AGING AND END OF LIFE WEBINAR SERIES

Dementia Among Adults with Down Syndrome: Individual Differences in Risk and Progression

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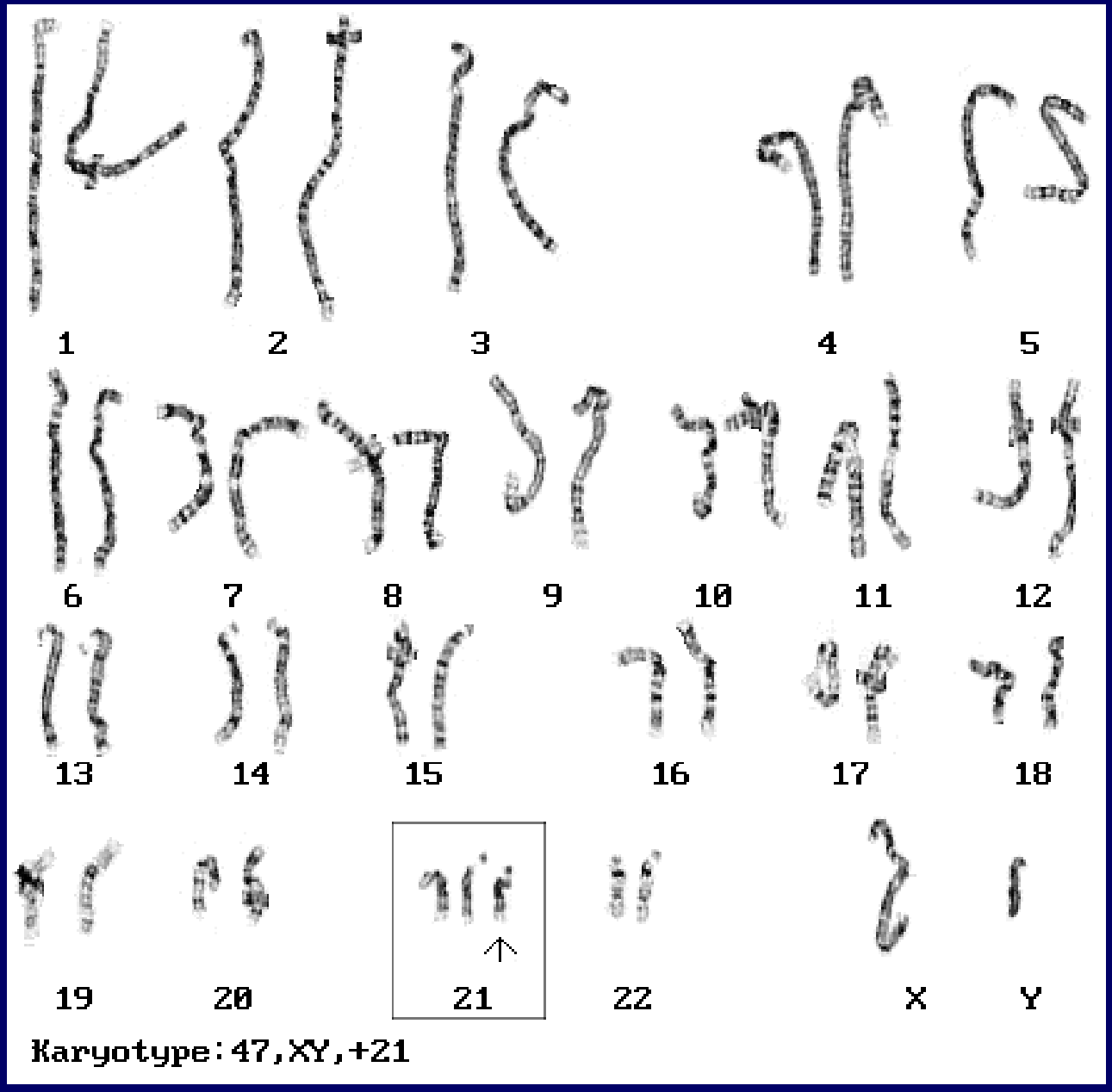
Webinar Outline

- Overview of Down syndrome (DS)
  - And the public health significance of aging
- Overview of Alzheimer's disease (AD)
- Connection between DS and AD
- Review of individual differences in risk
- Review of individual differences in progression
- Summary of gaps in current knowledge

Overview of Down Syndrome (Trisomy 21)

- The most prevalent genetic cause of intellectual disability.
- Results from the presence of an extra (third) copy of chromosome 21
  - Usually an entire copy, but variants can occur
    - Partial trisomy
    - mosaicism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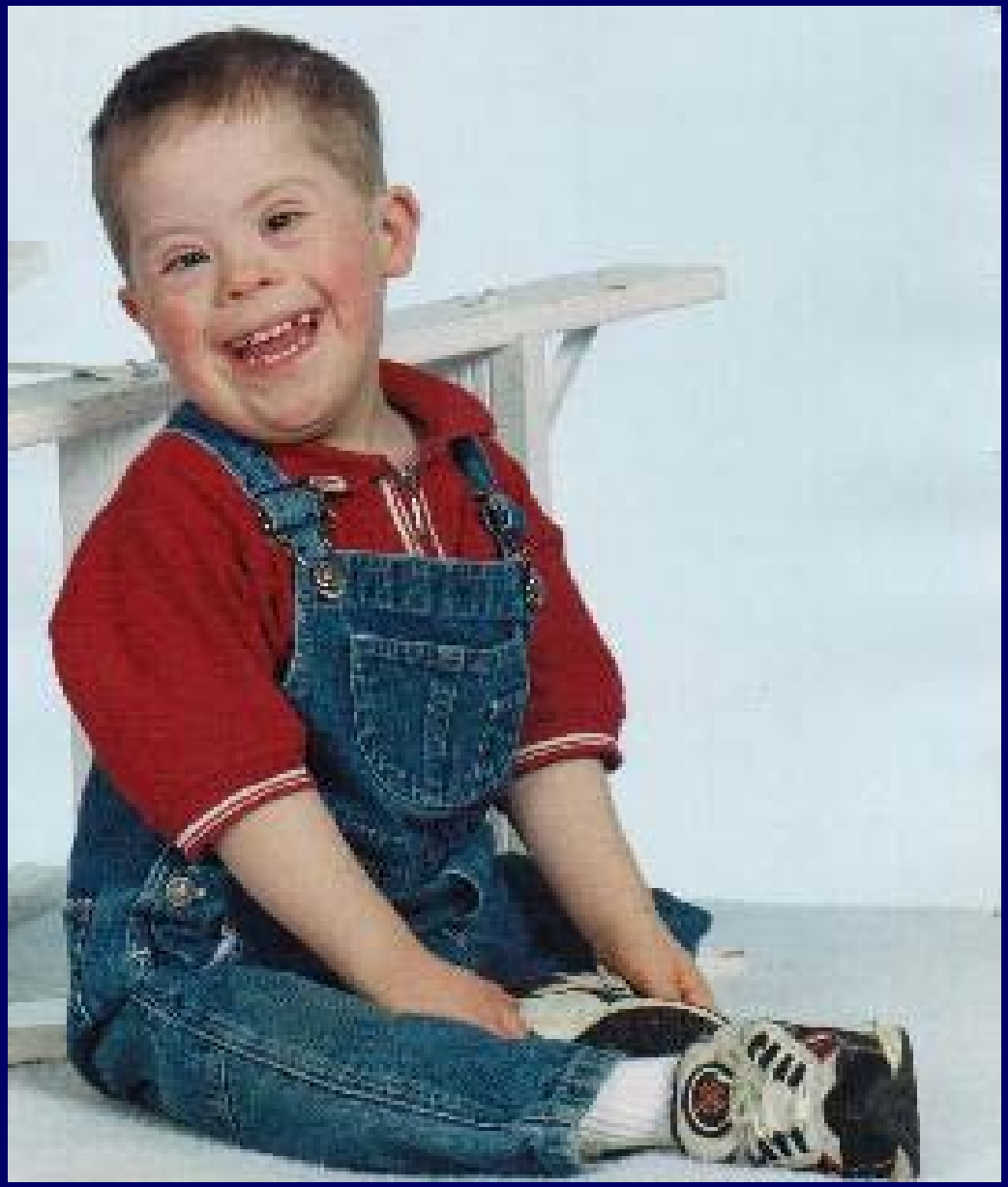
X
Y
Karyotype:47,XY,+21

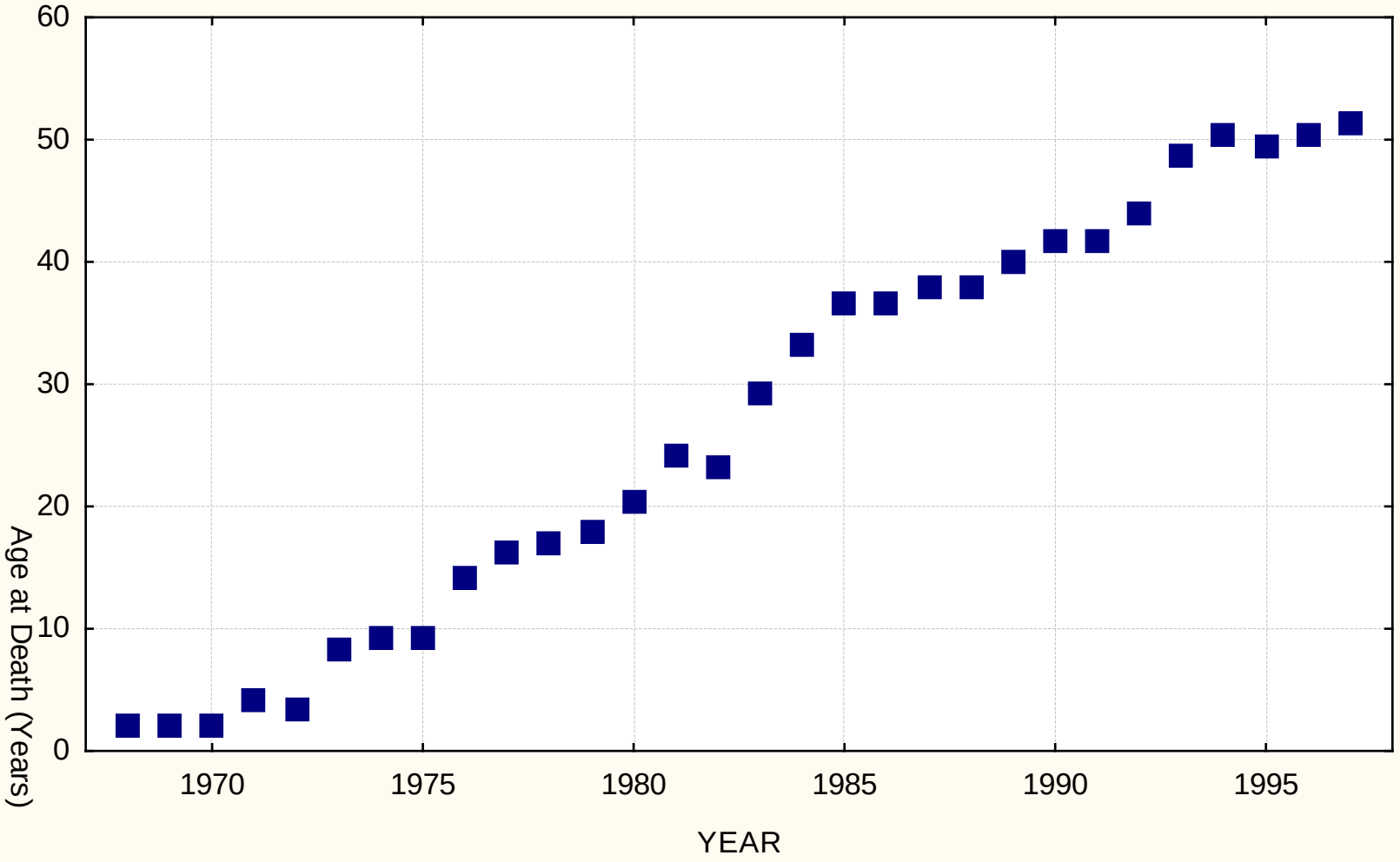
Overview of Down Syndrome (Trisomy 21)

- The most prevalent genetic cause of intellectual disability
  - Incidence of approximately 1 in 740 live births.
  - Risk increases with maternal age, but most affected births occur for “younger” mothers.
  - Characteristic phenotype.

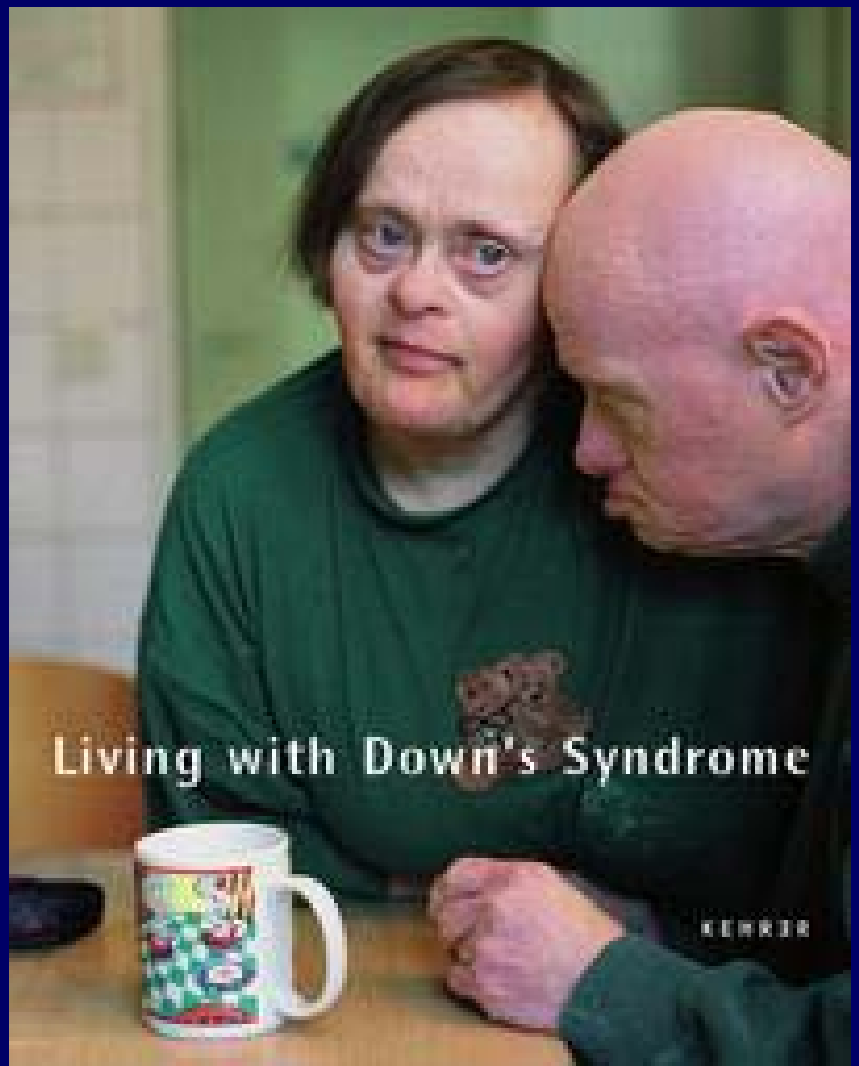


Median Age at Death of Persons with Down Syndrome:
U.S. White Population - 1968 to 1997

From Morbidity & Mortality Weekly Report, 2001
Vol. 50, 463-465.



