Delving into Alzheimer disease in Down syndrome – how a lifespan approach can help.

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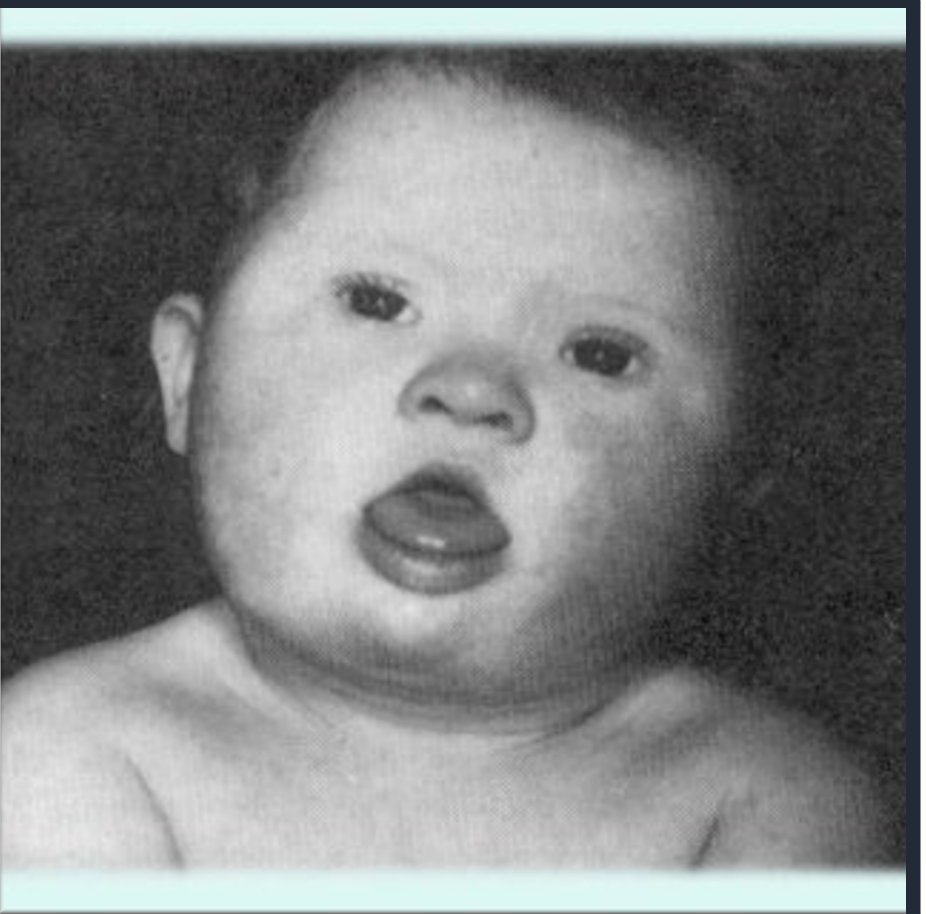
CFAR-DS

- What is Down syndrome and what causes it
- What is the link between Down syndrome and Alzheimer disease?
- What does Alzheimer disease in people with Down syndrome look like?
- What treatments are available for Alzheimer disease in people with Down syndrome
- Why is a lifespan approach so helpful for people with Down syndrome?
- How might we prevent Alzheimer disease?
- What is ABC-DS

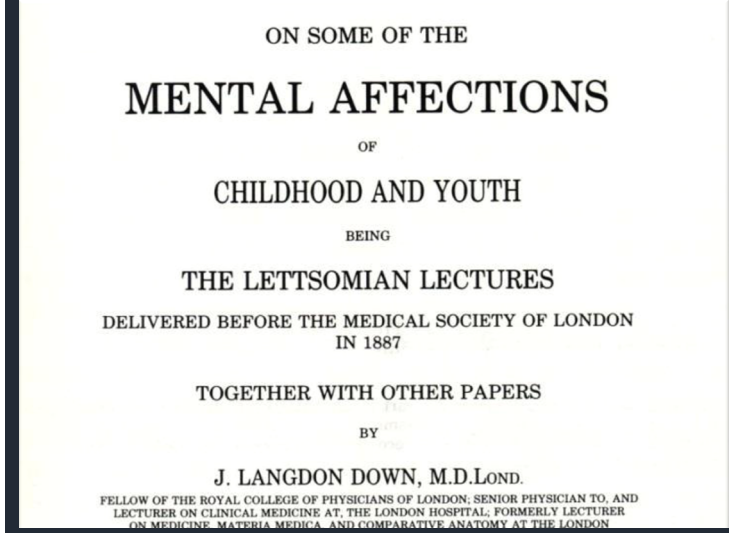
Down syndrome



First described by Langdon Down in 1887.

Down Syndrome (DS) is the most common cause of intellectual disability

About 400,000 people with Down syndrome in the USA



ON SOME OF THE

MENTAL AFFECTIONS

OF

CHILDHOOD AND YOUTH

BEING

THE LETTSOMIAN LECTURES

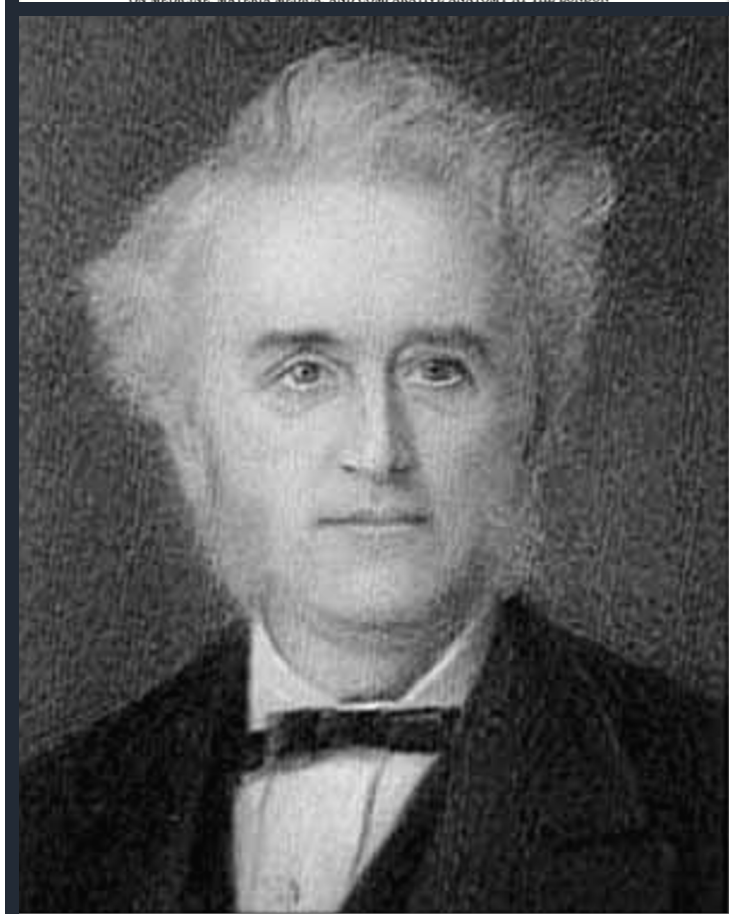
DELIVERED BEFORE THE MEDICAL SOCIETY OF LONDON IN 1887

