Promoting Healthy Aging in People with Down syndrome

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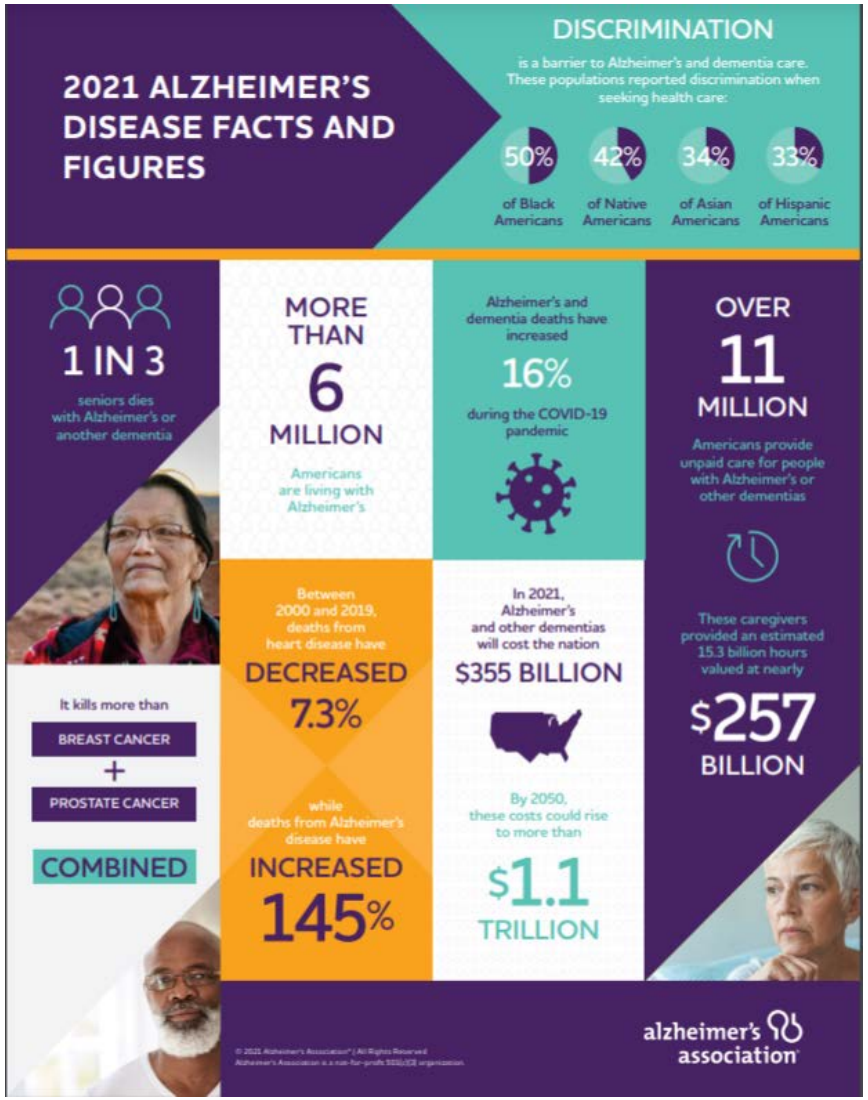
Brief Outline

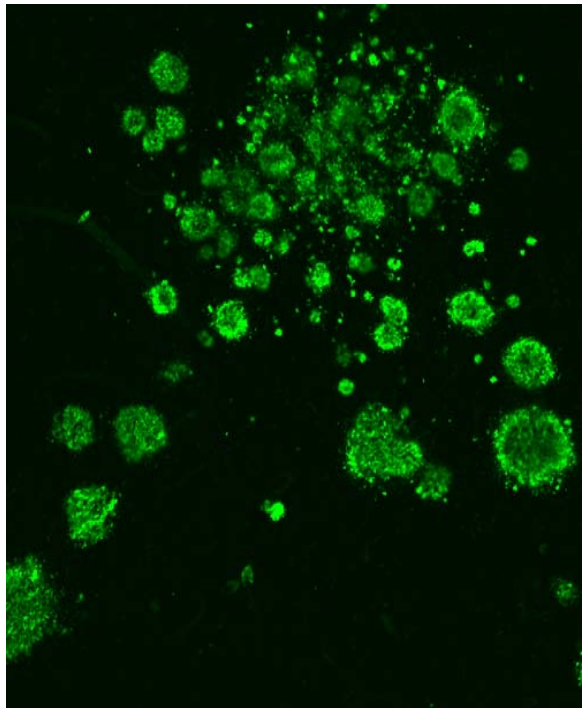
- What is Alzheimer's disease
- The link between Down syndrome and Alzheimer's Disease
- Treatments – pharmacological
- Treatments – managing behavioral changes
- Prevention
- What are researchers doing?
- Take home message

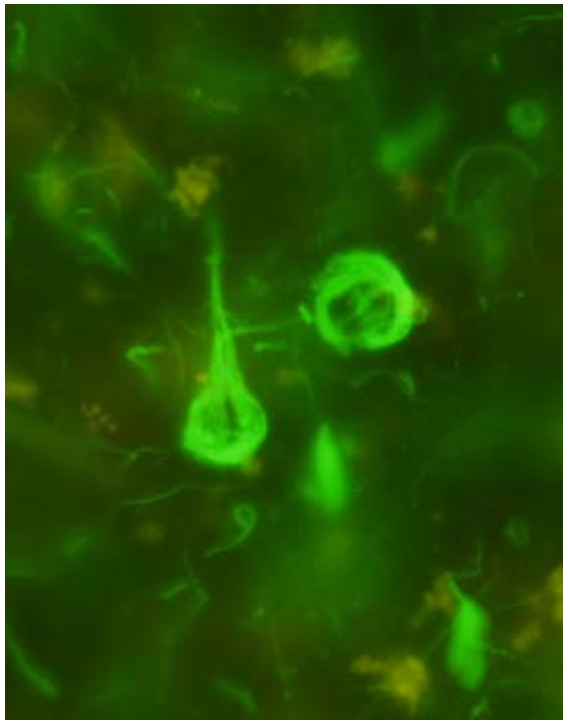
What is Alzheimer disease?



- Most common cause of dementia in the elderly
- Progressive neurodegenerative disease
- Associated with changes in learning and memory ability
- First described by Alois Alzheimer in 1901
- Risk factors – age and ApoE
- Alzheimer Association – Facts and Figures (https://www.alz.org/alzheimers-dementia/facts-figures)

Alzheimer Disease – Two Hallmarks



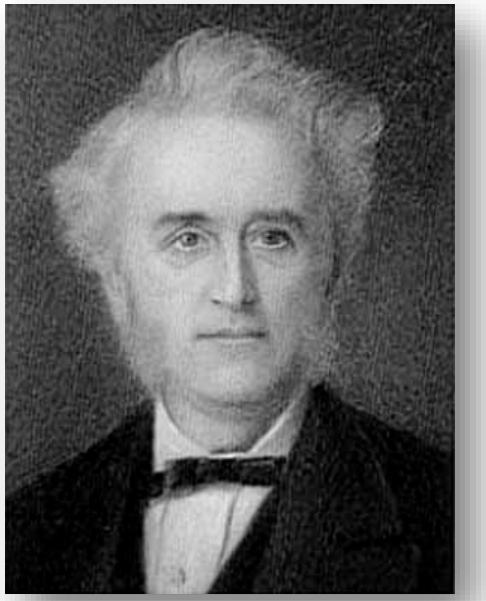


Beta-amyloid plaques

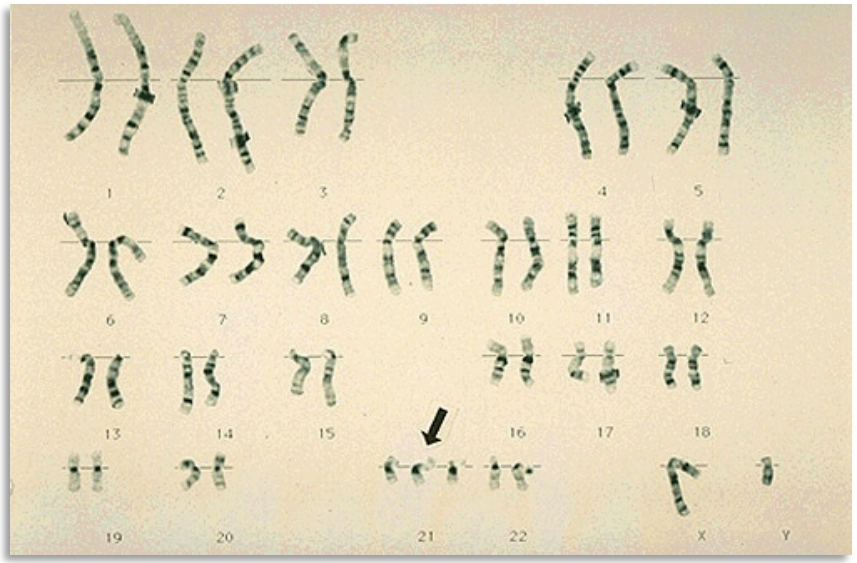
Neurofibrillary tangles

What is the link between Down syndrome and Alzheimer disease?