We now need to support a rapidly expanding older population with DS.



Characteristics of Atypical Aging Associated with Down Syndrome

- premature changes in skin and hair greying
- early menopause
- increased frequency of senile cataracts
- increased frequency of hearing loss
- age-related increase in hypothyroidism
- age-related increase in seizures
- **Dramatically increased risk of AD**
- **Reduced life expectancy**

Not All Bad News for Aging with Down Syndrome: Medical Conditions with Low Risk

- Solid Tumor Cancers
- Type 2 Diabetes (RR=0.4, despite prevalent obesity)
- Cardiovascular and cerebrovascular disease
  - Heart Disease (ischemic heart disease) (RR=0.7)
  - **Hypertension (RR=0.1)**
  - Stroke

“Public Health” Importance of Understanding Dementia among Adults with Down Syndrome

Projected “elderly” U.S. population with DS

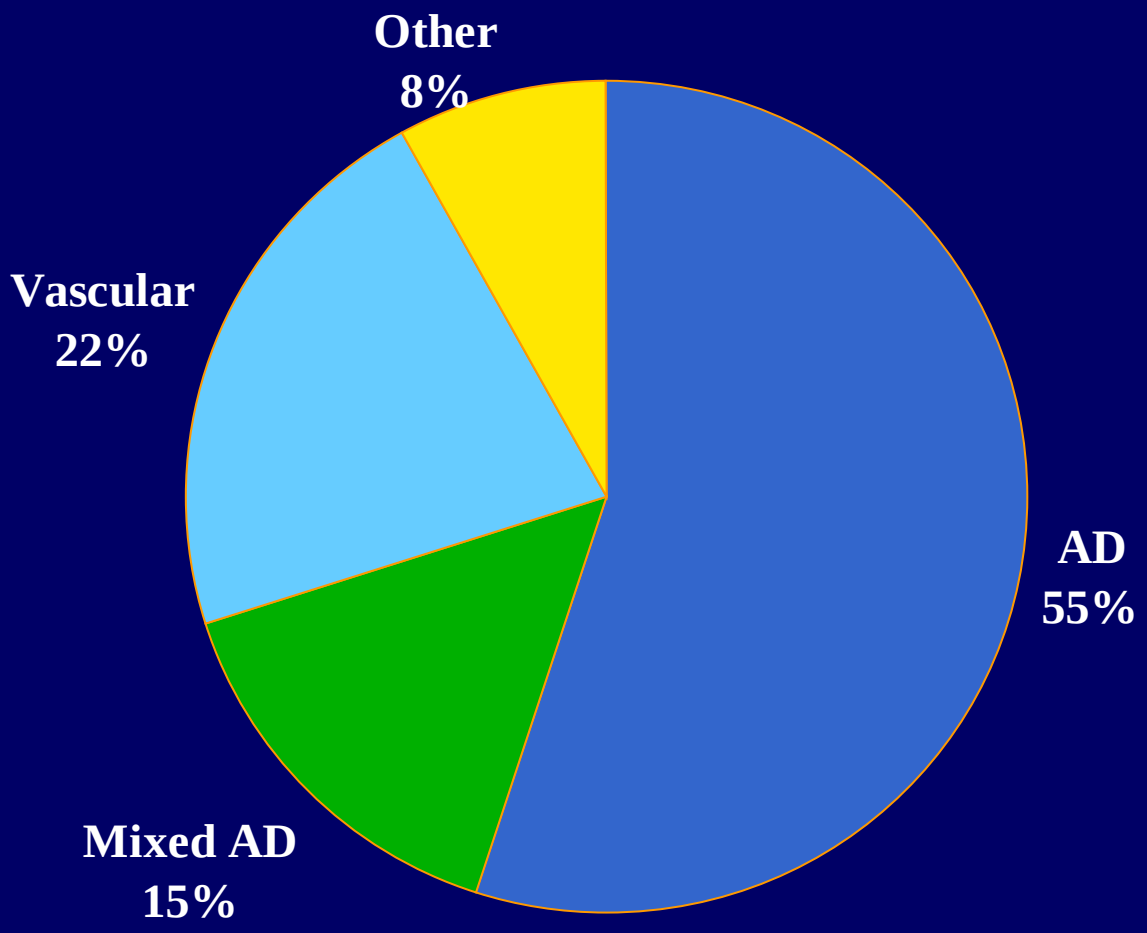
- 200,000 over 55 (based upon current incidence and survival rates), and
- 85,000 likely to develop AD

Potential annual cost of care > $10 billion.

Overview of Alzheimer's disease

- The most prevalent cause of dementia in old age.
- Cause remains unknown
- Risk increases substantially after age 65-70
  - Except for rare cases with genetic predisposition
- Has a distinctive profile
  - Slowly progressing clinical dementia
  - Broad spectrum of neuropathology

Alzheimer's Disease: Most Common Cause of Old-Age Associated Dementia



DSM-IV Definition of Dementia

Development of multiple cognitive deficits…,

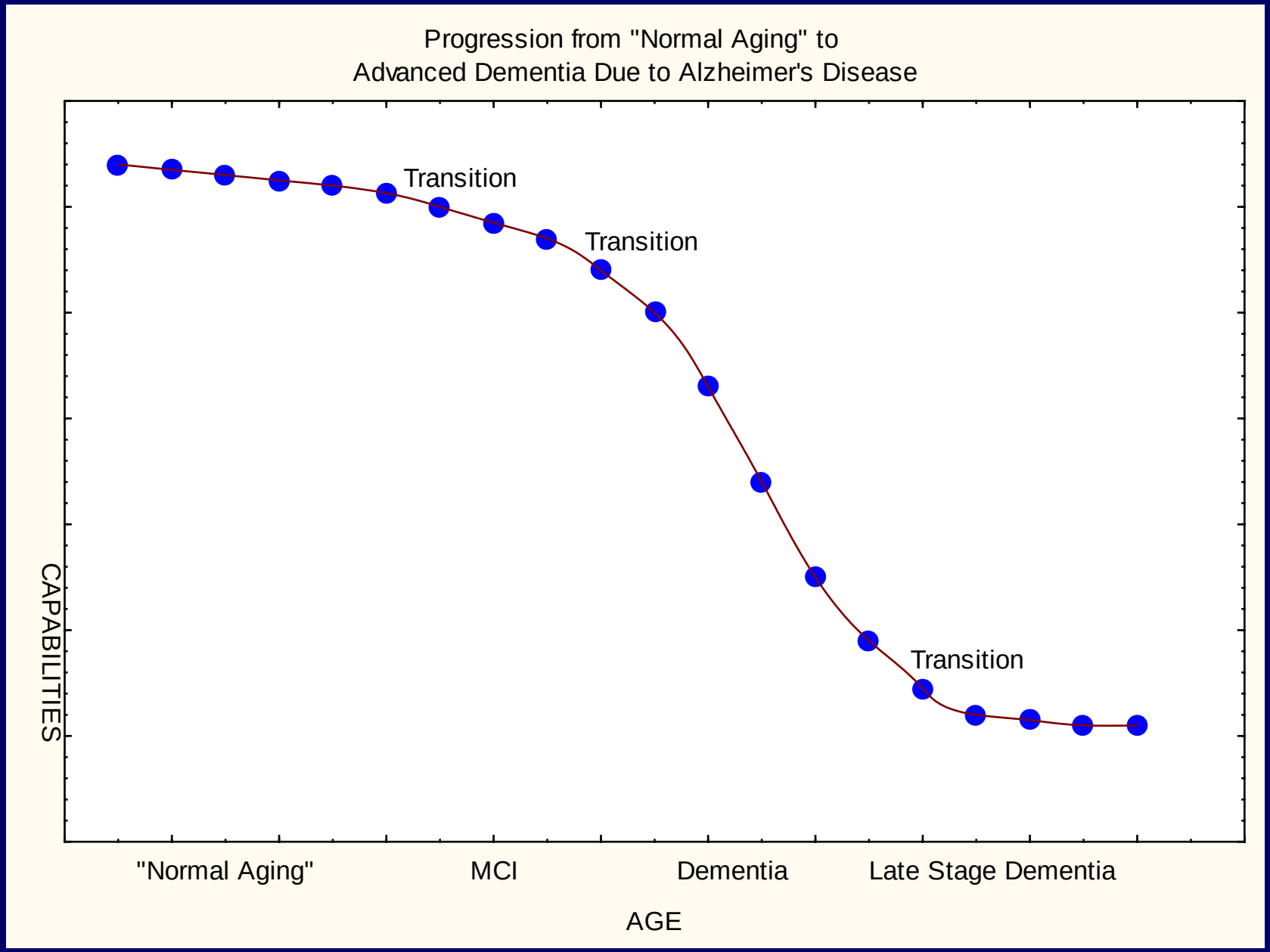
Characterized by a substantial decline in abilities associated with functional impairment.

Nonspecific with regard to underlying cause.

Complication

Lots of other illnesses or conditions can cause clinical dementia, some not even related to CNS function (e.g., untreated hypothyroidism, HIV, TBI, drug toxicity, poorly recognized systemic illness).

This complicates diagnosis, practice, planning and research, but it's topic for another day.


Progression from "Normal Aging" to
Advanced Dementia Due to Alzheimer's Disease
Transition
Transition
Transition
CAPABILITIES
"Normal Aging"
MCI
Dementia
Late Stage Dementia
AGE

Duration of decline for Adults with Alzheimer's Disease Without ID

No Decline

"Normal Aging"