TOGETHER WITH OTHER PAPERS

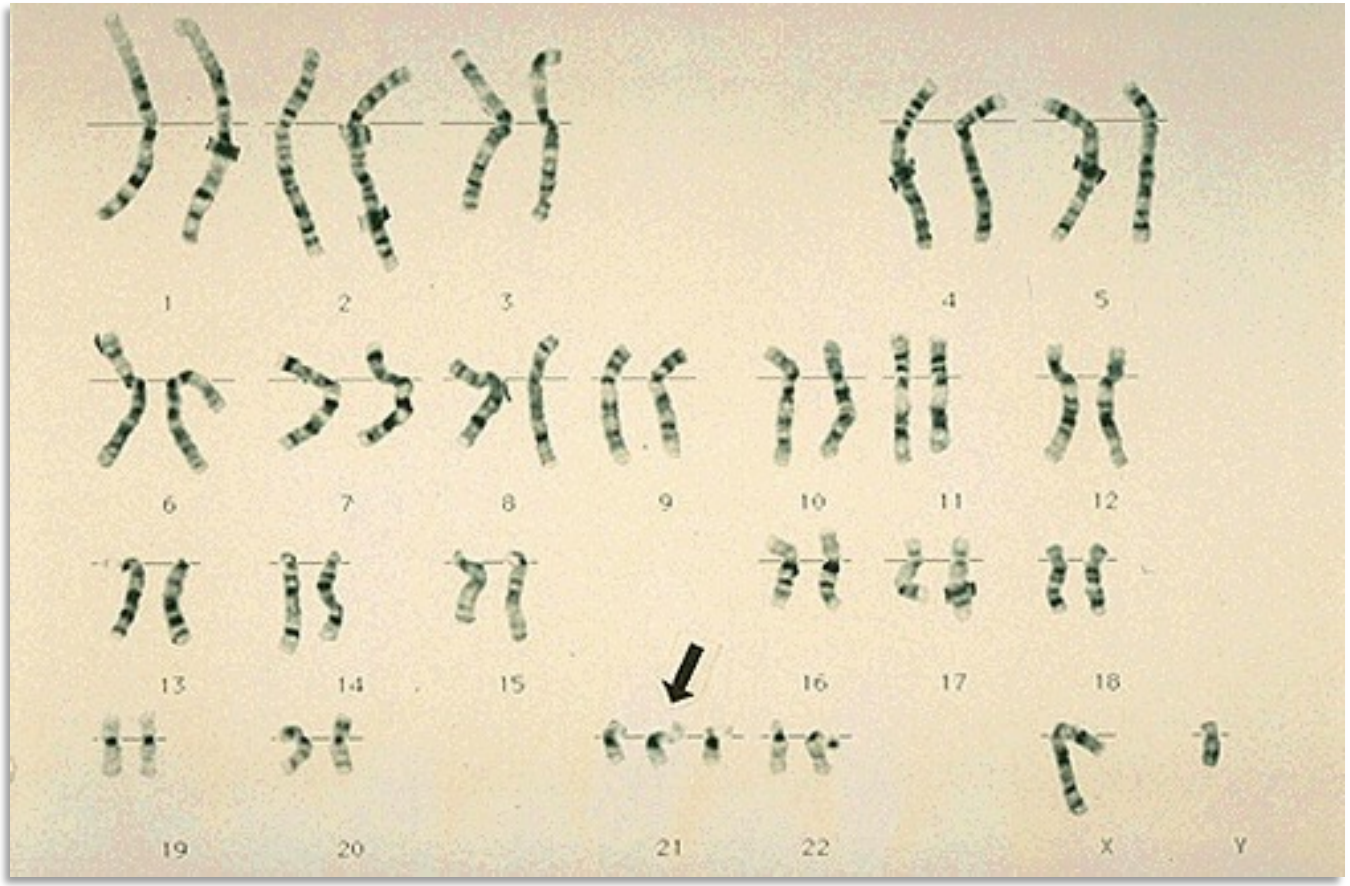
BY

J. LANGDON DOWN, M.D.LOND.

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON; SENIOR PHYSICIAN TO, AND LECTURER ON CLINICAL MEDICINE AT, THE LONDON HOSPITAL; FORMERLY LECTURER ON MEDICINE, MATERIA MEDICA, AND COMPARATIVE ANATOMY AT THE LONDON

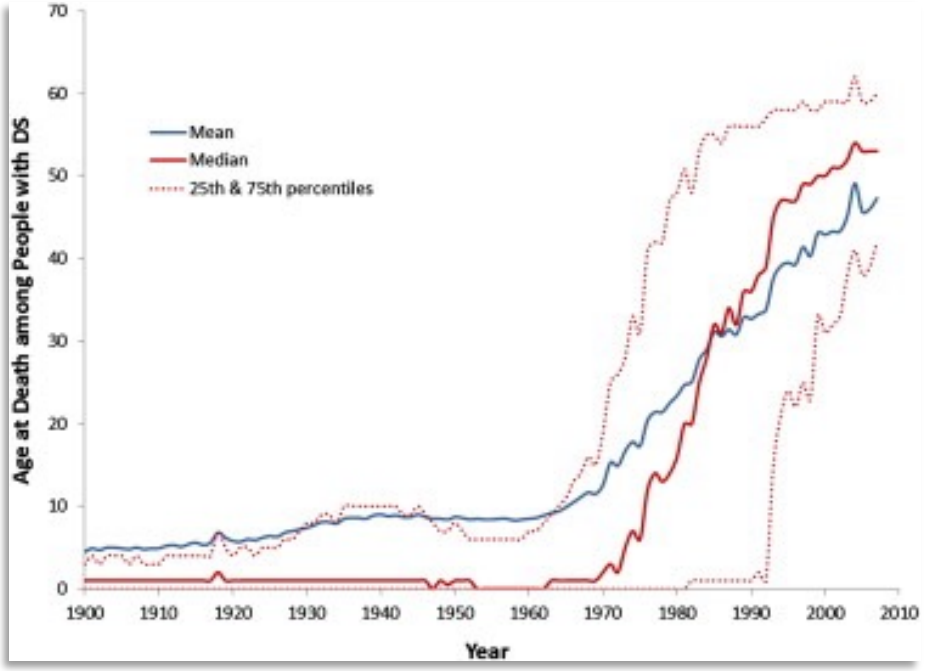


What causes Down syndrome?

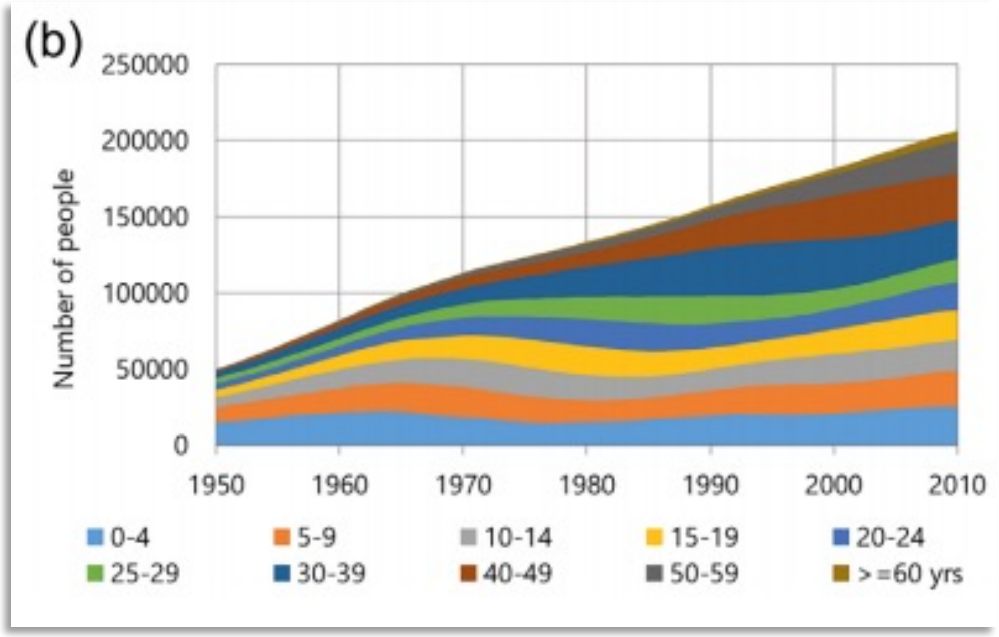


LeJeune and Gautier, 1959

People with Down syndrome are living longer

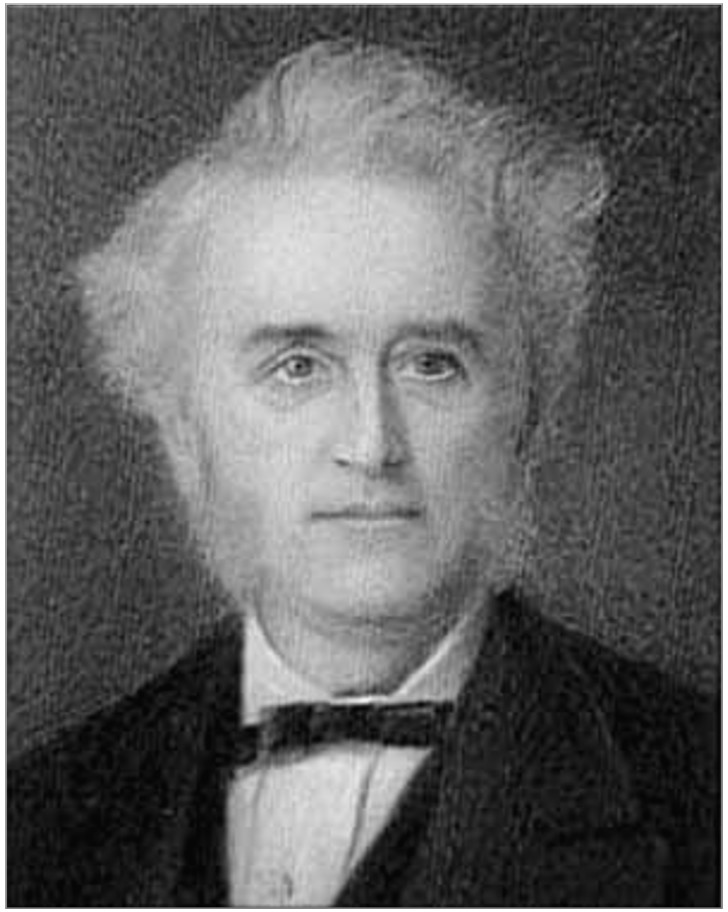


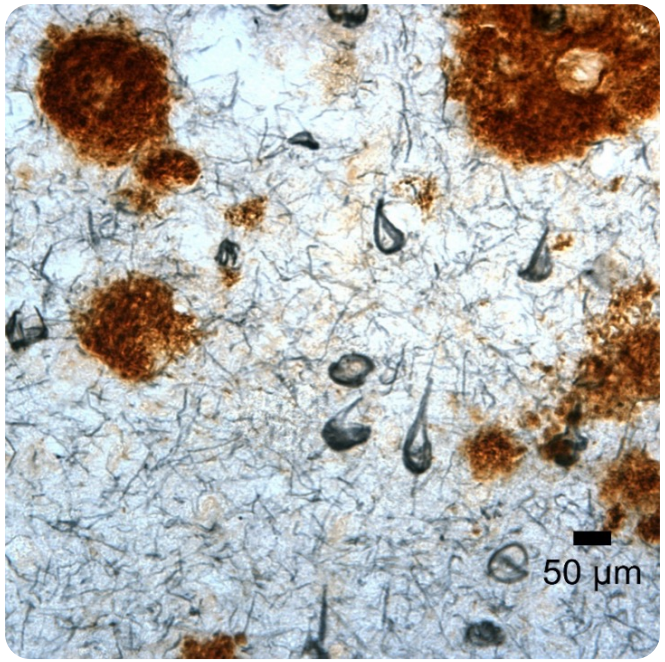
A 3.75-fold increase in average life expectancy since 1970 (Presson et al., J Peds., 2013).



