Down Syndrome –
Aging & Alzheimer's Disease Study

UK

# What do we know about Alzheimer's and Down syndrome?

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ADS

# Down Syndrome

CLASSICS IN
DEVELOPMENTAL MEDICINE
NO. 5

(Series Editor: Ross G. Mitchell, M.D.)

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 HOSPITAL; AND PHYSICIAN TO THE EARLSWOOD ASYLUM

With a Foreword by
*Ann Gath*

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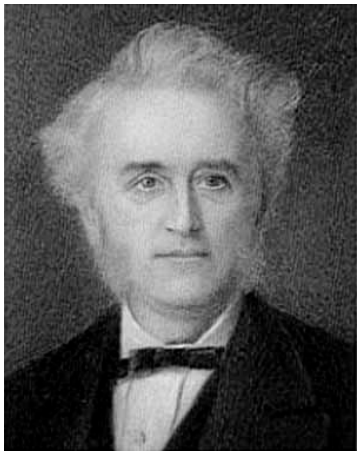
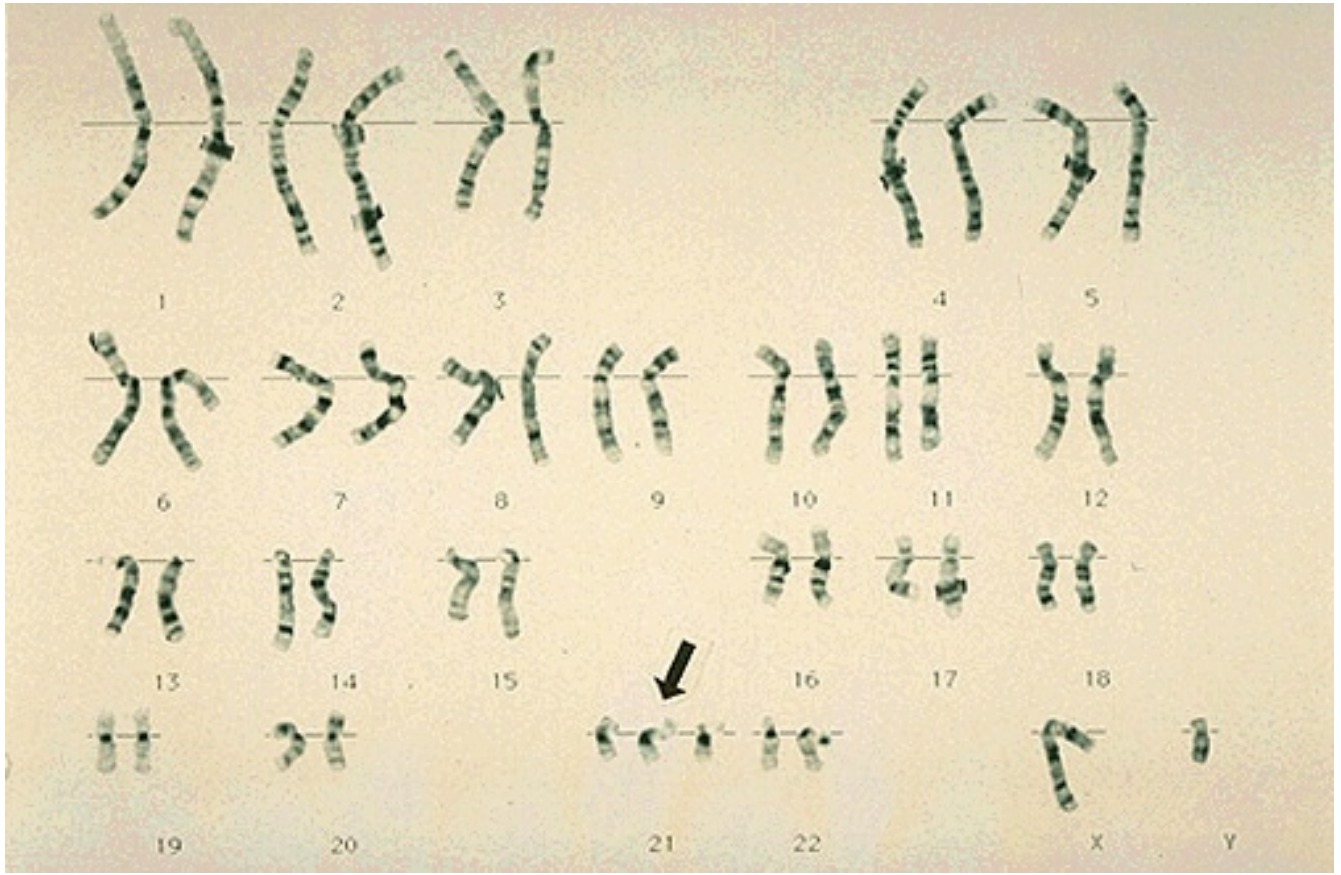
1887



# What causes Down syndrome?

LeJeune, 1959



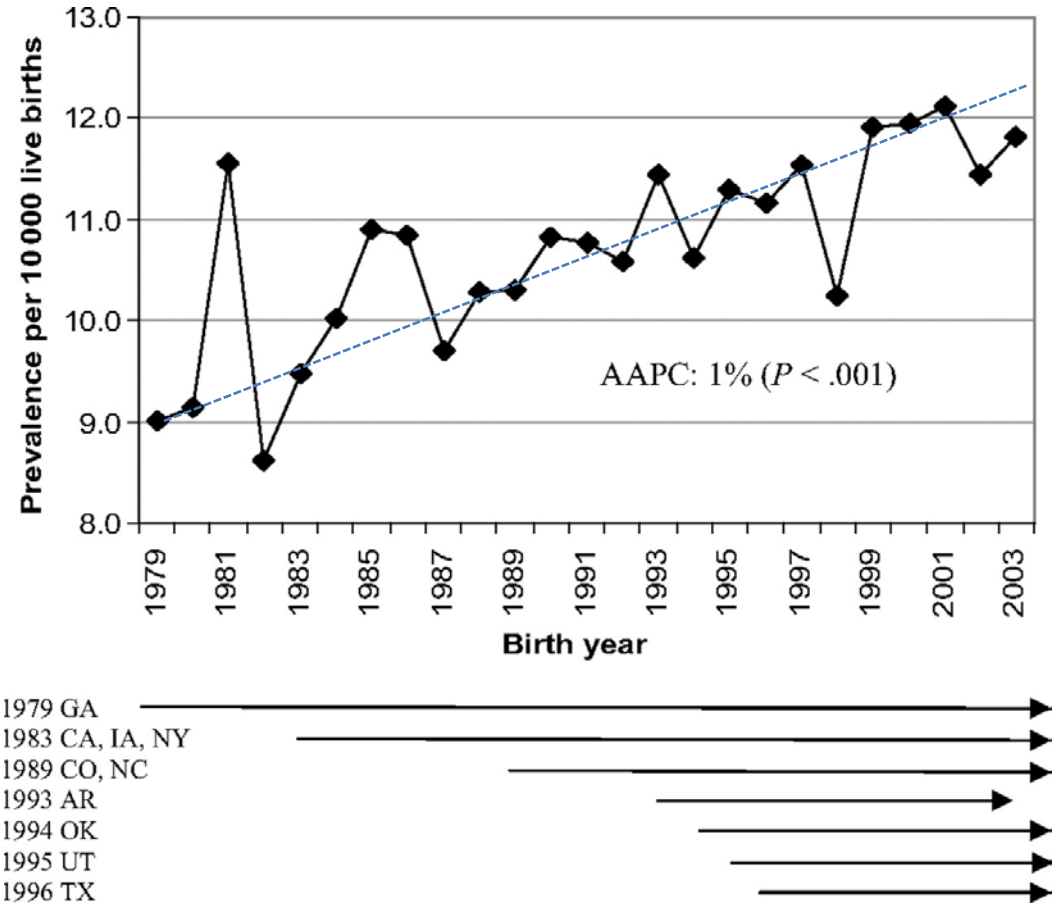

95% of people with Down syndrome have a full extra copy of chromosome 21
3-4% have a part of chromosome 21 triplicated
1-2% are mosaic

# Down Syndrome in the US

- Down Syndrome (DS) is the most common cause of intellectual disability.
- There are more than 5,000 DS births/year in the USA (2009).
- After age 35 years, mortality rates double every 6.4 years vs. 9.6 years for non DS. (Strauss & Eyman, 1996)
- Average life expectancy has improved from 25 years in 1983 to 60 years today.
- Current prevalence rates?