Mild Cognitive Impairment

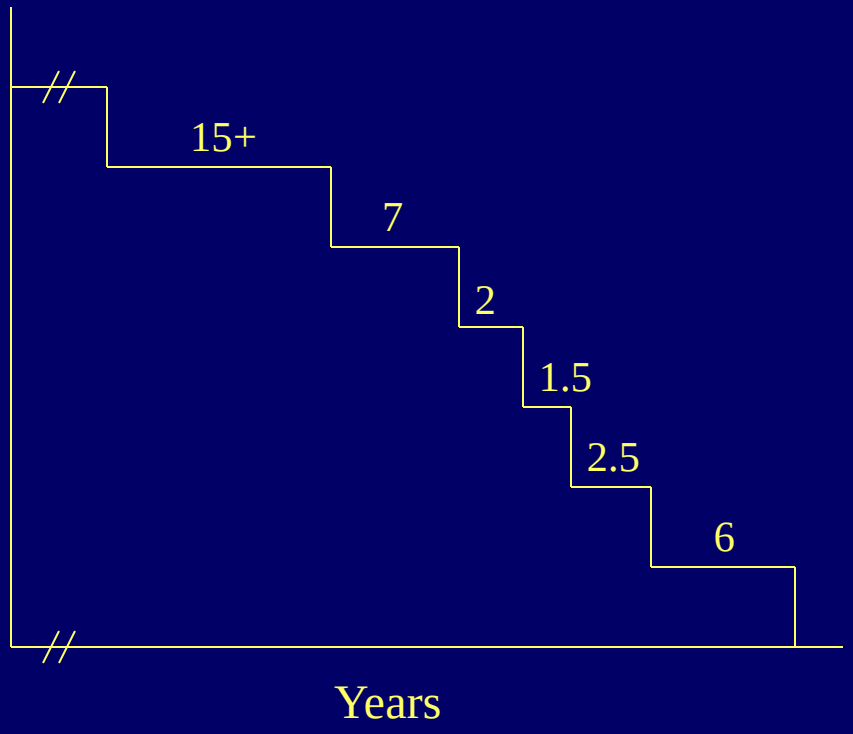
Moderate Cognitive Impairment

Early Dementia

Severe Dementia

Profound Dementia

Death

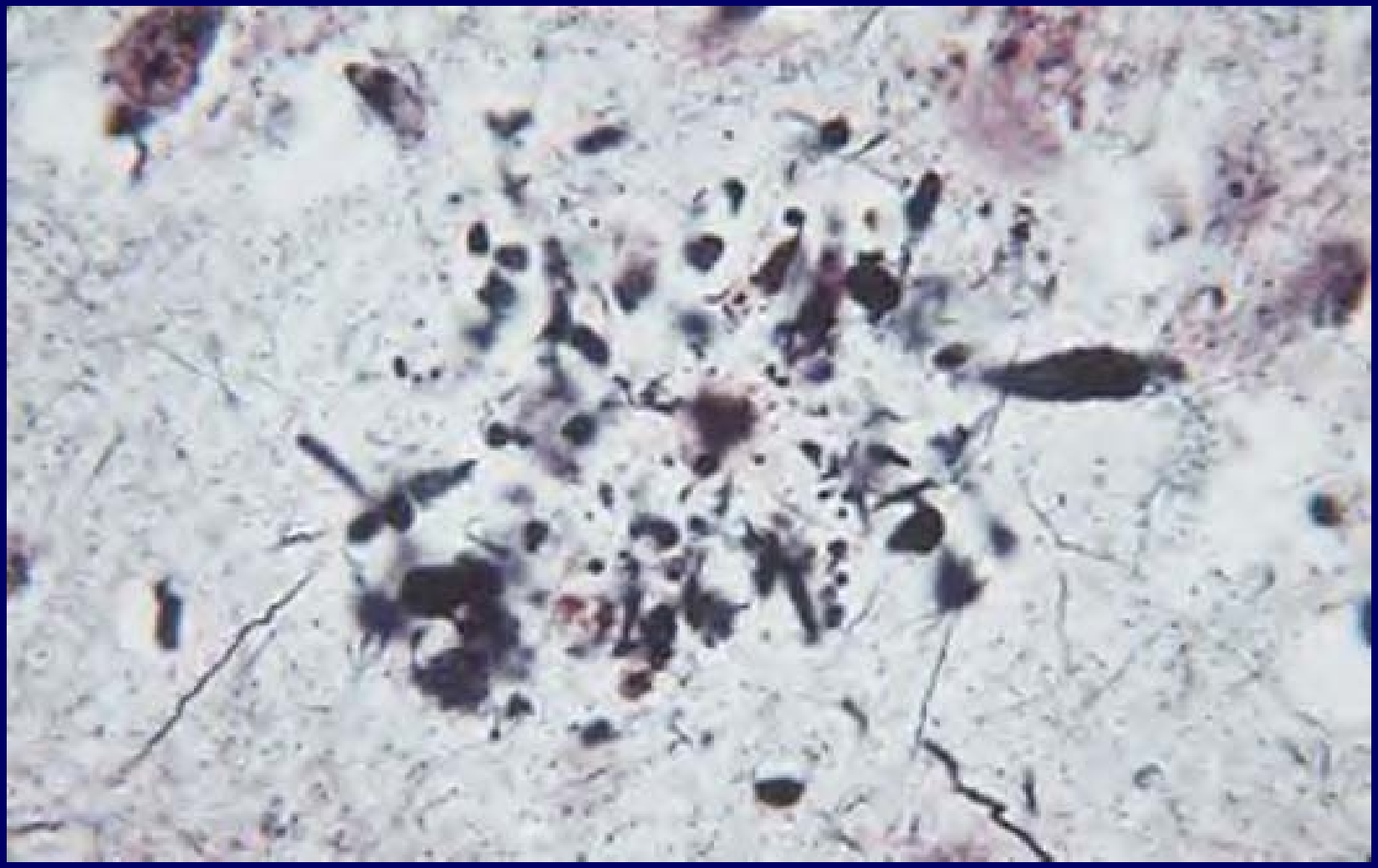


Adapted From: Reisberg, B. (1986). *Geriatrics*,41, 430-446.

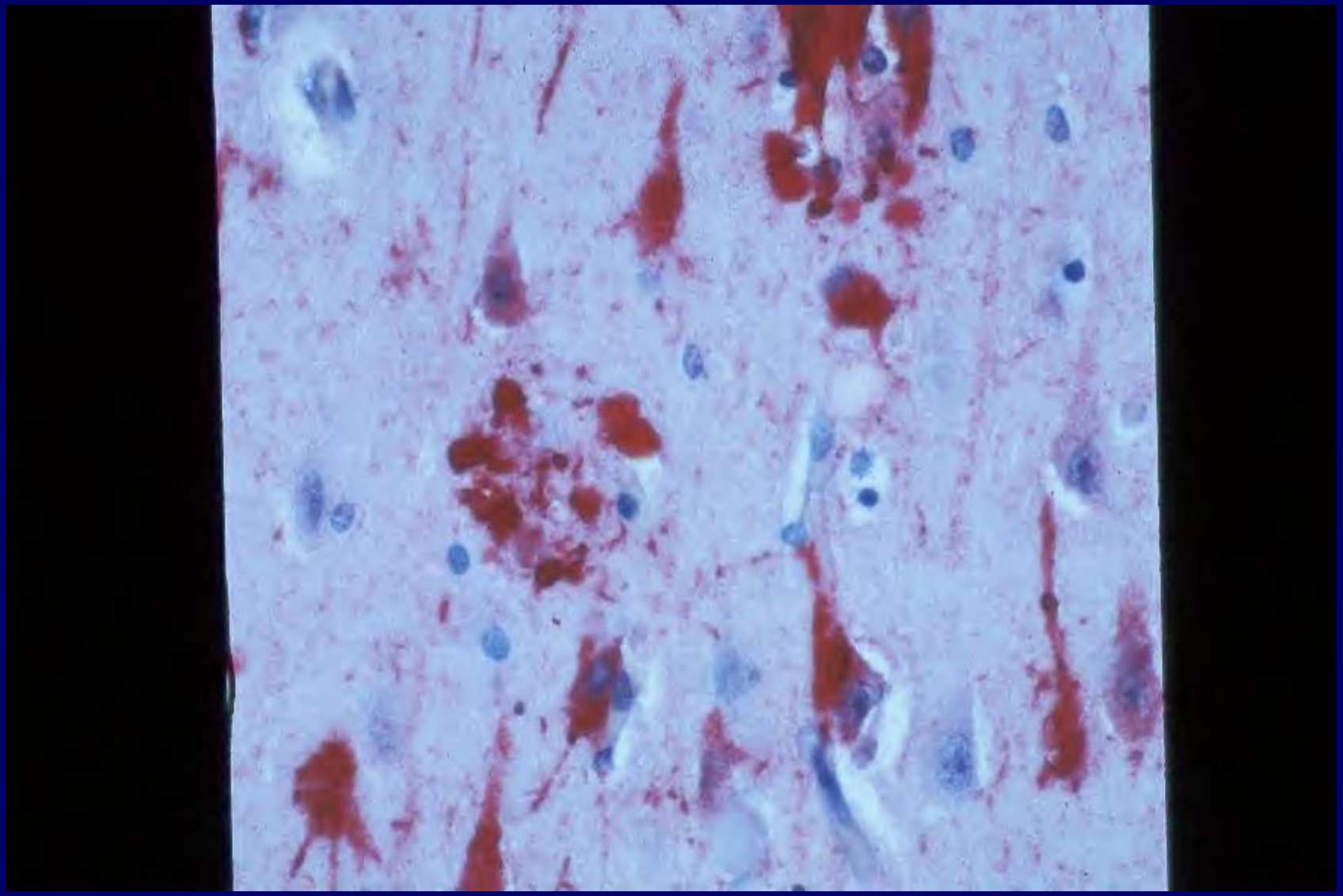
Neuropathological Characteristics of AD ("Gold standard" for diagnosis)

- Amyloid plaque deposits (substantial numbers)
- Neurofibrillary pathology
- Neuron loss and gross atrophy
- Distinct topographic progression
- Etc.

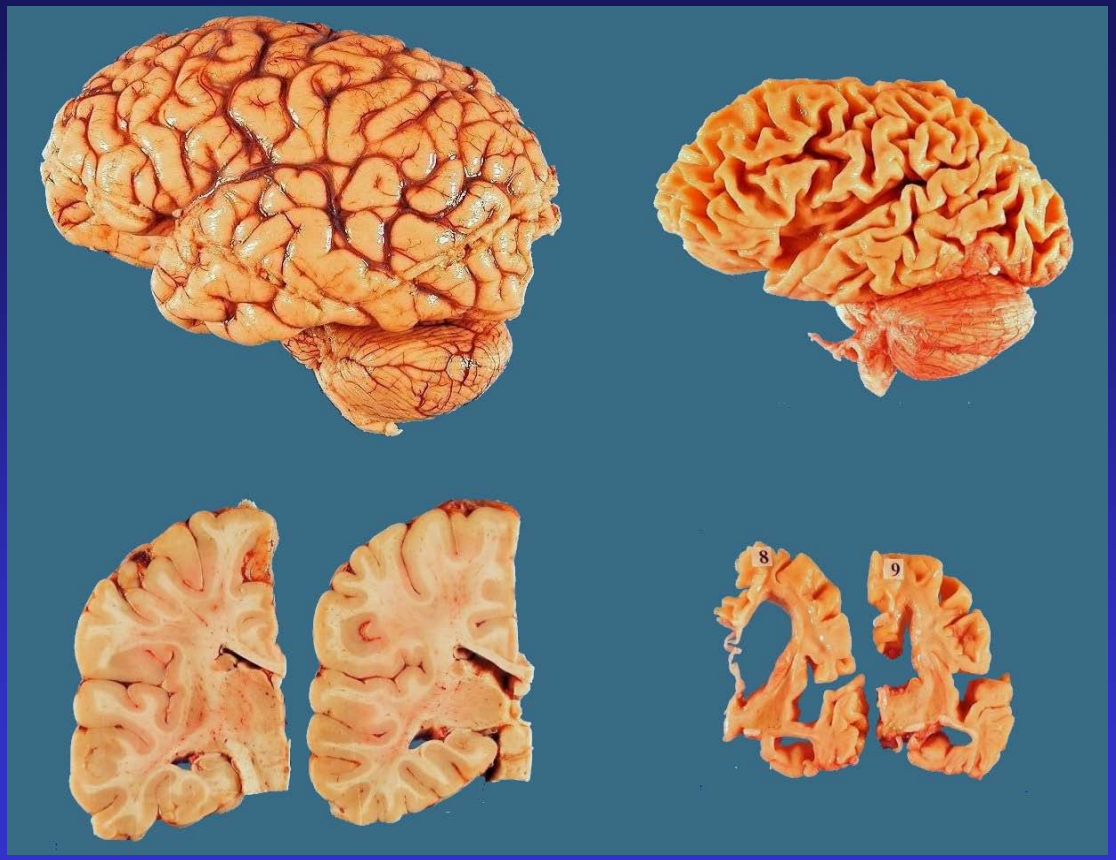
Neuritic Plaque



Neurofibrillary Tangles



Alzheimer's Disease Associated Gross Pathology



Down Syndrome and “Alzheimer’s Disease”

Reports of dementia in older adults with Down syndrome date back to the late 1800’s -

Even before Alzheimer described AD.

However, early reports were only of academic interest because very few individuals lived long enough to be at risk. It has only been since the 1980’s that the public health significance of this association was appreciated and relevant issues began to attract “serious” attention.

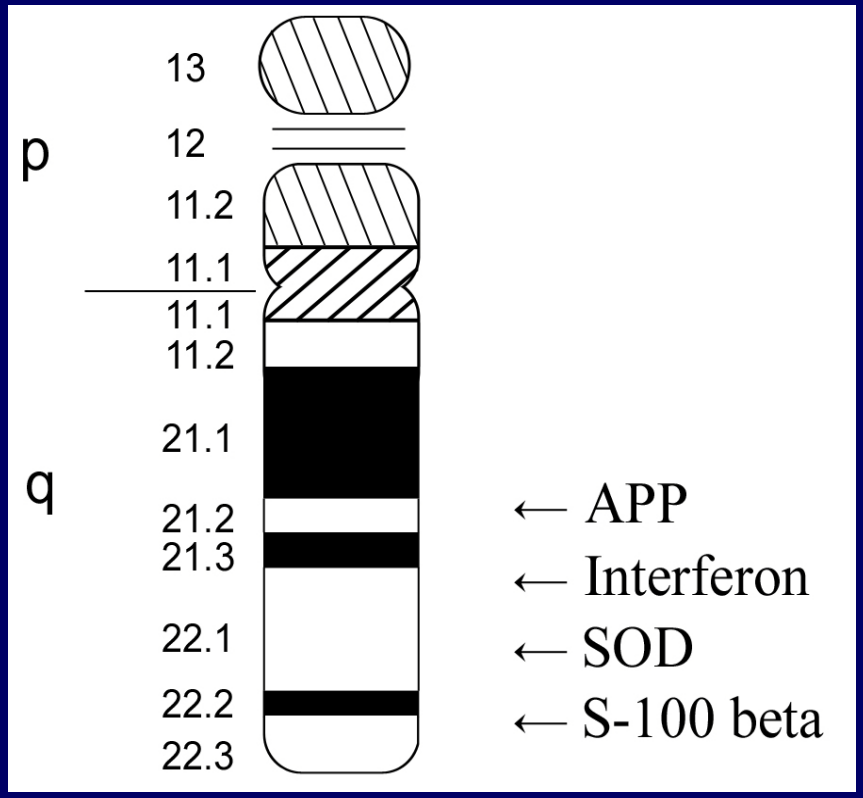
Why is there an association between AD and DS?

AD Cause: Amyloid Cascade Hypothesis

β-amyloid deposition causes AD by triggering a complex pathological cascade that leads to the broad spectrum of neuropathological changes seen in AD together with clinical dementia.

β-amyloid is formed from a larger protein needed for normal cell function, called amyloid precursor protein (APP).