Fastest growing segment is 40-49 years of age (Hithersay et al., 2019)

What is the link between Down syndrome and Alzheimer disease?

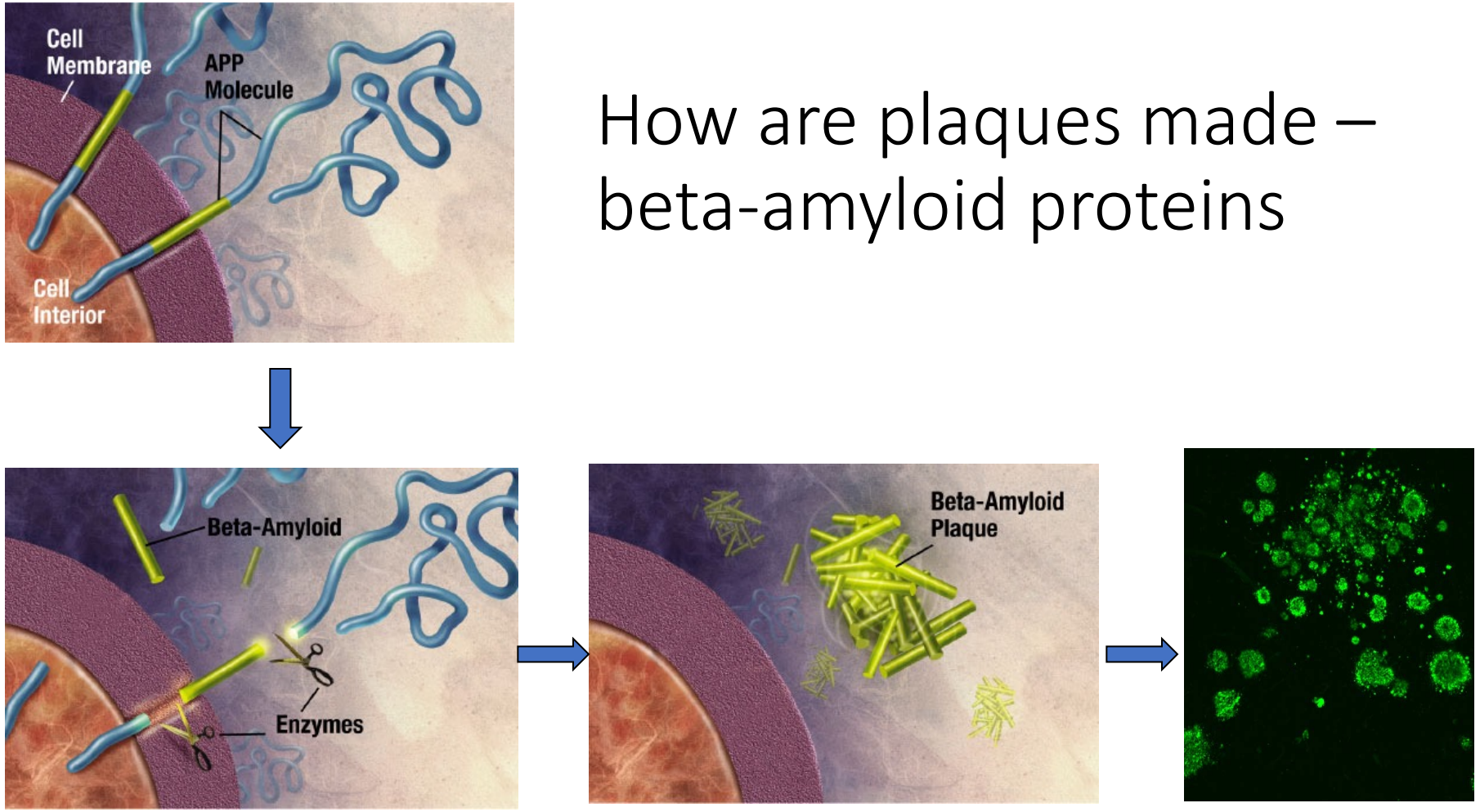




Alzheimer disease

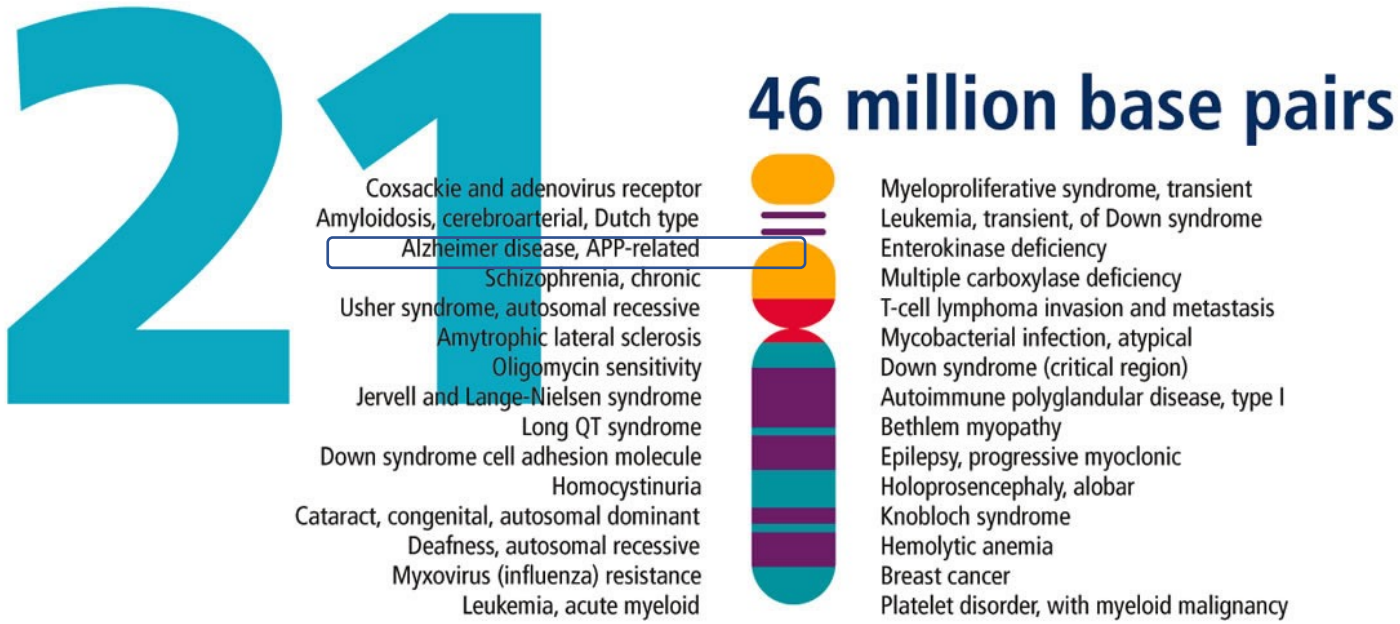
- Described by Alois Alzheimer in 1906
- Associated with a change in cognition and function that interferes with activities of daily living
- Presence of beta-amyloid plaques and neurofibrillary tangles

How are plaques made – beta-amyloid proteins



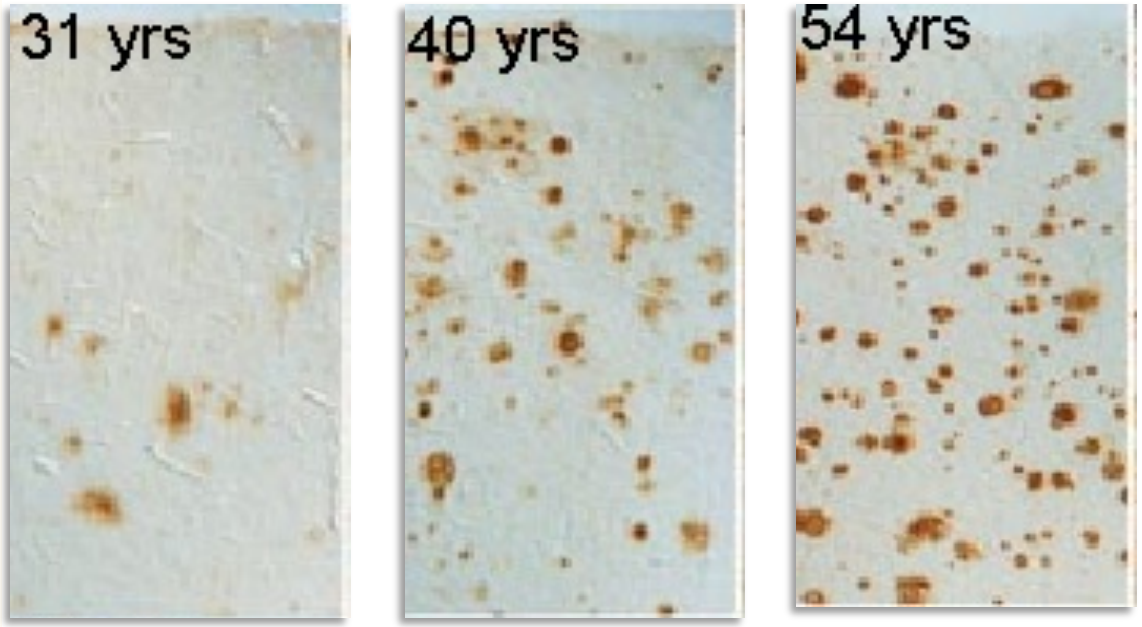
http://www.rienstraclinic.com/newsletter/2006/November/