# Overall prevalence of DS among live births in 10 US regions, 1979-2003

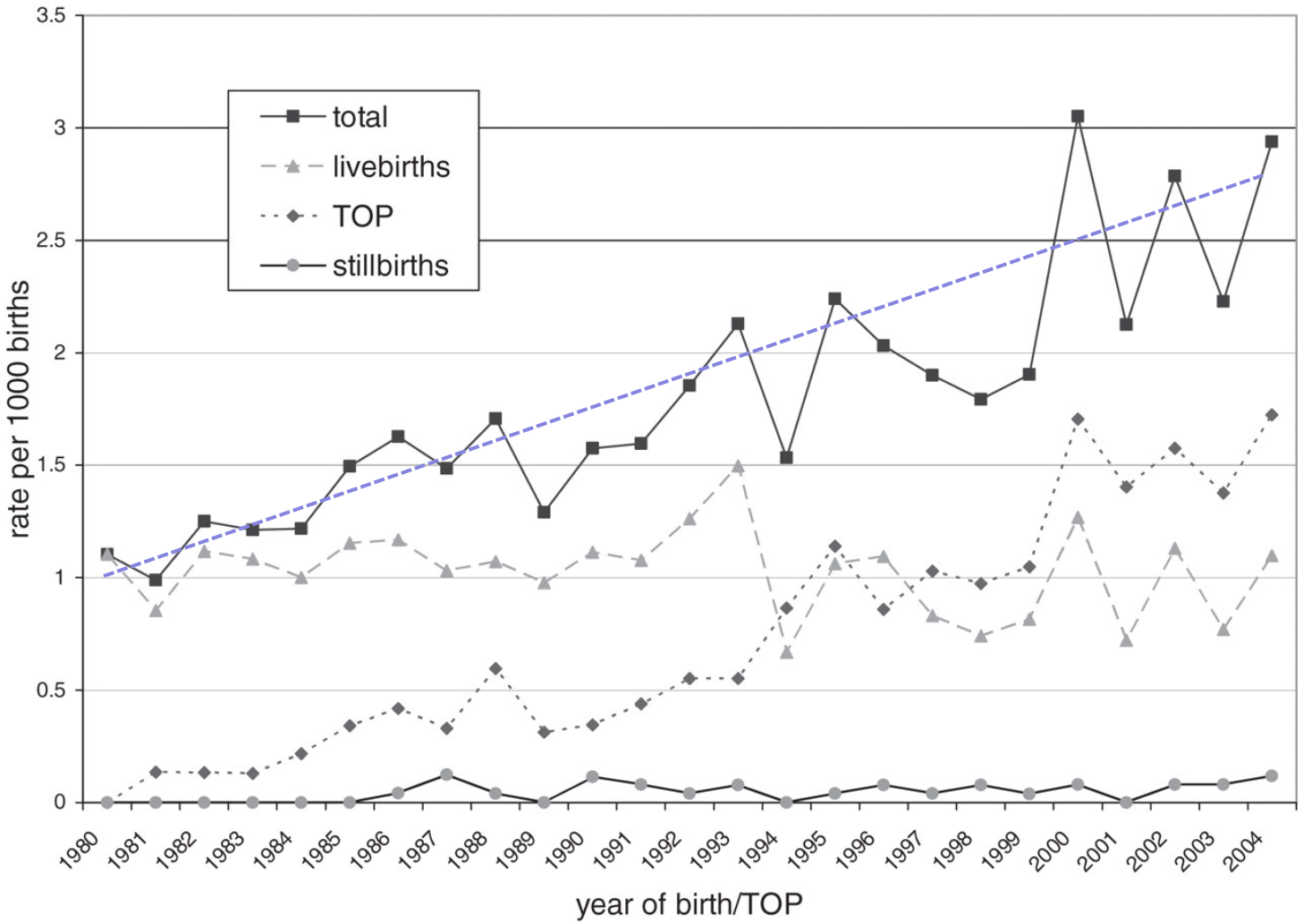
From 1979 through 2003, the **prevalence of DS at birth increased by 31.1%**, from 9.0 to 11.8 per 10,000 live births in 10 US regions. In 2002, the prevalence among children and adolescents (0–19 years old) was 10.3 per 10,000.




Shin, M. et al. Pediatrics 2009;124:1565-1571


PEDIATRICS®

**Down syndrome births, stillbirths, and terminations of pregnancy (TOP) per 1000 births in Western Australia 1980–2004.**