Down syndrome and APP

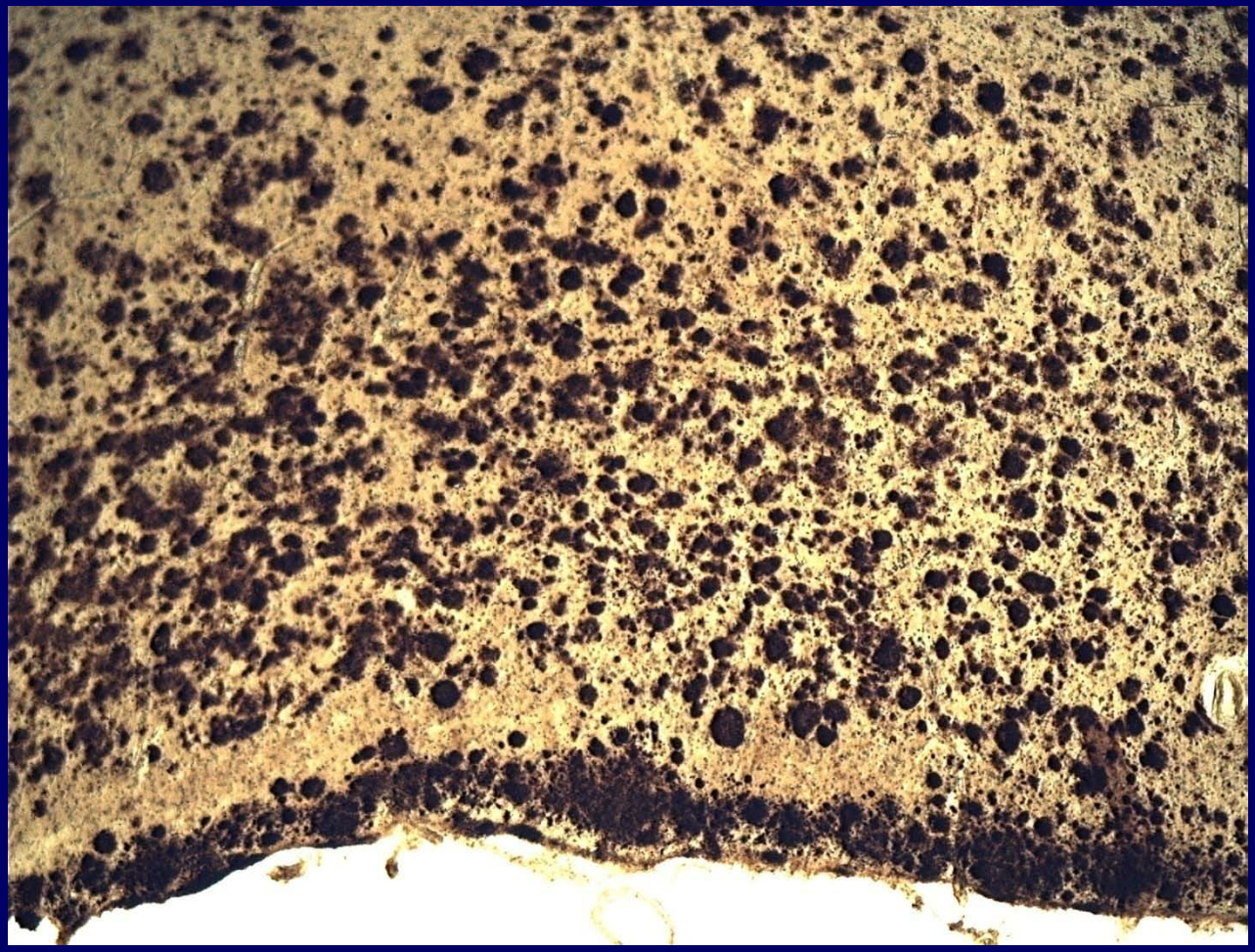


- The gene coding for APP is on chromosome 21
- Individuals with DS have 3 copies of this gene and produce excess APP
- Over many years, this excess APP leads to β-amyloid plaque formation and eventual AD

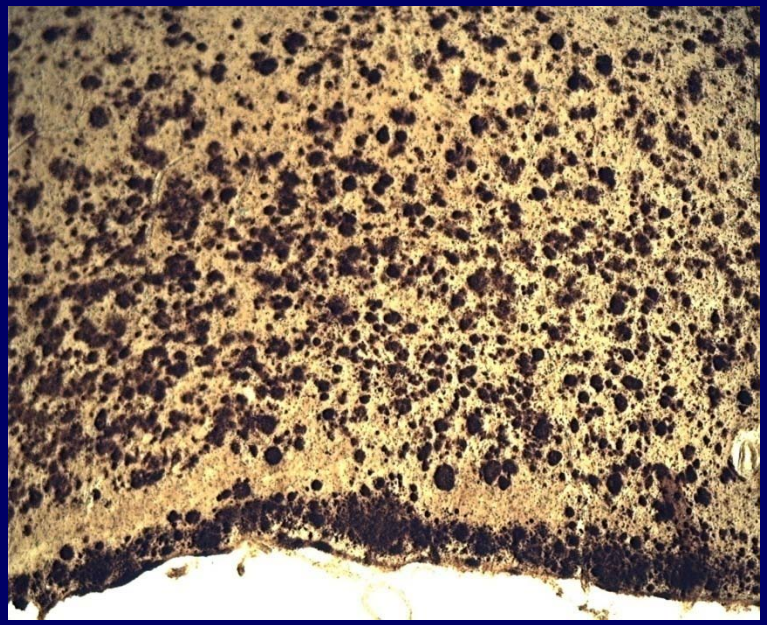
DS and AD: Neuropathological Criteria

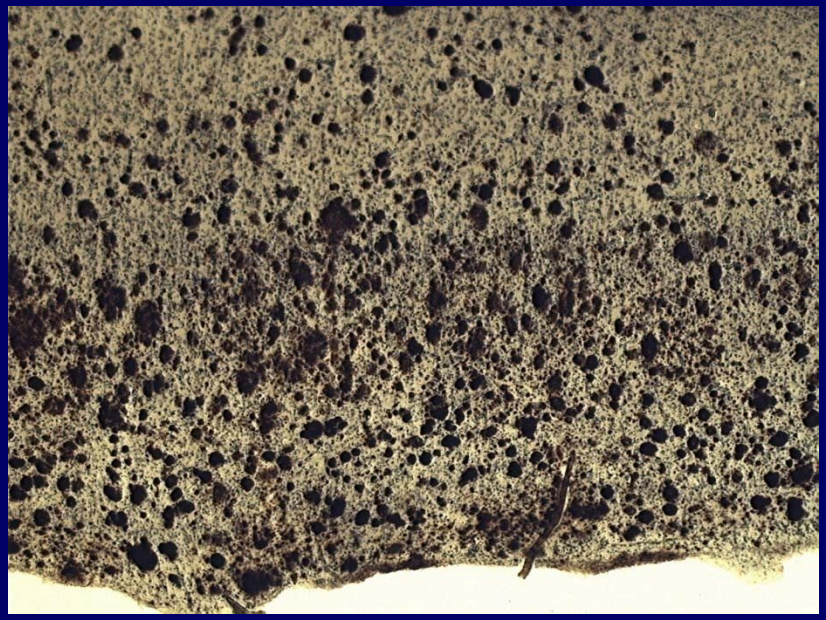
- Virtually all individuals with DS have amyloid deposits in their brains consistent with a diagnosis of AD by the time they are 35-40 years of age.

DS (Age 65): Parahippocampus immunostained to show βA plaques

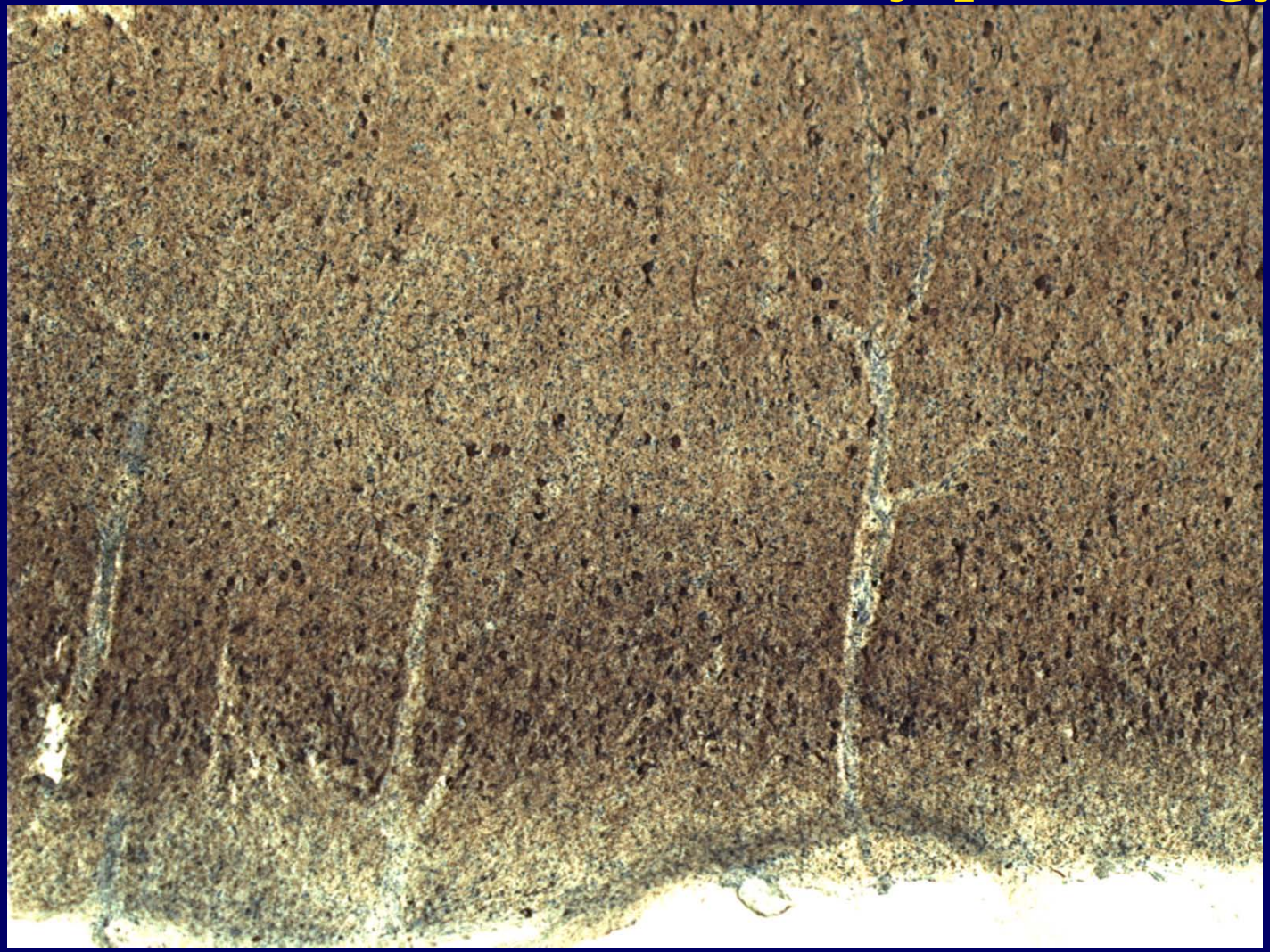


Parahippocampus stained to show plaques:
65 year old with DS on left,
78 year old with advanced AD on right





DS Age 65: Parahippocampus stained with Tau1 to show neurofibrillary pathology



DS and AD: Neuropathological Criteria

- Virtually all individuals with DS have amyloid deposits in their brains consistent with a diagnosis of AD by the time they are 35-40 years of age.
- What about dementia?

Complication

It is difficult to recognize dementia for individuals having preexisting cognitive impairments that vary widely in their severity. There are no “standard” methods for assessment or diagnostic criteria. Nevertheless, we can:

- Document substantial decline from previous status and rely on these findings to inform clinical judgment.

Well Defined Clinical Characteristics of AD can be Useful in Recognizing Transitions in Adults with DS

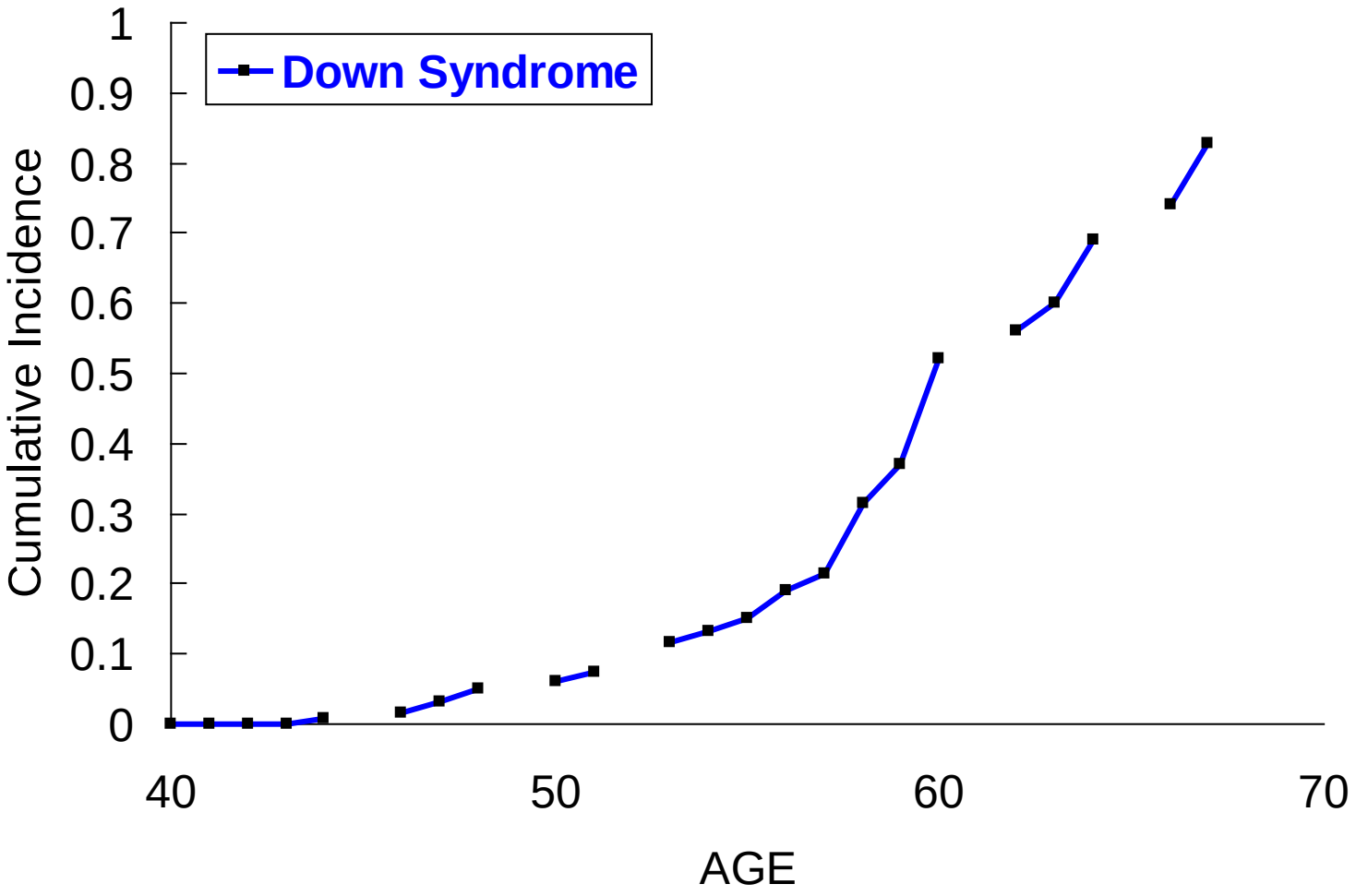
- Progressive Decline in
  - Memory and Cognition
  - Motor Function
  - Activities of Daily Living
  - Changes in Mood and Behavior
- Severity of deficits increase dramatically over extended time