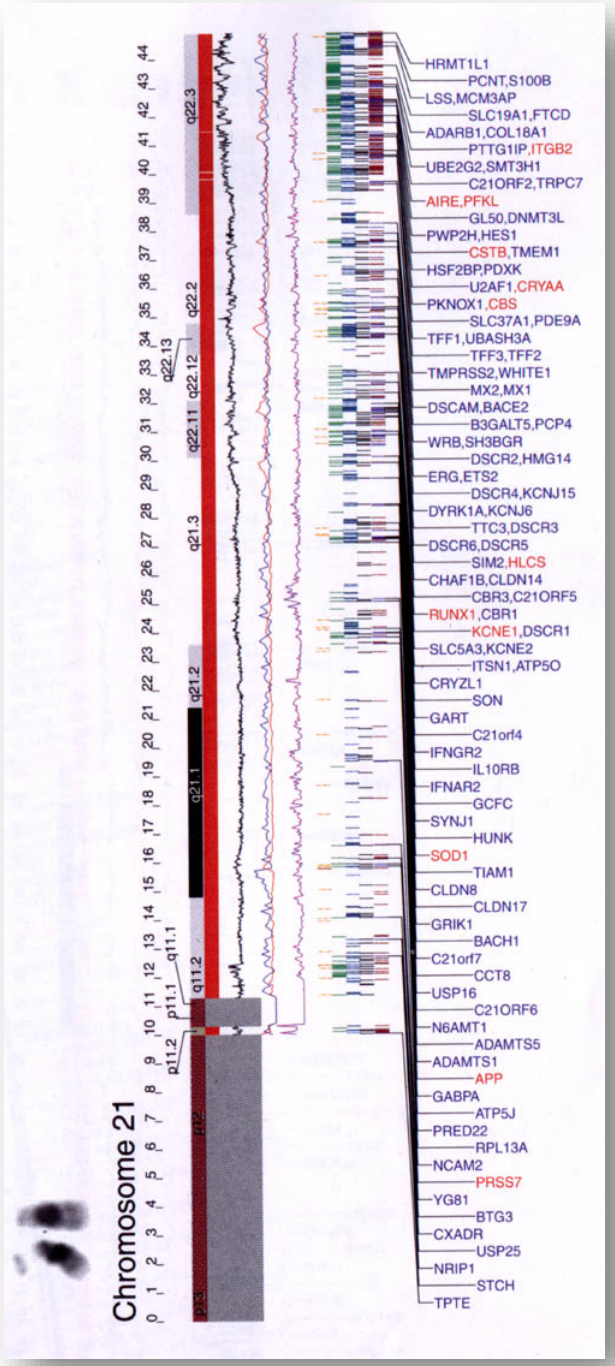
What causes Down syndrome?



J. Langdon Down - 1887



LeJeune and Gautier, 1959

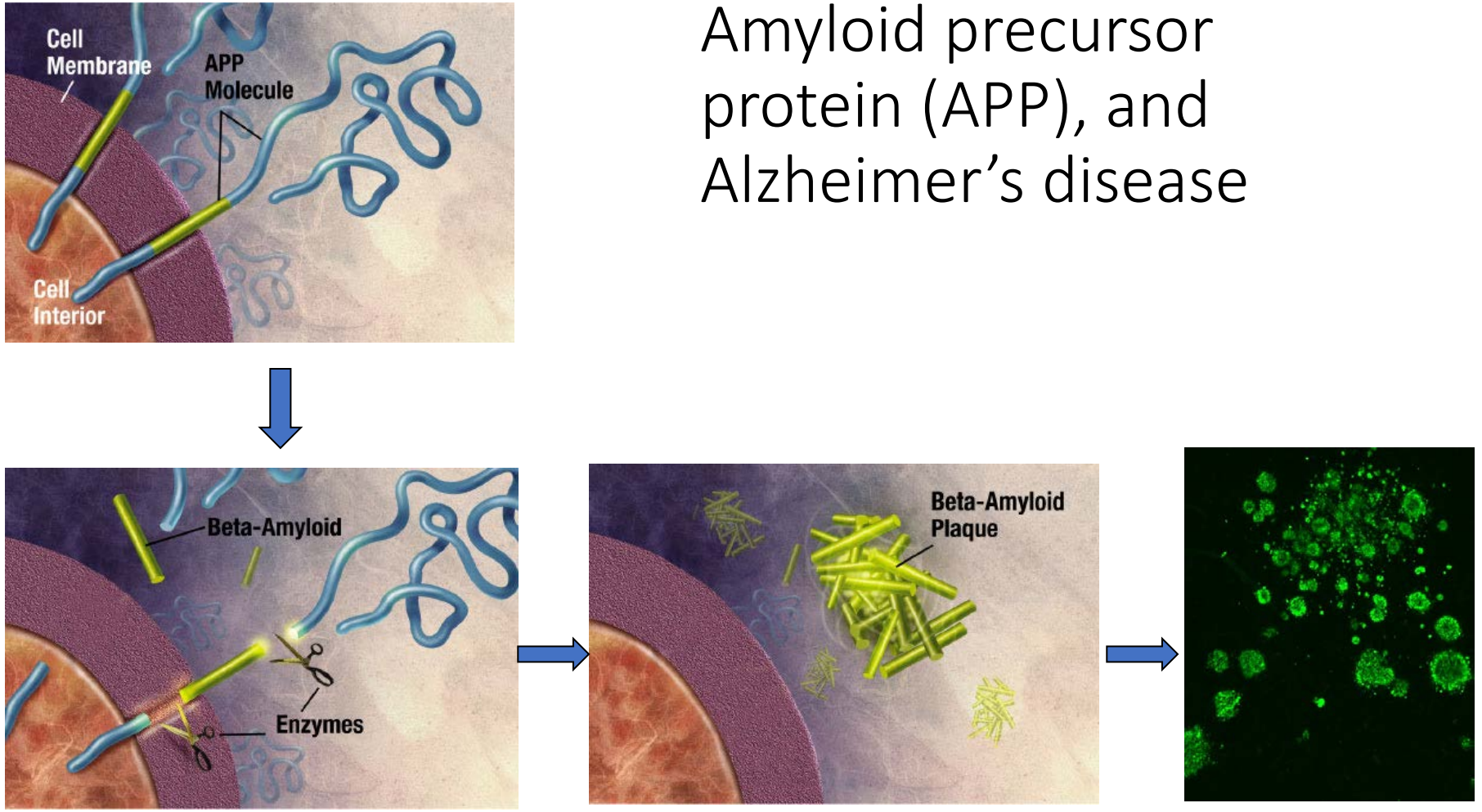


APP

Chromosome 21 has many genes associated with Alzheimer disease.

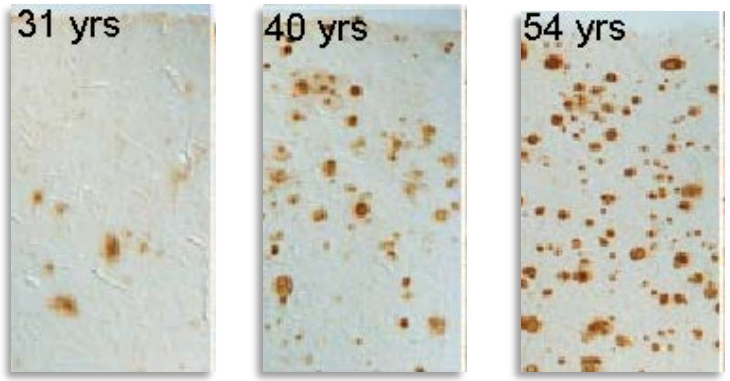
People with Down syndrome make more of these Alzheimer disease related proteins compared to people without Down syndrome.

