Disentangling the effects of normative and non-normative cognitive decline

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Bronx Aging and Einstein Aging Studies

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Overview

- Perspectives on normative cognitive aging and dementia
- Change point models
- Transitional models
- (Parental longevity, longevity genes, cognitive aging and dementia)

Factors associated with both cognitive decline and AD: AHRQ-Duke Evidence Report (2010)

- Increased risk of AD and CD

  -ApOE4 -Diabetes

  -Smoking -Depression

- Decreased risk of AD and CD

  -Cognitive engagement

  -Physical activity

  -Mediterranean diet

Williams, J et al., 2010

Parsing sources of cognitive decline in older adults

- Normative cognitive decline
- Non-normative cognitive decline

  -Neurodegenerative ←←

  -Vascular disease

  -Systemic/homeostatic

  -Other neuropsychiatric

The relative contribution of these factors varies with sample characteristics

Steinerman and Lipton JAGS, 2010

Factors influencing measured overlap in risk factors

- Study design: cross-sectional, longitudinal
- Sample characteristics: Age, health status
- Exposure assessment
- Definition of outcomes: categorical vs. continuous, single domain vs. global

Why the overlap: Hypotheses

- AD and CD differ only in degree and not in kind
- Designs do not fully distinguish normative and non-normative cognitive decline
- Outcomes are poorly measured

  A → decreases reserve; B → AD path;
  C→ Vascular disease. All lower MMSE

Designs do not fully distinguish normative and non-normative cognitive decline

- Hypothesis: Overlap of risk factors is do, at least in part, to the inclusion in normative aging samples of individuals with preclinical dementia.
- Dementia related cognitive decline is attributed to “normative aging”
- Dementia risk factors are mistaken for normative aging risk factors

Studies of Cognitive Performance and Age

- Dementia and preclinical dementia increases exponentially with age
- Proportion of a normative sample with preclinical dementia increases with age.
- Consequences: Cognitive decline and cognitive variability are over-estimated. Effect increases with age
- Suboptimal cut-scores for diagnosis
- One solution: Robust norming

One approach to assessing effects of risk factors on CD and dementia

- Excludes prodromal or preclinical dementia
- Separately examine the effects of risk factors on the cognitive course in persons on a trajectory to AD
- Strategies: Exclusion based on long-term follow-up, clinical course, predictive modeling or biomarkers (endophenotyping)
- Misclassification is inevitable

Separating normative aging and preclinical dementia in the Bronx Aging Study (BAS)

-488 community dwelling individuals age 75-85 enrolled 1980-1982 followed for up to 28 years

-Study started by Dr. Robert Katzman

-121 developed incident dementia.

-367 non-cases. Only one subject still alive.

- Clinical and neuropsychological assessments given every 12 to 18 months including:

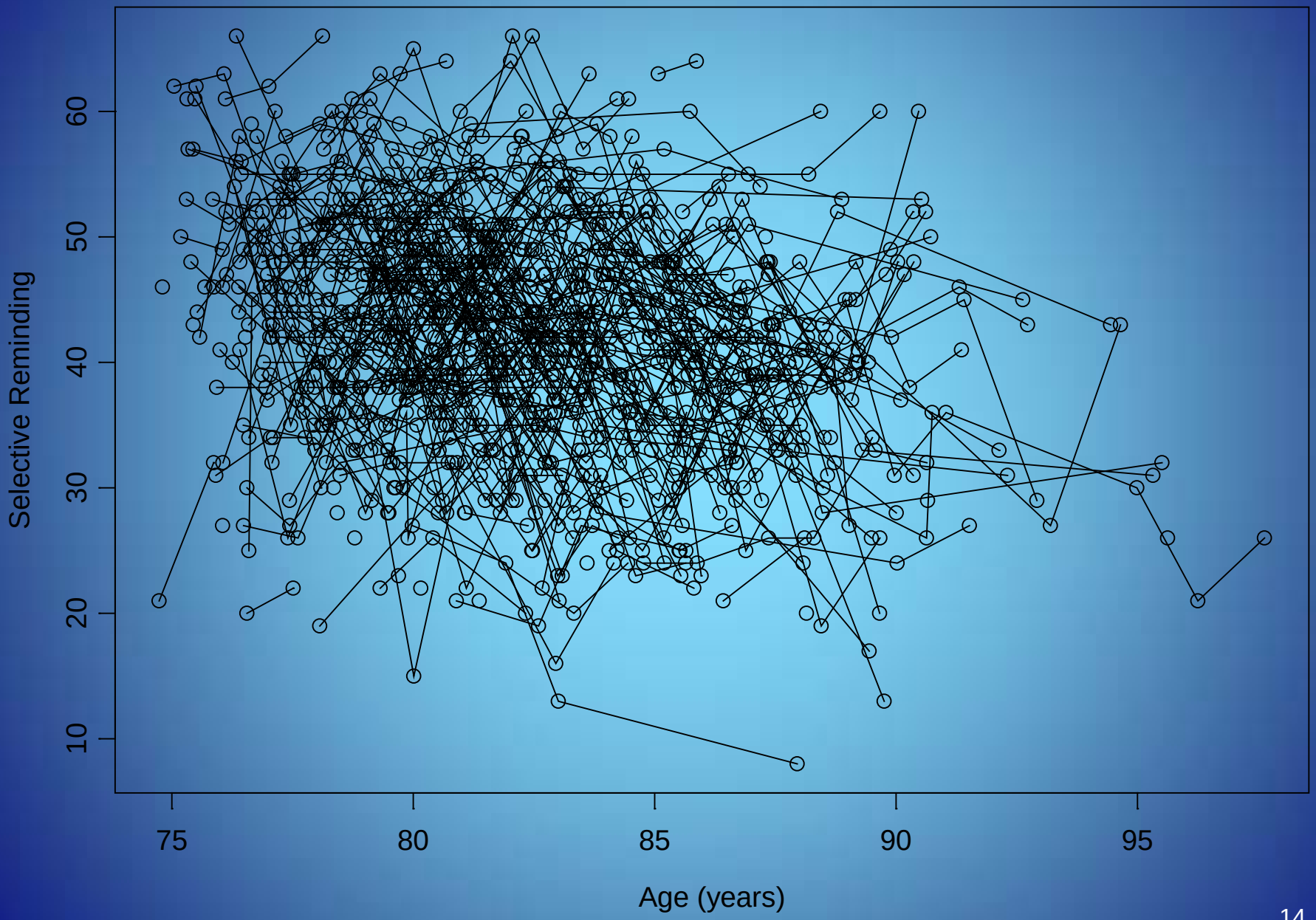
Buschke Selective Reminding (memory).

WAIS IQ subtests, including Digit Symbol, Block Design.

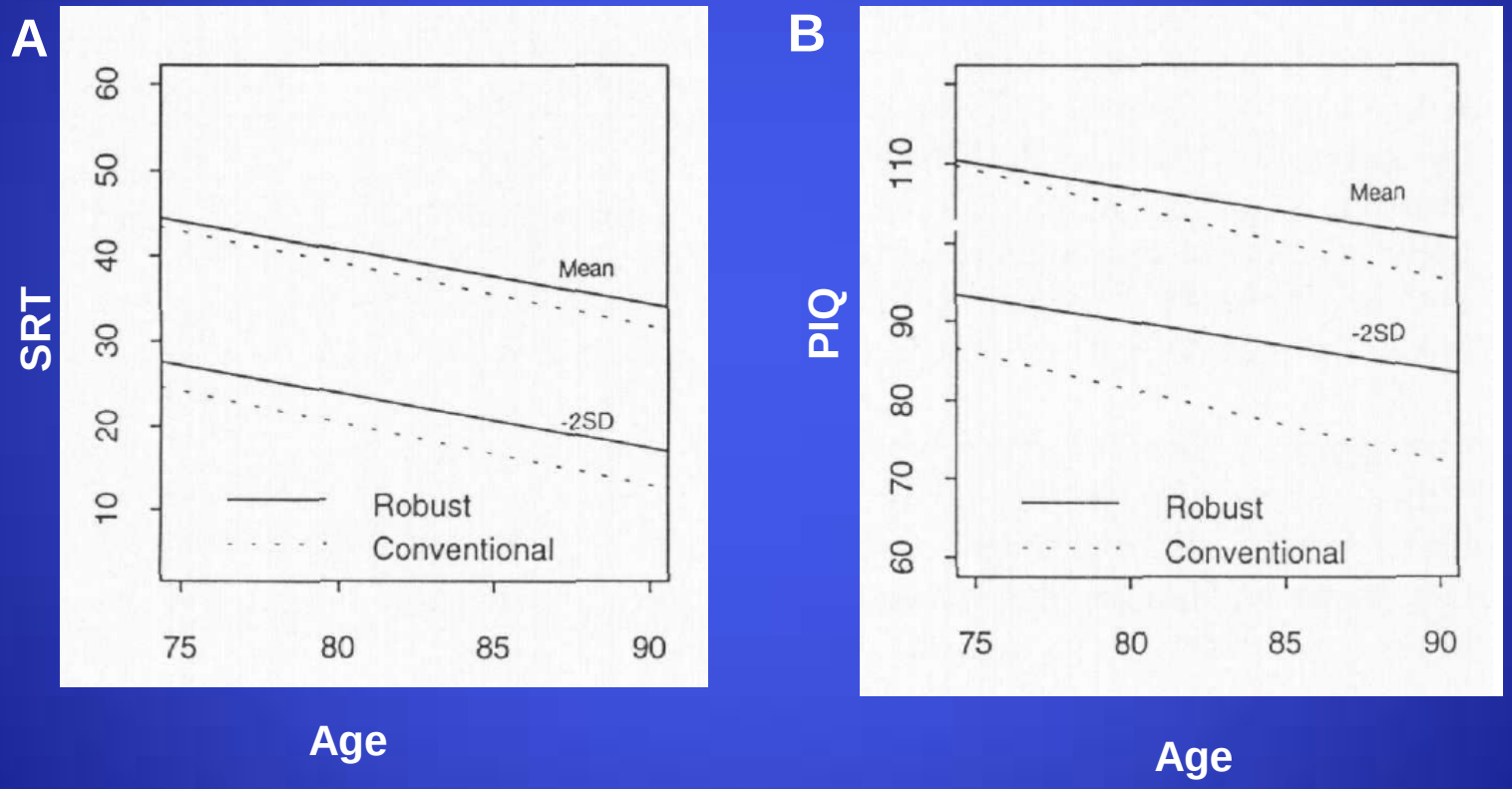
Timescales for Describing Cognitive Decline and Dementia

- Study wave
- Chronological age
- Time of dementia as the temporal referent and then look backwards in time

Non-Cases



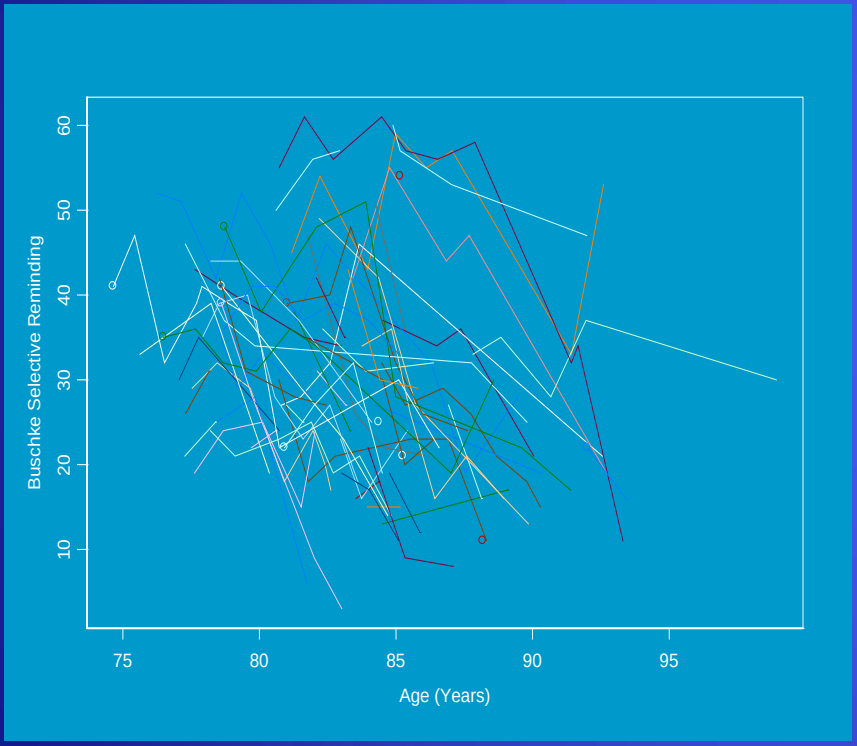
Conventional and Robust Norms for the SRT and WAIS PIQ