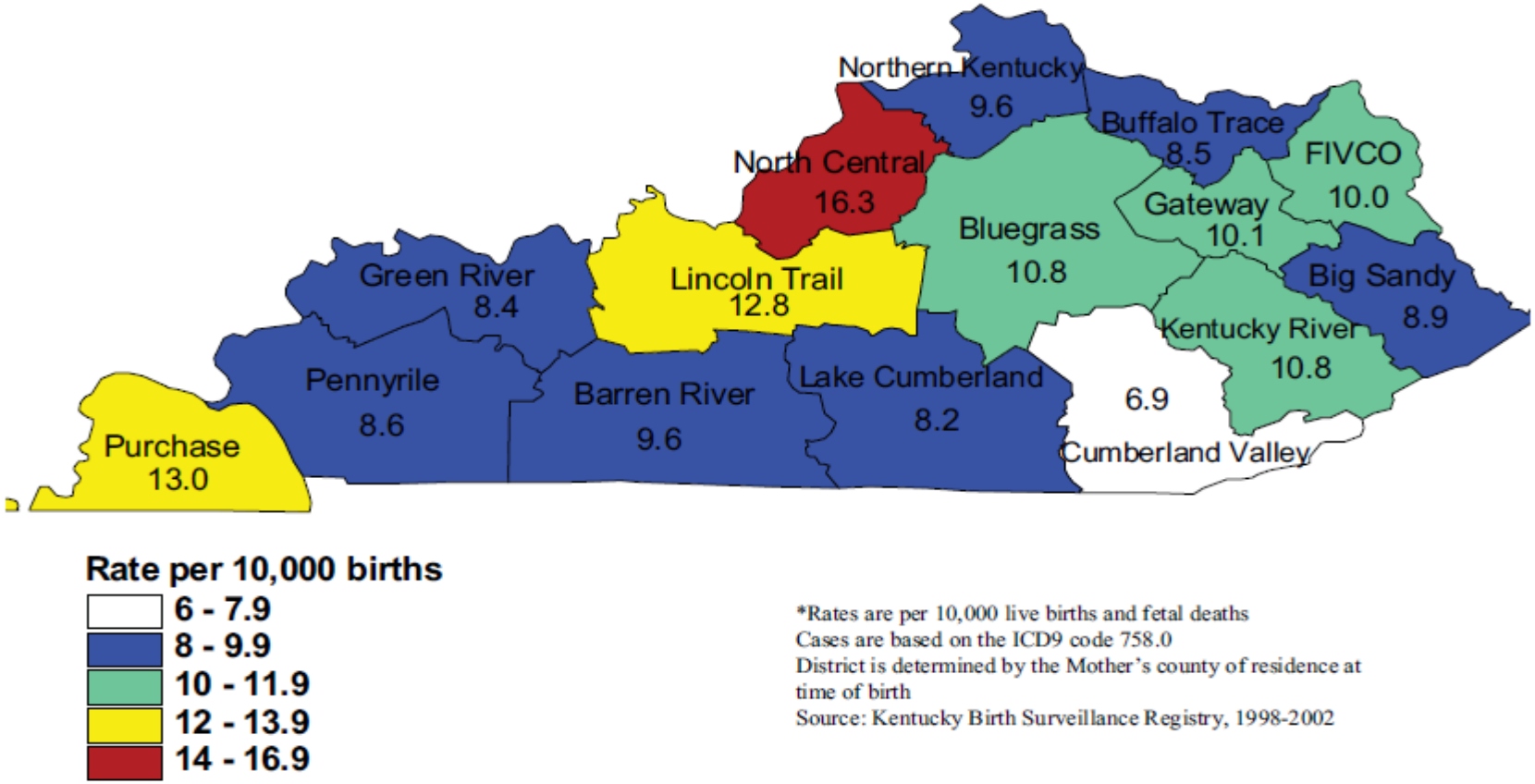



**Bittles A H et al. Eur J Public Health 2007;17:221-225**



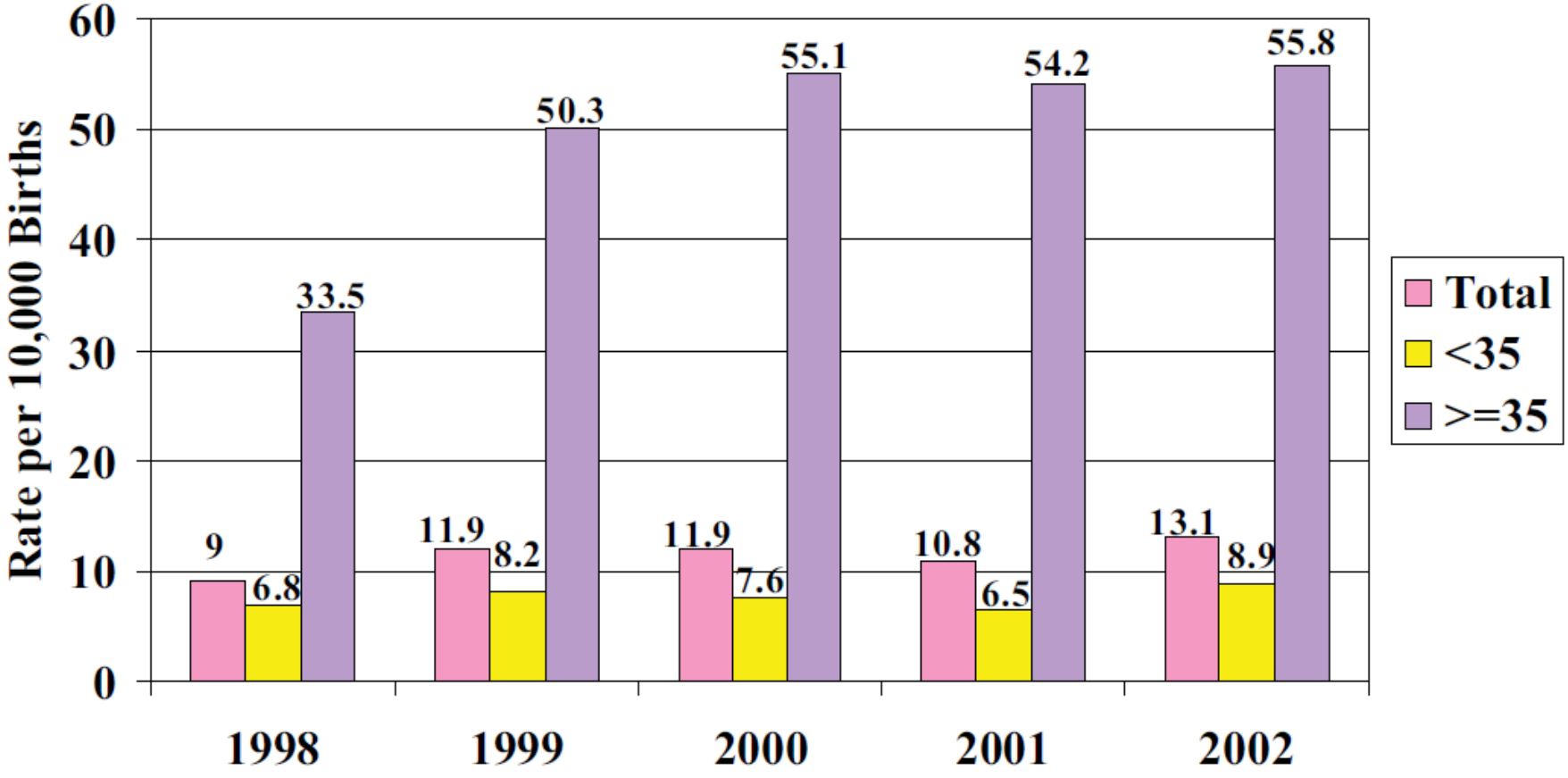
EUROPEAN JOURNAL OF PUBLIC HEALTH

# Rates* of Down Syndrome Among Kentucky Residents by Area Development District; 1998-2002




| Down syndrome (per 10,00 live births): | Annual Cases | Prevalence |
|---|---|---|
| KENTUCKY | 77 | 13.78 |
| USA | 5,132 | 12.78 |

# Rates* of Down Syndrome by Maternal Age** Among Kentucky Residents, 1998-2002; Kentucky Birth Surveillance Registry Data

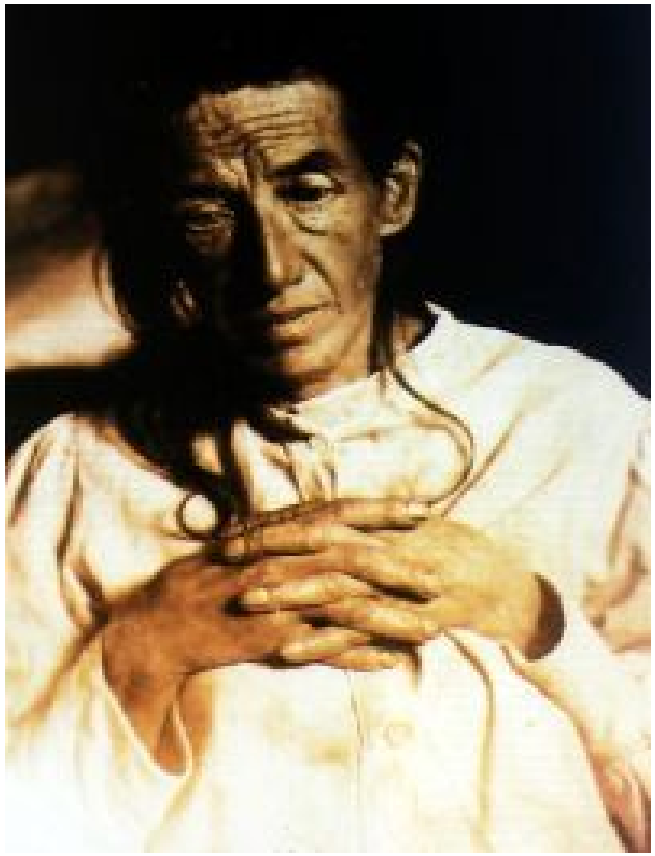


Adults with Down syndrome are at a higher risk for developing Alzheimer's disease than people in the general population.

Why?

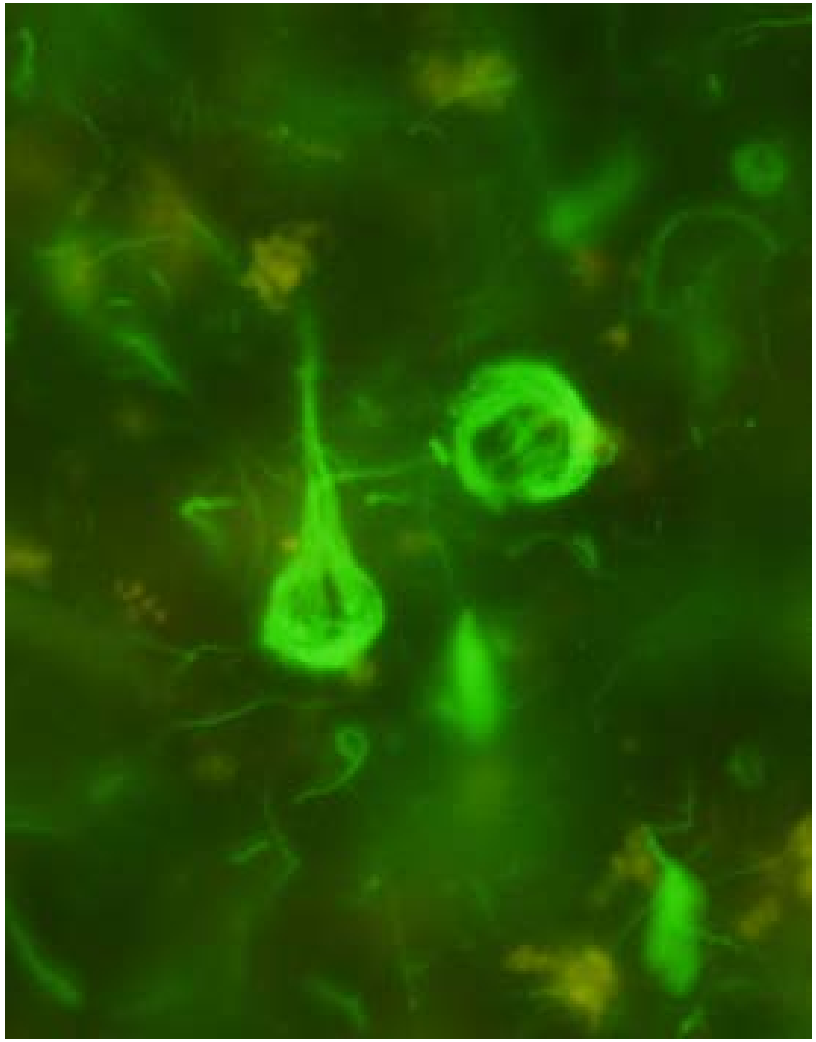
# Alzheimer disease

- Progressive dementia
- Senile plaques
- Neurofibrillary tangles
- Extensive neuronal loss
- Final diagnosis cannot be made until autopsy