Amyloid precursor protein (APP), and Alzheimer's disease



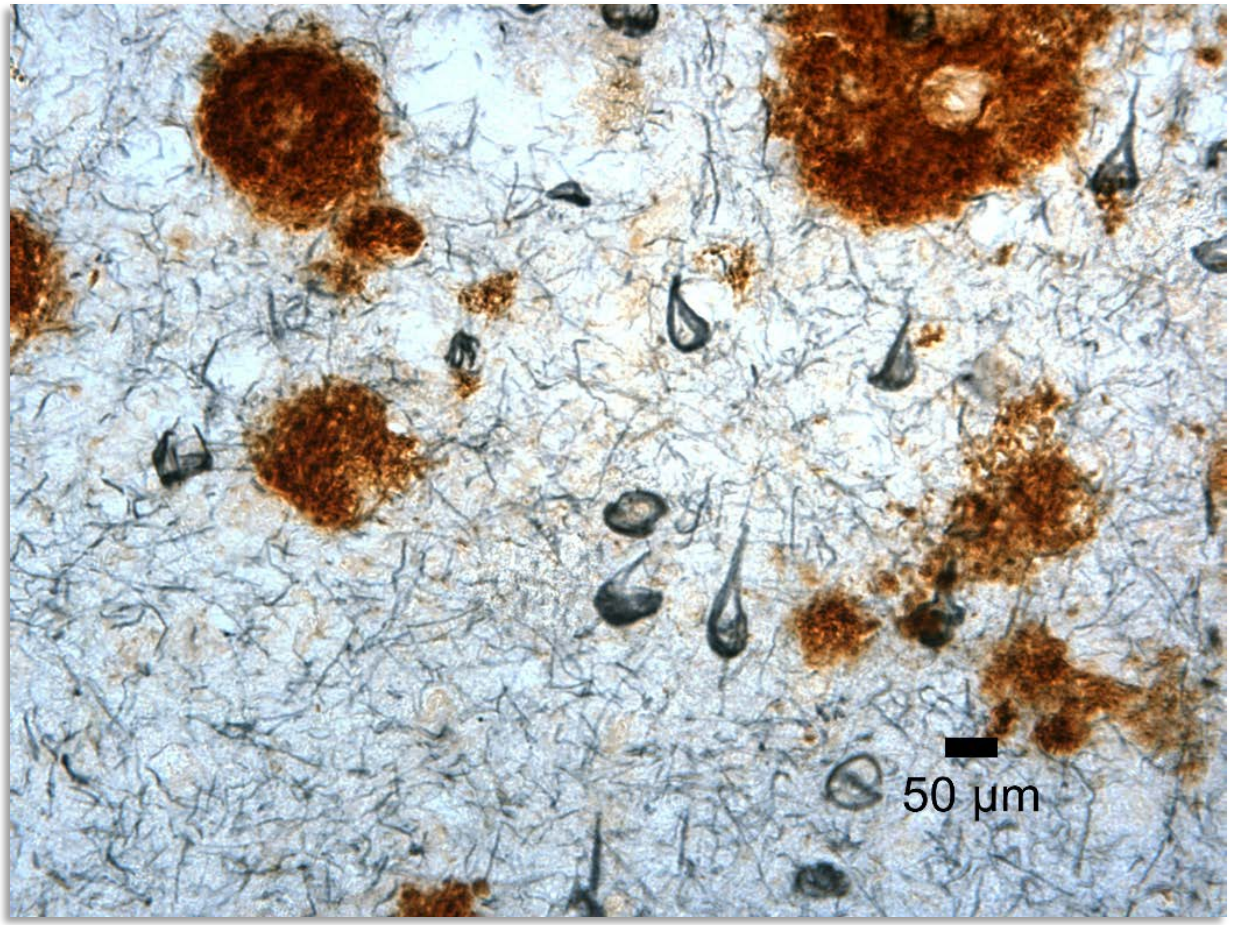
http://www.rienstraclinic.com/newsletter/2006/November/

Adults with DS are vulnerable to AD with an earlier age of onset



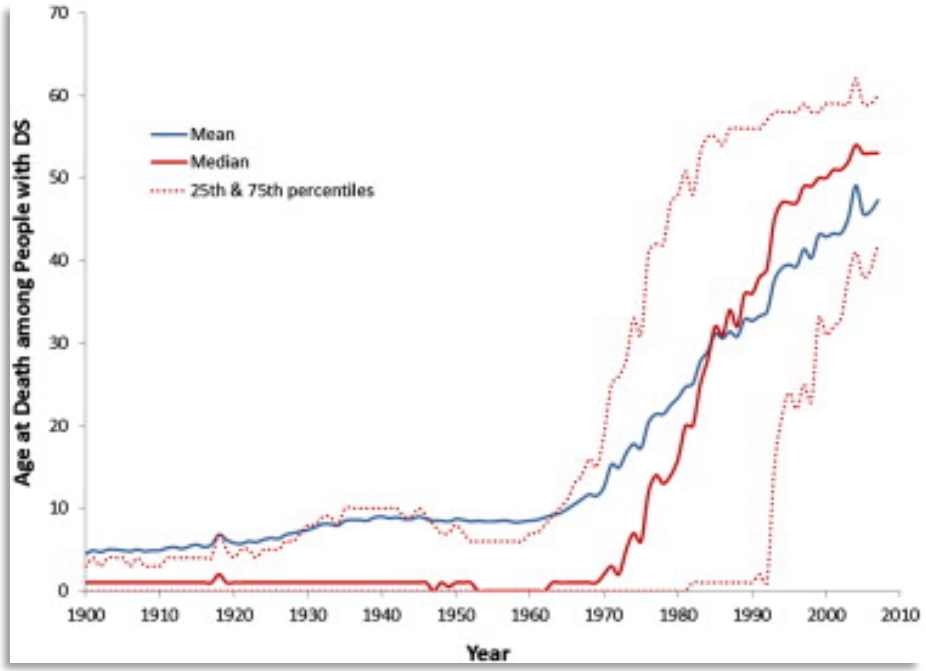
Head, Azizeh, Lott, Tenner, Cotman & Cribbs, 2001

Virtually all adults with DS over the age of 40 years have sufficient neuropathology for AD (Struwe, 1929; Jarvis, 1948) – including plaques and tangles