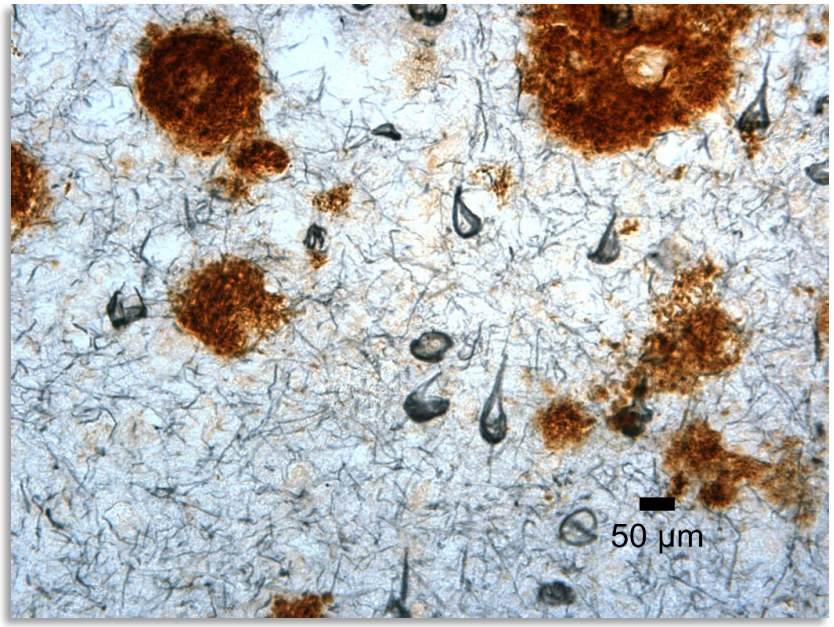
Where is the amyloid precursor protein gene (APP)?



https://web.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/chromo21.shtml

Adults with DS are vulnerable to AD



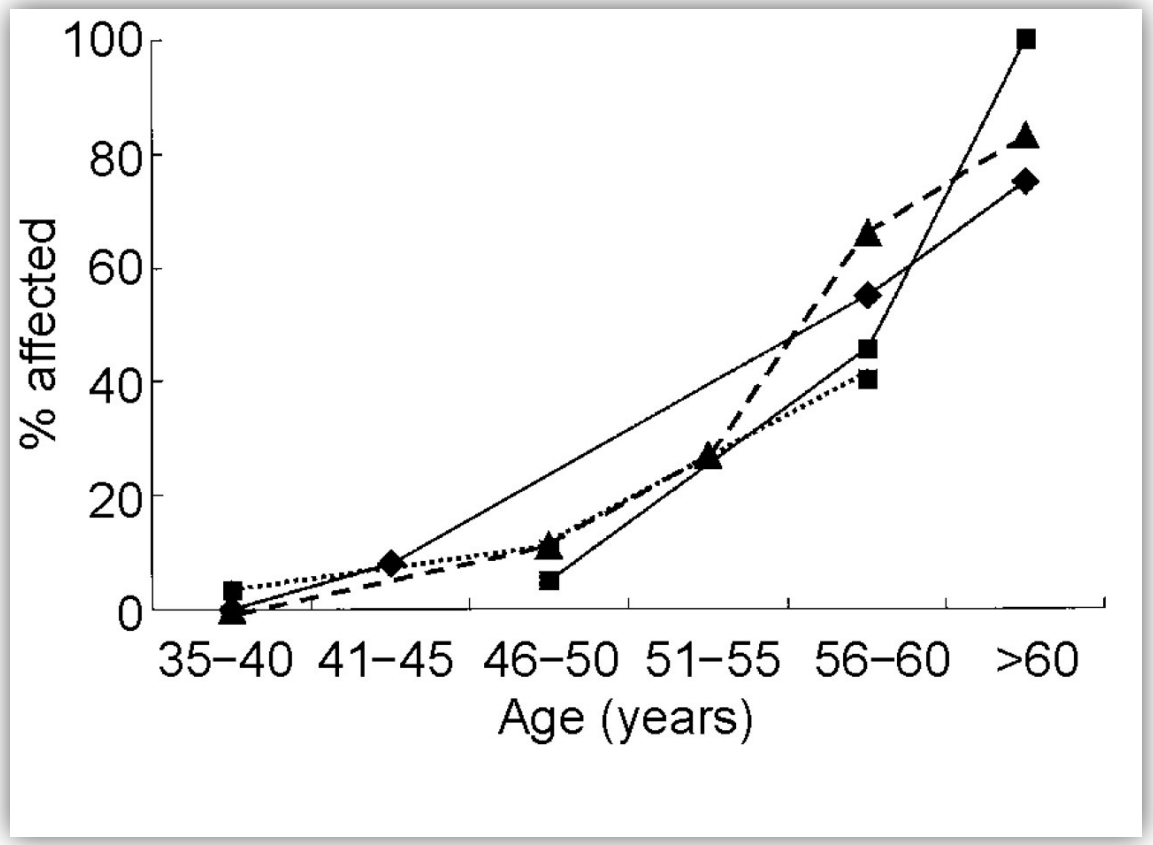


Virtually all adults with DS over the age of 40 years have sufficient neuropathology for AD

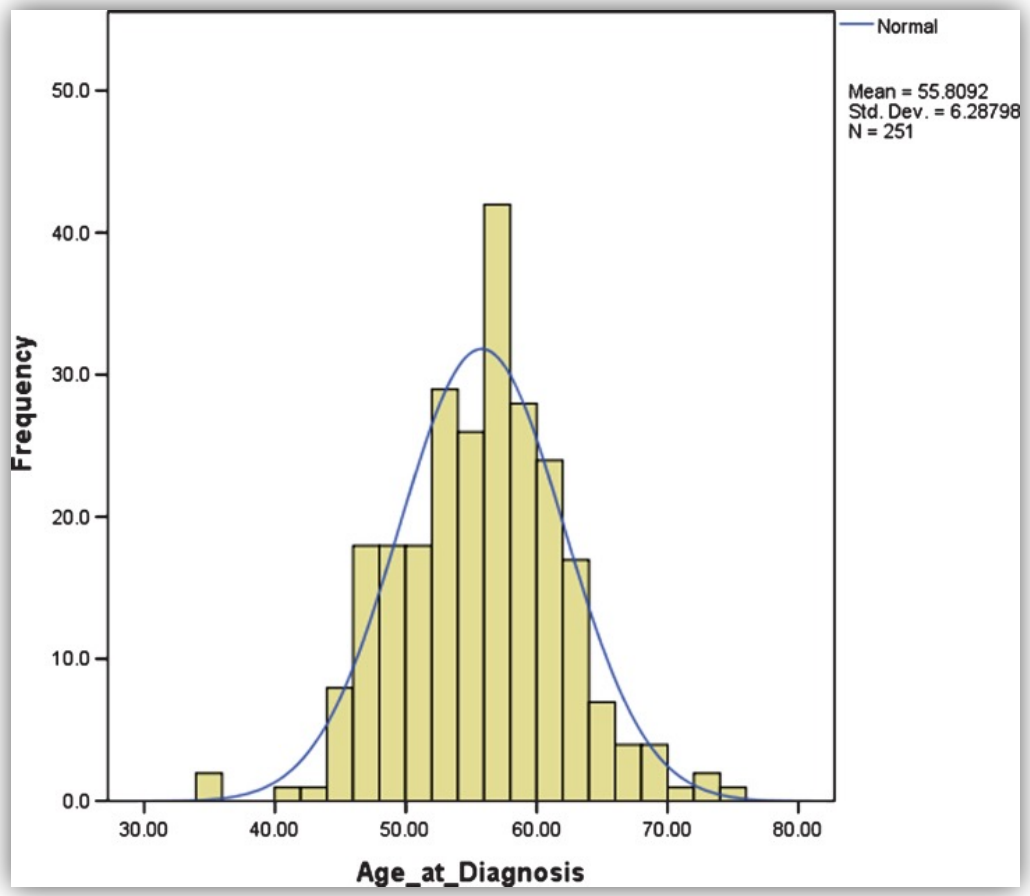
How do we diagnose dementia?

- We have a background of intellectual disability
- We have a different set of tests that can help us assess learning, memory, visuospatial skills etc
- We consider other factors (co-occurring illnesses, changes in living situation, external factors)
- Look for change over time – decline in function
- Consensus diagnosis

When do people with DS show signs of dementia?