Sliwinski, Lipton, Buschke and Stewart
Journal of Gerontology, 1996

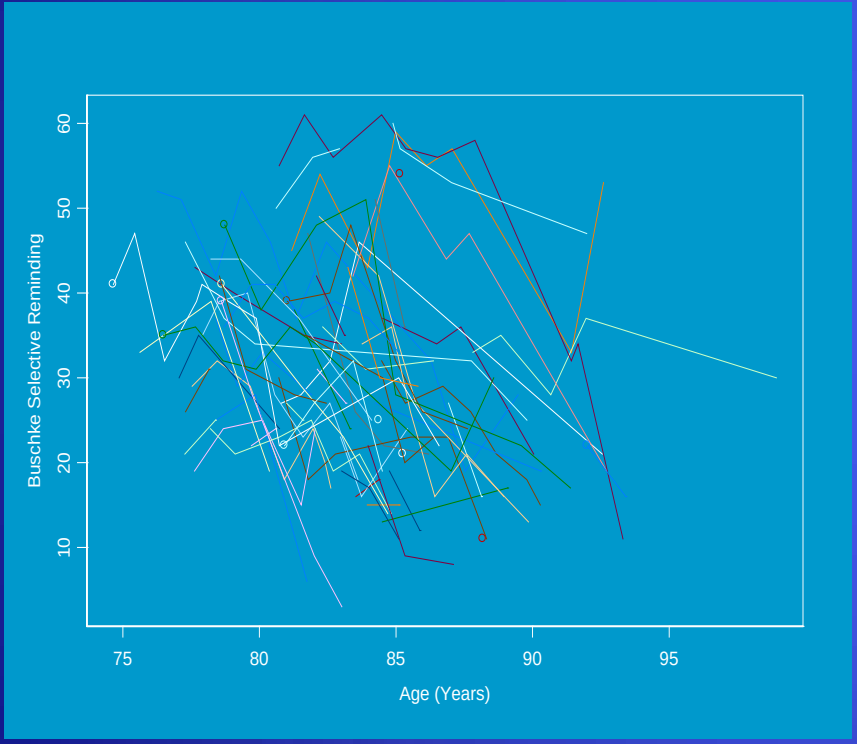
Selective Reminding: Trajectories in 121 Individuals who Developed Incident Dementia

Timescale: Age

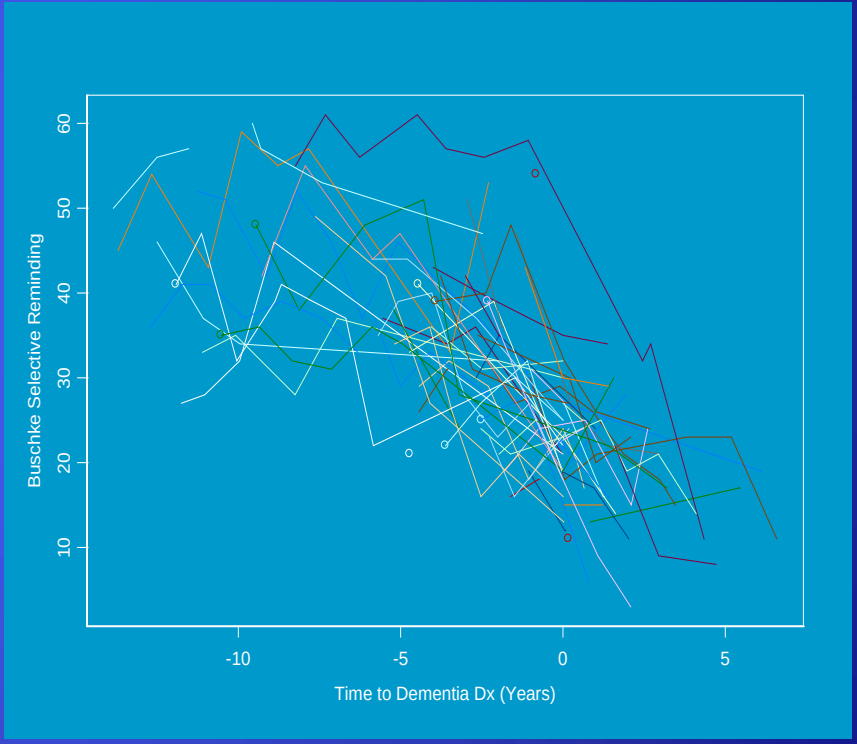


Selective Reminding

Timescale: Age



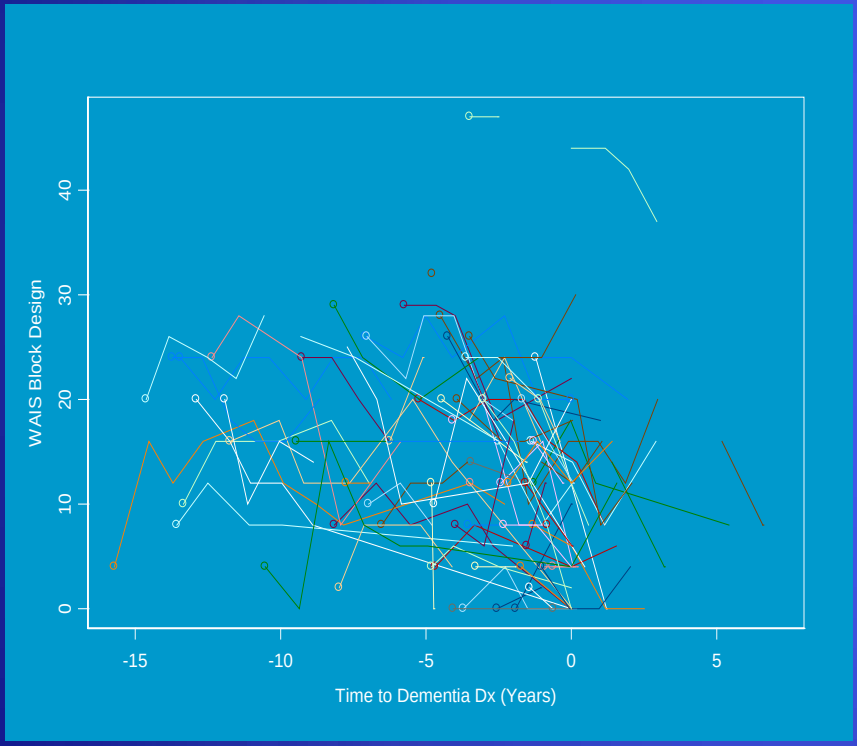
Years prior to dementia



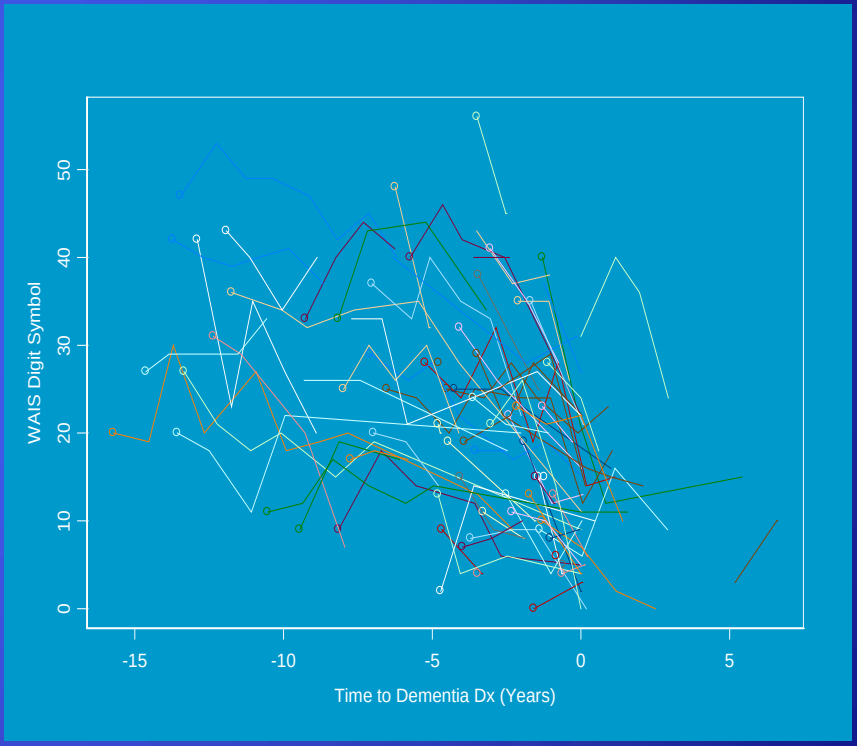
Hall et al., 2000

WAIS: Block Design, Digit Symbol

Block design: Years prior to dementia

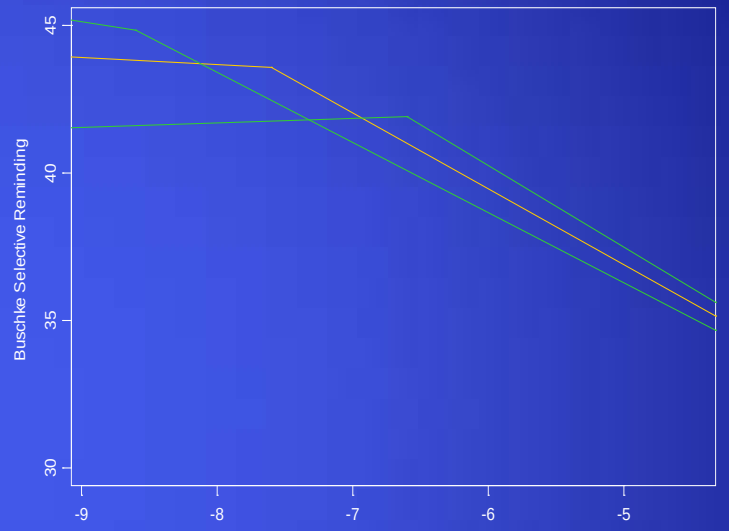


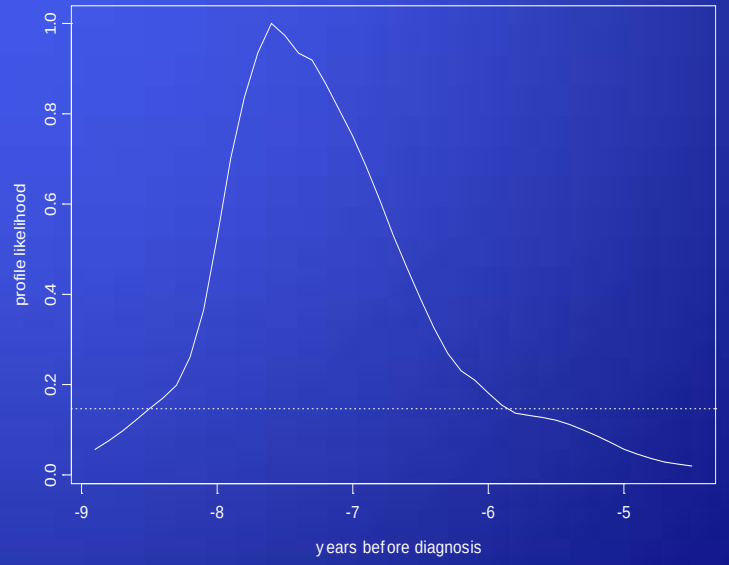
Digit symbol: Years prior to dementia



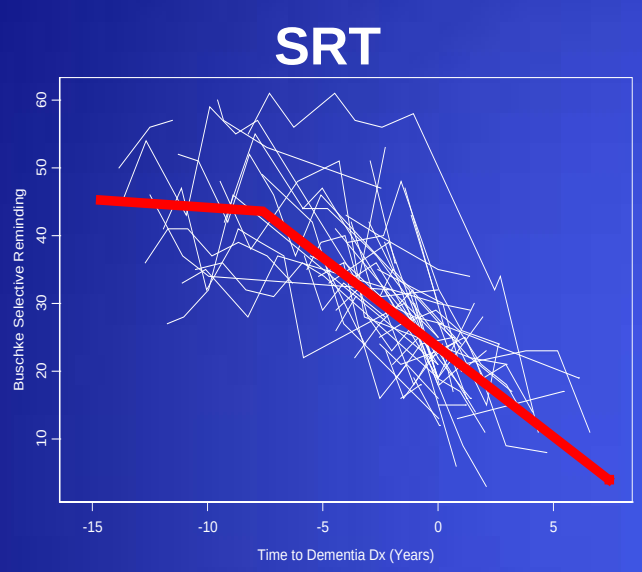
Fitting the Change Point Model

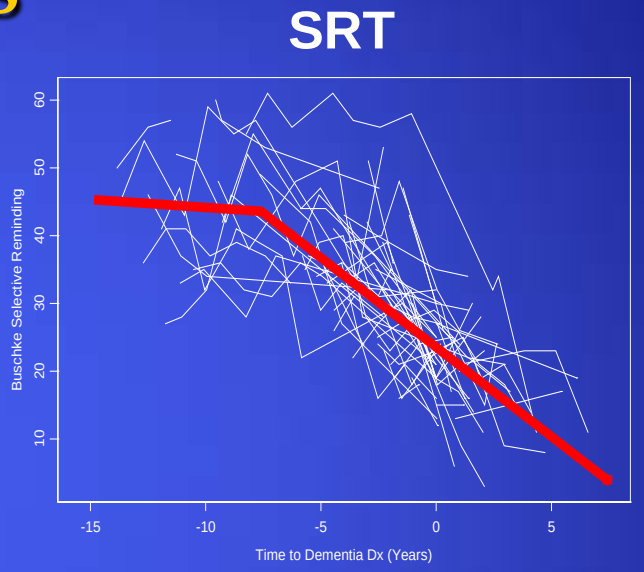
- Try a range of change points, computing goodness of fit.
- Select the one that fits the best.
- Easy in SAS, S-Plus.
- Statistical theory: profile likelihood.
- Confidence intervals as well!