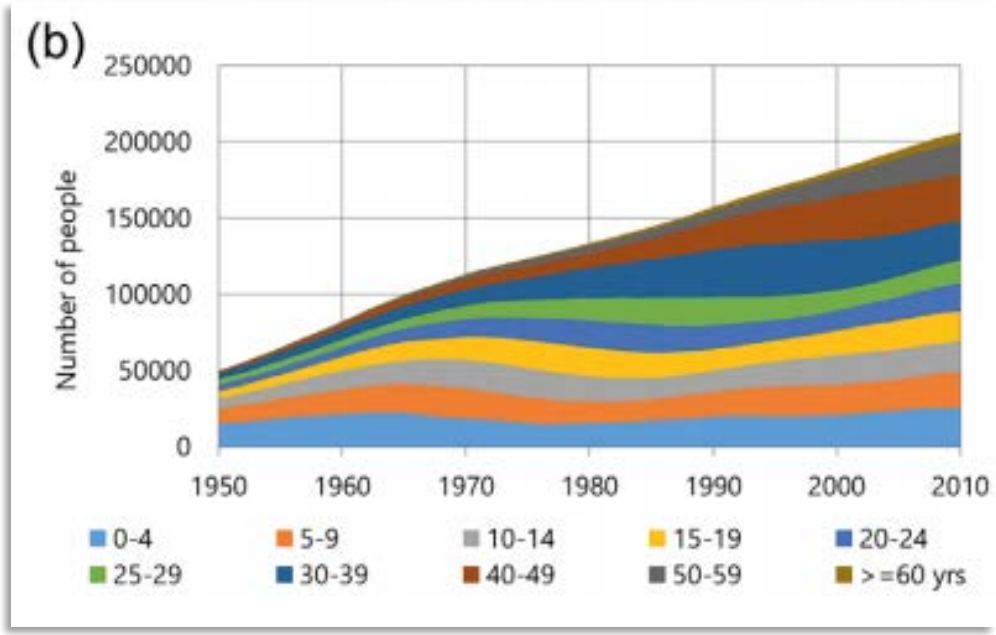


Head & Lott, 2019

Age and AD in Down syndrome - People with Down syndrome are living longer

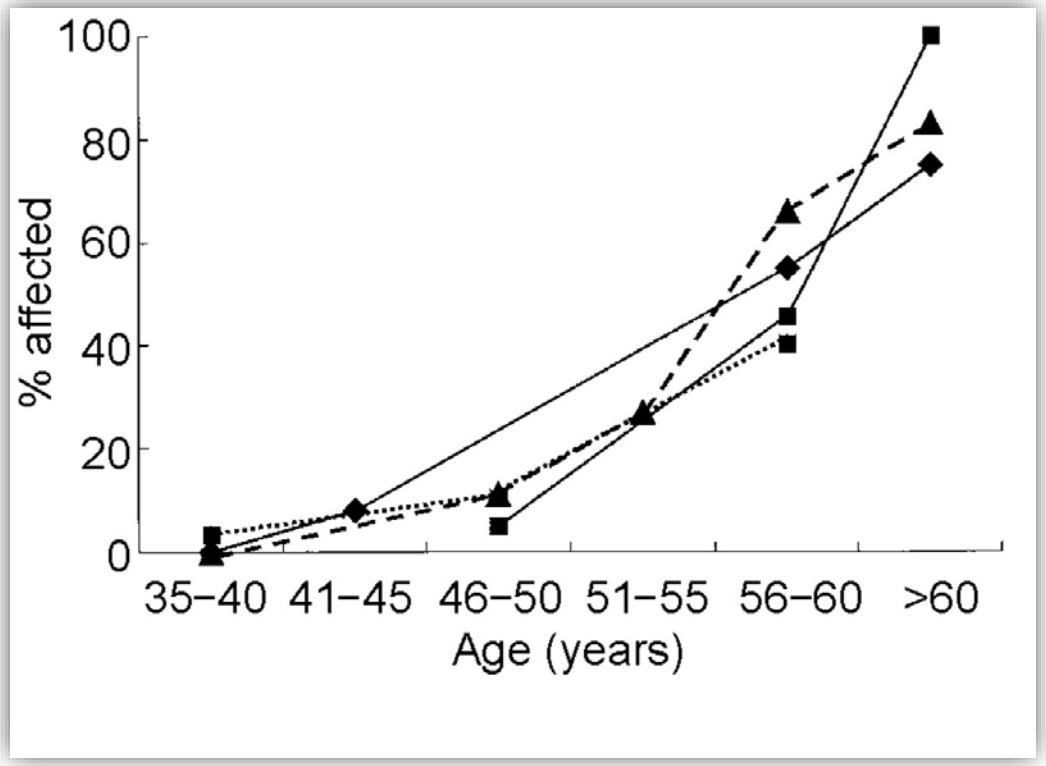


The mean and median age at death for persons with Down syndrome has increased significantly over the past 40 years. In 2007, the mean and median ages at death were 47.3 and 53 years, respectively, reflecting a 3.75-fold increase in average life expectancy since 1970 (Presson et al., J Peds., 2013).

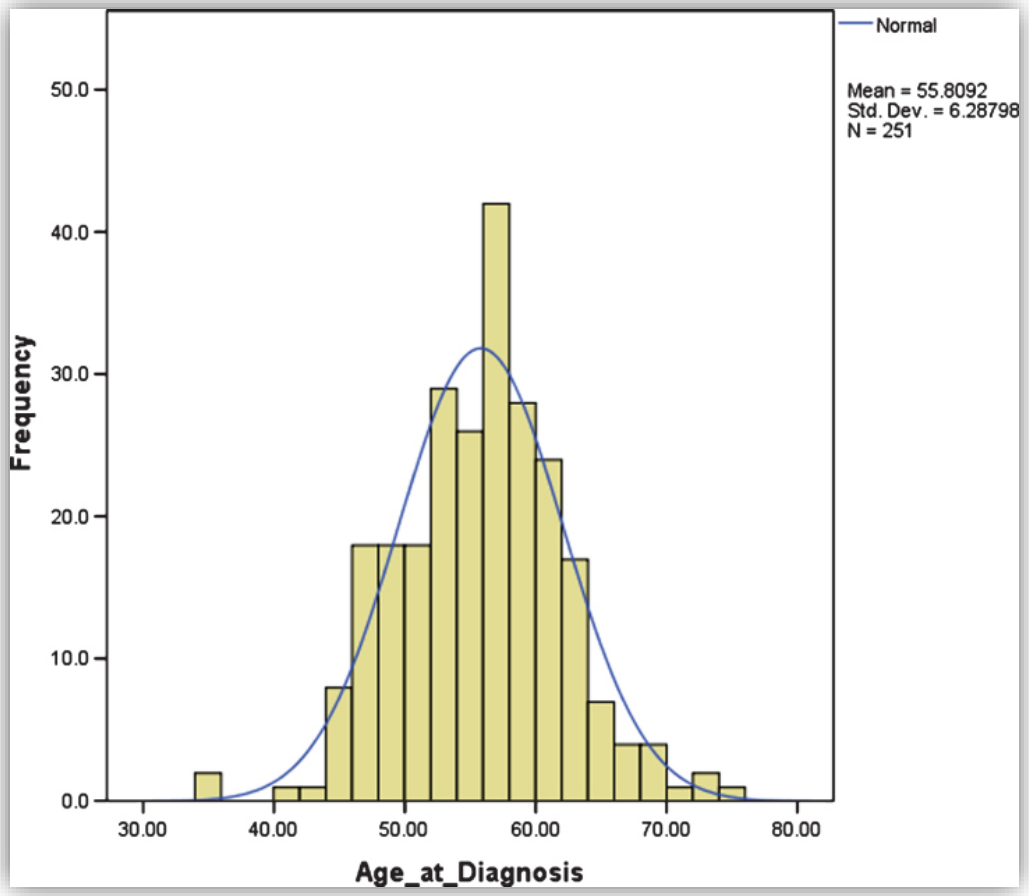


Fastest growing segment is 40-49 years of age. De Graaf et al., 2017 – based on 2010 census
Dementia was associated with mortality in 70% of older adults with DS – Hithersay et al., 2019

When do people with DS show signs of dementia?



SCHUPF, N. et al. The British Journal of Psychiatry 2002;180:405-410



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

But!!! We see up to 15% of people with Down syndrome reaching their 60's and older without significant changes in cognition.

Treatment of Dementia for People with Down syndrome

From Mario D. Garrett PhD

Treatments for AD

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)

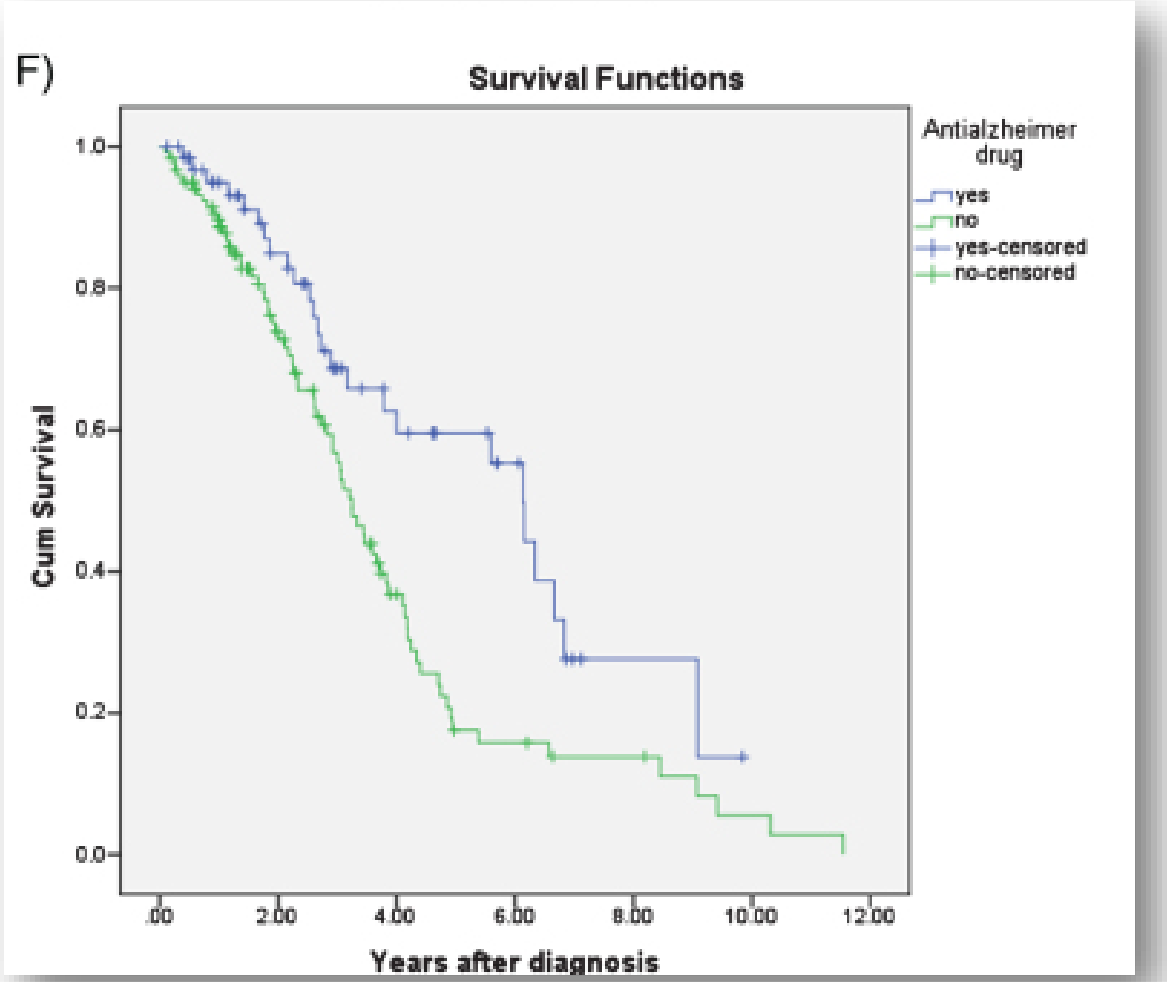
- Memantine just failed in a clinical trial in demented adults with DS, no improvement but no increase in adverse effects
- Donepezil - studies small and show modest or no effect with high adverse events (2009), recent 2011 study in women suggests improvement, 2015 review suggests no improvement and 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*.