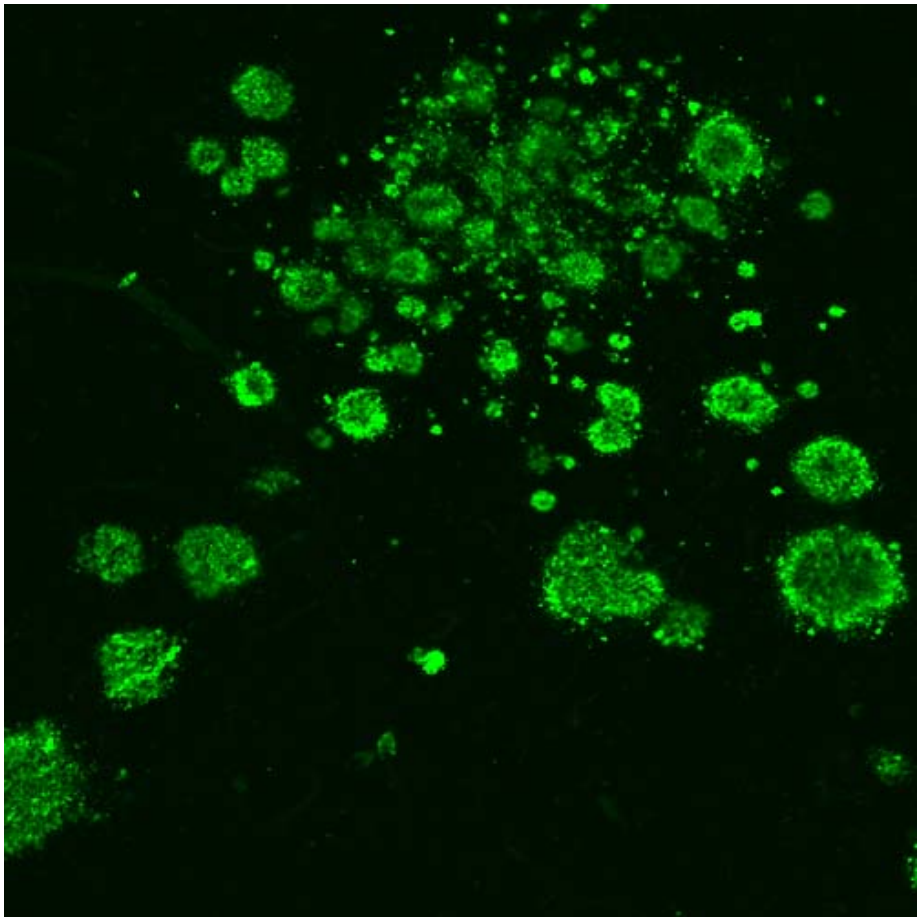
Frau D (1901-1906) Alois Alzheimer's first patient

# Neurofibrillary Tangles - tau



- Contain hyperphos-phorylated tau protein
- Tau protein is coded on chromosome 17
- Forms into paired helical filaments
- Impairs cytoskeletal transport

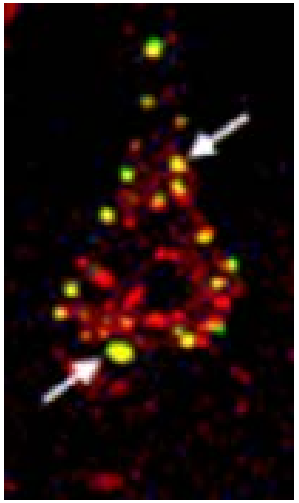
# Senile plaques - Aβ

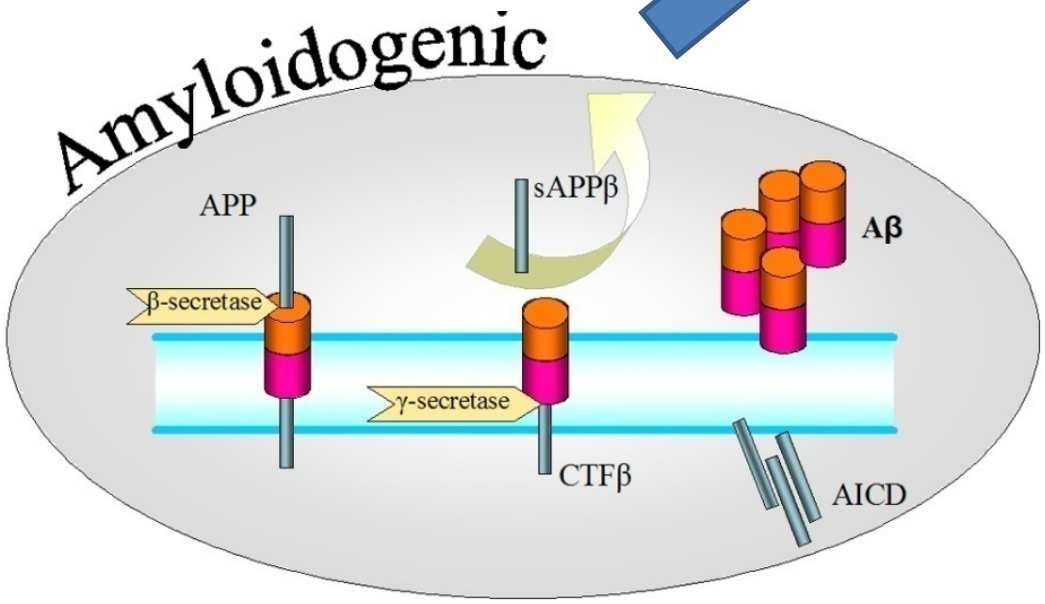


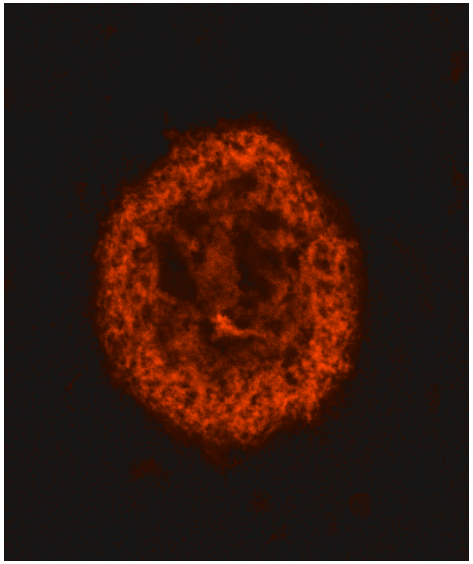
- Several familial types of AD are linked to an increase in the production of beta-amyloid
- The protein is very damaging to neurons
- Beta-amyloid hypothesis (John Hardy)

# Where do plaques come from?

- Beta-amyloid protein (42 amino acids long) comes from a longer protein called amyloid precursor protein (~750 amino acids long)