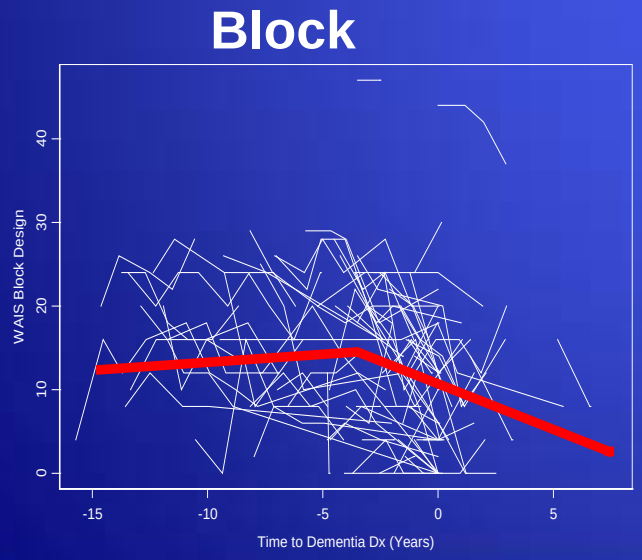


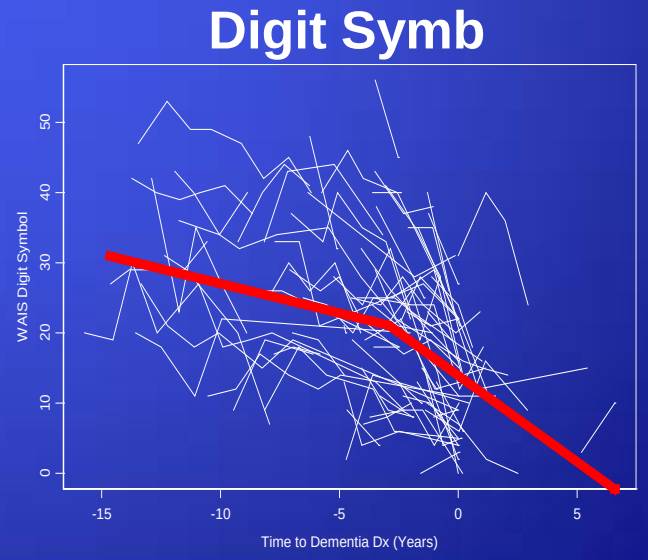


Comparison of Memory with Speeded Tasks

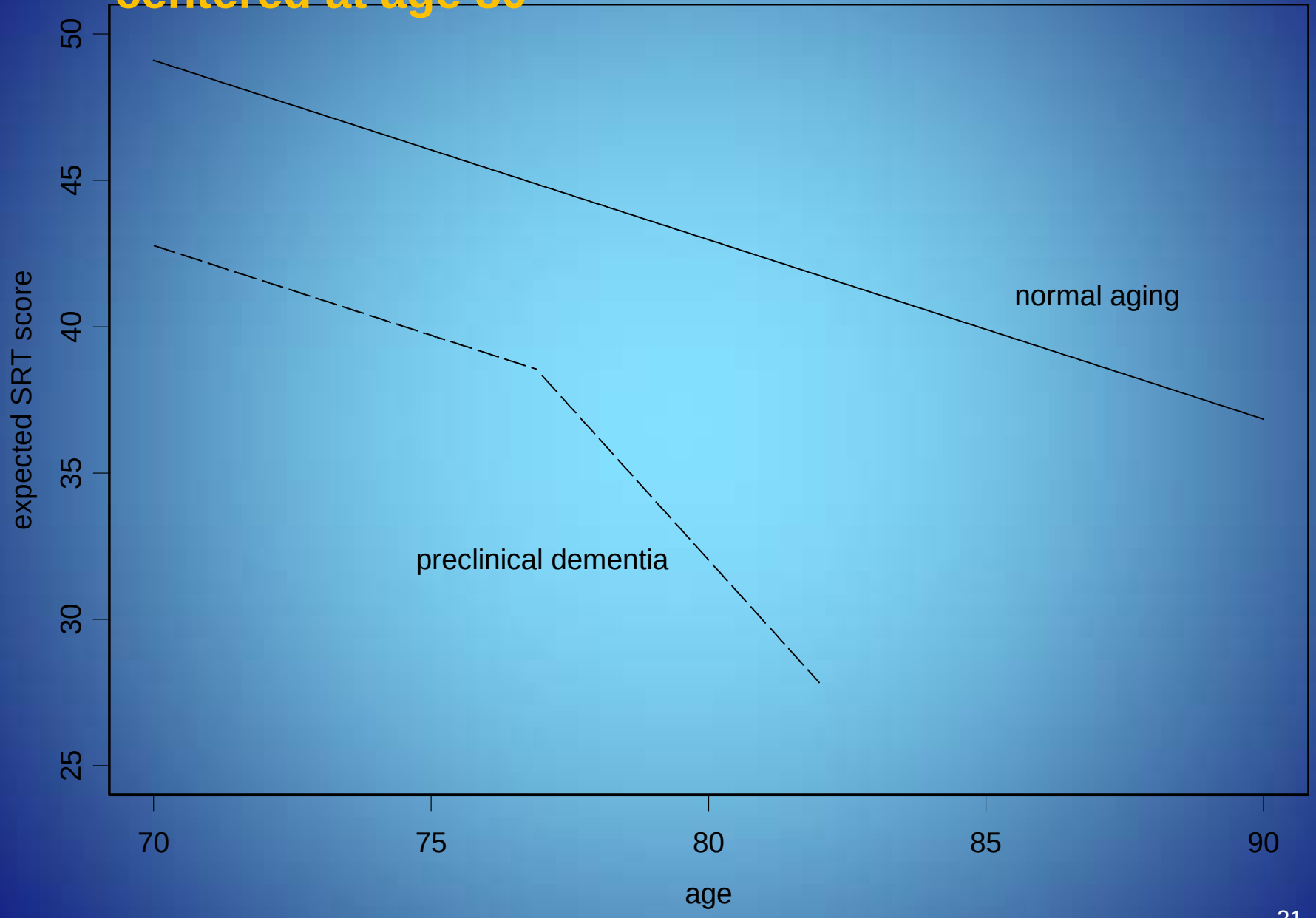








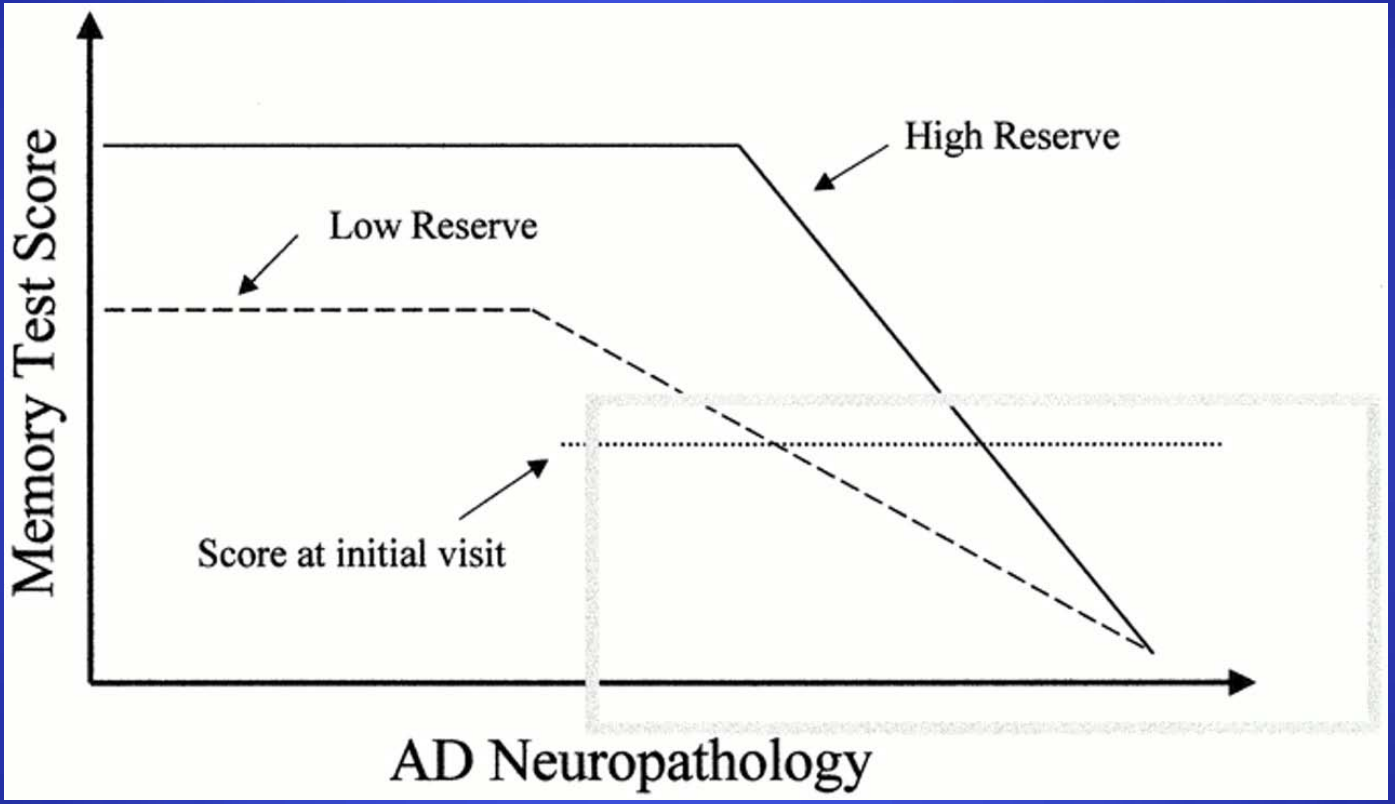
Normative aging and preclinical dementia sample centered at age 80



Assessing risk factors using change point models: Education

- In a traditional non-demented samples low education is associated with a more rapid rate of memory decline
- In a robust sample, low education does not predict memory decline
- In a sample on a trajectory to dementia the Stern predictions for cognitive reserve are demonstrated

