with baselines ~age 30 yrs
- Need for clinical DSAD trials for adults with Down syndrome (Aladdin & Abate)
- There is variability in the timing of DSAD and opportunity for primary and secondary prevention
- Lifestyle is related to positive aging in people with Down syndrome

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Acknowledgements

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