Schupf, N. et al. 2002



Sinai et al., JAD, 2018 (61): 717-728

Treatment of Dementia for People with Down syndrome

From Mario D. Garrett PhD

Treatments for AD – anti-cholinesterases

Generic	Brand	Approved For	Side Effects
donepezil	Aricept	All stages	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
galantamine	Razadyne	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
memantine	Namenda	Moderate to severe	Headache, constipation, confusion and dizziness.
rivastigmine	Exelon	Mild to moderate	Nausea, vomiting, loss of appetite and increased frequency of bowel movements.
memantine + donepezil	Namzaric	Moderate to severe	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness.

http://www.alz.org/alzheimers_disease_standard_prescriptions.asp

Drugs approved for use to treat AD in DS (as of 2021)

- Memantine failed in a clinical trial in demented adults with DS, **no improvement** but no increase in adverse effects (2021)
- Donepezil - studies small and show **modest or no effect with high adverse events** (2009), recent 2011 study in women suggests improvement, 2015 review suggests no improvement and more adverse effects
- Exelon – one small study of rivastigmine patch n=10 (2012)
- Galantamine – no studies
- Tacrine – no studies

Overall

- “Due to the low quality of the body of evidence in this review, it is difficult to draw conclusions about the effectiveness of any pharmacological intervention for cognitive decline in people with Down syndrome.” *Livingstone et al., 2015*.

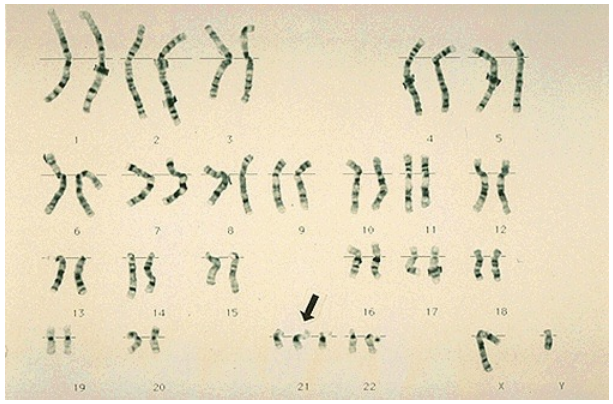
But – individual people may respond well to these treatments for a period of time and are well worth exploring for people with Down syndrome

Clear needs.

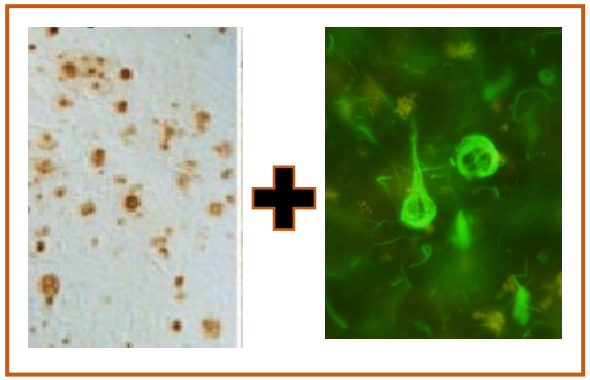
- People with Down syndrome are typically excluded from Alzheimer disease clinical trials
- We need to learn what types of treatments we should target and when they should be considered (treatment vs prevention)
- A lifespan approach is critical

Let us put the development of Alzheimer disease in people with Down syndrome as a lifespan question

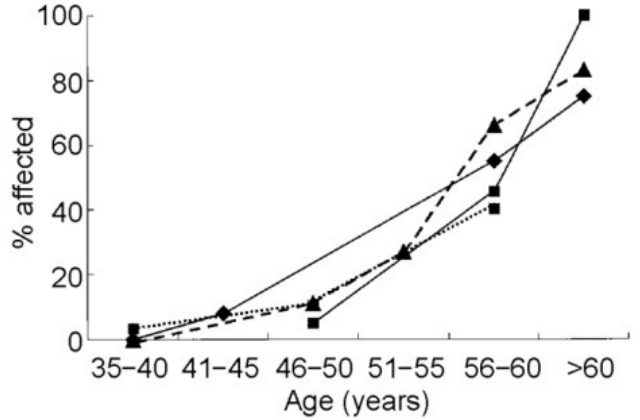
Trisomy 21



AD Pathology



Dementia

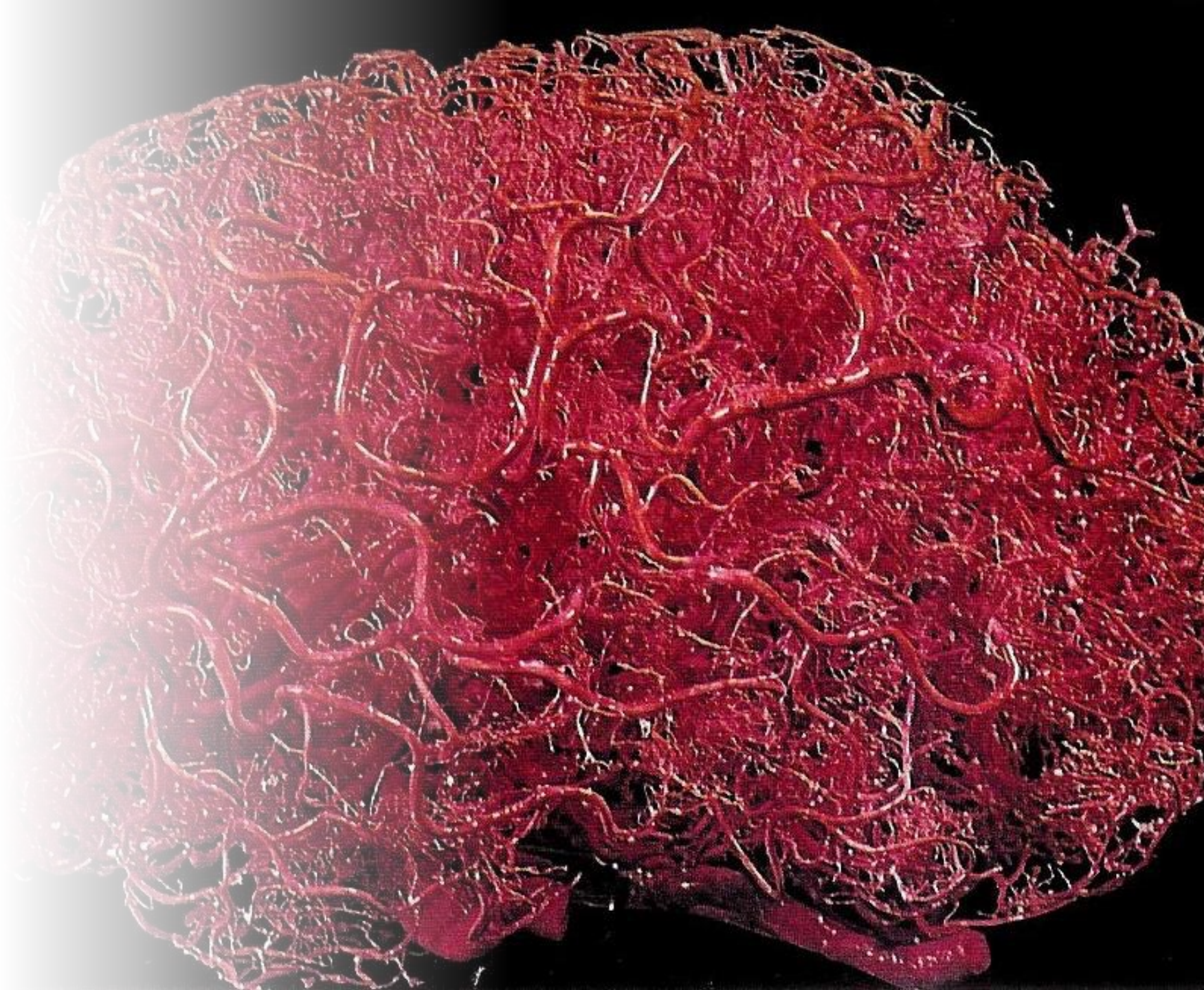


Birth 30 40 50 60+ YEARS

Can we fill in more events across the lifespan that tells us about earlier changes than the development of plaques and tangles?

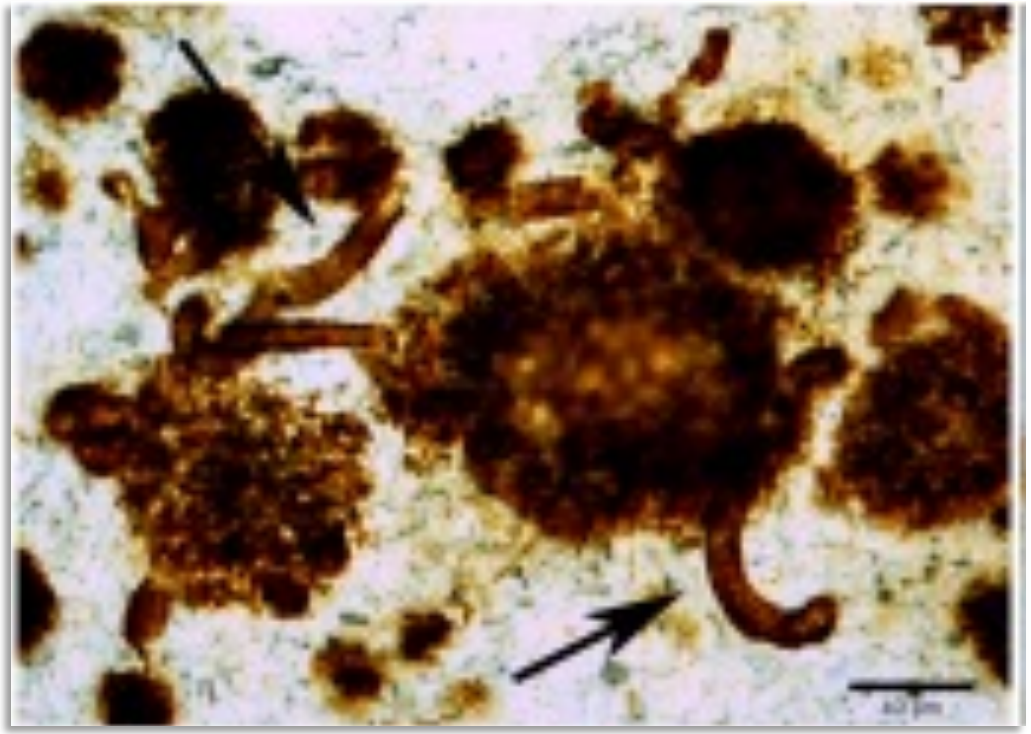
- Atheroma free
- Very little hypertension