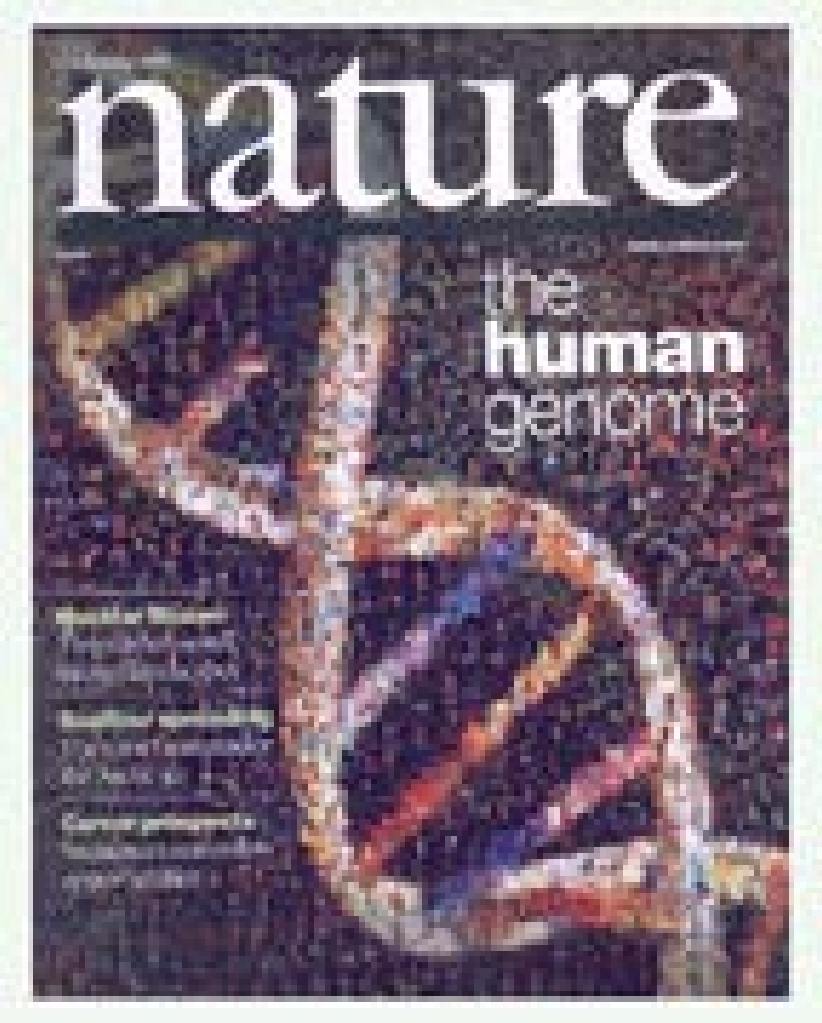


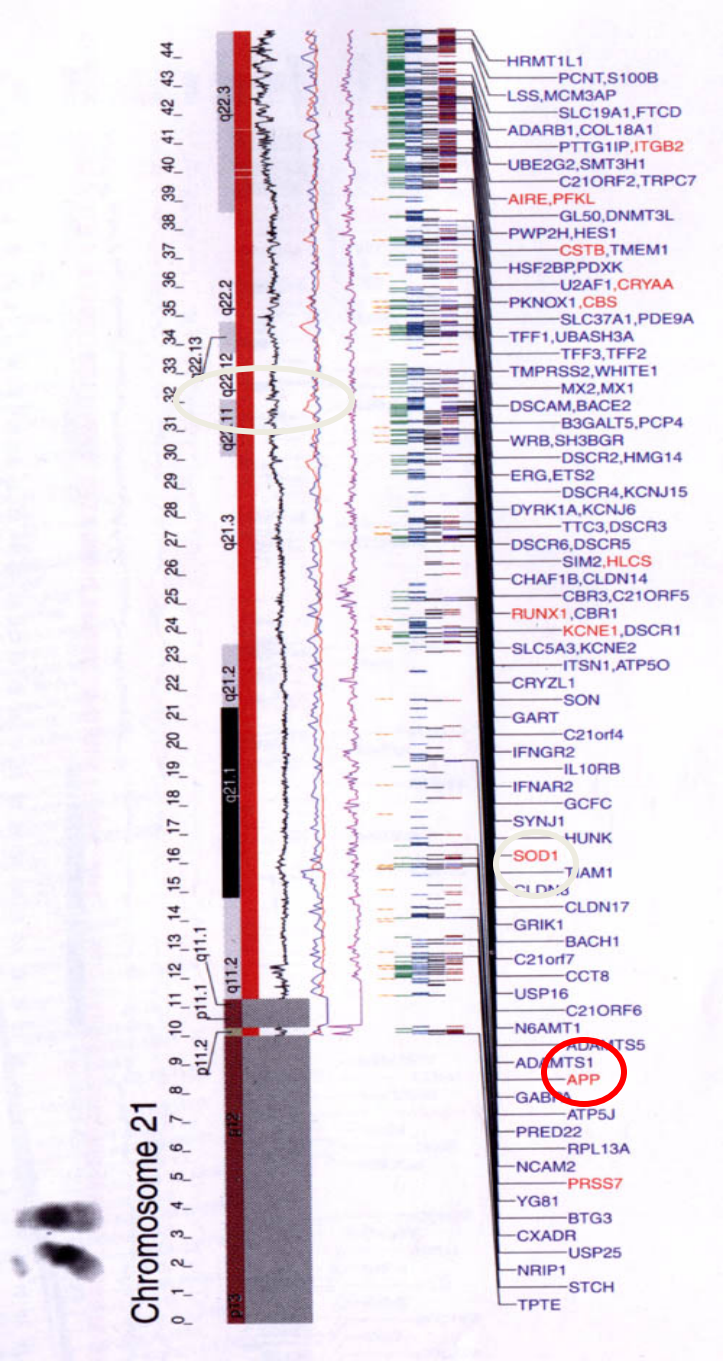



Where is the gene for the amyloid precursor protein?

# Chromosome 21

2001

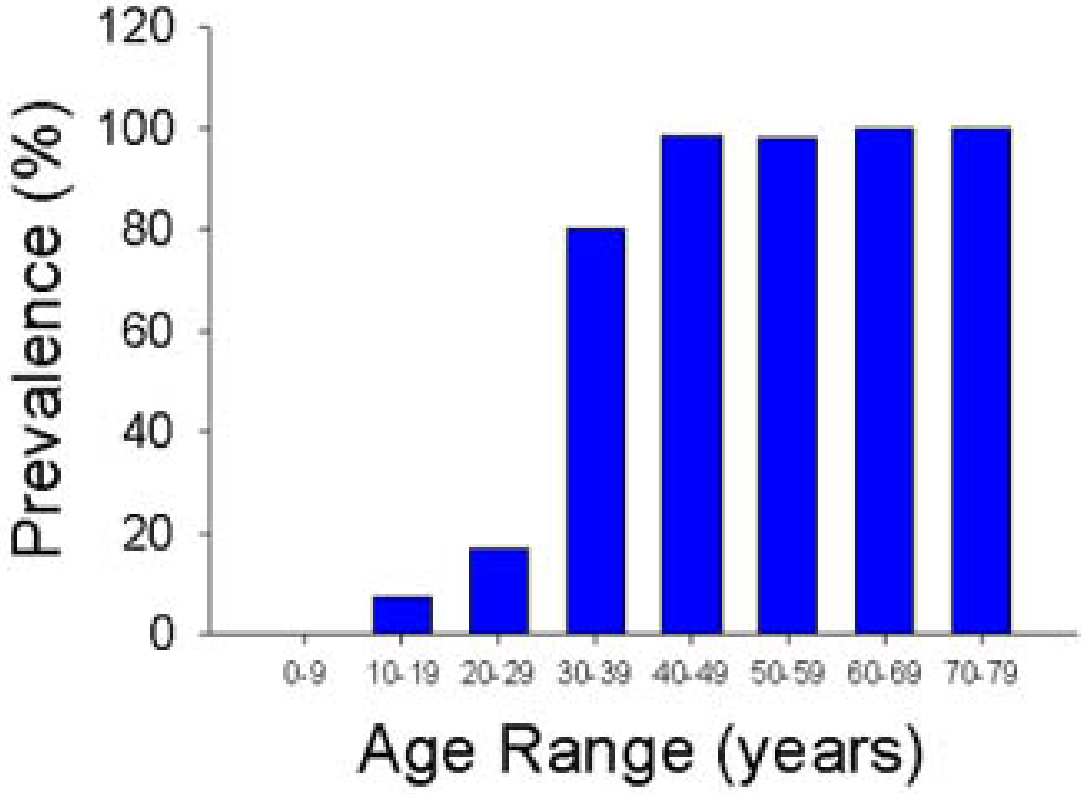


Virtually all adults with DS over the age of 40 years have sufficient neuropathology for AD

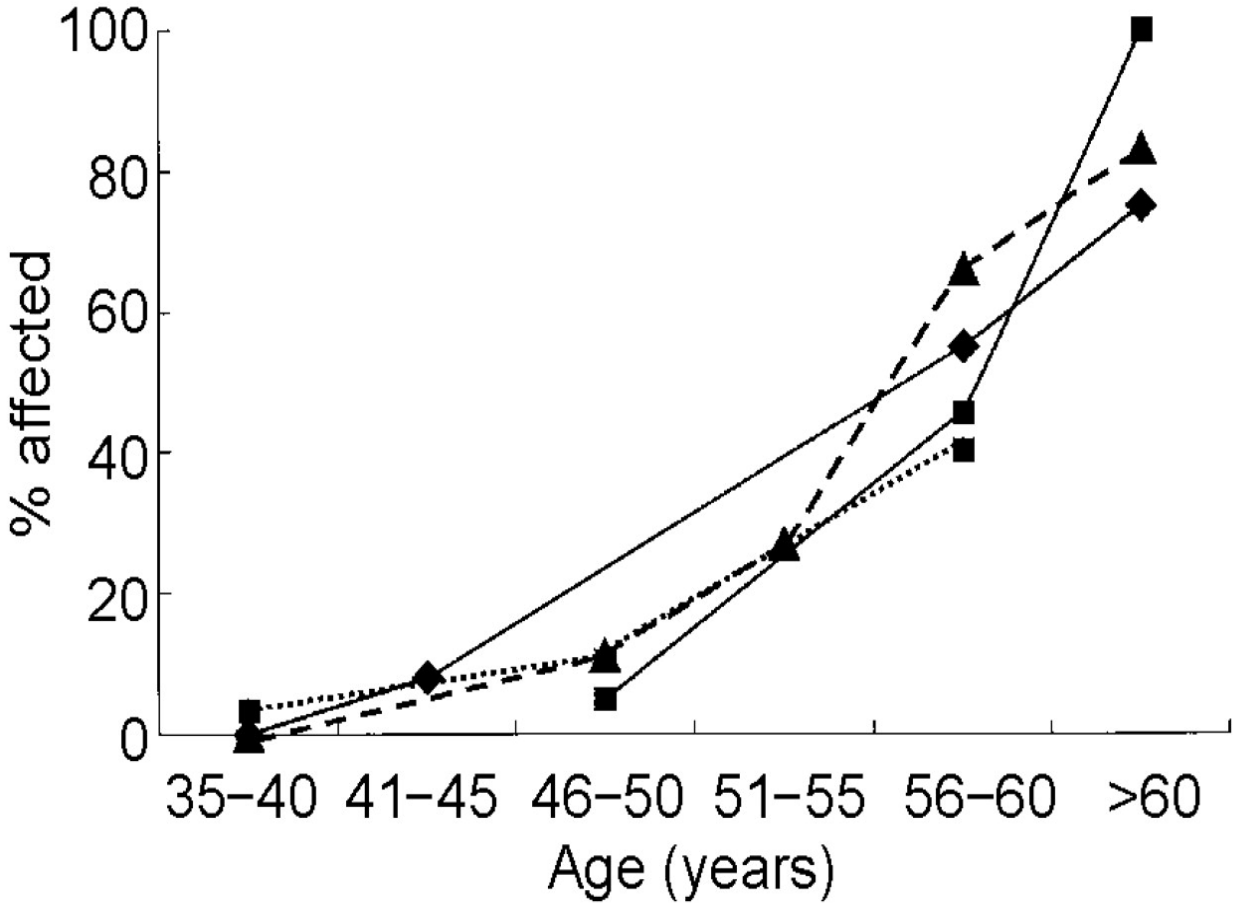
(Struwe, 1929; Jarvis, 1948)