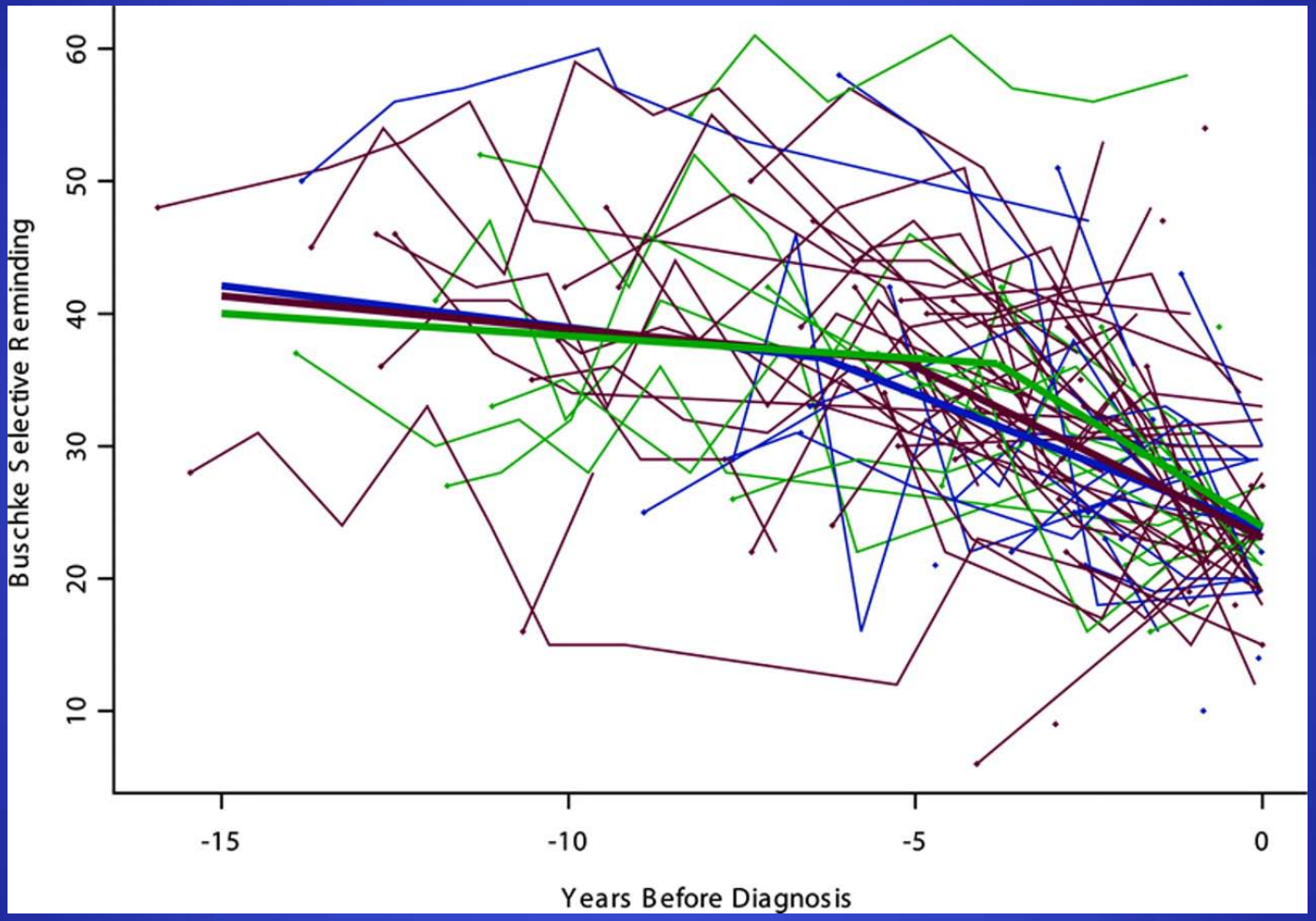
Theoretical model to explain the observation of more rapid progression in patients with higher educational or occupational attainment



NEUROLOGY

Stern, Y. et al. Neurology 1999;53:1942

Higher education is associated with delayed onset of accelerated decline and a more rapid rate



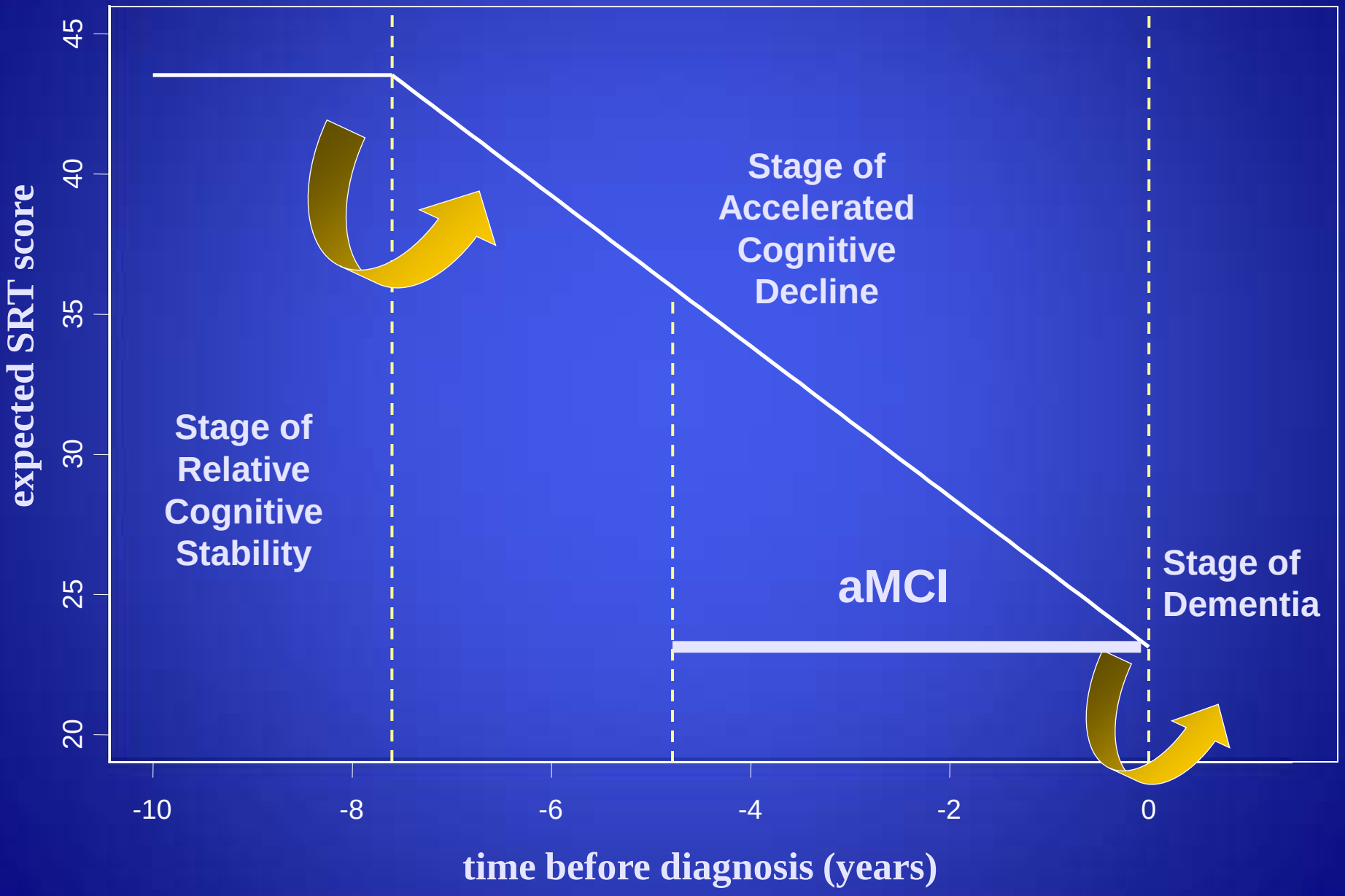
Neurology®

Hall, C. B. et al. Neurology 2007;69:1657-1664

Problems – and Some Solutions

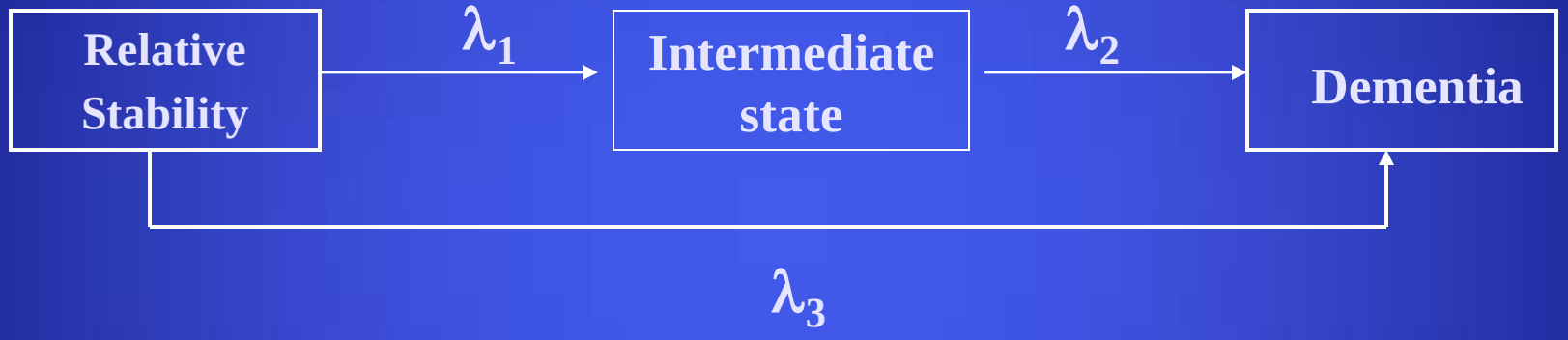
- Misclassification of cases and controls.
- Cognitive measures are "noisy"
- Death and loss to follow-up are associated with cognitive decline resulting in informative loss to follow-up/missing data
- Very long follow-up required /low power for confirmed cases

Cognitive Transitions



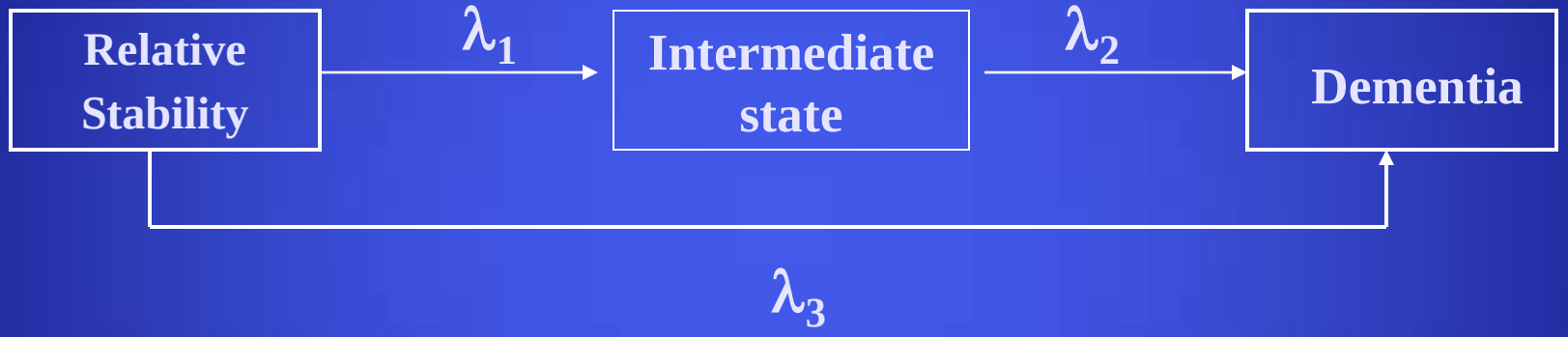
Hall et al. 2000, 2001, 2003

Transitional Models



- Framework for assessing risk factors by stage
- Model allows for back transitions (not shown)
- Traditionally studies of risk factors and categorical outcomes consider λ3 or λ2 and λ3

Transitional Models: Aligning risk factor discovery and interventions



- Primary prevention: Reduce λ_1
- Secondary prevention: Reducing $\lambda 2$ preventing AD
- Tertiary prevention: Treating dementia
- Stage specific influence of risk factors may account for treatment failures in prevention studies

Modeling approach

- Assess the influence of risk factors on first order Markov transitions assuming dementia is an absorbing state
- Normals have 3 possible outcomes: remain normal, develop MCI or develop dementia.
- MCIs have 3 possible outcomes: transition to normal, remain MCI or develop dementia
- Random effects used to account for within subject correlation

Modeling approach

- Examined 7 risk factors:

  -Demographics: Age, gender, education

  -Medical conditions: hx of MI and stroke, depression, diabetes

Evaluated 4 polychotomous logit models and 4 proportional odds models (fixed effect, shared random effect, previous stage dependent random effects model, generalized random effects model)

Sample: EAS

- 812 subjects with 2239 transitions
- 1874 transitions from normal (to normal 1666; to aMCI 178; to dementia 30)
- 365 transitions from aMCI (to normal 127; to aMCI 173; to dementia 65)

Results of multilevel polychotomous logit models

Risk factor	Normal to aMCI	aMCI to Dementia
Age (Continuous)	**1.11 (1.05-1.16)**	**1.13 (1.03-1.24)**
Gender (F vs M)	**0.55 (0.33-0.94)**	2.20 (0.88-5.94)
Education (Continuous)	**0.93 (0.87-0.99)**	1.04 (0.94-1.15)