We can talk about Aduhelm in the discussion period if there is interest.

Use of anti-AD drugs and survival in DS



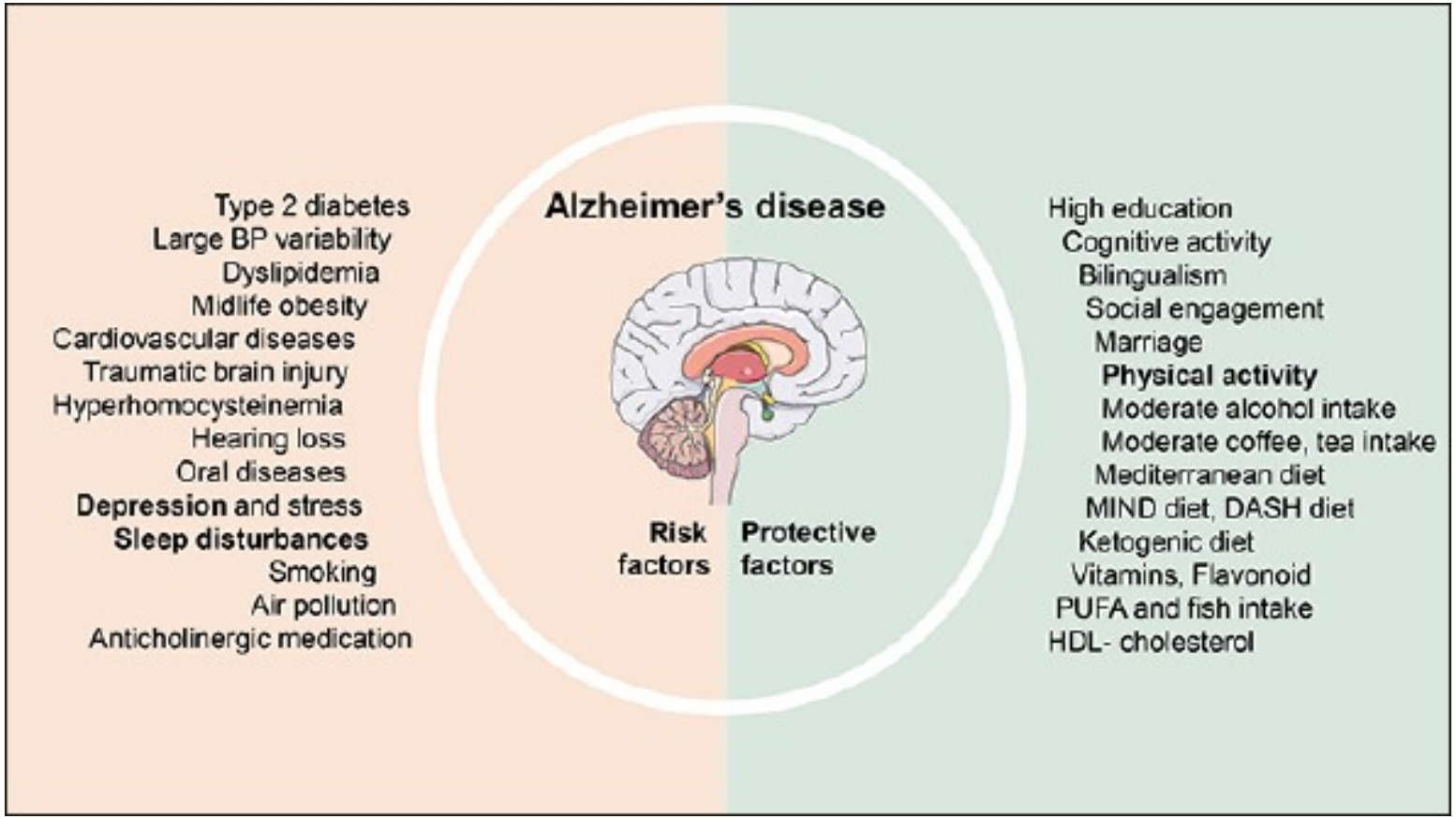
Sinai et al., JAD, 2018 (61): 717-728

Reduced mortality in people with DS taking anti-Alzheimer drugs – truly not sure of the nature of this effect.

How can we prevent Alzheimer's disease in people with Down syndrome?

Cornell hosts Camp PALS NY for adults with Down syndrome

The most important thing we can do RIGHT NOW is to control or minimize risk factors that are associated with Alzheimer disease



Zhang et al., The Journal of Prevention of Alzheimer's disease, 2021.

Control co-occurring illnesses as these are risk factors for dementia (medical interventions)

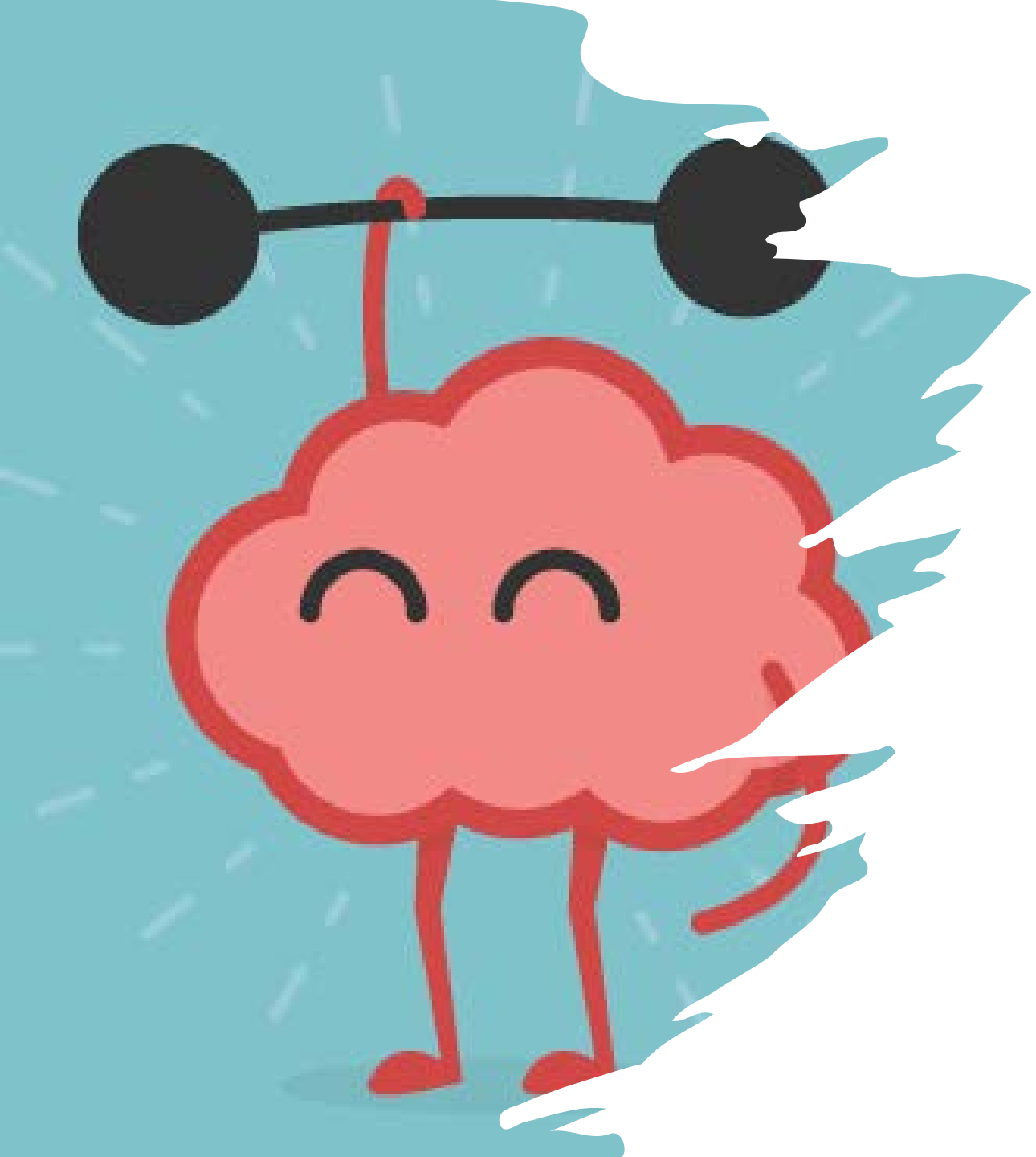
- Stay on top of hypothyroidism treatment (hypothyroidism linked to impaired cognition, reduced blood flow to brain and impaired glucose metabolism in the brain – (Figueroa et al., 2021)
- Vitamin deficiencies (e.g. vitamin D – frequent in people with regression - Santoro et al, 2020; associated with AD – Bivona et al., 2021)
- Diabetes and insulin resistance (may lead to more blood vessel pathology in the brain - Nelson et al., 2009)
- Epilepsy/seizures – (new onset seizures after 40 years of age may signal development of AD – Altuna, Gimenez, Fortea, 2021)