# Prevalence of senile plaques and neurofibrillary tangles




Mann et al., 1993

# Number of people with Down syndrome and dementia




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

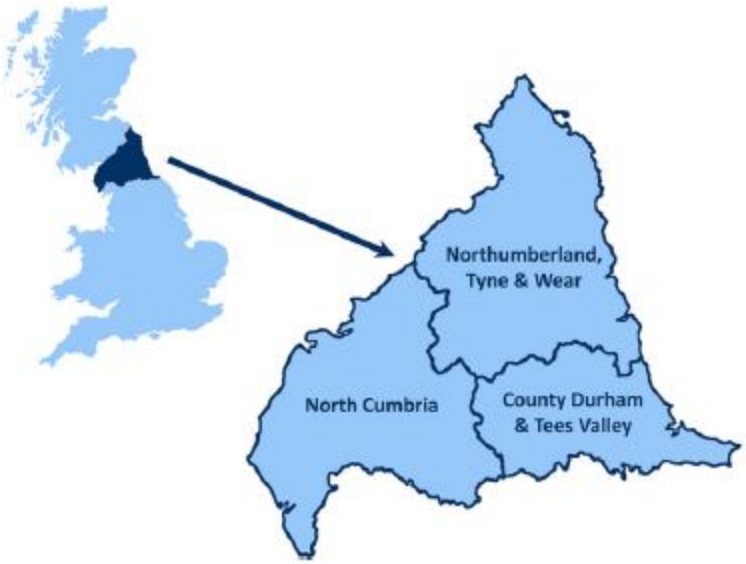
THE BRITISH JOURNAL OF PSYCHIATRY

# Why is this important for not only people with Down syndrome but everyone?

- Not everyone with Down syndrome over 40 years of age has dementia.
- Why?  Can we find what other proteins might be protecting the brain?
- If we can learn this – can we then find a way to promote healthy aging in both people with Down syndrome and all aging people?

# Epidemiology of Survival with DS

- 1115 Down syndrome pregnancies (01/01/85–12/31/03)
  - 19 years births followed-up with national mortality records (01/29/08)
- total prevalence of 16.8 per 10,000 live and stillbirths




5.4% spontaneous fetal loss, 31.7% pregnancy terminations

63% live births (702 cases)

Survival status determined for 95.3% of live births

16.6% documented deaths

Rankin et al., Pediatrics 2011

# Mortality Risk Factors in Pediatric DS

- Infant mortality decreased significantly from 14.0% (1985–1990) to 5.8% (1997–2003).
- Year of birth, gestational age at delivery, birth weight, karyotype and presence of additional structural anomalies were significant predictors of survival.

| Health Problem | Mortality Risk |
|---|---|
| Cardiovascular | 5.01 (3.10–8.11) |
| Digestive system | 6.50 (2.62–16.13) |
| Cardiovascular/digestive | 7.84 (3.76–16.37) |

Rankin et al., Pediatrics 2011

# Developmental Aspects of Cognition in DS

From Chapman & Hesketh, MRDDRR, 2000

Infancy (0-4 years)

| Domain | Behavioral Phenotype |
|---|---|
| Cognition | Learning delays at ages 0–2<br>accelerating at ages 2–4 |
| Speech | No difference in vocalization types;<br>slower in transition from babbling to speech; poorer intelligibility |
| Language | Delays relative to cognition in:<br>-frequency of nonverbal requesting<br>-rate of expressive vocab. development<br>-rate of increase in mean length of utterances<br>(no relative delay in comprehension) |

# Developmental Aspects of Cognition in DS

Childhood (4-12 years)

| Domain | Behavioral Phenotype |
| --- | --- |
| Cognition | Selective deficits in verbal STM |
| Speech | Longer period of phonological errors & more variability; poorer intelligibility |
| Language | Expressive language delays continue relative to comprehension |
| Adaptive behavior | Fewer behavior problems compared to controls with cognitive disability<br>More behavior problems than sibs w/o DS<br>Anxiety, depression, and withdrawal correlate positively with increasing age. |

# Developmental Aspects of Cognition in DS

Adolescence (13–18 years)

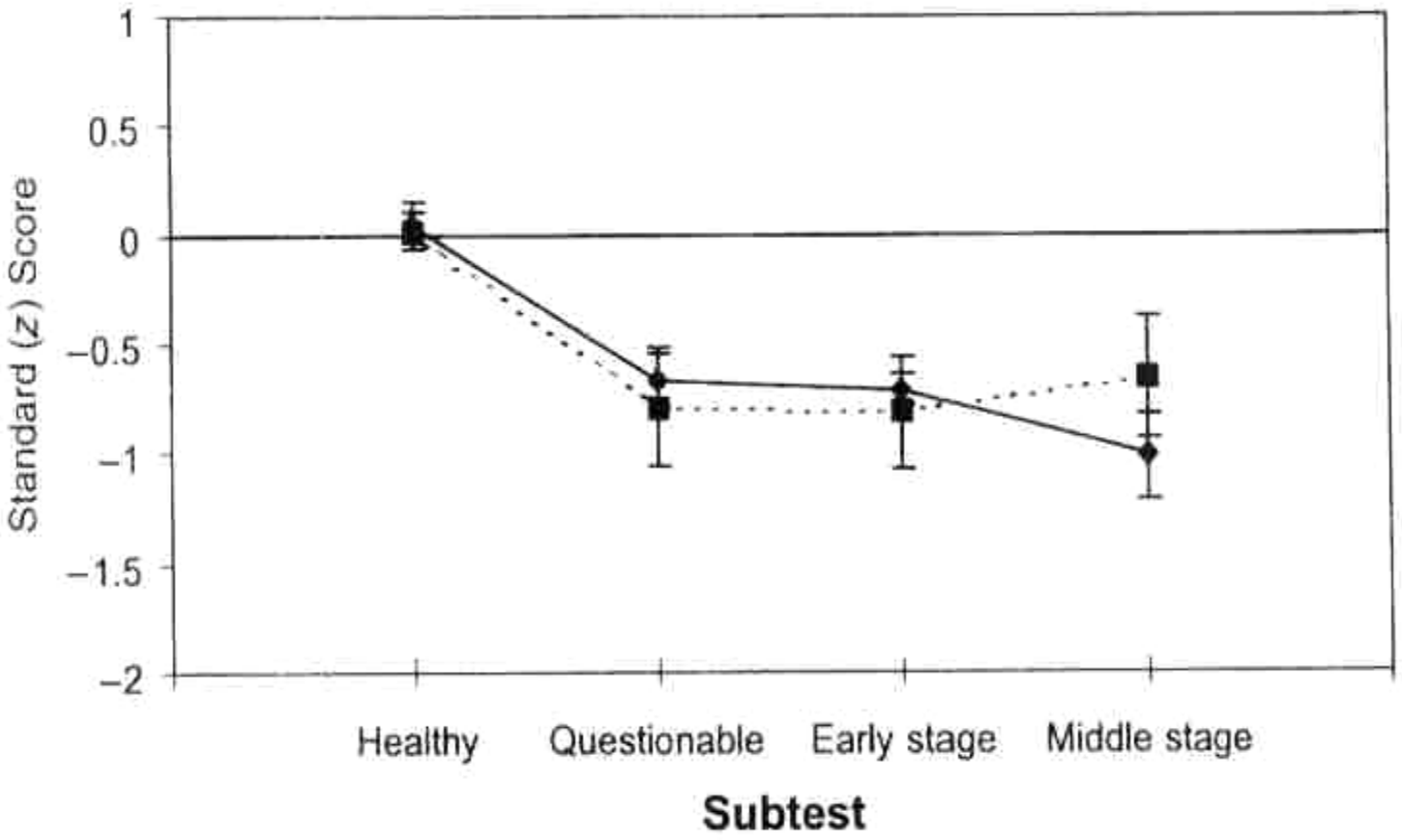
| Domain | Behavioral Phenotype |
| --- | --- |
| Cognition | Deficits in verbal working-memory and delayed recall |
| Speech | More variability in fundamental frequency, rate control & placement of sentential stress |
| Language | Expressive language deficit in syntax > expressive language deficit in the lexicon<br>Comprehension of words typically more advanced than nonverbal cognition<br>Syntax comprehension beginning to lag behind nonverbal cognition |