Song et al., 2010 (in press)

Summary

- Traditional neuropsychological tests are only moderately reliable reducing power to measure decline, intra-individual change and the influence of risk factors
- Normative aging samples contain individuals on a trajectory leading to dementia
- Removing those individuals provides a strategy for assessing the influence of risk factors on normative aging minimizing the effect of dementia

Summary

- Time scales of age and study wave are poorly correlated with disease
- Meaningful temporal referents help: time of dementia, time of MCI, achievement of a biological endpoint
- Using these methods memory decline accelerates 7 years prior to dementia diagnosis in Bronx Aging, EAS and BLSA
- For other domains cognitive decline accelerates later

Summary

- In robust normative samples and in the pre-change point dementia samples cognitive slopes are not different
- Though low education is associated with memory decline and risk of dementia important complexity is revealed by assessing robust normals and individuals on a trajectory to dementia separately
- Transitional models

Einstein Aging Study

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Possible Protective Factors Against AD

- High education
- Anti-inflammatory drugs
- Estrogens (in women)
- Antioxidants (Vitamins C, E and flavanoids).
- Statins
- Cognitive and physical activity
- Exceptional parental longevity
- Longevity or successful cognitive aging genes

Overview

- Perspectives on normative cognitive aging and dementia
- Parental longevity, longevity genes, cognitive aging and dementia
- Closing thought on overlapping risk factors

Offspring of Parents with Exceptional Longevity (OPELs) in the Bronx Aging Study

- Bronx Aging Study: From 1981-83 we enrolled 488 community residing 75 to 85 year olds (born between 1896 and 1908)
- Followed 424 subjects to dementia (n=113) or death (or loss to follow-up)
- Parents of BAS subjects were born prior to 1880 on average
- Defined OPEL as having at least one parent reaching the age of 85 (n=149)

OPELs Have Less Memory Decline and a Reduced Risk of AD

- OPELs have a markedly reduced rate of longitudinal decline in memory
- Hazard ratio for AD is 0.60 (95% CI: 0.37-0.99) after adjusting for age, gender education, race/ethnicity, hypertension, history of MI and diabetes.
- Hazard ratio for all dementia is similar in magnitude but loses significance after all adjustments (0.69, 95% CI: 0.46-1.05)

Why are OPELs Protected Against Cognitive Decline and AD?

- OPELs may have healthier life styles
- OPELs may carry "longevity genes" that protect against dementia by:

  -Increasing cognitive reserve (the ability to withstand pathology)

  -Protecting against vascular disease

  -Protecting against AD pathology

Studying Exceptional Longevity

- Only ~1/10,000 individuals lives to 100 years old
- Exceptional longevity occurs with greater frequency in the siblings and offspring of Centenarians
- Do longevity genes contribute to successful cognitive aging, protect against dementia/AD or both
- Are the effects specific to particular longevity genes?

Approaches to Identifying Longevity Genes

- Cohort studies are impractical
- Case control studies but what is the appropriate control group?

  -Age mates of centenarians

  -Birth cohort of persons who would be centenarians had they survived
- Assess gene frequency by age

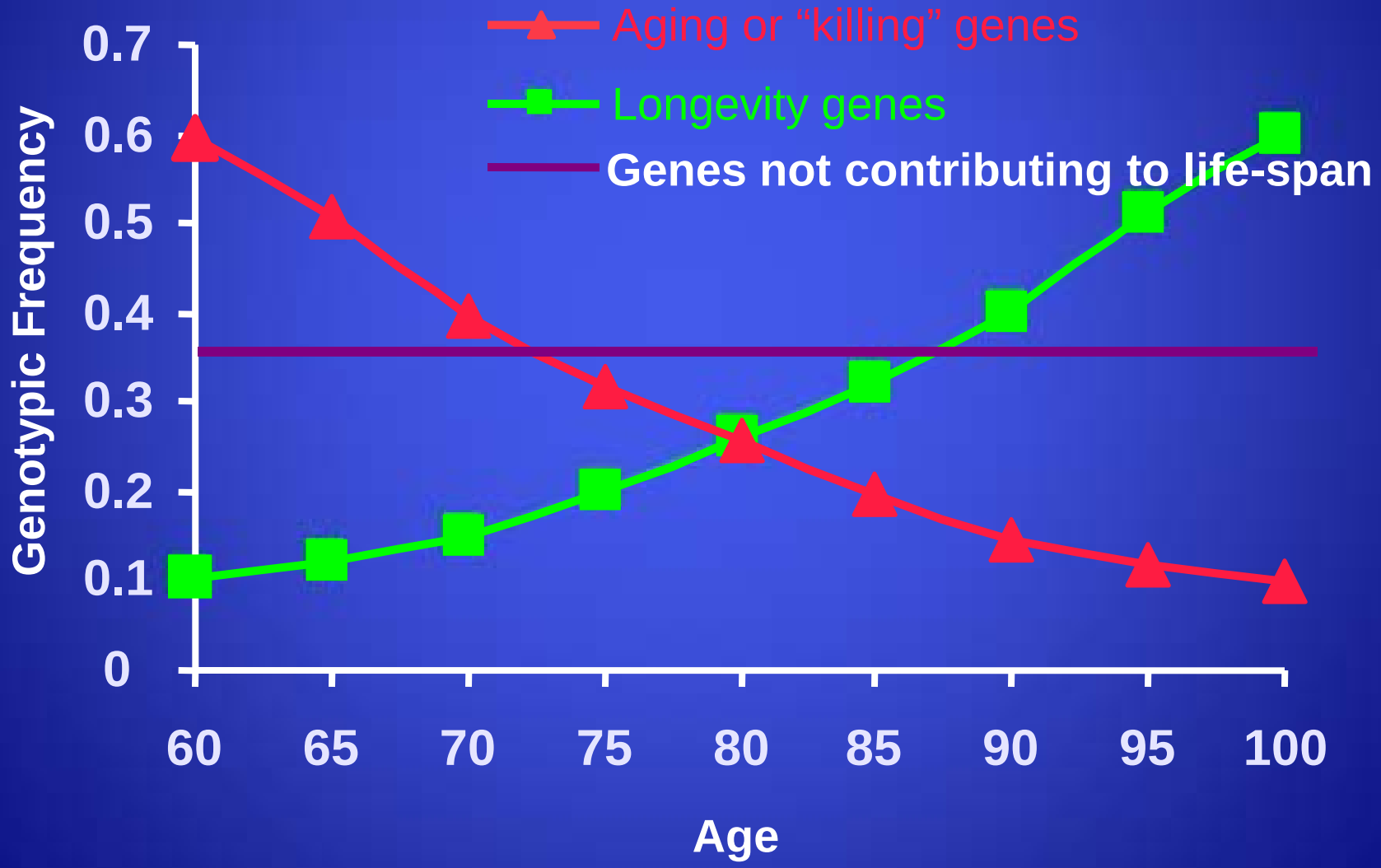
A Major Barrier to Genetic Studies in Centenarians

What is the appropriate control group?

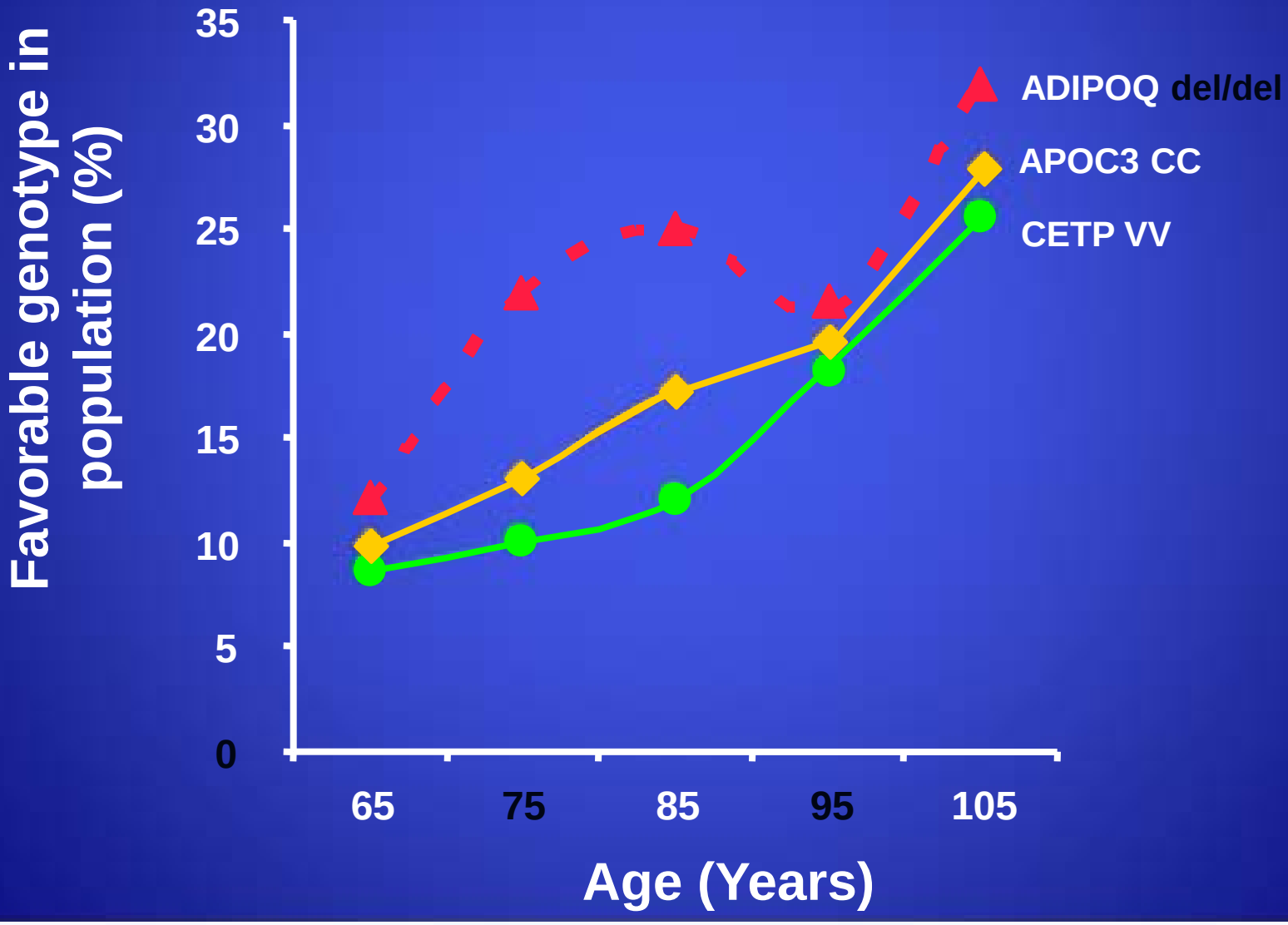
- Study centenarians their offspring and ages mates of their offspring
- Method 1: Gene frequency goes up with age for longevity genes
- Method 2: Longevity gene frequency