Our Consensus Dementia Ratings

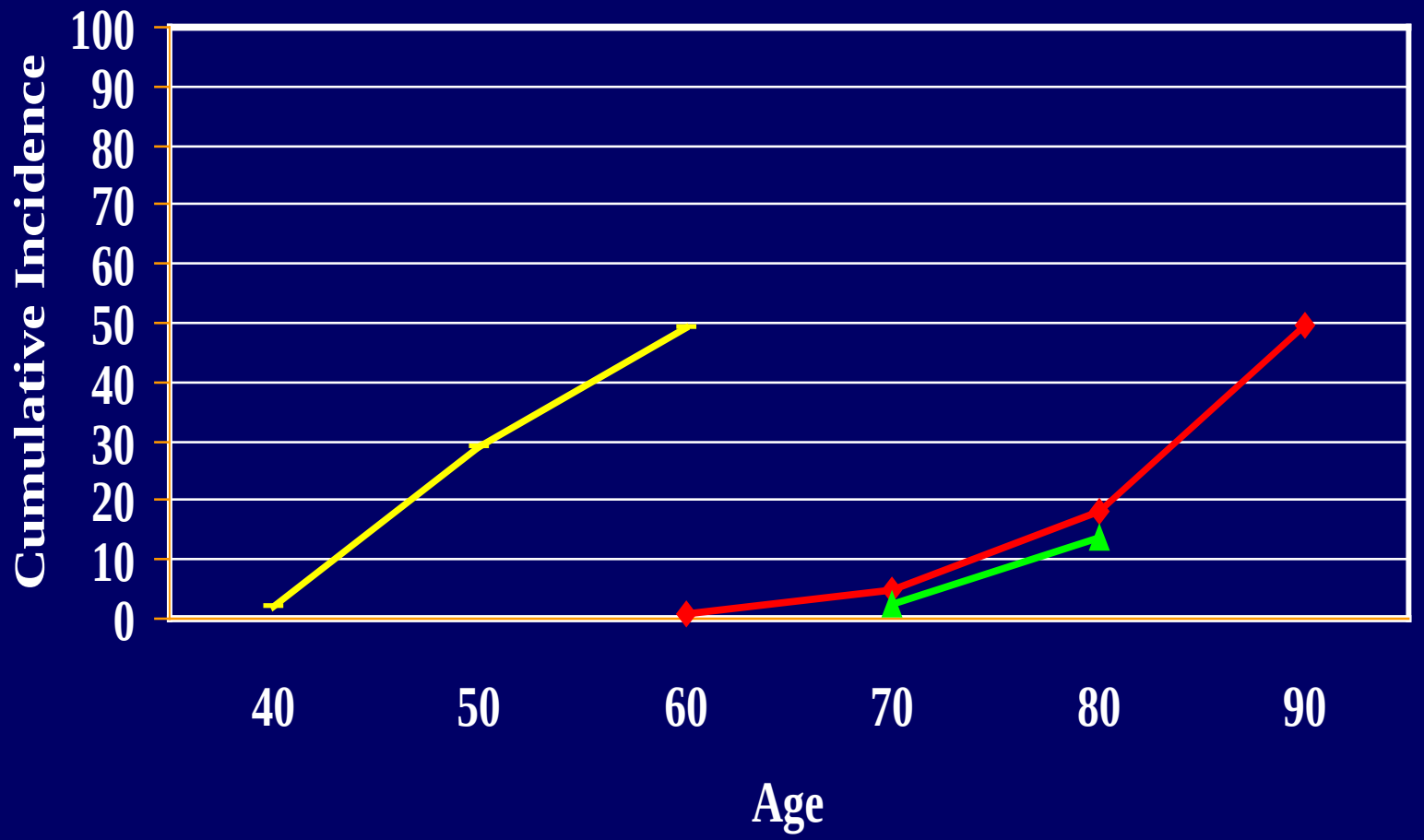
Overall classification established every 14-18 months based upon a comprehensive evaluations.

Not demented	Stable or age-related changes
Questionable	Some declines or concerns; unlikely due to aging, per se
With complications	Substantial declines that may be due to “other” condition
Possible dementia	Substantial declines of late onset
Definite dementia	Substantial declines of extended duration
Unknown status	Circumstances prevent determination

Cumulative Incidence of Dementia/AD in Down Syndrome



Cumulative Incidence of Dementia/AD in Adults with Down Syndrome (Yellow), the Overall Population (Red), and Other ID (Green)



Alzheimer's Disease and Down Syndrome: The Big Picture

Increased risk and younger age of onset;

AD neuropathology present from 30s;

Incidence of dementia increases in 50s;

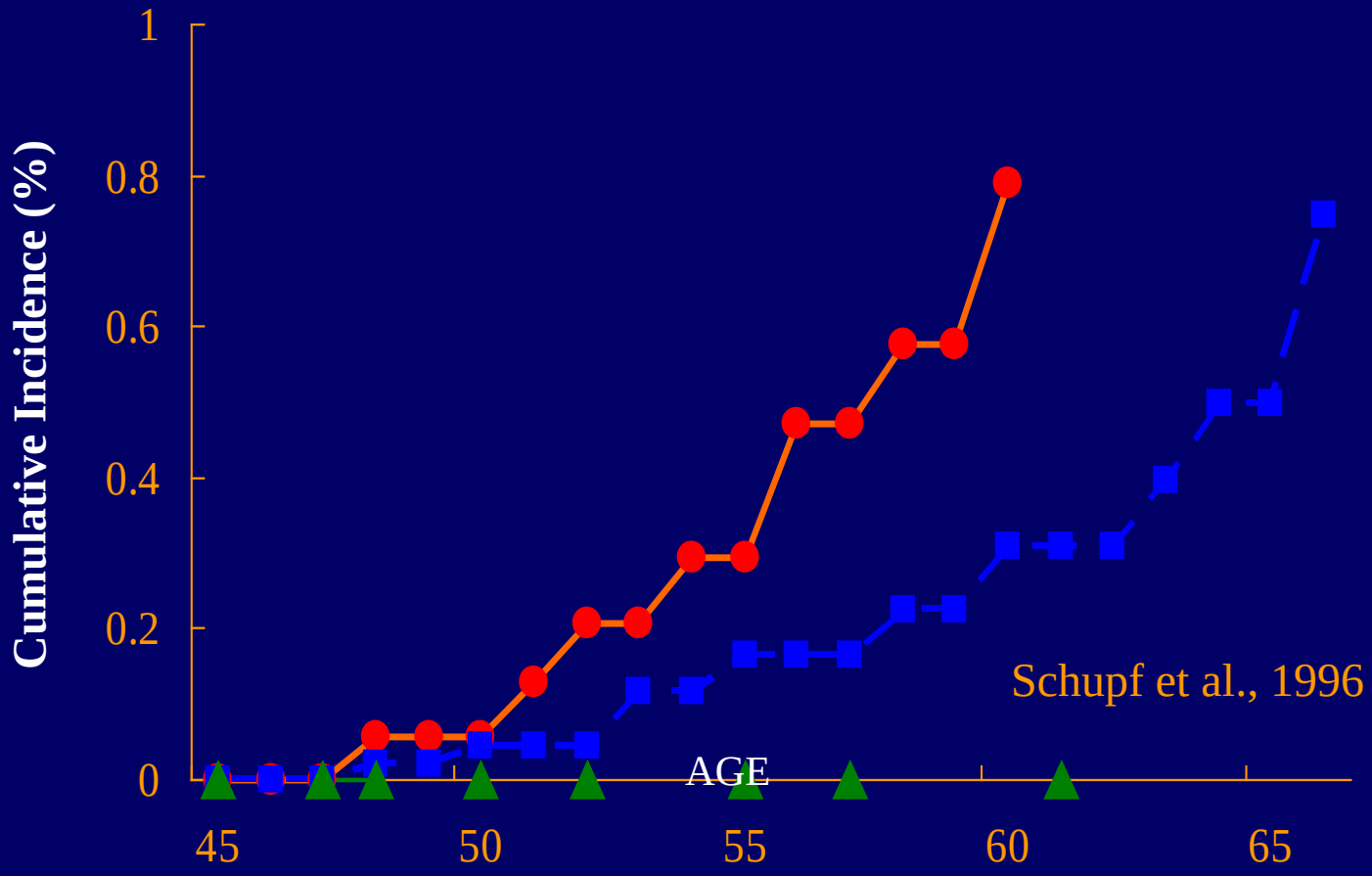
Substantial individual differences.

DS and AD:
Examining Individual Differences in Risk

DS and AD: Apolipoprotein E genotype:
(Schupf et al, 1996)

- Gene on chromosome 19;
  - Three common alleles -- e2, e3, e4
  - One allele is inherited from each parent
    - e3 is most common;
    - e2 is associated with decreased risk for AD;
    - e4 is associated with increased risk.

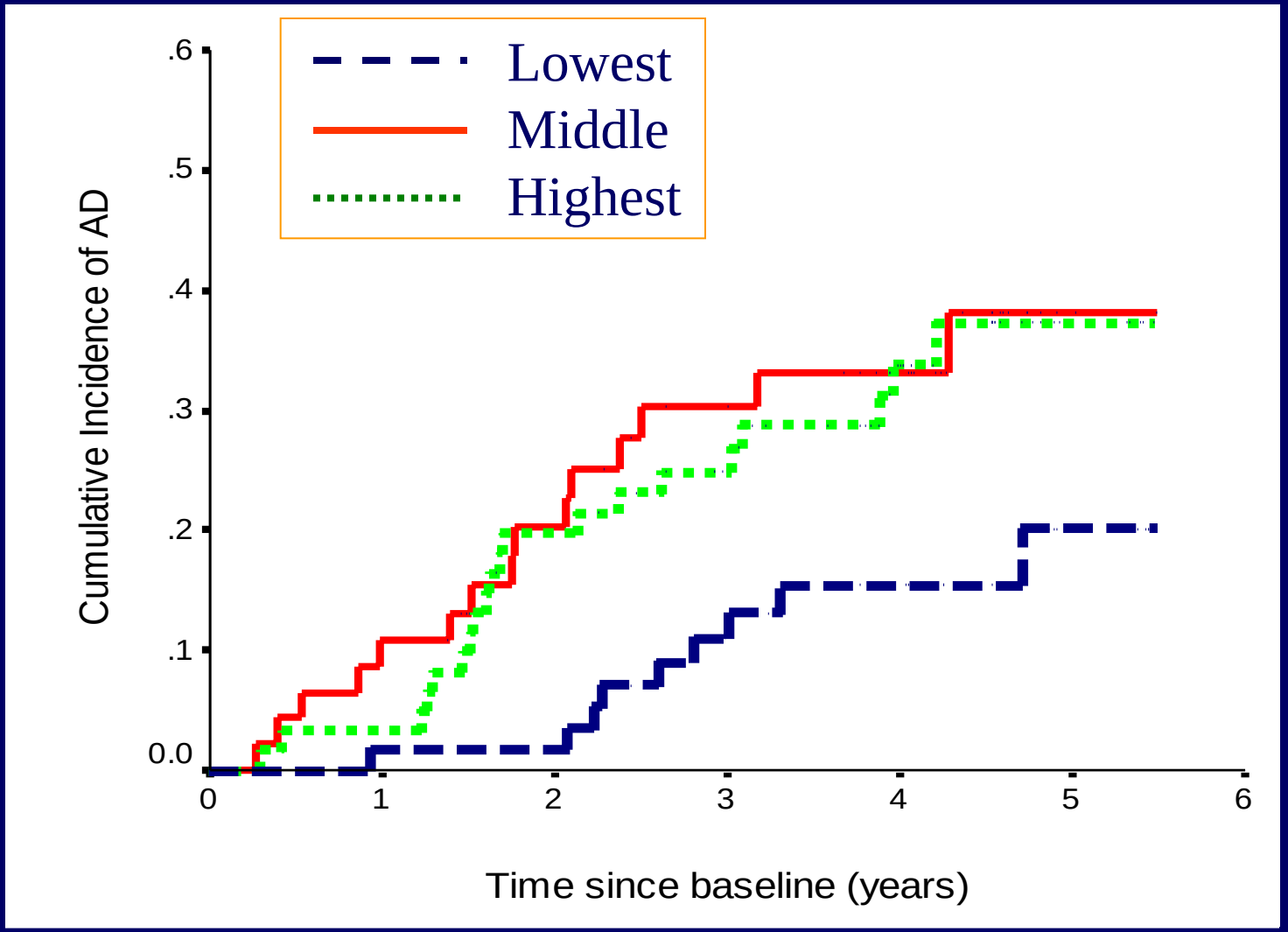
Early onset of AD in those with the e4 allele (Red) and delay in onset with the e2 allele (Green).