# Developmental Aspects of Cognition in DS

Adulthood (18+ years)

| Domain | Behavioral Phenotype |
| --- | --- |
| Cognition: | Behavioral symptoms of dementia begin to emerge at 50 years for up to 50% |
| Speech: | Higher incidence of stuttering/hypernasality |
| Language: | Syntax comprehension continues to lag |
| Adaptive behavior | Fewer behavior problems compared to controls with cognitive disability |
| | Higher rates of depression with increased age |
| | Dementia in Down syndrome is not associated with increased rates of aggression |

# Cognitive Change with Evolving AD




WISC-R Block Design & Coding data from: Devenny et al, JIDR, 2000

# The Down syndrome and Aging Study

- The goal of this study is to follow people with Down syndrome over 35 years of age, and who are not demented as they get older
- Measure learning and memory every 6 months
- Participants seen by a neurologist every year
- Participation lasts 5 years

# Learning and Memory Procedures

- Severe Impairment Battery
- Fuld Object Memory Test
- Peabody Picture Vocabulary Test
- Rapid Assessment for Developmental Disabilities
- Brief Praxis Test
- Trail Making Test
- Reiss Screen

## Brief Praxis Test (BPT)

Scoring:

**4 Points:** A correct response on request (1 repeat) without any prompts within 5-8 seconds.

**3 Points:** A correct response following additional verbal cues and verbal hints.

**2 Points:** A correct response following a display by the examiner of how the correct response should be executed.

**1 Point:** A correct response following "physical prompting" using hand-over-hand, in which the examiner may place his/her hand over the person's hand, or doing something for the person.

**0 Points:** Person is unable or unwilling to perform the response.

**Note:** **Scores of 0, 1, 2, 3, or 4 are used for items 1-16 only. Scores of 0 or 4 only are used for items 17-20 with no prompting.**

### WHILE STANDING

**1. Clap your hands**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**2. Lift one arm over your head**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**3. Lift the other arm over your head**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**4. Turn your head to the side**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**5. Turn your head to the other side**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**6. Lift one leg**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**7. Lift the other leg**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

*CONTINUED ON NEXT PAGE*

### WHILE SEATED

**8. Place each of the coins in the jar**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**9. Place each of the coins in the jar with the other hand**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**10. Salute**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**11. Scratch your head**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**12. Snap your fingers**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**13. Open the jar**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**14. Close the jar**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**15. Unlock the padlock**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

**16. Lock the padlock**
☐ 4 ☐ 3 ☐ 2 ☐ 1 ☐ 0

*Scores of 0 or 4 only are used for items 17-20*

**17. Point to your index finger**
☐ 4 ☐ 0

**18. Give me a nickel**
☐ 4 ☐ 0

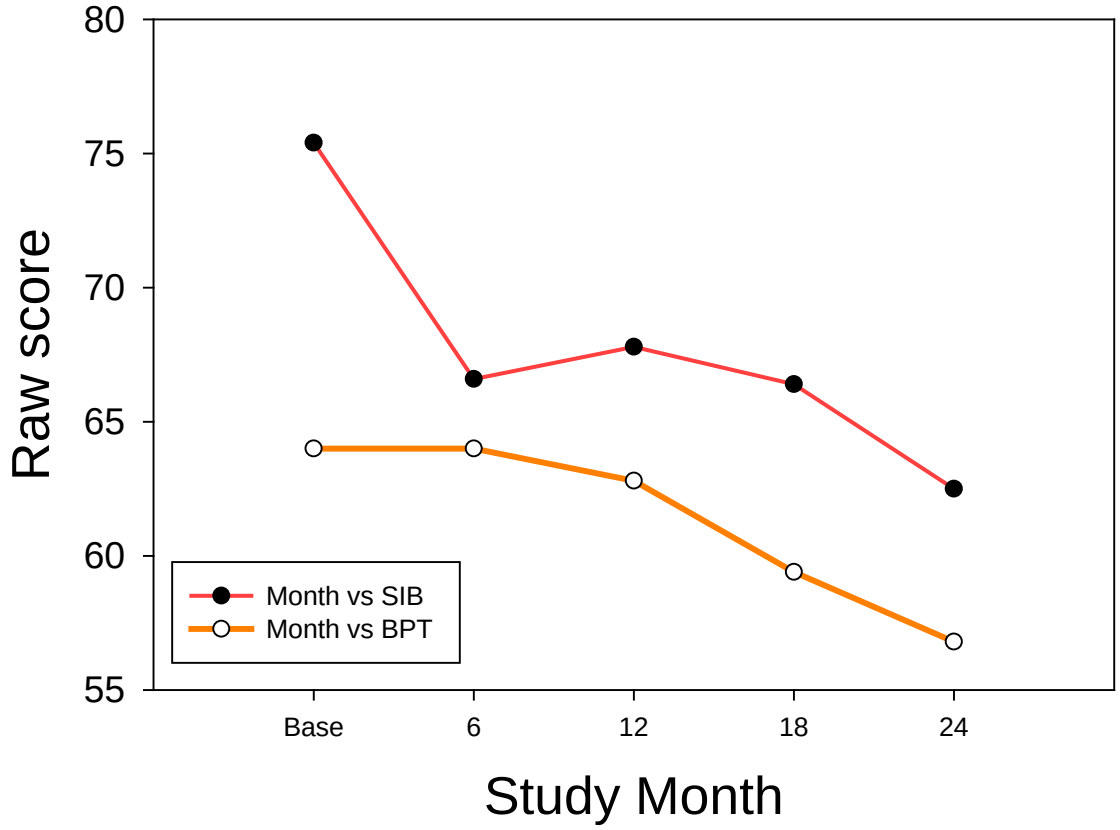
**19. Give me a quarter**
☐ 4 ☐ 0

**20. Give me a dime**
☐ 4 ☐ 0

# Dementia Progression in DS

Mental status losses over two years in a trial of antioxidant therapy in persons with DS

Data derived from Lott, et al., 2011, Am J Med Genet A



# Useful Clinical Screening Tools

- Adaptive Behaviour Dementia Questionnaire
  - (ABDQ)
  - ➢ Prasher, Farooq & Holder (2004, *Res. Devel. Disab.*)
- Dementia Screening Questionnaire for Individuals with Intellectual Disabilities
  - (DSQIID)
  - ➢ Deb, Hare, Prior & Bhaumik (2007, *Brit. J. Psychiat.*)

Both show 92% sensitivity to DS with dementia

# Informant-based

ABDQ

- 15 items rated better/same/worse
- Probes group activities, cooperation, praxis, awareness, conversation, dressing, initiative and other skills

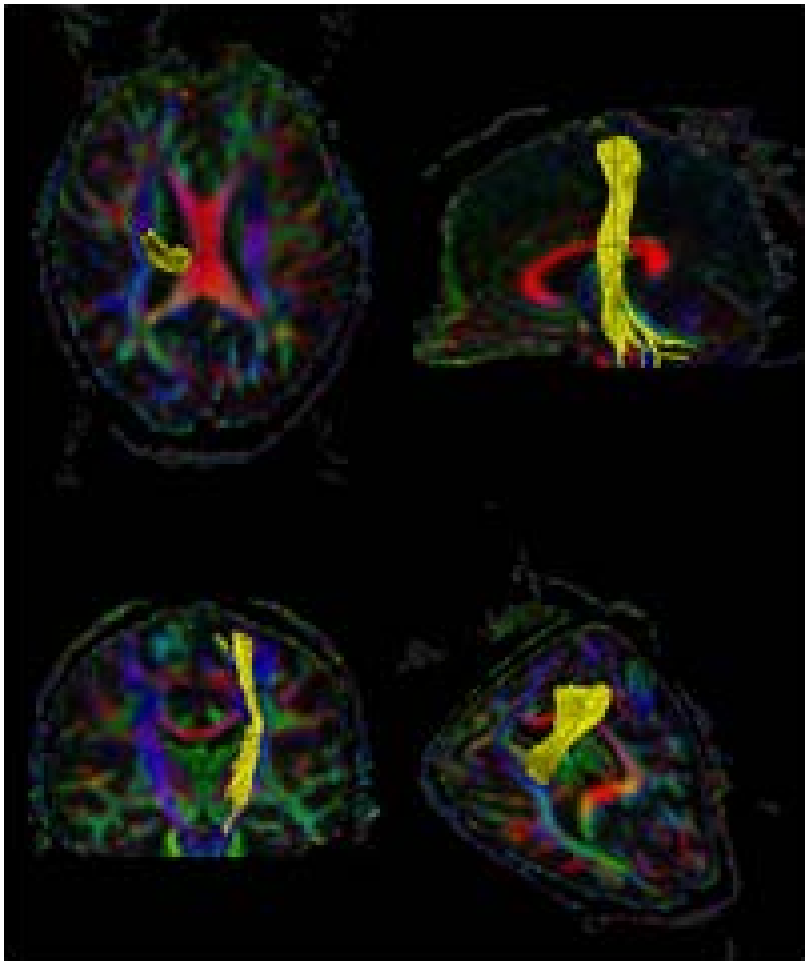
DSQIID – 3 parts and 56 questions

- Rated: always, always but worse, new symptom, not applicable and yes/no
  - Speech, daily living skills, behavior, cognitive, motor, orientation