Dr. Brian Chicoine

Control co-occurring illnesses as these are risk factors for dementia (medical interventions)

- Psychiatric conditions (e.g. depression increases risk of developing dementia – Byers & Yaffe, 2011)
- Hypertension (far less frequent in people with DS)
- Hyperlipidomia (high cholesterol)
- Periodontitis (Kamer et al., 2016)
- Sleep apnea (associated with increased risk of AD – Mullins et al., 2020)

Dr. Ira Lott



Lifestyle interventions to promote healthy brain aging

- Sleep
- Diet
- Exercise
- Cognitive training
- Social engagement

Sleep disturbances

- OSA
- Difficulty sleeping (may be disruptive to caregiver)
- Daytime napping and shifts in sleep/wake cycle (sundowning – restlessness or agitation in the early evening)
- Depression may be a major contributor to sleep problems

http://www.sleepapnoeablog.com/downs-syndrome-is-high-risk-for-sleep-apnoea-volunteers-needed-for-new-study/

Managing Sleep Disturbances

- Non pharmacological
  - Maintain regular schedule
  - Bed is only for sleeping – if awake – get out of bed
  - Safety lights
  - Regular exercise
  - Cholinesterase inhibitors – try to give in am not pm
  - Treat pain
  - Temperature
  - Discourage TV if awake

Managing Sleep Disturbances

- Pharmacological
  - Must be very careful with using sleep-inducing medications
  - Start with low doses and slowly increase if needed
  - Increased risk of falls and fractures
  - Increased confusion
- Examples
  - Tricyclic antidepressants
  - Benzodiazepines
  - “sleeping pills” – zolpidem, zaleplon, chloral hydrate
  - “atypical” antipsychotics – risperidone for example
  - Classic antipsychotices – older – e.g. haloperidol

Poor sleep in people with Down syndrome may lead to reduce brain connectivity

brain sciences

MDPI

Article

Sleep and White Matter in Adults with Down Syndrome

Victoria Fleming [1,2], Brianna Piro-Gambetti [1,2], Austin Bazydlo [1,3], Matthew Zammit [1,3], Andrew L. Alexander [1,3,4], Bradley T. Christian [1,3,4], Benjamin Handen [5], David T. Plante [4] and Sigan L. Hartley [1,2,*]

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Abstract: Adults with Down syndrome are at a high risk for disordered sleep. These sleep problems could have marked effects on aging and Alzheimer's disease, potentially altering white matter integrity. This study examined the associations between disordered sleep assessed via an actigraph accelerometer worn on 7 consecutive nights, presence of diagnosis of obstructive sleep apnea, and diffusion tensor imaging indices of white matter integrity in 29 non-demented adults with Down Syndrome (48% female, aged 33–54 years). Average total sleep time was associated with lower mean diffusivity in the left superior longitudinal fasciculus ($r = -0.398$, $p = 0.040$). Average sleep efficiency, length of awakenings, and movement index were related to fractional anisotropy in the right inferior longitudinal fasciculus ($r = -0.614$ to 0.387, $p \leq 0.050$). Diagnosis of obstructive sleep apnea was associated with fractional anisotropy in the right inferior longitudinal fasciculus ($r = -0.373$, $p = 0.050$). Findings suggest that more disrupted sleep is associated with lower white matter integrity in the major association tracts in middle-aged adults with Down syndrome. Longitudinal work is needed to confirm the directionally of associations. Sleep interventions could be an important component for promoting optimal brain aging in the Down syndrome population.

check for updates

Citation: Fleming, V.; Piro-Gambetti, B.; Bazydlo, A.; Zammit, M.; Alexander, A.L.; Christian, B.T.; Handen, B.; Plante, D.T.; Hartley, S.L. Sleep and White Matter in Adults with Down Syndrome. *Brain Sci.* **2021**, *11*, 1322. https://doi.org/10.3390/brainsci11101322

Keywords: Down syndrome; Alzheimer's disease; white matter; sleep; diffusion tensor imaging

- 29 people, 33-54 years of age
- Actigraph to measure sleep/wake cycles, MRI to measure brain connectivity
- Total sleep time, wake after sleep onset, sleep efficiency, number of awakenings, average length of awakenings, movement index and sleep fragmentation index
- Sleep log for 7 nights
- Presence/absence of OSA
- Less sleep, more awakenings, more sleep fragmentation and presence of OSA = poorer brain connectivity in white matter
- *note – in mouse models of Down syndrome – enhancing sleep leads to better memory (Pittaras et al., 2021)

Healthy Diet

- Obesity, type II diabetes – raises risk for AD - exercise/diet
- Fruits and vegetables are high in antioxidants – better than supplements
- Mediterranean diet – lots of fish, nuts and healthy oils, fruits and vegetables – very nice evidence of protection from AD
- A healthy diet can reduce obesity and associated risk factors

http://www.medicinenet.com/mediterranean_diet/article.htm

Antioxidants

- Some of the genes on chromosome 21 that are overexpressed lead to oxidative damage to a greater extent in Down syndrome
- Antioxidant supplements – clinical data?
- The importance of well controlled clinical trials

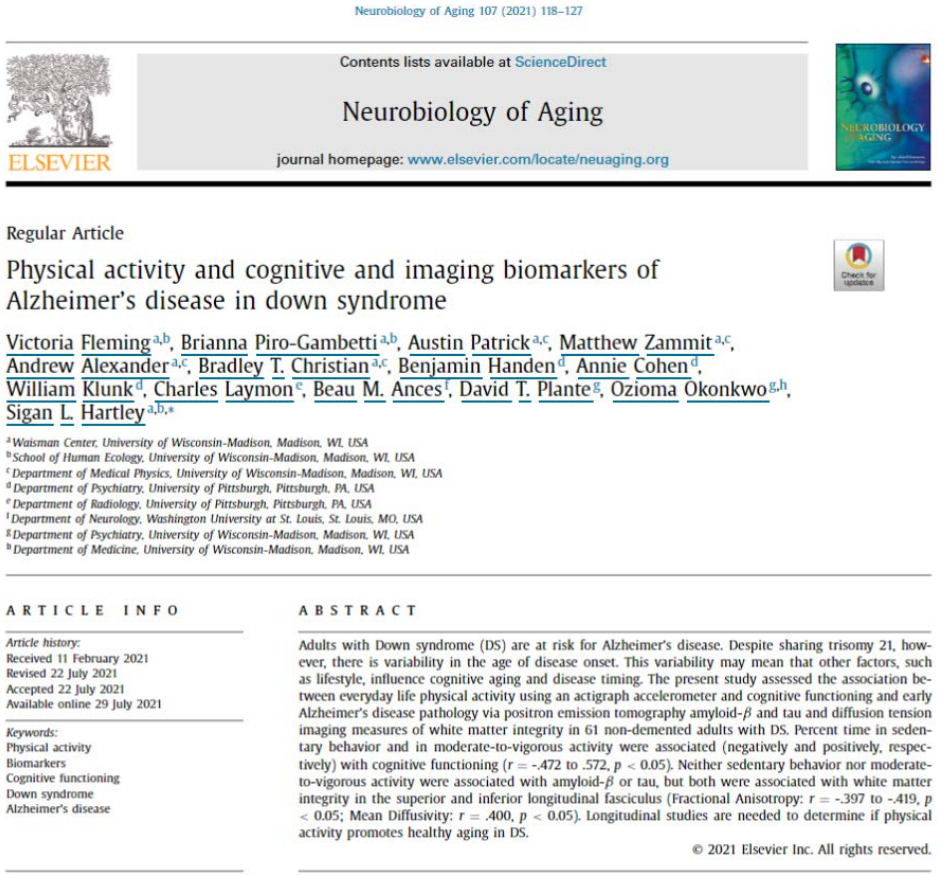
Prevention - Exercise

- Reduces risks associated with obesity and cardiovascular function
- Can help the brain grow new neurons!
- May reduce inflammation
- Stimulates the brain to make growth factors to support healthy cells