Down syndrome and amyloid beta-peptides

- Aβ 1-42 is the earliest form of Aβ deposited
  - Aβ 1-42 can be observed in diffuse plaques as early as 12 years of age
  - even in older DS (> 50 years), Aβ 1-42 is more abundant in plaques than Aβ (1-40)

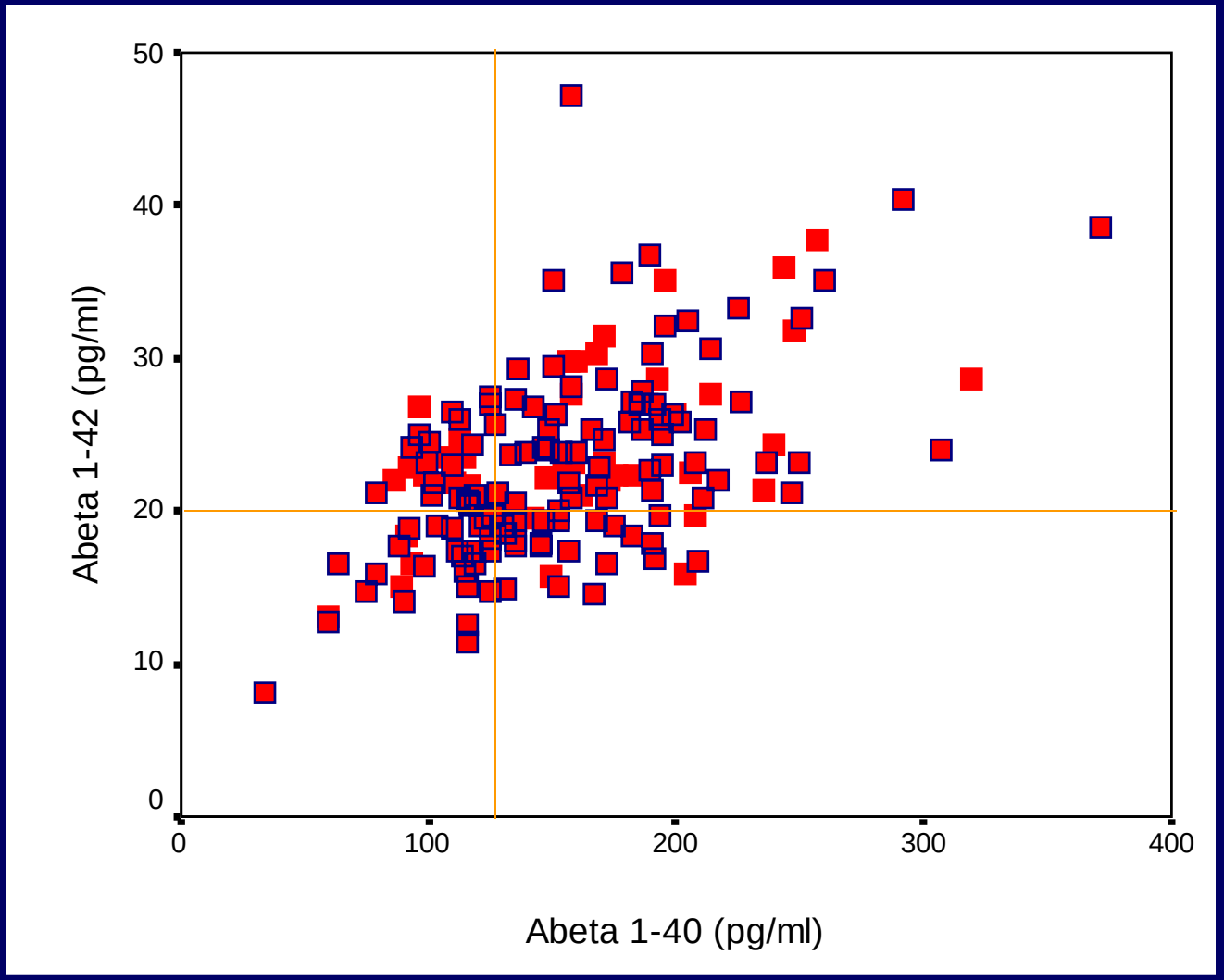
Risk of Dementia/AD by tertiles of Aβ 1-42 in blood: Incident cases



Schupf et al., 2007

Can Aβ 1-42 be used as a biomarker to inform diagnosis?

Aβ1-42 and Aβ1-40 for adults with (red) and without dementia



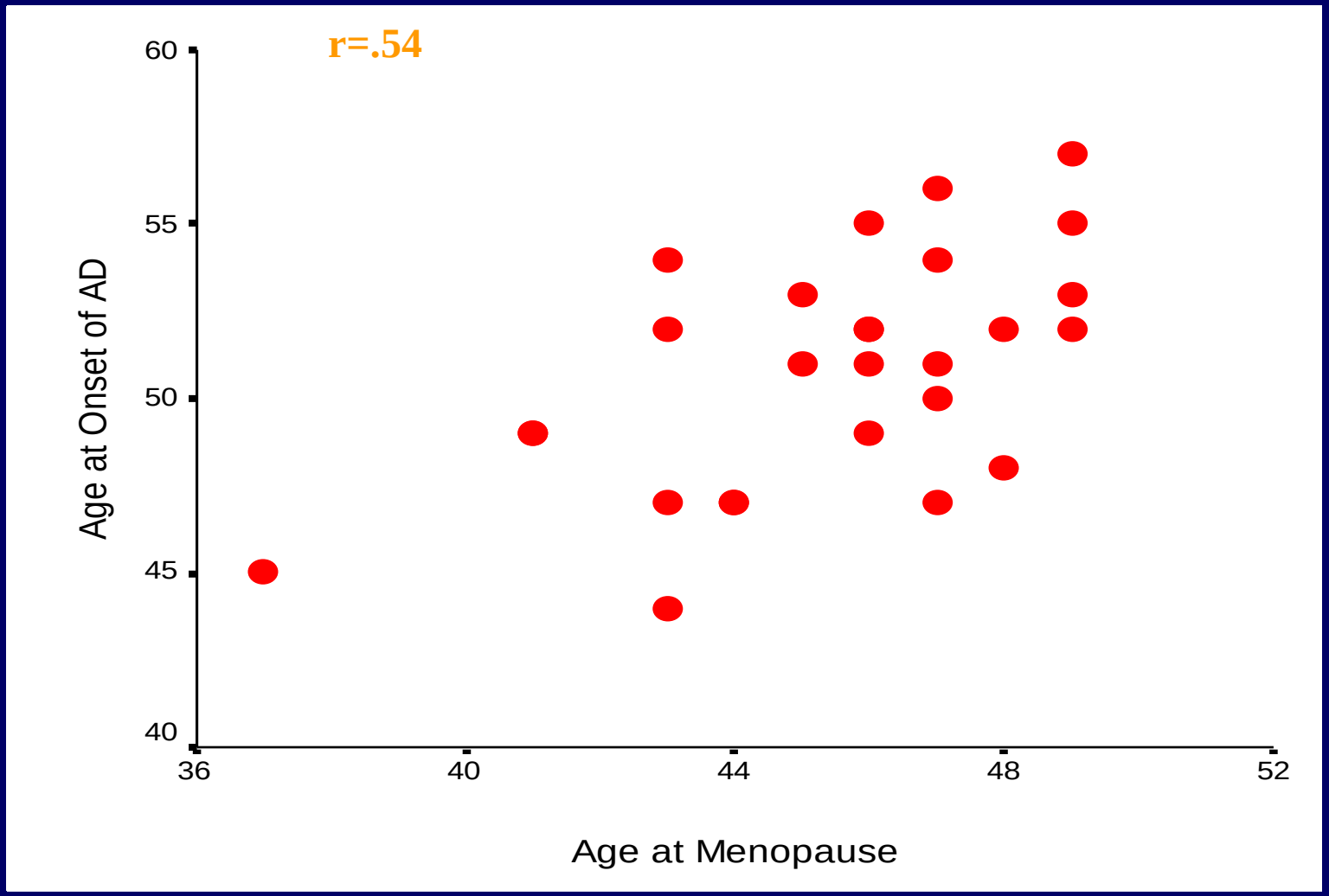
Estrogen and Alzheimer's disease (Schupf, et al.)

- Estrogen:
- Promotes the growth of cholinergic neurons and regulates the metabolism of APP to protect against Aβ deposition
- Seems to affect cognition in post-menopausal women
- Higher levels may delay or prevent the onset of AD, although large HRT trials have generated conflicting results.

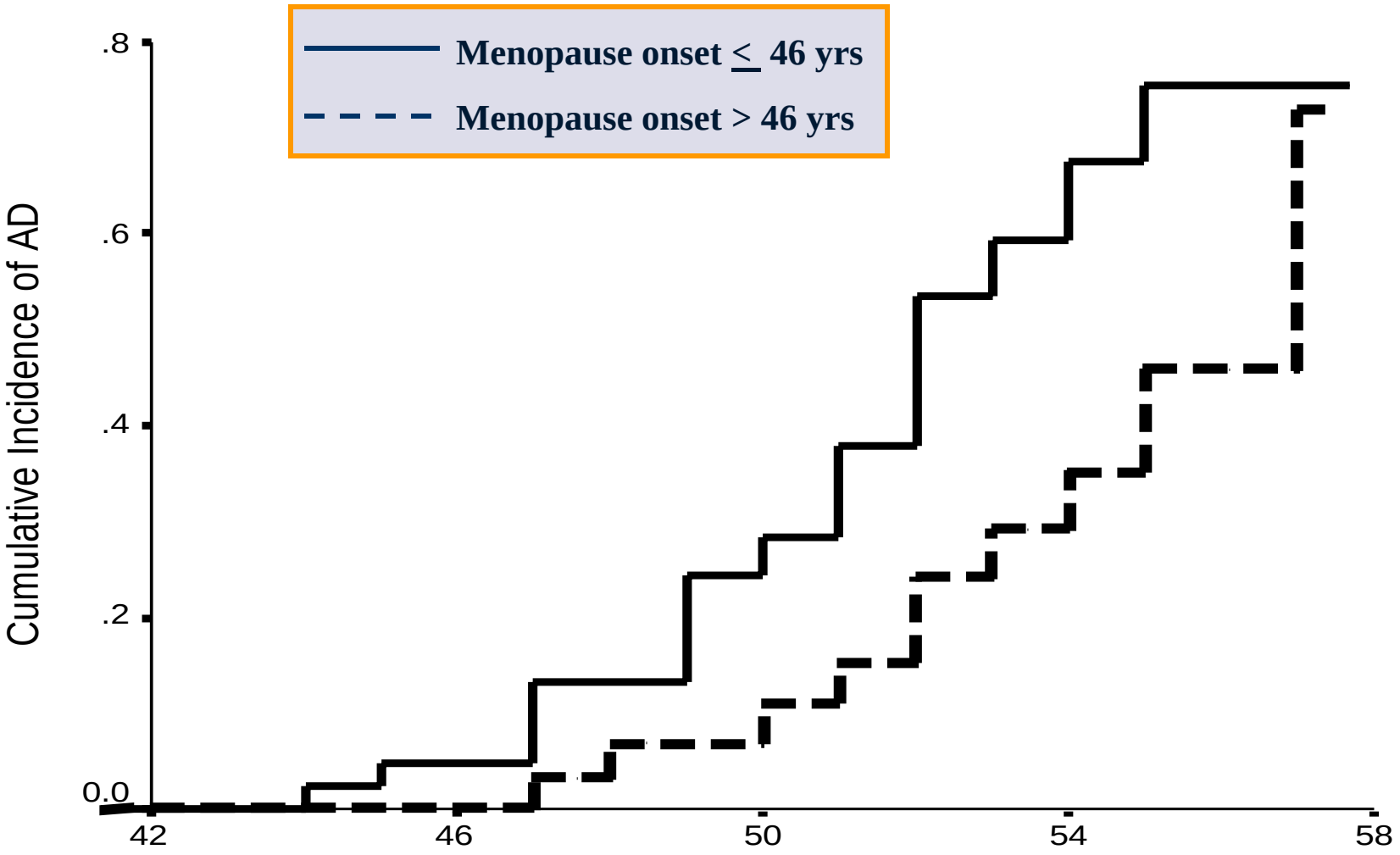
Menopause

- Menopause results in lowered bioavailability of estrogen
- Women with Down syndrome have early menopause
  - Median age of 46 (versus 51 for general population) with some variation