# ABDQ

Weightings for questions in questionnaire

| Question | Item | Weighting |
|---|---|---|
| 1 | Are they able to dress themselves better/same/worse than normal? | 1 |
| 2 | Can they use their hands better/same/worse than normal? | 4 |
| 3 | Is their ability to buy/shop better/same/worse than normal? | 1 |
| 4 | Are they able to have a conversation better/same/worse than normal? | 1 |
| 5 | Is their awareness of time better/same/worse than normal? | 4 |
| 6 | Do they help to prepare food better/same/worse than normal? | 1 |
| 7 | Do they help to clear the table better/same/worse than normal? | 6 |
| 8 | Are they able to perform simple jobs better/same/worse than normal? | 4 |
| 9 | Do they carry out simple jobs better/same/worse than normal? | 5 |
| 10 | Is their initiative in doing activities better/same/worse than normal? | 1 |
| 11 | Is their persistence in doing activities better/same/worse than normal? | 1 |
| 12 | Do they take care of their personal belongings better/same/worse than normal? | 3 |
| 13 | Is their cooperation better/same/worse than normal? | 3 |
| 14 | Do they participate in group activities better/same/worse than normal? | 1 |
| 15 | Is their ability to do things independently better/same/worse than normal? | 1 |



# Brain imaging

Brian Gold & David Powell

Our MRI Research Team Members

How long does the MRI take? 28 minutes
What is the purpose for the MRI?
DTI, MRS, fMRI, Structural images

# Blood samples

- Check for overall health
- Measure the levels of different proteins – Dr. Tony Wyss-Coray at Stanford University
- Measure the level of beta-amyloid protein in blood – Dr. Liz Head

# Who are we asking to participate?

Persons with Down syndrome age 35 and older and their family member or caregiver. We would like to recruit 40 people who do not have dementia yet and 10 people who do have dementia. The people with dementia will be asked to come for a single visit while those without dementia will be asked to return to see us every 6 months.

# What will happen on the first visit for the Down syndrome, Aging, and Alzheimer's disease research study.

No food from midnight, the night before, until after the blood sample at the first visit.

Morning of the visit - No Breakfast, Coffee, tea or water only.

**8:00 am** — Informed Consent

**8:30 am** — Blood sample

**9:00 am** — Snack provided

**9:30 am** — Memory and thinking tests

**10:30 am** — Medical and neurological exam

**12:30 pm** — Lunch provided

**1:30 pm** — MRI scan

**4:00 pm** — End of visit!

Thank you for being a volunteer. See you soon!

- ‘As individuals with DS continue to experience longer lives, the need to understand their aging and associated health conditions becomes more critical.’

- ‘The chronic disorders that onset in adults with DS, and the age-related change in other disorders, have important implications for health care management of this aging population’.

Esbensen 2010, Int Rev Res Ment Retard

# Medical Comorbidities in DS

- Alopecia areata effects 6-19% while atopic dermatitis, fungal infections, seborrhoeic dermatitis, and xerosis are also common (34-39% of DS adults vs. 0.1-0.2%)
  - May reflect 'premature aging', lower levels of DNA repair enzymes, or CuZnSoD metabolism linked to chromosome 21 as overexpression alters structure & function of tissue
- Women with DS have a median age of menopause 4 to 6 years earlier (47.1 vs. 51.3 years of age)
  - implications for health as menopause is a risk factor for heart disease, depression, osteoporosis, breast-cancer and dementia in general population

# Sensory Issues in DS

- Visual impairments / eye abnormalities are more common in adults with DS (44-71% vs. 8-50% in ID)
- Corneal degeneration (37% over age 40) & cataracts (30-68% vs. 17% gen. popn.) are common in DS
- High frequency hearing loss onset ~20-30 years earlier than in ID, ~30-40 years before general population
    - 80% of care providers and general practitioners unaware of the hearing loss (VanBuggenhout et al., 1999)

# Medical Conditions in DS

- Seizures: 7% in younger vs. 46% (age 50+)
  - possible link to myoclonus epilepsy gene on c21
  - possible dementia risk or prodrome?
- Thyroid disease: 35-40% DS adults
  - risk increases with advancing age (>GP)
- Diabetes: age of onset ~22 years for type 1
  - comparable to gen. popn.
  - Type 2 diabetes - preliminary report suggestes a lower rate than gen. popn.
- Obesity: 45-79% of males; 56-96% of females are reported to be overweight

# Medical Conditions in DS

## Musculoskeletal:

- Osteoporosis is common among adults with DS and adults are at greater risk as they age
  - May be due to early menopause, deceased physical activity, low muscle tone, decreased strength
- Osteoarthritis of the spine affecting 22% of middle-age adults and 40% of elderly adults
- Orthopedic problems (e.g., flat feet - congenital condition) seen in 70% of adults with DS

# DS Medical Conditions

- Rate of mitral valve prolapse is high
- Lower risk for cardiovascular and cerebrovascular disease observed in adults with DS compared to general population.
- Lower rates of emphysema, fractures, hypercholesterolemia and heart disease compared to adults with other ID causes.
- Individuals with DS have lower resting heart rates and lower blood pressure than gen. popn.

From: Esbensen 2010, Int Rev Res Ment Retard

# Percentages of Health Comorbidities in DS+AD

| Condition | AD+ | AD- | ModAD | SevAD |
|---|---|---|---|---|
| Epilepsy | 56 | 12 | 39 | 84 |
| Pulmonary | 56 | 8 | 33 | 92 |
| Poor Vision | 89 | 72 | 85 | 92 |
| Poor Hearing | 44 | 21 | 46 | 44 |
| Depression | 38 | 18 | 49 | 16 |
| Arthritis | 14 | 2 | 21 | 8 |
| GI Disorder | 16 | 2 | 18 | 16 |

Note: persons with AD 55.4yo vs. w/o AD 50.8yo

Data adapted from McCarron et al., JIDR, 2005

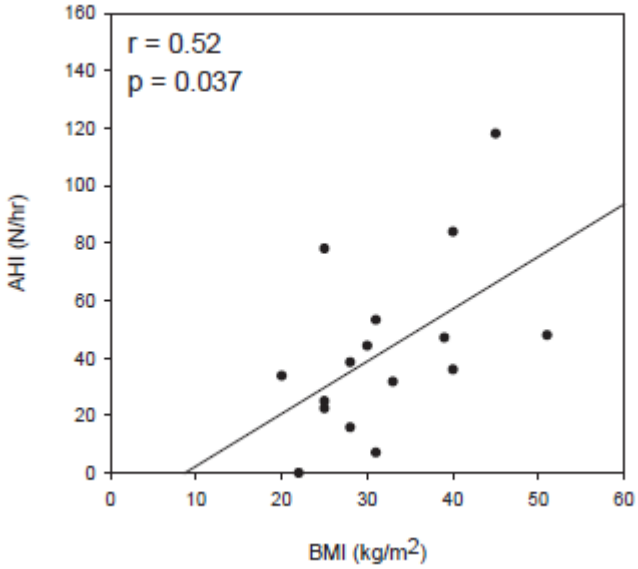
Table 1 Causes of death among people with Down syndrome at different life stages

| Cause of death | Childhood and early adulthood (0–18 yr), % (*n*) | Adulthood (19–40 yr), % (*n*) | Senescence (>40 yr), % (*n*) |
|---|---|---|---|
| Congenital heart defects | 12.8 (19) | 23.1 (9) | 0 (0) |
| Pneumonia and other respiratory infections | 33.1 (49) | 23.1 (9) | 39.6 (44) |
| Coronary artery disease | 1.4 (2) | 2.6 (1) | 9.9 (11) |
| Cerebrovascular accidents | 1.4 (2) | 5.1 (2) | 6.3 (7) |
| Cardiac, renal and respiratory failure | 11.5 (17) | 10.2 (4) | 9.0 (10) |
| Cancers | 3.4 (5) | 7.7 (3) | 5.4 (6) |
| Other causes | 36.5 (54) | 28.2 (11) | 29.7 (33) |
| Total (298 deaths) | 100 (148) | 100 (39) | 100 (111) |

From: Bittles et al., EurJPubHealth, 2006

# Obstructive Sleep Apnea in DS

- OSAS common in children with DS (30 to 55%)
- OSAS prevalence increases with age
- 94% of persons with DS, ages 17-56 have OSAS of varying severity
  - Contrasts with 2 to 4% of general population
- Compared to age-matched sample: 73 min less total sleep
- SpO2 nadir is 75% vs. 93%




Adapted from: Trois, et al., JCSM, 2009

**Our team and contact information:**

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