http://www.dailymail.co.uk/news/article-2407982/Meet-Downs-Syndrome-man-thats-elite-athlete--regularly-lifting-non-impaired-competitors.html

Boogie Down Crew – DS Association of Louisville

Exercise and brain connectivity



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journal homepage: www.elsevier.com/locate/neuaging.org

Regular Article

Physical activity and cognitive and imaging biomarkers of Alzheimer's disease in down syndrome

Victoria Fleming[a,b], Brianna Piro-Gambetti[a,b], Austin Patrick[a,c], Matthew Zammit[a,c], Andrew Alexander[a,c], Bradley T. Christian[a,c], Benjamin Handen[d], Annie Cohen[d], William Klunk[d], Charles Laymon[e], Beau M. Ances[f], David T. Plante[g], Ozioma Okonkwo[g,h], Sigan L. Hartley[a,b,*]

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ABSTRACT

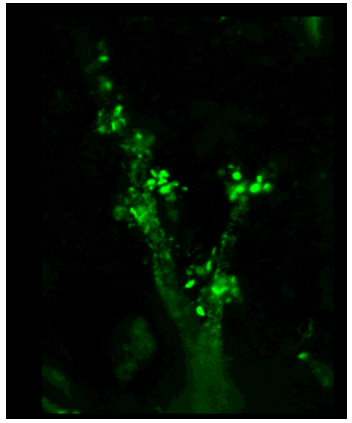
Adults with Down syndrome (DS) are at risk for Alzheimer's disease. Despite sharing trisomy 21, however, there is variability in the age of disease onset. This variability may mean that other factors, such as lifestyle, influence cognitive aging and disease timing. The present study assessed the association between everyday life physical activity using an actigraph accelerometer and cognitive functioning and early Alzheimer's disease pathology via positron emission tomography amyloid-β and tau and diffusion tension imaging measures of white matter integrity in 61 non-demented adults with DS. Percent time in sedentary behavior and in moderate-to-vigorous activity were associated (negatively and positively, respectively) with cognitive functioning (r = -.472 to .572, $p < 0.05$). Neither sedentary behavior nor moderate-to-vigorous activity were associated with amyloid-β or tau, but both were associated with white matter integrity in the superior and inferior longitudinal fasciculus (Fractional Anisotropy: r = -.397 to -.419, $p < 0.05$; Mean Diffusivity: r = .400, $p < 0.05$). Longitudinal studies are needed to determine if physical activity promotes healthy aging in DS.

- 66 people with Down syndrome 25 years and older

- All cognitively stable
- Neuroimaging (MRI – structural, PET-tau/amyloid
- Actigraph for 7 days – sedentary, light, moderate, vigorous and vey vigorous activity
- People with Down syndrome who spent more time in moderate to vigorous activity and less time being sedentary and better cognitive functioning (caveat – people with poorer cognition may be sedentary because of this vs sedentary behaviors causing cognitive decline)
- More time spent sedentary is associated with poorer connectivity in the brain

Prevention – Cognitive Exercises

- The more active your brain is – helps neurons to make more connections
- Leads to growing new neurons
- Leads to growth factors being released in the brain to make existing neurons happier and healthier
- The more connections you have, the more “damage” you can absorb
- Example – more years of education = less risk of AD

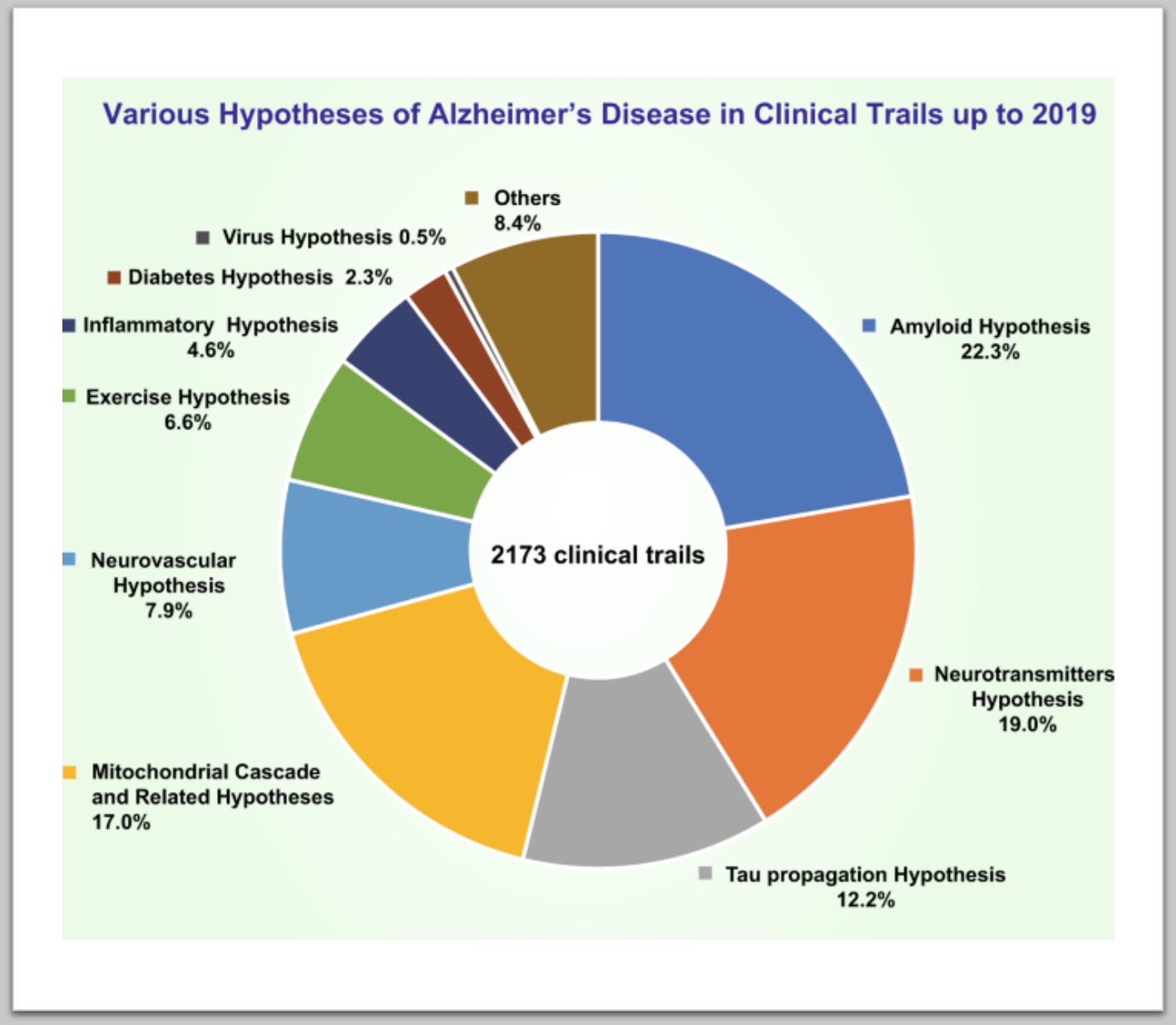


Prevention – Social Activities

- People with very active social lives, lots of friends tend to be more protected against AD
- Why? Social activity engages the brain and the more active your brain, the more neurons are stimulated to make connections and stay healthy