- Obesity
- Sleep apnea
- Cerebral Amyloid Angiopathy

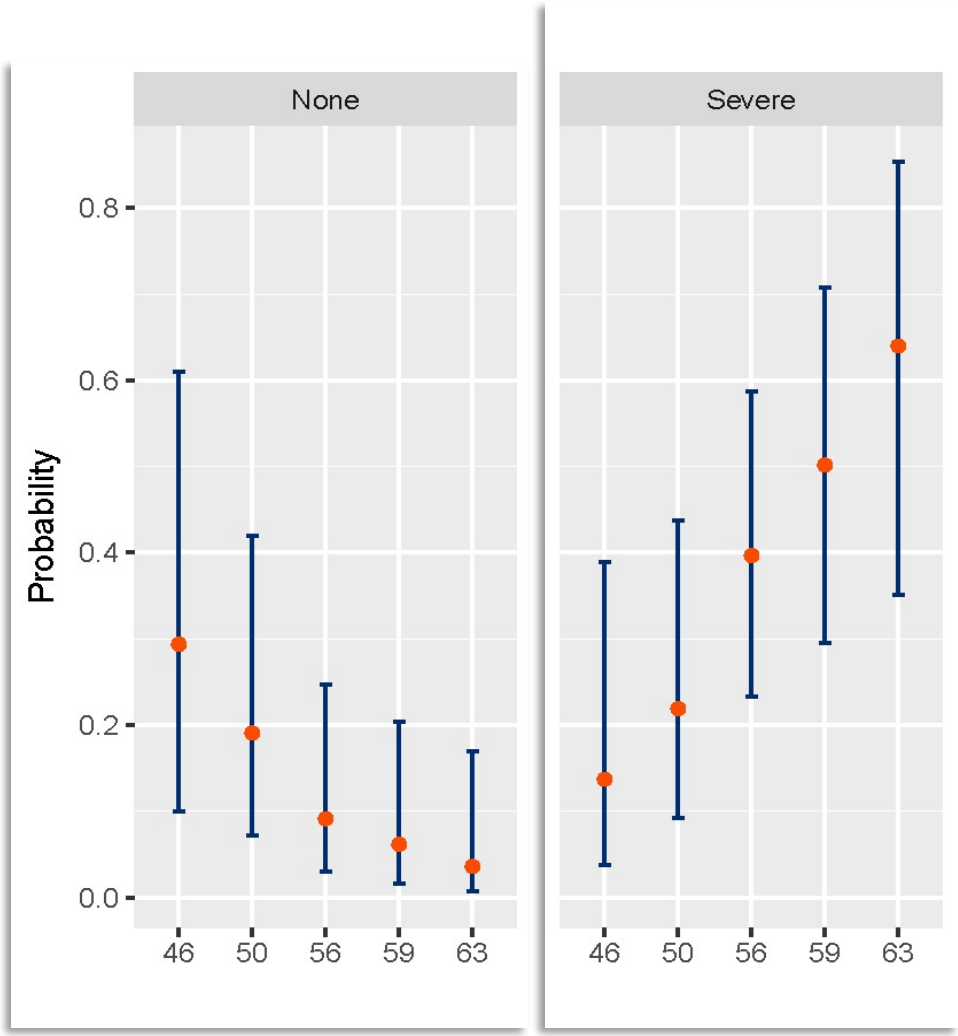


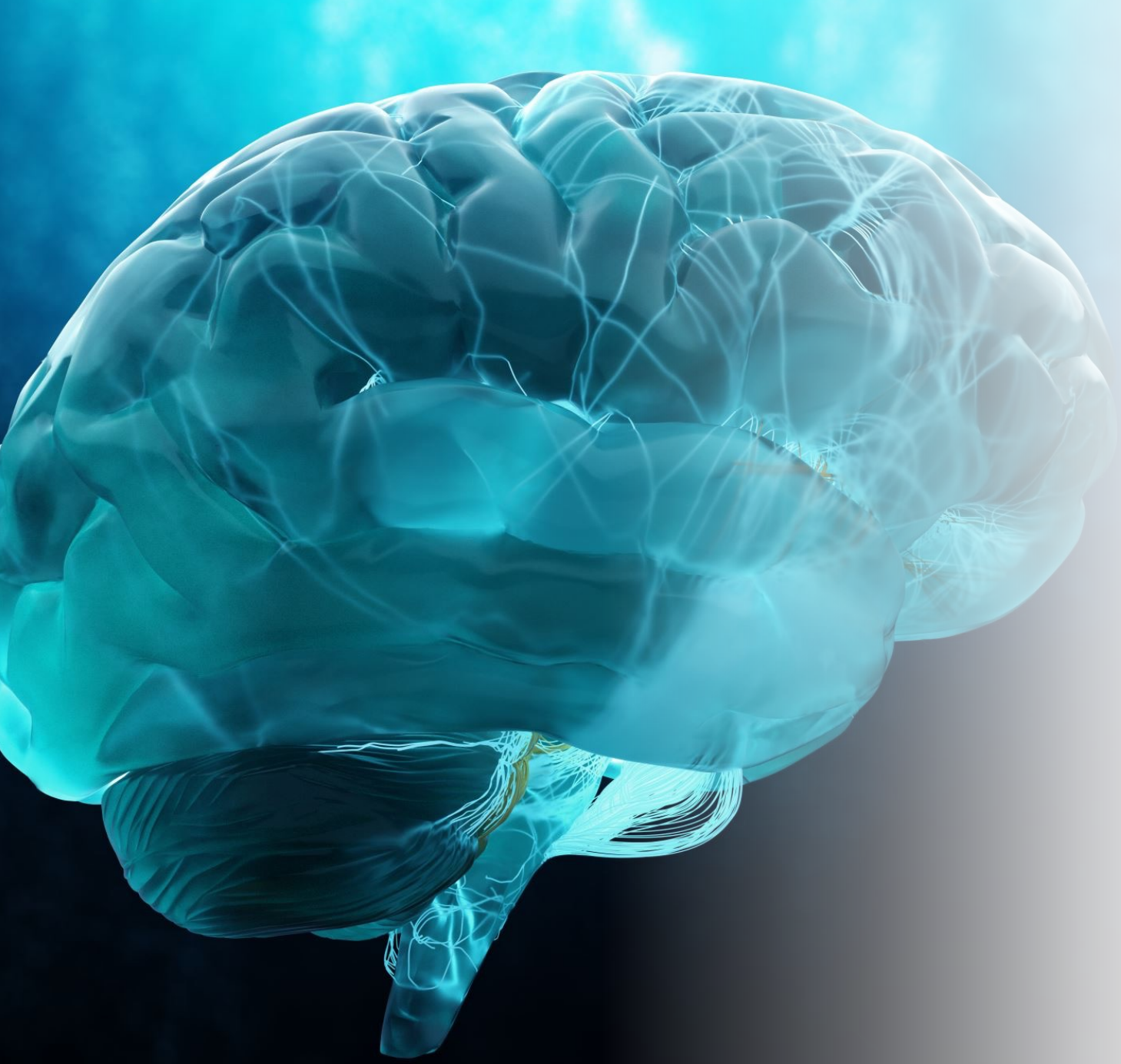
Cerebral amyloid angiopathy in DS

Beta-amyloid

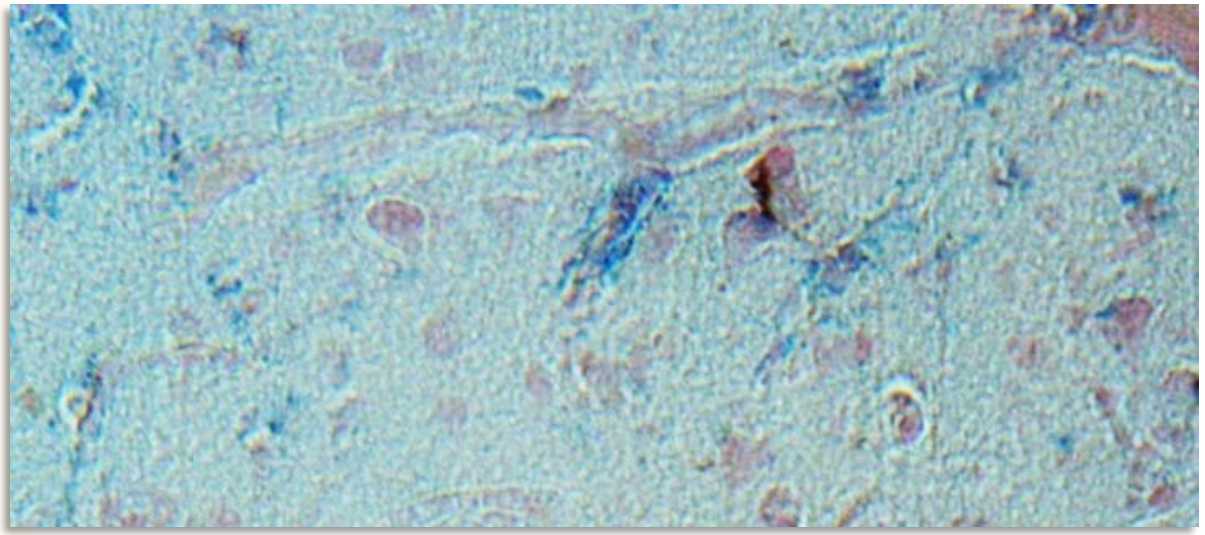


More frequent in Down syndrome compared to late onset Alzheimer disease

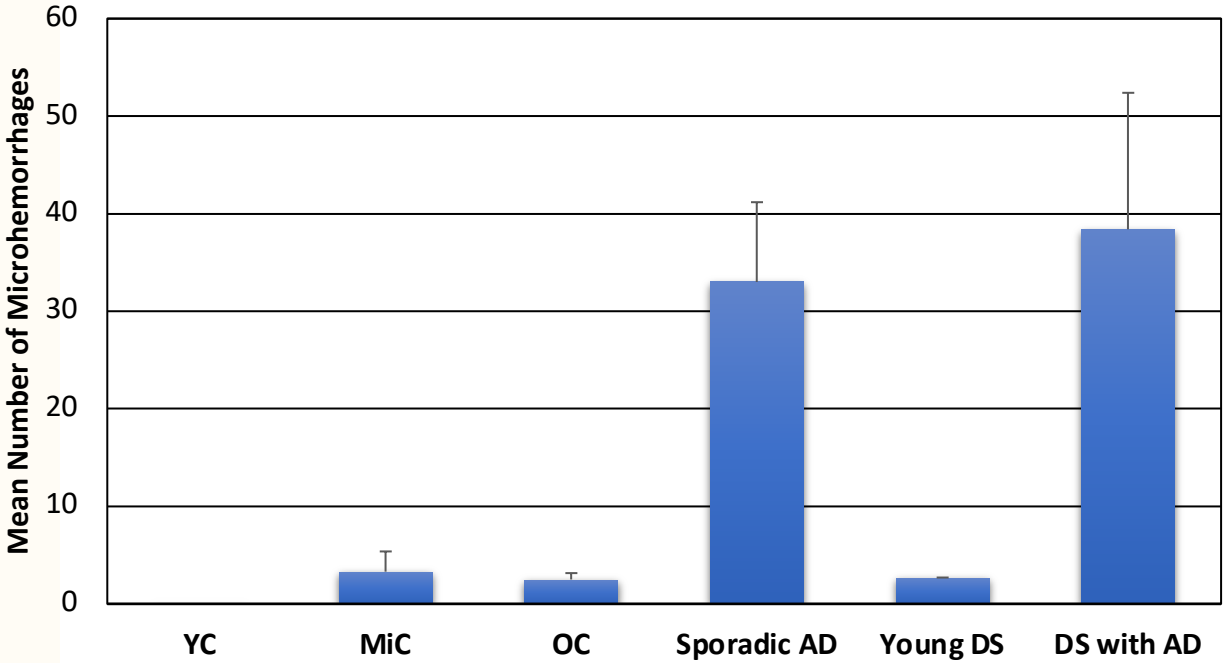




What happens when blood vessels have too much beta-amyloid?

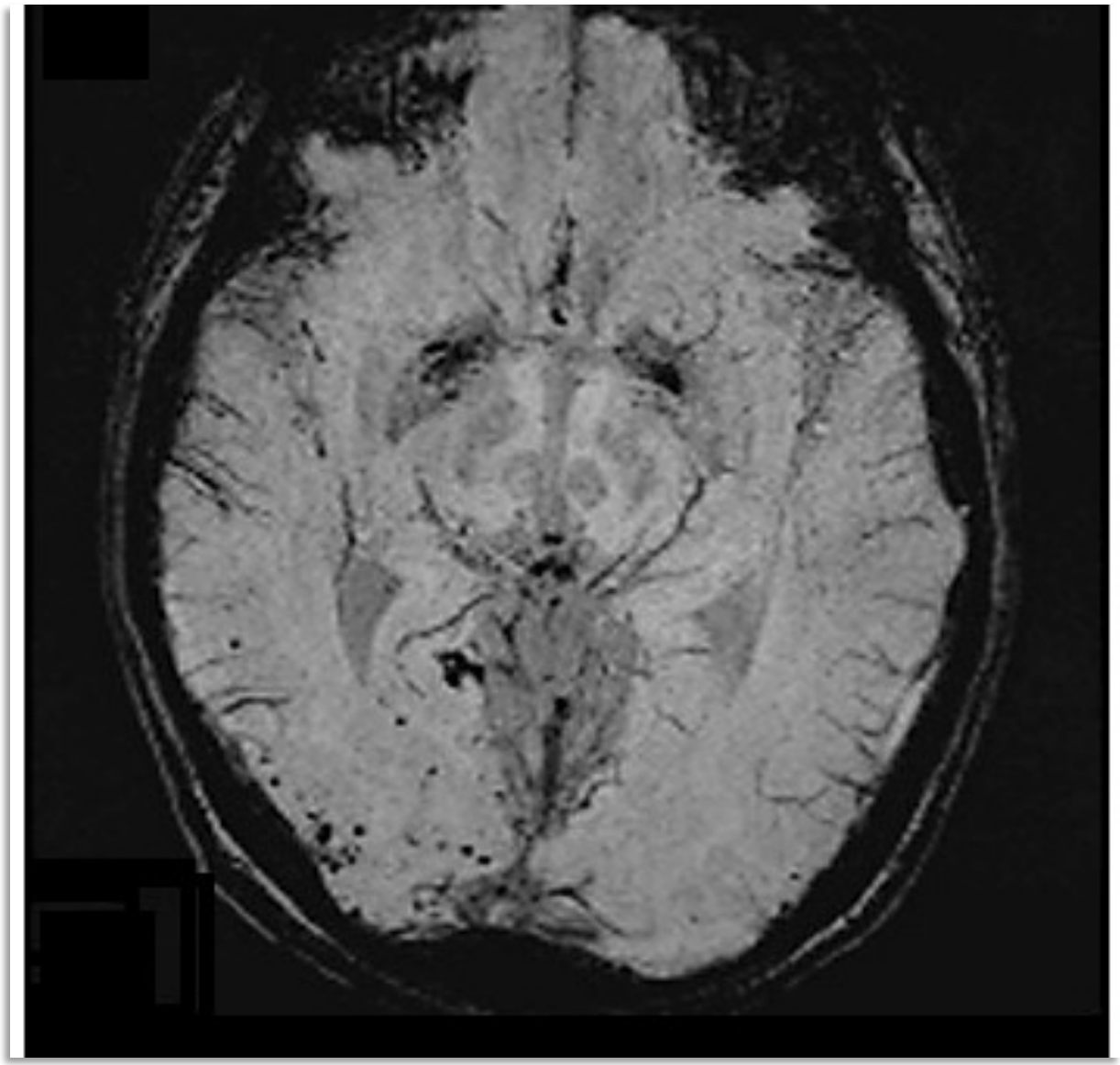