Onset of dementia by age at menopause for women with DS

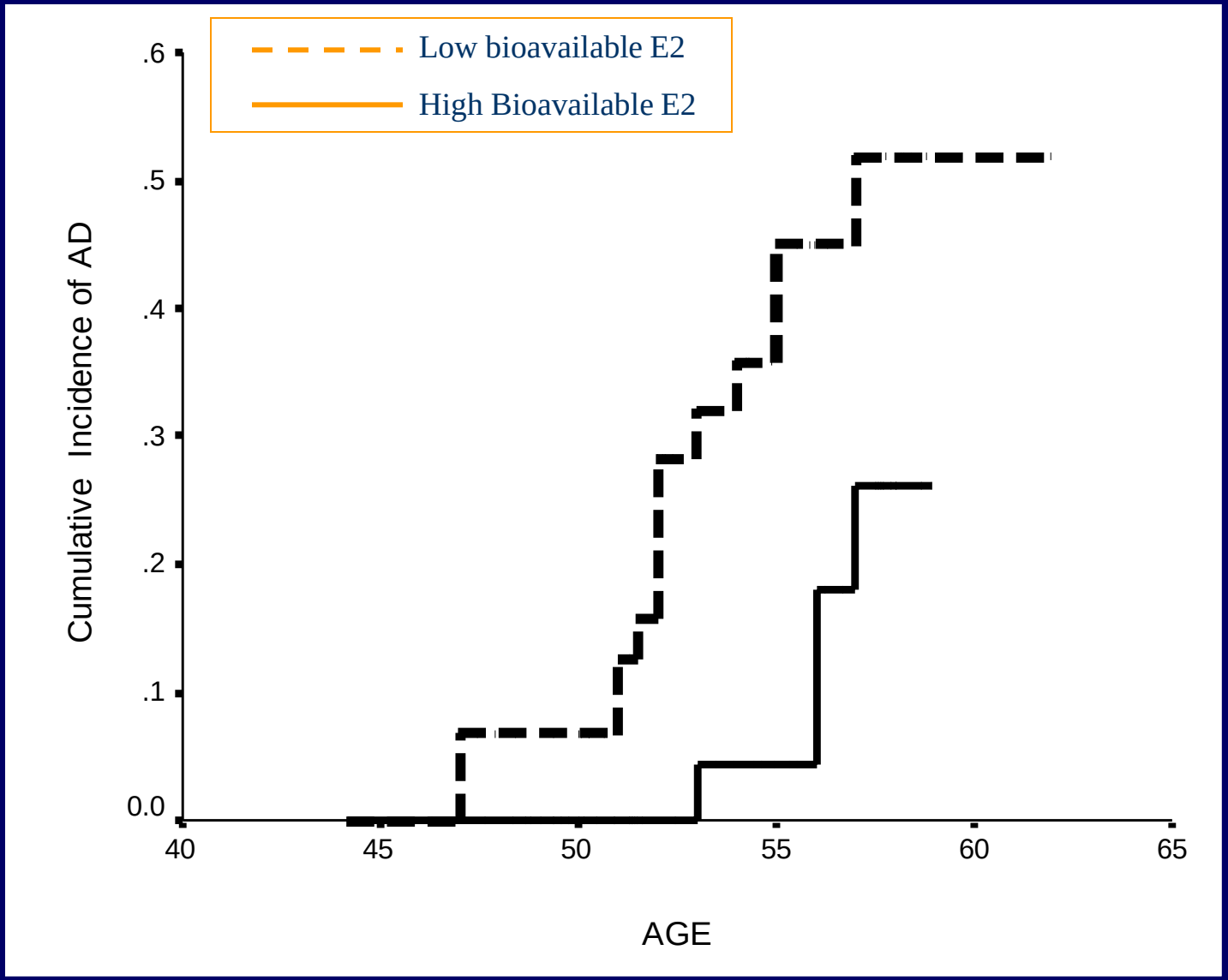


Incidence of AD by Age at Menopause in Women with DS



Schupf et al. 2003

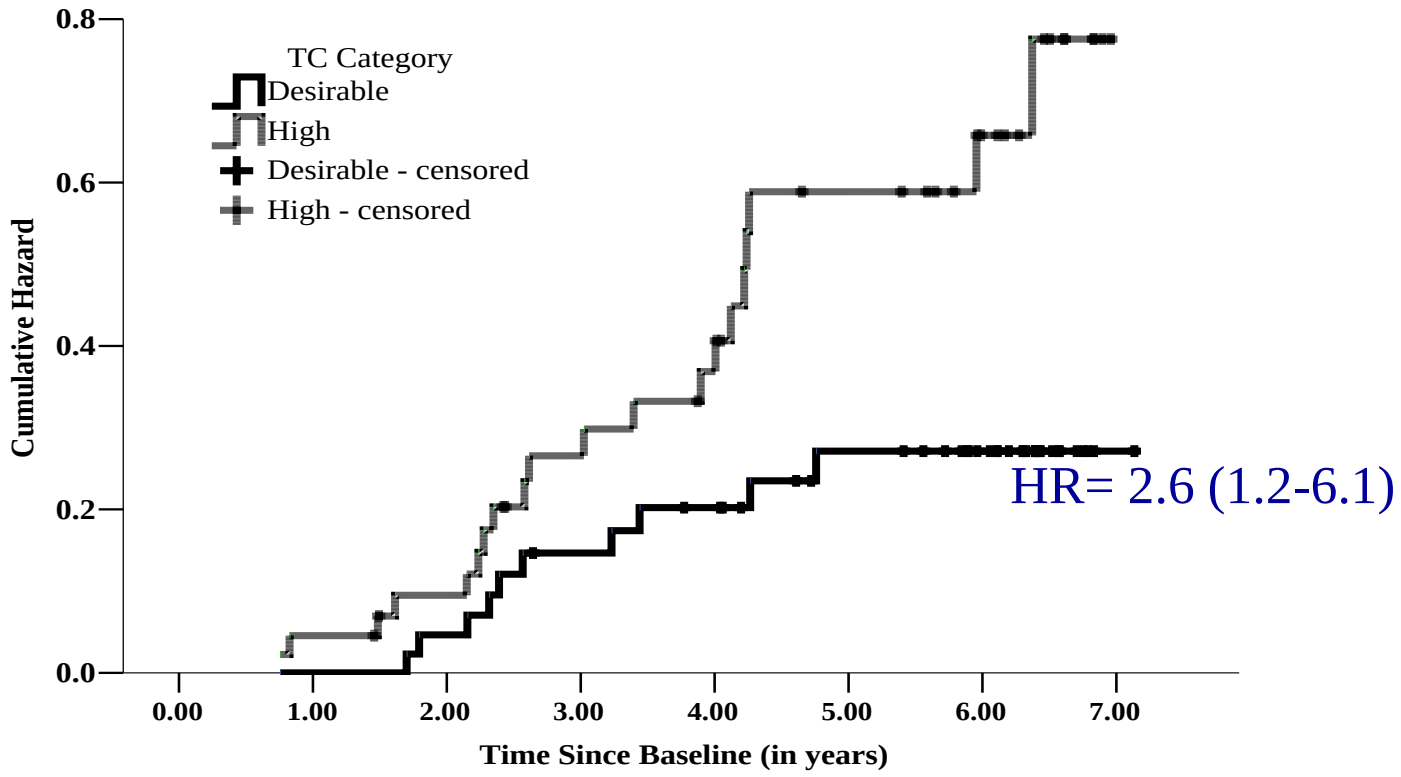
Incidence of Dementia Related to Estrogen Bioavailability



Cholesterol and AD (Zigman, et al.)

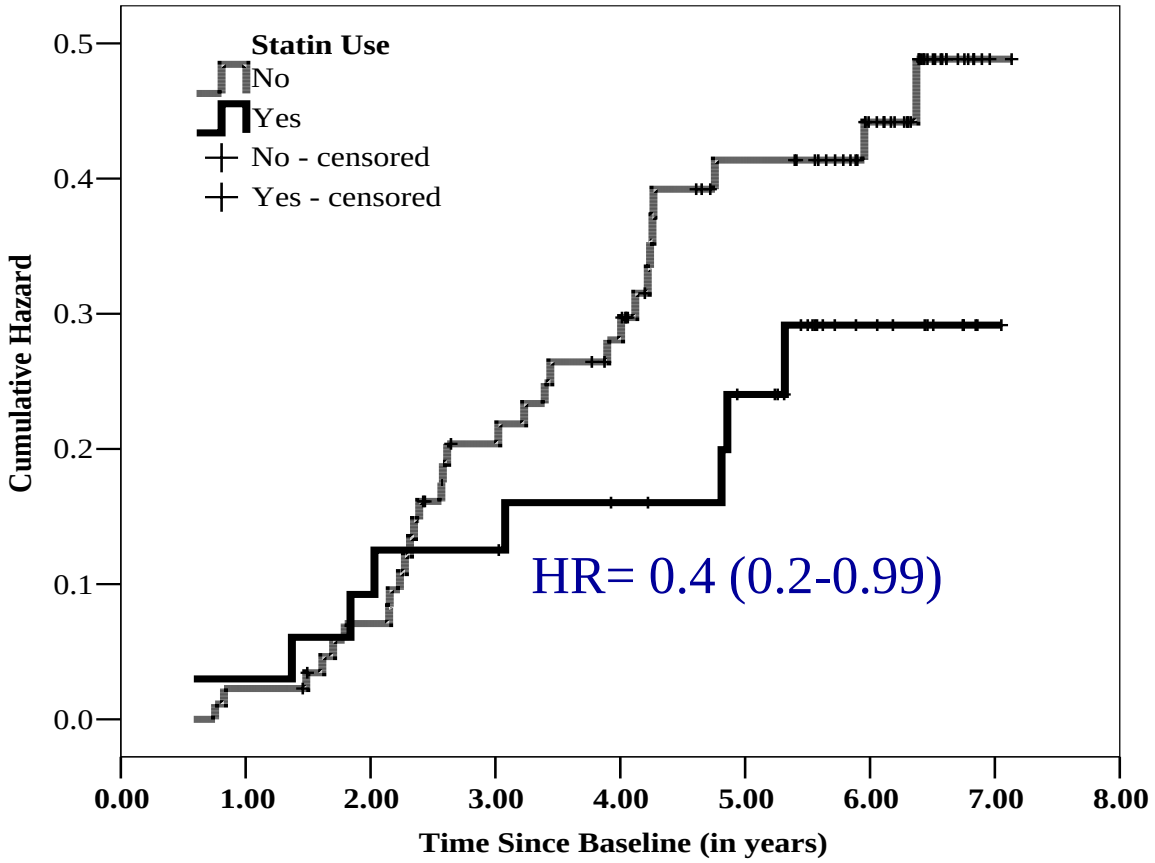
- Both the generation and clearance of Aβ are regulated by cholesterol.
- Elevated cholesterol levels increase risk in most animal models of AD.
- In the general population high total cholesterol levels during midlife increase risk of AD (a little), although findings have been inconsistent.
- What about for DS?

DS and AD: Cumulative incidence and cholesterol level



Zigman et al. 2006

DS and AD:High cholesterol and statin use



Conclusions

- Individual differences in risk for AD are evident among adults with DS, and we are beginning to understand contributing factors.
- There may be targets for intervention, and there is a pressing need for well controlled clinical trials specifically for adults with DS.

DS and AD: Individual differences in rate of progression

How Rapidly does Dementia Advance in Adults with DS, Gradually or Abruptly ("like falling off a cliff")? How much does the pattern vary across individuals?

We looked at 88 adults with dementia to see how long it took from diagnosis until they:

(a) developed seizures,

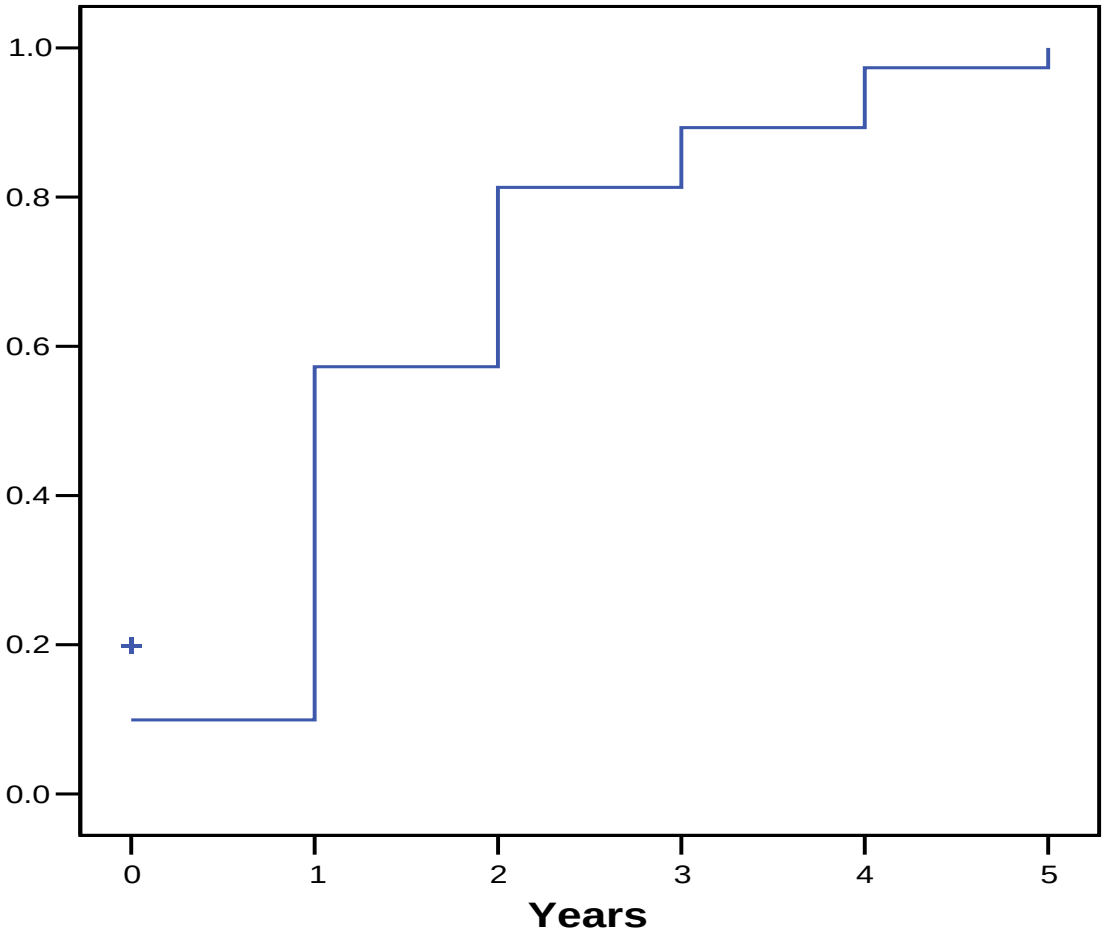
(b) moved to a more service-intensive program of supports, or

(c) died.

Qualification

- Clinicians vary in their diagnostic practices. This affects the precision of our estimates of time intervals.
- We’re working on something better, but for now this is what I have.

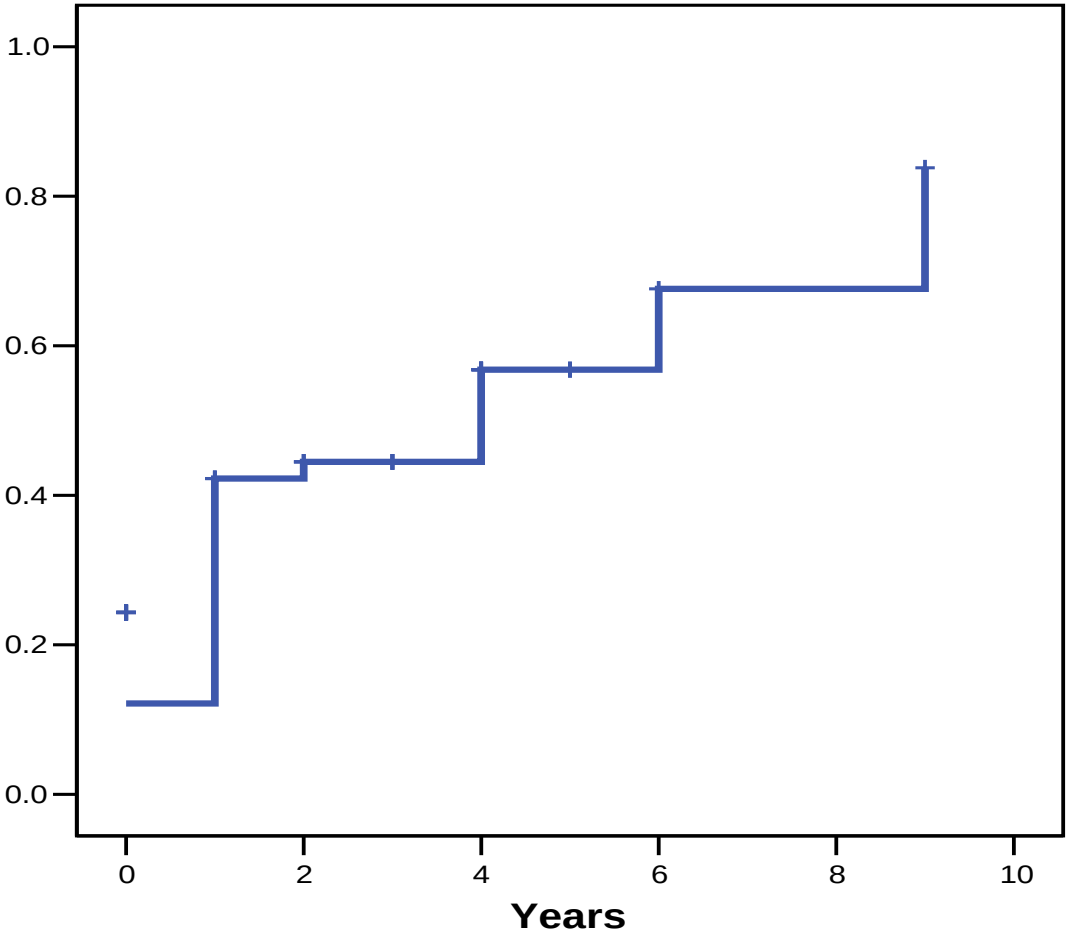
Duration Between the Earliest Symptoms of Dementia and Clinical Diagnosis for Adults with Down Syndrome



How quickly do seizures develop following diagnosis of AD?