  Centenarian > Offspring > Controls

Modeling Changes in the Frequency of a Genotype as a Function of Age



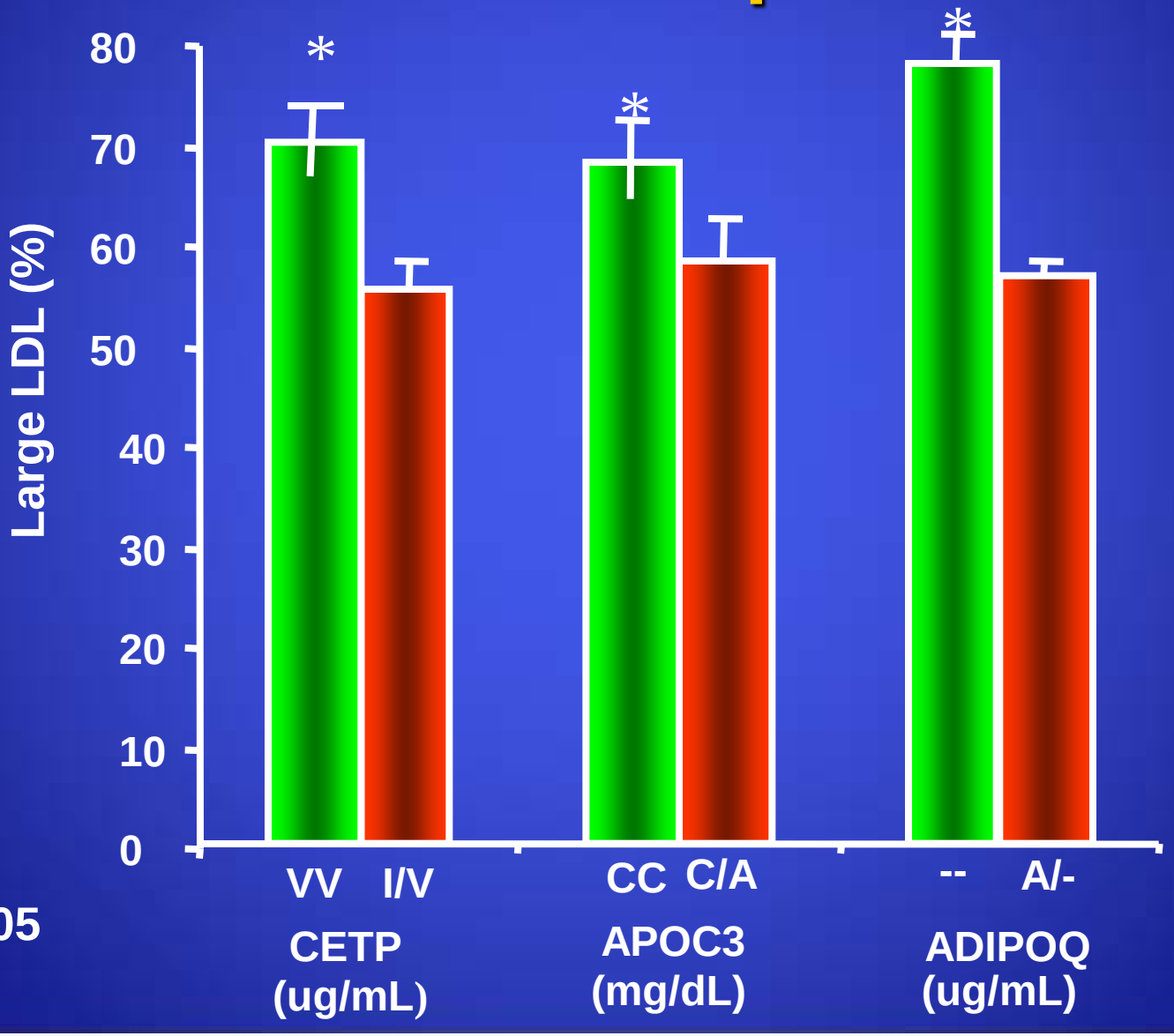
Favorable Longevity-Associated Genotypes in Unrelated 65-108 Year-Old Ashkenazi Individuals



Of These Three Longevity Genes

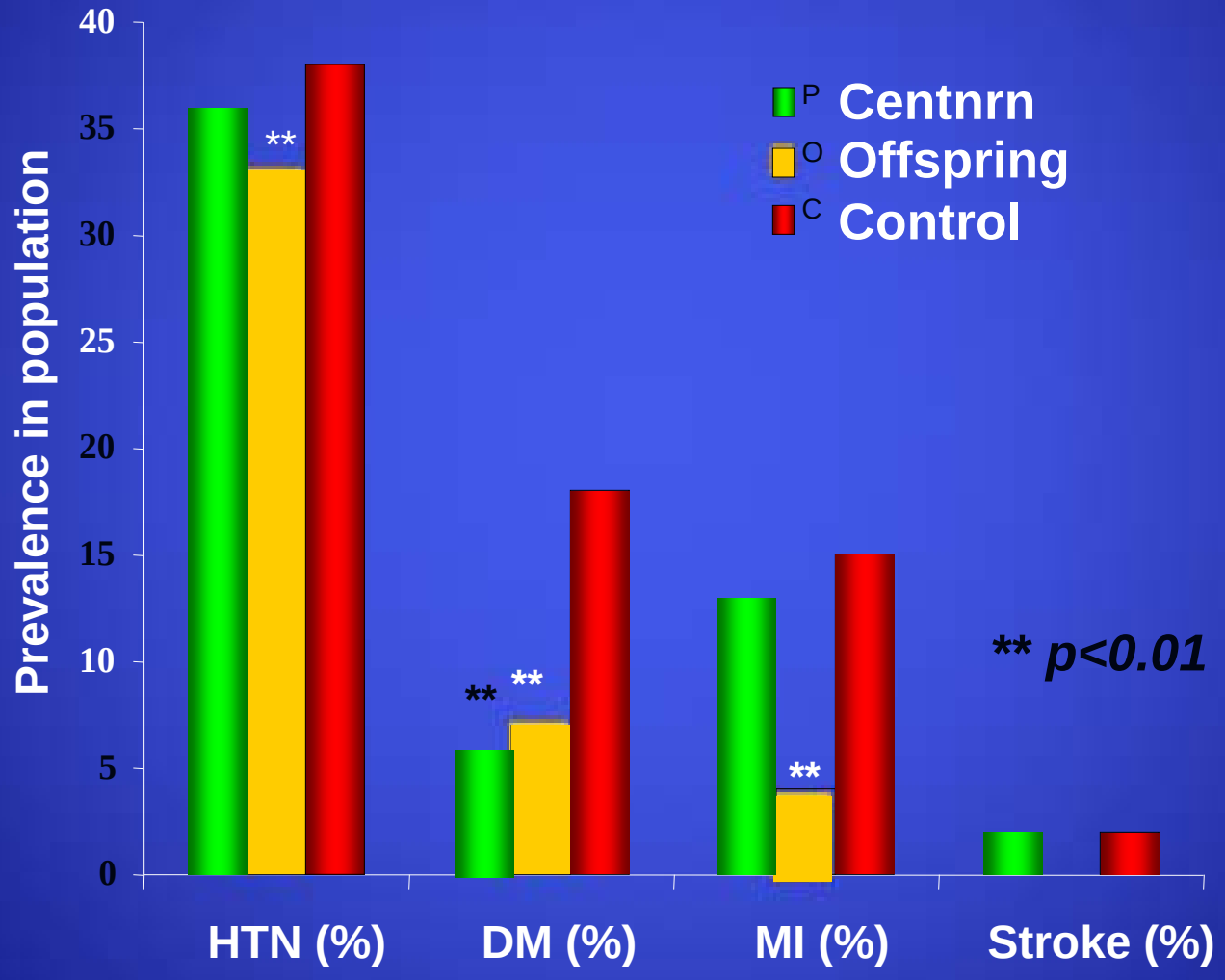
- All are associated with large lipoprotein particle size
- The CETP VV polymorphism is a loss of function mutation associated with reduced CETP levels
- The favorable form of CETP is associated with high HDL levels and large lipoprotein particle sizes

"Longevity Genotypes" are associated with HDL and LDL particle size



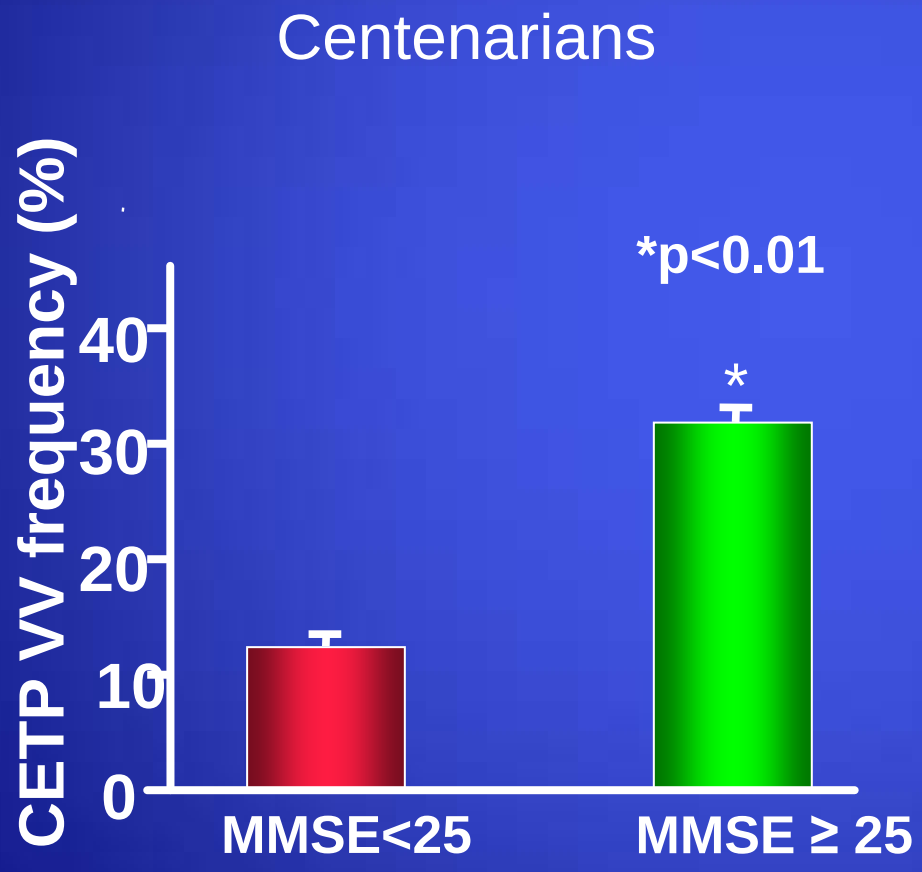
*p<0.05

Offspring of Centenarians are Less Likely to Have Age-Related Diseases



JAGS 2004; 52:274

CETP VV Genotype and Cognitive Function in AJ Centenarians



Barzilai et al, Neurology 2007

Background on CETP

- CETP SNPs modulate levels of CETP and influence cholesterol homeostasis
- CETP raises LDL and lowers HDL increasing the risk of CAD
- CETP loss of function and CETP inhibition is associated with increasing HDL levels
- Treatments which inhibit CETP are in development

Cholesterol Ester Transfer (CETP) is a Plausible Candidate in AD

- Plasma glycoprotein which regulates HDL and LDL levels and particle size
- Longevity gene involves a valine for isoleucine substitution in Codon 14 (I405V)
- CETP is found in the brain
  - Interthecal synthesis in CSF (human studies)
  - AntiCETP staining in astrocytes in gray matter in AD (Yamada et al, 1995)
- In AD, CETP levels and cholesterol esterification reduced (Knebl et al, 1994)

Do "Longevity Genes" Protect Against Dementia? – EAS Sample

- Systematically recruited initially nondemented individuals 70+
- At least 2 waves of follow-up

CETP V405V and Incident AD: EAS Sample

- We followed 520 initially non-demented individuals 70+ in the EAS for up to 10 years.
- The CETP VV genotype was associated with a reduced rate of incident dementia (HR =0.21, 95% CI: 0.06-0.75) using age as the time scale and adjusting for gender and education.
- Further adjustments for medical comorbidities and inflammatory markers (IL-6, TNF) did not alter the association (HR=0.20).

Baseline Features in the "CETP" Sample

	Non-Demented (n = 369)	Incident Dementia (n = 26)
Age	78.1	79.6
% Female	61	61
Ashkenazi Jewish	14%	4%
Follow-up	3.8 yrs.	4.5 yrs.
Comorbidity	1.1	1.4

Cholesterol Ester Transfer (CETP) and the Brain

- CETP is a plasma glycoprotein which regulates HDL level and particle size
- CETP is found in the brain
  - Interthecal synthesis in CSF studies in humans
  - AntiCETP staining in astrocytes in gray matter in AD (Yamada et al, 1995)

    and in vascular endothelium and in microglia (Dickson et al., in prep)
- In AD, CETP levels and cholesterol esterification reduced (Knebl et al, 1994)
- CETP is a drugable target

Summary

- Exceptional parental longevity "protects" against cognitive decline and dementia
- At least one longevity gene (CETP VV) appears to account for part of this effect in two large, independent samples (AJ Centenarians and the EAS)
- Identifying the biological mechanisms which prolong life while preserving cognitive function may lead to the identification of novel approaches to treatment- CETP itself provides a target