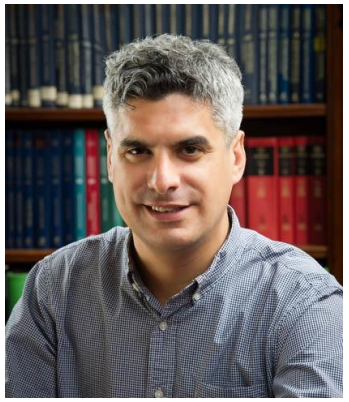
Dr. Alex Helman



We see microbleeds in the brains of people with Down syndrome and Alzheimer disease pathology to a similar extent as late onset Alzheimer disease

Magnetic Resonance Imaging can reveal small bleeds





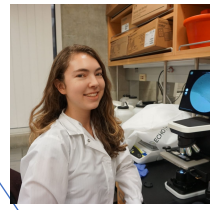
Dr. Adam Brickman – Columbia University

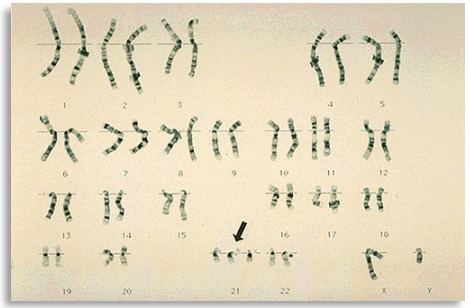
Dr. Lisi Flores Aguilar

Kelly Poon

A lifespan approach

Biological effects of sex?