- Of our 88 adults with Down syndrome who were demented:
  - 5 had a history of seizures from before the age of 40;
  - 44 (52%) developed seizures following onset of dementia;
  - 39 (44%) have, as yet, no history of seizures.

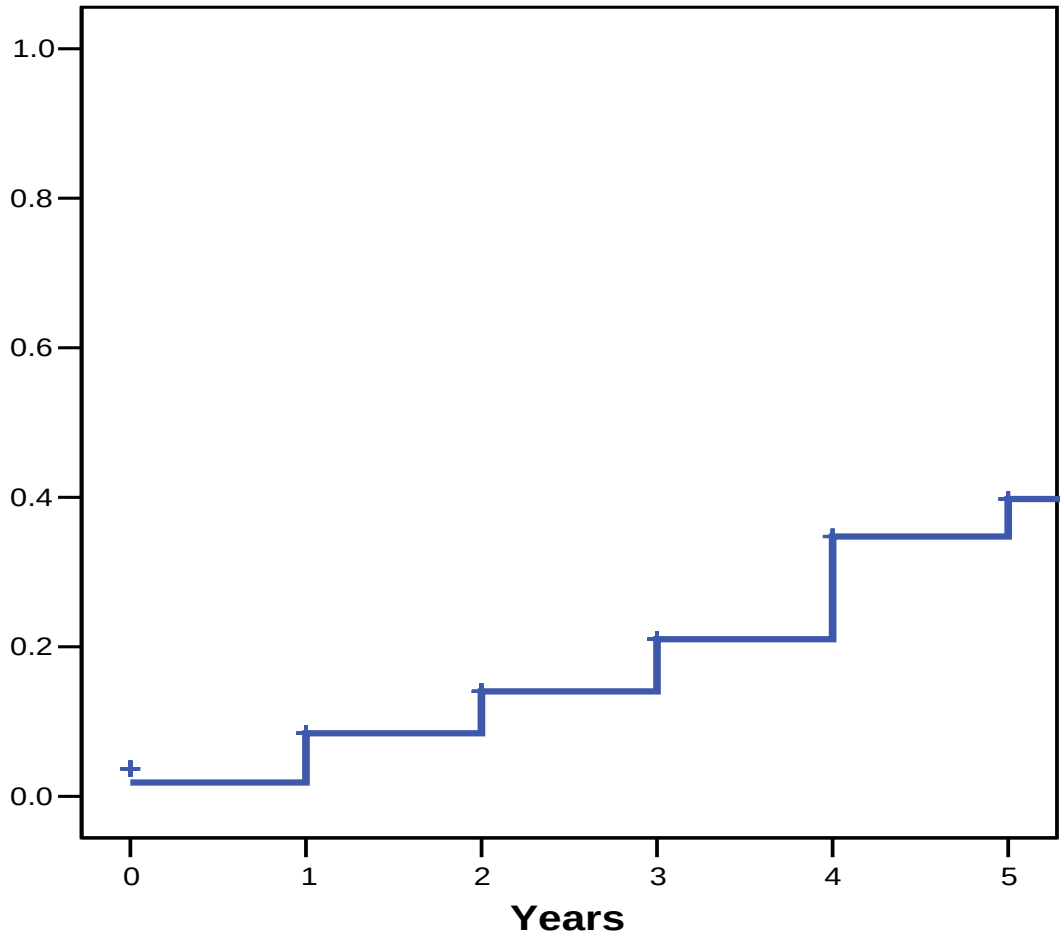
Development of Seizures Following A Diagnosis of Dementia in Adults with Down Syndrome



How long will it be before a move will have to be made to a more service intensive program?

- Of the 88 adults with Down syndrome and dementia, 8 were in nursing homes the first time we saw them:
  - 20 individuals moved to a more service intensive program following the onset of dementia.

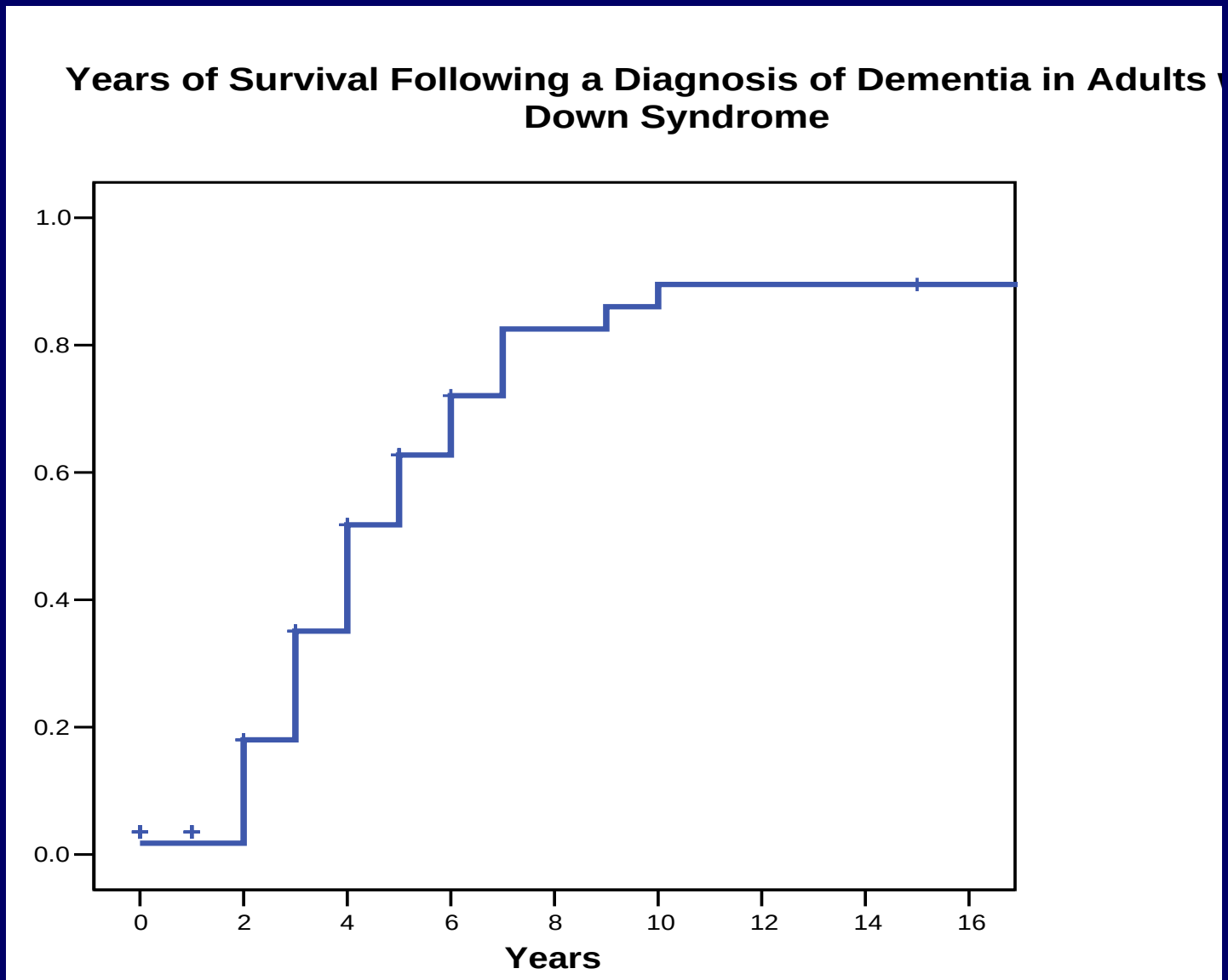
Movement to a More Intensive Program of Services Following a Diagnosis of Dementia for Adults with Down Syndrome



How does Alzheimer's Disease Affect Survival of Adults with Down Syndrome?

45 adults with Down syndrome and dementia have died since the beginning of our study and the time of this analysis. As expected, dementia is associated with increased mortality risk, reducing survival by 5-10 years.

What is life expectancy following diagnosis of dementia, and is it comparable to what we see in the general population?


Years of Survival Following a Diagnosis of Dementia in Adults
Down Syndrome
1.0
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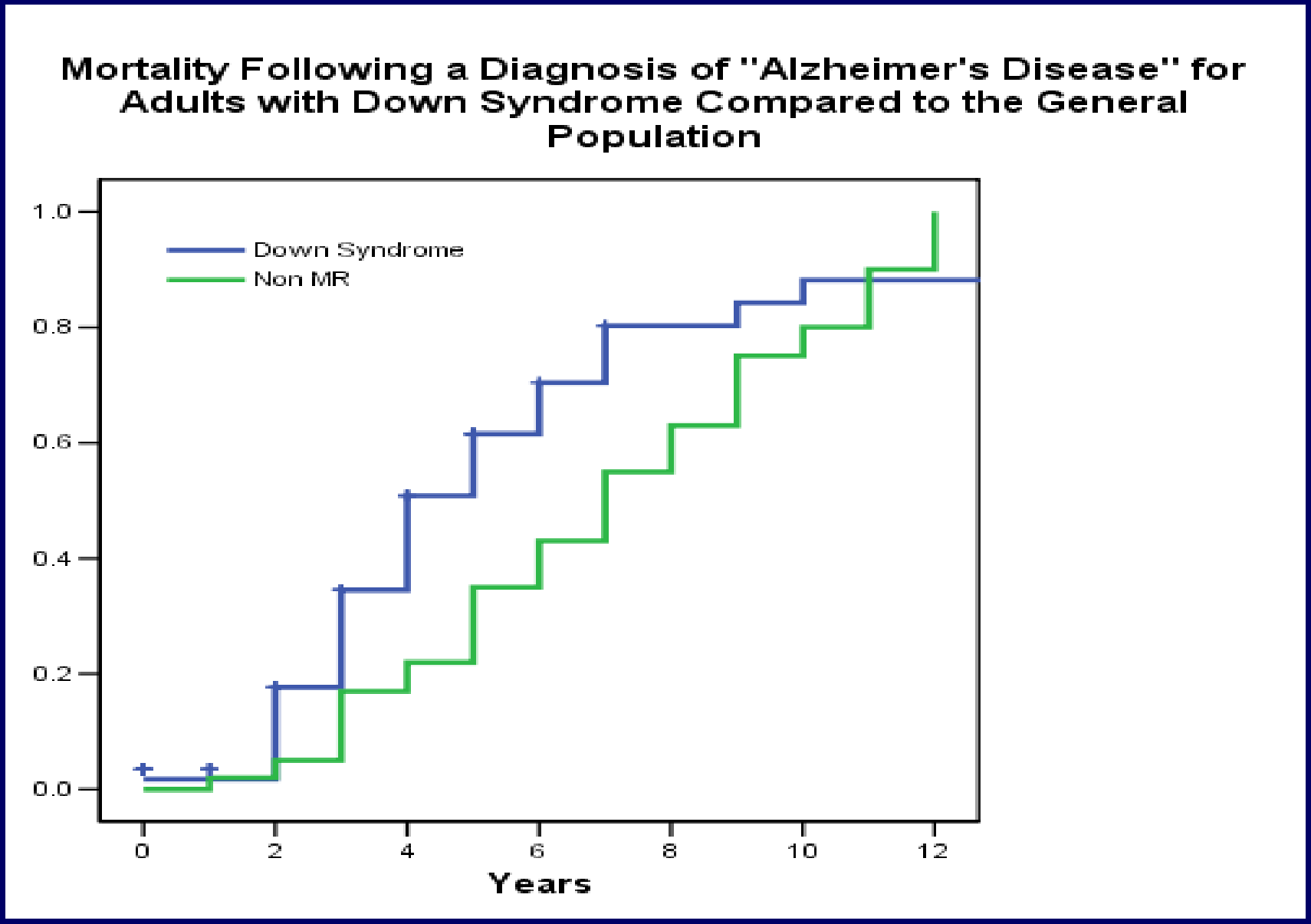
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
Years



Non MR data simulate Stern, et al. (1997). *JAMA*, *277*, 806-812.

Factors NOT Strongly Related to Rate of Progression

- Age at diagnosis of AD
- ApoE genotype
- Gender
- Severity of ID

- Note: These results are based on preliminary analyses of relatively small subsamples and must be interpreted cautiously.

Conclusions

Alzheimer's disease has devastating consequences for any affected individual. For adults with DS, rate of progression seems slightly increased, but, nevertheless:

- Mortality risk is low during the first few years following diagnosis.
- Rate of progression varies substantially among individuals.
- Anecdotal reports of adults with Down syndrome "falling off a cliff" reflect unusual cases.
  - In such cases, severe symptoms may be due to some additional, perhaps treatable problem.

DS and AD: Gaps in Knowledge

- There are no gold standard methods for evaluating symptoms of dementia.
- Nor are there criteria for defining dementia quantitatively or clinically.
- Standards for diagnosis in early stages of AD are needed, as are operational definitions of “mild cognitive impairment - MCI.”

Paradox

If all adults with DS in their mid-30s or older have key neuropathological hallmarks of AD, and

If most of these adults have no dementia,

Then the current “gold standard” for diagnosis of AD is meaningless for this population.

We need to develop valid diagnostic standards, and we need to determine what specific neuropathology actually causes dementia.

Gaps in Knowledge

- We need to understand why dementia occurs well after substantial neuropathology is present.
- We need to understand why some individuals with Down syndrome are far more vulnerable than others.

Gap in Knowledge

All current knowledge of “old age” reflect experiences of adults with DS born when they weren’t expected to survive past childhood. Are they therefore the fittest among their generation?

We need to learn how to anticipate cohort effects that could be very substantial.

Huge Gap in Knowledge

We need to discover how to treat and prevent AD (as well as other old-age associated conditions causing dementia).

Some resources that would be very helpful for future research

- Registry of possible research participants
  - Consensus core dataset
- Tissue repository
  - Clinically well characterized cases
  - Variety of tissues
  - System to encourage postmortem organ donations
- Support of collaborations across institutions.

My Co-Investigators

IBR: W. Zigman, D. Devenny, S. Krinsky-McHale, S.Y. Kim, P. Kittler, P. Mehta, E. Jenkins, W.T. Brown, M. Vilenov, C. Dobkin, N. Zhong, Y.W. Hwang, K. Dowjat, W. Kaczmarski, C.X. Gong, T. Adayev, M. Barua, H. Imaki, J. Wegiel, I. Kuchna, K. Nowicki.

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