The future for treating Alzheimer's disease in people with Down syndrome

- Several clinical trials are going on in sporadic AD including new drugs and vaccines
- We have to be careful about thinking these same drugs or vaccines might be directly applicable to people with Down syndrome without testing them directly
- Liu et al., Signal Transduction and Targeted Therapy, 2019



Current clinical trials – Clinicaltrials.gov as of 2019

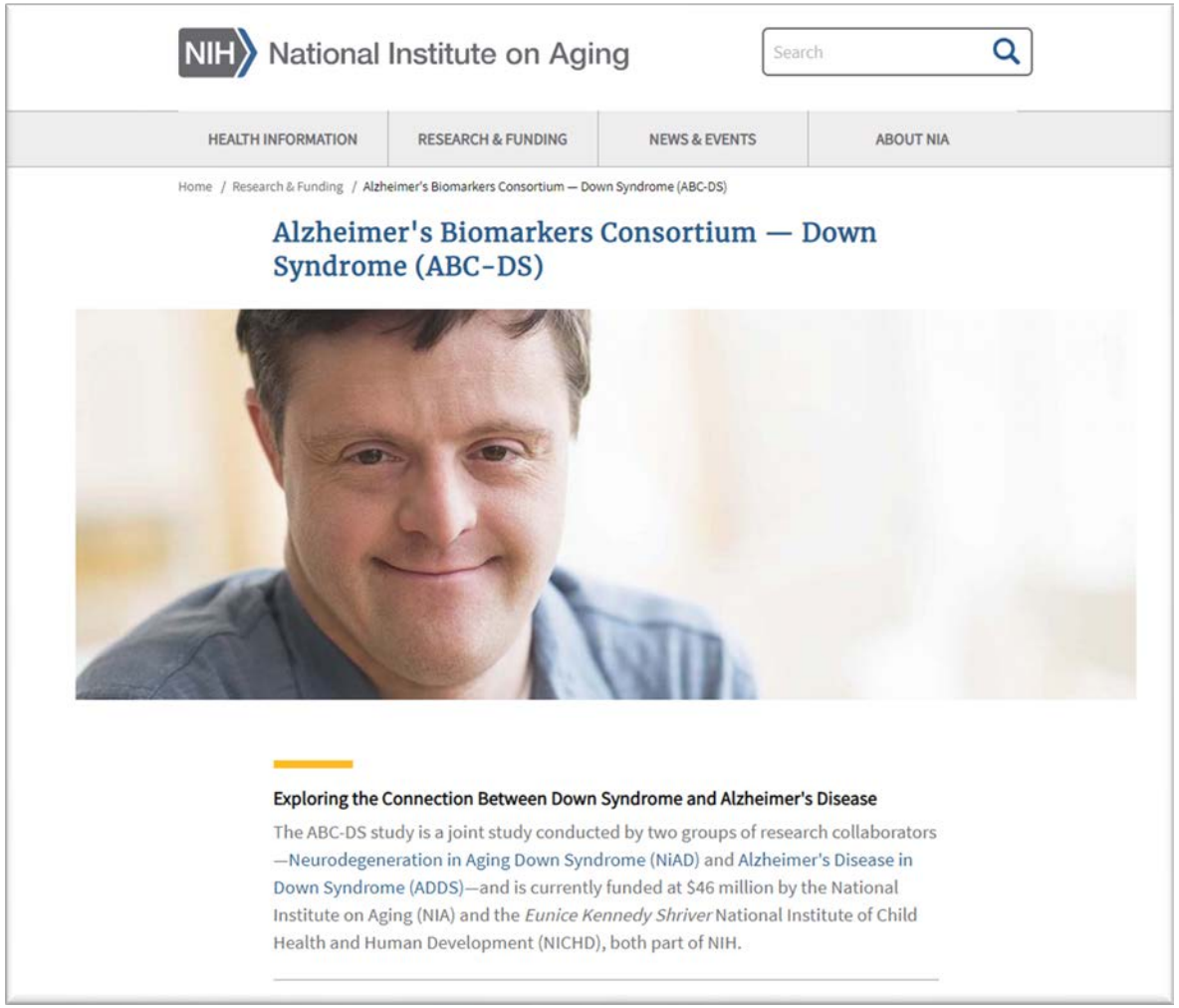
- 54 trials are recruiting for DS in total (2 years ago was 40!)
- 17 interventional trials are recruiting/completed for people with DS over 18 years of age (around the world)
- 6 are focused on DS with AD
  - Physical activity (University of Kansas)
  - LuMIND – observational study
  - TRC-DS – observational study

What are researchers doing?

- Find out what the earliest signs of dementia may be (more accurate diagnosis)
- Earlier we catch signs of dementia – the sooner we can start an intervention
- Which treatment and importantly, when?
- What measures should we make when we are planning clinical trials dedicated to people with Down syndrome to prevent Alzheimer’s disease?

ABC-DS

- N=550 people 25 years and older
- 8 cores
- 11 sites
- INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE)



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

TRCDS
Trial-Ready Cohort-Down Syndrome

www.trcds.org

lumind idsc
DOWN SYNDROME FOUNDATION

- https://www.lumindidsc.org

https://dsconnect.nih.gov/

Resources

Clinical Review & Education

JAMA | Special Communication

Medical Care of Adults With Down Syndrome
A Clinical Guideline

Amy Y. Tsou, MD, MSc; Peter Bulova, MD; George Capone, MD; Brian Chicoine, MD; Bryn Gelaro, MA, LSW; Terry Odell Harville, MD, PhD, D(ABMLI), D(ABHI); Barry A. Martin, MD; Dennis E. McGuire, PhD, LCSW; Kent D. McKelvey, MD; Moya Peterson, PhD, APRN, FNP-BC; Carl Tyler, MD, MSc; Michael Wells, BS; Michelle Sie Whitten, MA; for the Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup

IMPORTANCE Down syndrome is the most common chromosomal condition, and average life expectancy has increased substantially, from 25 years in 1983 to 60 years in 2020. Despite the unique clinical comorbidities among adults with Down syndrome, there are no clinical guidelines for the care of these patients.

OBJECTIVE To develop an evidence-based clinical practice guideline for adults with Down syndrome.

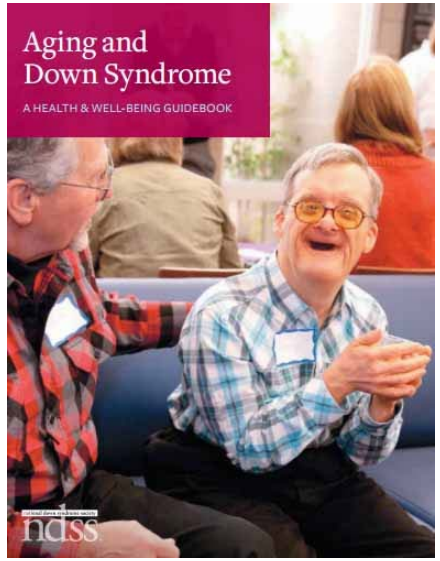
EVIDENCE REVIEW The Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup (n = 13) developed 10 Population/Intervention/Comparison/Outcome (PICO) questions for adults with Down syndrome addressing multiple clinical areas including mental health (2 questions), dementia, screening or treatment of diabetes, cardiovascular disease, obesity, osteoporosis, atlantoaxial instability, thyroid disease, and celiac disease. These questions guided the literature search in MEDLINE, EMBASE, PubMed, PsychINFO, Cochrane Library, and the TRIP Database, searched from

Editorial page 1509

Supplemental content

CME Quiz at jamacmelookup.com

https://jamanetwork.com/journals/jama/fullarticle/2771907



Dr. Julie Moran - www.ndss.org

Summary

- People with DS are at a higher risk for AD with an earlier age of onset but NOT EVERYONE DEVELOPS DEMENTIA
- Current treatments for Alzheimer’s disease include both pharmacological and nonpharmacological interventions
- Prevention approaches are very promising and include modifying lifestyle risk factors
- New treatments are in the pipeline

Take home messages

- A healthy diet – lots of fruits and vegetables
- Exercise – make it fun! Dancing counts ☺
- Make friends – and then make more friends and keep visiting with friends
- Play (board games, computer games), learn new things (music, drawing, cooking), take classes
- Make sure you are getting lots of good sleep
- All of these reduce your risk factors
- Prevention is more powerful than treating a disease

Be active and proactive!

Advocate and self-advocate for more research to help us find ways to improve health in aging people with Down syndrome

Volunteer ☺

Be positive!!

Many thanks to our volunteers with Down syndrome

Thank you to you, your families and to the Down syndrome Association of Wisconsin for all you do!