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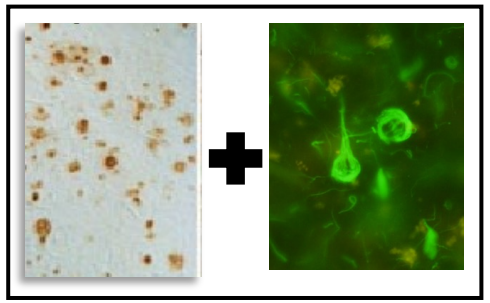
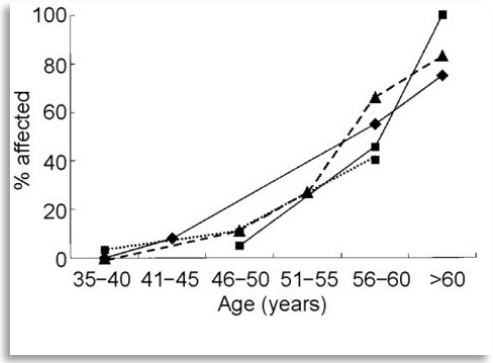


AD

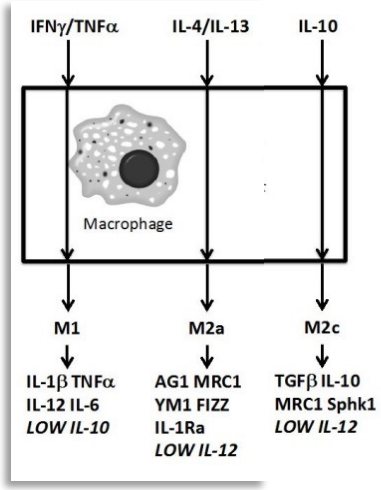
Dementia



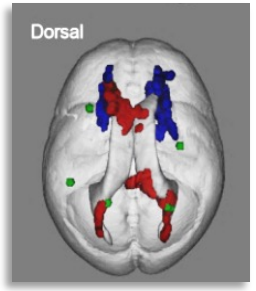
Fluid biomarkers in extracellular vesicles

Birth 40 50 60+ YEARS

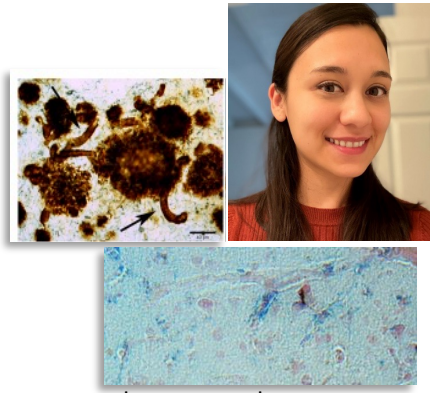
Obesity/leptin



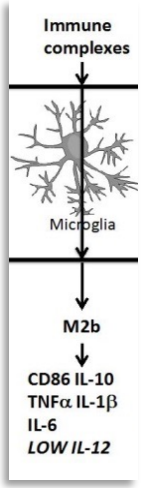
Pro and anti inflammatory markers



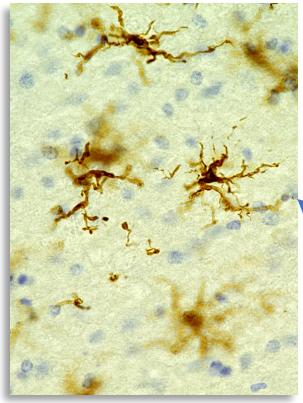
White matter integrity decreased



Cerebrovascular Pathology and microhemorrhages



Inflammation – (CD86, FCGR1B)



Glial senescence and death

🎯 Implications

- Aβ, tau, cerebrovascular pathology as well as other pathologies are all potential targets for intervention.
- The timing of each pathology suggests we have a moving target for intervention dependent upon age.
- People with DS may be among the first cohorts (ADAD) to benefit from prevention studies (what might these be – lets talk about this during the discussion!)
- **Critical need for longitudinal biomarker aging studies with multidisciplinary approaches to design and appropriately power clinical trials for AD in DS**

Alzheimer biomarker consortium – Down syndrome –

Handen, Christian, Mapstone and Head (MPIs)

https://www.nia.nih.gov/research/abc-ds

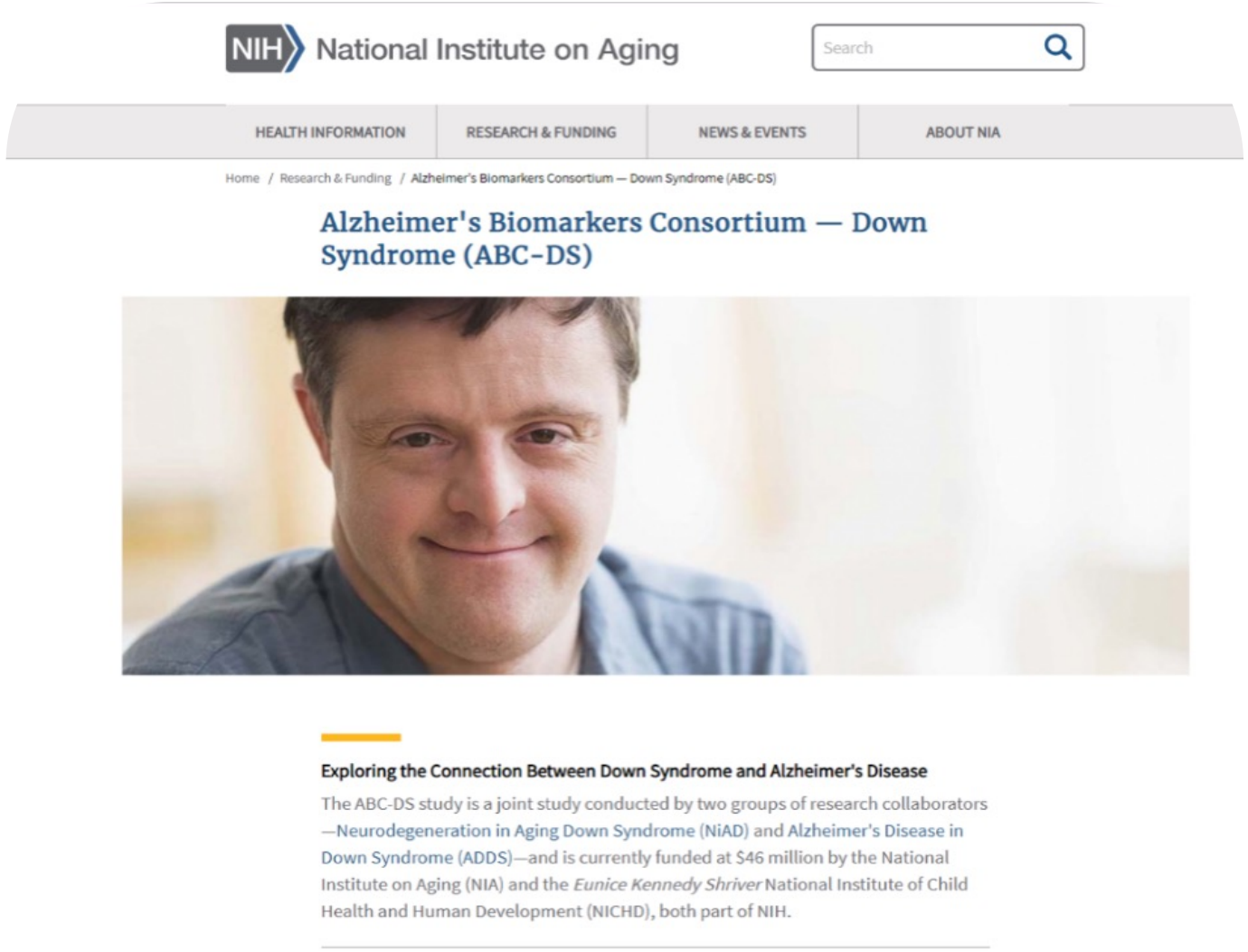
U Pittsburgh

Wisconsin U @ Madison

UCI

Alzheimer Biomarker Consortium – Down Syndrome

- https://www.nia.nih.gov/research/abc-ds
- N=550 people with DS
- > 25 years
- 18 clinical/research sites
- Clinical, neuropsychological, omics, neuroimaging and neuropathology data



TRCDS
Trial-Ready Cohort-Down Syndrome

www.trcds.org

lumind idsc
DOWN SYNDROME FOUNDATION

- https://www.lumindidsc.org

https://dsconnect.nih.gov/

Inspired by and collaborating with the following colleagues…

Heartfelt thank you to our participants and their families for their participation and brain donation.

Funded by:
NIH/NIA U19AG068054 (Christian Handen, Head, Mapstone)
NIH/NIA ADRC P30AG066519 (LaFerla/Grill)

UCI MIND

Dr. Mark Mapstone
Dr. Ira Lott
Dr. Christy Hom
Dr. Wayne Silverman
Eric Doran
Alicia Hernandez
Kelley Kilday
Dr. Mari Perez-Rosendahl
Dr. William Yong

Acknowledgements

Dr. Lorena Sordo
Dr. Lisi Flores Aguilar
Dr. Michael Phelan
Jesse Pascual
Elizabeth Andrews
Cherie Stringer
Jeremy Rouanet
Leslie Vasquez-Rangel
Phong (Billy) Ngo
Halyma Nguyen
Tamara Shamas
Brenna Phelan
Vinuta Sandadi
Haley Miyasato
Kelly Poon
Kevin Camey
Dr. Alessandra Martini

- NIH/NICHD support for the University of Kentucky (R01HD064993 –Schmitt & Head)
- NIH/NIA support for the Alzheimer Biomarker Consortium – Down syndrome (ABC-DS – U19AG068054 – Handen, Christian, Mapstone & Head)
- Brightfocus funding support for the Down syndrome International Brain Bank to Head and to Dr. Sordo
- UCI ADRC P30AG066519
- WAM pilot from UCI MIND
- Repository team – Justine Silva, Sierra Wright, Kelsey Leavy and Brianna Gawronski

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https://sites.mind.uci.edu/headlab/