Summary of CETP data

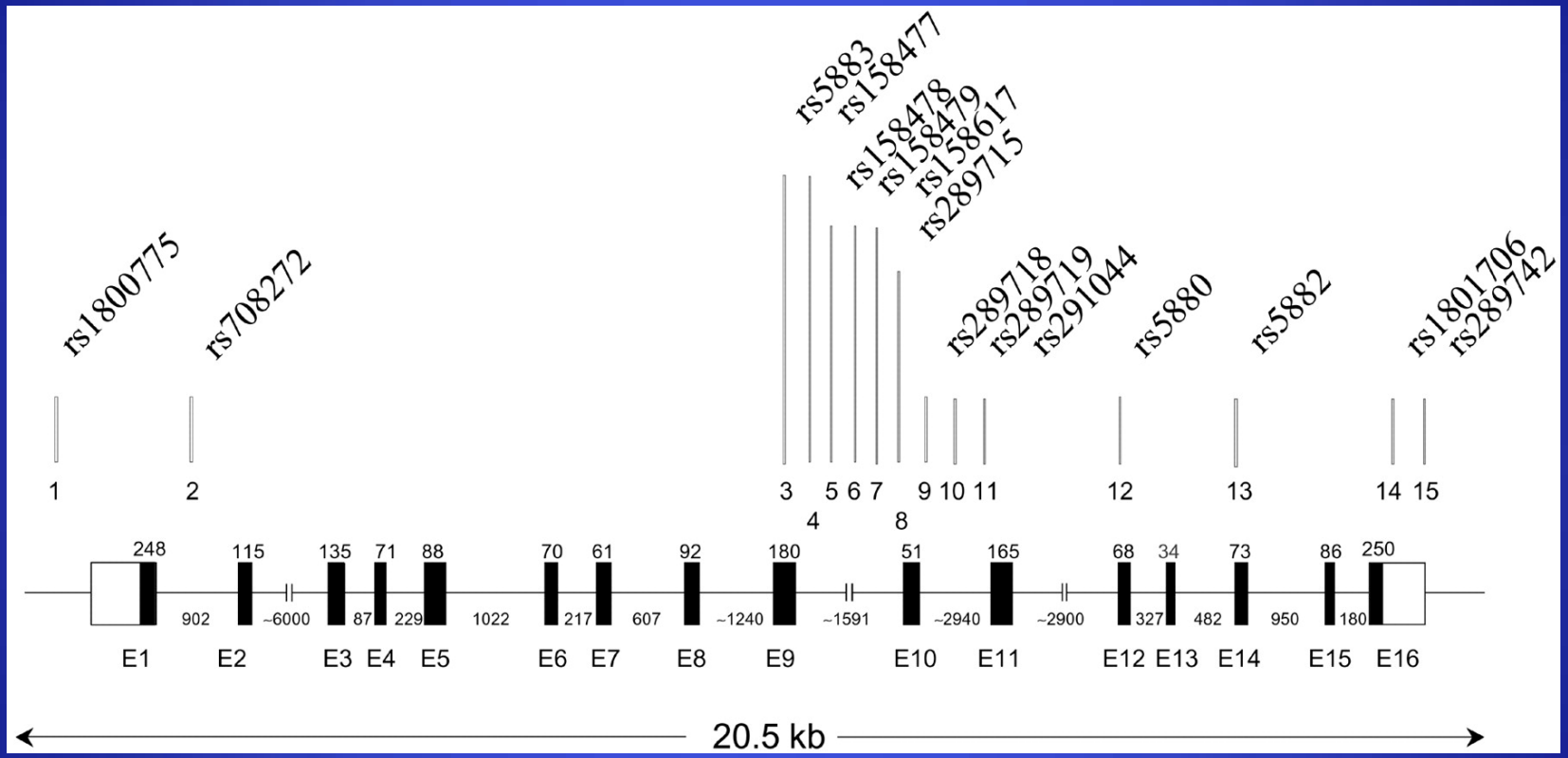
The favorable CETP genotype is associated with

- Exceptional longevity
- Reduced vascular risk: Less HTN, DM, MI and stroke, high HDL levels and large lipoprotein particle size
- Better scores on the MMSE in AJ Centenarians
- Reduced prevalence of dementia at cross-section in a diverse community sample
- A reduced incidence of dementia in a longitudinal community study

Overview

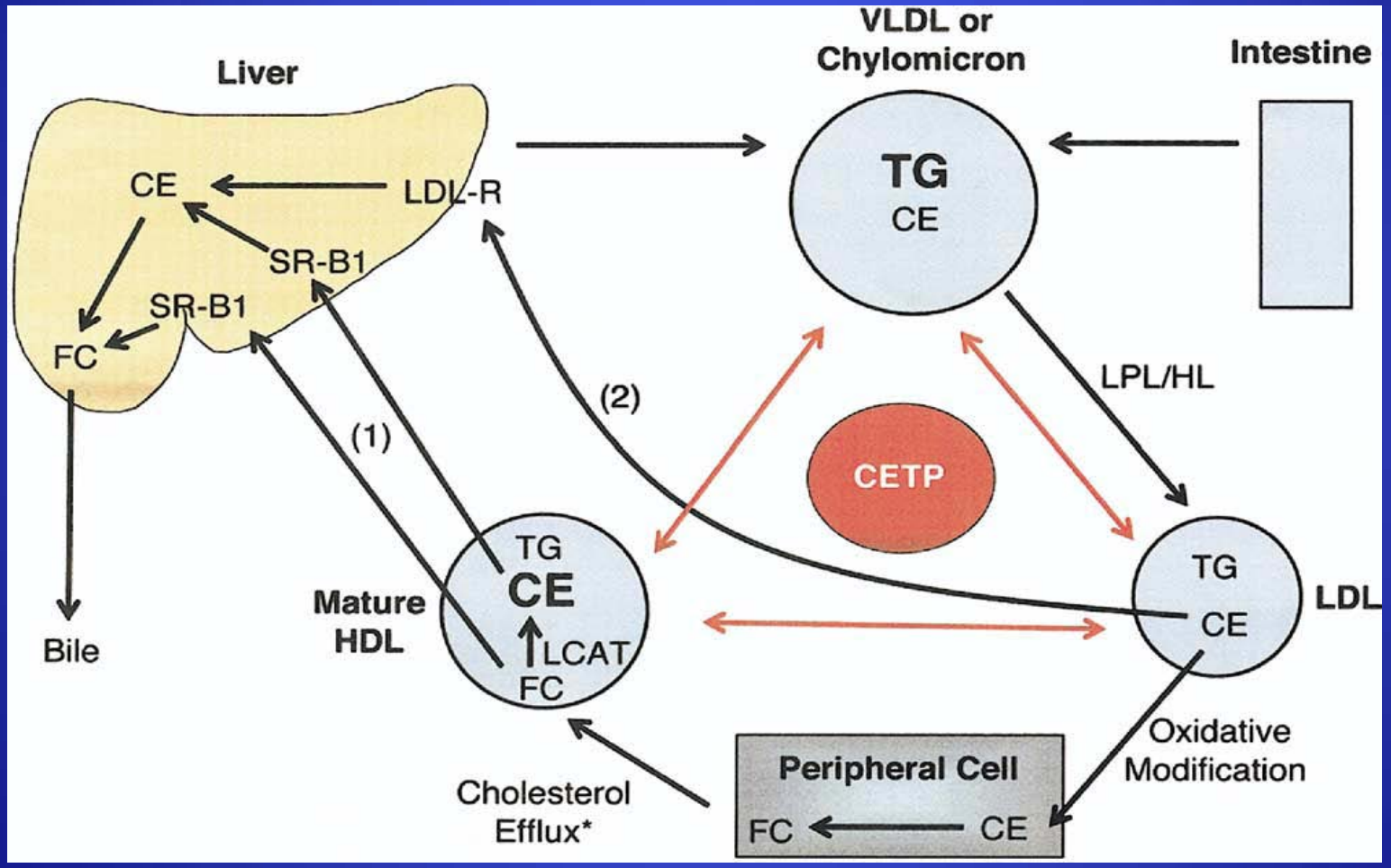
- Describing the preclinical onset of dementia
- Assessing the role of exceptional parental longevity as a protective factor against dementia

Structure of the CETP Gene and the Locations of SNPs Tested.



Bansal A et al. PNAS 2002;99:16871-16874

CETP in Plasma Lipid Transport



Barter et al, *JACC*, 2006

Why *CETP* and Dementia?

- *CETP* may be a "longevity gene"
  - Phenotype of increased lipoprotein particle size (HDL and LDL) and lower prevalence of hypertension, cardiovascular disease, and the metabolic syndrome in Ashkenazi Jewish centenarians and their offspring
  - Phenotype associated with increased cross-sectional frequency of V-allele homozygosity at rs5882: 24.8% of centenarians and 8.6% of unrelated controls

Barzilai et al, *JAMA*, 2003

Study Hypothesis

The V allele will be associated with lower risk of dementia and Alzheimer's disease

CETP

- Chromosome 16q21
- 16 exons
- Codon 405 located in exon 14
- Hydrophobic plasma glycoprotein

Why *CETP* and Dementia?

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Study Hypothesis

The V allele will be associated with lower risk of dementia and Alzheimer's disease

Why *CETP* and Dementia?

- *CETP* may be associated with reduced cardiovascular disease risk and healthy aging
  - In Framingham Offspring Study, OR for prevalent CHD associated with B2 allele of TaqIB polymorphism 0.73 in men
  - In Honolulu Heart Study, elderly Japanese men with Int14A variant showed trend for lower mortality along with significantly higher HDL-C and increased likelihood of "healthy survival"

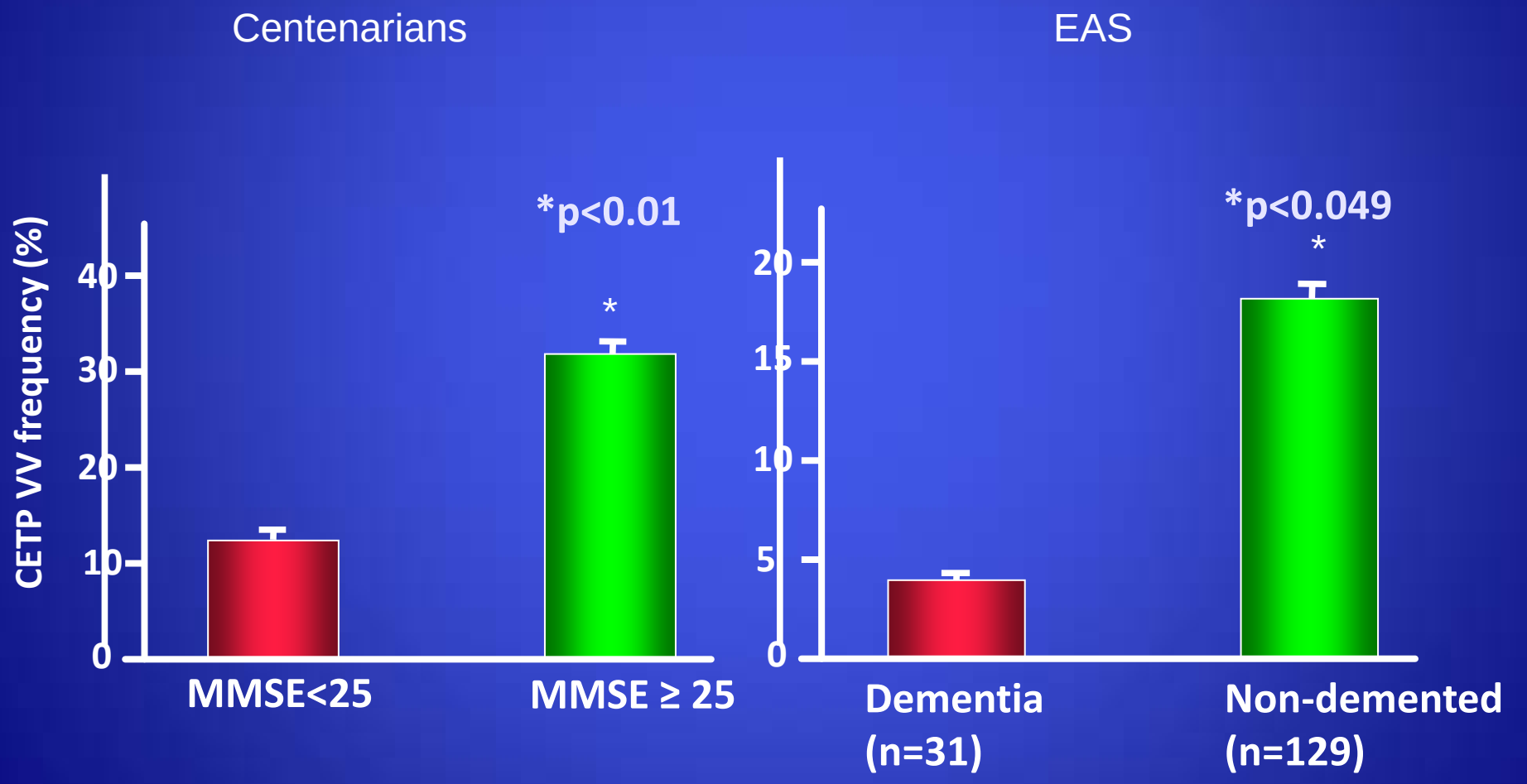
Ordovas et al, *Arterioscl Thromb Vasc Biol,* 2000; Koropatnick et al, *JG:MS, 2008*

Why *CETP* and Dementia?

- For late onset Alzheimer's disease, only *APOE* has been conclusively associated with disease susceptibility
- V405 homozygosity associated with preserved cognition (MMSE>25) in Ashkenazi Jewish centenarians
- V405 homozygosity in non-demented non-Ashkenazi subjects aged 75-85 in Einstein Aging Study occurred nearly fivefold more than in demented subjects

Barzilai et al, *Neurology,* 2006

CETP VV Genotype and Cognitive Function



Barzilai et al, Neurology 2006

Why *CETP* and Dementia?

- Genetic association studies examining *CETP* and dementia risk are inconclusive
  - Nine papers listed at *Alzgene* website
  - Numerous polymorphisms investigated
  - Six negative, two positive, one marginal ("trend")
  - All used case-control study designs
  - Eight of nine used clinic-based populations

Einstein Aging Study

- Longitudinal study of aging and cognition
- Systematic random sampling methods
- Since 1993, > 1900 individuals older than age 70, primarily English-speaking and Caucasian
- Non-demented at study entry

Einstein Aging Study

- Annual clinical visits:
  - Medical history (10-item scale)
  - Functional assessment (LB), GDS
  - Neurological examination
  - Neuropsychological testing
  - Fasting blood sample
  - Consensus dementia diagnosis using DSM-IV for dementia; NINCDS/ADRDA for Alzheimer's disease

Analysis Population

- *CETP* genotype available on 608 individuals
- Exclusions: prevalent dementia, < 2 visits
- 523 individuals in the analysis
- Mean age at baseline 78
- 61% female; 26% African American
- Mean education 14 years
- Mean follow-up time 4.3 years

Statistical Methods

- Cox Proportional Hazards Models
  - Age as time scale
  - Estimation of relative dementia risk in V405 homozygotes and heterozygotes
  - Isoleucine homozygotes were reference group

- Three nested models progressively adjusted for
  - Demographics (sex, education, race)
  - Medical co-morbidities (10-item scale)
  - Presence of *APOE ε4* allele

Results

- Relatively healthy: median 1.0 medical problems endorsed
- No functional decline: median score 7 out of 8 on Lawton-Brody scale
- Few depressive symptoms: median GDS 2
- Demographic characteristics and baseline neuropsychological test performance comparable among the three genotype groups, except for race and premorbid intelligence (homozygotes worse).

Results

- Allele frequency for valine 43.5%
- Genotype frequency: valine homozygotes 21% (110), heterozygotes 45% (235), isoleucine homozygotes 34% (178)
- Genotype frequencies differed slightly from Hardy-Weinberg equilibrium (chi-square 3.86, p=0.05)
- 40 incident dementia cases (35 met criteria for probable or possible Alzheimer's disease)

CETP V405 Genotype and Risk for Dementia and Alzheimer Diseasea

Table 4. *CETP* V405 Genotype and Risk for Dementia and Alzheimer Disease[a]

Category	Model 1[b]		Model 2[c]		Model 3[d]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Risk for dementia vs isoleucine homozygotes						
Valine heterozygotes (n = 16)	0.52 (0.26-1.06)	.07	0.53 (0.26-1.09)	.08	0.57 (0.28-1.15)	.12
Valine homozygotes (n = 5)	0.29 (0.10-0.85)	.02	0.28 (0.09-0.84)	.02	0.28 (0.10-0.85)	.02
Risk for Alzheimer disease vs isoleucine homozygotes						
Valine heterozygotes (n = 14)	0.52 (0.24-1.13)	.10	0.53 (0.25-1.2)	.11	0.56 (0.26-1.2)	.14
Valine homozygotes (n = 5)	0.31 (0.10-0.96)	.04	0.30 (0.10-0.94)	.04	0.31 (0.10-0.95)	.04

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] *P* values from Cox proportional hazard models with delayed entry and age as the time scale. There were 40 incident cases of dementia (19 in the reference group) and 35 incident cases of Alzheimer disease (16 in the reference group).

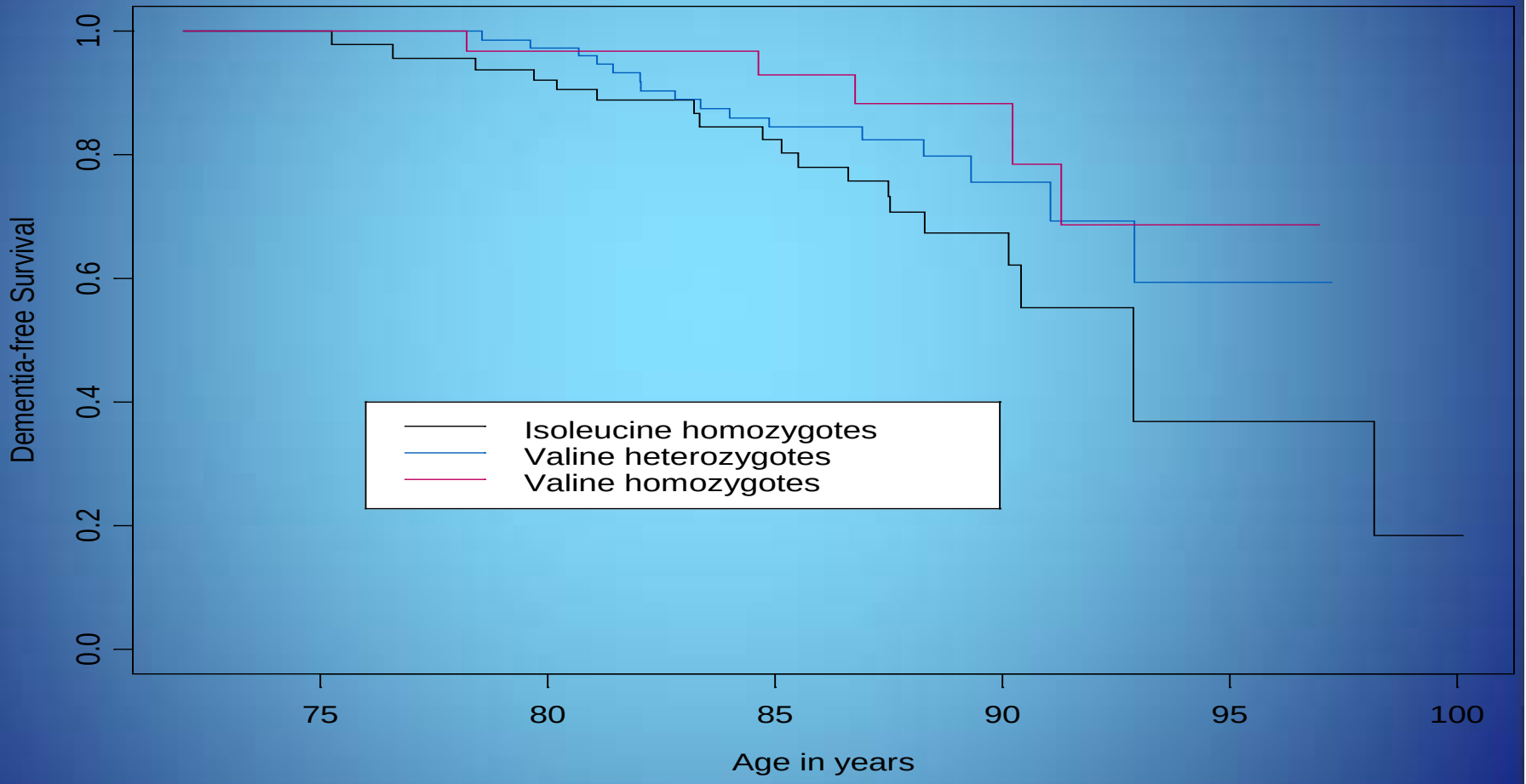
[b] Adjusted for sex, years of education, non-Ashkenazi white race, and black race.

[c] Adjusted for the covariates in model 1 plus an additional adjustment for medical comorbidities as measured by the Medical Comorbidity Index.

[d] Adjusted for the covariates in model 2 plus an additional adjustment for presence of an apolipoprotein E ε4 allele.

Sanders, A. E. et al. JAMA 2010;303:150-158.

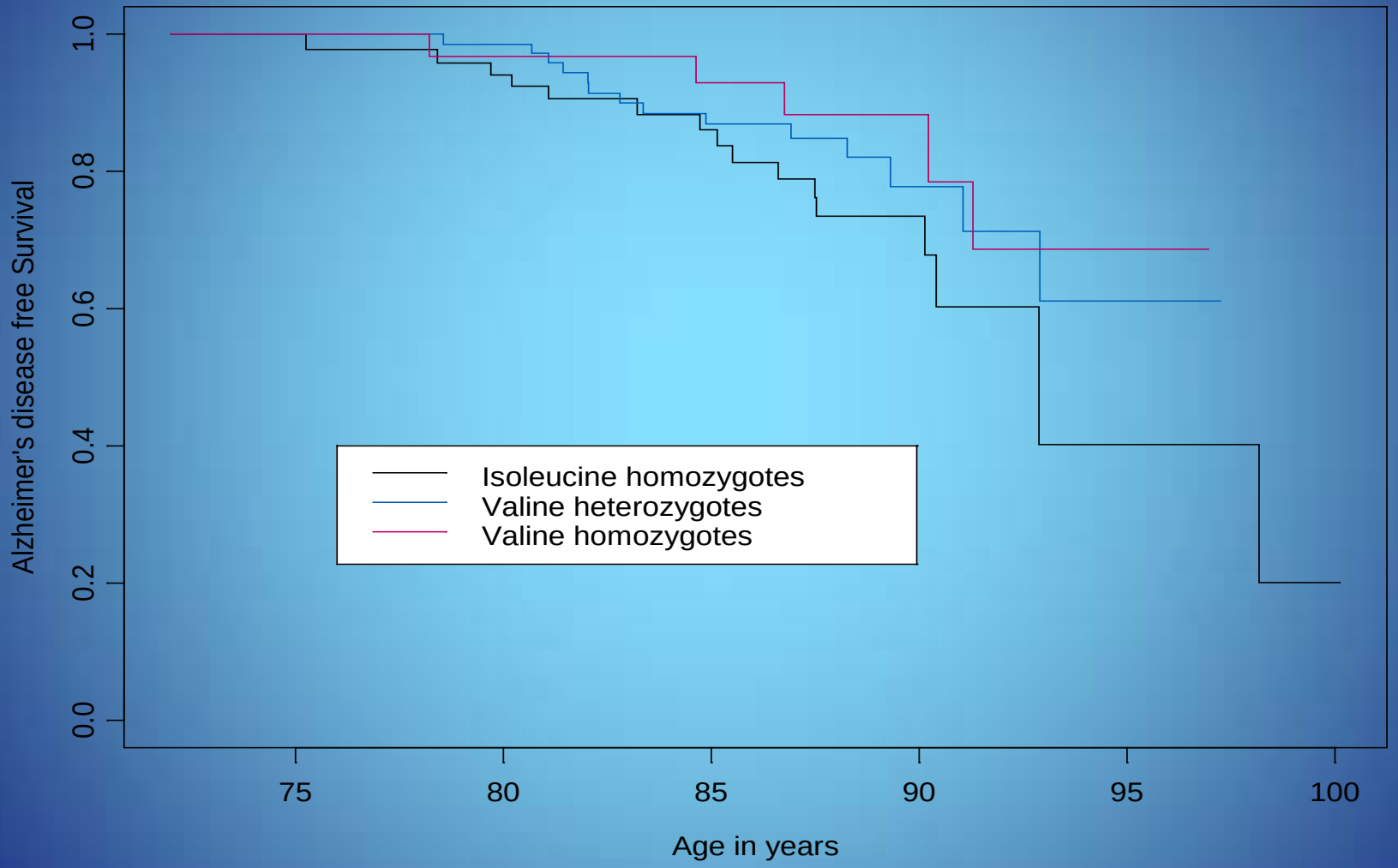
Dementia-Free Survival



Sanders, A. E. et al. JAMA 2010;303:150-158

JAMA

Alzheimer's-Free Survival



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JAMA

Summary and Implications

- Presence of V-allele at codon 405 in the *CETP* gene was associated with reduced incidence of both all-cause dementia and Alzheimer's disease
- Since *CETP* has also been associated with longevity, we hypothesize that in case-control studies protective effects may be attenuated by prolonged survival in cases having the beneficial allele

Limitations

- Sample size precluded analysis of dementia subtypes other than AD
- Community-residing relatively healthy population
- Diagnostic misclassification possible
- Selective attrition possible

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